International Journal of Surgery 25 (2016) 98–105

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original Research

# Peritoneal carcinomatosis with synchronous liver metastases from colorectal cancer: Who will benefit from complete cytoreductive surgery?

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## HIGHLIGHTS

- Combined treatment for peritoneal and liver metastases from colon cancer was evaluated.
- Toxicity to preoperative chemotherapy and size of LM were poor prognostic factors.
- These criteria could help in better selecting patients for such extensive surgery.

## ARTICLE INFO

*Article history:*
Received 14 September 2015
Received in revised form
1 November 2015
Accepted 6 November 2015
Available online 1 December 2015

*Keywords:*
Colorectal cancer
Peritoneal carcinomatosis
Liver metastasis
HIPEC
Cytoreductive surgery
Liver resection

## ABSTRACT

*Purpose:* Selection of patients for resection of synchronous liver metastases (LM) and peritoneal carcinomatosis (PC) of colorectal cancer (CRC) remains a debated issue since morbidity of this surgery is not negligible. We aimed to define overall survival (OS) prognostic criteria in patients undergoing PC surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) and LM resection.
*Methods:* This monocentric and comparative study included all consecutive patients operated for LM (LM group, n = 77), PC (HIPEC group, n = 18) and PC + LM (LM + HIPEC group, n = 9) from January 2007 to May 2011. Characteristics of the 3 groups were prospectively collected and retrospectively compared.
*Results:* Median follow-up was 56,5 months. Major morbidity and mortality were respectively 14% and 3%. Two-year disease free and overall survival rates were respectively 23% and 76%. There were significantly more Dindo grade III-IV complications in LM + HIPEC group. In multivariate analysis, grade II and III preoperative chemotherapy-induced toxicity and size of LM were identified as poor OS prognostic factors whereas response to preoperative chemotherapy significantly increases OS. OS was not different (p = 0.235) between the 3 groups.
*Conclusion:* Toxicity to preoperative chemotherapy and size of LM were identified as poor prognostic factors in patients undergoing simultaneous PC and LM surgery. These criteria could help in better selecting patients for such extensive surgery.


## 1. Introduction

The liver and peritoneum represent the two most common metastatic site of colorectal cancer (CRC). During the past two decades, the progresses achieved in perioperative chemotherapy regimens and surgical techniques allowed prolonged survival and even cure in selected patients with isolated liver metastases (LM) or peritoneal carcinomatosis (PC) from CRC. Peritoneal and liver spreading seems to be different diseases and their etiology remains unknown but probably linked to biological patterns of the primitive

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http://dx.doi.org/10.1016/j.ijsu.2015.11.025
1743-9191/

tumor. Particularly, mucinous subtype of CRC seems to be more likely associated with peritoneal spreading [1] and with LM showing a more aggressive behavior [2]. The synchronous occurrence of PC and LM from CRC have been considered for many years as an exclusive palliative scenario [3]. Later on, some authors used in this setting complete cytoreductive surgery (CCRS) associated with hyperthermic intraperitoneal chemotherapy (HIPEC) and liver resection in order to prolong survival [4]. However, initial surgical enthusiasm was lowered by a nearly prohibitive post-operative morbidity and low survival benefit [4,5].

More recently, because of a better selection of patients and improvements in perioperative management, some studies suggested that the simultaneous combination of CCRS-HIPEC and liver resection can effectively improve survival in patients with synchronous peritoneal and hepatic metastatic disease [6]. This aggressive treatment, in selected patients, offers improved survival compared with exclusive palliative chemotherapy [3]. Accurate criteria for selecting patients for such advanced procedure remain a debated issue since morbidity of this surgery remains high. Therefore, the aim of this study was to define prognostic criteria for survival in patients undergoing combined CCRS-HIPEC and LM resection.

## 2. Patients and methods

This study included all consecutive patients operated on in a curative intent for LM and/or PC from colorectal origin between January 2007 and May 2011 at two academic departments of the University hospital of Strasbourg, France. Data were prospectively collected into two dedicated databases and retrospectively analyzed. The study received institutional review board approval.

For isolated LM or PC indications for surgery were discussed during multidisciplinary meetings including surgeons, gastroenterologists, medical oncologists, radiologists and pathologists and followed national guidelines [7]. Briefly, patients for whom R0 resection was reasonably expected and controlled co-morbidities and no extra-abdominal cancerous spreading were considered candidates for surgery. For associated CCRS-HIPEC and LM resection, only patients with Peritoneal Carcinomatosis Index (PCI) less than 20/39 (since 2009) [8] and not requiring major liver resection ($\geq$3 liver contiguous segments according to the Coinaud definition [9]) were selected for surgery.

Data collected included: characteristics of the primary tumor (TNM classification, degree of differentiation, muciparity), patients characteristics, use of preoperative and postoperative chemotherapy, response to preoperative chemotherapeutic regimens, synchronous or metachronous character of PC and LM, PCI [10] and Gilly's score [11] for PC and number, size and location of LM, morbidity, mortality, and overall survival (OS) and disease-free survival (DFS).

### 2.1. Surgical procedures

- HIPEC with or without LM resection:

A median xyphopubic incision was systematically used, and the abdominal cavity was completely explored. The extent of peritoneal seeding was calculated for each patient using PCI and Gilly's score. CCRS-HIPEC was performed in all patients with confirmed resectable macroscopic PC by peroperative pathologic examination.

Following CCRS, mitomycin C (between 2007 and 2009) or oxaliplatin [8,12] (from 2009)-based HIPEC was performed in a closed abdominal cavity with abdominal massage. Mitomycin C was administered intraperitoneally at a dose of 0.8 mg/kg in a peritoneal dialysis solution for 90 min, with intraperitoneal temperature of 42 °C. For oxaliplatin-based HIPEC, patients received an intravenous perfusion of 5-fluorouracil (400 mg/m$^2$) with leucovorin (20 mg/m$^2$) just before starting HIPEC. Oxaliplatin was administered at a dose of 360 mg/m$^2$ in iso-osmotic 5% dextrose for 30 min, with intraperitoneal temperature of 42 °C. In case of liver resection for colorectal LM, parenchymal transection, the use of pedicular clamping and combined radiofrequency ablation were performed as described elsewhere [13].

### 2.2. Study definitions

#### 2.2.1. Mortality and morbidity

Short-term postoperative morbidity and 30-day mortality were evaluated using the Dindo-Clavien classification [14]. Complications graded III or higher were considered as major morbidity.

Liver failure was defined as serum bilirubin >50 μmol/L and prothrombin time <50% on postoperative day 5 [15]. Chemotherapy tolerance was evaluated using the International Classification CTAET (Common Terminology Criteria for Adverse Events). Response to chemotherapy was evaluated by clinical evaluation, CT scan and carcinoembryonic antigen (CEA) blood dosage and classified in “response”, “stabilization” or “progression” according to RECIST criteria [16]. After surgery patients were followed-up with a clinical examination 1 month after surgery. They were then followed-up every 3 months over 2 years and then every 6 months over 3 years with a clinical examination, imaging studies, and blood tumor marker dosage. OS was calculated from the date of surgery until the date of latest news in September 2013 or death. DFS was calculated from the date of surgery.

### 2.3. Statistical analysis

Patients' descriptive analysis was generated and their differences were investigated using non-parametric Mann–Whitney statistical tests for quantitative data and Fisher's exact test for qualitative data. In univariate analysis, a Cox model was used for quantitative data and the corrected chi-2 was used for dichotomic data in order to study the effect of different variables on OS and DFS. Significant variables in univariate analysis were tested in multivariate analysis by a Cox model. A Weibull model was used to estimate the risk linked to recurrence. A p-value less than 0.05 was considered as significant. Survival rates were estimated according to the Kaplan–Meier method. In order to define prognostic criteria for survival, the OS of patients operated on for synchronous LM and PC was compared with those operated on for isolated PC and isolated LM. The three groups were matched according to: primary tumor characteristics (T and N stage from TNM classification), metachronous or synchronous occurrence of PC or LM, uni or bilobar LM presentation, number and size of LM and PCI.

## 3. Results

### 3.1. Population

According to the above-mentioned criteria, a total of 104 consecutive patients were included in the study and divided into 3 groups. Nine patients had combined CCRS-HIPEC and LM resection (LM + HIPEC group), 18 patients had CCRS and HIPEC (HIPEC group) and 77 patients were operated on LM resection (LM group).

### 3.2. Patients' characteristics and comparability

Patient characteristics and comparability are summarized in Table 1. There were significantly more right colon cancer in the LM + HIPEC group and left colon tumor in the HIPEC group