Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from colorectal and appendiceal cancer: five-years of experience

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Abstract

An increasing promising evidence support the use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of peritoneal carcinosis from colorectal cancer (CRC) and appendiceal cancer (AC).

In our institute 18 patients with CRC and 4 patients with AC undergone to CRS and HIPEC were retrospectively analyzed from 2011 to 2016. Patients and tumor characteristics were analyzed. Overall survival and disease free survival were analyzed with Kaplan-Meier curves and log-rank testing.

Median disease free survival (DFS) is 20.5 and 31.4 months in CRC and AC respectively (P=0.76). Instead mean overall survival is 37.8 and 44.6 months in CRC and AC group respectively (P=0.46). Primary CRC have an improved DFS compared patients with relapse tumor (45.2 *versus* 19.4 months) (P=0.037).

Comparing with conventional chemotherapy regimens CRS and HIPEC from CRC and AC may obtain a better disease control particularly when a complete cytoreduction is achieved. The combined treatment can have a potential curative intent.

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Key words: Colorectal and appendiceal cancer; hyperthermic intraperitoneal chemotherapy; cytoreductive surgery; peritoneal mucinous carcinomatosis; high-grade non-mucinous carcinoma.

Contributions: GM and PF reviews the literature; GM, PF, LA, MC contributed equally to this work, manuscript conception and draft. GM, PF, VG and GCT contributed to collect data. FC, AG, LA critically revised the manuscript and contribute with important scientific knowledge giving the final approval.

Conflict of interest: the authors declare no conflict of interest.

Received for publication: 21 March 2016.
Accepted for publication: 19 April 2016.

Journal of Peritoneum (and other serosal surfaces) 2016; 1:3
doi:10.4081/joper.2016.3

Introduction

In Italy colorectal cancer (CRC) was accounted for more than 52,000 new cases in 2014 and 20,670 deaths in 2013 [data from the Italian Association of Medical Oncology (AIOM) in 2014]. In contrast appendiceal carcinoma (AC) is relatively rare, with only 0.9-1.4% cancers detected in over 280,000 appendectomies performed annually in USA.[1]

In the last two decades chemotherapy regimens (irinotecan and oxaliplatin, and biologic agents as bevacizumab and cetuximab in kRAS positive patients) have improved significantly overall survival (OS) and disease free survival (DFS).[2] In the same way in last years an advanced surgical treatment of hepatic and pulmonary metastases with curative intent has been achieved.[2] However despite the progresses of systemic chemotherapy and more extensive surgery, a synchronous peritoneal carcinosis (PC) is identified at primary surgery in approximately 5-10% of patient undergoing CRC resection and up to 20-50% of patients undergoing curative intent CRC resection can have a peritoneal recurrence.[2] In 3-28% of CRC the peritoneal washing is positive, while the serosal scraping is between 15 to 42%.[3] In case of AC peritoneal dissemination occurs over 40%.[4]

The presence of PC in the context of CRC and AC has always been seen as a poor prognosis condition. The natural history of PC gives an average life expectancy of 5-7 months.[2] Available literature shows a median survival after traditional treatment of 5-24 months for PC from CRC, with a decrease in overall survival from 30% to 4%,[2,5,6] and of 26 months for PC from AC (with a 10-year survival rate of 32% in low-grade appendiceal pseudomyxoma and 5-year survival rate of 6% in appendiceal adenocarcinoma).[4,7]

In the last decade the introduction of aggressive cytoreductive surgery (CRS) in combination with hypertermic intraperitoneal chemotherapy (HIPEC) has improved OS and DFS of PC from both CRC and AC.[8]

We evaluated our center experience with CRS+HIPEC for PC from CRC and AC, specifically looking at the influence of primary tumor on oncologic outcomes and at the main prognostic factors in terms of OS and DFS.

Materials and Methods

Twenty-two patients with PC from CRC (18 patients) and AC (4 patients) were treated with combined CRS and HIPEC from January 2011 to January 2016. The data were retrospectively analyzed. Initial selection was done regarding the origin of type of neoplasm: from colorectal or from appendiceal origin. The specimens from AC were classified according to the 2010 World Health Organization classification and the 7th American Joint Committee on Cancer (AJCC)[9] in disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA), high-grade non mucinous carcinoma (PCA), one regard any neoplastic epithelial proliferation confined to the appendiceal mucosa as an adenoma. Only PMCA and PCA were considered in OS and DFS analysis because similar to CRC in terms of outcomes. DPAM were excluded from the analysis.

Patient characteristics and pre-operative data are reported in Table 1 for AC group and in Table 2 for CRC group. In the AC group tumor characteristics analyzed were tumor stage (according to the Classification of Malignant Tumours), tumor histology (PMCA and PCA), presence or absence of positive peritoneal cytology (Table 1). In the CRC group the data that were analyzed were: tumor stage, the presence/absence of kRAS mutation, the neoplasm localization, the positive cytology at first surgery, the presence/absence of liver synchronous metastasis, the use of an adjuvant/neoadjuvant chemotherapy regimen, and the positive of exploratory laparoscopy (Table 3).

Intraoperative characteristics (volume of peritoneal disease during HIPEC in terms of peritoneal cancer index (PCI) [according to Sugarbacker's classification), operative time, delay of Intensive Care Unit (ICU) and total hospital stay] and post-operative morbidity of the two groups were report in Tables 4 and 5. All patients have an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, without extra-abdominal disease. According with the pre-operative images (computed tomography, positron-emission tomography, magnetic reso-

Table 1. Patients and tumor characteristics in appendiceal carcinoma group.

Characteristics (N=4)	Value	N (%)
Gender	Male	1 (25)
	Female	3 (75)
Age	Mean (SD), years	47 (±14.3)
	Median (range), years	45 (34-63)
ASA score	I	3 (75)
	II	1 (25)
Tumor stage	IV a	2 (50)
	IV b	2 (50)
Tumor histology	PMCA	3 (75)
	PCA	1 (25)
Previous tumor related-therapy	Chemotherapy	0 (0)
	Surgery	2 (50)
	None	2 (50)
Peritoneal citology at primary surgery	Positive	3 (75)
	Negative	0 (0)
	ns	1 (25)
HIPEC for	Primary tumor	3 (75)
	Recurrence	1 (25)
Time since surgery of the primary tumor and HIPEC	Mean (±SD), months	13 (±13.5)
	Median (range), months	9 (1-29)
Time since diagnosis of the primary tumor and HIPEC	Mean (±SD), months	13.7 (±14.5)
	Median (range), months	9 (1-31)

SD, standard deviation; ASA, American Society of Anesthesiologists; PMCA, peritoneal mucinous carcinomatosis; PCA, high-grade non mucinous carcinoma; HIPEC, hyperthermic intraperitoneal chemotherapy; ns, not specified.

Table 2. Patient characteristics in colorectal cancer group.

Characteristics (N=18)	Value	N (%)
Gender	Male	10 (55.6)
	Female	8 (44.4)
Age	Mean (SD), years	58 (±9.3)
	Median (range), years	57 (44-74)
ASA score	I	6 (33.3)
	II	7 (38.9)
	III	4 (22.2)
	IV	1 (5.6)

SD, standard deviation. ASA, American Society of Anesthesiologists.

nance) the peritoneal disease was debulkable. Patients with hepatic metastases were included only if hepatic lesions were easily resectable (wedge or segmentectomy resections). CRS was performed removing all peritoneum and visceral organs involved. The omentectomy, cholecystectomy and appendectomy were routinely removed.

HIPEC was performed according to the coliseum technique for 90 min at a temperature of 40-41°C. One inflow and four outflow catheters are placed with the open abdomen that was partially close with a surgical adhesive drape performing a *closed-HIPEC with open abdomen technique*. Chemotherapy regimens were: 35 mg/m^2 mitomycin-C (MMC) (or 16 mg/m^2 MMC if cisplatin was added) or 100 mg/m^2 cisplatin is added to the perfusate. Afterward, the perfusate is drained and the reconstructive time was performed. Adverse events were recorded with the Common Terminology Criteria for Adverse Events (CTCAE v. 4.03).[10] The completeness of resection (CC) was graded by the surgeon at the conclusion of the procedure according to the Sugarbacker classification: CC0 - complete cytoreduction of all visible disease; CC1 - minimal residual disease with nodules less than 2.5 cm; CC2 - residual disease with nodules of 2.5 mm to 2.5 cm; and CC3 - residual disease with nodules grater than 2.5 cm. Postoperative data as date of recurrence, date of death and date of last follow up were sought.

Statistical analysis

Continuous and categorical variables including frequencies and percentages for categorical data were reported in Tables 1-5. DFS and OS were calculated in the two groups (AC and CRC) as the interval between the date of CRS and HIPEC and the data of last follow-up or death. The curves of DFS and OS were analyzed using the Kaplan-Meier method, and survival estimates were compared using the log-rank test. Statistical significance was defined as P value <0.05. All analysis was performed using SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0; Released 2011. IBM Corp., Armonk, NY, USA).

Results

Patients, tumor and perioperative characteristics

In CRC group the 10 patients were male and 8 female. The median age was 57 years (range 44-74). The majority of patients had an American Society of Anesthesiologists (ASA) score between I to III.

More than half patients had a tumor stage IVa or IVb, with a kRAS mutation, and only 6 patients had a synchronous liver metastasis.

Table 3. Tumor characteristics in colorectal cancer group.

Characteristics (N=18)	Value	N (%)
Tumor stage	I	1 (5.6)
	II a	1 (5.6)
	II b	3 (16.7)
	III b	1 (5.6)
	IV a	2 (10.5)
	IV b	10 (56)
Synchronous hepatic metastasis	Yes	6 (33.3)
	No	12 (66.7)
Neoplasm localization	Right colon	11 (61.1)
	Transverse colon	1 (5.6)
	Left colon-rectum	6 (33.3)
kRAS mutation	Yes	10 (55.6)
	No	3 (16.6)
	ns	5 (27.8)
Peritoneal cytology at primary tumor surgery	Positive	2 (11.1)
	Negative	10 (55.6)
	ns	6 (33.3)
Previous tumor related-surgery	Yes	13 (72.2)
	No	5 (27.8)
Exploratory laparoscopy before HIPEC	Yes	5 (27.8)
	No	13 (72.2)
ACT of the primary tumor	Yes	11 (61.1)
	- FolfiriFolfox	
	- Bevacizumab+Xelox	
	- Folfiri+bevacizumab	
	- Xelox	
	- Folfiri+cetuxumab	
	No	7 (38.9)
NACT of the primary tumor	Yes	1(5.6)
	No	17 (94.4)
HIPEC for	Primary tumor	5 (27.8)
	Recurrence	13 (72.2)
Time since surgery of the primary tumor	Median (range), months	14 (0.5-71)
Time since ACT of the primary tumor	Median (range), days	90 (28-600)*

ns, not specified; HIPEC, hyperthermic intraperitoneal chemotherapy; ACT, adjuvant chemotherapy; NACT, non-adjuvant chemotherapy. *Data of the twelve patients who underwent to ACT.

Eleven patients had a right colon cancer and 6 a left colon-rectum cancer. In only 2 patients a positive peritoneal cytology at primary tumor surgery was reported. More than 70% of patients were treated for a peritoneal recurrence and 10 (55.6%) patients underwent to adjuvant chemotherapy (the chemotherapy regimen used are shown in Table 3). Neadjuvant chemotherapy was performed only in one case. The median time since primary tumor surgery and CRS+HIPEC was of 14 months (range 0.5-71 months), and since adjuvant chemotherapy and CRS+HIPEC was of 90 days (range 28-600 days). In the CRC group the median of PCI was 9 (range 0-32): 13 patients had PCI <10 and 2 patients had PCI >20. All patients achieve at a CC0 resection.

In AC group, 1 patient was male and 3 female, and the median age

Table 4. Perioperative data in appendiceal carcinoma group.

Characteristics (N=4)	Value	N (%)
PCI	Median (range)	20 (0-32)*
	<10	1
	11-19	0
	>20	2
Operative time	Median (range)	620 (570-955)*
Days in ICU	Median (days)	2 (2-70)*
Total hospital stay	Median (days)	20 (0-29)*
Postoperative morbidity	Yes°	2 (50)
	Hemorrhage	1
	- Anastomotic leak	1
	- Constipation	1
	- Meningoradiculitis	1
	Median grade CTCAE	4 (0-4)
	No	1 (25)
	ns	1 (25)
Reoperation before discharge	pts	1 (25)
Perioperative mortality	pts	1 (25)

PCI, peritoneal cancer index; ICU, Intensive Care Unit; CTCAE, Common Terminology Criteria for Adverse Events; ns, not specified; pts, patients. *In one patient data is not specified; °some patients have more than one complication.

Table 5. Perioperative data in colorectal cancer group.

Characteristics (N=18)	Value	N (%)
PCI	Median (range)	9 (0-32)
	<10	13
	11-19	3
	>20	2
Operative time	Median (range)	525 (340-720)
Days in ICU	Median (range), days	2 (1-15)*
Total hospital stay	Median (range), days	17 (8-62)*
Postoperative morbidity	Yes	8 (44.4)
	- Anemia	4
	- Infection/sepsis	3
	- Neurological disorders	3
	- Wound deiscence	2
	- Pleural effusion	1
	- Pneumonia	3
	- Anastomotic leak	3
	- Vein trombosis	1
	Median grade of CTCAE	3 (1-4)
	No	10 (55.6)
ACT post-HIPEC	Yes	4 (22.2)
	No	7 (38.9)
	No for poor clinical condition	5 (27.8)
	ns	2 (11.1)
Time since HIPEC from ACT	Median (range), days	56 (33-270)°
Surgical reintervention after HIPEC	pts	2 (11.1)

PCI, peritoneal cancer index; ICU, Intensive Care Unit; CTCAE, Common Terminology Criteria for Adverse Events; ACT, adjuvant chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; ns, not specified; pts, patients. *Data of the eleven patients who underwent to ACT before HIPEC; °data of the four patients who underwent to ACT after HIPEC.

was 45 years (range 34-63). The majority of patients had an ASA score I. All the patients had a tumor stage IVa or IVb (one patient classified with PCA had a signet ring cells adenocarcinoma). In 3 patients a positive peritoneal cytology was reported. Only 2 patients underwent to HIPEC+CRS immediately, the others had performed appendectomy in others Hospital. Only the patient with PCA was subjected to adjuvant chemotherapy with FOLFOX and he was treated with HIPEC for the malignancy recurrence. The median time since primary tumor surgery/diagnosis and CRS+HIPEC was the same (9 months). In this group PCI index was higher than in CRC group: 2 patients had more than 20 of PCI. All patients achieve at a CC0 resection.

Morbidity and mortality

In the CRC group 44.4% of patients had post-operative complications with a median grade of CTCAE of 3 (Table 5). The ICU and in ward stay were reasonable. However 5 patients did not underwent to adjuvant chemotherapy post HIPEC due to the poor condition give by the intervention, and only 2 patients needed of a surgical re-intervention for an anastomotic leak.

In the AC group 50% of patients had post-operative complications as show in Table 4. Only 1 patient needed a re-intervention for colic fistula.

In both groups no patients died during HIPEC procedure, however one patient died postoperatively for hemorrhage in AC group.

Survival and disease-free survival

DFS compared in the two groups have a median of 20.5 and 31.4 months in CRC and AC respectively (Figure 1) (P=0.76). The mean OS is 37.8 and 44.6 months in CRC and AC group respectively (Figure 2) (P=0.46).

The analysis of CRC group have showed that CRC operated for primary tumor have a DFS of 45.2 months compared to 19.4 months in patients with relapsed tumor (Figure 3) (P=0.037). OS in patients with primary tumor is 44.4 months *versus* 34.2 months in recurrence colic tumor (Figure 4) (P=0.42).

Discussion

For many years the OS of patients with PC from CRC and AC, treated by conventional chemotherapy, have been unchanged. Recently in patients treated with oxaliplatin, irinotecan and biologic monoclonal antibody has been reported a 31 months median OS and 12 months of progression-free survival (PFS).[11] Despite these results the long-term survival remains poor with a 5-year survival of less then 10% and with a complete response only in 4.8% of patients.[12] These data suggest that systemic chemotherapy alone, also with the addition of a monclonal antibody, has no curative potential and does not improve long-term outcomes.[12]

After the introduction and the good results of resective surgery in patients with liver metastases from CRC, the concept of *step-by-step* metastasis from CRC has diffused. This concept was first described by Weiss and refers to a well-ordered metastatic diffusion in subsequent steps or *metastases from metastases* mechanism.[13] From this diffusion modality can be understood the efficacy of peritonectomy has the intent to remove the disease at its last border. As a matter of fact, Chu[14] in the late 80s, and more recently Sadeghi,[15] observed that 25% of patients die without any signs of extraperitoneal disease. This shows that peritoneum, in this case, can be considered as the last border of the disease. The increase in OS due to the introduction of new chemotherapy regimens is the rationale for the introduction of combined modality strategy with cytoreductive surgery, loco-regional chemotherapy and adjuvant systemic chemotherapy with up to now unexpected results and a 5-years survival that reaches, in some studies, 50%.[13]

In literature there has been only two randomized controlled trials (RCTs) carried out to compare outcomes with CRS + intraperitoneal chemotherapy and conventional systemic chemotherapy for PC from CRC. In 2003 Verwaal[16] has reported a median survival of 22.2 months in CRS+HIPEC group compared with 12.6 months in patients receiving chemotherapy alone. This study has been criticized, as the systemic chemotherapy consisted only of 5-fluorouracil and leucovirin, which

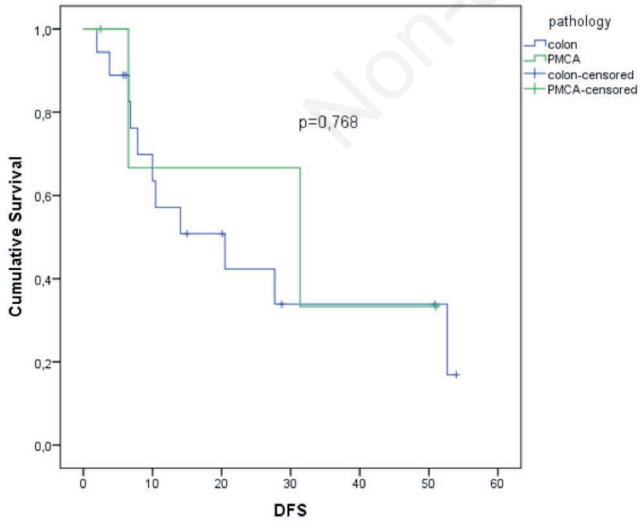

Figure 1. Comparison between disease free survival (DFS) (in months) in patients underwent to hyperthermic intraperitoneal chemotherapy+cytoreductive surgery for peritoneal mucinous carcinomatosis (PMCA) and high-grade non mucinous carcinoma (green line) and for colorectal cancer (blue line).

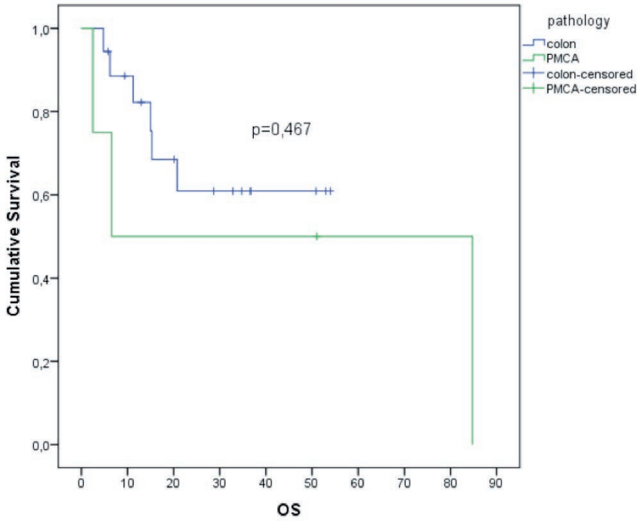

Figure 2. Comparison between overall survival (OS) (in months) in patients underwent to hyperthermic intraperitoneal chemotherapy+cytoreductive surgery for peritoneal mucinous carcinomatosis (PMCA) and high-grade non mucinous carcinoma (green line) and for colorectal cancer (blue line).

now is considered suboptimal. This year Cashin and coll.[12] has reported the data from the *Swedish peritoneal study* in which patients were randomized to CRS plus sequential postoperative intraperitoneal chemotherapy (SPIC) with 5-fluorouracil *versus* systemic chemotherapy with oxaliplatin and 5-fluorouracil regimen. The study was started in 2004 but was prematurely stopped in 2011 for the low accrual rate with only 48 eligible patients (the primary sample size calculated was 88 patients). Despite the decision to prematurely terminate the trial, the study showed that CRS+SPIC may be a superior treatment to systemic chemotherapy alone with a 5-years survival of 33% *versus* 4% (P=0.02) and a OS of 25 *versus* 18 months (P=0.04) (hazard ratio=0.51) compared with in systemic chemotherapy. Instead a promising results is suggesting from the PFS curves where the curative potential of CRS plus SPIC, in comparison with systemic chemotherapy alone [CRS+SPIC have better results: 12 months *versus* 11 months (P=0.16) and 17% *versus* 0% at 5 years (P=0.1)]. As comparison between SPIC and HIPEC indicates that HIPEC may be superior, it seems reasonable to conclude that the same benefit seen in CRS+SPIC is applicable to CRS+HIPEC.

The remaining available literature consists of case series or comparative study that clearly indicates that the greatest survival rates in patients with PC from CRC is achieved after treatment with CRS and HIPEC (OS 62.7 *versus* 23.9 months and 51% *versus* 13% 5-years survival for CRS+HIPEC group in for the standard treatment).[17]

In present study as shown in Kaplan-Meier curves OS and DFS are similar to the more recent literature despite the small simple size. Particularly interesting is found comparing the curves of primary and recurrence CRC, where the maximal effort with CRS+HIPEC in patients treated for primary CRC seems to be achieved with a significant difference of 45.2 months of DFS and 44.4 months of OS respectively. Regarding the role of neoadjuvant chemotherapy some authors reported a decrease in OS in patients undergone to pre-operative chemotherapy prior HIPEC+CRS compared to those who did not receive any pre-HIPEC systemic chemotherapy (14.4 months *versus* 20.4 months respectively, P=0.01).[18] However these data reported curves of patients undergone to CRS+HIPEC for different histopathology entities (high-grade primary appendiceal or colon cancer, signet-ring cells, any poorly differentiated lesion considered high-grade, and neuroendocrine tumors with or without goblet-cell features).[18]

Differently from CRC the classification of peritoneal disseminated mucinous appendiceal tumors remains a challenge for oncologists, surgeons and pathologists. Controversy exists among different systems of classification regarding reproducibility and prediction of long-term patient outcomes. However the histologic grade of malignancy seems to be the most important prognostic factors.[9,18-20]

PMCA is considered when the primary tumor is an appendiceal adenocarcinoma with peritoneal tumor having more proliferative epithelium with signet ring cells associated with a cytology atypia. This tumor is considered more aggressive than diffuse peritoneal adenomucinosis (DPAM) for the potentiality to give lymphatic, hematic and peritoneal metastases.[21] PCA is a high-grade non-mucinous neoplasm associated with the presence of extracellular mucin more than 50% which all have severe cytologic atypia and mitoses.[8] For this reason we have decide to exclude patients with DPAM from our analysis.

In a study by Glehen including 1290 patients who underwent 1154 CRS+HIPEC for PC from non-ovarian origin the overall median survival was 30 months for PC from CRC and 77 months for PC from appendiceal adenocarcinoma (5-years survival of 26% in CRC, of 73% in pseudomyxoma peritonei (PMP) and of 56% in appendiceal adenocarcinoma), showing etiology of PC as a principal independent prognostic factors for OS (P<0.001).[6] In a study by Bruin the multivariate analysis shows that histological classification and primary tumor site are strong prognostic factors for outcome after HIPEC treatment and in general patients with tumors of appendiceal origin show better survival than CRC ones and primary colon tumor hardly ever resulted in DPAM.[8] Similarly Milovanov compared OS and DFS in DPAM *versus* stage IVa PMCA (patients with well-differentiated mucinous carcinomas with negative lymphnodes) and *versus* stage IVb PMCA (moderately and

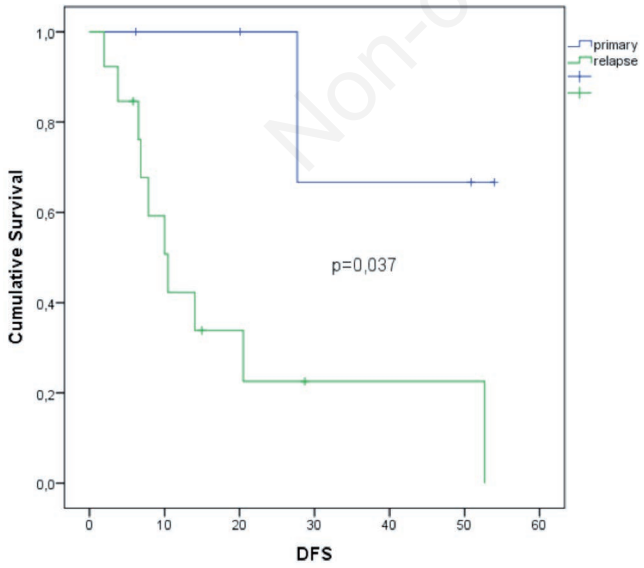

Figure 3. Comparison between disease free survival (DFS) (in months) in patients underwent to hyperthermic intraperitoneal chemotherapy+cytoreductive surgery for primary colorectal cancer (CRC) *versus* relapse for CRC.

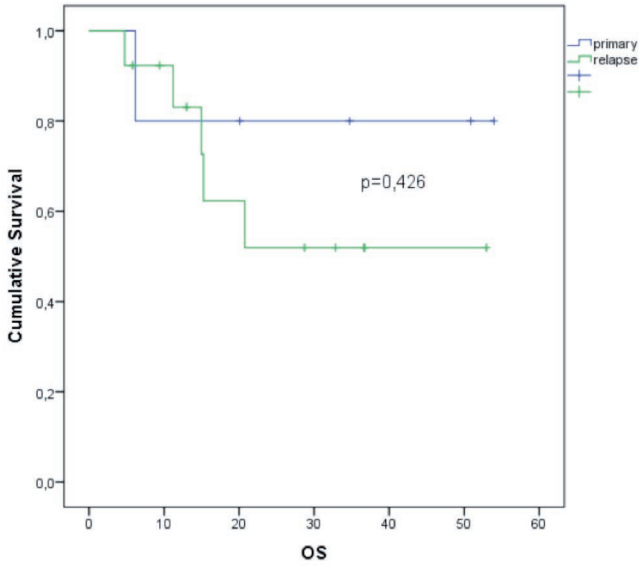

Figure 4. Comparison between overall survival (OS) (in months) in patients underwent to hyperthermic intraperitoneal chemotherapy+cytoreductive surgery for primary colorectal cancer (CRC) *versus* relapse for CRC.

poorly differentiated tumors irrespective of lymphnodes status and well-differentiated PMCA with positive lymphnodes) found a statistical significance difference with a 3-year survival of 88%, 67%, 27% respectively (P=0.025) and a 3-years DFS of 71%, 43% and 15% (P=0.004).[19] In the study by Winer the differences in oncologic outcome after CRC+HIPEC suggests a difference in underlying biology between signet ring carcinomas of appendiceal and colorectal origin (better OS in AC group), despite a similar phenotype.[4] However, despite the data reported in literature in our series AC OS and DFS are similar to CRC, probably for the small number of patients.

At present the role of pre-operative or post-operative chemotherapy in AC is not clear, particularly in most aggressive tumors, and the only treatment that can improve OS is a complete cytoreduction.[21] These findings are probably due to the different receptor expressed in appendiceal neoplasms and this could explain the reason for which the chemotherapy regimens more frequently used and similar to the regimens used in CRC do not work.[21] Also in cases of intraperitoneal recurrence surgical treatment may improve survival.[21]

Despite a lack of RCTs, systemic chemotherapy is offered to patients with high-grade AC, incomplete CRS, lymph node involvement and early recurrence, based on the proven effectiveness of systemic chemotherapy in CRC.[18,21] In 2012 Chua[7] reports a median survival rates of 4.2 years *versus* 1.7 years in patients underwent to CRS+HIPEC in high-grade adenocarcinoma of the appendix compared to systemic chemotherapy alone.[7]

Considering the complexity of the surgical procedure the frequency of complications after CRS+HIPEC from CRC and AC is predictably high (mortality 0.9-5.8% up to 20%, major morbidity rate 12-52% up to 70%).[21,22] However it could be considered acceptable given the circumstances and it is not superior to other mayor gastrointestinal surgery procedures.[23,24] Furthermore the experience acquired in this surgical technique, the careful patients selection and post-operative care have improved outcomes and decreased mortality and morbidity.[22] In our study near to 50% of patients had post-operative complications in both groups, however only 3 patients (1 in AC group and 2 in CRC group) needed a surgical re-intervention, and the median of ICU and ward stay was of 2 and 17-20 days respectively. However 5 patients did not underwent to adjuvant chemotherapy post HIPEC due to the poor condition give by the intervention. Mortality rates were 2.2% (1 patients of 22) considering both groups.

Recently prospective and RCTs trials confirmed that the most important prognostic factors remain the completeness of CC and the tumor histology for both CRC and AC.[1,6,9,16,13,23] The CC is crucial to improve outcomes and to achieve stability of the curves in terms of OS that DFS.[1,13,23,9] Patients with PC from CRC undergoing CCR0 prior to HIPEC have a 5-years survival of 20% and an OS of 25.9 months, than those with CCR1 (9.9% of 5-years survival and 8 months of OS).[2] Patients with PC from AC with CCR2 or CCR3 have a 5-years survival rate of 24% compared with 85% in CCR0, and 80% in CCR1 patients.[7] However the achieving of CC0 is strong related with the volume of malignancy (in terms of PCI). For CRC literature supports a PCI lower than 10 (5-years survival of 65%, 26% and 18% respectively).[2,24,25] According to that it could be reasonable to strongly advise against treatment of PC from CRC with PCI>20, even if a total contraindication judgment cannot be made on PCI alone.[13,24] As a matter of fact Elias *et al.* described a significant advantage in survival even when PCI was over 24 in CRC.

Regarding PC from AC Chua shows as the influence of PCI remained a significant prognostic variable for both patient with low-grade appendiceal pseudomyxoma and appendiceal adenocarcinoma treated by CRS+HIPEC. Nevertheless for patient with appendiceal PMP even in PCI ranging from 31 to 39, 5- and 10-years survival rates of 73% and 68% respectively, may still be achieved.[7] Likewise for patients with appendiceal adenocarcinoma, 5- and 10-years survival rates of 56% and 46% respectively, may still be achieved despite high volume peritoneal disease. Therefore, patients with high volume disease from mucinous appendiceal neoplasms should be considered for CRS+HIPEC despite PCI.[7] Moreover, according to many recent publications, PCI in AC is more related to post-operatory complications than to OS and DFS.[13] Our data are in line with the literature about the CC and the criteria of PCI, but the simple size of the two groups did not permit to perform univariate and multivariate analysis to evaluate the others prognostic factors (as PCI, different outcome related to the different tumor stages, in nodes positivity, the presence of liver metastasis, CC0, the role of neoadjuvant chemotherapy and also the role of adjuvant chemotherapy).

Conventional treatment also with recent new chemotherapy regimens have reported a minimal increase in disease control but do not have potential curative intent and do not improve long-term outcomes. At today clinical studies and RCTs suggest CRS and HIPEC as better treatment in case of advanced disease particularly in patients with low PCI, primary tumor, and aggressive appendiceal cancer as PMCA and PCA.

Conclusions

CRS and HIPEC for CRC and AC may achieve a better disease control particularly when a complete cytoreduction is achieved.

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