ISRCTN89947480 https://doi.org/10.1186/ISRCTN89947480

PIPAC for peritoneal metastases of colorectal cancer

Submission date 02/08/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 14/08/2017	**Overall study status** Completed	
Last Edited 12/03/2021	**Condition category** Cancer	

Plain English summary of protocol

Current plain English summary as of 16/01/2019:
Background and study aims
Approximately a quarter of the patients who are diagnosed with colorectal cancer with metastases have their metastases in the peritoneum. The vast majority of these patients cannot be cured by surgery, frequently due to too many peritoneal metastases. These incurable patients have a very short life expectancy. They are treated with chemotherapy through the veins. However, chemotherapy through the veins seems to be relatively ineffective against peritoneal metastases, probably because it does not reach the peritoneal metastases very well. Chemotherapy through the veins may also cause side effects that are sometimes severe. Recently, doctors developed PIPAC: a short laparoscopic procedure during which chemotherapy is sprayed in the abdomen for 30 minutes, directly against the peritoneal metastases. As a result, PIPAC may be equally effective against peritoneal metastases than chemotherapy through the veins. It may have less side effects, because the chemotherapy mainly stays in the abdomen, not in the veins. PIPAC indeed shows promising first results in the first European patients with peritoneal metastases of colorectal cancer who have been treated with this operation. However, still, little is known about its feasibility, safety, tolerability, and efficacy. This study investigates these parameters.

Who can participate?
Adults with inoperable peritoneal metastases of colorectal cancer without metastases elsewhere (e.g. liver, lung).

What does the study involve?
Instead of chemotherapy through the veins, participants receive PIPAC every 6 weeks. PIPAC is a laparoscopic operation under general anaesthesia. During PIPAC, chemotherapy is sprayed in the abdomen for about 30 minutes. After PIPAC, patients stay in the hospital for one night. Four weeks after each PIPAC, patients visit the hospital for a scan and to evaluate whether PIPAC can be continued. PIPAC is continued until (1) the cancer grows, (2) PIPAC causes unacceptable side effects, or (3) PIPAC is technically not possible to perform. In case no further PIPAC is performed, restarting chemotherapy through the veins is discussed with the patient.

What are the possible benefits and risks of participating?
PIPAC may potentially be similarly effective against peritoneal metastases than chemotherapy through the veins, with a potential lower risk of side-effects. PIPAC may cause side-effects. The most frequent potential side-effects are pain, nausea, fever, wound infection, diarrhea, obstipation, and minor damages to the kidney, liver, and bone marrow. These side-effects are mostly very mild. Moreover, the risk of side-effects of PIPAC is thought to be lower than the risk of side-effects of chemotherapy through the veins. Severe side-effects of PIPAC are extremely rare. The most important are a bowel perforation or a bleeding during PIPAC. So far, these severe side-effects have not been observed during PIPAC in patients with peritoneal metastases of colorectal cancer.

Where is the study run from?
Catharina Hospital (Netherlands)
St Antonius Hospital (Netherlands)

When is the study starting and how long is it expected to run for?
January 2017 to October 2019 (updated 14/10/2019, previously: October 2020)

Who is funding the study?
Catharina Hospital (Netherlands)
St Antonius Hospital (Netherlands)

Who is the main contact?
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Previous plain English Summary:
Background and study aims
Approximately a quarter of the patients who are diagnosed with colorectal cancer and metastases (when the cancer spreads to other parts of the body) have peritoneal (the tissue that lines the abdominal cavity) metastases. The vast majority of these patients cannot be cured by surgery, frequently due to too many peritoneal metastases. These incurable patients have a very short life expectancy. This is treated with chemotherapy through the veins. However, chemotherapy through the veins appears to be relatively ineffective against peritoneal metastases, probably because it does not reach the peritoneal metastases very well. Chemotherapy through the veins may also cause side effects that are sometimes severe. Recently, doctors developed PIPAC: a short laparoscopic operation (a minimially invasive surgery done through a small incision) during which chemotherapy is sprayed in the abdomen for 30 minutes, directly against the peritoneal metastases. As a result, PIPAC may be more effective against peritoneal metastases than chemotherapy through the veins. It may also have less side effects, because the chemotherapy mainly stays in the abdomen, not in the veins. PIPAC indeed shows promising results in the first European patients with peritoneal metastases of colorectal cancer who have been treated with this operation. The aim of this study is to investigate whether PIPAC is a safe, feasible, tolerable, and potentially effective treatment for patients with peritoneal metastases of colorectal cancer.

Who can participate?
Adults with peritoneal metises of colorectal cancer without metastases elsewhere (e.g. liver, lung), who cannot be cured by surgery due to too many peritoneal metastases.

What does the study involve?
Participants undergo the PIPAC procedure. This takes 90 minutes. After the procedure,

participants stay in hospital for at least one night. This is repeated every six weeks until participants have three PIPAC procedures. This may be done more or less depending on the participatns response to the procedure. Four weeks after each procedure, participants have a CT-scan to evaluate if they can another PIPAC. If not, they receive the usual chemotherapy treatment. After participants undergo their last PIPAC, they visit the outpatient centre every three months to evaluate how the cancer responds to the treatment.

What are the possible benefits and risks of participating?
Participants may benefit from a similar or more effective treatment against peritoneal metastases than chemotherapy, as well as a lower risk of side-effects. There are risks of side-effects such as pain, nausea, fever, wound infection, diarrhea, obstipation (severe constipation) and minor damage to the kidney, liver and bone marrow. There is a rare risk of bowel perforation or bleeding during PIPAC. These severe side-effects have not been observed during PIPAC in patients with peritoneal metastases of colorectal cancer.

Where is the study run from?
Catharina Hospital (Netherlands)

When is the study starting and how long is it expected to run for?
January 2017 to October 2019

Who is funding the study?
Catharina Hospital (Netherlands)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03246321

Clinical Trials Information System (CTIS)
2017-000927-29

Protocol serial number
NL60405.100.17

Study information

Scientific Title
Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX) as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a multicentre, open-label, single-arm, phase II study

Acronym
CRC-PIPAC

Study objectives
Current hypothesis as of 16/01/2019:
Repetitive ePIPAC-OX as a palliative monotherapy is safe, feasible, tolerable, and potentially effective for patients with isolated unresectable colorectal PM.

Previous hypothesis:
Upfront repeated laparoscopic PIPAC with oxaliplatin and simultaneous intravenous bolus 5-fluorouracil/leucovorin is a safe, feasible, and tolerable treatment for patients with isolated unresectable colorectal peritoneal metastases, with a potentially higher preliminary oncological efficacy compared to standard palliative systemic therapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics board: Medical Research Ethics Committees United, 31/07/2017, ref: R17.038

Primary study design
Interventional

Study design
Interventional single arm multicentre phase II study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Isolated unresectable colorectal peritoneal metastases

Interventions
Current interventions as of 16/01/2019:
Instead of standard palliative treatment, enrolled patients receive laparoscopy-controlled ePIPAC-OX (92 mg/m2 body-surface area [BSA]) with intravenous leucovorin (20 mg/m2 BSA) and bolus 5-fluorouracil (400 mg/m2 BSA) every six weeks. Four weeks after each procedure,

patients undergo clinical, radiological, and biochemical evaluation. ePIPAC-OX is repeated until clinical, radiological, or macroscopic disease progression, after which standard palliative treatment is (re)considered.

Previous interventions:
Instead of standard palliative systemic therapy, patients receive upfront laparoscopic PIPAC with oxaliplatin (92 mg/m2) and simultaneous intravenous bolus 5-fluorouracil/leucovorin (400/20 mg /m2), intentionally repeated with an interval of six weeks until intraperitoneal disease progression, unfitness for laparoscopy, or laparoscopic non-access.

In case of intraperitoneal disease progression, unfitness for laparoscopy, or laparoscopic non-access, patients intentionally receive standard palliative systemic therapy, while further PIPAC-procedures are cancelled. In case of systemic disease progression with intraperitoneal disease response or stable disease, patients intentionally receive standard palliative systemic therapy, while further PIPAC-procedures are intentionally continued until intraperitoneal disease progression, unfitness for laparoscopy, or laparoscopic non-access.

After the last PIPAC-procedure, patients are radiologically and biochemically evaluated at the oncological outpatient clinic every 3 months for a total of 3 times. Thereafter, patients enter regular oncological follow-up according to local protocol.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Oxaliplatin, 5-fluorouracil, leucovorin.

Primary outcome(s)
Current primary outcome measure as of 16/01/2019:
The number of patients with major toxicity, defined as grade ≥3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, up to four weeks after the last ePIPAC-OX.

Previous primary outcome measure:
Major mobidity. Method: Common Terminology Criteria for Adverse Events grade III-V, measured after each PIPAC-procedure up to 4 weeks after the last PIPAC-procedure . Expected timepoint: +/- 16 weeks after inclusion.

Key secondary outcome(s)
Current secondary outcome measures as of 16/01/2019:
1. The environmental safety of ePIPAC-OX, based on air concentrations and surface concentrations of oxaliplatin during the first three procedures, measured by atomic absorption spectrophotometry
2. Procedure-related characteristics of ePIPAC-OX (e.g. laparoscopic access, intraoperative complications, amount of adhesions, technical difficulties, operating time)
3. The number of procedures in each patient and reasons for discontinuation
4. Minor toxicity, defined as grade ≤2 according to CTCAE v4.0, up to four weeks after the last ePIPAC-OX
5. Organ-specific toxicity, based on bone marrow, liver, and kidney functions measured at

baseline, each postoperative day, and four weeks after each ePIPAC-OX
6. Major and minor postoperative complications, defined as grade ≥3 and grade ≤2 according to Clavien-Dindo, respectively, up to four weeks after the last ePIPAC-OX
7. Hospital stay, defined as the number of days between ePIPAC-OX and initial discharge;
8. Readmissions, defined as any hospital admission after initial discharge, up to four weeks after the last ePIPAC-OX
9. Radiological tumour response, based on central review of thoracoabdominal CT and DW-MRI at baseline and four weeks after each ePIPAC-OX, performed by two independent radiologists blinded to clinical outcomes (classification is not defined a priori)
10. Histopathological tumour response, based on central review of collected peritoneal biopsies during each ePIPAC-OX, performed by two independent pathologists blinded to clinical outcomes by using the Peritoneal Regression Grading Score
11. Cytological tumour response, based on collected ascites or peritoneal washing cytology during each ePIPAC-OX
12. Macroscopic tumour response, based on PCI and ascites volume during each ePIPAC-OX
13. Biochemical tumour response, based on tumour markers measured at different time points
14. Quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) at baseline and one and four weeks after each ePIPAC-OX
15. Costs, derived from the Dutch costing guidelines for health care research at the time of analysis, based on case report forms, hospital information systems, and questionnaires (iMTA PCQ, iMTA MCQ) at baseline and four weeks after each ePIPAC-OX
16. Progression-free survival, defined as the time between enrolment and clinical, radiological, or macroscopic progression, or death
17. Overall survival, defined as the time between enrolment and death
18. Platinum concentrations in plasma and plasma ultrafiltrate (collected before ePIPAC-OX and 5, 10, 20, 30, 60, 120, 240, 360, and 1080 minutes after oxaliplatin injection), urine (collected before ePIPAC-OX and on postoperative days 1, 3, 5, and 7), and two pieces of normal peritoneum and two peritoneal metastases collected during each ePIPAC-OX

Previous secondary outcome measures:
1. Platinum concentrations in the air of the operating room. Method: stationary measurements in the operating room and personal measurements at the working places of the personnel (e.g. surgeon, anesthesiologist) and at the position of the patient, measured during the first 3-5 PIPAC-procedures, depending on findings. Expected timepoint: +/- 1 week after inclusion.
2. Platinum concentrations on surfaces in the operating room. Method: measurements on the surface of equipment and devices (e.g. high pressure injector, filter system) and personal measurements at the working places of the personnel (e.g. clothing, gloves) and at the position of the patient, measured during the first 3-5 PIPAC-procedures, depending on findings. Expected timepoint: +/- 1 week after inclusion.
3. Platinum concentrations in plasma of the patient. Method: total and ultrafiltrated plasma concentrations of platinum, measured at t=0, t=0.5, t=0.75, t=1, t=2, t=4, t=6, and t=8 hours after start of oxaliplatin injection during/after the first 10-20 PIPAC-procedures, depending on findings. Expected timepoint: +/- 1 week after inclusion.
4. Platinum concentrations in excretes (urine, saliva) of the patient. Method: concentrations at t=1, t=3, t=5, and t=7 days after the first 10-20 PIPAC-procedures, depending on findings. Expected timepoint: +/- 1 week after inclusion.
5. Intraoperative characteristics. Method: laparoscopic (non-)access, amount of adhesions (Zühlke), ascites volume (ml), blood loss (ml), operating time (minutes), any intraoperative complications (e.g. bleeding, perforation), and any PIPAC-specific technical difficulties, measured during each PIPAC-procedure. Expected timepoint: +/- 12 weeks after inclusion.
6. Minor morbidity. Method: Common Terminology Criteria for Adverse Events grade II, measured after each PIPAC-procedure up to 4 weeks after the last PIPAC-procedure. Expected

timepoint: +/- 16 weeks after inclusion.
7. Hospital stay. Method: time between PIPAC-procedure and discharge, measured after each PIPAC-procedure up to 4 weeks after the last PIPAC-procedure. Expected timepoint: +/- 16 weeks after inclusion.
8. Number of readmissions. Method: hospital readmission after initial discharge, measured after each PIPAC-procedure up to 4 weeks after the last PIPAC-procedure. Expected timepoint: +/- 16 weeks after inclusion.
9. Number of PIPAC-procedures. Method: measured in each patient with reasons for discontinuation of further PIPAC-procedures. Expected timepoint: +/- 52 weeks after inclusion.
10. Organ functions. Method: renal, liver, and haematological function, measured at baseline as well as 12 hours and 4 weeks after each PIPAC-procedure. Expected timepoint: +/- 16 weeks after inclusion.
11. Histopathological tumour response. Method: Peritoneal Regression Scale (PRGS), measured after each second and subsequent PIPAC-procedure. Expected timepoint: +/- 12 weeks after inclusion.
12. Macroscopic intraperitoneal tumour response. Method: Peritoneal Cancer Index (PCI), measured after each second and subsequent PIPAC-procedure. Expected timepoint: +/- 12 weeks after inclusion.
13. Tumour markers. Method: carcinoembryonic antigen, measured at baseline as well as 12 hours and 4 weeks after each PIPAC-procedure, and during follow-up every 3 months. Expected timepoint: +/- 52 weeks after inclusion.
14. Peritoneal progression free survival. Method: time between inclusion and macroscopic intraperitoneal disease progression during a second or subsequent PIPAC, or time between inclusion and radiological evidence of intraperitoneal disease progression on CT-scan 4 weeks after each PIPAC or during follow-up every 3 months. Expected timepoint: +/- 52 weeks after inclusion.
15. Systemic progression free survival. Method: time between inclusion and radiological evidence of systemic disease progression on CT-scan 4 weeks after each PIPAC or during follow-up every 3 months. Expected timepoint: +/- 52 weeks after inclusion.
16. Disease-specific survival. Method: time between inclusion and death due to colorectal cancer. Expected timepoint: +/- 52 weeks after inclusion.
17. Overall survival. Method: time between inclusion and death due to any cause. Expected timepoint: +/- 52 weeks after inclusion.
18. Quality of life. Method: EQ5D5L, EORTC-QLQC30, and EORTC-QLQCR29, measured at baseline, 4 weeks after each PIPAC-procedure, and during follow-up every 3 months. Expected timepoint: +/- 52 weeks after inclusion.
19. Costs. Method: iMTA Productivity Cost Questionnaire and iMTA Medical Consumption Questionnaire, measured at 3, 6, 9, and 12 months after inclusion. Expected timepoint: +/- 52 weeks after inclusion.
20. Collection of tissue and ascites for translational research. Method: during each PIPAC-procedure, ascites or peritoneal fluid is sent for cytology and several peritoneal metastases are biopsied. Expected timepoint: +/- 12 weeks after inclusion.
21. Collection of blood for translational research. Method: an EDTA tube (10 ml) is drawn, processed, and frozen at baseline, t=0, t=0.5, t=1, t=2, t=4, t=6, t=8 during/after each PIPAC, 4 weeks after each PIPAC, and during follow-up every 3 months. Expected timepoint: +/- 52 weeks after inclusion.

Completion date
14/01/2019

Eligibility

Key inclusion criteria
Current inclusion criteria as of 16/01/2019:
1. A World Health Organisation (WHO) performance status of ≤1 and life expectancy >3 months
2. Histological or cytological proof of PM of a colorectal or appendiceal carcinoma
3. Unresectable disease determined by abdominal computed tomography (CT) and a diagnostic laparoscopy or laparotomy
4. Adequate organ functions (haemoglobin ≥5.0 mmol/L, neutrophils ≥1.5 x 109/L, platelets ≥100 x 109/L, serum creatinine <1.5 x ULN, creatinine clearance ≥30 ml/min, and liver transaminsases <5 x ULN)
5. No symptoms of gastrointestinal obstruction
6. No radiological evidence of systemic metastases
7. No contraindications for oxaliplatin or 5-fluorouracil/leucovorin
8. No contraindications for a laparoscopy
9. No previous PIPAC-procedures
10. Written informed consent

Importantly, enrolment is allowed for patients with an unresected primary tumour (if asymptomatic) and for patients in various lines of palliative treatment, including patients who refuse, have not had, or do not qualify for first-line palliative systemic therapy. All potentially eligible patients are discussed in a multidisciplinary team. Enrolled patients need to be informed about the potential consequences of postponing or discontinuing standard palliative treatment by a medical oncologist prior to enrolment.

Previous inclusion criteria:
1. Histologically confirmed unresectable peritoneal metastases of a colorectal or appendiceal carcinoma
2. Asymptomatic presentation (i.e. no disabling malignant ascites or obstructive symptoms)
3. WHO performance score 0-1
4. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
20

Key exclusion criteria
Current exclusion criteria as of 16/01/2019:
See ‘inclusion criteria’

Previous exclusion criteria:
1. Radiological evidence of extra-abdominal metastatic disease

2. Inadequate organ functions (hemoglobin <5.0 mmol/L, absolute neutrophil count <1.5 x 10(9) /L, platelet count <100 x 10(9)/L, serum creatinine >1.5 x ULN, creatinine clearance <30 ml/min, liver transaminases >5 x ULN)
3. Known pregnancy or lactation
4. Known unstable or uncompensated respiratory or cardiac disease
5. Known bleeding diathesis or coagulopathy
6. Serious active infections
7. Any other condition not allowing for a safe laparoscopy or a safe administration of oxaliplatin, 5-fluorouracil, or leucovorin
8. Enrolment in another clinical study

Date of first enrolment
01/10/2017

Date of final enrolment
14/10/2019

Locations

Countries of recruitment
Netherlands

Study participating centre
Catharina Hospital
Michelangelolaan 2
Eindhoven
Netherlands
5623 EJ

Study participating centre
St. Antonius Hospital
Koekoekslaan 1
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Sponsor information

Organisation
Catharina Hospital

ROR
https://ror.org/01qavk531

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Catharina Hospital

Funder Name
St. Antonius Hospital

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/01/2021	12/03/2021	Yes	No
Protocol article	protocol	27/07/2019	07/08/2020	Yes	No