


BMJ Open Prophylactic surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC CO₂) versus standard surgery in colorectal carcinoma at high risk of peritoneal carcinomatosis: short-term and long-term outcomes from the CHECK study – protocol for a randomised, multicentre, phase 3 trial

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To cite: Pacelli F, Gerardi C, Rulli E, *et al.* Prophylactic surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC CO₂) versus standard surgery in colorectal carcinoma at high risk of peritoneal carcinomatosis: short-term and long-term outcomes from the CHECK study – protocol for a randomised, multicentre, phase 3 trial. *BMJ Open* 2022;**12**:e051324. doi:10.1136/bmjopen-2021-051324

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-051324>).

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Received 26 April 2021

Accepted 23 June 2022



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ABSTRACT

Introduction Up to one-fifth of patients with colorectal cancer will develop peritoneal metastases, frequently without other districts' involvement. Despite the recent unsuccesses of hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal cancer peritoneal metastases treatment, the rationale in the prophylactic setting remains strong. Several clinical and pharmacokinetic data suggest that the efficacy of intraperitoneal chemotherapy is highest when the disease is microscopic. However, robust evidence demonstrating whether the addition of HIPEC for high-risk colorectal cancers offers better control of local recurrence is lacking.

Methods and analysis This is a multicentre randomised phase 3 trial comparing prophylactic surgery plus HIPEC CO₂ with mitomycin, over standard surgical excision in patients with colorectal cancer at high risk of peritoneal carcinomatosis; 388 patients will be included in this study. The primary objective is to compare the efficacy of prophylactic surgery (radical colorectal resection, omentectomy, appendectomy, round ligament of the liver resection and bilateral adnexectomy) plus HIPEC CO₂ with mitomycin and standard surgery in terms of local recurrence-free survival. The main secondary endpoints are disease-free survival (DFS), overall survival (OS) and safety. The primary endpoint will be described with a cumulative incidence function and will be analysed with Grey test to take account of the competing risks. DFS and OS will be described with the Kaplan-Meier method.

Ethics and dissemination This trial has been evaluated by the Italian Medicines Agency, local ethics committees and will be submitted to the Ministry of Health to notify the start of the trial according to the regulation of trials on devices with CE mark/certification.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Novel hyperthermic intraperitoneal chemotherapy (HIPEC) system with simultaneous CO₂ infusion overcome drug distribution issues of the closed approach.
- ⇒ Multicentre randomised trial with homogeneity of the HIPEC technique and protocol.
- ⇒ No delay between surgery and HIPEC treatment.
- ⇒ Possible delay in starting adjuvant treatment in the experimental arm.
- ⇒ No preoperative stratification based on tumour pathology or mutational profile.

The results will be submitted for presentation at academic meetings and for publication in a peer-reviewed journal, whatever the findings.

Trial registration number NCT03914820.

INTRODUCTION

Background

It is estimated that about 50 000 new cases of colorectal cancer (CRC) are diagnosed yearly in Italy, with a number of deaths approaching 18 500 patients.¹ The 5-year survival rate is about 64%. Peritoneal carcinomatosis (PC) is a common mode of disease progression that can occur without involving other districts in a large percentage of cases. The reported incidence of PC from CRC is 4.3%–7% for the synchronous presentation and 4.2% for the metachronous form.^{2,3}

The prognosis of patients with PC has always been considered unfavourable. In recent decades, encouraging results have been obtained with new systemic antitublastic drugs^{4–7} and a multimodal therapeutic strategy based on the use of cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC).^{8–10}

Two main clinical factors prompted the idea to advance locoregional chemotherapy in order to prevent the development of PC: the struggles to control PC once it has spread and the limited sensitivity of current imaging methods for early diagnosis.

Pharmacological data on HIPEC also supported the rationale for prophylactic locoregional chemotherapy in a population at high risk of peritoneal relapse.¹¹ Drug penetration during HIPEC is limited to only a few cell layers under the tumour surface, and the efficacy of intraperitoneal chemotherapy is highest where there is microscopic disease.

Historical series on the prophylactic use of HIPEC after curative resection, although involving a small number of patients, showed promising outcomes both in terms of locoregional disease control and survival rates. A proactive treatment strategy, comprising HIPEC with oxaliplatin together with more extensive prophylactic surgery (removal of the omentum, appendix, round hepatic ligament and adnexa), in addition to colorectal excision, significantly improved disease-free survival (DFS) and overall survival (OS), compared with standard surgery.¹²

Although similar outcomes of adjuvant locoregional chemotherapy were reported in other case series,^{13–19} the latest clinical trials on CRC have cut HIPEC's reputation. In the ProphyloCHIP trial, systematic second-look surgery plus HIPEC did not offer any survival advantage, compared with adequate surveillance.²⁰ In the PRODIGE-7 trial, the addition of HIPEC to CRS for peritoneal metastases did not influence OS.²¹ Finally, the COLOPEC trial failed to find any improvement of peritoneal metastasis-free survival for adjuvant HIPEC with oxaliplatin in T4 or perforated colon cancer.²² Although numerous questions have been raised on the value of HIPEC itself, the van Driel trial in ovarian cancer provided solid proof of efficacy of this intraperitoneal treatment.²³

Several factors have been offered to explain the failure of HIPEC in the trial mentioned, in other settings than gynaecology. Most of them concern the use of oxaliplatin. They include uncertain drug efficacy after systemic exposure, the limited perfusion time (30 min), the drawbacks of carrier solution (5% dextrose) and the possible adverse effects of hyperthermia. Mitomycin-C has thus become more appealing for HIPEC, and while the results from a phase 3 trial are awaited,²⁴ comparative studies of the two drugs after CRS are not conclusive.^{25–28}

Adequate drug distribution during perfusion is another hot topic. Recently a novel closed-abdomen approach was proposed.²⁹ Based on continuous CO₂ infusion to generate turbulence during HIPEC and overcome the distribution issues of the closed abdomen technique, it

has given fair safety and efficacy outcomes.^{30–32} Hence, whether and how the optimisation of surgery and the HIPEC technique for CRCs can ever achieve the results obtained in gynaecology is still debate.

To address this question, we designed a multicentre randomised trial comparing prophylactic surgery plus HIPEC CO₂ with mitomycin, over standard surgical excision for CRC at high risk of PC.

Impact of the COVID-19 pandemic on prevention, cancer detection and treatments

A recent survey by the WHO showed that, 75% of countries reported a considerable degree of noncommunicable disruption of services due to the COVID-19 pandemic. This was consistent across all regions and income groups. The most common reasons for service disruptions were cancellation of elective care, lack of transport due to imposed lockdowns, insufficient staff and closure of hospital services. Globally, 2.3 million cancer surgeries have been cancelled or postponed during the peak 12-week period of COVID-19. One main reason for disruption of services was the closure of population-level screening programmes and lockdowns, hindering access to health facilities.³³

A paper from Nature points out that modelling the effect of COVID-19 on cancer screening and treatment for breast and CRC (which together account for about one-sixth of all cancer deaths) over the next decade will see almost 10 000 excess deaths from these cancers. This is a roughly 1% increase in deaths from these tumours during a period when one would expect to see almost 1 000 000 deaths from the two diseases. According to this predictive model, the number of excess deaths per year should peak in the next year or two.³⁴

Major oncology scientific societies have, therefore, recommended the use of telemedicine and boosting local medicine. At European level, telemedicine has been recommended for follow-up visits and monitoring of oral drug-based therapy.³⁵

Primary objective

The primary objective of the study is to determine whether prophylactic surgery plus mytomicin-based HIPEC CO₂ offers a better local recurrence-free survival (LRFS) in patients with CRC at high risk of developing PC compared with standard treatment.

Secondary objectives

- ▶ To compare the experimental treatment (prophylactic surgery plus mytomicin-based HIPEC CO₂) versus standard treatment on DFS and OS.
- ▶ To assess the safety (treatment-related morbidity and mortality) of this experimental treatment.

METHOD AND ANALYSIS

Hypothesis

In patients with CRC at high risk of PC, the treatment of minimal or unrecognised peritoneal disease together with primary tumour resection should reduce peritoneal recurrence.

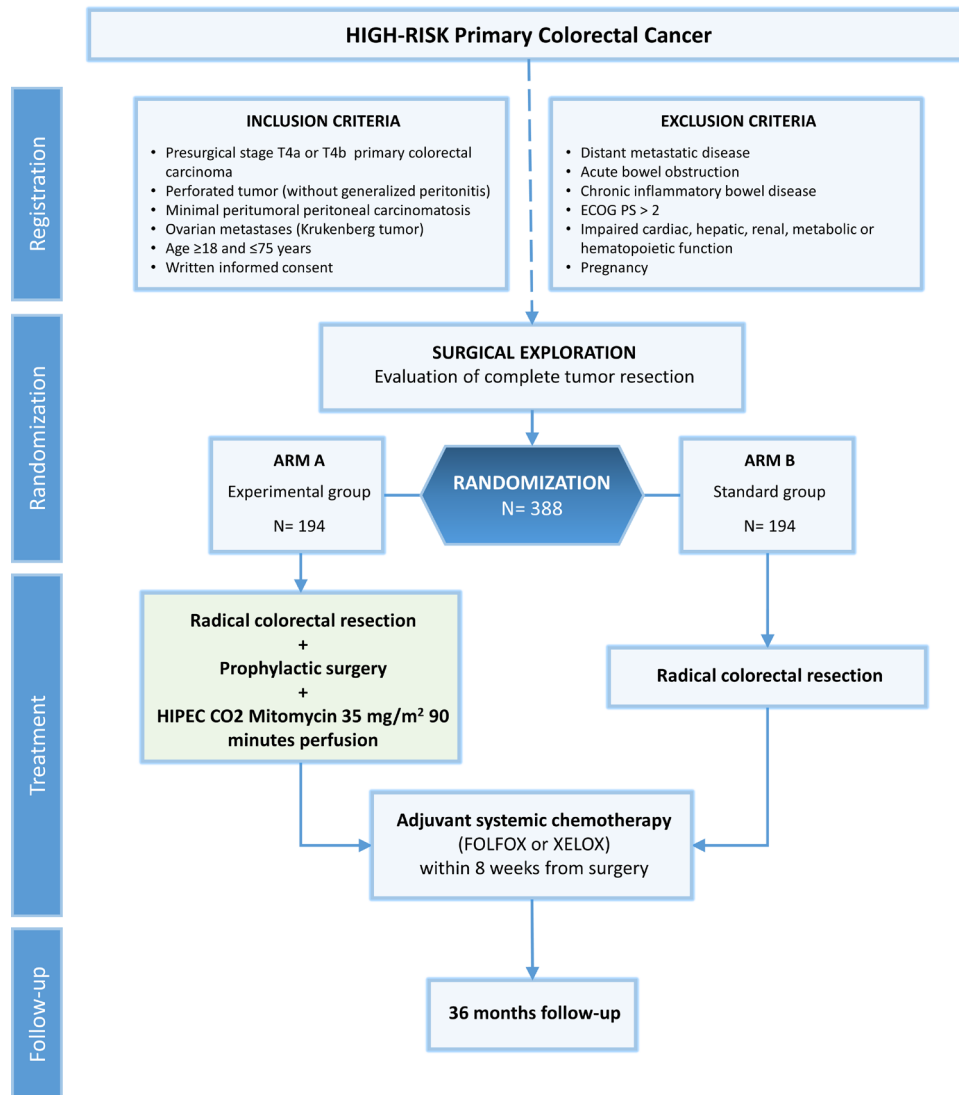


Figure 1 Study protocol flow diagram. HIPEC, hyperthermic intraperitoneal chemotherapy; ECOG, Eastern Cooperative Oncology Group Performance Status; FOLFOX, oxaliplatin, 5-fluorouracil, leucovorin; XELOX, oxaliplatin, capecitabine

Study design

CHECK is a phase 3, open-label, parallel-group, randomised, multicentre controlled trial. Patients will be randomly assigned (1:1 ratio) to receive one of the two treatment strategies: prophylactic surgery plus HIPEC CO₂ with mitomycin (arm A) or standard surgery (arm B). Adjuvant treatment after surgery is mandatory except for documented cases of non-eligibility (figure 1). Length of study is 6 years (3 recruitment +3 follow-up). This is a collaborative randomised controlled trial by Associazione Chirurghi Ospedalieri Italiani (ACOI), FONDAZIONE ASSOCIAZIONE ITALIANA DI ONCOLOGIA MEDICA (AIOM), SOCIETA' ITALIANA DI CHIRURGIA (SIC), SOCIETA' ITALIANA CHIRURGIA ENDOSCOPICA (SICE), SOCIETA' ITALIANA DI CHIRURGIA ONCOLOGICA (SICO).

Full list of ethics committee is reported in online supplemental material.

Participants

The target population is composed of patients with CRC at high risk of developing PC. The inclusion and exclusion criteria are reported below.

Inclusion criteria

Patients with colon or rectosigmoid junction (defined by the level of peritoneal reflection and the disappearance of taenia coli) cancer eligible for R0 with:

1. Histologically documented colorectal adenocarcinoma:
 - a. Presurgical stage T4a or T4b primary tumour (TNM eighth edition).
 - b. Urgent presentation: perforation without purulent generalised peritonitis or faecal peritonitis.
 - c. Peritumoural minimal PC: limited peritoneal disease in close proximity to the primary tumour, which may be removed en bloc
 - d. Ovarian metastases (Krukenberg tumour).
2. Age 18–75 years.

3. Written informed consent.

Exclusion criteria

1. Distant metastatic disease (even if limited and completely resected).
2. History of tumour diagnosed in the 3 years before entering the study, except for topical and healed pathologies that do not need further treatment (eg, non-melanoma skin carcinomas, superficial bladder carcinomas or in situ carcinoma of the breast or cervix).
3. Psychological, family or social conditions which may negatively affect the treatment and follow-up protocol.
4. Poor general conditions (European Cooperative Oncology Group (ECOG) performance status >2).
5. Impaired cardiac function (history of congestive heart failure or Ejection Fraction (EF) <40%). Clinically significant cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrolment), myocardial infarction (<6 months prior to enrolment), unstable angina, congestive heart failure (New York Heart Association Classification Class >II or serious uncontrolled cardiac arrhythmia requiring medication).
6. Impaired renal function (creatinine >1.5 upper limit of normal or creatinine clearance <60 mL/min).
7. Impaired hepatic function (Aspartate AminoTransferase (AST), Alanine AminoTransferase (ALT) >2.5 upper limit of normal, bilirubin >1.5 upper limit of normal).
8. Impaired haematopoietic function (leucocytes <4x10⁹/L, neutrophils <1.5 x10⁹/L, platelets <100 x10⁹/L).
9. Impaired pulmonary function (presence of Chronic Obstructive Pulmonary Disease (COPD) or other pulmonary restrictive conditions with Forced Expiratory Volume in the 1st second (FEV1) <50% or Diffusing Capacity for Carbon monoxide (DLCO) <40% of normal age value).
10. Pregnancy.
11. History or presence of other diseases, metabolic dysfunction or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of HIPEC or chemotherapy or patient at high risk from treatment complications.
12. Chronic inflammatory bowel disease.
13. Patients with acute bowel obstruction.
14. Refusal to join the study.

Surgical exploration

A complete abdominal exploration by laparoscopy or laparotomy will be done in order to confirm the preoperative indication and the possibility of complete radical tumour resection.

Randomisation

Randomisation will be done 24 hours before surgery. We will use a stratification procedure based on centre. Patients will be randomised in a 1:1 ratio. The treatment assignment will be retrieved within the electronic case report form (eCRFs); the randomisation will be produced by a computer software program that incorporates a randomisation list previously generated by the coordinating centre. Date of first enrolment is 19 June 2020, estimated primary completion date is 1 June 2023 (final data collection date for primary outcome measure).

Amendments

The original study design was based on intraoperative randomisation of the patients. However, organisational difficulties arose during the study conduction in apply the intraoperative randomisation, amplified by the COVID-19 pandemic, and in June 2021 an amendment was planned in order to guarantee the feasibility of the trial. The amendment modified the protocol, moving randomisation from intraoperative to before surgery (to a maximum of 24 hours before). By placing the randomisation before the intervention, patients with peritoneal carcinosis diagnosed during surgery and not identified at the presurgery diagnostic level, will be included and randomised. These patients will not receive the experimental treatment and are not part of the target population defined by the eligibility criteria.

Treatment regimen

Patients assigned to the experimental group will receive prophylactic surgery and mitomycin-based HIPEC CO₂ in addition to primary tumour resection. Patients randomised to standard surgery will be operated according to clinical practice, without HIPEC CO₂.

Surgery

Before surgical resection, peritoneal washing will be done for definitive cytological evaluation, according to TNM eighth edition. Both the laparotomic and laparoscopic surgical approaches are allowed.

In the experimental group, prophylactic surgery will include radical colorectal resection, according to AIOM and (European Society for Medical Oncology (ESMO) guidelines,^{36 37} omentectomy, round hepatic ligament resection, bilateral adnexectomy and appendectomy. In women of childbearing age, bilateral adnexectomy should be discussed.

In the control arm B, radical standard surgery will be done according to AIOM and ESMO guidelines.

HIPEC procedure

In the experimental group, patients will undergo HIPEC. In the CHECK STUDY, we will use a closed-abdomen HIPEC technique with CO₂ agitation with a specific CE marked device.^{38 39} HIPEC may be done after laparoscopic or laparotomic primary tumour resection. An adequate filling volume usually corresponds to 2.0–2.5 L/mq. The recommended temperature for HIPEC treatment is

41°C–42°C for 90 min of perfusion. The antiproliferative drug will be mitomycin (35 mg/mq in saline solution), in three shots: 50% at time 0 from the start of HIPEC (17.5 mg/mq), 25% (8.8 mg/mq) after 30 min and the remaining 25% after 60 min. During the recirculation of the perfusate, turbulence will be generated by the infusion of 0.6–0.7 L of CO₂ under controlled pressure (upper limit, 15 mm Hg). At the end of the perfusion, the perfusate will be evacuated and the abdomen re-explored for a thorough inspection of the abdominal viscera, in order to detect any thermal and/or mechanical lesions. If not already done, the reconstructive time will be completed.

Adjuvant chemotherapy

Adjuvant chemotherapy can be administered choosing between 6 months of oxaliplatin, 5-fluorouracil, leucovorin (FOLFOX) or oxaliplatin and capecitabine (XELOX).

Adjuvant treatment should start within 8 weeks from surgery. Toxicities for adjuvant treatment will be managed according to clinical practice on the basis of the schedule adopted.

Disease assessment

On days 1, 3, 5 after surgery the following exams will be done in both arms: white blood cells, platelets, haemoglobin; neutrophil, lymphocytes, creatinine, glycaemia, ALT, AST. Histological evaluation after surgery should be done according to TNM (eighth edition) staging and peritoneal cytology, mutational status of RAS, BRAF and MMR will be assessed.

A CT scan should be done 6 weeks after surgery and adjuvant treatment should start within 8 weeks.

Five and 9 months from randomisation, chest and abdomen CT scan with contrast will be taken and laboratory tests will be done. Laboratory tests will include complete blood count with formula, azotemia, creatinine, bilirubin dir/tot, ALT, AST, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transferase, CarcinoEmbryonic Antigen (CEA), Carbohydrate Antigen (CA) 19-9, albumin and ECOG performance status.

Then, every 3 months for 3 years and every 6 months for 2 years after that, chest and abdomen CT scan with contrast will be alternated with chest RX/abdomen ultrasound. A clinical visit, blood and biochemical tests will be scheduled, and 1 year from surgery, colonoscopy will be done and repeated after another 3 years.

Study endpoints

Efficacy

The primary efficacy endpoint is LRFS. LRFS is defined as the time from randomisation to the date of first local relapse, PC or death for any cause, whichever comes first. Local recurrence will be assessed by imaging or surgical exploration.

The secondary efficacy endpoints are DFS and OS. DFS is defined as the time from randomisation to the date of first local relapse, distant relapse, PC or death for any

cause, whichever comes first. Patients alive and without relapse will be censored at their last disease evaluation. OS is defined as the time from randomisation to death for any cause. Patients alive at the time of statistical analysis will be censored at their last information on vital status.

Safety

The safety endpoints will be:

- ▶ Mortality 30 and 90 days after surgery.
- ▶ Morbidity during and after surgery (within 30 postoperative days), graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 for adverse events related to chemotherapy and according to Clavien-Dindo for surgery complications.⁴⁰
- ▶ The number of postsurgery complications.
- ▶ The duration of surgery.
- ▶ The length of hospital stay.
- ▶ The number of patients receiving adjuvant chemotherapy.

Sample size

Setting a two-sided type I error of 4.9% and a power of 80%, to detect a relative reduction of 50% in the incidence of LRFS events in the experimental group compared with the control group, 72 events are required. Assuming 36 months of accrual and 36 months of follow-up, it will be necessary to include approximately 330 patients (165 per arm). Assuming a 15% of randomised patients not eligible because of the presence of PC undetected by CT scan and discovered only during the surgical procedure, it will be necessary to randomise a total of 388 patients (194 per arm) in order to reach approximately 330 patients evaluable for the analysis of the primary endpoint.

In this setting considering all types of recurrences (local and distant), we expect an incidence of local recurrence as primary site in 30%–40% of patients.

Reaching the target number of events of local recurrences (72 events), about 200 recurrences of any type (local or distant) will be observed. Therefore, the trial will have adequate power to analyse the secondary endpoint DFS: 80% power to detect a relative reduction in the risk of recurrence/death of at least 33%, with a 5% level of significance at two sides.

Statistical analysis

LRFS will be described with cumulative incidence function and will be analysed with the Grey test to take into account the competing risks (distant relapses). DFS and OS will be described with the Kaplan-Meier method. Differences in DFS and OS between arms will also be tested by univariable and multivariable Cox's models including stratification variables and other clinical-biological features as covariates.

The efficacy analysis will be performed on the modified intention-to-treat (m-ITT) population including all patients randomised, without major violation of eligibility criteria and without PC detected during surgery. Patients

will be analysed according to randomisation arm. An interim analysis on efficacy will be scheduled when half the events are observed. The conservative Haybittle-Peto boundary will be used as for guidance stopping in order to do the final analysis at the significance level of 0.049.

Data collection, management and analysis

Data will be collected using eCRFs using a centralised web database. A data timing plan and data validation plan, developed by the statisticians and data managers of the coordinating centre, will be used in order to request the input of the data in the electronic CRF and to check the data entered by data clarification forms (DCF). The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number.

Quality assurance

Each participating investigator will be responsible for ensuring data quality as planned in the data validation plan. Each item of information in the electronic CRF will be systematically checked for consistency, completeness or incongruity by the data coordinating centre that will issue DCFs in case of inconsistent data.

Local quality control will be provided by the coordinating centre, which will be responsible for monitoring all the centres.

Monitoring the trial

Source data

During the study, a sponsor's representative will have regular contacts with the study site, including visits to: Provide information and support for the investigator(s), confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the eCRFs, verify source data (comparison of the data in the eCRFs with the patient's medical records at the hospital or practice and other records relevant to the study) including verification of informed consent.

Trial management

Administrative structure

The coordinating centre is: Policlinico Universitario Agostino Gemelli IRCCS, Roma.

The sponsor is ACOI, which has delegated the Mario Negri Institute for Pharmacological Research as the Data Coordinating Centre for clinical operations oversight, data management support and clinical monitoring.

About 62 experimental centres are expected to participate. These centres have been selected on the basis of the report and recommendation of Italian National Agency for Regional Healthcare Services with at least 50 surgeries for colorectal disease per year. There is also the possibility to include international centres from other countries.

Independent data monitoring committee

An independent data monitoring committee (IDMC) comprising of three international experts (one oncologists one surgeon and one statistician), not involved in

the trial and with no conflict of interest with respect to the results, will monitor the progress of the trial from the ethical and scientific viewpoints.

The IDMC will review the interim efficacy analysis and the safety reports in order to monitor toxicity. Based on this, the IDMC will provide recommendation to the study Sponsor and the steering committee (SC).

Standard for protocol publication

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials guidelines. The trial was registered on ClinicalTrials.gov (NCT03914820).

Safety reporting

The collection, assessment and presentation of safety reports will be carried out in accordance with the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3').

Ethics and dissemination

The study will be conducted in accordance with the ethical principles set out in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and regulatory requirements for participant data protection.

Prior to entering the study, patients will receive a presentation of key information about the clinical trial, verbally and through a written consent form. Patients are notified that they are free to discontinue from the study at any time.

The study has been approved by the Ethics Committee of the Università Cattolica, Policlinico Agostino Gemelli IRCCS, Rome and has been approved or is under evaluation by the Ethics Committees of all the participating centres. Any substantial amendment made to the protocol by the coordinating investigator is sent to the local ethics committee and health authorities for approval, prior to implementation.

According to local and international regulation, results from the trial are the property of the sponsor who will share them with all participating investigators.

There is a commitment to post trial results in a public register 1 year after the trial is completed and to publish results irrespective of findings in a peer review journal.

Systematic individual patient data sharing is not intended, but all requests for the trial's data, full protocol and statistical analysis plan will be considered by the SC on request.

We planned to share the results of the study with the scientific community and national coloncancer patient associations.

Patient and public involvement

No patient involved.

DISCUSSION

The CHECK trial will assess whether adding prophylactic surgery and mitomycin-based HIPEC CO₂ to the standard treatment protects from peritoneal relapse patients undergoing CRC excision at high risk of PC. The literature questioned the role of HIPEC for PC of gastrointestinal origin. The French ProphylCHIP and PRODIGE-7 trials and the Dutch COLOPEC study found no advantage of HIPEC in the therapeutic and prophylactic settings of CRC PC.^{20–22} However, different pictures emerge in the treatment of ovarian cancer and prevention of gastric cancer peritoneal dissemination. In the van Driel trial, the addition of HIPEC to interval debulking surgery for advanced epithelial ovarian cancer resulted in longer RFS and OS than surgery alone,²³ while the efficacy of prophylactic HIPEC for gastric cancer is strongly supported by three Asian randomised trials^{41–43} and several comparative studies.^{44–48}

Hence, doubts remain whether the failures in CRC are due to biological differences between tumours or the drugs and protocols used for HIPEC.

Keeping in mind that different settings were under study, the successful above-mentioned studies on gastric and ovarian cancer used mitomycin and or cisplatin, whereas oxaliplatin-based HIPEC was administered in the three negative CRC trials. Several mechanisms have been proposed to explain the possible inefficacy of oxaliplatin-based HIPEC. As for pharmacokinetics, the limited perfusion exposure time (30 min), the short drug half-life as well as the possible adverse effects of hyperthermia and carrier solution (dextrose 5%) have been called into question.^{49–51} However, chemoresistance of consensus molecular subtype 4 to oxaliplatin, which is highly prevalent in peritoneal metastases of CRC, has even raised doubts over the antitumour activity of oxaliplatin against peritoneal metastases.⁵² On the other hand, the only other randomised controlled trial investigating CRS and HIPEC for colorectal or appendiceal carcinomatosis delivering mitomycin resulted in a significant survival improvement for the CRS-HIPEC group.⁵³

Based on this data, for the CHECK trial, we opted for the administration of mitomycin by a closed-abdomen technique, with 90 min perfusion, according to the Verwaal protocol.⁵³ In addition, a novel HIPEC system will provide simultaneous CO₂ infusion that generates intra-abdominal turbulence to overcome the drug distribution issues of the closed approach.

Another criticism of the COLOPEC trial was the possibility of scheduling HIPEC simultaneously or 5–8 weeks after primary tumour resection. Thus, around 90% of patients received locoregional treatment several weeks after surgery. This resulted in various unexpected consequences. First, a 1-month delay in starting adjuvant chemotherapy in the experimental group, which may be detrimental in local relapse and survival. Second, nearly 10% of patients presented with peritoneal metastases at the time of delayed HIPEC and although they required CRS they were not excluded from the study as the analysis

was on the ITT population. Finally, postoperative adhesions in the delayed HIPEC group could have hampered drug distribution in the abdominal cavity. Thus, in order to avoid this bias, the administration of HIPEC and colorectal excision will be simultaneous in the CHECK trial. This strategy has its own drawbacks as stratification on the base of histology or mutational status, specifically on the presence of BRAF V600E would have enhanced the design, so we will have to cope with them during subsets analysis.

Since drug penetration during HIPEC is limited to only a few cell layers under the tumour surface,⁵¹ and unrecognised or fast-developing PC it is not uncommon (10% of COLOPEC patients), the experimental treatment of our study incorporates the prophylactic surgical excision of organs at risk of peritoneal metastases. The rationale of this approach, which has already been successfully tested by Sammartino *et al* in a prospective study,¹² has been reinforced by the important value of CRS emerging from the PRODIGE-7 survival analysis.²¹ One might argue that adding two variables (prophylactic surgery and HIPEC) to standard treatment at the same time could act as a confounding factor, but the combination should be synergistic. Otherwise, we would have had to exclude prophylactic surgery in both arms, but then, even the control group would have been experimental and not given standard treatment.

Another strength of the CHECK trial is the homogeneity of the HIPEC technique since all centres will use the same HIPEC protocol. To overcome drug distribution issues related to the closed-abdomen technique, we opted for CO₂ recirculation HIPEC to offer adequate peritoneal surface drug exposure, stability and homogeneity of the intra-abdominal temperature, as previously demonstrated^{29–32 38}

A possible limitation of this trial, as in the other similar studies in literature, could be the challenging preoperative or early intraoperative identification of high-risk primary tumours (cT4a/b tumours). It has been reported that approximately 50% of T4 tumours are correctly identified by preoperative CT scan and surgical exploration combined.⁵⁴ CT scan is able to detect tumour invasion beyond the bowel wall (T1–T2 vs T3–T4), with sensitivity and specificity of 90% and 69%.⁵⁵

Hence, differentiating between pT3 and pT4 remains a surgical and radiological challenging task and it is even difficult macroscopically unless the tumour infiltrates clearly into adjacent organs. For this reason, the surgical specimen often requires a thorough pathological assessment for the T stage definition.⁵⁶ Some authors report a worse prognosis for patients who had suspected cT4 before surgery but had been diagnosed with pT3, because they were more likely to have perforation.⁵⁷ Moreover, in a previous report (COLOPEC trial) the authors showed a 3% (experimental group) and a 4% (control group) of patients with histologically pT2–pT3 and preoperative cT4. In our results, we will expect a similar rate of preoperative failure of pT4. CHECK STUDY will follow an ITT approach, therefore, all randomised

patients will be included in the primary endpoint analysis. The management of patients with pT2–pT3 tumours erroneously classified will be managed and treated with the same approach of the clinical practice. This approach along with the use of ITT will guarantee a high transferability of our study results.

Given the failure of the last three trials on oxaliplatin-based HIPEC and awaiting the outcomes of the HIPECT4 trial,²⁴ the present study might be useful for establishing national and international clinical practice. If the efficacy of mitomycin-based HIPEC CO₂ is demonstrated, guidelines on the adjuvant treatment of patients at high risk of peritoneal metastases from CRC will reduce the number of peritoneal recurrences and the subsequent burden of hospitalisation and need for care. Otherwise, if locoregional chemotherapy fails once again, it may become inevitable to avoid unnecessary treatment and HIPEC will become something of the past for CRC.

WHO trial registration data set information

1. Primary Registry and Trial Identifying Number: ClinicalTrials.gov - NCT03914820 (<http://clinicaltrials.gov>).
2. Date of Registration in Primary Registry: 16 April 2019.
3. Secondary identifying numbers: n/a.
4. Source(s) of monetary or material support: unconditional grant from ACTA group, Naples, Italy.
5. Primary sponsor: ACOI.
6. Secondary sponsor(s): n/a.
7. Contact for Public Queries: Fabio Pacelli - fabio.pacelli@policlinicogemelli.it.
8. Contact for Scientific Queries: Stefano Rotolo—stefano.rotolo@policlinicogemelli.it.
9. Public title: ‘Prophylactic surgery plus HIPEC CO₂ versus standard surgery in colorectal carcinoma at high risk of PCs. Short and long-term outcomes. CHECK STUDY. A collaborative randomised controlled trial by ACOI, FONDAZIONE AIOM, SIC, SICE, SICO.’
10. Scientific title: ‘Prophylactic surgery plus HIPEC CO₂ versus standard surgery in colorectal carcinoma at high risk of PC. Short-term and long-term outcomes. CHECK STUDY. A collaborative randomised controlled trial by ACOI, FONDAZIONE AIOM, SIC, SICE, SICO.’
11. Countries of Recruitment: Italy.
12. Health condition(s) or problem(s) studied: Colorectal carcinoma at high risk of PC.
13. Intervention(s):
 - Experimental: prophylactic surgery plus HIPEC CO₂ performed with mitomycin.
 - Comparator: standard surgery.
14. Key inclusion and exclusion criteria: see the Methods and analysis section.
15. Study type: Randomised, multicentre, controlled trial with two arms (1:1 allocation ratio).
16. Date of first Enrolment: 19 June 2020.
17. Target sample size: 330 (see page 11).
18. Recruitment status: recruiting.
19. Primary outcome(s): LRFS.
20. Key secondary outcomes: OS, DFS, postsurgery complications, morbidity, duration of surgery, number of patients performing the adjuvant chemotherapy, length of hospitalisation, mortality at 30 and 90 days from surgery.

Protocol Version: v3.0, 03/08/2021

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Funding This trial is supported by an unconditional grant from ACTA GROUP <https://www.actagroup.eu/https://www.actagroup.eu/> (Naples, Italy).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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