Clinical and Experimental Studies in Peritoneal Metastases from Gastric Cancer

BO HULTMAN
Gastric cancer (GC) is one of the leading causes of death in the world, and peritoneal metastases (PM) are a major site of recurrence. PM from GC implies a poor prognosis, with median overall survival (mOS) approximately 3 months and no survival at five years.

The aims of this thesis were to explore the incidence and evaluate prognostic factors for mOS of PM from GC in a defined population; to investigate the outcome of a new multimodal treatment; to analyse the treatment costs, and to investigate differences in drug sensitivity between individual patient samples and between various tumors.

The incidence of loco-regional advanced GC was 3.8 per 100,000 person-years. Synchronous loco-regional GC in combination with synchronous distant metastasis was a negative prognostic factor while chemotherapy and good performance status, and radiotherapy plus chemotherapy were positive prognostic factors. There were no significant differences in mOS for the group of patients included during the period 2000-2004 versus 2005-2009, and this lack of improvement in mOS during the past decade justifies new treatment approaches.

In a Phase II study of patients treated with neoadjuvant systemic chemotherapy followed by cytoreductive surgery + hyperthermic intraperitoneal chemotherapy, mOS was 14.3 months and for patients with macroscopically radical surgery mOS was 19.1 months. The mean overall cost of the loco-regional treatment was $145,700 compared to $59,300 with systemic chemotherapy treatment.

In an ex vivo chemo-sensitivity test, it was determined that GC samples were equivalent to colorectal cancer in chemo-sensitivity to standard drugs and targeted drugs, whereas ovarian cancer samples were more sensitive. The individual GC samples varied considerably in sensitivity to increasing concentrations of the drugs, arguing for individualized drug selection. The incidence of loco-regional advanced GC was more common than previously reported and there were no improvements in mOS over the past decade. The mOS for patients with neoadjuvant systemic chemotherapy followed by macroscopically radical cytoreductive surgery + hyperthermic intraperitoneal chemotherapy was better than in recent reports on treatment with systemic chemotherapy. Treatment of advanced GC patients is costly irrespective of treatment modality. The GC samples varied considerably between individuals in terms of sensitivity to increasing concentrations of the drugs and were comparable to colorectal cancer in chemo-sensitivity.

**Keywords**: gastric cancer, peritoneal metastases, peritoneal carcinomatosis, epidemiology, prognostic factor, survival, neoadjuvant chemotherapy, cytoreductive surgery, HIPEC, health economy, costs, systemic chemotherapy, cultured tumor cells, fluorometric analysis, cancer drug tests, chemo-sensitivity, anti tumor drugs.

Bo Hultman, Uppsala University, Department of Surgical Sciences, Colorectal Surgery, Akademiska sjukhuset ing 70 1 tr, SE-751 85 Uppsala, Sweden.

© Bo Hultman 2013

ISSN 1651-6206
ISBN 978-91-554-8635-8
urn:nbn:se:uu:diva-197776 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-197776)
“Wisdom is not a product of schooling but of the lifelong attempt to acquire it.”

Albert Einstein

To my beloved wife Fabiola and daughters Natalie & Caroline.
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


Reprints were made with permission from the publisher.
## Contents

Introduction...................................................................................................11  
Background.................................................................................................12  
Aim of the Thesis........................................................................................26  
   Specific aims .........................................................................................26  
Patients and methods..................................................................................27  
   Ethical considerations ........................................................................27  
   Study I .................................................................................................27  
   Study II ...............................................................................................28  
   Study III .............................................................................................28  
   Study IV .............................................................................................28  
Statistical Methods.....................................................................................30  
   Study I .................................................................................................30  
   Study II ...............................................................................................30  
   Study III .............................................................................................30  
   Study IV .............................................................................................30  
Results...........................................................................................................31  
   Study I .................................................................................................31  
   Study II ...............................................................................................34  
   Study III .............................................................................................36  
   Study IV .............................................................................................36  
General discussion.......................................................................................43  
Conclusions...................................................................................................50  
Future perspectives ....................................................................................51  
Sammanfattning på svenska........................................................................52  
   Delarbete I ..........................................................................................52  
   Delarbete II ........................................................................................53  
   Delarbete III ......................................................................................54  
   Delarbete IV ......................................................................................54  
   Avhandlingens nyhetsvärde ...............................................................56
Abbreviations

AJCC American Joint Committee on Cancer
ATP-CRA Adenosine Triphosphate-based Chemotherapy Response Assay
CC Completeness of Cytoreduction Scores
CEA Carcinoembryonic Antigen
CF Cisplatin+5-fluorouracil
CI Confidence Intervals
C_{max} The maximum concentration reached during intraperitoneal chemotherapy
CRC Colorectal Cancer
CRS Cytoreductive Surgery
ECF Epirubicin+Cisplatin+5-fluorouracil
ELF Etoposide+Leucovorin+5-fluorouracil
EOX Epirubicin+Oxaliplatin+Capecitabine
EPIC Early Postoperative Intraperitoneal Chemotherapy
EuroQoL European Quality of Life
5-FU 5-fluorouracil
FLOX 5-fluorouracil+Leucovorin+Oxaliplatin
FMCA Fluorometric Microculture Cytotoxicity Assay
FOLFIRI Leucovorin+5-fluorouracil+Irinotecan
GC Gastric Cancer
HIPEC Hyperthermic Intraperitoneal Chemotherapy
IPC Intraperitoneal Chemotherapy
IC_{50} The 50% Inhibitory Concentration
ILF Irinotecan+Leucovorin+5-fluorouracil
KPS Karnofsky Performance Status Scale
NIPS Neoadjuvant Intraperitoneal-Systemic Chemotherapy
NCI CTC 3.0 The National Cancer Institute’s Common Toxicity Criteria version 3.0
Nordic FLv Bolus 5-fluorouracil+Leucovorin
mOS Median Overall Survival
PM Peritoneal Metastasis
PMP Pseudomyxoma Peritonei
PCI Peritoneal Cancer Index
QALY Quality Adjusted Life Year
QoL Quality of Life
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
<td>Survival Index</td>
</tr>
<tr>
<td>TDs</td>
<td>Targeted Drugs</td>
</tr>
<tr>
<td>TS-1</td>
<td>Tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate</td>
</tr>
</tbody>
</table>
Introduction

The incidence of gastric cancer (GC) is falling. Although it was the most common neoplasm worldwide in 1975, it is currently the fourth most common cancer in the world (8% of all cancer cases) and it is the second most common cause of death globally (10% of all cancer deaths). Adenocarcinoma represents 90% of all gastric malignancies and it is spread widely across different regions of the world, with the highest incidence in East Asia, eastern Europe and South America. In Sweden GC has a comparatively low incidence of 11.2 per 100,000 person-years for males and 7.8 per 100,000 person-years for females, representing 1.6% of all cancer cases in the country. Symptoms usually develop at a late stage, and the incidence of advanced GC (Stage IV) is 20-30% from GC in general. Median survival in Stage IV cancer is up to 9 months with no long-term survival. For patients with PM from GC, median overall survival (mOS) is 3 months, if patients treated with an aggressive approach (intraperitoneal chemotherapy or cytoreductive surgery (CRS) followed by intraperitoneal chemotherapy) are excluded.

The most common site for metastases is the peritoneum, in two thirds of cases synchronous and in one third metachronous. In recurrent disease, 50% of the patients with GC has peritoneal metastases (PM) and in patients who undergo resection with curative intent for GC it is 10-20%. However, the true incidence, prognosis, treatment and outcome of patients with PM in GC are not well-known. The most common treatment for advanced GC is palliative chemotherapy, with a median overall survival (mOS) of 8-17 months. In cases with non-curable GC (distant lymph node metastases, liver metastases, remnant tumour or PM) treated with palliative resection, an mOS of 7-8 months has been observed and in patients not actively treated, it is shorter. This poor outcome of PM from GC underlines the importance of further investigation and the evaluation of a new treatment method that may improve survival rates.
Background

Histopathology
GC tumours are usually staged according to TNM\textsuperscript{18} (T = depth of invasion, N = presence and number of nodal metastases, M = metastases). They are histologically classified into poorly, moderately and well differentiated carcinoma\textsuperscript{19}, using differentiation grades from Lauren’s classification\textsuperscript{20} (diffuse, mixed and intestinal types, respectively); morphologically classified as adenocarcinoma or signet ring cell carcinoma and macroscopically classified by pathological type according to Borrmann’s system\textsuperscript{21} (polyp-like, ulcer with wall-like edge, ulcer without wall-like edge and diffuse/linitis plastica, respectively).

Stage-specific survival
There are many theories about the spread of incidence between geographic regions. Genetic differences have been speculated, but there is overwhelming epidemiological proof that the major reason is different incidences of Helicobacter pylori infection\textsuperscript{22,23}. The corrected five-year survival rate for surgery with potentially curative intent in Japan for all patients with GC is 71%, and in western countries 44-47\%\textsuperscript{24}. In the U.S.A., Stage III is the most common (35%), followed by Stage IV (30%), but in Japan Stage I is the most common (46%), followed by Stages III (22%) and IV (21\%)\textsuperscript{4}.

The reason for a majority of high-level stages at the time of diagnosis is that symptoms often present late (weight loss, anorexia, anaemia, fatigue, bleeding, obstruction, dysphagia, vomiting) and there is also a lack of surveillance programmes.

The major factor for overall survival in GC is the stage reached at diagnosis. For early GC (T1 according to TNM\textsuperscript{18} or in other words Stages I and II, T2N0-1 and T3N0 excluded) there is a five-year survival rate of 70-95\%\textsuperscript{25}.

For Stage III (T2N2, T3N1-2 and T4N0) there is a moderate five-year survival rate of 19-61\% and for Stage IV (advanced GC) the five-year survival rate is zero\textsuperscript{5,6}. During the nineties, three studies\textsuperscript{26-28} examined the effect of palliative systemic chemotherapy for patients with advanced GC: mOS was >7.5-12 months in the treated group and 3-4 months in the control group (best supportive care).
Liver metastases are not the major cause of failure and death in patients who have undergone surgery. In autopsy series, 30% of patients who died of GC had liver metastases, whereas 50% of them had peritoneal metastasis (PM)\(^{10}\). Thus, PM was a major site of recurrence even after extended lymphadenectomy, although the rate of local recurrence was considerably lower compared with more limited surgery\(^{10}\).

**Treatment of GC with curative intent**

At the beginning of 1817, Napoleon Bonaparte was treated for GC with large doses of tartar emetic and calomel. In 1879 the French surgeon Pean performed the first gastric resection for cancer\(^{29}\) but unfortunately the patient died five days postoperatively. The best treatment for early GC limited to the mucosa and submucosa is surgical, with a five-year survival rate of 70-95\(^{25}\). Surgical treatment for Stages I to III of the disease is usually total gastrectomy or subtotal gastrectomy in combination with resection of perigastric nodal stations (D1 lymphadenectomy)\(^{21}\). In some centres a more radical resection is performed: in addition to the perigastric nodal stations, nodes along a. gastrica sin, a. hepatica communis, truncus coeliacus, a. lienalis and the splenic hilum are also resected (D2 lymphadenectomy)\(^{21}\). This method improves overall survival and is today’s recommended surgical approach globally for patients with resectable GC\(^{30}\). An option is a modified D2 lymphadenectomy, the so-called “D1+” (resection of perigastric nodal stations plus nodes along a. gastrica sin, a.hepatica communis and truncus coeliacus). D1+ offers the advantage of a decreased risk for iatrogenous bleeding from the spleen during node resection which makes splenectomy necessary. If splenectomy can be avoided, morbidity and mortality are decreased. Historically there has been high in-hospital mortality (6-33\%) irrespective of surgical method for patients with GC in general. There has also been high severe morbidity for gastrojejunostomy, subtotal or total gastrectomy (20-48\%), with gastrojejunostomy close to 20\% and total gastrectomy close to 48\%\(^{31}\). With intraoperative assessment of non-curable disease, mOS for patients undergoing exploratory laparotomy with biopsy alone or gastrojejunostomy was 4-6 months with a zero 2-year survival rate, but this improved with palliative resection (16\% 2-year survival)\(^{31}\).

There has long been a lack of information to confirm the beneficial effects of neoadjuvant and adjuvant chemotherapy in patients who undergo resection with curative intent\(^{32}\) but during the past decade, two major studies have demonstrated improved mOS with postoperative radio-chemotherapy (the INT 0116 study)\(^{33}\) and perioperative chemotherapy (the MAGIC study)\(^{25}\) to curative resection for patients with no evidence of distant metastases (DM) or locally advanced disease. Yu et al. demonstrated a survival benefit with early postoperative intraperitoneal chemotherapy (EPIC) in patients with curative resections on serosal invasion\(^{34}\). There is an
on-going, international, multi-centre study, whose aim is to investigate the potential in adjuvant HIPEC in patients without PM undergoing curative surgery. This treatment may be an option in the future.

Treatment of non-curable GC
Advanced GC has a tumour doubling time of 69-305 days\(^{35}\), and PM from GC is an extremely aggressive tumour disease, with an estimated tumour doubling time of 18-60 days\(^{35}\). Moreover, if the only treatment is best supportive care, the disease is often fatal within a few months\(^{7,36}\). Based on current knowledge, this patient group is mostly treated with palliative chemotherapy\(^{12,26,27}\) and sometimes in combination with radiotherapy\(^{33}\).

Surgical treatment
The choice of treatment during an operation has always been made on the basis of the disease’s extent: exploratory laparotomy with biopsy alone, gastrojejunostomy, subtotal (Figure 1) or total gastrectomy and D2 lymphadenectomy\(^{34}\). In a randomised trial from Yu et. al.\(^{34}\) with GC patients treated with EPIC as an adjuvant treatment after gastric resection vs. surgery only, the 5-year survival rate was increased in patients with Stage III disease (53% vs. 23%) and with Stage IV disease (28% vs. 5%), favouring EPIC vs. surgery alone. However, this came at the price of increased mortality (6.4% vs. 1.6%) and increased morbidity (29% vs. 20%). In more advanced disease, patients often have metastasis in the N3 nodes (usually surrounding the superior mesenteric artery, retro-pancreatic region and hepatoduodenal ligament) or even another level away, in the N4 nodes (para-aortic region)\(^{37}\). This is probably a major reason for low mOS in the group of patients undergoing palliative resection.

More recently, with better options for staging GC, our understanding of high morbidity and mortality, combined with low mOS for palliative surgery, means that selectively applied surgery as a treatment is also an option.
Systemic chemotherapy treatment

There are various palliative regimens of systemic chemotherapy treatment for advanced GC, but they all have very similar mOS. In 2002, a meta-analysis revealed that some patients with advanced GC receive clinically important benefits from palliative chemotherapy \(^{32}\). In a randomised comparison of systemic chemotherapy (etoposide/leucovorin/5-fluorouracil; ELF) vs. best supportive care for patients with advanced GC, mOS was 8 months in the treated group and 5 months in the control group, and the quality of life (QoL) was prolonged or improved for a minimum period of 4 months in the treated group\(^{12}\).

Recently there has also been an improvement in mOS in randomised studies for a new generation of palliative chemotherapy drugs in patients with advanced GC, including irinotecan, docetaxel, oxaliplatin and capecitabine. Irinotecan/5-fluorouracil/leucovorin (ILF) revealed a higher response rate than ELF (35% vs. 17%)\(^{38}\) and than cisplatin/irinotecan (34% vs. 26% and 4 months’ increased mOS)\(^{39}\) and a higher response rate than cisplatin/5-fluorouracil (CF) in a Phase III study\(^{40}\). In another Phase III study (TAX 325) cisplatin/docetaxel/5-fluorouracil (DCF) demonstrated an increased response rate (39% vs. 23%) and two months’ increased mOS over CF\(^{41,42}\). Since the results of the REAL-2 study have become official\(^{43}\), EOX
(epirubicin/oxaliplatin/capecitabine) has more or less become the standard
treatment for GC. A meta-analysis from 2006\textsuperscript{44} demonstrated the fact that
anthracyclines have an independent value in the treatment of GC. In a
Swedish randomised Phase II study (GATAC trial)\textsuperscript{45}, there was no
difference between docetaxel/5-fluorouracil vs. irinotecan/5-fluorouracil.
Overall survival was 11 months in both arms of the study. FLOX (5-
fluorouracil/leucovorin/oxaliplatin) and FOLFIRI (leucovorin/5-
fluorouracil/irinotecan) have also been applied in recent years. Thus, the
standard treatment for patients with PM from gastric cancer is systemic
chemotherapy\textsuperscript{7,46}.

Radiotherapy as a palliative treatment for advanced GC is mostly loco-
regional, to reduce symptoms from skeletal or skin metastasis\textsuperscript{37}.

\textit{Targeted therapy}
A new field in the treatment of advanced GC is a group of drugs that attacks
the cell cycle of tumours, angiogenesis, cell signalling, matrix
metalloproteinases and growth factors. Bevacizumab, panitumumab and
trastuzumab have been studied in Phase I-III studies and it is apparent that
trastuzumab is a promising agent in this group in combination with cisplatin
and capecitabine or 5-fluorouracil (5-FU), with an mOS of 14 months\textsuperscript{48}. In a
recent clinical trial using modified docetaxel, cisplatin, and 5-FU (mDCF) in
combination with bevacizumab, mOS of 17 months was observed\textsuperscript{15}.

\textit{Loco-regional treatment of peritoneal metastasis}
A growing treatment option for PM (Figure 2) is CRS followed by
intraperitoneal chemotherapy, e.g. hyperthermic intraperitoneal
chemotherapy (HIPEC), with promising results for selected patients with
colorectal cancer\textsuperscript{49-52} (up to a 45\% 5-year survival rate). This treatment has
resulted in an 85\% 5-year survival rate in selected patients with
pseudomyxoma\textsuperscript{53, 54}. The rationale for CRS is the resection of all visible
tumours from the peritoneum and it is important when selecting patients to
exclude all those with DM or patients who cannot tolerate advanced
treatment. Loco-regional chemotherapy, i.e. intraperitoneal chemotherapy
(IPC), has been shown to provide higher chemotherapy concentrations in the
PM nodules compared to systemic chemotherapy treatment\textsuperscript{55}. CRS+HIPEC,
sometimes in combination with early postoperative intraperitoneal
chemotherapy (EPIC), in patients with gastric cancer and PM has
demonstrated an mOS ranging from 8.0 to 11.5 months\textsuperscript{56-61}. There is no
technical difference in the performance of CRS for PM from gastric cancer
compared to PM from colorectal cancer\textsuperscript{62-64}. However, data are still lacking
on the possible benefits from such an approach in patients with PM from
gastric cancer and there is debate as to whether this treatment should be
applied in this disease\textsuperscript{46}.
Cytoreductive surgery

Cytoreductive surgery (CRS), i.e. the removal of all macroscopic PM, is usually performed according to the Sugarbaker method. Briefly, depending on disease extent, one or more of the following surgical procedures is carried out: total or subtotal gastrectomy with D2 lymphadenectomy; greater omentectomy; ± cholecystectomy and dissection of the duodenal-hepatic ligament; ± splenectomy; ± parietal peritonectomy; ± right and left upper quadrant peritonectomy; ± colon and small bowel resection; ± pelvic peritonectomy; ± rectosigmoid resection and ± hysterectomy ± salpingoooforectomy.

Tumour load and completeness of cytoreduction for PM are recorded during the CRS procedure, using the Peritoneal Cancer Index (PCI) and Completeness of Cytoreduction Scores (CC) respectively. The PCI (range 1-39) consists of lesion size scores in 13 different regions of the abdomen: 0 = no tumour seen, 1 = tumour up to 0.5 cm, 2 = tumour up to 5 cm and 3 = tumour >5 cm. The PCI score is calculated by adding together the lesion size scores for the 13 regions.

Figure 2. Peritoneal metastases in colon and small bowel.
Figure 3. The Peritoneal Cancer Index (PCI) is a method of measuring the tumour load. The PCI (range 1-39) consists of lesion size scores in 13 different regions of the abdomen: 0 = no tumour seen, 1 = tumour up to 0.5 cm, 2 = tumour up to 5 cm and 3 = tumour >5 cm. The PCI score is calculated by adding together the lesion size scores for the 13 regions. This figure is published with permission from Dr. Sugarbaker and Dr. Yutaka Yonemura.
Hyperthermic intraperitoneal chemotherapy (HIPEC)

Hyperthermic intraperitoneal chemotherapy (HIPEC) is targeted to treat microscopic PM, and is mostly administered according to either the open (Coliseum) technique\textsuperscript{65} (Figure 5) or the closed technique\textsuperscript{67}. In the Coliseum technique, the skin edges of the abdomen are fixed to the frame of a retractor and a plastic sheet covers all. The hyperthermic (42°C to 44°C) chemotherapy solution enters the abdominal cavity via an intra-abdominal drain and leaves the abdominal cavity via four intra-abdominal drains. During the process, the surgeon stirs the solution by hand through a small opening in the covering plastic sheet. The closed technique is similar, but the abdomen is sutured together before the HIPEC procedure begins. In both methods, the chemotherapy solution circulates for 30–90 minutes, depending on which cytotoxic agent is used. These are usually oxaliplatin, doxorubicin, cisplatin, mitomycin C\textsuperscript{63} or irinotecan, and a majority of them are cell-cycle non-specific (i.e. drugs that act during any phase of the cell cycle). There is an on-going debate about the best choice of carrier solutions for the chemotherapeutic agents: hypotonic, isotonic or hypertonic. The gold standard is hypertonic solutions\textsuperscript{68}\textsuperscript{69}, with a reduced peritoneal clearance and prolonged drug activity compared to hypotonic solutions. In animal models, isotonic solutions offer an advantage with decreased systemic toxicity and retention of artificial ascites\textsuperscript{70} while hypotonic solutions have a pharmacokinetic advantage\textsuperscript{71}\textsuperscript{72}. A disadvantage of hypotonic solutions is
thrombocytopenia and postoperative bleeding. Hyperthermia damages PM through protein denaturation, the inhibition of oxidative metabolism in the microenvironment. It weakens DNA repair and augments the cytotoxic effect of some drugs.

*Figure 5. Hyperthermic intraperitoneal chemotherapy, open technique. This figure is published with permission from Dr. Mahteme.*

**Early postoperative intraperitoneal chemotherapy**

Another type of intraperitoneal chemotherapy is normothermic EPIC. The rationale for using EPIC is to eliminate the microscopic residual disease remaining from the contamination of cancer cells from the serosa, transected lymphatic channels or lost blood from the cancer specimen, or from resected PM. Another rationale is the possibility of repeated treatments and slow drug release in combination with cell-cycle specific drugs. EPIC is given daily during the first five postoperative days via the four intra-abdominal drains left in place after surgery. New solution is given every 24 hours. Both the route (intraperitoneal) and the timing (perioperative, before the formation of intra-abdominal adherences) are important factors for efficacy. The cytotoxic agents used most often are mitomycin C and 5-fluorouracil in combination with intravenous leucovorin or paclitaxel, and a majority of them are cell-cycle specific, i.e. drugs that act only during a specific portion of the cell cycle.
**Bidirectional chemotherapy**

A new and promising neoadjuvant therapy, so-called neoadjuvant intraperitoneal-systemic chemotherapy (NIPS), has recently been introduced by Yonemura et al.\(^8^3\). According to Dr. Yonemura’s protocol, patients are treated with oral TS-1 (tegafur, 5-cloro-2, 4-dihydroxypyridine and potassium oxonate)\(^8^4\) for 21 days and are synchronously given cisplatin and docetaxel with 500 ml of saline into the peritoneal cavity through a peritoneal port on days one, eight and 15. After NIPS, CRS+HIPEC follow. The rationale for this is to assault PM from two sides: from the peritoneal cavity (cisplatin and docetaxel) and from the subperitoneal blood vessels (TS-1), with repeated loco-regional and systemic chemotherapy.

With a similar technique, Kitayama et al. recently reached an mOS of 23.6 months with bidirectional treatment of systemic TS-1 (5-cloro-2, 4-dihydroxypyridine and potassium oxonate) and intraperitoneal paclitaxel followed by salvage gastrectomies in 100 patients, 90% of whom had PM detected all over the abdominal cavity\(^8^5\).

**Tailored treatment strategies**

One way to tailor drug treatment could be to test the chemo-sensitivity for tumours. Extrapolation from an ex vivo assay to the clinic is difficult. In vivo there is a more complex environment for the tumour cells regarding the immune system, pharmacokinetics and the influence of the surrounding stroma. There is an on-going discussion amongst medical oncologists on the potential advantage of an individual approach for drug selection. There are some studies trying this approach. Kubota and Weisenthal evaluated a new method of selecting adjuvant chemotherapy for advanced GC in a retrospective study\(^8^6\), and they revealed that drug sensitive ex vivo corresponded to improved survival. By using an adenosine triphosphate-based chemotherapy response assay (ATP-CRA) Kim et al.\(^8^7\) measured ex vivo chemo-sensitivity in patients with chemo-naïve advanced GC. They were treated with a paclitaxel-cisplatin combination. ATP-CRA might predict clinical response to paclitaxel and cisplatin with high accuracy: specificity and sensitivity were 96% and 46%, and positive and negative predictive values were 86% and 76%. Higher response rates (86%) were found in the in vitro chemo-sensitive group versus the chemo-resistant group (24%), but there were no differences in progression-free survival or mOS. It is important to keep in mind, that these data have not been validated in an independent cohort. The study from Kim et al. does not prove that drug selection based on an ex vivo assay are advantageous compared with the current empirical selection.
**Fluorometric microculture cytotoxicity assay**
The fluorometric microculture cytotoxicity assay (FMCA) has an established ability to predict clinical drug efficacy in solid tumours and in haematological malignancies, both at the diagnosis and the individual patient level. In detail, tumour cells from patient samples (5,000 cells per well for the solid tumour samples and 40,000 cells per well for MNCs and leukaemia) in 45 µl are seeded in the drug-prepared plates. The culture medium is washed away after 72 hours’ incubation and fluorescein diacetate is added to all wells. After incubation, the fluorescence from each well is read and displayed as survival index (SI): blank values are subtracted from the fluorescence of the test (expressed as a percentage of control cultures). The 50% inhibitory concentrations (IC$_{50}$, i.e. the drug concentration producing an SI of 50%) are calculated from the SI results.

**Patient selection for loco-regional treatment**
CRS+HIPEC is an extremely demanding treatment for the patient. This is why performance status is an important factor in the selection process. Performance status is usually measured with either the WHO International Classification of Functioning scale or the Karnofsky Performance Score (KPS). The WHO performance status can be converted to KPS with a conversion system based on a recommendation from the American Joint Committee on Cancer (AJCC) (see Table 1). Buccheri et al. suggested a modification with a three-point conversion table: grade 1 = WHO 0-1 = KPS 80-100, grade 2 = WHO2 = KPS 60-70 and grade 3 = WHO 3-4 = KPS 10-50.
Table 1. WHO International Classification of Functioning scale and the Karnofsky Performance Score.

<table>
<thead>
<tr>
<th>WHO</th>
<th>Grade</th>
<th>Scale</th>
<th>Karnofsky</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully active, able to carry on without restriction.</td>
<td>0</td>
<td>100</td>
<td>Normal, no evidence of disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>Able to carry on normal activity, minor symptoms.</td>
</tr>
<tr>
<td>Restricted activity, but able to carry out light house-work and office work.</td>
<td>1</td>
<td>80</td>
<td>Normal activity with effort, some symptoms of disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>Cares for self but unable to carry on normal activity or active work.</td>
</tr>
<tr>
<td>Ambulatory and capable of all self-care, but not work activities. Up and about &gt; half of waking hours.</td>
<td>2</td>
<td>60</td>
<td>Requires occasional assistance, but able to care for most personal needs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>Requires considerable assistance and needs medical care.</td>
</tr>
<tr>
<td>Only limited self-care. Up and about &lt; half of waking hours.</td>
<td>3</td>
<td>40</td>
<td>Requires assistance and medical care. Disabled.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>Hospital admission is indicated. Severely disabled.</td>
</tr>
<tr>
<td>No self-care. Not able to be up and about. Completely disabled.</td>
<td>4</td>
<td>20</td>
<td>Hospital admission and active supportive treatment necessary. Very sick.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>Rapidly fatal processes progressing. Moribund.</td>
</tr>
</tbody>
</table>
Quality-adjusted survival
There are no cost-effectiveness analyses in studies on GC with PM and there is also very little information in the literature about quality-adjusted life-years. Thus, new therapies must be assessed, not just in terms of clinical outcome but also in terms of costs. The impact of a disease can be measured in quality-adjusted life-years (QALY), which include both the quantity and quality of life. QALY is calculated as survived years multiplied by health utility weights (HUW). One year with perfect health is QALY 1.0 whereas one year with 50% health is QALY 0.5.

Health utility weights
In order to estimate QALYs, values for the patients’ health utility must be estimated. When utility weights for each state are obtained, they are multiplied by the time in each state and added together, with their sum being the QALY, e.g. half a year in the state 0.5 plus half a year in the state 0.7 gives 0.5 multiplied by 0.5 plus 0.5 multiplied by 0.7, i.e. 0.25+ 0.35 = 0.6. Sometimes authors use the terms “quality of life weight”, “value” or “preference score” instead of “utility”. Utility weights can be measured directly in patients by using preference-based techniques (i.e. time trade-off or standard gamble) or can be assigned indirectly by using a utility-weighted health status index (i.e. Quality of Well-Being Scale, EuroQoL or Health Utility Index). If no data on health utility in the patients are available, HUW can be estimated and derived for the patients based on the WHO performance status or KPS. KPS can be converted directly to HUW by a linear scale where HUW=KPS/100. WHO performance status can be converted to KPS with a conversion system based on a modification of the recommendation by Buccheri et al., and the WHO International Classification of Functioning, Disability and Health. Thus, WHO 0 is converted to HUW 0.980; WHO 0-1 to 0.955; WHO 1 to 0.855; WHO 1-2 to 0.755; WHO 2 to 0.630; WHO 2-3 to 0.505 and WHO 3 to 0.275. If data are missing, HUW can be based on an estimated utility weight, e.g. HUW 0.3/120 for every tenth of a month when a patient is hospitalised; 0.40/120 for every tenth of a month in a hospice; 0.45/120 for every tenth of a month when assistance by medical staff at home is indicated; 0.50/120 for every tenth of a month with parenteral nutrition; 0.60/120 for every tenth of a month during the first month postoperatively, if addicted to morphine, in periods with many side effects, fever or fatigue; 0.80/120 for every tenth of a month during the second month postoperatively, if experiencing pain or last month alive; 0.90/120 for every tenth of a month three months postoperatively, if experiencing diarrhoea or vomiting and 1.00/120 for every tenth of a month without residual tumour and more than three months
postoperatively or if information is recorded in a journal, like “feel very
good”.

The cost per life-year gained is defined as the difference in costs between
a treated group and a control group, divided by the difference in life-years
for the treated group and the control group93. The cost per QALY gained is
defined as the difference in costs for the two groups divided by the
difference in QALY for the two groups93.

Health Economy
Medical research will continue to produce an increasing number of
alternatives for the detection, prevention and treatment of diseases. Limited
budgets will not allow health-care systems to make all of the alternatives
available for everybody. Sweden and some other countries (United
Kingdom, Canada and Australia) approach this by guiding resource-
allocation decisions according to frequently used, formal health-economic
analysis93, the most popular approach currently being the cost-effectiveness
analysis. In the United States for many years, US$50,000/QALY has
frequently been quoted as being cost-effective93. The introduction of new
and advanced interventions is often costly, and the scarcity of health-care
resources makes it important to thoroughly assess the cost-effectiveness of
each such new intervention.

The mean cost of treatment with CRS+HIPEC in patients with PM (some
of them with GC) has been estimated in previous studies (Chua et al.97,  
Baratti et al.98, Bonastre et al.99 and Spiliotis et al.100). Chua had an estimate
of $58,378 for 136 patients. Baratti had an estimate of $53,073 per patient
for 376 patients. Bonastre had an estimate of $37,229 per patient, based on
all procedures during a two-year period for 73 patients, and Spiliotis had a
mean cost estimated from 24 patients of $23,700 per patient (range $12,800–
$51,200). In the Chua, Baratti and Spiliotis studies, only costs from the
primary hospital stay were included. Longer hospital stays in our study were
probably due to higher morbidity rates.
Aim of the Thesis

The overall aims of the thesis were to explore the incidence and evaluate prognostic factors for OS of PM from GC, to investigate the feasibility of multimodal treatment in patients with PM from GC, to analyse the treatment costs, and to investigate drug sensitivity in tumour cells from GC patients.

Specific aims

I To investigate epidemiological and prognostic factors as a base for the treatment of patients with loco-regionally advanced GC.

II To investigate whether multimodal treatment of PM from GC is feasible and to evaluate the clinical outcomes and clinical effectiveness of neoadjuvant systemic chemotherapy followed by CRS+HIPEC+EPIC in patients with PM from GC on an intention to treat basis.

III To evaluate the costs and clinical effectiveness of CRS+HIPEC+EPIC added to primary chemotherapy in patients with PM from GC compared with palliative systemic chemotherapy alone.

IV To describe patterns of drug sensitivity between individual patient samples and between various tumour types to provide an additional basis for drug selection in systemic and loco-regional treatment of GC.
Patients and methods

Ethical considerations
All studies were approved by the regional ethics committee and informed consent was obtained from each patient. Study II was registered in ClinicalTrials.gov, with identifier NCT01379482.

Study I
GC was defined as adenocarcinoma with the major tumour volume in the stomach. Patients with GC diagnosed in Uppsala County between 2000 and 2009 were identified and patients were matched against two registers at the National Board of Health and Welfare. Patient records from all identified patients with GC were assessed for the presence of loco-regional advanced GC, defined as tumour invading the parietal and/or visceral peritoneum, at diagnosis or at follow-up. Loco-regional advanced GC were regarded as synonymous with PM. Histopathological data, demographic data and data about symptoms, distant metastasis, treatment and mOS were extracted. The mOS was counted from the date of the diagnosis with loco-regional advanced GC until death.

To determine the possible impact of time-related changes in treatment, the patients were divided into two time periods for inclusion: 2000-2004 and 2005-2009. Patients were classified in separate groups according to histopathological data, according to information about loco-regional advanced GC (synchronous or metachronous), to information about distant metastasis (synchronous, metachronous or non) and according to information about palliative chemotherapy (yes or no), palliative radiotherapy (yes or no) or both (yes or no).

Patients were also classified in two groups according to their age (above 70, yes or no) and Karnofsky performance status (KPS 90-100 or below 90) at loco-regionally advanced GC diagnosis.
Study II

Between January 2005 and March 2009, eighteen consecutive patients (median age 57 years, range 38–74) with PM from gastric cancer were scheduled for neoadjuvant systemic chemotherapy followed by CRS+HIPEC+EPIC at Uppsala University Hospital, Uppsala, Sweden. The eligibility requirements for treatment were: histologically confirmed diagnosis of primary gastric adenocarcinoma; histologically and/or radiologically confirmed PM diagnosis; no DM; adequate renal, haematopoietic and liver functions, and a KPS of >70. Five serum tumour markers (CEA, CA 125, CA 19-9, CA 15-3 and CA 72-4) were taken one to six days before surgery and ten days after surgery, to analyse the frequency of the impact of gastric cancer with PM on these tumour markers. The National Cancer Institute’s common toxicity criteria version 3.0 (NCI-CTC 3.0) was used to grade therapy-related adverse events83.

Study III

Between January 2005 and July 2007, ten consecutive patients with PM from GC were scheduled for neoadjuvant chemotherapy followed by CRS+HIPEC+EPIC at Uppsala University Hospital, Uppsala, Sweden. These patients were also the first ten included in Study I above. The costs and clinical outcomes of the treatment for these patients were compared with ten patients, matched according to age, gender, performance status, tumour extent, American Society of Anaesthesiologists’ (ASA) classification grade ≤ 2, and treated during the same time period with systemic chemotherapy only. The eligibility requirements for treatment for both groups were: histologically confirmed diagnosis of primary GC; histologically and/or radiologically confirmed PM diagnosis; no DM; adequate renal, haematopoietic and liver functions; and a WHO performance status (WHO) of ≤ 2. Analyses of all patients included were done with intention to treat. NCI-CTC 3.0 was used to grade therapy-related adverse events83.

Study IV

Tissue samples were collected from patients with advanced GC, colorectal cancer (CRC) and ovarian cancer. For reference, healthy blood donors contributed with normal mononuclear cells (MNCs) from buffy coats and leukaemia cells were collected by vein puncture, since these cells are known to be generally drug sensitive. The tumour tissue was minced into small pieces followed by collagenase digestion88. MNCs and leukaemia cells were collected by centrifugation followed by purification on Ficoll-Hypaque
gradients\textsuperscript{89}. Small cell clusters or single cells from the solid tumours with < 30% contaminating non-malignant cells and with ≥ 90% viability were obtained, as estimated by morphological examinations of May-Grünwald Giemsa stained cytocentrifugate preparations. Prior to seeding onto culture plates, the cells were washed and re-suspended in complete culture medium. Included in this study were all the received samples which complied with the criteria for a successful assay (acceptable quality): ≥ 70% tumour cells in the cell preparation, a fluorescence signal in control cultures of ≥ five times mean blank values, and a coefficient of variation of cell survival in control cultures of ≤ 30%. The standard cytotoxic drugs 5-FU, cisplatin, oxaliplatin, irinotecan, mitomycin C, doxorubicin and docetaxel and also some recently introduced targeted drugs were tested. The FMCA was used to measure cell viability\textsuperscript{91}. The maximum concentrations as reported in the literature reached at intraperitoneal chemotherapy (\(C_{\text{max}}\)) of each drug were compared with IC\textsubscript{50}. 
Statistical Methods

Results are presented as the median values with range and confidence intervals (CI) with 95% limits and statistical significance was set at \( p \)-level \(<0.05 \) in all studies. The computer software package STATISTICA AXA version 10.0, StatSoft Scandinavia, Sweden, was used for statistical calculation in Studies I, II and III. The computer software package GraphPad Prism 5.0 was used for statistical evaluation in Study IV.

Study I
Proportional hazard (Cox) regression, Kaplan-Meier and the log-rank test were used for analysis of factors possibly influencing survival.

Study II
All analyses were performed according to intention-to-treat. Kaplan-Meier and the log-rank test were used for analysis of factors possibly influencing survival.

Study III
Survival was calculated by the Kaplan Meier-method. Confidence interval around mean costs was estimated with the bootstrap resampling method. Results are presented as the mean and/or the median.

Study IV
One-way ANOVA with Dunnett’s post test was used for statistical inferences between the mean IC\(_{50}\) values of samples. Spearman’s rank correlation was used for analysis of cross-resistance between selected drugs. The least squares method was used to calculate the regression line slope. Data are presented as mean values ± standard error.
Results

Study I

*Incidence and patient characteristics*

Figure 7 presents a flow chart depicting the selection process for patients with loco-regional advanced gastric cancer. One-hundred and twenty patients (47% of all patients with GC; 80 at diagnosis and 40 during follow-up) were eligible for detailed analyses. Diagnosis of GC mainly emanated from pathology specimen reports. Diagnosis of loco-regionally advanced GC was verified by histopathology (52%), assessment during surgery (15%) or radiology (32%).

![Flow chart](image)

*Figure 7. Flow chart depicting the selection process for patients with loco-regionally advanced gastric cancer.*

The median age of the 120 patients at loco-regionally advanced GC diagnosis was 70.5 years (range 26-91) and males represented a slight majority (54%). For the most part, both genders had a good performance
status (KPS 90 or higher in 65%). Seventy-one patients were free from DM (see Figure 7 and Table 2).

**Survival and prognostic factors**
The mOS of the 120 patients was 4.8 months (range 0.0-67.4). For the subgroup with DM mOS was 4.7 months (range 0.0-27.5) and for the subgroup without DM the mOS was 5.1 months (range 0.0-67.4). For details, see Figure 7. There were no significant differences in mOS for the group of patients with a diagnosis of loco-regional GC included during the period 2000-2004 (5.1 months, range 0.0-67.4) compared to that of the patients included during the period 2005-2009 (4.0 months, 0.0-28.3) and no significant differences in risk factors were identified when comparing the two groups.

Multivariate Cox analysis revealed the positive prognostic variables for mOS. Good performance status, palliative chemotherapy and palliative chemotherapy + palliative radiotherapy were related to good prognosis. Negative prognosis variables were synchronous DM and a combination of synchronous loco-regionally advanced disease and synchronous DM. Table 2 summarizes the details of the proportional hazard (Cox) regression analyses.
Table 2. Uni- and multivariate proportional hazard (Cox) regression from 120 included patients with loco-regional advanced gastric adenocarcinoma.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Univariate analysis</th>
<th></th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>2005-09</td>
<td>47</td>
<td>1.27</td>
<td>0.87-1.84</td>
<td>1.32</td>
<td>0.90-1.94</td>
<td></td>
</tr>
<tr>
<td>KPS &gt; 80</td>
<td>78</td>
<td>0.63</td>
<td>0.43-0.92</td>
<td>0.56</td>
<td>0.38-0.82</td>
<td></td>
</tr>
<tr>
<td>LR sy+DM sy</td>
<td>32</td>
<td>1.81</td>
<td>0.19-2.74</td>
<td>1.86</td>
<td>1.21-2.84</td>
<td></td>
</tr>
<tr>
<td>Pall chemo</td>
<td>53</td>
<td>0.66</td>
<td>0.45-0.95</td>
<td>0.45</td>
<td>0.30-0.66</td>
<td></td>
</tr>
<tr>
<td>Pall radio+chemo</td>
<td>7</td>
<td>0.29</td>
<td>0.13-0.65</td>
<td>0.17</td>
<td>0.08-0.40</td>
<td></td>
</tr>
<tr>
<td>No DM</td>
<td>71</td>
<td>0.82</td>
<td>0.57-1.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>49</td>
<td>1.22</td>
<td>0.84-1.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM sy</td>
<td>34</td>
<td>1.70</td>
<td>1.13-2.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM me</td>
<td>15</td>
<td>1.69</td>
<td>0.40-1.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR sy+no DM</td>
<td>44</td>
<td>0.78</td>
<td>0.53-1.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR sy+DM</td>
<td>36</td>
<td>1.28</td>
<td>0.87-1.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR sy+DM me</td>
<td>4</td>
<td>0.38</td>
<td>0.14-1.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR me+no DM</td>
<td>27</td>
<td>1.08</td>
<td>0.70-1.66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR me+DM</td>
<td>13</td>
<td>0.97</td>
<td>0.54-1.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR me+DM me</td>
<td>11</td>
<td>1.01</td>
<td>0.54-1.89</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N, number; HR, hazard ratio; CI, confidence interval; 2005-09, inclusion time period 2005-2009; KPS > 80, Karnofsky performance status 90-100; LR sy+DM sy, synchronous loco-regional advanced gastric cancer and synchronous distant metastases; Pall chemo, palliative chemotherapy; Pall radio+chemo, palliative radiotherapy + palliative chemotherapy; no DM, no distant metastases; DM, distant metastases; DM sy, synchronous distant metastases; DM me, metachronous distant metastases; LR sy+no DM, synchronous loco-regional advanced gastric cancer and no distant metastases; LR sy+DM, synchronous loco-regional advanced gastric cancer and distant metastases; LR sy+DM me, synchronous loco-regional advanced gastric cancer and metachronous distant metastases; LR me+no DM, metachronous loco-regional advanced gastric cancer and no distant metastases; LR me+DM, metachronous loco-regional advanced gastric cancer and distant metastases; LR me+DM me, metachronous loco-regional advanced gastric cancer and metachronous distant metastases.

Multivariate analyses were performed in groups between the lines. Significant hazard ratio in italics.
Figure 7 – Overall survival for subgroups synchronous and metachronous loco-regionally advanced gastric cancer +/- synchronous and metachronous distant metastases.

Locoreg sync/ no distmet, synchronous loco-regionally advanced gastric cancer without distant metastases; Locoreg sync/ distmet sync, synchronous loco-regionally advanced gastric cancer with synchronous distant metastases; Locoreg meta/ no distmet, metachronous loco-regionally advanced gastric cancer without distant metastases; Months, median overall survival in months; Locoreg meta/ distmet meta, metachronous loco-regionally advanced gastric cancer with metachronous distant metastases.

Study II

The mOS was 10.2 months (range 1.2–34.3, 95% CI 6.9–13.7). For the patients who received the entire treatment mOS was 14.3 months (range 6.1–34.3, 95% CI 6.6–20.3). Six of the 18 patients (33%) had macroscopically radical (CC0) surgery, and mOS for that subgroup was 19.1 months (range 6.1–34.3, 95% CI 6.9–27.1). Patient survival rates are presented in Figure 8. Postoperative 90-day mortality was one patient in ten (one in eight for the patients who received CRS+HIPEC) and the perioperative grade II-IV adverse event (AE) rate was 62.5%. All patients had poorly differentiated
tumours: 50% were of the diffuse type and signet ring cells were detected in 67% of the patients.

Tumour markers were normal in three of the eight patients who had CRS+HIPEC and in five of the eight patients at least one tumour marker was elevated. In the group of patients who received CRS+HIPEC and with no visible peritoneal seeding, one had two raised tumour markers, three had one raised tumour marker and two had none. In contrast, all ten patients without CRS+HIPEC treatment had at least one elevated tumour marker and four had more than one raised tumour marker. Amongst the tumour markers, raised values for CA72-2 were most frequent, in 11 of all 18 patients (61%); in four out of eight (50%) who received CRS+HIPEC and in seven out of 10 (70%) of the patients without CRS+HIPEC. CEA were normal for all the patients who received macroscopically radical CRS+HIPEC. In four out of 18 patients (22%) CEA was raised, all of them in the group of 12 patients with non-radical CRS+HIPEC or without CRS+HIPEC.

Figure 8. Overall survival for the CC0 and CC>0 subgroups from the CRS+HIPEC+EPIC group.

CC0, patients with macro radical cytoreduction surgery; CC>0, patients with non-macro radical cytoreduction surgery. Months, median overall survival in months.
Study III
The mean overall cost in the loco-regional group was $145,700 (range $49,900–$487,800) and $59,300 (range $23,000–$94,800) for the control group. The mean overall survival for the loco-regional group was 17.4 months (range 6.0–34.3), and 11.1 months (range 0.1–24.2) for the systemic chemotherapy only group. The gain in life-years was 0.52 and in quality-adjusted life-years 0.49, leading to incremental cost per life-year and quality-adjusted life-year gained of $166,716 and $175,164 for the loco-regional group compared to the systemic chemotherapy group.

Study IV
Sixteen tumour samples from 30 patients (53%) with GC fulfilled the quality criteria and were analysed for drug sensitivity. The overall technical success rate for the other samples included in the study was considerably higher (85%). The main reason for failure was fungus contamination in the primary tumour from GC. Thirty-four samples from ovarian cancer and 52 from CRC were also analysed for drug sensitivity. Thirteen tumour samples from patients with leukaemia and 44 samples of normal mononuclear cells were included as a normal cell reference.

The GC samples did not significantly differ from CRC samples with regard to sensitivity to standard drugs. The ovarian cancer samples were significantly more sensitive than the CRC and GC samples to cisplatin, irinotecan and 5-FU (Figure 9). For drugs that are the most clinically active in the systemic chemotherapy of GC, the GC samples had numerically lower IC50 values than CRC in 67% of the tested drugs.
Figure 9. IC₅₀ values for standard drugs. Statistical interference was calculated with the colorectal cancer samples as reference.

MNC, mononuclear cells; CLL, chronic lymphocytic leukaemia; Ovarian, ovarian cancer; Gastric, gastric cancer; Colorectal, colorectal cancer.* P<0.05; *** P<0.001; NS, not statistically significant.

Figure 10 displays a great inter-individual variability for the GC samples. Some samples are also resistant to the highest concentrations tested and some are sensitive at even the lowest concentrations. Thus, there is not only variability in the resistance when comparing different tumour types, but also when comparing different tumour samples in the same tumour type.
Figure 10. Concentration response curves. Tumour cell sensitivity, expressed as survival index at maximum concentration of drug tested, for standard drugs in tumour samples from gastric cancer.

Log, logarithm; 5-FU, 5-fluorouracil;

Figure 11 shows that the activity cisplatin correlated strongly to that of oxaliplatin, in the GC samples. Seemingly the choice of the platinum-based drugs has a similar effect on GC tumours. 5-FU correlated moderately to cisplatin but not at all to irinotecan, mitomycin C, doxorubicin and docetaxel. Furthermore, many individual samples were sensitive to one drug but resistant to the other.
Figure 11. Correlations (based on all tumour samples investigated) between survival index for pairs of standard cytotoxic drugs at concentrations selected to provide optimal activity variation.

P, the level of statistical significance; r, correlation coefficient.

The sensitivity patterns of the targeted drugs (TDs) were similar to those of the standard drugs (Figure 12). The CRC samples had numerically lower IC_{50} values than GC in 75% of the tested TDs (statistically significantly in 25%). In the clinic, the activity of these TDs is expected to be modest in GC.
Figure 12. IC_{50} values for targeted drugs in all tumour samples investigated divided for the subtypes indicated.

MNC, mononuclear cells; CLL, chronic lymphocytic leukaemia; Ovarian, ovarian cancer; Gastric, gastric cancer; Colorectal, colorectal cancer. * P<0.05; NS, not statistically significant.

Sunitinib showed low cross-resistance to the standard drugs (Figure 13). Sunitinib was significantly cross-resistant to sorafenib (not shown). This indicates that these two TDs would be suitable in 2nd line treatment, combined with standard drugs.
Figure 13. Correlations (based on all tumour samples investigated) between survival index for pairs of standard and targeted cytotoxic drugs at concentrations selected to provide optimal activity variation.

P, the level of statistical significance; r, correlation coefficient.

Which activity against GC tumour cells could be expected in the intraperitoneal chemotherapy (IPC) situation? In that type of chemotherapy the tumour cells are exposed to high drug concentrations. Figure 14 displays cell survival at the highest ex vivo concentrations used. Cell survival for GC follows the same pattern as for CRC.
Figure 14. Cell sensitivity of tumour. Survival index at maximum concentration of drug tested.

Colorectal, colorectal cancer; Gastric, gastric cancer; 5-FU, 5-fluorouracil.
General discussion

A growing treatment option for PM is CRS and HIPEC, which has shown promising results for PM from CRC and PMP. However, information is still lacking on the possible benefits from such an approach in patients with PM from GC and there is debate as to whether this treatment should be applied in this disease\textsuperscript{46}.

This summary aimed to explore the incidence and evaluate prognostic factors for mOS of PM from GC in a defined population, to explore whether multimodal treatment of PM from GC is feasible and to evaluate the clinical outcomes, costs and clinical effectiveness of neoadjuvant systemic chemotherapy followed by CRS+HIPEC+EPIC in patients with PM from GC, compared with palliative systemic chemotherapy alone, and to investigate differences in drug sensitivity between individual patient samples and between various tumour types.

\textit{Incidence and prognostic factors}
Loco-regional GC in Study I was far more commonly observed than indicated by previous studies, with an incidence of 3.8 per 100,000 person-years, and was found in 47\% of all patients with GC. However, it is reasonable to presume some degree of undiagnosed PM in our study population, with few autopsies. Memorial Sloan-Kettering Cancer Center\textsuperscript{23} reported PM at diagnostic laparoscopy in ten out of 50 patients (20\%) with GC and/or adenocarcinoma in the esophago-gastric junction, all judged as free from metastases on a clinical basis. Li et al. detected PM in 24\% (33/135) of proximal GC cases after curative resection\textsuperscript{101}. In a Japanese study, in patients who underwent gastrectomy (curative and palliative) for gastric cancer measuring ten centimetres or more in diameter, recurrent disease with PM was proven preoperatively in 15 of 95 patients (16\%), irrespective of which method of PM diagnosis was used (radiological or histopathological)\textsuperscript{102}. Douglass detected PM in half of the patients with recurrent GC\textsuperscript{103}. In Study I, loco-regionally advanced GC was discovered during follow-up in 40 (33\%) of all patients, a result well in line with the literature\textsuperscript{104 105}.

It is difficult to compare Study I with previous literature, since to the best of our knowledge this is the first time this particular group of patients (with loco-regionally advanced GC) has been studied. Prognostic factors for GC
have been studied quite well, but not on a group of patients with PM and/or distant metastasis. Synchronous (at primary diagnosis) DM were confirmed as a major negative independent prognostic factor in multivariate analysis, and mOS for this subgroup of 34 patients was 4.7 months, compared to 3 months in a French study on patients with advanced GC. Additionally, as expected, good performance status, palliative chemotherapy and palliative chemotherapy + palliative radiotherapy were confirmed as major positive independent prognostic factors. The result was not a surprise, and has been well supported in the literature.

There was no significant difference in mOS for patients included during the period 2000-2004 compared to the period 2005-2009. It is obvious that ten years’ research and development in patients with advanced GC had no major impact on mOS in a population-based setting. There is no effective treatment strategy today for advanced GC and the tumour biology is seemingly the reason. With this knowledge, multimodal therapies, i.e. bidirectional chemotherapy or cytoreductive surgery and hyperthermic intraperitoneal chemotherapy could be a beneficial treatment option in the future, representing few therapy options with potential for long time survival. The better survival in two recent studies, compared to Study I, is probably due to patient selection, with median age 11-13 years less and the majority of patients with a good performance status (KPS 80-100). In two older studies the mOS was 5.4-5.6 months in the group of patients who had no resection, which is similar to the current study. EPIC as an adjuvant treatment has demonstrated a survival benefit in patients with curative resections on serosal invasion. Despite the promising results, EPIC it is not a frequently used treatment strategy nowadays.

Loco-regional treatment
To the best of our knowledge, Study II is the first prospective study in the literature testing combined treatment with neoadjuvant systemic chemotherapy followed by CRS, HIPEC and EPIC, in patients with PM from GC.

Six studies testing various combinations of CRS+HIPEC+EPIC in patients with gastric cancer and PM have been published: two prospective, one non-randomised with case control patients, and three retrospective. The mOS for patients in Study II’s CRS+HIPEC group was in line with these six studies, as was mOS for the subgroup CC0 (19.1 months in Study I and 8.0–36.3 for the comparable studies). Signet ring cell carcinoma is considered a major and independent factor of poor prognosis in gastric cancer. Lauren, diffuse cancer as well as poor differentiation are considered independent factors of poor prognosis. The tumour histopathology of patients included in Study II was less favourable than in the comparable studies. In comparable studies patients had 56%
(range 33–82) poorly differentiated tumours whereas in Study II it was 100%. Only one group reported the presence of signet ring cells, in 4% of the patients (vs. 72% in Study II). It has been speculated that histopathologically, signet cell type cancer could also be an exclusion criterion. In a study by Fanelli et al., signet cell type cancers were significantly associated with the presence of PM at diagnosis, but were not a predictor for poor survival. In addition, patients in Study II underwent extensive CRS, even if tumour involvement was found in more than seven regions. Surgery was avoided only if PM was widespread on the small bowel. Careful patient selection seems essential for good results from CRS+HIPEC for patients with PM from gastric cancer. Baseline performance status seems to be an important tool in the selection process. All the patients in Study II who had macroscopically radical surgery had a good performance status (median KPS 100), and most who did not have macroscopically radical surgery had reduced performance status (median KPS 90).

Over the past two decades, many studies have shown that tumour markers are useful for checking the prognosis, for predicting a favourable outcome from the treatment and for predicting recurrence and risk of death for patients with advanced GC. Thus, tumour markers could also be potential tools in the selection process. The findings in Study II correlate with previous studies. Kim at al. certify that most patients with PM did not have raised CEA, compared to only 22% of the patients in Study II. Kodama et al. revealed that CA72-4 was more specific for GC than other tumours and was more frequently raised in higher GC stages. In Study II, 61% of the patients (50% of the patients in the CRS+HIPEC group and 70% of the patients who did not receive CRS+HIPEC) had raised CA72-4 levels.

Postoperative 30-day mortality in Study II was at the low end (0%) compared with patients in previously published studies (range 0-11%). However, the perioperative morbidity rate in our study was high (62.5%) compared to that in previously published studies (Table 2). Interestingly, Glehen et al. noted that the complication rate was higher in the EPIC subgroup (60%), well in line with the complication rate in the study by Farma et al., including patients receiving EPIC (67%). In a Korean randomised trial with GC patients treated with EPIC as an adjuvant treatment after gastric resection vs. surgery only, the 5-year survival rate was increased in patients with Stage III disease (53% vs. 23%) and with Stage IV disease (28% vs. 5%), favouring EPIC vs. surgery alone. However, this came at the price of increased mortality (6.4% vs. 1.6%) and increased morbidity (29% vs. 20%). According to Study I, about half of the patients with GC developed PM, and with this background, adjuvant EPIC may give a survival benefit for all Stage III - IV GC patients. The choice of drug for adjuvant EPIC may be individualised based on results from chemo-sensitive tests (see Study IV). Moreover, higher morbidity could be expected with the
use of platinum-based HIPEC\textsuperscript{63}, and this could be one reason for higher morbidity in our cohort, as both Glehen et al.\textsuperscript{56} and Hall et al.\textsuperscript{57} used mitomycin C only, while Yang et al.\textsuperscript{59} used relatively low doses of cisplatin.

Due to various methodologies, there is still a lack of information about the possible benefits from a multimodal treatment approach in patients with PM from gastric cancer. Six studies have been published testing various combinations of CRS+HIPEC+EPIC in patients with gastric cancer and PM. Table 3 presents details of these studies. The evidence grades were not so high in three studies since they were retrospective\textsuperscript{58, 60, 61} and in five studies, morbidity was not graded in an objective and reproducible way\textsuperscript{57-62}. All studies stressed the importance of macroscopic radical surgery, yet even so the number of patients who received macroscopic radical surgery was low (10-56\%). In a recently published, randomised Phase III study by Yang et al.\textsuperscript{128}, it is apparent that the majority of the patients from the CRS+HIPEC group are already presented in a study from 2010\textsuperscript{59} and the control group underwent CRS only. However, it seems that nowadays most centres prefer to combine CRS with intraperitoneal chemotherapy. The number of patients with metachronous PM was too small for a definite conclusion, but mOS for these patients was half of that of patients with synchronous PM (5.5 vs. 11 months). The same tendency was also observed by Glehen et al.\textsuperscript{56}. Four\textsuperscript{56, 58, 60, 61} of the six studies mentioned above included patients with metachronous PM (29\% - 56\% of all patients included). In Study II, just one patient had metachronous PM. One could speculate whether neoadjuvant treatment in patients with this heavy load of PM simply increases the morbidity rate with only a slight increase in mOS. NIPS\textsuperscript{83} is probably a better option in combination with CRS+HIPEC or CRS+HIPEC alone, without any neoadjuvant treatment at all. Study II describes the most unselected subgroup of patients with PM from GC in the literature. One could only speculate upon the results of a more careful patient selection in Study II. Still the results in Study II indicate that a formerly unproven multimodal treatment of PM from GC gives an mOS in line with comparable studies.
Table 3. Data from trials on CRS+HIPEC in patients with PM from GC.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>No of patients</th>
<th>Chemo EPIC</th>
<th>Mortality (%)</th>
<th>Morbidity (%)</th>
<th>mOS (months)</th>
<th>1-yr mOS (%)</th>
<th>2-yr mOS (%)</th>
<th>3-yr mOS (%)</th>
<th>5-yr mOS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossi</td>
<td>2003</td>
<td>13</td>
<td>No</td>
<td>0</td>
<td>26</td>
<td>15</td>
<td>md</td>
<td>md</td>
<td>md</td>
<td>0</td>
</tr>
<tr>
<td>Glehen</td>
<td>2004</td>
<td>49</td>
<td>No</td>
<td>4</td>
<td>27</td>
<td>10.3</td>
<td>39</td>
<td>14</td>
<td>10</td>
<td>8.2</td>
</tr>
<tr>
<td>Hall</td>
<td>2004</td>
<td>34</td>
<td>No</td>
<td>0</td>
<td>35</td>
<td>8</td>
<td>36</td>
<td>26</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Yonemura</td>
<td>2005</td>
<td>42</td>
<td>No</td>
<td>7</td>
<td>43</td>
<td>11.5</td>
<td>36</td>
<td>10</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>Farma</td>
<td>2005</td>
<td>9</td>
<td>Yes</td>
<td>11</td>
<td>67</td>
<td>9</td>
<td>22</td>
<td>11</td>
<td>11</td>
<td>5.6</td>
</tr>
<tr>
<td>Gusani</td>
<td>2007</td>
<td>2</td>
<td>No</td>
<td>md</td>
<td>md</td>
<td>md</td>
<td>md</td>
<td>md</td>
<td>md</td>
<td>0</td>
</tr>
<tr>
<td>Spiliotis</td>
<td>2008</td>
<td>3</td>
<td>No</td>
<td>md</td>
<td>md</td>
<td>10</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yang</td>
<td>2009</td>
<td>12</td>
<td>No</td>
<td>md</td>
<td>md</td>
<td>29</td>
<td>&gt;75</td>
<td>md</td>
<td>md</td>
<td>md</td>
</tr>
<tr>
<td>Yang</td>
<td>2010</td>
<td>28</td>
<td>No</td>
<td>0</td>
<td>14.3</td>
<td>9.2</td>
<td>28</td>
<td>14</td>
<td>7</td>
<td>md</td>
</tr>
<tr>
<td>Glehen</td>
<td>2010</td>
<td>150</td>
<td>Yes/No</td>
<td>6.5</td>
<td>27.8</td>
<td>9.2</td>
<td>43</td>
<td>23</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Yang</td>
<td>2011</td>
<td>34</td>
<td>No</td>
<td>0</td>
<td>md</td>
<td>11.0</td>
<td>43</td>
<td>20</td>
<td>10</td>
<td>md</td>
</tr>
<tr>
<td>Hultman</td>
<td>-</td>
<td>8</td>
<td>Yes</td>
<td>0</td>
<td>62.5</td>
<td>14.3</td>
<td>62.5</td>
<td>37.5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

EPIC, early postoperative intraperitoneal chemotherapy; mOS, median overall survival; md, missing data. This figure is reproduced with permission of the publisher.

Costs

There are few studies comparing the costs and clinical effectiveness of CRS and HIPEC treatment in patients with PM, compared to other tumour types such as colorectal cancer, and there are currently no studies of CRS and HIPEC treatment in patients with PM from GC only. Results from cost and cost-effectiveness analyses are important in deciding the allocation of health-care resources. Such analyses are therefore used increasingly in health-care decision making and the concept of cost-effectiveness thresholds (i.e. a maximum accepted cost per unit of health gain) is proposed and used in resource-allocation decisions.

To the best of our knowledge, Study III is the first prospective health-economic study on CRS+HIPEC+EPIC treatment in patients with PM from GC only. The number of patients that was possible to include was small and non-randomised comparisons are inherently hazardous. However, the controls were matched and treated during the same time period and within the same geographical area as the CRS+HIPEC+EPIC group.

The results in Study III indicate prolonged survival for the combined treatment approach compared to systemic chemotherapy only, but at
considerably higher costs and with a very high incremental cost per QALY gained. This leads to an incremental cost per additional life-year gained higher than what is usually considered cost-effective in Sweden and many other countries. A treatment like the one assessed here that adds a cost of about $86,000 per patient would probably need to also add at least one additional life-year (i.e. have an incremental cost per QALY gained below about $70,000-$80,000), to be considered reasonably cost-effective compared to other available health-care interventions. One patient in the CRS+HIPEC+EPIC group had a very high treatment cost ($487,756) due to complications with re-operations including a prolonged postoperative period in the intensive care unit. Although there will always be occasional patients with costs much higher than the average, it is difficult to draw a definite conclusion to what extent this could potentially occur, given the small number of patients in Study III. It could therefore be interesting to also assess the outcome after excluding such patients, if they are assumed to occur with a very low frequency in a larger patient population or at a similar frequency in the two groups. If the patient who had the very high treatment cost were excluded, the difference between the CRS+HIPEC+EPIC group and the systemic chemotherapy group would be $48,411. The gain in survival would be 0.56 years, the cost per life-year gained $86,938, and the cost per QALY gained $86,292. Although this is still a fairly high incremental cost, it is more in accordance with currently accepted cost-effectiveness thresholds in Sweden.

The mean cost of treatment with CRS+HIPEC+EPIC in patients with PM has already been estimated in a prospective study by Chua et al.; in a retrospective study by Baratti et al.; in a retrospective study by Bonastre et al. and in a prospective study by Spiliotis et al.

Patient selection criteria between different studies could influence the results. Patients reported in this thesis were not excluded from CRS+HIPEC treatment due to a higher PCI score. The only reason for not being treated by loco-regional procedure was extensive tumour growth on the entire small bowel surface. This could explain the extended duration of surgery (mean 9.1 hours including HIPEC time, compared with 5.2 hours excluding HIPEC time for Glehen), and probably the increased morbidity too. Moreover, higher morbidity with the use of platinum-based HIPEC could be expected and this could be one reason for higher morbidity in our cohort, as neither Glehen nor Hall used platinum-based HIPEC, but mitomycin C.

**Tailored treatment: the future?**
The results in Study IV reveal quite a good correspondence between the ex vivo findings for drug sensitivity in GC and the clinical activity for the standard drugs as published: 1st line treatment with similar standard drug combinations in GC and CRC result in similar tumour response rates.
These results could be used as guidance in the selection of drugs for which there is clinical experience for CRC, but which have not previously been used for GC. Furthermore, in Study IV tumour samples from GC and CRC displayed very similar drug sensitivity, not only for the standard drugs but also for the TDs. Still, the survival rates for GC and CRC clearly differ in clinical trials, with GC showing mOS in the range 14 – 17 months compared with 20 – 24 months\textsuperscript{14 15 134-136} for CRC. One explanation might be the wider use of 2\textsuperscript{nd} and 3\textsuperscript{rd} line therapy in CRC. Another explanation is the possibility of a lower stage of disease for CRC compared to GC, at the time of diagnosis. Disease-free survival for IPC/HIPEC is shorter for PM from GC versus CRC. The obvious differences in mOS for GC with or without PM compared to CRC point to differences in tumour biology beyond drug sensitivity\textsuperscript{61 137 138}.

The platinum drug mostly used in the treatment of GC is cisplatin, and its activity correlated strongly to that of oxaliplatin (Fig. 11), well in line with findings in clinical trials\textsuperscript{13 139}. Oxaliplatin is at least as active as cisplatin. Thus, there is support for substituting cisplatin with oxaliplatin, a drug with less negative side effects.

5-FU correlated moderately to cisplatin but not at all to mitomycin C, irinotecan, docetaxel and doxorubicin in Study IV. If there is disease progression on standard 1\textsuperscript{st} line platinum/5-FU based chemotherapy, there may be some activity of mitomycin C, irinotecan, docetaxel and doxorubicin in 2\textsuperscript{nd} line treatment. These observations have also been presented recently in clinical trials with docetaxel and irinotecan\textsuperscript{140 141}. Cisplatin, oxaliplatin, 5-FU, mitomycin C and irinotecan are the drugs mostly used for IPC/HIPEC for PM from CRC as well as from GC\textsuperscript{61 62 128 137}. The observations from Study IV, that similar standard drug combinations in GC and CRC result in similar tumour response rates, support the notion of also choosing drugs for IPC with proven efficacy for PM of CRC origin for IPC for PM from GC.

One common standpoint is that an optimal drug choice in an individual patient should be tailored to optimize drug treatment. The considerable variability between individual GC samples in sensitivity to increasing drug concentrations and to different drugs lends support for an individual approach.
Conclusions

The results of Study I show that loco-regionally advanced GC is far more common than revealed by previous studies. No differences in mOS between the two time periods were observed, despite some reported progress in systemic treatment options in advanced disease. These results demand novel treatment strategies. From this perspective, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in combination with palliative systemic chemotherapy may represent a potentially beneficial option for patients with PM without DM.

Neoadjuvant chemotherapy followed by CRS+HIPEC+EPIC is not associated with long mOS in patients with PM from GC, unless macroscopically radical surgery is achieved. If the survival benefit from adding loco-regional treatment to systemic chemotherapy indicated from this comparison is true, the incremental cost is considered high. However, treatment of PM from GC is costly irrespective of treatment modality. Morbidity from this new treatment is considerable and it cannot be recommended for routine care until there is supportive evidence from a prospective randomised trial. Study II describes a rather unselected subgroup of patients, whose PM is more widespread than in the majority of the comparable publications. Still, the results indicate that a formerly unproven multimodal treatment of PM from GC (neoadjuvant chemotherapy + CRS+HIPEC+EPIC) gives an mOS in line with other studies in the literature, for patients with this disease. With more careful patient selection, accepting only those with good performance status and limited PCI (maximum of 12 suggested⁶¹), one can assume that it is possible to achieve better results for CRS+HIPEC in patients with PM from GC.

FMCA for ex vivo assessment of drug activity in GC seems to provide clinically relevant data that could be of guidance in efforts to improve the systemic and intraperitoneal drug treatment for GC. The two tumour types, GC and CRC, have similar drug sensitivity profiles, which is why extrapolation from the experience in CRC seems reasonable. There are large differences in drug sensitivity between individual patient samples and between various tumours, arguing for a more individualized selection of drug for chemotherapy.
Future perspectives

To date, there is a very limited number of studies of patients with GC and PM. Epidemiological information is lacking in the literature about this patient group. There is also a lack of concordance between different medical specialities in definitions of the terminology and a dearth of knowledge about understanding prognostic factors, especially concerning mOS. The tables may be turned, where East Asia will dominate in the development of this disease the next decade. The incidence of the disease is still high in this area of the world with the greatest economic growth, whereas Europe and North America with declining incidence in GC and shrinking economies will lose the leading role.

To curb the galloping rising costs for the treatment of patients with cancer, societies will concentrate more on cost-effectiveness analyses for all different cancer treatments, and there will be a focus on highly responsive disease. It seems reasonable to believe that good performance status will be essential for surgery with curative attempt and for chemotherapy. Sequential mono-therapies will be the gold standard for 2nd and 3rd line therapy of GC with PM, and there will be a step back to best supportive care and enhanced cognitive services for disease with lower response.

A new and interesting scientific field is the tailoring of anti-cancer treatment. To definitively address this question, a prospective randomized trial comparing therapy based on information from an ex vivo assay with therapy based on the clinician’s choice is needed. Both accuracy for predicting tumour response (a surrogate endpoint for mOS) and mOS is important, and the assay should be validated according to those issues. To define chemo-sensitivity, patients with stable disease should be included and not just responders, and there should be an independent review of response evaluation.

In the near future, the dominant treatment strategy in East Asia will seemingly be bidirectional treatment followed by CRS+HIPEC in patients with good performance status and limited PM (PCI not more than 6) or bidirectional treatment followed by salvage gastrectomy in patients with a PCI higher than 6. EPIC with a tailored choice of drug will be the gold standard for patients with GC and serosal invasion. With growing frequency, treatment options will be based on cost-effectiveness analyses and small budgets.
Sammanfattning på svenska


Delarbete I

Det första delarbetet syftar till att studera epideimiologiska- och prognostiska faktorer, som är kopplade till överlevnad hos patienter med loco-regionalt avancerad ventrikelcancer. Den nya informationen kan ligga som bas till val av behandling av patienter med denna sjukdom.


Totalt 255 patienter med ventrikelcancer studerades och journaluppgifter för bedömning av loco-regional sjuka fanns hos 47 % av patienterna, en incidens på 3,8 per 100 000 personår. Komplett datainsamling har gjorts för 120 patienter med loco-regional ventrikelcancer. Medianöverlevnaden för de 120 patienterna var 4.8 månader och för de 71 patienter med enbart loco-

Slutsats: loco-regional ventrikellcancer verkar vara vanligare än tidigare studier visat. Då ingen förbättring i överlevnad har skett det senaste decenniet väcks tanken om behovet av ändrad behandlingsstrategi av denna sjukdom, där man bör överväga CRS+HIPEC eller kombinerad systemisk och intraperitoneell cytostatika-behandling.

Delarbete II

Delarbetet syftar till att undersöka om multimodal behandling av patienter med peritoneala metastaser från ventrikellcancer är möjlig, samt att utvärdera den kliniska nyttan av neoadjuvant systemisk cytostatika (cytostatika innan kirurgi givet i blodbanan), CRS, hypertermisk (41,5-43 gradig) intraoperativ intraperitoneal cytostatika (HIPEC) och tidig postoperativ intraperitoneal cytostatika på denna grupp av patienter, med ”intention to treat”-ansats.

Arton patienter (medianålder 57 år, spann 38–74) med peritoneala metastaser inkluderades. Tre månaders neoadjuvant systemisk cytostatika planerades, följt av CRS, HIPEC och tidig postoperativ intraperitoneal cytostatika.

Medianöverlevnaden var 10,2 månader (spann 1,2–34,3, 95% konfidensintervall 6,9–13,7). För patienterna som erhöll full behandling var medianöverlevnaden 14,3 månader (spann 6,1–34,3, 95% konfidensintervall 6,6–20,3). Sex av de 18 patienterna (33 %) erhöll makroskopiskt radikal kirurgi och medianöverlevnaden för denna subgrupp var 19,1 månad (spann 6,1–34,3, 95% konfidensintervall 6,9–27,1) Postoperativ mortalitet (90 dagars) var en patient, 10% av alla opererade och 12,5% av alla som erhöll CRS+HIPEC. Perioperativa komplikationer grade II-IV ”adverse events” var 62,5%.

Slutsats: neoadjuvant systemisk cytostatika, följt av CRS, HIPEC och tidig postoperativ intraperitoneal cytostatika verkar inte leda till förlängd överlevnad, såvida inte makroskopiskt radikal kirurgi är möjlig. Dessutom leder behandlingen till en påtaglig morbiditet och kan därför inte rekommenderas som rutin-behandling innan en prospektiv randomiserad studie genomförts.
Delarbete III

I det tredje delarbetet var syftet att utreda kostnader och klinisk effektivitet av neoadjuvant systemisk cytostatika följt av CRS, HIPEC och tidig postoperativ intraperitoneal cytostatika för patienter med peritoneala metastaser från ventrikelcancer jämfört med enbart palliativ systemisk cytostatika.

Tio patienter planerades för systemisk cytostatika, följt av loco-regional behandling. En referensgrupp bestående av tio matchade kontrollpatienter behandlade enbart med palliativ systemisk cytostatika jämfört med de loco-regionalt behandlade.

Medelkostnaden i den loco-regionala gruppen var $145700 (spann 49900–487800) och $59300 (spann 23000–94800) för kontrollgruppen. Medelöverlevnaden i den loco-regionala gruppen var 17,4 månader (spann 6,0–34,3) och 11,1 månader (spann 0,1–24,2) för gruppen som enbart fick systemisk cytostatika. Vunna levnadsår var 0,52 och kvalitetsjusterade vunna levnadsår 0,49, vilket medförde ökad kostnad per vunnet levnadsår och per kvalitetsjusterat vunnet levnadsår med $166716 respektive $175164, för den loco-regionala gruppen jämfört med gruppen som enbart fick systemisk cytostatika.

Slutsats: kostnaden för behandling av patienter med PM från ventrikelcancer är hög, oavsett behandlingsregim. Om överlevnadsvinsten som ses i denna jämförelse mellan loco-regional behandling och systemisk cytostatika är korrekt, är den ökade kostnaden för denna överlevnadsvinst hög.

Delarbete IV

Det fjärde delarbetet syftar till att som bas till val av systemisk och loco-regional onkologisk behandling av ventrikelcancer beskriva mönster i cytostatika-känslighet in vitro mellan olika patienter och mellan olika tumörtyper.

Vävnadsprover (tumörceller) från 16 patienter med ventrikelcancer analyserades avseende känslighet för olika typer av cytostatika, som vanligen används i behandlingen av ventrikelcancer och kolorektal cancer (5-fluorouracil, cisplatin, oxaliplatin, irinotecan, mitomycin C, doxorubicin och docetaxel). Även känsligheten för ”targeted drugs” (bortezomib, sorafenib, sunitinib och rapamycin) analyserades. Vävnadsproverna preparerades och analyserades på FMCA (fluorometric microculture cytotoxicity assay)-plattor efter inkubering i 72 timmar. Därefter lästes mängden viable cancerceller av med en fluorometer. Dessutom analyserades vävnadsprover från kolorektal cancer (52), från ovarialcancer (34), från...
kronisk lymfatisk leukemi (13) och från normala mononuklerara celler (44) som en jämförelse.


Slutsats: ex vivio-analys av cytostatika-känslighet hos tumör-celler från patienter med ventrikelfakancer är möjlig att genomföra och kan ge information som kan vara andvändbar vid val av cytostatika. Cytostatika-känsligheten varierar betydligt mellan olika ventrikelfakancer-vävnadsprover, vilket talar för en skräddarsydd behandlingsstrategi i valet av kemoterapi för patienter med denna sjukdom.
Avhandlingens nyhetsvärde

Delarbete I är den första studien i litteraturen där man i en population av patienter studerat förekomsten av loco-regional spridning från ventrikeltumor, ett sjukdomstillstånd som verkar vara vanligare än tidigare studier visat. Det är så vitt vi vet inte tidigare studerat prognostiska faktorer i en population av patienter med loco-regional spridning från ventrikeltumor. I delarbete I kartläggs för första gången loco-regionalt spridd ventrikeltumor med och utan fjärrmetastaser och det konstateras att ingen förbättring i överlevnad har skett det senaste decenniet.

Avhandlingens fas-II-studie är den första studie där patienter behandlas med neoadjuvant systemisk cytostatika följt av CRS, HIPEC och EPIC. Denna multimodala behandling ger inte lång överlevnad för patienter med peritoneala metastaser från ventrikeltumor, såvitt inte makroskopiskt radikal kirurgi erhålls. Om överlevnadsvinsten som ses i denna jämförelse mellan loco-regional behandling och med systemisk cytostatika är korrekt, är den ökade kostnaden för denna överlevnadsvinste hög. Oavsett vilken behandling som ges till patienter med peritoneala metastaser från ventrikeltumor är kostnaden hög, men morbiditeten av denna nya behandling är påtaglig och därför kan den inte rekommenderas som rutinbehandling, om inte en framtida randomiserad studie kan påvisa en tydlig behandlingsvinste med det kombinerte terapikonceptet. Då morbiditeten i denna studie låg i överkant jämfört med studier gjorda med CRS och HIPEC, men utan EPIC, bör man i framtida randomiserade studier undvika att kombinera dessa olika kemoterapi-metoder.

Acknowledgements

Haile Mahteme, my main tutor, for inviting me into the enormously interesting world of cytoreductive surgery and for initiating this thesis; for generously sharing his great knowledge and his time to teach me how to produce good science and how to perform cytoreductive surgery;

Ulf Gunnarsson, my co-tutor, for inviting me into his Scientific Research Group and for encouraging me to accomplish the many steps along the road to my PhD; for great help in understanding the best way to analyse epidemiological data.

Peter Nygren, my co-tutor, for all the good scientific advices and sharp analysis; for teaching me about medical oncology and giving me new perspectives on how to think scientifically.

Magnus Sundbom, my co-tutor, for inviting me into the Department of Surgery at Uppsala University Hospital and for introducing me into the world of gastric cancer surgery and basic research;

Bengt Glimelius, co-author, for all the good scientific advice and sharp analysis and for adding refinements to our manuscripts;

Ulf Haglund, co-author, for all the good scientific and clinical advice and for adding refinements to our manuscripts;

Jonas Lundkvist, co-author, for sharing his great scientific knowledge with me and for adding refinements to our manuscript and Martin Ljungman, and Rolf Larsson, co-authors, for sharing data with me and for participation in work with our manuscripts;

Claes Juhlin, Staffan Wollert and Ewa Lundgren, current and former heads of the Department of Surgery, Uppsala University Hospital, and Olle Nilson and Lars Wiklund, current and former heads of the Department of Surgical Sciences, Uppsala University, for providing the conditions that made this research possible;

Göran Granath, for skilful help with statistical matters.
Mandy Trickett and Sue Pajuluoma, for proofreading and helping me improve my abilities in the golden scientific language;

Yutaka Yonemura, Osaka, Japan, for your generosity to me and my family, giving me the opportunity to widen my perspectives in the area of cytoreductive surgery in Japan;

Christina Bengtsson, secretary at the colorectal unit of the Department of Surgery, Uppsala University Hospital, for helping me obtain copies of patient journals from hospitals outside Uppsala;

Johan Hansson and Kurt van der Speeten, for being excellent role models for me on the road to my PhD, for proofreading the outline of my thesis and for their friendship;

Nakisa Esfahani, Hella Hultin, Ann Langerth, Zakaria Abdulla, Niclas Högberg, Gabriel Sandblom and Rikard Henricsson, my roommates at work, for good advice and friendship and for developing an enjoyable atmosphere in the room.

Helen Siilin, for your strong compassion and friendship, and for your assistance when I needed help in changing the schedule.

Nathlie Spång, Peter Cashin, Hella Hultin, Filip Sköldberg, Carl-Johan Drott and Lana Ghanipour for working on-call duties instead of me and all my colleagues and co-workers in the Department of Surgery, Uppsala University Hospital, for all their support, help and friendship;

Benkt-Åke, my father, for teaching me the importance of all kinds of knowledge and how to deal with Excel, and Lillemor, my mother, for all her moral support and advices. To both, my heartfelt thanks for all their support and help with my thesis celebration, my house, cars and daughters during all those double-working years;

Maria and Karin, my sisters, for proofreading the outline of my thesis.

Fabiola, my wife, for all your love, patience and support and for sacrificing so much for the sake of my research, and for all your wonderful food which has kept me alive;

Natalie and Caroline, my daughters, for bringing music to our home, for all your love for an often absent father and for always reminding me what is most important in life.
References


20. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. an Attempt at a Histo-Clinical Classification. *Acta pathologica et microbiologica Scandinavica* 1965;64:31-49.


86. Kubota T, Weisenthal L. Chemotherapy sensitivity and resistance testing: to be "standard" or to be individualized, that is the question. *Gastric Cancer* 2006;9(2):82-7.

88. Csoka K, Tholander B, Gerdin E, de la Torre M, Larsson R, Nygren P. In vitro
determination of cytotoxic drug response in ovarian carcinoma using the
fluorometric microculture cytotoxicity assay (FMCA). *Int J Cancer*
1997;72(6):1008-12.

Increased in vitro cellular drug resistance is related to poor outcome in
high-risk childhood acute lymphoblastic leukaemia. *British journal of

al. Detection of tumor-specific cytotoxic drug activity in vitro using the
fluorometric microculture cytotoxicity assay and primary cultures of

91. Lindhagen E, Nygren P, Larsson R. The fluorometric microculture cytotoxicity

92. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance
status scoring in lung cancer: a prospective, longitudinal study of 536

93. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-
effectiveness analysis in health-care resource allocation decision-making:
how are cost-effectiveness thresholds expected to emerge? *Value Health*

94. Brauer CA, Rosen AB, Greenberg D, Neumann PJ. Trends in the measurement
of health utilities in published cost-utility analyses. *Value Health*

95. Advertisement: NHS R & D Research Methodology Programme and the
National Institute for Clinical Excellence (NICE): RM03/JH12: The
societal value of health gains. Available from:
http://www.publichealth.bham.ac.uk/nccrm/invitations_to_tender.htm
[Last accessed February 8, 2004].

96. Weinstein M, Siegel J, Gold M, al. e. Recommendations of the panel on cost-

the cost-effectiveness of cytoreductive surgery and hyperthermic
intraperitoneal chemotherapy (peritonectomy) at the St George Hospital
peritoneal surface malignancy program. *Annals of surgery*

Cost analysis of the combined procedure of cytoreductive surgery and
hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol*

an intraperitoneal chemohyperthermia (IPCH) related to cytoreductive


Acta Universitatis Upsaliensis

*Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 886*

Editor: The Dean of the Faculty of Medicine

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.

Distribution: publications.uu.se
urn:nbn:se:uu:diva-197776