Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial

*Charlotte E L Klaver, Daniel D Wisselink, Cornelis J A Punt, Petur Snaebjornsson, Johannes Crezee, Arend G J Aalbers, Alexandra Brandt, Andre J A Bremers, Jacobus W A Burger, Hans F J Fabry, Floris Ferenschild, Sebastiaan Festen, Wilhelmina M U van Grevenstein, Patrick H J Hemmer, Ignace H J T de Hingh, Niels F M Kok, Gijsbert D Musters, Lotte Schoonderwoerd, Jurriaan B Tuynman, Anthony W H van de Ven, Henderik L van Westreenen, Marinus J Wiezer, David D E Zimmerman, Annette A van Zweeden, Marcel G W Dijkgraaf, Pieter J Tanis, on behalf of the COLOPEC collaborators group**

Summary

Background Nearly a quarter of patients with locally advanced (T4 stage) or perforated colon cancer are at risk of developing peritoneal metastases, often without curative treatment options. We aimed to determine the efficacy of adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with locally advanced colon cancer.

Methods This multicentre, open-label trial was done in nine hospitals that specialised in HIPEC in the Netherlands. Patients with clinical or pathological T4N0–2M0-stage tumours or perforated colon cancer were randomly assigned (1:1), with a web-based randomisation application, before resection of the primary tumour, to adjuvant HIPEC followed by routine adjuvant systemic chemotherapy (experimental group) or to adjuvant systemic chemotherapy alone (control group). Patients were stratified by tumour characteristic (T4 or perforation), age (<65 years or ≥65 years), and surgical approach of the primary tumour resection (laparoscopic or open). Key eligibility criteria included age between 18 and 75 years, adequate clinical condition for HIPEC, and intention to start adjuvant systemic chemotherapy. Patients with metastatic disease were ineligible. Adjuvant HIPEC consisted of fluorouracil (400 mg/m²) and leucovorin (20 mg/m²) delivered intravenously followed by intraperitoneal delivery of oxaliplatin (460 mg/m²) for 30 min at 42°C, delivered simultaneously or within 5–8 weeks after primary tumour resection. In all patients without evidence of recurrent disease at 18 months, a diagnostic laparoscopy was done. The primary endpoint was peritoneal metastasis free-survival at 18 months, measured in the intention-to-treat population, with the Kaplan-Meier method. Adverse events were assessed in all patients who received assigned treatment. This study is registered with ClinicalTrials.gov, number NCT02231086.

Findings Between April 1, 2015, and Feb 20, 2017, 204 patients were randomly assigned to treatment (102 in each group). In the HIPEC group, two patients withdrew consent after randomisation. In this group, 19 (19%) of 100 patients were diagnosed with peritoneal metastases: nine (47%) during surgical exploration preceding intentional adjuvant HIPEC, eight (42%) during routine follow-up, and two (11%) during diagnostic laparoscopy at 18-months. In the control group, 23 (23%) of 102 patients were diagnosed with peritoneal metastases, of whom seven (30%) were diagnosed by laparoscopy at 18-months and 16 during regular follow-up (therefore making them ineligible for diagnostic laparoscopy). In the intention-to-treat analysis (n=202), there was no difference in peritoneal-free survival at 18-months (80·9% [95% CI 73·3–88·5] for the experimental group *vs* 76·2% [68·0–84·4] for the control group, log-rank one-sided p=0·28). 12 (14%) of 87 patients who received adjuvant HIPEC developed postoperative complications and one (1%) encapsulating peritoneal sclerosis.

Interpretation In patients with T4 or perforated colon cancer, treatment with adjuvant HIPEC with oxaliplatin did not improve peritoneal metastasis-free survival at 18 months. Routine use of adjuvant HIPEC is not advocated on the basis of this trial.

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Introduction

Colorectal cancer is a highly prevalent disease worldwide, with an incidence of more than 1 million cases in 2018.[1] The peritoneum is a common site of dissemination, with approximately 10% of patients developing peritoneal metastases.[2] Important risk factors for metachronous peritoneal metastases are locally advanced disease (T4 stage) and tumour perforation, mucinous and signet ring cell histology, nodal stage, right-sided tumour location, and irradical resection (R1 or R2).[2–5] The true incidence might even be higher than reported because the clinical diagnosis of peritoneal metastases is complicated by the limited sensitivity of imaging methods.[6] Peritoneal metastases are often diagnosed at

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*Members listed in the appendix

Department of Surgery (C E L Klaver MD, D D Wisselink BSc, G D Musters PhD, P J Tanis PhD), **Department of Oncology** (Prof C J A Punt MD), **Department of Radiation Oncology** (J Crezee PhD), **and Department of Clinical Epidemiology, Biostatistics and Bioinformatics** (Prof M G W Dijkgraaf PhD), **Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; Department of Pathology** (P Snaebjornsson PhD), **and Department of Surgery** (A G J Aalbers PhD, N F M Kok PhD), **Antoni van Leeuwenhoek Hospital-Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Surgery, Erasmus Medical centre at Daniel den Hoed, Rotterdam, Netherlands** (A Brandt PhD); **Department of Surgery, Radboud University Medical Centre, Nijmegen, Netherlands** (A J A Bremers PhD, Prof I H J T de Hingh MD); **Department of Surgery, Catharina Hospital, Eindhoven, Netherlands** (J W A Burger PhD); **Department of Surgery, Bravis Hospital, Roosendaal, Netherlands** (H F J Fabry PhD); **Department of Surgery, Maasziekenhuis Pantein, Beugen, Netherlands** (F Ferenschild PhD); **Department of Surgery, Onze Lieve Vrouwen Gasthuis, Amsterdam, Netherlands** (S Festen PhD);

Department of Surgery, University Medical Centre Utrecht, Utrecht, Netherlands (W M U van Grevenstein PhD); **Department of Surgery, Universitair Medical Centre Groningen, Groningen, Netherlands** (P H J Hemmer PhD); **Department of Surgery, Bernhoven, Uden, Netherlands** (L Schoonderwoerd MD); **Department of Surgery, Amsterdam UMC, Free University, Cancer Centre Amsterdam, Amsterdam, Netherlands** (J B Tuynman PhD); **Department of Surgery, Flevo hospital, Almere, Netherlands** (A W H van de Ven MD); **Department of Surgery, Isala Hospital, Zwolle, Netherlands** (H L van Westreenen PhD); **Department of Surgery, St Antonius Hospital, CM Nieuwegein, Netherlands** (M J Wiezer PhD); **Department of Surgery, Elisabeth-Tweesteden Hospital, Tilburg, Netherlands** (D D E Zimmerman PhD); **and Department of Internal Medicine, Amstelland Hospital, Amstelveen, Netherlands** (A A van Zweeden MD)

Correspondence to: Prof Pieter Tanis, Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam 1105 AZ, Netherlands
p.j.tanis@amsterdamumc.nl

See Online for appendix

Research in context

Evidence before this study

We systematically searched PubMed, Embase, and Cochrane databases, from inception to August, 2013, for articles on adjuvant intraperitoneal chemotherapy for patients with stage II or III colorectal cancer. Among 1414 records, a total of 12 studies were identified, including four randomised controlled trials and three comparative cohort studies. The four randomised trials determined the efficacy of postoperative repeated fluoropyrimidine-based intraperitoneal chemotherapy delivered via peritoneal catheters for several days to several months. Two trials showed a significant reduction in peritoneal recurrence (91% *vs* 20% and 21% *vs* 8%). None of the trials reported a significant effect on overall survival. The three comparative cohort studies investigated intra-operative intraperitoneal chemotherapy delivered simultaneously with primary tumour resection with mitomycin C or oxaliplatin, which was combined with hyperthermia in two studies. An updated search in November, 2016, showed one additional comparative study using hyperthermic intraperitoneal chemotherapy (HIPEC). A significant reduction in peritoneal recurrence was found in three studies (60% *vs* 12%, 22% *vs* 4%, and 43% *vs* 9%). All four comparative cohort studies showed a significant improvement in overall survival after adjuvant HIPEC. The reported numbers of major complications related to adjuvant HIPEC were low among all studies. Because of substantial heterogeneity in patient selection, treatment protocols, and outcome measures, no meta-analyses were done.

Added value of this study

To our knowledge, this is the first multicentre randomised controlled trial to assess the added value of adjuvant intra-operative HIPEC with oxaliplatin in addition to routine adjuvant systemic chemotherapy after curative resection of T4 or perforated stage II–III colon cancer. Adjuvant HIPEC with oxaliplatin was not superior to routine adjuvant systemic chemotherapy with respect to 18-month peritoneal metastasis free-survival. Unexpectedly, early peritoneal recurrences were already found in nine (9%) of 100 patients at surgical re-exploration before adjuvant HIPEC could be administered.

Implications of all the available evidence

Overall, peritoneal recurrences were seen in 21% of patients, despite adjuvant systemic chemotherapy, similar to findings in published literature, indicating the magnitude of this clinical problem in patients with locally advanced stage II–III colon cancer. Given the proof of concept of HIPEC as an effective intraperitoneal treatment strategy based on a randomised controlled trial in ovarian cancer published in January, 2018, further research should aim to find an effective HIPEC regimen in colorectal cancer, both for the use in the adjuvant setting, as well as in combination with cytoreductive surgery in the metastatic setting to treat peritoneal recurrences. Cytoreductive surgery and HIPEC are still used worldwide after the PRODIGE-7 trial, which did not show a survival benefit of the addition of HIPEC to cytoreductive surgery. The worldwide use of cytoreductive surgery combined with HIPEC is because the trial results cannot be extrapolated to mitomycin C as a chemotherapeutic drug and to the up-front application without induction systemic therapy. Nevertheless, the negative result of the PRODIGE-7 trial has fueled discussion on the efficacy of HIPEC in colorectal cancer in general. Although in the adjuvant setting, the COLOPEC trial is another negative trial using oxaliplatin as intraperitoneal chemotherapy. Probably the next step should be to evaluate new HIPEC regimens in in-vitro models.

an advanced and symptomatic stage, are associated with poor prognosis (median survival of approximately 12 months) and are relatively resistant to palliative systemic therapy.[7,8] Only 20–25% of patients are in good enough clinical condition and have limited extent of disease to be considered candidates for treatment with curative intent with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC),[9] a procedure that is associated with substantial morbidity.[10]

Patients with pathological T4 stage colon cancer (both stage II and III) are commonly treated with adjuvant systemic chemotherapy. Nevertheless, peritoneal metastases develop in many patients. More effective adjuvant therapy to prevent the development of peritoneal metastases is warranted. Intraperitoneal chemotherapy in an ambulant setting with peritoneal catheters has previously been attempted, as well as intraoperative HIPEC with mitomycin or oxaliplatin.[11] These studies suggested that intraperitoneal chemotherapy might be efficacious in reducing the development of peritoneal metastases (three comparative studies comparing intraperitoneal chemotherapy regimens with intravenous chemotherapy or no chemotherapy showed significant reductions of 60% *vs* 12%, 22% *vs* 4%, and 43% *vs* 9%) and result in survival benefit.[11] Regarding treatment-related morbidity, previous studies,[11] as well as our pilot study,[12] showed that adjuvant HIPEC is well tolerated. However, these studies have substantial bias and no definitive conclusions can be drawn on the basis of these data. Together, these findings supported the conduct of the multicentre randomised COLOPEC trial. The primary aim of this study was to determine the efficacy of adjuvant HIPEC with oxaliplatin after a curative resection of T4 or perforated colon cancer in patients with locally advanced colon cancer.

Methods

Study design

COLOPEC is a multicentre, open-label, randomised controlled trial, designed and endorsed by of the Dutch Peritoneal Oncology Group and the Dutch Colorectal Cancer Group. The trial was done in nine Dutch hospitals

that specialised in HIPEC (appendix p 3). The study protocol was previously published.[13] The Amsterdam UMC was the coordinating centre and approval of the protocol was obtained from its institutional review board. Data collection and database management were done by the Netherlands Comprehensive Cancer Organization (Integraal Kankercentrum Nederland), and final data collection and analysis by researchers of the coordinating centre (CELK, MGWD, and PJT).

Participants

Patients with resectable primary clinical or pathological T4N0–2M0 stage or perforated colon cancer were screened for inclusion. Perforation was defined as tumour perforation, perforation of the efferent bowel, or a peritumoural abscess. Other key eligibility criteria were age between 18 and 75 years, adequate clinical condition for HIPEC (according to the evaluation of the physician), and intention to start adjuvant systemic chemotherapy. Patients with neuroendocrine tumours were excluded, as were patients with microsatellite instability stage II tumours, because the Dutch guidelines do not recommend adjuvant chemotherapy for those patients. A full list of inclusion and exclusion criteria is presented in the protocol.[13] All patients signed informed consent before randomisation.

Randomisation and masking

Randomisation was done centrally by CELK using a web-based randomisation application (ALEA, version 2.2). Randomisation was not blinded. We used block randomisation with a maximum block size of six and a block size factor of four. Stratification factors were tumour characteristic (T4 or perforation), surgical approach of the primary tumour resection (laparoscopic or open), and age (<65 years or ≥65 years). Randomisation was done before resection of the primary tumour (clinical T4 stage) or postoperatively (confirmed pathological T4 stage or perforation). Patients were randomly assigned (1:1) to adjuvant HIPEC followed by standard adjuvant systemic chemotherapy (experimental group), or adjuvant systemic chemotherapy alone (control group; appendix p 7). After randomisation, patients received a study identification number, being a sequence number starting with 1.

Procedures

Adjuvant HIPEC was delivered simultaneously or 5–8 weeks after resection of the primary tumour. HIPEC was done by either a laparoscopic or open approach, starting with exploration of the abdominal cavity for peritoneal staging and adhesiolysis when necessary. A bidirectional HIPEC protocol was used: fluorouracil (400 mg/m²) and leucovorin (20 mg/m²) were delivered intravenously followed by HIPEC using oxaliplatin (460 mg/m²) in a single dose for 30 min at a temperature of 42–43°C (further details can be found in the appendix p 5). In both study groups, patients received adjuvant systemic chemotherapy, consisting of 6 months of capecitabine and oxaliplatin every 3 weeks or fluorouracil and oxaliplatin every 2 weeks (according to the Dutch guidelines), which preferably started within 6–8 weeks, but no later than 12 weeks, after primary tumour resection.

Follow-up was done according to the Dutch guidelines during the first 18 months. Follow-up included imaging of the liver (ultrasound or CT) at 6 months and 12 months and CT imaging of the abdomen at 18 months, combined with blood carcinoembryonic antigen testing at 3–6 month intervals. If patients developed recurrent disease during this time interval, they were treated accordingly at the discretion of the treating physician. In patients without radiological or pathological diagnosis of recurrent disease at 18 months, or in patients with recurrent disease outside the peritoneal cavity who were still treated with curative intent, a diagnostic laparoscopy was done in both study groups for peritoneal staging. Omental and ovarian metastases were considered as peritoneal metastases. In cases of histopathologically confirmed peritoneal metastases, patients were treated with cytoreductive surgery with HIPEC if they fulfilled treatment criteria, and were switched to treatment with mitomycin in the experimental group. Patients with a negative diagnostic laparoscopy continued routine follow-up for at least 5 years from primary tumour resection, with yearly liver ultrasound or CT imaging of the abdomen, in combination with serum carcinoembryonic antigen measurement, starting 24 months after tumour resection.

Outcomes

The primary endpoint was peritoneal metastasis-free survival at 18 months and was centrally assessed. Secondary endpoints were hospital stay, treatment-related toxicity after adjuvant HIPEC, disease-free survival, overall survival, quality of life, and costs (quality of life and costs will be reported elsewhere). Post-hoc analyses were proportion of patients receiving adjuvant chemotherapy, time to adjuvant chemotherapy, time until diagnosis and extent of peritoneal metastases. Complications related to HIPEC were reported in case of a Clavien-Dindo score of 2 or higher and at 30 days. All serious adverse events related to adjuvant HIPEC with or without primary tumor resection, as well as adjuvant chemotherapy within 30 days after end of treatment, were reported according to received treatments and definition according to Good Clinical practice (Declaration of Helsinki) guidelines. We determined the extent of peritoneal metastases intra-operatively using the peritoneal cancer index.[14]

Statistical analysis

Adjuvant HIPEC was estimated to result in a 60% relative risk reduction in peritoneal metastases on the basis of available literature.[11] We estimated 18-month peritoneal metastasis-free survival to be 75% in the control group.[2–5]

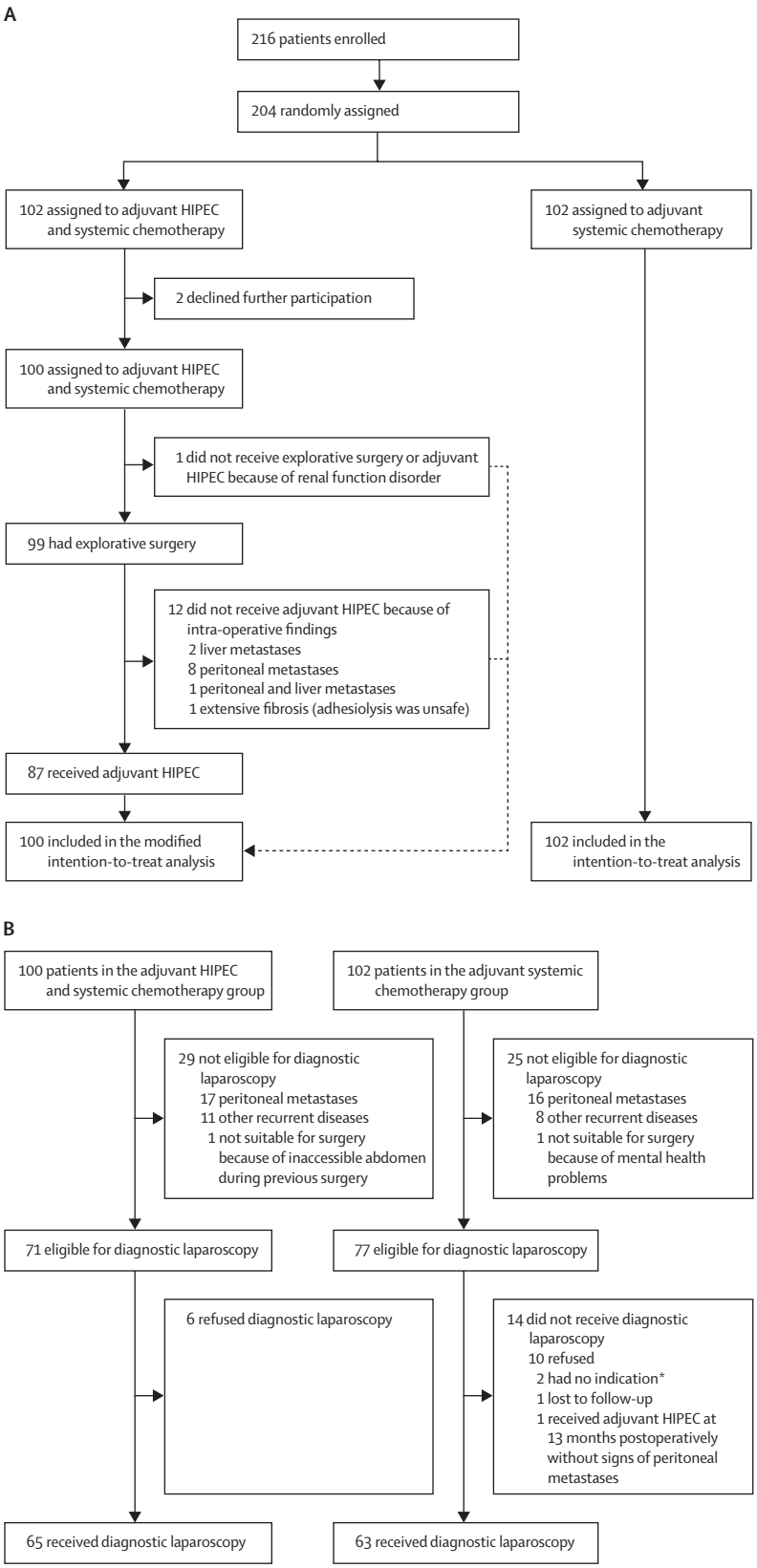

Figure 1: **Trial profile**
(A) Randomisation and administration of adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC). (B) 18-month diagnostic laparoscopy. *Treating physician did not consider that diagnostic laparoscopy was indicated because of low risk of peritoneal metastases based on histopathology (pathological T2–3 stage and pathological T4N0 with microsatellite instability).

To detect a 60% relative risk reduction (18-month peritoneal metastasis-free survival of 90% in the experimental group), 176 patients (88 in each group) were needed (Kaplan-Meier method, one-sided p value, α=0·05, power of 80%, drop-out rate of 5%). Because some patients had unexpected diagnosis of peritoneal metastases before receiving intended adjuvant HIPEC (and were therefore no longer suitable for adjuvant therapy), the ethics committee approved continuation of randomisation until the predefined number of adjuvant HIPEC procedures was done. We compared survival outcomes between the study groups using the Kaplan-Meier survival analysis (log-rank test with one-sided p value), using the intention-to-treat principle. We did post-hoc subgroup analyses of the primary endpoint to cautiously explore treatment effects within distinct clinical risk factors (eg, tumour stage, nodal stage, and histopathological features) using a log-rank test with a one-sided p value. We analysed continuous secondary outcome variables (eg, duration until start of adjuvant systemic chemotherapy) using independent samples *t* test or Mann-Whitney *U* test depending on the distribution, with two-sided significance level in the intention-to-treat population. A p value of less than 0·05 was considered statistically significant.

A data and safety monitoring board performed interim reviews after inclusion of 25, 50, and 100 patients, and advised on trial continuation on the basis of the incidence of serious adverse events and distant metastases.

We did all statistical analyses using SPSS (version 25). This study is registered with ClinicalTrials.gov, number NCT02231086.

Role of the funding source

The funders of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had responsibility for the decision to submit for publication.

Results

Between April 1, 2015, and Feb 20, 2017, 216 patients were enrolled in the trial. 204 patients had been randomly assigned to treatment, 102 in each study group (30 randomly assigned preoperatively and 172 postoperatively; appendix p 7, figure 1). In the experimental group, two patients withdrew consent after randomisation. After additional medical assessment,

	Experimental group (n=100)	Control group (n=102)
Median age, years	61 (56–68)	61 (54–68)
Sex		
Female	47 (47%)	50 (49%)
Male	53 (53%)	52 (51%)
American Society of Anesthesiologists score		
1	33 (33%)	49 (48%)
2	63 (63%)	49 (48%)
3	4 (4%)	4 (4%)
Setting		
Elective	76 (76%)	84 (83%)
Perforation		
No perforation	77 (77%)	83 (82%)
Perforation	23 (23%)	18 (18%)
Procedure		
Right hemicolectomy	38 (38%)	39 (39%)
Left hemicolectomy	14 (14%)	12 (12%)
Sigmoid resection	33 (33%)	32 (32%)
Anterior resection	13 (13%)	16 (16%)
Subtotal colectomy	2 (2%)	2 (2%)
Approach		
Laparoscopic	56 (56%)	55 (55%)
Converted	12 (12%)	8 (8%)
Open	32 (32%)	38 (38%)
Multivisceral resection		
No	66 (66%)	65 (64%)
Limited	13 (13%)	11 (11%)
Extended	21 (21%)	25 (25%)
cT		
cT1*	1 (1%)	0
cT2	7 (7%)	5 (5%)
cT3	29 (29%)	28 (28%)
cT4	41 (41%)	53 (52%)
cTx	22 (22%)	16 (16%)
pT		
T4a	71 (71%)	72 (71%)
T4b	16 (16%)	16 (16%)
T2 or T3 (perforation)	10 (10%)	9 (9%)
T2 or T3 (cT4)	3 (3%)	4 (4%)
(Continued from previous column)		
pN		
N0	24 (24%)	29 (29%)
N1	36 (36%)	34 (34%)
N2	40 (40%)	38 (38%)
Histopathology		
Well differentiated adenocarcinoma	75 (75%)	72 (71%)
Poorly differentiated or undifferentiated adenocarcinoma†	13 (13%)	12 (12%)
Mucinous carcinoma	8 (8%)	9 (9%)
Signet ring cell carcinoma	2 (2%)	8 (8%)
Medullar carcinoma	2 (2%)	0
Residual tumour		
R0	99 (99%)	99 (98%)
R1	1 (1%)	2 (2%)
R2	0	1 (1%)
Maximum tumour diameter, mm	42 (30–60)	42 (30–60)
Postoperative complications after primary tumour resection (Clavien-Dindo score ≥3)	10 (10%)	3 (3%)

Data are median (IQR) or n (%). cT=clinical T category. pT=pathological tumour status. pN=pathological nodal status. R=residual. *Case of a tubulovillous adenoma that could not be removed endoscopically; histopathology (biopsies) remained inconclusive with suspicion of carcinoma. †Also includes adenocarcinoma of unknown differentiation (n=4) due to neoadjuvant therapy.

Table 1: **Baseline characteristics of the intention-to-treat population**

five of 202 included patients (four in the control group and one in the experimental group) did not meet the inclusion criteria (appendix p 9), but were included in the intention-to-treat analysis. Baseline characteristics and details of the primary tumour resection are shown in table 1.

In total 87 (87%) of 100 patients in the experimental group received adjuvant HIPEC (table 2). One patient did not receive adjuvant HIPEC because of renal function disorder. Nine patients were diagnosed with peritoneal metastases preceding intentional adjuvant HIPEC (figure 1A): one patient during a simultaneous procedure and eight during a staged procedure at 5–8 weeks postoperatively. These patients did not receive adjuvant HIPEC and the eight patients with only peritoneal metastases were treated with cytoreductive surgery with HIPEC (appendix p 10). Three patients did not receive adjuvant HIPEC because of intraoperatively detected liver metastases (n=2) and extensive fibrosis (n=1). One patient in the control group received adjuvant HIPEC 13 months postoperatively. At 18 months after primary tumour resection, 148 (73%) patients (77 in the control group and 71 in the experimental group) were eligible for diagnostic laparoscopy, which was done for 128 (63%) patients (63 in the control group and 65 in the experimental group; figure 1B). At the time the last patient completed 18 months of follow-up (November, 2018), overall median follow-up was 23 months (IQR 18–26).

In the experimental group, 19 (19%) of 100 patients were diagnosed with peritoneal metastases, of which nine were diagnosed before receiving HIPEC, eight during routine follow-up, and two during diagnostic laparoscopy. The incidence of peritoneal recurrence depending on assigned treatment in the 91 patients without early detected peritoneal metastases were: nine (10%) of 87 patients after adjuvant HIPEC, and one (25%) of four patients after omission of adjuvant HIPEC

	Patients (n=87)
Timing	
Simultaneous	8 (9%)
Staged (5–8 weeks)	79 (91%)
Surgical approach	
Open	25 (29%)
Laparoscopic	62 (71%)
Converted (due to adhesions)	5/62 (8%)
Drug	
Oxaliplatin	86 (99%)
Mitomycin C	1 (1%)
Target organ resection	
None	86 (99%)
Omentum and ovaries	1 (1%)
Adhesions in case of staged HIPEC	
None	27/79 (34%)
Limited	25/79 (32%)
Moderate	12/79 (15%)
Extensive	15/79 (19%)
Median blood loss, mL	10 (0–225)
Intraoperative complications	
Minor bleeding (no red blood cells given)	1 (1%)
Minor serosal injury	1 (1%)
Median length of hospital stay, days	
Simultaneous HIPEC	17 (11–30)
Staged HIPEC (5–8 weeks)	4 (2–6)
Incidence of 30-day complication	
Simultaneous HIPEC	7/8 (88%)
Anastomotic leakage	2/8 (25%; CD3)
Wound infection	3/8 (38%; n=2 CD2, n=1 CD3)
Pneumonia	2/8 (25%; CD2)
Sepsis (due to intravenous catheter)	1/8 (13%; CD2)
Urinary tract infection	2/8 (25%; CD2)
Gastroparesis	2/8 (25%; CD2)
Paralytic ileus	1/8 (13%; CD2)
Delirium	1/8 (13%; CD2)
Staged HIPEC (5–8 weeks)	5/79 (6%)
Gastroparesis	2/79 (3%; CD2)
Anaemia	1/79 (1%; CD2)
Abdominal discomfort	1/79 (1%; CD2)
Venous thrombosis	1/79 (1%; CD2)
Reinterventions (within 30 days)	3 (3%)
Late complications	1 (1%)*

Data are n (%), n/N (%), or median (IQR). HIPEC=hyperthermic intraperitoneal chemotherapy. CD=Clavien-Dindo score. *Encapsulating peritoneal sclerosis

Table 2: **Characteristics of the adjuvant HIPEC procedures**

(omission because of liver metastases during early re-exploration [n=2], renal function disorder [n=1], and extensive fibrosis [n=1]). In the control group, 23 (23%) of 102 patients were diagnosed with peritoneal metastases, of which seven were detected during diagnostic laparoscopy and 16 during regular follow-up.

The intention-to-treat analysis showed no significant difference in 18-month peritoneal metastasis-free survival between the two study groups (figure 2): 80·9% (95% CI 73·3–88·5) in the experimental group and 76·2% (68·0–84·4) in the control group (one-sided log-rank p=0·28). There were no substantial differences between the two study groups regarding peritoneal metastasis-free survival in subgroup analyses (figure 3). In right-sided tumours, 18-month peritoneal metastasis-free survival was 81·0% (69·0–93·0) in the experimental group and 65·0% (51·1–78·9) in the control group (p=0·064). Corresponding 18-month peritoneal metastases-free survival in left-sided tumours was 80·9% (70·7–91·1) and 87·1% (78·1–96·1; p=0·84), respectively.

Median length of hospital stay was 16·5 days (IQR 11–29·5) after simultaneous HIPEC and 4 days (2–6) after staged HIPEC. Postoperative complications after adjuvant HIPEC occurred in 12 (14%) of 87 patients: seven (88%) of eight after simultaneous procedure, and five (6%) of 79 after staged procedure (table 2). Regarding long-term morbidity, one (1%) patient presented 12 months after adjuvant HIPEC with abdominal discomfort and inability of oral intake with subsequent need for parenteral nutrition, due to encapsulating peritoneal sclerosis. After laparotomy with full adhesiolysis, bowel function was restored and the patient fully recovered.

The proportion of patients who started adjuvant systemic chemotherapy in each study group was similar (85 [85%] in the experimental group *vs* 90 [88%] in the control group, p=0·50). Reasons for not receiving adjuvant chemotherapy are shown in the appendix (p 11). In the experimental group, median time to systemic chemotherapy was longer than in the control group (10 weeks [IQR 9–12] *vs* 6 weeks [5–7], Mann-Whitney *U* test two-sided p<0·0001). Median time to diagnosis of peritoneal metastases was 8 months (IQR 1–16) in the experimental group and 14 months (8–18) in the control group (Mann-Whitney *U* test two-sided p=0·059). Mean peritoneal cancer index score at first detection was 9·1 (SD 5·8) based on surgical exploration in 15 patients of the experimental group, and 7·5 (5·2) in 16 patients of the control group. In the remaining 11 patients, peritoneal metastases were diagnosed with imaging only and the peritoneal cancer index score was not systematically determined. Peritoneal metastases were treated with cytoreductive surgery with HIPEC in 13 (68%) of 19 patients in the experimental group and 15 (65%) of 23 patients in the control group. Serious adverse events were reported in the appendix (p 12).

18-month disease-free survival and overall survival for the entire study population (both control and experimental groups) were 69·2% (95% CI 62·7–75·7) and 93·5% (90·2–96·8), respectively. Disease-free survival and overall were comparable between the study groups (disease-free survival 69·0% [60·0–78·0] in the experimental group *vs* 69·3% [60·3–78·3] in the control

group, p=0·99; overall survival 93·0% [87·9–98·1] *vs* 94·1% [89·6–98·6], p=0·82).

Discussion

In this randomised trial of adjuvant bidirectional HIPEC in patients who had curative intent resection of T4 or perforated colon cancer, there was no difference in 18-month peritoneal metastasis-free survival between adjuvant HIPEC followed by adjuvant systemic chemotherapy and adjuvant systemic chemotherapy alone. 42 (21%) of 202 patients had peritoneal recurrence after a median follow-up of 23 months (19 [19%] of 100 patients in the experimental group and 23 [23%] of 102 patients in the control group). Unexpectedly, surgical exploration with the intention to do adjuvant HIPEC showed peritoneal metastases in nine (9%) of 100 patients in the experimental group. During routine follow-up, peritoneal metastases were identified in 24 patients and 18-month diagnostic laparoscopy in both groups showed that an additional nine patients had peritoneal metastases. Of the 42 patients with peritoneal metastases, 28 (67%) were eligible for cytoreductive surgery with HIPEC.

We chose a surrogate endpoint that enabled early assessment of the efficacy of HIPEC; because peritoneal metastases are associated with survival, and because of rapid disease progression in general, we considered 18-month peritoneal metastasis-free survival to be an appropriate surrogate endpoint. There was a sense of urgency among the Dutch Ministery of Health and the Zorginstituut Nederland (ie, the national institute that decides on reimbursement of new therapies) to decide on the continuation of adjuvant HIPEC in routine practice after completing accrual, including among patient advocates. Adjuvant HIPEC was already being used outside the trial setting during the study period, which is why one patient could receive the experimental intervention in the control group. To our knowledge, the COLOPEC trial was the first of its kind to provide evidence to guide the use of adjuvant HIPEC in daily practice. Within the study group, we decided to stop use of adjuvant HIPEC in the Netherlands between completion of accrual in the COLOPEC trial and analysis of the primary endpoint. Since superiority of the experimental intervention regarding 18-month peritoneal metastasis-free survival could not be shown, this policy is still enforced.

In the intention-to-treat analysis, the potential efficacy of adjuvant HIPEC might be masked by the substantial proportion of patients (9%) with peritoneal metastases at surgical exploration preceding adjuvant HIPEC, for whom there was no window of time to do a preventive intervention. Determination of the effect of adjuvant HIPEC in reducing the remaining 16% (of the a priori 25%) estimated risk of peritoneal metastases would have required a considerably larger sample size. Given the randomised study design, it is likely that a similar amount of early peritoneal metastases occurred in the control group. However, without early surgical re-exploration in the control group, those patients with either missed synchronous peritoneal metastases or rapid disease progression in the control group could not be identified, precluding an as-treated analysis.

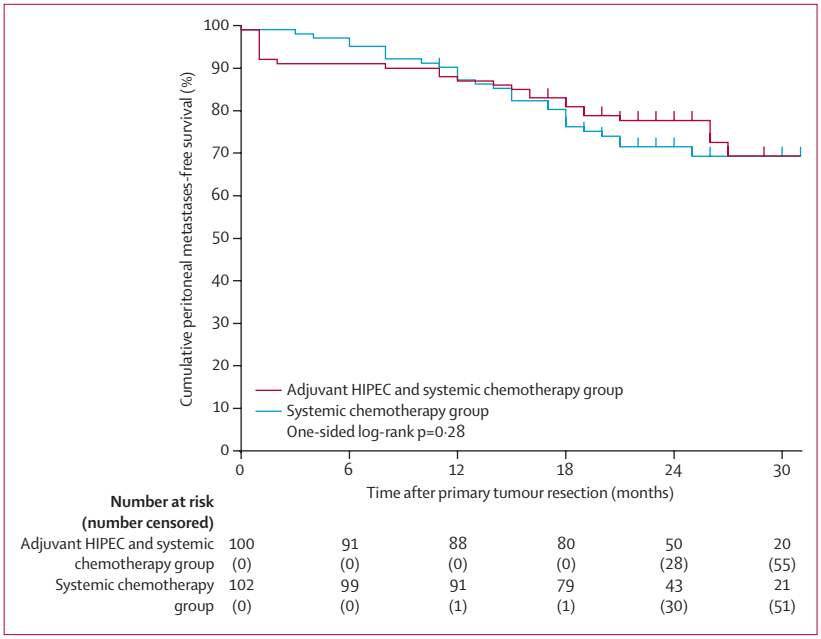

Figure 2: **Kaplan-Meier estimates of peritoneal metastasis-free survival of the control and the experimental groups**
HIPEC=hyperthermic intraperitoneal chemotherapy.

Previously published small cohort studies[15–18] reported promising results of adjuvant HIPEC for patients with high-risk colon cancer, with incidence of peritoneal metastasis of 0–4% after treatment. Considering the 87 patients who had adjuvant HIPEC in this study, nine (10%) patients developed peritoneal metastases despite adjuvant HIPEC using the bidirectional protocol, which raises the question whether it is the concept of staged adjuvant HIPEC or the HIPEC protocol that resulted in failure to prevent the outgrowth of these peritoneal metastases. In 2018, the outcomes of the randomised PRODIGE7 trial[19] were presented. Patients with peritoneal metastases of colorectal origin who were pretreated with systemic chemotherapy containing oxaliplatin for up to 6 months were subsequently randomly assigned to cytoreductive surgery alone or in combination with HIPEC using 30-min high-dose oxaliplatin (460 mg/m²). No difference was observed in median overall survival between the two groups (41·2 months *vs* 41·7 months, p=1·0). It is unclear to what extent neoadjuvant oxaliplatin-based systemic chemotherapy affected the effectiveness of subsequent intraperitoneal oxaliplatin in this trial, because this neoadjuvant treatment might have already induced a certain degree of resistance to oxaliplatin in the tumour cells. The PROPHYLOCHIP trial[20] also did not show

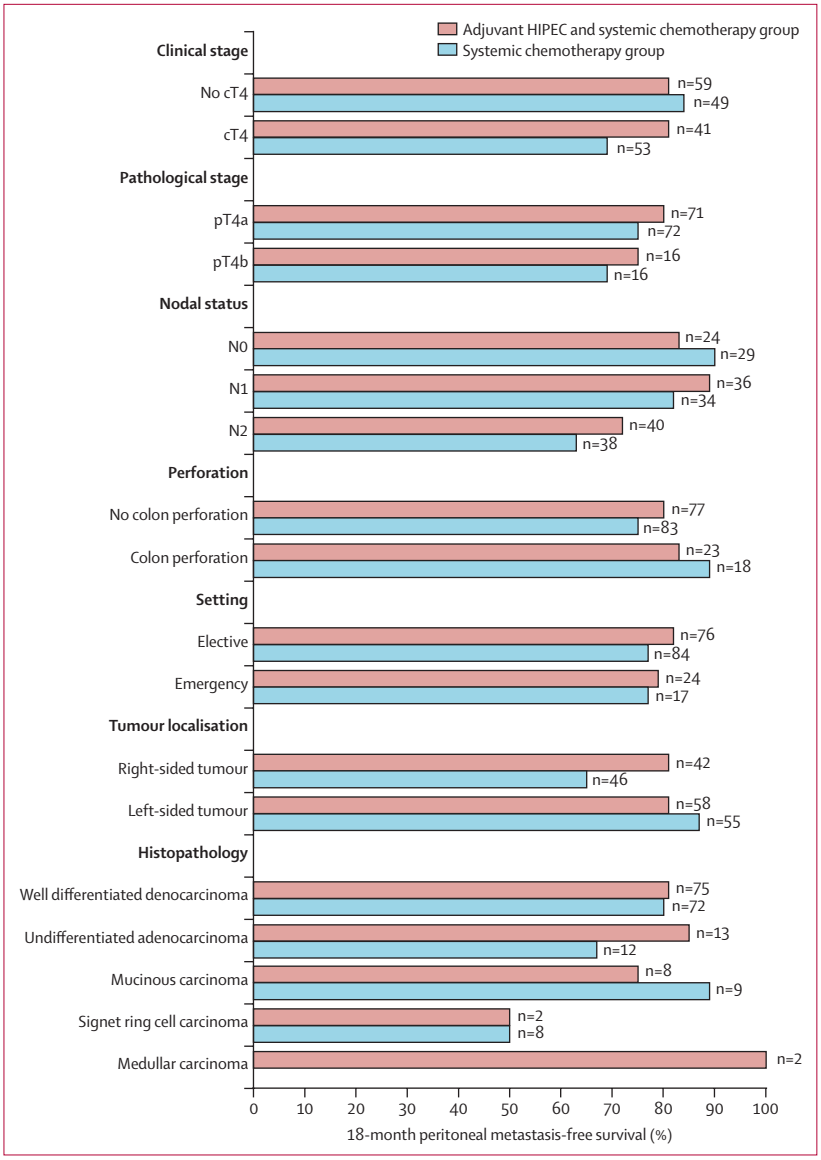

Figure 3: **Peritoneal metastasis free-survival analysed by subgroup stratification**
HIPEC=hyperthermic intraperitoneal chemotherapy. c=clinical. p=pathological. N=nodal.

benefits of this particular HIPEC protocol in patients with minimal resected peritoneal metastases, ovarian metastases, or a perforated primary tumour compared with surveillance (3-year disease-free survival 51% *vs* 44%, p=0·75). Although these trials were done in different clinical settings to the COLOPEC trial, the results of these three trials question the efficacy of the 30-min HIPEC protocol with oxaliplatin.

It might be hypothesised that a single 30-min exposure of malignant cells to oxaliplatin is too short to obtain a clinically relevant antitumour effect. The PROMENADE (NCT02974556) and HIPECT4 (NCT02614534) trials investigating simultaneous adjuvant HIPEC are currently recruiting patients, with the latter using mitomycin. The proof-of-concept of achieving a significant overall survival benefit after HIPEC in addition to cytoreductive surgery has been shown in ovarian cancer.[21] Altogether, this evidence suggests that future research should focus on optimising HIPEC regimens using oxaliplatin or other drugs in the treatment and prevention of peritoneal metastases from colorectal origin.[22]

The observation of peritoneal metastases at early re-exploration raises several questions. Metastases might have been missed at the time of resection of the primary tumour. Dutch population-based data have shown that transition from open to laparoscopic colon cancer surgery resulted in lower detection of synchronous peritoneal metastases.[23] But this transition is unlikely to be the only explanation. These tumours could also represent an aggressive type of colon cancer with rapid outgrowth of occult peritoneal metastases. Surgical stress from the primary tumour resection might have induced cancer cell growth.[24] For this reason, it could be argued that HIPEC should be done simultaneously with the primary resection. However, preoperative selection for simultaneous HIPEC is complicated by the restricted sensitivity and specificity of imaging methods to diagnose T4-stage disease.[25] Approximately 40% of clinical T4 tumours appear to be pathological tumour 2–3 stage[26] on the basis of histopathological examination, whereas a substantial number of pathological stage 4a tumours are diagnosed only postoperatively. Furthermore, a staged approach allows patient referral from non-HIPEC centres and inclusion of emergency cases.

In this study, 28 (67%) of 42 patients with established peritoneal metastases had cytoreductive surgery with HIPEC, which is substantially more than the seven (21%) of 33 patients undergoing this procedure in the T4 colon cancer cohort of van Santvoort and colleagues.[27] Our experimental intervention can be regarded as a combined therapeutic and preventive strategy. If peritoneal metastases are found at re-exploration, cytoreductive surgery with HIPEC can be applied at an early stage of the disease. If peritoneal metastases are absent, adjuvant HIPEC is done. Long-term results should show whether this combined strategy eventually results in improved survival. However, the control group of the study might also have benefited from an increased awareness of peritoneal metastases and from 18-month diagnostic laparoscopy, reflected by the remarkable high proportion of cytoreductive surgery with HIPEC procedures done.

Median length of stay of 4 days (IQR 2–6) after staged HIPEC was longer than expected based on our pilot study (median 1·5 days [1–2]) using mitomycin.[12] One patient developed encapsulating peritoneal sclerosis, a rare but life-threatening complication.[28]

One strength of this multicentre study is external validity. Patient referral from all hospitals in the Netherlands and the willingness to participate in the trial (appendix p 8) resulted in a population representative of daily clinical practice. The HIPEC procedures, as well as the 18-month

diagnostic laparoscopy, were all done in hospitals that specialised in HIPEC. Patients in both study groups received routine adjuvant chemotherapy in similar proportions and according to the Dutch guidelines. For the purpose of determining the primary endpoint, a diagnostic laparoscopy was done after a negative CT scan at 18-month follow-up. This examination identified an additional seven peritoneal metastases in the control group and two in the experimental group.

A limitation of this study is the fact that adjuvant chemotherapy was administered later in the experimental group than in the control group. However, all patients still received adjuvant chemotherapy within the recommended 12-week timeframe. Meta-analysis of comparative cohort studies showed that a 4-week increase in time to adjuvant systemic chemotherapy results in a significant decrease of overall survival (HR 1·14 [95% CI 1·10–1·17]).[29] However, this effect has never been confirmed in a randomised trial that compares different intervals between surgery and adjuvant chemotherapy. The cohort series included in the meta-analysis are confounded by factors delaying the start of adjuvant systemic chemotherapy that also affect survival (eg, age, comorbidity, postoperative complications), which raises questions regarding the causality of the association between interval to chemotherapy and survival. In the meta-analysis,[29] the authors tried to minimise the risk of confounding factors by only including studies that balanced the groups for prognostic factors or corrected the outcomes for these factors. To what extent residual confounding has affected this observed relationship is difficult to determine.

Another limitation of this study is the invasiveness of diagnostic laparoscopy to determine the primary endpoint. The need to undergo another surgical intervention under general anaesthesia might have been a reason for patients to refuse this study procedure. Altogether, 74 (37%) of 202 patients did not receive an 18-month diagnostic laparoscopy for various reasons which might have led to missed peritoneal metastases. Furthermore, diagnostic laparoscopy is less sensitive than laparotomy, thereby potentially affecting the primary endpoint. However, the proportion of patients undergoing 18-month diagnostic laparoscopy was similar in both groups (65% in the experimental group and 62% in the control group) and missed peritoneal metastases were likely to be evenly distributed between the study groups. Non-invasive but equally sensitive alternatives to detect occult peritoneal metastases are warranted. One of these methods could be circulating tumour DNA, because results have been promising for diagnosing occult residual disease after surgery.[30] Positive circulating tumour DNA might enable a more accurate selection for diagnostic laparoscopy with a higher diagnostic yield than diagnostic laparoscopy not preceded by circulating tumour DNA testing.

Other limitations of this trial are inherent methodological issues related to the experimental intervention, namely the unblinded intervention and outcome assessment. Lastly, because of tight time schedules of patient referral and subsequent treatment planning, including possibly HIPEC, five patients were randomly assigned to treatment but were not eligible after further assessment (appendix p 9).

In conclusion, this study did not show superiority of adjuvant HIPEC with oxaliplatin in terms of 18-month peritoneal metastasis free-survival in patients with T4 stage or perforated colon cancer. The 21% peritoneal recurrence noted in the overall study population indicates the magnitude of the clinical problem in locally advanced colon cancer and therapeutic strategies have to be further explored. Outcomes of other trials investigating adjuvant HIPEC are eagerly awaited.

Contributors

PJT, CELK, GDM, MGWD, CJAP, PS, and JC made substantial contributions for the conception or design of this trial. CELK, DDW, PJT, AGJA, AB, AJAB, JWAB, HFJF, FF, SF, WMUG, PHJH, IHJTH, NFMK, JBT, AWHV, HLW, MJW, DDEZ, LS, and AAZ acquired the data, which were analysed by CELK. PJT, CELK, DDW, and MGWD interpreted the results. CELK and PJT drafted the manuscript, which was critically revised by DDW, CJAP, PS, JC, AGJA, AB, AJAB, JWAB, HFJF, FF, SF, WMUG, PHJH, IHJTH, NFMK, GDM, LS, JBT, AWHV, HLW, MJW, DDEZ, AAZ, and MGWD. All authors approved the final version of the manuscript to be submitted. All authors agreed to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the Article are appropriately investigated and resolved.

Declaration of interests

We declare no competing interests.

Data sharing

Individual de-identified participant data, study protocol, statistical analysis plan, and analytic code will be available immediately after publication, for researchers who provide a methodologically sound proposal, for any scientific purpose. Proposals should be directed to the corresponding author.

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