Peritoneal Carcinomatosis from Colorectal Cancer: Fluorescence-Guided Surgery with Indocyanine Green

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Editorial

Peritoneal Carcinomatosis (PC) is a severe oncological condition originating from the mesothelium (primary PC) or, more frequently, from gastrointestinal or gynecological tumors (secondary PC). Every year, peritoneal carcinomatosis affects about 25,000 people in Italy [1]. Peritoneal involvement is considered the most serious event in tumor progression with a median survival of ≤ six months after diagnosis [2] and, even in patients resected for intra-abdominal carcinoma, PC is the most frequent cause of death [3]. Interestingly, POCC often develops as a “local” disease in the absence of hematogenous or distant metastases [4] and occurs in 30%-40% of patients with colorectal carcinoma (CRC) as a metachronous disease [5]. A positive peritoneal cytology at the time of the curative resection represents an important risk factor of secondary PC [6].

Peritoneal seeding is due to peritoneal dissemination of free tumor cells from the serosa of the organ involved, passage of malignant cells through the lymphatic lacunae and venous vessels of the peritoneum and deposition after trauma and surgical manipulation [7].

Since its local spread, PC can benefit of a potentially curative treatment in selected cases. In the last twenty years, Cytoreductive Surgery (CS) associated with hyperthermic intraperitoneal chemotherapy (HIPEC), with a 5-year survival rate ranging from 30% to 48%, is an aggressive therapeutic technique, based on both the direct cytotoxicity of hyperthermia on neoplastic cells, increased rate of the cytotoxicity of some chemotherapeutic agents determined by hyperthermia itself and, pharmacokinetically advantage obtained by the administration of intraperitoneal chemotherapy [8].

Since the inability to remove all microscopic residues, the concept of radicality is relative in PC; so that not only the complete cytoreduction (CCR-0) but also CCR-1 (residual tumor ≤ 2.5 mm) is deemed acceptable [9].

The diagnosis of peritoneal carcinomatosis is challenging; the gold standard for PC staging is still the direct laparotomic or laparoscopic visualization. Computed tomography (CT) and positron emission tomography (PET) provide the best results before surgery, but underestimation of the disease phase is frequently reported [10].

During laparotomy, the PC extension depends on visual inspection and palpation by the surgeon; nevertheless some subclinical peritoneal lesions may escape intraoperative detection. The Peritoneal Cancer Index (PCI) quantifies the extent of peritoneal disease and is related with the prognosis of CS + HIPEC [11].

Then one of the most critical trouble in PC treatment is represented by both correct diagnosis of peritoneal nodules and identification of smaller lesions. In recent years, new technologies have allowed surgeons to better address such limitations [12]. Intraoperative Fluoroscopy (FI) is a recently introduced imaging modality that can improve PC detection [13]. Indocyanine green (ICG), a near-infrared (NIR) contrast agent becoming fluorescent if excited by light with a wavelength of 800 nm-900 nm, has been recently proposed for FI due to its special affinity for the cancerous tissue [14].

The extravascular ICG accumulation is responsible for the hyperfluorescence observed in the tumor tissue in contrast to the surrounding normal tissue [15].

FI-guided surgery with ICG (ICG-FI), both in vivo (ICG-IF intraoperative) and ex vivo (on the ICG-FI table) seems to be particularly suitable for detecting PC in which superficial lesions are present. However, data on ICG-guided surgery in PC CRC treatment are still poor and the technique has not yet been standardized for this use.

At the Division of Surgical Oncology of the University of Naples “ Luigi Vanvitelli”, a prospective study was conducted to evaluate the role of ICG-FI in the improvement of outcome in patients affected by peritoneal carcinomatosis from CRC and undergoing CS + HIPEC. Inclusion criteria for CS + HIPEC were age of 18-70 years, PCI ≤ 20 at preoperative diagnosis, tumor limited to the peritoneal cavity without other distant metastases, absence of serious comorbidity with the performance status ≤ 1. Overall, seven patients with PC from CRC were
admitted. Three patients were excluded from surgical treatment due to high PCI (29 and 31, respectively), or poor general conditions (one patient). Ultimately, four patients underwent surgical exploration. All patients had previously been successfully submitted to a potentially curative resection for stage III colorectal adenocarcinoma. All patients underwent adjuvant chemotherapy with 5-fluorouracil plus oxaliplatin, and they were followed at 3-month intervals until tumor recurrence [16]. All operations were performed through open median relaparotomy. After clinical exploration of the entire peritoneal cavity and evaluation of the feasibility of CCR-0 or CCR-1 cytoreduction and localization of metastatic nodules, a dose of 0.25 mg/kg ICG was injected intravenously. FI-guided imaging was performed on the entire peritoneal cavity using Fluobeam, an open system for in vivo infrared fluorescence imaging: the peritoneum appears as a large gray area and a hyperfluorescent peritoneal nodule appeared as a well-defined area of intense bright light with clear margins. In our experience, 50 minutes after ICG intravenous injection, the intraoperative view with Fluobeam of the fluorescent areas in the abdomen was optimal. Our decision to perform the intraoperative injection of the fluorescent probe was influenced by our previous experience with ICG-FI guided surgery for liver cancers [17]. All peritoneal sites were checked again at the end of surgical resection to evaluate residual fluorescence. Finally, all specimens were observed ex vivo with Fluobeam to confirm their previous appearance and investigate the margins of resected tissue. A cytoreductive surgery classified as CCR-0 followed by HIPEC was performed in all patients. HIPEC was performed through a closed technique by using oxaliplatin (400 mg/m²) in 5 L of 5% glucose solution for 30 minutes at 42 °C. No patient had serious postoperative complications and all were discharged on post-operative days 9-11. The operation time ranged from 240 to 360 min. All samples were also examined with Fluobeam ex vivo, namely on the table in the operating room. There was a complete correspondence between in vivo and ex vivo observations. In addition, a hypo-fluorescent tissue boundary was identified around each lesion. Postoperative histopathology showed that in all cases, the hypo-fluorescent tissue around each lesion was negative for metastatic tissue. Of the 65 metastatic peritoneal nodules, the ICG-FI allowed to identify 16 nodules not diagnosed with conventional procedures, adding a 25% diagnostic improvement. Overall, the sensitivity of current diagnostic procedures (CT and PET) was 43.1% preoperatively and 76.9% intraoperatively (visual examination and palpation). With the ICG-FI sensitivity increased to 96.9%. Prior to ICG-FI, median PCI were 7 but after ICG-FI PCI increased significantly to a median of 10. However, the worsening of PCI did not prevent a complete cytoreduction in all patients. Cytological examination of the peritoneal liquid was positive for malignant cells in three out four cases before HIPEC and negative in all cases after HIPEC.

In conclusion, cytoreductive surgery achieving CCR-0 or at least CCR-1 should be the gold standard in the treatment of primary and metastatic peritoneal carcinomatosis, including PC from colorectal cancer. A technique that improves intraoperative detection of PC nodules would help to achieve complete cytoreduction and avoid resection of non-cancerous lesions. Despite the limited number of patients and PC nodules that are limitations of the present study, our results with intraoperative ICG-FI appear promising. A new interesting tool is represented by prophylactic HIPEC in CRCs at high risk of developing peritoneal metachronous carcinomatosis, such as tumors invading serosa (pT4a) or with positive peritoneal lavage [18]. In these patients, current clinical and imaging techniques do not have sufficient diagnostic sensitivity, and ICG-FI-guided surgery could identify small undiagnosed peritoneal metastatic nodules. Further studies are needed to standardize the technique and determine its role in this patient population.

References
