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ORIGINAL ARTICLE – COLORECTAL CANCER

Surgical Treatment of Colorectal Cancer with Peritoneal and Liver Metastases Using Combined Liver and Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Report from a Single-Centre Experience

Julie Navez, MD[1,2], Christophe Remue, MD[2], Daniel Leonard, MD, PhD[2], Radu Bachmann, MD[2], Alex Kartheuser, MD, PhD[2], Catherine Hubert, MD, PhD[1], Laurent Coubeau, MD[1], Mina Komuta, MD, PhD[3], Marc Van den Eynde, MD[4], Francis Zech, MD, PhD[5], and Nicolas Jabbour, MD, FACS[1]

[1]Hepatobiliary Surgery Unit, Department of Abdominal Surgery and Transplantation, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [2]Colorectal Surgery Unit, Department of Abdominal Surgery and Transplantation, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [3]Department of Pathology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [4]Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [5]Department of Internal Medicine, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

ABSTRACT

Background. Chemotherapeutic advances have enabled successful cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) expansion in treating metastatic colorectal cancer.

Objectives. The aims of this study were to evaluate the safety of combining liver surgery (LS) with HIPEC and CRS (which remains controversial) and its impact on overall survival (OS) rates.

Methods. From 2007 to 2015, a total of 77 patients underwent CRS/HIPEC for peritoneal carcinomatosis (PC) of colorectal cancer. Twenty-five of these patients underwent concomitant LS for suspicion of liver metastases (LM; group 2), and were compared with patients who underwent CRS/HIPEC only (group 1). Demographic and clinical data were reviewed retrospectively.

Results. Among the group 2 patients, two underwent major hepatectomies, six underwent multiple wedge resections, 16 underwent single wedge resections (one with radiofrequency ablation), and one underwent radiofrequency ablation alone. For groups 1 and 2, median peritoneal cancer index was 6 and 10 (range 0–26; $p = 0.08$), complication rates were 15.4 and 32.0 % (Dindo–Clavien ≥ 3; $p = 0.15$), and median follow-up was 34.2 and 25.5 months (range 0–75 and 3–97), respectively. One group 2 patient died of septic shock after 66 days. Pathology confirmed LM in 21 patients in group 2 (four with benign hepatic lesions were excluded from long-term outcome analysis). Two-year OS rates were 89.5 and 70.2 % ($p = 0.04$), and 2-year recurrence-free survival rates were 38.3 and 13.4 % ($p = 0.01$) in groups 1 and 2, respectively.

Conclusions. Simultaneous surgery for colorectal LM and PC is both feasible and safe, with low postoperative morbidity. Further longer-term studies would help determine its impact on patient survival.

Among patients with resected colorectal cancer, approximately half develop distant metastases, synchronously or metachronously. The most frequent metastatic sites are the liver (35–55 %), lungs (10–20 %), and peritoneum (10–25 %).[1–4] Over the past decade, advances in chemotherapy have allowed the expansion of surgical indications to treat metastatic colorectal cancer, with an overall 5-year survival of 40–50 % in patients with liver metastases (LM).[5] Peritoneal carcinomatosis (PC) in colorectal cancer used to be considered a terminal condition, with no curative treatment and a median survival of only 6–7 months;[1] however cytoreductive surgery (CRS)

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N. Jabbour, MD, FACS
e-mail: jabbourn@yahoo.com

combined with hyperthermic intraperitoneal chemotherapy (HIPEC), which has promising results for pseudomyxoma and ovarian cancers, has recently been introduced to treat patients with locally advanced abdominal cancers. This technique extended to PC from colorectal cancer was recently observed to lead to a 5-year survival rate of 34 % in selected patients.[6]

Simultaneous LM and PC, observed in 8 % of patients with colorectal cancer, was considered a surgical contraindication;[7] however, recent studies have shown potential benefit of a combined treatment of LM and PC by liver resection, CRS, and HIPEC.[8,9] Although this aggressive treatment can improve survival in selected patients with colorectal cancer,[10] its value and safety remain controversial. The purpose of the present study was to evaluate the safety of concomitant liver surgery (LS), HIPEC and CRS, and its impact on overall patient survival.

MATERIALS AND METHODS

Patient Selection

From October 2007 to November 2015, all patients operated for PC from colorectal cancer with curative intent at Saint-Luc University Hospital were retrospectively reviewed and analyzed. The present study was approved by the Institutional Review Board and was performed in accordance with the precept of the Declaration of Helsinki.

Preoperative assessment was performed to exclude extra-abdominal metastases, including thoracic and abdominopelvic computed tomodensitometry (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI), in cases of suspected LM. No patients had evidence of metastases other than PC and LM. All cases were discussed at tumor board meetings, which included oncologists, surgeons, radiologists, and a pathologist, to assess the eligibility of all patients for surgery alone or in combination with neoadjuvant chemotherapy. The presence of PC was determined preoperatively based on previous surgical findings and/or imaging. LMs were diagnosed either by imaging or intraoperatively. Inclusion criteria included a Peritoneal Cancer Index (PCI) inferior or equal to 26, based on Sugarbaker's method, i.e. separating the abdomen into nine regions and the small intestine into four regions;[11] no evidence of N3 lymph node involvement; number of LMs inferior or equal to 3; complete surgical resectability; no extra-abdominal disease; no severe comorbidities [American Society of Anesthesiologists (ASA) score <3], and good general health. The absence of disease progression after neoadjuvant chemotherapy was recommended.

Surgical Technique

Surgery was performed by midline laparotomy under general anesthesia. After a complete exploration of the abdominal cavity, the extent of PC was scored according to Sugarbaker's PCI, which ranges from 0 to 39, providing the abdominal tumor burden according to abdominal and small intestinal distribution and size of metastatic deposits. CRS was performed with the intention of removing all macroscopically detectable intraperitoneal tumor deposits, including regional peritonectomies, resection of visceral organs with major tumor involvement, and a systematic omentectomy. In cases of suspicion of LM, intraoperative ultrasonography of the liver was performed by exploration and palpation. Liver lesions diagnosed either preoperatively or intraoperatively were treated either by parenchyma-preserving liver resection and/or radiofrequency ablation. At the end of each surgical procedure, HIPEC was usually infused, using a closed abdomen technique, with oxaliplatin (460 mg/m^2 at 41–42 °C over 30 min). In case of contraindication to oxaliplatin, extensive surgery, a frail or old patient, or a previous history of HIPEC, mitomycin C (35 mg/m^2 at 42 °C over 90 min) was infused. All resected specimens were sent for final pathological examination.

Follow-Up

During the postoperative course, all patients were followed-up with clinical examination, tumor marker levels, and imaging studies at 1, 2, and 3 months, and every 6 months thereafter. Thoracic and abdominopelvic CTs were performed every 6 months, and a PET scan was performed every year. Postoperative chemotherapy was administered in the majority of patients regarding its use in the preoperative setting.

Statistical Analysis

Data for all patients included in the retrospective analysis were prospectively recorded in a database. For comparison of two percentages, we used the exact test of Nurminen and Mutanen, which was considered convenient for very small values.[12] We used the χ^2 test for comparison of more than two categorical variables, the Smirnov test for comparison of ordered variables, and the Wilcoxon rank-sum test for comparison of continuous variables. Survival curves were estimated using the Kaplan–Meier method. Yearly survival estimates were actuarial on a monthly basis, and the standard error was calculated according to Greenwood's method. For comparisons of survival, we used the log-rank tests, and a two-sided p value ≤ 0.05 was considered statistically significant.

Postoperative mortality and morbidity were defined according to the Dindo–Clavien classification, including all complications occurring until postoperative day 30 or until discharge from hospital.[13]

RESULTS

Patient Characteristics

Over the study period, 77 patients underwent CRS with HIPEC for PC from colorectal cancer. Patient baseline characteristics are reported in Table 1. Fifty-two (67.5 %) patients underwent CRS/HIPEC alone (group 1), while 25 (32.5 %) patients underwent CRS/HIPEC combined with LS (group 2). Among the group 2 patients, two underwent major hepatectomies (more than two segments), six underwent multiple wedge resections, 16 underwent single wedge resections (including one with radiofrequency ablation), and one underwent radiofrequency ablation alone. Significant differences were observed between groups in terms of the number of patients with preoperative chemotherapy.

Major complications (Dindo–Clavien $\geq$3) in group 2 were observed in 7 of 25 patients (32.0 %), and included thoracic drainage of pleural effusion ($n = 1$); reoperation for achieving a stoma for digestive anastomotic leakage ($n = 3$), including one patient with pancreatic fistula; intestinal obstruction ($n = 1$) and evisceration ($n = 1$) surgically treated; and pulmonary embolism with cardiac failure ($n = 1$) requiring intensive care unit management. One group 2 patient with multiple wedge liver resections died of septicemia and multi-organ failure after 66 days. No complications related to LS were observed in any of the patients in group 2. Major complication rates tended to be lower, but not significantly so, in group 1 (15.4 %; $p = 0.15$). Intensive care unit stay and hospital stay were significantly increased in group 2 compared with group 1 ($p = 0.02$ and $p = 0.05$, respectively). No significant difference was observed between groups in the reoperation rate and postoperative mortality rate. Perioperative chemotherapy was received by more patients in group 1 compared with patients in group 2 ($p = 0.03$). With respect to liver pathology, 21/25 patients had colorectal LM (13 synchronous, 8 metachronous LMs), while the remaining four patients had benign hepatic lesions (diagnosed as hepatocellular adenoma, nodular regenerative hyperplasia, steatonecrosis and sclerotic nodule). All resections were complete. Five lesions were discovered intraoperatively (25 %).

For comparison of oncological outcomes (Table 2), the four patients with benign hepatic lesions were excluded from group 2. Previous LS for colorectal metastases had

TABLE 1 Comparison of patient characteristics between the CRS/HIPEC and CRS/HIPEC + LS groups

	CRS/HIPEC	CRS/HIPEC + LS	*p* value
N	52	25	
Age at surgery, years [median (range)]	59 (17–77)	57 (33–72)	0.96
Sex, female/male (*n*)	25/27	16/9	0.10
ASA score			0.24
I	1 (1.9)	1 (4.0)	
II	38 (73.1)	21 (84.0)	
III	13 (25.0)	3 (12.0)	
Perioperative chemotherapy	51 (98.1)	21 (84.0)	0.03
PCI [median (range)]	6 (0–30)	10 (0–26)	0.09
$\leq$15	43 (82.7)	18 (72.0)	0.27
>15	9 (17.3)	7 (28.0)	
Any complication, minor or major			0.15
Minor (DC 2)	9 (17.3)	9 (36.0)	0.07
Major (DC $\geq$3)	8 (15.4)	8 (32.0)	0.10
Reoperation	5 (9.6)	5 (20.0)	0.20
Postoperative mortality	0	1 (4.0)	0.21
ICU stay, days [median (range)]	1 (0–7)	2 (1–58)	0.02
Hospital stay, days [median (range)]	13 (5–79)	19 (8–66)	0.05

Data are expressed as *n* (%) unless otherwise specified

ASA American Society of Anesthesiologists, *PCI* Peritoneal Cancer Index, *DC* Dindo–Clavien classification, *ICU* intensive care unit, *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *LS* liver surgery

TABLE 2 Comparison of oncological outcomes between the CRS/HIPEC and CRS/HIPEC + LS groups (exclusion of four patients from the CRS/HIPEC + LS group due to benign hepatic lesions)

	CRS/HIPEC	CRS/HIPEC + LS	*p* value
N	56	21	
Primary cancer			NS
Right colon	12 (21.4)	6 (28.6)	
Left colon	8 (14.3)	3 (14.3)	
Sigmoid	15 (26.8)	7 (33.3)	
Appendix	7 (12.5)	1 (4.8)	
Rectum	6 (10.7)	2 (9.5)	
Transverse colon	4 (7.1)	1 (4.8)	
Double location	1 (1.8)	1 (4.8)	
Previous surgery for liver metastases	5	6	0.03
CEA, ng/mL [median (range)]	2.5 (0.5–194.0)	3.7 (0.7–89.3)	0.40
Perioperative chemotherapy	53 (94.6)	19 (90.5)	0.51
Preoperative chemotherapy	30 (57.7)	19 (90.5)	0.01
Postoperative chemotherapy	49 (87.5)	11 (52.4)	0.01
Malignant ascites	10 (17.9)	3 (14.3)	0.50
K-ras mutation	11 (19.6)	6 (28.6)	0.60
Lymph node status			
Positive	39 (69.6)	17 (81.0)	0.37
Negative	17 (30.4)	4 (19.0)	

Data are expressed as *n* (%) unless otherwise specified

CEA carcinoembryonic antigen, *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *LS* liver surgery, *NS* non-significant

been performed in six patients in group 2 (28.6 %) and five patients in group 1 (2.7 %; $p = 0.03$). More patients in group 2 had been treated by preoperative chemotherapy ($p = 0.01$), and fewer patients in group 2 required post-operative chemotherapy compared with group 1 patients ($p = 0.01$).

Median follow-up was 34.2 months (range 0–76) for group 1 and 25.5 months (range 2–97) for group 2. Seven patients in group 2 (33.3 %) died from recurrence; initial PCI was >15 in two of these patients. Median overall survival (OS) and recurrence-free survival (RFS) was 59.2 and 18.4 months in group 1, and 27.5 and 6.7 months in group 2, respectively. Whereas OS only tended to be lower in group 2 compared with group 1 (log rank $p = 0.06$), the 2-year OS was significantly different between the two groups (group 1, 89.5 ± 4.5 % vs. group 2, 70.2 ± 11.5 %; $p = 0.04$). Recurrence appeared in 17 patients in group 2 (81.0 %), including six patients with extra-abdominal disease (Fig. 1). Recurrence in the liver occurred in 3 % of patients in group 1 and 24 % of patients in group 2 ($p = 0.03$). RFS was significantly lower in group 2 than in group 1 (log-rank $p = 0.01$), as was the 2-year RFS (group 2, 13.4 ± 8.6 % vs. group 1, 38.3 ± 7.2 %; $p = 0.01$) (Fig. 2). All patients who had undergone previous surgery for liver or lung metastases from colorectal cancer recurred ($n = 6$).

DISCUSSION

Each year, more than 1.3 million cases of colorectal cancer are diagnosed worldwide, resulting in 690,000 deaths.[14] Liver and peritoneal metastases are the first metastatic sites resulting in death within approximately 30 months when treated with chemotherapy alone.[15,16] When liver is the only metastatic site, surgical resection offers a 5-year survival rate of 50 %.[5] Over the last 20 years, surgical advances in the treatment of LM have become increasingly popular and have proven beneficial in cases of, for example, repeat liver resections, two-stage hepatectomy and portal vein embolization, associated liver partition and portal vein ligation for staged hepatectomy (ALPPS), and association of locoregional destruction (radiofrequency ablation, cryoablation).[17–22] Liver transplantation in combination with new and more effective chemotherapeutic agents has also led to equivalent outcomes in selected patients.[23]

For patients who have disease outside the liver, but still localized in the abdominal cavity, combined CRS + HIPEC was introduced, based on its success in treating ovarian cancer or regionally advanced pseudomyxoma.[24,25] The combination of CRS + HIPEC and hepatic resection for intra-abdominal colorectal metastases has been performed by a limited number of teams who reported its

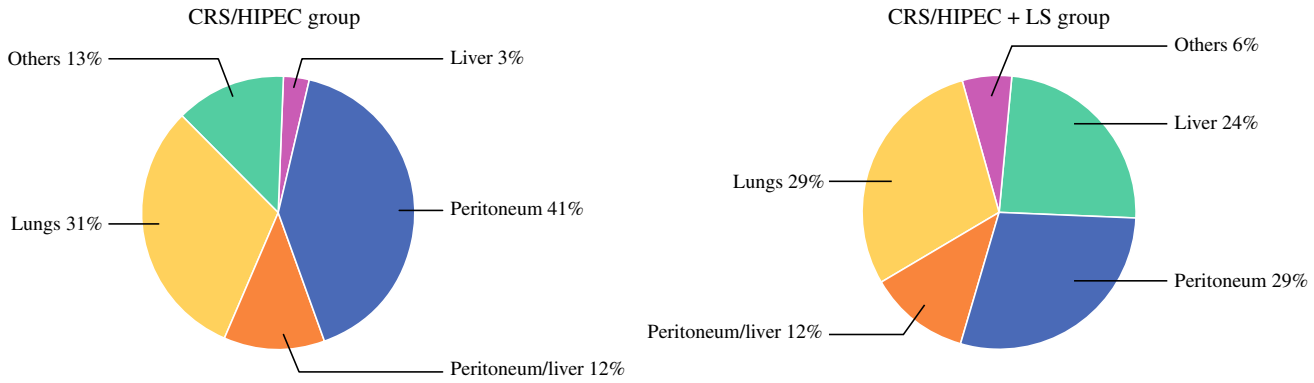
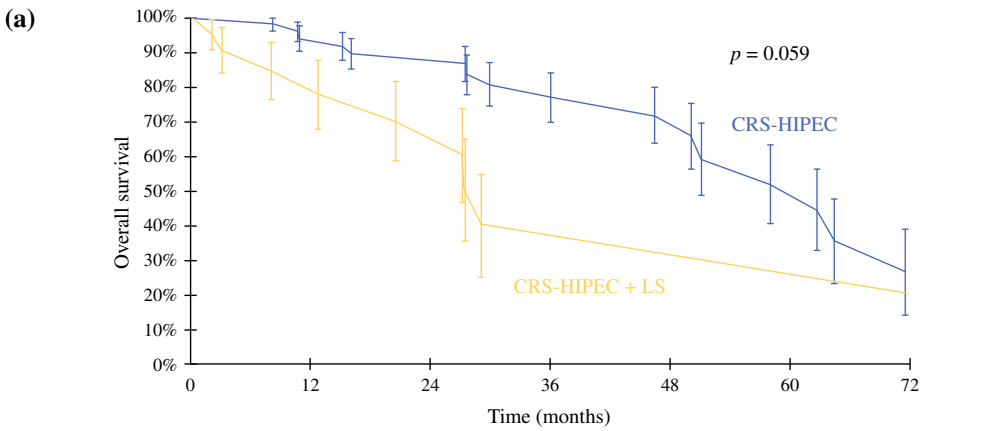
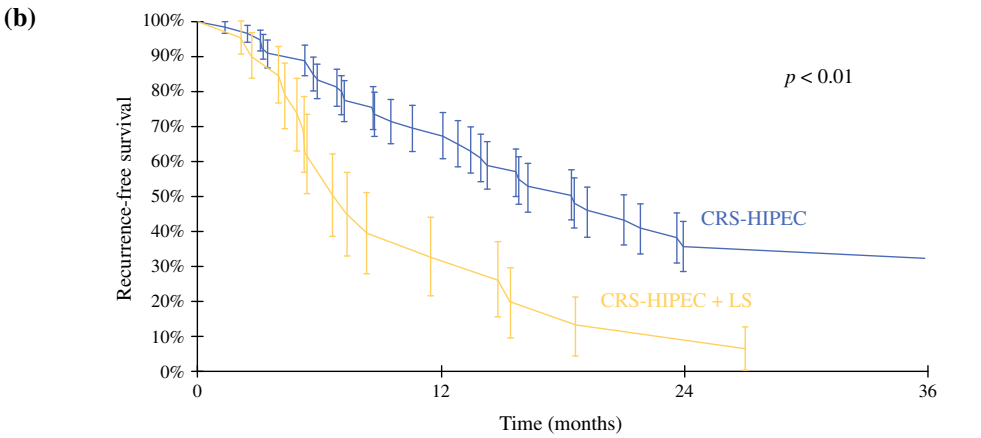


FIG. 1 Sites of recurrence in CRS/HIPEC and CRS/HIPEC + LS groups. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *LS* liver surgery

FIG. 2 Overall survival and recurrence-free survival curves in CRS/HIPEC and CRS/HIPEC + LS groups. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *LS* liver surgery



CRS-HIPEC	56	53	51	48	46	41	40
CRS-HIPEC + LS	21	18	16	13	13	13	13



CRS-HIPEC	56		40		26		25
CRS-HIPEC + LS	21		10		7		5

feasibility, despite higher morbidity and mortality rates ranging from 24 to 51 %.[26–28] Our series confirmed the safety and feasibility of the surgical procedure, with an acceptable morbidity rate of 32 % and one postoperative death. Comparison with previous studies is difficult as separate results and observations, such as the severity of

complications between patients with PC only versus those with PC + LM, are often not specified and some studies included patients without HIPEC.[9,29] The French team of Maggiori et al. described an overall major complication rate of 51 %, with 8 % of postoperative deaths in 98 patients followed between 1993 and 2009 (61 patients with PC and 37 patients with PC + LM). Almost half of their patients underwent major hepatectomy and were therefore at greater risk of postoperative complications, which appeared to be linked to LS combined with extensive CRS when the PCI was >12.[27] Recently, Delhorme et al. confirmed a significantly higher postoperative severe morbidity rate (44 %) when concomitant HIPEC and LS were performed, compared with both HIPEC alone (11 %) and LS alone (20 %).[30] In a retrospective study by Glockzin et al. pertaining to 63 patients who underwent CRS/HIPEC combined with hepatobiliary procedures, including liver and bile duct resection, 21 patients (33 %) had major complications such as pancreatitis and abdominal abscesses, whereas only three patients (4.8 %) had specific complications such as bile leakage.[31] According to our present study, major complication rates only tended to be higher when performing combined LS with CRS/HIPEC. Interestingly, none of these complications were related to LS, although 80 % of our patients had preoperative chemotherapy with possible hepatotoxicity. It would thus appear that intraperitoneal chemotherapeutic agents such as oxaliplatin and mitomycin do not expose the surgical liver margin to an increased risk of bile leakage or bleeding.

Even if recurrence rates after CRS/HIPEC + LS remain quite high, this surgical approach seems to have a positive effect on survival in selected patients. A relatively recent systematic review of studies identifying patients with concomitant CRS/HIPEC + LS for colorectal metastases demonstrated a median OS of 24–36 months and an RFS of 8–24 months.[10] This must be interpreted cautiously as a result of the great heterogeneity of the reviewed studies. For instance, the study by Abreu de Carvalho et al. included patients with a low PCI, which is the most powerful prognostic factor for the treatment of PC.[26,32] Their median OS of 44 months appeared to be both high and favorable, but more than one-third of patients had not yet reached 1-year follow-up. Our present results are in agreement with the Gustave Roussy group, who reported a median OS of 32 months, and concluded that the selected patients needed a PCI of <12 with fewer than 3 LMs.[27,33] Others reported median survivals of 23 and 36 months, but included patients who had concomitant lung metastases.[34,35] In our study, the median OS of 27.5 months and median RFS of 6.7 months were comparable to many series and significantly lower in the LM + PC group compared with the PC group. New chemotherapeutic agents have considerably changed the prognosis of colorectal cancer over the years, therefore it is both delicate and difficult to compare our oncological outcomes with earlier studies. The number of patients who received perioperative chemotherapy was not significantly different between groups. Only the timing of chemotherapy varied, which was administered preoperatively and/or postoperatively according to the surgical resectability of the metastatic disease, and for a total of 12 cycles.[36] Currently, the median survival of patients with stage IV colorectal cancer treated with chemotherapy is approximately 30 months.[15,16,37] Therefore, it is questionable whether surgery has an impact on the survival of patients with PC and LM compared with chemotherapy alone, knowing that almost all of the patients relapse after surgical treatment.

Complete CRS combined with HIPEC appeared to be the most effective treatment for micro- and macroscopic peritoneal disease. The median survival of these patients is currently around 32–47 months.[36] In the absence of extra-abdominal disease, PC occurs after direct serosal invasion or perforation of the primary tumor, leading to free circulation of malignant cells in the peritoneum; therefore, PC should be considered a 'locoregional disease'. The presence of LM does not necessarily imply generalized disease as the liver is the first organ reached by portal venous blood from the mesenteric tract. Therefore, a more aggressive approach to control locoregionally advanced disease may offer patients a chance for cure. In addition, the fact that, in our study, approximately 60 % of patients in both groups first recurred in the peritoneum and the liver without extra-abdominal disease supports the clinical concept of the benefits of locoregional disease control. A recent report regarding 60 % 5-year patient survival following liver transplantation performed in advanced liver disease not amendable for surgical resection points to the curious aspect of colon cancer that tends to remain localized to the abdominal cavity for a relatively long period of time prior to systemic dissemination.[23] The latter occurs as result of either hematogenous spread or overwhelming liver barrier.

CONCLUSIONS

Simultaneous surgical treatment of colorectal LM and PC by CRS/HIPEC + LS is both safe and feasible in patients with resectable disease, and is associated with an acceptable morbidity rate. Despite a high rate of disease recurrence, the potential benefits on survival of this approach over chemotherapy should be evaluated with regard to the concept of locoregional disease control. Further larger studies with a longer follow-up are needed to determine appropriate patient selection in order to improve long-term survival in locoregionally advanced colorectal disease.

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CONFLICTS OF INTEREST Julie Navez, Christophe Remue, Daniel Leonard, Radu Bachmann, Alex Kartheuser, Catherine Hubert, Laurent Coubeau, Mina Komuta, Marc Van den Eynde, Francis Zech, and Nicolas Jabbour declare no conflicts of interest.

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