HIPEC treatment of peritoneal carcinomatosis in colorectal and gastric cancer
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CHAPTER 13

Summary and future perspectives
This thesis focuses on the treatment of peritoneal metastases of gastric and colorectal cancer, specifically using cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). A large part of this thesis is based on retrospective analysis of patients treated with CRS + HIPEC in the St. Antonius hospital, Nieuwegein, and Catherina Hospital, Eindhoven. By combining the patients’ databases of both hospitals, we were offered a large unique set of colorectal cancer patients treated with CRS + HIPEC. This made it possible to establish statistically significant conclusions regarding specific subgroups of patients with peritoneal carcinomatosis of colorectal cancer.

Part 1 is concentrated on the early treatment of peritoneal metastases in gastric and colorectal cancer.

Chapter 2 describes the incidence and occurrence of peritoneal metastases in T4 colorectal cancer patients. A total of two hundred patients who underwent resection of T4 colorectal cancer were retrospectively analyzed after a median follow-up of 66 months. Approximately 1 in 5 patients had synchronous peritoneal metastases, and the same percentage of patients developed metachronous peritoneal metastases. Although in multivariate analysis, nodal stage was significantly associated with peritoneal metastases (OR: 1.62, 95%-CI 1.12–2.34, P = 0.01), further characterization of these patients did not reveal any clinicopathological factors predictive for the development of metachronous peritoneal metastases. These are important data when developing targeted early detection strategies and therapeutic interventions aimed at the prevention of peritoneal metastases.

In Chapter 3, a systematic review on the risk of metachronous peritoneal metastases following potentially curative treatment in gastric cancer patients is presented. This study aimed at identifying specific clinicopathological factors associated with an increased risk of peritoneal recurrence in gastric cancer patients. Forty-seven articles were included, incorporating a total of 18472 gastric cancer patients. The factors which strongest correlated with peritoneal recurrence were positive peritoneal cytology (OR: 18.49, 95%-CI 6.95–49.22, P < 0.00001), serosal invasion (OR: 5.95, 95%-CI 4.28–8.25, P < 0.00001) and lymph node involvement (OR: 3.82, 95%-CI 2.8–5.16, P < 0.00001). The pooled incidence rates of peritoneal recurrence were 64.1%, 27.3% and 19.6% for patients with positive peritoneal cytology, serosal invasion and nodal involvement,
respectively. Other factors associated with peritoneal recurrence were vascular invasion, lymphatic invasion, tumor differentiation and gender. The location of the primary tumor was not associated peritoneal recurrence. This information is crucial when designing studies aimed at the early detection, prevention and treatment of peritoneal metastases in gastric cancer patients.

Chapter 4 describes the differences in outcome of performing primary tumor resection and cytoreductive surgery and HIPEC in a one-stage procedure or a two-stage procedure. Seventy-two patients with synchronous peritoneal carcinomatosis of colorectal cancer were analyzed. Patients who underwent primary tumor resection and HIPEC in one procedure were compared to patients in whom the primary tumor was removed prior to HIPEC treatment. Although the majority of patients are currently treated within a two-stage fashion, we showed a significant benefit of the one-stage procedure. In the two-stage procedure a resection of earlier bowel anastomosis was frequently performed. These more extended resections resulted in more permanent colostomies. The one-stage procedure prevented these extended bowel resections and also resulted in a shorter treatment plan, with the benefit of early administration of adjuvant chemotherapy. We therefore conclude that early referral and combining primary tumor resection and HIPEC is preferable and efforts should be made to increase the rate of one-stage procedures.

In Chapter 5, a survey is presented which was sent to all Dutch surgical and medical oncologists. In total 185 eligible responses were received from 71 hospitals, which resulted in an overall response rate of 23% and a response rate of 85% of the respective hospitals. The most important finding of this survey was that approximately 30% of physicians treating colorectal cancer does not regard cytoreductive surgery combined with HIPEC as the standard treatment in patients with limited peritoneal carcinomatosis of colorectal cancer. Surgeons were generally more in favor of this treatment compared to medical oncologists. The majority of surgical respondents choose to perform a primary tumor resection in patients with intraoperatively discovered peritoneal carcinomatosis, resulting in a high prevalence of patients referred for a two-stage procedure. This survey showed a wide range of opinions regarding the optimal treatment in patients with peritoneal carcinomatosis. The results of this survey emphasize the need for clear guidelines on the treatment of peritoneal carcinomatosis of colorectal origin and the need for intensified efforts to disseminate the knowledge on the theoretical and practical aspects of the HIPEC treatment among medical and surgical oncologist and residents in the Netherlands.
Part 2 of this thesis explores the current borders of peritoneal carcinomatosis treatment with cytoreductive surgery and HIPEC.

In Chapter 6, patients with both an acute resection of the primary tumor and peritoneal carcinomatosis, were compared to patients without an acute resection of the primary tumor. Both emergency presentation and peritoneal carcinomatosis are known prognosticators of a poor survival. One hundred forty-nine patients treated with CRS+HIPEC for peritoneal carcinomatosis of colorectal cancer were retrospectively analyzed, of whom 24.2% initially presented with acute symptoms. Operative outcomes, complication rates and survival did not differ between patients with or without emergency presentation. The results from this study support the use of CRS + HIPEC treatment in patients following acute resection.

In Chapter 7, the influence of urological involvement of peritoneal carcinomatosis and subsequent urological resection during cytoreductive surgery was investigated. Of the 267 patients who underwent CRS + HIPEC for colorectal cancer, 38 patients underwent a urological procedure during CRS + HIPEC. Although complications were more frequent in these patients, these were not specifically related to the urological procedure. This probably reflected the more extensive peritoneal spread in these patients. The survival of patients following urological procedures and HIPEC was comparable to patients without urological involvement. We conclude that urological resections during cytoreductive surgery in combination with HIPEC are feasible and results in comparable long-term results, keeping in mind the higher rate of postoperative complications.

In Chapter 8, the treatment with CRS + HIPEC in patients with limited liver metastases and synchronous peritoneal carcinomatosis of colorectal cancer is described. In a cohort of 276 patients treated with CRS + HIPEC for colorectal peritoneal carcinomatosis, eighteen patients has synchronous liver metastases, of whom fourteen underwent liver metastasectomy. The results of this study show that in patients with limited synchronous liver metastases, CRS + HIPEC is feasible and results in similar long term results compared to patients without liver metastases. Additionally, severe complications were not more prevalent in patients with synchronous liver metastases. A gradual extension of treatment of more extensive liver disease in combination with HIPEC for peritoneal metastases, either in a one- or two-stage procedure seems justified under careful controlled conditions.

In Chapter 9, a literature review is presented on the selection of chemotherapy for hyperthermic intraperitoneal use in gastric cancer patients. Currently reported data of effect on gastric cancer, experience of intraperitoneal usage, either in humans or
animals, toxicity profiles, pharmacokinetic data, safety of administration and known effect status are presented of several potential chemotherapeutic drugs is presented. This report shows that the optimal drug regime is currently unknown and that more research is warranted to further elaborate the role of specific drugs and other parameters in the HIPEC treatment, such as patient selection, temperature of perfusate, and duration of perfusion. With both good systemic effect and favorable intraperitoneal pharmacokinetics, a regimen consisting of a platinum-based agent and a taxane appears the most promising combination of drugs.

In Chapter 10, we presented the study protocol of the PERISCOPE study. This study aims to investigate the feasibility of CRS + HIPEC using oxaliplatin and docetaxel in patients with limited peritoneal carcinomatosis of gastric cancer after neoadjuvant systemic chemotherapy, and to determine the maximum tolerated dose of intraperitoneal docetaxel in combination with a fixed dose regimen oxaliplatin in this treatment schedule. Patients with synchronous limited peritoneal carcinomatosis or positive peritoneal cytology of gastric cancer, confirmed with diagnostic laparoscopy, treated with neoadjuvant chemotherapy are eligible for inclusion. An open HIPEC technique is used with oxaliplatin for 30 minutes and a dose-escalation will be performed with docetaxel for 90 minutes. Additionally, perfusate- and plasma samples will be obtained for pharmacokinetic analysis. The study procedures are further described in this chapter and a discussion is presented on the specific choices made in the design of this study.

Part 3 of this thesis is aimed at exploring the outcome of patients in whom the treatment of peritoneal carcinomatosis with CRS + HIPEC was deemed not feasible and the outcome of patients presenting with recurrent disease following a previous HIPEC procedure.

In Chapter 11 we have described the characteristics of patients with recurrence following cytoreductive surgery and HIPEC. This study showed that approximately 75% of the patients with recurrence have peritoneal recurrence, and in half of these patients this is the only location of recurrence. The majority of recurrence after CRS + HIPEC occurred in the first two years following treatment, which supports intensive surveillance should occur in this period. We showed that initial nodal stage and the resectability of the recurrence are the most important prognostic factors in these patients. Consequently, timely detection of recurrence and an aggressive surgical approach may result in a substantial survival benefit in selected patients.

In Chapter 12, the outcome of patients who were scheduled for CRS + HIPEC, but who
at exploratory laparotomy were deemed unresectable are described. Prevention of this event is preferable, as the occurrence of open and close procedures results in preoperative uncertainty, emotional burden following open and close, and uses significant hospital resources. In our population, approximately one quarter of patients scheduled for CRS + HIPEC were labelled as open and close procedures. Prior to laparotomy, no strong clinical predictors could be identified for unresectability. Although three quarters of patients receives palliative chemotherapy, survival was poor in these patients with a median overall survival of approximately 10 months. This study emphasizes efforts should be made to improve patient selection, such as improving current imaging modalities to detect peritoneal nodules.

**Future perspectives**

In the last decade CRS and HIPEC has become an established procedure in the treatment of peritoneal carcinomatosis. The studies presented in this thesis may contribute to a further improvement in patient care. However, more research on the treatment of peritoneal surface malignancies using CRS + HIPEC is warranted. Improvements should be made by performing both clinical research and basic preclinical research.

In clinical research, patient selection remains one of the most important topics to address. Improving patient selection will prevent patients who will not benefit from CRS and HIPEC, to be exposed to the unnecessary burden of this treatment. On the other hand patients who are now excluded from CRS + HIPEC, but may benefit from HIPEC, may be included in the future. Improved patient selection may also result in more detailed preoperative prediction regarding benefits and morbidity of CRS + HIPEC treatment, which is a valuable asset in the process of shared-decision-making when choosing the most appropriate treatment in patients with peritoneal surface disease.

A more timely diagnosis and treatment of both synchronous as well as metachronous peritoneal dissemination can be achieved by increasing the diagnostic accuracy of current imaging modalities, which are frequently incapable of detection small peritoneal nodules. For instance, in a small study of fifteen patients, preoperative magnetic resonance imaging (MRI) correlated well with surgical peritoneal cancer index and the authors concluded that MRI might be a suitable technique for improved patient selection. Possibly other radiological innovations, such as radio-nuclear imaging, may improve preoperative
radiologic accuracy. By improving the accuracy of preoperative diagnostic imaging, a more specific estimate can be made whether peritoneal disease is resectable, conceivably resulting in a decrease in the rate of “open and close” procedures. Furthermore, possibly a more detailed projection can be made on the extent of cytoreductive surgery required and its associated risk of morbidity. Albeit its invasiveness, diagnostic laparoscopy is a valuable tool in the preoperative assessment of patients planned for CRS + HIPEC. However, in a subset of patients diagnostic laparoscopy is not successful, mainly resulting of adhesions, or results in an underestimation of the extent of peritoneal spread, especially in the retroperitoneal plane. The exact position of diagnostic laparoscopy in patients with peritoneal metastases is currently unknown and needs further characterization. Patient selection can also be improved by a more accurate preoperative physical assessment of the patient’s perioperative vulnerability. Numerous risk scoring systems including simple clinical tests have been described to determine individual patient’s risk of perioperative morbidity and mortality. Apart from the ASA classification, these tools are hardly incorporated in daily clinical decision making. New scoring systems should be validated in patients with peritoneal surface malignances. Specific interventions such as exercise therapy or nutritional support have been described to improve outcome following major abdominal surgery, their role in CRS + HIPEC has not yet been established. Prevention and early treatment of peritoneal metastases is believed to be an important part of the future of HIPEC treatment. As extensive surgical resections are not required, the related surgical morbidity will be limited in early treated patients. The currently performed COLOPEC study is a randomized multicenter trial investigating the prevention of peritoneal dissemination in patients with T4 or perforated colon cancer undergoing adjuvant HIPEC simultaneously or shortly after primary tumor resection. In gastric cancer, the randomized GASTRICHIP study aims to investigate the survival benefit of adjuvant HIPEC during primary resection in gastric cancer patients without manifest peritoneal metastases. In gastric cancer with its high risk of metachronous peritoneal metastases following curative resection, especially in patients with serosal invasion or positive peritoneal cytology, prevention of peritoneal metastases appears promising. With the results of the PERISCOPE study, outlined in Chapter 10, we hope to design a future randomized trial using HIPEC to prevent peritoneal metastases in patients at risk for peritoneal dissemination or treat limited peritoneal metastases of gastric cancer. Patients with disease located outside the peritoneal cavity are generally excluded for CRS + HIPEC. There is a definitive, but currently still ill-defined trend, to combine CRS + HIPEC
for peritoneal carcinomatosis with local treatment of limited extraperitoneal disease, i.e. limited pulmonary and/or liver metastases. The few available studies suggest a survival benefit for patients with well resectable disease but further studies are mandatory to establish clear guidelines for the indications and extent of these combined procedures.

Performing a radical resection of all peritoneal metastases is the most important predictor of long-term outcome following CRS + HIPEC. To improve outcome in patients with peritoneal metastases, an increase in the ability to perform a complete macroscopic resections is needed. New initiatives such as intraoperative techniques using fluorescence imaging could become an important tool in improving the rate of radical resections in peritoneal surface malignancy. Extensive analysis of patients treated with CRS + HIPEC can further determine to which extent different surgical resections are feasible in terms of perioperative morbidity and long-term outcome.

A topic of debate in the treatment in peritoneal metastases of both colorectal and gastric cancer remains the position of systemic chemotherapy. Currently, adjuvant chemotherapy following CRS + HIPEC is regarded as standard treatment in colorectal cancer; however the true benefit is unknown. Some authors have advocated the use of neoadjuvant chemotherapy, before CRS + HIPEC as this may result in improved survival. While other studies have shown that limited effect of systemic chemotherapy, since palliative treatment does not seem to improve survival in patients with peritoneal metastases and neoadjuvant chemotherapy does not increase resectability of unresectable peritoneal metastases. As shown in Chapter 2 and 3 of this thesis, adjuvant chemotherapy did not decrease the risk of peritoneal dissemination in patients with T4 colorectal cancer or curatively treated gastric cancer. Although, the known limitations of these retrospective analyses are present, these results support the theory that systemic chemotherapy has limited effect on peritoneal dissemination. Elias at el. described the intraoperative administration of intravenous leucovorin and 5-fluorouracil just before HIPEC perfusion, with the idea to potentiate the effect of intraperitoneal oxaliplatin. The effect of this bidirectional chemotherapeutic regimen has not been investigated, and there is currently no experimental or clinical data to support this method. More research is warranted on the timing and role of systemic chemotherapy in the treatment of peritoneal carcinomatosis.

In the Netherlands, currently all centers using CRS + HIPEC are united in the Dutch Peritoneal Surface Oncology Group, which permits the collective performance of clinical trials. Additionally, peritoneal carcinomatosis treatment is performed identically throughout these centers, which permits the retrospective analysis of large series of
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patients. Further collaboration between centers specialized in treating peritoneal surface malignancies should be encouraged. Apart from the aforementioned perspectives in clinical research, presumably basic and preclinical research has a major role in improving treatment of peritoneal surface malignancies. Major steps are expected by using tumor profiling and exploring underlying genetic patterns of peritoneal metastases. Personalized cancer treatment is aimed at tailoring diagnosis and treatment to each individual molecular tumor profile. More insight in tumor profiles will aid in a personalized prediction of disease development, progression and therapy response. New biomarkers, such as the already used HER2neu or KRAS, may become valuable tools in tailoring cancer treatment to the individual patient. For instance, in colorectal cancer, low levels of Bloom syndrome protein (BLM) have been associated with high mitomycin sensitivity and improved survival following CRS + HIPEC. This fundamental information can be both implemented for intraperitoneal as well as systemic chemotherapy. Ideally, a personalized chemotherapeutic regimen with a combination of systemic and intraperitoneal chemotherapeutic drugs can be formed for each individual patient based on the chemosensitivity of the primary tumor and the peritoneal metastases. Analysis of molecular biology of different metastatic patterns may also help designing tailored strategies in the early detection and prevention of different metastatic patterns in gastrointestinal malignancies.

The technique of performing CRS + HIPEC is currently mainly based on clinical experience and a limited body of experimental basic or preclinical data. The individual elements of HIPEC treatment, such as perfusion duration, temperature, selection of chemotherapeutic drugs, intraperitoneal pressure, should be further explored and more evidence is warranted to support each component of HIPEC treatment. Experimental and preclinical studies are needed to provide a basis for future clinical studies. For instance, animal studies by Klaver et al. have shown the efficacy of intraperitoneal chemotherapy using mitomcyin in a mouse model with colorectal cancer. However, the same animal model has shown no difference in survival of animals treated with intraperitoneal chemotherapy administered with or without hyperthermia. The results of these studies require further evaluation in clinical trials. More research is needed on the pharmacokinetics and pharmacodynamics of potential chemotherapeutic agents in HIPEC. Exploring alternative chemotherapeutic regimens or drugs is necessary. Current chemotherapeutic drugs are all derived from systemic therapies; however, the development of alternative drugs, primarily for intraperitoneal administration could be
promising. For instance, Catumaxomab, a monoclonal antibody targeting the EpCAM antigen located on the surface of many epithelial tumors, is a promising new agent registered only for intraperitoneal infusion.\textsuperscript{14} Further intraperitoneal drug development, based on tumor profiling, could become a fundamental part of HIPEC development.
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References


