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Long term survival analysis after hyperthermic intraperitoneal chemotherapy with oxaliplatin as a treatment for appendiceal peritoneal carcinomatosis

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ABSTRACT

Background and objectives: Complete cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) have been proven to lengthen survival in appendiceal peritoneal carcinomatosis (PC-A). The aim of this study was to analyze survival results of this therapy in our institution over the last 10 years.
Methods: Data was retrospectively reviewed and analyzed. Treatment consisted of CRS plus HIPEC with oxaliplatin. Ronnett's histologic classification was used (peritoneal mucinous carcinomatosis (PMCA), PMCA with intermediate features (PMCA-I) and disseminated peritoneal adenomucinosis (DPAM)). Overall survival (OS) and disease-free survival (DFS) estimates were calculated using Kaplan–Meier survival curves.
Results: 109 patients with PC-A underwent laparotomy with curative intent. Of those, 92 underwent CRS plus HIPEC. Median follow-up was 42 months. The 5 and 10-year OS rates for the HIPEC group were 82.2% and 76.5%. The 5 and 10-year OS estimates for DPAM and PMCA-I subgroups were 100% and 100%, 78.1% and 72.9%, respectively. For the PMCA subgroup, the 3 and 5-year OS were 61.4% and 40.1%, respectively. The 5 and 10-year DFS estimates were 71.9% and 42.7%.
Conclusion: CRS plus HIPEC with oxaliplatin represent an effective therapeutic approach for PC-A. Long term OS estimates for patients treated at our institution are encouraging.

1. Introduction

The incidence rate of appendiceal neoplasms varies between 0.12 and 2 cases per 1,000,000 people per year [1]. They are found in about 1% of appendectomy specimens [2]. Epithelial neoplasms of the appendix may present with peritoneal dissemination [2]. Mucin-producing tumors may cause pseudomyxoma peritoneii (PMP), characterized clinically by progressive abdominal distension [3] possibly leading to organ dysfunction and a variety of complications [4]. The outcome of peritoneal carcinomatosis arising from the appendix (PC-A) depends significantly on the histologic grade, with worse prognosis associated with high-grade tumors [5]. There are several classifications for PC-A, of which Ronnett's has had the widest use to date [6]. In that classification system, three grades are recognized: low grade disseminated peritoneal adenomucinosis (DPAM), high grade peritoneal mucinous carcinomatosis (PMCA) and PMCA with intermediate features (PMCA-I). The latter, as the name implies, has histologic atypia worse than found in DPAM and less than found in PMCA. Recently, a new concensus classification has been proposed in which PC-A is divided into low-grade, high-grade and high-grade with signet ring cells [3].

Traditionally, PC-A was treated with repetitive debulking surgery alone. The 10-year overall survival (OS) of these patients was 21–32% [7,8]. A more aggressive therapy consisting of complete cytoreduction surgery (CRS) and intra-peritoneal chemotherapy was introduced by Spratt et al., in 1980 [9]. Using this approach, Gonzalez-Moreno et al. reported 5 and 10 year OS rates of 71.9% and 54.5%, respectively [10]. The addition of hyperthermia to chemotherapeutic agents, termed hyperthermic intraperitoneal chemotherapy (HIPEC), has been shown to enhance tumoral cytotoxicity [11,12], drug penetration into tumors and reduce systemic toxicity [13].

There is now a large body of evidence to support the use of CRS-HIPEC in the treatment of PC-A. When compared to historical series of surgical debulking alone, OS is improved when CRS-HIPEC is used [4,14–22]. This approach is now considered to be the standard of care for PC-A [23,24].

Recently, several large series, including one multi-institution study

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with 2298 patients, have reported 5-year survival rates following CRS-HIPEC for PMP of between 69% and 74% [19,21,25]. However, in *Chua* et al.'s series, there was heterogeneity in the therapy, with up to 30% of patients receiving early postoperative intraperitoneal chemotherapy (EPIC) as well as HIPEC [25]. A more recent single institution study of 1000 patients with PMP due to perforated appendiceal neoplasms undergoing CRS-HIPEC with mitomycin C plus or minus EPIC showed OS rates at 3-, 5- and 10-years of 94.1%, 87.4% and 70.3%, respectively [26].

Other than the variability among studies regarding the use or not of EPIC, there is heterogeneity in regards to the agent used for HIPEC. Mitomycin C has been commonly administered during HIPEC but since, *Elias* et al. have shown that oxaliplatin (OX) can be used safely as a HIPEC agent for PC-A [27]. In a phase one study, intraperitoneal OX had an advantageous pharmacokinetic profile, displaying very high intraperitoneal concentrations with low systemic toxicity because of limited systemic absorption [28]. As shown in animal studies we have performed [13], its advantages also include a reduced duration of perfusion to 30 min versus 90 min for mitomycin C as well as increased peritoneal concentrations, with reduced systemic concentrations.

The primary objective of this study was to analyze long term survival of PC-A patients treated by our team over the last 10 years using CRS-HIPEC with OX. The secondary objectives were to evaluate overall surgical outcomes and to identify prognostic factors. This work is an update on our series published in 2014 [29]. It remains, to date, the first and only series to use OX exclusively as a cytotoxic agent in HIPEC in this population.

2. Materials and methods

After ethic and scientific boards' approval at our institution, we reviewed our prospective database of all patients with PC-A treated with curative intent in our centers between July 2004 and December 2015 (n = 109).

PC-A patients were treated with CRS-HIPEC with OX if they fulfilled the following criteria: confirmed histological diagnosis of peritoneal carcinomatosis arising from the appendix, no evidence of visceral metastasis on computed tomographic (CT) imaging of the chest and abdomen, no contra-indication to CRS-HIPEC and fully resectable disease.

The following factors were analyzed: survival, demographic data, surgical procedures, pathologic diagnosis, complications, length of hospital stay and status at follow-up.

Preoperative systemic chemotherapy was administered on a case-by-case basis. It was administrated to all PMCA or PMCA-I patients. Systemic chemotherapy was also administered preoperatively for 3–6 months in certain cases with lower grade disease but with high tumor load, defined as a preoperative estimated PCI greater than 25. This systemic treatment was aimed at diminishing the tumor burden in order to maximize the chance of complete surgical cytoreduction thereafter. Chemotherapy consisted of 5-fluorouracil based regimens.

Regarding operative technique, the abdomen was approached through a xyphopubic midline incision. After complete adhesiolysis, PC-A was confirmed pathologically by frozen section diagnosis. The extent of PC was scored according to Sugarbaker's peritoneal index [30]. When PC was deemed resectable, the primary tumor and all visceral or peritoneal surface tumor deposits were removed and selective peritonectomy procedures were performed [31]. Sugarbaker's completeness of cytoreduction (CCR) score [32] was used to assess efficacy of surgical debulking. Macroscopically detectable disease had to be resected either completely (CCR-0) or the largest implant measure < 2.5 mm (CCR-1) before intraperitoneal chemotherapy was administered. When electrovaporization of nodules located on the bowel or pelvis was performed the score was considered CCR-1. If, after thorough exploration, PC was determined to be incompletely resectable, HIPEC was not administered and palliative debulking was performed. Post-operative intravenous chemotherapy was offered on a case by case approach to these patients. Of note, from 2004 to 2007, all anastomoses were performed after HIPEC. Since 2008, all anastomoses have been performed before HIPEC.

HIPEC was performed with the open abdomen technique until October 2011, after which a closed abdomen technique was adopted and exclusively used. In the open abdomen technique, the coliseum technique was used [33]. In the closed abdomen technique, the same closed circuit lines were used, with the skin in the midline incision being sutured around the drains in a watertight manner to prevent leakage of chemotherapy.

In both techniques, intravenous fluorouracil (400 mg/m^2) and folinic acid (20 mg/m^2) were administered 30 min prior to HIPEC. The perfusat used for HIPEC was composed of 1.9 L/m^2 of 5% dextrose and OX (460 mg/m^2) [28]. OX was added to the 5% dextrose only once the target temperature had been reached (42°C-43 °C), usually after 10 min of perfusion. At this point, the 30 min countdown was started. To monitor temperature during perfusion, 4 thermal probes were placed inside the peritoneal cavity. The abdomen was perfused at 1 L/min. After HIPEC, the perfusat was evacuated and the abdominal cavity washed once.

Patients were seen and assessed every day following surgery. Complications were graded according to the Clavien-Dindo scale [34]. Minor complications (grade I or II) that were managed with pharmacological treatment (eg. urinary tract infection treated with antibiotics) or non-invasive procedures (eg. nasogastric tube for post-operative ileus) were not considered for analysis. Major complications were defined as grade III-V.

The pathology slides of the CRS procedure were analyzed by an experienced pathologist. Tumor grading of both primary (when available) and PC-A was done according to Ronnett's histologic classification [5].

After discharge, patients were followed at the outpatient clinic at 4-month intervals, where a physical examination was performed. CT scans of the abdomen and pelvis were performed every 4 months for 2 years, every 6 months for an additional 3 years, and yearly thereafter.

Simple descriptive statistics were used to report patient, disease and perioperative events characteristics. Overall and disease-free survival estimates were calculated and demonstrated using Kaplan–Meier survival curves with log-rank tests to compare different subgroups. Any type of tumor recurrence was accounted for in the disease-free survival (DFS) calculation and deaths from any cause was accounted for in the overall survival (OS) calculations. Univariate Cox regression analysis was used to assess the relation between different factors and disease recurrence. These covariates included: age, sex, histology, presence of obstruction or perforation at presentation, synchronous vs. metachronous presentation, peri-operative use of chemotherapy, PCI, operative duration, number or organs resected, CCR score, estimated blood loss, the use of blood transfusion and post-operative complications. A p-value of ≤ 0.05 was considered significant. Covariates that were found to be significant on univariate analysis were included in the final multivariate Cox regression model. To assess for violation of Proportional Hazard assumption, the scaled Schoenfeld residuals method was used. Statistical analyses were performed using RStudio program (Version 0.99.893 – © 2009–2016 RStudio, Inc).

3. Results

109 patients underwent laparotomy with curative intent for PC-A between July 2004 and December 2015 at our institution. The demographic characteristics are shown in Table 1. There were 67 females and 42 males, with a mean age of 52 years (range 33–70). A total of 15 patients were found to have unresectable disease. Of those, 7 were found to have PMCA-I at final pathology, and 8 had PMCA, with 5 having tumors with the presence of signet-ring cells.

Two patients who had initially been diagnosed with an appendiceal neoplasm, one of them being a low grade mucinous neoplasm (LAMN)

Table 1
Patient characteristics at time of diagnosis of peritoneal carcinomatosis.

All patients	109
PC-A status	
Resectable	92
Unresectable	15
Negative second-look	2
Sex	
Male	42
Female	67
Age	
Mean	52
ASA Class	
I	23
II	66
III	17
IV	1
Presentation of PC-A	
Synchronous	75
Metachronous	34
Bowel obstruction	8
Perforated appendix	44
Pathology of PC-A	
DPAM	35
PMCA-I	55
PMCA	19
Use of systemic chemotherapy	34

PC-A: appendiceal peritoneal carcinomatosis; ASA: American Society of Anesthesiologists; DPAM: disseminated peritoneal adenomucinosis; PMCA: peritoneal mucinous carcinomatosis; PMCA-I: PMCA with intermediate features.

and the other a low grade adenocarcinoma, both with limited PC at primary surgery at other institutions, had no evidence of residual disease when second-look laparotomy was performed. These patients had undergone appendectomy along with complete removal of visible peritoneal disease before being referred to us. Since they had no evidence of PC, these patients were not treated with HIPEC.

PC was found synchronous to the diagnosis of the primary tumor in 75 patients (68.8%), with 44 patients (40%) presenting with a perforated appendiceal neoplasm and 8 patients (0.1%) with clinical bowel obstruction.

Ninety-two patients underwent complete CRS followed by HIPEC with oxaliplatin. Perioperative and postoperative details are shown in Table 2. Fifty-five (59.8%) patients had open abdomen HIPEC, while 37 patients (40.2%) had closed abdomen HIPEC. The CCR score was 0 in 57 patients (61.9%) and 1 in 35 patients (38%). The median PCI was 15. Median operative time was 420 min (135–840) and median hospital stay was 16 days (6–104). 34.7% of patients required intensive care, with a median length of stay in the intensive care unit of 2 days (range 1–45). There was one postoperative mortality (1.1%) from sepsis and multi-organ failure. The overall major complication rate (Grades III-V) was 26% (24 patients), including anastomotic leak in 6 patients (6.5%), intra-abdominal abscess in 15 (16.3%), hemoperitoneum in 12 (13%) and surgical re-intervention in 18 (19.6%). Two patients (2.2%) in the HIPEC group experienced at least grade 3 hematologic toxicity, consisting of thrombocytopenia and coagulopathy, respectively. Six patients (6.5%) experienced grade 3–4 neuropathy in the postoperative period. With regards to the trend of complications over time, there was a significant lower rate of re-intervention between the years 2010–2015 compared to 2004–2009 (9.1% vs 30.1%, p = 0.017).

Final pathology reports for the whole cohort of 109 patients showed 35 patients (32.1%) had DPAM (HIPEC n = 33, negative second-look n = 2, unresectable n = 0), 55 (50.5%) had PMCA-I (HIPEC n = 48, negative second-look n = 0, unresectable n = 7) and 19 (17.4%) had PMCA (HIPEC n = 11, negative second-look n = 0, unresectable n = 8).

Table 2
Intra-Operative and Post-Operative characteristics of the 91 patients who underwent CRS and HIPEC.

All HIPEC patients	92
CCR score	
0	57
1	35
PCI	
Median (range)	15 (0–39)
Hollow organs resected	
Mean (range)	1.02 (0–4)
Anastomosis	
Mean (range)	0.68 (0–4)
Operative time (min)	
Median (range)	450 (135–840)
Open vs closed abdomen	
Open	55
Close	37
Chemotherapy synchronous	
Yes	30
No	62
Blood loss (ml)	
Median (range)	650 (0–10000)
Patients requiring ICU admission	32
Median length in days (range)	2 (0–45)
NPO days	
Median (range)	8 (2–41)
Length of hospitalization (days)	
Median (Range)	16 (6–104)
Transfusion required	30 (32.6%)
Grade III-IV-V Complications	24 (26.1%)
Anastomotic leak	6 (6.5%)
Abdominal abcess	15 (16.3%)
Hemoperitoneum	12 (13%)
Pleural effusion	15 (16.3%)
Surgical re-intervention	18 (19.6%)
Clostridium Difficile	3 (3.3%)
Chemotherapy related complications	
Overall	6 (6.5%)
Hematologic	2 (2.2%)
Systemic	6 (6.5%)

HIPEC: hyperthermic intraperitoneal chemotherapy; CCR: completeness of cytoreduction; PCI: peritoneal carcinomatosis index; ICU: intensive care unit; NPO: nothing by mouth.

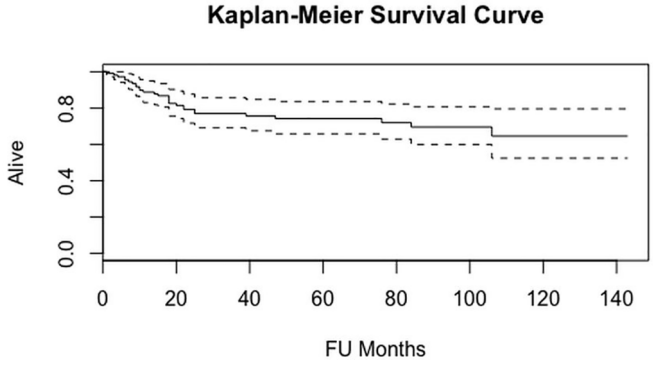

Fig. 1. Overall survival for entire series.
FU: follow-up.

Median follow-up for the whole cohort was 42 months (mean 53.1, range 1–143). The estimated 5- and 10-year OS rate for the entire cohort was 74.2% and 64.6%, respectively (Fig. 1). OS at median follow-up of 42 months was 75.6%. The 5- and 10-year OS rates for the HIPEC group were 82.2% and 76.5%, respectively (Fig. 2). Among the HIPEC group, the 5- and 10-year OS estimates for DPAM and PMCA-I subgroups were 100% and 100%, 78.1% and 72.9%, respectively. For the PMCA subgroup, the 3- and 5-year OS were 61.4% and 40.1%, respectively (Fig. 3). At median follow-up of 10 months, the OS for the

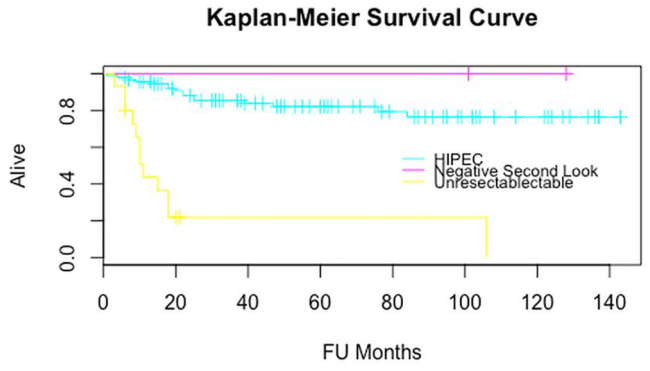

Fig. 2. Overall Survival curve by cohort group: HIPEC, unresectable and negative second-look.
HIPEC: hyperthermic intraperitoneal chemotherapy; FU: follow-up.

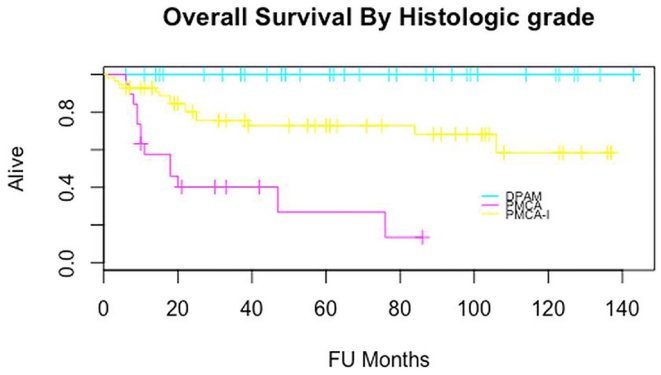

Fig. 3. Overall survival by histologic grade.
DPAM: disseminated peritoneal adenomucinosis; PMCA: peritoneal mucinous carcinomatosis; PMCA-I: PMCA with intermediate features.

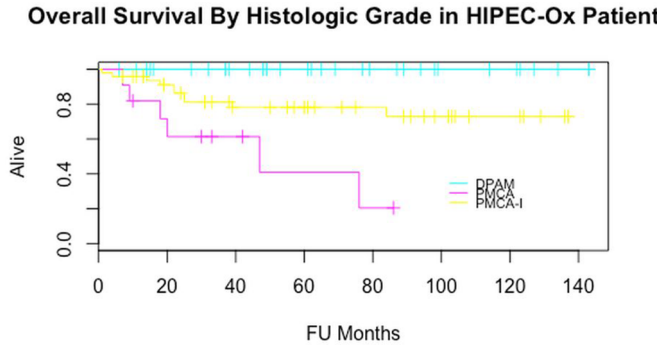

Fig. 4. Overall Survival by histologic grade in HIPEC patients.
DPAM: disseminated peritoneal adenomucinosis; PMCA: peritoneal mucinous carcinomatosis; PMCA-I: PMCA with intermediate features; HIPEC-OX: hyperthermic intraperitoneal chemotherapy with oxaliplatin.

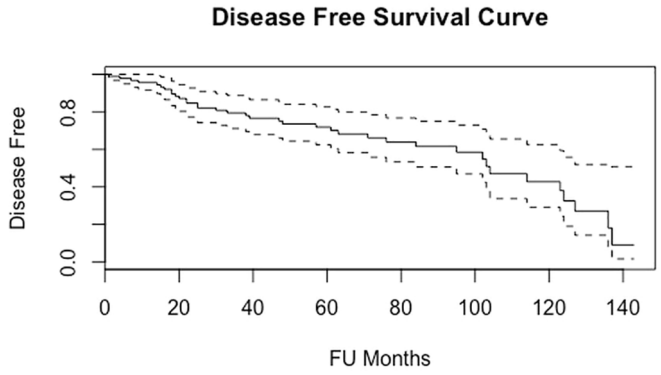

Fig. 5. Disease free survival curve for patients undergoing CRS and HIPEC.
FU: follow-up, CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy.

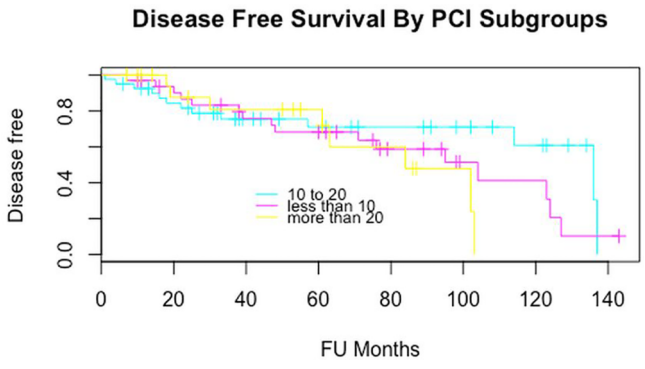

Fig. 6. Disease free survival by PCI subgroups.
FU: follow-up; PCI: peritoneal carcinomatosis index.

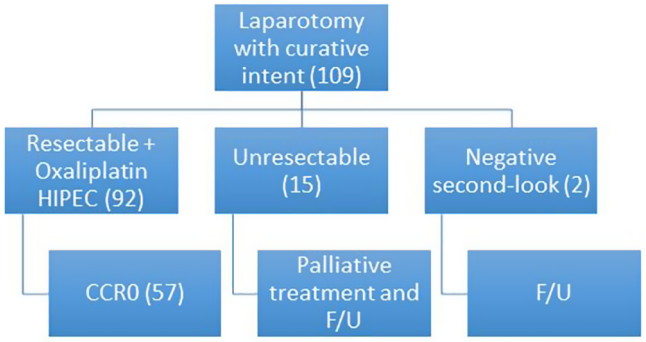

Fig. 7. Decisional algorithm for each group.
FU: follow-up, HIPEC: hyperthermic intraperitoneal chemotherapy, CCR: completeness of cytoreduction score.

unresectable group was 50.9% (Fig. 2). At time of data analysis, 34 patients had experienced recurrence (37%), with 21 (22.8%) having isolated peritoneal recurrence, 12 (13%) having peritoneal as well as visceral and/or other recurrence (bone), and one patient having isolated abdominal wall recurrence without any peritoneal recurrence. The 5- and 10-year DFS estimates for patients undergoing HIPEC were 71.9% and 42.7%, respectively (Fig. 5). Overall survival curves and DFS curves by histologic grade were significantly different ($p < 0.0001$). However, OS or DFS curves were not significantly different for CCR or PCI subgroups (Figs. 3, 4 and 6) (see Fig. 7).

Univariate Cox regression analysis was performed, followed by multivariate analysis on variables found to be significant in the univariate model (Table 3). At univariate analysis, significant poor prognostic factors for DFS were blood loss ($p = 0.0464$), use of systemic chemotherapy ($p = 3.89 \times 10^{-5}$), histology grade PMCA-I ($p = 0.00708$) and PMCA ($p = 2.57 \times 10^{-5}$) and the number of hollow organs resected ($p = 0.0484$). PMCA grade, systemic chemotherapy use and the number of hollow organs resected were found to be statistically significant after multivariate analysis, with a HR of 5.40, 3.51 and 1.46, respectively, for recurrence. Other variables, such as sex, age, PCI, duration of surgery, occurrence of major complications were not significant at univariate analysis.

Finally, among the patients who experienced PC recurrence after HIPEC with OX, 12 underwent second CRS-HIPEC with mitomycin C. Mean follow-up for these patients up to the date of analysis was 42 months (range 1–108). Eight of these patients were disease-free after

Table 3
Univariate and multivariate regression analysis.

	Univariate			Multivariate		
Covariates	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Age	1.013	(0.976, 1.051)	0.506			
Sex	Ref	(0.545, 2.075)	0.857			
Female	1.063					
Male						
Histology	Ref	(1.435, 9.891)	0.007*	2.181	(0.762, 6.245)	0.146
DPAM	3.767	(3.777, 38.30)	< 0.001*	5.401	(1.527, 19.1)	0.009*
PMCA-I	12.027					
PMCA						
Presentation	Ref	(0.266, 1.328)	0.204			
Metachronous	0.5937					
Synchronous						
Use of peri-operative chemotherapy	Ref	(2.05, 7.569)	< 0.001*	3.507	(1.586, 7.755)	0.002*
No	3.939					
Yes						
Obstruction at time of surgery	Ref	(0.727, 8.008)	0.15			
No	2.413					
Yes						
Perforation at time of surgery	Ref	(0.396, 1.677)	0.578			
No	0.8148					
Yes						
PCI	1.009	(0.968, 1.052)	0.659			
CCR score	Ref	(0.448, 1.748)	0.724			
0	0.885					
1						
No. of solid organs resected	0.871	(0.646, 1.175)	0.365			
No. of hollow organs resected	1.331	(1.002, 1.769)	0.048*	1.458	(1.041, 2.045)	0.029*
Operative duration (minutes)	1.001	(0.999, 1.003)	0.245			
Blood loss (100 ml)	1.016	(1.00, 1.032)	0.046*	0.995	(0.975, 1.016)	0.656
Transfusion	Ref	(0.524, 1.997)	0.946			
No	1.023					
Yes						
Post-operative complication grade 3-5	Ref	(0.774, 3.074)	0.218			
Yes	1.542					
No						

DPAM: disseminated peritoneal adenomucinosis; PMCA: peritoneal mucinous carcinomatosis; PMCA-I: PMCA with intermediate features; CCR: completeness of cytoreduction; PCI: peritoneal carcinomatosis index.

second CRS-HIPEC, 2 experienced recurrence and 2 are deceased.

4. Discussion

Although historically a disease having a poor prognosis, PC-A when treated with CRS-HIPEC now has a greatly improved OS. In the current series, after a median follow-up of 42 months, the 5 and 10-year OS rates for the HIPEC group were 82.2% and 76.5%, respectively and 74.2% and 64.6% for the entire cohort. These results are consistent with previous studies and support the fact that CRS plus HIPEC can improve OS in this population. For instance, *Ansari* et al. showed 5 and 10-year OS for their HIPEC group of 87.4% and 70.3% [26]. Similarly, larger series including one multi-institution study with 2298 patients have reported 5-year survival rates following CRS-HIPEC between 69% and 74% [19,21,25]. These results add to the growing body of evidence demonstrating the benefits of CRS-HIPEC as a treatment of PC-A.

In our study, the 5 and 10-year DFS rates for patients receiving HIPEC were 71.85% and 42.72%, respectively with an overall recurrence rate of 37%, which is in accordance with previously published studies [19,21,25,35].

In our study, 12 patients presenting with recurrence were eligible for repeat CRS and HIPEC using mitomycin C. From this cohort, 8 patients were disease-free, 2 had a secondary recurrence and 2 were deceased at the time of data analysis. Therefore, even though recurrence is frequent, it is often possible to treat selected patients with a second CRS-HIPEC with encouraging results.

Not surprisingly, histological grade was a significant prognostic factor for disease-free survival after multivariate analysis. There is debate as to the best pathological classification of the primary appendiceal pathology and the peritoneal implants. There has been a recent trend away from Ronnett's three grade classification of PC-A towards two categories. *Carr* et al. recently published an international consensus introducing 3 categories: low grade, high grade, and high grade with signet-cells [3]. The reproducibility of classification is currently being validated. We have chosen to use Ronnett's classification in order to allow for continuity with our previous results published in 2014 [29]. Our findings show that histologic grade is a significant prognostic factor for both OS and DFS (Figs. 3 and 4). In multivariate analysis, when compared to DPAM, PMCA histology had a 5.4 HR of recurrence (95% CI 1.53–19.1, p = 0.0089). Patients with PMCA developed recurrence almost invariably. As such, the question of whether these patients should undergo aggressive surgical therapy arises. Although recurrence in this population may be inevitable, CRS-HIPEC still provide these patients with an acceptable survival advantage over traditional debulking surgery alone. In our series, the 3 and 5-year OS were 61.4% and 40.1%, respectively, with no patient being alive at the 10 year mark. In this context, the modest survival advantage in PMCA patients should be weighed against the patient's fitness for surgery. Therefore, PMCA histology could be used as a patient selection tool preoperatively.

It is recognized that complete cytoreduction is one of the strongest predictors of long term survival in patients with PC-A [26]. However, achieving complete cytoreduction (CCR-0 or CCR-1) often requires a lengthy procedure, with extensive dissection and potentially numerous organ resections to allow for the administration of HIPEC. Every reasonable effort should be made to achieve complete microscopic tumor removal because HIPEC has limited ability to penetrate beyond a few

millimeters (2.5 mm, or CCR-1) [4]. In our series, among patients receiving HIPEC (n = 92), 57 (62%) had CCR-0 resection and 35 (38%) had CCR-1 resection. It has already been demonstrated that CCR score is a prognostic factor for DFS and OS (4, 10, 18). In our previous series, we found that CCR score was a significant prognostic factor for DFS but not for OS on univariate Cox regression analysis [29]. Our updated results now show that CCR is not a significant prognostic factor for DFS. While this conflicts with other studies, it might be explained by the variability in the definition of CCR score. We used a strict definition, in which electrovaporization of any nodules located on the bowel or pelvis lead to a CCR-1 score [32]. This is because 100% destruction of tumor cells cannot be guaranteed by electrovaporization as opposed to surgical resection. As a result, after detailed review of the surgical protocols, several patients previously classified in the database and in the previous study as having undergone CCR-0 resection were reattributed a CCR-1 score. As such, if some patients with previously attributed CCR-0 status and good survival were then assigned a CCR-1 status, this may explain why no difference was found among the CCR groups.

Median PCI in our HIPEC cohort was 15, which is comparable to other groups. However, in contrast with other studies, PCI was not found to be a significant prognostic factor for survival or for disease-free survival in our CRS-HIPEC cohort. This is compatible with the findings of *Polanco* et al., who analyzed outcomes of high-grade/high-volume PC-A and compared them to high-grade/low-volume PC-A [36]. They found that patients with high PCI had an overall worse prognosis for several reasons: higher peri-operative morbidity and mortality, but, more importantly, lower rates of CRS completion and thus lower rates of HIPEC administration. However, among patients having successful CRS-HIPEC, there was no difference in outcomes between high PCI and low PCI patients. Therefore, the prognostic value of PCI may stem primarily from its link to higher complication rates and higher incomplete CRS, hence the interest of accurately predicting PCI pre-operatively in order to select the patients who will most benefit from this intervention.

Pre-operative chemotherapy, consisting of 5-fluorouracil based regimens, was administrated to all patients with PMCA or PMCA-I histology before the CRS-HIPEC procedure. Patients with high tumor load as estimated pre-operatively, with an estimated PCI of 25 or more, were also given neo-adjuvant chemotherapy. On multivariate analysis, pre-operative chemotherapy was found to be significantly linked to increased recurrence. This finding can be explained by the patient selection to receive neo-adjuvant cytotoxic therapy being inherently at higher risk of recurrence because of the biology of their disease.

As to the 15 patients in our study with unresectable disease, they underwent debulking without CRS or HIPEC. None had low grade disease (DPAM), half had PMCA histology and the other half PMCA-I. The median PCI was 24 versus 15 for the HIPEC group. It is not clear in this situation whether debulking (eg: removal of the “omental cake”) provides survival benefit, although it may be important for symptom relief. At median follow-up of 10 months, the OS for the unresectable group was 50.9%. As of now, 12 out of 15 patients are deceased.

As mentioned in our previously published series, there were nine patients who had no PC at a second-look laparotomy after having had resection of primary tumor and all other peritoneal disease at another center [29]. Of these, 7 eventually presented with signs of recurrence and consequently were treated with CRS-HIPEC. They are now included in our HIPEC cohort for data analysis. Only two of the previously 9 negative second-look patients are alive and disease free at the time of analysis. These cases raise the question of whether prophylactic HIPEC should be used in cases of perforated appendiceal epithelial neoplasms, including low-grade tumors. To date, there has been no published studies of outcomes after prophylactic HIPEC in cases of PC-A. However, given the natural history of the disease, with high recurrence rates, even in low-grade tumors such as DPAM, prophylactic HIPEC is potentially justified, especially in cases where low-volume PC was previously resected at another center.

Finally, major complications often follow CRS-HIPEC. Reported mortality and morbidity rates vary. Recently, a multi-institutional retrospective study of 2298 patients from 16 institutions reported a postoperative major morbidity rate of 24% and 30-day mortality rate of 2% [25]. In our study, the overall major complication rate (Grades III-V) was 26% (24 patients), including 12 patients presenting with hemoperitoneum (13.04%) and 18 patients (19.56%) requiring surgical re-intervention. Our results (major morbidity 24%, and mortality 1.1%) are in accordance with previously published studies. With regards to the trend of complications over time, there was a significant lower rate of re-intervention between the years 2010–2015 compared to 2004–2009 (9.1% vs 30.1%, p = 0.017). One of the factors that may have led to reduced re-intervention rates may be the increased experience of surgeons over time in the CRS-HIPEC procedure, which could translate into less peri-operative blood losses and less operative time, both known factors linked to complication rates [37]. These were not quantified, however, for the different time periods. Moreover, another hypothesis for reduced re-intervention rates after 2010 may be the fact that bowel anastomoses were performed after HIPEC before 2010 compared to before HIPEC after 2010. A possible explanation may be related to tissue edema differences before and after the intra-peritoneal chemotherapy and the risk for anastomotic leak from sutures or staple lines.

Overall side effects of intra-peritoneal chemotherapy were low, occurring in 6 patients (6.5%), with two patients (2.2%) experiencing grade III-IV hematologic toxicity and 6 patients (6.5%) suffering from grade III-IV neuropathy. This is comparable with reports by Elias et al. [28]. These data support the need for referral of these patients to designated, high-volume centers to minimize morbidity.

5. Conclusion

CRS-HIPEC with OX represents an effective therapeutic approach for PC-A. Despite a high recurrence rate, the long term OS results at our institution are encouraging and consistent with the current literature. Although this aggressive therapy results in high morbidity rates, results from our series show that this improves with increasing experience, supporting the need for referral of these patients to designated centers.

Conflict of interests

The authors declare no conflict of interests.

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Summary

This study is a retrospective review of patients treated for appendiceal peritoneal carcinomatosis with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy with oxaliplatin. The primary objective of this study was to analyze long term survival of patients treated in our institution over the last 10 years. The secondary endpoints were to evaluate overall surgical outcomes and to identify prognostic factors.

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