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ORIGINAL ARTICLE

Synchronous liver metastases and peritoneal carcinomatosis from colorectal cancer: different strategies for curative treatment?

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Abstract

Background Management of patients with resectable hepatic metastases (HMs) and colorectal peritoneal carcinomatosis (CRPC) is not currently standardised.

Objective The aims of this study were to evaluate the safety of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) and hepatic surgery for patients with CRPC with synchronous hepatic metastases (HM), and its impact on survival rates.

Methods A retrospective analysis was performed, including patients undergoing CRS/HIPEC for CRPC from 2007 to September 2016 in two groups, with (HM+) and without (HM−) synchronous hepatic metastases. Patients with extra-abdominal metastases were excluded. The hepatic strategy was described. Morbimortality and survival were compared between the two groups.

Results One hundred nine patients underwent CRS/HIPEC for CRPC with or without hepatic surgery with curative intent: 33 patients with (HM+) and 76 patients without (HM−) synchronous HM. The median follow-up was 30 months. All patients with HM (HM+) received neoadjuvant chemotherapy vs. 88.1% in the HM− group ($p = 0.04$) associated with monoclonal antibody in 66.6% of cases in the HM+ group vs. 57% in the HM− group ($p = 0.01$). In the HM+ group, two steps were implemented to treat peritoneal and hepatic metastases in 15 patients (45%). In this group, planned hepatic resection in two procedures was performed for eight patients, all presenting bilobar HM. Postoperative morbidity did not differ between the two groups. No deaths occurred. Median overall survival (OS) and recurrence-free survival (RFS) were 31 and 65 months ($p = 0.188$), versus 21 and 24 months ($p = 0.119$), respectively, in the HM+ versus HM− groups. In multivariate analysis, the peritoneal cancer index (PCI) was the only significant prognostic factor whereas synchronous HM was not a significant prognostic factor.

Conclusion Curative surgical treatment for CRPC with synchronous HM seems to be feasible and safe, and could facilitate long survival rates, compared to patients without HM. The hepatic strategy is not standardised. However, a "two-step" surgical strategy could be proposed in order to reduce postoperative morbidity rates.

Keywords Colorectal cancer · Liver metastases · Peritoneal metastases · HIPEC

Introduction

Colorectal peritoneal carcinomatosis (CRPC), with an occurrence rate of 40% [1, 2], is the second most common colorectal metastatic disease after hepatic metastases (HMs) [3]. Peritoneal carcinomatosis (PC) alone is observed synchronously with the primary tumour in 10% of cases, or metachronously in about 25–35% of recurrences [4, 5]. CRPC is associated with an increased number of metastatic sites [6]. It is recognised as a negative prognostic factor in patients with metastatic colorectal cancer [7, 8]. Franko et al. [9] published a recent meta-analysis including individual patient data from first-line prospective controlled, randomised phase 3 trial patients with metastatic colorectal cancer. They reported a median overall survival of 19 months in patients with HM only, 16 months in patients with PC only and 12.6 months in patients with non-isolated PC [9]. The curative management of patients with metastatic colorectal cancer is based on surgical resection. CRPC was previously considered a terminal condition, and the therapeutic arsenal was limited.

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The median survival of these patients did not exceed 12 to 24 months with palliative chemotherapies [10, 11]. Moreover, with recent systemic chemotherapy, PC was associated with a 30% reduction in overall survival (OS) compared to patients with metastatic colorectal cancer without PC [6]. The standardisation of combined treatment involving cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has evolved over the last two decades [11–13]. PC can now be considered as a metastatic step eligible for locoregional treatment in combination with systemic chemotherapy. CRS/HIPEC can obtain an overall survival of about 40 months in the case of complete macroscopic resection [11, 12, 14, 15]. A complete CRS, a peritoneal cancer index (PCI) lower than 20, good performance status, postoperative chemotherapy and no synchronous HM were identified as factors associated with a better OS [11, 16, 17]. PC was associated with one or more HM in 8% of cases, with median OS of 5 months [18]. For a long time, the discovery of PC in patients with resectable HM was a contraindication to hepatectomy [19]. Since 2007, the occurrence of less than three resectable synchronous HM with CRPC was a relative contraindication for CRS/HIPEC [20, 21]. Some studies, with small cohorts, have shown that complete CRS of PC and liver resections followed by HIPEC was feasible with a better OS than systemic chemotherapy alone [14, 22–30]. However, no study has evaluated complete metastatic site resection (PC and HM) in two steps.

The purpose of this study is to describe and to evaluate the hepatic strategy for patients with synchronous HM and CRPC treated by CRS/HIPEC.

Patients and methods

Population

In this single-centre study, population characteristics were obtained from data collected prospectively and analysed retrospectively. Patients with synchronous liver metastases (HM+ group) or PC alone (HM− group), treated by CRS/HIPEC, were enrolled for this analysis. Patients with extra-abdominal disease were excluded from this study. HM was diagnosed before surgery in all patients via a CT scan and hepatic-specific imaging (magnetic resonance imaging or ultrasonography). The criteria selected for surgery were as follows: resectable PC, resectable HM (or accessible to radiofrequency ablation), under 70 years of age and in a good general condition (World Health Organisation performance status of 0–2). All patients with synchronous HM received initial neoadjuvant chemotherapy. After six cycles, a cycle every 3 weeks, imaging was repeated to assess the benefit of additional cycles. Surgery was performed in the absence of tumour progression. We proposed a surgical cohort; patients with tumour progression were not included. The decision of HM management was taken during a tumour board meeting, which included oncologists, surgeons, radiologists and pathologists. HM and PC resection were performed in one or two steps after considering the resectability of the PC and the difficulty of the hepatectomy.

Surgical and HIPEC procedure

CRS with or without hepatic resection

By laparotomy through a xiphopubic incision, a complete abdominal exploration was performed to assess and record the extent of tumour deposits according to the PCI, as described by Jacquet and Sugarbaker [31]. An intraoperative hepatic ultrasound scan was performed to confirm the number, size and resectability of the lesions. CRS was performed in all patients with confirmed resectable HM and macroscopic PC. Surgery was performed with curative intent in all cases. The gallbladder, appendix, omentum and ovaries were systematically removed. The PC was resected by peritonectomy with removal of digestive tissue, as required. The volume of residual disease following CRS was recorded using the completeness of cytoreduction (CC) score [31]. The aim was to achieve complete resection (R0) of all detectable liver lesions by hepatectomy or radiofrequency (RF) (for small-sized central HM). Final hepatic management required one or two procedures.

All surgical procedures except anastomoses, including minor or major hepatic resections, were performed before HIPEC.

HIPEC

Following CRS, microscopic residual PC was treated perioperatively, using Elias protocol: an open abdomen technique, with hyperthermic intraperitoneal oxaliplatin (460 mg/m^2 at 43 °C over 30 min). Moreover, patients received intravenous perfusion of 5-fluorouracil (400 mg/m^2) with leucovorin (20 mg/m^2) 1 h before starting HIPEC.

Outcomes

Mortality and outcomes 90 days following the HIPEC were reported. Major complications were defined according to the Dindo–Clavien classification (≥ 3) [32]. The duration of hospital stays was described.

Follow-up

Follow-up was performed 1 and 3 months after hospital discharge and every 6 months thereafter, with a clinical examination, imaging studies and determination of blood tumour

markers. The first CT scan was made three months after the hospitalisation and every six months after that. Postoperative chemotherapy was administered in some cases, depending on the neoadjuvant treatment. No patient was excluded from survival analyses.

End points

The primary endpoint was survival: recurrence-free survival (RFS) and OS. RFS was defined as the time from CRS and HIPEC surgery to relapse or death. OS was defined as the time from CRS and HIPEC surgery to the time of death due to any cause. In the case of a two-staged procedure, the CRS procedure date was considered as the first treatment day. The secondary endpoints were completeness of surgical resection, postoperative morbidity/mortality and duration of hospital stay. The Dindo–Clavien classification staged postoperative morbidity/mortality.

Statistical analysis

Data analysis was performed using IBM's Statistical Package for Social Sciences (SPSS) 20. Quantitative variables are expressed as mean (± standard deviation) or as median (interquartile 25–75). Qualitative variables are expressed as percentages. The Mann–Whitney *U* test or Kruskal–Wallis test were used for comparisons of quantitative variables as appropriate, whereas a chi^2 test or Fisher exact test was used to compare categorical data. The Kaplan–Meier method was used to estimate survival probabilities, which were compared using the log-rank test. The date of the patient's last contact was used as the end of follow-up in all censored patients. Follow-up was updated until August 2017. Postoperative deaths were included in the OS analysis but excluded from the RFS analysis. Multivariate analysis was performed using a Cox proportional hazard model to identify independent prognostic factors for OS and RFS. A p value < 0.05 was considered significant for all tests.

Results

Patient and preoperative characteristics

From January 2007 to August 2016, 130 patients with CRPC were treated in our surgical department with CRS/HIPEC. After exclusion of patients with extra-hepatic metastases and small bowel carcinomas, 109 patients were enrolled: 76 in the HM− group (70%) and 33 in the HM+ group (30%) (Fig. 1). Patient characteristics are reported in Table 1. HM+ patients received more preoperative chemotherapy than HM− patients (100% vs. 88.1%, $p = 0.04$). The chemotherapy protocol was preferentially bi-chemotherapy, three weekly protocol: 21 HM+ patients (64%) and 74 HM− patients (97%).

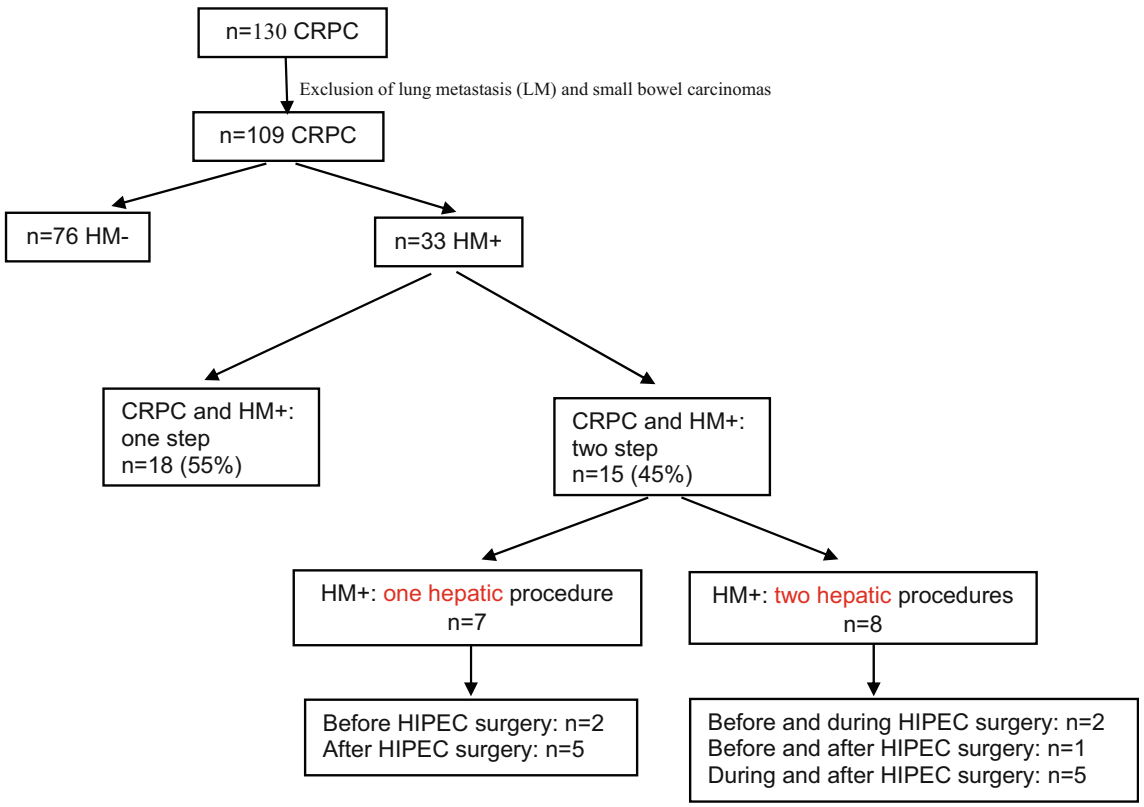

Fig. 1 Flowchart, hepatic management

Table 1 Preoperative characteristics

	HM−, $n = 76$	HM+, $n = 33$	p
Patient characteristics			
Age (years)*	57 (47–65)	58 (49–64)	0.742
Male gender	31 (40.8)	15 (45.5)	0.655
Perioperative treatment			
Neoadjuvant CT	67 (88.1)	33 (100)	0.040
Number of Neoadjuvant cycles*	6 (4–12)	6 (5–10)	0.348
Neoadjuvant monoclonal antibody with CT	38 (57.0)	22 (66.6)	0.014
Neoadjuvant CT: response	46 (60.0)	32 (97.0)	0.003
Neoadjuvant RT	2 (2.6)	0 (0)	0.999
Adjuvant CT	28 (10.5)	18 (56.3)	0.087
Primary tumour characteristics			
Primary tumour initially resected	60 (78.9)	23 (69.7)	0.250
TNM stage of the primary tumour resected			
T2	1 (1.0)	1 (3.0)	0.551
T3	19 (25.0)	8 (24.0)	0.936
T4	40 (52.6)	14 (42.4)	0.207
N+	58 (76.3)	22 (66.6)	0.299
Synchronous PC	45 (59.2)	21 (63.6)	0.683
Metachronous PC: length of time between primary and HIPEC (month)*	11 (7–21)	13.5 (6–25)	0.667
Right colon	23 (30.2)	11 (33.3)	0.755
Left colon	48 (63.1)	21 (63.6)	0.965
Rectum	5 (6.7)	1 (3.0)	0.668

Values in brackets are percentages unless indicated otherwise

*Values are median (interquartile 25–75)

Neoadjuvant monoclonal antibody therapy associated with chemotherapy was bevacizumab mainly ($n = 45$, 75%). HM+ patients received more neoadjuvant monoclonal antibody therapy than HM− patients (22 HM+ (66.6%) vs. 38 HM− (57%), $p = 0.01$) (Table 2).

Concerning primary tumour characteristics, no significant difference was observed.

A total of 46 patients received an adjuvant chemotherapy, 18 HM+ and 28 HM−. Adjuvant treatment prescription was decided according to neoadjuvant treatment: patients who received less than six cycles of neoadjuvant received an adjuvant therapy. We noted that some patients received more than six cycles of preoperative chemotherapy. These patients presented a pronounced carcinomatosis. Medical treatment was intensified before a surgery in curative intent. Response to the treatment was evaluated function of RECIST version 1.1, on CT scan. Complete response was no noted and stability of disease was note for 3% of HM+ patients ($n = 1$) and 40% of HM− patients ($n = 30$). Other patients of this cohort, 97% of HM+ group ($n = 32$) and 60% of HM− ($n = 46$) group, presented a partial response ($p = 0.003$).

Peroperative PC management

PC management, type of resection, intraoperative characteristics and margins are reported in Table 3. The PCI was higher for HM+ patients (9 versus 6, $p = 0.011$). Transfusions were more frequent in HM+ patients (30.3% vs. 13.1%, $p = 0.03$). There was no significant difference between the two groups with regard to other characteristics.

Hepatic management (Fig. 1)

Thirty-three patients (29%) had synchronous HM which was bilobar in 15 patients (45.5%). Hepatic and CRPC resection were performed in one step for 18 patients (55%) and in two steps for 15 patients (45%). Eight patients needed two procedures for total HM resection, with hepatic tumorectomy per HIPEC in 87.5% of cases (Fig. 1). All patients presented bilobar HM.

Twelve major hepatic resections were necessary: four before HIPEC (33%), one during HIPEC (8%) and seven after HIPEC (59%). Major hepatic resection was right hepatectomy in all cases.

Table 2 Neoadjuvant drug protocols

Chemotherapeutic	HM−, *n* = 76 *n* patients (%)	HM+, *n* = 33 *n* patients (%)
All protocols	67 (88.1) 6 cycles (± 3)	33 (100) 6 cycles (± 3)
FOLFIRI	7 (10) 7 cycles (± 3)	2 (6) 10 cycles (± 3)
FOLFIRI bevacizumab	20 (30) 8 cycles (± 3)	13 (39) 7 cycles (± 3)
FOLIFIRI cetuximab	9 (14) 7 cycles (± 3)	0
FOLFOX	19 (28) 8 cycles (± 3)	4 (12) 7 cycles (± 3)
FOLFOX bevacizumab	5 (7) 7 cycles (± 3)	0
FOLFOX cetuximab	2 (3) 6 cycles (± 3)	0
FOLFIRINOX	3 (4) 6 cycles (± 4)	9 (27) 6 cycles (± 3)
FOLFIRINOX bevacizumab	2 (3) 6 cycles (± 2)	5 (15) 6 cycles (± 2)

Twenty-five patients with HM (76%) received hepatic management during HIPEC surgery: one underwent major resection (4%), eight had RF (28%) and 20 had tumorectomies (80%), with a median of one metastatic resection [1, 2].

A total of 30 tumorectomies were made during HIPEC, nine in the segment IV (30%), eight in the segment II (27%), four in the segment VII (13%), three in the segment VI (10%) and one in segments III, V and VIII.

On the pathological analysis, the HM median size was 20 mm but larger for HM resection after HIPEC, namely 30 mm. The HM resection was incomplete (R1) for nine patients (27%): four had per HIPEC HM resection (44%) and five underwent hepatectomy after HIPEC (56%).

RF was the only form of liver management for five of these patients (71%), and this was combined with a tumorectomy for two patients. One RF was necessary for seven patients and three RFs for one patient. RF were particularly in le left lobe (*n* = 4 in the segment II).

Table 3 Peroperative management

	HM−, *n* = 76	HM+, *n* = 33	*p*
PCI*	6 (4–11)	9 (6–15)	0.011
Type of resection			
Small bowel	32 (42.1)	17 (51.5)	0.298
Colon	59 (77.6)	27 (81.8)	0.332
Rectum	41 (53.9)	13 (39.4)	0.242
Stomach	0 (0)	1 (3.0)	0.295
Spleen	8 (10.5)	4 (12.1)	0.738
Duodeno-pancreatectomy	2 (2.6)	0 (0)	0.999
Bladder	3 (3.9)	1 (3)	0.999
Ureter	5 (6.5)	1 (3.0)	0.671
Ovary	31 (40.7)	12 (36.4)	0.466
Uterus	19 (25.0)	5 (15.2)	0.310
Diaphragm	24 (31.6)	11 (33.3)	0.810
Enteric anastomosis	53 (69.8)	26 (78.8)	0.370
Number of enteric anastomoses*	1 (0–3)	1 (0–2)	0.901
Stoma	48 (63.1)	19 (57.6)	0.710
Intraoperative characteristics			
Duration of surgery (min)*	420 (360–495)	420 (330–480)	0.640
Transfusion	10 (13.1)	10 (30.3)	0.034
Blood loss (ml)*	500 (300–500)	500 (400–725)	0.080
Margins			
CCR0	58 (76.3)	22 (66.7)	0.499
CCR1	17 (22.4)	11 (33.3)	
CCR2	1 (1.3)	0 (0)	

Values in brackets are percentages unless indicated otherwise

PCI peritoneal cancer index

*Values are median (interquartile 25–75)

Morbidity and mortality

No postoperative deaths occurred. Morbidity and major morbidity rates were similar in both groups (Table 4). The rate of surgical site infection was higher for HM+ patients (33.3% versus 15.7%, $p = 0.03$). Intensive care unit stay and hospital stay did not differ in the two groups. The length of the hospital stay was 28 days for HM+ patients and 25 days for HM− patients ($p = 0.296$). Ten patients (30%) underwent hepatectomy after HIPEC (seven underwent major hepatectomy). No deaths occurred after this surgery, and three patients presented major complications (30%) with prolonged ICU hospitalisation.

Survival rate and recurrence

The median follow-up was 30 months. Median OS and RFS was 65 and 24 months for HM− patients, and 31 and 21 months for HM+ patients ($p = 0.188$ and $p = 0.119$), respectively (Fig. 2). One-year, 3-year and 5-year OS rates of 87.1% vs. 96.4%, 48.2% vs. 79.2% and 43.4% vs. 53.6% were recorded for HM+ vs. HM− patients, respectively ($p = 0.188$). One-year, 3-year and 5-year RFS rates of 58% vs. 79.8%, 38% vs. 49% and 24% vs. 39% ($p = 0.119$) were recorded for HM+ vs. HM− patients, respectively.

Sixty-one patients (56%) experienced a recurrence during follow-up—22 HM+ patients (66.6%) and 39 HM− patients (51.3%). Liver recurrences were more frequent for HM+ patients (12 patients in the HM+ group (36.4%) vs. 11 patients in the HM− group (14.5%), $p = 0.01$). Three patients underwent a second HIPEC procedure for recurrence: one patient in the HM+ group and two patients in the HM− group (Table 5).

Prognostic factors

In univariate analysis (Table 6), PCI > 15, synchronous PC and adjuvant chemotherapy were identified as prognostic factors for lower OS. PCI > 6 and synchronous PC were identified as prognostic factors for lower DFS.

Table 4 Outcomes following the HIPEC

	HM−, $n = 76$	HM+, $n = 33$	p
Global outcomes			
90-day postoperative mortality	0 (0)	0 (0)	–
90-day postoperative complications	35 (46.0)	14 (42.4)	0.730
90-day postoperative major complications	30 (39.4)	14 (42.4)	0.778
Repeat surgery	20 (26.3)	7 (21.2))	0.575
Repeat surgery for hemoperitoneum	13 (65.0)	2 (28.6	0.127
Length of time to repeat surgery (days)*	10 (6.5–15)	16 (11–22)	0.040
Details of complications			
EP	3 (3.9)	2 (6.1)	0.636
Surgical site infection	12 (15.7)	11 (33.3)	0.030
Radiological drainage	7 (9.2)	6 (18.2)	0.201
Evisceration	1 (1.3)	0 (0)	0.999
Enteric fistula	9 (11.8)	4 (12.1)	0.999
Peritonitis	4 (5.2)	3 (9.1)	0.418
Ileus	30 (39.4)	15 (45.5)	0.542
SDRA	10 (13.1)	4 (12.1)	0.999
Pleural effusion with drainage	2 (2.6)	3 (9.1)	0.151
Pulmonary infection	11 (14.4)	6 (18.2)	0.510
Urinary fistula	3 (3.9)	1 (3.0)	0.999
Urinary obstruction	1 (1.3)	1 (3.0)	0.504
Haemorrhage	13 (17.1)	2 (6.1)	0.143
Multivisceral insufficiency	6 (7.9)	3 (9.1)	0.910
Severe sepsis	21 (26.6)	6 (18.2)	0.343
Hospital stay			
ICU duration (days)*	2 (1–3)	2 (1–4)	0.216
Length of hospital stay (days)*	25 (17–32)	28 (20–42)	0.296

Values in brackets are percentages unless indicated otherwise

ICU intensive care unit

*Values are median (interquartile 25–75)

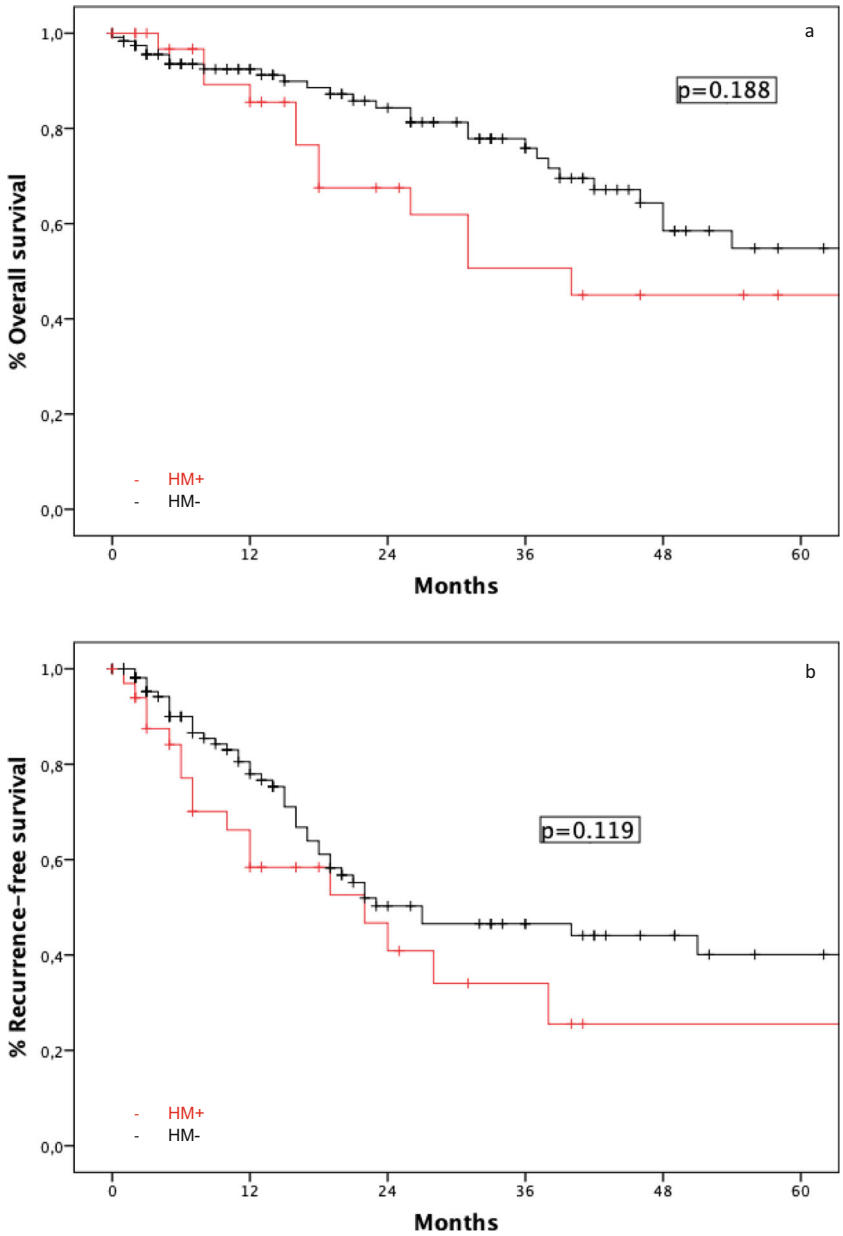

Fig. 2 OS (**a**) and RFS (**b**) survival curves in HM− and HM+ patients

In multivariate analysis (Table 6), PCI was the only significant prognostic factor [95% CI 1.101–1.190], $p = 0.001$.

Discussion

Management of patients with hepatic and CRPC is not currently standardised.

The combination of CRS/HIPEC is gradually becoming the standard of care for patients with PC of colorectal origin.

In our study, the median OS for HM− patients was 65 months. Prolonged survival can be explained by selecting patients with a low PCI (median: 9) and an aggressive strategy with neoadjuvant chemotherapy (88.1% of patients) and complete cytoreduction. Only patients with disease stability or response to neoadjuvant chemotherapy were included. This inclusion criterion explains that 97% and 3% of patients presented a partial response and a stability of disease, respectively. In Table 3, we note that 28 patients had a cytoreductive surgery noted CCR1. These results were mainly reported the first years but the evolution of the surgical practice permitted to obtain a complete cytoreductive surgery for other patients.

The chemotherapeutic agent used was oxaliplatin, function of Elias HIPEC protocol. Oxaliplatin became a reference in France, and it was preferred by many teams because of the duration of HIPEC protocol (30 min with oxaliplatin vs. 60 or 90 min with mitomycin C), despite the increase of the risk of postoperative hemorrhagic complications [33]. However, recently, this protocol failed to show a difference, in the randomised Prodige 7 trial, in overall survival between

Table 5 Type of recurrence and management

	HM−, $n = 76$	HM+, $n = 33$	p
Survival rates			
Median RFS (months)*	22 (17.9–26.5)	19 (5.3–32.6)	0.080
Median OS (months)*	65 (42.8–85.1)	31 (16.2–45.8)	0.079
Recurrence	39 (51.3)	22 (66.6)	0.140
Type of recurrence			
Hepatic recurrence	11 (14.5)	12 (36.4)	0.010
Pulmonary recurrence	10 (13.1)	7 (21.2)	0.291
Peritoneal recurrence	25 (32.9)	9 (27.3)	0.565
Retroperitoneal recurrence	5 (6.6)	3 (9.1)	0.700
Treatment of the recurrence			
Chemotherapy alone	28 (36.8)	13 (39.4)	0.789
Surgery	18 (23.7)	9 (27.2)	0.617
Intraabdominal CRS	14 (18.4)	7 (21.2)	0.671
2nd HIPEC	2 (2.6)	1 (3.0)	0.999
Radiotherapy (hepatic, bones, lung, etc.)	1 (1.3)	1 (3.0)	0.504
Hepatic radiofrequency	2 (2.6)	2 (6.3)	0.202
Pulmonary radiofrequency	1 (1.3)	0 (0)	0.999

Values in brackets are percentages unless indicated otherwise

*Values are median (interquartile 25–75)

patients undergoing CRS alone versus CRS combined with HIPEC using high-dose oxaliplatin [34]. The high morbidity could explain these results, and oxaliplatin could be replaced by other chemotherapeutic agents: traditionally mitomycin C was the most commonly used drug worldwide.

Surgical advances in the treatment of HM have proved beneficial with repeat liver resections, two-stage hepatectomy or a combination of locoregional destruction by radiofrequency ablation [35, 36]. Some series suggest that improved survival may be achieved for patients with CRPC and synchronous HM with aggressive management including the simultaneous resection of HM and PC [14, 22, 27]. In 2006, an initial study showed the results of combined treatment for HM+ patients. The study highlighted the feasibility of treating these selected patients with curative intent and the benefit gained (3-year OS, 41.5%, and 3-year RFS 23.6%): no more than three HMs, a moderate volume of PC, and known responders to chemotherapy [22]. Less than three HMs ($p < 0.01$) was the only significant prognostic factor [22]. Higher morbidity rates, from 24 to 51%, impacted these results [37–39]. In 2016, Navez et al. [40] showed a postoperative morbidity rate of 32% with a median OS of 27.5 months and median RFS of 6.7 months, which was significantly lower for HM+ patients. Other studies reported a median OS of 32 months and an overall major complication rate of 51%, with 8% of postoperative deaths [27, 41]. These authors concluded as follows regarding criteria selection: PCI < 12 with fewer than three HMs. It is interesting to note that many patients underwent major hepatectomy during HIPEC surgery in these studies.

In our surgical department, a standardised HM+ management strategy has been in place since 2007 with median OS and median RFS rates of 31 and 21 months, respectively. HM management did not improve major morbidity (HM+, 42.4%, vs. HM−, 39.4%, $p = 0.78$). All HM+ patients received neoadjuvant chemotherapy (100% of HM+ patients and 88.6% of HM− patients, $p = 0.05$). According to the scientific literature, neoadjuvant systemic chemotherapy response or nonprogression during treatment is a beneficial factor in selecting patients [24, 42]. However, the interest of perioperative systemic therapy in addition to CRS/HIPEC surgery for CRPC is unclear: no randomised studies have been carried out to assess the overall benefit. In our cohort, neoadjuvant monoclonal antibodies were more often associated with HM+ patients (66.6% vs. 57.0%, $p = 0.01$), mainly bevacizumab (75%). The superiority of neoadjuvant chemotherapy with bevacizumab vs. chemotherapy alone was shown [43]. Bevacizumab has been widely used for the treatment of metastatic colon cancer. In 2013, the results of the EORTC 40983 phase III trial comparing perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer were published [44]. Median overall survival was 61.3 months (95% CI 51·0–83·4) in the perioperative chemotherapy group and 54.3 months (41.9–79.4) in the group who underwent only surgery ($p = 0.34$). The 3-year RFS was 38.2% (95% CI 31.1–45.2) in the perioperative chemotherapy group versus 30.3% (23.7–37.1) in the surgery-only group ($p = 0.07$). Another multicentre randomised phase III trial, the FIRE-3 trial, investigated

Table 6 Univariate and multivariate analysis of prognostic factors of OS and RFS

Parameter		5-year OS (%)	OS				5-year RFS (%)	RFS			
			Univariate	Multivariate				Univariate	Multivariate		
			p	*p*	HR	(95% CI)		*p*	*p*	HR	(95% CI)
Patient characteristics											
Study group	HM−	53.6	0.188	0.811	1.001	0.501–3.330	39	0.119	0.640	1.050	0.898–2.11
	HM+	43.4					24				
Age	> 65 years	48.1	0.986				55.1	0.472			
Gender	Male	48.9	0.230				32.1	0.440			
PCI	> 6	41.0	0.050				49.7	0.013			
	≤ 6	59.0					50.1				
	> 15	27.1	0.006				6.8	0.001			
	≤ 15	59.1					42.0				
PCI (continuous variable)				0.040	1.082	1.004–1.166			0.001	1.099	1.101–1.190
Synchronous carcinosis		44.0	0.039	0.198	1.921	0.661–5.008	23.1	0.038	0.057	1.960	0.990–3.671
Disease-free interval	> 18 months	66.1	0.073				45.7	0.380			
Disease-free interval (continuous variable)			0.390	0.410	1.038	0.998–1.059					
Primary site											
Rectum		30.2	0.120				30.4	0.39			
Left colon		52.4	0.420				37.2	0.13			
Right colon		46.1	0.370				31.2	0.29			
N+		32.2	0.383	0.790	1.175	0.360–3.831	38.3	0.087	0.483	1.338	0.373–1.471
CCR0		50.2	0.180				36.5	0.144			
Outcomes											
Major complication		56.1	0.720				28.3	0.890			
Repeat surgery		56.2	0.501				21.7	0.921			
Chemotherapy											
Neoadjuvant CT		46.6	0.411				35.2	0.999			
Adjuvant CT		43.3	0.032	0.930	1.101	0.448–3.285	25.6	0.410			
Monoclonal antibody		49.8	0.899				31.4	0.877			

FOLFIRI (5-FU, folinic acid and irinotecan) plus cetuximab ($n = 297$) versus FOLFIRI plus bevacizumab ($n = 295$) in first-line treatment of metastatic colorectal cancer. Median OS was better in the cetuximab group (28.7 months vs. 25.0 months) [HR 0.77; 95% CI 0.62–0.96; $p = 0.017$] [45]. Cetuximab, in association with FOLFIRI, could be preferred for patients with KRAS exon 2 wild type. These results could be discussed regarding literature of these last years. Recent articles evaluated in the treatment of metastatic colorectal cancer for patients exhibited the wild-type RAS (RAS-WT) gene, the response of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies and antivascular endothelial growth factor (VEGF) therapy. A recent meta-analysis of randomised clinical trials [46] indicated that superior overall response rate and OS between the addition of anti-EGFR therapy versus anti-VEGF therapy in all RAS-WT patients. The benefit of these treatments differed in the primary tumour location. Matsuhashi et al. demonstrated, with anti EGFR first-line treatment, that the mean tumour shrinkage rate in the right side of the colon was − 11.1% (RECIST classification), versus − 54.0% on the left side ($p = 0.042$) [47]. A recent review concluded that in patients with RAS wild-type metastatic colorectal cancer, anti-EGFR therapy appears to be more effective than bevacizumab in the first-line setting in left-sided colorectal cancer, whereas bevacizumab seems to increase progression-free survival more than EGFR antibody therapy in right-sided colorectal cancer [48].

In our study, a two-step strategy was performed to prevent major hepatectomy during CRS/HIPEC surgery. Fifteen HM+ patients (45%) received curative intent treatment with a two-step procedure that has not yet been described in published studies. During HIPEC, radiofrequency HM ablation was recommended when the number of resections for surgical hepatic metastases could be reduced. We noted that our practices

changed between 2007 and 2017. Major hepatectomy after HIPEC is actually preferable to an initial resection. PC resectability appears to be the limiting factor in the curative strategy.

We did not report postoperative deaths in this cohort. The rate of complications 90 days after HIPEC (46% vs. 42.4%, $p = 0.73$) and the postoperative repeat surgery rate (26.3% vs. 21.2%, $p = 0.57$) were similar in the HM+ and HM− groups, respectively. Only the cause and length of time to repeat surgery were different. Repeat surgery was carried out earlier (at 10 postoperative days vs. 16 postoperative days, $p = 0.04$), mainly for hemoperitoneum (65% vs. 28.6%, $p = 0.12$), in the HM− group. In the surgical department, when patients presented a postoperative hemoperitoneum, we noted a faster favourable evolution with surgical revision than medical treatment. An abdominal lavage permitted to decrease ileus, pain and per cutaneous drainage. This strategy explains the high level of reoperation.

With this optimal hepatic strategy, synchronous HM was not identified as a significant factor of poor prognosis in this series ($p = 0.188$). However, inclusion of more patients with HM would induce a significative difference between the two groups. PCI was the only significant prognostic factor in the multivariate analysis. PCI is recognised as an independent prognostic indicator in patients with CRPC [46], and an inverse linear relationship between PCI and OS has been demonstrated [47, 49, 50].

In this cohort, a 3-year RFS rate of 49% was recorded for HM− patients. This result was similar for patients with resectable liver metastases from colorectal cancer treated with perioperative chemotherapy (38.2%) in the EORTC 40983 study. With the CRS and HIPEC strategy, patients with resectable PC or hepatic metastases seem to have a comparable RFS. In addition, the 3-year RFS rate did not differ significantly in the two groups (HM+ 38% vs. HM− 49%, $p = 0.119$). These results could be attributed to the selection of patients with a PCI < 10, systematic neoadjuvant chemotherapy and "two-stage" curative surgical treatment in the case of bilobar HM. We propose radiofrequency HM treatment during HIPEC to avoid hepatic resection morbidity. Major hepatectomy or multiple wedge resections are proposed as "dual surgery" options following HIPEC.

To our knowledge, this is the first patient series highlighting the results of combined treatment for HM+ patients with a major focus on hepatic strategy. Today, experts are thinking about the news indications of HIPEC in colorectal carcinomatosis: patients with high risk of recurrence. We propose to select patients with CRPC and HM.

However, caution should be exercised when interpreting these results because of the small patient cohort, the retrospective and nonrandomised design of the study. Prospective studies on a larger scale should confirm the interest of this type of surgical strategy.

In conclusion, we have shown that surgical treatment of synchronous colorectal HM and PC by CRS/HIPEC plus liver resection is both feasible and safe. HM management could be adapted depending on the need for major hepatectomy. A "dual strategy" would be proposed to avoid major hepatic resection during HIPEC and to reduce postoperative morbidity and mortality rates.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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