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Peritoneal carcinomatosis of colorectal origin

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Abstract

Peritoneal carcinomatosis is, after liver metastases, the second most frequent cause of death in colorectal cancer patients and at the present time, is commonly inserted and treated as a stage IV tumour. Because there is no published data that outlines the impact of new therapeutic regimens on survival of patients with peritoneal surface diffusion, the story of carcinomatosis can be rewritten in light of a new aggressive approach based on the combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Also if these treatment perhaps allow to obtain better results than standard therapies, we suggest, that a large prospective randomised control trial is needed to compare long-term and progression-free survival under the best available systemic therapy with or without

INTRODUCTION

Peritoneal carcinomatosis (PC) is, after liver metastases, the second most frequent cause of death in patients with colorectal cancer (CRC). The peritoneal surface is involved in 10%-30%^[1-3] of patients with CRC and in roughly 7%-8%^[3,4] at the time of primary surgery, in 4%-19% of cases during follow-up after curative surgery, in up to 44% of patients with recurrent CRC who require relaparotomy, and in 40%-80% of patients who succumb to CRC^[4]. However, in the 25% of patients with metastatic disease, the peritoneal cavity seems to be the only site of diffusion even after extensive diagnostic investigations^[5].

Presently, this last group of patients is commonly classified and treated as stage IV CRC, and there is no published data that outlines the impact of new therapeutic

regimens on survival^[6] and therefore research into new therapeutic approaches is widely justifiable and favourable.

NATURAL HISTORY OF PERITONEAL CARCINOMATOSIS

The PC occurs by a sequence of events: the spreading of cancer cells in the peritoneal cavity, their adhesion to the mesothelial surface and the invasion of the subperitoneal space for proliferation and vascular neogenesis^[7]. The high incidence of tumour implantation on the peritoneal surface in CRC can occur by intraperitoneal tumour emboli as result of serosal penetration, or can be the consequence of surgical management through leakage of the malignant cells from the lymphatic vessels or through their dissemination due to tumour trauma as result of dissection, with subsequent fibrin entrapment and tumour promotion of the entrapped cells^[8].

The three principal studies^[2,3,9] dedicated to the natural history of peritoneal carcinomatosis from CRC confirmed a poor prognosis with a median survival ranging between 6 and 8 mo and no 5-year survivors. Chu *et al*^[2] reported, in a series of 100 patients with PC of nongynecologic tumours, a median survival of 6 mo. Sadeghi *et al*^[3], in a multi-centre prospective study (EVOCAPE1) reported 118 patients with PC from CRC with a median survival of 5.2 mo. In a retrospective analysis^[9] of 3019 patients with CRC, 13% of these presented carcinomatosis and had a median survival of 7 mo. Verwaal *et al*^[10], in a phase III randomized controlled trial of 50 patients who were treated with systemic chemotherapy and palliative surgery obtained an overall median survival of 12.6 mo with a 2-year survival rate of 18% and a median time to disease progression of 7.6 mo.

CYTOREDUCTIVE SURGERY (CRS) AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

As reported by Esquivel *et al*^[6], in the light of a new aggressive approach based on the combination of CRS and HIPEC, the story of peritoneal carcinomatosis can probably be rewritten like the story of colorectal liver metastases.

In the 1930s, Meigs^[11] was the first to advocate CRS followed by adjuvant radiotherapy in patients with ovarian cancer but with poor results. Subsequently Munnell^[12] and Griffiths^[13], between the 1960s and 1970s, demonstrated that better survival rates could be achieved by more extensive surgery and that the size of residual disease is the most important prognostic factor^[11]. In 1980s, Spratt was the first to report, after an experimental study with hyperthermic peritoneal perfusion in dogs^[14], the results of CRS followed by HIPEC using thioTEPA in a patient with pseudomyxoma peritonei^[15]. After this first clinical report, Sugarbaker *et al*^[16,17] finally in the 1990s proposed and improved CRS and perioperative intraperitoneal che-

motherapy as a possible treatment, initially for peritoneal dissemination of the appendiceal neoplasms and diffuse malignant peritoneal mesothelioma^[14] and successively, for patients with PC from various gastrointestinal tumours. This was based on the realization that PC is a form of locoregional cancer dissemination rather than a systemic spread of the disease.

RATIONALE AND TECHNIQUE OF CRS AND HIPEC

Perioperative intraperitoneal chemotherapy consists of the intraperitoneal administration of drugs in a large volume of fluid either during the operation or postoperatively^[16]. Intraperitoneal chemotherapy can increase local exposure of the peritoneal surface to pharmacologically active molecules, especially those of high molecular weight (Mitomycin C, 5-FU, Doxorubicin, Cisplatin, Paclitaxel and Gemcitabine) resulting in a more uniform distribution throughout the abdominal cavity^[16]. This treatment can also be performed under hyperthermic conditions. Hyperthermia, associated with intraperitoneal chemotherapy, presents several advantages; it has a direct cytotoxic effect and enhances the activity and penetration depth of many cytotoxic drugs^[17-19]. Because it is estimated that the optimal target of thermochemotherapy is limited to few millimetres, is mandatory to resect all the macroscopic disease^[20,21]. According to Sugarbaker, the peritoneum can be divided into six parts, so between one and six peritonectomy procedures may be required, including visceral and parietal peritonectomies^[22]. Subsequently, when the resection of the cancer is complete, some catheters and suction drains are placed through the abdominal wall to permit perfusion, with open or closed abdomen techniques or with peritoneal cavity expander or a semi-opened or semi-closed technique. The duration of the perfusion varies according to investigators and drugs used, from 30 to 120 min, and a heat exchanger keeps the infused fluid at 46-48°C so that the intraperitoneal fluid is maintained at 41-43°C^[23,24]. When the perioperative intra-abdominal chemotherapy is over, the abdominal cavity must be revisited. As to the timing of bowel anastomoses, pre- or post-hyperthermic chemotherapy, there is no consensus.

The best choice of drugs and their dosage for intraperitoneal therapy are still under discussion. Although Mitomycin-C is the most frequently used cytostatic agent, either alone or in combination with 5-FU or Cisplatin, recently others drugs like Oxaliplatin and Irinotecan have been studied alone or in combination. Elias, in a phase II study, using Oxaliplatin after administration of 5-FU and Leucovorin iv before HIPEC, reported no case of mortality, 40% morbidity and a 5-year overall survival of 48.5% (median survival 60.1 mo) with a 73% rate of recurrence at 14 mo^[25]. In another study, the same author, in a retrospective comparison of HIPEC with Oxaliplatin *vs* standard systemic chemotherapy, found that median survival rate of the HIPEC group was significantly better than that of the other group (62.7 mo *vs* 23.9 mo)^[26].

EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY (EPIC)

Another modality of perfusion is the EPIC. In this technique, intraperitoneal chemotherapy is administered on postoperative days 1-5, and can be started immediately postoperatively and continued in the outpatient setting^[27]. EPIC has the advantage that it can be performed anywhere and at anytime because it does not necessitate any special apparatus and this is most relevant and useful when the carcinomatosis is a fortuitous discovery during laparotomy^[28]. Another advantage is the possibility to administer multiple cycles of chemotherapy^[29]. But EPIC has many deficiencies, such as the failure to uniformly treat all the peritoneal surfaces, and to provide the additive effect of hyperthermia, the greater risk of significant systemic absorption and adverse effects of a high concentration of chemotherapy which increases the possibility of complications^[23,24,27,28].

SURVIVAL AFTER CRS AND HIPEC

In the last decade, an increasing number of prospective studies investigated the effectiveness of the CRS and HIPEC in the management of PC of colorectal origin. Verwaal *et al*^[10] were the first who in 2003 conducted a randomized controlled trial comparing the efficacy of CRS and HIPEC with systemic chemotherapy and surgery. This trial clearly demonstrated longer survival in the combined treatment group with a median survival of 22.3 mo *vs* 12.6 mo obtained in the control arm. Subsequently, Glehen *et al*^[28] in 2004, in a multi-institutional registry study from 28 international treatment centres, showed that the median survival was 19 mo and 3-year survival was 39% after CRS and HIPEC for 506 patients with colorectal peritoneal carcinomatosis. However at present, the clinical outcomes, in the literature, vary considerably: the median survival from 12 to 32 mo, with 1-year, 2-year, 3-year and when reported 5-year survival rates ranging from 65% to 90%, 25% to 60%, 18% to 47% and 17% to 30%, respectively^[4]. Univariate and multivariate analyses of most series of patients with PC of colorectal origin revealed several clinical, surgical and pathologic factors predictive of survival^[4]. Clinical characteristics that have been correlated, in univariate analyses with an improved survival, are female gender, younger age and good clinical performance status^[4]. Surgical factors that have been correlated with survival are the extent of carcinomatosis encountered at laparotomy, the completeness of resection, bowel obstruction, the presence of ascites and the presence and resection of metastatic disease to the liver^[4]. Finally, the pathologic factors that have been correlated with impaired survival include site of the primary tumour, poor tumour differentiation, signet cell histology and lymph node involvement. However, the results of multivariate analyses on the abovementioned clinicopathologic factors were reported in 5 publications; in 4 of these, the extent of dis-

ease [measured by Peritoneal Cancer Index (PCI)] and the completeness of resection were the factors most related to treatment success and survival^[4]. Patients with localization in six or seven regions of the abdomen had a poor prognosis, with a median survival of 5.4 mo *vs* 29 mo in those with a lower number of regions affected^[7]. In a recent retrospective study, in 70 patients, da Silva and Sugarbaker demonstrated, by univariate analysis, that the patients with a PCI < 20 had a median survival of 41 mo compared with 16 mo for patients with PCI > 20 ($P = 0.004$)^[29].

Verwaal *et al*^[10], using their seven regions system, demonstrated that the survival benefit was low in patients with more than five regions involved, with a greater correlated morbidity. The completeness of resection was also linked to survival. Median survival following complete resection of all macroscopic disease varied from 17.8 mo to 39.0 mo, whereas the reported 5-year survival rates varied from 20% to 54% while median survival, after incomplete resection, resulted in median survival times of 12.5-24 mo, with 5-year survival rates between 10% and 29%. When macroscopic disease of more 5 mm in diameter had to be left behind, the reported median survival varied between 5 and 12 mo and none of these patients survived for 5 years^[4].

MORBIDITY AND MORTALITY AFTER CRS AND HIPEC

CRS followed by HIPEC carries a postoperative morbidity of 14% to 55% and a treatment-related mortality of 0% to 19%, which seem to be related to the extent of surgery as a function of peritoneal involvement rather than to the HIPEC^[4]. Yan *et al*^[30] suggested that there is a learning curve associated with the procedure for achieving an acceptable morbidity rate and Roviello affirms that postoperative complications could be resolved favourably in most cases with correct patient selection and adequate postoperative care^[31]. We also want to underline, as already demonstrated in our recent manuscript^[32], that 6 mo after surgery, the patients submitted to CRS and HIPEC, recover the same quality of life levels as the preoperative period.

CONCLUSION

A recent international conference was convened and a consensus statement on the appropriate use of CRS and HIPEC was developed and adopted by the Peritoneal Surface Malignancy Group in an attempt to standardize the indications and techniques for this treatment^[6]. However we retain, according with the conclusion of Glocks in his recent review^[33], that a large prospective RCT is needed to compare long-term and progression-free survival under best available systemic therapy with or without CRS and HIPEC.

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