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

Fabio Pacelli,[1] Chiara Gerardi,[2] Eliana Rulli,[2] Carlo Abatini,[3] Stefano Rotolo ,[1,4] Silvio Garattini,[2] Gianluigi Melotti,[5] Valter Torri,[2] Fabio Galli,[2] Erica Rulli,[2] Andrea Di Giorgio,[1] On behalf of CHECK Investigators

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).

FP and CG contributed equally.

Received 26 April 2021
Accepted 23 June 2022

For numbered affiliations see end of article.

Correspondence to
Dr Stefano Rotolo;
stefanorotolo@gmail.com

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.

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.

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.

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 antiblastic 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 mytomycin-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.

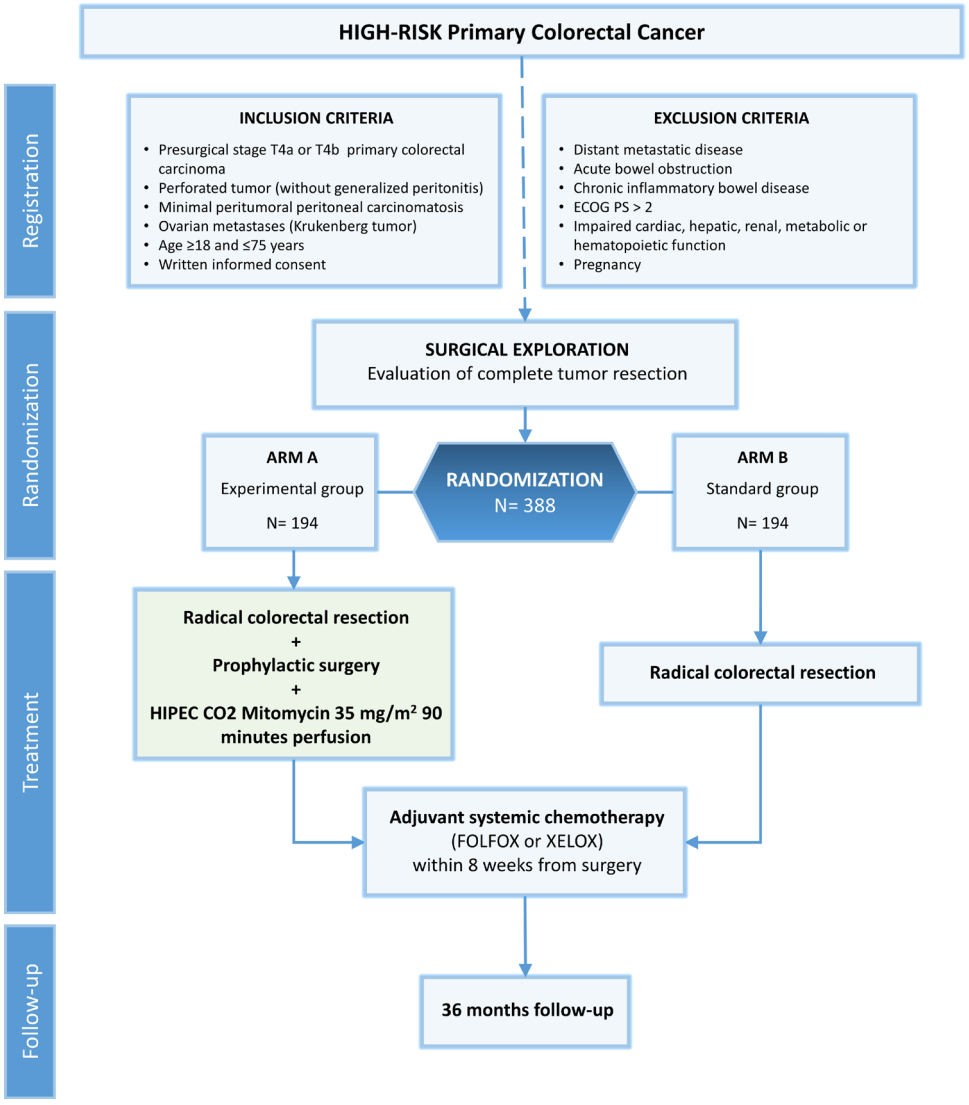

Figure 1 Study protocol flow diagram. HIPEC, hyperthermic intraperitoneal chemotherapy; ECOG, Eastern Cooperative Oncology Group Performance Status; FOLFOX, oxaliplatin, 5-fluorouracil, leucovorin; XELOX, oxaliplatin, capecitabine

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 arythmia 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 <4x10^9/L, neutrophils <1.5 x10^9/L, platelets <100 x10^9/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 CO_2.

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 antiblastic 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 a 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 ProphyloCHIP 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 mytomicin-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

Author affiliations
[1]Chirurgia del Peritoneo e del Retroperitoneo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[2]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy
[3]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[4]Dipartimento di Discipline Chirurgiche, Oncologiche e Stomatologiche (Di.Chir.On.S.), Università degli Studi di Palermo, Palermo, Italy
[5]Associazione Chirurghi Ospedalieri Italiani, Roma, Italy

Collaborators CHECK Investigators - Fondazione Policlinico Universitario A. Gemelli, Roma: F. Pacelli; ASST Grande Ospedale Metropolitano Niguarda, Milano: G. Ferrari; Ospedale Sacro Cuore Don Calabria, Negrar: G. Ruffo; IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG): F. Bazzocchi; ULLS1 1 Dolomiti - Ospedale di Feltre (BL): U. Montin; IRCCS Istituto Tumori Giovanni Paolo II, Bari: M. Simone; Ospedale dell'Angelo, Venezia Mestre: M. Rizzo; IRCCS Policlinico San Donato, S. Donato Milanese (MI): L. Bonavina; Ospedale Evangelico Betania, Napoli: V. Bottino; Azienda Ospedaliera S. Camillo Forlanini, Roma: P. Marini; Azienda Ospedaliera Universitaria Federico II, Napoli: F. Corcione; A.O.R.N. A. Cardarelli, Napoli: C. Antropoli; Azienda Ospedaliera S. Croce e Carle, Cuneo: V. Pruiti Ciariello; ASREM Ospedale Cardarelli, Campobasso: G. Cecere; Fondazione Giovanni Paolo II, Campobasso: F. Rotondi; Ospedale A. Perrino, Brindisi: G. Manca; Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo: G. Gulotta; Azienda Ospedaliera Santa Maria, Terni: A. Parisi; A.R.N.A.S. Ospedali Civico Di Cristina Benfratelli, Palermo: P.E. Marchesa; Ospedale Umberto I, Siracusa: P. Tinè; Azienda Sanitaria Provinciale Ospedale di Lentini, Lentini (SR): G. Trombatore; Policlinico di Milano, Milano: L. Boni; Ospedale Madonna delle Grazie, Matera: G. Pacifico; Azienda Sanitaria Provinciale PO Sant'Elia, Caltanissetta: G. Ciaccio; Ospedale Giovanni Paolo II, Ragusa: G. Di Mauro; Azienda Ospedaliera Universitaria Sant'Orsola Malpighi, Bologna: G. Poggioli; Ospedale Mazzini - ASL Teramo: E. Colangelo; ASP Messina Ospedale San Vincenzo, Taormina: F. Vasta; Ospedale San Carlo, Potenza: A. Giuliani; Fondazione Policlinico Universitario A. Gemelli, Roma: S. Alfieri; Fondazione Policlinico Universitario A. Gemelli, Roma: R. Persiani; Ospedale Bonomo, Adria (BT): E. Restini; Ospedale di Erba, Como: A. Porta; Azienda Ospedaliero Universitaria Careggi, Firenze: S. Scaringi; Ospedale San Donato, Arezzo: G. Mura; Ospedale Cardinale G. Panico, Tricase (LE): M. Viola; Ospedale Generale Regionale F. Miulli, Acquaviva delle Fonti (BA): A. Verbo; Policlinico di Bari: L. Vincenti; Ospedale Molinette, Torino: P. De Paolis; ASST Fatebenefratelli Sacco, Milano: M.A. Zappa; ASST Santi Paolo e Carlo, Milano: E. Opocher; Policlinico di Abano Terme (PD): C. Huscher; Ospedale Infermi di Rimini: G. Garulli; AOU Modena presidio Baggiovara (MO): M. Piccoli; Azienda Ospedaliera Universitaria di Parma: F. Catena; Ospedale Cisanello, Pisa: P. V. Lippolis; Ospedale Cisanello, Pisa: P. Buccianti; Presidio Ospedaliero Santo Spirito, Azienda USL Pescara: M. Basti; Ospedale SS Annunziata, Chieti: F. Mucilli; Ospedale Veris delli Ponti, Scorrano (LE): C. Mastria; Ospedale Vito Fazzi, Lecce: M. Spampinato; IRCCS de Bellis, Castellana Grotte (BA): G. Lantone; Azienda Sanitaria Locale, Presidio Ospedaliero di Gallipoli (LE): D. DeGiorgi; Università di Bari: A. Pezzolla; AO Bianchi Melacrino Morelli, Reggio Calabria: S. Costarella; Azienda Sanitaria Provinciale Ospedale G. Jazzolino, Vibo Valentia: F. Zappia; Presidio Ospedaliero San Giovanni di Dio, Crotone: G. Brisinda; Casa di Cura La Maddalena, Palermo: P. Mezzatesta. IRFMN (Istituto Ricerche Farmacologiche Mario Negri) – Laboratorio di Metodologia della Ricerca Clinica: Erica Rulli, Eliana Rulli, M. De Luca, F. Galli, D. Poli, S. Martini, L. Carlucci, V. Torri. – Centro di Politiche Regolatorie in Sanità: C. Gerardi, V.Bertelè, - President: S. Garattini

Contributors Study concept: FP and CG. Study design: VT, ER, CG. FP, ADG, CA, VT, GM and SR prepared the first draft of the manuscript. SG, ER, ErR and FG revised the manuscript. All authors approved the manuscript.

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.

ORCID iD

Stefano Rotolo http://orcid.org/0000-0002-3981-0794

REFERENCES

1 AIRTUM. AIRTUM – I numeri del cancro in Italia 2017, 2017. Available: http://mediaaiomit/userfiles/files/doc/documenti_scientifici/2017_numeri_del_cancropdf
2 Segelman J, Granath F, Holm T, *et al*. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg*, 2012;99, :699–705.
3 Koppe MJ, Boerman OC, Oyen WJG, *et al*. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006;243:212–22.
4 Grothey A, Sargent D, Goldberg RM, *et al*. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004;22:1209–14.
5 Sorich MJ, Wiese MD, Rowland A, *et al*. Extended Ras mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. *Ann Oncol* 2015;26:13–21.
6 Tabernero J, Yoshino T, Cohn AL, *et al*. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (raise): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015;16:499–508.
7 Cremolini C, Loupakis F, Antoniotti C, *et al*. Folfoxiri plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 tribe study. *Lancet Oncol* 2015;16:1306–15.
8 Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Ann Surg* 1995;221:124–32.
9 Elias D, Blot F, El Otmany A, *et al*. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. *Cancer* 2001;92:71–6.
10 Levine EA, Stewart JH, Shen P, *et al*. Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. *J Am Coll Surg* 2014;218:573–85.
11 Jacquet P, Averbach A, Stephens AD, *et al*. Heated intraoperative intraperitoneal mitomycin C and early postoperative intraperitoneal 5-fluorouracil: pharmacokinetic studies. *Oncology* 1998;55:130–8.
12 Sammartino P, Sibio S, Biacchi D, *et al*. Long-Term results after proactive management for locoregional control in patients with colonic cancer at high risk of peritoneal metastases. *Int J Colorectal Dis* 2014;29:1081–9.
13 Baratti D, Kusamura S, Iusco D, *et al*. Hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of primary curative surgery in patients with colorectal cancer at high risk for metachronous peritoneal metastases. *Ann Surg Oncol* 2017;24:167–75.
14 Graf W, Westlin JE, Påhlman L, *et al*. Adjuvant intraperitoneal 5-fluorouracil and intravenous leucovorin after colorectal cancer surgery: a randomized phase II placebo-controlled study. *Int J Colorectal Dis* 1994;9:35–9.
15 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;74:2224–33.
16 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;47:725–33.
17 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;77:1349–54.
18 Tentes AAK, Spiliotis ID, Korakianitis OS, *et al*. Adjuvant perioperative intraperitoneal chemotherapy in locally advanced colorectal carcinoma: preliminary results. *ISRN Surg* 2011;2011:1–6.
19 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;231:449–56.
20 Goere D, Glehen O, Quenet F, *et al*. Results of a randomized phase 3 study evaluating the potential benefit of a second-look surgery plus HIPEC in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP- NTC01226394). *Journal of Clinical Oncology* 2018;36:3531.
21 Quenet F, Elias D, Roca L, *et al*. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *Journal of Clinical Oncology* 2018;36:A3503.
22 Klaver CEL, Wisselink DD, Punt CJA, *et al*. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. *Lancet Gastroenterol Hepatol* 2019;4:761–70.
23 van Driel WJ, Koole SN, Sikorska K, *et al*. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 2018;378:230–40.
24 Arjona-Sánchez A, Barrios P, Boldo-Roda E, *et al*. HIPECT4: multicentre, randomized clinical trial to evaluate safety and efficacy of hyperthermic intra-peritoneal chemotherapy (HIPEC) with mitomycin C used during surgery for treatment of locally advanced colorectal carcinoma. *BMC Cancer* 2018;18:183.
25 Cavaliere F, De Simone M, Virzì S, *et al*. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. *Eur J Surg Oncol* 2011;37:148–54.
26 Ceelen W, Van Nieuwenhove Y, Putte DV, *et al*. Neoadjuvant chemotherapy with bevacizumab may improve outcome after cytoreduction and hyperthermic intraperitoneal chemoperfusion (HIPEC) for colorectal carcinomatosis. *Ann Surg Oncol* 2014;21:3023–8.
27 Leung V, Huo YR, Liauw W, *et al*. Oxaliplatin versus mitomycin C for HIPEC in colorectal cancer peritoneal carcinomatosis. *Eur J Surg Oncol* 2017;43:144–9.
28 Prada-Villaverde A, Esquivel J, Lowy AM, *et al*. The American Society of peritoneal surface malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. *J Surg Oncol* 2014;110:779–85.
29 Sánchez-García S, Villarejo-Campos P, Padilla-Valverde D, *et al*. Intraperitoneal chemotherapy hyperthermia (HIPEC) for peritoneal carcinomatosis of ovarian cancer origin by fluid and CO2 recirculation using the closed abdomen technique (PRS-1.0 combat): a clinical pilot study. *Int J Hyperthermia* 2016;32:488–95.
30 Cianci S, Vizzielli G, Fagotti A, *et al*. A novel HIPEC technique using hybrid CO_2 recirculation system: intra-abdominal diffusion test in a porcine model. *Updates Surg* 2018;70:529–33.
31 Padilla-Valverde D, Sanchez-Garcia S, García-Santos E, *et al*. Usefulness of thermographic analysis to control temperature homogeneity in the development and implementation of a closed recirculating CO_2 chemohyperthermia model. *Int J Hyperthermia* 2017;33:220–6.
32 Sánchez-García S, Padilla-Valverde D, Villarejo-Campos P, *et al*. Hyperthermic chemotherapy intra-abdominal laparoscopic approach: development of a laparoscopic model using CO_2 recirculation system and clinical translation in peritoneal carcinomatosis. *Int J Hyperthermia* 2017;33:684–9.

33 Noncommunicable diseases S, Monitoring and Reporting. *The impact of the COVID-19 pandemic on noncommunicable disease resources and services: results of a rapid assessment*, 2020.
34 Sharpless NE. COVID-19 and cancer. *Science* 2020;368:1290.
35 Smrke A, Younger E, Wilson R, *et al*. Telemedicine during the COVID-19 pandemic: impact on care for rare cancers. *JCO Glob Oncol* 2020;6:1046–51.
36 AIOM - Linee guida tumori del Colon 2021.
37 Argilés G, Tabernero J, Labianca R, *et al*. Localised colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31:1291–305.
38 Cianci S, Abatini C, Fagotti A, *et al*. Hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal malignancies using new hybrid CO_2 system: preliminary experience in referral center. *Updates Surg* 2019;71:555–60.
39 Rotolo S, Di Giorgio A, Santullo F, *et al*. Cytoreductive surgery and mitomycin C hyperthermic intraperitoneal chemotherapy with CO 2 recirculation (HIPEC-CO 2) for colorectal cancer peritoneal metastases: analysis of short-term outcomes. *Updates in Surgery* 2021;29:1–6.
40 Clavien PA, Barkun J, de Oliveira ML, *et al*. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187–96.
41 Kaibara N, Hamazoe R, Iitsuka Y, *et al*. Hyperthermic peritoneal perfusion combined with anticancer chemotherapy as prophylactic treatment of peritoneal recurrence of gastric cancer. *Hepatogastroenterology* 1989;36:75–8.
42 Koga S, Hamazoe R, Maeta M, *et al*. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer* 1988;61:232–7.
43 Yonemura Y, de Aretxabala X, Fujimura T, *et al*. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. *Hepatogastroenterology* 2001;48:1776–82.
44 Coccolini F, Celotti A, Ceresoli M, *et al*. Hyperthermic intraperitoneal chemotherapy (HIPEC) and neoadjuvant chemotherapy as prophylaxis of peritoneal carcinosis from advanced gastric cancer-effects on overall and disease free survival. *J Gastrointest Oncol* 2016;7:523–9.
45 Kim JY, Bae HS. A controlled clinical study of serosa-invasive gastric carcinoma patients who underwent surgery plus intraperitoneal hyperthermo-chemo-perfusion (IHCP). *Gastric Cancer* 2001;4:27–33.
46 Kunisaki C, Shimada H, Nomura M, *et al*. Lack of efficacy of prophylactic continuous hyperthermic peritoneal perfusion on subsequent peritoneal recurrence and survival in patients with advanced gastric cancer. *Surgery* 2002;131:521–8.
47 Kunisaki C, Shimada H, Nomura M, *et al*. Therapeutic strategy for scirrhous type gastric cancer. *Hepatogastroenterology* 2005;52:314–8.
48 Murata S, Kaida S, Kodama H, *et al*. A propensity-matched analysis comparing hepatic recurrence after curative gastrectomy followed by adjuvant HIPEC to surgery alone for advanced gastric cancer. *JCO* 2016;34:4056.
49 Ceelen W. HIPEC with oxaliplatin for colorectal peritoneal metastasis: the end of the road? *Eur J Surg Oncol* 2019;45:400–2.
50 Johnson B, Eng C. More questions regarding HIPEC in colorectal carcinomatosis. *Lancet Gastroenterol Hepatol* 2019;4:744–5.
51 Panteix G, Guillaumont M, Cherpin L, *et al*. Study of the pharmacokinetics of mitomycin C in humans during intraperitoneal chemohyperthermia with special mention of the concentration in local tissues. *Oncology* 1993;50:366–70.
52 Song N, Pogue-Geile KL, Gavin PG, *et al*. Clinical outcome from oxaliplatin treatment in stage II/III colon cancer according to intrinsic subtypes: secondary analysis of NSABP C-07/NRG oncology randomized clinical trial. *JAMA Oncol* 2016;2:1162–9.
53 Verwaal VJ, van Ruth S, de Bree E, *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;21:3737–43.
54 van Santvoort HC, Braam HJ, Spekreijse KR, *et al*. Peritoneal carcinomatosis in T4 colorectal cancer: occurrence and risk factors. *Ann Surg Oncol* 2014;21:1686–91.
55 Nerad E, Lahaye MJ, Maas M, *et al*. Diagnostic accuracy of CT for local staging of colon cancer: a systematic review and meta-analysis. *American Journal of Roentgenology* 2016;207:984–95.
56 Stewart CJR, Hillery S, Platell C, *et al*. Assessment of serosal invasion and criteria for the classification of pathological (P) T4 staging in colorectal carcinoma: confusions, controversies and criticisms. *Cancers* 2011;3:164–81.
57 Choo J-M, Baek S-J, Kwak J-M, *et al*. Clinical characteristics and oncologic outcomes in patients with preoperative clinical T3 and T4 colon cancer who were staged as pathologic T3. *Ann Surg Treat Res* 2020;99:37–43.

Studio clinico CHECK
Informativa e consenso al trattamento dei dati personali
Versione 2.0 del 08/01/2021

INFORMATIVA PER IL TRATTAMENTO DEI DATI PERSONALI

Titolo dello studio: Chirurgia profilattica e chemioterapia intraperitoneale in ipertermia (HIPEC CO2) versus chirurgia standard nel carcinoma colorettale ad alto rischio di carcinosi peritoneale. Risultati a breve e a lungo termine. Studio collaborativo randomizzato controllato di: ACOI, Fondazione AIOM, SIC, SICE, SICO_STUDIO CHECK (di seguito denominato lo "Studio")
Centro di Sperimentazione:_____ (nome/indirizzo dell'Ospedale/Ente) (di seguito denominato il "Centro di Sperimentazione")
Promotore: Associazione Chirurghi Ospedalieri Italiani (ACOI) (di seguito denominato il "Promotore")
Coordinatore dello Studio: Istituto di Ricerche Farmacologiche Mario Negri IRCCS (di seguito denominato il "Coordinatore dello Studio")

Titolare e Responsabile della Protezione dei dati Il Centro di Sperimentazione e il Promotore che ha commissionato lo Studio (inclusi suoi partner di ricerca, designati e rappresentanti che collaborano allo Studio), in qualità di Titolari del Trattamento, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme di Buona Pratica Clinica (D.L. 211/2003), dal Regolamento UE 2016/679 del Parlamento e del Consiglio Europeo relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati (di seguito GDPR), dall'Autorizzazione generale n.9/2016 al trattamento dei dati personali effettuato a scopi di ricerca scientifica del 15 dicembre 2016, dall'Autorizzazione generale n.8/2016 al trattamento dei dati genetici del 15 dicembre 2016 e dalla Delibera del Garante per le "Linee guida per i trattamenti di dati personali nell'ambito delle sperimentazioni cliniche di medicinali" del 24 luglio 2008 e successive modifiche, tratteranno i Suoi dati personali, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello Studio e per le finalità di seguito indicate.
Il Promotore ha delegato il Coordinatore dello Studio alla raccolta, trattamento, analisi dei dati, gestione dello studio e monitoraggio.

La informiamo che i Titolari, ai sensi dell'articolo 37 del GDPR EU 2016/679, hanno proceduto ad individuare e nominare il Responsabile della Protezione dei dati (anche "Data Protection Officer" o "DPO":
DPO del Centro di Sperimentazione:
[compilare campo]

DPO del Coordinatore dello Studio, delegato del Promotore:
CDR Cattaneo Dall'Olio Rho & Partners Tax & Legal
Email: DPO@marionegri.it

Categorie di dati oggetto del trattamento
Il presente trattamento avrà ad oggetto i Suoi dati personali, di seguito meglio specificati:

a) Dati identificativi: data di nascita;
b) Dati particolari ex art. 9 GDPR, relativi al Suo stato di salute; al Suo peso, alla Sua statura, alla Sua origine, ai Suoi stili di vita.

Finalità del trattamento
I dati sopra descritti verranno trattati per le seguenti finalità:

- consentire lo svolgimento della ricerca in parola e di tutte le relative operazioni ed attività connesse,
- farmacovigilanza.

Studio clinico CHECK
Informativa e consenso al trattamento dei dati personali
Versione 2.0 del 08/01/2021

Base giuridica del trattamento
Il consenso informato costituisce la base giuridica per il trattamento dei Suoi dati per gli scopi descritti nella scheda informativa. In assenza di consenso firmato non potremo utilizzare i Suoi dati per la conduzione e le analisi dello Studio.
Potrà interrompere la Sua partecipazione in qualsiasi momento e senza fornire alcuna motivazione; in tal caso, i Suoi dati verranno trattati come descritto nella scheda informativa dello Studio. Non saranno inoltre raccolti ulteriori dati che La riguardano, ferma restando l'utilizzo di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

Natura del conferimento dei dati
La partecipazione alla sperimentazione avviene su base volontaria, pertanto, il conferimento dei dati personali è assolutamente volontario, nel senso che Lei può decidere di non conferire i Suoi dati personali e, quindi, di non partecipare allo Studio.

Modalità di Trattamento dei dati
Le finalità sopra indicate prevedono lo svolgimento del trattamento dei dati personali mediante strumenti manuali ed informatici con logiche strettamente correlate alle finalità stesse e, comunque, in modo da garantire la sicurezza e la riservatezza dei dati stessi.
I dati raccolti per i fini dello Studio verranno gestiti in forma codificata.
Il medico che La seguirà nello Studio, La identificherà con un codice che non permetterà di risalire direttamente alla Sua identità, se non presso il Centro Partecipante. I dati che La riguardano, raccolti nel corso dello Studio, ad eccezione del Suo nominativo, saranno trasmessi al Promotore e dallo Stesso registrati, elaborati e conservati.
Soltanto il medico, il personale responsabile del monitoraggio dello Studio (Istituto di Ricerche Farmacologiche Mario Negri IRCCS) e il personale delegato dalle Autorità Competenti per attività di verifica, potranno collegare questo codice al Suo nominativo quando necessario.

Ambito di comunicazione dei dati
La Sua partecipazione allo Studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale del Promotore o suo delegato o delle società esterne che eseguono per conto del Promotore il monitoraggio e la verifica dello Studio, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.
La diffusione dei dati scientifici risultanti dalle analisi dei dati dello Studio, potrà avvenire solo in forma anonima e per sole finalità scientifiche. In pratica, i risultati delle ricerche scientifiche, potranno essere presentati in forma aggregata nell'ambito di Convegni o pubblicati su riviste specializzate senza mai permettere la precisa identificazione dei pazienti.
Se previsto dal protocollo, i Suoi dati personali potranno essere trasferiti a Centri esterni per le finalità previste dal protocollo, designati dai Titolari quali "Responsabili del trattamento".
Potrà conoscere l'elenco aggiornato dei Responsabili del Trattamento, inviando una comunicazione ai riferimenti sopra riportati.

Politica in materia di conservazione dei dati personali
I dati personali raccolti nell'ambito di questo Studio verranno conservati presso il Centro sperimentale, il Promotore e le strutture coinvolte nello Studio, per un periodo minimo di 7 anni dopo la conclusione dello Studio o per un periodo più lungo, se necessario, in base ad ulteriori requisiti di legge.

Diritti dell'Interessato

Diritto di accesso ai dati

Può chiedere di consultare le informazioni che sono state raccolte su di Lei. Tuttavia, per salvaguardare l'integrità scientifica dello Studio, potrebbe non essere possibile accedere ad alcuni dati prima della conclusione dello Studio stesso.

Diritto di rettifica ai dati

Può richiedere la modifica dei dati che La riguardano, qualora fossero errati o incompleti. Durante la valutazione di tale richiesta, ha il diritto di limitare il trattamento dei dati che La riguardano.

Diritto di portabilità dei dati

Può richiedere il trasferimento dei dati che La riguardano a Lei stesso o a qualcun altro in un formato comunemente utilizzato (cartaceo o elettronico).

Diritto di cancellazione dei dati

Può ritirare il consenso in qualsiasi momento senza darne motivazione alcuna. Può ritirare il consenso per il trattamento dello Studio e/o il follow up successivo, anche senza ritirare il consenso per il trattamento dei dati. Qualora cambiasse idea sul trattamento dei Suoi dati, non sarà possibile rimuovere le informazioni personali già elaborate per lo Studio prima del Suo ritiro (coperte dal consenso originale). In seguito, al ritiro del consenso al trattamento dei Suoi dati non verrebbero acquisite ulteriori informazioni che La riguardano.

Diritto di reclamo

Può presentare un reclamo presso l'autorità incaricata della protezione dei dati:
Garante della privacy, E-mail: garante@garanteprivacy.it Sito web: http://www.garanteprivacy.it/

In merito all'esercizio di tali diritti, potrà rivolgersi direttamente al Centro di sperimentazione [indicare il nome di una persona fisica o di un ufficio responsabile e un recapito] o, per il suo tramite, al Responsabile della protezione dei dati del Promotore.

Studio clinico CHECK
Informativa e consenso al trattamento dei dati personali
Versione 2.0 del 08/01/2021

Consenso al trattamento dei dati personali
ai sensi del GDPR UE 2016/679

Preso atto dell'informativa di cui all'art. 13 del GDPR UE 2016/679, il sottoscritto_____,
nato a_____, il_____,
in qualità di

□ interessato

□ amministratore di sostegno dell'incapace naturale/rappresentante legale_____, nato a_____, il _____.

□ dà il proprio consenso □ nega il proprio consenso
al trattamento dei dati per finalità relative alla sperimentazione clinica

□ dà il proprio consenso □ nega il proprio consenso
alla eventuale cessione dei dati in forma anonima ad aziende farmaceutiche o ad altri soggetti che utilizzino gli stessi a scopo di studio o ricerca.

□ dà il proprio consenso □ nega il proprio consenso
affinché i risultati delle analisi e di eventuali scoperte inattese che emergano durante le attività di sperimentazione siano comunicate a:

□ me medesimo
□ familiare (Cognome e nome _____)
□ convivente /coniuge (Cognome e nome _____)
□ medico di famiglia (Cognome e nome _____)

Firma del/della paziente _____

Data _____

Studio clinico CHECK
Modulo di revoca del consenso
Versione 2.0 del 08/01/2021

MODULO PER LA REVOCA DEL CONSENSO INFORMATO

ALLA PARTECIPAZIONE ALLO STUDIO e AL TRATTAMENTO DEI DATI

Chirurgia profilattica e chemioterapia intraperitoneale in ipertermia (HIPEC CO_2) versus chirurgia standard nel carcinoma colorettale ad alto rischio di carcinosi peritoneale. Risultati a breve e a lungo termine. Studio collaborativo randomizzato controllato di: ACOI, Fondazione AIOM, SIC, SICE, SICO

STUDIO CHECK

Numero identificativo assegnato al/alla paziente: _____

Io sottoscritto/a _____ _____,
(Nome e Cognome in stampatello)

Dichiaro di voler revocare volontariamente il mio consenso alla partecipazione allo studio e al trattamento dei dati personali, come mi era stato descritto nel modulo di consenso informato da me precedentemente sottoscritto, senza pregiudicare le mie cure mediche né i miei diritti legali e senza che tale scelta modifichi in alcun modo i miei rapporti con il personale medico e sanitario della struttura.

Sono consapevole che le informazioni personali già ottenute saranno conservate per assicurare la corretta valutazione dei risultati dello studio e la conformità alle disposizioni di legge.
Sono altresì a conoscenza del fatto che i dati raccolti fino al momento del mio ritiro rimangono parte dei risultati dello studio.

Firma del/della paziente _____ data _____

Firma del rappresentante legale /testimone/amministratore di sostegno

_____ data _____

Studio clinico CHECK
Modulo di revoca del consenso
Versione 2.0 del 08/01/2021

DICHIARAZIONE DEL MEDICO

Io sottoscritto/a _____dichiaro di aver fornito l'informazione sulla revoca del consenso, di aver documentato in cartella clinica la volontà del/della paziente e di aver fornito copia del presente modulo.

Data: _____

Nome e cognome del medico _____
(in stampatello)

Firma del medico: _____
(leggibile)

REDATTO IN DUE COPIE: L'ORIGINALE DA CONSERVARSI A CURA DEL MEDICO DELLO STUDIO E LA COPIA DA CONSEGNARE AL/ALLA PAZIENTE

Pacelli F, *et al. BMJ Open* 2022; 12:e051324. doi: 10.1136/bmjopen-2021-051324