Loco-regional Treatment of Peritoneal Carcinomatosis: Survival, Morbidity and Quality of Life

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Abstract


Peritoneal carcinomatosis (PC) is traditionally regarded as a terminal stage of disease with a poor prognosis and systemic chemotherapy is regarded as palliative treatment. In order to improve survival and even to achieve cure for selected patients with PC, cytoreductive surgery and intraperitoneal che-motherapy have been advocated. Despite complete macroscopic removal of tumour, residual microscopic malignant cells might result in recurrence. Intraperitoneal chemotherapy aims to kill residual malignant cells and thereby needs to be distributed in the entire peritoneal cavity. This aggres-sive combined loco-regional treatment has a high risk of morbidity and mor-tality. Whether the increased risks are acceptable to improve survival re-quires investigation and the impact of loco-regional treatment of PC on health-related quality of life (HRQL) needs to bee explored.

The overall aim of this thesis was to analyse the impact of cytoreductive surgery and intraperitoneal chemotherapy on patients with peritoneal carci-nomatosis.

A significant survival improvement (median 32 months) was seen in 18 patients with PC of colorectal origin subjected to loco-regional treatment, in comparison to matched controls treated with systemic chemotherapy (me-dian survival 14 months, Paper I). The results of single-photon emission computer-tomography (SPECT) in 51 patients were correlated to the number of intraperitoneal chemotherapy courses that could be performed without further surgery (Paper II). Postoperative 30-days morbidity and 90-days mortality was investigated in 123 PC-patients after loco-regional treatment. Severe adverse events occurred in 51 (41%) patients. Five patients (4%) had treatment-related mortality. Stoma formation, duration of surgery, periopera-tive blood loss, and extent of PC was associated with morbidity (Paper III). HRQL was investigated in 64 patients. HRQL was negatively affected at 3 months but a partial recovery was seen at 8 months. 30-day morbidity did not have any impact on HRQL at 8 months (Paper IV). This treatment there fore appears justified despite considerable toxicity in view of possible life prolongation.

Keywords: Peritoneal carcinomatosis, Cytoreductive surgery, Intraperitoneal chemotherapy, Survival, SPECT, Morbidity, Mortality, Quality of life

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“No struggle without victory”
Roald Dahl, 1916-1990
List of Papers

This thesis is based on the following Papers, which are referred to in the text by their Roman numerals (I-IV).


II Hansson J, Mahteme H, Maripuu E, Garske U and Graf W. Single-photon emission computed tomography for prediction of treatment results in sequential intraperitoneal chemotherapy at peritoneal carcinomatosis. *Submitted*


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Abbreviations

5-FU  5-Fluorouracil  
AE    Adverse Events  
ASA   American Society of Anaesthesiologists  
CC    Completeness of Cytoreduction  
CI    Confidence Interval  
CRC   Colorectal Carcinoma  
CRS   Cytoreductive Surgery  
CT    Computerized Tomography  
DV    Detected Volume  
ECRS  Extent of CRS  
EORTC European Organization for Research and Treatment of Cancer  
EPIC  Early Postoperative Intraperitoneal Chemotherapy  
Global QoL Global Quality of Life  
HIPEC Hyperthermic Intraperitoneal Chemotherapy  
HRQL  Health Related Quality of Life  
i.p.  Intraperitoneal  
i.v.   Intravenous  
IPC   Intraperitoneal Chemotherapy  
LS    Lesion Size  
LV    Leucovorin  
MCS   Mental Component Summary  
PC    Peritoneal Carcinomatosis  
PCI   Peritoneal Carcinosis Index  
PCS   Physical Component Summary  
PMP   Pseudomyxoma peritonei  
PSS   Prior Surgical Score  
QLQ-C30 Quality of Life Questionnaire Core 30 Items  
R1    No residual macroscopic tumour  
R2    Residual macroscopic tumour  
SD    Standard Deviation  
SF-36  Short Form 36  
SPECT Single Photon Emission Computer Tomography  
SPIC  Sequential Postoperative Intraperitoneal Chemotherapy
Introduction

Background

The word carcinoma, “malignant tumour”, resembles the Latin carcinoma, which derives from the Greek word Karkinoma, meaning “a crab”: karkinos (“Crab”) also meant “hard”. Cancer was known to the ancient Greek-Roman physician Galen of Pergamon (129-200 CE), among others, who noted the similarity of cancerous tumours to crabs with the sometimes swollen veins as the “legs” (http://www.etymonline.com/index.php?term=cancer).

Colorectal carcinoma (CRC) is the third most frequent cancer in the Nordic countries with 15,000 new cases a year, with a five year survival rate of generally around 50 % (Moller, Fekjaer et al. 2002; Malila and Hakulinen 2003). Fifty percent of CRC patients develop metastatic disease, whereas, peritoneal carcinomatosis (PC) is encountered in 7 % of patients at primary surgery (Koppe, Boerman et al. 2006). PC can also appear as a recurrence after curative resection for colorectal cancer. PC originating from neoplasia of the appendix is rare, resulting in pseudomyxoma peritonei (PMP) in 1-2/1,000,000/year (Smeenk, van Velthuysen et al. 2008). Mesothelioma of the peritoneum is estimated to occur in 1-3/1,000,000/year (Connelly, Spirtas et al. 1987). In gastric cancer, 50% of patients have PC at exploration (Sugarbaker and Yonemura 2000). Ovarian cancer accounts for 9/100,000 cases per year, of which the majority are locally advanced at exploration (Deraco, Raspagliesi et al. 2003). Metastases of carcinoma of gastrointestinal origin disseminate via different routes: haematogenous, lymphatic, peritoneal, and locally advanced tumour growth involving adjacent intra- or retroperitoneal organs. These routes are considered essential for explaining the pattern of metastases, although other theories, proposing cancer cell fusion with migratory bone marrow-derived cells as an unifying explanation of the mechanism behind metastasis (Pawelek and Chakraborty 2008; Shabo, Stal et al. 2008).

Disseminated disease in the peritoneal cavity also occurs because of spillage of tumour during cancer surgery, carcinoma cells implant in a random fashion near the contamination site. PC cells can also move in the peritoneal cavity, especially in the case of mucinous content like PMP, the laws of gravity, normal flow and reabsorption of peritoneal fluid, and the surface of peritoneum enhance cancer cell migration called the “redistribution phenomenon” resulting in the typical location of tumour lesions at the greater
and lesser omentum and right hemidiaphragm (Sugarbaker 1994). When sufficient nutrition is provided, tumour cell implants progress and metastasis can be extensive before the disease is clinically significant.

Traditionally, PC is regarded as a disseminated and terminal stage of disease and patients suffering from this condition usually have very poor prognosis (Mahteme, Pahlman et al. 1996; Shepherd, Baxter et al. 1997; Assersohn, Norman et al. 1999). Systemic chemotherapy is used in order to achieve regression of tumour and to improve outcome in terms of survival and quality of life (Glimelius 2003).

In order to improve survival and also to obtain cure for selected patients with PC, cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) have been advocated (Cunliffe and Sugarbaker 1989; Markman 2003). In selected patients, total removal of advanced tumours and/or PC is feasible with CRS. Although complete CRS results in total macroscopic elimination, residual microscopic disease, or dissemination and implantation of malignant cells associated with surgical trauma might result in tumour recurrence. IPC aims to kill residual malignant cells and obtain complete cancer eradication in the peritoneal cavity. Curative intent by loco-regional treatment is based on the assumption that metastatic disease (haematogenous or lymphatic) is absent. This aggressive combined treatment has a risk of morbidity and mortality (Stephens, Alderman et al. 1999). The increased risk appears acceptable in view of possible improved survival, compared to traditional palliation (Slevin, Stubbs et al. 1990). There are indications that loco-regional treatment initially affects health related quality of life (HRQL) negatively (McQuellon, Loggie et al. 2001). Therefore, the efficacy, safety, and the impact of this treatment on HRQL need to be evaluated.

Peritoneal Anatomy and Physiology

The periphery of the abdominal cavity is lined by the peritoneum parietale and the viscera are covered by peritoneum viscerale. The peritoneal surface area approximates the skin surface area (Albanese, Albanese et al. 2009). Histologically the peritoneum consists of a monolayer of mesothelial cells supported by a basement membrane and connective tissue which contains a collagen matrix, interstitial cells and blood capillaries. The peritoneal fluid enters the vascular system by diffusion past the restricting blood capillary wall from the intraperitoneal compartment or by absorption to the peritoneal lymphatic network thru the lymphatic stomata mainly located on the diaphragmatic surface and the omentum (Bettendorf 1978; Stelin and Rippe 1990).
Pharmacokinetics

Tissue penetration is one of the key issues in IPC. The penetration into tumour tissue by IPC is by diffusion and the highest concentration therefore occurs in the peripheral 1-3 mm (Los, Mutsaers et al. 1989). The intratumoral drug concentration is increased by heat (Los, Sminia et al. 1991) and by increased concentration of the intraperitoneal (i.p.) drug (Elias, Bonnay et al. 2002). Drainage via the visceral peritoneum is into the portal circulation and this route has been suggested for drug distribution in treatment of hepatic metastases (Mahteme, Larsson et al. 1998). Drainage via the peritoneum parietale by diffusion results in flow to the systemic circulation and drainage to the lymphatic system has been shown to be at most 50% of the total peritoneal to blood absorption (Stelin and Rippe 1990).

Prognostic indicators

PC is often diagnosed and / or quantified peroperatively since a preoperative diagnosis of this condition is difficult. In the case of PC from CRC, preoperative conventional computerized tomography (CT)-scan has limited capacity to detect smaller tumour noduli (de Bree, Koops et al. 2006). Different scoring systems for assessing the extent of PC have been suggested (Gilly, Carry et al. 1994; Sugarbaker 1998; van der Vange, van Goethem et al. 2000; Yonemura, Bandou et al. 2006). Two prognostic indicators are the Prior Surgical Score (PSS) and the Peritoneal Cancer Index (PCI) (Sugarbaker and Jablonski 1995; Sugarbaker, Ronnett et al. 1996).

The tumour cell entrapment theory advanced by Sugarbaker is a hypothesis to explain the rapid progress of PC in patients that undergo CRS without using IPC (Sugarbaker 1999). As definitive treatment of PC preferably is done with minimal prior surgery the PSS has been developed. PSS (0-3) estimates the extent of abdominal and pelvic dissection performed before definitive CRS. The PCI developed by Sugarbaker is validated and used by several PC-centres. PCI is a peroperative quantitative assessment of the distribution and size of tumour implants inside the abdomen and pelvis. PCI (1-39) is calculated by summing lesion size (LS) scores (LS-0 no malignant deposits, LS-1 tumor nodules < 0.5 cm, LS-2 tumour nodules 0.5-5 cm, LS-3 tumour nodules > 5 cm) in 13 different regions of the abdomen. The prognostic value of PCI is dependent on the cancer type, whereas, the possibility of obtaining complete CRS is related to the extent of disease, location and to invasiveness associated with histology (Sugarbaker, Ronnett et al. 1996; Sugarbaker, Schellinx et al. 1996; Sugarbaker 1998).

The prognostic value of histology is evident, not only for distinguishing between CRC and PMP, but also for differentiation between prognostic features in PMP (Schellinx, von Meyenfeldt et al. 1996). PMP was introduced as a description of the mucinous tumour and ascites associated with the rup-
ture of appendiceal mucocele. The term PMP is loosely applied in the case of abdominal mucinous tumours, without regarding the histological features of the primary lesion. However, histologically, PMP is defined by subtypes associated with different prognoses. The different histological subtypes may initially have similar clinical features, but peritoneal mucinous carcinomatosis has a poorer prognosis than disseminated peritoneal adenomucinosis (Ronnett, Zahn et al. 1995).

Completeness of cytoreduction (CC) is scored and recorded the end of surgery (CC-0: no peritoneal seeding at exploration, CC-1: remaining tumour < 2.5 mm, CC-2. remaining tumour < 2.5 cm, and CC-3: remaining tumour > 2.5 cm or confluence of unresectable tumor). Therefore CC-0 / CC-1 is designated as complete cytoreduction (Sugarbaker 1999). CC-0 corresponds to no residual macroscopic tumour (R1) and CC-1 or more to residual macroscopic tumour (R2), according to the International Union Against Cancer (Wittekind, Compton et al. 2002).

Treatment of metastasis
Radical surgical removal of all disease is to this date the only major possible treatment that can cure cancer. Chemotherapy has a central role in treatment of advanced cancer of colorectal origin (Van Halteren, Roumen et al. 1999; Glimelius 2003). Adjuvant treatment using systemic chemo- and radiation therapy can improve results in terms of cure (Glimelius and Isacsson 2001; Ragnhammar, Hafstrom et al. 2001).

Surgical treatment
Surgical treatment for PC started as a ‘debulking’ surgery in combination with IPC, mainly used in the field of gynaecological oncology to achieve palliative advantages (van der Burg, van Lent et al. 1995). In recent years, this surgical approach has been further developed to a more aggressive technique evolved into the peritonectomy procedures, described by Sugarbaker (Sugarbaker 1995). Briefly, peritonectomy is performed by defined procedures concerning all anatomical regions in the abdomen. Depending on extent of disease and location, one or more of the following surgical procedures is undertaken: greater omentectomy ± splenectomy; parietal peritonectomy; right and left upper quadrant peritonectomy; colon and small bowel resection; pelvic peritonectomy ± recto sigmoid resection ± salpingoooforectomy ± hysterectomy; cholecystectomy ± lesser omentectomy, and dissection of duodenal-hepatic ligament. A ball-tip electro-surgical hand piece with pure cut at a high voltage of 200/300 W is used to facilitate dissection and induce tumour kill in the tissue interface (Sugarbaker 1994).
Chemotherapy treatment modalities

Previous standard systemic chemotherapy treatment for PC have been estab-
lished mainly in a palliative setting (Glimelius 2003) resulting in slightly
prolonged survival, alleviated symptoms, and increased quality of life
(Glimelius, Hoffman et al. 1994). The lack of drug delivery to the PC nod-
ules has been suggested as one of the main reason for the failure of systemic
chemotherapy treatment. In order to obtain a maximum drug concentration
in the target organ, i.p. administration has emerged as an optimal route (Los,
Verdegaal et al. 1991; Mahteme, Larsson et al. 2004).

The loco-regional treatment approach in combination with extensive sur-
gical procedures, i.e. CRS in combination with IPC, is promoted in selected
patients (Verwaal, van Ruth et al. 2003; Glehen, Kwiatkowski et al. 2004;
Yan, Bijelic et al. 2007).

IPC with different modalities has developed over the last decades, and
two different settings include: sequential postoperative i.p. chemotherapy
(SPIC) (Markman, Cleary et al. 1986) and hyperthermic i.p. chemotherapy
(HIPEC) (Spratt, Adcock et al. 1980), with the addition of early postopera-
tive i.p. chemotherapy (EPIC) (Sugarbaker, Zhu et al. 1993). Loco-regional
chemotherapy is valuable, as complete cytoreduction (CC-0 / CC-1) only
means complete removal of macroscopic disease; thus, residual microscopic
tumour remnants remaining in the abdominal cavity leads to recurrence.

SPIC can be administered postoperatively through a Port-a-Cath placed
subcutaneously just above the perist of the lower ribs, with the i.p. catheter
directed at the main area of carcinomatosis. Infusion starts within 1 day of
surgery to prevent implantation of residual cancer cells and to treat residual
tumour noduli. Limited distribution of active agents in the abdomen might
be due to the formation of postoperative adhesions. Historically, the main
drug for CRC treatment has been 5-Fluorouracil (5-FU), and this drug has
also been used for i.p. infusion in SPIC to treat PC of different gastrointesti-
nal origin (Carlsson, Graf et al. 1990; Oman, Blind et al. 2001). An intrave-
nous (i.v.) infusion of Leucovorin (LV) is administered 60 minutes after the
start of the i.p. infusion to optimise the 5-FU anti tumour activity (Spears,
Gustavsson et al. 1989). SPIC is given sequentially during six days and re-
peated at 4–6 weeks intervals. The chemotherapy-resistance of the tumour
can be tested and the choice of drug adjusted accordingly (Csoka, Nygren et
al. 1995).

HIPEC is performed at the end of the operation. The drug is heated to
42°C and is evenly administered throughout the abdominal cavity in an open
or closed abdomen technique. The heating of the fluid is important, as the
high temperature enhances cytotoxicity and increases the depth of penetra-
tion by the drug into the tumour tissue (Los, van Vugt et al. 1994; Witkamp,
de Bree et al. 2001a; Elias, Bonnay et al. 2002). Drugs routinely used in
HIPEC are oxaliplatin, mitomycin C, cisplatin, doxorubicin and irinotecan
(Witkamp, de Bree et al. 2001a; Sugarbaker, Mora et al. 2005; Hadi, Saunders et al. 2006; Elias, Goere et al. 2007). EPIC is applied for 5-days postoperatively (i.p. 5-FU and i.v. LV) (Hadi, Saunders et al. 2006; Esquivel, Sticca et al. 2007; van Leeuwen, Graf et al. 2008).

Distribution of intraperitoneal fluids

In HIPEC, the distribution of the chemotherapeutic agent is manually controlled by the surgeon in the coliseum technique (Stephens, Alderman et al. 1999), or by changing the flow rate into the abdominal cavity and shifting the patient side-wise in the closed technique (Witkamp, de Bree et al. 2001a). Repeated IPC treatment, as in SPIC, requires access to the intraperitoneal space. The distribution of the chemotherapeutic agents to tumour-affected areas in the peritoneal cavity is a prerequisite for successful treatment. Feasibility and possible effects of repeated IPC-treatment are affected by the formation of postoperative adhesions that form at a high rate as a result of abdominal surgery (Menzies and Ellis 1990).

Single-photon emission computed tomography (SPECT) has been suggested as a useful instrument for defining the extent and location of i.p. administered fluids (Wahl, Gyves et al. 1989). The technique provides detailed anatomic information on the distribution of the fluid administered, in regions such as the peri-hepatic region, the lesser sac, and the pelvic region (Figure 1). Also, there is methods developed to measure anatomical volumes by summing up the volume elements (voxels) lying within the contour in each constructed slice (Murase, Tanada et al. 1989).
Quality of Life

Quality of Life has become an increasingly important factor in the development of new treatment strategies. However, for patients with cancer treatment effect generally precede over inconvenience of the treatment (Slevin, Stubbs et al. 1990). Phase II and phase III clinical trials (Cunliffe and Sugarbaker 1989; Markman 2003; Verwaal, van Ruth et al. 2003), has forwarded loco-regional treatment to improve survival in PC. Consequently, an increasing number of centres treat PC with his combination; however, this aggressive treatment is associated with high morbidity and mortality (Stephens, Alderman et al. 1999; Witkamp, de Bree et al. 2001b) and the impact of this treatment on HRQL needs further evaluation.

There are limited reports that CRS + IPC improve HRQL (McQuellon, Loggie et al. 2001; McQuellon, Loggie et al. 2003; Schmidt, Dahlke et al. 2005; Tuttle, Zhang et al. 2006; McQuellon, Russell et al. 2008), however,
there is scepticism towards this treatment modality (Jaaback and Johnson 2006) because of the concern that treatment reduces HRQL. Thus, there is a strong need for evaluation of CRS and IPC, not only with respect to efficacy and safety, but also to assess the impact on HRQL. It would also be of great interest to identify variables that might affect the risk of morbidity and quality of life.
Aim of the thesis

The overall aim of this thesis was to analyse the impact of cytoreductive surgery and intraperitoneal chemotherapy on patients with peritoneal carcinomatosis.

Specific aims:

I To determine the effect of CRS followed by repeated courses of i.p. chemotherapy on side effects, and survival compared to the results obtained with systemic chemotherapy in patients with PC of colorectal origin (Paper I).

II To investigate whether SPECT data can predict successful SPIC treatment without further surgical intervention after CRS and if clinical data correlate to SPECT data and feasibility of SPIC (Paper II).

III To assess survival and morbidity after CRS combined with IPC and identify clinical variables that may increase the risk of postoperative morbidity and mortality (Paper III).

IV To determine the extent by which HRQL in patients with PC is influenced by treatment with CRS combined with IPC and to analyse the influence of clinical variables (Paper IV).
Patients and methods

Ethical considerations
All studies were approved by the regional ethics committee and informed consent was obtained from each patient.

Eligibility requirements and procedures
The diagnosis of PC in patients included in this thesis was through surgical exploration or CT-scan, and was confirmed by histopathological analyses. Inclusion criteria were: no distant metastasis; adequate haematopoietic, liver and renal function; functional status: World Health Organisation performance status ≤ 2 or similar; and, American Society of Anaesthesiologists (ASA) classification ≤ 2.

The extent of PC was recorded retrospectively in a separate system for classification of local/peritoneal spread, based on which, all patients could be classified (Paper I). For paper II-IV, quantitative prognostic indicators for PC were recorded retrospectively for patients treated before January 2003, and thereafter, prospectively; PCI score was simplified as follow: PCI 1-10 as PCI-I, PCI 11-21 as PCI-II and PCI 21-39 as PCI-III.

Before February 2003, peritonectomy was not performed on the right and left upper quadrant, lesser omentum or duodenal-hepatic ligament in our unit. Instead, tumours on these sites were treated by electro-cautery at 70-100 W.

Paper I
Eighteen patients (nine women and nine men, with a mean age of 54 years, range 31–74) were included in this study. The protocol was established in 1991 and the last patient was included in September 1999. The inclusion criteria were primary colorectal adenocarcinoma, with local or peritoneal tumour deposits, either resectable or suitable for debulking surgery, and no evidence of tumour growth outside the abdomen.

One patient was not treated according to the protocol due to extensive non-resectable peritoneal tumour growth. The remaining 17 patients were
treated with either total macroscopic removal (n=11) or debulking of the metastases (n=6) followed by chemotherapy according to SPIC. A system for classification of local/peritoneal spread was developed by which all patients could be classified.

Eighteen patients (nine women, nine men, mean age 56 years, range 36–69) treated for advanced colorectal adenocarcinoma within the Nordic chemotherapy trials (1992; Glimelius 1993; Glimelius, Jakobsen et al. 1998) were randomly selected as a reference group. The selection was made without any knowledge of survival. The selection criteria were: resected primary colorectal adenocarcinoma; and, local and/or peritoneal tumour deposits treated by intravenous i.v. chemotherapy (8 patients received Methotrexate-Fluorouracil-Leukovorin and 10 received Fluorouracil-Leukovorin). The control group was matched with the experimental group according to age and gender, and the tumour burden was assured not to be lower than in the experimental group.

Paper II

Between May 1991 and August 2004, 51 patients (20 women, mean age 52 years, range 14-74) were investigated by SPECT to assess the i.p. distribution of infused fluid. The time interval between CRS and SPECT ranged between 5 and 25 weeks (median 7). Pre-, per- and postoperative clinical variables were extracted from the medical files and listed in a database.

Surgical treatment and parameters

To estimate the extent of surgical trauma in the abdominal cavity as a result of CRS, the extent of surgical dissection was defined as extent of CRS (ECRS) and summarised in nine different regions with a score 0-9.

Chemotherapy parameters

A Porth-a-Cath was used to administer SPIC treatment, which was started the day after surgery, and was administered daily for six days and then repeated monthly for eight courses. The chemotherapy consisted of i.p. 5-FU and i.v. LV. In six patients, additional IPC agents were added after the first SPIC course based on in vitro chemotherapy-resistance tests (Csoka, Nygren et al. 1995). Two patients had HIPEC treatment (Mitomycin C). Clinical assessment was performed before each SPIC course.
SPECT
Before the second SPIC course, SPECT was performed with $^{99m}$Technetium labelled macro-aggregated albumin i.p. administered via the PaC. SPECT acquisition was made in 60 projections (30 per head) and stored in a 64 x 64 matrix. The distribution of the radioactivity detected by SPECT resulted in a detected volume (DV). The DV was calculated at four different threshold settings: 1% (DV$_1$%), 2% (DV$_2$%), 5% (DV$_5$%), and 10% (DV$_{10}$%). Clinical data and the number of SPIC-courses that could be administered after the SPECT examination without further surgical intervention, was compared to SPECT data.

Paper III
Between May 1991 and November 2004, 123 patients (57 women and 66 men with a mean age of 54 years, range 14-77) were treated with CRS and IPC because of PC. Toxicity was scored according to the Common Toxicity Criteria (version 3.0) of the National Cancer Institute. Adverse Events (AE) data (grades 3 and 4) on 30-days postoperative morbidity and 90-days mortality were analysed. Clinical data concerning preoperative status, perioperative procedures, postoperative events, and survival were assessed.

Paper IV
Between November 2001 and March 2005, two quality of life instruments, European organization for research and treatment of cancer, core quality of life questionnaire v 3.0 (QLQ-C30) and 36-Item Short-Form Health Survey (SF-36), were completed (preoperatively, and 3- and 8- months postoperatively) by 64 PC patients (29 women and 35 men, with a mean age 54 years, range 21–76). The patients were treated with CRS (38 complete CRS) + IPC. IPC was given as SPIC for 44 and as HIPEC for 20 patients. Thirty-six patients received a stoma (colo- or ileostomy). Clinical data was assessed and the impact on HRQL analysed. As a reference, the HRQL values for the Swedish population, matched for gender and age, were used.

HRQL instruments
The QLQ-C30 is a self-administered cancer-specific structured questionnaire designed for the use in clinical trials containing 30 questions, 24 of which form nine multi-item scales representing various dimensions of HRQL: five functional scales, three symptom scales, and one global scale (Global QoL). The remaining six questions reflect cancer-oriented symptoms. The combi-
nation of items to be calculated into multi-item scales is pre-defined (Aaronson, Ahmedzai et al. 1993) i.e. to a 0-100 scale. Higher scores indicate a higher level of symptoms or a lower functioning level.

SF-36 is a generic questionnaire with 36 questions summarised into two major health summary scales (Physical and Mental Health) and eight multi-item scales. It is categorized into five functional scales and three comfort scales. The combination of items to be calculated into multi-item scales is pre-defined (Sullivan, Karlsson et al. 2002) to a 0-100 scale. A higher score indicates a better state of health, meaning lower degree of symptoms or better functioning level. Two higher-order summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS) are recommended for interpreting the findings in the subscales (Ware, Kosinski et al. 1994).
Statistical methods

In all Papers, confidence intervals (CI) were used with 95% limits and statistical significance was set at a \( p \)-level <0.05. Analyses were performed with Statistica 7.0 in Paper I and Statistica 8.0 in Papers II-IV (Statsoft. Inc., Tulsa, OK, USA).

Paper I

Survival curves were constructed according to the Kaplan–Meier method and differences were analysed with the log-rank test. Differences in proportions were evaluated with Fisher’s exact test.

Paper II

Data were presented as median (range) unless otherwise indicated. Clinical data and DV relation to number of SPIC treatments were analysed by Spearman Rank-correlation test and linear regression tests. Mann-Whitney U-test and Kruskal & Wallis tests were used to assess differences between groups. Survival curves were constructed with the Kaplan Mayer method and compared by the log rank test. For relation to continuous data, survival was analysed with Cox-regression.

Paper III

Univariate analysis of each clinical variable was performed with Fisher’s exact test or \( \chi^2 \) test. Where appropriate, the Mann–Whitney \( U \)-test and the Kruskal–Wallis test investigated the probability of association with grades 3 – 4 AE. A logistic regression model was used in a multivariate analysis to determine the odds ratios for the correlation between clinical variables and grades 3 – 4 AE. The backward-elimination method determined which clinical and surgical variables best predicted AE. Survival curves were constructed according to Kaplan–Meier method and differences were analysed with the log-rank test.
Paper IV

Missing data concerning non-participating patients, unit non-response, item non-response and item non-response due to a missing last page were assessed by separate analyses. As the mechanism behind the missing last page was administrative and analyse indicated randomness, an imputation was made in an effort to compensate for the missing data, which resulted in 11 additional complete cases.

Descriptive statistics, i.e. frequencies and proportions for categorical data and means, medians, standard deviation (SD), and ranges for continuous variables were calculated. Mann-Whitney U-test, Kaplan–Meier- and Log-Rank-tests were used to investigate influence of missing data as described by Park and Davis (Park and Davis 1993). To test for any differences between groups, the Mann-Whitney U-test, Spearman Rank correlation-test and t-test were used.

HRQL values for the Swedish population matched for gender and age were retrieved as means and used as reference (Michelson, Bolund et al. 2000; Sullivan, Karlsson et al. 2002). To investigate differences between reference and baseline, Wilcoxon matched pairs test were used. Mann-Whitney U-test was used to investigate outcome between different points in time. All statistical analyses were with Statistica 8.0 (Statsoft. Inc., Tulsa, OK, USA). A p-value <0.05 was considered as significant.
Results

Paper I

There was no treatment-related mortality. Median survival was 32 months among patients treated with CRS and IPC, and 14 months in the control group (Figure 2). In all, 11 patients who underwent macroscopically radical surgery had a longer survival than those who were not radically operated ($p=0.02$: Figure 3).

Of the 18 patients treated, 13 terminated the planned treatment prematurely: seven due to catheter-related problems; five due to other reasons (ileus $n=1$, liver metastases $n=1$, decline in general status $n=1$, and two patients refused further treatment); and treatment was withdrawn in one patient after SPECT due to lack of widespread distribution in the abdominal cavity.

Figure 2. Survival: i.p. patients vs. Control group.
Figure 3. Survival: Radically-operated vs. Non-radically-operated.
Paper II

The DV at a threshold of 2% (Figure 4) had the highest correlation to the number of SPIC courses. Patients with a DV$_{2\%}$ lower than mean reached two SPIC courses and patients with DV$_{2\%}$ higher than mean reached six SPIC courses. SPECT examination revealed an inverse relationship between DV and threshold level (Table 1).

![Figure 4. Comparison of number of SPIC-courses after SPECT against detected volume (DV) (ml) at threshold 2%.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Detected volumes (DV) (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Minimum</td>
</tr>
<tr>
<td>DV, Threshold 1%</td>
<td>6919</td>
</tr>
<tr>
<td>DV, Threshold 2%</td>
<td>4734</td>
</tr>
<tr>
<td>DV, Threshold 5%</td>
<td>2313</td>
</tr>
<tr>
<td>DV, Threshold 10%</td>
<td>1085</td>
</tr>
</tbody>
</table>
The median number of SPIC courses was five (range 0-7). Feasibility of SPIC was dependent of diagnosis \((p=0.03)\), the median number of SPIC courses was three for CRC (range 0-7) and seven for PMP (range 0-7).

The number of SPIC courses was lower if there had been previous systemic chemotherapy (median 1.5, range 0-7), compared to systemic chemotherapy naive patients (median 6, range 0-7, \(p=0.001\)). Previous systemic chemotherapy also had a negative impact on DV (DV\(_{2\%}\) \(p=0.03\)). Previous radiotherapy did not affect DV or the number of subsequent SPIC courses.

Height correlated to DV and number of SPIC courses. Patients with a height lower than mean reached DV\(_{2\%}\) \((r=0.29)\) at mean 3930 ml (95% CI, 2660-5199) ml, and patients with a height greater than mean reached DV\(_{2\%}\) at mean 5507 ml (95% CI, 4149-6865). A taller person could also tolerate more SPIC courses \((r=0.28)\). Patients with a height lower than mean, reached four SPIC courses and higher than mean reached six SPIC courses.

R1-resection did not correlate to number of SPIC courses, although when stratified by diagnosis, there was a difference between CRC+R1-resection and CRC+R2-resection, \((p<0.05, \text{Table 2})\).

The ECRS did not correlate to DV or to the number of SPIC courses. ECRS did not correlate to clinical variables except for operation time, operative bleeding, and time of hospital stay (Data not shown).

Table 2. Number of sequential intraperitoneal chemotherapy (SPIC) courses comparing completeness of cytoreductive surgery, R1=R1-resection, R2=R2-resection, stratified for diagnosis, CRC=colo-rectal cancer, PMP=pseudomyxoma peritonei.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Descriptive Statistics, SPIC courses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valid N</td>
</tr>
<tr>
<td>CRC+R2</td>
<td>11</td>
</tr>
<tr>
<td>CRC+R1</td>
<td>15</td>
</tr>
<tr>
<td>PMP+R2</td>
<td>12</td>
</tr>
<tr>
<td>PMP+R1</td>
<td>10</td>
</tr>
</tbody>
</table>

There was no treatment related mortality. The initial planned treatment was not fulfilled by 30 patients (59%) for different reasons (progress of disease, \(n=9\), PaC problems (breakage of the catheter \(n=3\), infection \(n=3\), obliteration \(n=3\)), fistula formation \(n=3\), ileus \(n=1\), general health deterioration \(n=3\), and insufficient i.p. distribution at SPECT \(n=1\)). Four patients terminated the treatment for unknown reasons.

Patients treated with systemic chemotherapy before CRS had a longer hospital stay (mean 19, range 8-54 days) than systemic chemotherapy native patients (mean 12, range 6-52 days, \(p=0.003\)). Seven of the patients with prior systemic chemotherapy had a R1 resection. There was no correlation between DV and overall survival (data not shown).
Grade 3–4 AE were observed in 51 patients (41 %) Grade 3-5 AE were associated with stoma formation, duration of surgery, peroperative blood loss and peritoneal cancer index (PCI) in the univariate analysis. Stoma formation remained correlated to morbidity in the backward elimination analysis after multivariate logistic regression. Small bowel anastomoses were associated with AE but no correlation was found for colo-colonic anastomoses. Excision, or electro-cautery evaporation, of the tumour from small bowel surface was correlated to bowel morbidity but the same procedure performed on colon was not associated with bowel morbidity. Patients treated with HIPEC + EPIC had a longer hospital stay compared to those treated with SPIC. Five patients had treatment-related mortality (4%) within 90 days. Overall median survival was 27 months for the CRC patients and 30 months for the PMP patients. Survival was associated with macroscopic radical surgery, prior surgical score, PCI, and primary tumour type (Figure 5).

*Figure 5.* Survival according to primary tumour type, Colon and Rectal cancer, Pseudomyxoma peritonei (PMP).
Compliance

Preoperatively, 62 (97%) completed QLQ-C30 and 60 (94%) SF-36. The number of completed questionnaires declined at 3- and 8-months as an effect of attrition. A complete set of units at all three occasions (complete case) was reached in 69% (44/64) for QLQ-C30 and 67% (42/64) for SF-36. Patients who declined to participate in the study were older than participating patients \((p=0.02)\). The patients who did not return the questionnaires at 8 months had worse scores in several scales at baseline, than patients who did. This difference was seen in both instruments.

Baseline

The QLQ-C30 scores were worse in several scales (global QoL \(p=0.0001\), role functioning \(p=0.001\), emotional functioning \(p=0.001\), social functioning \(p=0.001\) and insomnia \((p=0.0001)\) than the scores in the reference population.

In SF-36, most scales were lower than in the reference population (role physical \(p=0.0001\), general health \(p=0.01\), vitality \(p=0.001\), social function \(p=0.0001\), role-functioning emotional \(p=0.001\) and mental health \(p=0.0001\)). The physical component summary score was unaffected and the mental component summary score was lower \((p=0.0001)\).

There was no difference between the imputed and the non-imputed scores at any assessment.

Trends over time

Mean scores and trends in complete cases for QLQ-C30 are presented in Figure 6 and Figure 7 and for SF-36 in Figure 8 and Figure 9.

There was no difference between the imputed and the non-imputed scores at any assessment.

3-months

At 3-months, the QLQ-C30 indicated a decline in the physical \((p=0.001)\), role \((p=0.001)\) and social functioning \((p<0.05)\) scales, compared to baseline; Global QoL, emotional and cognitive functioning, and all symptom scales were unchanged.

For SF-36 at 3-months, physical functioning \((p<0.05)\) and role physical \((p=0.01)\) declined. General health score decreased although not significantly compared to baseline. PCS declined \((p=0.01)\) and MCS was unchanged compared to baseline.
8-months

For QLQ-C30 at 8-months, all scales remained unchanged compared to the 3-month values. However, there was a return towards baseline levels in most scales, although physical functioning was lower \((p=0.01)\) and dyspnoea was higher than baseline \((p<0.05)\).

All SF-36 scales also remained unchanged between 8 and 3-months, except role physical which improved \((p=0.01)\). General health was unchanged compared to the 3-months scores. All SF-36 scales and both component summary scores at 8-months returned to baseline level, showing no difference to the preoperative scores.

![Figure 6. EORTC QLQ-C30, Complete cases, Global QoL & Functional scales.](image)

Global quality of life (Global QoL), Physical functioning (PF), Role functioning (RF), Emotional functioning (EF), Cognitive functioning (CF), Social functioning (SF).

![Figure 7. EORTC QLQ-C30, Complete cases, Symptom scales & Single items.](image)

(Fatigue (FA), Nausea & Vomiting (NV), Pain (PA), Dyspnoea (DY), Insomnia (SL), Appetite (AP), Constipation (CO), Diarrhoea (DI) and Financial difficulties (FI)).
Distribution of high and low HRQL scores in the complete cases

In order to be able to study the impact of HRQL domains in greater depth, thou mean scores were rather stable from baseline to 8-months; the distribution of the patient scores according to the assessment was explored.

A typical pattern that emerged for several scales was that the number of patients with the more favourable scores at baseline, decreased to 3-months and then increased at 8-months again, whereas an increase of the number of the worst score was seen at 8-months. In physical component summary there was a marked shift of patients with high scores to a lower score at 3-months and to be returned at 8-months. The mental components summary both decreased the number of low scores and increased the number of high scores over time.
Results of QLQ-C30 in relation to clinical data and morbidity

At baseline PCI II-III did not have impact on HRQL and diagnosis only had an impact on diarrhoea, with increased symptoms \((p=0.01)\) in patients with CRC. Patients with a perioperative bleeding above median had worse scores in physical functioning \((p<0.05)\), role functioning \((p<0.05)\), and fatigue \((p<0.05)\) at 3-months and worse scores in global QoL \((p<0.05)\), role functioning \((p<0.05)\) and dyspnoea \((p<0.05)\) at 8-months. Patients with a duration of surgery above median had worse scores in role functioning \((p<0.05)\) and fatigue \((p=0.001)\) at 3-months, but not at 8-months. Patients with a stoma had lower social function \((p<0.05)\) at 8-months. PCI II-III worsened global QoL \((p=0.01)\) and social functioning \((p=0.01)\) at 8-months. HIPEC had a negative impact on physical functioning at 3-months \((p<0.05)\) and complete CRS increased pain at 3-months \((p<0.05)\) but these variables had no impact at 8-months. 30-days morbidity with AE \(\geq 3\) had no impact on HRQL at 3 or 8-months (data not shown).
General Discussion

The clinical outcome after a diagnosis of PC has radically changed during the last two decades due to combined loco-regional treatment. Development of different regimens in systemic chemotherapy treatment has moderately improved in outcome from metastatic disease in terms of survival and quality of life (Glimelius, Hoffman et al. 1994; Glimelius 2003). Although the diagnosis still is associated with a poor prognosis the loco-regional combined treatment of surgery and intraperitoneal chemotherapy is a promising treatment alternative.

In Paper I, survival from CRS of PC of CRC origin in combination with SPIC treatment was compared with matched control patients treated with systemic chemotherapy. Median survival (32 months) with treatment was more than double than in controls (14 months). However, interpretation must consider that patient selection may influence the results despite efforts to match the groups. The results in terms of survival in Papers I and III is of a magnitude making randomisation per se difficult due to patients expectancy, as indicated by others (Smith and Pell 2003; Verwaal, van Ruth et al. 2003; Elias, Delperro et al. 2004)

The systemic chemotherapy used to treat the controls was from an older regimen i.e. methotrexate-fluorouracil-leucovorin or fluorouracil-leucovorin in 1985-1995. Moreover, treatment in the experimental group would not be currently recommended, instead peritonectomy and HIPEC is considered “the golden standard”. However, this study demonstrated the benefits in terms of survival with a loco-regional approach for patients with PC from CRC.

One of the major obstacles to obtain IPC treatment, especially in the SPIC setting, is lack of distribution of drugs in the peritoneal cavity. This was illustrated in Paper I, as five of 18 patients prematurely terminated planned treatment due to catheter-related obstruction. The catheter related problems were investigated (Paper II), and SPECT data correlated with feasibility of repeating SPIC. The predictive value of SPECT might be useful for selecting patients that would benefit from SPIC and those who would be better off with additional surgery for improving i.p. distribution or to be transferred to systemic treatment.

Some results in Paper II implied there was a difference in the feasibility of SPIC relating to diagnosis. The impact of diagnosis on survival was de-
monstrated in Paper III, which was in concordance with previous results (Ronnett, Zahn et al. 1995; Schellinx, von Meyenfeldt et al. 1996).

The benefit of complete cytoreduction was verified (Papers I, II and III). Macroscopically radical surgery, later defined as R1-resection, benefited survival in CRC patients (Paper I) which was subsequently confirmed, as complete cytoreduction was associated with improved survival in different diagnoses (Paper III). R1-resection benefited the number of SPIC courses (Paper II) and the number of SPIC courses might affect survival, although no such difference was determined (Paper II). This might be due to the number of SPIC courses given without further surgical intervention being investigated and not the total number of SPIC courses for each patient (Paper II). One conclusion (Paper II) was that SPECT might be an instrument for selecting patients that would benefit from surgical intervention to facilitate drug distribution: this was applied in the group of patients but not investigated (Paper II). It was not possible to predict SPECT data or the feasibility of SPIC with the clinical data (except height), including the ECRS defined in paper II. The correlation of height was controversial as it implied that shorter patients are less likely to benefit from SPIC treatment. A number of patients achieved seven courses despite negligible DV; this might be due to temporary occlusion of the catheter or the abdominal cavity, i.e. methodological error. If these patients were excluded, the relationship between DV and number of courses would be much stronger.

A 30-day morbidity of about 40% was confirmed (Paper III), which is in agreement with previous data (Stephens, Alderman et al. 1999; Elias, Blot et al. 2001; Verwaal, van Tinteren et al. 2004): 90-day mortality was 4%. The 90-day mortality was reported since advanced treatment in the intensive care unit for patients with multiple and emergency organ failure and life-treating conditions has improved increasing the likelihood for 30-days survival, therefore, 90-day postoperative mortality is more realistic for describing treatment-related mortality.

Major morbidity was associated with four clinical variables: PCI, peroperative blood loss, duration of surgery, and stoma formation. PCI, peroperative blood loss, and duration of surgery have previously been reported. (Stephens, Alderman et al. 1999; Witkamp, de Bree et al. 2001b). Stoma formation did not reduce the risk for intra-abdominal complications; however, providing the patient with a stoma was a risk factor for morbidity. A confounding mechanism could influence this finding, as patients with a stoma had higher PCI scores than those without a stoma. In multivariate analysis, stoma creation remained correlated to morbidity and this finding has not previously been reported. The reason for this finding is difficult to explain and a confounding mechanism can not be excluded and we still consider a stoma indicated in selected patients.

Thirty-six patients had multiple tumour involvement on the small bowel surface. In these patients, tumour excision from small bowel serosa or elec-
tro-cautery tumour evaporation was performed and correlated to bowel-associated morbidity. Major small bowel resection was not considered an appropriate method due to the risk of developing short bowel syndrome. However the present finding has made us more reluctant to use diathermy on small bowel.

One concern with IPC is anastomotic dehiscence. Morbidity is related to a number of anastomoses (Glehen, Cotte et al. 2004; Younan, Kusamura et al. 2005), although this contrasts with the work presented here. Intraperitoneal 5-FU after surgery does suppress collagen accumulation (Graf, Ivarsson et al. 1994). However, correlation of anastomotic leakage and IPC-related toxicity have been investigated in clinical studies, and IPC administration per se is not associated with an increased leak rate (Graf, Westlin et al. 1994; Vaillant, Nordlinger et al. 2000). In Paper III, small bowel anastomoses were correlated with increased morbidity, although this was not identified after colon-colon or colorectal anastomoses. This finding could be explained by the routine protection of low colorectal anastomoses by stoma, which is still the current policy for such anastomoses and is in line with data reported by Moran and Cecil (Moran and Cecil 2003) and Verwaal et al. (Verwaal, van Tinteren et al. 2004).

The risk of adverse events is connected to surgical trauma. Some centres advocate that CRS should not be performed if seven or more regions are involved with tumour (Elias, Blot et al. 2001; Verwaal, van Ruth et al. 2003). However, controversies still exist, as decisions should not be based on PCI score only, but rather on tumour histology, patient’s performance status, and the surgeon’s ability to safely perform CRS.

Reports on treatment with CRS + IPC improving HRQL are limited (McQuellon, Loggie et al. 2001; McQuellon, Loggie et al. 2003; Schmidt, Dahlke et al. 2005; Tuttle, Zhang et al. 2006; McQuellon, Russell et al. 2008) and there is scepticism to this treatment modality (Jaaback and Johnson 2006) partly due to concern over negative impact on HRQL. There were clinical indications in Paper I suggesting impact on HRQL during chemotherapy, although these were not separately assessed. These reports included: pain during or immediately after the i.p. infusion; repeatedly suffering from nausea and vomiting during the i.p. treatment period; premature termination of the treatment due to a decline in general status; and refusal of further i.p. treatment.

The patients’ HRQL was assessed (Paper IV) and indicated a decrease at 3-months postoperatively, and a trend of a return towards baseline values in most scales in both instruments at 8-months. Global QoL of the QLQ-C30 and general health of SF-36 were unaffected over time. The changes in the average scores were with the exception of role functioning and dyspnoea in QLQ-C30 and role physical in SF-36 less than 10 points and regarded as minor ((Wyrwich, Bullinger et al. 2005; Osoba, Bezjak et al. 2007)
The mean scores were rather stable over time, although there was a pattern of deterioration at 3 months and a recovery at 8-months, not all patients recover. In the analyses of distribution of scores it was seen that the number of patients having the lowest possible score increased at 8-months. It could be speculated of the reason but apparently, there are patients suffering from complications during the whole span of time covered by the questionnaires.

In studies of patients with advanced cancer, attrition is often marked and usually selective. This was clearly seen in this study as the scores at baseline were worse in the entire group compared to the complete cases. Evaluation of changes over time must then be based on complete cases only, as comparisons that relate to baseline scores of the entire group would be misinterpreted. The complete cases represent patients with a favourable treatment outcome, i.e. at least surviving 8-months and interest and ability to completing the questionnaires, and thus a selection of patients with a better state of health.

The correlation between QLQ-C30 and SF-36 of the same pattern of parallel changes in similar scales is mainly investigated in non-surgical diagnosis treated with systemic chemotherapy (Apolone, Filiberti et al. 1998; Kuenstner, Langelotz et al. 2002). The difference in results could be related to the different sensitivity of the instruments: QLQ-C30 is cancer specific and SF-36 is generic. Cancer related HRQL assessed in palliative settings often reflects the impact of the disease and the systemic treatment. The combination of CRS and IPC is a new treatment modality and existing instruments may not completely address the affect on HRQL after this treatment.

The interpretation of the outcome of the two summary scores in SF-36 is debated and the inter-relationship, relationship, and relative influence of the subscales to the summary components have been investigated (Taft, Karlsson et al. 2001). The relation between the summary components implies that part of the decline at 3-months in PCS can be related to the improvement in MCS; although, the increase at 8-months in MCS, as PCS returns to baseline levels, indicates an overall improvement in HRQL. However this improvement might partly be explained by response shift, as patients try to maintain HRQL despite stressful negative events (Padilla, Grant et al. 1992).

Increased morbidity is generally associated with loco-regional treatment and in particular, with PCI, perioperative blood loss, duration of surgery (Stephens, Alderman et al. 1999; Witkamp, de Bree et al. 2001b), and the application of a entero-cutaneous stoma at loco-regional treatment (Paper III). Application of a stoma had a negative impact on social function at 8-months. Permanent stoma among rectal cancer long-time survivors produces impairment in physical functioning, but improved social functioning compared to rectal cancer patients without a stoma presumably due to poor bowel function (Rauch, Miny et al. 2004). An unexpected result was that high PCI had no impact at preoperative HRQL. PCI influenced several scales negatively at later assessments which were expected as PCI is an indi-
cator of a more advanced disease. Peroperative bleeding, duration of surgery and completeness of CRS had impact at 3-months which implies that the 3-months decrease of HRQL is related to the surgical trauma. But the use of HIPEC also had negative impact on physical functioning at 3-months which implies that the effect is of a combined nature. The use of HIPEC + EPIC in paper III resulted in a longer hospital stay, which might be related to lower physical function. The absence of impact from 30-days morbidity on HRQL was unexpected; this finding might be explained by the selection process of the complete cases and must be seen as one of the limitations of the method using self administered questionnaires as a patient suffering from a severe complication which would be expected to have a low HRQL might not be able to answer the questionnaires. Survival appears dependent on diagnosis (Sugarbaker, Ronnett et al. 1996; Sugarbaker, Schellinx et al. 1996; Sugarbaker 1998) and an associated deterioration would affect HRQL, the absence of impact at 8-months might be explained by the selection process of the complete cases as previously mentioned.

Participation rate was 85% in the study of paper IV and the only detectable difference between those participating and not participating was that non-participants were older. Thus, the group investigated was considered as representative of the PC patients treated at the Department of Surgery at Uppsala University Hospital during this period (November 2001 - March 2005).

The observed unit non-response pattern over time could be explained by attrition or a worsened state of health, as PC, despite adequate treatment, is a fatal disease in many cases (Cunliffe and Sugarbaker 1989; Markman 2003). Although studies by Schmidt et al. (2005) and McQuellon et al. (2003) do not address the impact of loco-regional treatment on HRQL, they assess HRQL in long time survivors (mean, 4 years (Schmidt, Dahlke et al. 2005) and > 3years (McQuellon, Loggie et al. 2003)). The postoperative pattern of HRQL presents a postoperative decline in HRQL and a later recovery at 8-months is shown (Tuttle et al. (Tuttle, Zhang et al. 2006) McQuellon et al. (McQuellon, Russell et al. 2008) and was confirmed in this study. However, the interpretation of the results in the study by Tuttle et al (2006) is hampered by a low number of patients, and the analysis of missing data and patients declining participation is limited in the study by McQuellon et al. (2008). Although later assessments of HRQL in long time survivors would be beneficial, the aim of the present study was to assess the impact of the treatment on HRQL in the post-treatment period; thus, 8-months of follow-up was considered sufficient.
Conclusions

Loco-regional treatment has evolved from a palliative modality in an experimental setting, with the aim of attaining local tumour control or treating malignant ascites with i.p. chemotherapy, into a highly specialised treatment that benefit survival. The treatment of PC with CRS + HIPEC of today, aims at curative results in selected patients as demonstrated in this thesis.

It was confirmed that a combination of CRS and IPC results in improved survival compared with systemic chemotherapy.

The feasibility of repeated intraperitoneal chemotherapy could be predicted by SPECT, which could influence the selection of patients suitable for this treatment.

High morbidity and mortality in this loco-regional treatment is associated with the magnitude of disease and surgical trauma but also to some specific surgical procedures, such as stoma formation and electro-cautery on the small bowel.

Formation of stoma, high PCI and perioperative bleeding, all have a negative influence on various aspects of HRQL. CRS and IPC result in reasonable long-term HRQL despite high initial morbidity and an initial decrease in HRQL. Thus, this treatment appears justified in light of probable life prolongation, and possible cure.
Peritonealcarcinos (PC) utgående från gastrointestinal-, ovarial- och primär bukhinnecancer är ofta förenad med dålig prognos trots konventionell systemisk kemoterapi. Den dåliga effekten av intravenös cytotatika kan bero på dåligt upptag av läkemedlet i sämre kärförsörjda och ibland relativt stora metastaser. Tidigare har tumörreducerande kirurgi av dessa metastaser ej varit framgångsrik, då obehändlad mikrometastasering i bukhinnan leder till recidiv. Rapporter har indikerat en förbättrat överlevnad hos patienter med isolerad PC (frånvaro av generell metastasering) vid loko-regional behandling där cytoreduktiv kirurgi (CRS) kombineras med intraperitoneal cytostatika (IPC).

Kirurgin har utvecklats till ett antal definierade kirurgiska procedurer (peritonektomi) omfattande alla regioner i bukhålan som leder till optimal kirurgi med makroskopisk radikalitet. För att uppnå optimalt behandlingsresultat krävs IPC för eradikering av mikrometastaser som obehändlade leder till recidiv.

Flera prognostiska indikatorer har identifierats såsom histologisk diagnos, föregående kirurgiskt trauma (PSS) och tumörbörda (PCI), vilka på olika sätt påverkar inte bara utfallet av kirurgin utan också genomförbarheten att uppnå makroskopisk radikalitet.

IPC förekommer som hyperterm intraperitoneal cytostatika (HIPEC) där buken behandlas med 42°C cytostatika under slutfasen av det kirurgiska ingreppet. Tidig postoperativ intraperitoneal cytostatika (EPIC) ges i tillägg för optimal behandling vid vissa diagnoser. IPC kan även ges som sekventiell postoperativ intraperitoneal cytostatika (SPIC) distribuerad med kateter till bukhålan via en subkutan injektionsport (Port-A-Cath). Cytostatika ges då dagligen under 6 dagar och upprepas var 4-6 vecka, totalt 8 gånger.

En av svårigheterna vid IPC är att åstadkomma jämn distribution av cytostatika. Vid HIPEC kan detta lösas genom manuell spridning av kirurgen. Vid SPIC kan distributionen begränsas av postoperativt uppkomna sammanväxningar. Distributionen av cytostatika i bukhålan kan uppskattas med single-photon emission computed tomography (SPECT).

Den aggressiva loko-regionala behandlingen medför förhöjd morbiditet och mortalitet där vissa riskfaktorer identifierats som påverkat kirurgins utformning. Denna ökade risk förefaller dock acceptabel då behandlingen ger en ökad överlevnad.
Livskvalitet (HRQL) är en alltmer aktualiserad frågeställning vid olika behandlingar och har rönt särskilt intresse vid behandling av sjukdomar med dålig prognos såsom cancer. Aktuella behandlingar bör utvärderas inte bara vad gäller förlängd överlevnad utan också dess påverkan på patientens HRQL, då ett sammantaget övervägande av dessa faktorer leder till bästa behandling för patienten. Patienter som genomgår loko-regional behandling har ofta en långdragen postoperativ återhämtning där endast ett fåtal studier har beskrivit förloppet i termer av HRQL och hur den påverkas av behandlingen.

Det pågår en omfattande debatt på många håll i världen, även här i Sverige, om den loko-regionala behandlingens värde vid PC. Då behandlingsformen är ifrågasatt är det viktigt att utvärdera, utveckla samt förbättra behandlingsmetoden.

Delarbete I

Detta delarbete syftade till att värdera effekten av tumörreducerande kirurgi följt av SPIC avseende genomförbarhet, bieffekter och överlevnad, jämfört med konventionell systemisk cytostatikatherapi.


Av de planerade IPC kurerna, uppnåddes i median tre kurer. Fyra patienter hade smärta i anslutning till cytostatika infusionen. Två patienter upplevde återkommande illamående och kräkning i samband med infusion. 13 patienter avbröt behandlingen i för tid, 7 av dem p.g.a. kateterrelaterade problem, ileus 1, levermetastaser 1, nedsatt allmäntillstånd 1, två vågrade fortsatt behandling. Hos en patient avbröts behandlingen efter single photon emission computerised tomography (SPECT) av bukhålan påvisat otillräcklig distribution av i.p. infused i bukhålan. En patient i i.p. gruppen var ej möjlig att behandla med kirurgi och i.p. cytostatika.

En drygt fördubblad överlevnad noterades i i.p. gruppen (median 32 månader) jämfört med kontrollgruppen (14 månader). 5-års överlevnad var 28 % i i.p. gruppen och 5 % i kontrollgruppen. I i.p. gruppen noterades en skillnad mellan de 11 radikalt opererade som hade en medianöverlevnad på 34 månader och de 7 icke radikalt opererade som hade en medianöverlevnad på 10 månader.

Denna studie antyder att överlevnaden vid lokalt/peritonealt metastaserad kolorektal cancer kan förbättras genom tumörreducerande kirurgi kombine-

Delarbete II
Det andra delarbetet behandlar klarläggandet av IPC distribution i bukhålan med SPECT undersökning samt möjligheten att förutsäga genomförandet av SPIC behandling utan ytterligare kirurgisk intervention.


SPECT data korrelerade till antalet SPIC kurer (r=0.45). Patienter diagnostiserade med pseudomyxoma peritonei (PMP) erhöll fler, i median 7 SPIC kurer efter SPECT jämfört med patienter diagnostiserade med kolorektal cancer (CRC) som erhöll i median 3 kurer. Föregående systemisk kemoterapi korrelerade negativt till SPECT data och till antalet SPIC kurer. Radikal kirurgi hos patienter med CRC korrelerade med antalet SPIC kurer. Kroppsänd korrelerade positivt till SPECT data och antalet SPIC kurer. Kirurgiska parametrar korrelerade inte med SPECT data eller antalet SPIC kurer.

Det fanns ingen korrelation mellan antalet SPIC kurer uppnådda utan ytterligare kirurgi och överlevnad.

Denna studie pekar på möjligheten att förutsäga antalet SPIC kurer som kan uppnås utan ytterligare kirurgi vilket kan användas för att avgöra vilka patienter som kan ha fördel av förråd kirurgi för att förbättra distributionen eller överföras till systemisk behandling. Kortväxthet och föregående systemisk kemoterapi var associerad med sämre genomförbarhet av SPIC.

Delarbete III
Detta delarbete fokuserade specifikt på omfattningen och eventuella orsaker till komplikationer efter loko-regional behandling av PC. Överlevnad utifrån histopatologiskt ursprung analyserades också.

Studien av 123 konsekutiva patienter vid Uppsala Akademiska Sjukhus mellan maj 1991 och november 2004 innefattar PC av olika histologiskt ursprung: kolon 51, rektum 8, PMP 52 (höggradig 38, låggradig 14). 85 patienter erhöll SPIC, 28 HIPEC+EPIC, 2 HIPEC+EPIC+SPIC. 8 patienter erhöll ej IPC. Arbetet visade att allvarliga komplikationer inom 30 dagar in-
träffade postoperativt hos 41 % av patienterna och behandlingsrelaterade dödsfall inom 90 dagar hos 4 % av patienterna. Möjliga orsaker till komplikationer var; diatermibehandling av tumör på tunntarm, uppläggning av stomi, perioperativ blödning, lång operationstid, samt hög tumörbörda i bukhålan.

Sambandet mellan stomi och komplikationer är ej tidigare visat, övriga riskfaktorer för komplikationer är tidigare kända och bekräftas i denna studie. Resultatet har bidragit till att vikten av en noggrann selektion av patienter till loko-regional behandling har kommit i fokus samt undvikande av diatermibehandling av tumörer på tunntarmen.

**Delarbete IV**

Avhandlingens fjärde och sista delarbete behandlar patientens upplevelse och livskvalité (HRQL) efter loko-regional behandling av PC. Redovisning av HRQL hos dessa patienter har varit mycket begränsad i litteraturen, där man huvudsakligen beskrivit situationen vid olika tidpunkter. I detta arbete tillfrågades 75 patienter tiden november 2001 till mars 2005 varav 11 avstod från att delta. Studien innefattade 64 patienter där behandlingen och kliniska variablars påverkan på HRQL över tiden undersöcktes. Två livskvalitéinstrument, EORTC QLQ-C30 och SF-36 användes preoperativt, vid 3- och 8-månader postoperativt.

De patienter som avstod från att delta, skilde sig från deltagarna endast genom högre ålder. Preoperativt besvarade 62 (97 %) patienter EORTC QLQ-C30 och 60 (94 %) patienter SF-36. Resultaten visade att den generella livskvalitén var sänkt hos patienterna före operation. Hos de patienter som svarat vid alla tre tillfällen registrerades övergripande en tydlig försämring de första 3 månaderna efter loko-regional behandling, som dock förbättrades upp mot preoperativ nivå 8 månader efter operationen, utfallet påvisade viss skillnad i resultat mellan de två olika instrumenten.

Kliniska variabler som peroperativ blödning, operationstidens längd och radikal kirurgi påverkade HRQL (negativt) vid 3 månaders uppföljning vilket talar för att sänkningen av HRQL vid 3-månader är av kirurgiskt ur sprung. Dock ger användande av HIPEC ökad smärta vid 3-månader, sannolikt är det en kombinerad effekt av CRS och IPC. Patienter med perioperativ blödning över medianvärde hade sämre värden i flera skalar vid 3 månader som förbättrades vid 8 månader, dock kvarstod bland annat nedsatt global livskvalitet och rollfunktion. Patienter som fick stomi hade lägre social funktion vid 8 månader. Hög tumörbörda minskade global livskvalitet och social funktion. Behandling med HIPEC minskade fysisk funktion vid 3 månader, men hade ingen påverkan vid 8 månader. Förekomst av 30-dagars postoperativ morbiditet påverkade ej HRQL. Diagnos gav ingen påverkan vid 3 eller 8 månaders uppföljning. En av problemställningarna med självskattade HRQL
enkäter är att svar endast erhålls från de patienter som har vilja och förmåga att besvara instrumenten, vilket kan förklara en del av utfallet för kliniska variablers påverkan på HRQL.

Slutsatsen av detta delarbete är, att de undersökta patienterna är representerativa för denna grupp av patienter och att denna behandling innebär ett långdraget postoperativt förlopp med nedsatt livskvalitet som sedan förbättras över tiden. Påverkan av de kliniska parametrarna, indikerar att kirurgin sannolikt har stor betydelse för den initiala nedgången av livskvaliteten.

Slutsatser

Loko-regional behandling med cytoreduktiv kirurgi kombinerat med i.p. cytostatika har utvecklats från en experimentellt betingad palliativ behandling, där målet varit att uppnå lokal tumörkontroll eller att behandla malign ascites med i.p. cytostatika, till en högspecialiserad behandling som ger förlängd överlevnad och bot hos selekterade patienter.

En av begränsningarna vid upprepad i.p. kemoterapi är bildandet av sammanväxningar i bukhålan som ger försämrad distribution av cytostatika. Möjligheten att upprepa i.p. cytostatika kan förutsättas genom SPECT, vilket kan påverka selektionen av vilka patienter som är lämpliga för denna behandling.

Loko-regional behandling är förknippad med hög morbiditet och mortalitet som är associerade med specifika kirurgiska procedurer såsom anläggande av stomi och diatermisk behandling på tunntarm, denna kunskap tillämpas idag vid många PC-centra.

Denna aggressiva loko-regionala behandling har en negativ postoperativ påverkan på livskvaliteten som dock återtas över tiden. Den loko-regionala behandlingens nackdelar förefaller acceptabla i ljuset av förlängd överlevnad och möjlighet till bot.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)