Peritoneal carcinomatosis from colorectal cancer

Preclinical and clinical studies into surgical and medical treatment

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Peritoneal carcinomatosis from colorectal cancer
Preclinical and clinical studies into surgical and medical treatment

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 13 april 2012
om 10.30 uur precies

door
Yvonne Louisa Bertha Klaver
geboren op 25 april 1985
te Eindhoven

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Journal of Surgical Oncology 2012; Accepted for publication

Introduction

Peritoneal carcinomatosis is a condition characterised by the development of solid tumor deposits on the peritoneal surface following detachment of tumour cells from the primary tumour[1]. Shedding of tumour cells may occur spontaneously or as a result of spill during surgical procedures. The process of attachment of tumour cells to the mesothelial cells of the peritoneum involves neoangiogenesis and is mediated by several growth factors. Tumour implantation and growth may lead to invasion of any organ or structure that is covered by the peritoneum. Besides the presence of solid tumours, occlusion of lymphatic drainage and excessive fluid production caused by increased capillary permeability lead to intraperitoneal fluid accumulation and eventually result in ascites[2;3].

In patients with colorectal cancer, spread of tumour cells to the peritoneal cavity and the subsequent development of peritoneal carcinomatosis is usually regarded as metastatic disease (stage IV). Because this condition has always been considered to be an end stage of disease, treatment was offered with palliative intent only, consisting mostly of supportive care and occasionally systemic chemotherapy. The role of surgery used to be restricted to minimally invasive interventions aiming for symptom relief. Results of palliative treatment in this group of patients are infamous for a poor prognosis with invariably fatal outcome[4-7]. Therefore, peritoneal carcinomatosis of colorectal origin has received little interest from oncologic research perspectives. This has resulted in a lack of data regarding incidence, clinical course of disease and accurate treatment evaluation.

In the 1980's, peritoneal carcinomatosis gained more interest, triggered by the observation that a subgroup of patients presented solely with peritoneal tumour implants in the absence of systemic metastases[8;9]. This initiated the development of aggressive surgical treatment modalities combining radical cytoreductive surgery with intraperitoneal application of chemotherapy[10-14]. With this approach, prolonged overall survival and even cure of disease has been reported[15-22].

Until now, only one completed phase III randomised trial investigating the outcome of surgical intraperitoneal treatment has been published. Verwaal et al. reported a significant increase in median overall survival in patients treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) as compared to patients receiving standard palliative care consisting of systemic 5-fluorouracil and leucovorin[21-23]. The promising outcomes of this study have convinced many surgeons to accept this technique as standard of care for selected patients with peritoneal carcinomatosis, and HIPEC treatment is nowadays offered in specialised centres all over the world. However, this study was heavily criticised for not including a control group receiving cytoreductive surgery only. Therefore it remained unclear whether both cytoreductive surgery and HIPEC are indeed required for the reported

improvement in survival, or if the observed benefit may have been the result of one of both components only[24]. Interestingly, until recently no experimental data at all were available that investigated the efficacy of this treatment.

Meanwhile, the availability and use of palliative systemic treatment for patients with metastasised colorectal cancer has markedly increased. The development of new combinations of chemotherapy regimens and additional new agents has resulted in a significant increase in survival in patients with metastasised colorectal cancer[25-27].

With both new surgical and medical treatment strategies available, the choice of care for the patient presenting with peritoneal carcinomatosis requires an individual approach, exploration of all options of cure and care and detailed counseling. The present colorectal cancer treatment guidelines that are used for treatment of patients with peritoneal carcinomatosis are based on results among patients with metastatic colorectal cancer in general. More evidence regarding the baseline characteristics of the group of patients with peritoneal carcinomatosis and the natural course of this disease is required, in order to facilitate interpretation of outcomes of new treatment strategies. Furthermore, a better understanding of treatment mechanisms and effectiveness of different components of treatment is essential for an optimal patient selection and prevention of unnecessary morbidity and mortality.

Incidence & prognosis
Very little has been documented on incidence, natural course and prognosis of peritoneal carcinomatosis in patients with colorectal cancer. This can be explained by a lack of sensitive imaging tools for accurate diagnosis, and the traditional view of this condition as an end-stage of disease. In a single hospital-based study including 2756 patients with colorectal cancer, 214 (8%) patients were diagnosed with synchronous peritoneal carcinomatosis and 135 (5%) with metachronous disease[6]. Two older studies, also single-hospital based, reported 10% to 15% of patients with colon cancer to present with peritoneal carcinomatosis[5;28]. Peritoneal carcinomatosis developing metachronously is reported in 4-12% of patients after curative resection for colon cancer and in 2-19% of patients after curative resection for rectal cancer[29]. In patients undergoing repeat procedures for colorectal cancer after primary curative resection, 21%-44% of patients is diagnosed with peritoneal tumour deposits[30;31]. In autopsy studies, peritoneal carcinomatosis is found in up to 40% of patients who succumb to colorectal carcinoma[32;33].

The prognosis of patients with peritoneal carcinomatosis is poor, even with systemic treatment. In a French prospective multicenter study including 118 patients with peritoneal carcinomatosis of colorectal origin a median survival was reported of only 5.2 months[7]. In a large series of colorectal cancer patients presented by Jayne et al., including 392 patients with peritoneal involvement, a median survival of 7 months was reached[6]. Chu et al. reported a median survival of 6 months in a series of 45 patients, mainly treated with 5-fluorouracil and leucovorin[5]. An analysis performed by Kohne et al. on 3825 patients with metastatic colorectal cancer treated with 5-fluorouracil (5-FU)-based therapy showed a median survival of 7.7 months in patients with peritoneal carcinomatosis[34]. In a phase III randomised controlled trial (RCT) conducted by Verwaal et al., a group of 50 patients with peritoneal carcinomatosis but without haematogenous metastases who were fit for surgery were treated with systemic chemotherapy and palliative surgery. Overall median survival was 12.6 months, with a 2-year survival rate of approximately 18%[4;21].

Surprisingly few studies have been published on the epidemiological and clinical features of this disease, and no population-based data are currently available. Yet population-based data are essential for the evaluation of the impact of treatment developments on survival outcomes of the general population. Furthermore, these data can be used to assess risk factor profiles and address complex questions regarding determinants of outcomes of disease.

Clinical features

Deposition and growth of tumour cells on the peritoneal surface may lead to bulky tumours which can involve any organ in the abdomen. Preference sites for peritoneal implants are the omentum, mesentery, bowel surface, pouch of Douglas, right paracolic gutter, and diaphragm[35;36]. Patients initially present with aspecific symptoms like abdominal discomfort, nausea, weight loss, cachexia, and fatigue, which are often indistinguishable from more general features of malignant disease. The tumour growth on intestinal surfaces and associated fluid accumulation eventually result in signs of bowel obstruction[37] and invalidating amounts of ascites. However, a considerable number of patients does not report any symptoms at the moment of diagnosis, especially when only small nonobstructing tumour implants are present without ascites.

Diagnosis

The assessment of peritoneal tumour spread is important for the initial diagnosis and staging of disease as well as for the evaluation of treatment response. Quantification of tumour volume and registration of tumour distribution is essential for selecting those patients who may benefit from an aggressive surgical approach. Unfortunately, despite technological

developments, the accuracy of the currently available imaging techniques is far from optimal and radiological findings often do not correlate with surgical observations[38;39].

The sensitivity and specificity of imaging techniques like abdominopelvic ultrasound and computed tomography (CT) are limited for peritoneal carcinomatosis. The sensitivity is negatively influenced by the small size of the tumour deposits, typically well below 1 cm[38;40;41], and the characteristic appearance of peritoneal spread that follows the outline of normal structures in the abdomen. Consequently, the extent of peritoneal disease is frequently underestimated by imaging modalities[39], and the presence of peritoneal involvement often remains unknown until laparotomy is performed.

Laparoscopy remains the most reliable tool for the diagnosis of peritoneal carcinomatosis. Yet, this invasive procedure necessitates anaesthesia and is associated with a risk for complications. Furthermore, adhesions from prior surgery may preclude adequate examination and complete inspection of the abdomen[42].

Thus, currently the role of diagnostic imaging in the diagnosis and evaluation of peritoneal tumour deposits is limited and inaccurate. However, radiologists should be aware of the importance of adequate preoperative assessment of peritoneal involvement and should be triggered to detect and describe the often subtle signs of peritoneal carcinomatosis. Furthermore, preoperative imaging remains essential in the evaluation of the presence of extraperitoneal disease and may assist surgeons in the design of cytoreductive procedures by revealing encasement of organs in the peritoneal tumour mass.

Treatment

Systemic treatment

Only few data have been published describing the effectiveness of systemic chemotherapy in this specific group of patients. Due to the lack of possibilities for accurate measurement and treatment response evaluation, peritoneal tumours usually do not meet the inclusion criteria for randomised trials. The scarce studies describing the results of chemotherapeutic treatment mainly review treatment with systemic 5-fluorouracil and leucovorin in retrospective analyses. The results of these studies invariably show a poor prognosis of patients with peritoneal carcinomatosis as compared to other metastatic sites, with disappointing results of systemic treatment. Median survival is typically around six months[6;7;34;43;44]. A few studies have aimed to describe the influence of newer combinations of chemotherapeutic agents, including oxaliplatin and irinotecan[15;43;44]. Reported results with these therapies are contradictive and require a careful interpretation. Many of these studies are carried out to compare systemic treatment with surgical treatment, which introduces a selection bias, only including patients in a good condition with limited extent of disease and without systemic metastases. The introduction of targeted therapies including monoclonal antibodies specifically targeted at growth factors like Epidermal Growth Factor

Receptor (EGFR) and Vascular Endothelial Growth Factor (VEGF) has resulted in a significant prolongation of overall survival in patients with metastasised colorectal cancer[25;26]. Although these agents are now routinely included in the treatment of patients with stage IV disease, there are no studies available at all that have evaluated the effect of these targeted therapies in patients with peritoneal carcinomatosis.

Cytoreductive surgery and intraperitoneal chemotherapy

Nowadays, the surgical treatment of solitary hepatic and pulmonary metastases from colorectal cancer is well accepted. The observation that a subgroup of patients presents with peritoneal carcinomatosis in the absence of systemic metastases has led to the hypothesis that peritoneal carcinomatosis should be regarded as locoregional spread of disease rather than as systemic metastasis. This approach has encouraged surgical oncologists to explore possibilities for locoregional therapies. In the last two decades of the last century, new treatment strategies have been developed consisting of aggressive cytoreductive surgery and the intraperitoneal application of chemotherapy, often combined with hyperthermia.

Surgical procedures invariably start with a careful and systematic exploration of the abdomen and registration of the extent of peritoneal disease. The abdomen is divided in 13 regions, and for each region the number and size of tumour deposits is assessed and recorded. The sum of these scores represents the Peritoneal Cancer Index (PCI), ranging from 0-39. For peritoneal carcinomatosis from colorectal cancer, a PCI score of 15 or more is a generally accepted exclusion criterion. In the Netherlands a simplification of this score is commonly used (simplified PCI, sPCI) describing the involvement of 9 regions of the abdomen[21]. The PCI or sPCI is a well-known predictive factor for the outcome of patients undergoing cytoreductive surgery and perioperative chemotherapy[45].

During cytoreductive surgery, an attempt is made to remove all visible tumour deposits from the peritoneal surface. In order to achieve a radical resection, resection of grossly involved organs may be required. In addition, peritonectomy procedures can be performed[12]. The completeness of resection is recorded using the Completeness of Cytoreduction Score (CCR). A CCR-0 score indicates that no macroscopic peritoneal tumour deposits remain after cytoreduction. A CCR-1 score is reported in case tumour nodules less than *2.5* mm persist after cytoreduction. Residual disease between *2.5* mm and 2.5 cm is scored as CCR-2. A CCR-3 score represents tumour nodules greater than 2.5 cm or a confluence of unresected tumour nodules at any site within the abdomen or pelvis[46]. An alternative scoring system is the R1-R2a-R2b classification, in which R1 resection represents no macroscopic residual tumour, R2a macroscopic residual disease less than 2.5 mm, and R2b represents the situation when tumour deposits of more than 2.5mm are left behind[21]. Treatment outcome is negatively influenced by the presence of residual tumour after optimal cytoreduction, especially when the diameter of the remaining tumour mass is greater than 2.5 mm. This is thought to be the maximum penetration depth of chemotherapeutic agents[45].

After macroscopically complete cytoreduction, intraperitoneal chemotherapy is given to eradicate microscopic disease. This chemotherapy can be administrated immediately following the surgical procedure in the operating room, usually combined with hyperthermia (hyperthermic intraperitoneal chemotherapy, HIPEC) or started from the first postoperative day on and be continued for 5 days (early postoperative intraperitoneal chemotherapy, EPIC). HIPEC perfusion may be performed with a closed abdomen, or with an open technique (also known as 'coliseum technique'). Chemotherapeutic agents and doses vary widely between centres worldwide. In the Netherlands, HIPEC perfusion during 90 minutes is routinely performed with mitomycin C in a dose of 35 mg/m^2 body surface (maximum dose 70 mg) at a temperature of 41-42°C.

Experimental studies
Several questions remain to be answered after the completion of a randomised trial performed to evaluate the effect of cytoreduction and intraperitoneal chemotherapy as compared to systemic palliative chemotherapy using 5-fluorouracil and leucovorin[21;24]. For example, the contribution of each of the components (cytoreductive surgery and HIPEC) remains unknown and also the individual effects of hyperthermia and presence of chemotherapy. Nevertheless, the combination treatment is currently widely accepted as standard of care. Ideally, these questions should be addressed in future randomised trials but this appears to be difficult if not impossible as was demonstrated by a phase III trial in France which failed to reach the required number of patients due to patient dissatisfaction with randomisation[47]. Best available clinical evidence now comes from multi-institutional registries but this requires careful interpretation as experience of the surgeons, techniques and perioperative care differ between institutions.

Animal models simulating peritoneal carcinomatosis provide an interesting alternative for studying separate components of treatment techniques under standardised conditions, allowing randomisation of treatment between homogenous groups. Surprisingly few experimental studies have been performed.

Rats are the most frequently used animals in experimental studies for peritoneal carcinomatosis of colorectal origin. Administration of 1,2-dimethylhydrazine in syngeneic WAG/Rij rats results in growth of moderately differentiated colon carcinoma, known as CC531[48;49]. One week after percutaneous intraperitoneal injection of these isolated tumour cells in healthy rats, macroscopic tumour deposits have developed providing a validated and reproducible model of peritoneal carcinomatosis of colorectal origin that resembles the clinical situation in humans[48;50]. The CC531 cell line has been shown to be sensitive to mitomycin, making this experimental model an attractive option to study the effect of HIPEC

with this particular anticancer drug[51]. The feasibility of performing cytoreductive surgery has been demonstrated in this model[52] and the model has been proven to be suitable for performance of HIPEC after cytoreductive surgery[53;54].

Outline of the thesis

The content of this thesis is divided into three parts. The first part aims to clarify the incidence and prognosis of patients with peritoneal carcinomatosis receiving palliative treatment for metastasised colorectal cancer. In the second part, the efficacy of cytoreductive surgery and HIPEC as well as the individual contribution and necessity of the separate components are evaluated in experimental studies, using an established animal model for peritoneal carcinomatosis which is suitable for the assessment of survival outcomes. The third part of the thesis questions some of the clinical selection criteria for cytoreductive surgery and perioperative intraperitoneal chemotherapy. Outcomes of different groups of patients undergoing cytoreductive surgery and intraperitoneal chemotherapy were evaluated by means of retrospective analysis of data from tertiary referral centres in the Netherlands and Australia.

Part I Palliative treatment

In **chapter 1**, a study is presented aiming to identify predictive factors for the synchronous presentation with peritoneal carcinomatosis at diagnosis of primary colorectal cancer, and to provide incidence and survival data. For this purpose the population-based registry of the Eindhoven Cancer Registry was used, which covers a population of 2.4 million inhabitants in the South of the Netherlands, and is representative for the general Dutch population.

By use of the same database, trends in chemotherapeutic treatment in patients with peritoneal carcinomatosis and the effect of treatment on population-based survival are evaluated and reported in **chapter 2**. Factors influencing the likeliness of receiving chemotherapy are analysed and the effectiveness of chemotherapy regimens is assessed in different time periods between 1995 and 2008 in the South of the Netherlands.

Chapter 3 reports the results of a subanalysis of the CAIRO and CAIRO2 randomised controlled trials. In these analyses the effectiveness of modern systemic combination chemotherapy including irinotecan, oxaliplatin and targeted agents (bevacizumab and cetuximab) were separately evaluated in patients with signs of peritoneal carcinomatosis and compared with the outcomes among patients with metastases on other locations.

The results of palliative surgery and outcomes in terms of survival, morbidity and mortality are investigated in **chapter 4**. Different surgical approaches are compared and factors predicting survival are identified.

Part II Surgical combination therapies with curative intent in experimental studies
The second part of the thesis consists of preclinical studies investigating the necessity of various components of the combined surgical treatment strategies.
The additional benefit of HIPEC after cytoreductive surgery on survival was investigated in an animal model for peritoneal carcinomatosis by means of a randomised controlled study. Results are described in **chapter 5**. In this experiment, animals were randomised between treatment with cytoreductive surgery only or cytoreductive surgery followed by HIPEC using two different concentrations of mitomycin.

In **chapter 6**, an experimental study designed to evaluate the necessity of the separate elements hyperthermia and chemotherapy for the effectiveness of the HIPEC therapy as a whole on survival is reported. In this study, cytoreductive surgery only was compared to hyperthermic perfusion with chemotherapy, normothermic perfusion with chemotherapy and hyperthermic perfusion without chemotherapy.

The impact on survival of the two most widely used treatment regimens for application of intraperitoneal chemotherapy, HIPEC and EPIC, was compared to that of treatment with cytoreductive surgery only in rats. The results of this experimental study are described in **chapter 7**. In addition, the effect of a combination of both therapies on survival was investigated.

Part III Clinical aspects of surgical combination therapies with curative intent
The selection of patients for cytoreductive surgery and perioperative intraperitoneal chemotherapy remains essential for successful treatment. In **chapter 8** it is investigated whether patients who developed intraperitoneal recurrent disease during or shortly after the use of adjuvant systemic chemotherapy, and thus show a relative resistance against systemic chemotherapy, should be eligible for local treatment with cytoreductive surgery and HIPEC.

Another group of patients in which the performance of aggressive surgery is debatable is the group of elderly patients. The ageing population and the associated increased cancer incidence lead to an increased demand for oncological surgery. Outcomes of elderly patients (aged 70 years or older) undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy are described in **chapter 9**.

Despite aggressive treatment with cytoreductive surgery and intraperitoneal chemotherapy, a significant proportion of patients develops a peritoneal recurrence. This raises the question whether a second procedure consisting of cytoreductive surgery and intraperitoneal chemotherapy should be offered. In **chapter 10,** a study is described evaluating the oncologic efficacy and feasibility of repeat cytoreductive surgery and intraperitoneal chemotherapy for recurrent disease.

Reference List

(1) Ceelen WP, Bracke ME. Peritoneal minimal residual disease in colorectal cancer: mechanisms, prevention, and treatment. *Lancet Oncol* 2009; 10(1):72-79.

(2) Tamsma J. The pathogenesis of malignant ascites. *Cancer Treat Res* 2007; 134:109-118.

(3) Tamsma JT, Keizer HJ, Meinders AE. Pathogenesis of malignant ascites: Starling's law of capillary hemodynamics revisited. *Ann Oncol* 2001; 12(10):1353-1357.

(4) Bloemendaal AL, Verwaal VJ, van Ruth S, Boot H, Zoetmulder FA. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: a prospective study. *Eur J Surg Oncol* 2005; 31(10):1145-1151.

(5) Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989; 63(2):364-367.

(6) Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89(12):1545-1550.

(7) Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88(2):358-363.

(8) Sugarbaker PH. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. *Semin Surg Oncol* 1998; 14(3):254-261.

(9) Sugarbaker PH. Management of peritoneal-surface malignancy: the surgeon's role. *Langenbecks Arch Surg* 1999; 384(6):576-587.

(10) Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, Alexander R et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. *Ann Surg Oncol* 2007; 14(1):128-133.

(11) Katz MH, Barone RM. The rationale of perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies. *Surg Oncol Clin N Am* 2003; 12(3):673-688.

(12) Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995; 221(1):29-42.

(13) Sugarbaker PH, Schellinx ME, Chang D, Koslowe P, von Meyerfeldt M. Peritoneal carcinomatosis from adenocarcinoma of the colon. *World J Surg* 1996; 20(5):585-591.

(14) Sugarbaker PH. Carcinomatosis--is cure an option? *J Clin Oncol* 2003; 21(5):762-764.

(15) Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; 27(5):681-685.

(16) Kecmanovic DM, Pavlov MJ, Ceranic MS, Sepetkovski AV, Kovacevic PA, Stamenkovic AB. Treatment of peritoneal carcinomatosis from colorectal cancer by cytoreductive surgery and hyperthermic perioperative intraperitoneal chemotherapy. *Eur J Surg Oncol* 2005; 31(2):147-152.

(17) Pilati P, Mocellin S, Rossi CR, Foletto M, Campana L, Nitti D et al. Cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis arising from colon adenocarcinoma. *Ann Surg Oncol* 2003; 10(5):508-513.

(18) Piso P, Dahlke MH, Ghali N, Iesalnieks I, Loss M, Popp F et al. Multimodality treatment of peritoneal carcinomatosis from colorectal cancer: first results of a new German centre for peritoneal surface malignancies. *Int J Colorectal Dis* 2007; 22(11):1295-1300.

(19) Schneebaum S, Arnold MW, Staubus A, Young DC, Dumond D, Martin EW, Jr. Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. *Ann Surg Oncol* 1996; 3(1):44-50.

(20) Shen P, Hawksworth J, Lovato J, Loggie BW, Geisinger KR, Fleming RA et al. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma. *Ann Surg Oncol* 2004; 11(2):178-186.

(21) Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(22)   Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; 15(9):2426-2432.

(23)   Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12(1):65-71.

(24)   Khatri VP. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer: a panacea or just an obstacle course for the patient? *J Clin Oncol* 2010; 28(1):5-7.

(25)   Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol* 2007; 8(10):898-911.

(26)   Meulenbeld HJ, van Steenbergen LN, Janssen-Heijnen ML, Lemmens VE, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. *Ann Oncol* 2008; 19(9):1600-1604.

(27)   Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009; 360(6):563-572.

(28)   Minsky BD, Mies C, Rich TA, Recht A, Chaffey JT. Potentially curative surgery of colon cancer: patterns of failure and survival. *J Clin Oncol* 1988; 6(1):106-118.

(29)   Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006; 243(2):212-222.

(30)   Gunderson LL, Sosin H, Levitt S. Extrapelvic colon--areas of failure in a reoperation series: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 1985; 11(4):731-741.

(31)   Tong D, Russell AH, Dawson LE, Wisbeck W. Second laparotomy for proximal colon cancer. Sites of recurrence and implications for adjuvant therapy. *Am J Surg* 1983; 145(3):382-386.

(32)   Gilbert JM, Jeffrey I, Evans M, Kark AE. Sites of recurrent tumour after 'curative' colorectal surgery: implications for adjuvant therapy. *Br J Surg* 1984; 71(3):203-205.

(33)   Russell AH, Pelton J, Reheis CE, Wisbeck WM, Tong DY, Dawson LE. Adenocarcinoma of the colon: an autopsy study with implications for new therapeutic strategies. *Cancer* 1985; 56(6):1446-1451.

(34)   Kohne CH, Cunningham D, Di CF, Glimelius B, Blijham G, Aranda E et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002; 13(2):308-317.

(35)   Gerber SA, Rybalko VY, Bigelow CE, Lugade AA, Foster TH, Frelinger JG et al. Preferential attachment of peritoneal tumor metastases to omental immune aggregates and possible role of a unique vascular microenvironment in metastatic survival and growth. *Am J Pathol* 2006; 169(5):1739-1752.

(36)   Meyers MA. Distribution of intra-abdominal malignant seeding: dependency on dynamics of flow of ascitic fluid. *Am J Roentgenol Radium Ther Nucl Med* 1973; 119(1):198-206.

(37)   Ketcham AS, Hoye RC, Pilch YH, Morton DL. Delayed intestinal obstruction following treatment for cancer. *Cancer* 1970; 25(2):406-410.

(38)   Jacquet P, Jelinek JS, Steves MA, Sugarbaker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. *Cancer* 1993; 72(5):1631-1636.

(39)   Koh JL, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2009; 16(2):327-333.

(40)   de Bree E, Koops W, Kroger R, van Ruth S, Witkamp AJ, Zoetmulder FA. Peritoneal carcinomatosis from colorectal or appendiceal origin: correlation of preoperative CT with intraoperative findings and evaluation of interobserver agreement. *J Surg Oncol* 2004; 86(2):64-73.

(41)   Franiel T, Diederichs G, Engelken F, Elgeti T, Rost J, Rogalla P. Multi-detector CT in peritoneal carcinomatosis: diagnostic role of thin slices and multiplanar reconstructions. *Abdom Imaging* 2009; 34(1):49-54.

(42)   Rau B. Diagnostic laparoscopy: indications and benefits. *Langenbecks Arch Surg.* 2005; 390(3):187-96.

(43)   Folprecht G, Kohne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Cancer Treat Res* 2005; 134:425-440.

(44)   Pelz JO, Chua TC, Esquivel J, Stojadinovic A, Doerfer J, Morris DL et al. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer* 2010; 10:689.

(45)   Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg* 2004; 91(6):739-746.

(46)   Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996; 82:359-374.

(47)   Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol* 2004; 11(5):518-521.

(48)   Lopes Cardozo AM, Gupta A, Koppe MJ, Meijer S, van Leeuwen PA, Beelen RJ et al. Metastatic pattern of CC531 colon carcinoma cells in the abdominal cavity: an experimental model of peritoneal carcinomatosis in rats. *Eur J Surg Oncol* 2001; 27(4):359-363.

(49)   Zedeck MS, Sternberg SS. A model system for studies of colon carcinogenesis: tumor induction by a single injection of methylazoxymethanol acetate. *J Natl Cancer Inst* 1974; 53(5):1419-1421.

(50)   Los G, Ruevekamp M, Bosnie N, De Graaf PW, McVie JG. Intraperitoneal tumor growth and chemotherapy in a rat model. *Eur J Cancer Clin Oncol* 1989; 25(12):1857-1866.

(51)   Dirix LY, Gheuens EE, van der HS, van Oosterom AT, De Bruijn EA. Cytotoxic activity of 7-N-(2-(-gamma-L-glutamylamino)- ethyl)dithio)ethyl)-mitomycin C and metabolites in cell lines with different resistance patterns. *Anticancer Drugs* 1994; 5(3):343-354.

(52)   Koppe MJ, Hendriks T, Boerman OC, Oyen WJ, Bleichrodt RP. Radioimmunotherapy is an effective adjuvant treatment after cytoreductive surgery of experimental colonic peritoneal carcinomatosis. *J Nucl Med* 2006; 47(11):1867-1874.

(53)   Aarts F, Hendriks T, Boerman OC, Koppe MJ, Oyen WJ, Bleichrodt RP. A comparison between radioimmunotherapy and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of colonic origin in rats. *Ann Surg Oncol* 2007; 14(11):3274-3282.

(54)   Aarts F, Bleichrodt RP, de Man B, Lomme R, Boerman OC, Hendriks T. The effects of adjuvant experimental radioimmunotherapy and hyperthermic intraperitoneal chemotherapy on intestinal and abdominal healing after cytoreductive surgery for peritoneal carcinomatosis in the rat. *Ann Surg Oncol* 2008; 15(11):3299-3307.

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Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study

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Abstract

Background

The aim of this study was to provide population-based data on incidence and prognosis of synchronous peritoneal carcinomatosis, and to evaluate predictors for its development.

Methods

Diagnosed in 1995-2008, 18 738 cases of primary colorectal cancer were included. Predictors of peritoneal carcinomatosis were analyzed by multivariable logistic regression analysis. Median survival in months was calculated by site of metastasis.

Results

In the study period, 904 patients were diagnosed with synchronous peritoneal carcinomatosis (4.8% of total, constituting 24% of patients presenting with M1 disease). The risk of peritoneal carcinomatosis was increased in case of advanced T-stage (T4 vs. T1,2: odds ratio (OR) 4.7, confidence interval 4.0-5.6), advanced N-stage (N0 vs. N1,2: OR 0.2 (0.1-0.2)), poor differentiation grade (OR 2.1 (1.8-2.5)), younger age (< 60 years vs. 70-79 years: OR 1.4 (1.1-1.7)), mucinous adenocarcinoma (OR 2.0 (1.6-2.4)), and right-sided localisation of primary tumour (left vs. right: OR 0.6 (0.5-0.7). Median survival of patients with peritoneum as single site of metastasis remained dismal (1995-2001: 7 (6-9) months; 2002-2008: 8 (6-11) months), contrasting the improvement among patients with liver metastases (1995-2001: 8 (7-9) months; 2002-2008: 12 (11-14) months.

Conclusion

To conclude, synchronous peritoneal metastases from colorectal cancer are more frequent among younger patients, and among patients with advanced T-stage, mucinous adenocarcinoma, right-sided tumours, and tumours which are poorly differentiated. The prognosis of synchronous peritoneal carcinomatosis remains poor with a median survival of 8 months, and even worse if concomitant metastases in other organs are present.

Introduction

Approximately one fourth of newly diagnosed colorectal cancer patients presents with disseminated disease, the liver being the most commonly affected. The recognition that early treatment of liver metastases may lead to a favourable outcome has resulted in high levels of radiological screening for synchronous liver metastases[1]. Consequently, the incidence and prognosis of patients with liver metastasis is currently well documented.

Besides the liver, a common site of synchronous metastases is the peritoneum. Until recently, medical oncologists and gastrointestinal surgeons considered peritoneal carcinomatosis (the implantation of tumour cells throughout the peritoneal cavity[2]) to be a virtually untreatable condition, suitable for palliative measures at most. Since several years, peritoneal carcinomatosis regained interest because of the introduction of locoregional therapies. Several centres worldwide have published their experiences offering cytoreductive surgery combined with intra-operative intra-peritoneal chemotherapy to selected patients with peritoneal carcinomatosis from colorectal cancer, with promising results[3-8].

However, surprisingly few studies have been published on the epidemiological and clinical features of this disease; none of them on a population-based level. The best available data are currently derived from single or multicenter studies of at most 214 patients with synchronous peritoneal carcinomatosis of colorectal origin[9;10].

Therefore, the primary aim of this study including all patients diagnosed with synchronous peritoneal carcinomatosis of colorectal origin between 1995 and 2008 in the south of the Netherlands was to provide reliable population-based data on the incidence of synchronous peritoneal carcinomatosis related to relevant patient and tumour characteristics, and to identify predictors for the development of synchronous peritoneal carcinomatosis. Furthermore, data were provided on the prognosis of these patients, representing an era of evolving treatment.

Methods

The Eindhoven Cancer Registry collects data on all patients with newly diagnosed cancer in a large part of the southern Netherlands, which comprises about 2.4 million inhabitants. This population-based registry is notified by 6 pathology departments, 10 community hospitals at 17 locations, and 2 radiotherapy institutions.

Between 1995 and 2008, 18 738 cases of primary colorectal cancer (C18.0-C20.9) were diagnosed in the Eindhoven Cancer Registry area. Information on patient and tumour characteristics is routinely extracted from the medical records by specially trained administrators of the cancer registry. Anatomical sites of distant metastasis at time of diagnosis are registered according to ICD-O (International Classification of Disease

– Oncology). Registration takes place 6 to 12 months after diagnosis. By means of an independent case ascertainment method, the completeness of the registration is estimated to exceed 95%[11]. TNM-stage in this study was based upon the TNM Classification of Malignant tumours by the International Union Against Cancer (UICC), 6th edition[12]. Vital status of all patients diagnosed until 31st of December 2008 was assessed on 1st of January 2009 through merging with the Municipal Administrative Databases, where all deceased and emigrated persons in the Netherlands are registered.

Statistical analyses

Incidence rates are shown as the 5-year moving average of the number of new patients per 100 000 inhabitants per year. The rates are age-standardised, using the European Standardised Rate (ESR)[13]. Patient and tumour characteristics of patients with different sites of metastases were compared and analysed using a two-sided Chi^2 test. In case of unknown postoperative T or N stage, clinical T or N stage was used. The proportion of patients undergoing resection of the primary tumour, and/or cytoreductive surgery with or without intra-operative hyperthermic intra-peritoneal chemotherapy (HIPEC) was calculated by period of diagnosis (1995-2001, 2002-2005, and 2006-2008). The independent influence of relevant patient and tumour characteristics on the risk of presenting with peritoneal carcinomatosis was analysed by means of a multivariable logistic regression analysis. Crude survival proportions were presented up to 200 weeks (46 months) after diagnosis, for patients diagnosed between 1995 and 2008. Survival time was defined as the time from diagnosis to death; patients still alive at January 1st 2009 were censored. A log rank test was used to compare survival proportions between patients with different sites of metastases. The independent influence of relevant patient and tumour characteristics on the risk of death (hazard ratio) was analysed by means of a multivariable proportional hazards regression analyses. Median survival in months and corresponding 95% confidence interval were calculated by site of metastasis. All tests of statistical significance were two-sided. SAS/STAT® statistical software (SAS system 9.1, SAS Institute, Cary, NC) was used for all analyses.

Results

Of the 18 738 patients who were diagnosed with colorectal cancer between 1995 and 2008, 3 817 patients (20%) were diagnosed with synchronous M1 disease (stage IV) (figure 1). 2 086 patients had metastases confined to the liver ($M1_{liver}$), 102 had synchronous lung metastases only, and 160 patients presented with metastases limited to one other location. The patients with stage IV disease included 904 patients (24%) with peritoneal carcinomatosis. Of the 904 patients with peritoneal carcinomatosis, 395 patients (44%) had the peritoneum as the only site of disseminated disease ($M1_{PC}$), while 509 patients (56%) had metastases next to the peritoneal carcinomatosis ($M1_{pc+}$).
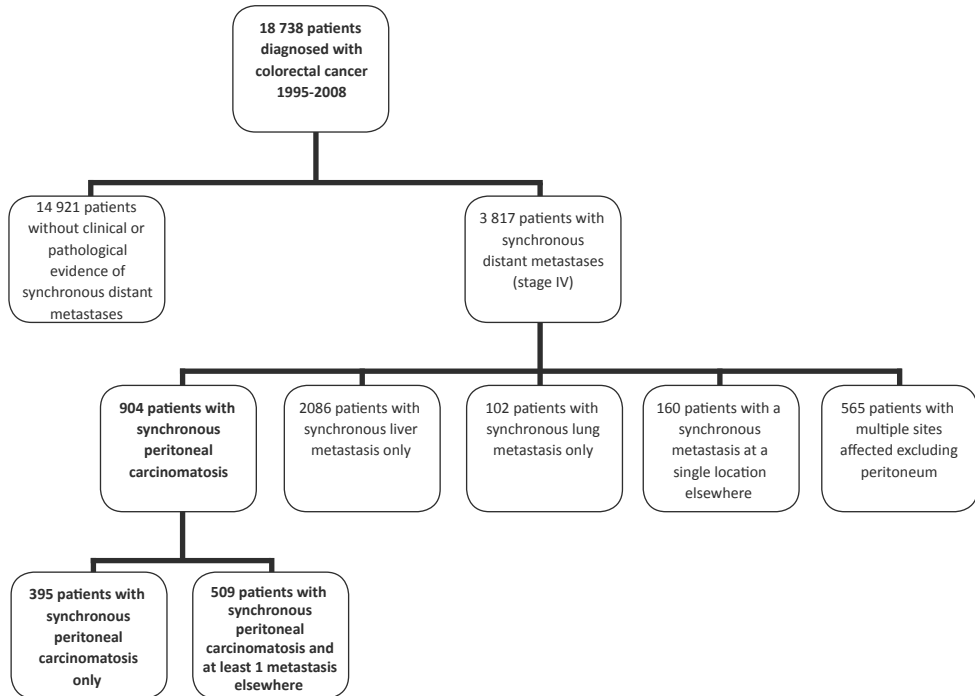
Figure 1. Numbers of patients with colorectal cancer and synchronous metastases in the south of the Netherlands diagnosed between 1995 and 2008.

The incidence of patients with newly diagnosed colorectal cancer and concurrent peritoneal carcinomatosis remained stable, being somewhat higher among men than among females (2-3 per 100 000 individuals per year, standardised for age) (figure 2). However, since 2001 an increase among females could be noted, the incidence catching up with males in the most recent years.

$M1_{PC}$ patients appeared to be somewhat older than $M1_{pc+}$ patients (table 1). Forty-five percent of $M1_{PC}$ patients were younger than 70 years, compared to 58% of $M1_{pc+}$ patients.

Table 1. General characteristics of patients diagnosed with colorectal cancer between 1995 and 2008 in the south of the Netherlands: patients with synchronous peritoneal carcinomatosis compared to patients with liver metastases, and no synchronous metastases.[a]

	Synchronous peritoneal carcinomatosis only		Synchronous peritoneal carcinomatosis and 1 or more metastases elsewhere		Synchronous liver metastases only		No synchronous metastases		P-value[b]
	n	(%)	n	(%)	n	(%)	n	(%)	
Age									
< 60	89	(23)	136	(27)	494	(24)	3125	(21)	
60-69	89	(22)	160	(31)	645	(31)	4209	(28)	
70-79	133	(34)	158	(31)	667	(32)	5057	(34)	
80+	84	(21)	55	(11)	280	(13)	2530	(17)	<0.0001
Gender									
Male	194	(49)	249	(49)	1233	(59)	7940	(53)	
Female	201	(51)	260	(51)	853	(41)	6981	(47)	<0.0001
Number of comorbid conditions									
0	117	(30)	191	(38)	742	(35)	4863	(35)	
1	114	(29)	140	(28)	581	(28)	4131	(28)	
2+	101	(26)	108	(21)	550	(26)	4262	(29)	
Unknown	63	(16)	70	(14)	219	(10)	1673	(11)	<0.0001
Period of diagnosis									
1995-2001	180	(46)	203	(40)	882	(42)	6459	(43)	
2002-2008	215	(54)	306	(60)	1210	(58)	8470	(57)	<0.0001
Localisation of primary tumour									
Colon, caecum	86	(22)	102	(20)	261	(13)	1748	(12)	
Colon, appendix	2	(0.5)	13	(3)	7	(0.3)	85	(0.6)	
Colon, ascending	60	(15)	62	(12)	184	(9)	1472	(10)	
Colon, hepatic flexure	24	(6)	29	(6)	98	(5)	564	(4)	
Colon, transverse	33	(8)	27	(5)	90	(4)	771	(5)	
Colon, splenic flexure	21	(5)	21	(4)	55	(3)	415	(3)	
Colon, descending	13	(3)	21	(4)	60	(3)	406	(3)	
Colon, sigmoid	78	(20)	122	(24)	545	(26)	3769	(25)	
Colon, overlapping, not otherwise specified	13	(3)	16	(3)	49	(2)	170	(1)	
Rectosigmoid	25	(6)	34	(7)	164	(8)	1083	(7)	
Rectum	40	(10)	62	(12)	573	(27)	4438	(30)	<0.0001
T stage of primary tumour (cT in case of unknown pT)									
T1	2	(0.5)	0	(0)	17	(0.8)	1304	(9)	
T2	7	(2)	2	(0.4)	74	(4)	2790	(19)	
T3	136	(34)	163	(32)	1057	(51)	8435	(57)	
T4	139	(35)	185	(36)	306	(15)	1356	(9)	
Tx	111	(28)	159	(31)	635	(30)	1033	(7)	<0.0001
N stage of primary tumour (cN in case of unknown pN)									
N0	70	(18)	51	(10)	414	(20)	6564	(44)	
N1	106	(27)	152	(30)	674	(32)	3321	(22)	
N2+	71	(18)	105	(21)	369	(18)	1182	(8)	
Nx	148	(37)	201	(39)	629	(30)	3854	(26)	<0.0001

	Synchronous peritoneal carcinomatosis only		Synchronous peritoneal carcinomatosis and 1 or more metastases elsewhere		Synchronous liver metastases only		No synchronous metastases		P-value[b]
	n	(%)	n	(%)	n	(%)	n	(%)	
Number of examined lymph nodes [c,d]									
0-6	64	(41)	81	(40)	340	(36)	4768	(44)	
7-11	24	(15)	39	(19)	256	(27)	2749	(26)	
12+	32	(20)	35	(17)	193	(20)	2092	(19)	
Unknown	38	(24)	50	(24)	162	(17)	1167	(11)	<0.0001
Number of positive lymph nodes [c,d]									
0	33	(21)	26	(13)	205	(22)	6222	(58)	
1-3	39	(25)	59	(29)	352	(37)	2354	(22)	
4+	50	(32)	73	(36)	277	(29)	958	(9)	
Exact number unknown [e]	36	(23)	47	(23)	117	(12)	1242	(12)	<0.0001
Lymph node ratio [c,d]									
0	26	(16)	21	(10)	169	(18)	5596	(52)	
0.01-0.24	12	(8)	17	(8)	146	(15)	1195	(11)	
0.25-0.49	26	(16)	20	(10)	151	(16)	827	(8)	
0.5-1	42	(27)	76	(37)	271	(29)	1001	(9)	
Unknown	52	(33)	71	(35)	214	(23)	2157	(20)	<0.0001
Differentiation grade of primary tumour									
Well/moderately	151	(38)	186	(37)	1098	(53)	10118	(68)	
Poorly/undifferentiated	127	(32)	159	(31)	412	(20)	2369	(16)	
Unknown	117	(30)	164	(32)	576	(28)	2434	(16)	<0.0001
Histology of primary tumour									
Adenocarcinoma, non-mucinous	266	(67)	375	(74)	1787	(85)	12859	(86)	
Adenocarcinoma, mucinous	105	(27)	106	(21)	155	(7)	1776	(12)	
Other/not specified	24	(6)	28	(6)	150	(7)	294	(2)	<0.0001

[a] The 'other' group, consisting of patients with simultaneous liver metastases and metastases in other organs, and patients with metastases in other organs than those described above (N=827), is not depicted here for reasons of clarity.

[b] Chi² test for equal proportions, the null hypothesis specifies equal proportions of the sample size for each class

[c] Excluding patients diagnosed between 1995 and 1998 since this item was not registered in that period

[d] Excluding patients who did not undergo resection of the primary tumour

[e] Often stated in the medical file as: 'several' or 'a number of'

M1$_{liver}$ patients had a clear divergent gender distribution, with 59% males compared to 53% males among M0 patients, and 49% among M1$_{pc+}$ patients. M1$_{PC}$ and M1$_{pc+}$ patients more often had a right-sided primary tumour location. A T4 tumour was much more frequently present among M1$_{PC}$ patients (35%) and M1$_{pc+}$ patients (36%) than among M1$_{liver}$ patients (15%) or M0 patients (9%). N stage did not differ among M1 patients, but was more often unknown among M1$_{PC}$ and M1$_{pc+}$ patients. The number of lymph nodes examined seemed not be lower among M1$_{PC}$ and M1$_{pc+}$ patients who underwent resection than among M0 patients. However, the number of positive nodes was much higher among M1$_{PC}$ and M1$_{pc+}$ patients, going together with a higher lymph node ratio. Differentiation grade was more unfavourable among M1$_{PC}$ and M1$_{pc+}$ patients. Mucinous adenocarcinoma was much more frequent among M1$_{PC}$ (27%) and M1$_{pc+}$ (21%) patients compared to M1$_{liver}$ (7%) and M0 (12%) patients. Only for a subset of patients, information was available on microsatellite instability (MSI) status (18% instable), and on the proportion of patients presenting with perforation (2%) and obstruction (8%) (data not shown).
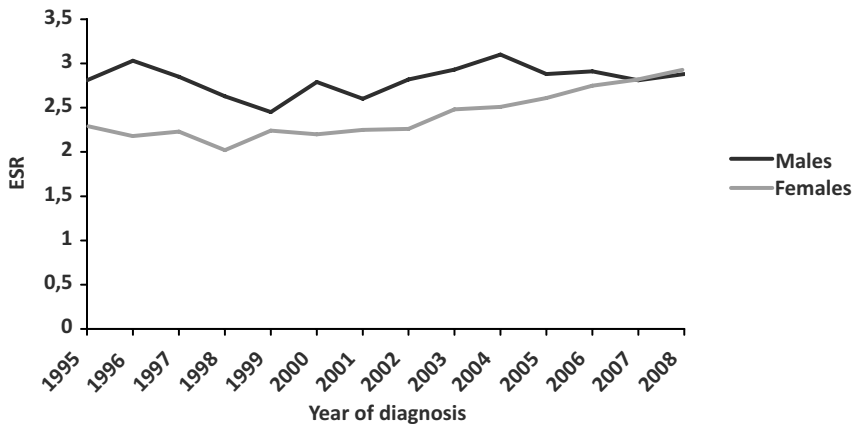
Figure 2. Trends in incidence of patients with newly diagnosed colorectal cancer and synchronous peritoneal carcinomatosis (n=904) between 1995 and 2008 in the south of the Netherlands (European Standardised Rate, 5-year moving averages).

In a multivariable logistic regression analysis, the risk of synchronous peritoneal carcinomatosis (including M1$_{PC}$ and M1$_{pc+}$) among patients with colorectal cancer clearly decreased by age (table 2). Females tended to have a higher risk, while patients with left-sided tumours had an apparent lower risk of developing peritoneal carcinomatosis. With increasing T and N stage, the risk of peritoneal carcinomatosis expanded. Poor/moderately differentiated tumours and mucinous adenocarcinoma showed a higher risk of peritoneal carcinomatosis. Sensitivity analyses repeating the multivariable logistic regression analysis calculating the risk of peritoneal carcinomatosis *only* (M1$_{PC}$) showed similar results, only

here there was a smaller age effect and no influence of gender (results not shown).

The proportion of patients who did not undergo resection of the primary tumour or cytoreduction of peritoneal metastases remained high (46% in 2006-2008); in the most recent period HIPEC was introduced: 11% of $M1_{PC}$ patients underwent this procedure in 2006-2008 (supplemental data).

Table 2. Multivariable logistic regression modelling the risk of peritoneal carcinomatosis among patients with colorectal cancer diagnosed between 1995 and 2008 in the south of the Netherlands.

	OR[b]	95% CI[c]
Age		
< 60	1.36	1.11-1.66
60-69	1.14	0.94-1.37
70-79 [a]	1.00	
80+	0.65	0.52-0.81
Gender		
Male [a]	1.00	
Female	1.07	0.92-1.24
Period of diagnosis		
1995-2001 [a]	1.00	
2002-2008	1.26	1.08-1.47
Localisation of primary tumour		
Right-sided tumour [a]	1.00	
Left-sided tumour	0.57	0.48-0.66
T stage of primary tumour (cT in case of unknown pT)		
T1,2	0.09	0.05-0.17
T3 [a]	1.00	
T4	4.72	3.95-5.64
N stage of primary tumour (cN in case of unknown pN)		
N0	0.17	0.13-0.23
N1,2 [a]	1.00	
Differentiation grade of primary tumour		
Well/ Moderately [a]	1.00	
Poorly/undifferentiated	2.10	1.76-2.51
Histology of primary tumour		
Adenocarcinoma, non-mucinous [a]	1.00	
Adenocarcinoma, mucinous	1.97	1.64-2.38
Other/not specified	0.58	0.39-0.79

[a] Reference group
[b] Odds ratio, adjusted for all variables listed in the table
[c] 95% Confidence Interval

There were evident differences in survival between patients with different metastatic location patterns (figure 3 and table 3). Patients with liver metastases exhibited an improved survival in time (median survival 8 months in 1995-2001 vs. 12 months in 2002-2008).

Patients with peritoneal carcinomatosis ($M1_{PC}$) had a median survival of 8 months in the most recent period. $M1_{pc+}$ patients had a dismal prognosis of only 5 months. There was no improvement in time during the study period.

The dismal prognosis of $M1_{pc+}$ patients compared to $M1_{PC}$ patients was confirmed by multivariable survival (proportional hazards regression) analyses (hazard ratio 1.16, 95% confidence interval 1.07-1.25) (supplemental data). Furthermore, age, T stage, N stage, differentiation grade and histology of the primary tumour had a prognostic impact among patients with peritoneal carcinomatosis.
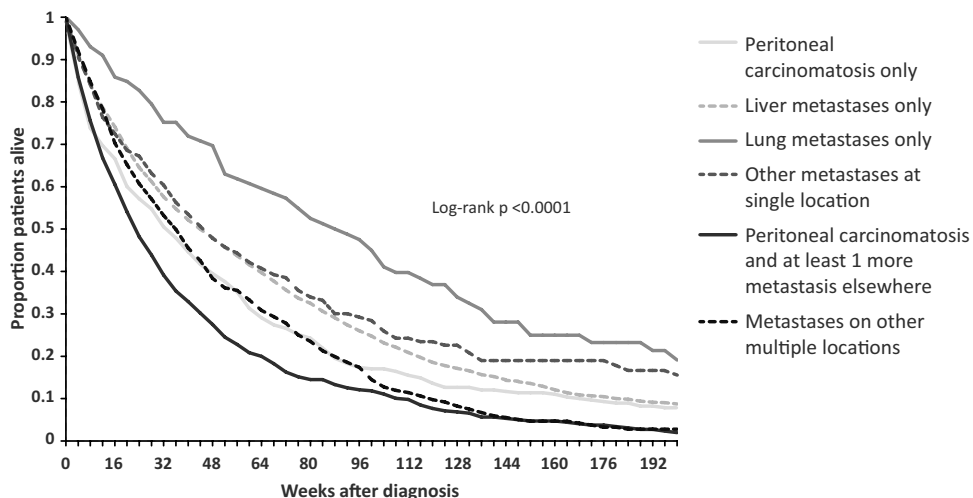
Figure 3. Crude survival of patients with synchronous metastatic colorectal cancer diagnosed between 1995 and 2008 in the south of the Netherlands, by site of metastasis.

Table 3. Median survival of patients with synchronous metastatic colorectal cancer diagnosed between 1995 and 2008 in the south of the Netherlands, by site of metastasis and period of diagnosis.

	Median survival in months (95% CI)	
	1995-2001	2002-2008
Peritoneal carcinomatosis only	7 (6-9)	8 (6-11)
Liver metastases only	8 (7-9)	12 (11-14)
Lung metastases only	22 (17-29)	20 (11-29)
Other distant metastases at a single location	8 (6-12)	12 (10-20)
Peritoneal carcinomatosis and ≥ 1 metastasis at other location	5 (5-8)	5 (4-7)
Other distant metastases at multiple locations	7 (6-8)	8 (7-10)

CI=Confidence Interval

Discussion

Despite the significant burden of peritoneal carcinomatosis in terms of incidence and especially mortality, very little has been documented on its clinical features and natural course. The present study including 904 patients with synchronous peritoneal carcinomatosis of colorectal origin is the largest series published to date, and unique in its population-based nature, representing 2.4 million inhabitants over a 14-year-period. These 904 patients constituted nearly a quarter of all patients diagnosed with M1 disease in the south of the Netherlands between 1995 and 2008. They represented almost 5% of patients of all patients with colorectal cancer. This proportion is slightly lower than the 7% stated in another relatively large cohort of patients with synchronous peritoneal carcinomatosis of colorectal origin described in literature, a single hospital-based study which included 214 patients[9]. Two older studies excluding rectal cancer reported 10% to 15% of patients with colon cancer to present with peritoneal carcinomatosis, which is higher than the well-over 6% of patients with colon cancer and peritoneal carcinomatosis at initial diagnosis in our study, but those studies were single-hospital based series comprising selected patients[14;15]. Since peritoneal carcinomatosis is best diagnosed during an operative procedure, one might speculate that our population-based study may have underestimated the true incidence of peritoneal carcinomatosis in the population. However, in over 93% of the patients eventually diagnosed with non-metastasised colorectal cancer (being 97% under the age of 80) the peritoneal surface was explored during a surgical procedure and therefore the chance that patients with peritoneal carcinomatosis were missed was likely to be very small. The only category for which this may be partly true is the group of patients aged 80 years or older. In this category 86% of the patients underwent a surgical exploration as part of the treatment. In the remaining patients, the abdominal cavity was usually screened for peritoneal carcinomatosis by various imaging modalities such as CT-scanning but these studies are all known for their moderate 60%-79% sensitivity in diagnosing peritoneal carcinomatosis[16-19]. Indeed, patients older than 80 years exhibited a smaller risk of presenting with peritoneal carcinomatosis. However, this does not explain the significant higher risk of presenting with peritoneal carcinomatosis at a younger age, especially younger than 60 years, for which we do not have a straightforward explanation. Besides a correlation with younger age, the present study also showed a positive relation between a more advanced T-stage and the risk of presenting with peritoneal carcinomatosis. The highest incidence of peritoneal carcinomatosis is found in patients with T4 tumours, while lower T-stages contribute less to the incidence of peritoneal carcinomatosis. This phenomenon has been documented before and lends support to the hypothesis that peritoneal carcinomatosis is caused by serosal infiltration of the primary tumour and subsequent shedding of malignant cells into the peritoneal cavity[2;20-23]. In contrast, the risk of patients with T3 tumours compared to T4

tumours to present with liver metastases is more or less similar, which suggests a different pathophysiological mechanism. The risk to present with peritoneal carcinomatosis was also associated with the location of the primary tumour in the colorectal tract, with a clearly higher risk for right-sided tumours. This relation has not been quantified previously in peer-reviewed literature. A possible explanation for this phenomenon may be the observation that, due to a longer asymptomatic period, right-sided T4 tumours are usually larger in diameter at the time of diagnosis than left-sided T4 tumours. Larger tumours infiltrate the serosal surface over a larger area which consequently may result in increased shedding of tumour cells into the peritoneal cavity, again confirming the previously mentioned pathophysiological mechanism of peritoneal carcinomatosis. Another explanation may be the hypothesised inherent difference in right-sided and left-sided colonic tumours caused by their distinct embryological origin and exposure to luminal agents, also resulting in survival differences[24]. Indeed, typical genetic differences have been found when comparing right- and left-sided tumours and these genotypes might result in a phenotype with a different likelihood to be associated with peritoneal carcinomatosis[25]. The higher risk of right-sided tumours to present with peritoneal carcinomatosis is also reflected in the age-adjusted incidence by sex, which showed an initially lower but more increasing incidence of peritoneal carcinomatosis among females over time. This can be explained by a sharply increased incidence of right-sided colon tumours among females in the south of the Netherlands within the study period[26]. Last but not least, mucinous adenocarcinoma was associated with the risk of peritoneal carcinomatosis. A negative prognostic impact of mucinous histologic cell type, including a lower effectiveness of oxaliplatin- and irinotecan based chemotherapy and a higher tendency to metastasise towards the peritoneal surface, has been described earlier[27-29]. However, once the disease has spread to the peritoneal surface, mucinous tumours interestingly appeared to be associated with a lower risk of death in our study.

The median survival of patients with peritoneal carcinomatosis as the only site of disseminated disease did not improve during the study period. The survival of 7-8 months is somewhat longer the median survival of 5-6 months previously reported by the two other studies which reported on the natural course of the disease[14;21]. While survival of patients with metastases confined to the liver was equal to that of peritoneal carcinomatosis in 1995-2001, population-based survival of these patients rose considerably from 8 to 12 months in the most recent period thanks to the introduction of more efficient chemotherapeutics[30]. Patients with peritoneal carcinomatosis do not seem to benefit at population level from the availability of the new treatment arsenal.

Efforts have been made to develop locoregional treatment strategies for patients with potentially resectable peritoneal metastases. A recent systematic review concluded that the current evidence suggests that radical cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is associated with improved survival compared to systemic

chemotherapy alone[5;31]. In a consensus statement following the Society of Surgical Oncology Annual meeting in 2006 it was advised that all patients suffering from peritoneal carcinomatosis should be eligible for such treatment in whom a complete cytoreduction can be achieved in the absence of systemic metastases[32]. In our study, from 2006 onwards indeed a growing proportion of patients has been treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy (11%). Future studies will have to monitor the effect of a growing proportion of patients undergoing this procedure on population-based survival of patients with peritoneal carcinomatosis.

The results of the present study may help to understand the natural history of the disease, and contribute to identifying subgroups of patients at risk of peritoneal carcinomatosis. The prognosis of patients suffering from peritoneal carcinomatosis remains dismal, especially compared to the improvements that have been reported for patients with liver metastases from colorectal origin. This underlines the importance of initiating studies on new treatment strategies for this population[32-35].

Reference list

(1)   Alberts SR, Wagman LD. Chemotherapy for colorectal cancer liver metastases. *The oncologist* 2008;13(10): 1063-1073.

(2)   Ceelen WP, Bracke ME. Peritoneal minimal residual disease in colorectal cancer: mechanisms, prevention, and treatment. *Lancet Oncol* 2009;10(1): 72-79.

(3)   Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004;22(16): 3284-3292.

(4)   Kianmanesh R, Scaringi S, Sabate JM, Castel B, Pons-Kerjean N, Coffin B, et al. Iterative cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. *Ann Surg* 2007;245(4): 597-603.

(5)   Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. *J Clin Oncol* 2006;24(24): 4011-4019.

(6)   Hagendoorn J, van Lammeren G, Boerma D, van der Beek E, Wiezer MJ, van Ramshorst B. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal and gastrointestinal origin shows acceptable morbidity and high survival. *Eur J Surg Oncol* 2009;35(8): 833-837.

(7)   Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008;15(9): 2426-2432.

(8)   Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* 2010;28(1): 63-68.

(9)   Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002;89(12): 1545-1550.

(10)   Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006;243(2): 212-222.

(11)   Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993;22(3): 369-376.

(12)   UICC. TNM Classification of Malignant Tumours (6th edn). Wiley-Liss: New York, 2002.

(13)   Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (eds). Cancer incidence in five continents. IARC Scientific Publications: Lyon, 1997.

(14)   Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989;63(2): 364-367.

(15)   Minsky BD, Mies C, Rich TA, Recht A, Chaffey JT. Potentially curative surgery of colon cancer: patterns of failure and survival. *J Clin Oncol* 1988;6(1): 106-118.

(16)   Franiel T, Diederichs G, Engelken F, Elgeti T, Rost J, Rogalla P. Multi-detector CT in peritoneal carcinomatosis: diagnostic role of thin slices and multiplanar reconstructions. *Abdominal imaging* 2009;34(1): 49-54.

(17)   de Bree E, Koops W, Kroger R, van Ruth S, Witkamp AJ, Zoetmulder FA. Peritoneal carcinomatosis from colorectal or appendiceal origin: correlation of preoperative CT with intraoperative findings and evaluation of interobserver agreement. *J Surg Oncol* 2004;86(2): 64-73.

(18)   Jacquet P, Jelinek JS, Steves MA, Sugarbaker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. *Cancer* 1993;72(5): 1631-1636.

(19)   Davies J, Chalmers AG, Sue-Ling HM, May J, Miller GV, Martin IG, Johnston D. Spiral computed tomography and operative staging of gastric carcinoma: a comparison with histopathological staging. *Gut* 1997;41(3): 314-319.

(20) Knorr C, Reingruber B, Meyer T, Hohenberger W, Stremmel C. Peritoneal carcinomatosis of colorectal cancer: incidence, prognosis, and treatment modalities. *Int J Colorectal Dis* 2004;19(3): 181-187.
(21) Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000;88(2): 358-363.
(22) Sugarbaker PH. Intraperitoneal chemotherapy for treatment and prevention of peritoneal carcinomatosis and sarcomatosis. *Dis Colon Rectum* 1994;37(2 Suppl): S115-122.
(23) Shepherd NA, Baxter KJ, Love SB. The prognostic importance of peritoneal involvement in colonic cancer: a prospective evaluation. *Gastroenterology* 1997;112(4): 1096-1102.
(24) Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N. Is there a difference in survival between right- versus left-sided colon cancers? *Ann Surg Oncol* 2008;15(9): 2388-2394.
(25) Glebov OK, Rodriguez LM, Nakahara K, Jenkins J, Cliatt J, Humbyrd CJ, et al. Distinguishing right from left colon by the pattern of gene expression. *Cancer Epidemiol Biomarkers Prev* 2003;12(8): 755-762.
(26) van Steenbergen LN, Lemmens VEPP, Louwman MJ, Straathof JW, Coebergh JWW. Increasing incidence and decreasing mortality of colorectal cancer due to marked cohort effects in southern Netherlands. *Eur J Cancer Prev* 2009;18(2): 145-152.
(27) Catalano V, Loupakis F, Graziano F, Torresi U, Bisonni R, Mari D, et al. Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy. *Br J Cancer* 2009;100(6): 881-887.
(28) Yan TD, Chu F, Links M, Kam PC, Glenn D, Morris DL. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma: non-mucinous tumour associated with an improved survival. *Eur J Surg Oncol* 2006;32(10): 1119-1124.
(29) Nozoe T, Anai H, Nasu S, Sugimachi K. Clinicopathological characteristics of mucinous carcinoma of the colon and rectum. *J Surg Oncol* 2000;75(2): 103-107.
(30) Meulenbeld HJ, van Steenbergen LN, Janssen-Heijnen ML, Lemmens VEPP, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. *Ann Oncol* 2008;19(9): 1600-1604.
(31) Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009;27(5): 681-685.
(32) Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, Alexander R, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. *Annals of surgical oncology* 2007;14(1): 128-133.
(33) Liberale G, Van Den Eynde M, Hendlisz A, El Nakadi I. Recommendations for general surgeons facing incidental peritoneal carcinomatosis of colorectal origin. *Eur J Surg Oncol* 2008;34(7): 725-726.
(34) Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. *Ann Surg Oncol* 2006;13(5): 635-644.
(35) Piso P, Dahlke MH, Ghali N, Iesalnieks I, Loss M, Popp F, et al. Multimodality treatment of peritoneal carcinomatosis from colorectal cancer: first results of a new German centre for peritoneal surface malignancies. *Int J Colorectal Dis* 2007;22(11): 1295-1300.

2

Population-based survival of patients with peritoneal carcinomatosis from colorectal origin in the era of increasing use of palliative chemotherapy

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Abstract

Background

Palliative chemotherapy improves survival in patients with metastasised colorectal cancer. However, there is a lack of data regarding effectiveness of modern chemotherapy in patients with isolated peritoneal carcinomatosis (PC).

Patients and methods

All patients with synchronous PC of colorectal origin diagnosed in the Eindhoven Cancer Registry registration area between 1995 and 2008 were included (n = 904). We assessed use of chemotherapy and overall survival in three time periods related to availability of different chemotherapy regimens.

Results

Chemotherapy use gradually increased over time. Median survival (MS) for patients with PC without other metastases diagnosed in 1995–2000 was 35 weeks (95% confidence interval (CI) 24-43) and 34 weeks (25-54) in 2005-2008. MS in patients diagnosed with PC plus other metastases was 21 weeks (15-27) in 1995–2000 and 26 weeks (18-33) in 2005-2008. In multivariable regression analysis, use of chemotherapy had a beneficial influence on survival only in 2005-2008. In the first two periods, chemotherapy treatment did not decrease the risk of death.

Conclusion

Despite increasing usage of palliative chemotherapy and availability of new agents population-based survival of patients with PC did not improve until very recently. Response to palliative chemotherapy in PC should be evaluated separately from haematogenous metastases.

Introduction

In the past two decades, chemotherapeutic treatment of patients with metastatic colorectal cancer has rapidly evolved. Subsequent randomised trials have defined the standard combination chemotherapy containing 5-fluorouracil (5-FU) derivatives together with oxaliplatin or irinotecan and a monoclonal antibody such as bevacizumab or cetuximab[1-5]. Several studies have reported a median survival of >20 months with these regimens, which implies a dramatic improvement as compared with historical series usually reporting a median survival of less than 6 months in untreated patients[6]. Therefore, palliative systemic chemotherapy is considered standard of care for most patients with metastatic colorectal cancer.

However, in a subset of patients the beneficial effect of systemic chemotherapy remains questionable, the patients being diagnosed with peritoneal carcinomatosis (PC). Peritoneal metastases are difficult to detect by imaging techniques, and often classified as 'non-measurable disease' and considered ineligible for response evaluation. As a result, these patients are not included in randomised studies. The sparse knowledge concerning patients with PC that is currently available is derived from a few non-randomised studies revealing that survival in the presence of PC is poor with reported median survival typically around 6 months[3;7-9].

In spite of this lack of evidence it is entirely conceivable that in daily clinical practice patients suffering from PC are considered as 'regular' metastasised colorectal cancer patients to whom palliative chemotherapy should be offered. The aim of this retrospective study was to investigate over time in a large unselected population the usage and the effect of palliative chemotherapy on survival in patients with PC.

Patients and Methods

The Eindhoven Cancer Registry (ECR) maintains a population-based cancer registry in a large part of the south-eastern Netherlands, collecting data on all patients with newly diagnosed cancer in an area with approximately 2.3 million inhabitants. The ECR is notified by 6 pathology departments, 10 community hospitals at 17 locations, and two large radiotherapy institutions.

Analyses for this study were based on data of all patients diagnosed with primary colorectal cancer (C18.0-C20.9) in the registration area of ECR between 1995 and 2008. Specially trained administrators of the cancer registry routinely extract data on patient and tumour characteristics on the basis of information in medical files, 6 to 18 months after diagnosis. By means of an independent case ascertainment method, the Dutch cancer registries attain an estimated completeness of >95%[10].

Subsites of systemic metastasis at time of diagnosis are registered according to the International Classification of Diseases for Oncology. Stage of the primary tumour is established according to the TNM (tumour- node-metastasis) classification. In patients who were treated surgically, the pathological TNM system was used for stage classification. Otherwise, the clinical stage was used. Chemotherapy (yes versus no) was defined as prescription of cytostatic drugs of any kind at initial diagnosis. Three periods were separately analysed according to the availability of chemotherapy regimens for metastasised colorectal cancer.

All colorectal cancer cases in this area have been documented in the ECR[11;12]. All patients diagnosed with primary colorectal cancer (C18.0– C18.9) between 1995 and 2008, who presented with synchronous peritoneal were selected from the database (n = 904). In all patients, follow-up of vital status was complete until January 2009. This information was obtained from the municipal administrative databases, in which data on all deceased and emigrated persons in the Netherlands are collected.

Analyses

Trends in treatment across the three periods (1995–1999, 2000–2004, and 2005-2008) were analysed by means of a Cochran-Armitage trend test. Crude survival proportions were presented up to 60 months after diagnosis. Survival time was defined as the time from diagnosis to death or last follow-up date (January 2009) for patients who were still alive.

Factors influencing the probability of receiving chemotherapy treatment were evaluated by multivariable logistic regression analysis. Differences between hospitals were included and corrected for in the analysis but are not shown in the results.

Changes in the percentages of patients treated with chemotherapy in the hospitals were evaluated over time. Survival proportions of patients diagnosed with PC in different periods and treated with chemotherapy were compared by means of the log-rank test. Multivariable survival analyses, using Cox proportional hazards regression modeling, were performed to estimate hazard ratios (HRs) for the various patient and tumour characteristics, including year of diagnosis. The model was first built without treatment variable (chemotherapy yes versus no); this was added separately to the model to investigate the effect of therapy on the HR of dying according to period of diagnosis. If adjustment for chemotherapy attenuated this association, this would suggest that increasing chemotherapy administration had contributed to the reduced mortality over time. Conversely, if adjustment did not attenuate this association, other reasons were more likely to be responsible for reduced mortality over time. Median survival in weeks and corresponding 95% confidence intervals (CIs) were calculated.

SAS/STAT® statistical software (SAS system 9.1, SAS Institute, Cary, NC) was used for all analyses.

Table 1. General characteristics of patients with peritoneal carcinomatosis, diagnosed between 1995 and 2008 in the South of the Netherlands (n=904), by extent of metastatic disease.

	Synchronous peritoneal carcinomatosis with or without other metastases	
	n	(%)
Age		
< 70 years	474	(52)
70+ years	430	(48)
Gender		
Male	443	(49)
Female	461	(51)
Period of diagnosis		
1995-1999	272	(30)
2000-2004	316	(35)
2005-2008	316	(35)
Comorbidity		
Yes	308	(34)
No	463	(51)
Unknown	133	(15)
Localisation of primary tumour		
Caecum	188	(21)
Appendix	15	(2)
Colon	511	(58)
Rectosigmoid	59	(7)
Rectum	102	(12)
T stage of primary tumour **(clinical stage in case of unknown pathological stage)**		
T1	2	(0.2)
T2	9	(1)
T3	299	(33)
T4	324	(36)
Tx	270	(30)
N stage of primary tumour **(clinical stage in case of unknown pathological stage)**		
N0	155	(17)
N1,2	434	(48)
Nx	315	(35)
Differentiation grade of primary tumour		
Well/moderate	337	(37)
Poorly/undifferentiated	286	(32)
Unknown	281	(31)
Extent of metastatic disease		
Peritoneal carcinomatosis only	395	(44)
Peritoneal carcinomatosis plus other metastases	509	(56)

Results

Between 1995 and 2008, 904 patients were diagnosed with synchronous PC in the registration area of ECR. The age-standardised incidence of synchronous PC in patients diagnosed with colorectal cancer remained stable over this time period. Patient and tumour characteristics are shown in table 1.

The prescription of chemotherapeutic agents increased significantly over time from 16% of all patients diagnosed with PC in 1995 to 46% in 2008 (p<0.0001) (figure 1). In younger patients (<70 years), the percentage of patients treated with chemotherapy was even greater, increasing from 29% of patients to 64%. In total, 292 patients (32%) of the study population received chemotherapy. Details are shown in table 2.
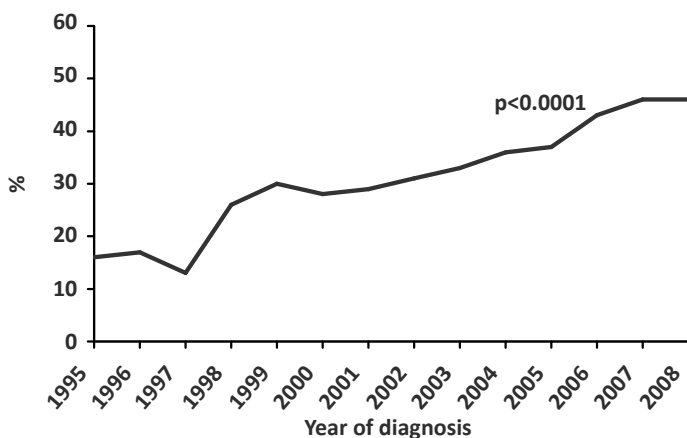
Figure 1. Percentage of patients who received chemotherapy per period.

Several factors influenced the probability of receiving chemotherapy. In multivariable analysis, patients diagnosed with PC between 2000 and 2004 were more likely to receive chemotherapy than patients diagnosed between 1995 and 1999 (Odds Ratio (OR) 2.1, 95% CI 1.37-3.15, p= 0.0005). This was even more pronounced in the most recent time period (OR=4.3, 95% CI 2.86-6.61, p<0.0001).

Table 2. Percentage of patients who received chemotherapy, by period and according to a number of relevant patient- and tumour characteristics.

| | 1995-1999 | | 2000-2004 | | 2005-2008 | |
	Total	Of which chemo	Total	Of which chemo	Total	Of which chemo
	n	(%)	n	(%)	n	(%)
Overall	272	21%	316	32%	316	43%
Age						
<70 years	151	29%	174	48%	149	64%
70+ years	121	10%**	142	12%**	167	25%**
Gender						
Male	137	27%	160	36%	146	48%
Female	135	14%*	156	27%	170	39%
Comorbidity[a]						
No	114	26%	95	45%	99	56%
Yes	123	15%*	167	26%*	173	36%
Extent of metastatic disease						
Peritoneal carcinomatosis only	137	18%	134	25%	124	35%
Peritoneal carcinomatosis plus other metastases	135	23%	182	36%*	192	48%

[a] Comorbidity unknown for 13%, 17%, and 14% of patients in the respective periods.
* P-value of Chi^2 test (within period) <0.05
** P-value of Chi^2 test (within period) <0.0001

Furthermore, patients diagnosed with rectal cancer were more often treated with chemotherapy (OR=1.6, 95% CI 1.05-2.39, p=0.03). Characteristics decreasing the probability of receiving chemotherapy treatment were older age (>70 years) (OR=0.2, 95% CI 0.15-0.30, p<0·0001), presence of comorbidities (OR=0.6, 95% CI 0.45-0.91, p=0.01), and female gender (OR=0.7, 95% CI 0.52-0.99, p=0.04) (table 3). Palliative surgery remained constant over time. (59% in 1995-1998 to 53% in 2003-2007, p=0.4). Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for PC was introduced in the ECR registration area in 2006. Between 2006 and 2008, 10 patients out of the presented population were treated with cytoreductive surgery and HIPEC.

Overall survival of the total population of patients with PC did not increase significantly over time (table 4). However, a trend towards improvement in survival up to 66 weeks (95% CI 57-91) was seen in patients treated with palliative systemic chemotherapy between 2005 and 2008 (p=0.064). Crude survival curves of patients treated with and without chemotherapy in the three different time periods are shown in figure 2.

Table 3. Multivariable logistic regression analysis modelling the chance of treatment with chemotherapy among patients with colorectal cancer and synchronous peritoneal carcinomatosis, diagnosed between 1995 and 2008 in the south of the Netherlands.

	OR	95% CI	P value
Age			
< 70 years[a]	1.0		
70+ years	0.2	0.15-0.30	<.0001
Gender			
Males[a]	1.0		
Females	0.7	0.52-0.99	0.04
Period of diagnosis			
1995-1999[a]	1.0		
2000-2004	2.1	1.37-3.15	0.0005
2005-2008	4.3	2.86-6.61	<.0001
Comorbidity			
No[a]	1.0		
Yes	0.6	0.45-0.91	0.01
Localisation			
Colon (incl. caecum and appendix)[a]	1.0		
Rectum (incl. rectosigmoid)	1.6	1.05-2.39	0.03
T stage			
T1-2	1.0	0.22-4.52	0.9
T3[a]	1.0		
T4	1.0	0.72-1.39	0.9
N stage			
N0	0.9	0.53-1.39	0.5
N1,2[a]	1.0		
Differentiation grade of primary tumour			
Well/moderately[a]	1.0		
Poorly/undifferentiated	0.8	0.54-1.08	0.1
Resection of primary tumour			
No[a]	1.0		
Yes	1.3	0.91-1.85	0.1
Extent of metastatic disease			
Peritoneal carcinomatosis only[a]	1.0		
Peritoneal carcinomatosis plus other metastases	1.4	0.99-1.88	0.06

Data are adjusted for all variables listed and differences between treatment hospitals.
OR=odds ratio
CI=Confidence Interval
[a] Reference category

Table 4. Median survival (in weeks) of patients with peritoneal carcinomatosis **(n = 904)**, according to extent of disease and period.

	1995-1999		2000-2004		2005-2008	
	n	Survival in weeks (95% CI)	n	Survival in weeks (95% CI)	n	Survival in weeks (95% CI)
Overall	272	26 (20-33)	316	24 (19-30)	316	28 (22-36)
Chemotherapy						
Yes	56	52 (39-75)	100	50 (42-62)	136	66 (57-91)
No	216	21 (16-27)	216	14 (11-17)	180	11 (8-15)
Age						
< 70 years	151	29 (22-39)	174	31 (27-39)	149	59 (48-72)
70+ years	121	22 (18-34)	142	16 (11-21)	167	17 (12-21)
Gender						
Male	137	32 (22-41)	160	24 (17-31)	146	30 (21-47)
Female	135	23 (18-28)	156	23 (17-34)	170	26 (19-35)
Comorbidity						
No	114	31 (22-41)	95	31 (23-39)	99	47 (28-69)
Yes	123	22 (16-34)	167	19 (16-29)	173	25 (18-32)
Sites of metastases						
PC only	137	35 (24-43)	134	31 (19-43)	124	34 (25-54)
PC plus other metastases	135	21 (15-27)	182	22 (17-28)	192	26 (18-33)

CI = Confidence Interval
PC = peritoneal carcinomatosis

Multivariable proportional hazards regression analysis modelling the risk of death for patients with colorectal cancer and synchronous PC is shown in table 5. A beneficial influence of time period on the risk of dying was observed in favour of patients diagnosed between 2005-2008 as compared with both earlier periods of time (HR 0.8, CI 0.64-0.92, p=0.004). The difference was not observed any more after adjusting for chemotherapy treatment. Comparison of the first two periods of time showed an equal risk of dying among patients with PC independent of chemotherapy treatment. Other beneficial prognostic factors identified by multivariable analysis were younger age (<70 years), absence of lymph node metastases, well or moderate differentiation grade of the primary tumour, and the performance of palliative surgery.

PC was the only site of metastasis in 395 patients in this population (44%). This group showed a higher median survival than patients with PC and additional other metastases in all time periods.
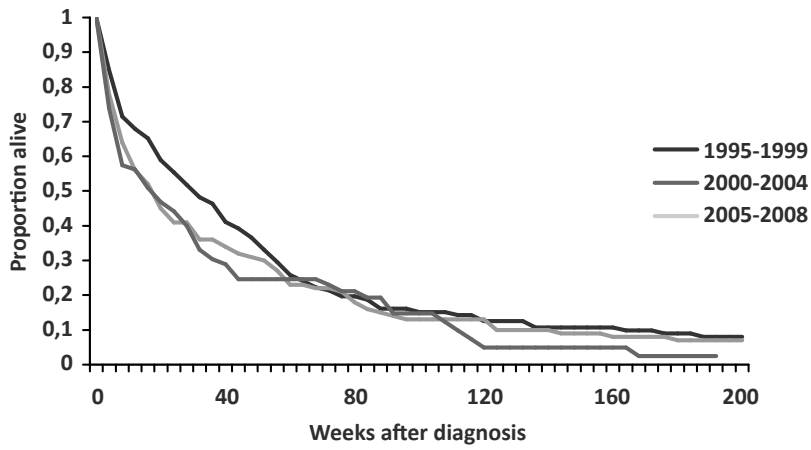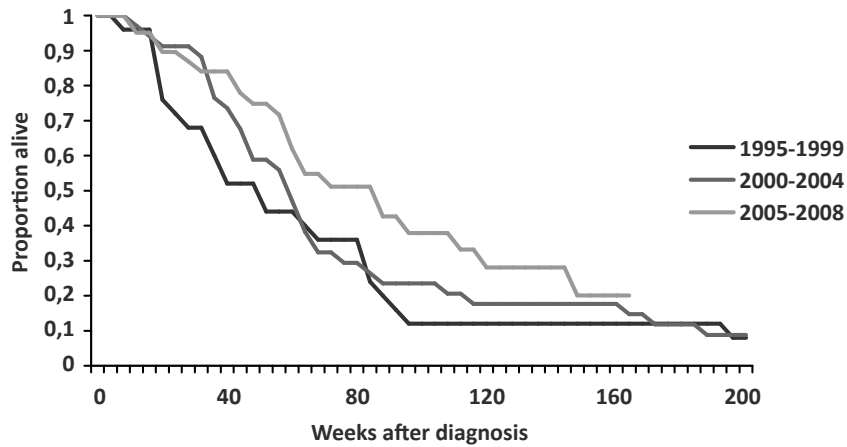
Figure 2a. Crude survival of patients with peritoneal carcinomatosis not treated with chemotherapy, according to period of diagnosis.

Log-rank, p=0.064

Figure 2b. Crude survival of patients with peritoneal carcinomatosis treated with chemotherapy, according to period of diagnosis.

Table 5. Multivariable proportional hazards regression analysis modelling the risk of death for patients with colorectal cancer and synchronous peritoneal carcinomatosis, diagnosed between 1995 and 2008 in the South of the Netherlands. Data are adjusted for all variables listed and differences between treatment hospitals.

	HR	95% CI	P value
Age			
< 70 years[a]	1.0		
70+ years	1.3	1.10-1.85	0.002
Gender			
Males[a]	1.0		
Females	1.0	0.86-1.14	0.8
Period of diagnosis			
1995-1999[a]	1.0		
2000-2004	1.1	0.92-1.29	0.3
2005-2008	1.0	0.83-1.20	0.9
Comorbidity			
No[a]	1.0		
Yes	1.0	0.87-1.20	0.8
Localisation			
Colon (incl. caecum and appendix)[a]	1.0		
Rectum (incl. rectosigmoid)	0.9	0.76-1.11	0.4
T stage			
T1-2	1.1	0.59-2.11	0.7
T3[a]	1.0		
T4	1.0	0.88-1.18	0.8
N stage			
N0	0.6	0.51-0.79	<0.0001
N1,2 [a]	1.0		
Differentiation grade of primary tumour			
Well/moderately[a]	1.0		
Poorly/undifferentiated	1.4	1.17-1.58	<0.0001
Resection of primary tumour			
No[a]	1.0		
Yes	0.5	0.41-0.57	<0.0001
Extent of metastatic disease			
Peritoneal carcinomatosis only[a]	1.0		
Peritoneal carcinomatosis plus other metastases	1.2	1.15-1.33	<0.0001
Chemotherapy			
Yes	0.4	0.34-0.47	<0.0001
No[a]	1.0		

HR=hazard ratio
CI=Confidence Interval
[a] Reference category

Without adjustment for 'chemotherapy': period of diagnosis 2000-2004 HR 1.0 (CL 0.83-1.17, p=0.9); 2005-2008 HR 0.8 (CL 0.64-0.92, p=0.004).
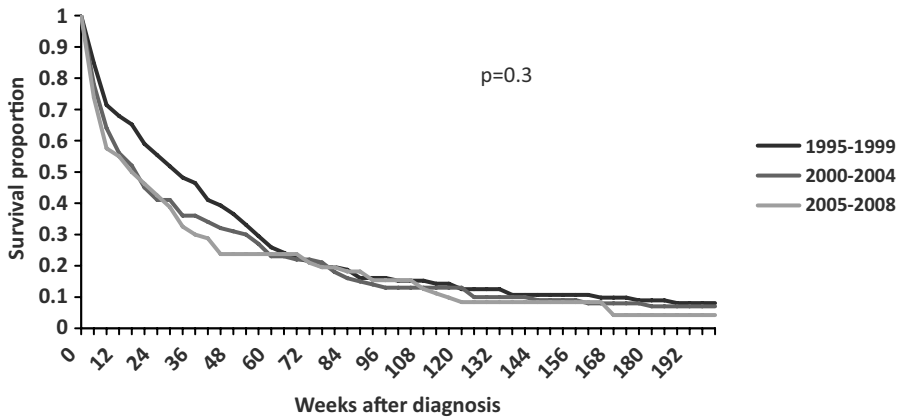
Figure 3a. Crude survival of patients with peritoneal carcinomatosis only, not treated with chemotherapy, according to period of diagnosis.

Figure 3b. Crude survival of patients with peritoneal carcinomatosis and other metastases, not treated with chemotherapy, according to period of diagnosis.

Figure 3c. Crude survival of patients with peritoneal carcinomatosis only, treated with chemotherapy, according to period of diagnosis.
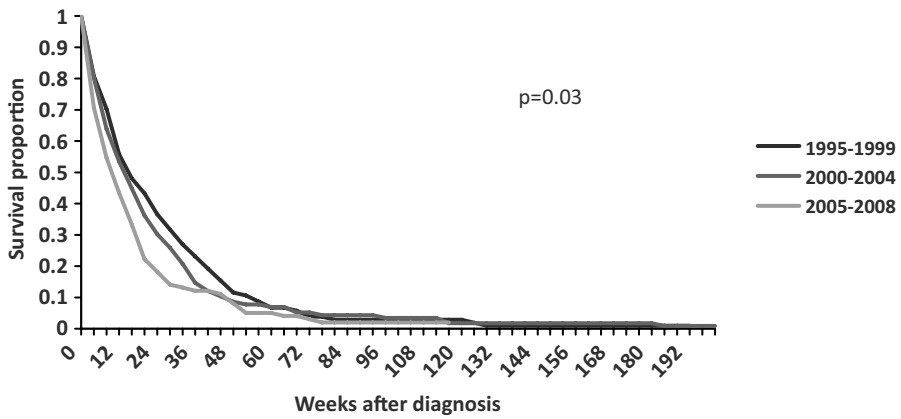

Figure 3d. Crude survival of patients with peritoneal carcinomatosis and other metastases, treated with chemotherapy, according to period of diagnosis.

Figure 4a. Crude survival of patients with synchronous liver metastases, not treated with chemotherapy, according to period of diagnosis.

Figure 4b. Crude survival of patients with synchronous liver metastases, treated with chemotherapy, according to period of diagnosis.

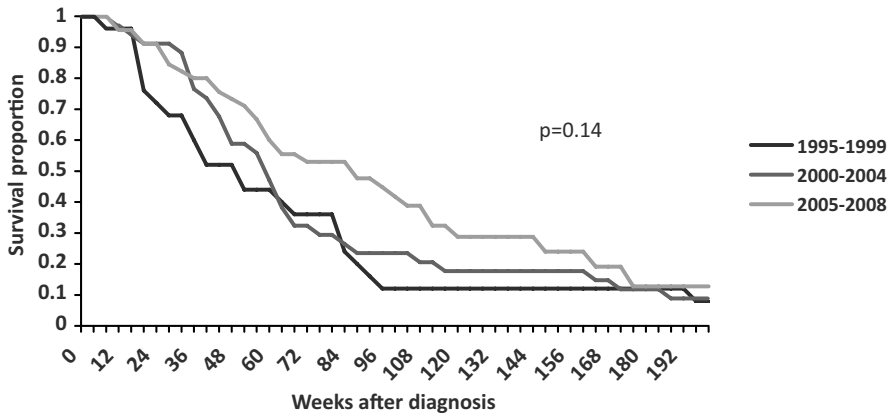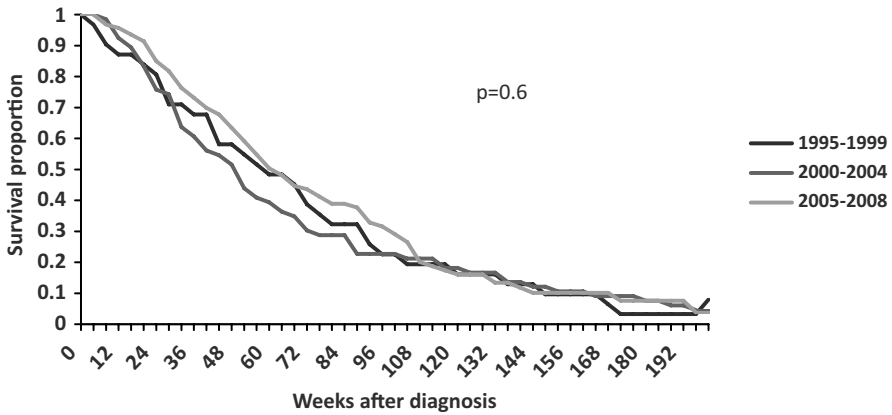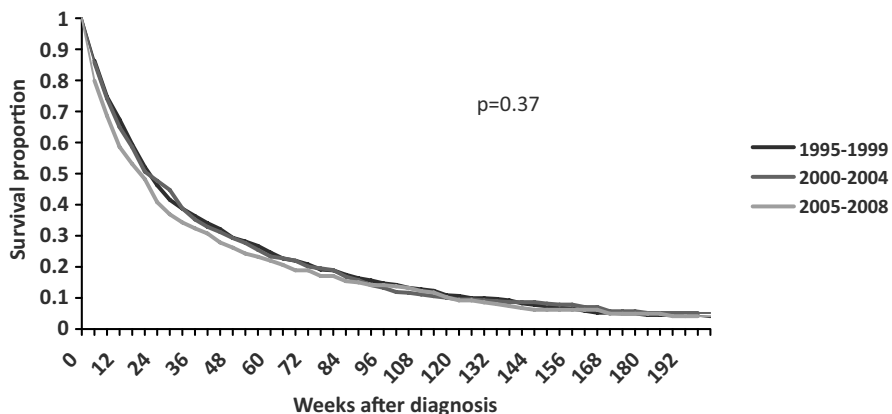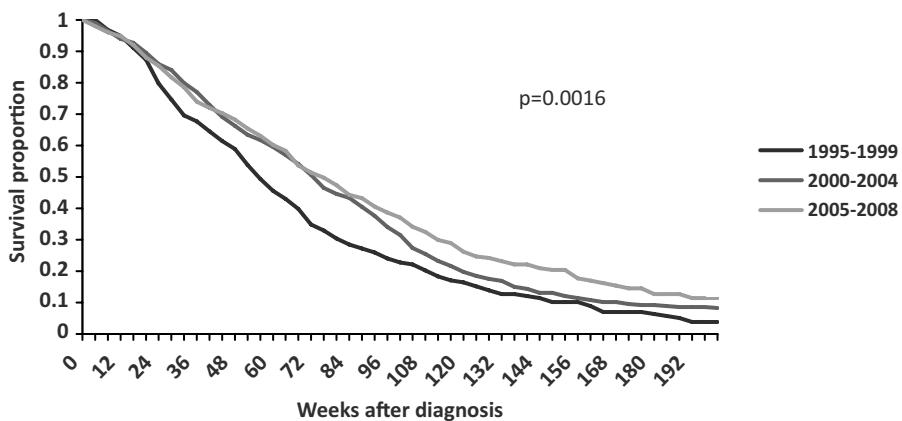Separate crude survival curves of patients with and without systemic metastasis in addition to PC are shown in figure 3, according to treatment with systemic palliative chemotherapy. As a comparison, survival data of patients with synchronous liver metastases as the only site of metastatic disease treated with chemotherapy in the same area and time interval were studied (figure 4). In this analysis, patients who underwent liver resection for their metastases were excluded. In these patients, an evident increase in survival was seen over time (p = 0.0016), in contrast to survival of patients with PC. Survival of patients with liver metastases who were treated with chemotherapy increased in each period of time, whereas survival of patients with PC remained stable between 1995 and 2004.

Discussion

The peritoneal surface is a common site of metastasis in patients with colorectal cancer, occurring in 13% of patients[8]. PC has long been considered to be an incurable condition, with a poor prognosis with a median survival of approximately 6 months[8;9;11].

Although the favourable effect of modern chemotherapy treatment on the survival of patients with metastatic disease in general has been well described, it remains unclear whether these systemic therapies have the same beneficial impact on the outcomes of the subset of patients diagnosed with PC. In recent years, the systemic treatment of metastasised colorectal cancer has rapidly evolved with the addition of oxaliplatin or irinotecan to 5-FU-based chemotherapy regimens[2;13;14]. New insights in carcinogenesis and angiogenesis contributed to the development of increasingly targeted and potentially more effective combinations of systemic treatment including agents like cetuximab and bevacizumab, resulting in a median survival of more than 20 months[15-17]. For this reason, systemic chemotherapy is now offered to an increasing number of patients with stage IV colorectal cancer, and this study shows that also in patients with PC, systemic chemotherapy use has significantly increased over time, from 21% in the period 1995-1999 to 43% in the period 2005-2008. Especially in patients <70 years, the prescription of chemotherapy increased: in the recent years, chemotherapy was used in 64% of the patients.

5-FU-based chemotherapy was the mainstay of treatment in the first two periods. Despite a significant increase in the use of chemotherapy over the two time periods, survival did not improve in this large unselected population. The most recent time period evaluated in this study (2005-2008) reflects a time in which combination therapies including oxaliplatin or irinotecan in combination with a monoclonal antibody like cetuximab or bevacizumab were introduced and became standard of care in the Netherlands. In the present study, including a large population of 904 patients, a trend in improvement in overall survival was observed in the period 2005-2008 in comparison with the two earlier periods. Data from small pooled analyses also suggest that patients with PC may profit from addition of irinotecan

and oxaliplatin to 5-FU based chemotherapy treatment[18;19]. Although this benefit may be partially explained by patient selection, this observation strengthens the evidence for an effect of modern combination chemotherapy treatment on survival in patients with PC.

In this study population, a marked difference in survival is seen between patients treated with or without systemic chemotherapy in all time periods in favour of chemotherapy treatment. The selection of patients receiving chemotherapy is mainly based on performance status, which indicates tumour load and co-morbidities. The observation that overall survival of patients who were not treated with chemotherapy in the last period of time has decreased to 11 weeks, even though more patients have been offered chemotherapy treatment, indicates a beneficial effect of palliative chemotherapy which cannot be explained by patient selection. Still, the effect is less pronounced than the effects observed in other localisations of metastatic disease like liver metastasis, and even with effective chemotherapy the prognosis of patients with PC remains worse than that of patients with metastases elsewehere[20]. There is no clear explanation for this observation. Yet, it might indicate that PC should be evaluated separately from systemic metastases. New insights in biological mechanisms cancer dissemination and the pathophysiology of PC from colorectal origin contributed to the understanding that PC can be regarded as a local-regional extension of disease, rather than a manifestation of systemic metastasis[21-25]. Furthermore, it has been suggested that gene expression patterns in the primary tumour determine not only the metastatic potential and the occurrence of peritoneal dissemination of colorectal cancer cells[23;25;26] but also variation in response to treatment with chemotherapeutic agents[27]. According to this hypothesis, gene expression in peritoneal disseminated cells may differ from expression patterns in metastases localised elsewhere, thereby modulating the sensitivity and response of tumour cells to different kinds of systemic administrated chemotherapy. In addition, it is known that the microenvironment at the site of metastasis affects molecular and cellular aspects of tumour growth[28]. Interactions between cancer cells and the peritoneum may differ from those involved in hematogenous and lymphogenous spread and thereby react differently to the available chemostatic agents. From the results of the current study, it may be postulated that PC (as opposed to, e.g. liver metastases) is not sensitive to 5-FU monotherapy, while modern chemotherapy schedules seem more effective.

The notion that a subgroup of patients presents with isolated intraperitoneal metastases without evidence of systemic disease contributed to the development of new locoregional treatment strategies consisting of cytoreductive surgery and HIPEC. In selected patients, this aggressive surgical approach combined with HIPEC results in a significant survival benefit[29]. Unfortunately, only a small and highly selected group of patients with limited disease confined to the peritoneal cavity is eligible for this treatment and so most patients suffering from PC are dependent on palliative surgery and/or systemic treatment.

The results of this study support the rationale for palliative treatment with the best available systemic chemotherapy schedules for patients with PC who do not meet the inclusion criteria for cytoreductive surgery and HIPEC. Still, the prognosis of patients with PC is worse than that of patients with other sites of metastases, even with the availability of more potent chemotherapy regimens. Future research should focus on developing the optimal combination of palliative chemotherapy regimens for patients suffering from PC of colorectal origin.

Reference List

(1)   Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351(4):337-345.

(2)   de Gramont A., Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18(16):2938-2947.

(3)   Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18(1):136-147.

(4)   Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol* 2005; 23(15):3502-3508.

(5)   Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005; 23(16):3697-3705.

(6)   Bengtsson G, Carlsson G, Hafstrom L, Jonsson PE. Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 1981; 141(5):586-589.

(7)   Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989; 63(2):364-367.

(8)   Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89(12):1545-1550.

(9)   Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88(2):358-363.

(10) Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993; 22(3):369-376.

(11) Lemmens VEPP, Klaver YLB, Verwaal VJ, Rutten HJT, Coebergh JW, de Hingh IHJT. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; 128(11):2717-2725.

(12) Lemmens VEPP, van Steenbergen L, Janssen-Heijnen M, Martijn H, Rutten H, Coebergh JW. Trends in colorectal cancer in the south of the Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. *Acta Oncol* 2010; 49(6):784-796.

(13) Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355(9209):1041-1047.

(14) Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; 343(13):905-914.

(15) Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22(1):23-30.

(16) Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350(23):2335-2342.

(17) Jonker DJ, Maroun JA, Kocha W. Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. *Br J Cancer* 2000; 82(11):1789-1794.

(18) Folprecht G, Kohne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Cancer Treat.Res.* 134, 425-440. 2007.

(19) Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; 27(5):681-685.

(20)   Meulenbeld HJ, van Steenbergen LN, Janssen-Heijnen ML, Lemmens VE, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. *Ann Oncol* 2008; 19(9):1600-1604.

(21)   Fermor B, Umpleby HC, Lever JV, Symes MO, Williamson RC. Proliferative and metastatic potential of exfoliated colorectal cancer cells. *J Natl Cancer Inst* 1986; 76(2):347-349.

(22)   Baskaranathan S, Philips J, McCredden P, Solomon MJ. Free colorectal cancer cells on the peritoneal surface: correlation with pathologic variables and survival. *Dis Colon Rectum* 2004; 47(12):2076-2079.

(23)   Kotanagi H, Saito Y, Yoshioka T, Koyama K. Characteristics of two cancer cell lines derived from metastatic foci in liver and peritoneum of a patient with colon cancer. *J Gastroenterol* 1998; 33(6):842-849.

(24)   Rekhraj S, Aziz O, Prabhudesai S, Zacharakis E, Mohr F, Athanasiou T et al. Can intra-operative intraperitoneal free cancer cell detection techniques identify patients at higher recurrence risk following curative colorectal cancer resection: a meta-analysis. *Ann Surg Oncol* 2008; 15(1):60-68.

(25)   Varghese S, Burness M, Xu H, Beresnev T, Pingpank J, Alexander HR. Site-specific gene expression profiles and novel molecular prognostic factors in patients with lower gastrointestinal adenocarcinoma diffusely metastatic to liver or peritoneum. *Ann Surg Oncol* 2007; 14(12):3460-3471.

(26)   McHugh SM, O'Donnell J, Gillen P. Genomic and oncoproteomic advances in detection and treatment of colorectal cancer. *World J Surg Oncol* 2009; 7:36.

(27)   Del Rio M., Molina F, Bascoul-Mollevi C, Copois V, Bibeau F, Chalbos P et al. Gene expression signature in advanced colorectal cancer patients select drugs and response for the use of leucovorin, fluorouracil, and irinotecan. *J Clin Oncol* 2007; 25(7):773-780.

(28)   Gout S, Huot J. Role of cancer microenvironment in metastasis: focus on colon cancer. *Cancer Microenviron* 2008; 1(1):69-83.

(29)   Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

3

Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy

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Abstract

Background
Although systemic therapies have shown to result in a survival benefit in patients with metastatic colorectal cancer (mCRC), the outcome of this treatment in patients with peritoneal carcinomatosis (PC) is poor. No data are available on the outcome of current chemotherapy schedules plus targeted agents in mCRC patients with PC. We evaluated the efficacy and toxicity in mCRC patients with PC receiving systemic treatment in two phase III studies (CAIRO and CAIRO2).

Methods
Previously untreated mCRC patients treated with chemotherapy in the CAIRO study and with chemotherapy and targeted therapy in the CAIRO2 study were included in this analysis, and retrospectively analysed according to the presence or absence of PC at randomisation. Patient demographics, primary tumour characteristics, progression free survival (PFS) and overall survival (OS), and occurrence of toxicity were evaluated.

Results
Thirty-four patients with PC were identified in the CAIRO study, and 47 patients in the CAIRO2 study. In the CAIRO2 study patients with PC more often had a WHO classification 1 than patients without PC. No other differences in baseline patient characteristics were observed between patients with and without PC.
The median OS was significantly decreased for patients with PC compared with patients without PC, with 10.4 versus 17.3 months, respectively in the CAIRO study (p≤0.001) and 15.2 versus 20.7 months, respectively, in the CAIRO2 study (p<0.001).
The median number of treatment cycles did not differ between patients with or without PC in both studies. The occurrence of major toxicity was more frequent in patients with PC treated with sequential chemotherapy in the CAIRO study as compared to patients without PC. However this was not reflected in the reasons to discontinue treatment in this study arm. In the CAIRO2 study, no differences in the occurrence of major toxicity were observed between patients with or without PC.

Conclusion
Our data demonstrate a decreased efficacy of the current standard chemotherapy with and without targeted agents in mCRC patients with PC. The median number of treatment cycles did not differ between patients with and without PC. This suggests that the poor outcome of these patients cannot be explained by undertreatment or increased susceptibility to toxicity, but rather by a relative resistance to treatment.

Introduction

Peritoneal carcinomatosis (PC) is frequently observed in patients with colorectal cancer and is notorious for its poor prognosis[1-3]. PC is found in approximately 5% of patients diagnosed with colorectal cancer, representing 24% of patients with synchronous metastasis at the time of diagnosis[4]. Another 8% of colorectal cancer patients develops PC during their course of disease[1].

Peritoneal spread is present in up to 15% of patients included in randomised trials investigating new palliative systemic treatment strategies for metastatic colorectal cancer (mCRC)[5-9]. Yet little is known about the effects of modern chemotherapy treatment and the effect of targeted agents in patients with PC, in contrast to patients with hepatic or pulmonary metastases[10].

There are no randomised trials evaluating the effect of systemic treatment in patients with PC. In retrospective studies investigating clinical determinants of outcome in patients with mCRC treated with chemotherapy, the presence of PC appears to be a negative prognostic factor[11;12]. Possible explanations for the reported poor median survival outcomes of patients with PC from these retrospective studies[1;3;12-14] include an increased susceptibility to chemotherapy-induced toxicity causing an early discontinuation of treatment, or an unfavourable biological profile of tumours spreading to the peritoneal cavity. However, detailed data are scarce and no clear explanation is currently available. The chemotherapy regimens used in these studies mainly concern 5-fluorouracil and leucovorin (5-FU/LV), which was the standard of care at that time. With the development of novel cytotoxic agents and targeted antibodies the systemic treatment has changed over the years, and its outcome has significantly improved[15;16]. Therefore we analysed the outcome of mCRC patients with PC treated with current standard systemic treatments.

Methods

Patients

Data were obtained from mCRC patients enrolled in two phase III studies of the Dutch Colorectal Cancer Group (DCCG). In the CAIRO study[17;18], 820 patients were randomised between sequential treatment (first-line: capecitabine, second-line: irinotecan, and third-line: oxaliplatin plus capecitabine, arm A) and combination treatment (first-line: irinotecan plus capecitabine, second-line: oxaliplatin plus capecitabine, arm B) (ClinicalTrials.gov NCT00312000). In the CAIRO2 study[19;20], 755 patients were randomised between capecitabine, oxaliplatin, and bevacizumab (CB regimen), and the same regimen plus weekly cetuximab (CBC regimen) (ClinicalTrials.gov NCT00208546).

Eligibility criteria of both randomised trials were: age >18 years, histologically proven diagnosis of colon or rectum carcinoma, presence of metastatic disease not amendable to curative surgery, measurable or assessable disease parameters, no previous systemic chemotherapy for metastatic disease, World Health Organization (WHO) performance status 0-2 (CAIRO) or 0-1 (CAIRO2), and adequate bone marrow, liver and renal function. Tumour response was assessed every 3 cycles (9 weeks) according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria[21].

For the current analysis patients were analysed according to the presence of PC at randomisation. Presence of PC was defined as reported presence of PC at previous laparotomy, the presence of ascites, or documented peritoneal tumour deposits by CT scanning at randomisation.

Statistical analysis
Overall survival (OS) and progression-free survival (PFS) were determined according to the methods described in the original study reports[17-20] and were estimated using the Kaplan–Meier method and compared with the log-rank test. The comparison of baseline patient characteristics between patients with and without PC was done using Wilcoxon's rank sum test or Chi square test where appropriate.
SAS 8.2 software was used for the analyses. All tests were two-sided and P-values of less than 0.05 were considered statistically significant.

Results

Baseline patient characteristics
In total, 803 eligible patients were enrolled in the in the CAIRO study and 736 patients in the CAIRO2 study. Thirty-four patients (4%) with PC at randomisation were identified in the CAIRO study cohort and 47 patients (6%) in the CAIRO2 study cohort. Baseline patient characteristics are shown in Table 1. In the CAIRO2 study patients with PC more often had a WHO performance status of 1 than patients without PC (as compared to WHO performance status 0). There were no other differences in patient characteristics between the patients with and without PC.

Table 1. Patient characteristics.

		CAIRO			CAIRO2		
		No PC	PC		No PC	PC	
		n (%)	n (%)	P value	n (%)	n (%)	P value
Overall		769	34		689	47	
Mean age (SD)		62.5 (9.5)	60.6 (13.0)	0.500	61.9 (9.4)	59.6 (10.0)	0.133
Female		283 (37)	13 (38)	0.857	276 (40)	21 (45)	0.532
WHO performance score							
	0	481 (63)	20 (59)	0.397	438 (64)	22 (47)	0.021
	1	257 (33)	11(32)		250 (36)	25(53)	
	2	31 (4)	3 (9)				
Prior adjuvant therapy							
	Yes	107 (14)	4 (4)	0.175	95 (14)	9 (81)	0.307
	No	662 (86)	30 (88)		594 (86)	38 (20)	
No of organs affected							
	1				242 (35)	10 (21)	0.051
	>1				445 (65)	37 (79)	
Site of primary tumour							
	Colon	451 (59)	27 (79)		273 (45)	21 (48)	
	Rectum	255 (33)	5 (15)	0.722	172 (28)	11 (26)	0.863
	Rectosigmoid	58 (8)	2 (6)		167 (27)	11 (26)	
	Multiple tumours	4 (1)	0 (0)		0 (0)	0 (0)	
LDH							
	Normal	489 (64)	24 (71)	0.406	383 (56)	26 (55)	0.937
	>UNL	280 (36)	10 (29)		302 (44)	21 (45)	
	Unknown				4		
Primary tumour in situ							
	No	161 (21)	8 (24)	0.717	542 (79)	36 (77)	0.859
	Yes	608 (79)	26 (74)		141 (20)	10 (21)	
	Unknown				6 (1)	1 (2)	
Site of metastasis							
	PC only		4 (12)			5 (11)	
	PC plus other sites		30 (88)			42 (89)	

UNL = Upper Normal Limit

Survival and toxicity outcomes

CAIRO

The median OS was significantly decreased for patients with PC compared to patients without PC, with 10.4 versus 17.3 months (p=<0.001) respectively. Kaplan Meier survival curves are shown in Figure 1. These differences were maintained when data were analysed per treatment arm. Detailed results on outcome are shown in Table 2.

Table 2. Overall survival (OS) and progression-free survival (PFS) of patients with and without PC in the CAIRO and CAIRO2 studies.

		No PC		PC		P value (PC vs. no PC)
		Median survival (months)	95% CI	Median survival (months)	95% CI	
CAIRO						
OS	Arm A: Sequential chemotherapy	16.8	14.8-18.5	10.4	5.7-12.0	<0.001
	Arm B: Combination chemotherapy	17.9	15.4-19.3	7.8	5.3-11.8	0.001
PFS	Arm A: Sequential chemotherapy	5.8	5.1-6.3	4.6	3.2-6.0	0.044
	Arm B: Combination chemotherapy	7.7	7.0-8.3	5.7	2.0-9.9	0.301
CAIRO2						
OS	Arm A: CB	21.4	18.9-24.8	15.2	7.2-17.9	0.002
	Arm B: CBC	20.4	18.4-21.7	13.9	10.2-20.2	0.035
PFS	Arm A: CB	10.8	9.8-12.5	6.6	5.3-12.8	0.048
	Arm B: CBC	9.7	8.6-10.7	7.2	6.2-10.3	0.028

95% CI = 95% Confidence Interval
CB = Capecitabine + Oxaliplatin + Bevacizumab
CBC = Capecitabine + Oxaliplatin + Bevacizumab + Cetuximab

No significant differences in OS were observed between treatment arms for patients with PC (Arm A vs. Arm B, p =0.5499). In the sequential treatment arm patients with PC had a decreased median PFS on first-line treatment as compared to patients without PC (4.6 months vs. 5.8 months, respectively, p=0.0443).

The median number of treatment cycles given in the first line of treatment did not differ between patients with or without PC (Table 3a). In the combination arm, the occurrence of grade 3 or 4 toxicity did not differ between patients with and without PC (75% vs. 59% respectively, p=0.19). In the sequential arm major toxicity was observed in 67% of the patients with PC and in 43% of patients without PC (p=0.0489). This higher incidence of grade 3 or 4 toxicity was not reflected in the reason to discontinue treatment.

In the combination arm, the most frequent reason to discontinue treatment was no further believed benefit or a poor performance status in patients with PC, and progression in patients without PC. In the sequential arm, acknowledgement of no further benefit was the main reason to discontinue treatment in both patients with and without PC (Table 3a).

CAIRO2

OS of patients with PC treated in the CAIRO2 study was significantly decreased as compared to the OS of patients without PC (15.2 vs. 20.7 months, respectively (p<0.001). Kaplan Meier survival curves are shown in Figure 2. PFS was also significantly decreased in patients with PC as compared to patients without PC in both treatment arms. These differences were maintained when data were analysed per treatment arm (table 2).

No significant differences in OS were observed between treatment arms for patients with PC (Arm A. vs. Arm B, p =0.981).

No differences were observed in the median number of cycles given. A summary of the main reasons for discontinuation of treatment is shown in Table 3b. Progression of disease was the most frequently reported reason for discontinuation of therapy in both treatment arms for patients with and without PC (75% vs. 55% in arm A, and 64 vs. 49 % in arm B, respectively).

The incidence of grade 3-4 toxicity in both treatment arms did not differ between the patients with and without PC (40% vs. 24 % in the CB arm p=0.073 and 77% vs. 84% in the CBC arm, p=0.400), respectively).
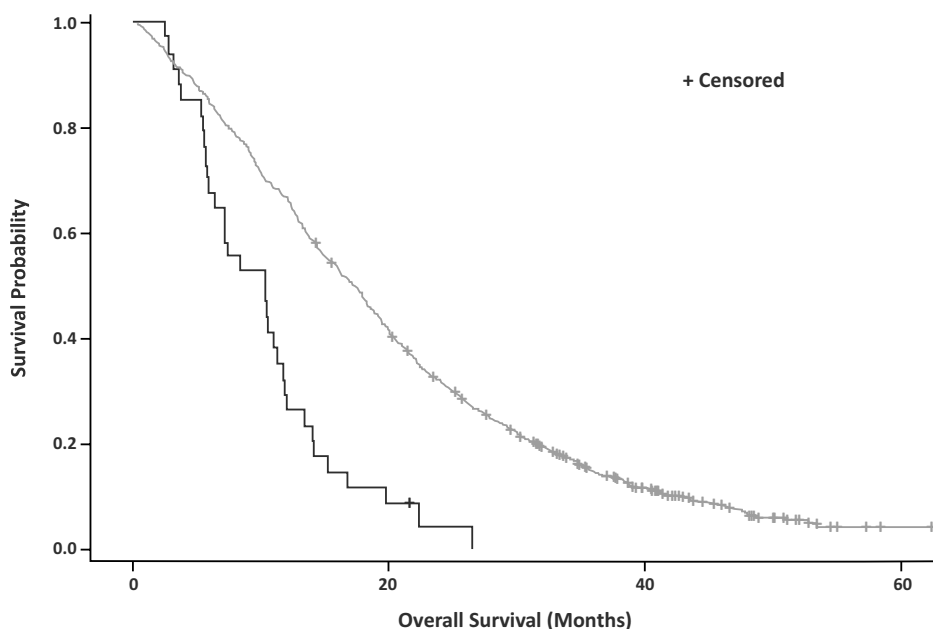

Figure 1. Kaplan-Meier curve for overall survival of metastatic CRC with and without PC at time of inclusion in the CAIRO trial.
—— Patients without PC.
—— Patients with PC
Median overall survival was 10.4 months for patients with PC versus 17.3 months in patients without PC (p≤0.001).

Table 3a. Number of treatment cycles given during the first line of treatment and primary reasons for treatment discontinuation for patients in the CAIRO trial, by treatment arm and presence of PC.

	Arm A: Sequential chemotherapy arm			Arm B: Combination chemotherapy arm		
	No PC	PC	P value (PC vs. no PC)	No PC	PC	P value (PC vs. no pc)
Number of treatment cycles given in 1st line of treatment	median (range)	median (range)		median (range)	median (range)	
	6.0 (0-53)	6.0 (1-14)	0.158	7.0 (0-42)	6.5 (1-18)	0.918
Reasons for treatment discontinuation	n (%)	n (%)		n (%)	n (%)	
Progression	103 (27)	3 (17)		134 (35)	2 (13)	
Toxicity	51 (13)	4 (22)		91 (24)	1 (6)	
Patients refusal	46 (12)	2 (11)		40 (10)	3 (19)	
Intercurrent death	32 (8)	3 (17)	0.873	25 (6)	2 (13)	0.008
Major protocol violation	3 (1)	0 (0)		2 (1)	0 (0)	
No further benefit/poor performance status/other illness	107 (28)	5 (28)		53 (14)	5 (31)	
Resection of metastases	2 (1)	0 (0)		8 (2)	0 (0)	
Other	30 (8)	1 (6)		28 (7)	1 (6)	
Missing data	0 (0)	0 (0)		5 (1)	2 (13)	

Table 3b. Number of treatment cycles given and primary reasons for treatment discontinuation for patients in the CAIRO2 trial, by treatment arm and presence of PC.

	Arm A: CB			Arm B: CBC		
	No PC	PC	p value (PC vs. no PC)	No PC	PC	p value (PC vs. no PC)
Number of treatment cycles given	median (range)	median (range)		median (range)	median (range)	
	9.0 (9-48)	8.5 (3-24)	0.388	9.0 (1-52)	9.0 (0-34)	0.732
Reasons for treatment discontinuation	n (%)	n (%)		n (%)	n (%)	
Progression	175 (55)	18 (75)		164 (49)	14(64)	
Toxicity	76 (24)	4 (17)		92 (28)	5 (23)	
Patient refusal	18 (6)	0 (0)		17 (5)	2 (9)	
Intercurrent death	7 (2)	0 (0)	0.606	2 (1)	0 (0)	0.571
Major protocol violation	2 (1)	0 (0)		12 (4)	1 (5)	
Lost to follow-up	1 (0)	0 (0)		1 (0)	0 (0)	
Other	40 (13)	2 (8)		44 (13)	0 (0)	
Missing data	24 (7)	1 (0)		14 (4)	0 (0)	

CB = Capecitabine + Oxaliplatin + Bevacizumab
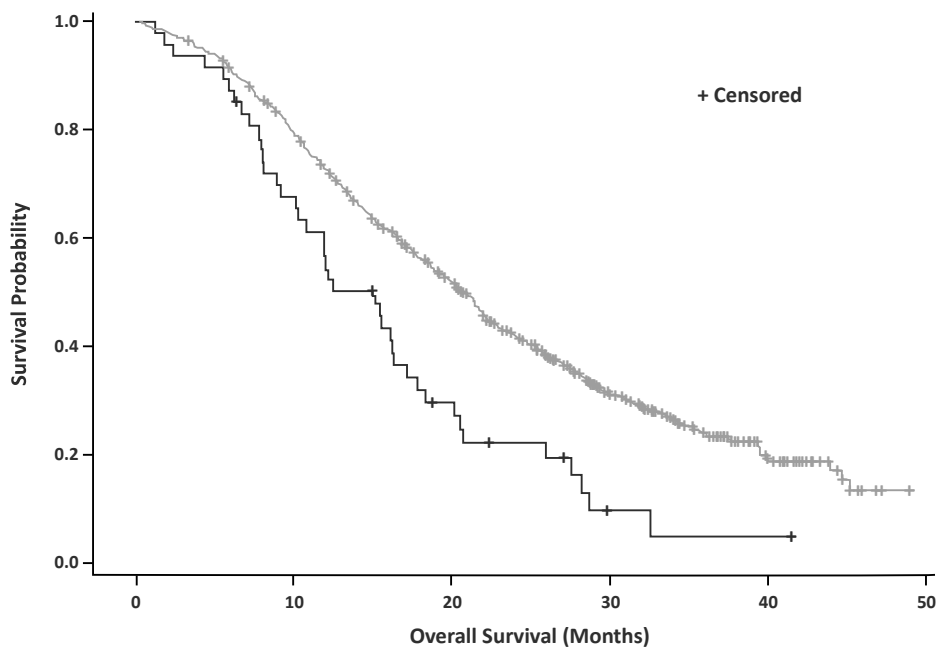CBC = Capecitabine + Oxaliplatin + Bevacizumab + Cetuximab

Figure 2. Kaplan-Meier curve for overall survival of metastatic CRC with and without PC at time of inclusion in the CAIRO2 trial.
―――― Patients without PC.
―――― Patients with PC
Median overall survival was 15.2 months for patients with PC versus 20.7 months in patients without PC (p≤0.001).

Discussion

We demonstrate that with the currently available standard systemic regimens the outcome for mCRC patients with PC remains poor as compared to patients without PC. The results of our analysis suggest an improved outcome in mCRC patients with PC when targeted agents are used, as the median OS of patients in the CAIRO2 study is longer than the median OS in the CAIRO study. However a formal comparison between the trials cannot be made due to differences in patient selection criteria, and caution is warranted with cross-study comparisons. Our data do not support inadequate treatment due to an increased susceptibility to systemic treatment-induced toxicity as an explanation for the poor outcome in mCRC patients with PC. Therefore a difference in biological behaviour of tumours spreading to the peritoneal cavity is more likely.

In the 1980s new treatment strategies have been introduced for patients presenting with PC in the absence of systemic metastases. These treatment strategies combine an aggressive surgical cytoreduction with the application of intraperitoneal chemotherapy, usually under hyperthermic conditions. In a randomised trial, the performance of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) has shown to result in a significant survival benefit as compared to systemic chemotherapy treatment with 5-fluorouracil/leucovorin[22]. With the availability of novel chemotherapy regimens and targeted therapies, it may be questioned whether an aggressive surgical approach still prolongs survival as compared to systemic treatment.

Another explanation for the scarce availability of data on outcomes of PC patients treated with chemotherapy is the lack of diagnostic tools. Despite technological developments, the accuracy of the currently available imaging techniques is insufficient for quantifying peritoneal tumour deposits. The small size of the tumour deposits, typically well below 1 cm, and the characteristic appearance of peritoneal spread that layers the outline of normal structures in the abdomen negatively influences the sensitivity of abdominopelvic ultrasound and CT-scans[23-25]. Consequently, radiological findings often do not correlate with observations during surgery[26].

This also implies that a number of patients in the present study who were included in the group without macroscopic PC may have had peritoneal tumour deposits which have not been identified with radiological examination.
Furthermore, since peritoneal lesions are usually qualified as "non-measurable disease", patients do not meet the inclusion criteria for response evaluation in randomised trials evaluating systemic treatment.

In conclusion, this subanalysis of two randomised controlled trials demonstrates a negative impact of the presence of PC on overall and progression-free survival in patients treated with currently available palliative chemotherapy with or without targeted therapy for mCRC. This study also suggests that the observed effect cannot be explained by undertreatment or increased susceptibility to toxicity. With the availability of both surgical and medical treatment options in this group of patients, a careful consideration of all options and an individual approach for each patient should be advocated. Further research should provide explanations for the different biologic behaviour of PC, and novel treatment approaches are warranted to improve the outcome in this subgroup of patients.

Reference List

(1) Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89(12):1545-1550.

(2) Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006; 243(2):212-222.

(3) Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88(2):358-363.

(4) Lemmens VEPP, Klaver YLB, Verwaal VJ, Rutten HJT, Coebergh JWW, de Hingh IHJT. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: A population-based study. *Int J Cancer* 2011; 128(11):2717-2725.

(5) Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005; 23(22):4866-4875.

(6) Diaz-Rubio E, Tabernero J, Gomez-Espana A, Massuti B, Sastre J, Chaves M et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. *J Clin Oncol* 2007; 25(27):4224-4230.

(7) Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355(9209):1041-1047.

(8) Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; 370(9582):143-152.

(9) Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001; 19(21):4097-4106.

(10) Gonzalez-Moreno S, Gonzalez-Bayon L, Ortega-Perez G, Gonzalez-Hernando C. Imaging of peritoneal carcinomatosis. *Cancer J* 2009; 15(3):184-189.

(11) Assersohn L, Norman A, Cunningham D, Benepal T, Ross PJ, Oates J. Influence of metastatic site as an additional predictor for response and outcome in advanced colorectal carcinoma. *Br J Cancer* 1999; 79(11-12):1800-1805.

(12) Kohne CH, Cunningham D, Di CF, Glimelius B, Blijham G, Aranda E et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002; 13(2):308-317.

(13) Folprecht G, Kohne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Cancer Treat.Res.* 134, 425-440. 2007.

(14) Pelz JO, Chua TC, Esquivel J, Stojadinovic A, Doerfer J, Morris DL et al. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer* 2010; 10:689.

(15) Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol* 2007; 8(10):898-911.

(16) Meulenbeld HJ, van Steenbergen LN, Janssen-Heijnen ML, Lemmens VE, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. *Ann Oncol* 2008; 19(9):1600-1604.

(17) Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL et al. Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer, an interim safety analysis. A Dutch Colorectal Cancer Group (DCCG) phase III study. *Ann Oncol* 2006; 17(10):1523-1528.

(18) Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; 370(9582):135-142.

(19) Tol J, Koopman M, Rodenburg CJ, Cats A, Creemers GJ, Schrama JG et al. A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. *Ann Oncol* 2008; 19(4):734-738.

(20) Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009; 360(6):563-572.

(21) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92(3):205-216.

(22) Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(23) de Bree E, Koops W, Kroger R, van Ruth S, Witkamp AJ, Zoetmulder FA. Peritoneal carcinomatosis from colorectal or appendiceal origin: correlation of preoperative CT with intraoperative findings and evaluation of interobserver agreement. *J Surg Oncol* 2004; 86(2):64-73.

(24) Franiel T, Diederichs G, Engelken F, Elgeti T, Rost J, Rogalla P. Multi-detector CT in peritoneal carcinomatosis: diagnostic role of thin slices and multiplanar reconstructions. *Abdom Imaging* 2009; 34(1):49-54.

(25) Jacquet P, Jelinek JS, Steves MA, Sugarbaker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. *Cancer* 1993; 72(5):1631-1636.

(26) Koh JL, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2009; 16(2):327-333.

4

Surgery for colorectal cancer in the presence of synchronous peritoneal carcinomatosis

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Abstract

Background
The detection of peritoneal carcinomatosis (PC) in colorectal cancer patients frequently results in a dilemma with regard to the optimal treatment strategy, especially when PC is encountered unexpectedly. Aim of this study was to evaluate outcomes of patients undergoing palliative surgery for colorectal carcinoma with synchronous PC.

Patients and methods
Patients diagnosed with primary colorectal cancer and synchronous PC in three community hospitals were selected from the Eindhoven Cancer Registry database. Outcomes on post-operative complications, in-hospital mortality and overall survival were analysed according to the type of intervention performed.

Results
Between 1995 and 2009, 169 colorectal cancer patients were diagnosed with synchronous PC. Surgery was performed in 142 patients. PC was encountered unexpectedly in 130 patients. Median survival was 14 weeks without surgery (n=22), 12 weeks after a derivative procedure (n=46) and 55 weeks after primary tumour resection (n=91). Derivative procedures resulted in a 30% complication rate and an in-hospital mortality of 41%. Performance of derivative procedures or no surgery were negative prognostic factors (Hazard ratio for dying 2.33, p=0.0001 and 3.09, p=0.0007, respectively). Other factors increasing the risk of death were age (>70 years), second primary tumour, poor differentiation grade, and systemic metastases.

Conclusion
PC is often encountered unexpectedly during surgery for colorectal cancer. Primary tumour resection can be safely performed with good outcomes, but some patients may have benefited from an even more radical approach. If possible, derivative surgery should be avoided given its high morbidity and mortality. Ideally, PC should be diagnosed prior to an operative procedure.

Introduction

The peritoneum is a commonly encountered site of metastasis in patients with colorectal cancer, being present in 4.8% of patients at the moment of diagnosis of the primary tumour[1]. Another 4 to 12% of patients will develop clinically evident peritoneal dissemination later in the course of their disease[2].

The presence of peritoneal carcinomatosis (PC) in patients with colorectal cancer represents a challenge for health care workers and for surgeons in particular. Currently, preoperative staging is inadequate to diagnose PC and it is therefore often discovered accidentally during surgery.

Taking into account the relatively high incidence of peritoneal metastases in colorectal cancer patients, surprisingly few data are available reporting on the outcomes of the surgical procedures performed in these patients. As a result, the role of surgery in patients with PC is yet to be defined. One may postulate that surgical exploration should always be considered even with widespread systemic disease since it has been show that resection of the primary tumour has a beneficial influence on survival in patients with other metastasised malignancies[3-6]. On the other hand, the limited accessibility of the abdomen caused by peritoneal deposits and resulting in an increased risk for complications may deter a surgeon from operating, especially since PC is traditionally regarded as an incurable condition.

Aim of this study was to report on the outcomes in terms of morbidity, mortality and survival of patients undergoing surgery for colorectal carcinoma with synchronous PC, in order to clarify the advantages and disadvantages of palliative surgical interventions. This may provide tools for clinical decision making in case of incidentally encountered PC during surgery or when PC is diagnosed during preoperative work-up.

Patients and methods

Patients

The Eindhoven Cancer Registry (ECR) collects data on all patients with newly diagnosed primary colorectal cancer (C18.0-C20.9) in a large part of the south-eastern Netherlands, and maintains a population based cancer registry in an area with approximately 2.3 million inhabitants. The ECR is notified by 10 community hospitals at 17 locations, 6 pathology departments, and 2 large radiotherapy institutions. By means of an independent case ascertainment method, the Dutch cancer registries attain an estimated completeness of more than 95%[7].

Data on patient and tumour characteristics are routinely extracted on basis of information in medical files by specially trained administrators of the cancer registry, 6 to 9 months after diagnosis. Routinely extracted data include the subsites of metastasis present at the time of

diagnosis according to the International Classification of Diseases for Oncology (ICD-O). The tumour-node-metastasis (TNM) classification is used for stage notification of the primary tumour, according to the edition of the TNM classification by the International Union Against Cancer (UICC), valid at time of cancer diagnosis.

For the analysis in the current study, patients diagnosed with primary colorectal cancer (C18.0– C20.9) and synchronous PC in three community hospitals between 1995 and 2008 were selected from the ECR database (n=169), and additional data regarding surgical procedures and postoperative outcome were collected by a specially trained administrator of the ECR.

Follow-up of vital status was complete until January 2009 in all patients as obtained from the Municipal Administrative Databases, containing data on all deceased and emigrated persons in the Netherlands.

Surgery

The radicality of resection of the primary tumour was reported using the following classification. An R-0 score indicates microscopically radical resection, R1 indicates macroscopic resection of disease but evidence for microscopic residual disease during pathological examination, e.g. microscopic tumour present in the intersection plane, R2 is noted when residual macroscopic tumour was present after the removal attempt.

Additional Therapy

Decisions regarding chemotherapy regimens were made on an individual patient basis by the medical oncologists. In the first years of this study period, treatment with 5-fluoruracil and folic acid was the standard palliative treatment for metastasised colorectal cancer in the Netherlands. From 2004 on, irinotecan and oxaliplatin were incorporated in standard palliative treatment regimens. Targeted therapies like cetuximab and bevacizumab were introduced in the Netherlands in 2006 and have been added to the chemotherapy combination therapies since then.

Statistical analysis

In addition to follow-up via the hospitals, information on vital status was actively obtained from the Dutch municipal personal records database (Central Bureau for Genealogy). Survival time was defined as the time from diagnosis to death or 1 January 2010 for the patients who were still alive. Median survival rates were computed according to patient and tumour characteristics. Ninety-five percent confidence intervals were calculated. A multivariable proportional hazards regression analysis was used to discriminate independent risk factors for death. P-values < 0.05 were considered statistically significant. All analyses were performed using SAS/STAT statistical software (SAS system 9.1.3, SAS Institute, Cary, NC).

Results

Patients

Between 1995 and 2009, 169 colorectal cancer patients (93 male) with a mean age of 67.4 years were diagnosed with synchronous PC in the three community hospitals. Patient characteristics are shown in table 1. The majority of patients reported symptoms of disease at the moment of diagnosis. Only 4 patients were asymptomatic. Most common symptom was pain, followed by weight loss.

In 22 patients it was decided not to perform surgery at all. The main considerations for this decision were the presence of wide-spread systemic disease and a poor performance status.

Table 1. General characteristics of patients with peritoneal carcinomatosis, diagnosed between 1995 and 2008 in the South of the Netherlands (n=169).

	n	(%)
Mean age (yrs)	67.4	
Male : Female	93:76	
Comorbidity		
Yes	50	(30)
No	109	(64)
Unknown	10	(6)
Localisation of primary tumour*		
Caecum	33	(20)
Appendix	3	(2)
Colon	100	(58)
Rectosigmoid	12	(7)
Rectum	22	(13)
T stage of primary tumour (cT in case of unknown pT)		
T1	1	(1)
T2	4	(2)
T3	53	(31)
T4	70	(41)
Tx	41	(26)
N stage of primary tumour (cN in case of unknown pN)		
N0	21	(12)
N1,2	92	(55)
Nx	56	(33)
Differentiation grade of primary tumour		
Well/moderate	73	(43)
Poorly/undifferentiated	42	(25)
Unknown	54	(32)
Extent of metastatic disease		
Peritoneal carcinomatosis only	66	(39)
Peritoneal carcinomatosis plus other metastases	103	(61)

* 5 patients were diagnosed with a synchronous primary tumour located in the colon and the rectum

Surgical procedures

In 142 patients, at least one surgical procedure was performed. Interestingly, the presence of PC was known before the operation in only 8 patients while in 130 patients PC was found unexpectedly during surgery. In 4 patients these data are missing. During surgery, ascites was noted in 37% of patients (n=62). A summary of the surgical decision making is shown in figure 1.

The primary tumour was resected in 91 patients. In most of these patients a microscopic (R-0) resection was achieved (n=66). In 4 patients, R1 resection was reported and in another 4 patients macroscopic tumour was left behind; no information on completeness of resection was found in the medical files for the remaining 17 patients.

In all other patients, the primary tumour was not resected. Main reasons for this decision were the knowledge that the patient was diagnosed with extensive synchronous metastases on other locations during preoperative work-up (n=21), irresectability of the primary tumour (n=16) or widespread peritoneal disease (n=11).

In five patients the abdomen was closed immediately after exploration without additional procedures.

In 46 patients a derivative procedure was performed, including an intestinal bypass in 11 patients and stoma formation in 34 patients. In one patient both an intestinal bypass and a stoma were made. Table 2 shows the number of procedures performed in patients with PC, according to a number of relevant patient and tumour characteristics.
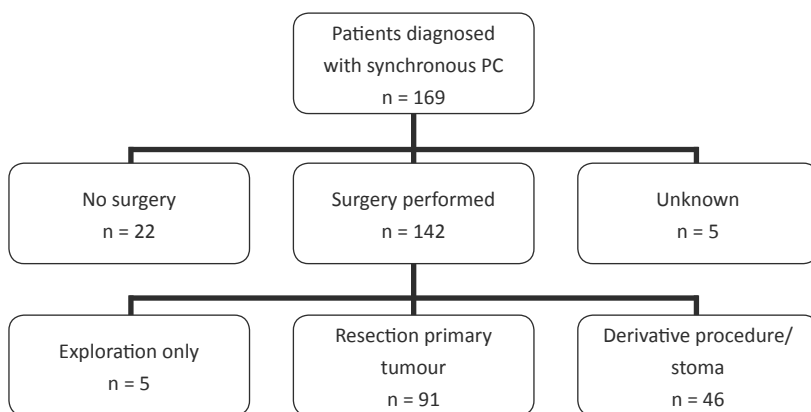

Figure 1. Summary of procedures performed in colorectal cancer patients diagnosed with synchronous peritoneal carcinomatosis (PC).

Adjuvant therapy

None of the 91 patients undergoing resection of the primary tumour received neoadjuvant chemotherapy. Six patients (7%) received preoperative radiotherapy. Resection of the primary tumour was followed by adjuvant chemotherapy in 45 patients (49%). Another 45 patients did not receive adjuvant treatment, and in 1 patient these data were missing. None of the patients received postoperative radiotherapy.

Table 2. Procedures and outcomes in patients with peritoneal carcinomatosis who underwent surgery, according to a number of relevant patient and tumour characteristics (n=142).

	Exploration only		Resection primary tumour		Derivative procedure (incl stoma)	
	n	(%)	n	(%)	n	(%)
Overall	5	(100)	91	(100)	46	(100)
Age						
<70 years	3	(60)	49	(54)	22	(48)
70+ years	2	(40)	42	(46)	24	(52)
Gender						
Male	3	(60)	50	(55)	25	(54)
Female	2	(40)	41	(45)	21	(46)
Comorbidity[a]						
Yes	2	(40)	56	(62)	30	(65)
No	3	(60)	32	(35)	10	(22)
Unknown	0	(0)	3	(3)	6	(13)
Extent of metastatic disease						
Peritoneal carcinomatosis only	3	(60)	36	(40)	17	(37)
Peritoneal carcinomatosis plus other metastases	2	(40)	55	(60)	29	(63)
PC known before operation						
Yes	1	(20)	4	(4)	3	(7)
No	4	(80)	85	(94)	41	(89)
Unknown	0	(0)	2	(2)	2	(4)
Median hospital stay (days)	5		10		11	
Postoperative complications	1	(20)	13	(14)	14	(30)
In-hospital mortality		20%		14%		41%

Morbidity

Postoperative complications occurred in 14% of patients who underwent resection of the primary tumour (n=91), and 30% of patients with a derivative procedure (n=46). In the group with derivative procedures, in-hospital mortality was 41%, as opposed to 14% in patients in whom the primary tumour was resected.

The most frequently reported complications in both the resection and the derivative group were prolonged ileus and systemic infections, such as pneumonia. In the resection group, this was followed by fascia dehiscence and wound infection. In the derivative group, renal failure was the next most frequent postoperative complication.

The performance of a derivative procedure was a significant negative prognostic factor as compared to resection of the primary tumour (Hazard ratio (HR) for risk of death 2.33, 95% CI 1.51-3.59). So was the performance of no surgery (HR 3.09, 95% CI 1.61-5.91). Other factors negatively influencing the risk of dying by multivariate analysis were age (>70 years), presence of a second tumour, poor differentiation grade, and presence of systemic metastases. Results of the multivariate analysis are shown in table 3.

Table 3. Multivariable proportional hazards regression analysis modelling the risk of death for patients with colorectal cancer and synchronous peritoneal carcinomatosis, diagnosed between in the south of the Netherlands between 1995 and 2008. Data are adjusted for all variables listed.

	HR	95% CI	P value
Age			
< 70 years[a]	1.00		
70+ years	1.66	1.17-2.35	0.005
Gender			
Male[a]	1.00		
Female	0.95	0.68-1.34	0.8
Comorbidity			
No[a]	1.00		
Yes	0.96	0.66-1.40	0.8
Localisation			
Colon (incl. caecum and appendix)[a]	1.00		
Rectum (incl. rectosigmoid)	0.86	0.55-1.33	0.5
Synchronous colon and rectal tumour			
No[a]	1.00		
Yes	2.28	1.02-5.13	0.046
T stage			
T1-2	1.50	0.49-4.58	0.5
T3[a]	1.00		
T4	1.17	0.80-1.72	0.4
N stage			
N0	0.70	0.38-1.28	0.2
N1,2[a]	1.00		
Differentiation grade of primary tumour			
Well/moderate[a]	1.00		
Poorly/undifferentiated	1.52	1.02-2.28	0.04
Operation performed			
Resection of tumour[a]	1.00		
Derivative procedure	2.33	1.51-3.59	0.0001
Exploration only	1.68	0.65-4.38	0.3
No surgery	3.09	1.61-5.91	0.0007
Extent of metastatic disease			
Peritoneal carcinomatosis only[a]	1.00		
Peritoneal carcinomatosis plus other metastases	1.29	1.05-1.58	0.01
Ascites present?			
Yes[a]	1.00		
No	0.72	0.35-1.47	0.4

HR=hazard ratio
CI=Confidence Interval
[a] Reference category

Survival

Median survival, calculated according to the surgical interventions that were performed is shown in table 4. Patients who did not undergo surgery had a median survival of only 14 weeks (95% CI 4-34). In the group with a derivative procedure, median survival was 12 weeks (95% CI 6-19). However in the group in which the primary tumour was resected, a median survival of 55 weeks (95% CI 46-70) was observed.

Table 4. Median survival (in weeks) of patients with peritoneal carcinomatosis (PC) **(n =164)**, *All: 34 weeks (23-46).*

	No surgery/ exploration only		Resection primary tumour		Derivative procedure	
	n	Survival in weeks (95% CI)	n	Survival in weeks (95% CI)	n	Survival in weeks (95% CI)
Overall	27	14 (4-34)	91	55 (46-70)	46	12 (6-19)
Age						
< 70 years	13	23 (11-71)	49	76 (50-117)	22	12 (5-34)
70+ years	14	5 (2-32)	42	46 (26-55)	24	14 (5-18)
Gender						
Male	14	28 (4-71)	50	55 (46-84)	25	13 (5-26)
Female	13	5 (2-14)	41	54 (36-80)	21	11 (6-24)
Comorbidity						
No	12	12 (1-53)	32	47 (22-76)	10	12 (5-19)
Yes	20	14 (4-49)	56	55 (47-84)	30	25 (5-39)
Sites of metastases						
PC only	12	10 (2-71)	36	80 (55-135)	17	11 (4-34)
PC + other metastases	15	14 (4-34)	55	46 (26-50)	29	18 (6-24)

CI = Confidence Interval

Discussion

The presence of PC in colorectal cancer patients is frequently discovered unexpectedly during surgery. Also in this study, PC was unknown before surgery in no less than 130 out of the 142 patients (91%) operated for PC. This causes the operating surgeon to be faced with a dilemma, since several surgical options are available: an attempt to resect the primary tumour with or without the peritoneal metastases, the performance of a derivative procedure or enterostomy, closure of the abdomen without further intervention. Currently, evidence from clinical studies to support one of these options is lacking.

This study reports a high incidence of postoperative complications (30%) and in-hospital mortality (41%) associated with the performance of a derivative procedure. Prognosis in these patients is very poor with a median survival of only 12 weeks. Since survival is comparable to non-operated patients (14 weeks) one may speculate that it would have

been better not to operate on these patients at all. Instead, less invasive techniques such as stenting of enteral stenoses and drainage of ascites may have been more suitable to palliate symptoms. This however requires a more specific and reliable preoperative work-up in order to diagnose PC preoperatively.

Patients in whom a resection of the primary tumour was performed achieved a median overall survival of 55 weeks with an acceptable morbidity and mortality. Although these survival outcomes remain unfavourable as compared to patients presenting with other sites of synchronous colorectal cancer metastases[1], one may conclude that resection of the primary tumour should always be considered even in the presence of PC. However, recent developments give rise to the question whether all patients in this study were optimally treated by resection of the tumour alone. In the 1980's, new treatment strategies have been introduced consisting of a combination of aggressive cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC). With this combined treatment modality, a significant increase in survival outcomes has been reported in clinical and experimental studies[8-17]. Eligibility criteria include fitness for major surgery, resectable peritoneal disease, limited extent of PC and absence of systemic metastases[10;18-20]. It is not unlikely that several of the patients with resectable tumours in the present study would have benefited from referral to a specialised HIPEC-center. Ideally, such referral is done before the performance of any operation since surgery induces the release of growth factors into the peritoneal cavity, which is thought to enhance the growth of peritoneal metastases. Once again, the preoperative discovery of PC is crucial in this respect since only then timely referral of the patient can be considered.

The currently available imaging techniques that are used for preoperative staging in colorectal cancer are contrast-enhanced multi-sliced computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and laparoscopy. The sensitivity of CT in detecting PC varies between 60 to 90% for lesions greater than 5 cm, but decreases to 10-30% for lesions smaller than 1 cm[21;22]. In addition, the accuracy of detecting peritoneal tumour nodules depends on the quality of the image, the expertise of the radiologist and the abdominopelvic regions examined[21-23]. Functional imaging by PET has shown to be a valuable tool in detecting metastases from colorectal cancer, with an overall sensitivity of 97%[24]. Yet this technique also has the drawback of a limited sensitivity for small (<1 cm) lesions. Thus, especially in patients presenting with limited PC in whom treatment is most likely to be beneficial, the non-invasive imaging techniques CT and PET are not reliable. This was also demonstrated by a recent study reporting a discovery of macroscopic PC during systematic second look surgery in 23 out of 41 (56%) asymptomatic patients without radiological signs of peritoneal involvement[25]. MRI is not routinely used for abdominal imaging but may be a technique of interest with new developments like contrast enhancement and faster pulse

sequences[26]. The decision to use MRI for preoperative evaluation of PC will also depend on radiologist's expertise, availability and costs.

Although the sensitivity of the currently available imaging techniques is insufficient to accurately quantify PC lesions and radiological findings often do not correlate with surgical observations[27-29], a high index of suspicion for the presence of PC should be raised with (often subtle) signs on imaging studies such as ascites, omental thickening and mesenterial implants. In the current study the presence of ascites –an indirect sign of PC - was mentioned in the operation notes in 37% of the patients in this study while PC was diagnosed preoperatively in only 5% of the patients. Part of this understaging may be explained by the fact that abdominal CT scans were not routinely performed for preoperative staging for a significant time-frame in the study period.

In case PC is suspected on preoperative imaging, an exploratory laparoscopy to provide more information on the presence and extent of PC may be considered. This has been shown to be feasible and safe but at the cost of an invasive procedure[30-32]. Nevertheless, since the present study reveals the great importance of being informed about the presence of PC prior to an operative procedure, a diagnostic laparoscopy should be part of the work-up whenever signs of PC are present. By doing so futile operations may be avoided, patients with widespread and untreatable disease may be palliated less invasively with stenting of intestinal stenoses and drainage of ascites and selected patients with resectable disease may be offered a chance for long-term survival in specialised HIPEC-centers.

As stated previously there is very little evidence from clinical studies investigating the effect of surgery in patients with PC. Bloemendaal et al. describe a series of 50 patients treated with conventional palliative care, of whom 8 patients underwent a bypass and 29 patients resection of the primary tumour[33]. Similar to the current study, median survival was better in patients in whom resection of the tumour was performed as compared to patients undergoing a derivative procedure or exploration only (17.3 versus 8.3 months respectively). No details were provided on postoperative morbidity and mortality. The better survival reported by these authors for both groups can be explained by the strict selection criteria in this study, including only patients with proven PC of colorectal origin without distant metastases, age 70 years or younger, and fit enough to undergo major surgery.

The present study has a few limitations inherent to its retrospective design. First of all, a selection bias cannot be avoided as data are collected retrospectively, and the decision making process regarding surgery is influenced by the performance status of patients and the surgeon's expertise and opinion. Furthermore, no description of the extent of PC that is found during laparotomy is available. This can be explained by the fact that exploration of the abdomen is not routinely performed, especially not if the surgical procedure is performed with palliative intent. Yet, the information presented here is unique since it describes (to our knowledge) the largest cohort of patients operated with palliative intent in the presence of

PC known in literature. Moreover, the cohort consists of an unselected group of consecutive patients and contains data on post-operative complications and in-hospital mortality. From these data it can be concluded that a careful and thorough preoperative staging is of crucial importance to improve the care for these patients. However, even then PC will be encountered frequently unexpectedly during surgery and despite the bad prognosis of PC on the long term, resection of the primary tumour should be considered whenever possible.

Reference List

(1) Lemmens VEPP, Klaver YLB, Verwaal VJ, Rutten HJT, Coebergh JW, de Hingh IHJT. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; 128(11):2717-2725.

(2) Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006; 243(2):212-222.

(3) Blanchard DK, Shetty PB, Hilsenbeck SG, Elledge RM. Association of surgery with improved survival in stage IV breast cancer patients. *Ann Surg* 2008; 247(5):732-738.

(4) Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; 345(23):1655-1659.

(5) Ruiterkamp J, Ernst MF, van de Poll-Franse LV, Bosscha K, Tjan-Heijnen VC, Voogd AC. Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. *Eur J Surg Oncol* 2009; 35(11):1146-1151.

(6) Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. *Breast Cancer Res Treat* 2010; 120(1):9-16.

(7) Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993; 22(3):369-376.

(8) Cavaliere F, De Simone M, Virzi S, Deraco M, Rossi CR, Garofalo A et al. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. *Eur J Surg Oncol* 2011; 37(2):148-154.

(9) Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; 27(5):681-685.

(10) Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, Alexander R et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. *Ann Surg Oncol* 2007; 14(1):128-133.

(11) Glehen O, Cotte E, Schreiber V, Sayag-Beaujard AC, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. *Br J Surg* 2004; 91(6):747-754.

(12) Klaver YLB, Hendriks T, Lomme RMLM, Rutten HJT, Bleichrodt RP, de Hingh IHJT. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model. *Br J Surg* 2010; 97(12):1874-1880.

(13) Mahteme H, Hansson J, Berglund A, Pahlman L, Glimelius B, Nygren P et al. Improved survival in patients with peritoneal metastases from colorectal cancer: a preliminary study. *Br J Cancer* 2004; 90(2):403-407.

(14) Piso P, Dahlke MH, Ghali N, Iesalnieks I, Loss M, Popp F et al. Multimodality treatment of peritoneal carcinomatosis from colorectal cancer: first results of a new German centre for peritoneal surface malignancies. *Int J Colorectal Dis* 2007; 22(11):1295-1300.

(15) Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(16) Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12(1):65-71.

(17) Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. *J Clin Oncol* 2006; 24(24):4011-4019.

(18)   Cao C, Yan TD, Black D, Morris DL. A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2009; 16(8):2152-2165.

(19)   Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg* 2004; 91(6):739-746.

(20)   Yan TD, Sim J, Morris DL. Selection of patients with colorectal peritoneal carcinomatosis for cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2007; 14(6):1807-1817.

(21)   de Bree E, Koops W, Kroger R, van Ruth S, Witkamp AJ, Zoetmulder FA. Peritoneal carcinomatosis from colorectal or appendiceal origin: correlation of preoperative CT with intraoperative findings and evaluation of interobserver agreement. *J Surg Oncol* 2004; 86(2):64-73.

(22)   Jacquet P, Jelinek JS, Steves MA, Sugarbaker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. *Cancer* 1993; 72(5):1631-1636.

(23)   de Bree E, Koops W, Kroger R, van Ruth S, Verwaal VJ, Zoetmulder FA. Preoperative computed tomography and selection of patients with colorectal peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol* 2006; 32(1):65-71.

(24)   Huebner RH, Park KC, Shepherd JE, Schwimmer J, Czernin J, Phelps ME et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. *J Nucl Med* 2000; 41(7):1177-1189.

(25)   Elias D, Goere D, Di Pietrantonio D, Boige V, Malka D, Kohneh-Shahri N et al. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg* 2008; 247(3):445-450.

(26)   Low RN, McCue M, Barone R, Saleh F, Song T. MR staging of primary colorectal carcinoma: comparison with surgical and histopathologic findings. *Abdom Imaging* 2003; 28(6):784-793.

(27)   Franiel T, Diederichs G, Engelken F, Elgeti T, Rost J, Rogalla P. Multi-detector CT in peritoneal carcinomatosis: diagnostic role of thin slices and multiplanar reconstructions. *Abdom Imaging* 2009; 34(1):49-54.

(28)   Gonzalez-Moreno S, Gonzalez-Bayon L, Ortega-Perez G, Gonzalez-Hernando C. Imaging of peritoneal carcinomatosis. *Cancer J* 2009; 15(3):184-189.

(29)   Koh JL, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2009; 16(2):327-333.

(30)   Denzer U, Hoffmann S, Helmreich-Becker I, Kauczor HU, Thelen M, Kanzler S et al. Minilaparoscopy in the diagnosis of peritoneal tumor spread: prospective controlled comparison with computed tomography. *Surg Endosc* 2004; 18(7):1067-1070.

(31)   Pomel C, Appleyard TL, Gouy S, Rouzier R, Elias D. The role of laparoscopy to evaluate candidates for complete cytoreduction of peritoneal carcinomatosis and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol* 2005; 31(5):540-543.

(32)   Valle M, Garofalo A. Laparoscopic staging of peritoneal surface malignancies. *Eur J Surg Oncol* 2006; 32(6):625-627.

(33)   Bloemendaal AL, Verwaal VJ, van Ruth S, Boot H, Zoetmulder FA. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: a prospective study. *Eur J Surg Oncol* 2005; 31(10):1145-1151.

5

Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model

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Abstract

Background

The combination of cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is the treatment of choice for selected patients with peritoneal carcinomatosis (PC) of colorectal origin. However, it remains to be proven whether the addition of HIPEC to CS is essential for the reported survival benefit.

Methods

Sixty WAG/Rij rats were inoculated intraperitoneally with the rat colon carcinoma cell line CC-531. Animals were randomised into three treatment groups. Group 1: CS alone, group 2: CS followed by HIPEC (mitomycin 15 mg/m^2), group 3: CS followed by HIPEC (mitomycin 35 mg/m^2). Survival was the primary outcome parameter.

Results

Median survival of rats treated with CS alone was 43 days. Rats receiving HIPEC 15 mg/m^2 and HIPEC 35 mg/m^2 both had a significantly longer median survival of 75 days (p=0.003) and 97 days (p<0.001), respectively. Rats receiving HIPEC showed a significantly lower tumour load at autopsy compared to rats treated with CS alone.

Conclusions

A combination of CS and HIPEC results in longer survival than CS alone in rats with PC of colorectal origin.

Introduction

Peritoneal carcinomatosis (PC) is an important cause of morbidity and mortality in patients with colorectal cancer. Synchronous peritoneal metastases are found in 7% of patients[1] and during follow-up a further 4-19% will develop PC[2]. Median survival in conservatively treated patients varies between 5.2 and 12.6 months[3-5]. PC has long been considered to be a manifestation of systemic metastasis with no curative treatment options. Recently, local treatment strategies have been developed combining cytoreductive surgery (CS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). The only phase III randomised trial comparing CS and HIPEC with standard palliative care found median survival in the CS + HIPEC group to be 22.4 months, compared with 12.6 months patients treated with standard palliative care alone[6]. Although these results are certainly encouraging, it remains unclear whether the combination of CS and HIPEC is indeed required to achieve the survival benefit. Unfortunately, no experimental arm was included where patients were treated with CS alone. At this time, it cannot be ruled out that the gain in survival was mainly or entirely due to CS[7].

The addition of HIPEC to CS prolongs operating time and increases the risk of postoperative morbidity and mortality[8;9]. Therefore, the additional benefit of HIPEC should be demonstrated unequivocally before it is widely accepted as standard of care.

Efforts to define the role of adjuvant intraperitoneal chemotherapy after CS in a randomised trial failed to attain the required number of patients, because of patient dissatisfaction with randomisation[10]. Thus, it seems unlikely that this issue will be resolved shortly in randomised clinical trials. Therefore, an experimental study was performed in rats with PC of colorectal origin, aiming to establish the benefit of HIPEC as adjuvant therapy after CS for PC.

Materials and methods

Animals

Sixty male WAG/Rij rats, 10-12 weeks old and median weight 269 (range 236-303) g, were obtained from Harlan, Horst, The Netherlands. The animals were allowed to accustom to laboratory conditions for at least 1 week before experimental use. Rats were housed in filter-topped cages (three rats per cage) under clean, non-sterile standardised conditions (temperature 20-24⁰C; relative humidity 50-60%, 12h light/12 h dark cycle), with free access to food (ssniff®, Bio services, Uden, The Netherlands) and water. All experiments were approved by the Animal Welfare Committee of the Radboud University and carried out in accordance with the Dutch Animal Welfare Act of 1997.

Experimental design

PC was induced in all animals. Seven days after intraperitoneal tumour induction, animals were randomised into three groups of 20 animals each: exploration and CS alone (CS group), CS followed by HIPEC, total dose of mitomycin 0.5 mg (15 mg/m^2) (HIPEC-15 group), and CS followed by HIPEC, total dose of mitomycin 1.2 mg (35 mg/m^2) (HIPEC-35 group). Survival was the primary outcome parameter.

Induction of peritoneal carcinomatosis

The tumour cell line used was the syngeneic rat colonic carcinoma cell line CC-531, originally induced in WAG/Rij rats by intravenous injection of 1,2-dimethylhydrazine[11]. The cell line was cultured and maintained as described previously[12] and two ml of a cell suspension (10^6 cells/ml) was injected intraperitoneally.

Surgery

One week after tumour cell inoculation, CS was performed under general anaesthesia using isoflurane 3%, O$_2$ and 1:1 nitrous oxide. For analgesia, rats were given carprofen (Rimadyl®; Pfizer Animal Health, Capelle aan de Ijssel, The Netherlands) 5 mg per kg per day 30 min before surgery and once daily until the third day after the operation. During surgery, rats were placed on a warmed mattress to limit body heat loss.

After laparotomy, the abdomen was carefully inspected for tumour growth at ten different sites, as shown in table 1. The tumour load at each site was scored semiquantitatively: 0, no macroscopic tumour; 1, limited tumour growth (diameter 1–2 mm); 2, moderate tumour growth (diameter 2–4 mm); or 3, abundant (diameter more than 4 mm). The sum of scores from all sites represented the Peritoneal Cancer Index (PCI) for that animal.

Subsequently, CS including standard omentectomy was performed in all animals, aiming at complete removal of the macroscopic tumour deposits. Unresectable tumour deposits were cauterized using an electrocoagulation device. After CS the amount of residual tumour was scored using a system currently employed in clinical practice. Absence of residual tumour was recorded as R1, a residual tumour of 2.5 mm or less was scored as R2a, and a tumour larger than 2.5 mm as R2b.

In the CS group, the abdomen was closed after surgery. In HIPEC-15 and HIPEC-35 groups, surgery was followed immediately by HIPEC.

Hyperthermic Intraperitoneal chemotherapy

Two multiperforated catheters were introduced into the abdominal cavity through the flanks, as described previously[13]. The catheters were connected to a closed perfusion system containing 250 ml 0.9% sodium chloride. The peritoneal perfusate was warmed in a tube coil using a thermostatically regulated water bath. Perfusion of the peritoneal cavity

was performed for 90 min at 10 ml/min. Mitomycin C (Nycomed Christiaens, Breda, The Netherlands) was dissolved in 0.9% sodium chloride to the appropriate concentration and added to the perfusate in three separate doses at 30-min intervals, each containing 50, 25 and 25% of the total dose. During HIPEC, the abdomen was massaged gently to achieve a uniform heat distribution.

After completion of the perfusion, the abdominal cavity was irrigated with warmed (42°C) saline during 5 min. The catheters were removed and the abdominal wall was closed in two layers using continuous polyglactin 910 (Vicryl™; Ethicon, Edinburgh, UK) sutures for the muscular layer and wound clips for the skin. All rats were given 10 ml 0.9% sodium chloride subcutaneously for rehydration.

Follow-up

The primary endpoint of the experiment was survival. Rats were observed and weighed daily for the first 7 days following surgery, and three times a week thereafter. Body weight was expressed as relative body weight compared to the body weight on the day of operation, and taken to reflect toxicity of the treatment.

When the humane endpoint was reached (physical inactivity, signs of intra-abdominal tumour growth with invalidating consequences or signs of massive haemorrhagic ascites), rats were killed by administration of carbon dioxide, and subjected to autopsy. Ultimately, the decision regarding the humane endpoint was made by an experienced biotechnician who was unaware of the experimental group to which the animal belonged.

After autopsy, the intraperitoneal tumour load was scored as described above. In addition, the weight of ascites was measured. The study was terminated 140 days after surgery. Remaining rats were killed and subjected to autopsy.

Statistical Analysis

Statistical analysis was performed using Graphpad® Prism (Graphpad Software, San Diego, California, USA) and SPSS® version 16.0 (SPSS, Chicago, Illinois, USA) software. The primary objective of the study was to demonstrate an improvement in median survival from 48 days in the CS group to 90 days in the HIPEC groups. Sample size was calculated by lifespan analysis assuming exponential survival from day 35 onwards and using a power of 0.90, $\alpha = 0.05/2 = 0.025$ and an one-sided test. The various assumptions were based on data from previous studies using the same animal model and surgical cytoreductive procedures[13-15]. For the comparison of dichotomous values, chi square or Fisher's Exact tests were used. One-way ANOVA or Kruskall-Wallis testing was used for comparison of continuous values. Survival outcomes were analysed and expressed using Kaplan–Meier curves, and compared with the log-rank test. Cox survival regression analysis was applied to correct for confounding factors. $P < 0.050$ was considered statistically significant.

Results

Surgical procedures

Sixty animals were randomised. Preoperative clinical condition and bodyweight did not differ between the groups. Findings at laparotomy and results of CS are shown in table 1. Peritoneal tumour deposits were present in 59 animals (Figure 1). In the rat with no macroscopic tumour growth omentectomy and exploration were followed by HIPEC as determined by randomisation. The mean PCI score was similar in the three groups. There were no differences between groups regarding residual disease in situ after resection. The mean time taken for the CS procedures, without HIPEC, was 45 min and did not differ between groups.

One rat in the HIPEC-15 group died from respiratory failure immediately after the procedure, and one rat in the CS group died shortly after the surgical procedure as a result of excessive blood loss. On postoperative day 11, one rat from the HIPEC-35 group died with signs of peritonitis and sepsis.

Table 1. Tumour score before cytoreduction, and results of cytoreductive surgery.

Group		CS (n = 20)	HIPEC-15 (n = 20)	HIPEC-35 (n = 20)
Body weight (g)		270 (15)	269 (17)	271 (16)
Tumour score per site				
	Subcutaneous	0 (0-3)	0 (0-2)	0 (0-2)
	Injection site	1 (0-2)	1 (0-2)	1 (0-2)
	Greater omentum	1 (1-1)	1 (1-1)	1 (0-1)
	Liver hilum	1 (0-1)	1 (0-2)	1 (0-2)
	Liver	0 (0-1)	0 (0-1)	0 (0-1)
	Perisplenic	1 (0-2)	1 (0-1)	1 (0-1)
	Mesentery	1 (1-1)	1 (0-2)	1 (0-2)
	Gonadal fatpads	0 (0-3)	0 (0-2)	0 (0-2)
	Diaphragm	0 (0-1)	0 (0-1)	0 (0-1)
	Parietal peritoneum	0 (0-2)	0 (0-2)	0 (0-3)
Overall PCI		6 (1.9)	6 (1.4)	6 (3.0)
Splenectomy				
	Yes	5	5	6
	No	15	15	14
Completeness of resection				
	R1	14	16	16
	R2a	6	3	4
	R2b	0	1	0

CS = cytoreductive surgery, HIPEC-15 = CS + hyperthermic intraperitoneal chemotherapy (HIPEC) with 15mg/m^2 mitomycin C, HIPEC-35 = CS + HIPEC with 35mg/m^2 mitomycin C, PCI = Peritoneal Cancer Index; R1 = no macroscopic residual tumour after CS, R2a = residual tumour 2.5 mm or less after CS, R2b = residual tumour greater then 2.5 mm after CS. Tumour score per site is expressed as median (range). Body weight and overall PCI are expressed as mean (SD).

Figure 1. Macroscopic aspect of peritoneal metastases found at laparotomy at (A) greater omentum and (B) abdominal wall.

Perfusion characteristics

During the HIPEC procedure, the intra-abdominal temperature was similar in both groups, with a mean (SD) of 42.0 (0.9)°C. Mean (SD) rectal temperature at the start of the procedure was 32.8 (0.7)°C in the HIPEC-15 group and 32.7 (0.7)°C in the HIPEC-35 group (p=0.443). This increased to increased to 36.7 (1.9)°C in the HIPEC-15 group and 36.2 (1.4)°C in the HIPEC-35 group by the end of perfusion (p=0.372). The course of rectal and intra-abdominal temperatures during the HIPEC procedures is shown in Figure 2.
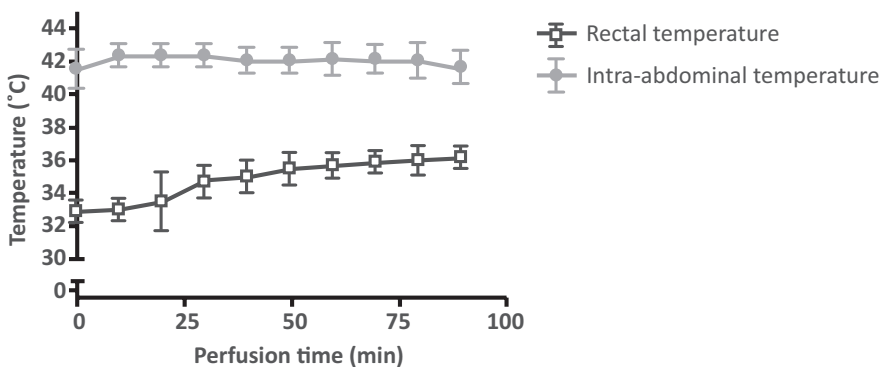
Figure 2. Rectal and intra-abdominal temperatures during the hyperthermic intraperitoneal chemotherapy procedure. Values are means (SD) of all 40 procedures.

Clinical appearance

Figure 3 shows the course of mean body weight in the three groups during the first week after surgery. Rats in the CS group generally gained weight from the second postoperative day onwards. In the HIPEC groups, the lowest mean (SD) bodyweight was recorded on the third day after surgery: reduction of 4.1 (0.6) versus 5.2 (0.6) % in HIPEC-15 and HIPEC-35 groups respectively. In the HIPEC-35 group, mean (SD) maximum weight loss was significantly higher than that in the CS group (5.2 (0.6) versus 3.0 (0.2) % respectively; p=0.042).
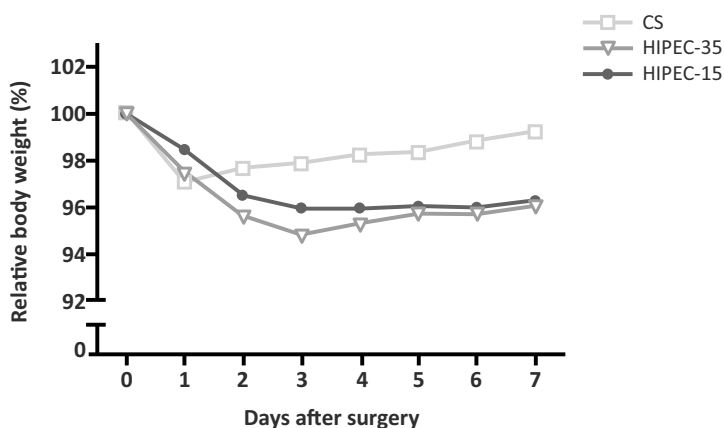

Figure 3. Course of mean body weight, relative to weight at operation, during the first week after surgery. Body weight is given relative to weight at operation. CS = cytoreductive surgery, HIPEC-15 = CS + hyperthermic intraperitoneal chemotherapy (HIPEC) with 15mg/m² mitomycin C, HIPEC-35= CS + HIPEC with 35mg/m² mitomycin C.

Survival

Survival curves are shown in figure 4. During follow-up two rats died from non-tumour related causes. Median survival was 43 (95% confidence interval (CI) 39-64) days in the CS group and 75 (67-99) days in the HIPEC-15 group. The highest median survival of 97 (76-113) days was achieved in the HIPEC-35 group. This difference in survival outcome was significant for both HIPEC groups in comparison with the CS-group: p=0.003 versus HIPEC-15, hazard ratio for dying 0.42 (95% CI 0.22-0.78); p <0.001 versus HIPEC-35, hazard ratio 0.31 (95% CI 0.16-0.59). Survival in the HIPEC-35 group tended to be higher than that in the HIPEC-15 group (p = 0.197). After 20 weeks, 11 rats were still alive (1 CS, 3 HIPEC-15, 7 HIPEC-35). Three of these animals showed no macroscopic evidence of tumour growth (1 CS, 2 HIPEC-35).

At autopsy, rats from the CS group were found to have a higher mean PCI than rats from the HIPEC-35 group (p < 0.001). One rat in the CS group had extensive lung metastases. Post mortem findings are shown in table 2.

In the rats treated with HIPEC, haemorrhagic ascites was the most common reason for reaching the humane endpoint. Rats in the CS group were most often removed from the experiment because of significant weight loss and palpable tumours in the abdomen. Differences in the mean ascites weight were observed between both HIPEC groups and the CS group, but, owing to massive variation, remained non-significant (p =0.355).

In a multivariable analysis, the only other independent factor influencing survival was completeness of resection. Rats with a complete (R1) resection had a longer survival (median 75 days) than rats in which tumour had been left behind (R2a or R2b, median 49 days), independent of treatment (hazard ratio 2.5, 95% CI 1.3-4.9, p=0.008).
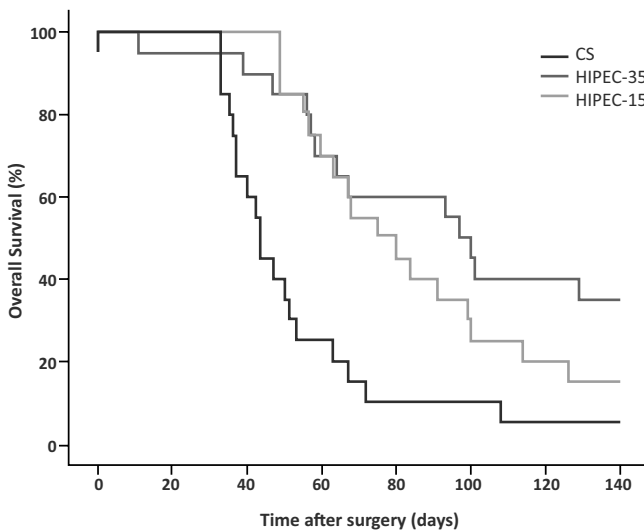
Figure 4. Kaplan-Meier survival curves for the three treatment groups. CS = cytoreductive surgery, HIPEC-15 = CS + hyperthermic intraperitoneal chemotherapy (HIPEC) with 15mg/m^2 mitomycin C, HIPEC-35 = CS + HIPEC with 35mg/m^2 mitomycin C. CS versus HIPEC-15, p= 0.003; CS versus HIPEC-35, p<0.001 (log rank test).

Table 2. Tumour score and ascites weight at autopsy.

Group	CS	HIPEC-15	HIPEC-35
Tumour score per site			
Scar	2 (0-3)	1 (0-3)	0 (0-2)
Injection site	0 (0-3)	0 (0-3)	0 (0-0)
Greater omentum	3 (0-3)	3 (0-3)	3 (0-3)
Liver hilum	3 (0-3)	3 (0-3)	3 (0-3)
Liver	2 (0-3)	1 (0-3)	0 (0-3)
Perisplenic	3 (0-3)	3 (1-3)	1 (0-3)
Mesentery	3 (0-3)	3 (1-3)	2 (0-3)
Fatpad 1	3 (0-3)	3 (0-3)	3 (0-3)
Fatpad 2	3 (0-3)	2 (0-3)	2 (0-3)
Diaphragm	3 (0-3)	3 (0-3)	3 (2-3)
Parietal peritoneum	3 (0-3)	2 (0-3)	1 (0-3)
Overall PCI	24 (6)	23 (5)	17 (6)
Ascites weight (g)	24 (18)	38(19)	37 (20)

CS = cytoreductive surgery, HIPEC-15 = CS + hyperthermic intraperitoneal chemotherapy (HIPEC) with 15mg/m^2 mitomycin C, HIPEC-35 = CS + HIPEC with 35mg/m^2 mitomycin C, PCI = Peritoneal Cancer Index. Tumour score is expressed as median (range). Overall PCI and ascites weight are expressed as mean (SD).

Discussion

This is the first experimental study that demonstrates that HIPEC is an effective adjuvant intraoperative therapy after CS for PC of colorectal origin. Complete macroscopic removal of the tumour from the peritoneal cavity is a second independent factor that improves outcome.

The experiments were performed using a validated and reproducible model of PC of colorectal origin that resembles the clinical situation. After inoculation of CC-531 syngeneic colonic carcinoma cells, PC without distant metastasis develops within three to five days[12;16]. As this cell line has been shown to be sensitive to mitomycin, the experimental model is attractive to determine the effect of HIPEC with this particular anticancer drug[17]. The model is also suitable for performing CS[15] and the feasibility of performing HIPEC after CS has been demonstrated[13;18].

The present experimental HIPEC procedure was designed to mimic the procedure used in the only reported randomised clinical trial[6] as closely as possible; the perfusion time was 90 min and mitomycin was introduced into the flow system in 3 sequential doses. The total dose of 1.2 mg, equivalent to 35 mg/m^2 body surface area, was similar to dosages used to treat patients with PC in the Netherlands. A second dose of 15 mg/m^2 mitomycin was chosen as it has been reported to reduce intraperitoneal tumour growth in rats[19]. Increasing doses

appeared to be increasingly effective when used in the HIPEC procedures as performed in the current model.

HIPEC proved to be highly effective in prolonging survival and in delaying outgrow of intraabdominal recurrence. A previous study carried out in the authors' laboratory failed to demonstrate a significant gain in survival after HIPEC, although median survival time increased from 57 days following CS alone to 76 days with CS and HIPEC[13]. It is entirely conceivable that the toxicity resulting from the very high dose (120 mg/m^2) of mitomycin used, delivered in a single administration, may have neutralised its potential benefits. Adaptation of the dose regimen resulted in a much lower toxicity in the present experiment, as indicated by a less severe loss of bodyweight, and a much improved outcome.

Rats treated by CS alone showed weight loss, palpable tumours in the abdomen and signs of bowel obstruction, most likely caused by rapid tumour growth. This is reflected by a significantly higher tumour load at autopsy than in either HIPEC group. In the latter groups the humane endpoint was based mainly on respiratory failure as a consequence of ascites. Most likely, tumour growth in these rats was inhibited and a fatal volume of ascites developed before tumour growth caused clinical symptoms. The beneficial effect of HIPEC on survival is therefore believed to be a result of tumour growth inhibition.

An interesting observation from this study is that a macroscopically complete removal of tumour is an independent favourable prognostic factor determining outcome. This is in accordance with observations in clinical practice[2;20;21].

Effects of intraperitoneal treatment in addition to CS for PC in rats have been reported previously[22-24]. Postoperative intraperitoneal administration of cisplatin and adrenaline (epinephrine) improved survival, whereas CS alone did not[22]. In addition, intraperitoneal apoptogenic agents administered after CS diminished tumour growth and ascites after 20 days[23]. Although these results support the rationale for performing HIPEC, the models used were not entirely relevant for dealing with questions concerning HIPEC because hyperthermia is not a component of treatment and chemotherapy is not applied during surgery. Recently, Raue and colleagues[24] showed that HIPEC with 15mg/m^2 mitomycin after CS can indeed lead to reduced tumour weight 21 days after surgery. However, the effect of treatment on survival was not evaluated in this study.

Although an experimental model, the results of the present study have provided an answer to the question whether the application of HIPEC is mandatory after CS to improve survival. This question has been under debate ever since publication of the only randomised trial currently available[6]. Although data on side effects remain limited, the available studies[9;25] report acceptable morbidity and mortality rates. Most common complications appear to be associated with CS rather than the addition of HIPEC[9;25]. These data, together with the results of the present study, show that HIPEC is a safe and effective intraoperative adjuvant to CS as therapy for PC of colorectal origin.

Reference List

(1)   Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89(12):1545-1550.
(2)   Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006; 243(2):212-222.
(3)   Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989; 63(2):364-367.
(4)   Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88(2):358-363.
(5)   Bloemendaal AL, Verwaal VJ, van Ruth S, Boot H, Zoetmulder FA. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: a prospective study. *Eur J Surg Oncol* 2005; 31(10):1145-1151.
(6)   Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.
(7)   Khatri VP. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer: a panacea or just an obstacle course for the patient? *J Clin Oncol* 2010; 28(1):5-7.
(8)   Yan TD, Zappa L, Edwards G, Alderman R, Marquardt CE, Sugarbaker PH. Perioperative outcomes of cytoreductive surgery and perioperative intraperitoneal chemotherapy for non-appendiceal peritoneal carcinomatosis from a prospective database. *J Surg Oncol* 2007; 96(2):102-112.
(9)   Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Toxicity of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy. *J Surg Oncol* 2004; 85(2):61-67.
(10)   Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol* 2004; 11(5):518-521.
(11)   Zedeck MS, Sternberg SS. A model system for studies of colon carcinogenesis: tumor induction by a single injection of methylazoxymethanol acetate. *J Natl Cancer Inst* 1974; 53(5):1419-1421.
(12)   Lopes Cardozo AM, Gupta A, Koppe MJ, Meijer S, van Leeuwen PA, Beelen RJ et al. Metastatic pattern of CC531 colon carcinoma cells in the abdominal cavity: an experimental model of peritoneal carcinomatosis in rats. *Eur J Surg Oncol* 2001; 27(4):359-363.
(13)   Aarts F, Hendriks T, Boerman OC, Koppe MJ, Oyen WJ, Bleichrodt RP. A comparison between radioimmunotherapy and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of colonic origin in rats. *Ann Surg Oncol* 2007; 14(11):3274-3282.
(14)   Aarts F, Koppe MJ, Hendriks T, van Eerd JE, Oyen WJ, Boerman OC et al. Timing of adjuvant radioimmunotherapy after cytoreductive surgery in experimental peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2007; 14(2):533-540.
(15)   Koppe MJ, Hendriks T, Boerman OC, Oyen WJ, Bleichrodt RP. Radioimmunotherapy is an effective adjuvant treatment after cytoreductive surgery of experimental colonic peritoneal carcinomatosis. *J Nucl Med* 2006; 47(11):1867-1874.
(16)   Los G, Ruevekamp M, Bosnie N, De Graaf PW, McVie JG. Intraperitoneal tumor growth and chemotherapy in a rat model. *Eur J Cancer Clin Oncol* 1989; 25(12):1857-1866.
(17)   Dirix LY, Gheuens EE, van der HS, van Oosterom AT, De Bruijn EA. Cytotoxic activity of 7-N-(2-((2-(-gamma-L-glutamylamino)- ethyl)dithio)ethyl)-mitomycin C and metabolites in cell lines with different resistance patterns. *Anticancer Drugs* 1994; 5(3):343-354.
(18)   Aarts F, Bleichrodt RP, de Man B, Lomme R, Boerman OC, Hendriks T. The effects of adjuvant experimental radioimmunotherapy and hyperthermic intraperitoneal chemotherapy on intestinal and abdominal healing after cytoreductive surgery for peritoneal carcinomatosis in the rat. *Ann Surg Oncol* 2008; 15(11):3299-3307.

(19)   Pelz JO, Doerfer J, Hohenberger W, Meyer T. A new survival model for hyperthermic intraperitoneal chemotherapy (HIPEC) in tumor-bearing rats in the treatment of peritoneal carcinomatosis. *BMC Cancer* 2005; 5:56.

(20)   Yan TD, Sim J, Morris DL. Selection of patients with colorectal peritoneal carcinomatosis for cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2007; 14(6):1807-1817.

(21)   Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg* 2004; 91(6):739-746.

(22)   Benoit L, Duvillard C, Beltramo JL, Brunet-Lecomte P, Chauffert B. [Intraperitoneal cisplatin plus epinephrine and surgical debulking for the treatment of advanced peritoneal carcinomatosis in the rat]. *Gastroenterol Clin Biol* 2000; 24(1):26-30.

(23)   Monneuse O, Mestrallet JP, Quash G, Gilly FN, Glehen O. Intraperitoneal treatment with dimethylthioampal (DIMATE) combined with surgical debulking is effective for experimental peritoneal carcinomatosis in a rat model. *J Gastrointest Surg* 2005; 9(6):769-774.

(24)   Raue W, Kilian M, Braumann C, Atanassow V, Makareinis A, Caldenas S et al. Multimodal approach for treatment of peritoneal surface malignancies in a tumour-bearing rat model. *Int J Colorectal Dis* 2010; 25(2):245-250.

(25)   Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Sebbag G et al. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol* 1999; 6(8):790-796.

6

Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study

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Abstract

Background
Hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C can improve survival if used as an adjunct to cytoreductive surgery (CS) for treatment of peritoneal carcinomatosis (PC). It remains unclear if both hyperthermia and chemotherapy are essential for the reported survival benefit.

Methods
Eighty WAG/Rij rats were inoculated intraperitoneally with the rat colon carcinoma cell line CC-531. Animals were randomly assigned to one of the four treatment groups (n=20): CS only, CS followed by HIPEC (mitomycin 35 mg/m^2 at 41°C), CS followed by intraperitoneal mitomycin perfusion at 37°C, CS followed by intraperitoneal saline perfusion at 41°C. Survival was the primary outcome with a maximum follow up of 126 days.

Results
Median survival was 62 days in rats treated with CS only and 57 days in rats treated with CS followed by hyperthermic saline perfusion. Rats receiving HIPEC had a median survival of 121 days (p=0.022 when compared to CS only). In the group treated with chemotherapy at 37°C, 13 of 20 animals were still alive at the end of the experiment so median survival was not reached (CS versus IPEC: p = 0.002). Rats treated with hyperthermic saline perfusion did not have an increased survival as compared to CS only.

Conclusion
The effectiveness of intraoperative intraperitoneal perfusion after CS is highly dependent on the presence of chemotherapeutic agents in the perfusate but not on hyperthermia. The need to include hyperthermia in the adjuvant intraoperative treatment after CS for PC should be further investigated.

Introduction

The combination of cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is widely accepted as a treatment strategy for selected patients suffering from peritoneal carcinomatosis (PC) from colorectal origin who are considered to be fit for major surgery. With palliative treatment, these patients have a poor prognosis of approximately 6 months[1-3]. Results of a randomised controlled trial demonstrated a survival benefit in patients treated with CS and HIPEC, when compared to palliative treatment only[4;5]. Nevertheless, many questions remain unanswered regarding the optimal approach for this multimodality treatment[6].

In PC the presence of residual microscopic disease after cytoreductive surgical procedures is assumed to be inevitable due to the fact that tumour cells have entered the continuous volume of the peritoneal cavity. The adjuvant application of intraoperative intraperitoneal chemotherapy is aimed at the destruction of this residual microscopic disease. In most institutions performing surgical procedures for PC, hyperthermia is a standard component of the treatment[7;8]. Hyperthermia is defined as an increase of temperature in a tumour-affected body region to 39-43°C by using an external energy source[9]. Next to a direct cytotoxic effect, hyperthermia is believed to enhance the antitumour effect of several cytostatic agents at markedly lower temperatures by increasing blood flow and oxygen content within tumours[10;11]. This phenomenon is thought to increase intratumoural drug concentrations and thereby the cytostatic efficiency.

So far, no randomised controlled trials have been published comparing normothermic versus hyperthermic intraoperative chemotherapy for PC from colorectal origin. Moreover, the additional value of chemotherapeutic agents in the intraperitoneal perfusion fluid has never been assessed in prospective studies. For clinical practice, it is very relevant to ascertain the necessity of both elements being included in the treatment since performance of these procedures is technically demanding. Also, some of the of reported side effects resulting from HIPEC procedures are possibly associated with either the use of the relatively high dose of mitomycin C or the hyperthermic conditions during the perfusion[12-14]. Recently, an animal model for PC was established which allows the performance of CS and HIPEC[15;16]. It was shown that the adjuvant application of HIPEC after CS indeed significantly prolonged survival when compared to CS only[17]. This study was designed to evaluate the necessity of the separate elements hyperthermia and chemotherapy for the effectiveness of the HIPEC therapy as a whole on survival.

Methods

Experimental design

In all animals PC was induced seven days before the surgical procedures. Animals were randomly assigned to one of four treatment groups, consisting of 20 animals each: Group 1: exploration and cytoreductive surgery only (CS), group 2: cytoreductive surgery followed by hyperthermic intraperitoneal perfusion with saline at 41°C (hyperthermic intraperitoneal perfusion: HIPE), group 3: cytoreductive surgery followed by normothermic intraperitoneal perfusion with mitomycin at 37°C (intraperitoneal chemotherapy: IPEC), group 4: cytoreductive surgery followed by hyperthermic intraperitoneal perfusion with mitomycin at 41°C (HIPEC). Primary outcome parameter was survival.

Animals

Eighty 10-12 weeks old male WAG/Rij rats with a mean weight of 263 ± 13 grams were obtained from Harlan, Horst, The Netherlands. The animals were accustomed to laboratory conditions for at least one week before experimental use and housed under clean, non-sterile standardised conditions (temperature 20-24°C; relative humidity 50-60%, 12h light/12 h dark) in filter-topped cages (three rats per cage). The animals were allowed free access to chow (Ssniff, Bio services Uden, The Netherlands) and water. All experiments were carried out in accordance with the Dutch Animal Welfare Act of 1997 and approved by the Animal Welfare Committee of the Radboud University Nijmegen Medical Centre.

Induction of peritoneal carcinomatosis

PC was induced by intraperitoneal injection of syngeneic rat colon carcinoma CC-531 cells as described before[18]. All animals were inoculated by intraperitoneal injection of 2ml of this cell suspension one week before surgical procedures.

Surgery

CS was performed in all animals one week after tumour cell inoculation under general anaesthesia using isoflurane 3%, O_2 and N_2O 1:1. Carprofen (5 mg/kg/day) was given 30 min before surgery and once daily until the third postoperative day for analgesia. Rats were placed on a warmed mattress during all procedures to limit body heat loss.

A complete midline laparotomy was performed in all animals. Subsequently, the abdominal cavity was inspected and the number of tumour deposits at 11 different sites was scored semiquantitatively with a score of 0 for no macroscopic tumour, 1 for limited tumour growth (diameter of 1–2 mm), 2 for moderate tumour growth (diameter of 2–4 mm), or 3 for an abundant presence of tumour nodules (diameter >4 mm or >10 deposits). The sum of scores from all sites represented the peritoneal cancer index (PCI) as described before[15;17].

After inspection, CS was performed in all animals, aimed at radical removal of all macroscopic tumour deposits with standard resection of the greater omentum. In case of irresectable tumour deposits cauterisation using an electrocoagulation device was performed. Residual tumour load after CS was scored using the R1-R2a-R2b classification in accordance to current clinical practice: R1: Absence of residual tumour, R2a: a residual tumour smaller than 2.5 mm, R2b: tumour mass larger than 2.5 mm left behind.

In the CS group, the abdomen was closed after exploration and cytoreductive procedures. In all other groups, surgery was followed immediately by intraperitoneal perfusion during 90 minutes according to the assigned treatment.

Intraperitoneal perfusion procedure

While the abdominal cavity was still exposed, two multiperforated catheters were introduced through the flanks into the abdominal cavity to perform perfusion as described before[15;17]. In short, the peritoneal perfusate consisting of 250 ml NaCl (0.9%) was warmed and infused into the abdomen during 90 min at 10 ml/min using a roller pump (Ismatec, Idex corporation, Northbrook). In the IPEC and HIPEC group, Mitomycin-C (Nycomed Christiaens BV, Breda, The Netherlands) was dissolved in saline to the appropriate concentration. A dose of 35 mg/m^2 was added to the perfusate in three separate administrations at 30 min intervals, each containing 50%, 25% and 25% of the total respectively. The abdomen was gently massaged throughout the perfusion to achieve an equal fluid distribution throughout the peritoneal cavity. After 90 minutes, the abdominal cavity was perfused with saline during 5 min, the catheters were removed and subsequently the abdominal wall was closed in two layers using continuous Vicryl 3/0 sutures. Ten ml of NaCl 0.9% were given subcutaneously to all animals for rehydration.

Follow-up

Survival was the primary endpoint of this study. Body weight and the general condition were assessed daily for the first week after surgical procedures, and at least twice a week thereafter. The humane endpoint was determined by an experienced biotechnician who was blinded for which treatment the animals had received. Bodyweight was used to evaluate toxicity of the treatment and expressed as relative bodyweight compared with the bodyweight on the day of surgery.

When the humane endpoint was reached (physical inactivity, signs of intra-abdominal tumour growth with invalidating consequences or signs of massive haemorrhagic ascites), rats were killed by O_2/CO_2-asphyxation and autopsied. Postmortem, the same PCI scoring system as described above was used to record the intraperitoneal tumour load. In addition, the weight of ascites was measured. At 126 days post-operatively, the experiment was terminated and the remaining rats were euthanised and autopsied.

If no macroscopic tumour was found at autopsy, the greater omentum and diaphragm were removed for microscopic evaluation. Samples were stained with hematoxylin & eosin (H&E) and murine MG1 antibody in combination with a horseanti-mouse IgG antibody, HRP conjugated (Vector Laboratories Inc., Burlingame, CA).

Statistical Analysis

Graphpad Prism (version 4.0, 2003, Graphpad Software Inc., San Diego CA) and SPSS (version 16.0, 2007, Chicago, IL) software were used for all statistical analyses. Chi square or Fisher's Exact test were used for the comparison of dichotomous values, and for comparison of continuous values one-way ANOVA testing or Kruskall-Wallis testing was used. Survival analysis was performed using Kaplan–Meier curves and compared by means of the log-rank test. Cox survival regression analysis was used to correct for confounding factors.

Results

Surgical procedures

CS was performed on eighty animals. Preoperative clinical condition and mean body weight were similar in all treatment groups.

All animals had macroscopic tumour deposits during laparotomy. Details are given in table 1 and examples of tumour deposits are shown in figure 1. Most frequently affected tumour sites were the greater omentum, perisplenic area, liver hilum, mesentery and intraabdominal site of tumour inoculation. At initial exploration during surgery, mean PCI did not differ between the treatment groups (p = 0.452).

Complete macroscopic resection of tumour deposits (R1 resection) was achieved in 72 animals (90%). In the animals with residual tumour, no deposits with a diameter larger than 2.5 mm were left behind. The results of CS in terms of residual disease did not differ between the treatment groups (p = 0.918). The CS procedures took a mean time of 30 minutes in all groups.

Two rats (one each in the HIPE and IPEC groups) died during the perfusion procedures due to respiratory failure. One rat in the CS group died shortly after the surgical procedure due to hypovolemia as a consequence of extensive blood loss during surgery. An unexpected death occurred in the HIPEC group on day 13 after surgery. At autopsy a herniation of small bowel through a mesentery defect was found, causing obstruction. One rat from the IPEC-treatment group died after 50 days due to an unknown cause. At autopsy, no evidence of tumour growth was found, nor any other signs which would explain the premature death. These rats were marked as censored in the survival analyses.
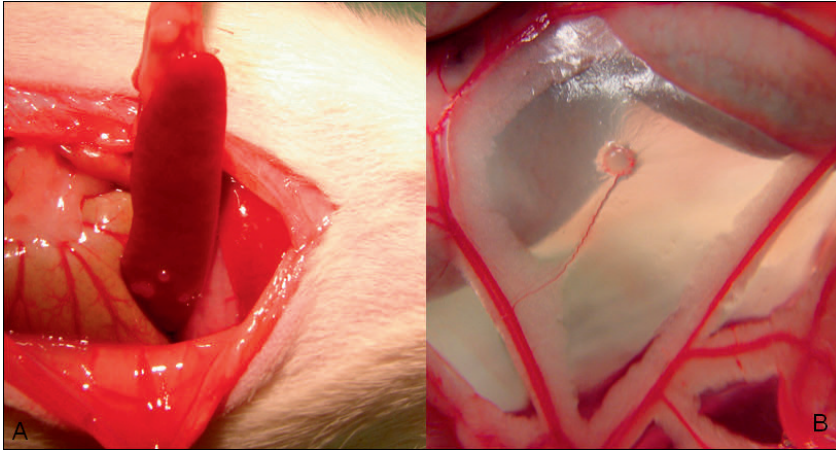
Figure 1. Examples of macroscopic tumour deposits found at spleen (A) and mesentery (B) during laparotomy.

Table 1. Tumour score before cytoreduction and results of cytoreductive surgery.

Group	CS	HIPE	IPEC	HIPEC
Preoperative weight (g) (mean, SD)	264 (16)	265 (10)	264 (15)	261 (12)
Tumour score per site (median, range)				
Subcutaneous	1 (0-1)	1 (0-2)	1 (0-1)	1 (0-3)
Inoculation site intraabdominal	1 (0-3)	1 (0-1)	1 (0-1)	1 (0-1)
Greater omentum	1 (1-1)	1 (1-2)	1 (1-1)	1 (1-1)
Liver hilum	1 (1-2)	1 (1-2)	1 (0-2)	1 (1-2)
Liver surface	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-1)
Spleen	1 (0-1)	1 (0-1)	1 (0-2)	1 (1-1)
Mesentery	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
Fatpad left	0 (0-1)	0 (0-2)	0 (0-2)	0 (0-2)
Fatpad right	0 (0-3)	0 (0-1)	0 (0-1)	0 (0-1)
Diaphragm	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Parietal peritoneum	0 (0-1)	0.5 (0-1)	0.5 (0-2)	0 (0-1)
Overall PCI (mean, SD)	5.9 (2.0)	6.6 (2.0)	5.8 (1.9)	6.1 (1.6)
Splenectomy (n)				
Yes	0	1	2	2
No	20	19	18	18
Completeness of resection (n)				
R1	18	17	18	19
R2a	2	3	2	1
R2b	0	0	0	0

CS = cytoreductive surgery, HIPE = CS + perfusion with NaCl at 41°C, IPEC = CS + perfusion with mitomycin at 37°C, HIPEC = CS + perfusion with mitomycin at 41°C. PCI = Peritoneal Cancer Index, R1 = no macroscopic residual tumour after cytoreduction, R2a = residual tumour <2.5mm after cytoreduction, R2b = residual tumour >2.5mm after cytoreduction.

Perfusion characteristics

During the perfusion procedures, the intraabdominal temperature at the inflow site was similar in both hyperthermic groups, with a mean of 41.3°C (figure 2A). Mean rectal temperatures during the experiment are shown in figure 2B. Rats in the IPEC group (normothermic perfusion) had a significantly lower rectal temperature at the end of perfusion than rats from both groups with hyperthermic perfusion (p<0.001).
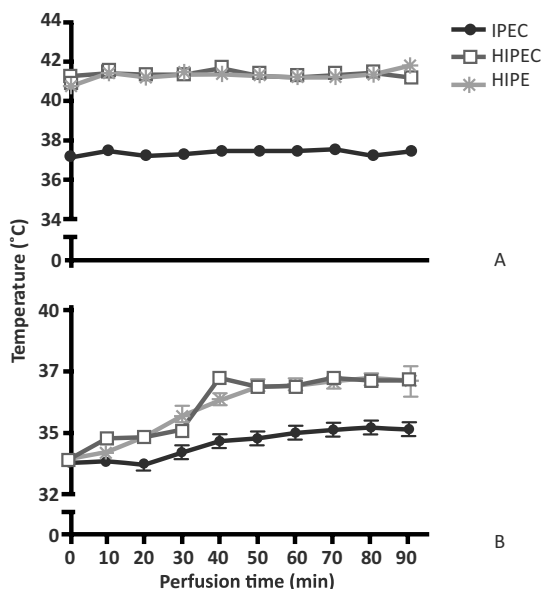

Figure 2. A. Intra-abdominal temperatures at the site of inflow and B. rectal temperatures during perfusion procedures.
Data represent means ± SD (n=20) of all procedures. HIPE = CS + perfusion with NaCl at 41°C, IPEC = CS + perfusion with mitomycin at 37°C, HIPEC = CS + perfusion with mitomycin at 41°C.

Clinical appearance

Apart from the surgery-related complications mentioned above, and one nontumour related death the procedures were well tolerated. In figure 3, the course of mean body weight in the various treatment groups is shown for the first week after operation. In the CS group the lowest postoperative body weight was recorded on the second day after surgery. In the other treatment groups rats generally gained weight from the fourth postoperative day onwards. After reaching a nadir, the rats gained weight again and recovered completely. The mean maximum weight loss was significantly higher in all groups that underwent peritoneal perfusion after CS than in rats in the CS group (CS versus HIPE, p = 0.034, CS versus IPEC and CS versus HIPEC, p <0.001). In addition, rats in the HIPEC group lost significantly more weight than rats in the HIPE group (p = 0.034).
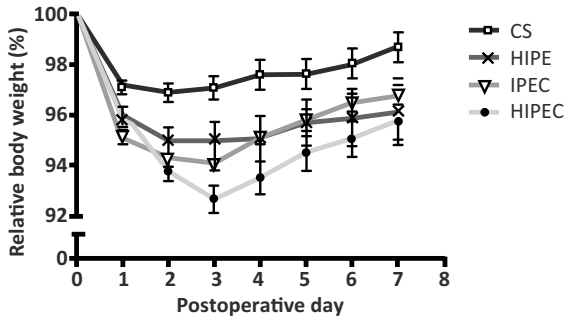
Figure 3. Course of mean relative bodyweight during the first week after surgery.
CS = cytoreductive surgery, HIPE = CS + perfusion with NaCl at 41°C, IPEC = CS + perfusion with mitomycin at 37°C, HIPEC = CS + perfusion with mitomycin at 41°C.

Survival

Kaplan-Meier survival analyses are shown in figure 4. In the group treated with CS only, median survival was 62 days (95% confidence interval (CI) 46-78) Median survival in rats receiving HIPE perfusion was 57 days (95% CI 50-64). In the group treated with HIPEC, median survival was 121 days. At the end of the follow-up, 13 rats in the IPEC-group were still alive and median survival was therefore not reached in this group. The difference in survival outcome when compared to the CS-group was significant for both the HIPEC group (p = 0.022, hazard ratio for dying 0.46, 95% CI 0.24-0.89) and the IPEC group (p = 0.002, hazard ratio 0.36, 95% CI 0.19-0.69).

After the maximum follow-up of 126 days was reached, 27 rats were still alive. In 21 of these rats no ascites or macroscopic tumour deposits were found at autopsy (2/3 CS, 2/2 HIPE, 10/13 IPEC, 7/9 HIPEC). In one of the rats from the IPEC-group, microscopic tumour deposits were found in a coagulated tumour. In the other rats, no residual tumour tissue was found at microscopic evaluation.

In rats from the CS group that reached their humane endpoint during the follow-up, a higher mean PCI was found when compared to the postmortem PCI of rats in the HIPEC-group (p = 0.050). A similar trend was observed when comparing the HIPEC group with the rats treated with HIPE, but this remained non-significant (p = 0.070). The amount of ascites present at autopsy did not differ between groups (p = 0.083). Post mortem findings are given in table 2. No predictors of outcome other than treatment group were identified in multivariate analysis.
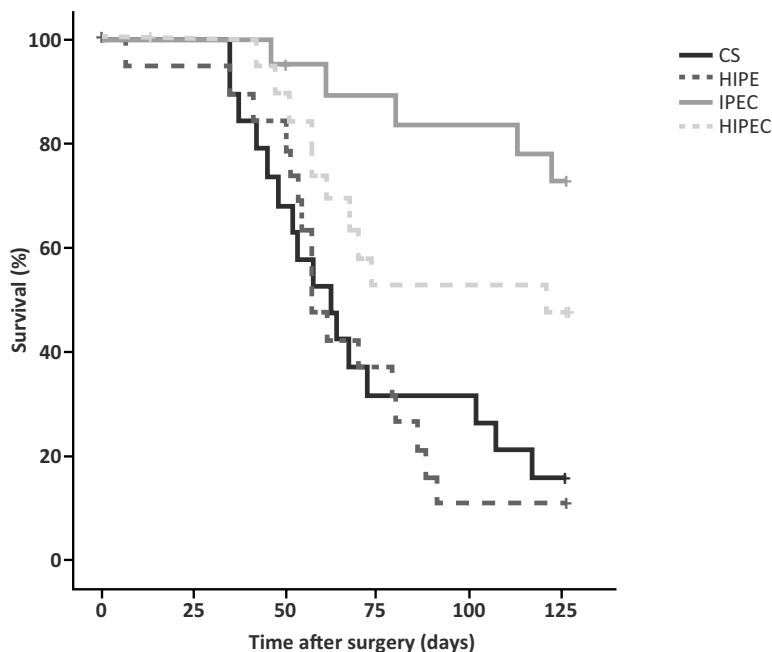
Figure 4. Kaplan Meier survival curves, per group.
CS = cytoreductive surgery, HIPE = CS + perfusion with NaCl at 41°C, IPEC = CS + perfusion with mitomycin at 37°C, HIPEC = CS + perfusion with mitomycin at 41°C.
CS versus HIPEC: p = 0.022, CS versus IPEC: p = 0.002, CS versus HIPE: nonsignificant.

Table 2. Post mortem findings.

Group	CS	HIPE	IPEC	HIPEC
Overall PCI (mean, SD)	26 (5)	25 (6)	21 (3)	20 (7)
Ascites weight (g) (mean, SD)	31 (28)	34 (23)	37 (13)	47 (15)

CS = Cytoreductive Surgery, HIPE = CS + perfusion with NaCl at 41°C, IPEC = CS + perfusion with mitomycin at 37°C, HIPEC = CS + perfusion with mitomycin at 41°C. PCI = Peritoneal Cancer Index

Discussion

This study shows that the effectiveness of intraoperative intraperitoneal perfusion after CS is highly dependent on the presence of chemotherapeutic agents in the perfusate but not on hyperthermia.

Although most procedures for PC nowadays are performed under hyperthermic conditions, the additional effect of hyperthermia as a component of the combined treatment for patients with PC from colorectal origin has never been demonstrated. Only one randomised

trial comparing intraoperative intraperitoneal perfusion with mitomycin C and cisplatin under normothermic and hyperthermic conditions has reported a survival benefit in the hyperthermic group[19]. However, this trial was performed in patients with advanced gastric cancer after curative gastrectomy without macroscopic peritoneal involvement, and treatment was applied in a prophylactic setting to prevent recurrent disease. The addition of hyperthermia to standard malignancy treatment strategies like radiotherapy or chemotherapy has been associated with improved tumour control and survival in patients with locally advanced cervix carcinoma[20], breast cancer[21], and soft tissue sarcoma[22]. However the available evidence is very limited, warranting further research to establish the value of hyperthermia in clinical practice.

Preclinical studies report conflicting results regarding the effect of hyperthermia on several outcome parameters varying from no effect on pharmacokinetics and pharmacodynamic outcomes[23-25] to a significant increase in concentration of chemotherapeutic agents in tumour cells or tissue under hyperthermic conditions[26]. Pelz et al. evaluated the histological response of PC in rats treated with hyperthermic perfusion with or without mitomycin, or with an intraperitoneal mitomycin injection under normothermic conditions. In all locoregional treatment groups a delay of tumour growth was observed as compared with sham operated animals, which was most pronounced in the group treated with HIPEC[27]. Yet in none of these preclinical studies CS was performed and overall survival was not used as an outcome parameter.

In this study, the application of hyperthermic saline did not have a beneficial effect on survival as compared to CS only. Moreover, no difference in postmortem PCI scores was found between the CS only and HIPE group, whereas the rats in the IPEC and HIPEC group showed a lower tumour load as expressed by PCI scores at autopsy. This inhibition of tumour growth by HIPEC is in accordance with results from a previous study performed in our laboratory[17], but was not seen in the group treated with hyperthermia only in this experiment. It should be taken into account that in the current study the temperature used for hyperthermic conditions was 41°C, which is used in the only completed randomised clinical trial evaluating the effect of HIPEC[5;15]. It cannot be ruled out that the application of higher temperatures (exceeding 42°-43°C) would have resulted in a decrease in tumour growth, as these temperatures have been demonstrated to have a direct cytotoxic effect on to both normal and tumour cells under experimental conditions[9;10]. However, in this study we aimed to evaluate the separate components of the clinical multimodality HIPEC treatment, which is routinely performed at a temperature of 41°C.

At the end of the follow up period of this study, 10 animals in the IPEC group and 7 animals in the HIPEC-group were alive without any microscopic evidence of disease, which compares favourably to 2 animals in both the CS and HIPE group. This study demonstrates that the application of normothermic chemoperfusion can successfully eliminate microscopic tumour

cells after cytoreductive procedures, and that normothermic intraperitoneal chemotherapy certainly does not lead to inferior results as compared to hyperthermic treatment. This is an important finding as application of hyperthermic circumstances in intraperitoneal perfusion may result in additional toxicity in clinical practice[12;14]. Indeed, in the current experiment the mean weight loss in the first week which is considered to be a marker of treatment-related toxicity was most pronounced in the HIPEC group. Furthermore, in clinical practice the heating of chemotherapy is time-consuming, increases the technical demands to operating room personnel and raises costs. Thus, the observation that normothermic application of intraperitoneal chemotherapy may be equally effective in the treatment of PC should stimulate further research in this area, to critically assess the necessity of hyperthermia. If feasible, a simplification of the current multimodality treatment may benefit the patients with PC.

Reference List

(1)   Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89(12):1545-1550.

(2)   Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88(2):358-363.

(3)   Lemmens VEPP, Klaver YLB, Verwaal VJ, Rutten HJT, Coebergh JW, de Hingh IHJT. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; 128(11):2717-2725.

(4)   Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12(1):65-71.

(5)   Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(6)   Khatri VP. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer: a panacea or just an obstacle course for the patient? *J Clin Oncol* 2010; 28(1):5-7.

(7)   Esquivel J. Technology of hyperthermic intraperitoneal chemotherapy in the United States, Europe, China, Japan, and Korea. *Cancer J* 2009; 15(3):249-254.

(8)   Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. *J Clin Oncol* 2006; 24(24):4011-4019.

(9)   Hildebrandt B, Wust P. The biologic rationale of hyperthermia. *Cancer Treat Res* 2007; 134:171-184.

(10)   Song CW, Park HJ, Lee CK, Griffin R. Implications of increased tumor blood flow and oxygenation caused by mild temperature hyperthermia in tumor treatment. *Int J Hyperthermia* 2005; 21(8):761-767.

(11)   Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T et al. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002; 43(1):33-56.

(12)   Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Toxicity of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy. *J Surg Oncol* 2004; 85(2):61-67.

(13)   Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H et al. Hyperthermia in combined treatment of cancer. *Lancet Oncol* 2002; 3(8):487-497.

(14)   Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. *Ann Surg* 2009; 249(6):900-907.

(15)   Aarts F, Hendriks T, Boerman OC, Koppe MJ, Oyen WJ, Bleichrodt RP. A comparison between radioimmunotherapy and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of colonic origin in rats. *Ann Surg Oncol* 2007; 14(11):3274-3282.

(16)   Aarts F, Bleichrodt RP, de Man B, Lomme R, Boerman OC, Hendriks T. The effects of adjuvant experimental radioimmunotherapy and hyperthermic intraperitoneal chemotherapy on intestinal and abdominal healing after cytoreductive surgery for peritoneal carcinomatosis in the rat. *Ann Surg Oncol* 2008; 15(11):3299-3307.

(17)   Klaver YLB, Hendriks T, Lomme RMLM, Rutten HJT, Bleichrodt RP, de Hingh IHJT. Intraoperative hyper-thermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model. *Br J Surg* 2010; 97(12):1874-1880.

(18)   Lopes Cardozo AM, Gupta A, Koppe MJ, Meijer S, van Leeuwen PA, Beelen RJ et al. Metastatic pattern of CC531 colon carcinoma cells in the abdominal cavity: an experimental model of peritoneal carcinomatosis in rats. *Eur J Surg Oncol* 2001; 27(4):359-363.

(19)   Yonemura Y, de Aretxabala X, Fujimura T, Fushida S, Katayama K, Bandou E et al. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. *Hepatogastroenterology* 2001; 48(42):1776-1782.

(20)   Lutgens L, van der Zee J, Pijls-Johannesma M, De Haas-Kock DF, Buijsen J, Mastrigt GA et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. *Cochrane Database Syst Rev* 2010; 3:CD006377.

(21)   Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. *Int J Radiat Oncol Biol Phys* 1996; 35(4):731-744.

(22)   Issels RD, Lindner LH, Verweij J, Wust P, Reichardt P, Schem BC et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* 2010; 11(6):561-570.

(23)   Pestieau SR, Stuart OA, Chang D, Jacquet P, Sugarbaker PH. Pharmacokinetics of intraperitoneal gemcitabine in a rat model. *Tumori* 1998; 84(6):706-711.

(24)   Zeamari S, Floot B, van der Vange N, Stewart FA. Pharmacokinetics and pharmacodynamics of cisplatin after intraoperative hyperthermic intraperitoneal chemoperfusion (HIPEC). *Anticancer Res* 2003; 23(2B):1643-1648.

(25)   Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. *Cancer Chemother Pharmacol* 1998; 41(2):147-154.

(26)   Los G, van Vugt MJ, Pinedo HM. Response of peritoneal solid tumours after intraperitoneal chemohyperthermia treatment with cisplatin or carboplatin. *Br J Cancer* 1994; 69(2):235-241.

(27)   Pelz JO, Doerfer J, Dimmler A, Hohenberger W, Meyer T. Histological response of peritoneal carcinomatosis after hyperthermic intraperitoneal chemoperfusion (HIPEC) in experimental investigations. *BMC Cancer* 2006; 6:162.

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Intraoperative versus early postoperative intraperitoneal chemotherapy after cytoreduction for colorectal peritoneal carcinomatosis. An experimental study

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Abstract

Background

Perioperative intraperitoneal chemotherapy is used as an adjunct to cytoreductive surgery (CS) for peritoneal carcinomatosis (PC) in order to prolong survival. Worldwide, hyperthermic intraperitoneal chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC) and combinations of the two are used. It remains unclear which regimen is most beneficial.

Methods

The rat colon carcinoma cell line CC-531 was injected into the peritoneal cavity of eighty WAG/Rij rats to induce PC. Animals were randomised into four treatment groups (n=20): CS only, CS followed by HIPEC (mitomycin 35 mg/m^2 at 41.5°C), CS followed by EPIC during 5 days (intraperitoneal injection of mitomycin on day 1 and 5-fluorouracil on day 2-5), and CS followed by HIPEC plus EPIC. Primary outcome was survival.

Results

In rats treated with CS only, median survival was 53 days (95% confidence interval (CI) 49-57). In rats treated with CS followed by HIPEC, survival was significantly (p = 0.001) increased (median survival 94 days, 95% CI 51-137). In the group treated with EPIC after CS, 12 out of 20 rats were still alive at the end of the experiment (p<0.001 as compared with CS only). In the group receiving both treatments, eleven rats died of toxicity, and therefore this group was not included in the survival analysis.

Conclusion

Both EPIC and HIPEC were effective in prolonging survival. The beneficial effect of EPIC on survival seemed to be more pronounced than that of HIPEC. Further research is indicated to evaluate and compare the possible benefits and adverse effects associated with both treatments.

Introduction

The combination of cytoreductive surgery (CS) and perioperative intraperitoneal chemotherapy is the only available curative option for patients with peritoneal carcinomatosis (PC) from colorectal cancer. By now, it has been widely accepted as the treatment of choice for patients with limited peritoneal carcinomatosis who are fit for major surgery. The aim of this treatment is to radically remove all visible tumour deposits from the peritoneal cavity, and to eradicate residual microscopic disease by adjuvant application of intraperitoneal chemotherapy. Promising results have been shown by several centres, achieving a median survival which compares favourably to the outcomes of patients treated with palliative care in whom life expectancy is usually limited to approximately 6 months[1-5].

The adjuvant intraperitoneal chemotherapy can be applied directly after cytoreduction under hyperthermic conditions (hyperthermic intraperitoneal chemotherapy, HIPEC) as a part of the surgical procedure, or can be started on the first postoperative day and continued for several (usually five) days (early postoperative intraperitoneal chemotherapy, EPIC). Both techniques are currently offered to patients with colorectal PC, either as separate treatments or in combination, depending on the preference of the center and surgeon.

The choice for HIPEC and/or EPIC has major consequences for the scheduling of procedures and the capacity of the treatment centre. This becomes relevant as growing awareness among physicians about the availability of treatment possibilities for PC results in increasing numbers of patients being referred to specialised centres.

No randomised controlled trials have been published comparing the survival outcomes after EPIC and HIPEC. Furthermore, it is unclear whether the combination of both HIPEC and EPIC results in superior outcomes.

In a recent experimental study, it was shown that the adjuvant application of HIPEC after CS can prolong survival as compared with CS only[6]. A second study demonstrated beneficial results for both adjuvant normothermic and hyperthermic intraoperative perfusion[7].

In the present study, the effectiveness of HIPEC and EPIC as adjuvant treatment after CS was evaluated in a well-established model for PC in rats. In addition, the combination of the two treatments was investigated. Survival was the primary outcome parameter.

Methods

Experimental design

PC was induced in all animals seven days before the surgical procedures. Rats were assigned to one of four treatment groups (n=20 each) by randomisation. Treatment per group was as follows: Group 1 (CS): exploration followed by cytoreductive surgery only; group 2 (HIPEC):

cytoreductive surgery plus hyperthermic intraperitoneal perfusion with mitomycin at 41°C for 90 minutes; group 3 (EPIC): cytoreductive surgery followed by early postoperative chemotherapy from the first day postoperatively using mitomycin on the first day and 5-fluorouracil (5-FU) on day 2 -5; group 4 (HIPEC+EPIC): cytoreductive surgery followed by HIPEC and EPIC. Primary outcome parameter was survival.

Animals
Eighty male WAG/Rij rats (10-12 weeks old, mean weight 267 ± 8.2 g) were obtained from Harlan, Horst, The Netherlands. The animals were housed in filter-topped cages (three rats per cage) under clean, non-sterile standardised conditions (temperature 20-24°C; relative humidity 50-60%, 12h light/12 h dark) with free access to water and chow (Ssniff, Bio services Uden, The Netherlands). Accustomization to laboratory conditions was allowed for at least one week before the start of the experiment. All experiments were approved by the Animal Welfare Committee of the Radboud University Nijmegen Medical Centre and carried out in accordance with the Dutch Animal Welfare Act of 1997.

Induction of peritoneal carcinomatosis
Two ml of a suspension containing a concentration of 10^6 cells/ml of the syngeneic rat colon carcinoma cell line CC-531 were injected intraperitoneally in all animals as described elsewhere to induce peritoneal carcinomatosis[8].

Surgery
One week after tumour cell inoculation, CS was performed in all animals under general anaesthesia using isoflurane 3%, O_2 and N_2O 1:1. Carprofen (5 mg/kg/day) was given for analgesia 30 min prior to surgery and once daily until the third postoperative day. To limit body heat loss, all rats were placed on a warmed mattress during the procedure.
The abdominal cavity was opened and exposed by a complete midline laparotomy, and all abdominal regions were systematically inspected for tumour deposits. The peritoneal cancer index (PCI) representing the extent of PC was recorded as the sum of all scores, as described previously[6;7].
All animals underwent CS with standard resection of the greater omentum aiming at radical removal of all macroscopic tumour deposits. CS may include resection of fatpads, spleen, parts of the mesentery and peritonectomy. No bowel resections are performed in this experimental model and no anastomoses are made. Due to the small size of the animals, some tumour localisations are impossible to reach for performing surgical resection. Small lesions that are not suitable for resection due to their localisation are cauterised using an electrocoagulation device. These cauterised deposits are considered as completely treated, as no visible vital tumour tissue is left behind. After the best achievable cytoreduction, the

amount of residual tumour was scored in accordance to current clinical practice using the R1-R2a-R2b classification: R1, no macroscopic disease left; R2a, tumour smaller than 2.5 mm left behind; R2b, residual tumour mass larger than 2.5 mm.

In both the CS and EPIC groups the abdomen was closed. In the HIPEC and HIPEC+EPIC groups, surgery was followed immediately by heated intraperitoneal perfusion.

HIPEC

Perfusion of the abdomen was performed with a closed technique as described before[6;9]. The peritoneal perfusate consisting of 250 ml NaCl (0.9%) was warmed to 41.5°C and infused into the abdomen at 10 ml/min during 90 min. Mitomycin-C (Nycomed Christiaens BV, Breda, The Netherlands) was dissolved in saline and added to the perfusate in three separate administrations at 30 min intervals, each containing 50%, 25% and 25% of the total dose of 35 mg/m^2 mitomycin. During the perfusion, gentle massage of the abdomen was applied to equalise fluid distribution in the peritoneal cavity. Subsequently the abdominal wall was closed in two layers using continuous Vicryl 3/0 sutures. All animals received a subcutaneous injection with ten ml of NaCl 0.9% for rehydration.

EPIC

Intraperitoneal chemotherapy was administered with a single daily intraperitoneal injection (0.75 ml). On the first day following surgery, mitomycin was given in a dose of 10 mg/m^2 (1.36 mg/kg). From the second postoperative day onwards a dose of 15 mg/kg 5-fluorouracil was given to each rat intraperitoneally. The last dose of 5-fluorouracil was administered on day five.

Follow-up and Autopsy

During the first week after surgery, general condition and body weight of the animals was assessed daily. After the first week, general condition and bodyweight were recorded at least twice weekly and more often if symptoms of discomfort were present. Survival was the primary endpoint of this study.

Humane endpoints were chosen to minimise or terminate the pain or distress of the experimental animals via euthanasia rather than waiting for their deaths as the endpoint. The following humane endpoints were used:

The animal refuses intake of food and fluids, shows rapid weight loss, severe circulation or breathing problems, strongly abnormal behaviour, severe clinical symptoms or disabling consequences of ascites or tumour growth, or the expectation is raised that the animal will die shortly.

Whether these endpoints were reached was determined by an experienced biotechnician blinded to the animals' assigned treatment groups.

When the humane endpoint was reached, rats were killed by O_2/CO_2-asphyxation and autopsied.

At autopsy, the weight of ascites (if present) was measured and the extent of intraperitoneal tumour load was recorded using the same PCI scoring system as described above. The experiment was terminated at 168 days post-operatively (24 weeks). The rats that were still alive at that time were euthanized and autopsied.

In case no macroscopic tumour deposits were found at autopsy, the greater omentum and diaphragm were removed and microscopically examined for presence of tumour growth. Hematoxylin & eosin (H&E) staining and murine MG1 antibody in combination with a horse anti-mouse immunoglobin G (IgG) antibody, horseradish peroxidise (HRP) conjugated (Vector Laboratories Inc., Burlingame, CA, USA) were used for microscopic evaluation of the samples.

Statistical Analysis

Statistical analysis was performed using Graphpad Prism (version 4.0, 2003, Graphpad Software Inc., San Diego CA) and SPSS (version 17.0, 2007, Chicago, IL) software. One-way analysis of variance (ANOVA) testing was used for comparison of continuous values. The comparison of dichotomous values was performed with Chi-square or Fisher's Exact test.

Kaplan–Meier curves were used for survival analysis and compared by means of the log-rank test. To correct for confounding factors, Cox regression analysis was performed.

Results

Surgical procedures

All animals underwent CS. No differences were observed between groups regarding preoperative clinical condition or mean bodyweight.

Macroscopic PC was present in all animals. An example of macroscopic tumour growth is shown in figure 1a. The greater omentum, perisplenic area, liver hilum, mesentery and intra-abdominal site of tumour inoculation were the most commonly affected sites of tumour growth. Detailed PCI is given in table 1. Median PCI before cytoreduction was similar in all treatment groups (p = 0.429).

No difference in results of CS in terms of residual disease were observed between the treatment groups (p = 0.343). Mean time of the CS procedures was 26 (standard deviation, SD 6) min without differences between groups (p=0.221).

Table 1: Tumour score before cytoreduction and results of cytoreductive surgery.

Group	CS	EPIC	HIPEC	HIPEC+EPIC
Preoperative weight (g) (mean, SD)	267 (7)	265 (9)	268 (9)	267 (8)
Tumour score per site (median, range)				
Subcutaneous	1 (0-2)	1 (0-1)	1 (0-1)	1 (0-2)
Inoculation site intraabdominal	1 (0-3)	1 (0-3)	1 (0-2)	1 (0-3)
Greater omentum	1 (1-1)	1 (0-2)	1 (1-3)	1 (1-1)
Liver hilum	1 (0-1)	1 (0-1)	1 (1-3)	1 (1-2)
Liver surface	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)
Spleen	1 (0-1)	1 (0-1)	1 (1-2)	1 (0-2)
Mesentery	1 (1-3)	1 (0-3)	1 (1-2)	1 (0-3)
Fatpad left	0 (0-1)	0 (0-1)	0.5 (0-1)	0 (0-1)
Fatpad right	0 (0-2)	0.5 (0-2)	1 (0-2)	0 (0-2)
Diaphragm	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-2)
Parietal peritoneum	0 (0-3)	0 (0-2)	0 (0-3)	0 (0-3)
PCI (mean, SD)	8.0 (2.9)	7.3 (2.0)	8.3 (1.8)	7.4 (2.0)
Splenectomy (n)				
Yes	1	1	3	3
No	19	19	17	17
Completeness of resection (n)				
R1	16	19	18	18
R2a	2	1	2	2
R2b	2	0	0	0

CS = cytoreductive surgery, EPIC = early postoperative intraperitoneal chemotherapy, HIPEC = hyperthermic intraperitoneal chemotherapy, PCI = Peritoneal Cancer Index

Perfusion characteristics

Mean intra-abdominal temperature at the inflow site was 41.5°C (SD 0.44). Mean rectal and intra-abdominal temperatures during the perfusion are shown in figure 2. The perfusion characteristics were similar in both HIPEC and HIPEC+EPIC groups.
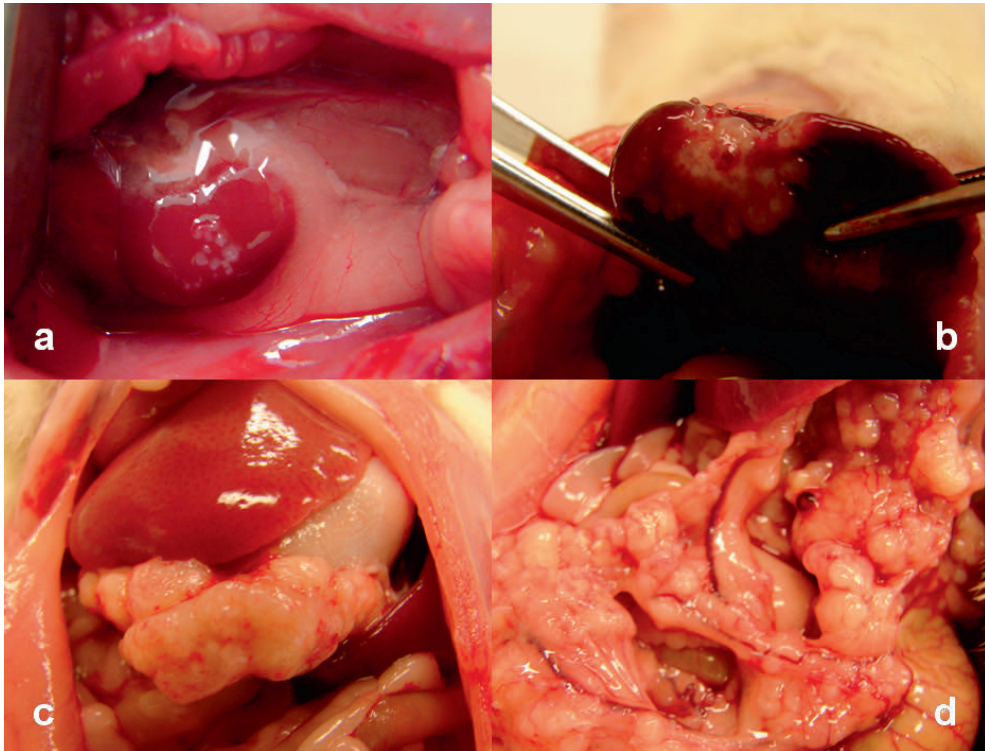
Figure 1. Examples of macroscopic tumour deposits found at during initial exploration of the abdomen on the kidney (a) and during autopsy at liver (b), omentum (c) and mesentery (d).
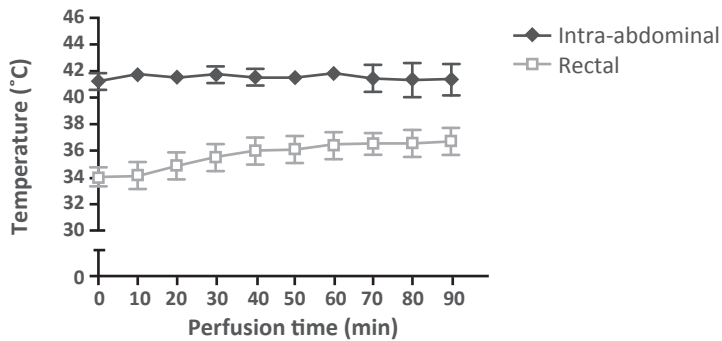

Figure 2. Rectal and intra-abdominal temperatures during perfusion procedures. Data represent means ± SD of temperature measurements during HIPEC in all animals from both HIPEC and HIPEC+EPIC groups (n=40).

Early follow-up

Figure 3 shows the course of bodyweight during the first 14 days after surgery in the four groups.

Rats in the CS group generally gained weight from postoperative day 2 onwards. In the HIPEC group, rats started gaining weight after day 6. Rats receiving EPIC (with or without HIPEC) reached their minimum weight on day 7. In both groups receiving EPIC, the maximum weight loss was higher than in the CS group (CS versus HIPEC, $p = 0.056$, CS versus EPIC and CS versus HIPEC+EPIC, $p < 0.001$).
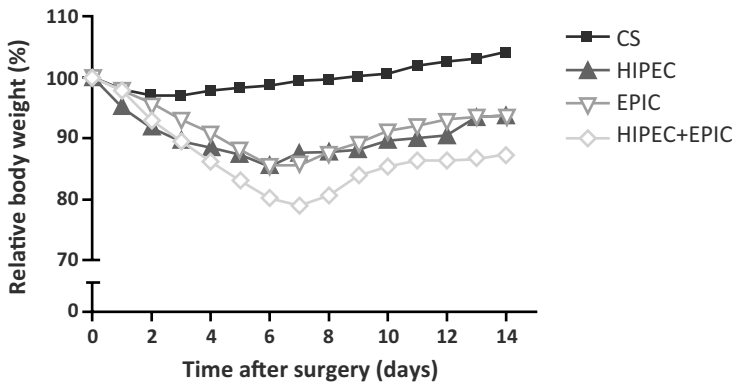

Figure 3. Postoperative course of mean relative body weight.

Eight deaths occurred in the early postoperative course (two HIPEC, three HIPEC+EPIC, two CS and one EPIC) unrelated to tumour growth. In the CS group, one rat died of postoperative ileus after 4 days. The other rat died of unknown reasons after 3 days. In the EPIC group, one rat died after 12 days because of obstruction caused by herniation of the ileum through a mesentery defect. In the HIPEC group, two unexpected deaths occurred, one after 7 days because of an abscess in the upper abdomen, and one caused by respiratory failure immediately following the surgical procedure, possibly related to excessive blood loss during CS. In the HIPEC+EPIC group, deaths were caused by bowel perforation and necrosis after 2 days and abscess formation in the liver hilum resulting in obstruction and progressive icterus after 15 days. One rat was found dead after 8 days, and the cause of death remained unclear.

In the HIPEC+EPIC group, a late unexpected death occurred after 86 days. At autopsy, herniation of the small bowel was found. All rats mentioned above were marked as censored in the survival analysis.

Rats in the HIPEC+EPIC group initially recovered from the procedures and gained weight from day 8 onwards. However, after several weeks rats started to lose weight again to die eventually from excessive weight loss. This course was observed in eleven rats. At autopsy,

no tumour was found in these animals, nor any evidence for another cause of death. Only four rats died from the consequences of tumour growth. At the end of the experiment, two rats were alive. Given the large amount of rats dying from not tumour related causes in this group, the effect of treatment on survival could not be evaluated and therefore it was decided not to include this group in the survival analysis.

Survival and post mortem findings

Figure 4 shows the Kaplan-Meier survival analysis for each group. Median survival in the group treated with CS only was 53 days (95% confidence interval (CI) 49-57 days). In the group of rats receiving HIPEC perfusion, a median survival of 94 days (95% CI 51-137 days) was observed. In the EPIC-group, 12 animals were still alive when the experiment was ended and therefore median survival could not be recorded, but it was at least 168 days.

Survival outcomes were compared between groups, correcting for completeness of resection and pre-operative PCI. Survival outcomes in both adjuvant treatment groups were significantly better as compared to the CS-group: HIPEC versus CS (p = 0.001, hazard ratio for dying 0.24, 95% CI 0.10-0.55) and EPIC versus CS (p < 0.001, hazard ratio 0.10, 95% CI 0.04-0.28).
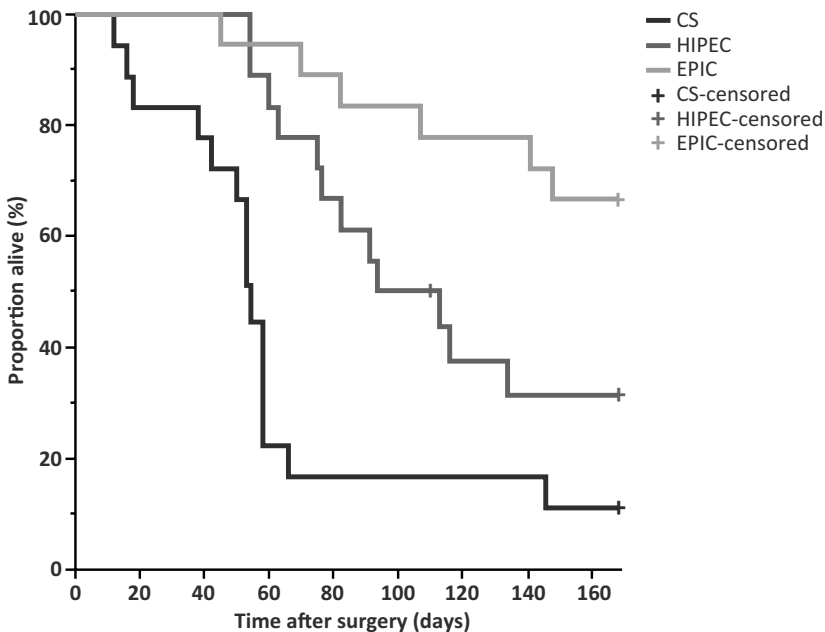

Figure 4. Kaplan-Meier analysis of overall survival, per group.

Nineteen rats were still alive at the time of the maximum follow-up of 168 days. At autopsy 11 of these rats appeared to be macroscopically free of tumour and ascites (1/2 CS, 3/5 HIPEC, 7/12 EPIC). In all of these rats, the remaining omentum and diaphragm were removed and stained for histological examination. No microscopic evidence of disease was found.

Rats from the CS group that reached their humane endpoint during follow-up showed a higher mean PCI at autopsy than rats treated with HIPEC (p=0. 004) or EPIC (p<0.001). The differences in the amount of ascites present at autopsy remained statistically insignificant for both adjuvant treatment groups as compared with the CS group. Post mortem findings are summarised in table 2.

In multivariate analysis, the influence of PCI and completeness of resection on survival outcomes did not reach significance (p=0.065 and p=0.164, respectively).

Table 2: Post mortem findings.

Group	CS	EPIC	HIPEC	p-value
PCI (mean, SD)	27 (4)	14 (10)	19 (6)	<0.001
Ascites weight (g) (mean, SD)	27 (23)	40 (26)	43 (20)	0.136

CS = Cytoreductive Surgery, EPIC = Early Postoperative Intraperitoneal Chemotherapy, HIPEC = Hyperthermic Intraperitoneal Chemotherapy, PCI = Peritoneal Cancer Index

Discussion

In this experimental study, both EPIC and HIPEC were effective in prolonging survival when applied as adjuvant treatment after CS. Always keeping in mind the difference between rodents and humans, this finding may have important implications for clinical practice.

The scheduling of EPIC treatment has several logistical advantages when compared with HIPEC. For the performance of a HIPEC procedure, a careful and punctual scheduling of the surgical procedure is essential. Intraoperative administration of heated chemotherapy requires the availability of the chemotherapeutic agent in the operating room, safety precautions for both the patient and the personnel involved in the procedures, specialised technical equipment which is adequately cleaned and/or sterilised and the presence of an experienced perfusionist. In contrast, for administration of EPIC, insertion of a peritoneal port at the end of a surgical procedure is an easier and less time consuming procedure. The intraperitoneal treatment itself can be performed at an intensive care unit or even hospital ward. Furthermore, EPIC can be offered ad hoc to patients in whom peritoneal carcinomatosis is discovered incidentally during laparotomy, which is a common way of diagnosing this disease. However, performance of EPIC has been associated with an increased risk of complications after extensive abdominal surgery in some retrospective studies[10;11].

This theoretically may be a consequence of the prolonged contact of chemotherapy with newly performed anastomoses and operated surfaces, thereby delaying wound healing and recovery. Indeed, experimental studies have shown that both HIPEC and intraperitoneal injection of chemotherapy have a negative influence on wound strength[12;13].

Other disadvantages of EPIC may be a less equal distribution of fluid in the abdomen and patients experiencing physical discomfort (nausea, impaired mobility) associated with the intraabdominal presence of the chemotherapy for 5 days. However, other studies reported no differences in complications between HIPEC and EPIC[14;15]. Currently no randomised controlled trials have been reported comparing the two techniques in this respect.

Previously published animal experiments have shown that the timing of intraperitoneal chemotherapy treatment after tumour cell application is a relevant factor influencing the effectiveness of treatment. It has been described that administration of anticancer agents immediately after tumour cell inoculation can eliminate all disease, whereas late administration (later than 3 days after tumour inoculation, when usually macroscopic disease is present) may slow down tumour growth but cannot be used with curative intent[16-20]. The current study shows, in accordance with the experimental literature mentioned, that the application of intraperitoneal chemotherapy 1 day after surgery is still effective to eliminate microscopic tumour cells after cytoreductive procedures, without the use of hyperthermic circumstances. Twelve animals from the EPIC group and 5 animals from the HIPEC group were alive at the end of the follow-up period of 24 weeks. Three animals from the HIPEC and 7 from the EPIC group were free of microscopic tumour.

Due to the experimental design of this study, choices such as the HIPEC conditions applied had to be made, which always constitute a certain degree of bias. Although the flow rate in rats may be lower than in the human situation, it is thought unlikely that this would explain the survival outcomes of this study. To our knowledge, the flow rate is not a commonly reported prognostic factor in patients treated with HIPEC. In the rats receiving EPIC, chemotherapy was given as a low volume intraperitoneal injection, resulting in no flow or pressure at all.

A direct cytotoxic effect of higher temperatures (exceeding 42°C–43°C) on both normal and tumour cells has been observed under experimental conditions[21;22]. In HIPEC treatment, however, direct cytotoxicity by hyperthermia is not a primary goal. The hyperthermia applied in this treatment is aimed at a synergetic effect with chemotherapy. Therefore in this animal model, lower temperatures are used, based on the HIPEC technique that was described in the only completed randomised phase III trial evaluating the effectiveness of HIPEC using an inflow temperature of 41-42°C[1].

The necessity of hyperthermia in the treatment of peritoneal carcinomatosis has never been proven. Although mild hyperthermia as applied in HIPEC is thought to increase blood flow and oxygen content within tumours, thereby increasing drug concentrations and enhancing the antitumour effect, the presumed beneficial effect on patient survival has never been investigated in randomised trials[22;23]. In retrospective studies, no difference between normothermic and hyperthermic administration of mitomycin followed by EPIC was found[24]. In a recent experimental study normothermic and hyperthermic intraoperative perfusion were both effective in prolonging overall survival in rats with peritoneal carcinomatosis and with both treatments several animals remained free of disease until the end of the follow-up period[7]. In a study by Zeamari et al., similar results were obtained, although no CS was performed[25]. Also in the current study, the performance of EPIC (under normothermic conditions) showed to be at least equally effective to the treatment including hyperthermia. Therefore, further research into the necessity of hyperthermia should be performed to investigate if indeed simplification of the current multimodality treatment for peritoneal carcinomatosis is possible.

In theory, EPIC and HIPEC may be combined to obtain optimal oncologic outcome. However, a risk of toxicity of the high dose of chemotherapy should always be taken into account when considering the combination of treatments. In the current study most rats treated with HIPEC+EPIC suffered from severe toxicity as illustrated by the weight loss during the first two postoperative weeks. In the end most rats died after several weeks with symptoms suggesting late toxicity. For further evaluation of the combination of HIPEC and EPIC in experimental studies, it may be useful to use only 5-fluorouracil in the EPIC regimen in order to decrease toxicity.

In conclusion, both HIPEC and EPIC prolonged survival when used as adjuvant therapy after cytoreductive surgery for peritoneal carcinomatosis from colorectal cancer in an experimental model. Further research is required to evaluate and compare the possible beneficial and adverse affects associated with both treatments in daily clinical practice. In this way the optimal treatment strategy for patients suffering from peritoneal carcinomatosis of colorectal origin will be further improved.

Reference List

(1)   Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(2)   Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12(1):65-71.

(3)   Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89(12):1545-1550.

(4)   Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88(2):358-363.

(5)   Lemmens VEPP, Klaver YLB, Verwaal VJ, Rutten HJT, Coebergh JW, de Hingh IHJT. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; 128(11):2717-2725.

(6)   Klaver YLB, Hendriks T, Lomme RMLM, Rutten HJT, Bleichrodt RP, de Hingh IHJT. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model. *Br J Surg* 2010; 97(12):1874-1880.

(7)   Klaver YLB, Hendriks T, Lomme RMLM, Rutten HJT, Bleichrodt RP, de Hingh IHJT. Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study. *Ann Surg* 2011; 254(1):125-130.

(8)   Lopes Cardozo AM, Gupta A, Koppe MJ, Meijer S, van Leeuwen PA, Beelen RJ et al. Metastatic pattern of CC531 colon carcinoma cells in the abdominal cavity: an experimental model of peritoneal carcinomatosis in rats. *Eur J Surg Oncol* 2001; 27(4):359-363.

(9)   Aarts F, Hendriks T, Boerman OC, Koppe MJ, Oyen WJ, Bleichrodt RP. A comparison between radioimmunotherapy and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of colonic origin in rats. *Ann Surg Oncol* 2007; 14(11):3274-3282.

(10)   Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De SM et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004; 22(16):3284-3292.

(11)   Elias D, Benizri E, Di PD, Menegon P, Malka D, Raynard B. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2007; 14(2):509-514.

(12)   van der Kolk BM, de Man BM, Wobbes T, Hendriks T. Is early post-operative treatment with 5-fluorouracil possible without affecting anastomotic strength in the intestine? *Br J Cancer* 1999; 79(3-4):545-550.

(13)   Aarts F, Bleichrodt RP, de Man BM, Lomme RMLM, Boerman OC, Hendriks T. The effects of adjuvant experimental radioimmunotherapy and hyperthermic intraperitoneal chemotherapy on intestinal and abdominal healing after cytoreductive surgery for peritoneal carcinomatosis in the rat. *Ann Surg Oncol* 2008; 15(11):3299-3307.

(14)   Gomez PA, Barrios P, Rufian S, Camps B, Bretcha P, Gonzalez BL et al. Management of peritoneal surface malignancy with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Eur J Surg Oncol* 2006; 32(6):628-631.

(15)   Elias D, Blot F, El Otmany A, Antoun S, Lasser P, Boige V et al. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* 2001; 92(1):71-76.

(16)   Hribaschek A, Pross M, Kuhn R, Kruger S, Ridwelski K, Halangk W et al. Prevention and treatment of peritoneal carcinomatosis in experimental investigations with CPT-11 and oxaliplatin. *Anticancer Drugs* 2002; 13(6):605-614.

(17)   Hribaschek A, Meyer F, Schneider-Stock R, Pross M, Ridwelski K, Lippert H. Comparison of intraperitoneal with intravenous administration of taxol in experimental peritoneal carcinomatosis. *Chemotherapy* 2007; 53(6):410-417.

(18)   Jacquet P, Stuart OA, Dalton R, Chang D, Sugarbaker PH. Effect of intraperitoneal chemotherapy and fibrinolytic therapy on tumor implantation in wound sites. *J Surg Oncol* 1996; 62(2):128-134.

(19)   Duvillard C, Benoit L, Moretto P, Beltramo JL, Brunet-Lecomte P, Correia M et al. Epinephrine enhances penetration and anti-cancer activity of local cisplatin on rat sub-cutaneous and peritoneal tumors. *Int J Cancer* 1999; 81(5):779-784.

(20)   Monneuse O, Mestrallet JP, Quash G, Gilly FN, Glehen O. Intraperitoneal treatment with dimethylthioampal (DIMATE) combined with surgical debulking is effective for experimental peritoneal carcinomatosis in a rat model. *J Gastrointest Surg* 2005; 9(6):769-774.

(21)   Hildebrandt B, Wust P. The biologic rationale of hyperthermia. *Cancer Treat Res* 2007; 134:171-184.

(22)   Song CW, Park HJ, Lee CK, Griffin R. Implications of increased tumor blood flow and oxygenation caused by mild temperature hyperthermia in tumor treatment. *Int J Hyperthermia* 2005; 21(8):761-767.

(23)   Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T et al. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002; 43(1):33-56.

(24)   da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. *J Am Coll Surg* 2006; 203(6):878-886.

(25)   Zeamari S, Floot B, van der Vange N, Stewart FA. Pharmacokinetics and pharmacodynamics of cisplatin after intraoperative hyperthermic intraperitoneal chemoperfusion (HIPEC). *Anticancer Res* 2003; 23(2B):1643-1648.

8

Results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy after early failure of adjuvant systemic chemotherapy

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Abstract

Background
Failure to respond to systemic chemotherapy is considered an exclusion criterion by some institutions for treatment with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). However, it is unknown if these patients benefit from HIPEC treatment. This study aimed to report on outcomes of HIPEC in patients who failed to respond to adjuvant systemic chemotherapy.

Methods
Patients were selected from a prospective database containing data on all patients who underwent HIPEC, using the following criteria: (1) Metachronous peritoneal carcinomatosis (PC) from colorectal origin, (2) adjuvant chemotherapy after primary tumour resection, (3) development of PC or local recurrence within 18 months after start of chemotherapy. Treatment and survival data were retrospectively collected.

Results
Twenty-one patients (29% male, mean age 57 years) were included. Median time to recurrence of disease was 9 months (range 2-15) after first chemotherapy administration. Median survival was 28 months (range 3-100). One-year and 2-year survival were 71% and 43%, respectively.

Conclusion
Patients who initially failed to respond to systemic adjuvant treatment showed a survival after HIPEC similar to results reported in literature in patients with unknown responsiveness. Failure to respond to previous adjuvant systemic treatment should therefore not be considered an exclusion criterion for HIPEC treatment.

Introduction

Peritoneal carcinomatosis (PC) originating from colorectal tumours has long been considered to be an incurable condition. Patients have therefore been treated in palliative support programs. Median survival is less than 13 months in patients receiving leucovorin and 5-fluorouracil (5-FU)-based chemotherapy schedules and might reach survival rates up to 18 months with combination therapies[1;2]. Recently, treatment of patients suffering from PC from colorectal origin has gained new interest because PC without visceral metastases is now considered as regional spread of disease rather than systemic metastasis. The availability of new local treatment strategies like cytoreductive surgery, hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC) has been based on this disease concept[3;4]. Multiple institutions have reported promising results with these techniques[5-14].

A careful patient selection for this complex treatment is essential to prevent unnecessary toxicity. There is currently no uniformity in selection criteria worldwide, but good clinical performance status, age <75 year, absence of visceral and retroperitoneal lymph node metastasis and no massive peritoneal disease. One of the controversies is the inclusion of patients in whom previous systemic therapy has failed, as it is unclear whether or not this group benefits from HIPEC. Response to systemic chemotherapy has been suggested as a selection criterion in patients in whom cytoreductive surgery and HIPEC is considered as a therapy, as this may allow selection of patients with biologically favourable tumour characteristics[15]. Patients who fail to respond to systemic chemotherapy, are excluded from intraperitoneal treatment in some studies reporting on treatment effects[13;16]. However, there is no evidence available in literature to date discussing whether or not these patients could derive benefit from treatment with HIPEC.

Aim of this study is to report on the outcomes of cytoreductive surgery and HIPEC in patients who failed to respond to adjuvant systemic chemotherapy after primary resection preceding HIPEC procedures.

Methods

Patient selection and data collection

Data were obtained from a prospective database, including all patients who underwent cytoreductive surgery and HIPEC between 1997 and 2008 in the Netherlands Cancer Institute, Amsterdam. In our institute, cytoreductive surgery in combination with HIPEC has been performed in patients with colorectal carcinoma since 1996. Eligibility of patients is based on performance status and resectability of the tumour. Data on previous treatments are recorded, but response to systemic chemotherapy is currently not used as a patient selection criterion[17].

Patients were selected by using the following criteria: (1) diagnosis of PC from colorectal origin, (2) metachronous presentation of disease, (3) treatment with adjuvant chemotherapy after primary resection, (4) presentation of recurrence of disease or development of PC within 18 months after start of adjuvant systemic chemotherapy, (5) treatment with cytoreductive surgery and HIPEC. A total of 21 patients was identified according to these inclusion criteria.

The time to recurrence of disease was defined as the period between the start of chemotherapy treatment and the first evidence of local recurrence or discovery of PC during follow-up.

Data on patient and tumour characteristics, HIPEC procedures and survival were retrieved from the database. Additionally, data on the time of diagnosis of recurrence of disease and development of PC and information on chemotherapy schedules was registered retrospectively. If necessary, reports from surgical procedures, laboratory tests and imaging studies were reviewed.

Operative procedures

Cytoreduction followed by HIPEC with mitomycin C was performed in the Netherlands Cancer Institute in all patients. After laparotomy, the number of regions involved was assessed and recorded by use of a simplified peritoneal cancer index (PCI)[17]. Stripping of the parietal peritoneum was routinely performed as described by Sugarbaker et al[18]. In all patients the greater omentum was removed. The construction of anastomoses was performed after HIPEC.

Completeness of cytoreduction was recorded using the following score system: absence of macroscopic residual tumour after completion of cytoreduction was recorded as R-1, macroscopic residual tumour nodules smaller than 2.5 mm as R-2a and a tumour residue in any region larger than 2.5 mm as R-2b.

After cytoreductive procedures, lavage of the abdominal cavity with mitomycin C (35 mg/m^2 for 90 min at 41°C) was carried out using an open technique as described in detail elsewhere[17].

Statistical analysis

Survival time was calculated from the date of diagnosis of PC to the time of death or last follow up. Patients alive at the time of analysis were marked as censored in the analysis at the date of their last follow-up contact. Data were analysed by Kaplan Meier analysis using SPSS 17.0 (Chicago, IL, 2008) software.

Results

Twenty-one patients (6 male), with a mean age of 57 years (standard deviation, SD 11) were included in this study. Tumour characteristics are shown in table 1.

Table 1: Tumour characteristics (n = 21).

Localisation		n (%)
	Rectum	2 (9.5%)
	Sigmoid	1 (4.8%)
	Left colon	6 (28.6%)
	Transverse colon	2 (9.5%)
	Right colon	2 (9.5%)
	Caecum	8 (38.1%)
T stage of primary tumour		
	T3	12 (57.1%)
	T4	9 (42.9%)
N stage of primary tumour		
	N0	3 (14.3%)
	N1	10 (47.6%)
	N2	8 (38.1%)

Diagnosis of PC

The median time between the primary tumour resection and the development of PC was 11 months (range 5-81). In two patients, PC was diagnosed more than 18 months after the primary tumour resection (23 and 81 months, respectively). In these patients, systemic chemotherapy was applied in a palliative setting. During this treatment these patients developed PC as sign of progression of disease and were referred for cytoreductive surgery and HIPEC. In all other patients, chemotherapy treatment was given in an adjuvant setting directly following resection of the primary tumour.

During chemotherapy treatment, follow-up routinely included assessment of tumour markers, in particular CEA, and CT scans. In addition, PET-CT was used if indicated. In all patients, a rise in CEA levels or a changing aspect of the abdomen on CT scans raised the suspicion of peritoneal disease. Diagnosis was confirmed in all patients by histological examination of the specimens resected during explorative laparotomy or cytoreductive surgery procedures.

Systemic chemotherapy treatment

Adjuvant systemic chemotherapy regimens used following resection of the primary tumour (but before HIPEC treatment) are shown in table 2. Most frequently used chemotherapy regimen was 5-fluorouracil combined with leucovorin. Median time of chemotherapy treatment was 21 weeks (range 3-27 weeks). Fourteen patients (67%) completed their

intended chemotherapy treatment. Toxicity was the reason of discontinuation in four patients, progression of disease in two patients and one patient oluntary withdrew from continuation of adjuvant systemic chemotherapy treatment. Mean time to recurrence of disease was 9.3 months from the first administration of chemotherapy.

Table 2: Details on adjuvant chemotherapy treatment following primary tumor resection before HIPEC procedures.

Adjuvant systemic chemotherapy schedules		n (%)
	5-FU and leucovorin	13 (62%)
	5-FU and leucovorin and oxaliplatin (FOLFOX)	4 (19%)
	Oxaliplatin and capecitabine	4 (19%)
Reasons for discontinuation chemotherapy		
	Completed	14 (67%)
	Progression during chemotherapy	2 (9%)
	Toxicity/Fever	4 (19%)
	Voluntary withdrawal	1 (5%)
Mean (SD) time from start chemo to diagnosis to recurrence of disease, preceding HIPEC treatment	Months	9.3 (3.4)

5-FU = 5-fluorouracil

HIPEC procedures

Simplified PCI scores are shown in table 3. In four patients (19%), more than 5 of the regions were involved. In most patients (76%) a complete macroscopic resection of PC was achieved (R1). All other patients underwent R2a resection.

Adjuvant systemic chemotherapy after HIPEC was routinely offered to all patients in whom physical condition was sufficient within 6-12 weeks after the surgical procedures. Three patients (14%) received 5-FU/leucovorin, four patients (19%) received capecitabin/oxaliplatin, and one patient received irinotecan as adjuvant treatment after HIPEC. All these patients completed 6 months of adjuvant treatment except for one case. This patient showed severe toxicity to the adjuvant treatment after HIPEC and did not continue the course after one cycle of chemotherapy. Twelve patients (57%) were not eligible for adjuvant treatment after their HIPEC procedure. Main reason for not starting chemotherapy after HIPEC was the occurrence of complications from surgery prolonging recovery. One patient moved overseas and details of treatment could not be retrieved. The outcomes of this patient were censored at the time of last known follow-up.

Another five patients received palliative chemotherapy treatment for recurrent disease diagnosed during follow up after their HIPEC procedure.

Table 3: Findings and results during cytoreductive surgery procedures.

		n (%)
Simplified PCI before surgery		
	Number of regions involved	
	0	2 (9%)
	1	2 (9%)
	2	5 (24%)
	3	5 (24%)
	4	3 (14%)
	5	0 (0%)
	6	3 (14%)
	7	1 (6%)
Radicality of cytoreductive surgery		
	R1	16 (76%)
	R2a	5 (24%)
	R2b	0 (0%)

PCI = Peritoneal Cancer Index

Survival

Kaplan-Meier analysis of survival data is shown in figure 1. Two patients moved abroad and therefore these follow-up data were incomplete. Median overall survival was 28 months (range, 3-100 months) One-year and 2-year survival were 71% and 43%, respectively.
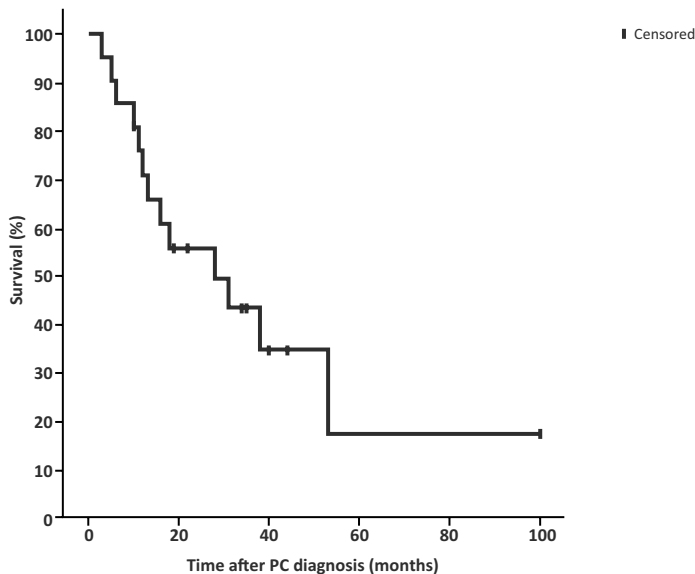

Figure 1. Kaplan-Meier analysis of survival in the presented study population.

Discussion

This study shows that patients with recurrence of disease or development of PC during or within 18 months after the start of adjuvant systemic chemotherapy after curative resection for colorectal cancer may benefit from HIPEC procedures. Their median survival of 28 months is similar to the overall median survival reported in the literature and, more specifically, to the result of a randomised controlled trial from our institute comparing HIPEC plus systemic chemotherapy with systemic chemotherapy alone. In that trial the median survival was 22.2 months[17] in an intention-to-treat analysis.

In general, treatment strategies for stage IV colon carcinoma are applied independent of the localisations of metastases. All possible different dissemination patterns, including liver, lung, bone or peritoneum have been treated with systemic chemotherapy as a standard of care for a long time. There has been a shift in this paradigm to a more anatomic and surgical approach since the successful introduction of liver resections. During the inclusion period of the study presented here, both adjuvant and palliative treatment of colorectal cancer underwent a rapid development. In the first years of this study period, 5-fluorouracil combined with leucovorin was the only available chemotherapy for patients with colorectal cancer. Since 1998-2000, irinotecan and oxaliplatin have been introduced and oxaliplatin has been incorporated in standard combination schedules. Oxaliplatin for adjuvant treatment has been used since 2004. These developments explain the differences in adjuvant chemotherapy schedules applied in this study.

Although overall survival of patients with metastasised colorectal cancer has increased over time with the availability of combination therapies and the more recent introduction of targeted monoclonal antibodies[19-22], the effect of these developments in patients with PC remains unclear. This group of patients is known to have a reduced response rate to systemic chemotherapy as compared to patients without peritoneal metastases[2]. Currently no data from randomised trials are available that evaluate the effect of new palliative chemotherapy treatment strategies. Elias et al.[16] reported a median survival of 24 months in 48 highly selected and relatively young (mean age 51 years) PC-patients with limited disease, treated with combination schedules including oxaliplatin and irinotecan. However, in the same study a median survival of 62.7 months was reported in patients who underwent HIPEC. A retrospective study from our institution showed a median survival of 12.6 months in patients with PC treated with 5-fluorouracil or irinotecan[1].

The development of new treatment strategies including HIPEC has been based on the hypothesis that PC could be considered as a regional dissemination pattern rather than as a sign of systemic disease[23-25]. This supports the possible beneficial effect of a regional treatment using the combination of cytoreductive surgery and HIPEC.

Although the performance of cytoreductive surgery and application of intraperitoneal chemotherapy is nowadays more widely accepted as a treatment strategy in patients with PC, patient selection for these procedures remains an important subject of discussion. Well-known and commonly used selection criteria for HIPEC procedures include good performance status, a limited extend of PC, and absence of systemic metastases. In a review by Yan et al.[15] it is acknowledged that response to preoperative chemotherapy could potentially be a useful criterion for selecting patients with biologically favourable tumour characteristics. Indeed in patients with metastatic disease, evidence indicates that genomic profiling may be related to chemotherapeutic treatment response[26]. Nevertheless, this study shows that failure of systemic adjuvant chemotherapy is not associated with an unfavourable outcome in patients treated with intraperitoneal chemotherapy. This suggests that the susceptibility to systemic chemotherapy treatment, at least in an adjuvant setting, in patients with PC cannot be associated with outcomes after local application of chemotherapy. A possible explanation for this could be that systemic administration of chemotherapy fails to reach the peritoneal metastases in a therapeutic concentration. In contrast, during HIPEC a direct contact between chemotherapy and the presumed presence of loose tumour cells is established. This contact is independent of blood supply of the metastasis and depends on direct penetration up to a depth of 2.5 mm and diffusion. In addition, the dose of chemotherapeutic agents that can be applied in intraperitoneal administrations is higher than the maximum systemic dose tolerated. Furthermore heating of the chemotherapy is presumed to enhance the cytotoxic effect of chemotherapeutic agents used[27]. As stated before, no data are currently available considering the effects of modern chemotherapy schedules, and therefore it remains unclear whether the results of chemotherapy reported in this study represent a failure of systemic treatment in general, or a failure in adjuvant chemotherapy treatment.

Some limitations of this study should be taken into account. Although data presented in this study were collected prospectively, this report has a retrospective design. Furthermore, only a small number of patients was included resulting in a wide range of data. Yet the fact that the results achieved in this highly selected patient group do not differ from the overall outcomes of the previous randomised clinical trial from our institute suggests that patients who fail to respond to systemic adjuvant treatment may still benefit from locoregional treatment. It also supports the hypothesis that PC should be considered as a local dissemination rather than a subgroup of systemic metastasis.

No evidence was found to support the exclusion of patients who failed to respond to systemic adjuvant chemotherapy from treatment with HIPEC. In the group of patients presented here, a median survival of 28 months was achieved after performing cytoreductive surgery and HIPEC, at least comparable to reported results of HIPEC in patients with an unknown response. Therefore, failure to respond to systemic adjuvant chemotherapy treatment should not be regarded as a selection criterion when assessing patient eligibility for HIPEC procedures.

Reference List

(1)   Bloemendaal A, Verwaal V, van Ruth S, Boot H, Zoetmulder FAN. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: A prospective study. *Eur J Surg* 2005; 31:1145-1151.

(2)   Folprecht G, Kohne CH, Lutz MP. Systemic chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Cancer Treat.Res.* 134, 425-440. 2007.

(3)   Sugarbaker PH, Graves T, De Bruijn EA, Cunliffe WJ, Mullins RE, Hull WE et al. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. *Cancer Res* 1990; 50(18):5790-5794.

(4)   Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995; 221(1):29-42.

(5)   Glehen O, Cotte E, Schreiber V, Sayag-Beaujard AC, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. *Br J Surg* 2004; 91(6):747-754.

(6)   Kecmanovic DM, Pavlov MJ, Ceranic MS, Sepetkovski AV, Kovacevic PA, Stamenkovic AB. Treatment of peritoneal carcinomatosis from colorectal cancer by cytoreductive surgery and hyperthermic perioperative intraperitoneal chemotherapy. *Eur J Surg Oncol* 2005; 31(2):147-152.

(7)   Mahteme H, Hansson J, Berglund A, Pahlman L, Glimelius B, Nygren P et al. Improved survival in patients with peritoneal metastases from colorectal cancer: a preliminary study. *Br J Cancer* 2004; 90(2):403-407.

(8)   Pilati P, Mocellin S, Rossi CR, Foletto M, Campana L, Nitti D et al. Cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy for peritoneal carcinomatosis arising from colon adenocarcinoma. *Ann Surg Oncol* 2003; 10(5):508-513.

(9)   Piso P, Dahlke MH, Ghali N, Iesalnieks I, Loss M, Popp F et al. Multimodality treatment of peritoneal carcinomatosis from colorectal cancer: first results of a new German centre for peritoneal surface malignancies. *Int J Colorectal Dis* 2007; 22(11):1295-1300.

(10) Schneebaum S, Arnold MW, Staubus A, Young DC, Dumond D, Martin EW, Jr. Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. *Ann Surg Oncol* 1996; 3(1):44-50.

(11) Shen P, Hawksworth J, Lovato J, Loggie BW, Geisinger KR, Fleming RA et al. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma. *Ann Surg Oncol* 2004; 11(2):178-186.

(12) Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; 15(9):2426-2432.

(13) Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol* 2004; 11(5):518-521.

(14) Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De SM et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004; 22(16):3284-3292.

(15) Yan TD, Sim Junyang, Morris DL. Selection of patients with colorectal peritoneal carcinomatosis for cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2007; 14(6):1807-1817.

(16) Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; 27(5):681-685.

(17) Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(18) Sugarbaker PH, Schellinx ME, Chang D, Koslowe P, von Meyerfeldt M. Peritoneal carcinomatosis from adenocarcinoma of the colon. *World J Surg* 1996; 20(5):585-591.

(19) Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351(4):337-345.

(20) de Gramont A., Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18(16):2938-2947.

(21) Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol* 2005; 23(15):3502-3508.

(22) Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; 343(13):905-914.

(23) Katz MH, Barone RM. The rationale of perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies. *Surg Oncol Clin N Am* 2003; 12(3):673-688.

(24) Schott A, Vogel I, Krueger U, Kalthoff H, Schreiber HW, Schmiegel W et al. Isolated tumor cells are frequently detectable in the peritoneal cavity of gastric and colorectal cancer patients and serve as a new prognostic marker. *Ann Surg* 1998; 227(3):372-379.

(25) Sugarbaker PH. Carcinomatosis--is cure an option? *J Clin Oncol* 2003; 21(5):762-764.

(26) Del Rio M., Molina F, Bascoul-Mollevi C, Copois V, Bibeau F, Chalbos P et al. Gene expression signature in advanced colorectal cancer patients select drugs and response for the use of leucovorin, fluorouracil, and irinotecan. *J Clin Oncol* 2007; 25(7):773-780.

(27) Sticca RP, Dach BW. Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents. *Surg Oncol Clin N Am* 2003; 12(3):689-701.

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Outcomes of elderly patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal cancer peritoneal carcinomatosis

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Abstract

Background
The combined treatment of cytoreductive surgery (CS) and perioperative chemotherapy (PIC) for colorectal peritoneal carcinomatosis (PC) is a rigorous surgical treatment most suited for fit and young patients. With technical maturity and improved perioperative care, we examined the outcomes of elderly patients undergoing CS and PIC for colorectal PC.

Methods
All consecutive patients treated in two tertiary centres for PC of colorectal cancer who were 70 years of age or older at the time of surgery were included. Data on patient characteristics, concomitant diseases, operation details, perioperative course and follow-up were retrieved from medical charts. Primary outcomes were perioperative morbidity and mortality. Secondary outcomes were disease-free and overall survival.

Results
Twenty-four patients (11 male) were included in this study (mean age 73.5 years). In eight patients major complications occurred. In six patients the postoperative course was complicated by minor adverse events. There was no perioperative mortality. Median overall survival was 35 months with a 6-, 12- and 18-months survival rate of 94%, 83% and 68%, respectively.

Conclusion
CS and PIC for colorectal PC may be safely performed with acceptable morbidity in selected elderly patients. When considering patients for surgery, performance status and the disease extent should be used as eligibility criteria rather than age.

Introduction

The incidence of colorectal cancer increases with age. With the increase in life expectancy, the ageing population is expected to rise. A considerable number of patients presenting with colorectal cancer are aged 75 or older. To offer a safe and appropriate treatment to elderly patients with colorectal cancer represents a challenge for health care resources with surgery in particular. As age is traditionally associated with more frequently occurring comorbidities and a reduced physical capacity to recover from adverse events[1;2], it is questionable whether elderly patients will tolerate aggressive surgery. Fortunately, over the last few years, there have been advances in the perioperative care of colorectal cancer surgery leading to a decrease in morbidity and mortality rates in elderly patients treated, and a good quality of life after surgery[3-5]. Several recent studies have shown that age alone does not influence the outcomes of surgery for colorectal cancer, and cancer-specific survival in these patients is similar to that of younger patients[6-9]. For example, hepatectomy for colorectal liver metastases has been shown to achieve reasonable 3-year survival at an acceptable morbidity in octogenarians[10].

The combination of cytoreductive surgery (CS) and perioperative intraperitoneal chemotherapy (PIC) has been established as a treatment strategy for patients with peritoneal carcinomatosis of colorectal origin. Traditionally, this condition has been regarded as a terminal disease that is often managed palliatively. Nowadays, many patients are treated worldwide with extensive surgical procedures including CS combined with PIC aiming for cure. Encouraging disease-free and overall survival results have been reported. In the few randomised trials that were performed, age was used as a selection criterion, including only patients younger than 71 or 65 years of age, respectively[11;12]. Yet, the majority of patients who present with synchronous peritoneal carcinomatosis as the only site of metastatic disease is 70 years of older at the time of diagnosis[13]. The risks and benefits of cytoreductive surgery and PIC in elderly patients have not been clearly defined. In a multi-institutional study, age over 65 years appeared to be an unfavourable prognostic factor in both univariate and multivariate analysis[14]. Many surgeons are therefore reluctant to offer these procedures to patients who are above 70 years of age. Given that surgical techniques, anaesthetic management and perioperative medical care have improved with increased experience over the years, we are now observing lower complication rates, improved selection of patients and anticipation to perioperative factors that may influence morbidity and mortality[15]. With these advances in the management of patients undergoing CS and PIC, it remains to be seen whether these procedures, being the only curative option available for peritoneal carcinomatosis, should only be reserved for younger patients. Using prospectively collected data from two tertiary institutions with specialised interest in peritoneal surface

malignancies, we examined the outcomes of elderly patients who underwent CS and PIC for PC from colorectal cancer.

Patients and Methods

Patients

All patients with a histologic diagnosis of PC from colorectal adenocarcinoma who underwent CS and PIC in two tertiary referral centres in Australia and the Netherlands at an age of 70 years or older were included in this study. The evaluation process to determine eligibility for CS and PIC procedures consists of physical examination by the surgeon who performs the procedures and discussion of the cases during a weekly multidisciplinary team meeting attended by representatives of surgical oncology, medical oncology, radiology, cancer care nurses and research staff.

Data regarding baseline patient characteristics, surgical procedures, perioperative outcomes and survival outcomes were prospectively collected and included in an electronic database. Regular follow-up was performed at monthly intervals for the first 3 months and at 6-monthly intervals thereafter. Additional details regarding the primary tumour, comorbidities and blood test results were retrieved from the medical charts. Redo CS and PIC procedures were excluded from the analysis.

Preoperative management

As per protocol, all patients underwent physical examination and double contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis.

In addition, positron emission tomography (PET) was performed to assess the extent of disease if necessary. Subcutaneous heparin is given routinely as thrombosis prophylaxis in both institutions.

Mechanical bowel preparation was performed in all patients. All patients received an intrajugular or subclavian central venous catheter. Prophylactic antibiotic treatment consisted of metronidazole 500 mg every 6 hours during surgery in both institutes combined with a pre-operative gift of cefotaxime 1000 mg (Australia) or cefalozine 2000mg (the Netherlands). Patient position was supine.

Cytoreductive surgery

In both institutions (STG and CHE), procedures were performed by a specialised surgical team, led by a single surgeon (D.L.M and I.H.J.T.H.). Midline laparotomy was performed in all patients, followed by assessment of the extent of disease by use of the Peritoneal Cancer Index (PCI)[16]. The PCI involves an assessment combining thickness of lesion size (LS) (LS 0: no macroscopic tumour; LS 1: tumour <0.5 cm; LS 2: tumour 0.5–5 cm; and LS3: tumour >5

cm) with distribution of tumour deposits in different abdominal regions (abdominopelvic region 0–12), resulting in a numerical score which represents a quantification of the extent of disease (PCI 0–39).

All surgical procedures were aimed at complete removal of all visible tumour deposits from the abdominal cavity. CS was performed using Sugarbaker techniques[17] in both centres. CS may include total anterior parietal peritonectomy, greater omentectomy, splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy, lesser omentectomy, cholecystectomy, rectosigmoidectomy, right colectomy, total abdominal colectomy, hysterectomy, salpingoovariectomy, and small bowel resection, depending on the presence of macroscopically visible tumour deposits. Furthermore, dissection of ureters and bladder may be required in order to achieve complete cytoreduction. Additionally, electrocoagulation was used. The macroscopic result of cytoreduction was assessed and recorded by means of the completeness of cytoreduction (CCR) score[15]. A score of CC0 represents no residual macroscopic tumour deposits; CCR1, remaining tumour does not exceed 2.5mm; CCR2, tumour nodules between 2.5 mm and 2.5 cm in diameter remain; and CCR3, nodules of more than 2.5 cm in diameter are present after best achievable cytoreduction.

Hyperthermic intraperitoneal chemotherapy

After cytoreduction, but prior to bowel anastomoses or repair of seromuscular tears, HIPEC was performed in a subset of patients by instillation of a heated chemoperfusate into the abdomen using the coliseum technique at approximately 42°C for 90 minutes. The chemoperfusate was made up of the cytotoxic drug diluted in 3 L of 1.5% dextrose peritoneal dialysis. To improve drug distribution, stirring of the abdomen was performed throughout the perfusion. The intraperitoneal temperature was monitored by a thermometers placed in the abdominal cavity.

After perfusion, the cytotoxic drugs were removed from the abdominal cavity and anastomoses were performed consequently. Two axion sump drains (on each side of the hemidiaphragm) were inserted before closure of the abdomen. If diaphragmatic resection was performed, 2 chest drains were placed.

Early postoperative intraperitoneal chemotherapy

Early postoperative intraperitoneal chemotherapy (EPIC) on postoperative day 1 to 5 was offered to selected patients who underwent CS. EPIC was not considered in case of leakage of the intraperitoneal chemotherapy system, early postoperative complications, or major organ failure. Furthermore, patients should be tolerating the increased intraabdominal fluid volume, as evaluated by an adequate urine output. During the years, a dose reduction of EPIC was introduced for patients with extensive prior treatment, long duration of surgery (>12 hours), unprotected bowel anastomoses and suboptimal preoperative conditions.

EPIC was administrated in the intensive care unit (ICU) or high dependency unit (HDU) through a peritoneal catheter port that was placed during surgery. Perfusion fluid consisted of 5-fluorouracil (650–800 mg/m^2 per day) in 1 L of 1.5% dextrose peritoneal dialysis solution, which remained intraperitoneally for 23 hours. After this time, the intraperitoneal chemotherapy was removed by closed suction drains over the course of 1 hour. During EPIC treatment, sump drains were clamped. Once all the perfusion fluid was removed, the next instillation was commenced.

Postoperative Management

All patients were given subcutaneous heparin for deep venous thrombosis prophylaxis. All patients who had a splenectomy were given pneumococcal polysaccharide vaccine. Clinical suspicions of deep venous thrombosis were assessed by Doppler ultrasound, and ventilation/perfusion scan or CT pulmonary angiogram was performed when pulmonary embolus was suspected. For the assessment of intra-abdominal collections or abscesses, oral contrast-enhanced abdomen and pelvic CT was performed in symptomatic patients. Total parenteral nutrition was only started on indication, including prolonged gastroparesis or inadequate intake for several days.

Statistical Analysis

Perioperative morbidity and mortality were the primary outcomes of this study. Survival was evaluated using Kaplan-Meier survival analysis. Overall survival was defined as time between the CS and PIC and the date of death or last follow-up. Disease-free survival was defined as time between the CS and PIC and the date of recurrence or death. Survival curves of subgroups were assessed by means of the log rank test. SPSS for Windows version 17.0 (SPSS, 2008) was used for all statistical analyses. A p-value of <0.05 was considered statistically significant.

Results

Patient demographics

Between January 1996 and August 2010, 106 CS procedures for peritoneal carcinomatosis of colorectal carcinoma were performed in STG and 41 in CHE. Twenty-four patients (13 female) of 70 years or older underwent combined treatment of CS and PIC, with a mean age of 73.5 years. Eight patients were 75 years or older at the time of surgery. Details on concomitant diseases and medical history are given in table 1.

Table 1. Patient characteristics (n=24).

	n
Gender M/F	11/13
Age (years) Mean (SD)	73.5 (3.4)
70-74	16
75-79	7
>80	1
Concomitant diseases/Medical history	
None	2
Metabolic	
Hypercholesterolaemia	3
Diabetes	3
Hypothyroidism	1
Cardiovascular	
Hypertension	6
Abdominal Aorta Aneurysm	2
Peripheral Arterial Disease	1
Ischaemic heart disease	1
Wolff-Parkinson-White syndrome	1
Transient ischaemic attack/Cerebrovascular accident	1
Malignancies	
Breast cancer	1
Prostate cancer	1
Bronchus carcinoma	1
Other	
Peptic ulcer disease	3
Deep venous thrombosis/pulmonary embolus	2
Parkinson	1
Primary tumour	
Caecum	4
Ascending colon	5
Hepatic flexure	1
Transverse colon	1
Splenic flexure	2
Sigmoid	7
Rectosigmoid	1
Rectum	1
Unknown	1
Time between primary tumour resection and CS + PIC in months Median (range)	13 (0-214)

CS = cytoreductive surgery, PIC = perioperative intraperitoneal chemotherapy

Clinical characteristics

In 14 patients, PC was discovered during follow-up for their primary tumour. In 9 patients PC was present at the time of the resection of the primary tumour.

Median time between the primary tumour resection and CS was 13 months (range 0-214)

The median PCI was 8 (1-22), with a mean of 8.3. Three patients had a PCI of 15 or higher. In 16 patients, PCI was lower than 10. A complete removal of the peritoneal tumour (CCR0) was achieved in 22 patients (92%). In 2 patients, residual tumour deposits of less than 2.5mm were present after cytoreduction (CCR1).

In twelve patients CS was directly followed by the administration of HIPEC, and in 6 patients EPIC was given during the first postoperative days. Five patients received both treatments after CS.

Morbidity and mortality

The median duration of the procedure was 5 hours and 45 minutes (range 2-7), with a mean of 5.7 (standard deviation, SD 2) hours. The median number of resections performed per patient was 4 (range 2-8), with a median of 1 anastomosis per patient (range 0-3). Twelve patients required blood transfusion during surgery, with a median of 4 units of blood per patient (range 2-16). Details on the CS procedures are shown in table 2.

Table 2: Cytoreductive surgery procedures.

		n
CCR		
	CCR0	22
	CCR1	2
	CCR2	0
	CCR3	0
Stoma		
	None	17
	Colostomy	2
	Ileostomy	4
	Unknown	1
Number of resections	Mean (SD)	Median (range)
	4 (1)	4 (2-8)
Number of peritonectomy sites	Mean (SD)	Median (range)
	1 (1)	1 (0-3)
PIC		
	HIPEC	12
	EPIC	6
	HIPEC+EPIC	5
Drugs used for HIPEC perfusion		
	Mitomycin	13
	Oxaliplatin	4

CCR = completeness of cytoreduction score, PIC = perioperative intraperitoneal chemotherapy, HIPEC = hyperthermic intraperitoneal chemotherapy, EPIC = early postoperative intraperitoneal chemotherapy.

Patients were admitted to the ICU as per protocol and had a median stay in this unit of 2 days (range 1-6), with a mean of 2 (SD 1) days. Thereafter, some patients were admitted to the HDU, staying there for a mean of 2 (SD 4) days. Patients were discharged from the hospital after a median total stay of 15 days (range 8-74), with a mean of 20 (SD 14) days.

In nine patients (38%) the procedures were uncomplicated. In six patients, postoperative complications were observed which could be managed conservatively or with medical intervention. In five patients (21%), radiological intervention was required and three patients (13%) required surgical intervention or admission to the ICU to deal with major complications.

Details regarding the complications and their management are shown in table 3. In the 3 patients (13%) requiring surgical intervention to deal with severe complications, no predisposing factors could be identified. They were aged 70, 71 and 77, respectively, and did not suffer from major concomitant diseases. Furthermore, their PCI scores were 8, 10 and 11 respectively, representing a moderate amount of peritoneal tumour.

The median time to the occurrence of morbidity was 14 days (range 2-26). No deaths occurred within 30 days after treatment, represented by a mortality rate of 0%. Twelve patients received adjuvant chemotherapy after their surgical treatment.

Table 3. Complication details.

Required management	n	Complication
None	9	
Conservatively treated	4	Ileus
	3	Atrial fibrillation
	1	Renal impairment
Medical intervention	1	Ileus requiring total parental nutrition
	3	Hypertension
	2	Pulmonary embolism
	1	Seizure
	1	Pneumonia
	1	Diabetic keto-acidosis
	1	Urinary tract infection causing delirium
	1	Fever without focus
Radiological intervention	5	Drainage intra-abdominal collection
	1	Drainage pulmonary fluid
Surgical intervention	1	Pancreatic leakage/necrotic pancreas fistula
	1	Splenic infarction
	1	Big subcutaneous abcess

Survival outcomes

Median follow-up time was 10.5 months (range 1-52). Median overall survival was 35 months (95% Confidence Interval 20.0-49.9), with a 6-, 12- and 18-months survival rate of 94%, 83% and 68%, respectively. Kaplan-Meier survival analysis for overall survival is shown in figure 1. Median disease-free survival was 12 months (95% confidence interval 7.7-16.3). In 13 patients, recurrent disease was discovered during follow-up after the CS. Most frequent site of recurrent disease was the liver (n=6), followed by the peritoneal surface (n=4) and lung (n=2). Median time to recurrence after the CS in these patients was 9 months (range 3-21).

Univariate analysis was performed to assess the influence on overall survival of the following factors: Age >75 years, histologic type of tumour (mucinous adenocarcinoma versus adenocarcinoma), completeness of cytoreduction score, amount of blood transfused, completeness of cytoreduction as represented by CCR, performance of HIPEC, administration of EPIC, and occurrence of a postoperative complication requiring radiological drainage or surgical intervention. None of these factors influenced overall survival.
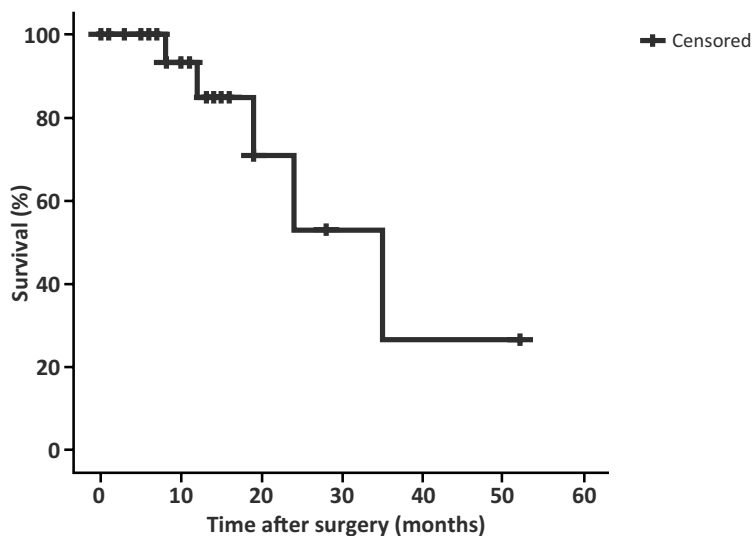

Figure 1. Kaplan-Meier survival analysis of overall survival in patients aged 70 years or older undergoing cytoreductive surgery and perioperative chemotherapy for colorectal cancer peritoneal carcinomatosis.

Discussion

The ageing population and the associated rise in prevalence of malignancy lead to an increase in demand for oncological surgery. In 2004, it was estimated that about 13% of the total Australian population was aged 65 years or older. It is expected that the proportion of elderly people will increase over time to 26% in 2051, and to 27% in 2100[18;19]. Furthermore, life expectancy grows up to ages over 80 years in children born in this decade. These developments together with the availability of specialised centres offering high standards of anaesthetic and perioperative care may allow a reconsideration of the use of age as a selection criterion.

This study shows that CS and PIC can be performed safely in patients aged 70 years or older without compromising the perioperative mortality rate and with an acceptable morbidity. Two patients who developed recurrence during follow up were also treated with a second cytoreductive procedure and recovered without complications. Although long term results could not be reported at this time due to a limited follow-up, the estimated median survival of 35 months is encouraging and comparable with results reported in the available randomised trials that included younger patients[11;20] and in a meta-analysis of the results of multiple centres worldwide by Yan et al[21].

To optimise the outcomes of elderly patients undergoing CS and PIC, it is important to avoid unnecessary resections to prevent potential added morbidity and mortality. It should be noted that the patients included in the current study represent a highly selected group, considered fit for major surgery and without any absolute contraindications for general anaesthetics.

Especially in elderly patients, the value of a detailed and careful counseling of patients being referred to a specialised centre for assessment for the combined procedures should be acknowledged. Truly, elderly patients often have less functional reserve when compared with a younger patient. The insult of an extensive surgical effort may therefore be potentially fatal in a poorly selected patient with significant comorbidities. Detailed explanation of the risks and benefits of the combined treatment modality and the awareness that major surgery, ICU stay, and the existence of comorbidities may potentially complicate the recovery and increase the morbidity and mortality is of utmost importance.

However, it can be concluded from the results of this study that eligibility assessment for CS and PIC should be based on performance status and the presence of concomitant diseases that may potentially increase the risks of anaesthesia and compromise the recovery process, rather than focus on age as a single factor.

Age has traditionally been regarded as a limiting factor towards the pursuit of curative therapies. Current data emerging in the surgical literature of metastasectomy suggest a need for change in this opinion. In other malignancies in which major abdominal surgery is the only curative option, selection criteria regarding age have been critically assessed. Recent reports have shown acceptable outcomes in terms of morbidity and mortality in patients older than 70 years of age undergoing pancreatectomy for pancreatic cancer[22-25] or gastrectomy for gastric cancer[26-30]. Further, clinical studies have shown that elderly patients undergoing chemotherapy treatment for colorectal cancer often receive suboptimal chemotherapy and are not offered modern effective polychemotherapy regimens and adjuvant therapy as a result of poorer tolerance towards chemotherapy toxicities[31;32]. Hence, if surgery may be safely performed in elderly patients, it may potentially be an appropriate therapy.

To our knowledge, this is the first study reporting on the outcomes of CS and PIC in elderly patients. Previous studies have evaluated the feasibility, safety and effectiveness of other metastasectomy procedures for colorectal cancer in the elderly population. Several centers have reported their results of liver resections for colorectal metastases in an elderly patient population (65 or older), repeatedly showing a low mortality and acceptable morbidity[33-35]. Even in octogenarians, the performance of liver surgery has been shown to be feasible and safe with a careful patient selection process[36;37].

The application of PIC worldwide is variable. The effectiveness of the combined approach of aggressive CS and HIPEC as compared to palliative care has been shown in both experimental studies and a randomised controlled trial[12;38;39]. The additional value of EPIC as early adjuvant after CS is less clear. Some studies suggest no additional effect of EPIC after cytoreduction[11], other studies have shown prolongation of survival with the combination of CS and EPIC as compared to standard care[40-42]. Also a trend towards prolonged survival has been described when hyperthermia is applied[43], whereas others do not show a difference between normothermic and hyperthermic treatment[41].

Unfortunately, data on quality of life in this elderly patient group were not available. Nonetheless, in this highly functional group of patients who are selected for surgery and expected to make a reasonable recovery, the ability to impact on life extension may be considered significant. Therefore, CS and PIC should not be withheld for elderly patients in whom a potential to prolong a good quality of life is to be expected. Further studies with

larger numbers of patients are needed to assess the quality of life after CS and PIC, and to identify factors of influence on morbidity, mortality and long-term survival in elderly patients. In addition, it may be useful to investigate quality of life outcomes of patients receiving CS combined with adjuvant systemic rather than intraperitoneal chemotherapy treatment. This modification of the current standard of care would aim to reduce complications associated with the intraperitoneal chemotherapy and shorten hospital stay, if the beneficial effects in terms of survival appear to be similar.

In conclusion, the results of this study should encourage surgeons to judiciously select elderly patients aged 70 years for potentially curative surgery for colorectal PC. Furthermore, these data should stimulate the inclusion of well selected elderly patients in clinical trials to determine the best treatment modality for patients with colorectal PC.

Reference List

(1) Marusch F, Koch A, Schmidt U, Steinert R, Ueberrueck T, Bittner R et al. The impact of the risk factor „age" on the early postoperative results of surgery for colorectal carcinoma and its significance for perioperative management. *World J Surg* 2005; 29(8):1013-1021.

(2) Shahir MA, Lemmens VEPP, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. *Eur J Cancer* 2006; 42(17):3015-3021.

(3) Arveux I, Boutron MC, El Mrini T, Arveux P, Liabeuf A, Pfitzenmeyer P et al. Colon cancer in the elderly: evidence for major improvements in health care and survival. *Br J Cancer* 1997; 76(7):963-967.

(4) Iversen LH, Pedersen L, Riis A, Friis S, Laurberg S, Sorensen HT. Age and colorectal cancer with focus on the elderly: trends in relative survival and initial treatment from a Danish population-based study. *Dis Colon Rectum* 2005; 48(9):1755-1763.

(5) Mastracci TM, Hendren S, O'Connor B, McLeod RS. The impact of surgery for colorectal cancer on quality of life and functional status in the elderly. *Dis Colon Rectum* 2006; 49(12):1878-1884.

(6) Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet* 2000; 356(9234):968-974.

(7) Barrier A, Ferro L, Houry S, Lacaine F, Huguier M. Rectal cancer surgery in patients more than 80 years of age. *Am J Surg* 2003; 185(1):54-57.

(8) Faivre J, Lemmens VE, Quipourt V, Bouvier AM. Management and survival of colorectal cancer in the elderly in population-based studies. *Eur J Cancer* 2007; 43(15):2279-2284.

(9) Vironen JH, Sainio P, Husa AI, Kellokumpu IH. Complications and survival after surgery for rectal cancer in patients younger than and aged 75 years or older. *Dis Colon Rectum* 2004; 47(7):1225-1231.

(10) Adam R, Frilling A, Elias D, Laurent C, Ramos E, Capussotti L et al. Liver resection of colorectal metastases in elderly patients. *Br J Surg* 2010; 97(3):366-376.

(11) Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. *Ann Surg Oncol* 2004; 11(5):518-521.

(12) Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(13) Lemmens VEPP, Klaver YLB, Verwaal VJ, Rutten HJT, Coebergh JW, de Hingh IHJT. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; 128(11):2717-2725.

(14) Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De SM et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004; 22(16):3284-3292.

(15) Yan TD, Links M, Fransi S, Jacques T, Black D, Saunders V et al. Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy--a journey to becoming a Nationally Funded Peritonectomy Center. *Ann Surg Oncol* 2007; 14(8):2270-2280.

(16) Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996; 82:359-374.

(17) Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995; 221(1):29-42.

(18) Health of Older People in Australia: A Snapshot, 2004-05. http://www abs gov au/ausstats/abs@ nsf/mf/4833 0 55 001 [2011

(19) World Health Organisation. World Health Statistics 2010. http://www who int/whois/whostat/EN_ WHS10_Part2 pdf [2010

(20)   Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; 15(9):2426-2432.

(21)   Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. *J Clin Oncol* 2006; 24(24):4011-4019.

(22)   Brozzetti S, Mazzoni G, Miccini M, Puma F, De AM, Cassini D et al. Surgical treatment of pancreatic head carcinoma in elderly patients. *Arch Surg* 2006; 141(2):137-142.

(23)   Hodul P, Tansey J, Golts E, Oh D, Pickleman J, Aranha GV. Age is not a contraindication to pancreaticoduodenectomy. *Am Surg* 2001; 67(3):270-275.

(24)   Kang CM, Kim JY, Choi GH, Kim KS, Choi JS, Lee WJ et al. Pancreaticoduodenectomy of pancreatic ductal adenocarcinoma in the elderly. *Yonsei Med J* 2007; 48(3):488-494.

(25)   Scurtu R, Bachellier P, Oussoultzoglou E, Rosso E, Maroni R, Jaeck D. Outcome after pancreaticoduodenectomy for cancer in elderly patients. *J Gastrointest Surg* 2006; 10(6):813-822.

(26)   Kunisaki C, Akiyama H, Nomura M, Matsuda G, Otsuka Y, Ono HA et al. Comparison of surgical outcomes of gastric cancer in elderly and middle-aged patients. *Am J Surg* 2006; 191(2):216-224.

(27)   Kunisaki C, Makino H, Takagawa R, Oshima T, Nagano Y, Ono HA et al. Efficacy of laparoscopy-assisted distal gastrectomy for gastric cancer in the elderly. *Surg Endosc* 2009; 23(2):377-383.

(28)   Mochiki E, Ohno T, Kamiyama Y, Aihara R, Nakabayashi T, Asao T et al. Laparoscopy-assisted gastrectomy for early gastric cancer in young and elderly patients. *World J Surg* 2005; 29(12):1585-1591.

(29)   Wu CW, Lo SS, Shen KH, Hsieh MC, Lui WY, P'eng FK. Surgical mortality, survival, and quality of life after resection for gastric cancer in the elderly. *World J Surg* 2000; 24(4):465-472.

(30)   Yamada H, Kojima K, Inokuchi M, Kawano T, Sugihara K. Laparoscopy-assisted gastrectomy in patients older than 80. *J Surg Res* 2010; 161(2):259-263.

(31)   Lemmens VEPP, van Halteren AH, Janssen-Heijnen ML, Vreugdenhil G, Repelaer van Driel OJ, Coebergh JW. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 2005; 16(5):767-772.

(32)   Aparicio T, Navazesh A, Boutron I, Bouarioua N, Chosidow D, Mion M et al. Half of elderly patients routinely treated for colorectal cancer receive a sub-standard treatment. *Crit Rev Oncol Hematol* 2009; 71(3):249-257.

(33)   Aldrighetti L, Arru M, Catena M, Finazzi R, Ferla G. Liver resections in over-75-year-old patients: surgical hazard or current practice? *J Surg Oncol* 2006; 93(3):186-193.

(34)   Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ. Outcomes after major hepatectomy in elderly patients. *J Am Coll Surg* 2006; 203(5):677-683.

(35)   Zacharias T, Jaeck D, Oussoultzoglou E, Bachellier P, Weber JC. First and repeat resection of colorectal liver metastases in elderly patients. *Ann Surg* 2004; 240(5):858-865.

(36)   Riffat F, Chu F, Morris DL. Liver resection in octogenarians. *HPB (Oxford)* 2006; 8(3):206-210.

(37)   Shirabe K, Kajiyama K, Harimoto N, Gion T, Tsujita E, Abe T et al. Early outcome following hepatic resection in patients older than 80 years of age. *World J Surg* 2009; 33(9):1927-1932.

(38)   Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12(1):65-71.

(39)   Klaver YLB, Hendriks T, Lomme RMLM, Rutten HJT, Bleichrodt RP, de Hingh IHJT. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model. *Br J Surg* 2010; 97(12):1874-1880.

(40)   Elias D, Benizri E, Di Pietrantonio D, Menegon P, Malka D, Raynard B. Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2007; 14(2):509-514.

(41)   da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. *J Am Coll Surg* 2006; 203(6):878-886.

(42)   Mahteme H, Hansson J, Berglund A, Pahlman L, Glimelius B, Nygren P et al. Improved survival in patients with peritoneal metastases from colorectal cancer: a preliminary study. *Br J Cancer* 2004; 90(2):403-407.

(43)   Elias D, Blot F, El Otmany A, Antoun S, Lasser P, Boige V et al. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* 2001; 92(1):71-76.

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Secondary cytoreductive surgery and peri-operative intraperitoneal chemotherapy for peritoneal recurrence of colorectal peritoneal carcinomatosis following prior primary cytoreduction

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Abstract

Background
Primary cytoreductive surgery (CS) and peri-operative intraperitoneal chemotherapy (PIC) is the only curative option for patients with colorectal cancer peritoneal carcinomatosis (PC). A significant proportion of patients develop peritoneal recurrence despite the aggressive treatment. Outcomes of patients undergoing secondary CS and PIC for recurrent PC were examined.

Methods
All patients undergoing second procedures with curative intent for recurrent colorectal cancer PC in three centres, one in Australia and two in the Netherlands, were included. Relevant data were retrieved from medical charts. Morbidity and mortality, overall survival and disease-free survival were primary outcomes.

Results
The study included eighteen patients (13 female, mean age 47 years). At primary CS, mean Peritoneal Cancer Index (PCI) was 9.1, and in 13 patients (72%) complete resection was achieved. Median time to recurrence was 14 months (range: 1-33). At secondary CS, mean PCI was 6.3 and CS was complete in 13 patients. In one patient severe adverse events occurred requiring surgical intervention. There was no mortality in the first 30 days after surgery. One-year and two-year survival after secondary CS were 74% and 50%, respectively. However, fourteen patients showed recurrence after the second procedure with a median disease-free survival of only 4.5 months.

Conclusion
A secondary CS for recurrent colorectal cancer PC is safe and feasible, however, relapse is frequent. Further investigations are required to critically assess the efficacy of a secondary procedure and to define optimal patient selection criteria in the era of effective modern chemotherapy.

Introduction

Peritoneal carcinomatosis (PC) from colorectal cancer is often considered an incurable disease associated with a poor prognosis and a median survival of approximately 6 months[1;2]. Since the 90's of the last century, new treatment strategies have been developed aiming for cure, combining cytoreductive surgery (CS), including peritonectomy procedures, with perioperative intraperitoneal chemotherapy (PIC). The effectiveness of this therapy was evaluated in a randomised trial, showing a median survival of 24 months in patients treated with CS and HIPEC, which compared favourably to median survival of 12 months reported in the patients treated with palliative care[3]. Since then many centers worldwide have reported positive results with these techniques in terms of survival with acceptable morbidity and mortality rates. Although CS and PIC are performed with a curative intent, a considerable number of patients develop disease recurrences during follow-up[4-7]. The abdominal cavity is the most common site of recurrence, often without evidence of systemic metastasis. This raises the question of whether this group would benefit from a second surgical procedure to extirpate recurrent disease and repeated use of PIC. Recently, it was shown that repeated peritonectomy procedures are feasible in patients with different gastrointestinal malignancies[8]. It remains unclear whether this aggressive approach to managing recurrence is justifiable. Using the peritoneal surface malignancy databases of three major referral centers, we identified consecutive patients with PC of colorectal origin who underwent secondary CS and PIC to evaluate its oncologic efficacy and feasibility.

Methods

Selection criteria

Between June 2000 and October 2010 eighteen consecutive secondary CS procedures were performed for recurrent colorectal metastases. In all these patients hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC) was administered. Informed consent was obtained from all patients prior to the procedures. The suitability of patients for an iterative procedure was assessed and discussed during a weekly multidisciplinary team consisting of treating surgeons, radiologists and medical oncologists. All patients underwent preoperative investigations consisting of complete history, physical examination, contrast enhanced abdominal, pelvic and chest CT and blood tests including tumour markers. Eligibility criteria for the procedures were age <80 years, a good performance status (World Health Performance Status ≤2), absence of haematological abnormalities and adequate hepatic and cardiac functioning. Patients with extra-abdominal metastases were excluded.

Preoperative management

All patients were admitted on the day before surgery and received thrombosis prophylaxis. One hour prior to surgery cefotaxime 1000 mg (Australia) or cefalozine 2000mg (the Netherlands) was given as prophylactic antibiotic treatment, followed by metronidazole 500 mg every 6 hours during surgery in both institutes.

Cytoreductive surgery

Cytoreductive procedures were performed by a team supervised by a single experienced surgeon in each centre (D.L.M., V.J.V. and I.H.J.T., respectively). The extent of peritoneal disease was recorded using the peritoneal cancer index (PCI) as described elsewhere[9], and CS was performed using Sugarbaker's peritonectomy techniques[10]. The completeness of cytoreduction score (CCR score) was used to record the amount of residual tumour after the cytoreductive procedures[9].

Perioperative intraperitoneal chemotherapy

Following CS, HIPEC with mitomycin using the coliseum technique was initiated in a subset of patients, according to availability of the technique at the time of surgery. In the Netherlands, oxaliplatin is standardly used for hyperthermic perfusion in the second procedure. In Australia, mitomycin was used for all procedures.

Bowel anastomoses and repair of serosal defects were performed after perfusion.

Selected patients received EPIC containing of 5-fluorouracil (650–800 mg/m2 per day) in 1 L of 1.5% dextrose peritoneal dialysis solution, in the intensive care unit (ICU) or high dependency unit (HDU) on postoperative day 1 to 5. EPIC was only available in Australia and was applied as adjuvant treatment after CS in the first years of the inclusion of patients. Patients were considered eligible for EPIC treatment in addition to HIPEC if they recovered from the surgery without early postoperative complications or major organ failure.

Postoperative management

Subcutaneous heparin was administered to all patients per protocol for deep venous thrombosis prophylaxis. In symptomatic patients the presence of intraabdominal collection or abscesses was evaluated by oral contrast-enhanced abdomen and pelvic CT scan. Total parenteral nutrition was reserved for patients with prolonged gastroparesis or inadequate intake for several days.

Adjuvant chemotherapy was offered to all patients who recovered well from surgery and were fit enough to receive this treatment.

Follow-up

Data regarding baseline patient characteristics, surgical procedures, perioperative outcomes and survival outcomes were prospectively collected and included in an electronic database. Additional details regarding the primary tumour, comorbidities and blood test results were retrieved from the medical charts. For the assessment of complications, postoperative complications were registered according to their severity in terms of required management. Regular follow-up was performed at monthly intervals for the first 3 months and at 6-monthly intervals thereafter, including clinical examination, assessment of tumour markers and CT scans.

Study methods

The time between the first incision and closure of the abdomen was recorded as the operation time. Data regarding surgical and anaesthetic procedures including intraoperative administration of fluids and blood products were prospectively recorded in operative anaesthetic charts.

Grade I/II adverse events were defined as events managed with conservative or medical interventions. Moderate complications requiring radiological drainage of collections or fluid under CT- or ultrasound-guidance were recorded as grade III, whereas a severe complication (grade IV) was registered if a patient required reoperation or return to the intensive care unit (ICU). Perioperative death was defined as death occurring within 30 days after the CS or during the primary hospital admission.

Statistical analysis

All analyses were performed using SPSS software (Version 17.0). Data are reported as mean (standard deviation, SD) or median (range). Survival outcomes were assessed with Kaplan Meier survival analysis.

Results

Patient demographics

In total, 604 procedures combining CS and PIC for PC of colorectal carcinoma were performed between January 1996 and August 2010 in the three centers. Eighteen secondary procedures were performed for recurrent PC after prior primary CS and PIC treatment (seven in Australia and eleven in the Netherlands: ten in the NKI and one in the CHE). The study cohort comprised of 5 male and 13 female, with a mean age of 47 (SD 3.8) years at the time of the first CS. In two patients, an additional third procedure for recurrence after the second operation was performed.

Clinical characteristics

Relevant pathological characteristics of the primary tumours are shown in table 1. In 4 patients, PC was present at diagnosis of the primary tumour. Eleven patients received adjuvant chemotherapy after the resection of their primary tumour.

At the time of the primary CS and PIC, the mean PCI was 9.1 (SD 4.8) with a median of 10 (1-19). Five patients had incomplete cytoreduction (4 patients with CCR2 and one with CCR3) at primary CS and PIC. The median time to peritoneal recurrence after the primary CS and PIC was 14 months (1-33), and the median time interval between primary and secondary cytoreduction was 22 months (range 8-125). At the secondary CS and PIC, a complete removal of the peritoneal tumour (CCR0) was achieved 13 patients. In 2 patients a CCR2 resection was recorded, and in 3 patients a CCR3 resection.

Table 1. Primary tumour characteristics (n=18).

Primary tumour		n
Location		
	Ascending colon	4
	Transverse colon	1
	Descending colon	1
	Sigmoid	3
	Recto sigmoid	3
	Appendix	5
	Unknown	1
T-stage		
	T2	1
	T3	10
	T4	3
	Unknown	4
N-stage		
	0	9
	1	2
	2	2
	Unknown	5
Differentiation grade		
	Poor	4
	Moderate	2
	Well	10
	Unknown	2
Previous adjuvant chemotherapy		
	No	6
	Yes	11
	Unknown	1

The administration of PIC after the primary CS consisted of HIPEC in 12 patients, EPIC for five postoperative days in 3 other patients and a combination of both treatments was given to 3 patients. During the second treatment, 14 patients received HIPEC, 3 patients were given EPIC only and 1 patient received a combination of the treatments.

From the three patients receiving only EPIC after their secondary CS procedure, the first procedure was combined with HIPEC in two of these patients. The third had EPIC only in both procedures.

Morbidity and mortality

The first procedures had a median duration of 7 hours (2.0-12.5), with a mean of 6.8 (3) hours. During the second procedure the median operating time was 6.5 (2.5-9.5) hours with a mean of 6.3 (1.9) hours. The median number of resections performed per patient during the first CS and PIC was 3 (1-10), and 2 (0-5) during the second procedure. Details on the CS procedures are shown in table 2.

Table 2. Details of cytoreductive surgery and perioperative intraperitoneal chemotherapy.

		1st CS + PIC procedure		2nd CS + PIC procedure	
Operating hours		**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
		6.8 (3)	7.0 (2-12.5)	6.3 (1.9)	6.5 (2.5-9.5)
Blood transfusions		**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
		2.4 (3.6)	0.5 (0-14)	1.4 (2.2)	0 (0-7)
CCR					
	CCR0	13		13	
	CCR1	0		0	
	CCR2	4		2	
	CCR3	1		3	
No of resections		**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
		3.4 (2.1)	3 (1-10)	1.9 (1.3)	2 (0-5)
PCI		**Mean (SD)**	**Median (Range)**	**Mean (SD)**	**Median (Range)**
		9.1 (4.8)	10.0 (1-19)	6.3 (3.3)	6.5 (1-13)
PIC					
	HIPEC	12		14	
	EPIC	3		3	
	HIPEC+EPIC	3		1	

CS = cytoreductive surgery, PIC = Peri-operative Intraperitoneal Chemotherapy, CCR = Cytoreduction Completeness Score, PCI = Peritoneal Cancer Index

All patients were admitted to the ICU after the surgical procedures as per protocol. Median time of stay was 2 (1-21) days for the first procedure and also 2 (0-6) days for the second CS and PIC. Some patients in Australia were transferred to the High Dependency unit (HDU)

before going to the surgical ward, staying in this unit for a mean of 2.1 (2.7) days during the first admission, and 2.7 (3.9) days during the second. The median time of total hospital stay was 16 days for the first procedure (8-45), and 15.5 (8-61) days for the second procedure.

Table 3. Perioperative course.

	1st CS + PIC		2nd CS + PIC	
ICU days	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
	3.9 (5.1)	2 (1-21)	2.5 (1.5)	2 (0-6)
HDU days	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
	2.1 (2.7)	0.5 (0-6)	2.7 (3.9)	0 (0-10)
Total days of hospital admission	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
	19.9 (10.3)	16.0 (8-45)	18.5 (12.4)	15.5 (8-61)
Severity of morbidity per patient (n)				
	None	15		11
	Conservatively treated	2		4
	Medical intervention	1		0
	Radiological intervention	0		2
	Surgical intervention	0		1

CS = cytoreductive surgery, PIC = Peri-operative Intraperitoneal Chemotherapy, ICU = Intensive Care Unit, HDU = High Dependency Unit

The perioperative course of the initial CS and PIC procedure was uncomplicated in 15 patients. In 3 patients, mild adverse effects occurred, which could be managed with conservative or medical treatment. The first CS and PIC procedure was followed by adjuvant chemotherapy treatment in 9 patients.

During the second procedure, conservatively manageable complications occurred in 4 patients. In two patients, a collection had to be drained under radiological guidance. One patient required surgical intervention because of small bowel obstruction and sepsis. No deaths occurred within 30 days after treatment, represented by a mortality rate of 0%. Details about the complications observed are shown in table 4.

In 3 patients adjuvant chemotherapy was given after the second CS and PIC procedure.

Table 4. Details on adverse events during the postoperative courses of procedures.

1st procedure		2nd procedure
Required management	**Adverse event**	
	n	n
Uneventful recovery	15	None	11
Conservatively treated	1	Ileus	0
	0	Lesion N. femoralis	1
	1	Pneumothorax	0
	1	Pleural effusion	2
	1	Fistula	1
	0	Intra-abdominal collection	2
Medical intervention	0	Wound infection	1
	1	Pericarditis	0
Radiological intervention	0	Drainage intra-abdominal collection	2
Surgical intervention	0	Small bowel obstruction and sepsis	1

Survival outcomes

Median follow-up time was 33 months (15-157) after the first CS and PIC procedure, with a 2-year and 3-year survival rate of 83% and 72%, respectively.

Median follow up after the second CS was 10 months (range 1-76). After the secondary procedure, 1-year survival was 74% and 2-year survival was 50%. Kaplan Meier survival analysis for overall survival from the primary and secondary CS and PIC is shown in figure 1 and figure 2. Fourteen out of eighteen patients showed relapse of disease after the second CS and PIC procedure, with a median time to recurrence of 4.5 months (range 1-22). Most frequent sites of recurrence were intra-abdominal (n=7), hepatic (n=3), and pulmonary (n=2). At the time of analysis, the four patients that remained disease-free had a follow-up of 1, 3, 4 and 76 months, respectively, after the second procedure.

The patient receiving EPIC treatment only after both CS procedures had a survival of 25 months after the second procedure. Lung metastases were diagnosed 5 months after the second CS and PIC. In one of the patients receiving EPIC only after the second procedure, survival was 21 months in which liver metastases developed 2 months after the last CS and PIC. The third patient developed local recurrence of disease 9 months after the secondary CS and EPIC treatment. This patient is currently alive with disease 10 months after the second procedure and decided not to undergo further surgery.
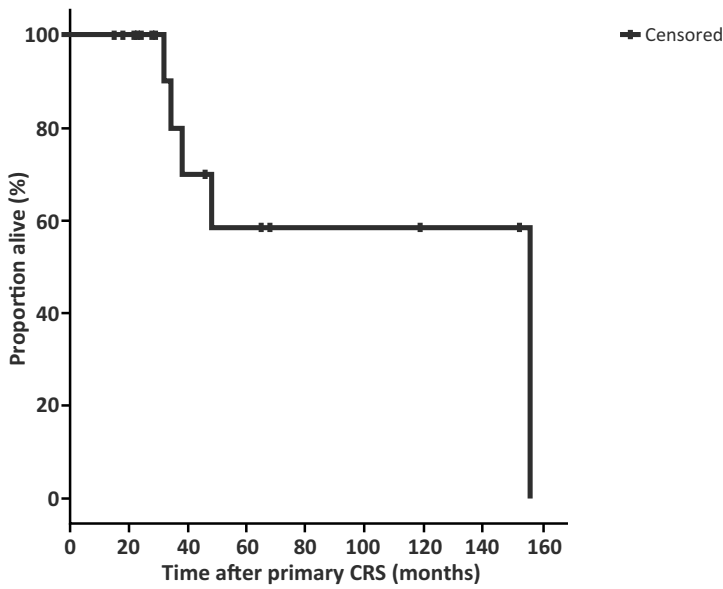
Figure 1. Kaplan-Meier survival analysis of patients undergoing secondary cytoreductive surgery, as assessed from primary cytoreduction.
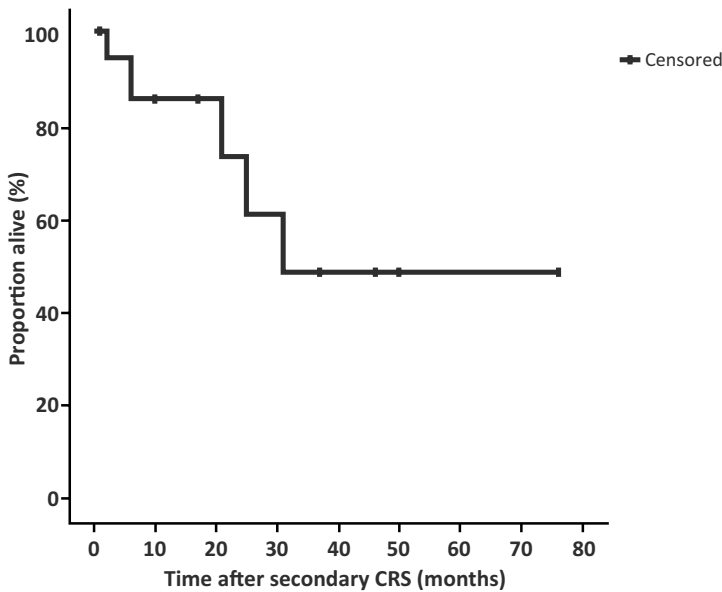

Figure 2. Kaplan-Meier survival analysis of patients undergoing secondary cytoreductive surgery, as assessed from secondary cytoreduction.

Discussion

Repeat surgery via secondary cytoreduction appears to be a feasible option for managing patients with isolated peritoneal recurrence from colorectal cancer PC following previous primary CS with acceptable morbidity and no mortality. The findings of our study suggest that secondary cytoreduction is able to prolong the survival of patients who would otherwise succumb to disease. However, the results may require further evaluation to determine its efficacy. Fourteen patients developed disease recurrence after secondary CS and PIC.

Recurrent disease after a CS and PIC is a frequently encountered problem. Verwaal et al. describe a recurrence in 69 out of 106 patients (65%) after CS and PIC[6]. In 39 of these patients, the recurrent disease remained limited to the abdominal cavity. These patients were treated with surgery if possible, but no intraperitoneal chemotherapy was applied for a second time. Bijelic et al. reported recurrent disease in 49 out of 70 patients with complete cytoreduction and PIC[7]. Survival of patients with localised recurrence was significantly better than survival with diffuse peritoneal recurrence (p=0.018) and isolated distance metastases (p=0.002). A diagnosis of recurrence within 6 months after CS was associated with a significantly shorter survival than late recurrent disease (17 vs. 36 months, p=0.001). In this study, 26 patients underwent a second operation and in 18 of these patients a complete secondary cytoreduction was achieved. Fourteen patients received intraperitoneal chemotherapy. The median survival in complete secondary CS was 42 months as compared to 30 months for whole recurrence group. In a study by Kianmanesh, secondary procedures were performed in 11 out of 43 patients (26%) undergoing CS and HIPEC for PC of colorectal origin. Overall median survival was 38.4 months, but unfortunately, outcomes of these patients were not analysed separately from those of patients treated with a single procedure[11]. Brouquet et al report on a series of 20 patients treated with repeated CS and PIC, four of which were treated for PC from colorectal origin. Strict inclusion criteria were used, e.g. an interval of >12 months between the first procedure and recurrence, limited extent of recurrence and complete cytoreduction at the repeated procedure. A median survival of 32 months was reported in these patients[12]. Gomez Portilla et al reported a median survival of 20 months in 18 patients undergoing a second procedure for recurrent PC, with six patients being disease-free three years after their initial CS and PIC treatment[5].

The comparison of survival results of patients undergoing a secondary CS versus palliative chemotherapy is difficult. It should be noted that the median disease-free survival time after second procedures for PC as reported in the literature and also in the current study is comparable to the progression-free survival reported in patients treated with modern chemotherapy regimens[13-15]. Yet, median follow-up time of the patients included in this study is relatively short. The follow-up of these patients should be continued to draw conclusions on long-term survival benefits.

Although the occurrence of adverse events associated with the secondary CS and PIC procedures in the present study is acceptable for a major oncological surgical procedure, the survival results and the risks of surgical complications question its role when compared to conservative medical treatment using palliative chemotherapy.

Surgery offers eradication of disease that may be the source of symptoms that impact on quality of life. In the setting of metastatic disease, issues of maximizing survivorship are an objective goal of treatment. With the variety of options available through local options including surgery and radiotherapy to systemic therapies comprising of chemotherapy and biological therapy, the decision-making process to select the optimal and appropriate choice is complex. It requires tailoring based on degree of tumour-related symptoms, peritoneal tumour burden, competing performance status, age and the acceptability of treatment-induced toxicities. Importantly, the estimates of duration of survival based on an understanding of tumour biology and the patient's disease behaviour together with the expected gains from treatment must be balanced in choosing optimal therapies.

The clinical behaviour of disease recurrence varies and holds a heterogenous pattern unique to each patient. There are variations in the extent and location of relapse that may be important in deciding on the ability to offer a secondary CS. In addition, the presence of systemic metastasis not only excludes many patients from a secondary CS procedure, but is also known to be an independent negative prognostic factor[16]. It is therefore inevitable that the group of patients that is considered eligible for a secondary CS procedure is a subset of patients with limited disease and favourable prognostic baseline characteristics, introducing a selection bias when comparing these patients with patients who have not been offered a second procedure.

The only way in which a surgical procedure could be beneficial in patients with recurrent disease is in case of the possibility of a curative treatment. Although our multidisciplinary tumour board may support a secondary CS and PIC through carefully selected young patients with a low PCI and favourable tumour biology, the current preliminary analysis of this management strategy have yielded results that require a re-evaluation given that the potential for long term survival is low. Although long term survivors after secondary CS and PIC have been described[7], the number of patients in whom this is achieved is limited and it is not clear which characteristics are of beneficial influence. It would be interesting to evaluate these patients in more detail to identify characteristics that influence long term outcomes after secondary procedures.

Owing to the high recurrence rates, some authors have advocated standard second-look surgery after CS and PIC[5]. The early discovery of recurrent disease (before this reaches the extent which is visible on imaging or causes symptoms) in patients after CS and PIC may

provide some advantages if a second procedure will be offered, for example limited extent of disease. The PCI is a well known prognostic factor in CS and PIC for colorectal PC. However, in the current study (in which PC was diagnosed during standard follow-up without second look procedures) the median PCI at the second procedure was 6.5 with a range of 1-13, and complete cytoreduction was achieved in most patients. Before offering standard second look procedures after CS and PIC, it should be clarified whether this has advantageous over standard follow up and can result in long term survival without evidence of disease, as it involves additional surgical procedures. Furthermore early discovery of disease also implies a shortening of the experienced disease-free life of patients.

In conclusion, secondary CS and PIC to treat isolated peritoneal recurrence of colorectal cancer PC following primary cytoreduction appears to be feasible with an acceptable morbidity and in this study without mortality. Unfortunately, early relapse from secondary CS is observed frequently. The optimal treatment strategy to manage recurrence after primary CS requires an individualised approach. Should secondary CS be pursued, it should be offered to patients who respond following a trial of systemic therapy, who are fit and have minimal and completely resectable disease.

A multi-disciplinary approach is essential to select patients who would benefit from secondary cytoreduction based on technical feasibility of further surgery, performance status and response to chemotherapy in an era when systemic therapies have shown to achieve survival prolongation[17].

Reference List

(1)   Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; 89(12):1545-1550.

(2)   Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; 88(2):358-363.

(3)   Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21(20):3737-3743.

(4)   Bijelic L, Yan TD, Sugarbaker PH. Treatment failure following complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from colorectal or appendiceal mucinous neoplasms. *J Surg Oncol* 2008; 98(4):295-299.

(5)   Portilla AG, Sugarbaker PH, Chang D. Second-look surgery after cytoreduction and intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer: analysis of prognostic features. *World J Surg* 1999; 23(1):23-29.

(6)   Verwaal VJ, Boot H, Aleman BM, van Tinteren H, Zoetmulder FA. Recurrences after peritoneal carcinomatosis of colorectal origin treated by cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment, and outcome. *Ann Surg Oncol* 2004; 11(4):375-379.

(7)   Bijelic L, Yan TD, Sugarbaker PH. Failure analysis of recurrent disease following complete cytoreduction and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Ann Surg Oncol* 2007; 14(8):2281-2288.

(8)   Saxena A, Yan TD, Morris DL. Critical assessment of preoperative and operative risk factors for complications after iterative peritonectomy procedures. *Eur J Surg Oncol* 2010; 36(3):309-314.

(9)   Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996; 82:359-374.

(10)   Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995; 221(1):29-42.

(11)   Kianmanesh R, Scaringi S, Sabate JM, Castel B, Pons-Kerjean N, Coffin B et al. Iterative cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. *Ann Surg* 2007; 245(4):597-603.

(12)   Brouquet A, Goere D, Lefevre JH, Bonnet S, Dumont F, Raynard B et al. The second procedure combining complete cytoreductive surgery and intraperitoneal chemotherapy for isolated peritoneal recurrence: postoperative course and long-term outcome. *Ann Surg Oncol* 2009; 16(10):2744-2751.

(13)   Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol* 2005; 23(15):3502-3508.

(14)   Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005; 23(16):3697-3705.

(15)   Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009; 360(6):563-572.

(16)   Lemmens VEPP, Klaver YLB, Verwaal VJ, Rutten HJT, Coebergh JWW, de Hingh IHJT. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: A population-based study. *Int J Cancer* 2011; 128(11):2717-2725.

(17)   Klaver YLB, Lemmens VEPP, Creemers GJ, Rutten HJT, Nienhuijs SW, de Hingh IHJT. Population-based survival of patients with peritoneal carcinomatosis from colorectal origin in the era of increasing use of palliative chemotherapy. *Ann Oncol* 2011; 22(10):2250-6.

Summary and future perspectives

Peritoneal metastases are frequently diagnosed in patients with colorectal cancer. Due to the fact that peritoneal carcinomatosis (PC) is thought to be relatively resistant to systemic chemotherapy and is associated with an inevitably fatal outcome, this pathology has received little interest in the past. The introduction of aggressive surgical treatments, combining cytoreductive surgery with intraperitoneal chemotherapy, has lead to a change in this attitude. With these techniques, an increased overall survival was achieved with even long-term disease-free survival in some patients. In order to optimise these treatment strategies, data regarding the natural course of disease, results of palliative treatment and insight into patient-dependent factors influencing outcome are of utmost importance. The lack of such data has stimulated research in this area and renewed the interest in information regarding different aspects of PC.

This thesis describes population-based, experimental and clinical studies. Aims of the thesis were to report the outcomes of patients with PC treated with systemic chemotherapy and palliative surgery, to clarify the role of several components of surgical treatment including cytoreductive surgery and intraperitoneal chemotherapy, and to evaluate patient selection criteria for this treatment.

Part I Treatment with palliative intent

The primary goal of the study described in **chapter 1** was to provide reliable population-based data on the incidence of synchronous PC. Including all patients diagnosed with synchronous PC of colorectal origin between 1995 and 2008 in the south of The Netherlands, relevant patient and tumour characteristics were related to incidence data to identify predictors for the development of synchronous PC. In addition, data on the overall survival of these patients were provided. In the study period, 904 colorectal cancer patients were diagnosed with synchronous PC (4.8% of all patients diagnosed with colorectal cancer, constituting 24% of patients presenting with metastatic disease). The risk of synchronous PC appeared to be increased in case of advanced T stage, advanced N stage, poor differentiation grade, younger age, mucinous adenocarcinoma and right-sided localisation of the primary tumour. The prognosis of synchronous PC remained poor especially compared to the improvements that have been reported for patients with liver metastases from colorectal origin. Median survival was 8 months and even worse if concomitant metastases in other organs were present. This underlines the importance of initiating studies on new treatment strategies for this population. The results of this study may help to understand the natural history of the disease and contribute to identifying subgroups of patients at risk for PC.

The beneficial effect of systemic chemotherapy in patients diagnosed with PC is questionable. The limited size of peritoneal tumour deposits precludes response evaluation of systemic treatment and therefore these patients are often not included or not separately analysed in

randomised trials, because they are qualified as presenting with "non-measurable" disease. In spite of any evidence as to its efficacy, it is entirely conceivable that in daily clinical practice, patients suffering from PC are considered as 'regular' metastatic colorectal cancer patients to whom palliative chemotherapy should be offered. In **chapter 2** the trends in usage of palliative chemotherapy and its effect on survival in a large unselected population of patients with PC in the south of the Netherlands were studied retrospectively. It was shown that the administration of chemotherapy gradually increased over time, from 16% of all patients diagnosed with PC in 1995 to 46% in 2008 (p=0.001). In younger patients (<70 years), the percentage of patients treated with chemotherapy was even greater, increasing from 29 to 64%.

However, median survival did not increase despite increasing usage of palliative chemotherapy and availability of new agents like oxaliplatin and irinotecan. Median overall survival was 35 weeks for patients with PC without other metastases diagnosed in 1995–2000 and 34 weeks in 2005-2008. Interestingly, a trend towards improvement in survival up to 66 weeks was seen in patients treated with palliative systemic chemotherapy between 2005 and 2008. Also, in multivariable regression analysis the use of chemotherapy showed a beneficial influence on survival only in 2005–2008. In previous periods, chemotherapy treatment did not reduce the risk for death. This study shows that even with effective chemotherapy the prognosis of patients with PC remains worse than that of patients with metastases elsewhere. From 2005 onwards, targeted agents were routinely included in palliative treatment for patients with metastasised colorectal carcinoma. This coincides with the increase in survival observed in this population. Yet, no data from randomised trials are available reporting on the outcome of chemotherapy plus targeted agents in stage IV colorectal cancer patients with PC.

To further evaluate the effects of the most recent chemotherapy regimens, the efficacy and toxicity in metastatic colorectal cancer patients with PC receiving systemic treatment were evaluated in two large phase III studies (CAIRO and CAIRO2). These results are presented in **chapter 3**. Patients with previously untreated metastatic colorectal cancer were treated with chemotherapy in the CAIRO study and with chemotherapy and targeted therapy in the CAIRO2 study. All patients were included in this analysis, and the outcomes were retrospectively analysed in relation to the presence or absence of PC at randomisation. Patient demographics, primary tumour characteristics, occurrence of toxicity and survival outcomes were evaluated.

Thirty-four patients with PC were identified in the CAIRO study, and 47 patients in the CAIRO2 study. In the CAIRO2 study patients with PC more often had a WHO classification 1 (as opposed to classification 0) than patients without PC. No other differences in baseline patient characteristics were observed between patients with and without PC.

The median overall survival was significantly decreased for patients with PC compared to patients without PC, with 10.4 versus 17.3 months, respectively in the CAIRO study (p=<0.001) and 15.2 versus 20.7 months, respectively, in the CAIRO2 study (p<0.001).

The median number of treatment cycles did not differ between patients with or without PC in both studies. The occurrence of major toxicity was more frequent in patients in PC treated with sequential chemotherapy in the CAIRO study as compared to patients without PC. However this was not reflected in the reasons to discontinue treatment in this study arm. In the CAIRO2 study, no differences in the occurrence of major toxicity were observed between patients with or without PC.

These data demonstrate a decreased efficacy of the current standard chemotherapy with and without targeted agents in metastatic colorectal cancer patients with PC. The median number of treatment cycles did not differ between patients with and without PC. This suggests that the poor outcome of these patients cannot be explained by undertreatment or increased susceptibility to toxicity, but rather by a relative resistance to treatment.

The detection of PC in colorectal cancer patients frequently results in a dilemma with regard to the optimal treatment strategy, especially when PC is encountered unexpectedly. It is unclear whether any surgical interventions of any kind should be advocated in patients with colorectal cancer and synchronous PC or if a non-invasive palliative treatment policy should be preferred. Several surgical options are available: an attempt to resect the primary tumour with or without the peritoneal metastases, the performance of a derivative procedure or enterostomy, closure of the abdomen without further intervention.

In **chapter 4** the morbidity, mortality and survival of patients undergoing palliative surgery for colorectal carcinoma with synchronous PC were evaluated, in order to clarify the advantages and disadvantages of different surgical approaches.

For this purpose, patients diagnosed with primary colorectal cancer and synchronous PC between 1995 and 2009 in three community hospitals were selected from the Eindhoven Cancer Registry database. Between 1995 and 2009, 169 colorectal cancer patients were diagnosed with synchronous PC. Surgery was performed in 142 patients. PC was encountered unexpectedly in 130 patients. Median survival was 14 weeks without surgery (n=22), 12 weeks after a derivative procedure (n=46) and 55 weeks after primary tumour resection (n=91). Derivative procedures resulted in a 30% complication rate and an in-hospital mortality of 41%. Performance of derivative procedures or no surgery were negative prognostic factors (Hazard ratio for dying 2.33, p=0.0001 and hazard ration 3.09, p=0.0007,

respectively). Other factors increasing the risk of death were older age (>70 years), the presence of a second primary tumour, poor differentiation grade, and systemic metastases. This study shows that PC is often encountered unexpectedly during surgery for colorectal cancer. Primary tumour resection can be safely performed with good outcomes, but some patients may have benefited from an even more radical approach. If possible, derivative surgery should be avoided given its high morbidity and mortality. Ideally, PC should be diagnosed prior to an operative procedure.

Part II Surgical combination therapies with curative intent in experimental studies
The only phase III randomised trial comparing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) with standard palliative care found median survival in the cytoreductive surgery and HIPEC group to be 22.4 months, compared with 12.6 months in patients treated with standard palliative care alone. Although these results are certainly encouraging, it remains unclear whether both cytoreductive surgery and HIPEC are indeed required to achieve the survival benefit. Unfortunately, no experimental arm was included with cytoreductive surgery alone. It is unlikely that a clinical trial will be able to resolve this issue since patients are not willing to participate in such studies. Instead an experimental study was performed in rats with PC of colorectal origin, aiming to establish the benefit of HIPEC as adjuvant therapy after cytoreductive surgery for PC. The results of this study are presented in **chapter 5**. The experiments were performed using a validated and reproducible model of PC of colorectal origin that resembles the clinical situation. After inoculation of CC-531 syngeneic colonic carcinoma cells, PC without distant metastasis develops within one week. One week after tumour cell inoculation, cytoreductive surgery was performed followed by no further treatment in the first group, and perfusion with hyperthermic mitomycin in a concentration of 15 or 35 mg/m^2 bodysurface in the second group and third group, respectively. Perfusion of the peritoneal cavity was performed for 90 min at 10 ml/min at a temperature of 41°C. Mitomycin C was dissolved in 0.9 per cent sodium chloride to the appropriate concentration and added to the perfusate in three separate doses at 30-min intervals, each containing 50, 25 and 25 per cent respectively of the total dose.

The median survival of rats treated with cytoreductive surgery alone was 43 days. Rats receiving HIPEC 15 mg/m^2 and HIPEC 35 mg/m^2 both had a significantly longer median survival of 75 days (p = 0.003) and 97 days (p < 0.001) respectively. Rats receiving HIPEC showed a significantly lower tumour load at autopsy compared with rats treated with cytoreductive surgery alone. Complete macroscopic removal of the tumour from the peritoneal cavity was identified as a second independent factor that improves outcome, similar to observations in clinical practice.

Concluding, HIPEC in both concentrations proved to be highly effective in prolonging survival and in delaying intra-abdominal recurrence when applied after cytoreductive surgery.

The HIPEC treatment consists of two factors, chemotherapy and hyperthermia. Next to a direct cytotoxic effect, hyperthermia is believed to enhance the antitumour effect of several cytostatic agents at markedly lower temperatures by increasing blood flow and oxygen content within tumours. This phenomenon is thought to increase intratumoural drug concentrations and thereby the cytostatic efficiency. Yet it remains unclear if both hyperthermia and chemotherapy are essential for the reported survival benefit.

In **chapter 6**, the necessity of the separate elements hyperthermia and chemotherapy for the effectiveness of the HIPEC therapy as a whole on survival was evaluated in the same experimental model as described above.

In this study, eighty WAG/Rij rats with PC were randomly assigned to 1 of the 4 treatment groups (n = 20): cytoreductive surgery only, cytoreductive surgery followed by HIPEC (mitomycin 35 mg/m^2 at 41°C), cytoreductive surgery followed by intraperitoneal mitomycin-C perfusion at 37°C and cytoreductive surgery followed by intraperitoneal saline perfusion at 41°C. Survival was the primary outcome with a maximum follow up of 126 days. Median survival was 62 days in rats treated with cytoreductive surgery only and 57 days in rats treated with cytoreductive surgery followed by hyperthermic saline perfusion. Rats receiving HIPEC had a median survival of 121 days (p=0.022 when compared with cytoreductive surgery only). In the group treated with chemotherapy at 37°C, 13 of 20 animals were still alive at the end of the experiment so median survival was not reached. (cytoreductive surgery versus normothermic perfusion: p=0.002) Rats treated with hyperthermic saline perfusion did not have an increased survival as compared with cytoreductive surgery only.

It is concluded that the effectiveness of intraoperative intraperitoneal perfusion after cytoreductive surgery is highly dependent on the presence of chemotherapy in the perfusate but not on hyperthermia.

Currently, the factor hyperthermia is not integrated in all treatment protocols for PC including cytoreductive surgery and intraperitoneal chemotherapy. The two most widely used treatment regimens for application of intraperitoneal chemotherapy are HIPEC and normothermic Early Postoperative Intraperitoneal Chemotherapy (EPIC). It remains unclear which regimen is most beneficial. In the experimental study described in **chapter 7**, the effectiveness of both treatment strategies was compared to treatment with cytoreductive surgery only. In addition, the effect of a combination of both therapies on survival outcomes was investigated.

PC was induced in Wag/Rij rats as described before, and the animals were randomised into four treatment groups (n=20): cytoreductive surgery only, cytoreductive surgery followed by HIPEC (mitomycin 35 mg/m^2 at 41°C), cytoreductive surgery followed by EPIC during 5 days

(i.p. injection of mitomycin 10 mg/m^2 on day 1 and 5-fluorouracil 15mg/kg on day 2-5), and cytoreductive surgery followed by HIPEC plus EPIC.

In rats treated with cytoreductive surgery only, median survival was 53 days. In rats treated with CS followed by HIPEC, survival was significantly increased to a median survival of 94 days (p = 0.001). In the group treated with EPIC after cytoreductive surgery, 12 out of 20 rats were still alive at the end of the experiment (p<0.001 as compared to cytoreductive surgery only). In the group receiving both treatments, eleven rats died of toxicity and therefore this group was not included in the survival analysis.

Both EPIC and HIPEC were effective in prolonging survival after cytoreductive surgery for PC from colorectal cancer. The beneficial effect of EPIC on survival seemed to be more pronounced than that of HIPEC. Further research is indicated to evaluate and compare the possible benefits and adverse effects associated with both treatments.

Part III Clinical aspects of surgical combination therapies with curative intent

In order to optimise the outcome of cytoreductive surgery and perioperative intraperitoneal chemotherapy, a careful patient selection remains one of the most important determinants. Well-known selection criteria are a physical condition fit enough for extensive surgery, resectable disease, absence of extensive hematogenous metastases and a limited extent of PC. Other criteria are applied on a theoretical basis only and therefore the selection of patients is still very much dependent on individual experience and preference of the surgical oncologist who performs the surgery.

In **chapter 8** the question is addressed whether patients who developed intraperitoneal recurrent disease during or shortly after the use of adjuvant systemic chemotherapy, and thus showed a relative resistance against systemic chemotherapy, should be eligible for local treatment with cytoreductive surgery and HIPEC. For this purpose, the outcomes of twenty-one consecutive patients who had an early recurrence after adjuvant systemic chemotherapy were analysed. Median time to recurrence of disease was 9 months after the first chemotherapy administration. Median survival after diagnosis of PC was 28 months. One- and 2-year survival was 71% and 43%, respectively. These results are similar to data reported in the literature on patients treated with HIPEC in whom data on response to previous chemotherapeutic treatment were not provided. No evidence was thus found to support the exclusion of patients who failed to respond to systemic adjuvant chemotherapy from treatment with HIPEC. Therefore, previous chemotherapy treatment should not be regarded as a selection criterion when assessing patient eligibility for HIPEC procedures.

Another group of patients where the indication for an aggressive surgical approach is debatable is the group of elderly patients. With advances in surgical techniques, anesthetic management and perioperative medical care complication rates of patients undergoing cytoreductive surgery and intraperitoneal chemotherapy have lowered considerably. It

remains to be seen whether these procedures, being the only curative option available for PC, should only be reserved for younger patients. This issue was addressed in **chapter 9**. In this chapter, morbidity, mortality and survival are reported for patients aged over 70 years at the time of surgery. Twenty-four patients were included with a mean age of 74 years. In eight patients major complications occurred. In six patients the postoperative course was complicated by minor adverse events. There was no perioperative mortality. Median overall survival was 35 months with a 6-, 12- and 18-months survival rate of 94, 83 and 68%, respectively. Thus, cytoreductive surgery and perioperative intraperitoneal chemotherapy can be safely performed with acceptable morbidity in elderly patients with PC from colorectal origin. When selecting patients for surgery, performance status and the disease extent should be used as eligibility criteria rather than age. This should encourage surgeons to consider elderly patients aged 70 years and older for cytoreductive surgery and perioperative intraperitoneal chemotherapy if indicated.

Despite aggressive treatment with cytoreductive surgery and intraperitoneal chemotherapy, a significant proportion of patients develops peritoneal recurrence. This raises the question whether a repeat procedure consisting of cytoreductive surgery and peri-operative intraperitoneal chemotherapy should be offered to these patients. In **chapter 10,** a study is described evaluating the oncologic efficacy and feasibility of repeat procedures including cytoreductive surgery and intraperitoneal chemotherapy for recurrent disease. The study included eighteen patients. During the repeat procedure, severe adverse events requiring surgical intervention occurred in one patient. There was no mortality in the first 30 days after surgery. One-year and two-year survival after repeat cytoreductive surgery were 74 and 50 %, respectively. However, fourteen patients developed a recurrence after the repeat procedure with a median disease-free survival of only 4.5 months. It was concluded that repeat cytoreductive surgery for recurrent colorectal cancer PC appears feasible, with an acceptable morbidity and without mortality. Unfortunately, early relapse from repeat cytoreduction is observed frequently. Further research and long-term follow up to explore the option of repeat cytoreduction for recurrent colorectal PC is required.

Should secondary cytoreduction be pursued, it should be offered to patients who respond following a trial of systemic therapy, who are fit and have minimal and completely resectable disease. A multi-disciplinary approach is essential to select patients who would benefit from secondary cytoreduction based on technical feasibility of further surgery, performance status and response to chemotherapy in an era when systemic therapies have shown to achieve survival prolongation.

Conclusion and future perspectives

Part I Treatment with palliative intent

Traditionally, patients with PC have been treated with palliative systemic chemotherapy for stage IV colorectal cancer. The introduction of cytoreductive surgery and intraperitoneal chemotherapy treatment has increased the need for data describing the results of palliative treatment, in order to compare this "standard" palliative care with aggressive surgical approaches. Furthermore, the presence of systemic metastases, extensive irresectable peritoneal involvement, or a poor physical performance status excludes patients from aggressive surgery. The majority of patients with PC thus remains dependent on palliative treatment.

The choices available to medical oncologists for the palliative treatment of patients with metastatic colorectal cancer have increased over the last few years with the approval of irinotecan and oxaliplatin, and with the introduction of targeted agents suppressing angiogenic growth factors. Although the presence of PC is associated with a worse prognosis as compared to other sites of metastasis, the data reported in this thesis show that the introduction of targeted agents may be beneficial in this group of patients. Also, it appears that the traditional chemotherapeutic agents have only a minor impact on this disease. Therefore, new developments in the systemic palliative treatment of peritoneal metastases should focus on pathways involved in tumour growth other than working mechanisms of conventional chemotherapy. The process of tumour induced neoangiogenesis may be a pathway of interest.

An individualisation of care is important to select those patients who will most likely benefit from different systemic treatment regimens. With an increasing number of cytotoxic and targeted agents available, the need is growing for selection parameters like tumour markers or mutational status to offer an appropriate and individualised treatment to every patient. Response evaluation studies investigating the predictive value of tumour related parameters in this group of patients are required to achieve more accuracy in treatment strategies, and to avoid unnecessary toxicity.

Finally, future studies should focus on quality of life in patients with PC to optimise treatment, and palliative care in particular.

Part II Surgical combination therapies with curative intent in experimental studies

From the preclinical experiments described in this thesis, it can be concluded that the addition of intraperitoneal chemotherapy after cytoreduction is an essential component of HIPEC in the combination treatment to achieve a survival benefit. There is no evidence for an additional value of hyperthermic over normothermic intraperitoneal treatment after cytoreduction. Also, EPIC after cytoreductive surgery certainly seems a treatment option worthwhile to pursue.

Animal studies remain important for studying cancer in humans, but caution is always warranted with extrapolation and application to the clinical situation. Although similarities among animal models and human clinical practice in terms of responses to hazardous exposures are well known, differences between species may be of influence on tumour pathogenesis and response to treatment. Yet, the possibilities for simplification of the procedures including intraperitoneal chemotherapy may be worthwhile to explore further. The results obtained in these experimental studies should stimulate further investigation in clinical phase III trials. A comparison between HIPEC and EPIC would be an interesting issue to address. Primary goals should be to evaluate differences in morbidity and mortality associated with these procedures. Secondly, long term survival benefits should be compared. Interesting groups of patients to include in this trial would be patients in whom PC is encountered unexpectedly during surgery, or patients considered to be at high risk for developing peritoneal metastases and in whom PC is found during a planned second look laparoscopy. Randomisation between direct application of EPIC and rescheduling for HIPEC treatment would be a possibility to compare these treatments.

Next to clinical evaluation of experimental conclusions, the availability of the animal model allows further investigation of questions regarding HIPEC techniques. Other questions that may be examined in this animal model are the influence of the concentration of the perfusate as compared to the dose used in an undefined volume of perfusion fluid. Furthermore, the duration of perfusion time is not standardised worldwide, and the perfusion time in HIPEC procedures varies between 30 and 90 minutes. No clear rationale for one of these variations exists, although the time needed for perfusion has important implications with regards to operating time scheduling, duration of anaesthesia and control of body temperature. In addition, it would be interesting to develop an animal model with an open (coliseum) technique HIPEC perfusion, to compare open and closed perfusion techniques.

Promising results have been reported with the application of adjuvant radioimmunotherapy after cytoreductive surgery in experimental studies. With this technique, monoclonal antibodies directed against tumour-associated antigens are labeled with radionuclides for targeted radiation. This may be a worthwhile alternative to chemotherapy and requires additional evaluation in phase I trials.

Part III Clinical aspects of surgical combination therapies with curative intent
A careful selection process of patients remains one of the most important factors in the effectiveness of surgical combination treatment. New insights into the biological mechanisms of cancer dissemination and the pathophysiology of PC from colorectal origin have contributed to the understanding that PC can be regarded as a locoregional

extension of disease, rather than a manifestation of systemic metastasis. Yet, the exact pathophysiological mechanisms and differences between patients in the behaviour of the disease remain to be clarified. It has been suggested that gene expression patterns in the primary tumour determine not only the metastatic potential and the occurrence of peritoneal dissemination of colorectal cancer cells, but also the variation in response to treatment with chemotherapeutic agents. According to this hypothesis, gene expression in peritoneal disseminated cells may differ from expression patterns in metastases localised elsewhere, thereby modulating the sensitivity and response of tumour cells to different kinds of systemically administrated chemotherapy. This would explain the observation that the prognosis of patients with PC is worse than that of patients with metastases at other sites, even with the availability of more potent chemotherapy regimens.

It can be expected that with advances in research regarding genetic expression patterns, it will at some point in time be possible to identify factors influencing patterns of disease spread and sensitivity to different treatments. For example, specific mutations (e.g. k-ras in colorectal cancer, HER2/neu receptors in breast cancer) have been shown to be associated with tumour behaviour and treatment response. For PC, it would be of interest to identify factors that determine whether the spread of colorectal cancer cells will remain limited to the peritoneal cavity, as in these patients long-term survival and even cure may be achieved with locally applied treatment like cytoreductive surgery and HIPEC. This will have a great impact on patient selection for an aggressive surgical treatment.

In addition, it is not unlikely that intraperitoneal chemotherapy will not only be applied as a treatment after cytoreduction, but also as adjuvant treatment after resection of primary colorectal carcinomas with high potential of peritoneal dissemination. This may prevent spilled cancer cells from attaching to the peritoneal surface and formation of solid peritoneal metastases. Another strategy aiming at increasing early diagnosis of PC is standard "second-look surgery", consisting of a scheduled laparoscopy or laparotomy in patients at high risk for developing metachronous PC. Factors increasing the risk for PC may for example be perforated tumours, malignant cells in ascites and unfavourable histology. Trials evaluating the feasibility and efficacy of this approach are currently undertaken.

Finally, for the evaluation of patient selection criteria, cooperation between centres and the integration of results in databases are essential. As the performance of randomised trials in this area of research has shown to be very difficult, multicentre studies combining large numbers of patients are required to further define patient selection criteria. Globally, several large institutes already collaborate and this should be encouraged further.

Samenvatting

Peritoneale uitzaaiingen komen frequent voor bij patiënten met colorectaal carcinoom. De diagnose 'peritoneale metastasering' is altijd beschouwd als een ongeneselijk stadium van ziekte, geassocieerd met een zeer slechte prognose. Bovendien leek de patiëntengroep die zich presenteerde met peritoneaalmetastasen nauwelijks baat te hebben bij systemische palliatieve chemotherapie. Deze factoren hebben ertoe geleid dat dit ziektebeeld in het verleden relatief weinig aandacht heeft gekregen.

De ontwikkeling van nieuwe chirurgische behandelstrategieën voor patiënten met peritoneale metastasen heeft gezorgd voor een hernieuwde belangstelling voor deze patiëntengroep. Deze technieken bestaan uit een combinatie van radicale cytoreductieve chirurgie en intraperitoneale chemotherapie. Met deze therapie kan een significante toename van de overleving bereikt worden ten opzichte van palliatieve zorg. Daarnaast wordt bij een deel van de behandelde patiënten langdurige ziektevrije overleving gerapporteerd.

Om een optimaal resultaat te kunnen bereiken met nieuwe behandelstrategieën is aanvullende informatie over onder andere het natuurlijke beloop van de ziekte, resultaten van 'standaard' palliatieve behandeling en patiënt-afhankelijke factoren die van invloed zijn op het effect van de behandeling essentieel. De afwezigheid van deze data in combinatie met de toegenomen interesse in deze patiëntengroep heeft wetenschappelijk onderzoek naar dit ziektebeeld gestimuleerd.

In dit proefschrift worden populatie-onderzoeken, dierexperimenten en klinische studies beschreven. Hiermee wordt beoogd enerzijds een beeld te schetsen van de resultaten van palliatieve behandeling van patiënten met peritoneaal gemetastaseerd colorectaal carcinoom met systemische chemotherapie en chirurgie, en anderzijds meer inzicht te geven in de factoren die van invloed zijn op de effectiviteit van behandeling met cytoreductieve chirurgie en intraperitoneale chemotherapie. Onder dit laatste worden zowel de invloed van de afzonderlijke componenten van de behandeling op de effectiviteit als patiëntselectiecriteria verstaan.

Deel I Palliatieve behandeling

Het doel van de studie beschreven in **hoofdstuk 1** was om een indruk te geven van de incidentie van synchrone peritoneale metastasen bij patiënten met een primair colorectaal carcinoom. Hiervoor werden gegevens uit de database van de kankerregistratie in de regio Eindhoven geanalyseerd. Deze gegevens worden routinematig verzameld door medewerkers van het Integraal Kankercentrum Zuid (IKZ). In deze analyse werden alle patiënten geïncludeerd bij wie tussen 1995 en 2008 de diagnose primair colorectaal carcinoom gesteld werd. De incidentiedata van peritoneaalmetastasen werden gerelateerd aan relevante karakteristieken van deze patiënten en gegevens over de primaire tumor, om predisponerende factoren voor het bestaan van peritoneaalmetastasen ten tijde

van diagnose van een primair colorectaal carcinoom te identificeren. Daarnaast werd de mediane overleving van deze patiëntengroep berekend. Tijdens de studieperiode werd bij 904 patiënten in de IKZ-regio de diagnose primair colorectaal carcinoom met synchrone peritoneaalmetastasen gesteld (dit komt overeen met 4.8% van het totale aantal patiënten gediagnosticeerd met colorectaal carcinoom, en 24% van de patiënten met synchroon gemetastaseerde ziekte). Het risico op synchrone presentatie met peritoneaalmetastasen bij diagnose van een colorectaal carcinoom was verhoogd bij een gevorderd T- stadium van de primaire tumor, gevorderd N stadium, slechte differentiatiegraad, jonge leeftijd, mucineuze classificatie van het adenocarcinoom en rechtzijdige localisatie van de primaire tumor. De overleving van patiënten met synchrone peritoneaalmetastasen is beperkt, en staat in contrast met de prognose van patiënten met levermetastasen, bij wie de laatste jaren veel vooruitgang in overleving gerapporteerd wordt. Mediane overleving van patiënten met peritoneaalmetastasen is 8 maanden. Indien behalve het peritoneum ook andere localisaties in het lichaam aangedaan zijn is de prognose zelfs nog slechter. Deze gegevens onderstrepen het belang van de ontwikkeling van nieuwe therapieën voor patiënten met peritoneaalmetastasen. De gegevens uit deze studie kunnen bijdragen aan een beter inzicht in het natuurlijke beloop van de ziekte en het identificeren van groepen patiënten met een verhoogd risico op peritoneaalmetastasen.

De toegevoegde waarde van systemische chemotherapie bij patiënten met peritoneaal gemetastaseerd colorectaal carcinoom is niet vastgesteld. Door de beperkte grootte van de peritoneale tumordeposities is het vaak moeilijk om een eventuele respons op chemotherapie aan te tonen met beeldvormende technieken. Om deze reden voldoen patiënten met peritoneaalmetastasen vaak niet aan de inclusiecriteria voor gerandomiseerde studies die het effect van systemische therapieën evalueren. Indien ze wel geïncludeerd worden, wordt slechts zelden een aparte analyse van de resultaten van deze groep van patiënten uitgevoerd en beschreven.

Hoewel er geen bewijs is over de effectiviteit van behandeling, kan worden aangenomen dat peritoneaalmetastasen in de kliniek beschouwd worden als "gemetastaseerde ziekte", en dat patiënten die zich presenteren met deze ziekte behandeld worden met systemische palliatieve chemotherapie. In **hoofdstuk 2** werden trends in het gebruik van palliatieve chemotherapie en het effect hiervan op de overleving in een grote ongeselecteerde populatie van patiënten met peritoneaalmetastasen retrospectief geanalyseerd. Er werd een toename van het gebruik van chemotherapie waargenomen in de tijd. In 1995 werd 16% van alle patiënten met peritoneaalmetastasen behandeld met chemotherapie. In 2008 was dit gestegen naar 46% (p=0.001). Bij jongere patiënten (<70 jaar oud) was deze toename nog sterker, van 29 naar 64%. Ondanks deze toename in behandelingsfrequentie en de beschikbaarheid van nieuwe middelen zoals oxaliplatin en irinotecan nam de mediane

overleving in deze tijdsperiode niet toe. Bij de totale groep van patiënten met peritoneale uitzaaiingen, maar zonder afstandsmetastasen werd een mediane overleving van 35 weken geregistreerd in de periode van 1995 tot 2000 en 34 weken tussen 2005 en 2008.

Een opmerkelijke observatie was een trend naar verbeterde overleving (tot 66 weken) bij selectie van patiënten die behandeld werden met chemotherapie in de periode van 2005-2008. In multivariate regressie analyse bleek het gebruik van chemotherapie het risico op overlijden te verlagen in de periode 2005-2008. In de tijd daarvoor werd het risico op overlijden niet gereduceerd door chemotherapie gebruik. Deze studie laat zien dat de prognose van patiënten met peritoneaalmetastasen slecht blijft ondanks ontwikkelingen in en betere beschikbaarheid van palliatieve chemotherapie. Sinds 2005 worden monoclonale antilichamen standaard toegevoegd aan palliatieve chemotherapieschema's voor de behandeling van patiënten met gemetastaseerd colorectaal carcinoom. Deze ontwikkeling valt samen met de toename in overleving die geobserveerd werd bij patiënten met peritoneaalmetastasen die met chemotherapie behandeld zijn. Echter, momenteel zijn er geen gerandomiseerde studies gepubliceerd die resultaten van deze therapie bij patiënten met gemetastaseerd colorectaal carcinoom met peritoneaalmetastasen beschrijven.

Teneinde de effecten van de meest recente chemotherapieschema's bij patiënten met peritoneaalmetastasen verder te evalueren, werden de uitkomsten met betrekking tot effectiviteit en toxiciteit van systemische behandeling bij patiënten met peritoneaal gemetastaseerd colorectaal carcinoom uit twee grote gerandomiseerde studies (CAIRO and CAIRO2) retrospectief geëvalueerd. De resultaten hiervan worden beschreven in **hoofdstuk 3**. Tevoren onbehandelde patiënten met gemetastaseerd colorectaal carcinoom werden behandeld met chemotherapie in de CAIRO studie en met chemotherapie en monoclonale antilichamen in de CAIRO2 studie. De resultaten van alle patiënten die deelnamen aan deze studies werden retrospectief geanalyseerd, waarbij onderscheid werd gemaakt in de aan- of afwezigheid van peritoneaalmetastasen ten tijde van randomisatie. Patiëntkarakteristieken, kenmerken van de primaire tumor, het optreden van toxiciteit en overlevingsuitkomsten werden vergeleken.

Bij 34 patiënten in de CAIRO studie en 47 patiënten in de CAIRO2 studie waren er aanwijzingen dat peritoneaalmetastasen aanwezig waren ten tijde van randomisatie. Patiëntkarakteristieken verschilden niet tussen patiënten met en zonder peritoneaalmetastasen, behalve een frequenter voorkomen van WHO classificatie 1 (ten opzichte van classificatie 0) bij patiënten met peritoneaalmetastasen in de CAIRO2 studie.

De mediane overleving van patiënten met peritoneaalmetastasen was significant minder dan die van patiënten zonder peritoneaalmetastasen, met 10.4 versus 17.3 maanden, respectievelijk, in de CAIRO studie ($p=<0.001$) en 15.2 versus 20.7 maanden in de CAIRO2 studie ($p<0.001$). Het mediane aantal behandelcycli met chemotherapie verschilde niet

tussen patiënten met en zonder peritoneaalmetastasen. In de groep patiënten die behandeld werd met sequentiële chemotherapie in de CAIRO studie trad meer toxiciteit op bij patiënten met peritoneaalmetastasen dan bij patiënten met metastasen op andere locaties. Dit kwam echter niet tot uiting in de redenen om de behandeling te discontinueren. In de CAIRO2 studie werden geen verschillen gevonden in het optreden van ernstige toxiciteit tussen patiënten met en zonder peritoneaalmetastasen.

Patiënten met peritoneaalmetastasen hebben derhalve een slechtere prognose dan patiënten met metastasen op andere locaties, ook wanneer zij behandeld worden met de huidige standaard chemotherapie voor gemetastaseerd colorectaal carcinoom met of zonder monoclonale antilichamen. De observatie dat het aantal behandelcycli niet verschilden tussen patiënten met en zonder peritoneaalmetastasen suggereert dat de negatieve impact op overleving niet verklaard kan worden door onderbehandeling of een frequenter optreden van toxiciteit in deze groep. Vervolgonderzoek is nodig om de oorzaak van de geobserveerde relatieve resistentie van peritoneaalmetastasen voor systemische palliatieve therapie te verhelderen.

Wanneer synchrone peritoneaalmetastasen onverwacht aangetroffen worden tijdens een operatie voor een primair colorectaal carcinoom staat de opererend chirurg voor een keuze. Besloten kan worden tot het uitvoeren van de geplande resectie van de primaire tumor, het aanleggen van een omleiding of stoma om obstructie te voorkomen, of het sluiten van het abdomen zonder verdere interventie. Het is niet bekend of chirurgische ingrijpen bij patiënten met colorectaal carcinoom en synchrone peritoneaalmetastasen zinvol is. In **hoofdstuk 4** werden de postoperatieve morbiditeit, mortaliteit en de overlevingsresultaten geanalyseerd van patiënten met colorectaal carcinoom en peritoneaalmetastasen die een palliatieve chirurgische ingreep ondergingen. Doel van deze studie was om de voor- en nadelen van de verschillende chirurgische benaderingen te evalueren. Hiervoor werden alle patiënten geïncludeerd bij wie tussen 1995 en 2009 in drie regionale ziekenhuizen de diagnose primair colorectaal carcinoom met synchrone peritoneaalmetastasen werd gesteld. Voor de selectie van deze patiënten werd gebruik gemaakt van de kankerregistratiedatabase van het IKZ.

Tussen 1995 en 2009 werd bij 169 patiënten met een primair colorectaal carcinoom synchrone peritoneale metastasen gediagnosticeerd. Bij 142 patiënten werd een operatieve ingreep verricht. Peritoneaalmetastasen werden aangetroffen als toevalsbevinding tijdens de operatie bij 130 patiënten. De mediane overleving van patiënten was 14 weken indien geen interventie plaatsvond (n=22), 12 weken voor patiënten met een omleiding of stoma (n=46) en 55 weken bij patiënten bij wie de primaire tumor gereseceerd werd (n=91).

Van de patiënten bij wie een omleiding of stoma werd aangelegd had 30% een gecompliceerd herstel, resulterend in een mortaliteit tijdens de opname van 41%. Het niet ondergaan

van een operatie of een operatie voor een omleiding of stoma was geassocieerd met een verhoogd risico op overlijden ten opzichte van resectie van de primaire tumor (Hazard ratio (HR) voor overlijden 2.33, p=0.0001 en HR 3.09, p=0.0007, respectievelijk). Andere factoren geassocieerd met een verhoogd risico op overlijden in multivariate analyse waren gevorderde leeftijd (>70 jaar), de aanwezigheid van een tweede primaire tumor, slechte differentiatiegraad van de primaire tumor en de aanwezigheid van metastasen op andere locaties naast het peritoneum.

Deze studie laat zien dat peritoneaalmetastasen vaak per toeval aangetroffen worden tijdens chirurgische ingrepen voor colorectaal carcinoom. Resectie van de primaire tumor is mogelijk met een acceptabele postoperatieve morbiditeit en mortaliteit, maar sommige patiënten zouden mogelijk baat hebben gehad bij een agressievere behandeling. Terughoudendheid is geboden met het uitvoeren van een omleiding, aangezien deze gepaard gaat met een hoge postoperatieve morbiditeit en mortaliteit. Idealiter zouden peritoneaalmetastasen preoperatief gediagnosticeerd moeten worden.

Deel II Experimenteel onderzoek naar in opzet curatieve chirurgische combinatiebehandelingen

De enige gerandomiseerde studie die cytoreductieve chirurgie plus hypertherme intraperitoneale chemotherapie (HIPEC) vergeleken heeft met standaard palliatieve zorg rapporteerde een mediane overleving van 22.4 maanden in de cytoreductieve chirurgie plus HIPEC groep, en 12.6 maanden in de groep met de standaard palliatieve behandeling. Hoewel deze resultaten veelbelovend zijn, blijft het onduidelijk of het noodzakelijk is om de cytoreductieve chirurgie met HIPEC te combineren om de beschreven overlevingswinst te behalen. Helaas was in de studie in kwestie geen behandelgroep opgenomen met alleen cytoreductieve chirurgie. Het is niet waarschijnlijk dat een klinische studie deze vraag zal beantwoorden aangezien patiënten niet bereid zijn deel te nemen aan een dergelijk studie-protocol.

Een dierexperimentele studie werd uitgevoerd bij Wag/Rij ratten met peritoneaalmetastasen van een coloncarcinoom, om de adjuvante waarde van HIPEC na cytoreductieve chirurgie in de behandeling van peritoneaalmetastasen vast te stellen. De resultaten van deze studie worden gepresenteerd in **hoofdstuk 5**. Voor het experiment werd gebruik gemaakt van een gevalideerd en reproduceerbaar model voor peritoneaalmetastasen van colorectale oorsprong, dat de klinische situatie simuleert. Na intraperitoneale injectie van cellen afkomstig van de CC-531 ratten colon carcinoom cellijn ontwikkelen de peritoneaalmetastasen zich binnen een week. Een week na de tumor inoculatie werd cytoreductieve chirurgie verricht bij alle ratten. Deze behandeling werd in de verschillende groepen (elk n=20) gevolgd door respectievelijk geen verdere behandeling of perfusie met hypertherme mitomycine, in een concentratie van 15 of 35 mg/m^2 lichaamsoppervlak.

De perfusie van de peritoneaalholte duurde 90 minuten bij een perfusiesnelheid van 10 ml/min en een temperatuur van 41°C. Mitomycine C werd opgelost in 0.9% natriumchloride en in drie afzonderlijke giften toegevoegd met intervallen van 30 minuten. Elke toediening bevatte respectievelijk 50, 25 en 25% van de totale dosis.

De mediane overleving van ratten die behandeld werden met alleen cytoreductieve chirurgie was 43 dagen. Bij de dieren waar de cytoreductie gevolgd werd door HIPEC 15 mg/m^2 of HIPEC 35 mg/m^2 werd een significant langere mediane overleving waargenomen van 75 dagen (p = 0.003) en 97 dagen (p < 0.001) respectievelijk. Ratten die een HIPEC-behandeling ondergaan hadden bleken een significant lagere hoeveelheid tumor te hebben op het moment van overlijden dan ratten die alleen met cytoreductieve chirurgie waren behandeld. Een complete macroscopische resectie van de peritoneale tumor deposities was geassocieerd met een gunstige uitkomst. Dit komt overeen met klinische observaties.

Er werd geconcludeerd dat HIPEC in beide concentraties, wanneer dit wordt toegepast als adjuvante therapie na cytoreductieve chirurgie, zeer effectief is in het verlengen van de overleving en het vertragen van recidiverende intra-abdominale tumorgroei. De toevoeging van HIPEC aan cytoreductieve chirurgie is dus essentieel om de overlevingswinst te bereiken zoals die beschreven wordt in de enige afgeronde gerandomiseerde klinische studie.

De HIPEC behandeling bestaat uit twee factoren, namelijk chemotherapie en hyperthermie. Naast een direct cytotoxisch effect wordt de werking van hyperthermie in deze setting vooral toegeschreven aan een versterking van het effect van cytostatica. Dit effect wordt bereikt op aanzienlijk lagere temperaturen dan die benodigd zouden zijn voor directe cytotoxiciteit. Het effect wordt toegeschreven aan stimulatie van de circulatie en verhoging van de zuurstofconcentratie in tumoren. Hierdoor zou de concentratie van cytostatica in tumorweefsel toenemen en daarmee de werking worden bevorderd. Echter, het is niet bekend of zowel de factoren hyperthermie als chemotherapie noodzakelijk zijn om een winst in overleving te bereiken na cytoreductieve chirurgie. Deze vraagstelling werd in **hoofdstuk 6** onderzocht, opnieuw gebruik makend van diermodel zoals hierboven beschreven.

In deze studie werden 80 Wag/Rij ratten middels randomisatie verdeeld over vier behandelgroepen (elk n=20) en behandeld met een van de volgende therapieën: cytoreductieve chirurgie zonder verdere interventie, cytoreductieve chirurgie gevolgd door HIPEC (35 mg/m^2 mitomycine verwarmd tot 41°C), cytoreductieve chirurgie gevolgd door intraperitoneale perfusie met mitomycine verwarmd tot 37°C, en cytoreductieve chirurgie gevolgd door intraperitoneale perfusie met fysiologisch zout verwarmd tot 41°C. Overleving was de primaire uitkomst van het onderzoek met een maximale follow-up van 126 dagen. Een mediane overleving van 62 dagen werd bereikt in de groep behandeld met alleen cytoreductieve chirurgie, en van 57 dagen in de groep behandeld met cytoreductieve chirurgie gevolgd door hypertherme perfusie met fysiologisch zout. Er werd geen verschil

in overleving gevonden tussen deze groepen. Ratten die een HIPEC procedure ondergingen hadden een mediane overleving van 121 dagen (p = 0.022 vergeleken met de groep die alleen cytoreductieve chirurgie onderging). In de groep die behandeld werd met normotherme chemotherapie perfusie waren aan het einde van het experiment nog 13 dieren in leven (cytoreductieve chirurgie alleen versus normotherme perfusie: p= 0.002).

Deze studie laat zien dat de effectiviteit van intraoperatieve intraperitoneale perfusie na cytoreductieve chirurgie met name toe te schrijven is van de aanwezigheid van cytostatica in de perfusievloeistof, en niet aan de toevoeging van hyperthermie.

De huidige behandelprotocollen voor peritoneaalmetastasen die cytoreductieve chirurgie en intraperitoneale chemotherapie combineren maken niet allemaal gebruik van hyperthermie. De twee meest gebruikte toepassingsmethoden voor de intraperitoneale chemotherapie zijn HIPEC en de vroeg postoperatieve intraperitoneale chemotherapie ("Early Postoperative Intraperitoneal Chemotherapy" (EPIC)). Bij deze laatste maakt hyperthermie geen onderdeel uit van de behandeling. De effectiviteit van beide technieken is nooit in gerandomiseerde studies vergeleken. **Hoofdstuk 7** beschrijft een experiment waarin de beide technieken werden toegepast na cytoreductieve chirurgie. De overlevingsresultaten van beide technieken werden vergeleken worden met de overleving na cytoreductieve chirurgie alleen. Tevens werd het effect van een combinatie van HIPEC en EPIC geëvalueerd. Een week na inoculatie van de tumor werden 80 Wag/Rij ingedeeld in een van de volgende vier behandelgroepen (elk n=20): cytoreductieve chirurgie alleen, cytoreductieve chirurgie gevolgd door HIPEC (35 mg/m^2 mitomycine verwarmd tot 41°C), cytoreductieve chirurgie gevolgd door EPIC gedurende 5 dagen (intraperitoneale injectie met mitomycine 10 mg/m^2 op dag 1 en 5-fluorouracil 15 mg/kg op dag 2 tot en met 5), en cytoreductieve chirurgie gevolgd door HIPEC plus EPIC.

Mediane overleving van de ratten die alleen cytoreductieve chirurgie ondergingen was 53 dagen. Ratten die behandeld werden met cytoreductieve chirurgie gevolgd door HIPEC lieten een significant langere overleving zien, met een mediaan van 94 dagen (p = 0.001). Twaalf dieren uit de EPIC groep waren nog in leven bij beëindiging van het experiment, na 167 dagen (p<0.001 vergeleken met cytoreductieve chirurgie alleen). In de groep die een combinatie van HIPEC en EPIC toegediend kreeg werd een vroegtijdige uitval van elf ratten waargenomen door toxiciteit. Daarom werd deze groep niet in de overlevingsanalyses meegenomen.

Uit deze resultaten blijkt dat zowel HIPEC als EPIC de overleving van ratten met peritoneaalmetastasen kan verlengen na cytoreductieve chirurgie. Het gunstige effect van EPIC op de overleving lijkt sterker te zijn dan dat van de HIPEC. Vervolgonderzoek zal moeten uitwijzen welke mogelijke voor- en nadelen bij beide technieken een rol spelen in de klinische praktijk.

Deel III Klinische aspecten van de in opzet curatieve chirurgische combinatiebehandelingen

Een zorgvuldige patiëntenselectie blijft een van de belangrijkste factoren van invloed op het resultaat van de behandeling met cytoreductieve chirurgie en intraperitoneale chemotherapie. Bekende en algemeen geaccepteerde selectiecriteria zijn een goede fysieke conditie die een grote chirurgische ingreep toelaat, resectabele tumoren, afwezigheid van niet curatief behandelbare metastasen op afstand en een beperkte uitgebreidheid van peritoneale ziekte. Andere criteria worden minder uniform toegepast en zijn vooral afhankelijk van de ervaring en individuele voorkeur van de behandelend chirurg.

In **hoofdstuk 8** wordt de vraag gesteld of patiënten die peritoneale metastasen ontwikkelden tijdens of kort na het gebruik van adjuvante chemotherapie (en dus een relatieve resistentie lijken te hebben tegen systemische chemotherapie) in aanmerking zouden moeten komen voor een behandeling met cytoreductieve chirurgie en HIPEC. Om deze vraag te beantwoorden werden de overlevingsresultaten geanalyseerd van 21 opeenvolgende patiënten die een vroeg recidief ontwikkelden na het ondergaan van adjuvante chemotherapie behandeling na resectie van een primair colorectaal carcinoom. Mediane tijd tot de diagnose van het recidief was 9 maanden na de eerste toediening van chemotherapie. De mediane overleving na diagnose van de peritoneale metastasen was 28 maanden. De een- en tweejaars overleving was respectievelijk 71% en 43%.

Deze resultaten zijn vergelijkbaar met de data die gerapporteerd worden in de literatuur voor patiënten die behandeld worden met HIPEC zonder gegevens over hun respons op systemische therapie. Er werd geen bewijs gevonden dat een beslissing zou rechtvaardigen om patiënten die niet op adjuvante systemische therapie reageren behandeling met cytoreductieve chirurgie en HIPEC te onthouden. Geadviseerd wordt dus om de reactie op systemische chemotherapie niet als selectiecriterium voor de HIPEC procedure te hanteren.

Een andere categorie patiënten voor wie de indicatie voor een agressieve chirurgische behandeling ter discussie staat is de groep van oudere patiënten met een peritoneaal gemetastaseerd colorectaal carcinoom. Met de huidige ontwikkelingen in chirurgische technieken, anesthesie en perioperatieve zorg is het optreden van complicaties bij patiënten die behandeling met cytoreductie en intraperitoneale chemotherapie ondergaan aanzienlijk verminderd. Dit geeft aanleiding tot de vraag of deze procedures, die nog steeds de enige curatieve behandeling zijn voor peritoneale metastasen, uitsluitend aan jonge patiënten aangeboden zouden moeten worden. **Hoofdstuk 9** beschrijft een studie naar de postoperatieve morbiditeit, mortaliteit en overleving van patiënten die een behandeling met cytoreductieve chirurgie en intraperitoneale chemotherapie ondergingen op 70-jarige leeftijd of ouder. Vierentwintig patiënten werden geïncludeerd met een gemiddelde leeftijd van 74 jaar. Bij acht patiënten traden ernstige complicaties op. Bij zes patiënten verliep het postoperatieve beloop licht gecompliceerd. Er was geen perioperatieve mortaliteit.

Mediane overleving was 35 maanden met een 6-, 12- and 18-maanden overleving van respectievelijk 94, 83 and 68%. Dit geeft aan dat de behandeling met cytoreductieve chirurgie en intraperitoneale chemotherapie veilig kan worden toegepast met een acceptabele morbiditeit bij oudere patiënten met peritoneale metastasen. Bij de selectie van patiënten voor deze behandeling zou bij voorkeur rekening moeten worden gehouden met de fysieke conditie en de uitgebreidheid van ziekte waarmee de patiënt zich presenteert in plaats van met kalenderleeftijd.

Ondanks agressieve behandeling met cytoreductieve chirurgie en intraperitoneale chemotherapie ontwikkelt een aanzienlijk deel van de patiënten met peritoneaal gemetastaseerd colorectaal carcinoom een intraperitoneaal recidief. Dit roept de vraag op of een tweede procedure, bestaande uit cytoreductieve chirurgie en intraperitoneale chemotherapie, deze patiënten voordeel kan bieden. De uitvoerbaarheid en oncologische effectiviteit van herhaalde procedures met cytoreductie en intraperitoneale chemotherapie voor recidief peritoneaalmetastasen werden onderzocht in **hoofdstuk 10**. De gegevens van achttien patiënten uit drie centra in Nederland en Australië werden hiervoor geanalyseerd. Tijdens de herhaalde procedure traden bij 1 patiënt ernstige complicaties op waarvoor een additionele chirurgische ingreep noodzakelijk was. Er was geen mortaliteit in de eerste 30 dagen na de procedures. Een- en tweejaarsoverleving na de tweede procedure waren respectievelijk 74 en 50%. Bij veertien patiënten werd een recidief gediagnosticeerd na de tweede procedure, met een mediane ziektevrije overleving van slechts 4.5 maanden. Hieruit werd geconcludeerd dat herhaalde cytoreductie en intraperitoneale chemotherapie voor recidief peritoneaalmetastasen na een eerdere agressieve behandeling uitvoerbaar en veilig is, met een acceptabele morbiditeit en zonder mortaliteit. Helaas is het recidiefpercentage na de tweede ingreep hoog, met een beperkte ziektevrije overleving.
Om een definitieve uitspraak te kunnen doen over de waarde van herhaalde procedures zijn uitgebreider onderzoek en de rapportage van lange termijn resultaten noodzakelijk.
Indien herhaalde cytoreductie overwogen wordt, zou dit aangeboden moeten worden aan patiënten die een goede respons laten zien op een kuur van systemische chemotherapie, die fit zijn en minimale, compleet resectabele ziekte hebben. Een multi-disciplinaire benadering is essentieel om die patiënten te selecteren die zouden kunnen profiteren van herhaalde cytoreductie aangezien inmiddels ook van systemische therapieën bekend is dat ze de overleving kunnen verlengen.

About the author

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Yvonne Klaver was born on 25 April 1985 in Eindhoven, the Netherlands. She grew up in Veldhoven as the oldest child in a family of five children.

After completing secondary school at the Sondervick College in Veldhoven (Gymnasium) in 2003, she started her medical studies at Maastricht University. In 2007 she did an elective of 10 weeks at the Department of Pediatric Cardiology at Starship Children's Hospital in Auckland, New Zealand in 2007. Yvonne's involvement in research concerning treatment of peritoneal carcinomatosis from colorectal cancer started during her last year of medical school in the Department of Surgery at the Catharina Hospital, Eindhoven.

In 2009, Yvonne received her Medical Degree cum laude and started working as a fulltime PhD student in the Department of Surgery at the Catharina Hospital. Her PhD project involved close collaboration with the Radboud University Nijmegen Medical Centre, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam and the Eindhoven Cancer Registry, Eindhoven. In 2010 a scientific collaboration with the Hepatobiliary and Surgical Oncology Unit of the St George Hospital, Sydney, Australia, was established. Yvonne joined this team as a research fellow from October 2010 until January 2011. The results of the studies performed in these years were presented at many national and international conferences.

In November 2011, Yvonne started working in clinical practice at the Department of Internal Medicine of the Catharina Hospital, Eindhoven.

Publications

Publications

YLB Klaver, TC Chua, VJ Verwaal, IHJT de Hingh, DL Morris
Secondary cytoreductive surgery and peri-operative intraperitoneal chemotherapy for peritoneal recurrence of colorectal peritoneal carcinomatosis following prior primary cytoreduction.
J Surg Oncol 2012 – In press

YLB Klaver, VEPP Lemmens, SW Nienhuijs, GAP Nieuwenhuijzen, HJT Rutten, IHJT De Hingh
Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy combined with intraoperative radiotherapy for locally advanced rectal cancer with peritoneal carcinomatosis: A series of 5 consecutive cases.
J Surg Oncol 2012 – In press

YLB Klaver, BJM Leenders, GJ Creemers, HJT Rutten, VJ Verwaal, VEPP Lemmens, IHJT de Hingh
Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin.
Am J Clin Oncol 2012 – Feb 6 (published online ahead of print)

YLB Klaver, T Hendriks, RMLM Lomme, HJT Rutten, RP Bleichrodt, IHJT de Hingh
Intraoperative versus early postoperative intraperitoneal chemotherapy after cytoreduction for colorectal peritoneal carcinomatosis: An experimental study.
Ann Surg Oncol 2011 – Aug 12 (published online ahead of print)

YLB Klaver, TC Chua, IHJT de Hingh, DL Morris
Outcomes of elderly patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal cancer peritoneal carcinomatosis.
J Surg Oncol 2012;105:113-8.

MCG van de Poll, YLB Klaver, BJM Leenders, VEPP Lemmens, SW Nienhuijs, IHJT de Hingh
C-reactive protein concentration is associated with prognosis in patients with colorectal peritoneal metastases receiving palliative chemotherapy.
Int J Colorectal Dis 2011;26:1067-73.

YLB Klaver, VEPP Lemmens, GJ Creemers, HJT Rutten, SW Nienhuijs, IHJT de Hingh
Population-based survival of patients with peritoneal carcinomatosis from colorectal origin in the era of increasing use of palliative chemotherapy.
Ann Oncol 2011;22:2250-6.

YLB Klaver, T Hendriks, RMLM Lomme, HJT Rutten, RP Bleichrodt, IHJT de Hingh
Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study.
Ann Surg 2011;254:125-30.

YLB Klaver, IHJT de Hingh, H Boot, VJ Verwaal
Results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy after early failure of adjuvant systemic chemotherapy.
J Surg Oncol 2011;103:431-4.

VEPP Lemmens, YLB Klaver, VJ Verwaal, HJT Rutten, JWW Coebergh, IHJT De Hingh
Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study.
Int J Cancer 2011;128:2717-25.

JCM Verzijden, YLB Klaver, IHJT de Hingh, RP Bleichrodt
Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis in patients with colorectal cancer. [Protocol]
Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD008479.

YLB Klaver, T Hendriks, RMLM Lomme, HJT Rutten, RP Bleichrodt, IHJT de Hingh
Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model.
Br J Surg 2010;97:1874-80.

YLB Klaver, SW Nienhuijs, GAP Nieuwenhuijzen, HJT Rutten, IHJT de Hingh
Omentoplasty in rectal cancer surgery prolongs post-operative ileus.
Int J Colorectal Dis 2008;23:165-9.

Dankwoord

Dankwoord

Onderzoek doe je nooit alleen. In de afgelopen jaren zijn veel mensen op hun eigen manier betrokken geweest bij mij en mijn promotie-traject. Aan iedereen die er zo voor gezorgd heeft dat dit proefschrift tot stand kon komen ben ik veel dank verschuldigd. Hoewel het onmogelijk is om iedereen te noemen, maak ik graag van deze gelegenheid gebruik om een aantal mensen persoonlijk te bedanken.

Professor Bleichrodt. Als promotor bij dit project wist u altijd de klinische toepasbaarheid van onze studies te benadrukken en een brede denkwijze te stimuleren. Een bespreking van een experiment leidde zonder uitzondering tot nieuwe invalshoeken in de discussie. Bedankt voor uw deskundige begeleiding als promotor.

Ignace de Hingh. Ons gezamenlijke onderzoek begon met je woorden: "volgens mij verveel jij je". Sindsdien is 'me vervelen' geen moment meer in me opgekomen. Jouw aanstekelijke enthousiasme en energie hebben dit project succesvol gemaakt. 'Waar een wil is, is een weg' gold zowel voor onderzoeken, publicaties, als voor een reis naar Australië. Je bent een fantastische copromotor voor me geweest. Ik hoop dat we de komende jaren nog vele gezamenlijke publicaties toe zullen voegen aan de lijst.

Thijs Hendriks. Het lab in Nijmegen is deze jaren voor mij een stabiele en vertrouwde uitvalsbasis geweest, waar jij als copromotor altijd aanwezig was om advies, zorgvuldig onderbouwde kritiek of een luisterend oor te bieden. Ik heb met heel veel plezier onder jouw leiding in Nijmegen gewerkt. Zoals Ignace zegt: "Als Thijs zegt dat het goed is, is het goed." En zo is het. Dankjewel.

Valery Lemmens. Bedankt voor je enthousiaste en betrokken begeleiding als copromotor. Jouw expertise op het gebied van statistiek en je bereidheid om geduldig een heldere uitleg te geven (en zo nodig te herhalen) heeft mij deze jaren veel geleerd. Ondanks je drukke agenda maakte je altijd tijd voor me. De volgende Piña Colada in Barcelona is voor mijn rekening.

Vic Verwaal. Bij een project als dit is de steun van een autoriteit op het gebied van HIPEC-chirurgie onmisbaar. Bedankt voor het delen van je ervaring en expertise. Of het nu ging om samenwerkingsverbanden, wetenschappelijk onderzoek of surfscholen, een advies was nooit teveel gevraagd. Ik hoop dat we onze samenwerking nog lang voort kunnen zetten.

Roger Lomme. Het dierexperimenteel onderzoek was nooit iets geworden zonder jouw handigheid, vele praktische oplossingen en eindeloos geduld. Bedankt voor je hulp, maar vooral ook voor alle leuke uren die we op het lab hebben doorgebracht met opereren, ratten

wegen, voetbalwedstrijden beluisteren en koffie drinken. Ook nu mijn promotie erop zit geldt: bellen mag altijd.

Ben de Man. Ondanks dat je vanaf het begin van mijn promotietraject je eigen strijd aan het voeren was, bracht je regelmatig je inbreng in dit project. Je was daarbij altijd even optimistisch, betrokken en behulpzaam. Dat heb ik ontzettend gewaardeerd. Tijdens de afsluiting van mijn promotie-onderzoek ben je in gedachten bij ons.

Onderzoekers in Nijmegen. Bedankt voor alle gezellige uren in het 'onderzoekshok'. **Michel**, **Thamar** en **Jillis**: mijn dartkwaliteiten zullen nooit meer het niveau evenaren dat ik bereikte tijdens jullie deskundige leiding en met jullie muurbeschermende maatregelen. **Guus**, **Ronald**, **Sharonne**, **Ankit**, **Rozemarijn**: van het foute uur beluisteren tot de vele taart die ik heb moeten trakteren: voor jullie heel graag gedaan.

Centraal Dieren Laboratorium, en met name **Kitty** en **Bianca**. Bedankt voor jullie hulp, tijd en goede zorgen en adviezen tijdens de dierexperimentele studies. De deskundige, zorgvuldige en betrokken manier waarop jullie met proefdieren omgaan is een voorbeeld voor alle onderzoekers. Jullie creëren een veilige omgeving waarin dierexperimenteel onderzoek op een verantwoorde manier uitgevoerd kan worden met het respect dat de dieren verdienen. Dank jullie wel.

Maatschap chirurgie van het Catharina Ziekenhuis, en in het bijzonder **Harm Rutten** en **Grard Nieuwenhuijzen**. Bedankt voor het vertrouwen dat jullie in mij gesteld hebben, en voor de kansen die jullie mij geboden hebben door mij aan te nemen als arts-onderzoeker. Ik heb genoten van mijn jaren bij de chirurgie en ik hoop in de toekomst nog veel met de Heelkunde in het Catharina Ziekenhuis samen te mogen werken.

Assistenten Heelkunde in het Catharina Ziekenhuis. Bedankt voor de fijne samenwerking en alle mooie momenten van de afgelopen jaren. Ik kijk met veel plezier terug op onder andere de skiweekenden, het chirurgencabaret en jullie trouwe support bij mijn praatjes op congressen. Mijn onderzoekstijd bij de chirurgie in 'het Cathrien' waren jaren met een gouden randje.

David and Milja Morris. Thank you for offering me a home far away from home. My first Christmas overseas felt like celebrated with family. I will never forget the great time I had in Sydney, thanks to you.

Hepatobiliary and Surgical Oncology Unit, St George Hospital, Sydney. Thank you for your warm welcome in 'the office'. I was deeply impressed by the way you work as a team to offer every patient the best available care and treatment in a very personal way. I have really enjoyed working in St George with you and I hope to come back for a coffee and a chat soon.

Alle co-auteurs. In deze twee jaar heb ik met vele collega's, werkzaam in verschillende vakgebieden, mogen samenwerken en gebruik gemaakt van de grote expertise en ervaring die bestaat in en buiten onze regio op het gebied van de behandeling van colorectaal carcinoom. Ik wil al mijn co-auteurs hartelijk bedanken voor deze multidisciplinaire samenwerking en feliciteren met de mooie resultaten die we samen behaald hebben.

Martine en Karin, als paranimfen én vriendinnen zijn jullie er onvoorwaardelijk voor me met een theetje, advies en een helpende hand waar nodig. Al voor, maar ook tijdens mijn jaren als onderzoeker kon ik altijd op jullie rekenen, en ik ben er trots op dat jullie op deze bijzondere dag naast me staan. Ik had me geen betere paranimfen kunnen wensen.
Aimée, bedankt voor al je inzet en betrokkenheid bij het organiseren van mijn promotiefeest als officiële 'hulp-paranimf'. Ik ben ontzettend blij dat je dit voor me wilde doen. Je peptalks en de gezellige MTB-tjes in Den Haag hebben me er regelmatig doorheen gesleept als het even niet allemaal zo soepel liep.

Rob, Niels, Dorien, Merel, Sandra. Bij jullie kan ik altijd terecht voor een lach, een traan, gekke verhalen, spontane acties, een drankje, een kopje thee of iets sterkers. De afgelopen jaren heb ik heel veel met jullie kunnen delen, en ik hoop dat nog vele jaren te kunnen doen. Dank jullie wel.

Mariano, "A journey is best measured in friends, rather than miles". After we met in the Australian desert, you have always been there for me, no matter the distance. Thank you for your support and for being so close.

Opa en oma. Of het nu gaat om mijn onderzoek, reizen of andere bezigheden, jullie zijn altijd even geïnteresseerd in mijn doen en laten en bereid om hulp te bieden waar nodig. Zelfs het tijdelijk bieden van een thuis voor mij tijdens mijn onderzoek in Nijmegen was niet te veel gevraagd. Ik vind het heel bijzonder om deze mijlpaal met jullie te vieren. Dank jullie wel.

Bart, Paul, Marianne en Ruud. Een oudste zus die om de wereld reist, regelmatig verhuist en met de vreemdste verhalen thuiskomt levert altijd genoeg stof voor gesprekken en humor. Bedankt voor jullie betrokkenheid en jullie hulp de afgelopen jaren.

En last but not least: **pap en mam**. Zonder jullie steun had ik niet hier kunnen staan. Ondanks dat mijn plannen en ideeën voor jullie niet altijd even logisch en verwacht zijn, hebben jullie me steeds gestimuleerd mijn eigen keuzes te maken om mijn dromen waar te maken. Jullie staan altijd voor me klaar. Dank jullie wel.