

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

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ABSTRACT

Introduction Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX) is offered as a palliative treatment option for patients with isolated unresectable colorectal peritoneal metastases (PM) in several centres worldwide. However, little is known about its feasibility, safety, tolerability, efficacy, costs and pharmacokinetics in this setting. This study aims to explore these parameters in patients with isolated unresectable colorectal PM who receive repetitive ePIPAC-OX as a palliative monotherapy.

Methods and analysis This multicentre, open-label, single-arm, phase II study is performed in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM. Eligible patients are adults who have histologically or cytologically proven isolated unresectable PM of a colorectal or appendiceal carcinoma, a good performance status, adequate organ functions and no symptoms of gastrointestinal obstruction. 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 6 weeks. Four weeks after each procedure, patients undergo clinical, radiological and biochemical evaluation. ePIPAC-OX is repeated until disease progression, after which standard palliative treatment is (re)considered. The primary outcome is the number of patients with major toxicity (grade ≥3 according to the Common Terminology Criteria for Adverse Events v4.0) up to 4 weeks after the last ePIPAC-OX. Secondary outcomes are the environmental safety of ePIPAC-OX, procedure-related characteristics, minor toxicity, postoperative complications, hospital stay, readmissions, quality of life, costs, pharmacokinetics of oxaliplatin, progression-free survival,

Strengths and limitations of this study

- This is the first study that prospectively explores predefined endpoints regarding the feasibility, safety and efficacy of repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX) as a palliative monotherapy in patients with isolated unresectable colorectal peritoneal metastases.
- Unlike other studies, repetitive ePIPAC-OX is administered as a palliative monotherapy, thereby minimising the influence of concurrent palliative systemic therapy on study outcomes.
- Apart from exploring clinical outcomes such as feasibility, safety and efficacy, this study includes assessment of quality of life and costs, as well as pharmacokinetic and translational side studies.
- The broad eligibility criteria could lead to enrolment of prognostically heterogeneous patients in different lines of palliative treatment, which could impede the interpretation of efficacy outcomes.

overall survival, and the radiological, histopathological, cytological, biochemical and macroscopic tumour response. **Ethics and dissemination** This study is approved by an ethics committee, the Dutch competent authority and the institutional review boards of both study centres. Results are intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals and other stakeholders.

Trial registration number NCT03246321, Pre-results; ISRCTN89947480, Pre-results; NTR6603, Pre-results; EudraCT: 2017-000927-29, Pre-results.

INTRODUCTION

After the liver, the peritoneum is the second most common isolated metastatic site of colorectal cancer.^{1 2} The majority of patients with isolated colorectal peritoneal metastases (PM) do not qualify for curative intent surgical treatment,³ mostly due to insufficient condition or unresectable disease. Palliative systemic therapy is the standard treatment for patients with isolated unresectable colorectal PM.⁴ Although its increasing use has improved the outcomes of these patients,³ palliative systemic therapy appears less effective for isolated colorectal PM than for isolated non-peritoneal colorectal metastases.⁵ This phenomenon may be explained by a relatively low intraperitoneal concentration of systemically administered chemotherapy.⁶ Moreover, a relatively high systemic concentration could cause systemic toxicity. Intraperitoneal administration of chemotherapy is thought to increase locoregional efficacy and decrease systemic toxicity through a favourable peritoneum-plasma concentration ratio.^{6–8} However, intraperitoneal chemotherapy seems to have three major limitations: a poor direct tissue penetration, an inhomogeneous intraperitoneal drug distribution and dose-limiting local toxicity.^{9 10} This has encouraged development of new intraperitoneal drug delivery systems that aim to overcome these limitations. Currently, pressurised intraperitoneal aerosol chemotherapy (PIPAC) is one of these systems that internationally gains the most attention.

PIPAC

PIPAC is a laparoscopy-controlled repetitive intraperitoneal administration of low-dose chemotherapy as a pressurised aerosol.^{11 12} It combines the theoretical pharmacokinetic advantages of low-dose intraperitoneal chemotherapy (ie, low toxicity, high intraperitoneal concentration, low systemic concentration) with the principles of an aerosol (homogeneous intraperitoneal distribution) and intra-abdominal pressure (deep tissue penetration).^{13–20} Two groups systematically reviewed the results of non-comparative clinical studies that assessed the feasibility, safety, tolerability and preliminary efficacy of PIPAC with various drugs for PM of various origins.^{21 22} They concluded that PIPAC is a safe, feasible and well-tolerated treatment with good preliminary response rates.^{21 22} These preliminary conclusions have led to an increasing acceptance of PIPAC as a palliative treatment option for PM in several centres worldwide.²³ In these centres, patients with isolated unresectable colorectal PM usually receive PIPAC with oxaliplatin (PIPAC-OX) in an empirically chosen dosage of 92 mg/m² body surface area (BSA) every 4–6 weeks.²³ Some centres use electrostatic precipitation of the aerosol during PIPAC-OX (ePIPAC-OX),^{24 25} since this could increase tissue penetration of oxaliplatin.²⁶

PIPAC for colorectal PM

Several clinical studies included patients who received repetitive PIPAC-OX for colorectal PM.^{27–36} However, the

vast majority of these studies reported outcomes of entire cohorts that received repetitive PIPAC with various drugs for PM of various origins without presenting subgroup analyses of patients who received PIPAC-OX for colorectal PM.^{27–34} Only two studies reported separate outcomes of repetitive PIPAC-OX for colorectal PM.^{35 36} By using a prospectively maintained database, Teixeira Farinha *et al* retrospectively included 20 patients with isolated colorectal PM who received 37 procedures.³⁵ They concluded that repetitive PIPAC-OX causes a modest and transitory inflammatory response without haematological, renal or hepatic toxicity.³⁵ Demtröder *et al* retrospectively included 17 patients with isolated colorectal PM who received 48 procedures within an off-label programme.³⁶ They concluded that repetitive PIPAC-OX induces regression of pretreated colorectal PM and that the toxicity seems to be low.³⁶ Both studies have a retrospective design without predefined eligibility criteria and endpoints. Moreover, both studies included patients who received repetitive PIPAC-OX as a monotherapy as well as patients who received PIPAC-OX in combination with palliative systemic therapy. These shortcomings strongly impede the interpretation of these studies. Besides, recently published case reports suggested that PIPAC-OX could lead to severe hypersensitivity reactions and peritoneal sclerosis.^{37 38}

Rationale for this study

In conclusion, little is known about the safety, tolerability and efficacy of repetitive PIPAC-OX in patients with isolated unresectable colorectal PM, whereas nothing is known about its costs and pharmacokinetics. Specifically for repetitive ePIPAC-OX, all these outcomes have never been reported. This questions the current use of repetitive ePIPAC-OX as a palliative treatment option for isolated unresectable colorectal PM outside the framework of clinical study protocols. Ideally, these patients are included in prospective studies with predefined eligibility criteria, interventions and endpoints. However, by the knowledge of the investigators, such studies are currently lacking and not ongoing.³⁹ Therefore, this study aims to prospectively explore the safety, tolerability, preliminary efficacy, costs and pharmacokinetics of repetitive ePIPAC-OX as a palliative treatment for isolated unresectable colorectal PM. Although implementation of PIPAC appears feasible and occupationally safe,^{21 22 24 40–43} there is no experience with PIPAC in the Netherlands. Hence, this study also aims to assess the feasibility of implementation of ePIPAC-OX in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM.

Rationale for intervention

Repetitive ePIPAC-OX may be administered as part of a bidirectional therapy with palliative systemic therapy or as a monotherapy. The bidirectional therapy hypothetically maximises tumour response, probably at the cost of an increased treatment burden that could interfere with quality of life. Repetitive ePIPAC-OX as a monotherapy

could temporarily stabilise the intraperitoneal disease burden with minimal toxicity and preservation of quality of life. For this study, the investigators decided to administer repetitive ePIPAC-OX as a palliative monotherapy with (re)consideration of standard palliative treatment after progression. According to internationally used protocols, ePIPAC-OX is administered in a dosage of 92 mg/m² at 6-weekly intervals.²³ The investigators will actively follow two ongoing phase I studies in which repetitive PIPAC-OX is administered in various preplanned dosage levels to evaluate whether the dosage of oxaliplatin in this study needs to be modified.^{44 45} Before administration of ePIPAC-OX, the patients receive intravenous low-dose leucovorin with bolus 5-fluorouracil, since this is thought to potentiate the effect of intraperitoneal oxaliplatin.^{46 47}

METHODS AND ANALYSIS

Design and setting

This prospective, open-label, single-arm, phase II study is performed in two Dutch teaching hospitals qualified as tertiary referral hospitals for the surgical treatment of colorectal PM.

Eligibility criteria

Eligible patients are adults who have:

- ▶ A WHO performance status of ≤ 1 .
- ▶ Histological or cytological proof of PM of a colorectal or appendiceal carcinoma.
- ▶ Unresectable disease determined by the treating physician, based on abdominal CT and a diagnostic laparotomy or laparoscopy, the latter being a standard tool in the diagnostic work-up of patients with isolated colorectal PM in the Netherlands.
- ▶ Adequate organ functions (haemoglobin ≥ 5.0 mmol/L, neutrophils $\geq 1.5 \times 10^9$ /L, platelets $\geq 100 \times 10^9$ /L, serum creatinine $< 1.5 \times$ upper limit of normal (ULN), creatinine clearance ≥ 30 mL/min and liver transaminases $< 5 \times$ ULN).
- ▶ No symptoms of gastrointestinal obstruction.
- ▶ No radiological evidence of systemic metastases.
- ▶ No contraindications for oxaliplatin or 5-fluorouracil/leucovorin.
- ▶ No contraindications for a laparoscopy.
- ▶ No previous PIPAC procedures.

Thereby, enrolment is allowed for patients with a signet ring cell carcinoma, patients with a history of prior cytoreductive surgery or hyperthermic intraperitoneal chemotherapy (HIPEC) and patients with unresected ovarian metastases or an unresected primary tumour (if not causing symptoms of gastrointestinal obstruction). Importantly, enrolment is allowed 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 by a multidisciplinary team. Enrolled patients are informed about the potential consequences of postponing or

discontinuing standard palliative treatment by a medical oncologist prior to enrolment.

Interventions and procedures

Figure 1 shows a flowchart of the study. Table 1 presents a schedule of enrolment, interventions and assessments.

ePIPAC-OX

The procedure-related principles of (e)PIPAC have been extensively described by Willaert *et al* and Giger-Pabst *et al*.^{24 48} In this study, ePIPAC-OX is performed at 6-weekly intervals by at least one PIPAC-qualified surgeon in a standard operating room with laminar airflow. In both study centres, the operating personnel attended procedures in experienced PIPAC centres before performing their first procedure. All procedures are performed under general anaesthesia. Antibiotic prophylaxis and venous thromboembolism prophylaxis are not regularly administered. Before each procedure, a checklist is used to ensure all materials are available. The operating personnel wears appropriate chemotherapy-protective clothes according to existing HIPEC protocols.

The Hasson technique is used to insert a 10 mm blunt tip balloon trocar through the abdominal wall. After obtaining a normothermic 12 mm Hg capnoperitoneum, a second 10 mm blunt tip balloon trocar is inserted under direct vision and explorative laparoscopy is performed. Only if needed, careful adhesiolysis may be performed to create sufficient working space. In case of an iatrogenic bowel lesion, the procedure is ended after closure of the lesion, and ePIPAC-OX may be postponed by 2–4 weeks. If the procedure is considered feasible, leucovorin (20 mg/m² BSA in 10 min) and bolus 5-fluorouracil (400 mg/m² BSA in 15 min) are administered intravenously. In the meantime, ascites (or injected saline if ascites is not present) is completely evacuated, sent for cytology and translational research, and the ascites volume is documented. Adhesions are scored with the Zühlke score, the peritoneal cancer index (PCI) is registered and photographs are taken throughout the peritoneal cavity.^{49 50} A piece of normal peritoneum and three peritoneal metastases, preferably from different areas, are biopsied, sent for histopathology and translational research, and their locations are documented and marked with clips to enable biopsies of the same locations during subsequent procedures.

Then, the ePIPAC setup is installed. A stainless steel brush electrode (Ionwand, Alesi Surgical, Cardiff, UK) is inserted through a mini-trocar under direct vision, secured with its tip at least 2 cm away from other structures, and connected to its generator (Ultravision, Alesi Surgical, Cardiff, UK). A nebuliser (CapnoPen, Capnomed GmbH, Villingendorf, Germany) is inserted through one of the trocars and secured with its nozzle just inside the peritoneal cavity at a safe distance from visceral organs. The camera, inserted through the other trocar, is secured by a laparoscope holder in a way it permanently visualises the electrode and the nebuliser. The valve of

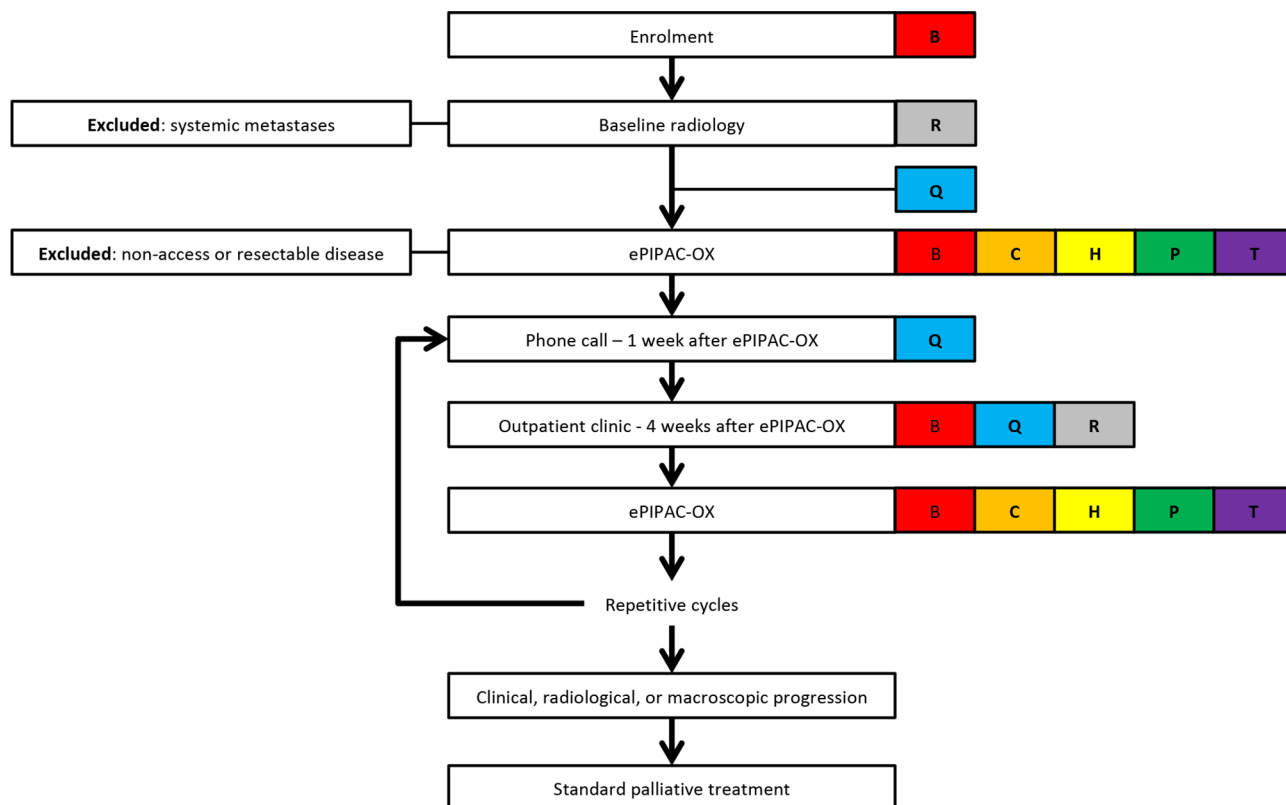


Figure 1 Flowchart of the CRC-PIPAC study. **B** Bloods (organ functions, tumour markers); **C** Cytology (ascites or peritoneal washing with saline); **H** Histopathology (peritoneal biopsies); **P** Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum); **Q** Questionnaires (quality of life, costs); **R** Radiology (thoracoabdominal CT, diffusion-weighted MRI); **T** Translational research (blood, ascites, PM). ePIPAC-OX, electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin; PM, peritoneal metastases.

the trocar connected to the CO₂ insufflation remains opened, whereas the other trocar is connected to a closed aerosol waste system (CAWS) with its valve closed. The CAWS consecutively consists of a smoke evacuation filter, a water seal drainage system, an infant-paediatric electrostatic microparticle filter, and the air waste system of the hospital. The preoperatively prepared syringe with oxaliplatin (92 mg/m² BSA diluted in a total volume of 150 mL 5% dextrose) is vented, placed in a standard angiographic injector and connected to the nebuliser with a saline-flushed high-pressure line protected by a plastic camera cover. A leak-free capnoperitoneum is ensured by zero flow of CO₂. If necessary, the external fascia may be additionally sutured and Luer lock caps may be placed on balloon valves of trocars. The angiographic injector is installed at a flow rate of 30 mL/min and a maximum pressure of 200 psi. Protective films are placed on the floor below the angiographic injector and around the patient. The angiographic injector is positioned above a chemotherapy waste bin. The peripheral venous line of the patient is connected to a 60 mL saline-containing syringe outside the operating room. Vital parameters of the patient, real-time videolaparoscopy and a patient-aimed camera are displayed on three screens outside the operating room. The screen of the angiographic injector is positioned in front of the window

of the operating room. General anaesthesia is ensured for at least another 40 min. A checklist is used to confirm that all aforementioned steps have been adequately taken. After completion of the checklist, the entire operating personnel leaves the operating room.

Oxaliplatin is injected through the nebuliser by remote controlled activation of the angiographic injector from outside the operating room. After complete formation of the oxaliplatin-containing aerosol in 5 min, the surgeon enters the operating room and turns on the Ultravision generator, which results in electrostatic precipitation of the aerosol. The electrostatic field and the capnoperitoneum are maintained for another 25 min. During this phase, the patient and the procedure are monitored through the three screens and the window of the operating room. Drugs may be administered to the patient through the intravenous access outside the operating room if necessary.

After 25 min, the surgeon enters the operating room, turns off the Ultravision generator, closes the trocar valve connected to the CO₂ insufflation and opens the trocar valve connected to the CAWS. After complete evacuation of the aerosol, the electrode and the nebuliser are removed, the entire operating personnel enters the operating room and a new capnoperitoneum is obtained. Ascites and peritoneal biopsies are collected for

Table 1 Schedule of enrolment, interventions and assessments

	Study period				
	Enrolment/ allocation	Post-enrolment			
		Outpatient clinics	Baseline radiology	Each ePIPAC-OX	1 week after each ePIPAC-OX
Enrolment/Allocation					
Eligibility screen	X				
Informed consent	X				
Interventions					
ePIPAC-OX			X		
Blood (organ functions, tumour markers)	X		X*		X
Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum)†			X		
Translational research (blood, ascites, PM)			X‡		
Thoracoabdominal CT		X			X
Diffusion-weighted MRI		X			X
Cytology (ascites or peritoneal washing)			X		
Histopathology (peritoneal biopsies)			X		
Questionnaires: quality of life		X		X	X
Questionnaires: costs§		X			X
Assessments					
Baseline characteristics	X	X	X		
Toxicity			X	X	X
Environmental safety of ePIPAC-OX¶			X		
Procedure-related characteristics			X		
Number of procedures in each patient, reasons for discontinuation			X	X	X
Postoperative complications			X	X	X
Hospital stay			X		
Readmissions				X	X
Clinical evaluation			X	X	X
Radiological tumour response		X			X
Histopathological tumour response			X		
Cytological tumour response			X		
Macroscopic tumour response			X		
Biochemical tumour response			X		X
Quality of life		X		X	X
Costs		X			X
Progression-free survival			X	X	X
Overall survival			X	X	X

*Drawn on each postoperative day.

†Blood is drawn before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360 and 1080 min after oxaliplatin injection during/after the first three procedures, urine is collected before ePIPAC-OX and on postoperative days 1, 3, 5 and 7, ascites/PM/normal peritoneum are collected directly after oxaliplatin injection.

‡Blood is drawn before ePIPAC-OX.

§Medical Consumption Questionnaire 4 weeks after each procedure, Productivity Cost Questionnaire 4 weeks after each second procedure.

¶Only during the first three procedures in the study.

ePIPAC-OX, electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin; PM, peritoneal metastases.

pharmacokinetic purposes. In case no bleeding or perforations are observed, instruments are removed and incisions are closed with absorbable sutures. All instruments and materials are directly disposed in chemotherapy

waste bins and the operating room is cleaned according to existing HIPEC protocols. Any procedure-related mistake or difficulty during ePIPAC-OX is recorded directly after occurrence.

After ePIPAC-OX, the patients are admitted to the general surgical ward. To relieve postoperative pain, the patients receive paracetamol (1 g, four times per day), on-demand morphine and 1 g of metamizole directly after the procedure. To minimise postoperative nausea and vomiting, the patients receive perioperative dexamethasone and on-demand granisetron (1 mg, three times per day). Standard postsurgical clinical evaluations are performed a few hours after the procedure and on every postoperative day. Blood is drawn for bone marrow, liver, and kidney functions, albumin and C-reactive protein on every postoperative day. If the postoperative period is uneventful, the patients are discharged on the first postoperative day. All body excretions are considered oxaliplatin-contaminated for up to 5 days after the procedure.

Dose reduction, prohibited and permitted concomitant care, and strategies to improve adherence are not specified a priori, but left to the discretion of the treating physician. ePIPAC-OX is repeated until clinical progression, radiological progression (Response Evaluation Criteria In Solid Tumours or at physician's discretion in case of non-measurable disease), macroscopic progression (ie, ascites volume, PCI), unacceptable toxicity, physician's decision to discontinue or at patient's request to discontinue. In patients who develop systemic metastases, continuation of ePIPAC-OX can only be considered if the patient has no systemic palliative treatment options and stable peritoneal disease.

Outpatient evaluations

One week after each ePIPAC-OX, the patients undergo clinical evaluation by phone. Four weeks after each ePIPAC-OX, the patients undergo radiological evaluation (ie, thoracoabdominal CT, diffusion-weighted MRI (DW-MRI)), biochemical evaluation (ie, bone marrow, liver, and kidney functions, albumin, C-reactive protein, tumour markers) and clinical evaluation.

Questionnaires

The patients are asked to complete EQ-5D-5L, QLQ-C30 and QLQ-CR29 at baseline and 1 and 4 weeks after each ePIPAC-OX.^{51–53} iMTA Productivity Cost Questionnaire (PCQ) and iMTA Medical Consumption Questionnaire (MCQ) are sent to the patients at baseline and 4 weeks after each ePIPAC-OX (PCQ) and each second ePIPAC-OX (MCQ).^{54,55}

Pharmacokinetics

Blood is collected during and after the first three procedures in each patient. Four mL of whole blood is drawn and collected in heparin tubes before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360 and 1080 min after injection of oxaliplatin. After immediate centrifuging, an aliquot of plasma is stored at -80°C until analysis. Another aliquot of 1 mL of plasma is centrifuged through an ultrafiltration membrane and stored at -80°C until analysis. Urine, ascites, PM and normal peritoneum are collected during and after all procedures. Four mL of urine is collected in

urinalysis tubes before ePIPAC-OX and on the first postoperative day. These are stored at -20°C until analysis. After discharge, the patients are asked to collect 4 mL of urine in urinalysis tubes on the third, fifth and seventh postoperative day, and to store these specimens at their home address at -20°C until analysis. After electrostatic precipitation of the aerosol, the surgeon aspirates a few milliliters of ascites and biopsies two peritoneal metastases and two pieces of normal peritoneum, preferably from different locations. These are collected in aliquots and directly stored at -80°C until analysis. Concentrations of oxaliplatin are measured by using atomic absorption spectrophotometry.

Translational research

Before each ePIPAC-OX, 20 mL of blood is drawn and collected in 10 mL cell-free DNA BCT tubes (Streck, La Vista, Nebraska, USA). According to the manufacturer's instructions, these tubes are sent to a central laboratory for isolation and storage (-80°C) of plasma and cell pellet. Collected ascites or saline is centrifuged twice (5 min, 420 g, zero break) under sterile conditions. The supernatant is snap frozen and stored at -80°C for further analysis on soluble components. The cell pellet is suspended in organoid culture medium at 4°C for transport and further work-up. Of each collected PM, three parts are snap frozen and stored at -80°C for sequencing analysis.

Outcomes

An assessment schedule is presented in [table 1](#). The primary outcome is the number of patients with major toxicity, defined as grade ≥ 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0,⁵⁶ up to 4 weeks after the last ePIPAC-OX. Secondary outcomes are as follows:

- ▶ The environmental safety of ePIPAC-OX, based on air and surface concentrations of oxaliplatin during the first three procedures, measured by atomic absorption spectrophotometry.
- ▶ Procedure-related characteristics of ePIPAC-OX (eg, intraoperative complications, amount of adhesions, procedure-related mistakes and difficulties, operating time).
- ▶ The number of procedures in each patient and reasons for discontinuation.
- ▶ Minor toxicity, defined as grade ≤ 2 according to CTCAE v4.0,⁵⁶ up to 4 weeks after the last ePIPAC-OX.
- ▶ Major and minor postoperative complications, defined as grade ≥ 3 and grade ≤ 2 according to Clavien-Dindo,⁵⁷ respectively, up to 4 weeks after the last ePIPAC-OX.
- ▶ Hospital stay, defined as the number of days between ePIPAC-OX and initial discharge.
- ▶ Readmissions, defined as any hospital admission after initial discharge, up to 4 weeks after the last ePIPAC-OX.
- ▶ Radiological tumour response, based on central review of thoracoabdominal CT and DW-MRI at baseline and 4 weeks after each ePIPAC-OX, performed

by two independent radiologists (JN, MJL) blinded to clinical outcomes (classification is not defined a priori).

- ▶ Histopathological tumour response, based on central review of collected peritoneal biopsies during each ePIPAC-OX, performed by two independent pathologists (eg, CH) blinded to clinical outcomes by using the Peritoneal Regression Grading Score.⁵⁸
- ▶ Macroscopic tumour response, based on PCI and ascites volume during each ePIPAC-OX.
- ▶ Biochemical tumour response, based on tumour markers measured at different time points (table 1).
- ▶ Cytological tumour response, based on collected ascites or peritoneal washing cytology during each ePIPAC-OX.
- ▶ Quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) at different time points (table 1).
- ▶ Costs, derived from the Dutch costing guidelines for healthcare research at the time of analysis, based on case report forms, hospital information systems, and questionnaires (iMTA PCQ, iMTA MCQ) at different time points (table 1).
- ▶ Progression-free survival, defined as the time between enrolment and clinical, radiological, or macroscopic progression, or death.
- ▶ Overall survival, defined as the time between enrolment and death.
- ▶ The pharmacokinetics of oxalipatin during and after ePIPAC-OX.

Sample size

Given the absence of evident clinical endpoints in this patient category, the investigators pragmatically determined the sample size of this exploratory study. The investigators agreed that 60 procedures are required to explore the feasibility, safety, tolerability and preliminary efficacy of repetitive ePIPAC-OX in this setting. Since the expected mean number of procedures is three per patient,³⁶ the initial sample size is determined at 20 patients. This pragmatically determined sample size is approved by the central ethics committee. Enrolled patients who do not undergo a first ePIPAC-OX (eg, systemic metastases on baseline radiology, non-access, resectable disease) are replaced to enrol 20 patients who receive at least one ePIPAC-OX.

Recruitment

The study started in October 2017 and is currently enrolling patients. The investigators anticipate that 20 patients will be enrolled within a maximum of 3 years. Strategies for achieving adequate participant enrolment are not defined a priori.

Data collection and data management

Outcomes are collected in all patients who receive at least one ePIPAC-OX. All baseline characteristics and clinical outcomes are prospectively collected and entered in an

ISO 27001 certified central study database (De Research Manager, Deventer, The Netherlands) with study-specific electronic case report forms by a local investigator in each study centre (RL, EW). This ISO 27001 certified system ensures adequate data integrity, including data coding, security and storage. Questionnaires (quality of life, costs), peritoneal biopsies (histopathological response) and radiological examinations (radiological response) are collected by the coordinating investigator (KR) throughout the study and centrally analysed after study completion. Plans to promote data quality, participant retention and complete follow-up are not specified a priori.

Statistical methods

Repetitive continuous outcomes (eg, quality of life, operating time) are analysed by using the Wilcoxon signed-rank test, the paired samples t-test, the Friedman test or repeated measurements analysis of variance where appropriate. Repetitive categorical outcomes (eg, intraoperative complications, postoperative complications) are analysed by using the McNemar test, the Wilcoxon signed-rank test, the Cochran's Q test or generalised estimating equations where appropriate. Time-to-event variables (ie, overall and progression-free survival) are analysed and displayed by using the Kaplan-Meier method. Other outcomes are analysed by using descriptive statistics. All statistical tests are two-sided and $p < 0.05$ is considered statistically significant.

Data monitoring

Interim analyses are performed after 8 and 20 procedures. The study is terminated after these interim analyses if CTCAE grade ≥ 3 toxicity, directly related to ePIPAC-OX, is observed after ≥ 4 and ≥ 10 procedures. Furthermore, the study is directly terminated if more than one CTCAE grade 5 toxicity, directly related to ePIPAC-OX, occurs during the study. The coordinating investigator and the principal investigator (IH) have access to these interim results. The principal investigator makes the decision to terminate or continue the study. The investigators decided that a data monitoring committee is not needed given the clear stopping rules and the low expected toxicity of repetitive ePIPAC-OX.

Harms

Local investigators report all serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) to the coordinating investigator within 24 hours. The coordinating investigator reports SAEs/SUSARs to the ethics committee within 7 days of first knowledge for lethal or life-threatening SAEs/SUSARs, and within 15 days for other SAEs/SUSARs. The time window for reporting SAEs/SUSARs is from enrolment up to 4 weeks after the last ePIPAC-OX.

Auditing

The study is audited by independent qualified monitors of Clinical Trial Centre Maastricht (Maastricht,

The Netherlands) as a high-risk study according to the brochure 'Kwaliteitsborging mensegebonden onderzoek 2.0' by the Dutch Federation of University Medical Centres. This means that study centres are audited at least three times per year, depending on enrolment, with 100% auditing of the study master file, investigator site files, informed consent forms, eligibility criteria, source data verification and SAEs/SUSARs.

Patient and public involvement

Patients were not involved in the study design before the start of the study. Shortly after the start of the study, the investigators presented the study design to a patient advisory group. Major topics of discussion were the rationale for the study, outcome parameters, recruitment strategies, the patient information sheet, dissemination strategies and the potential risks, benefits and burden of participation from the patient's perspective. The patient advisory group supported the presented study design. Although the patient advisory group is not involved in the recruitment and the conduct of the study, they will be involved in plans to disseminate the study results to relevant patient groups.

ETHICS AND DISSEMINATION

Protocol amendments

Important protocol modifications are communicated to the ethics committee, the Dutch competent authority, the institutional review boards of both study centres, all investigators and trial registries.

Consent or assent

Written informed consent is obtained by local investigators at the outpatient clinic of the study centres. The patients are given the possibility to give separate permission for undergoing DW-MRI and for storage of specimens for translational research.

Confidentiality

Personal information about potential and enrolled patients is collected, shared and maintained according to the Dutch law (Wet Bescherming Persoonsgegevens).

Ancillary and poststudy care

The sponsor (Catharina Hospital, Eindhoven, The Netherlands) is insured to provide cover for patients who suffer harm from study participation. After discontinuation of ePIPAC-OX, the patients receive standard palliative treatment for unresectable metastatic colorectal cancer according to Dutch guidelines.⁴

Dissemination policy

Results of the study are personally communicated to participants and intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals and other stakeholders. Authorship eligibility guidelines for the main manuscript and manuscripts of side studies are not defined a priori. The

full protocol and Dutch informed consent forms are available on reasonable request.

DISCUSSION

To the knowledge of the investigators, this is the first study that prospectively explores the feasibility, safety, tolerability, costs, preliminary efficacy and pharmacokinetics of repetitive ePIPAC-OX as a palliative monotherapy in patients with isolated unresectable colorectal PM.

This study protocol has potential limitations. The broad eligibility criteria could lead to a heterogeneous cohort with various primary tumours (ie, colon, appendix) and histologies (eg, signet ring cell carcinoma, high-grade appendiceal mucinous neoplasm) in different lines of treatment. This clinical heterogeneity could impede the interpretation of survival outcomes. However, survival outcomes are not the major focus of this study. Enrolment is also allowed for patients with an unresected primary tumour and patients who did not receive prior palliative systemic therapy. In these patients, administration of repetitive ePIPAC-OX as a monotherapy could theoretically lead to undertreatment and subsequent systemic progression or progression of the primary tumour. However, it is thought that the frequent clinical and radiological evaluations detect such progression in a sufficiently early stage. Moreover, the patients need to be informed by a medical oncologist about the potential consequences of postponing or discontinuing their standard palliative treatment prior to enrolment. Conclusively, the investigators feel that these controlled circumstances justify enrolment of these patients.

This study protocol has potential strengths. All endpoints are predefined and prospectively assessed. Independent 100% auditing ensures an appropriately conducted study and high-quality data. Unlike other studies, repetitive ePIPAC-OX is administered as a palliative monotherapy in all patients. Thereby, outcomes are not influenced by concurrent palliative systemic therapy. Extensive assessment of quality of life provides insights in the tolerability of ePIPAC-OX from a patient perspective, whereas pharmacokinetic analyses provide the first insights in the systemic absorption repetitive ePIPAC-OX. Insights in the costs of ePIPAC-OX could be valuable for policy makers and other teams that aim to implement this procedure or apply for scientific grants, while translational side studies may open new avenues for research.

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REFERENCES

- van Gestel YR, de Hingh IH, van Herk-Sukel MP, *et al.* Patterns of metachronous metastases after curative treatment of colorectal cancer. *Cancer Epidemiol* 2014;38:448–54.
- van der Geest LG, Lam-Boer J, Koopman M, *et al.* Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis* 2015;32:457–65.
- Razenberg LG, Lemmens VE, Verwaal VJ, *et al.* Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: Results of a population-based study. *Eur J Cancer* 2016;65:113–20.
- Landelijke werkgroep Gastro Intestinale Tumoren. Richtlijn colorectaal carcinoom. 2014 <https://www.oncoline.nl/colorectaalcarcinoom> (Accessed 10 Dec 2018).
- Franko J, Shi Q, Meyers JP, *et al.* Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol* 2016;17:1709–19.
- Sugarbaker PH, Stuart OA, Vidal-Jove J, *et al.* Pharmacokinetics of the peritoneal-plasma barrier after systemic mitomycin C administration. *Cancer Treat Res* 1996;82:41–52.
- Dedrick RL, Myers CE, Bungay PM, *et al.* Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1978;62:1–11.
- Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. *Cancer Treat Res* 1996;82:53–63.
- Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. *J Natl Cancer Inst* 1997;89:480–7.
- Markman M. Chemotherapy: limited use of the intraperitoneal route for ovarian cancer—why? *Nat Rev Clin Oncol* 2015;12:628–30.
- Solass W, Hetzel A, Schwarz T, *et al.* PIPAC Technology. In: Reymond MA, Solass W, eds. *Pressurized IntraPeritoneal Aerosol Chemotherapy – Cancer under Pressure*. De Gruyter, 2014.
- Reymond MA, Hu B, Garcia A, *et al.* Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporiser. *Surg Endosc* 2000;14:51–5.
- Jacquet P, Stuart OA, Chang D, *et al.* Effects of intra-abdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration. *Anticancer Drugs* 1996;7:596–603.
- Esquis P, Consolo D, Magnin G, *et al.* High intra-abdominal pressure enhances the penetration and antitumor effect of intraperitoneal cisplatin on experimental peritoneal carcinomatosis. *Ann Surg* 2006;244:106–12.
- Solass W, Herbette A, Schwarz T, *et al.* Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. *Surg Endosc* 2012;26:847–52.
- Solaß W, Hetzel A, Nadiradze G, *et al.* Description of a novel approach for intraperitoneal drug delivery and the related device. *Surg Endosc* 2012;26:1849–55.
- Facy O, Al Samman S, Magnin G, *et al.* High pressure enhances the effect of hyperthermia in intraperitoneal chemotherapy with oxaliplatin: an experimental study. *Ann Surg* 2012;256:1084–8.
- Solass W, Kerb R, Mürdter T, *et al.* Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. *Ann Surg Oncol* 2014;21:553–9.
- Blanco A, Giger-Pabst U, Solass W, *et al.* Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Ann Surg Oncol* 2013;20:2311–6.
- Eveno C, Haidara A, Ali I, *et al.* Experimental pharmacokinetics evaluation of chemotherapy delivery by PIPAC for colon cancer: first evidence for efficacy. *Pleura Peritoneum* 2017;2:103–9.
- Grass F, Vuagniaux A, Teixeira-Farinha H, *et al.* Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. *Br J Surg* 2017;104:669–78.
- Tempfer C, Giger-Pabst U, Hilal Z, *et al.* Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal carcinomatosis: systematic review of clinical and experimental evidence with special emphasis on ovarian cancer. *Arch Gynecol Obstet* 2018;298:243–57.
- Nowacki M, Alyami M, Villeneuve L, *et al.* Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: an international survey study. *Eur J Surg Oncol* 2018;44:991–6.
- Willaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Pleura Peritoneum* 2017;2:121–8.
- Graversen M, Lundell L, Frstrup C, *et al.* Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) as an outpatient procedure. *Pleura Peritoneum* 2018;3.
- Kakchekeeva T, Demtröder C, Herath NI, *et al.* In Vivo feasibility of electrostatic precipitation as an adjunct to Pressurized Intraperitoneal Aerosol Chemotherapy (ePIPAC). *Ann Surg Oncol* 2016;23(Suppl 5):592–8.
- Odendahl K, Solass W, Demtröder C, *et al.* Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). *Eur J Surg Oncol* 2015;41:1379–85.
- Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. *World J Surg Oncol* 2016;14:128.
- Teixeira Farinha H, Grass F, Kefleyesus A, *et al.* Impact of pressurized intraperitoneal aerosol chemotherapy on quality of life and symptoms in patients with peritoneal carcinomatosis: a retrospective cohort study. *Gastroenterol Res Pract* 2017;2017:1–10.
- Hübner M, Teixeira Farinha H, Grass F, *et al.* Feasibility and safety of pressurized intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis: a retrospective cohort study. *Gastroenterol Res Pract* 2017;2017:1–7.
- Hübner M, Grass F, Teixeira-Farinha H, *et al.* Pressurized intraperitoneal aerosol chemotherapy - practical aspects. *Eur J Surg Oncol* 2017;43:1102–9.
- Alyami M, Gagniere J, Sgarbura O, *et al.* Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. *Eur J Surg Oncol* 2017;43:2178–83.

33. Graversen M, Detlefsen S, Bjerregaard JK, *et al.* Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. *Ther Adv Med Oncol* 2018;10:17.
34. Kurtz F, Struller F, Horvath P, *et al.* Feasibility, safety, and efficacy of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for peritoneal metastasis: a registry study. *Gastroenterol Res Pract* 2018;2018:1–8.
35. Teixeira Farinha H, Grass F, Labгаа I, *et al.* Inflammatory response and toxicity after pressurized intraperitoneal aerosol chemotherapy. *J Cancer* 2018;9:13–20.
36. Demtröder C, Solass W, Zieren J, *et al.* Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. *Colorectal Dis* 2016;18:364–71.
37. Graversen M, Detlefsen S, Pfeiffer P, *et al.* Severe peritoneal sclerosis after repeated pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC OX): report of two cases and literature survey. *Clin Exp Metastasis* 2018;35:103–8.
38. Siebert M, Alyami M, Mercier F, *et al.* Severe hypersensitivity reactions to platinum compounds post-pressurized intraperitoneal aerosol chemotherapy (PIPAC): first literature report. *Cancer Chemother Pharmacol* 2019;83:425–30.
39. <https://clinicaltrials.gov/ct2/results?cond=&term=pipac&cntry=&state=&city=&dist=>. Accessed 10 Dec 2018.
40. Solass W, Giger-Pabst U, Zieren J, *et al.* Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. *Ann Surg Oncol* 2013;20:3504–11.
41. Graversen M, Pedersen PB, Mortensen MB. Environmental safety during the administration of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). *Pleura Peritoneum* 2016;1:203–8.
42. Ndaw S, Hanser O, Kenepekian V, *et al.* Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination. *Toxicol Lett* 2018;298:171–6.
43. Ametsbichler P, Böhlant A, Nowak D, *et al.* Occupational exposure to cisplatin/oxaliplatin during Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)? *Eur J Surg Oncol* 2018;44:1793–9.
44. Dumont F, Senellart H, Pein F, *et al.* Phase I/II study of oxaliplatin dose escalation via a laparoscopic approach using pressurized aerosol intraperitoneal chemotherapy (PIPOX trial) for nonresectable peritoneal metastases of digestive cancers (stomach, small bowel and colorectal): Rationale and design. *Pleura Peritoneum* 2018;3.
45. Kim G, Tan HL, Chen E, *et al.* Study protocol: phase 1 dose escalating study of Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) with oxaliplatin in peritoneal metastasis. *Pleura Peritoneum* 2018;3.
46. Elias D, Bonnay M, Puizillou JM, *et al.* Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. *Ann Oncol* 2002;13:267–72.
47. Giacchetti S, Perpoint B, Zidani R, *et al.* Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000;18:136–47.
48. Giger-Pabst U, Tempfer CB. How to perform safe and technically optimized pressurized intraperitoneal aerosol chemotherapy (pipac): experience after a consecutive series of 1200 procedures. *J Gastrointest Surg* 2018;22:2187–93.
49. Zühlke HV, Lorenz EM, Straub EM, *et al.* [Pathophysiology and classification of adhesions]. *Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir* 1990:1009–16.
50. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996;82:359–74.
51. Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
52. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
53. Stiggelbout AM, Kunneman M, Baas-Thijssen MC, *et al.* The EORTC QLQ-CR29 quality of life questionnaire for colorectal cancer: validation of the Dutch version. *Qual Life Res* 2016;25:1853–8.
54. Bouwmans C, Krol M, Severens H, *et al.* The iMTA Productivity cost questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. *Value Health* 2015;18:753–8.
55. iMTA. Questionnaires. <https://www.imta.nl/questionnaires/> (Accessed 10 Dec 2018).
56. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. 2009 https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf (Accessed 10 Dec 2018).
57. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
58. Solass W, Sempoux C, Carr NJ, *et al.* Reproducibility of the peritoneal regression grading score for assessment of response to therapy in peritoneal metastasis. *Histopathology* 2019;74:1014–24.