HIPEC treatment of peritoneal carcinomatosis in colorectal and gastric cancer
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CHAPTER 1

Introduction and general outline of the thesis
Introduction

Definition and epidemiology

Peritoneal dissemination, or peritoneal carcinomatosis, is a condition in which cancer cells outgrowth into metastatic tumor nodules on the peritoneal surface. Peritoneal metastases develop when malignant cells detach from the primary tumor and spread in the peritoneal cavity. This can occur in the natural course of the disease following invasion of the serosa or spontaneous perforation. Iatrogenic causes, such as irradical resection of the primary tumor or intraoperative tumor spill also play a role in the development of peritoneal metastases. Intraoperative spill can occur by iatrogenic perforation of the primary tumor or by the dissection of blood or lymph vessels containing malignant cells. The majority of peritoneal metastases are originated from gastrointestinal or gynecologic malignancies, however numerous other solid type cancers, such as breast, lung, prostate and melanoma, have been described to metastasize to the peritoneum. Colorectal and gastric cancers are responsible for approximately fifty percent and twenty-five percent of all peritoneal metastases in male and female patients, respectively. In patients with colorectal cancer approximately 5% of the patients present with synchronous peritoneal metastases and about 3.5% of patients develop metachronous peritoneal metastases after curative treatment of colorectal cancer. In gastric cancer, 14% of patients are diagnosed with synchronous peritoneal carcinomatosis, and about 16% of patients develop peritoneal recurrence after potentially curative treatment. Survival in patients with peritoneal carcinomatosis treated conservatively is poor. Even with modern systemic chemotherapy, survival is frequently limited to 6 to 12 months in colorectal cancer and 3 to 6 months in gastric cancer.

Historical overview

The first descriptions of the intraperitoneal administration of drugs for the treatment of malignancies originate from the 1950s, when in patients with disabling malignant ascites favorable result were reported on the administration of radioactive gold or nitrogen mustard. In the 1970s, interest renewed after several studies described the administration of chemotherapy through catheters in patients with ovarian cancer. The pharmacokinetic advantage of intraperitoneal administration of chemotherapeutic drugs was established. The limited permeability of the peritoneum allowed the local intraperitoneal application of significant higher concentrations of chemotherapy.
compared to intravenous administration. New techniques of intraperitoneal administration of chemotherapy were further explored such as continuous perfusion and the addition of hyperthermia. Simultaneously, emphasis shifted from palliating disabling malignant ascites to treating microscopic residual disease either after systemic chemotherapy or surgery. In 1995, Sugarbaker first described cytoreductive surgery using various peritonectomy procedures for the resection of peritoneal surface malignancies in combination with intraperitoneal chemotherapy. Initial studies focused on early postoperative intraperitoneal chemotherapy following cytoreductive surgery. After the first completed randomized controlled trial using cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastases of colorectal cancer, this treatment strategy became the foundation for further studies in the treatment of peritoneal surface malignancies. The long-term results of this study showed a significant survival benefit compared to systemic palliative chemotherapy. Patients with colorectal peritoneal metastases treated with CRS+HIPEC had a median disease-specific survival of 22.2 months, compared to 12.6 months in patients treated with palliative chemotherapy alone. In recent years, with improved patient selection, the median survival of patients with peritoneal metastases of colorectal cancer has increased to approximately 36 months.

Present situation
In the Netherlands, yearly approximately 350 CRS + HIPEC procedures are performed for the treatment of peritoneal carcinomatosis in eight designated HIPEC centers. Following laparotomy, cytoreductive surgery is performed with the aim to remove all visible tumor nodules. Afterwards, the abdominal cavity is filled with perfusion fluid, in which chemotherapeutic drugs are dissolved, and the intraperitoneal cavity is continuously perfused for thirty minutes to two hours, depending on the chemotherapeutic drug. Following the study by Verwaal et al. mitomycin C is generally used as chemotherapeutic drug, however, several studies have investigated other chemotherapeutic drugs. Resulting from the direct cytotoxic effect of hyperthermia and enhanced in vitro cytotoxicity of several chemotherapeutic drugs under hyperthermic condition, the perfusion fluid is generally heated till 39 to 42 degrees Celsius. Hyperthermia is also believed to increase chemotherapeutic drug penetration in the peritoneal tissue. Tissue penetration of intraperitoneal chemotherapeutic drugs can be regarded as the Achilles' heel of intraperitoneal chemotherapeutic drug administration, as penetration is generally
limited to three to five millimeters. Consequently, complete macroscopic cytoreductive surgery, is regarded mandatory for long-term survival following CRS + HIPEC.

**Present issues**

Patient selection remains a major topic in treatment of peritoneal surface malignancies. The extent of peritoneal carcinomatosis is considered to be one of the most important factors in patient selection. Survival is significantly correlated to the extent of peritoneal spread and the ability to achieve a complete macroscopic cytoreduction at surgery. Additionally, extensive spread may reflect the biologic aggressiveness of the underlying malignancy. Postoperative morbidity is increased in patients with extensive peritoneal dissemination as a result of more major surgical resections.

Unexpected inoperability at surgery remains a prevalent issue in patients with peritoneal carcinomatosis. This undesirable situation is often due to the inability of current imaging modalities to accurately document the extent of the disease and especially the involvement of the small bowel and its mesentery. Failure of present imaging techniques to detect small tumor nodules in early disease may lead to unnecessary delay in treatment. Second-look laparoscopy has been suggested as an option to improve early detection in patients at risk of peritoneal dissemination, the exact role of this strategy is currently unknown. Prevention of peritoneal metastases using HIPEC has been suggested by some authors. To correctly design and study these innovative treatment strategies, it is of importance to accurately determine which patients are at risk for the development of peritoneal metastases.

Although there are sufficient relevant clinical data regarding the survival following CRS+HIPEC, controversy still exists among physicians whether CRS+HIPEC is beneficial and can be regarded as standard treatment in patients with peritoneal dissemination of colorectal cancer. This may result in withholding treatment or delay in referral of patients who may potentially benefit from CRS and HIPEC.

In Asian countries CRS + HIPEC is widely applied in the treatment and prevention of peritoneal metastases in patients with gastric cancer, the role of this treatment in Western gastric cancer is unknown. The high risk of peritoneal metastases in gastric cancer, suggests that gastric cancer may be a suitable disease for this treatment. Several issues such as patient selection, appliance of perioperative chemotherapy and selection of drugs to be used intraperitoneally need to be addressed before larger studies in gastric cancer can be initiated.
General outline of the thesis

The studies presented in this thesis focus on three main issues: The risk and early treatment of peritoneal carcinomatosis (Part I), exploring borders in peritoneal carcinomatosis treatment (Part II) and failure of peritoneal carcinomatosis treatment (Part III). A large part of this thesis is based on in-depth analysis of a large population of patients treated with CRS + HIPEC in the St. Antonius hospital, Nieuwegein, and Catherina Hospital, Eindhoven (Chapter 6, 7, 8, 11 and 12).

Part I

Chapter 2 describes the occurrence and risk factors associated with the development of PC in patients with T4 colorectal cancer. Chapter 3 presents a systematic review on the risk of PC following curative resection of gastric cancer. Both studies emphasize the magnitude of the problem in both patient groups. The data derived from these studies provide a basis for further studies on the prevention, early detection and treatment of PC in these patients. Following the hypothesis that cytoreductive surgery and HIPEC should be performed early in the course of the disease, the outcome of performing CRS and HIPEC in one procedure compared to tumor resection followed by secondary CRS and HIPEC in a second stage procedure is presented in Chapter 4.

Chapter 5 describes the current attitude of medical and surgical oncologists in the Netherlands towards the indication and outcome of CRS and HIPEC in colorectal cancer patients. The survey provides important information to support further efforts to promote CRS and HIPEC among both medical students and professionals both in basic courses and continuing medical education curriculae at different levels.

Part II

In Chapter 6, patients treated with CRS + HIPEC after emergency presentation of colorectal cancer are described. As emergency presentation is a known poor prognostic factor in colorectal cancer, we investigated whether CRS + HIPEC is safe in patients with peritoneal carcinomatosis following acute resection, and results in equal long-term survival. In Chapter 7, urological resections as a part of CRS + HIPEC are investigated. As urologic involvement may result in more extensive resections, we studied whether a urologic resection during CRS + HIPEC is safe and affects long-term survival. Chapter 8, describes patients with limited synchronous liver and peritoneal metastases treated
with CRS + HIPEC. This investigates whether in carefully selected patients, CRS + HIPEC is feasible, and whether further exploration of combined treatment of hepatic and peritoneal metastases is feasible. With the three preceding studies we aimed at improving patient selection and individual patient counselling for CRS + HIPEC in patient with peritoneal metastases of colorectal cancer.

One important question when initiating studies with CRS + HIPEC in gastric cancer is which intraperitoneal chemotherapeutic regimen should be used. **Chapter 9** provides a comprehensive literature review on possibly suitable chemotherapeutic drugs for intraperitoneal perfusion in gastric cancer patients; several aspects on the selection of chemotherapeutic drugs are discussed. Subsequently, in **Chapter 10** a study protocol is presented of a study currently being performed in patients with limited peritoneal carcinomatosis of gastric origin. In this chapter the outline and expected results of this study are further described.

**Part III**

In **Chapter 11**, patients who experienced recurrence following cytoreductive surgery and HIPEC for peritoneal metastases of colorectal cancer are analyzed. Analysis of prognostic factors and treatment of recurrence is performed to gain insight in recurrence patterns and prognosis. In these patients further treatment options, including surgical resection, are explored. In **Chapter 12**, patients with colorectal peritoneal carcinomatosis who were not suitable for cytoreductive surgery and HIPEC treatment are described. Risk factors, prognosis and possible treatment options following an open and close procedure are investigated. With these results we hope to decrease the percentage of open and close procedures. Both studies in part III improve patient counselling concerning treatment options and prognosis following an open and close procedure or recurrence following CRS + HIPEC.

**Chapter 13** provides a summary of the results of the complete thesis, and provides future perspectives of peritoneal carcinomatosis treatment in colorectal and gastric cancer.
Chapter 1

References


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