

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

### Interventional procedure overview of pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis

Peritoneal carcinomatosis is cancer that has spread inside the peritoneal cavity (the space between the 2 membranes that separate the organs in the abdomen from the abdominal wall). It can happen with cancers in the pelvis, such as ovarian cancer, or in the abdomen, such as bowel cancer, and occasionally with cancers elsewhere in the body. In this procedure, chemotherapy is sprayed inside the peritoneal cavity through a small tube inserted into the abdomen for several minutes. The aim is to apply the chemotherapy directly to the cancer.

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IP overview: Pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis

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## Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

### ***Date prepared***

This overview was prepared in March 2019.

### ***Procedure name***

- Pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis

### ***Specialist societies***

- British Association of Surgical Oncology
- Faculty of Clinical Oncology
- Association of cancer physicians
- British Society of Gastroenterology
- Association of Coloproctology of Great Britain and Ireland
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Gynaecological Cancer Society
- Royal College of Surgeons Edinburgh
- Royal College of Surgeons of England
- The Royal College of Physicians and Surgeons of Glasgow.

## Description of the procedure

### ***Indications and current treatment***

Peritoneal metastases commonly result from the regional spread of gastrointestinal, gynaecological and other malignancies. Peritoneal carcinomatosis is an advanced form of cancer associated with short survival and IP overview: Pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis

poor quality of life. It may lead to bowel obstruction, fluid build-up in the peritoneal cavity and pain.

There is no curative treatment. Current standard treatment uses systemic chemotherapy or surgery for short-term palliation of complications such as bowel obstruction.

### ***What the procedure involves***

Pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis is a laparoscopic procedure usually done under general anaesthesia. The aim is to distribute the drug uniformly to all surfaces of the abdomen and pelvis.

Trocars are inserted and the abdomen insufflated with carbon dioxide. Peritoneal biopsies or local partial peritonectomy may be done at this time. The chemotherapy is delivered using an aerosol device containing normothermic chemotherapy solution. This device is connected to a high-pressure injector, which is inserted into the abdomen through an access port. For operator safety, the procedure takes place in an operating room with laminar air flow. Once in position, the device is operated remotely. A laparoscopic camera can be used to visualise the treatment. The chemotherapy is kept in the insufflated peritoneum for about 30 minutes. The chemotherapy aerosol is then exsufflated via a closed extraction system. Trocars are removed and laparoscopy completed. The procedure is usually repeated several weeks later. One standard course of treatment comprises 3 procedures, usually given 6 weeks apart, although the timing can vary.

## **Efficacy summary**

### **Overall survival**

In a systematic review of 24 observational studies, including a total of 1,547 patients with peritoneal carcinomatosis [PC] of various primary tumour origins (but mainly ovarian cancer) treated with pressurised intraperitoneal aerosol chemotherapy (PIPAC), a pooled analysis of 17 of the studies showed a mean overall survival duration of 13.7 months (range 2.8 months to 26.6 months).<sup>1</sup>

In a systematic review of 13 observational studies, including patients with PC of various primary tumour origins treated with PIPAC, overall median survival after PIPAC was 11.0 to 14.1 months for ovarian and gynaecological PC (3 studies, 184 patients), 13.4 to 15.4 months for gastric cancer PC (2 studies, 34 patients) and 15.7 months for colorectal PC (1 study, 17 patients).<sup>2</sup>

### **Progression-free survival (PFS months)**

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In the systematic review of 24 studies, in a pooled analysis of 3 studies, mean PFS was 5.8 months (range 5.8 to 6.0 months).<sup>1</sup>

### **Objective tumour response (OTR)**

In the systematic review of 24 studies, in a pooled analysis of 16 studies, the overall histological tumour regression rate was 69% (184/264) as assessed by consecutive PC samples taken during repetitive PIPACs.<sup>1</sup>

In the systematic review of 13 studies, the histological OTR rate was between 62% and 100%. In 1 study, the tumour response according to RECIST was 62% to 88%. OTR for PC of gynaecological origin (in 3 studies) was between 62% and 88%, for PC of colorectal origin (in 1 study) was between 71% and 86% and for PC of gastric origin (in 2 studies) was between 70% and 100%.<sup>2</sup>

### **Improvement of peritoneal carcinomatosis index (PCI)**

In the systematic review of 24 studies, improvement of PCI was seen in 69% (116/168) of patients in whom PCI changes were analysed.<sup>1</sup>

### **Quality of life**

In the systematic review of 24 studies, in a pooled analysis of 10 studies (a total of 396 patients), quality of life (assessed by the European organisation for research and treatment of cancer quality-of-life [EORTC-QLQ] 30+3 and SF-36 questionnaires) was maintained or improved during PIPAC in all studies. Improvements were reported for EORTC-QLQ-30+3 scores for global physical health (in 4 studies), and functional scores related to physical functioning (in 2 studies), emotional functioning (3 studies), cognitive functioning (1 study) and social functioning (2 studies). Gastrointestinal problems such as nausea and vomiting, appetite loss, constipation and diarrhoea improved during PIPAC therapy in 3 studies and did not deteriorate in all other studies. Pain scores increased in 1 study and did not change in 5 studies. Fatigue scores improved in 2 studies, deteriorated in 1 study, and were constant in 3 studies.<sup>1</sup>

In the systematic review of 13 studies, quality of life (assessed by the EORTC-QLQ-30 and SF-36 questionnaires) was maintained or improved during PIPAC in 5 studies (266 patients). All studies reported improved EORTC-QLQ-30 scores for global physical health, gastrointestinal problems such as nausea or vomiting, appetite loss and constipation during therapy. In 3 studies, there was an increase in pain score during PIPAC therapy.<sup>2</sup>

In a retrospective case series of 42 patients who had PIPAC for PC from gynaecological or digestive cancers, the overall quality of life (assessed by the EORTC-QLQ-30 questionnaire) was not statistically significantly different before and after first (p=0.57), second (p=0.89) and third (p=0.58) treatments

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respectively. Similarly, no changes were noted for quality-of-life components such as cognitive, physical emotional, role and social functioning. No statistically significant increase in digestive symptoms (appetite loss, constipation, diarrhoea) was reported after treatment sessions. Non-digestive symptoms (insomnia, fatigue, pain, and dyspnoea) did not show statistically significant changes throughout PIPAC treatment.<sup>3</sup>

### **Access failure**

In the systematic review of 24 studies, PIPAC was technically feasible in 89% (1,433/1,547) of patients, but access to the abdomen was not possible in 11% (114/1050) patients.<sup>1</sup>

In the systematic review of 13 studies, PIPAC was technically feasible in most patients. The rate of failed access (unsuccessful procedures) varied between 0 and 17%.<sup>2</sup>

### **Nutritional status**

In a retrospective case series of 84 patients with PC from recurrent ovarian and fallopian cancer, which assessed nutritional status longitudinally during palliative pressurised intraperitoneal aerosol chemotherapy (PIPAC), a severe nutritional deficit for nutritional parameters such as resting metabolism, skeletal muscle mass, visceral fat, upper arm and lower leg circumference, and serum parameters (albumin, total protein and transferrin) was noted. However, it was stabilised during repeated PIPAC treatment cycles. Cachexia-anorexia syndrome deterioration occurred in 16% (9/55) of patients and stabilisation or improvement of cachexia-anorexia syndrome was seen in 84% (46/55) patients with follow-up data.<sup>4</sup>

## **Safety summary**

### **Mortality**

In the systematic review of 24 studies, in 22 studies (a total of 1,197 patients) with a follow up of 4 to 22 months, the mortality rate was 2% (19/1197). Twelve events were judged to be procedure related and 7 events were judged as being unrelated to the procedure.<sup>1</sup>

In the systematic review of 13 studies there were 3 deaths (in 2 studies), which were unrelated to the procedure.<sup>2</sup>

### **Morbidity**

In the systematic review of 24 studies, in 22 studies (a total of 1,197 patients), mild adverse events occurred in 59% patients and severe adverse events in 9%

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patients. Procedure-related morbidity or toxicity, graded according to common terminology criteria for adverse events (CTCAE), was seen in 45% (537/1,197), 14% (167/1,197), 7% (83/1,197), 1% (10/1,197) and 2% (19/1,197) of patients for grades 1, 2, 3, 4 and 5 respectively.<sup>1</sup>

**Grade 1 or 2 adverse events** included abdominal pain (117), nausea and vomiting (15), fatigue (18), sleep disorder (8), diarrhoea (5), fever, elevated C reactive protein (7), bowel obstruction (2), anaemia (9), infection (4), hypocalcaemia (1) and leucocytosis.<sup>1</sup>

**Grade 3 adverse events** included colon perforation (1), small bowel perforation (1), trocar hernia (2), ileus (2), cholangitis (1), liver toxicity (1), bowel obstruction (4), duodenum obstruction (1), abdominal pain (2), hematoma (1), cholestasis (1), intraoperative bleeding (1), cystitis with urosepsis (1), anaemia (4), sepsis (2), trocar metastasis (1), breast cancer (1), hypertension (1), bile duct stenosis (1), diarrhoea needing hospitalisation (1), evacuation of large amounts of ascites and volume resuscitation with temporary kidney insufficiency, electrolyte disturbances and cardiopulmonary decompensation.<sup>1</sup>

**Grade 4 adverse events** included anaphylactic shock after application of metamizole (1), small bowel fistula (1), rectovaginal fistula (1), colon perforation (1), iatrogenic perforation of the jejunum (1) and bowel anastomosis insufficiency (1). Three of these events occurred in patients who had combined treatment with cytoreductive surgery.<sup>1</sup>

**Grade 5 adverse events** included death within 30 days (14 deaths were due to iatrogenic perforations of bowels followed by peritonitis).<sup>1</sup>

In the systematic review of 13 studies, CTCAE grade 1 or 2 events such as abdominal pain or nausea were common. Grade 3 to 5 events occurred in 0 to 35% of patients, and highest rates were reported in 1 study that combined PIPAC with cytoreductive surgery. Surgery-related complications occurred in from 0 to 12% of patients.<sup>2</sup>

### **Renal and hepatic toxicity**

In the systematic review of 24 studies, renal and hepatic functions were not impaired, and no renal or hepatic toxicity was seen after repeated PIPAC procedures.<sup>1</sup>

In the systematic review of 13 studies, hepatorenal toxicity (in 2 studies) was absent and all parameters were within normal range.<sup>2</sup>

### **Severe peritoneal sclerosis**

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Severe peritoneal sclerosis caused by repeated PIPAC treatment applications with oxaliplatin 92 mg/m<sup>2</sup> in 2 patients with PC from mucinous adenocarcinoma of the appendix and appendiceal goblet cell carcinoid was reported in a case report. Imaging showed small intestine covered with adhesions, and a thickened peritoneum enveloped by a secondary thick cocoon-like plaque resulting in bowel obstruction.<sup>5</sup>

### **Environmental and occupational safety**

In the systematic review of 22 studies, there was no risk of chemotherapy exposure for healthcare workers (in 4 studies). No detectable concentration of platinum particles was found when air in the operating room was analysed during the procedures. No traces of cisplatin were detected in the blood samples from the surgeons.<sup>1</sup>

### ***Anecdotal and theoretical adverse events***

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse event: extravasation of chemotherapy from port sites during the postoperative period. They considered that the following were theoretical adverse events: intra-operative mortality, disease progression indicating a failure of the technique, complications related to accessing the peritoneum, complications related to chemotherapy agents, life threatening massive tumour lysis, safety breaches in theatre causing contamination and exposure of staff to chemotherapy agents.

## **The evidence assessed**

### ***Rapid review of literature***

The medical literature was searched to identify studies and reviews relevant to pressurised intraperitoneal aerosol chemotherapy for PC. The following databases were searched, covering the period from their start to 26.09.2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the [literature search strategy](#)). Relevant published

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studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

**Table 1 Inclusion criteria for identification of relevant studies**

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with peritoneal carcinomatosis.
Intervention/test	Pressurised intraperitoneal aerosol chemotherapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

### ***List of studies included in the IP overview***

This IP overview is based on 1,675 patients from 2 systematic reviews<sup>1-2</sup>, 2 case series<sup>3-4</sup> and 1 case report<sup>5</sup>.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the [appendix](#).



## **Table 2 Summary of key efficacy and safety findings on pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis**

### **Study 1 Tempfer C (2018)**

#### **Details**

Study type	<b>Systematic review</b>
Country	Germany
Study period	Search period inception to April 2018; databases searched: Medline, PubMed, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled trials. Cross-reference searches were done to identify further articles on PIPAC. Study authors were contacted for additional information.
Study population and number	n=24 observational studies (n=1,547 patients with synchronous or metachronous peritoneal carcinomatosis [PC] of various primary tumours). 1 phase I study, 4 phase II studies, 9 retrospective cohort studies, 6 case series and 4 case reports. 16 studies included patients with PC from ovarian cancer
Age and sex	Not reported
Study selection criteria	Studies on PIPAC (clinical or experimental in vitro, in vivo, and ex vivo studies as a means of treatment of malignant disease) with no language restrictions were included. Studies reporting on intraperitoneal chemotherapy in the form of heated intraperitoneal chemotherapy (HIPEC) or intraperitoneal chemotherapy done as application of chemotherapy into the abdomen via indwelling transperitoneal catheter; on PITAC, double publications, book chapters and corrections to previous articles were excluded.
Technique	Pressurised intraperitoneal aerosol chemotherapy (PIPAC) -3515 procedures Procedure and technique standardised – chemotherapy protocols used were combination of cisplatin and doxorubicin at a dosage of 7.5 and 1.5 mg/m <sup>2</sup> or oxaliplatin at a dosage of 92mg/m <sup>2</sup> given. Mean time between procedures was 6 to 8 weeks. An average of 2.6 applications were done (range 1-12). Routine histological analysis and radiological evaluations were done. <u>Simultaneous treatment</u> : PIPAC associated with systemic chemotherapy was given in 2 studies and cytoreduction surgery in 1 study.
Follow-up	<b>Varied in studies (4 months to 22 months)</b>
Conflict of interest/source of funding	Primary author received research grants from Reger Medical and Capnomed. This study was not funded.

#### **Analysis**

**Follow-up issues:** follow up varied in studies.

**Study design issues:** a systematic review of clinical and experimental evidence was done, a comprehensive search strategy was used, quality assessment of studies was not done. Outcomes assessed in clinical studies were toxicity (either descriptive as the rate of complications and mortality or according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0), objective therapy response (either in the form of histological tumour regression or in the form of radiological response according to RECIST criteria or both), quality of life (in the form of validated questionnaires), and time to progression, overall and/or progression-free survival.

**Study population issues:** 16 studies reported on patients with ovarian cancer. PIPAC for mixed patients with PC from various primary tumour origins (gastric, gynaecologic, ovarian, colorectal cancer, primary peritoneal, pseudomyxoma peritonei (PMP), malignant mesothelioma or other origins) was assessed in studies. Most patients had had some form of previous treatments.

**Other issues:** evidence from experimental studies (n=18) about mechanism and pharmacokinetics was not extracted from this review. Only clinical evidence about safety and efficacy was considered.

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## Key efficacy and safety findings

Efficacy	Safety																
<p>Number of patients analysed: <b>1,547 (3,515 PIPAC procedures)</b></p> <p><b>Access failure</b></p> <p>PIPAC was technically feasible in 89% (1,433/1547) of patients, since access to the abdomen was not possible in 10.9% (114/1,050) patients.</p> <p><b>Objective tumour response % (defined as tumour regression on histology) (16 studies)</b></p> <p>In a pooled analysis of 16 studies, the overall histological tumour regression rate was 69% (184/264) as assessed by consecutive PC samples taken during repetitive PIPACs.</p> <p><b>Improvement of PCI</b> Improvement of PCI was seen in 69% (116/168) of patients in whom PCI changes were analysed.</p> <p><b>PFS (months)</b></p> <p>In a pooled analysis of 3 studies, the mean progression-free survival (PFS) was 5.8 months (range 5.8 to 6 months).</p> <p><b>OS (months)</b></p> <p>In a pooled analysis of 17 studies, the mean overall survival duration was 13.7 months (range 2.8 months to 26.6 months).</p> <p><b>Quality of life (10 studies with 396 patients assessed by the EORTC-QLQ-30 and SF-36 questionnaires)</b></p> <p>Quality of life maintained or improved during PIPAC in all studies. Improvements were reported for EORTC QLQ-30+3 scores for global physical health (in 4 studies), and functional scores related to physical functioning (in 2 studies), emotional functioning (3 studies), cognitive functioning (1 study), and social functioning (2 studies).</p> <p>Gastrointestinal problems such as nausea/vomiting, appetite loss, constipation, and diarrhoea improved during PIPAC therapy in some studies (3) and did not deteriorate in all other studies.</p> <p>Pain scores increased in 1 study and did not change in 5 studies. Fatigue scores improved in 2 studies, deteriorated in 1 study, and were constant in 3 studies.</p> <p><b>Environmental/occupational safety (4 studies)</b></p> <p>There was no risk of chemotherapy exposure for healthcare workers. No detectable concentration of platinum particles was found at analysis of the air in the operating room during the procedures. No traces of cisplatin were detected in the blood samples from the surgeons.</p>	<p><b>Procedure related morbidity/toxicity (% , according to CTCAE criteria) (in 22 studies, n=1,197 patients)</b></p> <table border="1" data-bbox="824 300 1511 594"> <thead> <tr> <th>CTCAE grade</th> <th>% (n)</th> </tr> </thead> <tbody> <tr> <td>Grade 1</td> <td>45 (537/1,197)</td> </tr> <tr> <td>Grade 2</td> <td>14 (167/1,197)</td> </tr> <tr> <td>Grade 3</td> <td>7 (83/1,197)</td> </tr> <tr> <td>Grade 4</td> <td>0.8 (10/1,197)</td> </tr> <tr> <td>Grade 5</td> <td>1.6 (19/1,197)</td> </tr> <tr> <td>Mild adverse events</td> <td>59%</td> </tr> <tr> <td>Severe adverse events</td> <td>9%</td> </tr> </tbody> </table> <p><b>Grade 1/2 events</b> included fatigue (18), abdominal pain (117), nausea/vomiting (15), sleep disorder (8), diarrhoea (5), fever elevated C reactive protein(7), bowel obstruction (2), anaemia (9), infection (4), hypocalcaemia (1), leucocytosis.</p> <p><b>Grade 3 toxicities</b> included colon perforation (1), small bowel perforation (1), trocar hernia (2), ileus (2), cholangitis (1), liver toxicity (1), bowel obstruction (4), duodenum obstruction (1), abdominal pain (2), hematoma (1), cholestasis (1), intraoperative bleeding (1), cystitis with urosepsis (1), anaemia (4), sepsis (2), trocar metastasis (1), breast cancer (1), hypertension (1), bile duct stenosis (1), diarrhoea needing hospitalisation (1), evacuation of large amounts of ascites and volume resuscitation with temporary kidney insufficiency, electrolyte disturbances and cardiopulmonary decompensation.</p> <p><b>Grade 4 events</b> included anaphylactic shock after application of metamizole (1), small bowel fistula (1), rectovaginal fistula (1), colon perforation (1), iatrogenic perforation of the jejunum (1), and bowel anastomosis insufficiency (1). 3 of these events occurred in patients who had combined treatment with cytoreductive surgery.</p> <p><b>Grade 5 events</b> included death within 30 days (14 deaths were due to iatrogenic perforations of bowels followed by peritonitis).</p> <p><b>Mortality rate %</b></p> <p>The mortality rate was 1.6% (19/1197) with 12 events judged related and 7 events judged unrelated to the procedure.</p> <p><b>Renal and hepatic functions</b> were not impaired; no renal or hepatic toxicity was seen after repeated PIPAC procedures.</p>	CTCAE grade	% (n)	Grade 1	45 (537/1,197)	Grade 2	14 (167/1,197)	Grade 3	7 (83/1,197)	Grade 4	0.8 (10/1,197)	Grade 5	1.6 (19/1,197)	Mild adverse events	59%	Severe adverse events	9%
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<p>Abbreviations used: CTCAE, common terminology criteria for adverse events; EORTC-QLQ, European organisation for research and treatment of cancer quality of life questionnaire-30+3; OS, overall survival; PCI, peritoneal carcinomatosis index; PC, peritoneal carcinomatosis; PCI, peritoneal carcinomatosis index; PIPAC, pressurised intraperitoneal aerosol chemotherapy; PFS, progression-free survival.</p>																	

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## Study 2 Grass F (2017)

### Details

Study type	<b>Systematic review</b>
Country	Switzerland
Study period	Search period 2010 to October 2016; databases searched: Medline, PubMed, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled trials. Hand searching and cross-reference searches were done to identify further articles on PIPAC.
Study population and number	<b>n=13 observational studies (n=346 patients with peritoneal carcinomatosis [PC] of 12 different primary tumours)</b> mainly gynaecological (3 studies, n=184), gastric (2 studies, n=34) and colorectal (1 study, n=17) 5 prospective studies including 1 phase II study, 6 retrospective cohort studies, 2 case reports.
Age and sex	Not reported
Study selection criteria	Scientific reports on PIPAC (pre-clinical and clinical studies) with no language restrictions were included. Studies reporting on intraperitoneal chemotherapy by conventional lavage- heated intraperitoneal chemotherapy (HIPEC) or via indwelling transperitoneal catheter; book chapters and reviews were excluded.
Technique	Pressurised intraperitoneal aerosol chemotherapy (PIPAC) -801 procedures Procedure and technique standardised – chemotherapy protocols used were combination of cisplatin and doxorubicin at a dosage of 7.5 and 1.5 mg/m <sup>2</sup> for PC of non-colorectal origin or oxaliplatin at a dosage of 92mg/m <sup>2</sup> was given for PC of colorectal origin. Mean time between procedures was 6 weeks. An average of 3 applications were done. Routine histological analysis and radiological evaluations were done. <u>Simultaneous treatment:</u> PIPAC associated with systemic chemotherapy was given in 2 studies and cytoreduction surgery in 1 study.
Follow-up	<b>Varied in studies (4 months to 22 months)</b>
Conflict of interest/source of funding	Authors declare no conflicts of interest.

### Analysis

**Follow-up issues:** follow up varied in studies.

**Study design issues:** a systematic review of clinical and experimental evidence was done, a comprehensive search strategy was used, data was extracted into a database, quality assessment of studies was not done. Outcomes assessed were toxicity (according to Common Terminology Criteria for Adverse Events (CTCAE), complications, mortality, objective tumour response (either in the form of histological tumour regression or in the form of radiological response according to RECIST criteria or both), quality of life (in the form of validated questionnaires), and time to progression, overall or progression-free survival. Data were presented in accordance with PRISMA statement. Data analysis was descriptive because of limited and heterogenous data. Most of the studies were done by 1 group in Germany.

**Study population issues:** PIPAC for mixed patients with PC from various primary tumour origins (gynaecologic cancer, ovarian cancer, appendiceal cancer, pseudomyxoma peritonei, primary peritoneal cancer, fallopian tube cancer, colorectal cancer, mesothelioma, cancer with unknown primary origin, colon cancer, endometrial cancer, breast cancer) was assessed in studies. Most patients had gynaecological, gastric or colorectal cancer and had had some form of previous treatments.

**Other issues:** evidence from preclinical studies (n=16) was not extracted from this review. Only clinical evidence about safety and efficacy was considered. There is some overlap of studies between the 2 systematic reviews.

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## Key efficacy and safety findings

Efficacy	Safety																						
<p>Number of patients analysed: <b>346 (801 PIPAC procedures)</b></p> <p><b>Access failure</b></p> <p>PIPAC was technically feasible in most patients. The rate of failed access (unsuccessful procedures) varied between 0 to 17%.</p> <p><b>Repeated treatment cycles</b></p> <p>Repeated PIPAC applications (a mean of 2 applications) were done in 32% to 82% of patients.</p> <p><b>OTR % (defined as tumour regression on histology) (13 studies)</b></p> <p>The treatment response according to RECIST was 62% to 88% in 1 study. In other studies, the histological tumour regression rate between 62% to 100% was reported but pathological assessment was inconsistent.</p> <p><b>OTR according to tumour origin</b></p> <table border="1" data-bbox="110 747 795 856"> <tbody> <tr> <td>PC of gynaecological origin</td> <td>62% to 88%</td> </tr> <tr> <td>PC of colorectal origin</td> <td>71% to 86%</td> </tr> <tr> <td>PC of gastric origin</td> <td>70% to 100%</td> </tr> </tbody> </table> <p><b>Quality of life (5 studies with 266 patients assessed by the EORTC-QLQ-30 and SF-36 questionnaires)</b></p> <p>Quality of life was maintained or improved during PIPAC in all studies. All studies reported improved EORTC QLQ-30 scores for global physical health, gastrointestinal problems such as nausea or vomiting, appetite loss and constipation during therapy. 3 studies showed increase in pain score during PIPAC therapy.</p> <p><b>Survival</b></p> <p>The median survival after PIPAC therapy was 11.0 to 14.1 months for ovarian and gynaecological related peritoneal carcinomatosis (PC) and 13.4 to 15.4 months for gastric related PC and 15.7 months for colorectal related PC.</p>	PC of gynaecological origin	62% to 88%	PC of colorectal origin	71% to 86%	PC of gastric origin	70% to 100%	<p><b>Adverse events (assessed according to CTCAE grading system) (in 13 studies, n=346 patients)</b></p> <table border="1" data-bbox="824 300 1507 785"> <tbody> <tr> <td><b>CTCAE grade 1 or 2 events</b> (abdominal pain and/or nausea were commonly reported)</td> <td>n=287</td> </tr> <tr> <td><b>CTCAE grade 3-5 events*</b></td> <td><b>n=61 (0-37%)</b></td> </tr> <tr> <td>PC of gynaecological origin</td> <td>15% to 28%</td> </tr> <tr> <td>PC of colorectal cancer</td> <td>23%</td> </tr> <tr> <td>PC of gastric cancer</td> <td>20% to 37%</td> </tr> <tr> <td><b>Surgery related complications</b></td> <td><b>n=44 (0-12%)</b></td> </tr> <tr> <td><b>Mortality</b></td> <td><b>n=3</b> (1 due to lung oedema, 1 disease progression and 1 from anasarca).</td> </tr> <tr> <td><b>Hepatorenal toxicity</b> (assessed in 2 studies)</td> <td><b>Absent;</b> all parameters in normal range</td> </tr> </tbody> </table> <p>*Highest toxicity rates were reported in 1 study that had combined PIPAC with systemic chemotherapy and cytoreduction surgery and another study on gastric PC.</p> <p>Leucocytosis and an increase in C reactive protein was reported after PIPAC therapy.</p>	<b>CTCAE grade 1 or 2 events</b> (abdominal pain and/or nausea were commonly reported)	n=287	<b>CTCAE grade 3-5 events*</b>	<b>n=61 (0-37%)</b>	PC of gynaecological origin	15% to 28%	PC of colorectal cancer	23%	PC of gastric cancer	20% to 37%	<b>Surgery related complications</b>	<b>n=44 (0-12%)</b>	<b>Mortality</b>	<b>n=3</b> (1 due to lung oedema, 1 disease progression and 1 from anasarca).	<b>Hepatorenal toxicity</b> (assessed in 2 studies)	<b>Absent;</b> all parameters in normal range
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<b>CTCAE grade 1 or 2 events</b> (abdominal pain and/or nausea were commonly reported)	n=287																						
<b>CTCAE grade 3-5 events*</b>	<b>n=61 (0-37%)</b>																						
PC of gynaecological origin	15% to 28%																						
PC of colorectal cancer	23%																						
PC of gastric cancer	20% to 37%																						
<b>Surgery related complications</b>	<b>n=44 (0-12%)</b>																						
<b>Mortality</b>	<b>n=3</b> (1 due to lung oedema, 1 disease progression and 1 from anasarca).																						
<b>Hepatorenal toxicity</b> (assessed in 2 studies)	<b>Absent;</b> all parameters in normal range																						
<p>Abbreviations used: CTCAE, common terminology criteria for adverse events; EORTC-QLQ, European organisation for research and treatment of cancer quality of life questionnaire-30+3; OTR, objective tumour response; PC, peritoneal carcinomatosis; PCI, peritoneal carcinomatosis index; PIPAC, pressurised intraperitoneal aerosol chemotherapy; SF-36, short form 36.</p>																							

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## Study 3 Farinha HT (2017)

### Details

Study type	<b>Case series (retrospective cohort study)</b>
Country	Switzerland
Recruitment period	2015-16
Study population and number	<b>n=42 patients with peritoneal carcinomatosis</b> 21 of gynaecological origin and 14 patients with PC of colorectal and 3 of gastric origin (1 each for small bowel, appendicular, pseudomyxoma, and mesothelioma).
Age and sex	Median age 66 years; 80% (34/42) female.
Study selection criteria	Patients with chemoresistant isolated peritoneal carcinomatosis who were not eligible for cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) because of medical or surgical contraindications had PIPAC were included.
Technique	Pressurised intraperitoneal aerosol chemotherapy (PIPAC) -91 procedures, 3 sessions scheduled at 6-week intervals. 1 patient also had systemic chemotherapy.
Follow-up	<b>3 months</b>
Conflict of interest/source of funding	Authors declare no conflicts of interest.

### Analysis

**Study design issues:** a small study assessing quality of life (QoL; 0–100: optimal) and symptoms (no symptom: 0–100), measured prospectively before, at discharge and after every PIPAC procedure using EORTCQLQ-C30. QLQ-C30 is a 30-question self-administered questionnaire assessing global health status, 9 individual symptoms, and 5 functional scales. The 30 scores were linearly converted to a 0–100 scale. High functional scores indicate a high level of function (optimum: 100), while high symptom scores represented high degree of symptoms (optimum: 0).

QoL was compared between patients with PC of gynaecological versus digestive origin to detect potential differences between those different patient groups.

**Key efficacy and safety findings**

Efficacy			Safety
Number of patients analysed: <b>42 (91 PIPAC procedures)</b>			Overall complication rate was 8.8%
<b>Quality of life (assessed using EORTC QLQ-30)</b>			
<b>Quality of life</b>		<b>P value</b>	
Baseline	66 ± 2.6		
PIPAC 1	64 ± 3.75	0.57	
PIPAC 2	61 ± 4.76	0.89	
PIPAC 3	70 ± 6.67	0.58	
<b>Fatigue symptom score</b>			
Baseline	32 ± 4.3		
PIPAC 1	44 ± 4.86		
PIPAC 2	47 ± 6.69		
PIPAC 3	34 ± 7.85	0.40	
<p>No statistically significant changes were noted under PIPAC treatment for the quality-of-life components cognitive, physical, emotional, role, and social functioning.</p> <p>The digestive group had lower scores throughout the treatment course with statistically significant differences after PIPAC 1 (discharge: p=0.03; 4 weeks: p=0.02) and after PIPAC 2 (discharge: p=0.01).</p> <p>Digestive symptoms such as diarrhoea (p=0.31), constipation (p=0.76), and nausea (p=0.66), appetite loss did not change statistically significantly after PIPAC treatment.</p> <p>Non-digestive symptoms insomnia, fatigue, pain, and dyspnoea did not show statistically significant changes.</p> <p>No statistically significant changes were seen in quality of life and symptoms after first and repeated sessions.</p>			
Abbreviations used: EORTC-QLQ, European organisation for research and treatment of cancer quality of life questionnaire-30+3; PIPAC, pressurised intraperitoneal aerosol chemotherapy; SF-36, short form 36.			

## Study 4 Hilal Z (2017)

### Details

Study type	<b>Case series (retrospective cohort study)</b>
Country	Germany
Recruitment period	2014-16
Study population and number	<b>n=84 patients with peritoneal carcinomatosis</b> from ovarian cancer (n=77), fallopian tube cancer (n=2), and peritoneal cancer (n=5)
Age and sex	Median age 60 years
Study selection criteria	Women with peritoneal cancer or peritoneal metastases from recurrent gynaecologic malignancies such as ovarian cancer or fallopian tube cancer were included in the study. Patients with extraperitoneal disease were not included in this study with the exception of isolated pleural carcinomatosis/effusion.
Technique	Pressurised intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin repeated every 4–6 weeks. Concomitant systemic therapy was done in 7 patients.
Follow-up	<b>Median 2.4 months (range 0.3 to 27.1 months)</b>
Conflict of interest/source of funding	Authors declare no conflicts of interest.

### Analysis

**Follow up issues:** 23% (20/84) were lost to follow up.

**Study design issues:** small retrospective cohort study.

**Study population issues:** all patients had prior systemic chemotherapy.

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**Key efficacy and safety findings**

Efficacy		Safety			
Number of patients analysed: <b>82</b>					
<b>Nutritional and serum parameters</b>					
	Baseline	Cycle 1	Cycle 2	Cycle 3	P value
No of patients (procedures)	84	53 (53)	30 (30)	15 (40)	
BMI (kg/m <sup>2</sup> )	24.3 (21.8–28.1)	23.6 (20.8–27.3)	23.5 (20.0–26.3)	26.5 (24.5–28.3)	0.010
<b>Bioelectrical impedance analysis</b>					
RM (kcal/day)	1,399 (1,321–1,491)	1,389 (1,308–1,485)	1,364 (1,321–1,416)	1,398 (1,375–1,444)	0.300
Body fat mass (%)	36.6 (30.9–41.7)	32.8 (27.4–39.4)	31.9 (26.2–39.8)	34.8 (29.1–40.4)	0.700
Skeletal muscle mass (%)	26.4 (24.3–28.9)	27.7 (25.4–30.0)	28.4 (25.4–30.2)	28.3 (25.3–31.1)	0.800
Visceral fat level	7 (5–10)	7 (4–9)	7 (4–10)	9 (7.25–11)	0.005
Caliper body fat (%)	36.0 (32.6–40.3)	35.9 (31.6–38.8)	35.9 (31.9–38.1)	34.3 (31.6–38.6)	0.900
Arm circumference (cm)	27.0 (25.1–30.0)	27.2 (24.0–29.0)	27.3 (24.9–29.0)	28.0 (26.0–29.3)	0.300
Leg circumference (cm)	35.0 (33.0–37.2)	34.5 (32.5–36.3)	33.1 (31.9–36.9)	33.8 (32.3–35.6)	0.700
<b>Serum parameters</b>					
CRP (mg/dL)	2.1 (0.48–5.3)	0.8 (0.3–4.2)	0.9 (0.2–3.3)	1.2 (0.6–4.3)	0.300
Albumin (g/dL)	3.7 (3.2–4.1)	3.7 (2.9–4.0)	3.7 (3.3–3.9)	3.6 (3.2–4.0)	0.900
Total protein (g/dL)	6.5 (5.7–6.8)	6.6 (5.8–6.9)	6.2 (5.7–6.9)	6.7 (5.9–7.1)	0.400
Transferrin (mg/dL)	203 (151–244)	195 (146–270)	206 (157–235)	184 (161–261)	0.900
Iron (microgram/dL)	44 (30–69)	51 (36–69)	62 (40–79)	56 (29–74)	0.400
Haemoglobin (g/dL)	11.3 (10.1–12.2)	11.1 (10.1–12.6)	11.1 (10.1–12.8)	11.6 (10.4–12.8)	0.600
<b>Cachexia-anorexia syndrome (CAS) during PIPAC (n=55)</b>					
Deterioration of CAS	16.4 (9/55)				
Stabilisation of CAS	83.6 (46/55)				
Parenteral nutrition support	3.9 (5/84)				
In a multivariate analysis, none of the parameters (body fat mass, visceral fat level, skeletal muscle mass, caliper body fat, presence of CAS, weight, BMI, ascites, Karnofsky index, RM, CRP, parenteral nutrition support, and tumour response) were predictors of CAS deterioration.					
Abbreviations used: BMI, body mass index; CAS, Cachexia-anorexia syndrome; CRP, C-reactive protein; RM, resting metabolism; PC, peritoneal carcinomatosis; PIPAC, pressurised intraperitoneal aerosol chemotherapy;					

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## Study 5 Graversen M (2018)

### Details

Study type	<b>Case report</b>
Country	Denmark
Recruitment period	2016-17
Study population and number	<b>n=2 patients</b> <b>1 patient with peritoneal carcinoma from mucinous adenocarcinoma of the appendix</b> <b>1 patient with peritoneal carcinoma from mucinous adenocarcinoma of the appendiceal goblet cell carcinoma</b>
Age and sex	44- and 71-year males
Patient selection criteria	Not reported
Technique	Pressurised intraperitoneal aerosol chemotherapy (PIPAC) Both patients had 4 sessions of PIPAC with oxaliplatin 92mg/m <sup>2</sup> per session (flowrate 0.5 ml/s, maximum pressure of 200 per square inch).
Follow-up	<b>5-8 months</b>
Conflict of interest/source of funding	Authors declare no conflicts of interest.

### Analysis

**Study population issues:** both patients previously had systemic chemotherapy.

### Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: <b>2</b> <b>2 patients developed severe peritoneal sclerosis after PIPAC therapy characterised by anorexia, nausea, abdominal pain and abdominal distension</b> The first patient had mild abdominal distention and pain, bloating, constipation, minimal loss of appetite (grade 1) after the procedures. After third and fourth sessions, the peritoneum was covered with a grey-white to yellow confluent plaque like material, with excessive fibrosis and no signs of progressive disease. The second patient had 4 PIPAC treatments. After first session the patient had a small bowel perforation (grade 3 complication) needing reoperation. At the second session, grey white to yellow confluent plaque like material at the surface of the peritoneum was noted. Biopsies showed fibrosis/sclerosis of the peritoneum. At fourth session, the small intestine is enveloped with severe cocoon like plaques resulting in obstruction and compression of the bowel. After 5 weeks he had fluids and laxatives. Patient needed nutritional support by the parenteral route.	
Abbreviations used: PC, peritoneal carcinomatosis; PIPAC, pressurised intraperitoneal aerosol chemotherapy.	

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## Validity and generalisability of the studies

- There are no studies evaluating the effect of PIPAC compared with other standard treatments (sequential or simultaneous applications with systemic chemotherapy).
- Studies were mainly small retrospective observational studies with short-term follow up in patients with end stage peritoneal carcinomatosis of various origins.
- The procedure and administration of the technique was standardised, and chemotherapy drugs mainly used in studies were cisplatin, doxorubicin and oxaliplatin. Concentration of drugs, duration of treatment, pressure, temperature and intervals between treatment were not consistent in studies.
- Three studies included in the systematic review<sup>1</sup> used combined treatments (systemic chemotherapy and PIPAC or PIPAC followed by cytoreductive surgery) and the risk of grade 3 or 4 adverse events was high.
- Toxicity related to PIPAC treatment might be drug- or dose-dependent.

## Existing assessments of this procedure

**Statement by European groups** (the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) from Germany, Austria, and Switzerland and the Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO) **on the use of PIPAC (2018)**

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a highly experimental method for treating patients with ovarian, tubal, and peritoneal cancer. Only 3 studies have assessed PIPAC in a total of 184 patients with peritoneal carcinomatosis. Only some of those studies were phase I/II studies that included PIPAC for patients with different indications and different cancer entities. PIPAC treatment is associated with relatively high toxicity and to date, no systematic dose-finding studies have been reported. Moreover, no studies have reported improvements in progression-free or overall survival associated with PIPAC therapy. Randomized controlled trials are required to evaluate the effect of PIPAC compared to other standard treatments (sequential or simultaneous applications with systemic chemotherapy). In cases of ovarian, tubal, and peritoneal cancer, PIPAC should not be performed outside the framework of prospective, controlled studies.<sup>6</sup>

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## Related NICE guidance

Below is a list of NICE guidance related to this procedure.

### Interventional procedures

- Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis, NICE interventional procedure guidance 331 (2010). Available from <http://www.nice.org.uk/guidance/IPG331>

### Technology appraisals

- Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy. NICE technology appraisal 381 (2016). Available from <http://www.nice.org.uk/guidance/TA353>
- Bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. (terminated appraisal) NICE technology appraisal 353 (2015). Available from <http://www.nice.org.uk/guidance/TA353>

### NICE guidelines

- Ovarian cancer: recognition and initial management. NICE guideline 122 (2011). Available from <http://www.nice.org.uk/guidance/CG122>

## Additional information considered by IPAC

### *Specialist advisers' opinions*

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are

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considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Adviser Questionnaires for pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis were submitted and can be found on the [NICE website](#).

### ***Patient commentators' opinions***

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

### ***Company engagement***

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

### ***Issues for consideration by IPAC***

- Ongoing studies:
  - **NCT02604784:** Feasibility, efficacy and safety of Pressurized IntraPeritoneal Air-flow Chemotherapy (PIPAC) With Oxaliplatin, Cisplatin and Doxorubicin in patients with peritoneal carcinomatosis from colorectal, ovarian, gastric cancers and primary tumors of the peritoneum: an open-label, two-arms, phase I-II clinical trial. PI-CaP; n=105, non-randomised study, completion date: October 2018, location: Italy.
  - **NCT02735928:** Feasibility, efficacy and safety of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Cisplatin in women with recurrent ovarian cancer: an open-label, single-arm phase I-II clinical trial (Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) applied to Platinum-Resistant Recurrence of Ovarian Tumor (PARROT)); n=50, single group assignment-phase I/II; completion date October 2018, location Italy.
  - **NCT03100708:** Register study of patients with peritoneal carcinomatosis treated with PIPAC (Pressurized Intra-peritoneal Aerosol-Chemotherapy) (PIPAC\_01) (evaluation of molecular and pathophysiological mechanisms of peritoneal carcinomatosis and monitoring of the efficiency of PIPAC (Pressurized Intra-peritoneal Aerosol-Chemotherapy) as a local chemotherapeutical treatment). n=500; location; international; completion date: April 2021; status recruiting.

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- **NCT03124394:** Prospective intraperitoneal chemotherapy in carcinomatosis, cohort study-registry; n=100; completion date December 2020; location Switzerland; status: recruiting.
- **NCT03172416:** Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) With Oxaliplatin in patients with peritoneal carcinomatosis (PIPAC); n=21 gastric cancer patients with PC; phase I study; completion date: January 2019; location Singapore; status: recruiting.
- **NCT03246321:** PIPAC for peritoneal metastases of colorectal cancer (CRC-PIPAC), 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 (CRC-PIPAC)); n=20, study completion date October 2019, location Netherlands; status: not yet recruiting.
- **NCT03280511:** Adjuvant Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in resected high-risk colon cancer patients -The PIPAC-OPC3 CC trial; n=60; phase 2 cohort study; completion date 2025; location Denmark; status: recruiting.
- **NCT03294252:** Oxaliplatin in PIPAC for non-resectable peritoneal metastases of digestive cancers (PIPOX); phase I / II dose escalation of Oxaliplatin via a laparoscopic approach of aerosol pressurized intraperitoneal chemotherapy for nonresectable peritoneal metastases of digestive cancers (stomach, and colorectal) n=50; study completion date: June 2021, location France; status: recruiting.
- **NCT03287375:** Treatment of peritoneal carcinomatosis with Pressurized IntraPeritoneal Aerosol Chemotherapy - (The PIPAC-OPC2 Trial), n=137; cohort study; completion date: December 2020; location Denmark; status: recruiting.
- **NCT03304210:** PIPAC Nab-pac for stomach, pancreas, breast and ovarian cancer (PIPAC-nabpac); Intraperitoneal aerosolization of albumin-stabilized Paclitaxel nanoparticles for stomach, pancreas, breast and ovarian cancer n=20; completion date: December 2020, location Belgium; status: recruiting.
- **NCT03210298:** International registry of patients treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) (PIPACRegis); n=1000; completion date May 2019; status: recruiting.
- **EUCTR2016-003394-18-DK** -[Treatment of peritoneal carcinomatosis with Pressurized IntraPeritoneal Aerosol Chemotherapy - PIPAC-2 trial](#).
- **ISRCTN12469865:** [Patient perspectives on peritoneal metastasis treatments](#), status: ongoing.

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## References

1. Tempfer C, Giger-Pabst U et al. (2018) Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal carcinomatosis: systematic review of clinical and experimental evidence with special emphasis on ovarian cancer. *Archives of Gynecology and Obstetrics* 298: 243–57
2. Grass F, Vuagniaux A et al. (2017) Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. *British Journal of Surgery* 6(104): 669–78
3. Farinha HT, Grass F et al. (2017) Impact of pressurized intraperitoneal aerosol chemotherapy on quality of life and symptoms in patients with peritoneal carcinomatosis: a retrospective cohort study. *Gastroenterology Research and Practice* Article ID 4596176, 10 pages
4. Hilal Z, Gunther A (2017) Nutritional status, cachexia, and anorexia in women with peritoneal metastasis and intraperitoneal chemotherapy: a longitudinal analysis. *J Gynecol Oncol* 28(6): e80
5. Graversen M, Detlefsen S et al. (2018) Severe peritoneal sclerosis after repeated pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC OX): report of two cases and literature survey. *Clinical & Experimental Metastasis* 35: 103–8
6. Dueckelmann AM, Fink D et al. (2018) The use of PIPAC (pressurized intraperitoneal aerosol chemotherapy) in gynecological oncology: a statement by the German "Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR)", the Swiss and Austrian AGO, and the North-Eastern German Society of Gynaecologic Oncology. *Archives of Gynecology & Obstetrics* (297) 4: 837–46

## Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	26/09/2018	Issue 9 of 12, September 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	26/09/2018	Issue 9 of 12, September 2018
HTA database (CRD website)	26/09/2018	n/a
MEDLINE (Ovid)	26/09/2018	1946 to September 25 2018
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	26/09/2018	September 25, 2018
EMBASE (Ovid)	26/09/2018	1974 to 2018 September 25
BLIC	26/09/2018	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

- 1 Aerosols/
- 2 ((pressur\* or laparoscopic\*) adj4 (intra-periton\* or intra?periton\* or "intra periton\*" or intra-abdominal\* or intra?abdominal or "intra abdominal\*") adj4 (chemo?therap\* or chemo or therap\* or treat\*)).tw.
- 3 (electrostatic\* adj4 pressur\* adj4 (intra-periton\* or intra?periton\* or "intra periton\*" or intra-abdominal\* or intra?abdominal or "intra abdominal\*") adj4 (chemo?therap\* or chemo or therap\* or treat\*)).tw.
- 4 PIPAC\*.tw.
- 5 (ePIPAC\* or PITAC\*).tw.
- 6 CapnoPen\*.tw.
- 7 Capnomed\*.tw.
- 8 Ultravision\*.tw.
- 9 Alessi\*.tw.
- 10 or/1-9
- 11 Peritoneal Neoplasms/
- 12 Carcinoma/
- 13 ((periton\* or (intra-periton\* or intra?periton\* or "intra periton\*")) adj4 (carcinomato\* or carcino\* or disseminat\* or metast\* or neoplasm\* or cancer or malign\* or tumo?r\* or lump\*)).tw.
- 14 ((intra-abdom\* or intra?abdom\* or "intra abdom\*") adj4 (carcinomato\* or carcino\* or disseminat\* or metast\* or neoplasm\* or cancer or malign\* or tumo?r\* or lump\*)).tw.
- 15 or/11-14
- 16 10 and 15

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## Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ametsbichler P, Bohlandt A, et al (2018). Occupational exposure to cisplatin/oxaliplatin during Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)? European Journal of Surgical Oncology (22) 22.	Retrospective analysis 14 PIPAC procedures in 2 hospitals (air samples 14, wipe samples 223 before and after PIPAC: 56 samples from the operating room floor, 84 from the injector, 28 from trocars and 55 from gloves.) analysed for platinum (Pt).	Contamination on various OR surfaces widely ranged and can lead to a distribution of cytotoxic drug residues. However, the air contamination was very low. The results indicate that PIPAC performance seems to be possible with low occupational exposure risk, but adequate safety and cleaning standards for PIPAC must be developed and monitored.	Operational safety, exposure, and room contamination outcomes reported.
Alyami M, Gagniere J et al (2017). Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. European Journal of Surgical Oncology (43) 11 2178-2183.	Case series N=73 patients with non-resectable PC (from colorectal, gastric, ovarian, malignant mesothelioma, pseudomyxoma peritonei or other origins in 20, 26, 13, 8, 1 and 5 patients) PIPAC with cisplatin, doxorubicin, oxaliplatin (164 procedures)	PCI improved in 64.5% of patients, 63.5% of patients presented with complete disappearance of symptoms. Major complications occurred in 16 PIPAC (9.7%) and 5 (6.8%) patients died within 30 days of the PIPAC procedure. Rate of mortality and major complications 40% and 62% respectively occurred in first 20 patients who had treatment. For 64 (88%) patients, systemic chemotherapy was associated with PIPAC and could be administered after PIPAC with a median delay of 14 days (2-28).	Included in systematic review added to table.
Blanco A., Giger-Pabst U et al (2013). Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). Annals of Surgical Oncology (20) 7 2311-6.	Prospective case series (toxicity study) N=3 end stage patients with treatment resistant peritoneal carcinomatosis (1 OC, 1GC, 1AC) 8 PIPAC procedures with doxorubicin (1.5 mg/m <sup>2</sup> body surface) and cisplatin (7.5 mg/m <sup>2</sup> body surface)	PIPAC did not induce clinically relevant liver cytotoxicity. Liver metabolism and function were not altered. Renal function remained within the normal range. No cumulative toxicity was seen after repeated PIPAC. PIPAC appears to be associated with very limited hepatic and renal toxicity.	Included in systematic review added to table.

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<p>Demtroder C, Solass, W et al (2016). Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Disease (18) 4 364-71.</p>	<p>Retrospective case series N=17 women with pre-treated colorectal peritoneal metastasis (All had previous surgery and 16 had systemic chemotherapy)</p> <p>Treatment with 48 PIPAC procedures (with oxaliplatin (92 mg/m<sup>2</sup>) every 6 weeks at 37 degree C and 12 mmHg for 30 min)</p> <p>Follow-up: mean 22 months</p>	<p>No intra-operative complications. Postoperative adverse events (CTCAE level 3) were seen in 4 patients (23%), no CTCAE level-4 adverse events were reported. The hospital mortality was zero. Objective tumour responses were seen in 12/17 patients (71%), and the overall responses were as follows: complete pathological response (7 patients), major response (4 patients), partial response (1 patient), no response (2 patients) and not eligible (3 patients). The mean survival after first PIPAC was 15.7 months.</p>	<p>Included in systematic review added to table</p>
<p>Falkenstein TA, Gotze TO et al (2018). First clinical data of pressurized intraperitoneal aerosol chemotherapy (PIPAC) as salvage therapy for peritoneal Metastatic biliary tract cancer. Anticancer Research (38) 1 373-378.</p>	<p>Case series (retrospective analysis) N=13 patients with PM from biliary tract cancer had PIPAC with low dose cisplatin and doxorubicin (17 procedures) at 6-week intervals. Mean 1.3 applications.</p>	<p>Access failure in 2, histological response in 4, An overall median survival of 85 days after the first PIPAC application was seen. No complications greater than Common Terminology Criteria of Adverse Events (v4.0) level 2 occurred. Grade 1: 8, grade 2: 6 events were reported.</p>	<p>Included in systematic review added to table.</p>
<p>Farinha HT, Grass F et al (2018). Inflammatory response and toxicity after Pressurized Intraperitoneal Aerosol Chemotherapy. Journal of Cancer (9) 1 13-20.</p>	<p>Retrospective case series N=42 patients with PM from gynaecologic cancer, ovarian cancer, colon cancer, pseudomyxoma peritonei, small bowel cancer and mesothelioma) (91 PIPAC procedures) 20 had oxaliplatin and 22 had cisplatin and doxorubicin.</p>	<p>Creatinine, aspartate transaminase (AST), alanine aminotransferase (ALT) were not statistically significantly altered after PIPAC (p=0.095, p=0.153 and p=0.351) and not different between oxaliplatin and cisplatin+doxorubicin regimens (p=0.371, p=0.251 and p=0.288). C-reactive protein (CRP) and procalcitonin (PCT) increased on post-operative day 2: DELTAmax 29+/-5 mg/L (p&lt;0.001) and DELTAmax 0.05+/-0.01 mug/L (p=0.005), respectively. Leucocytes increased at day 1: DELTAmax 2.2+/-0.3 G/L (p&lt;0.001). Albumin decreased at day 2: DELTAmax -6.0+/-0.5 g/L (p&lt;0.001). CRP increase</p>	<p>Included in systematic review added to table.</p>

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		correlated positively with Peritoneal Cancer Index (tumour load) ( $\rho = 0.521$ , $p < 0.001$ ). No haematological, renal or hepatic toxicity was seen even after repetitive administration.	
Giger-Pabst U, Solass W et al (2015). Low-dose pressurized intraperitoneal aerosol chemotherapy 9PIPAC) as an alternative therapy for ovarian cancer in a octogenarian patient. Anticancer Research 35, 4: 2309-2314.	Case report N=1 84-year-old woman with ovarian cancer who refused systemic chemotherapy. Treatment with 8 courses q 28-104 days of low-dose PIPAC with cisplatin at 7.5 mg/m <sup>2</sup> and doxorubicin at 1.5 mg/m <sup>2</sup> at 12 mmHg and 37 degree C for 30 min. Follow up: 15 months.	The treatment was well-tolerated with no Common Terminology Criteria for Adverse Events (CTCAE) CTCAE greater than 2. At 15 months, the patient is alive and clinically stable. The quality of life measured by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 showed improvement over 5-6 months (global physical score, global health score, global quality of live) without cumulative increase of gastrointestinal toxicity.	Included in systematic review added to table.
Giger-Pabst, Urs and Tempfer CB (2018). How to perform safe and technically optimized Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Experience after a consecutive series of 1200 procedures. Journal of Gastrointestinal Surgery 22, 2187-2193.	Retrospective case series N=512 patients with PM had 1200 PIPAC procedures with low dose cisplatin, doxorubicin, and oxaliplatin (tumour type ovarian cancer, fallopian tube cancer, primary peritoneal cancer, colon cancer, gynaecologic cancer, endometrial cancer, cancer of primary unknown origin, pseudomyxoma peritonei, mesothelioma, cervical cancer).	Patient selection criteria, operative and technical details regarding PIPAC technology with a focus on "how to do it" were reported. Access failure in 52/512 reported. Grade 1 toxicity in 170, grade 3 in 4 and grade 5 in 7 patients were reported. Mortality in 7/512 reported.	Included in systematic review added to table.
Giger-Pabst U, Demtroer C et al (2018). Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for the treatment of malignant mesothelioma. BMC Cancer (2018) 18:442.	Retrospective case series N=29 patients with PM from recurrent malignant epithelioid mesothelioma (MM) had PIPAC (74 procedures) with doxorubicin and cisplatin after prior surgery and systemic therapy. Mean 2.5 procedures. 5 PITAC (thoracol) procedures were also done.	Major regression (TRG 3) or complete regression (TRG 4) was seen in 20% and 10%, respectively. PIPAC induced statistically significant tumour regression in 51.7% (15/29) of patients with a cumulative effect after repetitive PIPACs. Postoperative CTCAE grade 4 complications were seen in 2 patients (6.9%) who had cytoreductive surgery (CC2) and intraoperative PIPAC. 1	Included in systematic review added to table.

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		patient (3.4%) died due to postoperative kidney insufficiency. After a follow up of 14.4 months after the last PIPAC/PITAC application, median overall survival was 26.6 months (from the first application).	
Graversen M, Detlefsen S et al (2017). Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). <i>Clinical &amp; Experimental Metastasis</i> (34) 5 309-314.	Case series N=5 patients with peritoneal metastasis (PM) from pancreatic cancer had PIPAC (with low-dose cisplatin and doxorubicin) treatment (16 procedures).	4 patients had histological regression, and 1 patient had stable disease. 3 patients are still alive, and the median overall survival is 14 months (range 10-20) since the diagnosis.	Included in systematic review added to table.
Graversen M, Detlefsen S et al (2018). Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. <i>Therapeutic Advances in Medical Oncology</i> (10), 1-11.	Case series-phase 2 study N=35 patients with end stage PM (from gynaecologic cancer, ovarian cancer, pseudomyxoma peritonei, colon cancer, small bowel cancer, mesothelioma, pancreatic cancer) had PIPAC (129 procedures) with low dose cisplatin, doxorubicin and oxaliplatin. (median 3 procedures).	Intraperitoneal access achieved in all patients. Few complications and adverse events were noted. There was no risk of chemotherapy exposure for healthcare workers. The mean peritoneal regression grading score (PRGS) was reduced statistically significantly and a reduction of the PRGS was seen in 67% of patients. Conversion from positive to negative cytology was achieved in 23% of patients. Quality of life was stabilised from baseline to day 60.	Included in systematic review added to table.
Hovarth B, Bekert S et al (2018). Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases of pancreas and biliary tract cancer. <i>Clinical &amp; Experimental Metastasis</i> , 35:635–640.	Prospective case series N=12 (6 peritoneal metastases of pancreatic adenocarcinoma (PDAC) and 6 patients from cholangiocarcinoma (CC). PIPAC treatment with low-dose cisplatin 7.5 mg/m <sup>2</sup> and doxorubicin 1.5 mg/m <sup>2</sup> body surface area every 6 weeks. Median 2 cycles (total 23 applications).	Complete tumour regression was found in 4 patients and major regression in 1 patient. Median overall survival after first PIPAC cycle was 12.7 months for PDAC patients and 15.1 months for CC patients. 11 patients are still alive after a median follow up of 438 days. There were no CTCAE Grade 3 or 4 complications. PIPAC is an innovative and attractive treatment option in the salvage situation for patients with peritoneal metastases of pancreaticobiliary tumours after failure of systemic chemotherapy.	Larger studies included in table 2.

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<p>Hubner M, Teixeira Farinha H et al (2017). Feasibility and Safety of Pressurized Intraperitoneal Aerosol Chemotherapy for peritoneal carcinomatosis: A retrospective cohort study. <i>Gastroenterology research &amp; practice</i> (2017) 6852749.</p>	<p>Retrospective case series N=42 patients with PM from ovarian cancer, gynaecologic cancer and colon cancer (91 PIPAC procedures with cisplatin, doxorubicin, and oxaliplatin)</p>	<p>Abdominal accessibility rate was 95% (42/44); laparoscopic access was not feasible in 2 patients. Median initial peritoneal carcinomatosis index (PCI) was 10 (IQR 5-17). Median operation time was 94min (89-108). 1 PIPAC application was postponed because of intraoperative intestinal lesion. Overall morbidity was 9% with 7 minor complications (Clavien I-II) and 1 PIPAC-unrelated postoperative mortality. Median postoperative hospital stay was 3 days (2-3).</p>	<p>Included in systematic review added to table.</p>
<p>Khosrawipour T, Khosrawipour V et al (2017). Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. <i>PLOS ONE</i>   <a href="https://doi.org/10.1371/journal.pone.0186709">https://doi.org/10.1371/journal.pone.0186709</a> October 19.</p>	<p>Prospective case series N=20 patients with peritoneal carcinomatosis of pancreatic adenocarcinoma treated with PIPAC (doxorubicin 1.5 mg/m<sup>2</sup> and cisplatin 7.5 mg/m<sup>2</sup> of body surface delivered at intervals of 6 weeks) 41 procedures, mean 2.1 cycles</p>	<p>Data analysis for 10 patients show that complete or high-grade tumour regression was found in 2 (10%) and 5 (25%) patients, respectively. An overall median survival of 36.6 weeks after the first PIPAC application was seen. 1 patient died postoperatively because of small bowel obstruction. No CTCAE level 3 and 4 complications occurred.</p>	<p>Larger studies included in table 2.</p>
<p>Nadiradze G, Giger-Pabst U et al (2016). Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. <i>Journal of Gastrointestinal Surgery</i> (20) 2 367-73.</p>	<p>Retrospective case series N=24 patients with advanced peritoneal metastasis (PM) from recurrent, platinum-resistant gastric cancer (GC). 67 % patients had previous surgery, and 79 % previous platinum-based systemic chemotherapy. 60 PIPAC procedures with low-dose cisplatin and doxorubicin. Cisplatin 7.5 mg/m<sup>2</sup> and doxorubicin 1.5 mg/m<sup>2</sup> were given for 30 min at 37 degree C and 12 mmHg at 6-week intervals. Median follow up was 248 days (range 105-748)</p>	<p>Median survival time was 15.4 months. 17 patients had repeated PIPAC, and objective tumour response was seen in 12 (12/24=50 %): no vital tumour cells=6, major pathological response=6, minor response=3. Postoperative adverse events CTCAE greater than 2 were seen in 9 patients (9/24, 37.5 %). In 3/17 patients, a later PIPAC could not be done because of non-access. Two patients (ECOG 3 and 4) died in the hospital because of disease progression.</p>	<p>Included in systematic review added to table.</p>

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<p>Nowacki M, Alyami M et al (2018). 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. <i>European Journal of Surgical Oncology</i> (44) 7 991-996.</p>	<p>Retrospective case series (international survey) N=349 patients with PM (most common indications- gynaecologic cancer, ovarian cancer and colon cancer) had 832 PIPAC procedures with low dose cisplatin, doxorubicin, oxaliplatin.</p>	<p>60% response rate. Mean time between procedures was 6-8 weeks. All centres used same chemotherapy protocol. Routine radiological evaluation done before first and after third PIPAC treatment but only half of the centres used tumour markers. Overall survival 15.7 months reported. These data confirm that PIPAC is a standardised treatment done in established centres by experts.</p>	<p>Included in systematic review added to table.</p>
<p>Nowacki M, Grzanka D et al (2018). Pressurized intraperitoneal aerosol chemotherapy after misdiagnosed gastric cancer: Case report and review of the literature. <i>World Journal of Gastroenterology</i> (24) 19 2130-2136.</p>	<p>Case report N=1 40-year-old woman with PM (from Krukenberg tumour) PIPAC (with cisplatin and doxorubicin) as a rescue therapy before palliative D2 gastrectomy combined with liver metastasectomy was given.</p>	<p>The patient felt better and returned to her daily activities. Multicenter data should be gathered to confirm the usefulness of PIPAC as a rescue or neoadjuvant supportive therapy in a very select group of patients.</p>	<p>PIPAC as supportive therapy.</p>
<p>Odendahl K, Solass W et al (2015). Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). <i>European Journal of Surgical Oncology</i> (41) 10 1379-85.</p>	<p>Retrospective case series N=91 palliative patients with pre-treated advanced peritoneal metastasis (29 GC, 25 OC, 14 CRC, 6AC, 4 M, 6 CUP, 7 others) with 158 PIPAC applications. 86% had previous systemic chemotherapy. 48 patients had at least 2 PIPAC every 6 weeks.  Follow up: mean 12 months.</p>	<p>After PIPAC 1 the global physical score deteriorated slightly (from 82% to 75%) but improved after PIPAC 2 (up to 89%). Gastrointestinal symptoms (nausea/vomiting, constipation, diarrhoea, anorexia) remained stable under PIPAC therapy. Functioning scores and disease-related symptoms were not altered for 3 months. A transient moderate increase of pain scores noted, PIPAC did not cause therapy related QoL deterioration, especially no gastrointestinal symptoms.</p>	<p>Included in systematic review added to table.</p>
<p>Robella M, Vaira M. and De Simone M (2016). Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy an innovative approach</p>	<p>Retrospective case series N=14 patients with peritoneal carcinomatosis (from 6 GC, 2 CRC, 2M, 1 PMP) 40 PIPAC procedures (with oxaliplatin or cisplatin+doxorubicin</p>	<p>No major perioperative complications. CTCAE grades 1 and 2 were seen after 6 and 8 procedures, respectively for abdominal pain and nausea. Renal and hepatic functions were not impaired; no cumulative renal toxicity was seen after</p>	<p>Included in systematic review added to table.</p>

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to treat peritoneal carcinomatosis. World Journal of Surgical Oncology (14) 128 Apr 29.	every 6 weeks at 37 degree C and 12 mmHg for 30 min) done. 13 also had systemic chemotherapy with a washout interval of 2 weeks before and 1 week after each PIPAC. Follow-up: not reported.	repeated PIPAC procedures in association with systemic chemotherapy.	
Solass W, Kerb R et al (2014). Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Annals of Surgical Oncology (21) 2 553-9.	Prospective case series N=3 end-stage patients with advanced PC from gastric, appendiceal, and ovarian origin treated with PIPAC (12 applications) Follow-up: 567 days.	No side-effects CTCAE greater than 2 were seen, and the procedures were well tolerated. Early hospital discharge between days 2-5. PIPAC created no statistically significant adhesions, could be repeated, and was applied 6x, 4x, and 2x. 2 patients showed a complete and 1 a partial histological remission. Mean survival after the first PIPAC was 288 days. One patient is alive after 567 days.	Included in systematic reviews added to table.
Solass W, Giger-Pabst U et al (2013). Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): occupational health and safety aspects. Ann Surg Oncol 20(11):3504-11.	Case series N=2 PIPAC	No cisplatin was detected in air at the working position of the surgeon and the anaesthetist under real PIPAC conditions.	Operational safety, exposure, and room contamination outcomes reported.
Solab W, Giger-Pbst U et al (2013). Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Occupational Health and Safety Aspects Ann Surg Oncol 20:3504–3511	Case report N=2 patients who had PIPAC using chemotherapy drugs  Occupational health and safety assessed.	No cisplatin was detected in the air at the working positions of the surgeon and the anaesthesiologist under real PIPAC conditions. Workplace contamination remains below the tolerance margin. The safety measures and conditions as defined above are sufficient. Protecting devices, such as particulate masks, are not necessary.	Larger studies included in table 2.
Solanki SL, Kumar PP et al (2018). Perioperative concerns and management of pressurised intraperitoneal aerosolised chemotherapy: Report of two cases. Indian Journal of Anaesthesia (62) 3 225-228.	Case report N=2 patients with PM (1 from carcinoma caecum, and 1 from pseudomyxoma peritonei) had PIPAC	In this case report of 2 patients the perioperative concerns and management related to PIPAC were discussed.	Larger studies included in table 2.

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<p>Seitenfus R, Kalil AN et al (2018). Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) through a single port: alternative delivery for the control of peritoneal metastases. Rev Col Bras Cir;45(4):e1909.</p>		<p>The present study aims to describe a novel form of this innovative surgical technique done for the first time in Brazil, in a modification of the technique originally described for PIPAC: delivery through a single-port device.</p>	<p>Technical note.</p>
<p>Tempfer CB, Celik I et al (2014). Activity of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. Gynaecologic Oncology (132) 2 307-11.</p>	<p>Case series (Prospective cohort study) laparoscopic Pressurised IntraPeritoneal Aerosol Chemotherapy (PIPAC) in 21 women with recurrent, platinum-resistant ovarian cancer (34 procedures). 8 combined with CRS Median follow up was 192 days (min. 13-max. 639).</p>	<p>Objective tumour response seen in 6 (complete remission: 1; partial remission: 2; stable disease: 3). Five adverse events WHO grade 2 or more, 3 after combined CRS noted. No perioperative mortality noted. Cumulative survival after 400 days was 62% and mean actuarial survival time was 442 days. PIPAC independently predicted objective tumour response.</p>	<p>Included in systematic review added to table 2</p>
<p>Tempfer CB, Winnekendonk, G et al (2015). Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study. Gynaecologic Oncology (137) 2 223-8.</p>	<p>Case series-phase 2 study laparoscopic pressurised intraperitoneal aerosol chemotherapy (PIPAC) in women with recurrent ovarian, fallopian or peritoneal cancer (n=64, 130 procedures).  Patients had 3 courses q 28-42 days of PIPAC with doxorubicin 1.5 mg/m(2) followed by cisplatin 7.5 mg/m(2).</p>	<p>53 patients analysed. 33/53 (62%) patients had an OTR - in 3, there was a partial response and 30 patients had stable disease. Tumour regression on histology and PC Index improvement were seen in 26/34 (76%) and in 26/34 (76%) patients who had all 3 PIPACs. There were no treatment-related deaths. No grade 4 toxicity was seen. Grade 3 toxicities were trocar hernia (n=2), bowel obstruction (n=2), abdominal pain (n=2), hematoma (n=1), intraoperative bleeding (n=1), and cystitis with urosepsis (n=1). EORTC QLQ-30 global physical health scores, nausea and vomiting, appetite loss, diarrhoea, and constipation improved during therapy.</p>	<p>Included in systematic review added to table 2.</p>
<p>Tempfer CB, Rezniczek GA et al (2015). Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal</p>	<p>Retrospective cohort study N= 99 women with PC (from 84 OC, 6PPC, 3CC, 3 EC, 1BC, 1PMP, 1FTC) having repeated courses of PIPAC with 7.5 mg/m(2) of cisplatin</p>	<p>50 women who had more than 1 PIPAC procedures, had an OTR of 76% (38/50) and PCI improvement in 64% (32/50). Ascites volume statistically significantly decreased from 762+/-1170 ml to 167+/-456</p>	<p>Included in systematic review added to table 2.</p>

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carcinomatosis: a cohort study. Anticancer Research 35: 6723-6730.	and 1.5 mg/m <sup>2</sup> ) of doxorubicin. 252 procedures. Follow-up: 126 days.	ml (p=0.02). 20 adverse events of Common Terminology Criteria for Adverse Events grade 3 or more were noted. EORTC QLQ-30+3 scores for global physical health, nausea/vomiting, appetite loss, and constipation improved during therapy.	
Tempfer CB, Hartmann F et al (2017). Intraperitoneal cisplatin and doxorubicin as maintenance chemotherapy for unresectable ovarian cancer: a case report. BMC Cancer (17) 1 26 01 06.	Case report N=1 patient with unresectable OC treated with 13 cycles of intraperitoneal cisplatin 7.5 mg/mand doxorubicin 1.5 mg/m over 2 years using laparoscopic PIPAC.	Objective tumour response (tumour regression on histology, stable disease on repeated video-laparoscopy and peritoneal carcinomatosis index) was noted. No Common Terminology Criteria for Adverse Events (CTCAE) greater than grade 3 were seen. EORTC QLQ-C30 quality-of-life measurements were stable throughout the therapy.	Larger studies included in table 2. Included in systematic review added to table 2.
Tempfer CB, Solass W et al (2014). Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in a woman with pseudomyxoma peritonei: a case report. Gynecol Oncol Reports, 10: 32-35.	Case report N=1 woman with pseudomyxoma peritonei treated with PIPAC (3 courses q 28–42 days of PIPAC with cisplatin 7.5 mg/m <sup>2</sup> and doxorubicin 1.5 mg/m <sup>2</sup> at 12 mm Hg and 37 °C for 30 min)  6 months follow-up	The treatment was well tolerated. CTCAE events grade 1 (nausea) and grade 2 (abdominal pain) were noted within 72 h after the first, second, and third PIPACs. No CTCAE event grade 3 or more was seen. There was no haematologic toxicity. PIPAC achieved clinical and histological disease remission. At 6 months, the patient is alive and needed no further treatment.	Larger studies included in table 2. Included in systematic review added to table 2
Tempfer, CB, Solass W and Reymond MA (2014). Pressurized intraperitoneal chemotherapy (PIPAC) in women with gynaecologic malignancies: a review. Wiener Medizinische Wochenschrift (164) 23-24 519-28.	systematic literature review n=10 studies (2 ex/in vivo, 6 clinical and 2 ongoing trials) using PIPAC in women with recurrent ovarian cancer and pseudomyxoma peritonei.	PIPAC is technically feasible, has a safe local and systemic safety profile, and has antitumor activity in women with peritoneal carcinomatosis from recurrent ovarian cancer.	More comprehensive and recent systematic reviews added to table 2.
Tempfer CB, Giger-Pabst U et al (2018). A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and	Case series-phase 1 study N=15 patients with recurrent ovarian cancer and peritoneal carcinomatosis on average had 2.3 PIPAC cycles.	No dose limiting toxicities were found. Adverse side effects were 1 grade 3 event (colon perforation) and 85 grade 1/2 events including fatigue (n=19), abdominal pain (n=18), nausea/vomiting (n=14), sleep disorder (n=8),	Included in systematic review added to table 2.

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<p>peritoneal carcinomatosis. Gynecologic Oncology (150) 1 23-30.</p>		<p>diarrhoea (n=5), and fever (n=2). Liver and renal toxicity was not seen. No systemic hematologic toxicity, alopecia, or neurotoxicity was noted. The maximum tolerable dose was not reached. Histologic tumour regression was seen in 7/11 (64%) patients who had 2 or more PIPAC cycles. PIPAC with cisplatin and doxorubicin may be safely used at an intraperitoneal dose of 10.5mg/mand 2.1mg/m</p>	
<p>Tempfer CB et al (2018). Concentrations of cisplatin and doxorubicin in ascites and peritoneal tumor nodules before and after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with peritoneal metastasis. European Journal of Surgical Oncology (44) 7 1112-1117 07.</p>	<p>Retrospective cohort study of women with PC from gynaecological tumours comparing the concentrations of cisplatin and doxorubicin in ascites and peritoneum before and after PIPAC 59 PIPAC procedures were done in 32 women with PC.</p>	<p>The concentrations of doxorubicin and cisplatin in ascites statistically significantly increased after PIPAC (140.2 +/- 671.5 vs 9035.7 +/- 5328.6 ng/ml; p&lt;0.0001 and 95.2 +/- 106.4 vs 24,770.8 +/- 11,710.8 ng/ml; p&lt;0.0001 respectively). Concentrations of doxorubicin and cisplatin in peritoneal tissue also statistically significantly increased after PIPAC (5.1 +/- 0.7 vs 19.2 +/- 38.6 ng/g; p=0.007, and 81.9 +/- 7.8 versus 131.5 +/- 134.4 ng/g; p=0.005 respectively). On an individual patient level, a statistically significant uptake (greater than 2-fold) of doxorubicin and cisplatin was seen in 57/59 (97%) and 58/59 (98%) of cases in ascites and in 23/59 (39%) and 13/59 (22%) of cases in the peritoneum. Uptake of cisplatin and doxorubicin were statistically significantly correlated (Spearman correlation coefficient: 0.33; p=0.011). After repeated PIPACs, doxorubicin uptake increased in peritoneal tumour tissue (p=0.008). PIPAC leads to a statistically significant chemotherapy uptake in both ascites and peritoneum, suggesting a bimodal cytotoxic effect of</p>	<p>Drug uptake assessed.</p>

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		PIPAC via direct tissue uptake into peritoneal tumour nodules and via ascites.	
Vaira M, Robella M et al (2016). Single-port access for Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC): Technique, feasibility and safety. Pleura and Peritoneum (1) 4 217-222.	Case series Retrospective N=17 patients with PM of various origin who had PIPAC using single port access by mini laparotomy (intraperitoneal cisplatin, doxorubicin and/or oxaliplatin) 29 procedures done 9 patients had 1 PIPAC, 4 had 2 PIPAC and 4 had 3 PIPAC.	Access to peritoneal cavity was possible in all. There was no bowel access lesion. Tightness of the abdomen (CO-flow = 0) was achieved in all. No postoperative complications according to CTCAE greater than 2 were seen, no re-laparotomies needed, and no postoperative mortality recorded.	Minor modification of the procedure.
Reymond M, Dentreder C et al (2016). Electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC): First in-human application. Pleura and Peritoneum (1) 2 79-89.	Case series N=3 patients with PM of hepatobiliary-pancreatic (HBP) origin PIPAC with cisplatin 7.5mg/m <sup>2</sup> and doxorubicin 1.5 mg/m <sup>2</sup> applied intraperitoneally at a pressure of 12 mmHg and a temperature of 37% degree C for 30 min. Additionally, a voltage 7,500-9,500 V and a current 10 muA or more were applied over a stainless-steel brush electrode emitting a stream of electrons.	No intraoperative complication was noted. The procedures were well tolerated with no adverse event CTCAE greater than 2. Patient 1 with PM of unknown origin showed an objective histological and radiological response and survived 11 months. Patient 2 with ductal pancreatic cancer had secondary resection after ePIPAC with no residual PM; however, tumour recurred 5 months later. Patient 3 with adenocarcinoma of the gallbladder showed a radiological regression of liver infiltration and is alive after 22 months without histological evidence of PM.	Addition of electrostatic precipitation to this procedure with the aim of improving tissue penetration.

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