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Repeated cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from appendiceal cancer: Analysis of survival outcomes

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Abstract

Background: Cytoreductive surgery (CRS)/hyperthermic intraperitoneal chemotherapy (HIPEC) is the procedure of choice in patients with peritoneal dissemination from appendiceal cancer. Although recurrence rates are 26%–44% after first CRS/HIPEC, the role of repeated CRS/HIPEC has not been well defined. We hypothesize that patients undergoing multiple CRS/HIPEC's have meaningful long term survival.

Methods: A retrospective study of a prospective database of 294 patients with peritoneal carcinomatosis (PC) was conducted, of these 162 had PC of appendiceal origin. Twenty-six of these patients underwent 56 CRS/HIPEC. Survival and outcomes was analyzed.

Results: The percentage of patients with pre-surgical PCI scores ≥20 for the first, second, and third CRS/HIPEC was 65, 65, and 25%, respectively. Complete cytoreduction (CC 0-1) at first, second, and, third surgeries was 96, 65 and 75%, respectively.

The mean operating time was 10.1 h. There was no 30-day peri-operative mortality. Following the first, second, and third CRS/HIPEC 27, 42, and 50% experienced grade III complications, respectively.

Mean follow up was 51, 28, and 16 months from the first, second, and third CRS/HIPEC, respectively. Overall survival rate for the first CRS/HIPEC was 100, 83, 54, and 46% at years 1, 3, 5 and 10, respectively; from the second CRS/HIPEC 91, 53, and 34% at 1, 3, and 5 years, respectively; and from the third CRS/HIPEC was 75% at one year.

Conclusion: Repeat CRS/HIPEC can lead to meaningful long term survival rates in patients with appendiceal peritoneal carcinomatosis with morbidity and mortality similar to those of the initial CRS/HIPEC.

Keywords: Appendix cancer; Cytoreductive surgery; HIPEC; Peritoneal carcinomatosis; Repeated HIPEC; Survival

Introduction

Peritoneal dissemination is a common presentation of appendiceal cancer. Disease recurrence rates have been reported to be as high as 91% with debulking surgery,[1] decreasing to 26%–44% after cytoreductive surgery (CRS) and hyperthermic chemotherapy (HIPEC).[2,3] Multiple studies have led to the acceptance of CRS/HIPEC as the standard of care for peritoneal carcinomatosis (PC) with reported survival from 30 to 80% at 20 years.[4–6] This procedure (CRS/HIPEC) consists of a complete resection of all visible disease from the abdominal cavity, including effected viscera, followed by the administration of intraperitoneal hyperthermic chemotherapy.[7–9]

Limited data on outcomes and survival has been published regarding recurrence of PC from appendiceal origin treated with repeated CRS/HIPEC. This study is focused on identifying the long term outcomes of patients with PC arising from appendiceal cancer, who underwent repeated CRS/HIPEC procedures. We propose that patients who undergo multiple CRS/HIPEC's have improved long term outcomes with similar morbidity and mortality to the first CRS/HIPEC.

Patients and methods

A retrospective review of a prospective database of 294 patients with PC who underwent CRS/HIPEC between October 1994 and January 2012 at our institution was conducted. One-

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hundred-sixty-two patients with appendiceal origin were studied. Twenty-six of these patients underwent a total of 56 CRS/HIPEC procedures. Twenty-two patients had 2 CRS/HIPEC and four patients had 3 CRS/HIPEC.

Ronnett's histopathological classification was used to classify appendiceal cancer histology type: disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA).[10,11] For each patient, a CT scan of the chest, abdomen, and pelvis and tumor markers (TM) (CEA, CA19-9, and CA125) were obtained prior to each surgery. The Peritoneal Cancer Index (PCI), as previously described by Jacquet et al., was used to assess the extent of peritoneal involvement.[12] Lymph node (LN) status was obtained from previous surgeries and at the time of repeated CRS/HIPEC. The histology from the CRS/HIPEC case, as well as the pathology from biopsy or first surgeries were reviewed at our institution. All patients had suspected recurrent disease based on CT scan, elevated tumor markers (CEA, CA125, CA19-9) and/or clinical presentation (bowel obstruction). Grade III surgical complications were defined according to Dindo's Classification of Surgical Complications.[13] Patients with extra-abdominal metastatic disease were excluded. All patients participated in a protocol approved by the institutional review board and preoperative informed consent was obtained.

Patient selection criteria for repeated CRS/HIPEC

Repeated CRS/HIPEC is recommended for patients with evidence of recurrent peritoneal disease, evidenced by tumor marker elevation and/or CT findings, with absence of distant metastasis (brain, lung). When the criteria met, the patient case was discussed in a multidisciplinary meeting of experienced physicians, including surgical oncologists, medical oncologists, pathologists, radiologists, and interventional radiologists. The final decision was made by consensus of the group, taking into consideration the patients related variables as well as known adverse risk factors which could represent absolute contraindications, such as extensive small bowel segmentation, multiple small bowel obstruction, biliary obstruction, short bowel syndrome, uncompensated medical issues, severe malnutrition, or poor performance status (ECOG 2–3). This multidisciplinary approach allows close communication between specialties optimizing patient management, including the discussion of potential adjuvant chemotherapy.

It is our practice to admit patients 24 h prior to CRS/HIPEC for IV hydration and appropriate bowel preparation. At this time, a multi-disciplinary team meets and educates patients in the areas specific to post-operative nutrition, wound/ostomy care, and physical therapy.

Surgical technique and patient care

Under general anesthesia, a xypho-pubic incision was made. Resections were done as needed to achieve complete cytoreduction (CC 0-1), which is defined as no visible tumor nodules or nodules less than 2.5 mm in size, using the CC score adopted by the consensus panel recommendations on peritoneal surface malignancies.[14] Resections included excision of previous scar and port sites, anterior abdominal wall, diaphragmatic and pelvic peritonectomies, as well as stripping of peritoneum over omental bursa, porta hepatis, and visceral peritonectomies. Bowel and solid organs were removed, if unable to be cleared of disease. Every attempt was made to avoid stoma creation and extensive small bowel resections to help preserve quality of life.

Following the CRS procedure, HIPEC was performed using closed technique for 90 min prior to performing any anastomosis.[7] The following chemotherapeutic agents were used: Mitomycin-C (40 mg), combination of Mitomycin-C (12 mg) and Cisplatin (50 mg), Mitomycin-C (25 mg) and Doxorubicin (25 mg), Melphalan (50 mg/m^2), or Carboplatin (800 mg/m^2). The choice of chemotherapeutic agent for any specific patient at the repeated HIPEC was determined preoperatively based on either the international consensus or when possible, on tumor sensitivity assay (ChemoFx® – Precisions Therapeutics®). The target outflow temperature was maintained at 41–42 °C, which required an inflow temperature of 42–43 °C. Urine output was maintained between 250 and 400 cc/h during perfusion to avoid renal toxicity.

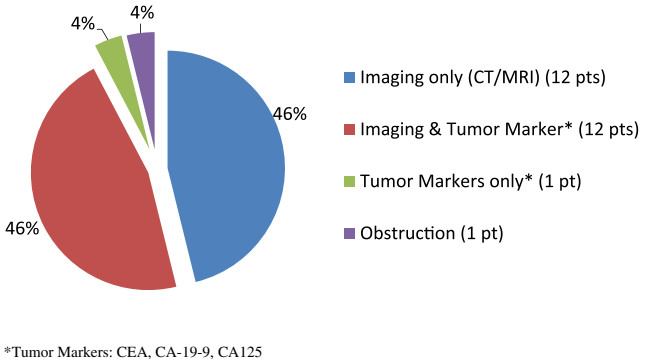
Patients were monitored in the intensive care unit during the first 24 h of the postoperative period or until stable and were subsequently transferred to the surgical oncology floor. Early mobilization was encouraged, with physical therapy assistance on post-operative day one. Low molecular weight heparin and compression stockings completed the deep vein thrombosis prophylaxis. Patients were discharged when clinically stable and low molecular weight heparin was continued on an outpatient basis for 21 days. All patients with PMCA were evaluated in medical oncology consultation. Follow-up was carried out at 3 weeks, 3 months, and every 6 months thereafter. CEA, CA19-9, and CA125 with CT scan of the chest, abdomen and pelvis were performed one-month post-operatively, at 6 month intervals for 5 years, and yearly thereafter. Disease recurrence was detected clinically, radiographically, and/or by tumor marker elevation. No patients were lost to follow up.

Statistical analysis

Overall survival (OS) was analyzed using survival analyses displayed as Kaplan Meier curves. The Log Rank test for the equality of survival curves was used to compare the survival distributions for tumor histology and location of first surgery. Statistically significant results are those with p-values ≤ 0.05. In addition, descriptive statistics are reported for time to follow-up, time between surgeries, Completeness of Cytoreduction (CC) score, pre-surgical Peritoneal Cancer Index (PCI) score, lymph nodes status (LN), and tumor histopathology.

Results

There were 26 patients who underwent more than one CRS/HIPEC procedure. Clinicopathologic patient characteristics are shown in Table 1. The mean age of patients at PC diagnosis was 48.9 years, with a range of 28.8–66.8 years. Fifty-four percent of the population was female and 46% male. There were no 30-day perioperative or hospital mortalities after the first, second, or third CRS/HIPEC. The mean time from diagnosis to first CRS/HIPEC was 15 months, from the first to second CRS/HIPEC was 23 months, and from the second to third CRS/HIPEC was 41 months.



*Tumor Markers: CEA, CA-19-9, CA125

Figure 1. Diagnostic Indication for Second CRS/HIPEC. CT: Computed Tomography; MRI: Magnetic Resonance Imaging; CEA: Carcinoembryonic antigen; Cancer antigen 19-9; Cancer antigen 125.

First CRS/HIPEC

The mean age at first CRS/HIPEC was 50.1 years (range: 33–67). Nine of the 26 patients had their first CRS/HIPEC at another institution. Sixty-five percent of patients (15/23) had a pre-surgical PCI greater than 20. The mean pre-surgical PCI score was 25 (range: 0–39). PCI scores were unavailable for three cases which were completed at outside institutions. A complete cytoreduction (CC 0-1) was achieved in 96% of the cases (25/26). Histopathology yielded 38.5% DPAM and 61.5% PMCA. Twenty-three patients (89%) received Mitomycin-C, 2 patients (7%) received a combination of Mitomycin-C/Cisplatin, and 1 patient (4%) received Mitomycin-C/Doxorubicin, as chemotherapeutic agents during HIPEC. Operating room time ranged from 6.5 to 14.4 h, with a mean time of 10.7 h. Mean hospital length of stay was 13 days. Grade III and IV complication were identified in 7 patients (27%).

Second CRS/HIPEC

Each of the 26 repeat procedures were completed at our institution. The mean age was 52 years (range: 34–69). All

Table 1
Clinicopathologic population characteristics.

Characteristic	Results		
	At diagnosis		
Number of patients (n)	26		
Mean age (range) years	48.9 (28.8–66.8)		
Gender distribution female/male	53.8% (14)/46.2% (12)		
	1st CRS/HIPEC	**2nd CRS/HIPEC**	**3rd CRS/HIPEC**
Number of patients (n)	26	26	4
Mean age (range) years	50 (33–67)	52 (35–70)	51 (37–60)
Gender distribution: female/male	53.8% (14)/46.2% (12)	53.8% (14)/46.2% (12)	50% (2)/50.0% (2)
DPAM	38.5% (10)	38.5% (10)	75% (3)
PMCA	61.5% (16)[a]	61.5% (16)[a]	25% (1)
Pre-surgical PCI > 20	65% (15/23)[b]	65% (17/26)	25% (1/4)
Mean pre-surgical PCI score (range)	25 (0–39)	23 (0–39)	17 (8–26)
CC 0-1 achieved	96% (25/26)	65% (17/26)	75% (3/4)
Mean OR time (range) hours	10.7 (6.5–14.4)	9.7/3.2–14.6	8.7/7.5–10
Mean hospital length of stay (days)	13	11	10
Grade 3 Complications[c]	27% (7)	42% (11)	50% (2)
Mortality (%)	0	0	0
Mean time between surgeries in months (range)	15 (0–107.1)	23.1 (8.7–45.9)	40.8 (14.3–96.4)
Mitomycin-C	89% (23)	35% (9)	–
Mitomycin-C/cisplatin	7% (2)	–	–
Mitomycin-C/doxorubicin	4% (1)	–	–
Carboplatin	–	4% (1)	–
Melphalan	–	61% (16)	100% (4)
Mean follow-up time	51	28	16
Mean follow-up (all surgeries)	65.8		

[a] 1 Patient converted from DPAM to PMCA, considered as PMCA at repeated HIPEC.
[b] 3 Missing PCI scores due to 1st HIPEC outside institution.
[c] Grade III/IV surgical. Annals of Surgery 2004.[15]

patients had radiographic or clinical evidence of resectable disease (Fig. 1). PCI > 20 was seen in 17 patients (65%) (range 0–39). CC 0-1 was achieved in 17 cases (65%). Chemotherapeutic agents included Mitomycin-C in 9 cases (35%), Melphalan in 16 cases (61%), and Carboplatin in 1 case (4%). The mean OR time was 9.7 h, ranging from 3.2 to 14.6 h. The mean hospital length of stay was 11 days and 11 patients (42%) experienced grade III/IV surgical complications.

Third CRS/HIPEC

Four patients underwent a third CRS/HIPEC. Three patients (75%) were classified as DPAM and 1 patient (25%) as PMCA. The mean age of the group was 50.6 years with 50% female. PCI > 20 was seen in 1 patient (25%) and a CC 0-1 resection was achieved in 3 patients (75%). All 4 patients (100%) received Melphalan as the chemotherapeutic agent during intraperitoneal chemoperfusion. The mean OR time was 8.7 h (range: 7.5–10 h), and the mean hospital length of stay was 10 days. Two patients (50%) suffered Grade III and IV complications.

Outcomes and survival

Mean length of follow-up was 51, 28, and 16 months from the first, second, and third CRS/HIPEC, respectively. Mean length of hospital stay for first, second, and third CRS/HIPEC was 13, 11, and 10 days, respectively. Median overall survival (OS) was 46.5 months, with a mean OS of 57.6 months.

OS rate from the first CRS/HIPEC was 100, 82.7, 53.6, and 45.9% at years 1, 3, 5 and 10, respectively. OS from the second CRS/HIPEC was 90.9, 54.3, and 33.9 at 1, 3, and 5 years, respectively. OS from the third CRS/HIPEC was 75% at one year. Fig. 2 shows the Kaplan–Meier survival curve for patients in the first (A) and second (B) CRS/HIPEC.

Survival related to CC and PCI scores

OS from the second CRS/HIPEC associated with CC 0-1 score at 1, 3, and 5-year was 92.9, 66.2, and 44.1%, respectively. OS in patients with incomplete cytoreduction (CC 2–3) at 1 and 3 years, were 83.3 and 41.7%, respectively ($p = 0.360$), 5 year OS was not obtained for this group due to the low number of patients. OS associated with PCI < 20 at 1 and 3 years was 100 and 53%, respectively, with no 5 year OS obtained due to low number of patients in this group. OS for PCI ≥20 was 85.6, 53.2, and 40.1% at 1, 3 and 5-years, respectively ($p = 0.667$) (Fig. 3).

Survival related to histopathology

Of the 10 patients (38.5%) identified as DPAM, 9 had negative LN and 1 had positive LN at the time of the first surgery. All were alive at the end of the study. Seven patients (70%) were alive with disease (AWD) and 3 patients (30%) had no evidence of disease (NED). The DPAM group had a mean follow-up of 38.2 months after the second CRS/HIPEC.

Of the 16 patients (61.5%) identified as PMCA, 9 had negative LN at the time of the first CRS/HIPEC. Four patients (44.5%) were NED, 3 patients (33.3%) were AWD, and 2 patients (22.2%) were dead of disease (DOD). All 7 patients who had positive LN were DOD at the end of the study. The mean follow-up time to death after the last CRS/HIPEC was 23.8 months for the 9 PMCA patients who are DOD. The median survival of all PMCA patients was 53 and 29.9 months after the first and second CRS/HIPEC, respectively.

Median follow up time of DPAM patients was 61, 46, 27, and 21 months after diagnosis, first, second and third CRS/HIPEC, respectively. Median follow up time of PMCA patients was 56, 41, 23, and 10 months after diagnosis, first, second and third CRS/HIPEC, respectively.

Of the 17 patients alive, an overall mean follow-up time from diagnosis was achieved at 72.7 months (range

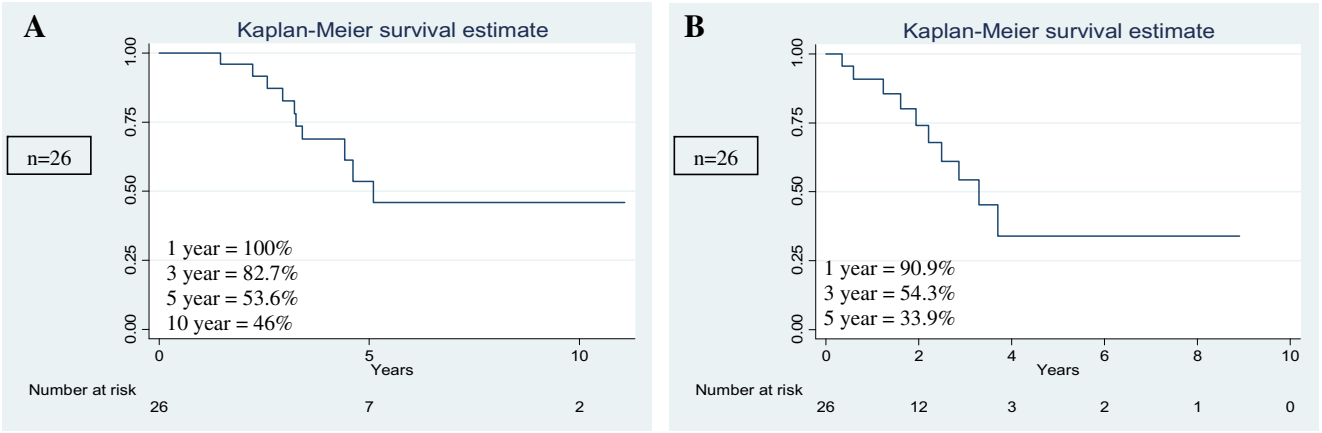


Figure 2. Kaplan–Meier Survival Curves Depicting the Overall Survival after the First (A) and Second (B) CRS/HIPEC.

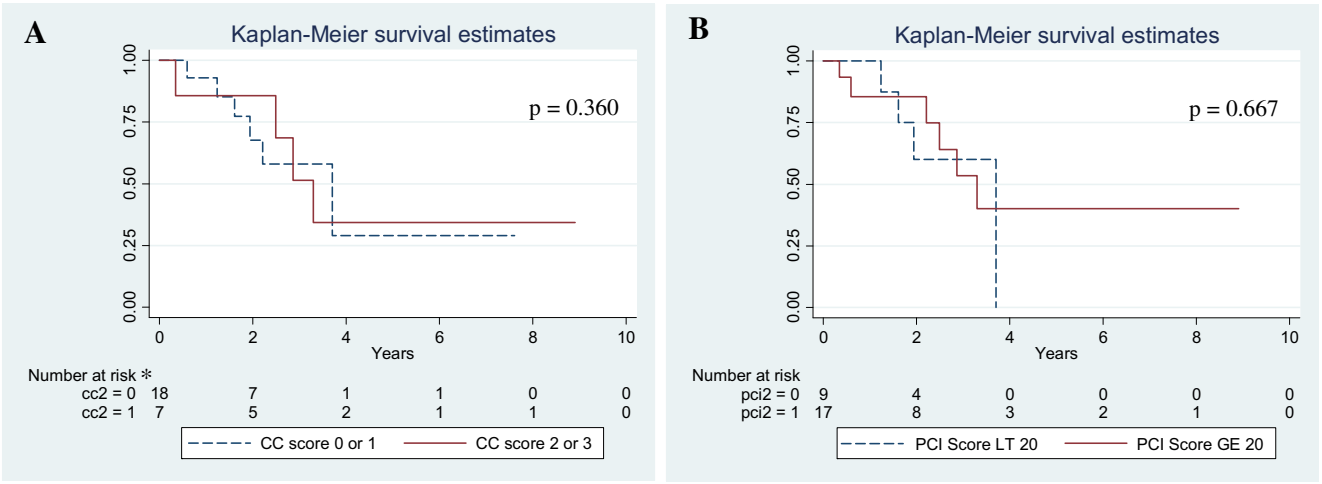


Figure 3. Kaplan–Meier Survival Curves Showing the Overall Survival related to CC scores (A) and PCI scores (B) after second CRS/HIPEC. CC: Completeness of Cytoreduction; PCI: Peritoneal Cancer Index*1 CC score was unavailable.

15–145) and overall mean follow-up time since the last CRS/HIPEC was 21.6 months (range: 2–92). CC score of 0–1 was obtained in 90% of DPAM and 100% of PMCA patients.

The 5-year survival for DPAM was 90% from initial CRS/HIPEC (10/11), and 100% after second CRS/HIPEC (10/10), while the 5-year survival for PMCA patients was 32% and 0% after the initial and second CRS/HIPEC, respectively ($p = 0.018$ and $p = 0.002$) (Fig. 4). The histopathology of one patient converted from DPAM to PMCA. The patient was considered as PMCA for the analysis of the second CRS/HIPEC.

Discussion

Outcomes and survival for patients with PC from appendiceal origin are related to the completeness of cytoreduction score (CC), tumor histopathology (DPAM vs. PMCA), lymph node status, and Peritoneal Cancer Index (PCI) score.[3,4,15–19] Patients with an incomplete cytoreduction and without re-interventions have a 5 and 10-year survival of 20% and 0%, respectively.[20]

Limited data has been published on second CRS/HIPEC for this condition. Esquivel et al., at the Washington Hospital Center (WHC), reported 98 patients with appendiceal cancer who underwent second look CRS/HIPEC, irrespective of clinical or radiological evidence of disease.[16] Votanopoulos et al. at Wake Forest (WF), reported repeated CRS/HIPEC's in a variety of abdominopelvic malignancies with evidence of recurrent disease, of which 53% of patients (33/62 patients) had malignancy of appendiceal primary.[17] The comparison of survival and outcomes from these reports is limited due to patient selection and variables measured.

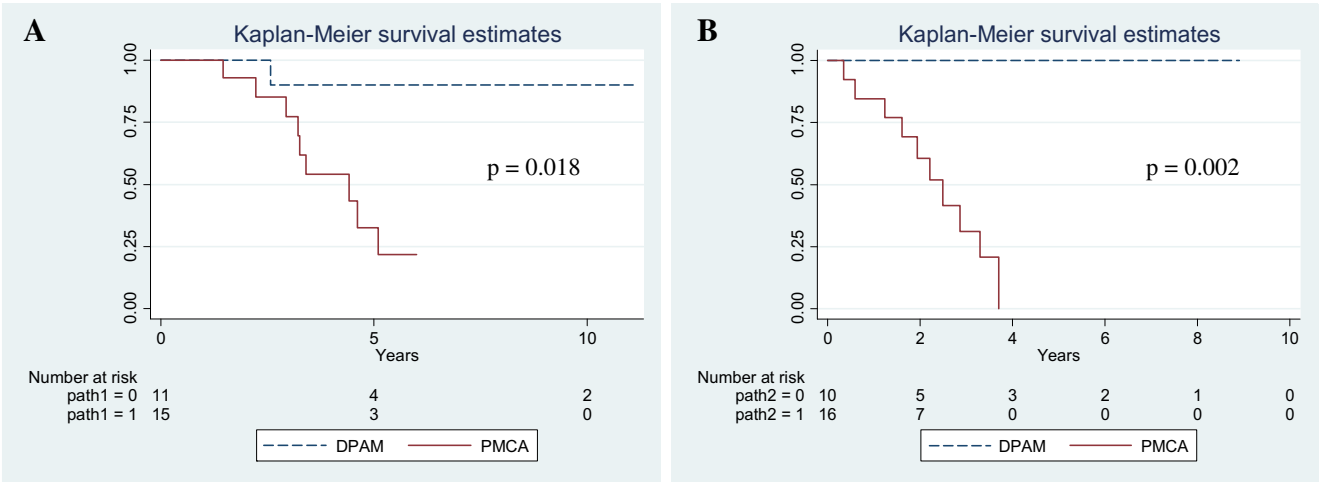


Figure 4. Kaplan–Meier Survival Curves Depicting the Overall Survival related to histopathologic diagnosis at first (A) and second (B) CRS/HIPEC. Note: One patient histopathology changed from DPAM at initial surgery to PMCA at the second surgery.

WHC group reported improved outcomes of patients selected for a second CRS/HIPEC, with a 5-year survival rate of 73.6%, compared to 68% survival rate for patients who did not receive a second procedure.[16] The WF group reported 1, 3, and 5-year OS rates of 78.7%, 48.6%, and 31.6%, respectively following the second CRS/HIPEC.[17] Similarly, our data shows a 1, 3, and 5-year OS after second CRS/HIPEC of 90.9, 54.3 and 33.9%, respectively. The mean survival time after the second CRS/HIPEC was again similar to the WF group with 52.1 and 57.6 months, respectively.[17] The OS differences between published studies and our data could be related to patient selection, documentation of recurrence of disease, and timing of the procedure.

Although there have only been 4 patients in our center who underwent a third CRS/HIPEC, the one year survival rate of 75% is encouraging. This is similar to the 5-year OS of 70% and a 10-year survival of 53% for patients undergoing three or more CRS/HIPEC reported by Mohamed et al.[21] (also from WHC), although neither histopathology type (DPAM vs. PMCA) nor preoperative evidence of disease recurrence was specified.

The histopathologic subtype remains one of the dominant factors in survival.[3] Outcomes of DPAM are significantly better than that of PMCA patients.[4,10] We obtained a significant higher OS for patients with DPAM compared to PMCA patients, after the first and second CRS/HIPEC ($p = 0.018$ and $p = 0.002$) (Fig. 4). PMCA histopathology is considered a negative predictor for survival in patients with PC from appendiceal origin.[15,22]

WF reported morbidity of 48.3% (30/62) and mortality of 4% (2/62).[17] The present study showed similar results with 43% experiencing grade III/IV surgical complications[13] and there was no 30-day or in-hospital mortality. We did not see any significant difference in morbidity or mortality between the first and repeated CRS/HIPEC.

In this study, no association was found between CC scores and survival perhaps due to the low number of patients with CC scores ≥ 2. However, in previous studies which included patients undergoing CRS/HIPEC for PC from appendiceal origin, there was a significant association between low survival rates and higher CC scores.[15] In addition, WHC group reported a 5-year survival in CC 0-1 and CC 2-3 of 84% and 44%, respectively.[16] Our study shows that a complete cytoreduction was more feasible at the first CRS/HIPEC. Although CC score appears to be a predictive factor,[22] the ability to achieve a complete resection is dependent not only on tumor histopathology and tumor extension, but also on operator expertise and skill.

In the present study, all PMCA patients with positive LN died of disease. A positive LN status is a negative prognostic factor in patients undergoing CRS/HIPEC. Patients with high grade tumors (PMCA) with positive LN had 5-year OS of 11%, compared to 76% for negative LN status ($p < 0.001$).[18]

PCI >20 has been associated with decreased survival.[22] The WHC demonstrated a negative impact on survival if the PCI score increased after the first CRS/HIPEC in patients undergoing repeated CRS/HIPEC.[16] However, as previously reported by our group, we have not considered high PCI scores as a contraindication for CRS/HIPEC. The survival rate of patients with PCI $>$ or $<$20 with a CC 0-1 achieved was statistically similar.[19]

In our patients with PMCA, the possibility of obtaining a CC 0-1 score differed depending on the PCI score. We previously reported that CC 0-1 was achieved in 65% of patients with PCI $\geq$ 20 and in 96% of patients with PCI $<$ 20, indicating that patients with a low tumor load are more likely to be completely resectable (CC 0–1) ($p = 0.004$). This would reflect better outcomes.[19]

It remains a challenge to identify which patients will benefit from repeated CRS/HIPEC procedures. Further studies will be required. There is evidence that stands a trend towards improved outcomes if patients are selected for multiple procedures.[16] In order to associate this procedure with prolonged survival and potentially disease-free survival, patient selection and timing is crucial for positive patient outcomes after repeated CRS/HIPEC.[17]

Based on our results, higher PCI scores, disease histology (PMCA), and/or LN status are factors that affect patient outcomes; however, are not absolute independent exclusion factors for repeated CRS/HIPEC procedures.[15,18,19] PMCA patients with positive LN should be carefully selected due to poorer survival following repeated CRS/HIPEC (all LN positive patients died of disease following the second procedure), but a significant median OS (30 months) is encouraging. Each patient should be individualized according to clinical status, and tumor biology to maximize repeated CRS/HIPEC benefit.

Our study suggests that re-operative CRS/HIPEC can lead to meaningful long term survival rates in patients with appendiceal peritoneal carcinomatosis. This procedure can be done with very low mortality and morbidity similar to that of the initial CRS/HIPEC.

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Jennifer Francis: Technical support.
Juan C Falla: Data collection.

Conflict of interest statement

The authors declare no conflict of interest.

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