Management of colorectal peritoneal metastases: Expert opinion

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Summary:

When peritoneal metastases are diagnosed (strong agreement of experts): i) seek advice from a multidisciplinary coordination meeting (MCM) with large experience in peritoneal disease (*e*.g. BIG RENAPE network), ii) transfer (or not) the patient to a referral center with experience in hyperthermic intraperitoneal chemotherapy (HIPEC), according to the advice of the MCM.

With regard to systemic chemotherapy (strong agreement of experts): i) it should be performed both before and after surgery, ii) for no longer than 6 months, iii) without post-operative anti-angiogenetic drugs

With regard to cytoreductive (excisional) surgery (strong agreement of experts): i) Radical surgery requires a xiphopubic midline incision, ii) no cytoreductive surgery *via* laparoscopy

With regard to HIPEC

HIPEC can be proposed for trials outside an HIPEC referral center (weak agreement between experts) : i) if surgery is radical, ii) if the expected morbidity is « reasonable », iii) if the indication for HIPEC was suggested by a MCM, and iv) Mitomycin is preferred to oxaliplatin (which cannot be recommended) for this indication.

Introduction

Management of colorectal peritoneal metastases is based on combined radical excisional (cytoreductive) surgery, systemic chemotherapy and, to a lesser extent, intraperitoneal chemotherapy, most often following a HIPEC modality during surgery. The UNICANCER PRODIGE 7 randomized clinical trial, presented at the 2018 American Society of Clinical Oncology (ASCO) meeting, reported no overall survival benefit i for complete peritoneal metastatic excision combined with oxaliplatin-based HIPEC based (1). These results gave rise to numerous exchanges, editorials and viewpoints, sometimes extremely divergent, ranging from complete rejection of the concept of HIPEC, abandonment of the tested protocol, or abandonment of the protocol according to the extent of disease (according to the peritoneal carcinomatosis index (PCI)) (2-4). It therefore seemed necessary to reflect on an overall strategy for this disease and to propose a revision based on expert opinion to the National Thesaurus of Gastro-intestinal Cancerology (Thésaurus National de Cancérologie Digestive (TNCD)) in order to harmonize practice.

A panel of 61 French experts, oncologists, surgeons, radiologists and pathologists, met in November 2018 at the Institut Curie in Paris to exchange ideas and to propose a consensus expert opinion for the management of peritoneal metastases of colorectal cancer (panel participants listed in annex). The goal of this meeting was to analyze the results of the PRODIGE 7 trial presented at the ASCO meeting in June 2018 (not yet published) and to provide consensus or strong agreement propositions for clinical practice. The PRODIGE 7 randomized trial evaluated the benefits of HIPEC after complete excision of synchronous or metachronous colorectal metastases.

The major elements of the trial, reflecting the activity of expert French centers who manage patients with colorectal peritoneal metastatic disease, were as follows.

1. A gain of more than 40 months in overall survival is remarkable, greater than ever reported previously in a controlled study and should be considered as the main goal to attain for all patients. In this study, 15% of patients can be considered cured at 5 years. These results are related to patient selection, complete resection of carcinomatosis and the expertise of the centers involved in management. This surgery is standardized: xiphopubic midline laparotomy, complete exploration, re-opening of all planes and complete radical excision.
2. This is the first study to evaluate the specific place of HIPEC at 43°C, using oxaliplatin 460 mg/m^2 (Glucose 5% solution) and intravenous 5-FU during complete cytoreductive surgery via laparotomy after initial IV chemotherapy. The principal goal of this trial was to show a benefit in median overall survival thanks to the addition of HIPEC. The overall result is negative. The seemingly positive effect of HIPEC in the subgroup of patients with a PCI between 10 and 15 who underwent complete excision was not validated by the majority of experts. No benefit of HIPEC was observed for patients when the PCI was less than 10. The average overall survival for patients with complete excision and PCI greater than 15 was limited to 24 months.
3. Given the absence of clear improvement of survival in the HIPEC arm, high-dose oxaliplatin can no longer be considered a preferential option. The associated morbidity is high, unlike results in more recent publications using HIPEC with Mitomycin C. The duration of high temperature and high dose oxaliplatin-based HIPEC was limited to 30 minutes, considered insufficient today. The majority of experts consider that whenever HIPEC is proposed, it should be based on mitomycin C with a longer hyperthermic exposure. Others consider that the usage of mitomycin C is still controversial.
4. Information concerning surgery for peritoneal metastases is currently limited and needs to be expanded through specific training both in France and Europe. This option seems preferable rather than addressing all patients to a referral center. All patients who have undergone surgery for peritoneal

metastases, whether judged to be complete or not, with or without HIPEC, should be included in the National data base under the auspices of BIGRENAPE.

Experts have proposed specific strategies adapted to the patient, according to the synchronous or asynchronous presentation of peritoneal disease, the histologic characteristics and whether the carcinomatosis was recognized before surgery for colorectal cancer or not.

1. In case of fortuitous discovery of peritoneal carcinomatosis, during laparoscopic colectomy, the majority of experts propose performance of biopsies without trying to resect the primary tumor, performance of a stoma as necessary (in case of obstruction), and then presentation of the case to a multidisciplinary coordination meeting (MCM).
2. If carcinomatosis that may be amenable to complete excision is suspected before surgery, and in the absence of other metastases, the majority of experts recommend initial systemic chemotherapy followed by discussion of the subsequent strategy in a MCM. The main elements for decisions include the histology (pejorative character of signet ring cells), tumor biology (BRAF, MSI, RAS), the estimated PCI, the response to chemotherapy, patient overall status, and expertise of the health care team.
3. When complete excision of peritoneal carcinomatosis is possible and the PCI is less than 20, there was no expert agreement as to whether HIPEC should be proposed or not. This should normally be decided before surgery in the MCM. HIPEC can be proposed outside of a trial, by an expert team in HIPEC.
4. For the majority of experts, cytoreductive surgery can still be proposed when pejorative prognostic elements are present: age over 70, more than 30% of signet cells, and/or BRAF mutation, need for minor hepatectomy and/or hepatic radiofrequency ablation.
5. When excision is possible, but the PCI is greater than 20, neither surgery nor HIPEC should be proposed, according to the majority of experts.

Key points:

Expert agreement for the management of patients with colorectal peritoneal metastases

1) When peritoneal metastases are diagnosed (strong agreement of experts)
    - Consult a MCM with extensive experience in peritoneal disease (for example in France, BIG RENAPE network)
    - Transfer (or not) the patient to a referral center for HIPEC, according to the proposition of the MCM

2) with regard to systemic chemotherapy (strong agreement of experts)
    - It should be administered before and after surgery
    - no longer than six months
    - without post-operative anti-angiogenesis drugs

3) with regard to excisional surgery (strong agreement of experts)
    - should be radical *via* an xiphopubic midline laparotomy
    - no laparoscopic cytoreductive surgery

4) HIPEC can be proposed outside of controlled trials by a referral center (weak expert agreement)
    - If the excision is radical
    - If expected morbidity is « reasonable»
    - If the indication of HIPEC is proposed by a MCM
    - Mitomycin is preferred over oxaliplatin (which is not recommended in this setting)

References:

1. Quenet F, Elias D, Roca L, *et al.* A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. Journal of Clinical Oncology 2018; 36: 18_suppl, LBA3503-LBA3503
2. Evrard S. Autopsie d'un consensus d'expert. Pour en finir avec la chimiothérapie hyperthermique intrapéritonéale dans la carcinose colorectale. Bull Cancer. 2018; 105: 839-841.
3. Königsrainer A, Rau B. Cytoreductive Surgery (CRS) and Hyperthermic IntraPeritoneal Chemotherapy (HIPEC): don't throw the baby out with the bathwater. Pleura Peritoneum. 2018; 3: 2018 0131.
4. Ceelen W. HIPEC with oxaliplatin for colorectal peritoneal metastasis: The end of the road? Eur J Surg Oncol. 2019; 45: 400-402.

Annex

List of authors by alphabetic order
coordination M. Pocard (last author)

Note :
This text was written and edited by the group of experts who made the presentations during this meeting, composed of ten senior authors, oncologists, surgeons dealing with carcinomatosis, surgeons who are not experts with regard to carcinomatosis, with different opinions and coming from different institutions. One expert did not sign the text, because he thought it to be too different from his own opinion, but he did not question the overall opinion.
The final version was validated by four different authors, all physicians, who were present during this meeting : one oncology gastro-enterologist, one surgeon performing HIPEC, one surgeon who is not an expert in carcinomatosis and a resident at the end of training in gastro-intestinal surgery.

Abbreviations:
HIPEC: hyperthermic intraperitoneal chemotherapy
MCM: multidisciplinary coordination meeting
PCI: Peritoneal carcinomatosis Index

List of participating experts
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Jérémie H/ Liberale, Gabriel/ Lo Dico, Rea/ Malgras, Brice/ Manceau, Gilles/ Mariani, Pascale/ Meillat, Hélène/ Michel, Pierre/ Neuzillet, Cindy/ Paquette, Brice/ Pinto, Amandine/ Pirro, Nicolas/ Pocard, Marc/ Quenet, François/ Rat, Patrick/ Sabbagh, Charles/ Samalin, Emmanuelle/ Sgarbura, Olivia/ Sourouille, Isabelle/ Taibi, Abdelkader/ Tessier, Williams/ Tuech, Jean-Jacques/ Tzanis, Dimitri/ Ulloa-Severino, Béatrice/ Vienot, Angélique/ Wernert, Romuald/ Ychou, Marc.