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Peritoneal carcinomatosis of colorectal cancer: novel clinical and molecular outcomes

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KRAS;
Signet ring cell

Abstract

BACKGROUND: The objective of this study was to identify the prognostic impact of parameters in peritoneal carcinomatosis from colorectal cancer.

METHODS: We collected data from patients treated by cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy for peritoneal carcinomatosis secondary to colorectal cancer.

RESULTS: Ninety-one procedures were performed. In univariate analysis, an increased peritoneal cancer index was associated with decreased survival ($P < .001$). The presence of signet ring cells was associated to a decrease in survival from 45.8 to 12.1 months ($P < .001$). Microsatellite sequences instability status was the only molecular prognostic factor correlated with an increase in median disease-free survival: 12.4 vs 24.9 months ($P = .01$). The presence of a mucinous component was associated with a decreased of survival from 51.9 to 35.1 months ($P = .02$).

CONCLUSIONS: Clinical factors were affecting the survival of patients. The absence of signet ring cells and mucinous component and the presence of microsatellite sequences instability may be favorable prognostic factors.

For peritoneal carcinomatosis for colorectal cancer, clinical factors were affecting the survival of patients such an increased peritoneal cancer index (P). The presence of signet ring cells was associated to a decrease in survival (P = .01). The presence of a mucinous component was associated with a decreased of survival (P = .02).

Peritoneal carcinomatosis (PC) is defined as a lesion of the peritoneum caused by a malignant tumor whatever its origin.[1] It can be primary, related to tumor development of peritoneal cells, or secondary, resulting from locoregional or metastatic extension of a tumor in the abdominal cavity. The incidence of colorectal cancer (CRC) in France was estimated in 2010 to be around 40,000 new cases.[2] It is the third most common cancer in the world.[3] The prognosis of CRC is

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favorable when diagnosed at an early stage: the 5-year relative survival is 91% for localized stage and 70% for a stage with locoregional invasion. In contrast, the 5-year survival is only 11% in metastatic situations, which represent nearly 25% of patients at the time of diagnosis. The natural history of CRC involves an evolution to PC in less than 10% of cases: synchronously in 4.8% of cases and metachronously in 4.2% of cases. PC is the first and only dissemination of a CRC in 4.8% of cases. Synchronous PC is more common for colon tumors (5.7%) than for rectal tumors (1.7%).[4]

For 20 years now, PC has been considered a locoregional extension of CRC.[5] Patients affected by PC need a specific medical and surgical management: the so-called Hyperthermic Intraperitoneal Chemotherapy (HIPEC),[6,7] which combines a surgical tumor cytoreduction with intraoperative or perioperative chemotherapy administered at 42°C to 43°C. According to the 2008 report of the French Surgical Association on HIPEC for nonovarian PC, median survival after HIPEC for PC of colorectal origin was 30 months. The survival at 3 and 5 years was 41% and 26%, respectively.[8]

One randomized trial published in 2003 demonstrated an oncological benefit from HIPEC for CRC.[9] Median survival was 12.6 months for systemic chemotherapy and 22.3 months for HIPEC, which represents a gain of nearly 10 months.[8]

Elias et al[10] reported that survival rates of the patients who received chemotherapy systemically and those who received systemic therapy and HIPEC were 65% vs 81% (2-year survival) and 13% vs 51% (5-year survival). Long-term survival (8 years) is also increased by HIPEC in PC from CRC.[11] However, despite its efficiency, HIPEC causes morbidity in nearly 30% of cases and mortality in 3% to 4%.[8,12] PC from CRC is the leading indication for HIPEC for primary or digestive peritoneal tumors.[8]

Objective

The objective of this study was to identify prospectively the prognostic impact of clinical and histologic parameters for PC of colorectal origin. In addition, we aimed to evaluate the impact of some molecular features. Indeed, data on prognostic factors in colorectal PC are currently needed, since previous studies were heterogeneous and from small cohorts.

Methods

This was a single-center prospective study. All patients underwent cytoreductive surgery and HIPEC for PC from CRC in the department of general and digestive surgery of Nice University Hospital from December 1999 to March 2013. The molecular biology analyses were performed a posteriori in 2013.

Inclusion criteria

After a biopsy that confirmed the diagnosis of CRC, preoperative evaluation including computer tomography of the chest, abdomen, and pelvis with oral and/or intravenous contrast agents was performed for all patients. After 2004, positron emission tomography was also performed, to evaluate the spread of the disease. A preoperative anesthetic evaluation that included echocardiography and lung-function tests was carried out for all patients. Patients were then selected preoperatively using the following criteria: (1) less than 70 years of age or good general condition (geriatric assessment after 70 years old: only Balducci 1 patient included); (2) PC colorectal adenocarcinoma, nonappendiceal; (3) no extra-abdominal metastatic dissemination; (4) absence of multiple or diffuse disease and absence of large peritoneal tumors on computer tomography; (5) absence of intestinal obstruction; (6) absence of biliary or ureteral obstruction; and (7) absence of massive abdominal invasion at the time of the clinical examination.

Criteria for noninclusion

Appendiceal adenocarcinomas were excluded from our study. Peritoneal cancer index (PCI) above 30 or lesions deemed unresectable were grounds for exclusion.

Surgical procedure

If an invasion was suspected of being major and/or unresectable, a laparoscopy was first performed. Otherwise, a median laparotomy was performed to assess the tumor load. The entire peritoneal cavity was exposed to carry out cytoreduction according to the HIPEC technique of "the open abdomen" or coliseum technique.[13]

HIPEC protocol

Mitomycin C was used according to the "Sugarbaker protocol"[14] at a dose of 10 mg/m^2 of body surface area for women and 12.5 mg/m^2 for men, associated with a solution of 2 L/m^2 of body surface. The duration of the procedure was 60 minutes at 42°C. The solution used for the chemotherapy bath was Dianeal PD4 Glucose 1.36% (Baxter AG, Vienna, Austria).

Data collection

For each patient, the following data were collected prospectively: demographic data (age and gender), morphological and clinical data (weight, height, body mass index [BMI], American Society of Anesthesiology classification, performance status), histology of the primary tumor (and recurrences when available), history of the disease (circumstances of discovery, treatment sequence, recurrence-free period, and length of time preceding the HIPEC), adjuvant or neoadjuvant therapy received by the patient (molecule, number of cycles), number and type of surgical procedures, information about the surgical procedure (duration, volume and temperature of the chemotherapy