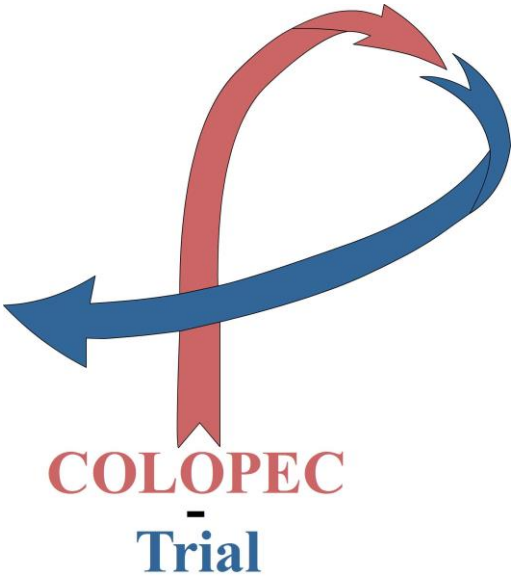
STUDY PROTOCOL



Adjuvant hyperthermic intraperitoneal chemotherapy in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial.

Principal investigators

P.J. Tanis[1], C.J.A. Punt[2], V. Verwaal[3], M.G.W. Dijkgraaf[4], W.A. Bemelman[1]

1 Department of Surgery, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
2 Department of Medical Oncology, Academic Medical Centre, University of Amsterdam
3 Department of Surgery, Catharina hospital, Eindhoven, the NetherlandsClinical Research Unit, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

PhD-students

C.E.L. Klaver[1], G.D. Musters[1]

1 Department of surgery, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Participating members / Writing committee:

R.J. van Ginkel[1], B. van Ramshorst[2], I.H.J.T. de Hingh[3], S.A. Radema[4],J.H.W. de Wilt[5], E.A. te Velde[6], J.W.A. Burger[7], A. Aalbers[8], W.M.U. van Grevenstein[9], C.J. Buskens[10], J.D.W. van der Bilt[10], L.A. ten Berg-Lammers[11], P. Evers[12], J. Pon[13], W.J.H.J. Meijerink[6], J. Tuynman[6], P.H.J. Hemmer[1], B. van Leeuwen[1], A. Bremers[5], S. Nienhuijs[3], M.J. Wiezer[2], D. Boerma[2] , P. Snaebjornsson[14]

1. Department of Surgery, University Medical Centre Groningen, Groningen, the Netherlands
2. Department of Surgery, Antonius hospital, Nieuwegein, the Netherlands
3. Department of Surgery, Catharina hospital, Eindhoven, the Netherlands
4. Department of Medical Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands
5. Department of surgery, Radboud University Medical Centre, Nijmegen, the Netherlands
6. Department of Surgery, VU Medical Centre, Amsterdam, the Netherlands
7. Department of Surgery, Erasmus Medical Centre / Daniel den Hoed, Rotterdam, the Netherlands
8. Department of Surgery, Antoni van Leeuwenhoek hospital / the Netherlands Cancer Institute, Amsterdam, the Netherlands
9. Department of Surgery, University Medical Centre Utrecht, Utrecht, the Netherlands
10. Department of Surgery, Academic Medical Centre, Amsterdam, the Netherlands
11. Department of Pharmacy, Academic Medical Centre, Amsterdam, the Netherlands
12. Dutch Cancer Patient Organization 'Leven met Kanker'
13. Society of patients with cancer of the gastrointestinal tract (SPKS), *Darmkanker Nederland*

14. Department of Pathology, Antoni van Leeuwenhoek hospital / the Netherlands Cancer Institute, Amsterdam, the Netherlands

Academic Medical Centre, Amsterdam, the Netherlands

Trial register: Clinicaltrial.gov
EudraCT number: **2014-002794-11**

Approval Medical Ethical Committee:
Protocol version 9. 11-11-2016

Protocol Title
Adjuvant hyperthermic intraperitoneal chemotherapy in patients with colon cancer at high risk of peritoneal carcinomatosis. The COLOPEC randomized multicentre trial.

Protocol ID	**NL49960.018.14**
Short title	**Adjuvant HIPEC in high risk CRC**
Version	**9**
Date	**11-11-2016**
Coordinating investigator/project leader	**Pieter J. Tanis, MD PhD, surgeon** Department of Surgery, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands Phone: +31-20-5669111 e-mail: p.j.tanis@amc.uva.nl
Principal investigator(s):	**Principle investigators:** **Pieter J. Tanis, MD PhD, surgeon** Department of Surgery, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands Phone: +31-20-5669111 e-mail: p.j.tanis@amc.uva.nl **Kees Punt, MD PhD, Professor of Medical Oncology** Department of Medical Oncology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands Phone: +31-20-5669111 e-mail: c.punt@amc.uva.nl **Victor Verwaal, MD PhD, surgeon** Currently not affiliated with an institute **Marcel G.W. Dijkgraaf, PhD, consultant in research methodology and statistics** Clinical Research Unit, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands Phone: +31-20-5669111 e-mail: m.g.dijkgraaf@amc.uva.nl

	Willem A. Bemelman, MD PhD, surgeon, Professor of Minimally Invasive Surgery Department of Surgery, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands Phone: +31-20-5669111 e-mail: w.a.bemelman@amc.uva.nl
Independent physician(s)	**O.R.C. Busch, MD PhD, surgeon** Department of Surgery, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands Phone: +31-20-5669111 e-mail: o.r.busch@amc.uva.nl

Protocol signature sheet

Name	Signature	Date
For non-commercial research, **Head of Department:** D. Legemate, MD PhD, Professor of Surgery		
Coordinating Investigator/Project leader/Principal Investigator: P.J. Tanis, MD PhD, oncological surgeon		

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CUA	Cost utility analysis
CRC	Colorectal cancer
CR	Cytoreductive surgery
CV	Curriculum Vitae
DALY	Disability adjusted life years
DSMB	Data Safety Monitoring Board
EU	European Union
GCP	Good Clinical Practice
HIPEC	Hyperthermic IntraPeritoneal chemotherapy
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
i.p.	Intraperitoneal administration
i.v.	Intravenous administration
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
PC	peritoneal carcinomatosis
QALY	Quality Adjusted Life-Year
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

1. SUMMARY

Background:

The peritoneum is the second most common site of recurrence in patients with colorectal cancer (CRC). Early detection of peritoneal carcinomatosis (PC) by imaging is difficult and adjuvant systemic treatment does not seem to affect peritoneal dissemination in contrast to haematogenous dissemination in the liver or lungs. Of all patients eventually presenting with clinically apparent PC, only a quarter have potentially curable disease. The curative option is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CR/HIPEC), but the effectiveness depends highly on the extent of disease and is associated with a considerable complication rate. These clinical problems underline the need for effective adjuvant intraperitoneal therapy in high risk CRC patients in order to prevent the development of PC with treatment at a subclinical stage.

***Objectives*:**

The aim is to determine the effectiveness of adjuvant HIPEC preceding routine adjuvant systemic therapy using i.p. oxaliplatin with concomitant i.v. 5-FU/LV following a curative resection of a T4 or intra-abdominally perforated colon cancer in preventing the development of PC in comparison to standard adjuvant systemic treatment alone.

Study design:

This will be a multicentre study in which eligible patients will be randomized to adjuvant HIPEC followed by adjuvant systemic chemotherapy in the experimental arm, or the standard adjuvant systemic chemotherapy alone in the control arm. Adjuvant HIPEC will be performed preferably simultaneously or within 10 days after resection of the primary tumour, either by laparoscopy or open approach, similar to the technique used for resection of the primary tumour. If adjuvant HIPEC cannot be performed within 10 days (i.e. complicated postoperative course), the procedure will be delayed until 5 to 8 weeks postoperatively. Subsequently, patients will receive routine adjuvant chemotherapy (CAPOX) within 3 weeks

from HIPEC. Diagnostic laparoscopy will be performed routinely after 18 months postoperatively in both arms of the study in patients without evidence of disease based on routine follow-up using CT imaging and CEA. If peritoneal carcinomatosis is found during staging laparoscopy, CR/ HIPEC will be performed in patients with a maximum of 5 involved regions and without evidence of systemic disease.

Study population:

Patients who underwent intentionally curative resection for a T4N0-2M0 or intra-abdominally perforated colon cancer.

Intervention:

Adjuvant HIPEC procedure: access to the abdominal cavity by laparoscopy or laparotomy under general anaesthesia, adhesiolysis if necessary, complete staging of the intra-abdominal cavity, positioning of in- and outflow catheters, perfusion with a minimum of 2l isotonic dialysis fluid at a flow rate of 1-2l/min and an inflow temperature of 42-43˚C. Before the beginning of HIPEC, 5-fluorouracil 400 mg/m^2 and leucovorin 20 mg/m^2 will be administered intravenously to potentiate oxaliplatin activity. Oxaliplatin (460 mg/m^2) is added to the perfusate after attaining at least 42 degrees inflow temperature with a total of 30 minutes perfusion time.

Outcomes:

Primary endpoint is peritoneal recurrence-free survival at 18 months. Secondary endpoints are treatment related toxicity, incidence of PC, sensitivity of imaging to detect PC during follow-up, differences in patterns of dissemination (peritoneal plus or minus distant metastases), disease-free survival, overall survival, quality of life and costs.

Sample size:

Based on the currently available literature, approximately 25% of colon cancer patients with a pT4 or perforated primary tumour will develop PC. Adjuvant HIPEC is expected to result in a 60% relative risk reduction. To detect a 15% difference in PC rate at 18 months, a total number of 176 assessable patients (88 in each arm) are needed (alpha=0.05, power of 80%, drop-out 5%).

Time schedule:

Accrual of 176 patients in nine centres in the Netherlands is planned between January 2015 and January 2017 with data analysis at the end of 2019. About 750 patients present each year with a pT4 and/or perforated colon cancer in the Netherlands yearly. Because the participating centres are all tertiary referral centres for PC with several referring hospitals each, timely accrual of 88 patients per year should be achievable**.**

2. INTRODUCTION AND RATIONALE

Colorectal cancer (CRC) is the second most common cancer in the Netherlands. On the 1st of January 2010, there were 57,768 CRC patients with an incidence of 12,319 new patients in 2009 (www.nationaalkompas.nl). In 2010, 5,111 patients died of CRC. The incidence of CRC is increasing in the Netherlands and is expected to be 15,000 patients in 2015 (www.oncoline.nl). The DALY for CRC is calculated to be 76,900 based on data from 2007 and is therefore one of the diseases with the highest disease burden (www.nationaalkompas.nl).

The peritoneum is the second most common site of recurrence in patients with colorectal cancer, accounting for 25 to 35% of all recurrences [1]. Synchronous peritoneal carcinomatosis (PC) is found in about 5% of the patients during the primary resection [2,3]. The incidence of metachronous PC is difficult to determine and ranges according to the literature between 4 and 19% [4]. The observed incidence of metachronous PC depends on the population characteristics (i.e. tumour stage), accuracy of imaging during follow-up, explorative relaparotomy of relaparoscopy rates during follow-up and autopsy rates. PC rates of up to 44% are reported during reoperation for CRC and in between 40 and 80% in autopsy series [4]. Because the clinical diagnosis of PC is much more difficult than the diagnosis of liver or lung metastases, it is likely that reported incidences of metachronous PC are underestimated.

Peritoneal dissemination is due to local serosal involvement of the tumour and subsequent detachment of free intraperitoneal tumour emboli. Other etiological mechanisms of free intra-abdominal tumour cells are leakage from transected lymphatic channels or blood vessels, or direct dissemination by surgical manipulation of the tumour [1,5].

Important risk factors for peritoneal tumour seeding of CRC identified in the literature are advanced stage of the primary tumour (pT4), tumour perforation and obstruction, and positive cytology of peritoneal lavage [6-8]. Based on the literature, the risk of developing PC for the different subpopulations of colorectal cancer is 17-50% for pT4, 14-58% for perforated

tumours, 63% for resected local peritoneal nodules, 75% for patients with ovarian metastasis, and 23-50% for patients with positive peritoneal cytology [6,9-15].

PC of colorectal cancer origin is associated with a poor prognosis. Median survival is only about 5 months if untreated and has a reported range between 5 and 15 months if treated with palliative systemic chemotherapy, being significantly worse compared to survival rates after palliative systemic chemotherapy for non-peritoneal localisations [16-19]. Quality of life is often significantly impaired because of ascites and bowel obstruction [19]. Palliative interventions like percutaneous drainage of ascites, intestinal bypass or stoma formation are associated with substantial morbidity, restricted effectiveness, and costs. During the last few months until death, the patient often requires intensive palliative care at a hospital, nursing home, hospice or home care setting (www.pallialine.nl). This translates into a significant disease burden.

In three quarter of the patients with PC of colorectal origin, only palliative treatment options remain at time of diagnosis. Less than half of the patients have sufficient clinical condition to tolerate systemic chemotherapy [20]. However, the effectiveness is restricted, even for modern chemotherapy regimens with or without targeted agents [17,18]. There seems to be a relative resistance of PC for systemic chemotherapy. In the remaining quarter of the patients without distant metastases and restricted peritoneal tumour load, cytoreductive surgery (CR) and HIPEC is an intentionally curative treatment option. A large number of phase II studies and two phase III trials have been published on CR/HIPEC, showing an improved survival in comparison with only systemic chemotherapy [16,21-32]. However, the effectiveness of CR/HIPEC highly depends on the extent of disease. If complete cytoreduction of PC is obtained, 5-year survival rates of 45% to 51% can be achieved in combination with HIPEC, but survival is significantly lower if not all visible tumour could be resected [33,34]. Furthermore, CR/HIPEC is associated with substantial morbidity, namely infectious complications (intra-abdominal abscesses, anastomotic leakage, enteric fistula, wound infection) and abdominal wall complications (hernias).

Because of the difficulties in treating PC at a clinically overt stage and the restricted sensitivity of imaging modalities to detect PC at an early stage, advancing the treatment to a subclinical stage may overcome the current problems in treating patients with PC of colorectal origin. In other words, effective adjuvant treatment to prevent development of PC in high risk CRC patients is warranted.

Prognosis of PC is poor despite the administration of systemic chemotherapy, with median survival rates between 5 and 13 months based on four studies [13,16,35,36]. Similarly, i.v. administration of chemotherapy in the adjuvant setting does not seem to affect the occurrence of peritoneal recurrences. Intraperitoneal (i.p.) administration of chemotherapy has been used to treat or prevent PC from various primary malignancies [5,27,37-43]. From a pharmacological point of view, this is an attractive approach given the peritoneal-plasma barrier which allows for higher peritoneal cavity concentrations resulting in higher efficacy while systemic toxicity is not increased.

In an attempt to prevent PC of CRC, i.p. 5-FU administration through a peritoneal catheter in the immediate postoperative period or as prolonged treatment up to 12 months has been used, as well as HIPEC using mitomycin-C or oxaliplatin [40,41,44-47]. The comparative studies are summarized in Table 1, with corresponding outcome data in Table 2. Cohort studies on adjuvant i.p. chemotherapy are summarized in Table 3, with corresponding outcome in Table 4. It can be concluded from these studies that i.p. chemotherapy seems to reduce intraperitoneal recurrence rates, and that even a survival benefit is suggested in studies using adjuvant HIPEC. These studies are subjected to significant bias and no definitive conclusions can be drawn based on these data. With regard to treatment related morbidity of adjuvant i.p. chemotherapy, these data as well as experience from the first 10 patients included in a Dutch feasibility study reveal that adjuvant HIPEC is a well-tolerated intervention with no significant morbidity, which can be performed in a short stay setting [48,49]. This supports conducting a randomized trial to determine the oncological effectiveness of adjuvant HIPEC in addition to routine adjuvant systemic therapy.

2.1 Standard care

According to the Dutch guidelines, adjuvant systemic chemotherapy in colon cancer is indicated for patients with node-positive disease (stage III) and can be considered in high risk stage II patients without MSI, including the following:

- T4 tumour;
- poorly differentiated,
- perforation or obstruction at presentation,
- less than 10 lymph nodes examined
- vascular invasion (oncoline.nl).

The most commonly used adjuvant chemotherapy regimen in the Netherlands is capecitabine and oxaliplatin in 8 courses of each 3 weeks.

Patients who already have PC but without evidence of systemic dissemination to other sites are candidates for CR/HIPEC, although the number of affected regions should not exceed 5 of 7 defined abdominal regions. CR/HIPEC entails a median laparotomy form xyphoid to pubic bone, with resection of all visible tumour in the abdominal cavity (R1 resection) if technically achievable, or debulking with a residual tumour thickness of less than 2.5 mm. If necessary, involved organs such as bowel segments, uterus, ovaries, stomach, or spleen are resected, together with omentum and involved parts of the peritoneum. Subsequently, the abdominal wall is retracted using a so-called Colosseum approach with positioning of inflow and outflow catheters in the abdominal cavity. These are connected to a pump with heat exchange and a perfusate is added to the circuit. If the desired temperature has been reached, chemotherapy is added. After perfusion, intestinal anastomoses are constructed and the abdomen is closed. Analysis of Dutch CR/HIPEC experience revealed a median hospital stay of 16 days (95%CI 13-22) [50]. Grade 3 to 5 morbidity was 34%, of which anastomotic leakage, abscess and fistula were the most commonly observed, often requiring re-operation and ICU admission. Postoperative mortality was 3%.

Patients with PC who are not candidate for CR/HIPEC can be treated with palliative systemic therapy if the clinical condition is sufficient, or palliative interventions like drainage of ascites or relief of obstruction by intestinal bypass or stoma.

2.2 Motivation for intervention

The intervention consists of a single HIPEC procedure using i.p. oxaliplatin combined with i.v. 5-FU/LV, either using a laparoscopic or open approach, and performed simultaneous with primary tumour resection or in the early postoperative period (< 10 days or between 5-8 weeks).

From a pharmacological point of view, the intraperitoneal route for adjuvant treatment has the advantage of administering much higher doses of chemotherapy without increasing systemic toxicity due to the peritoneum-plasma barrier. Furthermore, hyperthermia potentiates the effect of certain cytotoxic agents.

Although studies on adjuvant intraperitoneal administration of 5-FU in CRC patients at the end of the 20th century suggested a reduction of peritoneal recurrence rates, this did not uniformly translate into survival benefit [48]. In addition, repeated chemotherapy administration in an out-patient setting through peritoneal catheters was associated with discomfort and catheter related morbidity. This was the reason that the oncological community lost interest in the adjuvant i.p. treatment to prevent PC of CRC origin. Subsequently, HIPEC using mitomycin-C or oxaliplatin was shown to be effective in the treatment of macroscopic PC from CRC origin in addition to cytoreductive surgery. Based on the success of HIPEC as a combined procedure with cytoreductive surgery, initial small studies were conducted using HIPEC alone in the adjuvant setting[49,51-54]. These data are promising because of the suggested oncological effectiveness with minimal associated morbidity [48].

In addition to the conventional open approach, there is also the possibility to deliver HIPEC by a minimally invasive approach. If compared to an open procedure, laparoscopic HIPEC

avoids the risk and recovery time associated with a laparotomy while the temperature profiles and peritoneal perfusion flow rates are similar [55]. Experimental studies in pigs suggest even better penetration of chemotherapy in a closed abdomen probably due to increased abdominal pressure [56,57].

Timing of the adjuvant HIPEC procedure has been tailored to the individual patient within the COLOPEC trial. Both a simultaneous and a staged approach can be chosen. A theoretical disadvantage of a staged approach is the suggested phenomenon of residual cancer cells being encapsulated with fibrin, which probably make these cells less accessible for chemotherapy at an interval of more than two weeks after surgery [28,58-60]. Therefore, it is often stated that HIPEC should ideally be performed simultaneously with primary tumour resection, although this is not an evidence based recommendation. Simultaneous adjuvant HIPEC is often not feasible because pT4 stage is only found at definitive pathology, HIPEC is not available at time of primary tumour resection in an emergency setting for a perforated tumour, or surgery is being performed outside a HIPEC centre. In order to make results from a RCT transferable to daily clinical practice in the end, the possibility of early postoperative HIPEC has been included in the study protocol. Staged HIPEC may be performed within 10 days in case of adequate patient condition and logistics, or may be delayed to 5-8 weeks from primary resection. The theoretical advantage of staged adjuvant HIPEC is that healing of the anastomosis is not compromised by immunosuppression as a result of the administration of chemotherapeutic agents, and the more favourable logistics. Disadvantages of staged adjuvant HIPEC are the necessity of adhesiolysis, the risk of suboptimal distribution of chemotherapy in the abdominal cavity, and the potential delay of routine adjuvant systemic treatment.

Considering the different chemotherapeutic agents, oxaliplatin and Mitomycin-C are both cell cycle independent alkylating agents, interfering with DNA and DNA-synthesis. Because of a large molecular weight, there is limited systemic absorption of both agents. The enhancement of cytotoxicity under hyperthermia and a maximal tissue penetration of 2 mm is also comparable. Although there are no randomized studies comparing oxaliplatin and

Mitomycin-C for CR/HIPEC, literature suggests an equal antitumour effectiveness [61]. The advantage of oxaliplatin is the absence of neutropenia and shorter perfusion time (30 versus 90 minutes) compared to MMC.

2.3 Incidence

Colorectal cancer is the second most common cancer in men and second most common cancer in women. Approximately 13.000 new patients are diagnosed each year in the Netherlands, with an expected incidence of 15.000 in 2015. The population with a high risk of PC after curative resection considered to be the potential candidate for the COLOPEC study can be partly extrapolated from the Dutch Surgical Colorectal Audit (www.dsca.nl). The number of patients with a pT4 and/or perforated colon cancer and an age below 75 years was 547 in 2009, 660 in 2010, 706 in 2011 and 867 patients in 2012. Although there seems to be an increase of this subgroup of patients, this may be explained by more completeness of registration in recent years of the DSCA. Not all potential candidates will eventually be eligible for adjuvant HIPEC because of co-morbidity or complicated postoperative course. Based on an estimated drop-out of 10%, the estimated number of eligible patients for the COLOPEC study in the Netherlands is about 750 each year. But in daily practice, this number will appear to be much lower because of unfamiliarity with relevant trials and logistics in several Dutch hospitals.

2.4 Impact on clinical practice and healthcare system

There needs to be a good balance between associated costs and morbidity on one hand and effectiveness on the other hand for an adjuvant treatment modality. For routine adjuvant systemic chemotherapy in colon cancer, an absolute survival benefit as low as 5% is considered to be worthwhile despite duration of treatment for 6 months with treatment related toxicity such as hand-foot syndrome.

Based on published incidences of PC between 14 and 58% for perforated CRC and between 17 and 50% for pT4 stage, the estimated incidence of PC in the study population will be 25%. The relative risk reduction in PC by adjuvant HIPEC in the comparative studies of Sammartino et al. was 82% [53]. The older randomized studies using i.p. 5-FU showed relative risk reductions of 78% and 62% [46,47]. Based on these data, a conservative expected relative risk reduction of adjuvant HIPEC is 60%. The expected advantage of the experimental intervention is therefore an absolute reduction of 15% in PC (from 25% to 10%).

As a consequence of a 15% absolute risk reduction, from each cohort of 100 patients, 85 patients will undergo an additional treatment without any benefit. This is only acceptable if the associated morbidity is relatively low, which appears to be so based on systematic review of the literature and our own feasibility study [48,49].

Adjuvant HIPEC is expected to have a dual advantage. Prevention of PC will potentially reduce the application of CR/HIPEC. Secondly, part of advanced stage PC will be prevented, which would otherwise have led to palliative treatment. It is, however, difficult to predict the exact proportions of reduction in CR/HIPEC procedures or palliative treatment for advanced PC in the end based on the application of adjuvant HIPEC.

With regard to the cost-effectiveness, additional costs of routine adjuvant HIPEC should be weighed against gained life years and reduced costs of patients in whom PC has been prevented to develop. A 15% reduction of peritoneal recurrence is expected to result in at least a 5% survival benefit, given the dismal prognosis associated with development of PC and based on an update of the study by Sammartino et al. [abstract HIPEC congress Amsterdam 2014]. Reduced costs may be related to less expensive treatment for clinically manifest PC, such as CR/HIPEC (approximately €50.000 per procedure) and palliative systemic treatment including expensive targeted agents such as bevacizumab (€2.400 per month per patient). Furthermore, reduced costs may be related to a reduced use of other palliative treatment modalities (ascites drainage, palliative surgery) and less need for palliative care in a hospital or other institutional setting, or at home.

2.5 Studies with similar designs.

No similar studies are planned as far as our research group is aware of. Our research group is in close contact with the international HIPEC researchers and has organized the world congress on peritoneal surface malignancies to be held in October 2014 in Amsterdam. Therefore, we are well informed about current developments in this field. Also searching at www.clinicaltrials.gov did not reveal ongoing studies on early postoperative adjuvant HIPEC for patients with high risk colon cancer.

There is one French randomized controlled trial that has just completed inclusion using a different approach in a slightly different patient population. This trial randomly assigned patients with local peritoneal disease at primary tumour resection, isolated ovarian metastases or perforated tumours to routine follow-up or second look laparotomy after 12 months with 'in principle' HIPEC (NCT01226394) [62]. No data are available yet. A similar study design has been published by an American group [63], but this trial has been withdrawn prior to enrollment (NCT01095523). Another similar phase III trial is planned to start in October 2014 at the Zhejiang University, China, with second look laparotomy and HIPEC at 6 months, including also pT4 cancers in addition to the other three inclusion criteria of the French trial (NCT02179489). According to our opinion, this approach is essentially different because second look surgery with systematic HIPEC and cytoreduction on indication is not an adjuvant treatment approach. Furthermore, the patients to be included with local peritoneal disease or ovarian metastases have already developed PC. We consider these patients to be candidate for routine HIPEC outside a trial setting and feel that it is unethical to randomize these patients with a chance of not having effective treatment for proven PC. A third study from Naples, Italy, is a randomized phase II trial comparing routine follow-up with second look laparoscopy and HIPEC in case of PC at 6 months postoperatively for patients who underwent resection for mucinous colorectal cancer of any stage (I-III) (NCT01628211).

3. OBJECTIVES

Primary aim of this study is to determine the oncological effectiveness of adjuvant HIPEC, using i.p. oxaliplatin with concomitant i.v. 5-FU/LV, following a curative resection of a T4 or intra-abdominally perforated colon cancer in preventing the development of PC in addition to the standard adjuvant systemic treatment.

Secondary aims are:

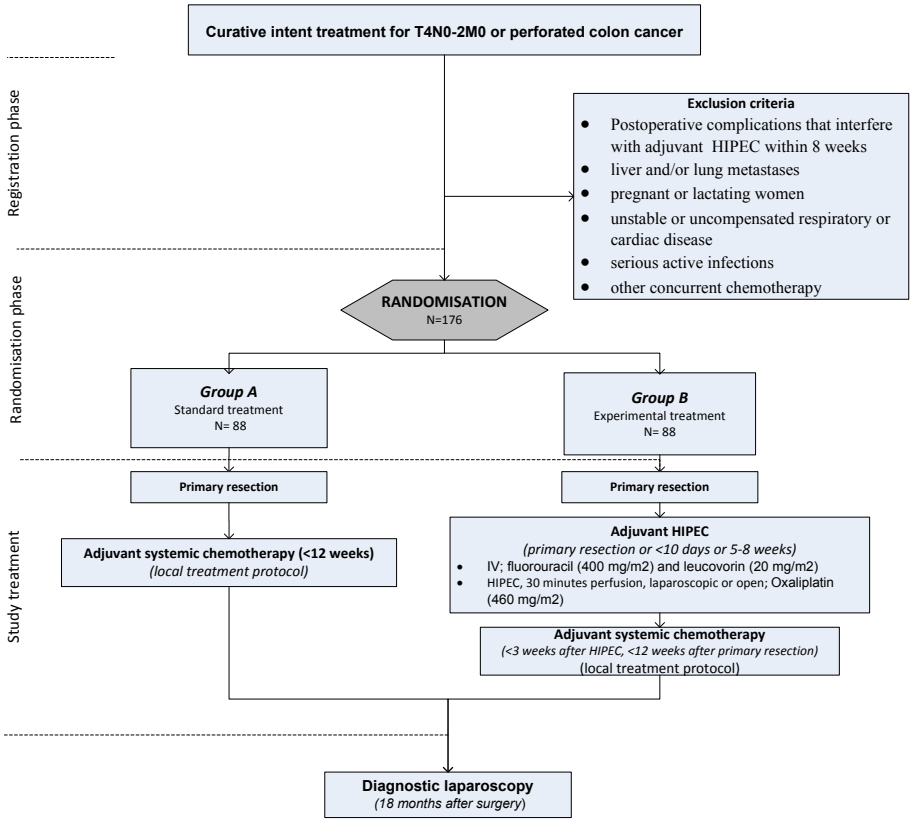
1. to determine the incidence of PC in pT4 and perforated colon cancer with metastatic patterns based on prospectively collected data and diagnostic laparoscopy at 18 months as a golden standard during follow-up.
2. to determine treatment related morbidity of open and laparoscopic adjuvant HIPEC
3. to determine treatment related morbidity of simultaneous and staged adjuvant HIPEC (both early postoperative (0-10 days) as well as delayed (3-8 weeks))
4. to determine several procedural characteristics of adjuvant HIPEC such as operating time, hospital stay, and re-admission rate
5. to compare quality of life and costs of adjuvant HIPEC with standard adjuvant systemic treatment

4. STUDY DESIGN

This will be a multicentre study in which eligible patients will be randomized to adjuvant HIPEC followed by adjuvant systemic chemotherapy in the experimental arm, or adjuvant systemic chemotherapy alone in the control arm (flow diagram). Stratification factors will be tumour characteristic (T4 or perforation), surgical approach (laparoscopy or open) and age (<65 years or ≥65 years). Adjuvant HIPEC will preferably be performed simultaneous with resection of the primary tumour or within 10 days thereafter, either by laparoscopy or open approach, similar to the technique used for resection of the primary tumour. If adjuvant HIPEC cannot be performed within 10 days (i.e. complicated postoperative course, inflammatory response in patients with perforation), the procedure will be delayed until 5 to 8

weeks postoperatively. Subsequently, patients will receive routine adjuvant systemic chemotherapy according to local treatment protocols within 3 weeks from HIPEC, preferably as soon as the clinical condition allows for systemic therapy. Diagnostic laparoscopy will be performed routinely after 18 months postoperatively in both arms of the study in patients without evidence of disease based on routine follow-up using CT imaging and CEA. Laparoscopy enables accurate assessment of the primary endpoint of the study and may have therapeutic implications for patients in whom asymptomatic PC is proven by laparoscopically taken biopsies. These patients will subsequently be treated by CR/HIPEC according to the national guideline, with a switch to mitomycine-C in patients who underwent adjuvant HIPEC with oxaliplatin previously. This approach is supported by the increasing data in the literature on the value of second look surgery for high risk patients [64,65]. All relevant data during work up, management and follow up will be collected in an electronic case record form. Data will be documented in line with 'Good Clinical Practice' and Dutch legal requirements.

Flow-diagram



5. INVESTIGATIONAL PRODUCT

5.1 Name and description of investigational product(s)

All patients will receive the standard adjuvant systemic treatment according to the local institutional protocol, which mostly consists of capecitabine and oxaliplatin (CAPOX) or 5-FU and oxaliplatin (FOLFOX). Patients who randomize for HIPEC (group B) will receive intra-operative leucovorin 20 mg/m^2 and 5-fluorouracil 400 mg/m^2 systemically and intraperitoneal oxaliplatin 460 mg/m^2 (maximal 920 mg) followed by standard adjuvant systemic treatment according to the local protocol.

5.2 Summary of findings from clinical studies

Prognosis of PC is poor despite the use of systemic chemotherapy, with disappointing median survival between 5 and 13 months based on four studies [13,16,35,36]. Similarly, IV administration of chemotherapy in the adjuvant setting does not seem to affect the occurrence of peritoneal recurrences.

Literature on intraperitoneal (i.p.) administration of chemotherapy in the adjuvant setting after curative resection of colorectal cancer was systematically reviewed [48]. A total of 12 studies were included. The studies were categorized as comparative studies (n=7) and prospective cohort studies (n=5) and displayed in Table one to four. Among the comparative studies, four randomized controlled trials (RCT) [40,41,46,47], two non–randomized comparative studies [6,54], and one case control study were identified [53].

The oldest of the selected articles was published in 1985 [47], and the most recent publication dated from 2012 [53]. The largest comparative study included 267 patients [41], and the largest cohort study included 87 patients [52]. In total, adjuvant (H)IPEC was administered in 463 patients. Five studies confined their inclusion to colon cancer patients only [41,44-46,53,66], whereas most studies did not exclude rectal cancer patients. One study included only rectal cancer patients [52].

Criteria for the inclusion of patients.

Nodal positive disease and/or T4 tumours were reported as inclusion criteria in most studies [41,44-47,51,52]. Three studies included all patients with T3 or T4 tumours, regardless of nodal status [53,54,66]. One study included all electively operated patients, with exclusion of patients with stage I disease [40]. Additional inclusion criteria were malignant obstruction or perforation [44,47,51,53], positive peritoneal lavage [6,51], CRC under the age of 30 [47], and signet ring cell or mucinous tumours [53].

(H)IPEC agents and combinations with systemic treatment.

5FU was used as single chemotherapeutic agent for intraperitoneal use in five studies [40,41,45,47,54]. Intraperitoneal LV was used in combination with a fluoropyrimidine analog (e.g. 5FU or floxuridine) in three studies [44,46,66], a combination of intraperitoneal 5FU and intravenous LV was used in one study [40], and three studies used concurrent intraperitoneal and intravenous 5FU administration either combined with intravenous LV or oral levamisole [44,46,66]. MMC was exclusively used during (H)IPEC in two studies [6,51], either MMC or oxaliplatin in one study [54], and exclusively oxaliplatin in another study [53]. Lygidakis et al. described the use of 5FU, oxaliplatin, LV, irinotecan, and mitomycin, but chemotherapy schedules were not further specified [52]. Hyperthermia was used to potentiate the effect of MMC or oxaliplatin in all studies, except for the study by Noura et al. [6] The effect of intraperitoneal oxaliplatin was further potentiated by intravenous administration of 5FU/LV just before the start of the (H)IPEC procedure.

Fluoropyrimidine or oxaliplatin based adjuvant systemic treatment was given in addition to adjuvant (H)IPEC in seven studies (Table 1 and 3). (H)IPEC was not followed by adjuvant systemic therapy in four studies [40,41,45,47]. In one of these studies, a combined adjuvant treatment schedule was used of repeated ambulatory intraperitoneal 5FU/LV administration and low doses of radiotherapy [45]. In one additional study the use of systemic treatment after adjuvant HIPEC was not mentioned [51].

Tolerance, morbidity and mortality of (H)IPEC.

The tolerance, morbidity and mortality for the different strategies is summarized in Table 2 and 4. Intolerance of intraperitoneal treatment was reported as dose limiting events, failure to complete the treatment, severe treatment associated side effects, and grading of (H)IPEC toxicity. Various grading systems or definitions, such as postoperative complications, serious complications, and life threatening side effects were used for the description of morbidity. Mortality was defined as treatment related mortality, in hospital mortality or mortality within 30 days.

Complications like infection [66], chemical peritonitis [45,47], diabetes [47], bowel perforation [66], abdominal discomfort and pain [41,46,47], intestinal obstruction or ileus [40] and intestinal poliposis [47] were specifically associated with repeated IPEC via intraperitoneal catheters. Seymour et al. studied the morbidity of repetitive intraperitoneal treatment with 5FU/LV by escalating the treatment frequency. The authors found that a weekly frequency was not tolerated; mostly due to abdominal pain [66]. Specific complications related to operative (H)IPEC were catheter or port site problems (such as cellulitis) [6,51] pancreatitis [53,54], and haematological toxicity with bone marrow aplasia in two patients from one study using a relative high dose of mitomycin-C [51]. Anastomotic failure was not associated with (H)IPEC in any of the studies.

Scheithauer et al. reported a severe adverse reaction rate of 13% in patients who received repeated IPEC with 5FU/LV compared to 3% in patients that did not receive intraperitoneal treatment [46]. This was the only study in which (H)IPEC showed a significantly higher rate of treatment related side effects compared to controls. However, the authors concluded that treatment associated side effects were infrequent and generally mild.

Graf et al. compared repeated IPEC using 5FU with repeated IPEC using a placebo [40]. Two patients in the 5FU group were diagnosed with localized peritonitis versus no patients in the placebo group. However, intestinal obstruction requiring surgery and wound infection occurred more often in the placebo group (1 vs. 2 and 4 vs. 9, respectively). The overall rate

of post-operative complications was not significantly different between the 5FU and placebo group.

In the study of Tentes et al., HIPEC with MMC or oxaliplatin simultaneously with the primary resection was compared to early postoperative repeated IPEC using 5FU via a peritoneal catheter [54]. Overall complications occurred significantly more often in the repeated IPEC group. In addition, a significant difference in hospital mortality rate was reported with nine out of 67 (13%) deaths in the repeated ambulatory IPEC group compared to one out of 40 (3%) in the intra-operative HIPEC group. Causes of death were not provided.

Survival and incidence of PC in comparative studies.

Oncological outcome parameters were analyzed in six out of seven comparative studies (Table 2) [6,41,46,47,53,54]. All three survival studies on operative (H)IPEC reported a significant impact on either overall or disease-free survival [6,53,54]. An absolute difference in 5-year cancer specific survival of 44.8% was found by Noura et al.[6]. Tentes et al. reported a significant difference in 3-year overall survival rate of 31.0%, in favour of the operative (H)IPEC group compared to the IPEC group (100% vs. 69%)[54]. Sammartino et al. showed a difference in median disease-free survival of 14.9 months in favour of the operative (H)IPEC group (36.8 vs. 21.9 months)[53]. From the studies that compare repeated ambulatory IPEC with no intraperitoneal chemotherapy, Vaillant et al. and Scheithauer et al. described absolute differences in overall survival rates of 6.0% and 18.0% respectively in favour of the IPEC groups, but these were not tested for significance [41,46]. The study by Sugerbaker et al. revealed no significant difference in overall survival [47].

Five studies compared the peritoneal recurrence rate after (H)IPEC with a control group [6,41,46,47,53]. Peritoneal recurrence rates varied between 4% and 91%. A significant difference in the incidence of PC in favour of adjuvant (H)IPEC was found in four studies (Table 2) [6,46,47,53]. Vaillant et al. reported a difference in the incidence of PC of 2.0% between the treatment and control group but this was not tested for significance [41].

5.3 Potential benefits and risks of adjuvant HIPEC

A potential benefit of adjuvant HIPEC is an expected 60% relative risk reduction in PC. As a consequence, survival is expected to increase with the use of adjuvant HIPEC in comparison to treatment with standard adjuvant systemic chemotherapy alone [48].

However, treatment related morbidity and mortality of adjuvant i.p. chemotherapy are potential risks. Potential adverse reactions of adjuvant HIPEC using oxaliplatin by a laparoscopic or open approach are wound infection, intraabdominal abscess formation, fascial dehiscence, bowel perforation due to adhesiolysis, delayed gastric emptying, ileus, chemical peritonitis and haematological toxicity. A systematic review and meta-analysis [48] as well as experience from the first 10 patients included in a Dutch feasibility study reveal that adjuvant HIPEC is a well-tolerated intervention with no significant morbidity [48,49].

Another potential risk of adjuvant HIPEC is a possible delay in the administration of adjuvant systemic chemotherapy. A meta-analysis of Biagi et al suggests that a delay to initiation of adjuvant chemotherapy decreases overall survival [67]. However, outcome of this analysis is biased by the effect of a patient's postoperative performance on time to adjuvant chemotherapy. Also, the chemotherapy used in the reviewed trials did not contain oxaliplatin and it is unknown whether the results can be extrapolated to oxaliplatin containing schemes. Another limitation of this study is that rates of completion and dosage reduction of adjuvant chemotherapy have not been reported. In the COLOPEC-trial, adjuvant HIPEC will preferably be performed during the primary resection or within ten days. Standard adjuvant chemotherapy is unlikely to be postponed by adjuvant HIPEC in these patients. When the HIPEC-procedure is yet 5-8 weeks postponed, this is in most cases due to a patient's (poor) postoperative performance. Poor postoperative performance itself would also delay systemic chemotherapy. The staged HIPEC-procedure is thus expected to cause a relative delay only. Furthermore, logistics will be optimized based on experiences from our feasibility trial [68] in order to reduce the time between staged adjuvant HIPEC and start of systemic

chemotherapy. This will be achieved by early consultation of the medical oncologist and planning of systemic chemotherapy administration in advance. Finally, we recently switched from mitomycin-C to oxaliplatin as first choice chemotherapeutic agent for HIPEC in CRC patients in the Netherlands. There will be some systemic exposure to oxaliplatin during HIPEC and a potentiating dose of 5FU/LV will be given systemically. Therefore, systemic treatment already starts at time of adjuvant HIPEC, although in a suboptimal dose.

5.4 Dosages, dosage modifications and method of administration

The chemotherapy during oxaliplatin-HIPEC consists of a intravenous phase with leucovorin 20 mg/m^2 (maximum 40 mg) and 5-fluorouracil 400 mg/m^2 (maximum 800 mg) and an intraperitoneal phase with oxaliplatin 460 mg/m^2 (maximal 920 mg). These three cytostatics are ordered one day in advance.

The HIPEC procedure will be performed as outlined below.

1. Abdominal exploration using an open or laparoscopic approach
2. 30 minutes before HIPEC, at least one inflow catheter in Douglas pouch and one outflow catheter in the right subphrenic space is inserted and connected to the perfusion system.
3. 30 min before HIPEC; the surgical gloves are changed.
4. 25 min before HIPEC; leucovorin 20 mg/m^2 in 100 cc of NaCl (0.9%) is intravenously administrated in 15 minutes by the anesthesiology personnel.
5. 10 minutes before HIPEC; 5-fluorouracil 400 mg/m^2 m^2 in 100 cc of NaCl (0.9%) is intravenously administrated in 10 minutes by the anesthesiology personnel.
6. Simultaneous with the administration of intravenous cytostatics, the abdominal cavity is filled with Dianeal© peritoneal dialysis solution (Baxter,

Peritoneal dialysis solutions, USA; Glucose 1.36 mg/100ml and is heated to 42°C (minimal flow 2L/min)

7. After completion of the intravenous 5-fluorouracil and reaching desired temperature and flow, complete dose of Oxaliplatin (460 mg/m^2) delivered in 50 cc syringes (concentration of 5 mg/ml) is added to the circuit in a single bolus by the perfusionist.
8. Perfusion for 30 minutes from time oxaliplatin was added to the perfusate.
9. After completion of the perfusion, the perfusion fluids are aspirated and collected together with all used materials following the local protocol of chemotherapy waste collection and disposal
10. Reconstruction with bowel anastomoses if indicated. Closure of the abdomen. The catheter in Douglas pouch is left in place as postoperative drainage.
11. All body excretions are collected as chemotherapy contaminated as long as the patient is admitted up to 7 days postoperatively.

5.5 Preparation and labelling of Investigational Medicinal Product and Drug accountability

This is a pragmatic clinical trial. All HIPEC centres in the Netherlands are switching from mitomycin-C to oxaliplatin as standard chemotherapeutic agent for CR/HIPEC procedures or have already done so. Therefore, oxaliplatin-HIPEC will become standard of care for CRC in the Netherlands from start of the COLOPEC trial in January 2015. For this reason, the HIPEC medication will be used from commercial stock and preparation and labelling will be performed on a patient named basis within the hospital pharmacy of each HIPEC centre. Therefore, no specific labelling for research purposes will be performed for the IMPs. . A certified monitor will be installed and a monitoring program is drafted in collaboration with the Clinical Research Unit of the Academic Medical Centre. The monitor will check adherence to

GCP guidelines and in particular the administration of serious adverse events and drug accountability registration. The monitor reports to the steering committee.

6. STUDY POPULATION

6.1 Population (base):

Patients diagnosed with adenocarcinoma of the colon and either one of the two following risk factors for PC or both will be considered for inclusion:

- T4N0-2M0 (stage T4 stage, either consisting of obvious clinical T4 stage based on preoperative imaging or intraoperative findings, or pathological T4 stage)
- Primary tumour presenting with perforation being curatively resected (N0-2M0 stage)

6.2 Inclusion criteria

- age between 18 and 75 years
- Intention to start standard adjuvant systemic therapy
- adequate clinical condition to undergo simultaneous HIPEC or re-laparoscopy or re-laparotomy with HIPEC within either 10 days or between week 5-8 from primary resection
- written informed consent
- white blood cell count of at least 3000/mm^3, platelet count of at least 100.000/mm^3 (< 3 months before surgery)
- no bleeding diathesis or coagulopathy
- normal creatinine or creatinine clearance of at least 50 ml/min (< 3 months before surgery)

6.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- postoperative complications that interfere with adjuvant HIPEC within 8 weeks (i.e. persisting intra-abdominal abscess, significant fascial dehiscence, enteric fistula)
- no intention or indication to start standard adjuvant systemic therapy
- non-curative intent treatment
- liver and/or lung metastases
- pathological T4N0 with microsatellite instability (or MMR deficiency based on immunohistochemistry)
- pregnant or lactating women
- unstable or uncompensated respiratory or cardiac disease
- serious active infections
- other concurrent chemotherapy
- hypersensitivity to fluorouracil, folinic acid or another substance of leucovorin or oxaliplatin
- stomatitis, ulceration in the mouth or gastrointestinal tract.
- severe diarrhea
- severe hepatic and / or renal dysfunction.
- plasma bilirubin concentrations greater than 85 µmol/l (measurement only necessary if indicated)
- pernicious anemia or other anaemias due to vitamin B12 deficiency.
- peripheral sensory neuropathy with functional impairment.

6.4 Sample size calculation

Approximately 25% of CRC patients with a pT4 or perforated primary tumour is suspected to develop PC. This is based on reported incidences of PC between 14 and 58% for perforated tumours [10,69,70] and between 17 and 50% for pT4 stage [3,13,71]. Reported incidences may have been underestimated because of the inaccuracy of routine follow-up examinations to detect PC and incomplete autopsy rates of patients who died of CRC. Adjuvant HIPEC is expected to result in a 60% relative risk reduction in peritoneal recurrence based on the currently available literature. The relative risk reduction in a comparative study of 25 patients undergoing prophylactic HIPEC compared to a 1:2 matched control group was 82% [53]. Older randomized studies using i.p. 5-FU showed relative risk reductions of peritoneal recurrence of 78%[72] and 62% in favour of the i.p. chemotherapy groups [73].

To detect an absolute 15% difference in PC recurrence-free survival at 18 months (90% peritoneal recurrence-free under HIPEC plus systemic chemotherapy against 75% peritoneal recurrence free under systemic chemotherapy), a total number of 176 patients (88 patients per arm, with at least 88 assessable patients in the experimental arm) is needed (Kaplan-Meier, one-sided, alpha=0.05, power of 80%, drop-out 5%). Actually, the power may even be higher, because the calculation ignores longer follow-up for the patients who have been included early on in the study. The term ‘assessable patient’ refers to a patient that can be evaluated regarding the study aim (i.e. in the experimental arm it means that a patient indeed received adjuvant HIPEC.).

7. TREATMENT OF SUBJECTS

7.1 Standard care of the control arm

Treatment in the control arm of the COLOPEC trial is in accordance with the current national guideline for adjuvant chemotherapy in colon cancer patients (www.oncoline.nl). Adjuvant intraperitoneal chemotherapy is currently not given to colon cancer patients with a high risk for peritoneal metastasis in the Netherlands. First line adjuvant systemic chemotherapy for colon cancer consists in the Netherlands of 6 months treatment with capecitabine and oxaliplatin (CAPOX) every 3 weeks or 5-FU and oxaliplatin (FOLFOX) every 2 weeks. Adjuvant chemotherapy is preferably started within 6-8 weeks after primary surgery and at a maximum of 12 weeks after primary resection.

Follow-up will be performed routinely according to the national guideline during the first 18 months. Patients who already developed recurrent disease during this time interval will be treated accordingly. In patients who have no clinical signs of recurrent disease at 18 months on CT scan of the thorax and abdomen in combination with non-elevated CEA levels, diagnostic laparoscopy will be performed. Patients with a negative laparoscopy will continue routine follow-up for at least 5 years, while patients with proven peritoneal recurrence found during laparoscopy will subsequently be treated according to the national guideline.

Patients fulfilling the criteria for CR/HIPEC will be treated accordingly using oxaliplatin as intraperitoneal chemotherapeutic agent. The first line treatment for patients with pathologically proven PC from colon carcinoma who do not qualify for CR/HIPEC is systemic therapy. The application of systemic therapy depends on the comorbidity and the clinical condition of the patient. Palliative relief of symptoms related to ascites or obstruction can most often be achieved by (minimally invasive) interventions such as percutaneous drainage, endoscopic stent placement or creation of a diversion ostomy (www.pallialine.nl).

7.2 Investigational product/treatment

Treatment in the experimental arm consists of adjuvant HIPEC followed by standard systemic chemotherapy. Timing of adjuvant HIPEC is tailored to the different clinical entities within the study population. Patients with obvious clinical T4 stage can be preoperatively asked for informed consent with simultaneous HIPEC if randomized in the experimental arm. If patients are randomized postoperatively based on intra-operative findings, early staged adjuvant HIPEC is preferably performed as soon as possible after primary resection but at a maximum of 10 days. When early postoperative HIPEC is not feasible, delayed staged adjuvant HIPEC will be performed in week 5 to 8 from primary resection. Staged HIPEC can be performed either by a laparoscopic or open approach to the discretion of the surgeon. In order to minimize delay in adjuvant systemic treatment, patients scheduled for delayed adjuvant HIPEC will preoperatively be seen by the medical oncologist to plan the adjuvant systemic chemotherapy within three weeks after the adjuvant HIPEC.

Laparoscopic adjuvant HIPEC

The patient is in French position on a bean bag under general anesthesia with prophylactic antibiotics. For a staged procedure, open introduction of a 10-12 mm trocar in the left upper quadrant is performed and a CO2 pneumoperitoneum is induced. Additional trocars of 10-12 mm are placed under direction vision in order to enable complete dissection of adhesions. In case of simultaneous laparoscopic HIPEC, minimally invasive access has already been obtained for the purpose of resection of the primary tumour without the need for adhesiolysis. The abdominal cavity is thoroughly inspected, including the Douglas pouch, the subdiaphragmatic spaces, the paracolonic gutters, and the entire small bowel. One multiperforated inflow catheter is placed through a 10-12 mm port in Douglas pouch. One multiperforated outflow catheter is placed in the right upper quadrant and positioned with the tip in the right subdiaphragmatic space. The patient's body temperature will be monitored in the oesophagus. All trocars are tightly fixed to the skin to avoid fluid leakage during the

procedure. Additionally, trocars are kept in an upright position with sutures connected to the trocar, which run over an Omnitract system and attached to a clamp as counter weight. Perfusion by an autoregulated pump system will be started with a minimum of 2l isotonic dialysis fluid at a flow rate of 1-2l/min and an inflow temperature of 42-43˚C. Before the beginning of HIPEC, fluorouracil 400 mg/m2 and leucovorin 20 mg/m2 will be administered intravenously to potentiate oxaliplatin activity. After attaining at least 42 degrees inflow temperature, Oxaliplatin (460 mg/m2) will be added to the circuit in a single dose. The operating table will be rotated and tilted every 5 minutes, and the abdomen will be agitated throughout the infusion to allow homogeneous exposure of the peritoneal surfaces to the heated chemotherapy. After a total perfusion time of 30 minutes, the peritoneal fluid is totally suctioned and the abdomen is examined for evidence of tissue injury or bleeding. A suction drain will be left in Douglas pouch for 24 hours. The other port sites are closed in a standard fashion. Postoperative care after simultaneous HIPEC will be according to the primary colonic resection following an enhanced recovery programme. After staged laparoscopic HIPEC, patients are fully mobilized at day 1 with normal diet and will intentionally be discharged at day 1-3 if the institutional discharge criteria are fulfilled. Hematologic parameters will be determined at day 14, followed by start of systemic chemotherapy.

Open adjuvant HIPEC

Open adjuvant HIPEC can be performed simultaneously in patients undergoing primary open resection, and staged open adjuvant HIPEC can be performed by re-laparotomy in patients who underwent primary open CRC resection. The decision to perform staged open or laparoscopic HIPEC in case of prior open resection will be left to the discretion of the surgeon. Besides the access to the peritoneal cavity, the procedure is similar to the laparoscopic approach as described above. Preferably, a closed perfusion is performed rather than a Colosseum technique to have similar pharmacokinetics as a laparoscopic approach. After positioning of the in- and outflow catheters, the abdomen will then be closed and subsequently perfusion will be started. Postoperative care is similar to the laparoscopic

approach with an anticipated day of discharge between day 2 to 5 if discharge criteria are fulfilled. Hematologic parameters will be determined at day 14, followed by start of systemic chemotherapy.

Follow-up after adjuvant HIPEC

Follow-up will be performed routinely according to the national guideline during the first 18 months. Patients who already developed recurrent disease during this time interval will be treated accordingly. In patients who have no clinical signs of recurrent disease at 18 months on CT scan of the thorax and abdomen in combination with non-elevated CEA levels, diagnostic laparoscopy will be performed. Patients with a negative laparoscopy will continue routine follow-up for at least 5 years, while patients with proven peritoneal recurrence found during laparoscopy will subsequently be treated according to the national guideline.
Patients who develop peritoneal recurrence after oxaliplatin based adjuvant HIPEC and fulfil the criteria of CR/HIPEC, mitomycin will be used as chemotherapeutic agent for re-HIPEC.
The first line treatment for patients with pathologically proven PC from colon carcinoma who do not qualify for CR/HIPEC is systemic therapy. The application of systemic therapy depends on the comorbidity and the clinical condition of the patient. Palliative relief of symptoms related to ascites or obstruction can most often be achieved by (minimally invasive) interventions such as percutaneous drainage, endoscopic stent placement or creation of a diversion ostomy (www.pallialine.nl).

7.3 Escape medication

Best supportive care for treatment-related symptoms will be offered as needed to all patients in this study.

8. METHODS

8.1 Main study parameter/endpoint

The primary endpoint of the study is peritoneal recurrence-free survival at 18 months determined by CT and if negative by laparoscopy. Although 3-year disease free survival (3-yr-DFS) using CT imaging is a commonly used endpoint in adjuvant setting, laparoscopy is more appropriate in this trial because of the restricted sensitivity of imaging modalities to detect PC at an early stage. Also, second look surgery is increasingly applied in patients at high risk of developing PC in- and out-side trial setting. Furthermore, evaluation at 18 months provides us with early data on the effectiveness of adjuvant HIPEC, as required by the Dutch government to decide on the coverage of adjuvant HIPEC by health insurance companies. It is likely that a significant reduction in peritoneal recurrence rate at 18 month will eventually translate into an overall survival benefit given the worse prognosis associated with peritoneal dissemination.

8.2 Secondary study parameters/endpoint

Secondary endpoints of the COLOPEC trial are:

- Treatment related toxicity of adjuvant HIPEC, including 30-day complication rate, re-intervention rate, and re-admission rate.
- Hospital stay for simultaneous and staged HIPEC, either open or laparoscopic
- Incidence of PC
- Sensitivity of imaging to detect PC during follow-up, using laparoscopy as a golden standard
- Inter- and intravariability amongst radiologist detecting PC using CT-imaging.
- Differences in patterns of dissemination (peritoneal plus or minus distant metastases)
- Disease-free survival
- Overall survival
- Quality of life

- Costs
- Costs per year free of PC
- Costs per quality adjusted life year

8.3 Other study parameters

A side study of the COLOPEC trial is:

Molecular prognostic parameters; Tissue of primary tumours (and their metachronous peritoneal metastasis) will be collected. RNA and protein levels of different biomarkers will be evaluated by microarray/ real time PCR, western blot and immunohistochemistry in order to identify prognostic molecular parameters to better select colon cancer patients who have a 'high risk' of developing peritoneal metastases in the future, providing evidence-based selection criteria for those who might benefit from adjuvant HIPEC.

8.4 Randomization and treatment allocation

Suitable patients will be approached for entry into the study at the surgical outpatient clinics or during hospital admittance. The rationale for the study is explained to the patient. A written patient information sheet is provided and patients will be given the opportunity to ask questions. After a sufficient reflection period, the willing patients are asked to sign the consent form. Once patient eligibility is confirmed, the patient may be consented for participation. Written informed consent is taken by surgeons, surgical registrars or trained research nurses prior to the primary resection. When consent has been obtained, the original form is kept in the study file and a copy is given to the patient. Baseline data as well as baseline questionnaires are collected.

Randomisation will take place after written informed consent has been obtained. Due to logistic issues, randomization can also take place in case patients orally confirm that they have signed or will sign the consent form. Patients will be randomised between standard adjuvant systemic chemotherapy (control arm) and adjuvant HIPEC followed by standard adjuvant systemic chemotherapy (intervention arm) in a 1:1 ratio. Randomisation will be performed by a member of the study team at the site pre-operatively, during the primary resection or thereafter. Randomisation will be performed by a central automated randomisation using the trial website, with stratification for tumour characteristic (T4 or perforation), surgical approach (laparoscopy or open) and age (<65 years of ≥ 65 years). The allocated treatment will be confirmed by e-mail within one working day. The allocation of treatment is not blinded to the patient or outcome assessor. Randomized patients will be assigned a sequential subject number. A log of the assigned subject numbers will be maintained by each site.

8.5 Study procedures

Standard care and the intervention of the experimental arm are described in paragraph 3. During the operative procedure, information about the surgical procedure will be collected. Postoperatively, adverse events and reintervention will be registered. In addition, information regarding the duration of pre- and postoperative hospitalization and inpatient resource utilization will be collected. During the entire postoperative period, concomitant medications, adverse events, procedures and adjuvant therapies will be reviewed and documented.
Blood testing for hematologic toxicity of adjuvant HIPEC will be performed at day 14. During routine outpatient clinic visits for oncological follow-up at 3, 6, 12, 18, 24, 36, 48 and 60 months, disease recurrence will be checked. A working window of 15 working days is allowed for all follow-up moments. In addition, at 18 months postoperatively, a diagnostic laparoscopy is performed to check for PC in both arms of the study if there are no signs of peritoneal recurrence by routine follow-up examinations including abdominal CT. This

diagnostic laparoscopy is currently no standard treatment according to the national guideline, although second look surgery is increasingly applied in patients at high risk of developing PC in- and out-side trial setting. During the 18 months diagnostic laparoscopy, a pneumoperitoneum is installed with insertion of additional 5-12 mm trocars as appropriate for adhesiolysis and careful inspection of all abdominal regions, including the local resection site. When PC is encountered, appropriate treatment is given in accordance with patient preferences and current treatment protocols (www.oncoline.nl) (i.e . systemic treatment, CR/ HIPEC). When applicable, cytoreduction with HIPEC can be performed in both treatment groups (adjuvant HIPEC/ adjuvant chemotherapy). Generic and cancer-specific quality of life assessments will be done with EQ-5D-5L and EORTC QLQ-C30 and CR-29 questionnaires respectively. For the purpose of economic evaluation, the iMTA Medical Consumption Questionnaire and iMTA Productivity Cost Questionnaire, adapted to the current study setting and target population, will be used at quarterly intervals during follow-up. The questionnaires will be sent to the patients' home addresses, accompanied by a return envelope provided with postage stamps and the address of the hospital.

All medical or surgical interventions and or re-operations or any procedure to treat an adverse event will be collected. Major violations of the protocol will be recorded.

For procedures and data sources related to costs, please see under 'Economic evaluation' in the Analyses section below. The data that will be collected are displayed in appendix 1.

8.6 Withdrawal of individual subjects

Subjects can leave the study at any time and for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study if he/she fails to comply with the study requirements or if the investigator feels it is in the best interest of the subject to discontinue participation. Reason for withdrawal or early termination will be documented and no further study assessments will be performed after the subject has withdrawn.

8.7 Follow-up of subjects withdrawn from treatment

Patients whom have withdrawn from the study but are still willing in participating in the follow-up will be followed according to the specifications of the patient.

An excessive rate of withdrawals can render the study uninterpretable. If more than 10% of patients withdraw from the study after 20% of patients have been included, the study will be terminated for being unfeasible. Based on reasons of withdrawal the study protocol will be amended if necessary.

8.8 Termination of the study

The entire clinical investigation will be terminated if a serious treatment-related adverse event occurs, making it impossible to recruit new patients or to continue the treatment of patients already recruited for medical or ethical reasons. The clinical investigation in an individual patient will be terminated in case of

1. insufficient compliance
2. a patients request
3. investigators request because of the onset of life-threatening adverse event.
4. changes in health status incompatible with continued participation in the clinical investigation, as judged by the clinical investigator.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the HIPEC procedure. All adverse events regardless of degree or causality with a severity degree of ≥ 2 (NCI-CTCAE) reported spontaneously by the subject or observed by the investigator or his staff, from the start of the study until one month after the last day of adjuvant systemic chemotherapy will be recorded. Incomplete data on severity and causality will not be retrospectively obtained. Because adjuvant chemotherapy is standard of care therefor not relevant to analysis of study outcome.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or affect that at any dose:

-results in death;

-is life threatening (at the time of the event);

-requires hospitalisation or prolongation of existing inpatients' hospitalisation;

-results in persistent or significant disability or incapacity;

- any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The clinical course of each event should be followed until resolution, stabilisation or until it has been determined that study treatment or participation is not the cause. SAEs, which are still ongoing at the end of the study period, must be followed up to determine the final outcome.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

SAEs that are clearly not related to trial participation will not be reported immediately but a list will be provided every six months.

A predefined list of SAE's will be reported every six months instead of individually using the CCMO-module 'toetsingOnline'. SAE's that will be listed and reported every six months are the following:

- SAE's related to postoperative complications
- SAE's related to the standard adjuvant chemotherapy treatment
- SAE's that are classified by the steering group as 'not related to the trial'

- SAE's related to diagnostic laparoscopy at 18 months

SAE's will only be recorded and reported if occurring in the following study period: from the start of the study until one month after the 18 months diagnostic laparoscopy or, in case a subject does not undergo the 18 months diagnostic laparoscopy, until one month after last day of adjuvant systemic chemotherapy.

Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2 'serious adverse events');
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the product under investigation
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

- Summary of Product Characteristics (SPC) for an authorised investigational product;

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials with the same investigational product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority. The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Information on all AEs / SAEs and SUSARs will be recorded in the CRF. Furthermore the investigators of the participating centers will report SAEs and SUSARs to the investigator via e-mail, fax or telephone (C.E.Klaver@amc.nl, G.D.Musters@amc.nl, and P.J.Tanis@amc.nl, Fax; 020-5666569, telephone; 020-5669111) upon occurrence.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.5 Data Safety Monitoring Board (DSMB)

A central DSMB consisting of a chairman (medical specialist), a medical and a surgical oncologist and a statistician who are not involved in the study will be installed to monitor quality and patient safety in this multicentre trial according to the standard operating procedures. All relevant data, including a full description of local treatments which have been performed in each individual patient, all serious adverse events and patient withdrawal, all specified per participating hospital will be made available to the DSMB by the study coordinators. The DSMB will review the safety data, report their findings to the principal investigator and advise on study continuation after 25, 50 and 100 patients are included. The principal investigator will submit these reports to the ethics committee along with all relevant data.

In order to monitor the potential risk of the delay in adjuvant systemic chemotherapy in the HIPEC group, the development of distant metastases will be closely monitored and continually reported to the DSMB. Additional information about nodal status at the time of the primary resection will be provided. Cessation of the study is warranted in case of a more than 10% higher proportion of distant metastases in the HIPEC group (as compared to the control group). This difference is only considered to be related to the delay in systemic chemotherapy if the proportion of stage III disease is similar in both groups. This stopping rule will be applied at the time of the second and third interim analysis (50 and 100 patients). As for the rest, the DSMB will counsel the steering committee on study continuation or cancellation based on their expertise.

A monitor will be installed and a monitoring program is being drafted in collaboration with the Clinical Research Unit of the Academic Medical Centre. The Monitor will check adherence to GCP guidelines; in particular the administration of serious adverse events and drug accountability registration. The monitor reports to the steering committee.

The practical implementation of the study will be thoroughly examined by means of interviews, evaluation of source documents and assessment of the Trial Master File and the Investigator File. The administration of essential documents will be evaluated, assessment of patient information, verification of all trial subjects' informed consent forms, studying whether the medical history of the trial subjects is in accordance with the in- and exclusion criteria, verification of the exclusion criteria related to the trial subjects' safety will be evaluated for a random 25% of trial subjects. Also source data, the reporting of SAEs and SUSARs, the administration of the accountability of the investigational medical products and studying whether and how the trial related procedures are described will be verified for 25% of subjects at random.

10. ANALYSES

This section contains the statistical analysis of the primary and secondary clinical outcome parameters (subsections 10.1 and 10.2).
In addition, the planned economic evaluation alongside the clinical trial is described in subsection 10.3. In absence of a suitable study protocol format to this end the related data sources and procedures of the economic evaluation are also described in **this** section of the protocol to prevent having these pieces of information scattered as loose ends over the sections mainly describing the clinical study.

10.1 Primary clinical study parameter(s)

The primary endpoint, peritoneal recurrence-free survival at 18 months, will be compared between the two study groups, using Kaplan Meier survival analysis with log rank test and a significance level of 0.05. Statistical analyses will be performed using SPSS software for Windows version 22.

10.2 Secondary clinical study parameter(s)

Treatment effects will be expressed as a relative risk with 95% confidence interval. Any binary secondary outcome measures (e.g. re-operation rate, death, etc) will be analysed by using a Fisher's exact or Chi-square test with a two-sided significance level of 0.05 on an intention to treat basis. Continuous variables will be analysed by independent sample t-test. Quality of life data (e.g. EORTC-QLQ-C30 and CR-29) will be graphically represented across all time points and analysed using a repeated measures analysis of variance. All analyses will be intention to treat, whereby patients will be analysed according to the treatment group to which they were randomised regardless of whether they complied with this treatment. A p-value of <0.05 will be considered statistically significant. Subgroup analyses will employ a test of interaction to explore whether there is evidence that the treatment effects differ across subgroups. As with all subgroups analyses, these will be interpreted with caution, and will be considered hypothesis generating.

10.3 Economic evaluation

General considerations

The economic evaluation of adjuvant HIPEC followed by systemic chemotherapy against adjuvant systemic chemotherapy alone will be performed from the societal perspective as a cost-effectiveness as well as cost-utility analysis. The primary outcomes will be the costs per year free of PC and the costs per quality adjusted life year (QALY) respectively. Incremental cost-effectiveness and cost-utility ratios will be calculated for these outcomes, along with

95% confidence intervals based on non-parametric bootstrapping to account for sampling variation. Explorative subgroup analyses will be done for patients presenting with or without perforation and for patients with early (simultaneous / <10 days postoperatively) or delayed (5-8 weeks postoperatively) HIPEC. Sensitivity analyses will be performed for the unit costs of adjuvant HIPEC and for alternative health valuation algorithms (see below). Results will be displayed graphically with cost-effectiveness planes and cost-effectiveness acceptability curves for willingness-to-pay values up to €100,000.

Initially, the time horizon will be 18 months with discounting (against generally accepted discount rates) of health effects and costs that occur during the second year. If a difference in peritoneal recurrence - clinically or subclinically at diagnostic laparoscopy – emerges, we will assess longer term (5 years) consequences in scenario-based disease modelling with progression parameters derived from literature and cohort studies. The type of modelling (simple decision tree, Markov state-transition model, or event history simulation) that best suits data availability, data quality, and decisional context at the time of analysis, will be selected and subsequently accounted for in a meeting with representatives of ZonMW, CvZ, NZa and patient organization ‘leven met kanker’ prior to its application.

Cost analysis

The analysis will include the direct and indirect medical and non-medical costs including the costs of HIPEC, systemic chemotherapy, inpatient stay, outpatient consultations (surgeon, gastroenterologist, oncologist, specialized nurse, dietician), out-of-hospital consultations (general practitioner, psychosocial care), home care, institutionalized stay (rehabilitation, nursing home, palliative care), informal care, out-of-pocket expenses, and production loss from sick leave (among members of the work force). Data on volumes will be gathered from case reports forms, hospital information systems and with short patient questionnaires at quarterly intervals during follow-up. The iMTA Medical Consumption Questionnaire and iMTA

Productivity Cost Questionnaire, adapted to the current study setting and target population, will be used.

Unit costing of resources will be in accordance with current national CvZ/EURiMTA-guidelines for costing in health care research. Unit costs of adjuvant HIPEC will be substantiated with activity based costing at the micro-level during application of the interventions in at least two participating centers. All costs will be expressed in euro with base year 2016, after price-indexing of unit costs from different calendar years.

Patient outcome analysis

Dissemination of cancer to the peritoneum may debilitate a person's quality of life on top of recovering from surgery for the primary cancer. In addition to the already mentioned cancer specific EORTC-QLQ-C30 and CR-29 questionnaires, patients will be asked to complete the short EQ-5D-5L generic health status questionnaire each quarter in order to gather health status profiles over time that can be transposed into QALYs using health utility scoring algorithms available from the literature (Dutch: Lamers et al; international: Dolan et al). These algorithms reflect preferences in the general population, which were elicited with time trade-off elicitation techniques.

Budget impact analysis

The economic evaluation will be expanded with a value of information analysis to assess the remaining uncertainty in decision making and the potential for further research.

Also, a budget impact analysis (BIA) will be performed linking data on disease incidence/prevalence, on inclusion criteria, and on health care expenses per case. Both, governmental and health care insurer perspectives will be addressed. The time horizon of this BIA will be in accordance with the time horizon of the health economic model (see

above): 5 years. This time horizon is a standard in clinical cancer research and it increases the likelihood of being able to derive model parameter estimates from the literature and cohort studies for the period beyond the initial observation period of 18 months in the current study.

Unit costing for the BIA will reflect the per case expenses that will actually be transferred from insurers to suppliers of health care, and may deviate from the 'real' unit costs used in the cost-effectiveness and cost-utility analyses.

The budget impact will be assessed under four different implementation scenarios: full (100%) or partial (50%) combined with immediate or gradual (linearly over four years) implementation of adjuvant HIPEC.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza,October 2013) *and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts*

11.2 Recruitment and consent

The information offered to the patient or representative contains:

-a statement that the trial involves research

-a full explanation of the procedure to be followed

-a full explanation of the nature, expected duration, and purpose of the study

-a description of any reasonable foreseeable risks or discomfort to the patient

-a description of any benefits which may reasonably be expected

-a statement that patient data will be handled with care and confidentiality

-a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care

11.3 Objection by minors or incapacitated subjects

Minors and legally incompetent adults are excluded from the trial.

11.4 Compensation for injury

The AMC Medical Research BV has insurance, which is in accordance with the legal requirements in The Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of June 23, 2003). This insurance provides cover for damage to research subjects through injury or death caused by the trial:

- € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the research;
- € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the research;
- € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the AMC as 'Sponsor (verrichter)' in the meaning of said Act in each year of insurance coverage. The insurance applies to the damage that becomes apparent during the study or within 4 years after.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

For UK participants NHS indemnity will apply.

11.5 Incentives

Enrolled patients will not receive any special incentives, compensation or treatment through participation in this trial.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Every randomised patient will be assigned a three digit study number. Communication occurs only with this number. The full name and birth date of the patient will only be recorded on the informed consent form.

A study coordinator coordinates the study, monitors patient inclusion and protocol steps, data collection, data entry, preparation and performs analyses and will report the data. Continuous data monitoring, and data collection on a CRF will guarantee complete and real-time prospective recording of data. Data will be collected and stored at the AMC in a separate, closed room.

12.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

12.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.5 Public disclosure and publication policy

Patients are entitled to public disclosure of the results of the trial on the basis of their participation in it. The results of research will be submitted for publication to peer-reviewed scientific journals. Agreements with respect to participation in publication will be made before the start of the trial. Besides the group of principle investigators and research fellows authorship is granted to the local investigator of each centre when at least five patients are included in the trial and when substantial contribution to the trial (e.g. full completion of CRF or intellectual input) is made. When a participating centre includes more than 17 patients (>10%), a second author of the participating centre will be added to the author list. Every other people who made substantial contribution to the trial will be added to the collaborator list.

References

[1] Brodsky JT, Cohen AM. Peritoneal seeding following potentially curative resection of colonic carcinoma: implications for adjuvant therapy. *Dis Colon Rectum* 1991; **34**(8):723-7.

[2] Lemmens VE, Klaver YL, Verwaal VJ *et al.* Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; **128**(11):2717-25.

[3] Segelman J, Granath F, Holm T *et al.* Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2012; **99**(5):699-705.

[4] Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006; **243**(2):212-22.

[5] de Bree E, Witkamp AJ, Zoetmulder FA. Intraperitoneal chemotherapy for colorectal cancer. *J Surg Oncol* 2002; **79**(1):46-61.

[6] Noura S, Ohue M, Seki Y *et al.* Long-term prognostic value of conventional peritoneal lavage cytology in patients undergoing curative colorectal cancer resection. *Dis Colon Rectum* 2009; **52**(7):1312-20.

[7] Rekhraj S, Aziz O, Prabhudesai S *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):60-8.

[8] Yang SH, Lin JK, Lai CR *et al.* Risk factors for peritoneal dissemination of colorectal cancer. *J Surg Oncol* 2004; **87**(4):167-73.

[9] Bosch B, Guller U, Schnider A *et al.* Perioperative detection of disseminated tumour cells is an independent prognostic factor in patients with colorectal cancer. *Br J Surg* 2003; **90**(7):882-8.

[10] Elias D, Goere D, Di PD *et al.* Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg* 2008; **247**(3):445-50.

[11] Gozalan U, Yasti AC, Yuksek YN, Reis E, Kama NA. Peritoneal cytology in colorectal cancer: incidence and prognostic value. *Am J Surg* 2007; **193**(6):672-5.

[12] Hase K, Ueno H, Kuranaga N *et al.* Intraperitoneal exfoliated cancer cells in patients with colorectal cancer. *Dis Colon Rectum* 1998; **41**(9):1134-40.

[13] Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; **89**(12):1545-50.

[14] Lee IK, Kim dH, Gorden DL *et al.* Prognostic value of CEA and CA 19-9 tumour markers combined with cytology from peritoneal fluid in colorectal cancer. *Ann Surg Oncol* 2009; **16**(4):861-70.

[15] Yamamoto S, Akasu T, Fujita S, Moriya Y. Long-term prognostic value of conventional peritoneal cytology after curative resection for colorectal carcinoma. *Jpn J Clin Oncol* 2003; **33**(1):33-7.

[16] Verwaal VJ, van RS, de BE *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):3737-43.

[17] Pelz JO, Chua TC, Esquivel J *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.

[18] Franko J, Shi Q, Goldman CD *et al.* Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol* 2012; **30**(3):263-7.

[19] Klaver YL, Lemmens VE, Nienhuijs SW, Luyer MD, de Hingh IH. Peritoneal carcinomatosis of colorectal origin: Incidence, prognosis and treatment options. *World J Gastroenterol* 2012; **18**(39):5489-94.

[20] Klaver YL, Lemmens VE, Creemers GJ *et al.* 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.

[21] Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999; **6**(8):727-31.

[22] Shen P, Levine EA, Hall J *et al.* Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. *Arch Surg* 2003; **138**(1):26-33.

[23] Schneebaum S, Arnold MW, Staubus A *et al.* Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. *Ann Surg Oncol* 1996; **3**(1):44-50.

[24] Cavaliere F, Perri P, Di FF *et al.* Treatment of peritoneal carcinomatosis with intent to cure. *J Surg Oncol* 2000; **74**(1):41-4.

[25] Beaujard AC, Glehen O, Caillot JL *et al.* Intraperitoneal chemohyperthermia with mitomycin C for digestive tract cancer patients with peritoneal carcinomatosis. *Cancer* 2000; **88**(11):2512-9.

[26] Fujimura T, Yonemura Y, Fujita H *et al.* Chemohyperthermic peritoneal perfusion for peritoneal dissemination in various intra-abdominal malignancies. *Int Surg* 1999; **84**(1):60-6.

[27] Witkamp AJ, de BE, Kaag MM *et al.* Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei. *Br J Surg* 2001; **88**(3):458-63.

[28] Elias D, Blot F, El OA *et al.* Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* 2001; **92**(1):71-6.

[29] Elias D, Delperro JR, Sideris L *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):518-21.

[30] Loggie BW, Fleming RA, McQuellon RP, Russell GB, Geisinger KR. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. *Am Surg* 2000; **66**(6):561-8.

[31] Piso P, Bektas H, Werner U *et al.* Improved prognosis following peritonectomy procedures and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from appendiceal carcinoma. *Eur J Surg Oncol* 2001; **27**(3):286-90.

[32] Rey Y, Porcheron J, Talabard JN, Szafnicki K, Balique JG. [Peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemohyperthermia]. *Ann Chir* 2000; **125**(7):631-42.

[33] Elias D, Lefevre JH, Chevalier J *et al.* Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; **27**(5):681-5.

[34] Verwaal VJ, Bruin S, Boot H, van SG, van TH. 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):2426-32.

[35] 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):364-7.

[36] Sadeghi B, Arvieux C, Glehen O *et al.* Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; **88**(2):358-63.

[37] 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):2152-65.

[38] Elias D, Gilly F, Boutitie F *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):63-8.

[39] Glockzin G, Schlitt HJ, Piso P. Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Surg Oncol* 2009; **7:5.**:5.

[40] Graf W, Westlin JE, Pahlman L, Glimelius B. Adjuvant intraperitoneal 5-fluorouracil and intravenous leucovorin after colorectal cancer surgery: a randomized phase II placebo-controlled study. *Int J Colorectal Dis* 1994; **9**(1):35-9.

[41] Vaillant JC, Nordlinger B, Deuffic S *et al.* Adjuvant intraperitoneal 5-fluorouracil in high-risk colon cancer: A multicenter phase III trial. *Ann Surg* 2000; **231**(4):449-56.

[42] Verwaal VJ, Kusamura S, Baratti D, Deraco M. The eligibility for local-regional treatment of peritoneal surface malignancy. *J Surg Oncol* 2008; **98**(4):220-3.

[43] Yonemura Y, Ninomiya I, Kaji M *et al.* Prophylaxis with intraoperative chemohyperthermia against peritoneal recurrence of serosal invasion-positive gastric cancer. *World J Surg* 1995; **19**(3):450-4.

[44] Kelsen DP, Saltz L, Cohen AM *et al.* A phase I trial of immediate postoperative intraperitoneal floxuridine and leucovorin plus systemic 5-fluorouracil and levamisole after resection of high risk colon cancer. *Cancer* 1994; **74**(8):2224-33.

[45] Palermo JA, Richards F, Lohman KK *et al.* Phase II trial of adjuvant radiation and intraperitoneal 5-fluorouracil for locally advanced colon cancer: results with 10-year follow-up. *Int J Radiat Oncol Biol Phys* 2000; **47**(3):725-33.

[46] Scheithauer W, Kornek GV, Marczell A *et al.* Combined intravenous and intraperitoneal chemotherapy with fluorouracil + leucovorin vs fluorouracil + levamisole for adjuvant therapy of resected colon carcinoma. *Br J Cancer* 1998; **77**(8):1349-54.

[47] Sugarbaker PH, Gianola FJ, Speyer JL *et al.* Prospective randomized trial of intravenous v intraperitoneal 5-FU in patients with advanced primary colon or rectal cancer. *Semin Oncol* 1985; **12**(3 Suppl 4):101-11.

[48] Sloothaak DA, Mirck B, Punt CJ *et al.* Intraperitoneal chemotherapy as adjuvant treatment to prevent peritoneal carcinomatosis of colorectal cancer origin: a systematic review. *Br J Cancer* 2014.

[49] Sloothaak DA, Gardenbroek TJ, Crezee J *et al.* Feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in a short stay setting in patients with colorectal cancer at high risk of peritoneal carcinomatosis. *Eur J Surg Oncol* 2014.

[50] Kuijpers AM, Mirck B, Aalbers AG *et al.* Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. *Ann Surg Oncol* 2013; **20**(13):4224-30.

[51] Chouillard E, Ata T, De JB *et al.* Staged laparoscopic adjuvant intraperitoneal chemohyperthermia after complete resection for locally advanced colorectal or gastric cancer: a preliminary experience. *Surg Endosc* 2009; **23**(2):363-9.

[52] Lygidakis NJ, Patil A, Giannoulis K, Fukuda T, Kumar R. Laparoscopic hyperthermic intraperitoneal chemotherapy as adjuvant modality following radical surgery for advanced rectal cancer a new look to an old problem. *Hepatogastroenterology* 2010; **57**(97):73-5.

[53] Sammartino P, Sibio S, Biacchi D *et al.* Prevention of Peritoneal Metastases from Colon Cancer in High-Risk Patients: Preliminary Results of Surgery plus Prophylactic HIPEC. *Gastroenterol Res Pract* 2012; **2012**:141585.

[54] Tentes AA, Spiliotis ID, Korakianitis OS, Vaxevanidou A, Kyziridis D. Adjuvant perioperative intraperitoneal chemotherapy in locally advanced colorectal carcinoma: preliminary results. *ISRN Surg* 2011; **2011**:529876.

[55] Knutsen A, Sielaff TD, Greeno E, Tuttle TM. Staged laparoscopic infusion of hyperthermic intraperitoneal chemotherapy after cytoreductive surgery. *J Gastrointest Surg* 2006; **10**(7):1038-43.

[56] Ferron G, Gesson-Paute A, Classe JM, Querleu D. Feasibility of laparoscopic peritonectomy followed by intra-peritoneal chemohyperthermia: an experimental study. *Gynecol Oncol* 2005; **99**(2):358-61.

[57] Gesson-Paute A, Ferron G, Thomas F *et al.* Pharmacokinetics of oxaliplatin during open versus laparoscopically assisted heated intraoperative intraperitoneal chemotherapy (HIPEC): an experimental study. *Ann Surg Oncol* 2008; **15**(1):339-44.

[58] Elias D, Raynard B, Bonnay M, Pocard M. Heated intra-operative intraperitoneal oxaliplatin alone and in combination with intraperitoneal irinotecan: Pharmacologic studies. *Eur J Surg Oncol* 2006; **32**(6):607-13.

[59] Glehen O, Osinsky D, Beaujard AC, Gilly FN. Natural history of peritoneal carcinomatosis from nongynecologic malignancies. *Surg Oncol Clin N Am* 2003; **12**(3):729-39, xiii.

[60] Glehen O, Gilly FN, Sugarbaker PH. New perspectives in the management of colorectal cancer: what about peritoneal carcinomatosis? *Scand J Surg* 2003; **92**(2):178-9.

[61] Hompes D, D'Hoore A, Wolthuis A *et al.* The use of Oxaliplatin or Mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. *J Surg Oncol* 2014; **109**(6):527-32.

[62] Elias D, Honore C, Dumont F *et al.* Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg* 2011; **254**(2):289-93.

[63] Ripley RT, Davis JL, Kemp CD *et al.* Prospective randomized trial evaluating mandatory second look surgery with HIPEC and CRS vs. standard of care in patients at high risk of developing colorectal peritoneal metastases. *Trials* 2010; **11:62.**:62.

[64] Sammartino P, Bolognese A, Chirletti P *et al.* [Video-assisted closed-thorax esophagectomy in cancer. A technical proposal]. *Minerva Chir* 1997; **52**(6):697-704.

[65] Chirletti P, Bolognese A, Cardi M, Sammartino P, Stipa V. [Decrease of the levels of PgE2 and alkaline gastritis after gastrectomy by the Billroth II technic (gastrojejunal anastomosis)]. *Ann Chir* 1988; **42**(5):323-6.

[66] Seymour MT, Trigonis I, Finan PJ *et al.* A feasibility, pharmacokinetic and frequency-escalation trial of intraperitoneal chemotherapy in high risk gastrointestinal tract cancer. *Eur J Surg Oncol* 2008; **34**(4):403-9.

[67] Biagi JJ, Raphael MJ, Mackillop WJ *et al.* Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA* 2011; **305**(22):2335-42.

[68] Sloothaak DA, Gardenbroek TJ, Crezee J *et al.* Feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in a short stay setting in patients with colorectal cancer at high risk of peritoneal carcinomatosis. *Eur J Surg Oncol* 2014.

[69] Cheynel N, Cortet M, Lepage C *et al.* Incidence, patterns of failure, and prognosis of perforated colorectal cancers in a well-defined population. *Dis Colon Rectum* 2009; **52**(3):406-11.

[70] Lefevre JH, Elias DM. Cytoreductive surgery plus intraperitoneal chemohyperthermia in patients with colorectal cancer at high risk for local-regional recurrence. *Cancer J* 2009; **15**(3):200-3.

[71] Hompes D, Tiek J, Wolthuis A *et al.* HIPEC in T4a colon cancer: a defendable treatment to improve oncologic outcome? *Ann Oncol* 2012; **23**(12):3123-9.

[72] Barillari P, Muttillo IA, Cioe I *et al.* [Localized pleural mesotheliomas. Clinicopathological considerations on a case report]. *Minerva Chir* 1992; **47**(20):1665-70.

[73] Barillari P, Ricci M, Broglia S *et al.* [Effectiveness of quarterly assessment of CEA, TPA and GICA serum levels in gastric and colorectal carcinomas: Prospective study of 174 patients undergoing radical surgery]. *Minerva Chir* 1994; **49**(10):953-61.

Table 1 characteristics of randomised and non-randomised comparative studies.

author, year, design	inclusion criteria	n	interval after resection	Drug, dosage, administration route	Duration and frequency	methods of ip administration
Sugerbaker, 1985, RCT	colorectal cancer N+, T4, obstruction, perforation, age <30 years	36	2 months	ip 5FU 1040mg;	daily for 5 days/ every month; 12 cycles	IPC
		30	2 months	iv 5FU 12mg/kg	daily for 5 days/every month; 12 cycles	
Graf, 1993 RCT	colorectal cancer electively operated with curative intent, exclusion of stage I	50	1 day after surgery	ip 5FU 500mg/m2/day & iv LV 60mg/m2/day	4 hours / daily for 6 consecutive days 1 cycle	IPC
		50	1 day after surgery	ip placebo	4 hours / daily for 6 consecutive days 1 cycle	IPC
Scheithauer, 1998, RCT	colon cancer T3/4 and/or N+	117	1-5 weeks	ip LV 200mg/m2 + ip 5FU 350mg/m2	day 1 and 3 of each iv cycle	IPC
				iv LV 200mg/m2& iv 5FU 350mg/m2	daily for 4 consecutive days/ each 4 weeks, total 6 cycles	
		119	1-5 weeks	po LE 50mg/m2& iv 5FU 450mg/m2	3 times daily for 3 days/ every 2 weeks; daily for 5days/ 2nd course after 4 weeks, weekly thereafter total 6 cycles	
Vaillant, 1999, RCT	colon cancer T3/4 and/or N+	133	4-14 days	ip 5FU 600mg/m2 iv 1gram 5FU	3 hours / daily for 6 consecutive days; 1 cycle Once during surgery	IPC
		134		no chemotherapy		
Noura , 2011, CS	colorectal cancer positive peritoneal lavage	31*	simultaneous with primary tumour resection	ip MMC 20mg T=37C°; t=1hour	Once during surgery	Closed IPEC procedure
				iv 5FU/LV or po 5FU derivates (n=23)	Schedule not specified	
		22		iv 5FU/LV or po 5FU derivates (n=19)	Schedule not specified	
Tentes, 2011, CS	colorectal cancer T3/4	40	simultaneous with primary tumour resection	ip MMC 15mg/m2 T= 42.5-43C° t=90min or Ox 130mg/m2 T= 42.5-43C° t=60min	Once during surgery	Open HIPEC procedure
				iv 5FU/LV in Stage III/IV	6 cycles	
		67	1 day	ip 5FU 600mg/m2 iv 5FU/LV in Stage III/IV)	23 hours / daily for 5 consecutive days; 1 cycle 6 cycles	IPC
Sammartino, 2012, matched CS	colon cancer T3/4NxM0, perforation (regardless of tumour stage), signet cell or mucinous tumours	25	simultaneous with primary tumour resection (with appendectomy, omentectomy, resection of the round hepatic ligament and bilateral ovariectomy)	ip Ox 460mg/m2 T=43C° t=30min iv 5FU 400mg/m2 + LV 20mg/m2	Once during surgery	Open HIPEC procedure
				iv 5FU/Ox (n=13)	not specified	
		50		iv 5FU/Ox (n=23)	not specified	

ip = intra peritoneal, RCT= randomised controlled trial, CS = non randomised comparitive study, T=temperature of intraperitoneal infusion, t= duration of infusion, 5FU =fluorouracil, LV =leucovorin, LE=levamisole, MMC =mitomycine-C, Ox =oxaliplatin, ip =intraperitoneal, iv =intravenous, po =oral *=selection based on general patient status and invasiveness of surgery, (H)IPEC=(hyperthermic) intraperitoneal chemotherapy, IPC = Intra peritoneal catheter, simultaneously placed with primary tumour resection or via a percutaneous approach, with or without a subcutaneous reservoir.

Table 2; endpoints in comparative studies.

author	group	overall / disease free survival	peritoneal recurrence rate	complications	Treatment related mortality	tolerance
Sugerbaker 1985		median overall survival (months)		serious complications (n)		dose limiting events
	ip 5FU	46.3	20%	15	nr	mucositis 25%, leucocyte suppression 60%, abdominal discomfort abdominal pain
	iv 5FU	47.5	91%	16	nr	mucositis 40%, leucocyte suppression 20%, abdominal discomfort abdominal pain
	p value	*ns*[A]	*0.003*[B]	*nr*	*nr*	*nr*
Graf 1993				postoperative complications (n)	in hospital or within 30days(n)	tolerance
	ip 5FU + iv LV	nr	nr	11	0	nausea 5%, diarrhoea 2%, allergic reaction 2%, infusion connected pain
	ip placebo	nr	nr	15	0	nausea 15%, diarrhoea 7% allergic reaction 0%, infusion connected pain
	p value	nr	nr		nr	nr
Scheithauer 1998		actuarial 4-year survival rate	4-year	life threatening side effects (n)	treatment related death (n)	severe treatment associated side effects
	ip + iv 5FU/LV	83%	8%	0	0	13%
	iv 5FU + po LE	65%	21%	0	0	3%
	p value	*nr*	*0.005*[C]	*nr*	*nr*	*0.01*
Vaillant 1999		actuarial 5-year survival rate	4-year	Postoperative complications (n)	Postoperative mortality (n)	
	ip 5FU	74%	8%	26	2	fair 14.9% poor 3.3%
	no CT	68%	10%	16	0	
	p value	*0.30*[A]	*nr*	*nr*	*nr*	*nr*
Noura 2011		actuarial 5-year cancer specific survival rate	actuarial 5-year	IPEC related postoperative complications (n)	Postoperative mortality	Grade 3 complications related to ip lavage
	ip MMC + (iv 5FU/Ox)	54.3%	12%	Grade III/IV=1	0	1
	(iv 5FU/Ox)	9.5%	59.9%	Grade III/IV=0	0	0
	p value	*0.0001*[A]	*0.0003*[A]	*Nr*	*nr*	*nr*
Tentes 2011		actuarial 3-year survival rate	nr	Overall complications (n)	Hospital mortality(n)	tolerance
	HIPEC MMC or Ox (iv 5FU/LV)	100%	nr	16	1	nr
	ip 5FU (iv 5FU/LV)	69%	nr	22	9	nr
	p value	*0.011*[A]	nr	*0.05*	*0.009*	nr
Sammartino 2012		median disease free survival (months)		Grade I-IV (n)		HIPEC toxicity Grade II
	HIPEC Ox (iv 5FU/Ox)	36.8	4%	Grade I/II =3 Grade III =0 Grade IV =1	nr	1
	(iv 5FU/Ox)	21.9	22%	Grade I/II =5	nr	0

			Grade III =1 Grade IV =3		
p value	*<0.01*[A]	*<0.05*[B]		*nr*	*nr*

nr = not reported, [A] =Log rank, [B] =Fisher exact, [C] =Chi square, 5FU =fluorouracil, LV =leucovorin, LE=levamisole, MMC =mitomycine-C, Ox =oxaliplatin, ip =intraperitoneal, iv =intravenous, po =oral

Table 3; characteristics of cohort studies

author, year	inclusion criteria	n	interval after resection	Drug, dosage, administration route	Duration / frequency	methods of ip administration
Kelsen , 1994	colon cancer N+; T4 with obstruction or perforation, or resected intra-abdominal M1	26	2-5 days after resection	ip floxuridine 500mg/m2 ip LV 120 mg/m2 po levamisol 50mg iv 5FU bolus 200-450 mg/m2 dose escalation iv 5FU 450mg/m2/week	Twice daily for 3 consecutive days/ every2 weeks 3 cycles 3 times a day for 3 days / every 2 weeks total 1 year During 3rd ip cycle, daily for 5 days Every week, total 1 year	IPC
Palermo 2000	colon cancer T3/4, N+	45	nr	ip 5FU 20mg/kg Radiotherapy 150cGy	Daily 60-90 minutes for 5 consecutive days/every 4 weeks 6 cycles daily for three weeks/ 2 cycles with 1 week interval	IPC
Seymour 2008	colon cancer T4	47*	Median 57 days (15-148)	ip 5FU 400 mg/m2 ip LV 20 mg/m2 iv 5FU/LV	Separate cohorts with frequencies of once per 4, 3, 2 or 1 week(s) total 24 weeks Once every week, max 24 weeks.	IPC
Chouillard 2009	colorectal cancer T4, pN2, perforation or obstruction (regardless of tumour stage); positive peritoneal lavage	16	5-8weeks	ip MMC 80mg/m2 : T=42-44C° & t=35-45min adjuvant iv treatment not mentioned	once	laparoscopic HIPEC procedure
Lygidakis 2010	rectal cancer N+, neurovascular involvement	87	22 days	ip 5FU, Ox, LV, Irinotecan T=43C°; t=60min iv 5FU, Ox, LV, Irinotecan	second lavage after 25 days and third lavage after 2 years. every month, 4 cycles	laparoscopic HIPEC procedure

ip = intra peritoneal, T=temperature of intraperitoneal infusion, t= duration of infusion, 5FU =fluorouracil, LV =leucovorin, MMC =mitomycine, Cis = cisplatinum, Ox =oxaliplatin, ip =intraperitoneal, iv =intravenous, po =oral; *=10/12 colorectal cancer histology in pharmacokinetic study and 37/44 colorectal cancer histology in frequency-escalation study; IPC = Intra peritoneal catheter

TABLE 4; endpoints in cohort studies

author	overall survival	peritoneal disease recurrence	complications	Treatment related mortality	tolerance
Kelsen 1994	nr	nr	No increase in postoperative morbidity 1 catheter removed of peritonitis	0%	ip: Gr 3+ myelosuppression 2/26 iv 5FU 300mg: Gr3+ myelosuppression 2/7, Gr3+ mucositis 4/7 iv 5FU 400mg: Gr3+ myelosuppression 2/3, Gr3+ mucositis 2/3
Palermo 2000	median follow-up 130 months (108-163) 5-year DFS 51% 5-year OS 56%	5/45 (n=4 relaparotomy because of small bowel obstruction)	Gr3 chemical peritonitis 7/45 patients, no bacterial peritonitis Gr3 nausea/vomiting 3/45 Gr4 nausea/vomiting 1/45 Gr3 haematologic toxicity 2/45 Small bowel obstruction 6/45	0%	Grade I toxicity =49% Grade II toxicity=19% Grade III toxicity =15% Grade IV toxicity =2%
Seymour 2008	nr	nr	failure of intraperitoneal access n=10: initial failure 7 (pain n=3; leakage n=2; infection n=1; bowel perforation n=1) secondary failure 3 (leakage n=1; blockage n=2) reason for stopping ip treatment: mostly abdominal pain	nr	tolerance per treatment frequency ip /4weeks nr ip/3weeks 87% ip/2weeks 77% ip/week 0%
Chouillard 2009	median follow-up 15.5 months 2/16 colorectal cancer patients died at end of FU. 3/14 alive with distant metastasis	peritoneal recurrence rate 0%	overall n=21 Major n=4 Minor n=11	0%	Major: bone marrow aplasia n=2 Minor: low platelet count n=11, leucopenia n=9, fatigue n=8, nausea n=7
Lygidakis 2010	1 year OS100%	2 year peritoneal recurrence rate 3%	0	0	no drug toxicity during hospital stay

nr = not reported, ip = intraperitoneal, iv = intranveneous, DFS = disease-free survival, OS = overall survival

Appendix 1

	Screening Visit / before surgery	Primary colon cancer resection	HIPEC Surgery (DOS)	14 days p.o.	3 -18 months p.o. (any visit during this time period)	18 months p.o.	18 -60 months p.o. (any visit during this time period)
Informed Consent	X						
Baseline case record form	X						
Pre-operative case record form	X						
Adverse Events		X	X	X	X	X	X
Intervention case record form		X	X			X	
Blood testing for hematologic toxicity				X			
Diagnostic laparoscopy						X	
Peritoneal carcinomatosis assessment					X	X	X
CRF corresponding with time interval from surgery				X	X	X	X
CEA and imaging according to local standard follow-up regimen (including one CT-scan thorax/abdomen at 18 months)				X	X	X	X
Quality of Life questionnaires (EORTC QLQ-C30, CR29**)**	X				X		X
iMTA Medical Consumption, iMTA Productivity Cost, EQ-5D-5L questionnaires	X				X	X	X