

Prophylactic surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC CO₂) versus standard surgery for gastric carcinoma at high risk of peritoneal carcinomatosis. Short and long-term outcomes. GOETH STUDY. A collaborative randomized controlled trial by ACOI, FONDAZIONE AIOM, SIC, SICE, SICO

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Research Article

Keywords: gastric cancer, prophylactic surgery, HIPEC CO2, hyperthermic intraperitoneal chemotherapy, mitomycin, cisplatin

Posted Date: March 14th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1304250/v1>

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Title Page

Prophylactic surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC CO2) versus standard surgery for gastric carcinoma at high risk of peritoneal carcinomatosis. Short and long-term outcomes. GOETH STUDY. A collaborative randomized controlled trial by ACOI, FONDAZIONE AIOM, SIC, SICE, SICO.

PROTOCOL NUMBER: IRFMN-GCC-7813

EUDRACT NUMBER: 2019-001478-27

CLINICALTRIALS.GOV NUMBER: NCT03917173

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ABSTRACT

Background: At the time of diagnosis, 15-20% of gastric carcinomas are in stage T4 or T4b.

Furthermore, 5-20% of patients undergoing potentially curative surgery suffer from synchronous or metachronous peritoneal metastases. To date, neither surgery nor systemic chemotherapy successfully controls peritoneal dissemination, offering a limited impact on survival. Peritoneal metastases are in fact responsible for death in around 60% of gastric cancer patients.

Several Eastern studies in the past have focused on HIPEC as a prophylactic measure in patients with serosal extension, nodal involvement and positive peritoneal fluid cytology. Therefore a new multimodal therapeutic strategy based on aggressive surgery plus new locoregional treatment may prolong survival in this particular clinical scenario.

Methods: This study compares the efficacy of prophylactic surgery (radical gastric resection, appendectomy, resection of the round ligament of the liver, and bilateral adnexectomy) plus HIPEC CO₂ versus standard surgery in patients with T3-T4 N0-N+ gastric adenocarcinoma. Patients will be randomly assigned (1:1 ratio) to the experimental arm or standard surgery. The primary endpoint is to establish the difference in disease-free survival between the groups. The secondary objective is to compare the safety and tolerability of prophylactic surgery plus HIPEC CO₂ versus standard surgery.

Discussion: Considering the poor prognosis of patients with peritoneal dissemination from gastric cancer, a prophylactic strategy to prevent peritoneal metastases may be beneficial. In patients with gastric cancer at high risk of peritoneal carcinomatosis, the treatment of minimal or unforeseen peritoneal disease together with primary tumor resection should reduce peritoneal recurrence. We

propose aggressive surgical treatment with radical gastric resection, removal of organs at risk of harbouring tumor cells, and HIPEC.

Trial registration: NCT03917173

Protocol version: v3, August 3, 2021

Keywords: gastric cancer, prophylactic surgery, HIPEC CO₂, hyperthermic intraperitoneal chemotherapy, mitomycin, cisplatin

World Health Organization Trial Registration Data Set information

1. Primary Registry and Trial Identifying Number: NCT03917173 (<http://clinicaltrials.gov>)
2. Date of Registration in Primary Registry: April 26, 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: Associazione Chirurghi Ospedalieri Italiani (ACOI)
6. Secondary Sponsor(s): n/a
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9. Public Title: “Prophylactic surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC CO₂) versus standard surgery in gastric carcinoma at high risk of peritoneal carcinomatosis. Short and long-term outcomes. GOETH STUDY. A collaborative randomized controlled trial by ACOI, FONDAZIONE AIOM, SIC, SICE, SICO.
10. Scientific Title:.. Prophylactic surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC CO₂) versus standard surgery in gastric carcinoma at high risk of peritoneal carcinomatosis. Short

and long-term outcomes. GOETH STUDY. A collaborative randomized controlled trial by ACOI, FONDAZIONE AIOM, SIC, SICE, SICO.

11. Countries of Recruitment: Italy

12. Health Condition(s) or Problem(s) Studied: Gastric carcinoma at high risk of peritoneal carcinomatosis

13. Intervention(s):

- experimental: prophylactic surgery plus HIPEC CO₂ with mitomycin and cisplatin
- comparator: standard surgery

14. Key Inclusion and Exclusion Criteria: see Methods and Analysis section

15. Study Type: Randomized, multicenter, controlled trial with two arms (1:1 allocation ratio)

16. Date of First Enrollment: June 1,2020

17. Target Sample Size: 240 patients

18. Recruitment Status: Recruiting

19. Primary Outcome(s): Disease-Free Survival

20. Key Secondary Outcomes: Overall survival, Local-recurrence free survival, post- surgery complications, morbidity, duration of surgery, number of patients receiving the adjuvant chemotherapy, length of hospitalization, mortality 30 and 90 days from surgery

Strengths and limitations of this trial

Strengths

- Rationale for CO₂ infusion that generates intra-abdominal turbulence to overcome the drug distribution issues of the closed approach
- Randomized controlled trial with a novel HIPEC system with simultaneous use of the HIPEC technique since all participating centers will follow the same HIPEC protocol
- No delay between surgery and HIPEC

Limitations

- Possible delay in starting adjuvant treatment in the experimental arm because of the added chemotherapy
- No preoperative stratification based on tumor pathology or mutational profile
- Different perioperative systemic chemotherapy regimens allowed

1. Background

Gastric cancer is the fifth most common form of neoplasm worldwide and third for mortality. [1] At diagnosis, 15-20% of gastric carcinomas are in stage T4 or T4b. [2] Synchronous or metachronous peritoneal metastases are very common in patients with locally advanced gastric carcinomas, [3,4] affecting 5-20% of those undergoing potentially curative surgery [5]. For diffuse adenocarcinomas, the incidence ranges between 30% and 60% and can be as high as 80% if peritoneal fluid cytology tests positive [3,5]. Moreover, after R0 gastrectomy surgery, the peritoneal recurrence rate is about 30%.

To date, neither surgery nor systemic chemotherapy ensure satisfactory control of peritoneal dissemination and have no significant impact on survival [6]. Systemic chemotherapy has a limited effect, with average survival 7 to 12 months [7 – 10] and peritoneal metastases are the cause of death in around 60% [11].

So far the literature seems to point towards perioperative systemic chemotherapy as a first-intention option in potentially resectable, locally advanced gastric carcinoma. Perioperative chemotherapy has an advantage over surgery alone in terms of survival, with reductions in the relative risk (19%) and absolute risk (9%) of recurrence of the disease. Perioperative poly-chemotherapy has also given a survival advantage over adjuvant chemotherapy alone. [12,13]

Hyperthermic intraperitoneal chemotherapy (HIPEC) is suggested as a treatment integrating cytoreductive surgery for carcinomatosis and as a precautionary strategy in locally advanced gastric carcinoma at risk of recurrence, with the aim of improving overall survival and reducing peritoneal recurrence [14]. The theoretical advantages of HIPEC consist in administering large quantities of

antiblastic drugs to the abdominal cavity, reducing their systemic toxicity, and exploiting the synergistic effect of hyperthermia which contributes to antitumoral efficacy in several ways. [15,16] Several Asiatic trials have focused on HIPEC as a prophylactic measure in patients with serosal extension, nodal involvement and positive peritoneal fluid cytology. Most of them were conducted between 1988 and 2001, using mitomycin and cisplatin for intraperitoneal chemotherapy and with variable HIPEC temperatures and flow rates. No adjuvant or neoadjuvant systemic chemotherapy was used in these studies and the five-years overall survival (OS) ranges from 42% to 66% in the experimental groups. These pioneering Asiatic experiences had encouraging oncological outcomes, theoretically supporting the use of HIPEC for the prevention of peritoneal recurrence in gastric cancer. [17-22].

These results are also confirmed by two meta-analyses: Cocolini et al. studied 20 randomized clinical trials on surgery with intraperitoneal chemotherapy in patients with advanced gastric cancer; 2145 patients were included, 1152 of them treated with surgery plus intraperitoneal chemotherapy and 993 surgery alone. The meta-analysis showed that surgery with intraperitoneal chemotherapy reduced overall mortality at 1, 2 and 3 years; mortality at 2 and 3 years in patients with locoregional lymph node metastasis; mortality at 1 and 2 years in patients with serosal involvement; the rates of hematogenous metastases and peritoneal recurrence.[5] Feingold et al. in a systematic review with 2029 treated patients, reported that intraoperative chemotherapy in patients at high risk of peritoneal carcinomatosis from gastric cancer reduced mortality at five years.[14] This considerations raise the question of whether the results apply to the western population. The lack of solid evidence has led national and international clinical guidelines not to support the use of adjuvant HIPEC outside a clinical trial.

The GOETH study was designed to address this knowledge gap.

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

A recent WHO survey 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 lockdowns, staff shortages and closure of hospital services. Globally, 2.3 million cancer surgeries were cancelled or postponed during the peak 12-week period of Covid-19. One main reason for these disruptions of services was the closure of population-level screening programmes and lockdowns, hindering access to health facilities. [23]

A paper from Nature points out that modelling the effect of COVID-19 on cancer screening and treatment for breast and colorectal cancer (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 tumors during a period when one could expect 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. [24]

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 oral drug-based therapy. [25]

2. Method and analysis

2.1. Hypothesis

In patients with gastric cancer at high risk of peritoneal carcinomatosis (PC), treatment of minimal or unforeseen peritoneal disease together with primary tumor resection should reduce peritoneal recurrence.

2.2. Primary objective

The primary objective of the study is to compare the efficacy of prophylactic surgery with HIPEC CO₂ versus standard surgery in terms of disease-free survival (DFS) in patients with gastric carcinoma (GC) at high risk of developing peritoneal carcinomatosis.

2.3. Secondary objectives

- To compare the experimental treatment (prophylactic surgery plus mitomycin and cisplatin-based HIPEC CO₂) versus standard treatment on local recurrence-free survival (LRFS) and OS.
- To assess the safety (treatment-related morbidity and mortality) of this experimental approach.

2.4. Study design

This is a phase III, randomized, open label, multicenter trial in patients with gastric carcinoma, at high risk of peritoneal carcinomatosis. Patients may have had neoadjuvant chemotherapy according to clinical practice, or direct surgery. If, after diagnostic exams, patients are eligible for the trial and resection of the tumor is total during surgery, patients will be randomly assigned (1:1 ratio) not more than 24 hours before surgery to prophylactic surgery plus HIPEC CO₂ (Arm A) or to standard surgery (Arm B), The primary objective is to compare the efficacy of prophylactic surgery (radical

gastric, appendectomy, resection of the round ligament of the liver and bilateral adnexectomy) plus HIPEC CO₂ versus standard surgery in terms of DFS. The secondary objective is to compare the safety profile and tolerability of prophylactic surgery plus HIPEC CO₂ versus standard surgery.

2.5. Participants

The target population comprises patients with gastric carcinoma, at high risk of peritoneal carcinomatosis. The inclusion and exclusion criteria are reported below.

Inclusion criteria

1. Patients with histologically documented gastric carcinoma (diffuse/intestinal histotype) eligible for R0 with :a) Presurgical or intraoperative stage T3-T4 N0-N+ primary tumour (TNM 8 th). b) Urgent presentation: perforation without purulent generalized peritonitis c) Positive cytology of peritoneal fluid (if previously obtained)
2. Age \geq 18 years and \leq 75 years.
3. Written informed consent.

Exclusion criteria

- 1.Gastroesophageal Junction (GEJ) cancer
- 2.Distant metastatic disease (even if limited and completely resected)
- 3.Peritoneal carcinomatosis

4. History of tumour diagnosed in the 3 years before entering the study, except for topical and healed pathologies that do not need further treatment (e.g. non-melanoma skin carcinomas, superficial bladder carcinomas or in situ carcinoma of the breast or cervix).
5. Psychological, family or social conditions which may negatively affect the treatment and follow-up protocol.
6. Poor general condition (ECOG > 2).
7. Impaired cardiac function (history of congestive heart failure or FE <40%). Clinically significant cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrolment), unstable angina, congestive heart failure (New York Heart Association Classification Class > II) or serious uncontrolled cardiac arrhythmia requiring medication
8. Impaired renal function (creatinine > 1.5 upper limit of normal or creatinine clearance <60 mL / min).
9. Impaired hepatic function (AST, ALT >2.5 upper limit of normal, bilirubin > 1.5 upper limit of normal).
10. Impaired hematopoietic function (leucocytes <4000 /mm³, neutrophils <1500 / mm³, platelets <100000 / mm³).
11. Impaired pulmonary function (presence of COPD or other pulmonary restrictive conditions with FEV₁ <50% or DLCO <40% of normal age value).
12. History or presence of other disease, metabolic dysfunction, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicate use of HIPEC or chemotherapy or patient at high risk from treatment complications.
13. Pregnancy.
14. Krukenberg tumor
15. Refusal to join the study

2.6. Randomization

Patients will be randomized no more than 24 hours before surgery if total resection of the tumor is intended, and a stratification procedure based on center and neoadjuvant chemotherapy will be used. Patients will be randomized in a 1:1 ratio. The treatment assignment will be retrieved within the eCRF; the randomization will be produced by a computer software program that incorporates a randomization list previously generated by the coordinating center.

2.7. Treatment regimen

Patients assigned to Arm A will receive prophylactic surgery and HIPEC CO₂ with cisplatin and mitomycin in addition to primary tumor resection. Patients randomized to standard surgery (Arm B) will be operated to clinical practice, without HIPEC CO₂.

During surgery, surgeons will assess the presence of peritoneal carcinomatosis; and if it is found, patients randomized to Arm A will not receive HIPEC and will be operated to surgery according to clinical practice.

2.8. Surgery

Diagnostic laparoscopy is suggested. Before surgical resection peritoneal washing will be done for definitive cytological examination. Both the laparotomic and laparoscopic surgical approaches are allowed according to clinical practice. In the experimental arm the prophylactic surgery will include radical gastrectomy with D2 lymphadenectomy and omentectomy, resection of the round ligament of the liver, bilateral adnexectomy and appendectomy. For women of child-bearing age, bilateral

adnexectomy should be discussed. In the comparator arm radical standard surgery will be done.

2.9. Hyperthermic intraperitoneal chemotherapy (HIPEC) procedure

In the experimental arm A, patients will undergo HIPEC. We will use a closed-abdomen HIPEC technique with CO₂ agitation, using a specific CE-marked device with multi-perforated catheters, two placed in the upper abdomen for the chemotherapy infusion and other two in the lower abdomen for fluid aspiration and CO₂ infusion. Chemotherapy with the perfusion solution at 42°C and CO₂ flowed into the abdominal cavity; turbulent flow was created to improve drug distribution. HIPEC may be done after laparoscopic or laparotomic primary tumor resection without interference with the standard surgical techniques.

The HIPEC CO₂ regimen will be as reported below: mitomycin 15 mg/mq and cisplatin 75 mg/mq both in physiologic solution 0.9%.

The recommended temperature for HIPEC treatment is 42°C for 60 minutes of perfusion

Sodium thiosulfate will be administered to prevent nephrotoxicity induced by cisplatin as follows:

Sodium thiosulfate 9 g/mq bolus and then sodium thiosulfate 1.2g/mq/h with continuous infusion for 6 hours. Adequate preoperative and postoperative intravenous hydration is necessary.

2.10. Perioperative and adjuvant chemotherapy

Clinically staged T3-4 N0-1 M0 patients should be considered for a perioperative approach.

Neo-adjuvant treatment consists of three months of chemotherapy followed, after surgery, by another three months of chemotherapy according to the same regimen used preoperatively. One can choose between epirubicin, cisplatin, fluorouracil/capecitabine (ECF/ECX) or oxaliplatin,

capecitabine (XELOX) or oxaliplatin, fluorouracil/leucovorin (FOLFOX-4) or fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT). For patients who receive FLOT before surgery, chemotherapy could be changed after surgery in case of toxicity or on the basis of a medical decision. Patients not receiving neoadjuvant chemotherapy will be given chemotherapy for six months in the adjuvant setting (consider ECF/ECX or FOLFOX/XELOX regimen). Adjuvant treatment should start within 8-12 weeks from surgery.

2.11. Disease Assessment

Before randomization, complete blood count (CBC), blood chemistry (glucose, sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), aspartate transaminase (AST), total and direct bilirubin, albumin and total protein), coagulation tests (prothrombin time (PT), activated partial thromboplastin time (aPTT), INR), tumour markers (CEA, CA 19.9), B-HCG test, electrocardiogram test, will be scheduled according to clinical practice. Thoraco-abdominal computed tomography is mandatory before surgery and evaluation with endoscopic ultrasound (EUS) is suggested. Moreover, will be collected information about patients' anamnesis and primary tumour characteristics.

A computed tomography scan (CT scan) should be done six weeks after surgery and adjuvant treatment should start within eight weeks from surgery. Histological examination after surgery is required in order to confirm clinical and radiological findings before surgery according to TNM.

2.12. Study endpoints

2.12.1. Efficacy

The primary efficacy endpoint is disease-free survival. DFS is defined as the time from randomization to the date of first local relapse, distant relapse, peritoneal carcinomatosis, or death for any cause, whichever comes first. Patients alive and without relapse will be censored at their last disease evaluation.

The secondary efficacy endpoints are: local recurrence free survival (LRFS) and Overall Survival. LRFS is defined as the time from randomization to the date of first local relapse, peritoneal carcinomatosis or death for any cause, whichever comes first. OS is defined as the time from randomization to death for any cause.

2.12.2. Safety

The safety endpoints will be:

mortality 30 and 90 days from surgery; morbidity during and after surgery (graded according to the NCI-CTAE version 4.03 for AE related to chemotherapy and according to Clavien Dindo for surgery complications); (34, 41-42) the number of post-surgery complications; the duration of surgery; the length of hospitalization; the number of patients receiving the adjuvant chemotherapy.

2.13. Sample size

Setting a two-side type I error of 4.9% and a 80% power to detect a relative reduction of 33% of risk of relapse/death events in arm A compared to arm B, 200 events are required. Assuming median DFS of one year in the control group, 36 months of accrual and 36 months of follow-up, approximately 240 patients (120 per arm) will be needed to get the required number of DFS events.

Assuming a 15% of randomized patients not eligible because of peritoneal carcinomatosis undetected by CT scan and discovered only during the surgical procedure, it will be necessary to randomize a total of 282 patients (141 per arm) so as to have approximately 240 patients for analysis of the primary endpoint.

2.14. Statistical analysis

Efficacy will be analysed on the modified intention to treat (mITT) population, including all patients randomized, without major violations of eligibility criteria and no evidence of peritoneal carcinomatosis (detected during surgery).

DFS and OS will be described with the Kaplan-Meier method. Differences between arms will be tested by the Log-rank test, and by univariate and multivariate Cox's models, including stratification variables and other clinical-biological features as covariates. LRFS will be described with a cumulative incidence function and will be analysed with a Grey test to take account of the competing risks.

An interim analysis of efficacy will be done when half of the events have been observed. The conservative Haybittle-Peto boundary will be used as stopping guidance in order to ensure final analysis at the significance level of 0.049.

2.15. Data collection, management and analysis

Data will be collected using an electronic case report form (CRF). A data timing plan and data validation plan, developed by the statisticians and data managers of the coordinating center, will be used to request data input (RID) in the electronic CRF and to check the data entered by data

clarification forms (DCF). The Sponsor maintains confidentiality standards by assigning a unique patient identification number to code.

2.16. Quality assurance

Each 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 Center, that will issue DCFs in case of inconsistent data. Local quality control will be provided by the coordinating center, which will be responsible for monitoring all the centers.

2.17. Monitoring the trial

During the trial a sponsor's representative will have regular contact 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, that data are being accurately and timely recorded in the eCRFs; to 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.

2.18. Trial management

2.18.1. Administrative structure

The coordinating center is the Policlinico Universitario Agostino Gemelli IRCCS, Roma.

The Sponsor is “Associazione Chirurghi Ospedalieri Italiani (ACOI)”, which has delegated the Mario Negri Institute for Pharmacological Research as the Data Coordinating Center for oversight of clinical operations, data management support, and clinical monitoring.

About 60 experimental centers are expected to participate. These centers have been selected on the basis of the report and recommendation of the Italian National Agency for Regional Healthcare Services (AGENAS) with at least 30 surgeries for gastric disease per year. It will also be possible to include centers from other Countries.

2.18.2. Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) comprising three international experts (one oncologist, 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 recommendations to the study Sponsor and the Steering Committee (SC).

2.18.3. 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’).

2.19. Ethics and dissemination

The trial 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 be given key information about the trial, verbally and in a written consent form. Patients are notified that they are free to withdraw the trial 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 centers. Any substantial amendment made to the protocol by the coordinating investigator is submitted to the local ethics committee and health authorities for approval, prior to implementation.

According to local and international regulation, the trial results 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 one year after the trial is completed and to publish results, irrespective of the findings, in a peer-reviewed 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 Steering Committee upon request.

We plan to share the results with the scientific community and national gastric-cancer patient associations.

2.20. Standard for protocol publication

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The trial is registered on clinicaltrial.gov (NCT039171730).

2.21. Patient and public involvement

No patient involvement

3. Discussion

The original study design was based on intra-operative randomization of the patients. However organizational difficulties arose during the study conduction in apply the intra-operative randomization, 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 randomization from intra-operative to 24 hours before surgery. In the previous design patients with peritoneal carcinosis detected during surgery did not access the randomized part of the study, allowing an ITT approach.

By placing the randomization before the intervention, patients with peritoneal carcinosis diagnosed during surgery and not identified at the pre-surgery diagnostic level, will be included and

randomized. These patients will not receive the experimental treatment and are not part of the target population defined by the eligibility criteria. In this group (assuming 10-20% of the sample) the difference between experimental and control treatment is expected to be null, with a consequent dilution of the total effect, i.e. the hazard ratio (HR) resulting from the primary analysis will approach 1 with respect to the hypothesized effect. In addition the final results would be difficult to interpret due to the population included. Therefore in the amended protocol a modified ITT was applied, excluding patients with peritoneal carcinosis diagnosed during surgery in order to obtain results on the target population without losing the generalizability.

Finally, the number of randomized patients was increased from 240 to 282, to take account of the expected number of patients (around 15%) with peritoneal carcinosis detected during surgery and excluded from the primary analysis.

Current, national and international guidelines do not include HIPEC for advanced or metastatic gastrointestinal cancer mainly because of the lack of large clinical trials in western Countries, and any clinical benefit of adjuvant HIPEC for gastric cancer has yet to be demonstrated. The GOETH trial has been designed to address this gap and test the clinical advantage of a surgical and chemotherapeutic prophylactic strategy to prevent recurrence. Therefore, we set DFS as the primary endpoint.

The HIPEC regimen of the present trial is based on cisplatin and mitomycin. This was supported by the results of past Asian prophylactic studies and the GYMSSA trial, which explored a similar HIPEC regimen after cytoreductive surgery, with curative intent.[26]

There is no standardized HIPEC protocol in clinical practice nor has a consensus been reached. The use of a single HIPEC technique in all centers in our trial appears to be one of the most important strengths of the protocol. The closed CO₂ recirculation offers adequate peritoneal surface drug exposure, stability, and homogeneity of the intra-abdominal temperature and should overcome the

shortcomings inherent to the closed technique. Both the laparoscopic and laparotomic surgical approaches can be safely used using this device. Another theoretical feature of this new HIPEC system, not been yet demonstrated, could be increased drug penetration through the mesothelial surface due to higher abdominal pressure. No deleterious impact on blood or hemodynamic parameters was found in an animal model and our own clinical experience has confirmed that the technique is safe and feasible, with good perioperative outcomes. [27-31]

The experimental arm surgery comprises prophylactic surgical excision of organs at risk of peritoneal metastases, in order to prevent microscopic peritoneal dissemination from the spread dynamics of peritoneal fluid. This strategy was already proposed by Sammartino et al. for colorectal cancer with promising results. [32-33]

Ovarian metastases are frequent in patients with gastric cancer, and this is the first most frequent site of origin. In a series of 2515 patients from the G.I.R.C.G. (Gruppo Italiano Ricerca Cancro Gastric), 30 presented with synchronous Krukenberg tumor, and 33 developed metachronous ovarian metastases. Survival in the metachronous group was better than in the synchronous group. [34] The introduction of another variable in the experimental treatment brings a confounding bias when assessing the role of HIPEC. However, the removal of organs at high risk of PM reduces the risk of primary ovarian or appendiceal cancer, removes microscopic synchronous metastases, and prevents metachronous relapse.

In our trial several neoadjuvant regimens are accepted and patients not receiving any preoperative chemotherapy can be enrolled. On this point, we opted to widen the indications, also considering the heterogeneity in current clinical practice in Italy. To minimize the bias introduced, the neoadjuvant chemotherapy regimen is considered a stratification variable for randomization.

All patients will receive adjuvant chemotherapy, unless there are clinical contraindications, this being current clinical practice in Italy.

Evidence from Western countries' currently available on adjuvant HIPEC for gastric cancer is recent and under development. Reutovich et al. recently published the results of a Belarus randomized trial including 154 advanced gastric cancer patients treated with surgery or surgery + HIPEC with cisplatin 50 mg/m² and doxorubicin 50 mg/m². No other adjuvant treatment was scheduled. The trial was powered on progression-free survival (PFS) and demonstrated that early peritoneal recurrence was reduced, showing a significant advantage on four-years PFS ($p < 0.001$). However, this did not translate into a significant survival benefit. The peritoneum may not be the only site of metastases and patients did not receive any adjuvant systemic chemotherapy. [35]

Various randomized clinical trials in Europe are enrolling in the prophylactic setting, investigating different drugs, perfusion techniques, and systemic treatments. The GASTRICHIP (NCT01882933) is a well-known actively recruiting European phase III trial that shares some characteristics with our study, mainly inclusion criteria. Differences are the extension of surgery in the experimental group (radical gastrectomy with D1-D2 lymphadenectomy), HIPEC technique (open or closed are permitted), and peritoneal drugs (oxaliplatin with intravenous 5-FU and calcium levofolinate induction). The primary endpoint is OS and secondary endpoints recurrence-free survival, morbidity, and quality of life.

The CHIMERA trial (NCT04597294) is a Polish phase III trial, not yet recruiting, testing the efficacy of perioperative FLOT4 chemotherapy in combination with HIPEC in 600 patients with advanced gastric cancer at high risk of peritoneal metastases. In the experimental arm, the HIPEC schedule is based on irinotecan 300 mg/m² infused for 45 minutes at 42 degrees. The primary endpoint is the rate of peritoneal recurrences at six months from randomization.

The PREVENT trial (NCT04447352) is a German recruiting phase III trial evaluating the efficacy

and safety of perioperative FLOT chemotherapy plus intraoperative cisplatin-based HIPEC (75 mg/m²) versus FLOT chemotherapy alone in patients with resectable locally advanced adenocarcinoma of the stomach and gastroesophageal junction (type II/III). In this study the primary outcome is the comparison of progression-/disease-free survival (PFS/DFS) between arms. Our study represents a novelty in this evolving context with some specific characteristics which, if proved, could improve the management of advanced gastric cancer.

4. Conclusion

The GOETH trial is the only one where prophylactic surgery and a new HIPEC technique with CO₂ agitation, are employed in patients with advanced gastric cancer, treated with an up-to-date multimodal strategy.

Considering the poor prognosis of peritoneal carcinomatosis from gastric cancer, maximum efforts are needed to identify and adequately treat patients with clinical and pathological risk factors.

In this randomized trial an aggressive surgical strategy comprising radical gastric resection, removal of organs at risk of harboring tumor cells and HIPEC, against standard surgery for advanced gastric cancer.

Trial Status

Actual Study Start Date: June 1, 2020

Estimated Primary Completion Date: June 1, 2023

Estimated Study Completion Date: June 1, 2025

Authors' contributions

All authors contribute equally to writing the manuscript

Funding statement

This trial is supported by an unconditional grant from ACTA srl.

Competing interest statement

The authors have no competing interest

List of abbreviations

HIPEC Hyperthermic Intraperitoneal Chemotherapy
ACOI Associazione Chirurghi Ospedalieri Italiani
AIOM Associazione Italiana Oncologia Medica
SIC Società Italiana di Chirurgia
SICE Società Italiana di Chirurgia Endoscopica e nuove tecnologie
SICO Società Italiana di Chirurgia Oncologia
OS Overall Survival
PC Peritoneal Carcinomatosis
DFS Disease-Free Survival
PFS Progression Free Survival
GC Gastric Carcinoma
LRFS Local Recurrence-Free Survival
GEJ Gastroesophageal Junction
ECOG Eastern Cooperative Oncology Group
ECF/ECX Epirubicin, Cisplatin, Fluorouracil/Capecitabine
XELOX Oxaliplatin, Capecitabine
FOLFOX Oxaliplatin, Fluorouracil/Leucovorin
FLOT Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel
ALP Alkaline Phosphatase
ALT Alanine Aminotransferase
aPTT Activated Partial Thromboplastin Time
AST Aspartate Transaminase
BUN Blood Urea Nitrogen
CBC Complete Blood Count
EUS Endoscopic Ultrasound
CT scan Computed Tomography scan
miTT modified Intention To Treat
CRF Case Report Form
RID Request Data Input

DCF Data Clarification Forms
IDMC Independent Data Monitoring Committee
AGENAS Italian National Agency for Regional Healthcare Services
SC Steering Committee

Appendix
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Declarations

- **Ethics approval and consent to participate**

Ethics Committee of the Università Cattolica, Policlinico Agostino Gemelli IRCCS, Rome, Prot. ID 2612. Written, informed consent to participate will be obtained from all participants.

- **Consent for publication**

Not applicable.

- **Availability of data and material**

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 Steering Committee upon request. We plan to share the results with the scientific community and national gastric-cancer patient associations.

- **Authors' information**

Not applicable.

- **Acknowledgements**

Not applicable.

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FLOW CHART

		Time 0	Day 1,3,5	6 week-8 week	5 month (adjuvant) 6 month (perioperative)	9 month	12 month
	Screening/pre-surgery exam	Surgery/Random	Post surgery	I assessment / start chemotherapy	II assessment	III assessment	IV assessment
informed consent	x						
demographic data	x						
medical history	x						
physical examination, PS	x				x	x	x
ECG	x			x			
bHCG	x			x			
HIV test	x						
HBsAG/anti Hbs/antiHbc/antiHcv	x						
Diagnostic laparoscopy	x						
cytological exam	x						
complete blood count (CBC)	x			x	x	x	x
chemistry test	x						
blood urea nitrogen (BUN)	x			x	x	x	x
creatinine	x			x	x	x	x
alanine aminotransferase (ALT)	x			x	x	x	x
aspartate aminotransferase (AST)	x			x	x	x	x
LDH	x			x	x	x	x
Alkaline phosphatase	x			x	x	x	x
Gamma glutamyl transpeptidase (GGT)	x			x	x	x	x
Bilirubin tot, direct bilirubin, albumin, total protein	x			x			
Coagulation tests (prothrombin time (PT), activated partial thromboplastin time (aPTT), INR	x			x			
Exam post surgery (HB, PLT, WBC, Glycaemia, Creatinine, ALT, ALB)	x		x				
CEA	x			x	x	x	x
EGDS	x						x
CT-scan MDC thorax-abdomen	x			x	x	x	
Ultrasound	x						x
EGDS will be performed at 1 year from surgery and if negative at 3 and 5 years							
Starting from ninth month from surgery, CT-scan and Ultrasound will be alternated every 3 months for 3 years and every 6 months in the following 2 years							
All clinical evaluation during chemotherapy treatment will be performed according to clinical practice							

Supplementary Files

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