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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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 August 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

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 using 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 using a closed extraction system. The trocars are removed, and the 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 meta-analysis of 21 studies, including a total of 668 patients with peritoneal carcinomatosis (PC) of various primary tumour origins treated with 1,480 pressurised intraperitoneal aerosol chemotherapy (PIPAC) cycles, the pooled mean overall survival (17 studies) was 11.9 months (range 2.8 to 26.6 months). In a subgroup analysis, the pooled survival was 11.4 months (range 3.9 to 16.4 months) for gastric cancer (5 studies), 12.0 months (range 8.9 to 13.6 months) for ovarian, tubal and primary peritoneal cancer (4 studies), 9.2 months (range 6.4 to 12.7 months) for pancreatic cancer (3 studies) and 9.0 months for hepatobiliary cancer (2 studies).[1]

In a systematic review of 45 studies (with 4 prospective and 16 retrospective studies), including a total of 838 patients with PC of various primary tumour origins treated with 1,810 PIPAC procedures, median survival of about 11 to 14 months was reported for patients with ovarian cancer, 8 to 15 months for gastric

cancer, 16 months for colorectal cancer and 27 months for peritoneal mesothelioma.[2]

In a systematic review of 24 observational studies, including a total of 1,547 patients with PC of various primary tumour origins (but mainly ovarian cancer) treated with 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).[3]

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).[4]

Progression-free survival (PFS months)

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).[3]

Objective tumour response (OTR)

In the meta-analysis of 21 studies, the pooled overall median pathological response rate was 44% (95% confidence interval [CI] 36 to 51 in the intention-to-treat population; people having at least 1 cycle of 1,480 cycles of PIPAC) as assessed using the peritoneal regression grading score system or other tumour regression grading systems.[1] In the subgroup analysis, the pooled pathological response rate in the intention-to-treat population was 39% (95% CI 32 to 46) for gastric cancer (5 studies), 46% (95% CI 36 to 56) for ovarian, tubal and primary peritoneal cancer (4 studies), 46% (95% CI 23 to 69) for pancreatic cancer (3 studies), 37% (95% CI 17 to 59) for hepatobiliary cancer (2 studies), 71% for colorectal cancer (1 study) and 60% for malignant mesothelioma (1 study).[1]

In the systematic review of 45 studies, an OTR of 62% to 88% was reported for patients with ovarian cancer, 60% to 91% for gastric cancer (in the per patient population), 71% (in the intention-to-treat population) to 86% (in the per patient population) for colorectal cancer and 75% for peritoneal mesothelioma.[2]

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.[3]

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%.[4]

In a case series of 48 patients who had PIPAC plus an electrostatic field for diverse tumours, in the 9 patients who had 2 treatment cycles, there was a response in 1 patient and no response in 8 patients. After 3 treatment cycles and concomitant chemotherapy in 28 patients, there was a response in 11 patients, no response in 15 patients and stable disease in 2 patientspeople.[7]

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.[3]

Quality of life

In the systematic review of 45 studies, there was consistent stable or improved quality-of-life scores in the 7 studies in which quality of life was assessed. Improvement or complete relief of peritoneal metastasis-related symptoms were reported in 64% (34/57) patients in 1 study.[2]

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.[3]

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.[4]

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 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.[5]

Access failure

In the meta-analysis of 21 studies, the overall access failure rate (calculated as the proportion of access failures over the number of PIPAC cycles administered) was 5% (ranging from 0 to 14%).[1] In the subgroup analysis, the pooled access failure rate was 2% for gastric cancer (5 studies), 7% for ovarian, tubal and primary peritoneal cancer (4 studies), 6% for pancreatic cancer (3 studies), 2% for hepatobiliary cancer (2 studies), 14% for malignant mesothelioma (1 study) and 13% for colorectal cancer (1 study).[1]

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.[3]

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%.[4]

Nutritional status

In a retrospective case series of 84 patients with PC from recurrent ovarian and fallopian cancer, which assessed nutritional status longitudinally during 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.[6]

Safety summary

Mortality

In the meta-analysis of 21 studies, the overall mortality rate was 1% (7/668) within the first 30 postoperative days. Two deaths were reported in the gastric cancer subgroup, 1 each in the ovarian, pancreatic cancer and malignant mesothelioma subgroups, and there were 2 deaths in mixed tumour subgroups. Deaths were unrelated to the procedure and were attributed to progressive disease in 3, acute renal failure in 2 and cardiopulmonary decompensation as a result of ascites removal in 2.[1]

In the systematic review of 45 studies, no mortality was reported in prospective studies but a rate of 2.7% was reported in the retrospective studies.[2]

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.[3]

In the systematic review of 13 studies there were 3 deaths (in 2 studies), which were unrelated to the procedure.[4]

Morbidity

In the meta-analysis of 21 studies, the overall severe (grade 3, 4 and 5) toxicities (graded according to common terminology criteria for adverse events [CTCAE]) were 8%, 2% and1% respectively.[1] In the subgroup analysis, 11 severe toxicity events were reported in gastric cancer studies (203 patients),15 were reported in ovarian cancer studies (103 patients), 4 were reported in colorectal cancer studies (17 patients), 3 were reported in malignant mesothelioma studies (29 patients) and 3 were reported in pancreatic cancer studies (31 patients).[1]

In the systematic review of 45 studies, adverse events (CTCAE greater than grade 2) were reported in 12% to 15% of procedures and commonly included bowel obstruction (0 to 5%), bleeding (0 to 4%) and abdominal pain (0 to 4%).[2]

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% patients. Procedure-related morbidity or toxicity, graded according to 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.[3]

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.[3]

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.[3]

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.[3]

Grade 5 adverse events included death within 30 days (14 deaths were due to iatrogenic perforations of bowels followed by peritonitis).[3]

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.[4]

In the case series of 48 patients, there were no CTCAE grade 4 or 5 events reported. The most common events reported include anaemia (10%, n=13), ileus (4%, n=5), anorexia (4%, n=6), nausea (4%, n=5) and vomiting (5%, n=7).[7]

Renal and hepatic toxicity

In the systematic review of 45 studies, no renal or hepatic toxicity was seen after repeated PIPAC procedures. A modest inflammatory response (C-reactive protein increase or leucocytosis) was seen in 2 studies.[2]

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.[3]

In the systematic review of 13 studies, hepatorenal toxicity (in 2 studies) was absent and all parameters were within normal range.[4]

Severe hypersensitivity reactions to drugs during PIPAC

The systematic review of 45 studies reported that 1 study showed severe hypersensitivity reactions to platinum compounds in 3% (4/132) 0f patients who had PIPAC for non-resectable PC. Two patients developed it after oxaliplatin and 2 after cisplatin-doxorubicin protocols. All reactions were managed by immediate intraperitoneal exsufflation without further complications.[2]

Severe peritoneal sclerosis

Severe peritoneal sclerosis caused by repeated PIPAC treatment applications with oxaliplatin 92 mg/m^2 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.[8]

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.[3]

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: intraoperative 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 09.08.2019: 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 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 3,575 patients from 4 systematic reviews[1-4], 4 case series[5-7] and 1 case report[8]. There is an overlap of patients between studies.

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 Giorgio (2019)

Details

Study type	**Systematic review and meta-analysis**
Country	Italy
Study period	Search period inception to February 2019; databases searched: PubMed, Scopus, Cross ref, Google Scholar. Hand searching and cross-reference searches were done to identify further articles.
Study population and number	**n=21 observational studies (n=668 patients with PC of 12 different primary tumours**) cancer origin: heterogenous cohort (6 studies), gastric cancer (5 studies) ovarian, tubal cancer or primary peritoneal cancer (4 studies), pancreatic cancer (2 studies), hepatobiliary cancer (1 study), pancreatic cancer and hepatobiliary cancer (1 study), malignant mesothelioma (1 study) and colorectal cancer (1 study). 8 prospective studies (including 1 phase 1 study, 6 phase 2 studies), 6 retrospective cohort studies and 2 conference proceedings.
Age and sex	Not reported
Study selection criteria	Prospective or retrospective case series, Phase 1, 2 or 3 clinical trials, conference proceedings with at least 3 patients who had PIPAC, in English language reporting pathological response using any tumour regression grading were included. Duplicate publications, overlapping accrual records, (for example, subgroup populations of another study), study protocols, methodology papers, in-vitro and in-vivo studies, environmental and occupational safety studies, those not reporting pathology response, studies on PIPAC alone, book chapters, reviews and non-English studies were excluded.
Technique	PIPAC -**1,480 procedures** across 20 studies. Median 26.5 patients per study (range 16.6-35 patients). Procedure and technique were standardised – chemotherapy protocols used were a combination of cisplatin and doxorubicin at a dosage of 7.5 and 1.5 mg/m^2 for PC of non-colorectal origin or oxaliplatin at a dosage of 92mg/m^2 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. Simultaneous treatment: 2 studies reported a combination of PIPAC and PITAC. PIPAC associated with systemic chemotherapy was reported in 36% patients across studies.
Follow up	**Varied in studies**
Conflict of interest/source of funding	Authors declare no conflicts of interest.

Analysis

Follow-up issues: follow up varied in studies. Only 30% of patients in the studies had 3 cycles.

Study design issues: the systematic review and meta-analysis was done according to the PRISMA statement. A comprehensive search strategy was used; data was extracted into a

database by 2 independent reviewers and any disagreements were resolved by a third reviewer. Quality assessment of studies was not done. Outcomes assessed were toxicity (according to CTCAE; v 4.0), mortality, tumour response (either in the form of pathological tumour response based on tumour biopsies) and overall survival. Data analysis was descriptive because of limited and heterogenous data. The median pathological response rate was calculated on the intention-to-treat population rather than per protocol population using a random effects model.

Studies were mainly case series with small sample size. Most of the studies were done by 1 group in Germany.

Study population issues: studies with heterogenous populations and various cancer origins were included in the review. Nearly 40% of patients had combined treatment with systematic chemotherapy except ovarian cancer patients. Most patients had gastric or ovarian cancer and had some form of previous treatments.

Other issues: There is some overlap of studies between the 4 systematic reviews.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **668 (1,480 PIPAC procedures)**

Repeated treatment cycles

Overall studies	**Mean % (range)**
Mean 2 cycles	59% (48-76%)
Mean 3 cycles	29% (26-53%)
Gastric cancer	
2 cycles	58
3 cycles	15
Ovarian, tubal and primary peritoneal cancer	
2 cycles	63
3 cycles	48
Pancreatic cancer	
2 cycles	58
3 cycles	35
Hepatobiliary cancer	
2 cycles	42
3 cycles	18

Efficacy outcomes

	Access failure % (range)	**Median PCI score**	**Treatment response* %**
Overall (n=21 studies)	5 (0-14)	NR	43.7% (95% CI 36.29-51.26)
Gastric cancer (n=5 studies)	2	15	38.96% (95% CI 32.34 – 45.78)

Safety

Toxicity

Overall toxicity (CTCAE) n=20 studies	**% (n)**
Grade 1	53 (352/668)
Grade 2	26 (174/668)
Grade 3	8 (54/668)
Grade 4	2 (15/668)
Grade 5	1 (7/668)
Mortality (within 30 days)*	1 (7/668)
Subgroup analysis	
Gastric cancer (n=203, 5 studies, 419 PIPAC procedures)	
Grade 1	20 (41/203)
Grade 2	4 (9/203)
Grade 3	4 (8/203)
Grade 4	0 (1/203)
Grade 5	1 (2/203)
Mortality (within 30 days)	n=2
Ovarian, tubal and primary peritoneal cancer (n=103 [90% ovarian cancer], 4 studies, 207 PIPAC procedures)	
Grade 1	150 (154/103)
Grade 2	63 (65/103)
Grade 3	12 (12/103)
Grade 4	2 (2/103)
Grade 5	1 (1/103)

Ovarian, tubal and primary peritoneal cancer (n=4 studies)	7	16.8	46.2% (95% ci 36.21 – 56.34)
Pancreatic cancer (n=3 studies)	6	20.2	45.54% (95% ci 23.24 – 68.82)
Hepatobiliary cancer (n=2 studies)	2	13.4	36.75% (95% CI 17.12 – 59.02)
Malignant mesothelioma (1 study)	14	19.9	60%
Colorectal cancer (1 study)	13	16	71%

***pathological response rate** according to PRGS [in 7 studies] and other TRG systems [in 14 studies] in the ITT population).

Overall survival

	Months (range)
Overall pooled survival (18 studies)	**11.9 (2.8 to 26.6)**
Gastric cancer (5 studies, n=203, 419 procedures)	11.4 (3.9-16.4)
Ovarian, tubal and primary peritoneal cancer (n=103, 4 studies, 207 PIPAC procedures)	12 (8.9-13.6)
Pancreatic cancer (n=31, 3 studies, 68 PIPAC procedures)	9.2 (6.4-12.7)
Hepatobiliary cancer (n=19, 2 studies, 29 procedures)	9

Mortality (within 30 days)	n=1
Pancreatic cancer (n=31, 3 studies, 68 PIPAC procedures)	
Grade 1	100 (31/31)
Grade 2	3 (1/31)
Grade 3-4	0
Grade 5	3 (1/31)
Mortality (within 30 days)	n=1
Hepatobiliary cancer (n=19, 2 studies, 29 procedures)	
Grade 1	8
Grade 2	6
Grade 3-5	0
Mortality (within 30 days)	0
Colorectal cancer (1 study, n=17, 48 procedures)	
Grade 3	n=4
Malignant mesothelioma (n=29, 1 study, 74 procedures)	
Grade 3-4	n=3
Mortality (within 30 days)	n=1

*3 cases related to progressive disease (of which 2 were due to bowel obstruction), 2 related to acute renal failure and 2 related to cardiopulmonary decompensation after ascites removal.

Abbreviations used: CI, confidence interval; CTCAE, common terminology criteria for adverse events; ITT, intention to treat; NR, not reported; PC, peritoneal carcinomatosis; PCI, peritoneal carcinomatosis index; PIPAC, pressurised intraperitoneal aerosol chemotherapy; PRGS, pathological tumour regression grading scores; TRG, tumour regression grading scores.

Study 2 Alyami M (2019)

Details

Study type	**Systematic review**
Country	France, Switzerland, Saudi Arabia, USA
Study period	Search period January 2011 to January 2019; databases searched: Medline, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled trials. Cross-referencing and hand searching were done to identify further articles on PIPAC.
Study population and number	N=**45 studies** (including 4 prospective studies and 16 retrospective cohort studies). **838 patients with PC of various primary tumours**) Cancer origin: ovarian 41% [354/838], gastric 22% [185/838], colorectal 12% [104/838], peritoneal mesothelioma 7% [58/838], and other cancers including pseudomyxoma peritonei, hepatobiliary and pancreatic origin 17% [146/838]
Age and sex	Not reported
Study selection criteria	Studies on PIPAC (prospective and retrospective clinical studies and systematic reviews) with no language restrictions were included. Ongoing studies were also identified. Studies reporting on other forms of intraperitoneal chemotherapy were excluded. Preclinical studies, narrative reviews and publications not reporting any clinical outcomes were excluded.
Technique	**PIPAC -1,810 procedures** Procedure and technique were standardised – chemotherapy protocols used were a combination of cisplatin and doxorubicin at a dosage of 7.5 and 1.5 mg/m^2 or oxaliplatin at a dosage of 92mg/m^2. Mean time between procedures was 6 to 8 weeks. An average of 3 applications were done (range 1-12). PIPAC was administered alone or associated with systemic chemotherapy.
Follow up	**Varied in studies (4 months to 22 months)**
Conflict of interest/source of funding	none

Analysis

Follow-up issues: follow up varied in studies.

Study design issues: systematic review was done using a comprehensive search strategy. Data was extracted in a structured database, but quality studies was not assessed. Outcomes assessed in studies were toxicity (according to CTCAE, version 4.0), 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, symptom relief or decreased ascites. Meta-analysis was not done because of the heterogeneity of data and outcome measures. Data was descriptively pooled according to the level of evidence.

Study population issues: studies were heterogenous in terms of indications. PIPAC for PC from various primary tumour origins (gastric, gynaecologic, ovarian, colorectal cancer, primary peritoneal, pseudomyxoma peritonei, malignant mesothelioma or other origins) was assessed in studies. Most patients had had some form of previous treatments.

Other issues: assessment of treatment response was not standardised and differed considerably between the studies. There is some overlap of studies between the 4 systematic reviews.

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: **838 (1810 PIPAC procedures)**

Treatment response (from 4 prospective and 11 retrospective cohort studies)

Tumour origin	**No of patients >2PIPAC**	**PCI**	**Objective tumour response % (n)**			**Survival**	
Ovarian	**% (n)**	**% (n)**	**Histological**	**RECIST**	**Other**	**OS**	**PFS**
PIPAC OV-1 (Tempfer 2015) N=64	81 (45/53)	76% (26/34)	ITT 62% (33/53)-72% (28/53) PP 76 (26/34) - 88% (30/34)	ITT 62% (33/53) PP 52% (16/31)		331 days (mean 95% CI 291-371)	144 days (mean 122-168)
Tempfer 2014 N=21	44 (8/18)		PP 75% (6/8)			442 days (mean)	
Tempfer 2015 N=99	61 (50/82)	64% (32/50)	PP 76% (38/50)			14.1 months (median)	
GASTRIC	**% (n)**	**% (n)**	**Histological**	**RECIST**	**Other**	**OS**	**PFS**
PIPAC GA-1 (Struller 2019) N=25	48 (12/25)		ITT 36% (9/25) PP 75% (9/12)	ITT 40% (10/25) PP 77% (10/13)		Mean 8.4 months	
PIPAC GA-2 (Khomykov 2016) N=31	48% (15/31)		PP 60% (9/15) to 91% (21/23)			Median 13 months 49.8% at 1 year	
Nadiradze 2016 N=25	71% (17/24)		ITT 50% (12/24) PP 71% (12/17)			Median 15.4 months	
Gockel 2018 N=24	58 (14/24)	57% (8/14)	PP 79% (11/14)		79% stable or <ascites	Median 210 days in all, Median 450 days in>3 PIPAC	
COLORECTAL	**% (n)**	**% (n)**	**Histological**	**RECIST**	**Other**	**OS**	**PFS**
Demtroder 2016 N=17	82 (14/17)		ITT 71% (12/17) PP 86% (12/14)			Median 15.7 months	
PANCREAS	**% (n)**	**% (n)**	**Histological**	**RECIST**	**Other**	**OS**	**PFS**
Graversen 2017 N=5	100 (5/5)		PP 80% (4/5)			Median 14 months	

Koshrawipour 2017 N=20	50 (10/20)		PP 70% (7/10)			36.6 weeks (95% ci 36.6 -5.11)	
BILIARY	**% (n)**	**% (n)**	**Histological**	**RECIST**	**Other**	**OS**	**PFS**
Falkenstein 2018 N=13	45% (5/11)		PP 80% (4/5)			Median 85 days (95% CI 59.2-110.4)	
MESOTHELIOMA	**% (n)**	**% (n)**	**Histological**	**RECIST**	**Other**	**OS**	**PFS**
Giger-Pabst 2018 N=29	91 (20/22)		PP 75% (15/20)			Median 26.6 months (95% CI 9.5-43.7)	
VARIOUS	**% (n)**	**% (n)**	**Histological**	**RECIST**	**Other**	**OS**	**PFS**
Graversen 2018 PIPAC OPC 1 N=35	86 (30/35)		ITT 57% (20/35) PP 67% (20/30)				
Alyami 2017 N=73	62 (45/73)	61% (PP), 65% (3rd PIPAC)			46-63% symptom relief		
Kurtz 2018 N=71	62 (39/63)		PP 67% (24/36)			Median 11.8 months (95% CI 7.45-16.2 months)	
Total weighted mean **N=552**	**65%**	**66.7%**	**PP 73.7; ITT 57.1%**	**PP 56.4%** **ITT 59%**		**Data not pooled (different primaries)**	

Safety (from 4 prospective and 16 retrospective studies)

Prospective studies **Origin, n**	**No of PIPAC**	**>2 PIPAC procedures % (n)**	**Surgical complications % (n)**	**Adverse events (CTCAE 4.0)**		
				Grade 3 %(n)	**Grade 4 %(n)**	**Grade 5 %(n)**
PIPAC OV-1 (ovarian), n=64	130	81 (43/53)	8 (4/53)	15 (8/53)	0	0
PIPAC GA-1 Gastric, n=25	43	48 (12/25)	NA	16 (4/25)	0	0
PIPAC GA-2 Gastric, n=31	56	48 (15/31)	3 (1/31)	13 (4/31)	0	0
PIPAC OPC-1 Various, n=35	129	86 (30/35)	6 (2/35)	11 (4/35)	3 (1/35)	0
Subtotal, weighted means, n=155	**358**	**69.4**	**5.95**	**13.9**	**0.7**	**0**

Retrospective studies	No of PIPAC	>2 PIPAC procedures % (n)	Surgical complications % (n)	Adverse events (CTCAE 4.0)		
				Grade 3	Grade 4	Grade 5
Tempfer 2014 Ovarian, n=21	34	44 (8/18)	17 (3/18)	17(3/18)	11 (2/18)	0
Tempfer 2015 Ovarian, n=99	252	61 (50/82)	6 (5/82)	21 (17/82)	37 (3/82)	0
Nadiaradze 2016 Gastric, n=25	60	71 (17/24)	5 (3/60 procedures)	25 (6/24)	4(1/24)	8 (2/24)*
Odendahl 2015 Various, n=91	158	53 (48/91)	3 (3/91)	9(8/91)	1 (1/91)	3 (3/91)
Robella 2016 Various n=14	40	100 (14/14)	0	0	0	0
Demtroder 2016 Colorectal, n=17	48	82 (14/17)	0	24 (4/17)	0	0
Graversen 2017 Pancreatic, n=5	16	100 (5/5)	0	0	0	0
Hubner 2017 Various, n=44	91	71 (30/42)	2 (1/42)	0	0	3 (1/42)
Alyami 2017 Various, n=73	164	62 (45/73)	NA	19 (14/73)	0	7 (5/73)
Khosrawipour 2017 Pancreatic, n=20	41	50 (10/20)	0	0	0	5 (1/20)
Falkenstein 2018 Biliary tract, n=13	17	45 (5/11)	0	0	0	0
Kurtz 2018 Various, n=71	142	62 (39/63)	5 (7/142)	16 (1/63)	0	16 (1/63)
Gockel 2018 Gastric, n=28	46	58 (14/24)	NA	0	0	0
Hovarth 2018 Pancreatic, n=12	23	50 (6/12)	0	0	0	0
Jansen-Winkeln 2019 Various, n=62	111	61 (33/54)	13 (7/54)	NA	NA	NA
Giger-Pabst 2018 Mesothelioma, n=29	74	91 (20/22)	0	5 (1/22)	9 (2/22)	5 (1/22)
Subtotal, weighted means, n=624	**1317**	**62.6**	**Not pooled, data heterogeneity**	**10.4**	**1.7**	**PIPAC related 0.8%; not related to PIPAC 1.9%**

Surgical complications were rare. Most common events were bowel obstruction (0-5%), bleeding (0-4%) and abdominal pain (0-4%). No mortality was seen in prospective studies, mortality of 2.7% was reported in retrospective studies. No hepatic or renal toxicity noted in 6 studies that evaluated. Inflammatory response (C-reactive protein increase or leucocytosis) noted in 2 studies. Severe hypersensitivity reactions (managed by intraperitoneal exsufflation) were noted in 1 study (3% [4/132]). **Occupational health** assessed in 5 studies reported a very low risk of exposure with adequate safety measures. **Quality of life** assessed in 7 studies showed stable or improved quality-of-life scores. **Peritoneal metastasis-related symptoms** assessed in 1 study showed improvement or complete relief in 64% (34/57) patients.
Abbreviations used: CI, confidence interval; CTCAE, common terminology criteria for adverse events; ITT, intention to treat; PP, per protocol population; NA, not available; OS, overall survival; PCI, peritoneal carcinomatosis index; PC, peritoneal carcinomatosis; PIPAC, pressurised intraperitoneal aerosol chemotherapy; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours.

Study 3 Tempfer C (2018)

Details

Study type	**Systematic review**
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 PC of various primary tumours). 1 phase 1 study, 4 phase 2 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 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	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^2 or oxaliplatin at a dosage of 92mg/m^2 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. Simultaneous treatment: PIPAC associated with systemic chemotherapy was given in 2 studies and cytoreduction surgery in 1 study.
Follow up	**Varied in studies (4 months to 22 months)**
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 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, 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. There is some overlap of studies between the 4 systematic reviews.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 1,547 (3,515 PIPAC procedures)
Access failure
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.

Objective tumour response % (defined as tumour regression on histology) (16 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.

Improvement of PCI Improvement of PCI was seen in 69% (116/168) of patients in whom PCI changes were analysed.

PFS (months)
In a pooled analysis of 3 studies, the mean PFS was 5.8 months (range 5.8 to 6 months).

OS (months)
In a pooled analysis of 17 studies, the mean overall survival duration was 13.7 months (range 2.8 months to 26.6 months).

Quality of life (10 studies with 396 patients assessed by the EORTC-QLQ-30 and SF-36 questionnaires)
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).

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.
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.</td><td>Procedure-related morbidity/toxicity (%, according to CTCAE criteria) (in 22 studies, n=1,197 patients)
<table>
<tr><th>CTCAE grade</th><th>% (n)</th></tr>
<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>
</table>
Grade 1/2 events 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.
Grade 3 toxicities 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.
Grade 4 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). 3 of these events occurred in patients who had combined treatment with cytoreductive surgery.
Grade 5 events included death within 30 days (14 deaths were due to iatrogenic perforations of bowels followed by peritonitis).
Mortality rate %
The mortality rate was 1.6% (19/1197) with 12 events judged related and 7 events judged unrelated to the procedure.</td></tr>
</table>

Environmental/occupational safety (4 studies) 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.	**Renal and hepatic functions** were not impaired; no renal or hepatic toxicity was seen after repeated PIPAC procedures.
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.	

Study 4 Grass F (2017)

Details

Study type	**Systematic review**
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	**n=13 observational studies (n=346 patients with PC of 12 different primary tumours**) mainly gynaecological (3 studies, n=184), gastric (2 studies, n=34) and colorectal (1 study, n=17) 5 prospective studies including 1 phase 2 study, 6 retrospective cohort studies, 2 case reports.
Age and sex	Not reported
Study selection criteria	Scientific reports on PIPAC (preclinical and clinical studies) with no language restrictions were included. Studies reporting on intraperitoneal chemotherapy by conventional lavage- heated intraperitoneal chemotherapy or via indwelling transperitoneal catheter; book chapters and reviews were excluded.
Technique	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^2 for PC of non-colorectal origin or oxaliplatin at a dosage of 92mg/m^2 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. Simultaneous treatment: PIPAC associated with systemic chemotherapy was given in 2 studies and cytoreduction surgery in 1 study.
Follow up	**Varied in studies (4 months to 22 months)**
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 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 4 systematic reviews.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 346 (801 PIPAC procedures)
Access failure
PIPAC was technically feasible in most patients. The rate of failed access (unsuccessful procedures) varied between 0 to 17%.
Repeated treatment cycles
Repeated PIPAC applications (a mean of 2 applications) were done in 32% to 82% of patients.

OTR % (defined as tumour regression on histology) (13 studies)
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.
OTR according to tumour origin
<table>
<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>
</table>
Quality of life (5 studies with 266 patients assessed by the EORTC-QLQ-30 and SF-36 questionnaires)
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.
Survival
The median survival after PIPAC therapy was 11.0 to 14.1 months for ovarian and gynaecological related PC and 13.4 to 15.4 months for gastric related PC and 15.7 months for colorectal related PC.
</td><td>
Adverse events (assessed according to CTCAE grading system) (in 13 studies, n=346 patients)
<table>
<tr><td>CTCAE grade 1 or 2 events (abdominal pain and/or nausea were commonly reported)</td><td>n=287</td></tr>
<tr><td>CTCAE grade 3-5 events*</td><td>n=61 (0-37%)</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>Surgery-related complications</td><td>n=44 (0-12%)</td></tr>
<tr><td>Mortality</td><td>n=3 (1 due to lung oedema,1 disease progression and 1 from anasarca).</td></tr>
<tr><td>Hepatorenal toxicity (assessed in 2 studies)</td><td>Absent; all parameters in normal range</td></tr>
</table>
*Highest toxicity rates were reported in 1 study that had combined PIPAC with systemic chemotherapy and cytoreduction surgery and another study on gastric PC.
Leucocytosis and an increase in C-reactive protein was reported after PIPAC therapy.
</td></tr>
<tr><td colspan="2">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.</td></tr>
</table>

Study 5 Teixeira- Farinha H (2017)

Details

Study type	**Case series (retrospective cohort study)**
Country	Switzerland
Recruitment period	2015-16
Study population and number	**n=42 patients with peritoneal carcinomatosis** 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 and Hyperthermic Intraperitoneal Chemotherapy because of medical or surgical contraindications had PIPAC were included.
Technique	PIPAC -91 procedures, 3 sessions scheduled at 6-week intervals. 1 patient also had systemic chemotherapy.
Follow up	**3 months**
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 EORTC-QLQ-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

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 42 (91 PIPAC procedures)

Quality of life (assessed using EORTC-QLQ-30)
<table>
<tr><th>Quality of life</th><th></th><th>P value</th></tr>
<tr><td>Baseline</td><td>66 ± 2.6</td><td></td></tr>
<tr><td>PIPAC 1</td><td>64 ± 3.75</td><td>0.57</td></tr>
<tr><td>PIPAC 2</td><td>61 ± 4.76</td><td>0.89</td></tr>
<tr><td>PIPAC 3</td><td>70 ± 6.67</td><td>0.58</td></tr>
<tr><td colspan="3">Fatigue symptom score</td></tr>
<tr><td>Baseline</td><td>32 ± 4.3</td><td></td></tr>
<tr><td>PIPAC 1</td><td>44 ± 4.86</td><td></td></tr>
<tr><td>PIPAC 2</td><td>47 ± 6.69</td><td></td></tr>
<tr><td>PIPAC 3</td><td>34 ± 7.85</td><td>0.40</td></tr>
</table>
No statistically significant changes were noted under PIPAC treatment for the quality-of-life components cognitive, physical, emotional, role, and social functioning.

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).

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.

Non-digestive symptoms insomnia, fatigue, pain, and dyspnoea did not show statistically significant changes.

No statistically significant changes were seen in quality of life and symptoms after first and repeated sessions.</td><td>Overall complication rate was 8.8%</td></tr>
<tr><td colspan="2">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.</td></tr>
</table>

Study 6 Hilal Z (2017)

Details

Study type	**Case series (retrospective cohort study)**
Country	Germany
Recruitment period	2014-16
Study population and number	**n=84 patients with peritoneal carcinomatosis** 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	PIPAC with cisplatin and doxorubicin repeated every 4–6 weeks. Concomitant systemic therapy was done in 7 patients.
Follow up	**Median 2.4 months (range 0.3 to 27.1 months)**
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.

Key efficacy and safety findings

Efficacy | Safety

Number of patients analysed: **82**

Nutritional and serum parameters

	Baseline	Cycle 1	Cycle 2	Cycle 3	P value
No of patients (procedures)	84	53 (53)	30 (30)	15 (40)	
BMI (kg/m^2)	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
Bioelectrical impedance analysis					
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
Serum parameters					
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

Cachexia-anorexia syndrome (CAS) during PIPAC (n=55)

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;

Study 7 Willaert W (2019)

Details

Study type	**Case series**
Country	Belgium
Recruitment period	2015-18
Study population and number	**n=48 patients with peritoneal carcinomatosis from diverse primary tumours** cancer origin: gynaecological origin (n=21), colorectal (n=21), gastric (n=3), and 1 each with small bowel cancer, appendicular, pseudomyxoma, and mesothelioma.
Age and sex	Median age 61 years; 58% (28/48) male.
Study selection criteria	Patients between 16 and 85 years, with evidence of unresectable progressive peritoneal metastases either before or after systemic chemotherapy, with no treatment options; absence of extraperitoneal cancer, those with liver or lung metastases treated with Pressurized IntraThoracic Aerosol Chemotherapy (PITAC) immediately after ePIPAC were included. Patients with partial small bowel obstruction, poor general condition (Karnofsky index < 60) intractable ascites, with impaired liver, renal, heart or bone marrow function or with known intolerance or allergy to platinum were excluded. Cytoreductive surgery in combination with ePIPAC was also a contra-indication.
Technique	Patients had PIPAC combined with an electrostatic field (typical voltage of 7.5-9.5 kV and current of _10 mA), using a generator (the Ultravision™ System). IPAC was performed with either oxaliplatin 92 mg/m^2 or cisplatin 7.5 mg/m^2 with or without doxorubicin 1.5 mg/m^2. After complete administration of chemotherapy (within 5-7 minutes), the generator was activated and switched off after 30 minutes to improve aerosol distribution and tissue penetration. Patients were scheduled for 3 ePIPACs every 6 weeks. Overall 135 procedures were done (median per patient, 3 [range 1-9]). 58% (28/48) patients received concomitant chemotherapy. 65.2% [88/135] procedures were done in outpatient setting. Median time from diagnosis to first ePIPAC was 5 months (range: 0-56).
Follow up	**Median 7.5 months**
Conflict of interest/source of funding	Authors declared no conflicts of interest.

Analysis

Follow-up issues: 42% (20/48) patients did not complete 3 ePIPAC procedures and dropped out due to disease progression (13), weakness (2), liver abscess (1), patient preference (1) and other reasons (3). Only 24 patients had 3 ePIPAC procedures and 4 had more than 3 procedures.

Study design issues: data was prospectively collected and retrospectively analysed. Treatment regimen was not standardised; adverse events were scored using the Common Terminology Criteria for adverse events (CTCAE 5.0). Treatment response was assessed after more than 1 PIPAC, using clinical symptoms, tumour markers, CT imaging and histological regression.

Patient population issues: patients and tumour characteristics were very heterogenous, and majority of the patients had previous treatments (cytoreductive surgery plus intraperitoneal chemotherapy [4], surgery 6], chemotherapy 25]).

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: **48 (135 ePIPAC procedures)**

The mean and highest PRGS after 2 and 3 ePIPACs

No o patients	**No of ePIPAC procedures**	**Mean PRGS**		**p**	**Highest PRGS**		**p**
9	**2**	**First**	**Second**	**p**	**First**	**Second**	**p**
		2.28 ± 0.83	1.78 ± 0.76	0.20	2.56 ± 0.69	1.89 ± 0.76;	0.06
28	3	**First**	**Third**	**p**	**First**	**Third**	**P**
		1.99 ± 0.71	1.88 ± 0.82	0.57	2.25 ± 0.69	2.11 ± 0.82	0.84

Treatment response

No o patients	**No of ePIPAC procedures**	**Responder**	**Stable**	**Non-responder**
9	2	1		8
28	3	11	2	15

Safety

Adverse event	**Overall % (n)**	**Grade 1**	**Grade 2**	**Grade 3**
Anaemia	9.6 (13)	3 (4)	3 (4)	3.7 (5)
Ileus	3.7 (5)	0	3 (4)	0.7 (1)
Abdominal pain	1.5 (2)	0.7 (1)	0	0.7 (1)
Nausea	3.7 (5)	0.7 (1)	2.2 (3)	0.7 (1)
Vomiting	5.2 (7)	3.7 (5)	0	1.5 (2)
Skin infection	0.7 (1)	0.7 (1)	0	0
Wound infection	2.2 (3)	2.2 (3)	0	0
Anorexia	4.4 (6)	0	3 (4)	1.5 (2)
Hypocalcaemia	0.7 (1)	0.7 (1)	0	0
Hypokalaemia	0.7 (1)	0.7(1)	0	0
Hyponatremia	0.7 (1)	0	0	0.7 (1)
Elevated ALT	0.7 (1)	0	0.7 (1)	0
Elevated AST	0.7 (1)	0	0	0.7 (1)
Haematuria	0.7 (1)	0	0.7 (1)	0
Arterial hypertension	1.5 (2)	0	1.5 (2)	0
Intraoperative gastrointestinal injury (small bowel perforation caused by a trocar repaired and recovery uneventful)	0.7 (1)	0.7 (1)	0	0
Total	**43 (58)**	**14 (19)**	**16.3 (22)**	**12.6 (17)**

No grade 4 or 5 morbidity noted. No patient needed a surgical reintervention.

77% (37/48) patients died after a median 7.5 months since first ePIPAC procedure.

Abbreviations used: ePIPAC, electrostatic pressurised intraperitoneal aerosol chemotherapy; ALT, alanine aminotransferase; AST aspartate transaminase; PRGS, peritoneal regression grading score.

Study 8 Graversen M (2018)

Details

Study type	**Case report**
Country	Denmark
Recruitment period	2016-17
Study population and number	**n=2 patients** **1 patient with peritoneal carcinoma from mucinous adenocarcinoma of the appendix** **1 patient with peritoneal carcinoma from mucinous adenocarcinoma of the appendiceal goblet cell carcinoma**
Age and sex	44- and 71-year males
Patient selection criteria	Not reported
Technique	PIPAC Both patients had 4 sessions of PIPAC with oxaliplatin 92mg/m^2 per session (flowrate 0.5 ml/s, maximum pressure of 200 per square inch).
Follow up	**5-8 months**
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: **2** **2 patients developed severe peritoneal sclerosis after PIPAC therapy characterised by anorexia, nausea, abdominal pain and abdominal distension** 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: PIPAC, pressurised intraperitoneal aerosol chemotherapy.	

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[1] 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)**

Pressurised 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 1 or 2 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.[9]

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 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 was able to gather patient commentary for this procedure from 1 patient. The patient commentator's views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

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 1-2 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 1 or 2; 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.

- **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 1 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 2 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 1 or 2 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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1. Di Giorgio A, Abatini A, Attalla El Halabeih et al (2019) from palliation to cure: PIPAC for peritoneal malignancies. Minerva Medica 110 (4):385-98
2. Alyami M, Hubner M, Grass F et al. (2019) Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence and potential evidence. The Lancet oncology,20 (7), e368-77
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Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	09/08/2019	Issue 8 of 12, August 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	09/08/2019	Issue 8 of 12, August 2019
HTA database (CRD website)	09/08/2019	n/a
MEDLINE (Ovid) & MEDLINE In-Process (Ovid)	09/08/2019	1946 to August 07, 2019
Medline ePub ahead (Ovid)	09/08/2019	August 08, 2019
EMBASE (Ovid)	09/08/2019	1974 to 2019 August 08

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

MEDLINE search strategy

1 Aerosols/ (29338)
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. (177)
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. (1)
4 PIPAC*.tw. (66)
5 (ePIPAC* or PITAC*).tw. (58)
6 CapnoPen*.tw. (0)
7 Capnomed*.tw. (4)
8 Ultravision*.tw. (20)
9 Alessi*.tw. (53)
10 or/1-9 (29611)
11 Peritoneal Neoplasms/ (14471)
12 Carcinoma/ (88666)
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. (17244)

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. (2027)
15 or/11-14 (112737)
16 10 and 15 (113)
17 Animals/ not Humans/ (4573928)
18 16 not 17 (94)
19 limit 18 to english language (84)
20 limit 19 to ed=20180901-20190831 (16)

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 2178-83	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.
Alberto M, Brandl A, Garg PK et al. (2019) Pressurized intraperitoneal aerosol chemotherapy and its effect on gastric-cancer-derived peritoneal metastases: an overview. Clinical & Experimental Metastasis (36) 11-4	Review of peritoneal metastasis (PM) from gastric cancer and treatment options.	This overview comprehensively addresses a novel and promising treatment (PIPAC) in the context of a scientifically and clinically challenging disease.	Review
Alyami M, Mercier F et al. (2019)	Retrospective case series	Median PIPAC procedure was 3 (1-8). Complications	Larger studies included in table 2.

Unresectable peritoneal metastasis treated by pressurized intraperitoneal aerosol chemotherapy (PIPAC) leading to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. European Journal of Surgical Oncology (21) 21	N=26 patients with unresectable PM (from gastric, peritoneal mesothelioma, ovarian, colorectal and small bowel in 13, 7, 4, 1 and 1), had 76 PIPAC procedures (systemic chemotherapy given)	occurred in 3 (4%) and there was no major complication (CTCAE III or higher). Complete cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) was achieved in 21 patients (14.4%). The remaining 5 patients were considered unresectable at the exploratory laparotomy. Among patients who had CRS and HIPEC, with median follow up of 7 (1-26) months, 14 patients (66.7%) were alive without recurrence, 2 patients (9.5%) were alive with recurrence and 5 patients (23.8%) died.	
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 Ovarian Cancer, 1 gastric cancer, 1 Adenocarcinoma) 8 PIPAC procedures with doxorubicin (1.5 mg/m(2) body surface) and cisplatin (7.5 mg/m(2) 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.
Bakrin N, Tempfer, C et al. (2018) PIPAC-OV3: A multicenter, open-label, randomized, two-arm phase III trial of the effect on progression-free survival of cisplatin and doxorubicin as Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) vs. chemotherapy alone in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. Pleura and Peritoneum (3) 3 20180114 Sep 01. Trial registration: The EudraCT number 2018-003664-31	Phase 3 randomised controlled trial protocol N=244 systematic palliative chemotherapy versus intraperitoneal chemotherapy 3 times every 6 weeks	The primary endpoint is PFS (according to RECIST v1.1) or death from any cause. The co-primary endpoint is the health-related quality of life (HRQoL) measured as the global health status (GHS, QLQ-30 of EORTC). Secondary outcomes comprise overall survival, safety (CTCAE 5.0), and tumour response according to peritoneal regression grading score (PRGS). Discussion: We expect PIPAC C/D to control peritoneal disease and preserve the QoL on this subset of patients.	Trial protocol.

Cazauran JB, Alyami M et al.(2018) Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Procedure for Non-resectable Peritoneal Carcinomatosis (with Video). Journal of Gastrointestinal Surgery (22) 2 374-5	surgical protocol accompanied by a short video	This video protocol provides a better understanding of the PIPAC procedure and the safety measures essential for this method of chemotherapy administration. It should help all teams wishing to implement a PIPAC therapy program.	Protocol
Demtroder C, Solass, W et al (2016). Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Disease (18) 4 364-71	Retrospective case series N=17 women with pretreated colorectal peritoneal metastasis (All had previous surgery and 16 had systemic chemotherapy) Treatment with 48 PIPAC procedures (with oxaliplatin (92 mg/m^2) every 6 weeks at 37 degree C and 12 mmHg for 30 min) Follow up: mean 22 months	No intraoperative 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.	Included in systematic review added to table
Delhorme JB, Klipfel A et al (2019). Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in an operating room without laminar airflow. Journal of Visceral Surgery	Sample analysis 26 samples with cellulosic wipes from surgeons and co-workers' environmental items and 5 specific polytetrafluoroethylene air-filtered collections were randomly performed for the first 2 cisplatin/doxorubicin-based PIPAC procedures	All air measurements were negative for cisplatin and doxorubicin. Only one wipe sample out of 26 was positive for cisplatin (4%) on the outer surgeon's pair of gloves but dosages on the surgeon's inner pair and hands were negative.	Occupational risk reported in studies added to table 2.
Dumont F, Senellart H et al (2018) 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	A multicentre phase 1 or 2 trial of oxaliplatin dose escalation during PIPAC	The aim is to determine the maximum tolerated dose of pressurised oxaliplatin administered by the intraperitoneal route (PIPAC) during 2 consecutive procedures at a 4-6-week interval for patients with extended peritoneal carcinomatosis from the gastrointestinal tract. Dose from 90mg/m	Rationale and study design.

(stomach, small bowel and colorectal): Rationale and design. Pleura and Peritoneum (3) 3 20180120 Sep 01		to 300mg/m. The hypothesis is that repeated local administration of high doses of oxaliplatin could improve tumour response and prognosis.	
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) 1 373-8	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.	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.	Included in systematic review added to table.
Teixeira-Farinha H , Grass F et al (2018). Inflammatory response and toxicity after Pressurized Intraperitoneal Aerosol Chemotherapy. Journal of Cancer (9) 1 13-20	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.	Creatinine, aspartate transaminase (AST) and alanine aminotransferase (ALT) were not statistically significantly altered after PIPAC (p=0.095, p= 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 postoperative day 2: DELTAmax 29+/-5 mg/L (p<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<0.001). Albumin decreased at day 2: DELTAmax -6.0+/-0.5 g/L (p<0.001). CRP increase 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.	Included in systematic review added to table.
Giger-Pabst U, Solass W et al (2015). Low-dose pressurized intraperitoneal aerosol chemotherapy 9PIPAC) as an alternative	Case report N=1 84-year-old woman with ovarian cancer who refused systemic chemotherapy.	The treatment was well tolerated with no Common Terminology Criteria for Adverse Events (CTCAE) CTCAE greater than 2. At	Included in systematic review added to table.

therapy for ovarian cancer in a octogenarian patient. Anticancer Research 35, 4: 2309-14	Treatment with 8 courses q 28-104 days of low-dose PIPAC with cisplatin at 7.5 mg/m(2) and doxorubicin at 1.5 mg/m(2) at 12 mmHg and 37 degree C for 30 min. Follow up: 15 months.	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.	
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, 2187-93	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 CRS (CC2) and intraoperative PIPAC. 1 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).	Included in systematic review added to table.

Graversen M, Detlefsen S et al (2017). Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Clinical & Experimental Metastasis (34) 5 309-14	Case series N=5 patients with 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. Therapeutic Advances in Medical Oncology (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 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.
Graversen M, Fristrup C et al. (2019) Detection of free intraperitoneal tumour cells in peritoneal lavage fluid from patients with peritoneal metastasis before and after treatment with pressurised intraperitoneal aerosol chemotherapy (PIPAC). Journal of Clinical Pathology (72) 5 368-372. Trial registration number: nct02320448	Retrospective study N=35 patients with PM of various origins	At the first PIPAC procedure, free intraperitoneal tumour cells (FITC) were detected by conventional cytology (sensitivity 0.58, specificity 1.00), carcinoembriyonic antigen (CEA) protein (cut-off 0.4 micro g/L, sensitivity 0.71), CEA mRNA (sensitivity 0.75, specificity 1.00), epithelial cell adhesion molecule (EpCAM) mRNA (sensitivity 0.71, specificity 1.00) and CA-125 mRNA (sensitivity 0.43, specificity 1.00). The combination of CEA/EpCAM mRNA had a sensitivity of 0.88 and a specificity of 1.00. The evaluation of ascites or peritoneal lavage fluid retrieved at the third PIPAC procedure failed to detect treatment response, when compared with the histological peritoneal regression grading score (PRGS). The evaluation of CEA and EpCAM mRNA	Cytology results

		detects FITC with a high sensitivity and an excellent specificity but is not useful for response evaluation in patients who had PIPAC.	
Graversen M, Lundell L et al. (2018) Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) as an outpatient procedure. Pleura and Peritoneum (3) 4 20180128. PIPAC-OPC2 study (ClinicalTrials.gov NCT03287375)	Retrospective case series N=41 patients with gastrointestinal or ovarian PM had 106 PIPAC procedures (C/D in 79 and OX in 27) 37/41 patients who had pretreatment with systemic chemotherapy and 8 received bidirectional chemotherapy.	24% (10/41) of the first PIPAC procedures were completed in an outpatient setting, increased to 65% (13/20) in PIPAC no 3 (p=0.008). In the PIPAC C/D cohort, 28% and 80% of the PIPACs were performed in the outpatient setting at PIPAC 1 and 3 respectively, contrasting to only 11% and 20% in the PIPAC OX group. No readmissions after outpatient care. The procedure can be performed in an outpatient setting. The critical component for success is pain control.	Larger studies added to table 2.
Garg PK, Jara M et al. (2019) The role of Pressurized IntraPeritoneal Aerosol Chemotherapy in the management of gastric cancer: A systematic review. Pleura and Peritoneum (4) 1 20180127 Mar 01, 2019	Systematic review to evaluate the current role of PIPAC in the management of gastric cancer associated PM.	Ten published studies (with 129 patients) have reported the use of PIPAC in gastric cancer associated PM. Only 2 studies had an exclusive cohort of gastric cancer patients while 8 other studies had a heterogeneous population with a small proportion of gastric cancer patients. There was only 1 study highlighting the role of PIPAC in neoadjuvant setting to downgrade the peritoneal carcinomatosis index. All the studies revealed that PIPAC is feasible and has minimal perioperative morbidity, even after repeated applications. Further studies are warranted to better define the role of PIPAC in gastric cancer associated PM.	More comprehensive reviews added to table 2. This review had only 2 studies with exclusive gastric cancer patients and these are included in other systematic reviews.
Gockel I, Jansen-Winkeln B et al. (2018) Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Gastric Cancer Patients	Case series N=24 patients with gastric cancer and PM had 46 PIPAC procedures cisplatin +	11 patients, who received 2 or more PIPAC procedures, had decreased and stable volumes of ascites, while	Study included in systematic review added to table 2.

with Peritoneal Metastasis (PM): Results of a Single-Center Experience and Register Study. Journal of Gastric Cancer (18) 4 379-391. ClinicalTrials.gov Identifier: NCT03100708	doxorubicin (laparoscopic access used)	only 3 patients displayed increasing volume of ascites. The median overall survival was 121 days (range, 66-625 days) after the 1st PIPAC procedure, while 8 patients who received more than 3 PIPAC procedures had a median survival of 450 days (range, 206-481 days) (P=0.0376).Patients, who received 2 or more PIPAC procedures, reported a stable overall quality of life.	
Glatz T, Horvath P et al. (2019) Staging laparoscopy and Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for peritoneal metastasis: safe access to the abdomen. Pleura and Peritoneum (4) 1 20190004		This finger-access technique has shown to be safe and effective.	Minor modified technique
Hovarth B, Bekert S et al (2018). Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases of pancreas and biliary tract cancer. Clinical & Experimental Metastasis, 35:635–40	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^2 and doxorubicin 1.5 mg/m^2 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.
Horvath, P, Yurttas C et al. (2019) Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastases in Solid Organ Graft Recipients: First Experience. Annals of Transplantation (24) 30-35	Retrospective analysis N=2 patients had combined chemotherapy and PIPAC (1 patient had metachronous PM of colonic cancer after liver transplantation, another patient had	No adverse events >CTCAE 2 were recorded. There was no measurable liver or renal toxicity. PIPAC procedures could be repeated without any interruption of immunosuppressive medication or impairment of respective plasmatic	Larger studies added to table 2.

Jan 15, 2019. (NCT03210298)	synchronous PM of pancreatic cancer after combined kidney-pancreas transplantation).	drug levels. The first patient passed away 7 months after the first PIPAC, the second patient was still alive after 8 months. PIPAC can induce objective regression of PM in solid organ transplant recipients without inducing organ toxicity or interfering with immunosuppressive therapy.	
Hubner M, Teixeira Farinha H et al (2017). Feasibility and Safety of Pressurized Intraperitoneal Aerosol Chemotherapy for peritoneal carcinomatosis: A retrospective cohort study. Gastroenterology research & practice (2017) 6852749	Retrospective case series N=42 patients with PM from ovarian cancer, gynaecologic cancer and colon cancer (91 PIPAC procedures with cisplatin, doxorubicin, and oxaliplatin)	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).	Included in systematic review added to table.
Katdare N, Prabhu R et al (2019) Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Initial Experience from Indian Centers and a Review of Literature. Indian Journal of Surgical Oncology (10) 1 24-30	Case series and review N=16 patients with peritoneal metastases from various primary sites had 17 PIPAC procedures	The median hospital stay was 1 day, minor and major complications were seen in 2 patients each (11.7%), and there was 1 postoperative death. Of the 6 patients who completed at least 6 weeks of follow up, there was disease progression in 2, unrelated problems in 2 patients, and a second procedure was performed in 1 patient. One patient had subsequent CRS and HIPEC.	Larger studies added to table 2.
Kurtz, F, Struller, F et al. (2018) Feasibility, Safety, and Efficacy of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastasis: A Registry Study. Gastroenterology research & practice (2018)	Retrospective analysis. N=71 patients who had had heavy pretreatment with PM from gastric (n = 26), colorectal (n = 17), hepatobiliary/pancreatic (n = 9), ovarian (n = 6), appendiceal (n = 5) origin, pseudomyxoma	Laparoscopic non-access rate was 11/142 procedures (7.7%). Mean number of PIPAC/patient was 2. There was no procedure-related mortality. There were 2.8% intraoperative and 4.9% postoperative complications. 39 patients	Study included in systematic review added to table 2.

2743985 2018. Trial registration:NCT03210298	peritonei (n = 4), and other tumours (n = 3). 142 PIPAC procedures	had more than 1 PIPAC and were eligible for efficacy analysis, and PRGS could be assessed in 36 of them. In 24 patients (67%), PRGS improved or remained unchanged at PIPAC#2, reflecting tumour regression or stable disease. Ascites was present in 24 patients and diminished statistically significantly under therapy. Median survival was 11.8 months (95% CI: 7.45-16.2 months) from PIPAC#1. Conclusion: PIPAC is feasible, safe, and well tolerated and can induce histological regression in a statistically significant proportion of patients with pretreated PM.	
Khosrawipour T, Khosrawipour V et al (2017). Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PLOS ONE | https://doi.org/10.1371/ journal.pone.0186709 October 19	Prospective case series N=20 patients with peritoneal carcinomatosis of pancreatic adenocarcinoma treated with PIPAC (doxorubicin 1.5 mg/m^2 and cisplatin 7.5 mg/m^2 of body surface delivered at intervals of 6 weeks) 41 procedures, mean 2.1 cycles	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.	Larger studies included in table 2.
Larbre V, Alyami, M et al. (2018) No Renal Toxicity After Repeated Treatment with Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Patients with Unresectable Peritoneal Metastasis. Anticancer Research (38) 12 6869-75	Case series N=43 patients with unresectable PM had 3 PIPAC cycles 175 procedures main were gastric 22 and ovarian 11 cancer.	Median PCI was 17 (range=5-39). Repeated PIPAC did not induce statistically significant acute nor cumulative renal toxicity in any patients. This study confirms the previous published results in a larger group of patients.	Larger studies included in table 2.
Ndaw S, Hanser O et al (2018) Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination. Toxicology Letters (298) 171-6	Wipe samples were collected from operating rooms, gloves, hands, devices and floor. Urines samples were collected from medical staff and from a control group. Platinum analysis was done by	Statistically significant contaminations were seen on the floor, gloves, shoes and devices. However, urinary platinum was below the limit of quantification (<10ng/L) for more than 50% of healthcare workers	Occupational risk reported in studies added to table 2.

	plasma mass spectrometry.	performing HIPEC and PIPAC. Concentrations did not differ statistically significantly from those reported for the control group. There appears to be little risk of exposure to platinum drugs during HIPEC and PIPAC providing the adequate safety measures are implemented.	
Nadiradze G, Giger-Pabst U et al (2016). Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. Journal of Gastrointestinal Surgery (20) 2 367-73	Retrospective case series N=24 patients with advanced PM from recurrent, platinum-resistant gastric cancer. 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(2) and doxorubicin 1.5 mg/m(2) 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)	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.	Included in systematic review added to table.
Nowacki, M. and Zegarski, W (2018) The scientific report from the first pressurized intraperitoneal aerosol chemotherapy (PIPAC) procedures performed in the eastern part of Central Europe. Journal of International Medical Research (46) 9 3748-58	Report	Analysed the 14-month preparation period prior to the performance of the first PIPAC procedure with respect to: (i) general preparations; (ii) patient referral and qualification; (iii) the first PIPAC procedure; (iv) the 2 weeks following PIPAC programme establishment; and (v) general problematic issues that arose.	General preparations
Nowacki M, Alyami M et al (2018). Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions	Retrospective case series (international survey) N=349 patients with PM (most common indications-gynaecologic cancer, ovarian cancer and	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	Included in systematic review added to table.

performed in 349 patients for peritoneal carcinomatosis treatment: An international survey study. European Journal of Surgical Oncology (44) 7 991-6	colon cancer) had 832 PIPAC procedures with low-dose cisplatin, doxorubicin, oxaliplatin.	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.	
Nowacki M, Grzanka D et al (2018). Pressurized intraperitoneal aerosol chemotherapy after misdiagnosed gastric cancer: Case report and review of the literature. World Journal of Gastroenterology (24) 19 2130-6	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.	The patient felt better and returned to her daily activities. Multicentre data should be gathered to confirm the usefulness of PIPAC as a rescue or neoadjuvant supportive therapy in a very select group of patients.	PIPAC as supportive therapy.
Odendahl K, Solass W et al (2015). Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). European Journal of Surgical Oncology (41) 10 1379-85	Retrospective case series N=91 palliative patients who had pretreated advanced peritoneal metastasis (29 gastric cancer, 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.	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.	Included in systematic review added to table.
Rovers KP, Lurvink Robin J et al. (2019) 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). BMJ Open (9) 7 e030408 Jul 27, 2019. TRIAL REGISTRATION NUMBER: NCT03246321, Pre-results;	Multicentre, open-label, single-arm, phase 2 study Patients with isolated unresectable colorectal PM or appendiceal carcinoma, received laparoscopy-controlled repetitive ePIPAC-OX with intravenous leucovorin and bolus 5-fluorouracil as every 6 weeks.	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. 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	Study protocol

ISRCTN89947480, Pre-results; NTR6603, Pre-results; EudraCT: 2017-000927-29, Pre-results		presentation to patients, healthcare professionals and other stakeholders.	
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 to treat peritoneal carcinomatosis. World Journal of Surgical Oncology (14) 128 Apr 29	Retrospective case series N=14 patients with peritoneal carcinomatosis (from 6 gastric cancer, 2 colorectal cancer, 3 epithelial ovarian cancer, 1 appendiceal cancer , 2 diffuse malignant peritoneal mesothelioma) 40 PIPAC procedures (with oxaliplatin or cisplatin+doxorubicin 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.	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 repeated PIPAC procedures in association with systemic chemotherapy.	Included in systematic review added to table.
Sgarbura O, Hubner M et al. (2019). Oxaliplatin use in pressurized intraperitoneal aerosol chemotherapy (PIPAC) is safe and effective: A multicenter study. European Journal of Surgical Oncology (09) 09 May	Retrospective cohort study N=101 patients with unresectable PC of various origins: 66 colorectal, 15 gastric, 5 ovarian, 3 mesothelioma, 2 pseudomyxoma, 10 other malignancies (biliary, pancreatic, endocrine) had PIPAC with oxaliplatin every 6 weeks (251 procedures)	Postoperative abdominal pain was present in 23 patients. Out of the 9 patients with grade 3 abdominal pain, only 3 needed a change of PIPAC drug. CTCAE 4.0 toxicity grade 4 or higher was encountered in 16 (15.9%) patients. The patients had a mean of 2.5 procedures/patient (SD=1.5). 50 subjects presented with symptom improvement. Oxaliplatin-based PIPAC appears to be a safe treatment that offers good symptom control and promising survival for patients with advanced peritoneal disease.	Comprehensive systematic reviews added to table 2.
Solass W, Kerb R et al (2014). Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for	Prospective case series N=3 end-stage patients with advanced PC from gastric, appendiceal, and ovarian origin treated with PIPAC (12 applications)	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,	Included in systematic reviews added to table.

efficacy. Annals of Surgical Oncology (21) 2 553-9	Follow up: 567 days.	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.	
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 20:3504–11	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) 3 225-8	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.
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		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.	Technical note.
Siebert M, Alyami M et al. (2019) Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in association with systemic chemotherapy and bevacizumab, evaluation	Retrospective case series N=134 patients had PIPAC for unresectable PM (397 procedures) 26 patients had concomitant systemic	Patients in the BEVA group showed a higher (PCI 20 vs. 16, p<0.001). There was no statistical difference in overall 30-day morbidity (BEVA: 13 (14.8%) vs NON-BEVA: 29 (9.4%); p=0.147).	Concomitant treatment (PIPAC associated with systemic chemotherapy - bevacizumab)

of safety and feasibility. A single center comparative study. European Journal of Surgical Oncology (20) 20	chemotherapy including bevacizumab (BEVA group) compared with 108 patients with systemic chemotherapy without bevacizumab (NON-BEVA group).	There was no statistical difference for grade III-IV complications (BEVA: 4 (4.5%) vs NON-BEVA 10 (3.2%); P=0.521). Major complications from BEVA group were as follow, 2 bowel obstructions, one hematoma and one severe hypersensitivity reaction to platinum compound. There was no 30-day mortality in the BEVA group compared to 6 (5.5%) mortality in the NON-BEVA group.	
Somashekhar, SP, Ashwin, KR et al. (2019) Pressurized IntraPeritoneal Aerosol Chemotherapy vs. intravenous chemotherapy for unresectable peritoneal metastases secondary to platinum resistant ovarian cancer - Study protocol for a randomized control trial. Pleura and peritoneum (4) 1 2019. Recruiting. REF/2018/08/021223 Registered on Clinical Trials Registry - India (CTRI); www.ctri.nic.in	Randomised controlled trial N=100 patients with PM secondary to platinum-resistant ovarian cancer will be randomised to PIPAC C/D group -3 cycles (n=50) or IV chemotherapy group-6 cycles (n=50).	We expect reduction of ascites with symptomatic relief and CA 125 levels. PIPAC is a novel technique for selected patients with platinum-resistant ovarian PM and further investigation in comparative clinical trials with conventional chemotherapy will establish its role as a good palliative treatment option.	Protocol for an RCT
Somashekhar SP, Ashwin KR et al. (2018) Randomized control trial comparing quality of life of patients with end-stage peritoneal metastasis treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC) and intravenous chemotherapy. Pleura and Peritoneum (3) 3 20180110. Trial registration: REF/2018/08/021225 Registered on Clinical Trials Registry-India (CTRI); www.ctri.nic.in	Randomised controlled trial N=120 patients with PM 60 had treatment with 3 cycles of PIPAC procedure versus 60 with 6 cycles conventional systemic intravenous chemotherapy	PIPAC is a novel minimally invasive repeatable treatment modality which showed potentially encouraging tumour response and only minimal toxicity in patients with PM of various origins. It can optimize local drug delivery and improve clinical outcome due to superior pharmacological properties as compared to systemic chemotherapy.	Trial protocol.
Struller, F, Horvath, P et al. (2019) Pressurized intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin (PIPAC C/D) in patients with gastric cancer and peritoneal	Case series N=25 patients who had heavy pretreatment and recurrent gastric cancer with peritoneal metastasis (RGCPM) had treatment with 3 courses low-dose	10 (40%) had a radiological complete, partial response or stable disease. Median OS [intention to treat (ITT)] was 6.7 months, median time to progression was 2.7 months. Complete or	Included in systematic review added to table 2.

metastasis: a phase II study. Therapeutic Advances in Medical Oncology (11) 1758835919846402	PIPAC C/D every 6 weeks after ≥1 line of intravenous chemotherapy.	major regression on histology were seen in 9/25 patients (36%, ITT) or 6/6 [100%, per protocol (PP)] patients. There were no suspected unexpected serious adverse reactions, no treatment-related deaths, no CTCAE grade 4 toxicity and 3 (12%) grade 3 toxicities. Changes in the QLQ-C30 scores during PIPAC C/D therapy were small and not statistically significant.	
Struller F, Solass W et al. (2018) Pressurized intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin (PIPAC C/D) in patients with gastric cancer and peritoneal metastasis: a phase-II trial (PIPAC-GA1). Pleura and peritoneum (3) sA393-2018. Phase II ICH-GCP Clinical Trial (NCT01854255)	Case series N=25 patients who had heavy pretreatment and RGCPM had treatment with 3 courses low-dose PIPAC C/D after ≥1 line of intravenous chemotherapy.	Complete or major regression on histology was seen in 9/12 (75%) patients who had at least 2 PIPAC cycles. Mean overall survival was 8.4 months (13.1 months in patients with PCI < 12). There were no treatment-related deaths, no grade 4 toxicity and 4 (16%) grade 3 toxicities.	Included in systematic review added to table 2
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	Case series (Prospective cohort study) laparoscopic 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).	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.	Included in systematic review added to table 2
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	Case series-phase 2 study laparoscopic 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	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	Included in systematic review added to table 2.

	mg/m(2) followed by cisplatin 7.5 mg/m(2).	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.	
Tempfer CB, Rezniczek GA et al (2015). Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal carcinomatosis: a cohort study. Anticancer Research 35: 6723-30	Retrospective cohort study N= 99 women with PC (from 84 ovarian cancer, 6 primary peritoneal cancer, 3 colon cancer, 3 endometrial cancer, 1 bladder cancer, 1 pseudomyxoma peritonei , 1 fallopian tube cancer) having repeated courses of PIPAC with 7.5 mg/m(2) of cisplatin and 1.5 mg/m(2) of doxorubicin. 252 procedures. Follow up: 126 days.	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 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.	Included in systematic review added to table 2.
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 ovarian cancer 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. Gyanecol Oncol Reports, 10: 32-5	Case report N=1 woman with pseudomyxoma peritonei who had treatment with PIPAC (3 courses q 28–42 days of PIPAC with cisplatin 7.5 mg/m^2 and doxorubicin 1.5 mg/m^2	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 haematological toxicity.	Larger studies included in table 2. Included in systematic review added to table 2

	at 12 mm Hg and 37 °C for 30 min) 6-month follow up	PIPAC achieved clinical and histological disease remission. At 6 months, the patient is alive and needed no further treatment.	
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 peritoneal carcinomatosis. Gynecologic Oncology (150) 1 23-30	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), diarrhoea (n=5), and fever (n=2). Liver and renal toxicity was not seen. No systemic haematological 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/m and 2.1mg/m.	Included in systematic review added to table 2.
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	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.	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<0.0001 and 95.2 +/- 106.4 vs 24,770.8 +/- 11,710.8 ng/ml; p<0.0001 respectively). Concentrations of doxorubicin and cisplatin in peritoneal tissue also statistically significantly increased after PIPAC (5.1 +/- 0.7 vs 19.2 +/-	Drug uptake assessed.

		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 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) 4 217-22	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, Demtroeder 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^2 and doxorubicin 1.5 mg/m^2 applied intraperitoneally at a pressure of 12 mmHg and a temperature of 37%	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	Addition of electrostatic precipitation to this procedure with the aim of improving tissue penetration.

	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.	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.	