Expanding Uses of HIPEC for Locally Advanced Colorectal Cancer: A European Perspective

Delia Cortes-Guiral, MD, PhD[1] Olivier Glehen, Prof, MD, PhD[2]

[1] General Surgery Department, Principe de Asturias University Hospital, Carretera de Alcala s/n, Alcalá de Henares, Madrid, Spain
[2] General Surgery Department (Surgical Oncology), Centre Hospitalier Lyon Sud (Hospices Civils de Lyon), Lyon, France

Address for correspondence Delia Cortes-Guiral, MD, PhD, General Surgery Department, Principe de Asturias University Hospital, Carretera de Alcala s/n, CP 28805, Alcalá de Henares, Madrid, Spain (e-mail: delia.cortes.guiral@gmail.com).

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Abstract

Locally advanced colorectal cancer is a challenge for surgeons and medical oncologist; 10 to 20% colorectal cancer debut as locally advanced disease, with tumors extending through the colon wall with perforation and/or invasion of adjacent organs or structures. Those locally advanced tumors have a worse prognostic at any stage due not only to systemic dissemination but also in a high percentage of patients, to locoregional recurrence, in fact, peritoneal carcinomatosis of colorectal origin is so predictable that we can assess the risk for each patient according to some histopathological and clinical features: small peritoneal nodules resected in the first surgery (70% probability), ovarian metastases (60%), perforated tumor onset or intraoperative tumor rupture (50%), positive cytology (40%), and pT4/mucinous pT3 up to 40%. Prophylactic or adjuvant hyperthermic intraperitoneal chemotherapy seems to be a promising strategy for patients with advanced colorectal cancer to prevent the development of peritoneal recurrence and improve prognosis of this group of patients.

Keywords

- locally advanced colorectal cancer
- high-risk patients
- peritoneal carcinomatosis
- hyperthermic intraperitoneal chemotherapy

Locally advanced colorectal cancer is a challenge for surgeons and medical oncologist; 10 to 20% colorectal cancer debut as locally advanced disease, with tumors extending through the colon wall with perforation and/or invasion of adjacent organs or structures.[1,2] Those locally advanced tumors have a worse prognostic at any stage (www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html). En bloc resection has been proposed as the most appropriate surgical treatment for tumors involving adjacent organs with 5-year survival ranging from 49[3] to 54%[4] and local relapse in 12% of patients and peritoneal carcinomatosis (PC) even up to 70% of patients.[5]

One of the most innovative concepts in colorectal cancer in recent years has been that of "patients at high risk of recurrence" and its identification, Honoré et al[5] defined patients at risk of developing PC: small peritoneal nodules present in the first surgery (70% probability of developing PC), ovarian metastases (60%), and perforated tumor (50%) as being high risk. Positive cytology and T3–T4 mucinous tumors have a risk of 30 to 40%. It is remarkable that positive cytology from colorectal cancer really worsens the prognosis according to the Lyon's series review[6] with median overall survival (OS) of 19 and 44 months for positive and negative intraperitoneal free cancer cells ($p = 0.018$).

A recent review on advanced primary tumors (T4) confirms that T4a tumors are worse than T4b as a prognostic factor for peritoneal metastases development after primary resection.[7]

Sugarbaker[8] defined the risk of peritoneal recurrence according to some clinical and histopathological characteristics of the tumor (►**Table 1**).

The identification of these groups allowed Segelman et al to develop an individualized prediction model to estimate each patient's risk.[9,10] At this model, the development of metachronous PC was associated independently with non-R0 surgery ($p < 0.001$), pN2 with lymphadenectomy with

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Table 1 Estimated incidence of peritoneal metastases observed in follow-up

Clinical characteristic	
Peritoneal nodules detected during primary cancer resection	70%
Ovarian metastases	60%
Perforation through the primary cancer	50%
Adjacent organ or structure invasion	20%
Signet-ring histology	20%
Fistula formation	20%
Obstruction of primary cancer	20%
Histopathological characteristic	
Positive resection margin	80%
Positive cytology before or after resection	40%
Positive imprint cytology	40%
Positive lymph nodes at or near resection margin	20%
T3/T4 mucinous cancer	40%

less than 12 nodes ($p < 0.001$), pT4 ($p < 0.001$), tumors located in the right colon ($p < 0.002$), and emergency surgery ($p < 0.001$), http://www.imm.ki.se/biostatistics/calculators/pcrisk, So, we can estimate the individualized risk for each patient.

It has been of high importance to identify these patients because they have poor survival rates at 5 years and new strategies are being developed to improve their prognosis.

New Strategies to Improve Outcome of Patients with Locally Advanced Colorectal Cancer

One of these strategies is neoadjuvant systemic chemotherapy, in this respect FOxTROT[11] is one of the most interesting trials. FOxTROT (NCT00647530) is a clinical trial developed by the National Cancer Research Institute Colorectal Cancer Clinical Studies Group to test if patients with radiological, preoperative staging of T4 or T3 (extramural depth ≥ 1 mm) could benefit from neoadjuvant chemotherapy. It is designed as a multicenter, phase II/III study with four arms: Arm A: 6 weeks of preoperative oxaliplatin/fluoropyrimidine chemotherapy followed by surgery, then 18 weeks of postoperative oxaliplatin/fluoropyrimidine chemotherapy. Arm B: the same chemotherapy with concomitant panitumumab for the first 6 weeks. Arm C: surgery, then 24 weeks of postoperative oxaliplatin/fluoropyrimidine chemotherapy. Arm D: schedule C with concomitant panitumumab for the first 6 weeks of postoperative therapy.

The pilot stage of 150 patients has already been completed[11] and they found that preoperative therapy resulted in significant downstaging of TNM5 compared with the postoperative group ($p = 0{\cdot}04$); therefore, they conclude that neoadjuvant therapy is feasible with acceptable toxicity and perioperative morbidity. We are waiting for the results to the phase 3 trial that reached recruitment of the 1,050 patients in December 2016 to see if pathological responses thanks to neoadjuvant therapy achieve improved long-term oncological outcomes.

Other strategy to try to improve outcomes of patients with locally advanced colorectal cancer is intensive follow-up after potentially curative resection. From a meta-analysis[12] (randomized trials published from 1995 to 2016) reviewing different schemes of follow-up with computed tomography (CT) scan, carcinoembryonic antigen (CEA) levels, and/or colonoscopy, no benefit in terms of survival has resulted from "earlier detection" of metastases or recurrence with these tests. It may be that the tests with greater precision allow us a diagnosis of recurrence with greater anticipation, in this regard, liquid biopsy seems one of the most promising and interesting tests, so first result reveals that circulating DNA is associated with worse outcome in solid tumors[13] and for colorectal cancer is that sensitive that even could be used as a noninvasive biomarker of drug resistance during disease progression,[14] but still have to determine how earlier anticipation with liquid biopsy will correlate with survival.

The third strategy is the early intervention and prevention of relapse from advanced colorectal cancer. It seems appropriate due to the high rates of peritoneal and local relapse from advanced colorectal cancer.

It is true that the treatment of PC of colorectal origin has dramatically evolved thanks to a multimodal approach with curative intent (cytoreductive surgery [CRS], hyperthermic intraperitoneal chemotherapy [HIPEC], and systemic chemotherapy) with survivals of up to 64 months with a mean 5-year survival of 51% in patients receiving a completeness of cytoreduction (CCR)-0[15] and with a 5-year disease-free survival of 16%.[16] From a median survival of ~6 months without treatment to a survival rate of ~24 months with palliative approach (palliative surgery and systemic chemotherapy with/without biologics). Management of peritoneal metastases from colorectal origin was recently reviewed in the meta-analysis performed by Klaver et al,[17] 21 guidelines were also analyzed, concluding that CRS with HIPEC was recommended in selected patients based on level 1b evidence. Actually, National Comprehensive Cancer Network (NCCN) clinical practice guidelines for colon and rectal cancers state that complete CRS and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom complete removal of all known tumor can be achieved (R0) (NCCN, 2017). As the treatment of established peritoneal disease has undergone a revolution, it is also interesting to delve into new treatment strategies for locally advanced colorectal cancer. As previously seen, despite intensive protocols of follow-up with the sensitive of the available tests, no benefit in terms of survival has resulted from this "earlier detection." One reason is that, in general, early PC (when peritoneal carcinomatosis index [PCI] is ≤ 5) cannot be detected with clinical, biological, or radiological methods

and it is mandatory to treat PC at the lowest possible PCI if we want to improve survival because both PCI and CCR-0 have been demonstrated to be the factors with the highest prognostic significance in the treatment of PC.[18,19]

Therefore, the strategy of early intervention consists of second-look surgery, that is, early detection of peritoneal or local relapse through a surgical review before relapse can be detected because of symptoms, biological abnormalities, and/or radiological signs of PC because at this point in time, patients usually present a higher PCI, and CRS + HIPEC offers a poorer outcome.[20] Second-look surgery consists of a laparotomy or laparoscopy to perform reduction-risk surgery (consisting of removal of the most frequent organs where PC develops: omentectomy, removal of the round ligament, appendectomy, and bilateral oophorectomy in postmenopausal patients), complete citoreduction if macroscopic PC is found and for all patients with and without macroscopic PC, perfusion on HIPEC with oxaliplatin or mitomycin. This second-look surgery is performed after oncological colorectal surgery and adjuvant therapy for 6 months in patients with negative findings in the follow-up studies or CEA increase without imaging correlation. Some centers perform second-look surgery after 3 months systemic chemotherapy, and then complete the remaining 3 months of adjuvant therapy. Most units select patients for second-look surgery according to the criteria from Sugarbaker[21] and follow his proposal sequence of treatment. That could be considered as early intervention, but also, a strategy of prevention of relapse from advanced colorectal cancer has been developed and consists of performing all these treatments simultaneously with resection of the primary tumor adding risk-reducing surgery and prophylactic or upfront HIPEC and then regular scheme of adjuvant therapy and follow-up for colorectal cancer.[8]

First results from second-look surgery came from the work by Elias et al,[22] a prospective series of 47 patients considered at very high risk of developing carcinomatosis, with adequate surgical and medical treatment for their colorectal cancer and negative follow-up after adjuvant therapy in which second-look surgery found macroscopic peritoneal disease in 49% of patients. Most patients of the series receive HIPEC and only 17% presented peritoneal relapse. The most interesting is that for this group of patients with advanced colorectal cancer and very poor prognosis, this second-look surgery plus HIPEC strategy got a 5-year survival of 90% and a 5-year disease-free survival of 44%. Prospective series from different countries have been published, with similar results.[23]

Sammartino et al[24] compared 25 patients with locally advanced colorectal cancer (pT3/T4 and mucinous or signetring cell) treated with second-look surgery and HIPEC to 50 patients treated with the conventional surgical and medical treatments with very interesting results that for the group treated with HIPEC presented a disease-free survival ($p < 0.05$) and OS ($p < 0.04$) significantly higher. In the follow-up, only 4% of patients treated with HIPEC presented peritoneal recurrence versus 28% of the patients following standard treatment ($p < 0.03$). Similar results were reported from the prospective study by Tentes et al,[25] again pT3 or pT4 patients could be treated with HIPEC with mitomycin as intraperitoneal adjuvant treatment (41 patients) or with conventional systemic adjuvant chemotherapy (40 patients). Again 5-year survival in HIPEC group was 100 versus 72% ($p = 0.0938$) without peritoneal relapses at the HIPEC group.

In light of these results, a large phase III trial began in France (Elias), ProphyloCHIP (NCT01226394). At this trial, patients with advanced colorectal cancer at high risk of PC (perforated onset, small nodules resected at first colorectal surgery, and/or ovarian metastases) are randomized in two groups. One group with standard surgical treatment of primary colorectal cancer, standard adjuvant systemic therapy, and regular follow-up versus adding to that conventional treatment second-look surgery with HIPEC (oxaliplatin) after adjuvant systemic chemotherapy. Results are available in June 2019.

A similar phase III trial is being conducted in the United States by Ripley et al, NCT01095523[26] that also randomizes patients to standard treatment versus standard treatment plus second-look surgery with HIPEC (oxaliplatin), but with broader inclusion criteria (presenting with PC, which was completely resected, and/or ovarian metastases, presenting with tumor perforation, T4 lesions that required adjacent organ resection, and/or emergency presentation with bleeding or obstructing lesions [incidence of recurrent PC < 40%]).

In Europe, the trial COLOPEC[27] randomizes patients with pT4 or perforated tumors in two groups, one group following standard treatment and the other group receives prophylactic HIPEC (intraperitoneal oxaliplatin and intravenous 5-FU) during the surgery of the primary tumor or within 5 to 8 weeks after the intervention. This study performs regular follow-up for both groups plus an exploratory laparoscopy at 18 months for all patients. All data will be available for analysis in 2022.

The PROMENADE trial (NCT02974556) is a prospective randomized trial in Italy (Sammartino et al) for patients with locally advanced colorectal cancer T3/T4 that compares standard oncological treatment (surgery and adjuvant therapy) versus surgery of the primary tumor with risk-reducing surgery and HIPEC (oxaliplatin) plus adjuvant systemic therapy with the goal to reduce the development of endoperitoneal metastases. Results will be available in 2025.

The HIPEC-T4 study (NCT02614534) in Spain (Arjona-Sánchez et al)[28] randomizes radiological T4 tumors to receive prophylactic HIPEC with mitomycin at the time of the primary tumor surgery versus standard treatment. The goal is to reduce the incidence of peritoneal recurrence from 36 to 18% at 36 months for T4 colorectal carcinoma.

A big prospective trial is about to begin in China NCT03221608, with 300 patients to be randomized. Patients with T4N0–2M0 will undergo conventional surgery and adjuvant therapy versus surgery with HIPEC with Lobaplatin for 60 minutes plus adjuvant therapy. Results will be analyzed in 2024.

As indications are evolving, also HIPEC technique does, and we can administer intraperitoneal chemotherapy with open abdomen or by laparoscopy, so patients undergoing

laparoscopic colorectal surgery can also receive HIPEC by laparoscopy with prophylactic intention or curative intention after laparoscopic second-look surgery or laparoscopic peritonectomy.[29] Another well-known indication of laparoscopic HIPEC is for refractory ascites.[30]

In this prophylactic setting, phase II trials are now ongoing analyzing a new way of intraperitoneal chemotherapy delivery: Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) NCT03280511 is a phase II study for radically resected colon cancer patients with adeno- or signet ring cell carcinomas with high-risk tumors defined as: perforated/pT4NanyM0 (UICC 8th edition)/pTanyNanyM1 with radically resected PM including ovarian metastases. They will be offered two PIPAC treatments with oxaliplatin after primary resection and standard adjuvant chemotherapy, so 2 months after colon resection or immediately after adjuvant chemotherapy, a standard laparoscopy including peritoneal lavage, peritoneal biopsies, and PIPAC treatment with oxaliplatin 92 mg/m^2 will be planned. This procedure will be repeated after another 5 weeks. Follow-up CTs after 12, 24, and 36 months will be planned.

Conclusion

One of the most interesting advances in colorectal cancer has been the identification of patients at high risk. Patients with locally advanced colorectal cancer are a group of patients with worse prognostic at any stage due not only to systemic dissemination but also in a high percentage of patients, to locoregional recurrence. To decrease probability of peritoneal disease, oncologic surgery and adjuvant systemic therapy are not enough, and local treatments on peritoneal surface, such as reduction risk surgery and HIPEC, are required. Therefore, prophylactic or adjuvant HIPEC seems to be a promising strategy for patients with advanced colorectal cancer to prevent the development of peritoneal recurrence and improve prognosis of this group of patients. The goal is to avoid peritoneal disease or to treat it at its earliest stages when citoreduction and HIPEC have the biggest impact. It is reasonable to enroll patients in those studies and to promote evaluation of patients with locally advanced colorectal cancer at units specialized in peritoneal surface malignancies. Fortunately, most colorectal surgeons are familiarized with the "high-risk patients" concept. New strategies are being developed to improve the outcome of these patients, most of them including prophylactic or adjuvant HIPEC as part of the treatment for locally advanced colorectal cancer.

Conflict of Interest
None.

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