Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer: a 13 years-retrospective monocentric study

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Abstract

Background and study aim: **Over the last 20 years, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has progressively become a therapeutic option for peritoneal carcinomatosis thanks to its favourable oncologic results. The aim of this study is to analyse the overall survival and recurrence-free survival, after complete CRS and closed abdomen technique HIPEC for peritoneal carcinomatosis from colorectal cancer.**

Patients and methods: **This retrospective study collected the data from all patients who underwent a CRS with HIPEC for colorectal cancer at "Cliniques universitaires Saint Luc" from October 2007 to December 2020. Ninety-nine patients were included.**

Results: **The median follow-up was 34 months. Post-operative mortality and Clavien-Dindo grade III/IV morbidity rates were 2.0% and 28.3%. The overall 2-year and 5-year survival rates were 80.1% and 54.4%. Using the multivariate analysis, age at surgery, liver metastases and PCI score >13 showed a statistically significant negative impact on overall survival. The 2-year and 5-year recurrence-free survival rates were 33.9% and 22%. Using the multivariate analysis, it was found that liver metastases, the extent of carcinomatosis with PCI>7 have a statistically significant negative impact on recurrence-free survival.**

Conclusions: **Despite a high recurrence rate, CRS followed by HIPEC to treat peritoneal carcinomatosis from colorectal origin offer encouraging oncologic results with a satisfying survival rate. When PCI>13, CRS and HIPEC does not seem to offer any survival benefit and to efficiently limit recurrence, our data are in favor of a maximum PCI of 7.** (Acta gastroenterol. belg., **2022,** 85, **573-579**).

Key words: cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; peritoneal carcinomatosis

Introduction

Peritoneal carcinomatosis (PC) from colorectal cancer is the second-most frequent cause of death in colorectal cancer after metastatic liver disease. Approximately 8% of patients with colorectal cancer had synchronous or metachronous peritoneal carcinomatosis and PC is the first and only localisation of metastases in almost 5% of cases (1). Patients with metastatic colorectal cancer with peritoneal-only involvement have significantly worse overall survival than those with other isolated sites of metastasis (2).

The treatment for patients with unresectable disease is systemic chemotherapy. For the resectable patients, the treatment has evolved since the 1980's and is still a matter of debate.

The combination of complete cytoreduction with hyperthermic intraperitoneal chemotherapy (HIPEC) showed good results. Indeed, some studies have shown an improved survival after cytoreductive surgery (CRS) followed by HIPEC over systemic chemotherapy alone (21.6 versus 12.6 months in the RCT of *Verwall et al*.) (3,4). The 5-year and 10-year survival after complete resection surgery followed by HIPEC is estimated to be 35% and 15%, respectively and the cure rate after complete resection surgery of colorectal PC, followed by HIPEC is estimated to be 16%, close to that obtained after resection of colorectal liver metastases (5).

However, this treatment carries a significant morbidity and mortality rate, and it is time and resources consuming. Also, some aspects of HIPEC remain controversial as the type of chemotherapeutic drug used, the means of drug administration (open versus closed abdomen technique) and the use of perioperative systemic chemotherapy. The recent French randomised trial "PRODIGE 7" (6) questioned the role and the benefit of HIPEC itself because they showed no evidence of an overall survival benefit with cytoreductive surgery associated with 30 minutes oxaliplatine HIPEC compared with cytoreductive surgery alone (41.2 months in the cytoreductive surgery group and 41.7 months in the cytoreductive surgery plus HIPEC group).

The aim of this study is to analyse the results in term of overall survival and recurrence-free survival after complete cytoreductive surgery and closed abdomen technique HIPEC for peritoneal carcinomatosis from colorectal cancer.

Methods

This retrospective study collected the data from all patients who underwent a cytoreductive surgery

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(CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal cancer in Colorectal Surgery Unit at "Cliniques universitaires Saint Luc" from October 2007 to December 2020.

Preoperative investigations

All the patients underwent physical examination, blood tests (including serum electrolyte, liver and kidney function) as well as evaluation of their nutritional status (body mass index, albuminemia and pre-albuminemia). Diagnostic tests included colonoscopy, upper endoscopic ultrasound, cerebral and thoraco-abdominal computed tomography (CT), as well as Positron Emission Tomography (PET) combined with CT. Operative risk was assessed with cardiac ultrasonography and lung spirometry.

Patient selection

The inclusion criteria were: [1] age > 18 years, [2] PC of colorectal origin, [3] PC considered resectable based on clinical and radiological investigations as previously described, and [4] signed informed consent.

The exclusion criteria were: [1] World Health Organization (WHO) performance status > 2, [2] cardiopulmonary failure: dyspnea > class 1 (New York Heart Association classification), or PaO_2 at rest <60 mmHg or left ventricular ejection fraction <60%, [3] renal failure: serum creatinine >120µmol/l, [4] hepatic failure: prothrombin level <70%, [5] leucopenia <1,500/µl, [6] thrombocytopenia <100,000/µl, [7] central nervous system disease (vascular or neoplastic), [8] extra-abdominal metastasis, [9] more than 3 resectable hepatic metastases, and [10] pregnancy. Patient with no peritoneal carcinomatosis (PCI of 0) during surgical exploration were excluded.

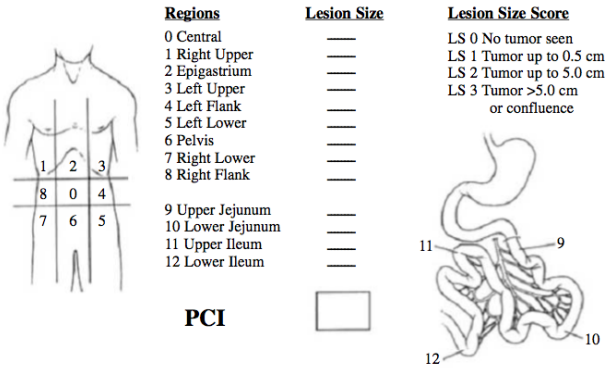
This study was performed in accordance with the Helsinki Declaration.

The study was approved by the Institutional Review Board of "Cliniques universitaires Saint Luc". Informed consent of patients was waived by the Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the standard of care.

Surgical and HIPEC procedure

Through a midline laparotomy the abdominal cavity was explored to obtain cytological and pathological samples. A precise description of disease distribution was performed and the decision to proceed with CRS and HIPEC was taken only if disease was deemed resectable (7). The Peritoneal Carcinomatosis Index (PCI) of Sugarbaker (8) was used to assess the extent of PC (Table 1). Cytoreductive surgery included primary tumour removal, complete resection of tumor nodules

Table 1. — **Sugarbaker's Peritoneal Cancer Index**



with gastrointestinal tract resection if necessary and peritonectomy. HIPEC was then performed. All patients underwent CRS with closed abdomen HIPEC under general anaesthesia. The HIPEC protocol was designed according to Glehen's published experience (9,10) using a closed sterile circuit. Before laparotomy closure, two inflow drains were inserted under the left and right hemi-diaphragms (30F silicone drain; William Harvey, Bard Cardiopulmonary Division, Haverhill, MA, USA) and a third outflow drain (32F) was positioned in the Douglas pouch. Temperature probes were also inserted into the abdominal cavity behind the liver pedicle and the mesentery. Other temperature probes were set up outside the abdominal cavity on the inflow and outflow drains 8 cm from the skin and inside the bladder within a Foley catheter. The laparotomy incision was then closed, and the inflow and outflow drains were connected to a closed sterile circuit with a perfusate of between 3 and 4 litres (Dextrose 5%) circulated at a flow rate of 500 ml/min using a dedicated device (Cavitherm®, EFS Electronics, Millery, France). Intra- and extra-abdominal temperatures, as well as intra-abdominal pressures were automatically monitored and recorded every 4 seconds through the Cavitherm computer system. The perfusate contained 360 mg/m^2 of Oxaliplatin or 35 mg/m^2 of Mitomycin-C in case of allergy or severe toxicity to Oxaliplatin. HIPEC was performed for 30 minutes with Oxaliplatin or 90 minutes with Mitomycin-C at inflow temperatures ranging between 41°C and 42°C. Respiratory and hemodynamic parameters were monitored during the whole procedure.

Post-operative course

All patients included in the study were transferred to the intensive care unit for at least 24 hours after operation.

During the first postoperative week, patients underwent daily blood sampling (full blood count, urea and electrolytes, liver function tests and clotting studies) then every two days for the second week and twice a week or when necessary until the patient's discharge. Radiological investigations were performed based on clinical and biochemical parameters if a postoperative complication was suspected.

All toxicities and postoperative complications that occurred during the initial 30 post-operative days were recorded.

Follow-up

All patients were followed every 3 months for the first two years, then every 6 months with clinical examination, serum carcinoembryonic antigen (CEA) measurement, thoraco-abdominal CT and PET-CT.

Statistical Analysis

Data were recorded retrospectively. The analysis of recurrence or death was based on the time from the surgery to the date of first recurrence, the date of death, the date of the latest news, or the cut-off date, whichever came first. For this analysis, only one patient was lost to follow-up.

A Kaplan-Meier survival curve was fitted to the data. Univariate analysis of factors influencing survival used log rank test and Cox model for categorical and continuous variables respectively. As missing data were very scarce (e.g. 3% for CEA level), no imputation was performed, especially as their respective effect on the outcome was lower than the threshold required for inclusion in the multivariable Cox Proportional Hazard model.

A p-value lower or equal to 5% was considered statistically significant. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients Characteristics

Between October 2007 and December 2020, 99 patients were operated in Colorectal Surgery Unit at "Cliniques universitaires Saint Luc" of colorectal adenocarcinoma for a combined treatment with CRS and HIPEC. There were 43 men and 56 women, with a median age of 57 years old (range: 18-76) at the time of CRS and HIPEC. Demographic data and tumour characteristics are presented in Table 2.

Twenty-nine patients (29.3%) presented synchronous liver metastases. These metastases were resected during the cytoreductive surgery in 21 patients. Twenty-one of the 56 women presented ovarian metastases.

There were 36 mucinous adenocarcinomas sub-type (36.4%).

The mean level of preoperative CEA was 14.8 µg/l (range 1-200).

Perioperative chemotherapy was prescribed to 71 patients (71.7%): 9 patients had neoadjuvant chemotherapy, 51 patients had adjuvant chemotherapy and 11 patients had both. Twenty-eight patients (28.2%) did not receive any perioperative chemotherapy.

Surgical Results

The median PCI was 8 (range: 1-30). The PCI score is presented in Table 2.

Table 2. — **Demographic and tumor characteristics**

Variables	n (%)
Sex	
Male	43 (43.4)
Female	56 (56.6)
ASA	
I	5 (5.0)
II	68 (68.7)
III	26 (26.3)
Smoker	
Yes	37 (37.4)
No	62 (62.6)
Site of primary tumor	
Appendix	10 (10.1)
Right colon	31 (31.3)
Transverse colon	4 (4.0)
Left colon	42 (42.4)
Rectum	11 (11.1)
vNo primary tumor found	1 (1.0)
Histology	
Adenocarcinoma	99
Mucinous	36 (36.4)
pT stage	
pT2	3 (3.0)
pT3	29 (29.3)
pT4	63 (63.6)
Unknown	3 (3.0)
pN stage	
pN0	24 (24.2)
pN1	33 (33.3)
pN2	38 (38.4)
Unknown	4 (4.0)
Primary tumor and carcinomatosis	
Synchronous	45 (45.5)
Metachronous	54 (54.5)
Synchronous liver metastases	
Yes	29 (29.3)
No	70 (70.7)
Peritoneal Carcinomatosis Index	
0-10	67 (67.7)
10-20	23 (23.2)
>20	9 (9.1)

A complete macroscopic cytoreduction was performed in all patients. Gastro-intestinal tract resection was necessary in 78 patients (78.8%) with a median number of anastomosis of 1 (range: 0-5). A stoma was performed for 33 patients (33.3%): 31 ileostomies and 2 colostomies.

HIPEC was performed in 87 cases (87.9%) with Oxaliplatin, in 12 cases (12.1%) with Mitomycin-C.

Postoperative mortality and morbidity

Two patients (1.9%) died within the 30 days after surgery: one from refractory septic shock after intra-

Table 3. — **Post-operative morbidity**

Variables	n (%)
Clavien-Dindo	
I	39 (39.4)
II	30 (30.3)
III	23 (23.2)
IV	5 (5.1)
V	2 (2.0)
Anastomotic fistula	
Yes	10 (10.1)
No	89 (89.9)
Reoperation	
Yes	12 (12.1)
No	87 (87.9)
Hematologic toxicity	
Yes	35 (35.4)
No	64 (64.6)
Pulmonary Complications	
Yes	15 (15.2)
No	84 (84.8)

abdominal bleeding, digestive fistula and abdominal compartment syndrome and the other one from acute respiratory distress syndrome (ARDS), medullary aplasia and septic shock.

Clavien-Dindo grade III complications occurred in 23 patients (23.2%) and grade IV complications in 5 patients (5.1%). Post-operative morbidity is presented in Table 3.

Thirty-five patients (35.4%) showed an hematologic toxicity (one patient with grade III thrombopenia associated with grade IV anemia, 7 patients with grade III thrombopenia associated with grade III anemia, 2 patients with grade IV anemia, 14 patients with grade III anemia, and 11 patients with grade III thrombopenia).

Ten patients (10.1%) had digestive fistula, all requiring reoperation. Two other patients needed reoperations for haemostasis.

Fifteen patients (15.2%) showed pulmonary complications: bilateral pleural effusion requiring percutaneous drainage in 7 patients, pulmonary embolism in 6 patients and association of bilateral pleural effusion requiring percutaneous drainage and pulmonary embolism in 2 cases.

The median hospital stay was 17 days (range: 8-71).

Overall survival

The median follow-up was 34 months (range: 0-142). One patient was lost to follow-up because he moved abroad. Median survival was 62.9 months. The Kaplan-Meier overall 2-year and 5-year survival rates were 80.1% and 54.4% respectively (Figure 1).

Using the univariate analysis, neodjuvant chemotherapy (p=0.01), presence of liver metastases (p=0.01) and the extent of carcinomatosis (p=0.04) have a statistically significant negative prognostic impact (Table 4).

A PCI cut-off value of 13 was found worsening statistically the overall survival (p=0.04) (Figure 2).

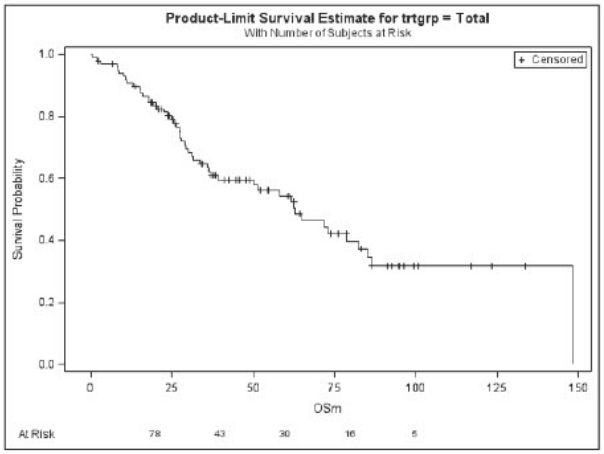


Figure 1. — Overall survival after cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis from colorectal origin.

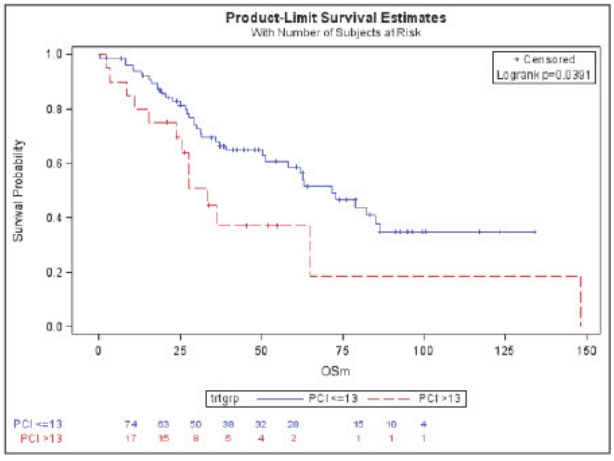


Figure 2. — Overall survival after cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis from colorectal origin. according to PCI value.

Median survival was 71.8 months when PCI <13 and 33.5 months when PCI>13.

In multivariate analysis, Cox regression model was performed to determine which clinical or therapeutic variables were more strongly correlated with overall survival. There were three independent prognostic indicators confirmed: age at surgery (p=0.02), presence of liver metastases (p=0.04) and PCI score >13 (p=0.01).

ASA>2, smoking patients, pre-operative CEA, mucinous sub-type or positive nodes did not have any prognostic impact.

Recurrence-free survival

During the follow-up, 74 patients (74.7%) showed recurrence: isolated PC recurrence in 16 patients, distant metastasis in 18 patients and association of PC with distant metastases in 40 patients. Nine patients had a second CRS + HIPEC surgery for PC recurrence of colorectal cancer.

Table 4. — **Univariate and Multivariate Analyses of Overall Surival**

	Univariate analysis			Multivariate analysis		
	Hazards ratio	**95% CI**	**p**	**Hazards ratio**	**95% CI**	**p**
ASA >2	1.01	0.53 – 1.93	0.98			
Age	0.98	0.96 – 1.00	0.10	0.97	0.95 – 0.99	0.02
Male sex	1.66	0.94 – 2.92	0.08			
Smoking	1.31	0.73 – 2.34	0.37			
CEA	1.00	1.00 – 1.01	0.48			
Neoadjuvant chemotherapy	2.21	1.20 – 4.07	0.01			
Adjuvant chemotherapy	0.72	0.49 – 1.65	0.90			
Liver metastases	2.07	1.17 – 3.65	0.01	2.32	1.30 – 4.13	0.004
Adenocarcinoma vs Mucinous Adenocarcinoma	1.56	0.84 – 2.89	0.16			
PCI>13	1.98	1.02 – 3.84	0.04	2.58	1.29 – 5.16	0.01
Synchronous PC	1.13	0.64 – 2.01	0.67			
Positive nodes	1.04	0.53 – 2.05	0.90			

Table 5. — **Univariate and Multivariate Analyses of Recurrence-Free Survival**

	Univariate analysis			Multivariate analysis		
	Hazards ratio	**95% CI**	**p**	**Hazards ratio**	**95% CI**	**p**
ASA >2	1.15	0.70 – 1.87	0.59			
Age	0.99	0.97 – 1.01	0.33			
Smoking	0.91	0.56 – 1.47	0.70			
CEA	1.00	1.00 – 1.01	0.37			
Neoadjuvant chemotherapy	1.70	0.99 –2.89	0.05			
Adjuvant chemotherapy	0.83	0.52 – 1.35	0.46			
Liver metastases	2.27	1.41 – 3.67	<0.001	2.51	1.54 – 4.08	<0.001
Adenocarcinoma vs Mucinous Adenocarcinoma	1.55	0.95 – 2.52	0.08			
PCI>7	1.84	1.15 – 2.95	0.01	2.04	1.27 – 3.27	0.003
Synchronous PC	1.00	0.63 – 1.58	0.99			
Positive nodes	0.95	0.55 – 1.66	0.86			

Median recurrence-free survival was 14.1 months. The Kaplan-Meier 2-year and 5-year recurrence-free survival rates were 33.9% and 22% respectively (Figure 3).

In the univariate analysis, neodjuvant chemotherapy (p=0.05), presence of liver metastases (p<0.001), the extent of carcinomatosis (p=0.01) have a statistically significant negative impact on recurrence-free survival (Table 5). A PCI cut-off value of 7 has been found worsening statistically the recurrence-free survival (p=0.01) (Figure 4). Median recurrence-free survival was 18.9 months when PCI <7 and 13.6 months when PCI>7.

Using the multivariate analysis, it was found that the presence of liver metastases (p<0.001), and the extent of carcinomatosis with PCI>7 (p=0.003) have a statistically significant negative impact on recurrence-free survival. (Table 5).

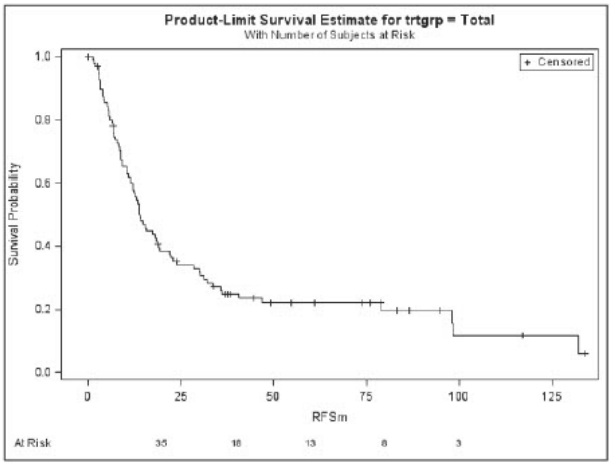


Figure 3. — Recurrence-free survival after cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis from colorectal origin.

Discussion

Our 2-year and 5-year overall survival rates of 80.1% and 54.4% respectively compares well with published survival rates from similar series. In *Goéré et al's* study (5), the 5-year and 10-year survival after complete resection surgery followed by HIPEC (with Oxaliplatin or Oxaliplatin + Irinotecan) was 35% and 15% respectively. *Quenet et al*. (11) using open abdomen technique and Oxaliplatin with or without Irinotecan for HIPEC presented results similar to ours with significant survival but an important recurrence: at 5 years, overall survival and recurrence-free survival rates were 41.8% and 13.8% in Oxaliplatin alone and 42.4% and 14.2% in Oxaliplatin + Irinotecan.

The main prognostic factors are completeness of resection and extent of the disease (4, 10). We found a PCI cut-off value of 13 worsening statistically overall

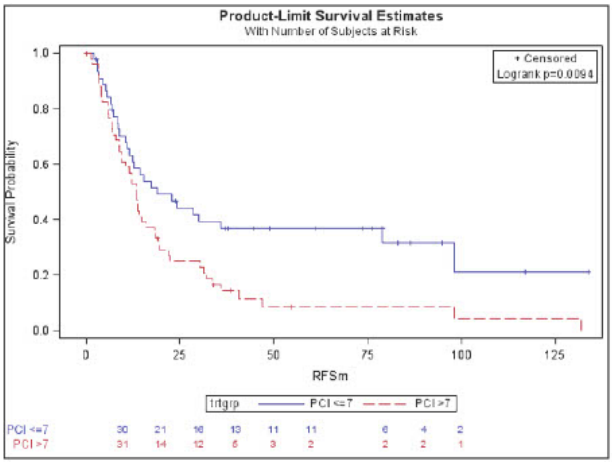


Figure 4. — Recurrence-free survival after cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis from colorectal origin according to PCI value.

survival. *Goéré et al*. (12) concluded that when PCI exceeds 17, CRS for colorectal peritoneal carcinomatosis followed by HIPEC for does not seem to offer any survival benefit. *Elias et al.* (13) showed a tremendous difference, on overall survival, between patients with a PCI score between 1 and 5, and patients with a PCI score ≥16 (respectively, 72.4 and 11.8 % at 5 years).

Post-operative mortality (2.0%) and Clavien-Dindo grade III or higher post-operative morbidity (28.3%) are similar to those reported recently by experienced group. *Elias et al* (4), on their 523 patients from 23 centres in four French-speaking countries had a post-operative mortality and grades 3 to 4 morbidity of 3 % and 31%, respectively. In *PRODIGE 7* study (6), the 30day mortality rate was 2%, and 42% of patients in the « cytoreductive surgery plus HIPEC group » had grade 3 or worse adverse events.

There is no consensus concerning the HIPEC modalities regarding the type of chemotherapeutic drug used, duration of exposure, temperature, technique (open versus closed)…(15) *Cavaliere et al.* (16) showed a trend toward improved survival with the closed technique as compared to the open (respectively 22 versus 17 months, p=0.08). We chose the closed abdomen technique because it theoretically provides higher tumour penetration through higher intra-abdominal pressure and limited thermic losses. Furthermore, it reduces exposure risks for healthcare workers in the operative room.

Regarding the drugs used for HIPEC, several multicentric retrospective studies showed an improved survival rate of patients treated with Oxaliplatin (4, 16). However, the recent French randomised trial "*PRODIGE 7*" (6) questioned the role and the benefit of HIPEC itself comparing 265 patients receiving HIPEC after cytoreductive surgery with cytoreductive surgery alone. They showed no evidence of an overall survival benefit with cytoreductive surgery plus HIPEC (Oxaliplatin in open or closed technique during 30 minutes) compared with cytoreductive surgery alone (41.2 months in the cytoreductive surgery group and 41.7 months in the cytoreductive surgery plus HIPEC group). In addition, they founded more frequent post-operative late complications with HIPEC group. So they concluded that high-dose Oxaliplatin-based HIPEC given over a short duration should no longer be used because it no confer any additional benefit to cytoreductive surgery and cytoreductive surgery alone should be the cornerstone of therapeutic strategies with curative intent for colorectal peritoneal carcinomatosis. Note the importance of management in expert centres to optimize the quality of cytoreduction (4, 14). These results are not sufficient to definitively renounce the concept of HIPEC for the treatment of peritoneal carcinomatosis of colorectal origin but must be put into perspective with the continuous progress of knowledge in terms of pharmacokinetics, individual tumor sensitivity and with those of the different categories of chemotherapies and delivery techniques.

As alternative to Oxalipatin-HIPEC, Mitomycin-C or Cisplatin, having shown longer recurrence-free survival and overall survival than surgery alone in stage III epithelial ovarian cancer (17).

Concerning the perioperative systemic therapy in patients with resectable peritoneal carcinomatosis, the results are not clear. *Repullo et al.* (18), in their retrospective study did not show any clear benefits of perioperative systemic chemotherapy in carefully selected patients undergoing R0/R1 cytoreduction surgery and HIPEC for colorectal peritoneal carcinomatosis.

In their RCT, *Rovers et al.* (19) did not find any significant difference between patients receiving perioperative systemic chemotheray or not regarding the proportions of macroscopic complete cytoreduction and Clavien-Dindo grade III or higher post-operative morbidity. They concluded that perioperative systemic therapy seemed feasible, safe, and able to induce response of peritoneal carcinomatosis from colorectal cancer.

Conclusion

Despite a high recurrence rate, cytoreductive surgery with HIPEC to treat peritoneal carcinomatosis of colorectal origin offers encouraging oncologic results with a satisfying overall survival rate. Despite the recent controversy regarding the use of Oxalipatin-HIPEC, our study shows favourable oncologic results comparable to published survival rates of similar series. Others studies are needed to analyse the specific role of HIPEC and standardised its use. However, macroscopically complete cytoreductive surgery should be considered the mainstay of treatment. When PCI>13, CRS and HIPEC does not seem to offer any survival benefit and to efficiently limit recurrence, our data are in favors of a maximum PCI of 7.

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