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Original Research

Peritoneal and extraperitoneal relapse after previous curative treatment of peritoneal metastases from colorectal cancer: What survival can we expect?

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Abstract ***Introduction:*** Over the last 20 years, complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) dramatically increased the survival of patients with colorectal peritoneal metastases (CRPM). However, despite better knowledge of the disease, around 70% of patients relapse after CRS with HIPEC. This study was designed to analyse the pattern of recurrence and the outcomes of different treatment modalities.

Methods: Patients relapsing after CRS plus HIPEC for CRPM were selected from a prospective database. The impact of iterative curative-intent treatments was analysed using Kaplan–Meier estimates and multivariate Cox regression models.

Results: Between April 1993 and December 2014, 190 of 274 (69%) patients previously treated by CRS plus HIPEC developed relapse, as an isolated peritoneal recurrence (31%), isolated distant recurrence (35%), or multisite recurrence (34%). The curative-intent treatment rate was 48% for isolated peritoneal recurrences, 49% for isolated distant recurrences and 22% for multisite recurrences ($p = 0.002$). From the diagnosis of relapse, 3- and 5-year overall survival were 77% and 46% after curative-intent treatment and 14% and 4.7% after non-curative treatment, with median survival of 59.7 and 18.3 months (log-rank $p < 0.0001$), respectively. Regression analysis identified the initial extent of CRPM (hazard ratio [HR]: 2.25; $p < 0.0001$), iterative curative-intent treatment (HR: 0.22; $p < 0.0001$) and disease-free interval (HR: 1.77; $p = 0.01$) as independent predictors of prolonged survival.

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Conclusions: Iterative curative-intent treatment can be performed in up to 40% of patients with relapse after CRS and HIPEC for CRPM, and is associated with prolonged survival in selected patients.

1. Introduction

The peritoneal cavity is the third most frequent metastatic site in patients with colorectal cancer (CRC), after the liver and lung [1,2]. The occurrence of colorectal peritoneal metastases (CRPM) worsens the prognosis [3,4] with median survival less than 16 [5] to 20 months [4,6], hinting at a CRC-specific pattern of peritoneal spread [5]. Complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has considerably increased survival in selected patients with CRPM, with 5-year overall survival (OS) reaching 40% [7] and a 16% cure rate [8], as observed after curative resection of colorectal liver metastases (CRLM) [9,10]. Unfortunately, in the same scenario of hepatic resection of CRLM [11], up to 70% of patients relapse [12–14]. Despite this, there is currently no consensus for the optimal management of recurrence after CRS and HIPEC in CRPM patients.

Iterative curative-intent surgery is currently proposed to a limited number of CRPM patients, particularly in cases of isolated peritoneal recurrence [14–17]. For the remaining patients with extraperitoneal relapse, curative-intent treatment is only exceptionally considered. Thus, the impact of iterative curative-intent treatment including further multimodal approaches, grouped under a 'reset the clock' policy, has not yet been explored. The aim of this study was to analyse the patterns of recurrence after CRS plus HIPEC and the clinical impact of these different treatment modalities.

2. Patients and methods

2.1. Study population

Data from all consecutive patients who underwent curative-intent surgery for CRPM at the Gustave Roussy Institute (France) from April 1993 to December 2014, and had at least 6 months of follow-up, were prospectively collected in a local database.

2.2. Patient selection for CRS and perioperative management

Patients were initially selected for CRS according to general clinical status (World Health Organization performance status 0–1), extent of CRPM, likelihood of achieving complete resection, absence of extra-abdominal disease and tumour control after at least two months of induction chemotherapy. Decisions regarding potentially curative treatment, type of surgery, and chemotherapy protocols were systematically discussed at a multidisciplinary tumour board composed of medical oncologists, one dedicated radiologist and two trained surgeons.

The extent of the peritoneal disease was assessed during the surgical exploration according to the peritoneal cancer index (PCI) [18]. The aim of the CRS was to resect all visible lesions, with only residual deposits of $\leq$1 mm allowed. Completeness of resection was evaluated according to the residual disease (CC-score) [19]. Thereafter, HIPEC was performed with concomitant intravenous administration of 5-fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2). The HIPEC protocol includes oxaliplatin alone (460 mg/m^2) or in combination (300 mg/m^2) with irinotecan (200 mg/m^2), as previously described [20,21]. In the early experience (before years 2000) HIPEC protocol included mitomycin C (35 mg/m^2 diluted in 2 L/m^2 of Ringer Lactate), this protocol was performed in a minority of patients. Postoperative adjuvant chemotherapy was discussed for each patient taking into account histological results, postoperative complications, response to preoperative chemotherapy and associated toxicity.

2.3. Postoperative follow-up and recurrence management

Postoperative follow-up included a physical examination, assessment of serum tumour markers (CEA and CA19.9) and thoracoabdominal and pelvic computed tomographic (CT) scans or magnetic resonance imaging (MRI) every 3 months during the first 3 years and every 6 months thereafter. Peritoneal or extraperitoneal relapses were defined as any newly detected lesion(s) during follow-up with or without tumour marker abnormalities. For isolated tumour marker increases, further diagnostic modalities such as positron emission tomography and/or MRI were performed.

When a recurrence was diagnosed, the site of recurrence was categorised anatomically. The extent of the peritoneal recurrence was evaluated during curative or palliative surgery, or retrospectively estimated by CT or MRI. For lymph node recurrence, involvement was categorised anatomically: retroperitoneal (para-aortic and aortico-caval), intra-abdominal (celiac, mesenteric