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ORIGINAL ARTICLE

Evaluation of cytoreductive surgery and HIPEC for peritoneal surface malignancies: analysis of 384 consecutive cases

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Abstract

Background Peritoneal surface malignancy (PSM) was historically associated with a poor survival. The adoption of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can now offer patients with PSM a favourable overall survival. Here, we report our single-institute outcomes following CRS and HIPEC for PSM and evaluate changes in our practice over time.

Methods This is a retrospective review from 2009 to 2018 of all patients undergoing CRS and HIPEC for PSM at a statewide peritoneal disease centre. Cases were divided into the first half and second to compare changes in practice over time.

Results Three hundred and eighty four CRS and HIPEC cases were performed during this time. The median age was 56 years with 59.6% female. The median peritoneal carcinomatosis index (PCI) was 11, with a reduction in PCI in the second cohort (9 v 15, $p < 0.01$). Complete cytoreduction rates were significantly higher in the second cohort (82.3% v 67.7%, $p < 0.01$). Overall, grade III/IV complications occurred in 101 cases (26.3%) with three (0.8%) perioperative mortalities. Median overall survival (OS) for the entire cohort was 85 months, with a 5-year survival of 52%. Median OS was 97 months for PMP, 34 months for colorectal peritoneal metastases and 27 months for other histologies. Completeness of cytoreduction, histology type, and PCI were factors independently associated with overall survival.

Conclusion CRS and HIPEC can offer highly favourable outcomes for PSM with low morbidity. Successful complete cytoreduction rates improved significantly with greater experience and better patient selection.

Keywords Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Peritoneal surface malignancy · Peritoneal carcinomatosis

Introduction

Peritoneal surface malignancy (PSM) was historically viewed as a terminal manifestation of gastrointestinal malignancies, with a median survival of 3.1 months [1]. Treatment with standard modalities such as systemic chemotherapy had poor efficacy in the treatment of peritoneal disease [2, 3]. Over the last two decades, however, the concept of treating PSM as a loco-regional disease led to the introduction of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).

The basis for cytoreductive surgery involves removal of all macroscopic intraperitoneal tumour deposits, with the addition of heated intraperitoneal chemotherapy aimed at eradicating any microscopic and isolated tumour cells. Hyperthermia to 41–43 °C acts synergistically to enhance the efficacy of the chemotherapy. Pioneered by Sugarbaker in the 1990s in the treatment of pseudomyxoma peritonei (PMP) [4, 5], CRS and HIPEC soon became the standard of care for patients with PMP. Studies reported a highly favourable 43–83% 5-year survival for patients undergoing CRS and HIPEC for PMP of appendiceal origin [6–9].

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Early studies also demonstrated a survival benefit from aggressive cytoreductive surgery for low volume peritoneal metastases in colorectal cancer [10, 11]. Verwaal et al. in 2003 demonstrated in a randomized trial that CRS and HIPEC offered a significant overall survival benefit of 22.3 months compared to 12.6 months with systemic therapy for patients with isolated colorectal peritoneal metastases (CRPM). Further studies have since reported highly favourable 20–31% 5-year survival, with a median overall survival of 32 to 41 months following CRS and HIPEC for CRPM [12–16]. This led to the widespread adoption of CRS and HIPEC for CRPM, with CRS and HIPEC now part of the treatment pathway for CRPM in many countries [17, 18]. In other cancers such as mesothelioma, CRS and HIPEC form the mainstay of treatment, offering patients a 40 to 53 months overall survival [19, 20].

Our institute has been the statewide peritoneal disease centre since 2009. In this study, we aim to evaluate our outcomes from CRS and HIPEC for PSM since the inception of the peritoneal disease service. In particular, we aim to explore the morbidity, mortality and survival following CRS and HIPEC and changes in our practice with increasing experience.

Methods

Patients and inclusion criteria

Data was retrospectively analysed from the prospectively maintained peritoneal disease database. All patients undergoing CRS and HIPEC from June 1, 2009 to May 31, 2018 were included in the study. Patient demographics, histology, operative details, complications and follow-up were recorded.

Perioperative management

Patients were pre-operatively assessed with routine full blood counts, liver function tests and coagulation studies. An FDG positron emission tomography-based computed tomography (PET/CT) scan of the chest, abdomen and pelvis was performed in most cases. All patients were discussed at the peritoneal disease multidisciplinary meeting (MDT) involving peritoneal surgeons, gastrointestinal (GI) oncologists, GI pathologists, radiologists and nuclear medicine physicians.

Diagnoses

Pseudomyxoma peritonei: PMP is a clinical syndrome characterized by mucinous, gelatinous ascites. While PMP can arise from various pathologies, the most common is an appendiceal mucinous neoplasm. In this manuscript, the term PMP refers to peritoneal disease originating from appendiceal mucinous neoplasms (low-grade or high-grade mucinous neoplasm) only.

Appendiceal carcinoma/cancer: peritoneal disease arising from appendiceal adenocarcinoma, mucinous adenocarcinoma (having clear pathological evidence of infiltrative invasion).

Colorectal peritoneal metastases: peritoneal metastases originating from colorectal adenocarcinoma.

Management strategy based on pathology

PMP: CRS and HIPEC were offered to all patients with PMP if they were medically fit. A high PCI was not a deterrent to offering CRS and HIPEC. The aim was always to achieve a macroscopically complete resection. If this was not possible due to areas of unresectable disease, maximal tumour debulking was performed, as debulking can also provide favourable survival.

Appendiceal carcinoma: Management strategy was similar to PMP. Patients with appendiceal adenocarcinoma with peritoneal metastases were offered CRS and HIPEC as long as they were medically fit. While the aim was always to try and achieve a complete macroscopic resection (CC 0/1), maximal tumour debulking was performed if there were areas of disease that were unresectable.

CRPM: Selection for CRS and HIPEC was more selective in patients with CRPM. The policy of the unit and the MDT consensus was to offer CRS and HIPEC to patients with a PCI ≤ 15, as the benefit of CRS and HIPEC diminishes in those with a higher PCI. Patients are thoroughly assessed with PET/CT to evaluate burden of disease. If disease is very low volume on imaging and clearly resectable, they are offered CRS and HIPEC. If disease is very high volume, they are given systemic chemotherapy and not offered CRS and HIPEC. Patients with intermediate disease burden are evaluated further with a diagnostic laparoscopy. The main purpose of laparoscopy was to identify patients who may have unresectable disease that was not detected on imaging. If laparoscopy cannot identify any clearly unresectable disease, the patient is offered CRS and HIPEC.

Less common histologies (ovarian, mesothelioma, sarcoma): These were discussed on a case-by-case basis at the MDT, before progressing to CRS and HIPEC.

Cytoreductive surgery and HIPEC

Following laparotomy and adhesiolysis, the PCI was scored from 0 to 39. Cytoreductive surgery was performed in accordance with Sugarbaker's techniques [4, 21]. Organ resections involved segmental colectomy, proctectomy, small bowel resections, cholecystectomy, splenectomy, gastrectomy (partial or rarely total), liver segmental resection and hysterectomy with bilateral salpingo-oopherectomy in females. If nodules

were present on the organs, they were resected as long as an R0 resection could be achieved. Nodules on the small bowel serosa were excised with primary closure, if a large number of nodules were present on a segment of small bowel, a small bowel resection was performed. Nodules on the colon led to a segmental colectomy. Similarly, for nodules on the spleen, a splenectomy was performed. For nodules on the stomach, they were generally excised with the defect primarily closed. If a large number of nodules were present, a formal partial or rarely, total gastrectomy was performed. Stripping of pelvic and diaphragmatic peritoneum was recorded when performed. Cytoreduction score was recorded at the end of each operation. CC 0 implied no residual macroscopic disease. CC 1, 2 and 3 implied residual disease less than 2.5 mm, 2.5 mm–2.5 cm and greater than 2.5 cm respectively. CC 0/1 was considered macroscopically complete resection, with subsequent administration of HIPEC. CC 2/3 cases were deemed incomplete cytoreduction and not given HIPEC, except in selected cases such as presence of intractable ascites. HIPEC was administered via open coliseum technique with a target intraperitoneal temperature of 41–43 °C.

HIPEC drugs and dosage

Pseudomyxoma peritonei of appendiceal origin: mitomycin C (15 mg/m^2) for HIPEC, with intravenous 5-FU (400 mg/m^2) for 90 min.

Appendiceal adenocarcinoma: oxaliplatin (350 mg/m^2) with intravenous 5-FU (400 mg/m^2) for 30 min.

Colorectal peritoneal metastases: oxaliplatin (350 mg/m^2) with intravenous 5-FU (400 mg/m^2) for 30 minutes. If there was known insensitivity to oxaliplatin, mitomycin C (15 mg/m^2) was used for 90 min.

Mesothelioma: cisplatin (100 mg/m^2) with mitomycin C (12.5 mg/m^2) for 90 min.

Ovarian cancer: cisplatin (100 mg/m^2) with intravenous 5-FU (400 mg/m^2) for 60 min.

Sarcoma (desmoplastic small round cell tumour): cisplatin (100 mg/m^2) was used for 60 min.

Gastric cancer: cisplatin (50 mg/m^2), doxorubicin (15 mg/m^2) with intravenous 5-FU (400 mg/m^2) for 60 min.

Systemic therapy

PMP: No patient with PMP received systemic chemotherapy. The use of systemic chemotherapy in both the neo-adjuvant setting (NAC) and adjuvant setting was an MDT-based decision.

Appendiceal carcinoma: NAC was given to patients when there were logistic reasons such as wait times before an operation date. Adjuvant chemotherapy was generally given when a CC 0/1 resection was not achieved. Adjuvant chemotherapy was also given at the discretion of the medical oncologists in high-risk patients, such as young patients, high tumour burden and presence of signet ring cells.

CRPM: The unit is very supportive of the use of systemic chemotherapy in patients with CRPM, aiming for patients undergoing CRS and HIPEC to receive either neo-adjuvant or adjuvant chemotherapy. Neo-adjuvant chemotherapy was given for 3 months in most cases when possible. Adjuvant chemotherapy was generally only given when patients had unresectable or very high volume disease at CRS and HIPEC (CC 2/3 resection). For patients who had a CC 0/1 resection, adjuvant chemotherapy was only given if they had not received neo-adjuvant chemotherapy.

Postoperative care and follow-up

Postoperatively, most patients were transferred to intensive care. An early recovery after surgery (ERAS)-based postoperative care program was implemented in all patients. Nasogastric tubes (NGT) were not routinely used. Patients were started on total parenteral nutrition (TPN) on day seven if there was ongoing evidence of postoperative ileus. No patient received postoperative intraperitoneal chemotherapy (EPIC).

There are no consensus guidelines regarding how follow-up should be performed for patients with PSM. We utilize an institutionally based follow-up program that was developed by the peritoneal service and is offered to all patients.

Following discharge, patients are seen in 2 to 4 weeks for clinical review. Subsequently, patients are followed up for clinical review at 3, 6 and 12 months. Blood tests with tumour markers when appropriate are performed at 6 and 12 months. PET/CT imaging is performed at 6 and 12 months. From the second year onwards, patients are followed up every 6 months for clinical review with blood tests and PET/CT.

Complications

Clavien–Dindo grades III, IV, and V were recorded [22].

Statistical analyses

Data was analysed with IBM SPSS version 22. Cases were divided into two cohorts based on the first half of cases performed and second half. Continuous parametric variables were expressed as means with standard deviations, with non-parametric variables expressed as medians with interquartile ranges. Categorical variables were expressed as numbers with percentages.

Differences between the two cohorts were evaluated by Student's *t* test for continuous parametric variables, with chi-Square and Mann–Whitney *U* test used for non-parametric categorical or continuous variables.

Kaplan–Meier survival analysis was performed to estimate the overall (OS) and disease-free survival (DFS). Log rank test was used to assess statistical significance. Overall and disease-free survival were calculated from date of cytoreductive surgery to date of last follow-up or death and date of last follow-up or relapse, respectively.

Factors affecting survival were identified using Cox univariate analysis. Cox multivariate hazards ratio model was developed to identify factors independently associated with overall survival. A p value < 0.05 was considered statistically significant.

Ethics

This project satisfied the Peter MacCallum Cancer Centre Ethics Committee and governance requirements and was granted ethical approval. Ethics approval number was 17/141R.

Results

Patient demographics

A total of 333 patients undergoing 384 CRS and HIPEC procedures were included in the study (Supplementary Figure 1).

Patient demographics are shown in Table 1. The median age of all patients was 56.0 years with a female preponderance (59.6%). Overall, the most common histology leading to CRS and HIPEC was PMP in 178 cases (46.4%). There was a significantly increased proportion of CRPM in the second cohort compared to the first (40.6% v 21.4%, $p < 0.01$), with a lower proportion of PMP cases in the second cohort compared to the first (36.5% v 56.3%, $p < 0.01$). Mesothelioma (8 cases), ovarian cancer (5 cases), sarcoma (3 cases), gastric cancer (2 cases) and mucinous carcinoma of unknown primary (5 cases) accounted for only 23 cases in total and therefore were classified together as "others". However, given the pathologies are significantly different, "others" have been excluded from the survival analysis.

The median PCI was 11 for the entire study population, with a lower PCI in the second cohort compared to the first (9 v 15, $p < 0.01$). In particular, there was a much higher proportion of cases with PCI < 10 in the second cohort (60.4% v 39.6%, $p < 0.01$) and lower proportion of cases with a PCI >30 in the second cohort compared to the first (7.8% v 19.3%, $p < 0.01$). Overall, there was a significantly higher rate of macroscopically complete resections (CC 0/1) in the second cohort compared to the first (82.3% v 67.7%, $p < 0.01$). This was further reflected in a higher proportion of CC 0/1 resections in PMP (81.4% v 69.4%, $p = 0.05$) and CRPM (83.3% v 63.4%, $p = 0.02$) cases in the second cohort compared to the first. Consequently, there was a higher use of HIPEC in the second cohort compared to the first (80.7% v 68.8%, $p < 0.01$).

In keeping with improvement in practice, there were fewer maximal debulking (CC 2) and laparotomy and biopsy cases (CC 3) in the second cohort compared to the first (8.9% v 20.3% for CC 2 and 8.9% v 12.0% for CC 3 respectively).

Approximately one in four cases received a blood transfusion (24.1%). There was no difference in blood transfusion rates between the two cohorts.

Resections and morbidity

Operative resections and morbidity are shown in Table 2. Organ resections were common, with a colectomy or proctectomy performed in 210 (54.7%) and 63 (16.4%) cases in the entire study. The majority of cases required up to two organ resections (82.0%), with almost one in five cases requiring more than two organ resections (18.0%). Overall, there was no difference in the type of organ resections, number of anastomoses, stoma formation or proportion of multi-visceral resections between the two cohorts.

Overall, 101 cases (26.3%) had a major complication (grade III/IV). Intra-abdominal collections occurred in 50 cases (13.0%), with most managed with percutaneous drainage. There were 18 anastomotic leaks (4.7%) in the study. Renal failure requiring renal replacement therapy was rare, occurring in seven cases (1.8%). There were three perioperative mortalities in the study (0.8%). There was no difference in morbidity or mortality rates between the two cohorts.

Systemic therapy

Appendiceal carcinoma

Twelve cases (20%) received systemic chemotherapy. Four cases received NAC and eight received adjuvant chemotherapy.

Colorectal peritoneal metastases

One hundred and four cases (87.4%) received systemic chemotherapy. Seventy cases (67.3%) received NAC. Median OS was the same for those who had NAC compared to those who did not (34 months, log rank $p = 0.65$).

Forty-nine cases (47.1%) received adjuvant chemotherapy. Of these, 27 cases received adjuvant chemotherapy after CC 0/1 resection (none of these had neo-adjuvant chemotherapy).

Overall, of the 91 cases that achieved a CC 0/1 resection, 76 (83.5%) received either neo-adjuvant or adjuvant chemotherapy. Median OS was 40 months for those who had systemic chemotherapy and 34 months for those who did not (log rank $p = 0.80$).

Table 1 Demographics of the cohort

Characteristic		Entire cohort	Cases 1–192	Cases 193–384	*p* value
Number of cases		384	192	192	
Median age		56.0 (47.0–66.0)	57.0 (48.0–66.0)	55.0 (46.0–65.5)	0.64
Gender	Male	155 (40.4%)	85 (44.3%)	70 (36.5%)	0.07
	Female	229 (59.6%)	107 (55.7%)	122 (63.5%)	
Median LOS		11.0 (8.0–18.0)	11.0 (8.0–16.0)	12.0 (8.0–19.0)	0.24
Histology	PMP	178 (46.4%)	108 (56.3%)	70 (36.5%)	*< 0.01*
	Appendix	64 (16.7%)	35 (18.2%)	29 (15.1%)	
	CRPM	119 (31.0%)	41 (21.4%)	78 (40.6%)	
	Others[a]	23 (6.0%)	8 (4.2%)	15 (7.8%)	
Median operation duration (min)		280 (240–360)	280 (220–360)	280 (240–320)	0.86
ASA		2 (1–3)	2 (1–3)	2 (1–3)	0.75
PCI	< 10	192 (50.0%)	76 (39.6%)	116 (60.4%)	*< 0.01*
	10–15	44 (11.5%)	24 (12.5%)	20 (10.4%)	
	16–20	28 (7.3%)	14 (7.3%)	14 (7.3%)	
	21–30	68 (17.7%)	41 (21.4%)	27 (14.0%)	
	> 30	52 (13.5%)	37 (19.3%)	15 (7.8%)	
	Median	11	15	9	
CC score	0/1	288 (75.0%)	130 (67.7%)	158 (82.3%)	*< 0.01*
	2	56 (14.6%)	39 (20.3%)	17(8.9%)	
	3	40 (10.4%)	23 (12.0%)	17 (8.9%)	
CC 0/1 based on histology	PMP	132/178 (74.2%)	75 (69.4%)	57 (81.4%)	*0.05*
	Appendix	51/64 (79.7%)	26 (74.3%)	25 (86.2%)	0.19
	CRPM	91/119 (76.5%)	26 (63.4%)	65 (83.3%)	*0.02*
	Others	14/23 (60.9%)	3 (37.5%)	11 (73.3%)	0.11
HIPEC	Yes	287 (74.7%)	132 (68.8%)	155 (80.7%)	*< 0.01*
	No	97 (25.3%)	60 (31.2%)	37 (19.3%)	
Blood	Yes	93 (24.2%)	48 (25.0%)	45 (23.4%)	0.41
	No	291 (75.8%)	144 (75.0%)	147 (76.6%)	

LOS length of stay, *PMP*, pseudomyxoma peritonei of appendiceal origin, *Appendix* appendiceal adenocarcinoma, *CRPM* colorectal peritoneal metastases, *ASA* American Society of Anesthesiologists, *CC* completeness of cytoreduction

[a] Others included mesothelioma (8), ovarian cancer (5), sarcoma (3), gastric cancer(2), mucinous adenocarcinoma of unknown primary (5)

Survival outcomes

Median follow-up for all cases was 24 months (range 0–135 months). Median OS for all cases was 85 months, with a 52% 5-year survival (Fig. 1a). Median DFS was 30 months for all cases, with a 37% 5-year DFS (Fig. 1b). There were significant differences in OS based on histology, with a median OS of 97 months for cases with PMP and 34 months for CRPM ($p < 0.001$) (Fig. 2a). Following macroscopically complete resection (CC 0/1), median OS was not reached for PMP and appendiceal cancers. Median OS for CRPM was 40 months (Supplementary Figure 2a). DFS was significantly better for PMP with a median DFS of 42 months, compared to 39 months for appendiceal cancer and 13 months for CRPM ($p < 0.001$) (Fig. 2b).

When comparing OS between the two cohorts, there was no discernible change in survival (log rank $p = 0.86$). Median OS in the first cohort was 85 months, with a 3-year survival of 67%. Median OS was not reached in the second cohort, with a 3-year survival of 65% (Fig. 3a). For PMP cases, 3-year survival was 80% in the first cohort compared to 83% in the second (log rank $p = 0.51$) (Fig. 3b). Similarly, for appendix cancers, 3-year survival was 72% compare to 82% in the second cohort (log rank $p = 0.69$) (Fig. 4a). For CRPM cases, there appeared to be a noticeable trend towards a difference, with median OS of 29 months in the first cohort compared to 37 months in the second cohort (log rank $p = 0.06$) (Fig. 4b).

Macroscopically complete resections significantly impacted on survival with CC 0/1 resections having a much better survival compared to CC 2 or CC 3 resections ($p < 0.001$) (Fig. 5a). PCI also significantly impacted on survival, with a lower PCI having a significantly better survival compared to cases with a higher PCI ($p < 0.001$) (Fig. 5b).

On univariable analysis, increasing age, colorectal histology, increasing PCI, completeness of cytoreduction and use of HIPEC were factors associated with overall survival. Cox multivariable analysis identified histology (appendiceal and colorectal), increasing PCI, and incomplete cytoreduction as independent predictors of worse overall survival (Table 3).

Table 2 Perioperative details

Characteristic		Entire cohort	Cases 1–192	Cases 193–384	*p* value
Number of cases		384	192	192	
Morbidity					
Grade III/IV	Yes	101 (26.3%)	48 (25.0%)	53 (27.6%)	0.32
	No	283 (73.7%)	144 (75.0%)	139 (72.4%)	
Intra-abdominal Collection	Yes	50 (13.0%)	21 (10.9%)	29 (15.1%)	0.14
	No	334 (87.0%)	171 (89.1%)	163 (84.9%)	
Anastomotic leak	Yes	18 (4.7%)	7 (3.6%)	11 (5.7%)	0.24
	No	366 (95.3%)	185 (96.4%)	181 (94.3%)	
Major respiratory[a]	Yes	59 (15.4%)	27 (14.0%)	32 (16.7%)	0.29
	No	325 (84.6%)	165 (86.0%)	160 (83.3%)	
Renal failure[b]	Yes	7 (1.9%)	3 (1.6%)	4 (2.1%)	0.71
	No	377 (98.1%)	189 (98.4%)	188 (97.9%)	
Return to theatre	Yes	21 (5.5%)	10 (5.2%)	11 (5.7%)	0.50
	No	363 (94.5%)	182 (94.8%)	181 (94.3%)	
Perioperative mortality	Yes	3 (0.8%)	2 (1.0%)	1 (0.5%)	0.50
	No	381 (99.2%)	190 (99.0%)	191 (99.5%)	
Resections					
Colectomy	Yes	210 (54.7%)	109 (56.8%)	101 (52.6%)	0.24
	No	174 (45.3%)	83 (43.2%)	91 (47.4%)	
Proctectomy	Yes	63 (16.4%)	28 (14.6%)	35 (18.2%)	0.20
	No	321 (83.6%)	164 (85.4%)	157 (81.8%)	
SB resection	Yes	70 (18.2%)	40 (20.8%)	30 (15.6%)	0.12
	No	314 (81.8%)	152 (79.2%)	162 (84.4%)	
Gastrectomy	Yes	11 (2.9%)	5 (2.6%)	6 (3.1%)	0.50
	No	373 (97.1%)	187 (97.4%)	186 (96.9%)	
HBSO	Yes	86 (22.4%)	44 (22.9%)	42 (21.9%)	0.45
	No	298 (77.6%)	148 (77.1%)	150 (78.1%)	
Splenectomy	Yes	46 (12.0%)	28 (14.6%)	18 (4.7%)	0.08
	No	338 (88.0%)	164 (85.4%)	174 (95.3%)	
Number of anastomoses	0	140 (36.5%)	66 (34.4%)	74 (38.5%)	0.54
	1	196 (51.0%)	99 (51.6%)	97 (50.5%)	
	> 1	48 (12.5%)	27 (14.1%)	21 (10.9%)	
Stoma	Yes	56 (14.6%)	28 (14.6%)	28 (14.6%)	0.56
	No	328 (85.4%)	164 (85.4%)	164 (85.4%)	
Organ resections	≤ 2	315 (82.0%)	157 (81.8%)	158 (82.3%)	0.50
	> 2	69 (18.0%)	35 (18.2%)	34 (17.7%)	

HBSO hysterectomy, bilateral salpingo-oopherectomy; *SB resection* small bowel resection

[a] Major respiratory includes pleural effusion, pneumonia, pneumothorax and respiratory failure

[b] Renal failure: those requiring renal replacement therapy

Workload

There has been a significant increase in the number of CRS and HIPEC procedures performed annually since the start of the peritoneal disease service in 2009 (Supplementary Figure 2b). Most notably, there has been a significant increase in the proportion of CRPM cases in the last few years.

Synchronous versus metachronous resections

Forty-three patients underwent a synchronous resection of the primary with peritoneal disease. Median OS was 97 months with synchronous resection compared to 63 months with metachronous resection (log rank $p = 0.10$) (Supplementary Figure 3a). Disease-free survival was 40 months in those having a synchronous resection compared to 29 months in those with a metachronous resection (log rank $p = 0.25$) (Supplementary Figure 3b).

Discussion

In its early years, the adoption of CRS and HIPEC was met with scepticism, largely due to concerns about morbidity and

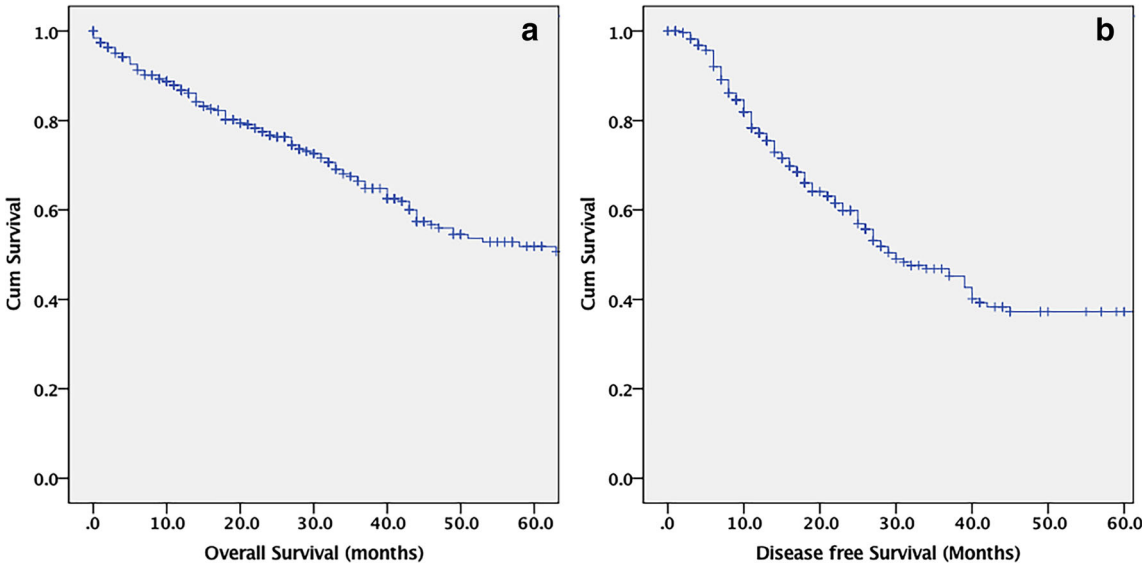

Fig. 1 **a** Overall survival of all cases, with 85 months median OS and 52% 5-year survival. **b** Median disease-free survival of 30 months after complete cytoreduction for all cases

the paucity of randomized evidence. However, with poor survival from standard systemic chemotherapy [1], there was a strong need to pursue a more aggressive treatment for PSM. With increased experience in surgical practice, advances in radiological imaging and better patient selection, CRS and HIPEC can now offer highly favourable results for PSM from gastrointestinal cancers [23–25]. CRS and HIPEC form a critical part of the treatment pathway for PMP, appendiceal, ovarian cancer, CRPM and mesothelioma and have an evolving role in the management of advanced gastric cancer and certain sarcomas [18, 20, 24, 26, 27].

This study is the second largest series reporting on outcomes following CRS and HIPEC for PSM in Australia and New Zealand. Our study demonstrated CC score, PCI and histology as independent predictors of overall survival. This is in keeping with published literature where completeness of cytoreduction, increasing PCI, more aggressive tumour histology as such colorectal histology, major complications and

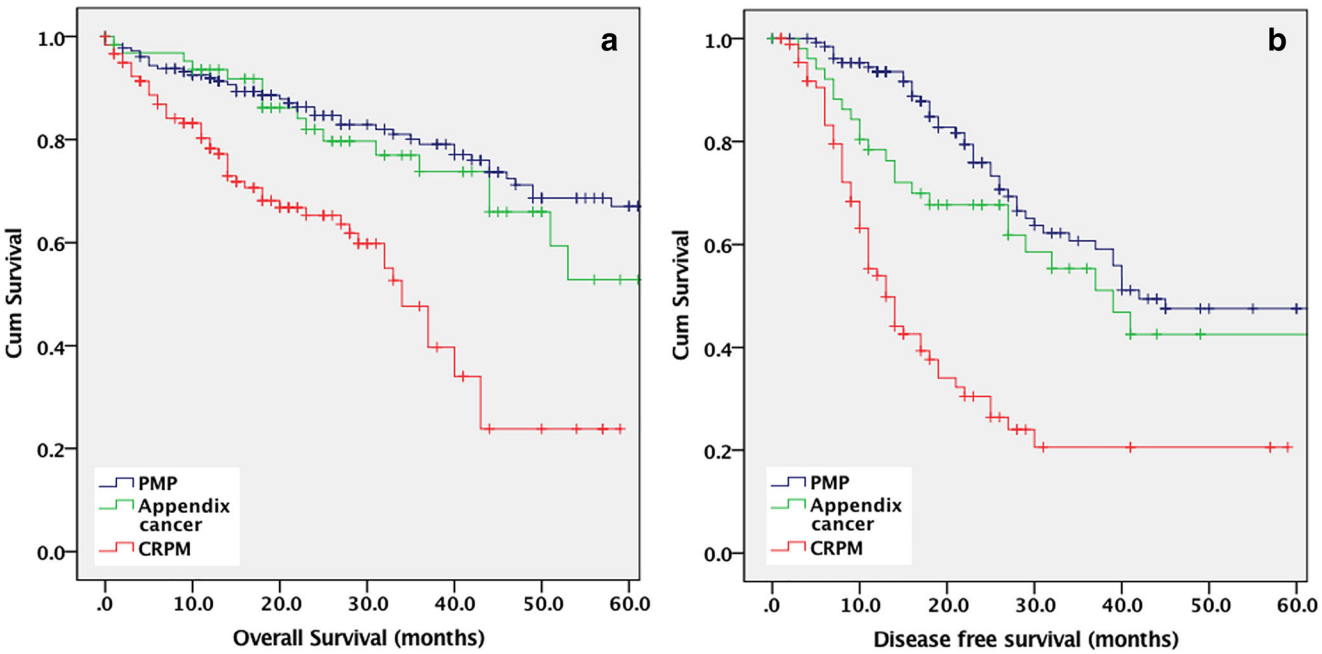

Fig. 2 **a** Overall survival based on histology. Median OS of 97 months for PMP, median OS not reached for appendiceal cancers (loss to follow-up) and 34 months for CRPM (log rank $p < 0.001$). Disease-free survival based on histology. Median DFS of 42 months for PMP, 39 months for appendiceal cancers and 13 months for CRPM (log rank $p < 0.001$)

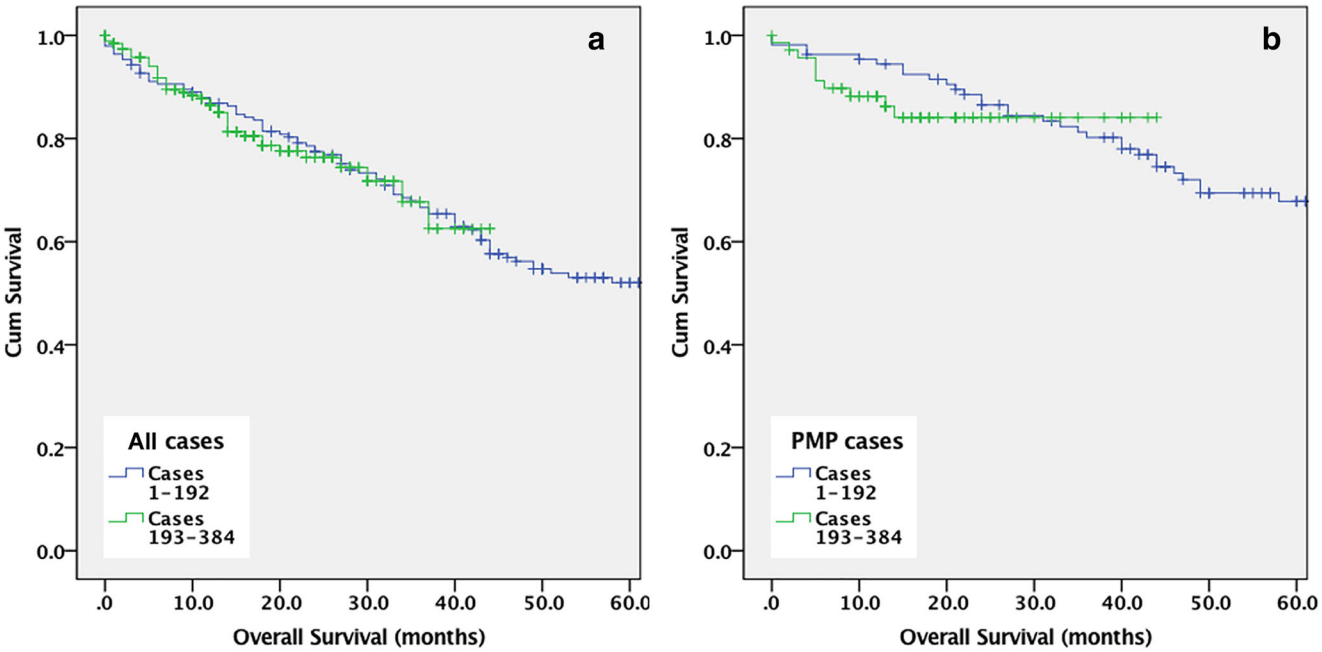

Fig. 3 **a** Overall survival based on cohort. Median OS of 85 months in the first cohort, with a 3-year survival of 67%. Median OS not reached for second cohort, with 3-year survival of 65% (log rank $p = 0.86$). **b** When comparing PMP cases, 3-year survival was 80% in the first cohort compared to 83% in the second cohort (log rank $p = 0.51$)

increasing age have been reported as factors independently influencing survival [6, 24, 28–30]. Our demonstrated OS of 97 months for PMP and 34 months for CRPM is similar to recently published series [6, 13, 23, 24, 28–30]. Following macroscopically compete resection, median OS is not reached for PMP and appendiceal cancer and is 40 months for CRPM, emphasizing the importance of clearing all visible disease. The overall morbidity and mortality rates of 26.3% and 0.8% in the study are low, in keeping with other centres who have reported morbidity and mortality rates of 22.9–50% and 2–3.9% respectively [13, 23, 24, 31, 32].

We believe there is evidence of improvement in our practice over the 9-year period of this study. This is reflected largely in the significantly increased complete cytoreduction

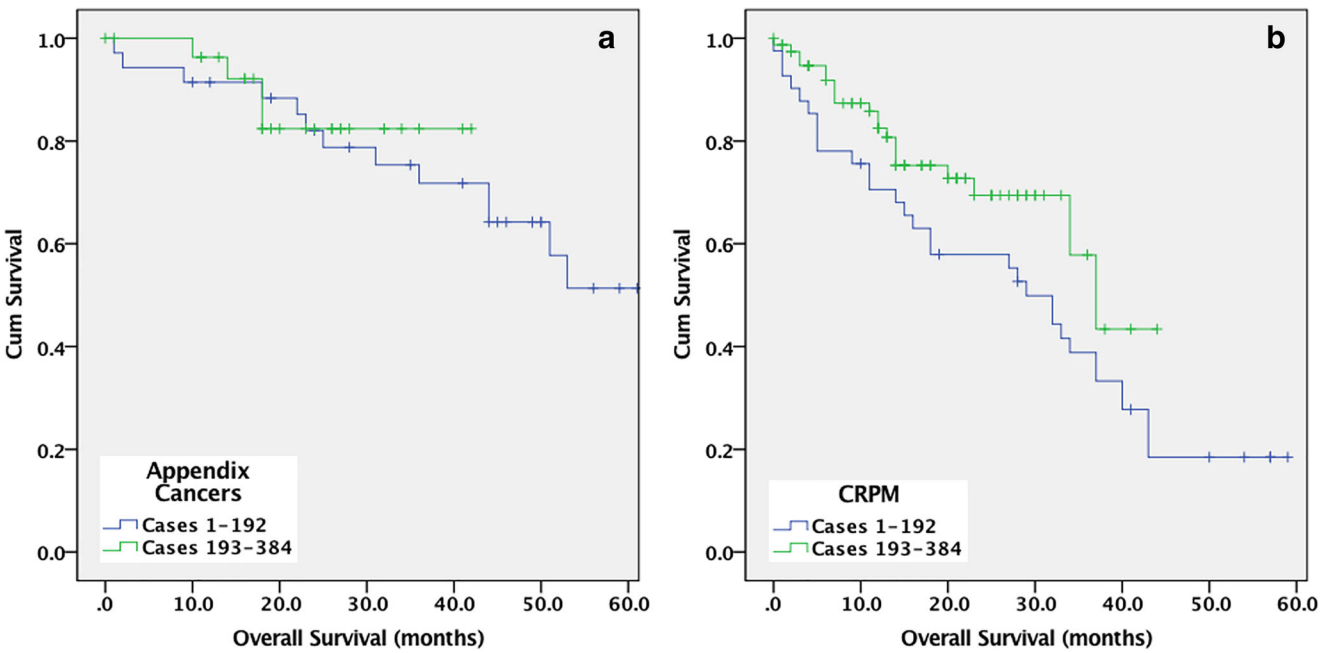

Fig. 4 **a** When comparing appendix cancer cases, 3-year survival was 72% in the first cohort compared to 82% in the second cohort (log rank $p = 0.69$). **b** When comparing CRPM cases, median OS was 29 months in the first cohort compared to 37 months in the second cohort (log rank $p = 0.06$)

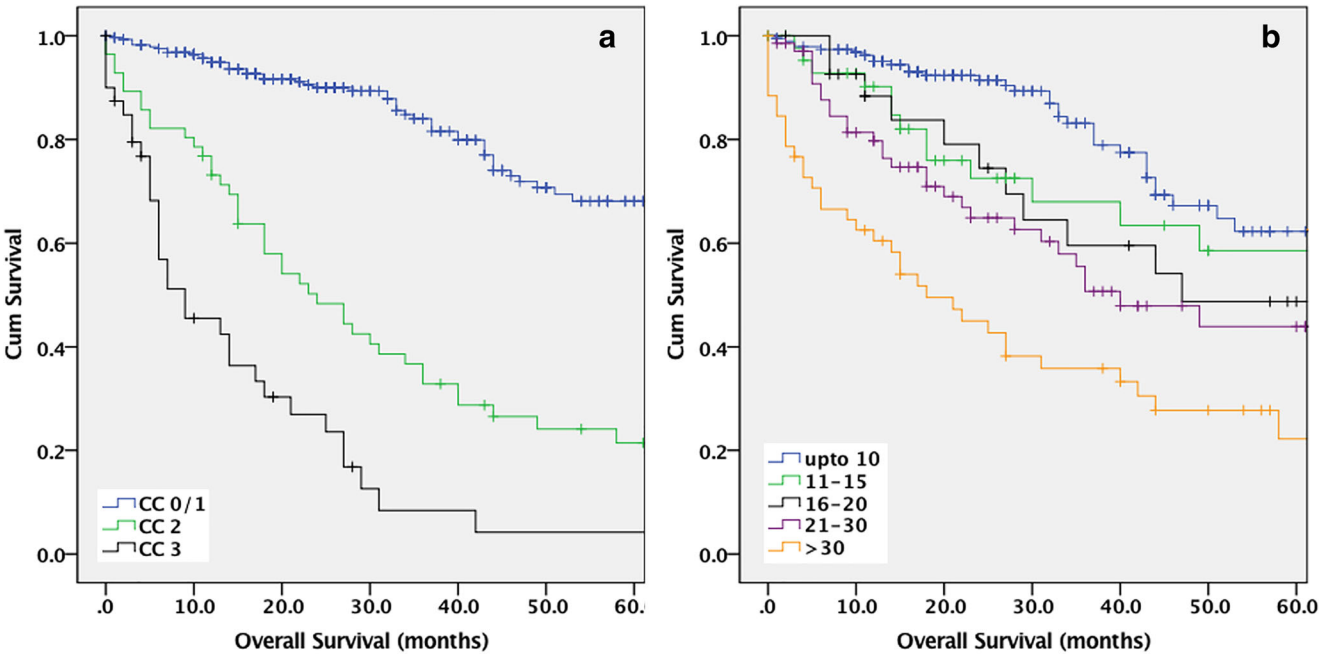

Fig. 5 **a** Overall survival based on completeness of cytoreduction. Following CC 0/1 resection, median OS not reached. Median OS of 24 months following CC 2 resection and 9 months following CC 3 resection (log rank $p < 0.001$). **b** Overall survival based on PCI. Median OS not reached for PCI 0–10 and 11–15. Median OS of 47 months for PCI 16–20, 40 months for PCI 21–30, 18 months for PCI > 30 (log rank $p < 0.001$)

rates in the second cohort compared to the first. Strikingly, there is an increase in complete cytoreduction rates for all histologies in the second cohort. The reasons for higher macroscopically complete resection (CC 0/1) rates in the second cohort are likely multifactorial. Having performed 192 cases in the first cohort, we believe the unit had gained adequate experience as part of overcoming the learning curve. Larger studies have explored the learning curve more extensively and reported that approximately 130–220 procedures are required before gaining proficiency [31, 33]. This would have led to better patient selection in the second cohort, along with improved technical expertise in clearing disease that may have been more challenging to clear early on in the experience. Better patient selection is a combination of improved preoperative, and intraoperative decision-making. For example, all patients now get a PET/CT scan as part of staging, which helps staging better than a contrast CT scan alone. Furthermore, most cases are now performed as two-surgeon procedures, allowing for more balanced intra-operative support, decision-making and technical assistance. Furthermore, for CRPM, diagnostic laparoscopy is employed selectively to try to better select those who would benefit from CRS and HIPEC. All these factors together combine to lead to an improved macroscopically complete resection (CC 0/1) rate in the second cohort without increased morbidity.

Patient selection is critical in ensuring good outcomes following CRS and HIPEC. This is particularly true in the case of CRPM, where benefit from CRS and HIPEC is strongly linked to a lower PCI. With almost double the number of CRPM cases in the second cohort compared to the first, complete cytoreduction rates were still much higher in the second cohort (83.3% v 63.4%), which translates into improved median OS in the second cohort compared to the first. This again reflects better patient selection, particularly as there is well-established benefit for CRS and HIPEC in CRPM when the PCI is less than 15 [26, 34].

While widely accepted in many countries, certain aspects of CRS and HIPEC remain in question. With regard to the treatment of CRPM, the overall role of oxaliplatin-based HIPEC has been put in question based on the recent PRODIGE 7 trial [15]. This French randomized trial demonstrated an excellent 41.2 months median OS following complete cytoreduction for CRPM. The addition of oxaliplatin-based HIPEC following CRS did not improve survival for the entire cohort (41.2 months v 41.7 months, $p = 0.995$). On subgroup analysis, however, HIPEC did offer a significant survival benefit for those with a PCI of 11–15. This trial has raised some questions about the overall efficacy of oxaliplatin-based HIPEC. While there is a survival advantage with the addition of HIPEC to those with a higher PCI, there is no reliable way to accurately select these patients pre-operatively. All patients in this trial received 6 months of perioperative systemic chemotherapy. It is unknown what role this had on survival. It is possible that oxaliplatin may not be the optimal agent for HIPEC, or alternatively that one dose of HIPEC in itself may not be adequate to treat microscopic

Table 3 Cox Univariate and Multivariate Hazard ratio model evaluating factors associated with overall survival

Variable		Univariate HR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Age at operation (continuous variable)		1.02 (1.00–1.04)	*0.01**	1.01 (1.00–1.03)	0.16
Gender	Male				
	Female	0.75 (0.52–1.08)	0.12	0.96 (0.65–1.43)	0.84
Histology	PMP				
	Appendix	1.19 (0.68–2.09)	0.54	2.72 (1.41–5.27)	*< 0.01**
	CRPM	3.31 (2.17–5.05)	*< 0.01**	9.97 (5.43–18.31)	*< 0.01**
Year group (cases)	1–192				
	193–384	1.04 (0.67–1.61)	0.86	1.18 (0.73–1.91)	0.47
PCI	0–10				
	11–15	1.78 (0.90–3.51)	0.10	2.10 (1.03–4.27)	*0.04**
	16–20	2.48 (1.26–4.88)	*0.01**	1.40 (0.58–3.39)	0.46
	21–30	3.16 (1.88–5.31)	*< 0.01**	2.40 (1.12–5.12)	*0.03**
	> 30	5.43 (3.28–8.99)	*< 0.01**	6.81 (2.90–16.03)	*< 0.01**
CC score	CC 0/1				
	CC 2	5.27 (3.45–8.05)	*< 0.01**	3.10 (1.18–8.03)	*0.02**
	CC 3	12.28 (7.54–19.97)	*< 0.01**	3.17 (1.06–9.46)	*0.04**
HIPEC	No				
	Yes	0.15 (0.11–0.23)	*< 0.01**	0.56 (0.24–1.29)	0.17
Grade III/IV complication	No				
	Yes	1.25 (0.84–1.86)	0.27	1.11 (0.72–1.71)	0.64
Organ resections	≤ 2				
	> 2	0.61 (0.36–1.04)	0.07	1.08 (0.58–1.98)	0.82
Transfusion	No	1.06 (0.71–1.61)	0.77	0.70 (0.49–1.27)	0.79
	Yes				
Synchronous resection	Yes				
	No	1.57 (0.92–2.70)	0.10	1.12 (0.59–2.10)	0.73

HR and 95% CI hazard ratio and 95% confidence interval, *PMP* pseudomyxoma peritonei of appendiceal origin, *Appendix* appendiceal adenocarcinoma, *CRPM* colorectal peritoneal metastases, *PCI* peritoneal carcinomatosis index, *CC* completeness of cytoreduction, *HIPEC* hyperthermic intraperitoneal chemotherapy

*Statistical significance on multivariate analysis

disease. It is also conceivable that systemic chemotherapy in the form of neo-adjuvant or adjuvant therapy as an adjunct to CRS may be of benefit, both areas that have not been well explored in the past. The CAIRO6 RCT [35] is currently recruiting to help evaluate this question further. This trial is evaluating the role of perioperative systemic therapy with CRS and HIPEC versus upfront CRS and HIPEC alone. At this stage, while this trial has generated a great deal of debate, we need to await the formal publication. It, however, has highlighted a number of areas to focus further research on.

On the other hand, Van Driel et al. recently demonstrated that CRS and HIPEC does offer a significant overall and recurrence free survival over surgery alone in ovarian cancer [36]. It is likely that this will contribute to more ovarian cancers referrals to peritoneal disease centres in the future.

Despite successful CRS and HIPEC, recurrence rates remain high. In PMP, over 25% recur [37]. In CRPM, up to 70% of patients undergoing complete cytoreduction recur, usually within 9–18 months [38–40]. While some can be offered iterative surgeries, there is a clear need to explore newer avenues of treatment. Newer treatment options like immunotherapy is changing the treatment landscape in many cancers yet remain largely unexplored in PSM [41]. Going forward, this is a rich area for collaborative translational research.

There are a number of limitations in this study that warrant mention. As a retrospective analysis, we remain reliant on the accuracy of the records previously kept. Thirty-nine patients in our cohort had more than one CRS and HIPEC procedure, with re-do procedures likely falling in the second cohort. Re-do procedures would be less likely to involve as many organ resections as the index procedure. This could contribute to the lack of a discernible difference in number of organ resections between the two cohorts. Selection bias is a major limitation that warrants mention. As the sole peritoneal service for the state, almost all our referrals are from other hospitals. It is very likely that treating clinicians at the index hospital only refer patients who are medically fit for consideration of CRS and HIPEC. Therefore, there are possibly other patients with PSM who we would not be capturing in our cohort. Another point of selection bias is more specifically in the case of CRPM. Given initial scepticism in the role of CRS and HIPEC for CRPM, it is possible that patients with CRPM were not referred early on. In recent years, with greater acceptance of CRS and HIPEC, referrals are increasing. This is reflected in Supplementary Figure 2, showing increasing workload at our service, particularly for CRPM. Furthermore, given we only offer CRS and HIPEC for patients with a PCI ≤ 15, contributing further to the patient selection bias. As a young peritoneal

disease centre, our patient selection has been strict, to ensure safety and minimize morbidity. Furthermore, only 6% of our study population had mesothelioma, ovarian cancer and other less common cancers. While this may be merely reflective of the referral patterns, we are unable to accurately report on outcomes of these cancers individually, owing to low numbers.

Conclusion

CRS and HIPEC can offer highly favourable survival for patients with PSM, with low morbidity. Histology, lower PCI and completeness of cytoreduction are factors that are associated with an improved overall survival.

Authors' contributions VN, JT, MM, RR and AH produced the study concept and design. VN and AD performed the scientific literature search and the data collection. VN performed all the statistical analysis. All authors were involved in refining the study design and data interpretation. VN, SW, CL, JM, MM, JT, RR and AH wrote the initial draft, with all authors involved in the editing process and final version of the manuscript. All authors have reviewed and approved the final manuscript. All authors agree to be accountable for all aspects of the work.

Compliance with ethical standards

All the authors have completed the Conflict of Interest Disclosure Form. This project satisfied Peter MacCallum Cancer Centre Ethics Committee and governance requirements and was granted ethical approval. Ethics approval number was 17/141R.

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

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