

Multimodality treatment of colorectal peritoneal metastases

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Chapter 17

Impact



PART 1 – CURRENT PRACTICE

The nationwide Dutch retrospective cohort study described in **chapter 2** showed an association of hospital of diagnosis with isolated colorectal peritoneal metastases (CPM) with the probability of undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) and survival, with a large variation in probability of CRS-HIPEC at individual hospital level (0% to 50%). These results were as unwanted as unexpected in a small and well-regulated country with a long history and high awareness of CRS-HIPEC.¹ The observed differences could even be more pronounced in other countries, in which both patients' accessibility to CRS-HIPEC and awareness of CRS-HIPEC among physicians may be lower.^{2,3} Results of this study appeared of (inter)national interest and were presented during plenary sessions at (inter)national surgical and oncology meetings.^{4,5} Dissemination of these results could increase attention for this potentially relevant issue and may initiate (inter)national initiatives to better spread the latest knowledge on CRS-HIPEC for CPM, especially among physicians working in non-specialized centers. Several examples of potential initiatives are proposed in the Discussion section of the chapter. Such initiatives may contribute to uniformization of treatment decision making for isolated CPM and to consideration of curative intent treatment in all (or at least an increasing number of) eligible patients regardless of hospital of diagnosis.

The survey among 19 PSOGI members from 19 countries described in **chapter 3** showed relevant between-country differences in integration of CRS-HIPEC for CPM in clinical practice and relevant between-hospital and between-participant differences in current surgico-oncological treatment practice of CPM. Several important topics of low consensus were identified. The observed between-country differences in estimated numbers of CRS-HIPEC procedures per million inhabitants, reimbursement of CRS-HIPEC by health insurers, and inclusion of CRS-HIPEC in guidelines may suggest that curative intent treatment is not equally accessible for patients across different countries and socioeconomic groups. Thereby, results of this survey may encourage international initiatives to better equalize and standardize integration of CRS-HIPEC across countries. Though the survey's methodology was not designed to provide evidence-based consensus statements, its findings should rather be used as a basis to form these. Several observed controversial topics have been addressed by randomized trials or this thesis,⁶⁻⁸ but remaining topics of low consensus may serve as a basis for future studies and consensus meetings.

PART 2 – CURATIVE INTENT SETTING

The systematic review described in **chapter 4** showed a striking lack of high-quality evidence on the value of perioperative (i.e. neoadjuvant, adjuvant) systemic therapy for resectable CPM. Despite this lack of evidence, perioperative systemic therapy in this setting has been widely used in many centers worldwide.⁹ In light of the lack of evidence shown by this review, one could question this widespread use in the era of evidence-based medicine, especially as perioperative systemic therapy is not without risks and may lead to relevant health care costs.¹⁰⁻¹² Results of this systematic review led to a change of clinical practice in the Netherlands, and probably also in other countries. Before the systematic review, the Dutch colorectal cancer guideline did not include recommendations on neoadjuvant treatment, but stated that adjuvant systemic chemotherapy could be considered after upfront CRS-HIPEC for CPM.¹³ After presenting results of the systematic review, the Dutch Peritoneal Oncology Group and the Dutch Colorectal Cancer Group uniformly decided that perioperative systemic therapy was no longer recommended for CPM until its benefit is proven in a randomized trial: CAIRO6. Ever since, upfront CRS-HIPEC alone has been the standard of care for patients with resectable CPM in all Dutch CRS-HIPEC centers.¹⁴

The retrospective cohort study described in **chapter 5** showed a strong association between adjuvant systemic chemotherapy and better overall survival relative to active surveillance following upfront CRS-HIPEC for isolated synchronous CPM. Results of this study again led to a discussion within the Dutch Peritoneal Oncology Group about whether upfront CRS-HIPEC alone is the appropriate standard of care for resectable CPM. However, as discussed in *chapter 5* and *chapter 16*, the retrospective study design inevitably led to a potentially relevant influence of selection bias on reported results. Therefore, it was decided that upfront CRS-HIPEC alone remained the standard of care until results of the CAIRO6 trial (which had then already enrolled about 150 patients) become available. In other countries, results of this study probably led to routine use of adjuvant systemic chemotherapy following upfront CRS-HIPEC for isolated synchronous CPM, especially given the current lack of data on this topic in this particular patient group.

The CAIRO6 randomized phase 2 trial described in **chapter 7** showed that perioperative systemic therapy in patients with resectable CPM seems feasible, safe, and able to induce relevant response of CPM. These results justified continuation to the CAIRO6 phase 3 trial. With almost 250 enrolled patients to date, results of the phase 3 trial will likely standardize the perioperative systemic treatment of patients with resectable CPM worldwide. The trial's radiological, pathological, and translational spin-off studies

will probably allow for identification of a subgroup of patients who benefit the most from perioperative systemic therapy, sparing its toxicity and burden to those who are unlikely to benefit. The phase 2 trial showed that about a third of all eligible patients were not approached for trial participation. Besides being caused by the first-time character of CAIRO6, this may be explained by the treating surgeons' fear of missing a window to operate because of progression or toxicity during neoadjuvant treatment. Moreover, based on previously published data,¹⁵ some surgeons may have had concerns about increased postoperative morbidity due to neoadjuvant administration of bevacizumab. Importantly, the phase 2 trial showed a higher absolute proportion of macroscopic complete CRS-HIPEC and a lower absolute proportion of major postoperative morbidity in patients receiving neoadjuvant treatment relative to those undergoing upfront CRS-HIPEC. Thereby, these results may contribute to the phase 3 trial's feasibility of accrual.

As part of the CAIRO6 randomized phase 2 trial, the study described in **chapter 8** showed no relevant differences in patient-reported outcomes (PROs) between patients receiving perioperative systemic therapy relative to those undergoing upfront CRS-HIPEC alone. Together with the previously discussed feasibility, safety, and tumor response data of the phase 2 trial, these findings contribute to the justification of the CAIRO6 phase 3 trial. The phase 2 trial showed that nearly half of approached patients refused trial participation, mainly because they feared the toxicity and burden of perioperative systemic therapy. Moreover, before trial initiation, several physicians involved in CAIRO6 thought the burden of perioperative systemic therapy would be too high in this setting, especially surgeons. Importantly, results of this study suggest acceptable tolerability of perioperative systemic therapy for resectable CPM and may be used by physicians to inform patients about its burden.

PART 3 – PALLIATIVE SETTING

The systematic review described in **chapter 9** showed a striking lack of evidence on the value of PIPAC-OX in patients with unresectable CPM. Despite this lack of evidence, PIPAC-OX has been adopted as a palliative treatment option for unresectable CPM in a rapidly increasing number of hospitals worldwide.^{16,17} Given results of this systematic review, one could question this rapidly increasing use in the era of evidence-based medicine. Though PIPAC was unavailable in the Netherlands, its seemingly promising initial results have been increasingly published in the Dutch lay press.¹⁸⁻²⁰ As a result, many Dutch patients with unresectable CPM went to other countries to undergo (non-evidence-based) PIPAC-OX in an off-trial setting, frequently at own costs of several thousands of euros: an unwanted and unethical situation. Together with the lack of

evidence, this trend has encouraged development of the first ethically approved, funded clinical trial that prospectively assessed the feasibility, safety, preliminary efficacy, PROs, costs, and systemic pharmacokinetics of repetitive PIPAC-OX in patients with unresectable CPM: the CRC-PIPAC trial.

The pharmacokinetic substudy of the CRC-PIPAC trial described in **chapter 11** showed that repetitive PIPAC-OX in the uniformly administered dose worldwide (92 mg/m^2) led to a relevant systemic oxaliplatin exposure that is comparable to that of intravenous oxaliplatin reported in the literature. Being the first in-human pharmacokinetic study of PIPAC-OX, results of this study challenged the popular belief of low systemic drug exposure after PIPAC.^{21,22} As the comparison with intravenous oxaliplatin was indirect, results of this study formed the basis of pharmacokinetic studies of the CRC-PIPAC-2 trial. In this ongoing trial, pharmacokinetic blood samples are collected after the first cycle of oxaliplatin-based systemic therapy and the first PIPAC-OX to provide the first direct comparison of systemic oxaliplatin exposure between these two methods of administration.²³

The phase 2 CRC-PIPAC trial in patients with unresectable CPM described in **chapter 12** showed that repetitive PIPAC-OX (92 mg/m^2) is associated with short hospital stay and low readmission rate, but has a risk of (sometimes severe) toxicity. Observed biochemical, pathological, cytological, and ascites responses may indicate biological activity of PIPAC-OX for CPM, but the clinical relevance of this biological activity remains to be determined, especially since no radiological or clinically relevant macroscopic responses were observed. Being the first prospective trial of repetitive PIPAC-OX monotherapy for unresectable CPM, this trial received international attention of several research groups and may serve as a reference trial in this new and still small area of research.^{24,25} Though the trial confirmed the feasibility of implementing PIPAC in a multicenter trial setting, reported safety data suggest that the risks of PIPAC-OX should not be underestimated. This further questions the current widespread off-trial use of repetitive PIPAC-OX in the absence of evidence proving its efficacy. Although PIPAC-OX appeared biologically active, the observed lack of radiological or clinically relevant macroscopic response may attenuate the seemingly promising efficacy of repetitive PIPAC-OX reported thus far,^{17,26} probably as the CRC-PIPAC trial is the first to assess repetitive PIPAC-OX monotherapy. Thereby, results of this trial could lead towards a shift from trials assessing repetitive PIPAC-OX monotherapy towards trials investigating more aggressive strategies such as first-line systemic therapy alternated with PIPAC-OX: the regimen investigated in the ongoing CRC-PIPAC-2 trial.

As part of the CRC-PIPAC trial, the study described in **chapter 13** showed that patients receiving repetitive PIPAC-OX monotherapy for unresectable CPM had transient but clinically relevant worsening of several PROs during treatment, with (abdominal) pain being the most relevant. Being the first study assessing PROs of PIPAC-OX for unresectable CPM, findings of this study may slightly attenuate the previously reported good tolerability of PIPAC-OX,²⁶ could be used by physicians to inform patients about the burden of PIPAC-OX, and should be taken into account by physicians when proposing PIPAC-OX in the palliative setting. These results will be put into more perspective by the ongoing CRC-PIPAC-2 trial, as patients in this trial are asked to complete PRO questionnaires after systemic therapy cycles and after PIPAC-OX.

The study described in **chapter 14** showed that cell-free tumor DNA (cftDNA) in plasma may not be a useful biomarker in patients with isolated CPM, in whom cftDNA in peritoneal fluid may be a relevant alternative requiring further research. This proof-of-concept study formed the basis of ongoing and future cftDNA-focused translational side studies with samples collected in CAIRO6, CRC-PIPAC, and CRC-PIPAC-2, as described in *chapter 16*. Furthermore, this proof-of-concept study may support the general assumption that CPM is a locoregional rather than systemic disease.

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