



Safety and preliminary efficacy of electrostatic precipitation during pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable carcinomatosis



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ABSTRACT

Introduction: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) was recently introduced to treat unresectable peritoneal metastases. Adding an electrostatic field may enhance charged droplet precipitation and tissue penetration, resulting in improved anticancer efficacy. We report for the first time its safety and preliminary efficacy.

Materials and methods: Patients underwent PIPAC combined with an electrostatic field, using the Ultravision™ apparatus. Adverse events were scored with the Common Terminology Criteria. Treatment response was assessed after more than one PIPAC, using clinical symptoms, tumor markers, CT imaging and histological regression.

Results: Forty-eight patients (median age, 61 y) with diverse primary tumors underwent 135 procedures (median per patient, 3). Most (65.2%) were treated as outpatient. Twenty-eight (58.3%) patients received concomitant chemotherapy. The most frequent treatment-related toxicities were anemia (grade 1 to 3, 13 [9.6%]), ileus (grade 1 to 3, 5 [3.7%]), anorexia (grade 1 to 3, 6 [4.4%]), nausea (grade 1 to 3, 5 [3.7%]) and vomiting (grade 1 to 3, 7 [5.2%]). There was no grade 4 or 5 morbidity. Twenty (41.7%) patients did not complete three treatments, mainly because of disease progression (n = 13). After two procedures, there were one responder and 8 non-responders. After three treatments, we observed 11 responders, two patients with stable disease, and 15 non-responders. All but one patient with therapy response received simultaneous chemotherapy.

Conclusion: Electrostatic precipitation during PIPAC is well tolerated and safe. After three procedures and concomitant chemotherapy, response or stable disease is achieved in approximately half of cases. These findings warrant prospective trials in homogeneous patient cohorts.

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Introduction

In selected patients with peritoneal metastases (PM), surgery combined with hyperthermic intraperitoneal chemoperfusion (HIPEC) may offer a meaningful survival benefit [1,2]. However, many patients present with unresectable disease, or are unfit to undergo major surgery. These patients may be offered laparoscopy

combined with pressurized intraperitoneal aerosol chemotherapy (PIPAC). This procedure, first described in November 2011, offers a novel approach to administer intraperitoneal (IP) chemotherapy, and is now a standardized procedure [3–6]. The perceived advantages of PIPAC include the benefits of a minimally invasive approach, the possibility to administer repeated treatments, and the potential for enhanced tissue penetration and enhanced anti-tumor efficacy due to the elevated IP pressure of the pneumoperitoneum [3]. In addition, repetitive PIPAC treatments can be combined with concurrent systemic anticancer drug treatment. Preliminary clinical data demonstrate the technical feasibility,

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safety, and antitumor activity of repeated PIPAC in PM of various origins [7–13].

When chemotherapy is nebulized in the peritoneal cavity, the forces acting on the aerosol particles include the acceleration provided by the nebulizer, gravity, and drag forces. In 2016, Reymond and coworkers proposed to combine PIPAC with the creation of an electrostatic field using a generator that is marketed to clear electrocautery smoke during laparoscopy [14]. In theory, application of an electrostatic field (typical voltage of 7.5–9.5 kV and current of $\leq 10 \mu\text{A}$) will accelerate aerosolized particles and improve aerosol distribution as well as tissue penetration. Experimental data in a large animal model confirmed that electrostatic precipitation PIPAC (ePIPAC) enhances tissue penetration of DT01 (noncoding small DNA fragments) [15]. In addition, preliminary data in three patients with PM has suggested that ePIPAC is technically feasible and well-tolerated [14]. Thus far, however, no reports from larger patient series have been published.

Here, we report the safety and preliminary efficacy of electrostatic precipitation combined with PIPAC in a consecutive series of 135 procedures.

Patients and methods

Patients

All patients signed an informed consent. Data of patients who underwent ePIPAC from September 2015 until April 2018 were prospectively collected and retrospectively analyzed. Data collection included demographic characteristics, details of the primary tumor and previous treatments, imaging findings (CT scan), and, if relevant, serum tumor marker levels. Inclusion criteria were based on previous reports and were as follows [16–18]: age between 16 and 85 years; clinical and/or radiological evidence of unresectable PM; progressive PM either before onset of systemic chemotherapy, after at least one line of chemotherapy or in the absence of treatment options; and absence of extraperitoneal cancer, with the exception of patients with a history of liver or lung metastases and no evidence of disease activity and patients with active pleural metastases who were treated with Pressurized IntraThoracic Aerosol Chemotherapy (PITAC) immediately after ePIPAC. Partial small bowel obstruction, poor general condition (Eastern Cooperative Oncology Group score 3 and 4 or Karnofsky index < 60) or intractable ascites were regarded as relative contra-indications. Patients with impaired liver, renal, heart (New York Heart Association class III or IV) 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.

ePIPAC

The technical details of the ePIPAC procedure have been previously reported [7,14]. To assess the impact of consecutive ePIPACs, biopsy sites were marked with metal clips. This allows repeated sampling at the same location to determine the mean and highest peritoneal regression grading score (PRGS) [19]. Additionally, digital photographs were taken throughout the peritoneal cavity to monitor the impact of serial ePIPACs on the normal and diseased peritoneum. PIPAC was performed with either oxaliplatin 92 mg/m^2 body surface area (BSA) in 150 mL of dextrose 5%, irinotecan 20 mg/m^2 in 200 mL of saline, or cisplatin 7.5 mg/m^2 in 150 mL of saline with or without doxorubicin 1.5 mg/m^2 in 50 mL of saline. After complete administration of chemotherapy (i.e. within 5–7 min, depending on the volume), the generator unit of the Ultravision™ System was activated. A high direct current voltage of 7.5–9.5 kV and a current of $\leq 10 \mu\text{A}$ were applied to the Ionwand™. The latter emits a

stream of electrons and forms negative gas ions that collide with the floating chemotherapy particles. The return electrode confers a weak positive charge on the patient, causing an electrostatic acceleration of the negatively charged aerosol particles to the peritoneum [15]. Thirty minutes after starting chemotherapy injection, the electrostatic field was switched off, the pneumoperitoneum was desufflated through a closed aerosol waste system and the laparoscopic incisions were tightly closed to prevent leakage of chemotherapy-containing wound fluid. Note that a PIPAC procedure generally comprises an injection time followed by a waiting period of 30 min. In our study, the waiting period of 30 min included the injection time as well, shortening the PIPAC procedure with 6–8 min. Pain relief was provided by local anesthesia (ropivacaine 0.75%, Aspen, Dublin, Ireland) and intravenous paracetamol or nonsteroidal anti-inflammatory drugs, on-demand. Postoperative nausea and vomiting were minimized with perioperative dexamethasone and ondansetron. Patients were scheduled for three ePIPACs every six weeks. Continuation of systemic chemotherapy was strongly recommended. Four-weekly ePIPACs were performed in the absence of systemic treatment options.

Postoperative morbidity and treatment toxicity

Treatment-induced toxicity was scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 until follow-up visits three weeks after the last ePIPAC [20]. Complication rate was calculated per procedure. Early in our experience, patients were hospitalized during a few days until clinical recovery and when blood samples did not show toxicity. With growing experience, ePIPAC has increasingly been performed as an outpatient procedure [21].

Response evaluation

Reasons for not completing the first three consecutive ePIPACs were noted. After two and three ePIPACs, the mean and highest PRGS per biopsy sample was noted and a multidisciplinary tumor board evaluated therapy response on the peritoneum (responder, stable or non-responder) based on CT imaging, changes in the mean PRGS, gastrointestinal complaints (i.e. any gastrointestinal symptom or disease - as described in CTCAE v5.0 - owing to treatment toxicity or progressive disease that precludes additional ePIPACs), and, if applicable, variation in ascites volume and tumor marker level. When both CT and the mean PRGS showed progression, the patient was considered as a non-responder, whereas patients with both iconographic and histological regression were defined as responders. When CT imaging showed stable disease, therapy response was based on the mean PRGS, being either regression, stable or progression. When CT revealed progressive PM and the mean PRGS demonstrated regression, other variables such as gastrointestinal complaints, ascites and tumor marker evolution were taken into account to determine therapy effect. Three extra ePIPACs were advised when responsive or stable disease was observed after three procedures. Likewise, after three extra ePIPACs, the multidisciplinary board reassessed therapy effect. The PRGS was calculated as proposed by Solass et al. [19]. The PRGS at the first ePIPAC indicates response to previous systemic chemotherapy and is the baseline for subsequent ePIPAC response evaluations [22].

Statistical analysis

Data are presented as mean \pm standard deviation (SD) or median (range) where appropriate. Data distribution was tested for normality and means were compared with a two-tailed student t-test. Statistical analysis was performed with SigmaPlot™ software

(version 13). A p value of ≤ 0.05 was considered to indicate statistical significance.

Results

Patients

From September 2015 until April 2018, 52 patients with unresectable PM were deemed eligible for ePIPAC. Four patients were excluded perioperatively due to inaccessibility ($n=3$) or portal hypertension-induced abdominal wall bleeding ($n=1$). Table 1 shows demographic and baseline disease characteristics and previous therapy information of 48 patients. The median time between diagnosis of PM and the first ePIPAC was five months (range: 0–56). In total, 135 procedures were performed. The median number of ePIPACs per patient was three (range: 1–9). Concomitant systemic chemotherapy was administered in 28 (58.3%) patients. Procedural characteristics, operative findings and treatment details are illustrated in Table 2.

Table 1
Demographic, baseline disease characteristics and previous therapy information.

Variable	Patients (N = 48)
Baseline characteristics	
Male sex - no. (%)	28 (58.3)
Median age - yr (range)	61 (16–85)
Karnofsky performance score - no. (%)	
>70	29 (60.4)
60–70	19 (39.6)
Disease characteristics	
Cancer type - no. (%)	
Appendiceal tumor	7 (14.6)
Goblet cell carcinoma	2 (4.2)
Low-grade appendiceal mucinous neoplasm	2 (4.2)
Mixed adenoneuroendocrine carcinoma	1 (2.1)
Signet ring cell adenocarcinoma	2 (4.2)
Cancer of unknown primary site	2 (4.2)
Cholangiocarcinoma	1 (2.1)
Colon adenocarcinoma	13 (27.1)
Ductal breast cancer	1 (2.1)
Endometrioid adenocarcinoma	1 (2.1)
Esophageal adenocarcinoma	3 (6.3)
Gastric adenocarcinoma	10 (20.8)
Diffuse type	7 (14.6)
Intestinal type	1 (2.1)
Undefined	2 (4.2)
Pancreas ductal adenocarcinoma	1 (2.1)
Peritoneal epithelioid mesothelioma	2 (4.2)
Ovarian cancer high grade type	3 (6.3)
Small bowel adenocarcinoma	2 (4.2)
Rectal adenocarcinoma	2 (4.2)
PM - no. (%)	
Synchronous	31 (64.6)
Metachronous	17 (35.4)
Median time until metachronous PM (range) - months	19 (5–118)
History of extraperitoneal disease - no. (%)	
Liver	4 (8.3)
Lung	3 (6.3)
Active pleural carcinomatosis	1 (2.1)
Previous treatment characteristics	
Cytoreductive surgery \pm intraperitoneal chemoperfusion - no. (%)	4 (8.3)
Surgery for gastrointestinal obstruction from PM - no. (%) ^a	6 (12.5)
Number of chemotherapy cycles before ePIPAC - no. (%)	
0	5 (10.4)
1	25 (52.1)
2	8 (16.7)
3	10 (20.8)

^a This includes stomy placement and palliative intestinal bypass. PM denotes peritoneal metastases. Seven patients had a history of liver and lung metastases, but did not show any evidence of active disease on the time of ePIPAC.

Morbidity and toxicity

The most frequent treatment-related toxicities were anemia (grade 1 to 3, 13 [9.6%]), ileus (grade 1 to 3, 5 [3.7%]), anorexia (grade 1 to 3, 6 [4.4%]), nausea (grade 1 to 3, 5 [3.7%]) and vomiting (grade 1 to 3, 7 [5.2%]). There was no grade 4 or 5 morbidity. Table 3 shows the adverse events related to ePIPAC. No patient needed a surgical reintervention. Most procedures (88/135 or 65.2%) were performed in an outpatient setting. In one patient, a 5 mm balloon trocar caused a small bowel perforation that was repaired and followed by ePIPAC. Recovery was uneventful. Another patient with duodenal adenocarcinoma and recurrent subobstruction was readmitted for rehydration. A patient with a colon adenocarcinoma treated with oxaliplatin was readmitted due to prolonged ileus, necessitating a temporary gastric tube and realimentation. Laparoscopic inspection demonstrated peritoneal inflammation during subsequent ePIPACs (Fig. 1).

Response evaluation

Twenty (41.7%) patients did not complete three ePIPACs due to disease progression ($n=13$), weakness ($n=2$), liver abscess ($n=1$), patient preference ($n=1$), or other reasons ($n=3$). Fig. 2 illustrates patient flow and the reasons for dropping out of treatment. Twenty-four patients underwent three ePIPACs while four patients were treated with three more procedures. One patient received nine ePIPACs. In the group treated twice, the mean PRGS before versus after the second ePIPAC was 2.28 ± 0.83 vs 1.78 ± 0.76 ($p=0.20$). Likewise, in terms of the highest PRGS, a trend towards statistical significance at the first versus the second procedure was detected (2.56 ± 0.69 vs 1.89 ± 0.76 ; $p=0.06$). Among those 9 patients treated twice, evaluation of peritoneal samples taken during the second ePIPAC showed an improvement of the mean PRGS in 5 (55.6%) cases while in four patients the score either remained unchanged (22.2%) or increased (22.2%). Within the group of 28 patients who underwent 3 ePIPACs, the mean PRGS prior to the first procedure was 1.99 ± 0.71 and 1.88 ± 0.82 at the third ePIPAC ($p=0.57$) and the highest PRGS before treatment was 2.25 ± 0.69 and 2.11 ± 0.82 at the third session ($p=0.84$). Within this group treated trice, an improvement of the mean PRGS was found in 15 (53.6%) patients while a stable or worse score was encountered in 6 (21.4%) and 7 (25%) cases, respectively. Fig. 3 illustrates the mean

Table 2
Characteristics of 135 ePIPACs and treatment information in 48 patients.

Open entry (Hasson technique) - no. (%)	129 (95.6)
Minilaparotomy - no. (%)	8 (5.9)
Ascites during 1st ePIPAC - no. (%)	18 (37.5)
Mean PCI (range) ^a	21.2 (2–39)
PITAC ^b - no. (%)	1 (0.7)
Type of chemotherapy - no. (%)	
Oxaliplatin (92 mg/m ²)	74 (54.8)
Oxaliplatin (23 mg/m ²)	1 (0.7)
Cisplatin (7.5 mg/m ²) and Doxorubicin (1.5 mg/m ²)	39 (28.9)
Cisplatin (7.5 mg/m ²)	15 (11.1)
Irinotecan (20 mg/m ²)	6 (4.4)
Mean duration of ePIPAC (SD) - min.	24.5 (0.77)
Median duration of surgery (range) - min.	110 (60–275)
Median duration of hospitalisation (range) - days	1 ^c (1–7)

^a Peritoneal Cancer Index (PCI) is based on 40 patients. In eight cases PCI was unknown because of extensive tumoral adhesions, preventing scoring.

^b Pressurized IntraThoracic Aerosol Chemotherapy (PITAC) was performed once in combination with ePIPAC in a patient with gastric adenocarcinoma with peritoneal and pleural carcinomatosis. The patient refused more PITACs because of thoracic wall pain.

^c 1 refers to ePIPAC in an outpatient setting.

Table 3
ePIPAC-related adverse events (CTCAE v5.0) until follow-up visit three weeks after the last procedure.^a

Adverse event	Any grade	Grade 1	Grade 2	Grade 3
	number of procedures (percent)			
Blood and lymphatic system disorders				
Anemia	13 (9.6)	4 (3.0)	4 (3.0)	5 (3.7)
White blood cell decreased	3 (2.2)	0	2 (1.5)	1 (0.7)
Lymphocyte count decreased	2 (1.5)	0	0	2 (1.5)
Platelet count decreased	2 (1.5)	1 (0.7)	1 (0.7)	0
Gastrointestinal disorders				
Abdominal pain	2 (1.5)	1 (0.7)	0	1 (0.7)
Ileus	5 (3.7)	0	4 (3.0)	1 (0.7)
Nausea	5 (3.7)	1 (0.7)	3 (2.2)	1 (0.7)
Vomiting	7 (5.2)	5 (3.7)	0	2 (1.5)
Infections and infestations				
Skin infection	1 (0.7)	1 (0.7)	0	0
Wound infection	3 (2.2)	3 (2.2)	0	0
Injury, poisoning and procedural complications				
Intraoperative gastrointestinal injury	1 (0.7)	1 (0.7)	0	0
Elevated liver enzyme levels				
ALT	1 (0.7)	0	1 (0.7)	0
AST	1 (0.7)	0	0	1 (0.7)
Metabolism and nutrition disorders				
Anorexia	6 (4.4)	0	4 (3.0)	2 (1.5)
Hypocalcemia	1 (0.7)	1 (0.7)	0	0
Hyperkalemia	1 (0.7)	1 (0.7)	0	0
Hyponatremia	1 (0.7)	0	0	1 (0.7)
Renal and urinary disorders				
Hematuria	1 (0.7)	0	1 (0.7)	0
Vascular disorders				
Arterial hypertension	2 (1.5)	0	2 (1.5)	0
Total	58 (43.0)	19 (14.1)	22 (16.3)	17 (12.6)

^a Shown are the adverse events of any grade that occurred in at least one patient. No grade 4 or 5 events were observed. ALT denotes alanine aminotransferase and AST aspartate transaminase.

and highest PRGS when either two or three ePIPACs were performed. Table 4 shows individual therapy response on the peritoneum based on CT, change in the mean PRGS, gastro-intestinal complaints and, if relevant, ascites and tumor marker. Of note, in 15 patients CT findings correlated with the mean PRGS. After two ePIPACs, assessment of therapy effect on the peritoneum revealed one responder and 8 non-responders. After three ePIPACs, 15 non-responders, 11 responders and two patients with stable PM were found. All but one patient with therapy response combined ePIPAC with systemic chemotherapy. Three additional ePIPACs in four cases resulted in two responders and two non-responders. Disease progression was present in one patient after nine operations. After a median follow-up of 7.5 months since the first ePIPAC, 37 of 48 patients died.

Discussion

Electrostatic precipitation involves the application of a high voltage, low power electrostatic charge to remove particles from an aerosol and was introduced in clinical practice to clear surgical smoke during laparoscopic surgery. Ansell et al. demonstrated that electrostatic precipitation improved visibility during laparoscopic cholecystectomy in a small randomized trial [23]. They did not observe any adverse events such as cardiac arrhythmia, ECG changes, bowel perforations, or skin burns. The potential benefits of adding electrostatic precipitation to PIPAC may include enhanced tissue penetration, and thus reduced risk of environmental exposure to residual aerosol, and shortened procedure times if maximal tissue uptake can be realized earlier in comparison with PIPAC. Kakchekeeva and coworkers found in a pig laparoscopy model that electrostatic precipitation during PIPAC significantly increased peritoneal tissue Cy5-labeled DT01 concentration compared to

PIPAC alone [15]. The first clinical application of ePIPAC was reported by Reymond et al., who treated three patients with PM from hepatobiliary-pancreatic origin, and found the procedure to be safe and well tolerated [14].

This study clearly demonstrates that ePIPAC is safe. Only minor adverse events were detected. The practice to perform ePIPAC in day clinic also stresses its safety. After three procedures and concomitant systemic chemotherapy, response or stable disease was achieved in approximately half of the patients.

We report the first large series of 135 procedures in 48 patients. Our results confirm that ePIPAC is safe and associated with limited treatment-related toxicity, comparable with reported side effects of PIPAC alone. A recent systematic review of 22 studies including 1197 patients showed adverse events of CTCAE grade 1, 2, 3, 4, and 5 in 537 (45%), 167 (14%), 83 (7%), 10 (0.8%), and 19 (1.6%) cases, respectively [24]. In our study, the most frequent adverse event was anemia, likely caused by systemic chemotherapy induced bone marrow suppression. In some patients, hemoglobin levels did not recover during the time interval between ePIPAC procedures. We did observe that ePIPAC with oxaliplatin was associated with more pronounced and frequent side effects including pain, ileus, nausea and vomiting that could last up to one week post-operatively. In addition, one patient treated with oxaliplatin developed gradually worsening peritoneal fibrosis, resulting in thickening and intestinal adhesions during subsequent procedures. Because of complete tumor response and only minor gastrointestinal complaints, the multidisciplinary board advised a fourth procedure. Despite the administration of a quarter of the dose (23 mg/m²) during the fourth ePIPAC, rehospitalization for prolonged ileus was needed. The patient was successfully treated with gastric drainage and corticosteroids. No additional ePIPACs were performed. The potential peritoneal toxicity of oxaliplatin, a

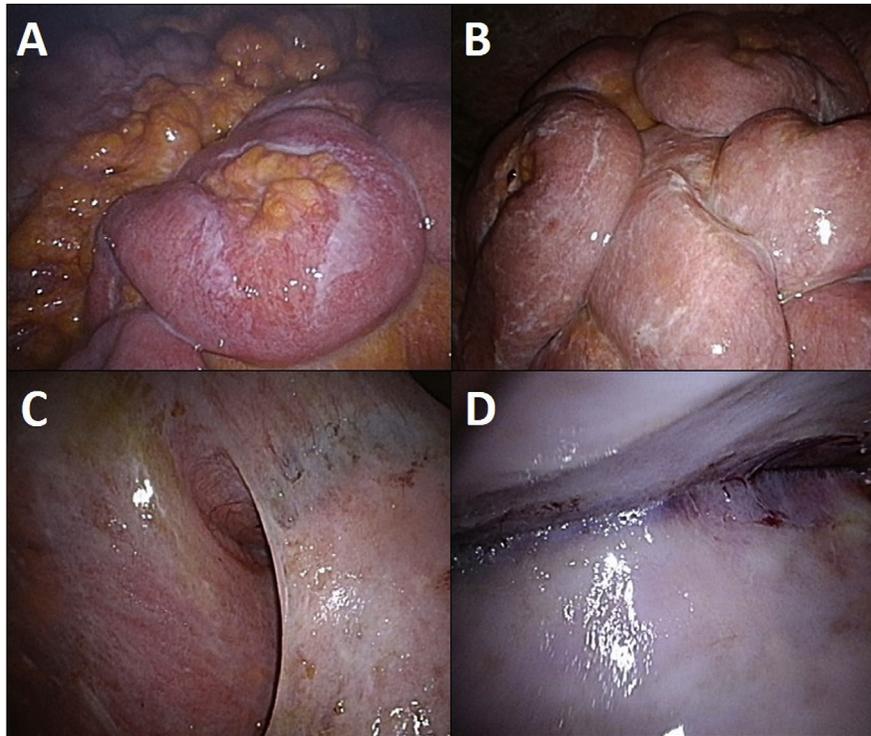


Fig. 1. Peritoneal inflammatory changes after several ePIPACs with oxaliplatin. A patient with peritoneal carcinomatosis from colonic origin. Before ePIPAC (A). After one procedure, a slight greyish peritoneal discoloration is noticed (B). Sticked intestinal loops after two procedures (C). After three ePIPACs, thickened peritoneum covers the intestines, impeding identification of the anatomy and causing temporary intestinal subobstruction that was treated with a gastric tube and realimentation (D).

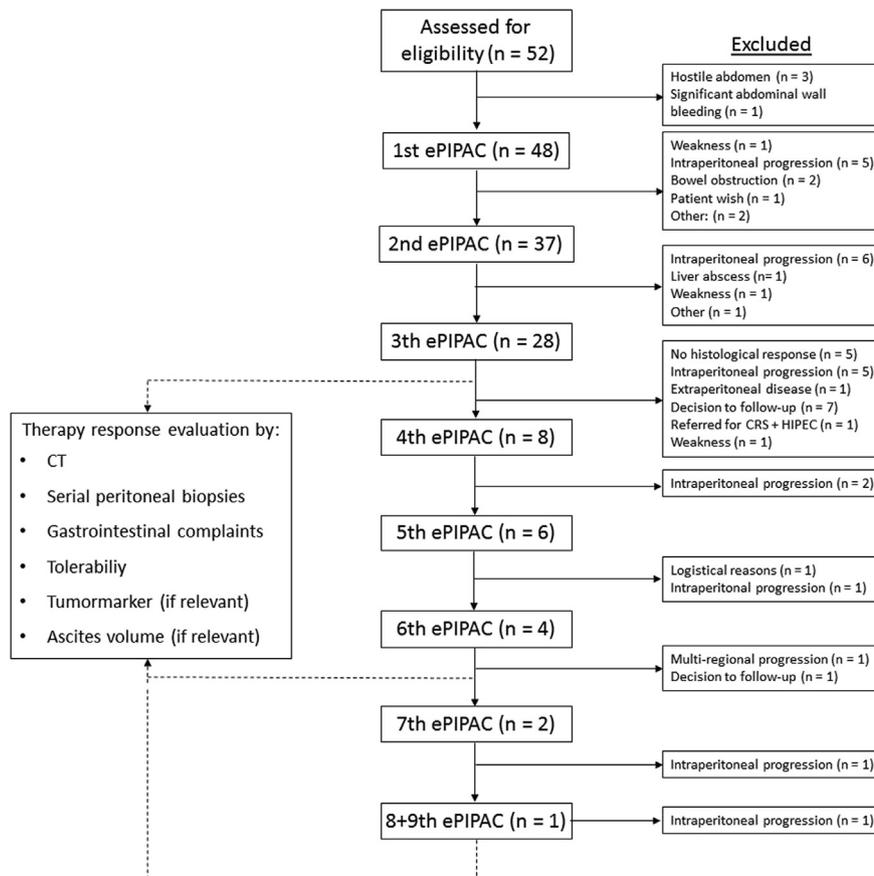


Fig. 2. Patient flow diagram. CRS: cytoreductive surgery; CT: computed tomography; HIPEC: hyperthermic intraperitoneal chemoperfusion.

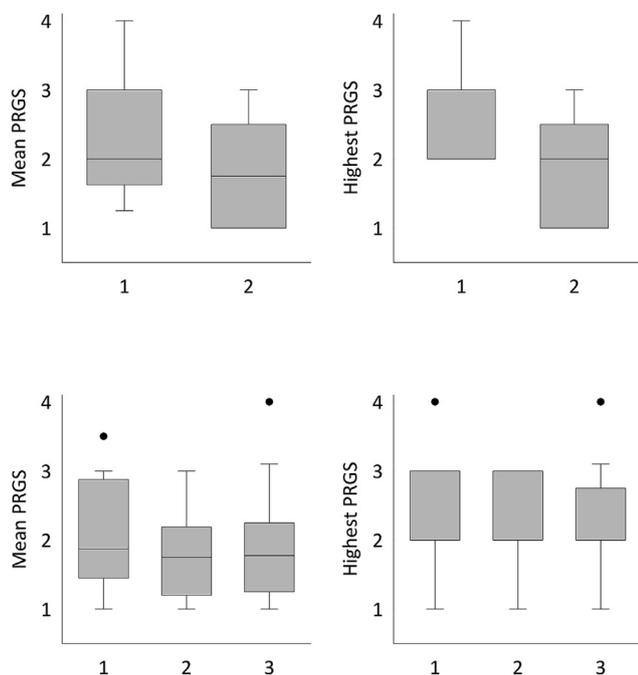


Fig. 3. Plots of the PRGS. The mean and highest PRGS in patients treated twice or thrice with ePIPAC.

known vesicant agent, has been highlighted by others, both after HIPEC and PIPAC [25]. These findings raise questions on the continued use of IP oxaliplatin. An ongoing dose escalation study (NCT03172416) with oxaliplatin will provide important answers on its safety and tolerability [26]. A potential alternative is irinotecan, which we have used at a dose of 20 mg/m² in patients with known intolerance to oxaliplatin. This dose is based on a phase 1 study of three-weekly repeated IP administrations of 200 mg/m² irinotecan in 1 L of saline solution [27]. Although it is known that irinotecan requires hepatic biotransformation by carboxylesterase to its active metabolite SN-38, a fraction of IP irinotecan is metabolized in situ to its active metabolite [28]. Repeated ePIPAC with irinotecan at 20 mg/m² did not result in any adverse events or peritoneal toxicity in the present study. However, the maximally tolerated dose and efficacy of irinotecan for PIPAC should be addressed in future prospective studies. In our study, a few patients were solely treated with cisplatin because doxorubicin was not a good indication (e.g. primary tumor type) or we considered its administration as hazardous in patients with known impaired cardiac function.

A major advantage of the addition of PIPAC in patients with unresectable PM is that it allows to assess, both visually and histologically, the extent of peritoneal disease. Assessing the effect of PIPAC is currently not standardized and uses various methods (i.e. response evaluation criteria in solid tumors, peritoneal cancer index, quality of life, histopathological tumor regression, survival and gene expression change), which are all subject to limitations [8,22]. In 2016, Solass et al. proposed a novel PRGS to improve standardization, using a mean PRGS and highest PRGS [19]. Graversen et al. used this classification and found a PRGS reduction in 67% of patients who underwent a median number of three PIPACs [22]. In our study, a mean PRGS reduction was present in slightly more than half of patients after 3 procedures. We observed stable disease or response in almost half of patients after three procedures. Repeated sampling from the same

biopsy sites is controversial as biopsies induce scarring. False positive therapy responses were minimized by placing clips at biopsy sites and resampling at sufficient distance (≥ 1 cm) and at PM that was macroscopically unaffected by prior sampling. Placing surgical clips is also debatable as most biopsy sites can be spotted again. In some cases, however, the use of clips can be beneficial. For example, repeated oxaliplatin administration can coat biopsy sites with inflammatory peritoneum or biopsy sites are covered with adherent tissue, demanding extensive adhesiolysis. In these cases, easy identification of clips can be advantageous.

Our findings underline the importance of a multimodal approach in these patients, and the need for adequate patient selection (no large volume disease, no gastrointestinal or urinary obstruction, adequate performance status). Obviously, the question can be raised what the respective contribution is of the systemic versus the locoregional treatment component in achieving peritoneal tumor response. Only randomized trials will establish this. Although there are no clinical trial results that have established the ideal number and timing of PIPAC procedures, most centers aim to administer at least three [22]. However, this number can often not be achieved, resulting in limited or uncertain efficacy of PIPAC [17,18,29].

The current study included a very heterogeneous patient population and therefore no firm conclusions can be made on survival benefit. Nevertheless, in some patients with early stage PM or progressive disease after several lines of systemic chemotherapy, a combination of ePIPAC and systemic chemotherapy led to a striking temporary disease regression and prolongation of expected survival, prompting further therapy. Ongoing randomized trials will define the effect of PIPAC and ePIPAC on survival in PM patients. In our study, a few patients had a history of liver and lung metastases. These patients were included because of absence of active disease on the time of ePIPAC. However, this indication is controversial and not recommendable because there is currently no evidence whether implementing ePIPAC in these patients is beneficial to survival. Of note, Nadiradze et al. treated 24 patients with PC from gastric cancer with PIPAC and found a worse survival in four patients with simultaneous extraperitoneal disease [18].

Several limitations apply to the interpretation of our findings. Considerable heterogeneity was present in terms of patient and tumor characteristics, previous treatments, disease extent and ePIPAC regimen. Although histological scoring with PRGS allows much more objective response assessment compared with CT imaging, sampling error, false positive results due to scarring, and variability as well as interobserver disagreement may limit its value. A PIPAC procedure generally comprises an injection time followed by a waiting period of 30 min. In our study, this waiting period included the injection time. As a consequence, the waiting period was shortened with 6–8 min. The impact of this time difference is of course unknown. Some technical and procedural questions remain on the use of electrostatic precipitation. As an example, it is unclear when and for how much time the electrostatic field should be activated.

In conclusion, we report the first large series of patients treated with electrostatic precipitation during PIPAC. Our findings suggest that ePIPAC does not enhance morbidity or drug toxicity compared to PIPAC alone. In addition, antitumor efficacy is promising, as evidenced by treatment response or stabilization in approximately half of patients treated three times in combination with systemic chemotherapy. Further prospective studies are needed in homogeneous patient cohorts in order to definitively establish the anticancer efficacy of ePIPAC.

Table 4
Characteristics of therapy response after at least two ePIPACs.

Number of ePIPACs per patients	Simultaneous systemic chemotherapy	CT	Mean PRGS	Tumormarker	Ascites volume	Gastrointestinal complaints	Therapy response
	Y/N	Regression/Decrease	Stable	±	Progression/Increase	-	Responder + Stable ± Non-responder -
Appendiceal tumor							
Goblet cell carcinoma	2 Y	–	±	NA	–	–	–
	2 Y	Not done	+	NA	+	±	+
Low grade mucinous neoplasm	3 Y	+	+	±	±	±	+
MANEC	3 N	–	±	–	–	±	–
Signet ring cell adenocarcinoma	3 Y	–	–	NA	–	±	–
	3 Y	±	+	NA	±	±	+
	6 Y	±	–	NA	–	±	–
Cancer of unknown primary site	2 N	Not done	–	NA	+	–	–
	3 N	–	–	NA	–	–	–
Colon adenocarcinoma	2 Y	–	–	NA	–	±	–
	3 Y	±	–	±	NA	±	–
	3 Y	+	+	+	NA	+	+
	3 Y	+	+	+	+	+	+
	3 Y	±	+	+	NA	+	+
	3 Y	±	+	±	NA	+	+
	3 Y	±	+	+	+	–	+
	3 Y	+	+	NA	–	±	±
	3 N	–	+	NA	NA	±	–
	3 N	–	±	–	NA	±	–
	3 Y	–	±	–	–	–	–
	3 Y	–	±	NA	+	±	–
	6 Y	±	+	+	+	±	+
Ductal breast cancer	2 N	–	±	–	–	±	–
Endometrioid adenocarcinoma	3 Y	±	+	NA	+	±	+
Esophageal adenocarcinoma	2 Y	Not done	+	NA	+	–	–
	3 Y	+	+	NA	NA	+	+
	6 Y	±	+	NA	NA	±	+
	9 Y	–	±	NA	NA	–	–
Gastric adenocarcinoma	2 Y	Not done	+	NA	NA	–	–
	2 Y	–	+	NA	–	±	–
	2 N	Not done	+	NA	NA	–	–
	3 Y	±	±	NA	±	±	±
	3 Y	±	–	NA	NA	±	–
	3 N	+	+	NA	NA	±	+
	3 Y	–	–	NA	NA	±	–
	3 Y	–	±	NA	+	±	–
	3 N	–	–	NA	NA	±	–
	3 Y	–	+	NA	–	–	–
	6 Y	–	–	NA	–	–	–
Peritoneal epithelioid mesothelioma	3 N	–	–	NA	–	±	–
Small bowel adenocarcinoma	3 N	–	±	NA	–	±	–
Rectal adenocarcinoma	3 Y	+	+	+	NA	±	+

When both CT and the mean PRGS showed progression, the patient was considered as a non-responder, whereas patients with dual regression were defined as responders. When CT showed stable PM, therapy response was based on the mean PRGS, being either regression, stable or progression. When CT revealed progressive PM and the mean PRGS demonstrated regression, other variables as gastrointestinal complaints, ascites and tumor marker were taken into account to determine therapy effect. CT was routinely done after three procedures. In four patients treated twice, this was not performed because progressive disease was obvious or due to logistical issues. CT indicates computed tomography. MANEC denotes Mixed AdenoNeuroEndocrine Carcinoma. PRGS indicates Peritoneal Regression Grading Score.

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References

[1] van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR,

Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 2018;378:1363–4.

[2] Bonnot PE, Piessen G, Kepenekian V, Decullier E, Pocard M, Meunier B, et al. Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastases (CYTO-CHIP study): a propensity score analysis. *J Clin Oncol* 2019; May;14:jco1801688. <https://doi.org/10.1200/JCO.18.01688> [Epub ahead of print].

[3] Solass W, Herbette A, Schwarz T, Hetzel A, Sun JS, Dutreix M, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. *Surg Endosc* 2012;26:847–52.

- [4] Solass W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond M. Description of a novel approach for intraperitoneal drug delivery and the related device. *Surg Endosc* 2012;26:1849–55.
- [5] Nowacki M, Alyami M, Villeneuve L, Mercier F, Hubner M, Willaert W, et al. Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: an international survey study. *Eur J Surg Oncol* 2018;44:991–6.
- [6] Alyami M, Gagniere J, Sgarbura O, Cabelguenne D, Villeneuve L, Pezet D, et al. Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. *Eur J Surg Oncol* 2017;43:2178–83.
- [7] Willaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Pleura Peritoneum* 2017;2:121–8.
- [8] Grass F, Vuagniaux A, Teixeira-Farinha H, Lehmann K, Demartines N, Hubner M. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. *Br J Surg* 2017;104:669–78.
- [9] Teixeira Farinha H, Grass F, Labгаа I, Pache B, Demartines N, Hübner M. Impact of pressurized intraperitoneal aerosol chemotherapy on quality of life and symptoms in patients with peritoneal carcinomatosis: a retrospective cohort study. *Gastroenterol Res Pract* 2017;4596176. <https://doi.org/10.1155/2017/4596176>.
- [10] Teixeira Farinha H, Grass F, Labгаа I, Pache B, Demartines N, Hübner M. Inflammatory response and toxicity after pressurized intraperitoneal aerosol chemotherapy. *J Cancer* 2018;9:13–20.
- [11] Giger-Pabst U, Demtröder C, Falkenstein TA, Ouaisi M, Götz TO, Rezniczek GA, et al. Pressurized IntraPeritoneal aerosol chemotherapy (PIPAC) for the treatment of malignant mesothelioma. *BMC Canc* 2018;18(1):442. <https://doi.org/10.1186/s12885-018-4363-0>.
- [12] Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Clin Exp Metastasis* 2017;34:309–14.
- [13] Hubner M, Grass F, Teixeira Farinha H, Pache B, Mathevet P, Demartines N. Pressurized IntraPeritoneal aerosol chemotherapy –practical aspects. *Eur J Surg Oncol* 2017;43:1102–9.
- [14] Reymond M, Demtröder C, Solass W, Winnekendonk G, Tempfer C. Electrostatic precipitation pressurized intraperitoneal aerosol chemotherapy (ePIPAC): first in-human application. *Pleura Peritoneum* 2016;1:109–16.
- [15] Kakchekeeva T, Demtröder C, Herath NI, Griffiths D, Torkington J, Solass W, et al. In vivo feasibility of electrostatic precipitation as an adjunct to pressurized intraperitoneal aerosol chemotherapy (ePIPAC). *Ann Surg Oncol* 2016;23:592–8.
- [16] Tempfer CB, Celik I, Solass W, Buerkle B, Pabst UG, Zieren J, et al. Activity of pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. *Gynecol Oncol* 2014;132:307–11.
- [17] Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst, Reymond M. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. *Colorectal Dis* 2016;18:364–71.
- [18] Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond M. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with low-dose cisplatin and doxorubicin in gastric peritoneal metastasis. *J Gastrointest Surg* 2016;20:367–73.
- [19] Solass W, Sempoux C, Detlefsen S, Carr NJ, Bibeau F. Peritoneal sampling and histological assessment of therapeutic response in peritoneal metastasis: proposal of the peritoneal regression grading score (PRGS). *Pleura Peritoneum* 2016;1:99–107.
- [20] Common terminology criteria for adverse events (CTCAE), version 5.0. National Institutes of Health, National Cancer Institute; November 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. [Accessed 31 May 2019].
- [21] Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond M. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Ann Surg Oncol* 2013;20:2311–6.
- [22] Graversen M, et al. Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. *Ther Adv Med Oncol* 2018;10. <https://doi.org/10.1177/1758835918777036>. eCollection 2018. 1758835918777036.
- [23] Ansell J, Warren N, Wall P, Cocks K, Goddard S, Whiston R, et al. Electrostatic precipitation is a novel way of maintaining visual field clarity during laparoscopic surgery: a prospective double-blind randomized controlled pilot study. *Surg Endosc* 2014;28:2057–65.
- [24] Tempfer C, Giger-Pabst U, Hilal Z, Dogan A, Rezniczek GA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal carcinomatosis: systematic review of clinical and experimental evidence with special emphasis on ovarian cancer. *Arch Gynecol Obstet* 2018;298:243–57.
- [25] Graversen M, Detlefsen S, Pfeiffer P, Lundell L, Mortensen MB. Severe peritoneal sclerosis after repeated pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC OX): report of two cases and literature survey. *Clin Exp Metastasis* 2018;35:103–8.
- [26] Kim G, Tan HL, Chen E, Teo SC, Jang CJM, Ho J, et al. Study protocol: phase 1 dose escalating study of Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) with oxaliplatin in peritoneal metastasis. *Pleura Peritoneum* 2018;3:20180118. <https://doi.org/10.1515/pp-2018-0118>.
- [27] Choi MK, Ahn BJ, Yim DS, Park YS, Kim S, Sohn TS, et al. Phase I study of intraperitoneal irinotecan in patients with gastric adenocarcinoma with peritoneal seeding. *Cancer Chemother Pharmacol* 2011;67:5–11. <https://doi.org/10.1007/s00280-010-1272-6>.
- [28] Ahn BJ, Choi MK, Park YS, Lee J, Park SH, Park JO, et al. Population pharmacokinetics of CPT-11 (irinotecan) in gastric cancer patients with peritoneal seeding after its intraperitoneal administration. *Eur J Clin Pharmacol* 2010;66:1235–45. <https://doi.org/10.1007/s00228-010-0885-3>.
- [29] Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond M. Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal carcinomatosis: a cohort study. *Anticancer Res* 2015;35:6723–9.