The changing landscape of colorectal peritoneal metastases

Summary and discussion

The aim of this thesis was to gain more insight into the emerging therapeutic options for the treatment of colorectal peritoneal metastases and their impact on quality of life.

Summary of results

Chapter 1. PSOGI 2020: Impact of PRODIGE 7

The only curative intent treatment available for patients with peritoneal metastases from a colorectal origin is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). However, CRS-HIPEC is not without controversy, especially since the publication of the PRODIGE 7 trial. The PRODIGE 7 trial investigated whether CRS combined with HIPEC would be beneficial over CRS alone. The results of this trial seemed not to be in favor of adjuvant HIPEC after radical CRS.[1] Many world-leading experts in the field of peritoneal surface malignancies have criticized the design and conclusions of the PRODIGE 7 trial, as the majority of patients were treated with systemic oxaliplatin-based neo-adjuvant therapy.[2-5] Only if patients responded favorably to the neo-adjuvant treatment were patients randomized into the CRS-HIPEC or CRS-alone treatment arms.[1] As a result of this systemic treatment, not only did the researchers introduce selection bias, but also induced acquired resistance to oxaliplatin of the peritoneal metastases. An additional course of oxaliplatin during 30 minutes of HIPEC might thus have yielded little result. However, despite its flaws, the PRODIGE 7 had rocked the proverbial HIPEC-boat and a survey amongst 19 worldwide experts from the Peritoneal Surface Oncology Group International (PSOGI) revealed that while their personal views on CRS-HIPEC remained largely unchanged after presentation of the PRODIGE 7 results, there were notable shifts in clinical practice. Changes that were reported included a transition away from oxaliplatin-based HIPEC regimens, an extension of HIPEC perfusion times, fewer referrals from non-HIPEC institutions, diminished national consensus, exclusion of HIPEC from national guidelines, and a decline in reimbursement rates by health insurance companies. Thus, the PRODIGE 7-trial has significantly affected the practice of CRS-HIPEC around the world. Despite the design flaws of the PRODIGE 7, the study has yielded important results and has contributed to new insights.[6, 7] Furthermore, by rocking the boat, the PRODIGE 7 has inspired other researchers to investigate the current CRS-HIPEC practice. One of the most remarkable outcomes of these investigations is the insight that peritoneal metastases from colorectal origin are intrinsically resistant to anti-neoplastic agents but may also develop an acquired resistance against oxaliplatin specifically.[8, 9] This insight has implications for HIPEC, as well as for other treatment techniques. Taken together, HIPEC remains interesting and rather than rejecting the concept of HIPEC as whole, more research should be conducted to

optimize the chemotherapeutic agent, regimen and means of delivery. In addition, the higher-than-expected overall survival that was reported by the PRODIGE 7 trial, confirms that CRS remains the cornerstone of colorectal peritoneal metastasis treatment and patients should thus be referred to experienced surgical treatment centers.

Chapter 2. CRC-PIPAC-II: Safety, feasibility and efficacy of PIPAC

The majority of patients with CPM does not benefit from treatment with CRS-HIPEC, but undergo palliative systemic therapy.[12, 13] Because palliative systemic therapy alone seems to be less effective for peritoneal metastases than it is for other systemic metastases, various treatments were developed in which the therapeutic agents are delivered directly into the peritoneum.[14-19] One of these techniques is pressurized intra-peritoneal aerosol chemotherapy (PIPAC).[20] PIPAC can be used as a monotherapy, as was done in the CRC-PIPAC-I study,[21] or it can be combined with systemic therapy as bidirectional therapy. Palliative systemic therapy combined with electrostatic precipitation oxaliplatin-based PIPAC (ePIPAC-OX) had not been examined prospectively for patients with CPM. The CRC-PIPAC-II study evaluated the safety, feasibility, and efficacy of this bidirectional therapy in patients with isolated, unresectable peritoneal metastases from a colorectal origin. In a two-center, single-arm, phase II trial, chemotherapy-naïve patients underwent three treatment cycles of systemic therapy and ePIPAC-OX. The primary outcome was the frequency of major treatment-related adverse events, while secondary outcomes included the frequency of minor treatment related adverse events, number of completed treatment cycles, tumor response measures, progression-free survival, and overall survival. Out of twenty participants, seven patients experienced major treatment related adverse events (15 major treatment related adverse events in total). All patients experienced minor treatment related adverse events, most commonly abdominal pain, nausea, and peripheral sensory neuropathy. Fifteen out of twenty patients (75%) completed all three planned treatment cycles and in total 52 cycles of bidirectional therapy were administered. After the treatment, a notable pathological and cytological response was seen in 88% and 38% of patients, respectively. The median progression-free survival was 10.0 months and the median overall survival was 17.5 months. This bidirectional therapy proved feasible for patients with unresectable colorectal peritoneal metastases, demonstrating a satisfactory safety profile. The treatment response and survival rates appear encouraging, but additional studies are needed to prove the benefit of this bidirectional treatment for patients with colorectal peritoneal metastases.

Chapter 3. CRS-HIPEC and IORT

For patients with CPM the benefit of CRS-HIPEC is dependent on different factors, an important one being the completeness of cytoreduction.[22] In locally advanced rectal cancer and locally recurrent rectal cancer additional intraoperative radiotherapy (IORT) might be necessary to achieve a complete cytoreduction.[23, 24] However, combining IORT with CRS-HIPEC might lead to unacceptable morbidity and mortality and is therefore rarely performed.[25] The study described in **chapter 3** aimed to evaluate the safety and long-term outcomes of a multimodal treatment regimen comprising radical surgery, IORT, and CRS-HIPEC for patients diagnosed with locally advanced/recurrent rectal cancer accompanied by colorectal peritoneal metastases. Conducted as a single-center retrospective cohort study, this research included all consecutive patients who underwent the specified treatment at a tertiary referral center specializing in locally advanced/recurrent rectal cancer and colorectal peritoneal metastases. Metrics such as postoperative complications, duration of stay in the intensive care unit (ICU), readmission rates, disease-free survival, and overall survival were assessed. The cohort comprised 14 locally advanced rectal cancer patients and 16 locally recurrent rectal cancer patients with peritoneal metastases. The median ICU stay was one day, and 57% of the patients encountered severe postoperative complications. No mortality was observed within 90 days post-surgery. The median disease free survival was 10 months (Interquartile Range 7-39), while the median overall survival was 31 months (Interquartile Range 16-144). Given that postoperative complications and survival were in line with treatments that are acceptable for locally advanced/recurrent rectal cancer and colorectal peritoneal metastases as separate procedures, the study concludes that a combination treatment involving IORT and CRS-HIPEC represents a viable therapeutic option. Therefore, this approach should be contemplated for carefully selected patients with locally advanced/recurrent rectal cancer and colorectal peritoneal metastases and performed in specialized tertiary referral centers.

Chapter 4. Palliative tumor resection for patients with colorectal peritoneal metastases

There is a lack of information to guide clinical decisions regarding palliative treatment options for patients presenting with isolated synchronous colorectal peritoneal metastases. The study described in **chapter 4** sought to elucidate the outcomes associated with various palliative interventions for these patients. From the Netherlands Cancer Registry (NCR), patients diagnosed with isolated synchronous CPM from 2009 to 2020 who received palliative care were included. Those who underwent emergency procedures or treatments with a curative intent were excluded, as clinical decision liberty is restricted in those instances. The

patient cohort was segmented based on treatment modality: those receiving an immediate palliative primary tumor resection (with potential supplemental systemic therapy) and those administered palliative systemic therapy exclusively. The study assessed overall survival across these groups and a multivariable Cox regression analysis was performed. From a total of 1,031 patients, 364 (35%) underwent primary tumor resection, while 667 (65%) received systemic therapy. A comparative evaluation revealed a 60-day mortality rate of 9% in the resection group, compared to 5% in the systemic therapy group (P = 0.007). Median overall survival stood at 13.8 months for those undergoing resection and 10.3 months for the systemic treatment group (P < 0.001). The multivariable analysis showed an association between primary tumor resection and enhanced overall survival (HR 0.68; 95%CI 0.57–0.81; P < 0.001). In patients with isolated synchronous colorectal peritoneal metastases, while palliative primary tumor resection was correlated with superior survival outcomes relative to mere systemic treatment, it also exhibited an increased 60-day mortality. Whilst awaiting the results from clinical trials, our observations offer clinicians and patients an additional perspective for informed decision-making, although they must be interpreted with care, due to residual biases.

Chapter 5. INTERACT II: study protocol

The peritoneum is the second most affected organ for the dissemination of colorectal cancer. Patients with unresectable CPM face a poor prognosis [12, 26]. The poor prognosis of unresectable CPM patients has resulted in the development of new treatment strategies where systemic therapy is combined with local, intraperitoneal chemotherapy. In addition to PIPAC, chemotherapy can be administered intraperitoneally in a catheter-based fashion. This is being investigated in the Netherlands. In the recently published phase I study (INTERACT I), the maximum tolerated dose and thus the recommended phase II dose of intraperitoneal irinotecan was investigated and determined to be 75 mg. In this single-arm phase II study performed in two Dutch tertiary referral centers, 85 patients with unresectable colorectal peritoneal metastases are enrolled. Patients may undergo up to 12 cycles of study treatment. Each cycle consists of intravenous mFOLFOX4 with bevacizumab and concomitant intraperitoneal irinotecan (75 mg). Cycles are repeated every two weeks, with a maximum of 12 cycles. The primary outcome is overall survival and key secondary outcomes are progression-free survival, safety, patient-reported outcomes and pharmacokinetics of irinotecan. It is hypothesized that the trial treatment will lead to a 4 month increase in overall survival from a median of 12 months to 16 months. In addition to a beneficial outcome in terms of overall survival, it is expected that INTERACT-treatment is less demanding of patients, as well as the healthcare system, than PIPAC.

Chapter 6. CRC-PIPAC-II: Patient reported outcome exploration

One of the secondary objectives of the CRC-PIPAC-II study encompassed the exploration of patient-reported outcomes (PROs) during trial treatment. PROs were obtained through the EuroQol EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires. Patients completed questionnaires at various timepoints: baseline, during the initial cycle, and at one and four weeks after each ePIPAC procedure. Patient reported outcome scores from these time points were compared to baseline scores, in order to investigate how scores were affected and changed during trial treatment. Most (30/37) patient-reported outcomes fluctuated during trial treatment but did not significantly deviate from baseline. Some patient-reported outcomes (7/37) deviated significantly from baseline reflecting both improvements and deteriorations, most notably were the patient-reported outcomes **"**pain**"** and **"**abdominal pain**"**. Pain improved initially during the first cycle but showed a temporary deterioration one week after the first two PIPAC procedures. Abdominal pain deteriorated one week after the first cycle but improved four weeks post-treatment. As most patient-reported outcomes were not significantly affected during treatment, and as all deteriorations appeared to be reversible, the bidirectional treatment used in the CRC-PIPAC-II study seemed reasonably well tolerated in terms of patient-reported outcomes.

Chapter 7. PIPAC vs PROCORE: a comparison of patient reported abdominal pain

While the CRC-PIPAC-II study examined ePIPAC-OX-based bidirectional therapy, the CRC-PIPAC-I study investigated ePIPAC-OX as a monotherapy. Similar to the patient reported outcome exploration in the CRC-PIPAC-II, the patient-reported outcomes were explored during treatment with ePIPAC-OX monotherapy as a secondary objective in the CRC-PIPAC I study. Most patient-reported outcomes remained unaffected during the CRC-PIPAC I trial while some patient-reported outcomes worsened temporarily. However, the patient reported outcome "abdominal pain" was more markedly affected and worsened significantly and to a clinically relevant extent after every PIPAC procedure. As PIPAC is a minimally invasive procedure whose premise is based on little negative impact on quality of life, it is important to put this observed abdominal pain into perspective. The study described in **chapter 7** aimed to compare the patient reported outcome "abdominal pain" after ePIPAC-OX monotherapy to abdominal pain after conventional surgery for colorectal cancer; The latter demographic represents a significant portion of the global population, exceeding a million new patients annually. Consequently, the implications of treatment and associated quality of life have been extensively examined for this cohort and are under-examined for the PIPAC cohort.

Using patient-reported abdominal pain scores (EORTC QLQ-CR29) from two prospective Dutch cohorts, abdominal pain at baseline and four weeks post-treatment were evaluated. The analysis encompassed 20 PIPAC-OX patients and 322 primary tumor surgery patients. Both groups demonstrated comparable baseline abdominal pain-levels. However, PIPAC-OX patients exhibited significantly increased abdominal pain at four weeks post-treatment. This differential effect over time was also statistically significant between groups. In conclusion, PIPAC-OX induces more severe postoperative abdominal pain compared to primary tumor surgery, underlining the importance of effective analgesia and suggesting further investigation to ameliorate post-PIPAC abdominal pain.

Chapter 8. CAIRO6 vs PROCORE: comparing patient-reported outcomes

This chapter described a comparative analysis of patient-reported outcomes between patients undergoing CRS-HIPEC and those subjected to standard surgery for primary colorectal cancer. CRS-HIPEC aims for resection of all visible tumor, often necessitating more extensive procedures compared to standard surgery, including potential multiple visceral resections. Such an extensive approach could increase morbidity and mortality rates, thereby affecting the disease burden for these patients. The study assessed nine predetermined outcomes (fatigue, diarrhea, C30 summary score, global health status, as well as physical, role, emotional, cognitive, and social functioning) at three timeframes: baseline, early postoperative, and one year postoperative. Findings indicated that CRS-HIPEC's influence on patient-reported outcomes was not markedly different from standard surgery for primary colorectal cancer. The early postoperative phase recorded deteriorated scores for fatigue, C30 summary, physical, and role functioning across both groups, and cognitive and social functioning in the standard surgery group. One-year post-operative, the scores reverted to their baseline values for both cohorts. The introduction of additional systemic chemotherapy exhibited no discernible effect on patient-reported outcomes. In conclusion, despite the extensive nature and augmented morbidity risks of CRS-HIPEC, its long-term impact on postoperative PROs was not more detrimental than standard surgery for primary colorectal cancer. These findings offer valuable insights into the treatment ramifications on patient-reported outcomes for patients receiving CRS-HIPEC, equipping clinicians and patients with enhanced information for optimized patient counseling in this specific patient category.