Cytoreduction and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis of colorectal origin
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Chapter one

Introduction and outline of the thesis
In November 1995, The Netherlands Cancer Institute embarked on the treatment of peritoneal carcinomatosis of colorectal cancer by means of cytoreduction followed by hyperthermic intraperitoneal chemotherapy. Peritoneal carcinomatosis is a manifestation of colorectal cancer in which intraperitoneal seeding of tumour cells occurs. After implantation on the peritoneal surfaces, the malignant cells may form tumour nodules throughout the abdominal cavity, which can cause bowel obstructions. Peritoneal carcinomatosis occurs commonly in colorectal cancer patients and is the second-most frequent cause of death after metastatic disease to the liver. In an estimated 25% of patients, no other tumour locations can be found, even if a detailed diagnostic work-up is performed. Sugarbaker and others have suggested that peritoneal carcinomatosis of colorectal cancer, like liver metastases, should probably not be equated with generalised disease, but can be seen as a first step of further dissemination.

The treatment - cytoreduction followed by hyperthermic intraperitoneal chemotherapy - consists of two elements. The first element is cytoreduction. The objective of the cytoreduction is to remove all macroscopic tumours or at least to have only limited residual disease (< 2.5 mm thickness). This is achieved by a surgical procedure in which a maximum exposure of the abdominal cavity is obtained, followed by resection of the affected peritoneum and infiltrated viscera. Reasons for not reaching a complete cytoreduction are extensive involvement of small bowel or its mesentery, and tumour infiltration in the porta hepatis or pancreas. In the latter cases, the tumour deposits are resected as far as is judged to be compatible with sufficient post-operative function. There are no further restrictions on the extent of surgery. Cytoreduction can include for example gastrectomy, splenectomy, cholecystectomy, peritonectomies of diaphragms, omentectomy, partial small and large bowel resections, rectal resection, resection of uterus and ovaries, and partial bladder or ureter resections. Of course, in many cases only a selection of these resections is needed.

The second element of the treatment is the hyperthermic intraperitoneal chemotherapy itself. Spratt was the first to describe this technique in 1980. The theoretical background has been studied well. The concept of intraperitoneal cytotoxic drug administration was developed from the ideas on peritoneal dialysis. A mathematical outline of intraperitoneal drug administration is based on the findings of Dedrick. He postulated that the intraperitoneal-to-plasma concentration ratio depends on molecular weight and the permeability of the peritoneal surfaces. He also concluded that a large proportion of the absorbed cytotoxic drug would pass through the portal system, which would result in high liver concentrations. Both situations are advantageous in peritoneal carcinomatosis. Brenner has provided guidelines for intraperitoneal drug selection. These guidelines consist of four points: (1) the drug should be capable of killing carcinoma cells either directly or by metabolic activation within tumour tissue, (2) it should possess a limited peritoneal permeability, (3) it should be rapidly cleared from plasma, and (4) there should be a dose-response relationship. Loss et al studied a rat model in which the temperature was increased to 41°C by means of submersion of the animal. They found that heat administration combined with intraperitoneal chemotherapy favours the response of solid intra-abdominal tumour cells to cytoreductive drugs. Although this model does not correspond completely with the method used in human beings, it supports the idea that hyperthermia is useful. The penetration depth after intraperitoneal administration was also
studied.\textsuperscript{12} They found that therapeutic concentrations were only reached within two mm from the exposed surface. Based on these observation, a complete or nearly complete cytoreduction is needed before intraperitoneal chemotherapy is started. It explains also why most intraperitoneal applications of cytotoxic drugs fail if applied without surgery.

The initiation of The Netherlands Cancer Institute project was based on the data known in 1995. Before that year, a number of institutes had started to treat patients affected by peritoneal carcinomatosis by the above described novel approach.\textsuperscript{13} Sugarbaker, as important promoter of this treatment, described the first clinical results in 1985.\textsuperscript{14} In that study, he and his co-workers found a significant decrease in recurrence when intraperitoneal 5-fluorouracil was given in comparison to intravenous use. They presented the clinical features of 66 patients affected by carcinomatosis in 1991.\textsuperscript{15} They briefly described the procedure of cytoreduction and hyperthermic intraperitoneal chemotherapy. The procedure has been explained in more detail in 1995 without providing survival data or other outcome features.\textsuperscript{16} These results were reported elsewhere that same year.\textsuperscript{17} A three-year survival rate of 61\% was found. The study consisted mainly of patients with low-grade tumours and had a median follow-up of two years. Results of selected patients with carcinomatosis of appendiceal carcinomas had been reported two years earlier.\textsuperscript{18} This evaluation of 69 patients showed a good survival rate in patients who were affected by pseudomyxoma peritonei (89\% three-year survival) and a worse survival in adenocarcinoma patients (38\% three-year survival). The latter group consisted of only six patients. A considerable toxicity was mentioned. Currently, Sugarbaker's group is working on an evaluation of the treatment of peritoneal carcinomatosis by hyperthermic intraperitoneal chemotherapy around the world.

In Japan Yamaguchi treated eight patients with peritoneal carcinomatosis in a similar way and found a two-year survival of 18\%.\textsuperscript{19} Another feasibility study was performed by Schneebaum et al.\textsuperscript{20} They encountered severe pulmonary and renal toxicity in one of their fifteen patients. In Europe, Gilly and colleagues treated 28 patients with various digestive cancers and reached a one-year survival rate of 54\%.\textsuperscript{21,22}

The above-mentioned studies up to 1995 provide only circumstantial evidence of the effectiveness of cytoreduction and hyperthermic intraperitoneal chemotherapy. The degree of evidence should be seen as level V.\textsuperscript{23,24} This was mainly because of the lack of information on other treatment options.

The initiating project at The Netherlands Cancer Institute ran between November 1995 and December 1997. This part consisted of a feasibility study of intraperitoneal Mitomycin C.\textsuperscript{25} The study contained 29 patients. From the experience of this study is that a dose above 35 mg/m\textsuperscript{2} give severe toxicity.

In the period of the feasibility study, a number of other institutes also started to treat peritoneal carcinomatosis by means of cytoreduction and hyperthermic intraperitoneal chemotherapy. Loggie et al in the USA treated 20 patients with peritoneal carcinomatosis of various origins in this fashion. Their main finding was that more patients were alive at six months when the cytoreduction was complete than when it was incomplete.\textsuperscript{26} Also, cytology of the peritoneal fluid became tumour-negative in case of successful cytoreduction. One year later, his group reported on 39 patients with
a one-year survival of 74% and a two-year survival of 48.5%. Their median survival time was 18.2 months. In this study, gastrointestinal and ovarian cancer were lumped together. Complete or near-complete cytoreduction was reached in only eight of the 36 patients. Complications were reported separately. The Sugarbaker group produced a large number of reports containing important clinical information, but did not provide new survival data.

In Europe, Elias et al reported on their successes. They described their approach in 1996 and the results the year thereafter. The two-year survival was 50%. The study population consisted of patients with sarcomas, neuroendocrine tumours, pseudomyxoma, various gastrointestinal tumours, a patient with ovarian cancer and another with testicular carcinoma.

In Japan, Nishimura et al treated fourteen patients successfully. These patients had a three-year survival rate of 25%. All patients had colorectal cancer. Fujimura treated eight patients, two with gastric cancer and six with colorectal cancer, of whom only one died within a year.

From the data available in 1997, one may gather that the two-year survival after cytoreduction and hyperthermic intraperitoneal chemotherapy is approximately 50% and the three-year survival 25%. Although these studies provided an abundance of useful information, there were also a number of flaws. Data were collected from patients with a wide variety of diseases and the populations were highly selected. There was also a lack of data on results of other treatments, such as systemic chemotherapy or debulking operations without chemotherapy. With the latter in mind, the degree of evidence was not improved above level V.

Partly based on the promising results of the above-mentioned reports and on our own results in the dose-finding study, a randomised trial was started. The trial was supported by the “College voor Zorgvoorzieningen (CVZ)”, a Dutch organisation that funds the development of new therapies and the research of their efficacy. The aim of this study was to provide level II evidence of the benefit of cytoreduction and hyperthermic intraperitoneal chemotherapy.

This thesis contains the results of this phase III study (Chapter 2), an evaluation of prognostic factors for survival and for toxicity (Chapters 3 and 4), the long-term results of peritoneal carcinomatosis when treated by conservative surgery and systemic chemotherapy (Chapter 5), the results of treatment of recurrence after the first management of peritoneal carcinomatosis (Chapter 6) and the evaluation of the follow-up (Chapter 7). The cost and quality of live consequences are given (Chapter 8). The survival data are updated until autumn 2003 (Chapter 9). This thesis closes with an general discussion in which remaining question are discussed and the lay-put for futures plans are given.

References
4. Sugarbaker PH: Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treat-
Chapter 1


