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# Is PIPAC a Treatment Option in Upper and Lower Gastrointestinal Cancer with Peritoneal Metastasis?

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**Abstract**

***Background:*** The survival prognosis of patients with peritoneal metastasis (PM) of gastrointestinal (GI) cancer is generally poor and treatment consists of, according to international guidelines, systemic chemotherapy. A multimodal treatment approach, including cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy, not only proved to be beneficial mainly in colorectal cancer, but also in selected patients with gastric cancer. The authors performed systematic research of articles and ongoing clinical trials using the keywords "PIPAC" and "gastric cancer" or "colorectal cancer" in PubMed in October 2021. Key findings, such as complications rates, treatment protocols, and overall survival were summarized and illustrated in Tables and critically discussed. ***Summary:*** Twenty years ago, the technique of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) was developed by Reymond et al. and delivered evidence to be recognized as a basic therapeutic tool in this multimodal therapy. Currently, there are several ongoing Phase II and III trials exploring the usage and efficacy of PIPAC as a neoadjuvant, adjuvant, or palliative component of treatment in patients with PM of GI cancer. ***Key Messages:*** The aim of this narrative review was to help navigate the reader throughout the most current evidence for the use PIPAC and to highlight its indication in patients with upper and lower GI cancer with PM. It also provides an outline of ongoing studies and future perspectives.



## Introduction

Patients with peritoneal surface malignancies represent a heterogeneous group of pathologies, including primary malignancies of the peritoneum, such as peritoneal mesothelioma, as well as secondary malignancies with varying risk for synchronous peritoneal metastasis (PM), such as ovarian (46%), gastric (14%), or colorectal cancer (CRC) (5%) [1–3]. The focus of this narrative review will lie on peritoneal disease from gastrointestinal (GI) cancers. Peritoneal metastasized CRC (CRC – pmCRC) confers the worst overall survival (OS) (approx. 16.3 months) when compared with non-peritoneal metastatic CRC (19.1 months for patients with liver metastasis and 24.6 months for lung metastasis) as Franko et al. [4] described. PM of gastric cancer (GC) predicts a dismal survival prognosis. Literature reports median survival of 3–4 months when left untreated and up to 10 months with systemic chemotherapy [5–7]. This is mainly explained by the fact that PM constitutes one of the most important factors predicting poor systemic cytotoxic response in both entities [4, 5, 8].

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Treatment modalities include systemic chemotherapy, cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for selected patients, or intraperitoneal chemotherapy (IPC). Advantages of IPC are seen in a higher peritoneal tissue concentration combined with less toxicity in comparison to systemic chemotherapy, which showed a diminished response in PM [4, 9, 10]. The application of IPC with atmospheric pressure or in the form of Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) is a minimal invasive procedure with growing evidence and represents an additional therapy for unresectable PM of adenocarcinoma of digestive origin among others. The aim of this review article was to provide an overview on the technique of PIPAC, its indication in patients with upper and lower GI cancer with PM, as well as an outline about ongoing studies and future perspectives.

## History

Reymond and colleagues [11] were the first to publish the idea of a chemotherapeutic enriched capnoperitoneum 20 years ago, testing a device in a porcine animal model. Still, they encountered technical difficulties concerning a stable dispersion of the aerosols. It took ten more years for a case series to be published, using a second-generation device developed for use in humans providing a stable system that led to the development of the standardized surgical technique we use today, which offers advantages in intra-abdominal distribution, tissue uptake, tolerability, and repeatability [11].

Tempfer et al. [12] first studied patients with PM of ovarian cancer and demonstrated both the feasibility and the local and systemic safety of PIPAC. It proved to induce regression (Reg) in PM of ovarian cancer by application of merely 10% of the common systemic dose [13]. During the last decade, the distribution and teaching of the PIPAC technique were secured by standardized training workshops. It was then adopted and validated by other expert groups to provide homogenous knowledge and ever-growing widespread practice [14].

The combination of high pressure and hyperthermia was demonstrated by Facy et al. [15] using oxaliplatin with an increased tissue concentration. Lagast et al. [16] reported in their review on results from mathematical models, in vitro experiments, animal studies, and clinical trials showing tissue penetration from 0.5 to 3 mm in depth, hence supporting superiority of PIPAC in terms of tissue penetration. A preclinical study focusing on tissue penetration of chemotherapy during PIPAC presented results of up to 4.1 mm depending on the distance from the nozzle, as well as good overall distribution in the abdominal cavity [17].

## Primary Indication in Upper and Lower GI Cancer with Peritoneal Metastases

Prior evaluating PIPAC as a suitable treatment for patients with potentially resectable or unresectable metastatic disease, the goals of treatment must be discussed and set. As per the guidelines used in European countries, provided by ESMO, these are: prolongation of survival, improving tumor-related symptoms, stopping tumor progression, and maintaining quality of life, among others [18]. The standard of care for unresectable metastatic GI disease according to these guidelines is systemic chemotherapy (ESMO Clinical Practice Guidelines) [18, 19].

If resection appears feasible and oncologically reasonable, considering the patient's overall constitution and the peritoneal cancer index, a multimodal treatment, including surgery should be evaluated. The effect of CRS and HIPEC in patients with pmCRC has been studied in important prospective randomized controlled trials. In 2003, Verwaal et al. [20] showed higher OS of 22.3 months in patients who underwent CRS and HIPEC followed by adjuvant systemic chemotherapy compared to those who only received systemic therapy with and without palliative surgery (12.6 months; $p = 0.032$).

More recently, a prospective randomized multicentric phase III trial (PRODIGE 7) concluded that patients would equally benefit from CRS with or without HIPEC and perioperative systemic chemotherapy regarding OS (41.7 vs. 41.2 months; $p = 0.99$), yet the complications (grade 3 or worse) after 60 days in the HIPEC group were higher (26% vs. 15%; $p = 0.035$). Quénet et al. [21] showed that CRS alone, without associated HIPEC, has a decisive impact in the multimodal therapeutic strategy for pmCRC. Conclusively, a strict patient selection is key to a successful treatment, improvement in survival, and symptom relief.

PIPAC can usually be considered in a palliative stage of cancer treatment, aiming to provide local control or even downstaging of PM. A Phase III trial included patients with PM of upper GI cancer randomizing more than 200 patients between standard of care palliative chemotherapy and intermittent PIPAC [22]. Results of these studies are keenly awaited to solidify the justification for this potentially life-prolonging approach.

## Complications of PIPAC – Comparison with Systemic Chemotherapy

A review article published in 2019 from Alyami et al. [23] investigates four prospective and 16 retrospective PIPAC studies, which have thoroughly proven safety, feasibility, and tolerance of repeated PIPAC sessions. Intra- and postoperative grade 4 complications (Common Ter-

**Table 1.** Publications for PIPAC and CRC

| Retrospective | Patients, *n* | PIPACs, *n* | Mean PCI | Drug and dose | Histological Reg, *n* (%) | | OS | Conclusion |
|---|---|---|---|---|---|---|---|---|
| Ellebæk et al. [37] | 24 | 75 | 10.7 (1–30) | Oxaliplatin 92 mg/m$^2$ BSA | After 1. PIPAC | Reg: 13 (68)<br>SD: 4 (21) | 37.6 months (10.2–47) | Intraperitoneal administered oxaliplatin can induce objective tumor Reg |
| | | | | | After 2. PIPAC | Reg: 10 (67)<br>SD: 4 (27) | | |
| Gockel et al. [33] | 13 | 26 | 14 (2–27) | Oxaliplatin 92 mg/m$^2$ BSA | 3 (43) | | 10.1 months (1–16.3) | Ascites production could be controlled with PIPAC. Histopathological Reg reported previously could not be reproduced |
| Demtröder et al. [34] | 17 | 48 | 16 (±10)$^+$ | Oxaliplatin 92 mg/m$^2$ BSA | Complete response: 7 (50)<br>Major response: 4 (29)<br>Partial response: 1 (1)* | | 15.7 months | Repeated PIPAC with oxaliplatin can induce the Reg of pretreated pmCRC |
| Siebert et al. [31] | 134<br>CRC: 26 | 397 | 18 (0–39) | Oxaliplatin 92 mg/m$^2$ BSA | Not specified | | Not specified | PIPAC associated with bevacizumab is "safe, feasible and well tolerated" |

CRC, colorectal cancer; pmCRC, peritoneal metastasized colorectal cancer; SD, stable disease; Reg, regression; PCI, peritoneal cancer index. $^+$standard deviation instead of range. * After at least 2 PIPACs.

minology Criteria for Adverse Events) were observed in 3% of included patients within prospective studies. In retrospective studies, complications were slightly higher reaching 11% (intraoperative) and 6% (postoperative).

The almost absence of systemic toxicity is another PIPAC strongpoint as established by various independent groups studying systemic drug uptake, renal and hepatic toxicity, inflammatory response, among other factors [23–28]. Neither renal nor hepatic toxicity could be demonstrated owing to a minimal systemic drug uptake. Two studies did observe a transitory inflammatory response and Siebert et al. [29] reported how 4 out of 132 patients presented a severe hypersensitivity reaction during or immediately after the nebulization with cisplatin (platinum-based compound). Absence of systemic toxicity is of particular importance when comparing it with, i.e., toxicity from systemic cytotoxic chemotherapy. A subgroup analysis of the safety of ramucirumab in patients from western countries in the 2016 RAINBOW trial showed an incidence of 79.1% of adverse events grade 3 or higher in patients receiving ramucirumab and paclitaxel [30].

As PIPAC is part of a combined therapy embedded between two cycles of chemotherapy, the tolerance and safety applying this treatment regimen was assessed, especially while treating patients with monoclonal antibodies, such as bevacizumab or ramucirumab, which are often used as 2nd line chemotherapy in patients with colorectal or GC, respectively. The studies by Siebert et al. [31] and Feldbrügge et al. [32] demonstrated the feasibility and safety of this therapeutic regimen.

## PIPAC for Lower GI Cancer

*Indication*

So far PIPAC has been administered as a palliative therapeutic option in patients with irresectable pmCRC. Nowacki et al. [14] published a study in 2018 compiling information on 9 centers that carry out PIPAC. In total 832 interventions were registered. After GC, pmCRC was the second most common indication for PIPAC across all centers with 20.1% of the 832 interventions being carried out in these patients [14].

Specific clinical trials, which include the neoadjuvant phase, are needed to investigate the potential role of sequential PIPAC with or without palliative systemic chemotherapy in increasing response rates and creating local tumor control in patients with unresectable pmCRC. Trials focusing on PIPAC as an adjuvant therapeutic tool either for patients after CRS with or without HIPEC or in high risk for peritoneal recurrence are ongoing.

*Treatment Regimen*

The surgical approach and PIPAC application are standardized [14]. For intraperitoneal administration, there is a shortage of approved drugs. Cisplatin, doxorubicin, and oxaliplatin are used off-label for HIPEC,

**Table 2.** Trials registered at the NIH of the United States National Library of Medicine

| Trial number | Acronym | Design | Research question | Characteristics | | |
|---|---|---|---|---|---|---|
| | | | | main primary | drug and dose | status |
| NCT04475159 | NASPIT | Open label, single-arm, single center, phase II trial | BORR | Colorectal | Not specified | Not yet recruiting |
| NCT03246321 | CRC-PIPAC – ePIPAC-OX | Multicenter, open label, single-arm phase II | Feasibility, safety, tolerability, efficacy, costs, pharmacokinetics | Colorectal | Bidirectional<br>**IP**: oxaliplatin: 92 mg/m$^2$ BSA*<br>**IV**: leucovorin: 20 mg/m$^2$ BSA and bolus 5-fluorouracil:<br>400 mg/m$^2$ BSA | Completed |
| NCT03280511 | PIPAC-OPC3 CC | Nonrandomized, nonblinded phase II cohort study | FITC after resection and adjuvant chemotherapy | Colorectal | Oxaliplatin: 92 mg/m$^2$ BSA | Recruiting |
| NCT04329494 | – | Single-arm, phase I Single center | Dose escalation, efficacy, safety | Ovarian, uterine, appendiceal, **colorectal,** and gastric | Cisplatin, doxorubicin. Dose not specified | Recruiting |
| NCT03210298 | PIPACRegis | Multicentric, international, web-based prospective documentation | Chemoresistance of PM of various origins | All entities | – | Recruiting |
| NCT03868228 | – | Single group assignment | Efficacy | Colorectal | Oxaliplatin: 92 mg/m$^2$ BSA | Recruiting |
| NCT02604784 | PI-CaP | Single center, open label, phase I–II, nonrandomized, two-cohort | Feasibility, efficacy, safety, and ORR | Ovarian, gastric, and CRC s | **Cohort A**: cisplatin: 7.5 mg/m$^2$ + doxorubicin:<br>1.5 mg/m$^2$ or **oxaliplatin**: 92 mg/m$^2$<br>**Cohort B**: cisplatin + doxorubicin: from 15 mg/m$^2$ + 3 mg/m$^2$ to 100 mg/m$^2$ + 30 mg/m$^2$<br>or **oxaliplatin**: from 92 mg/m$^2$ to 300 mg/m$^2$ | Completed |

http://clinicaltrials.gov. with focus on colorectal cancer. Date last accessed: September 2, 2021. Search items: colorectal cancer and PIPAC. BSA, body surface area; IV, intravenous; IP, intraperitoneal; NIH, National Institute of Health; BORR, best overall response rates; FITC, free intraperitoneal tumor cells; ORR, overall response rate. * Repetitive electrostatic PIPAC.

PIPAC, and other catheter-based systems. Each PIPAC procedure was applied approximately every 6–8 weeks. Most of the standardized chemotherapeutic protocols included oxaliplatin (dosage of 92 mg/m$^2$) for pmCRC and less frequent the combination of cisplatin and doxorubicin (dosages of 7.5 and 1.5 mg/m$^2$, respectively) (Table 1) [33].

*Oncologic Outcome*

PM, in addition to the metastatic pattern, was found to be crucial for the prognostic heterogeneity of metastatic CRC. Demtröder et al. [34] demonstrated that repeated use of PIPAC with oxaliplatin resulted in Reg of pretreated pmCRC, reaching a median OS of 15.7 months after the first PIPAC in pmCRC.

PIPAC, as an additional tool of a multidisciplinary multimodal treatment regimen in pmCRC patients, may improve the oncological management of patients regarding tumor control and OS. Preliminary results of PIPAC seem to be promising for quality of life as well as treatment tolerance, which are important treatment endpoints in addition to prolonging survival in palliative care [35].

*Ongoing Clinical Trials*

Currently, there are seven registered studies for PIPAC in pmCRC (Table 2). Two studies (NCT03246321: CRC-PIPAC-ePIPAC-OX; NCT02604784: PI-CaP) already completed the recruiting phase. PIPACRegis is recruiting for prospective documentation of all PM entities as a multicenter, international, web-based study.

## PIPAC for Upper GI Cancer

*Indication*

In the PIPAC context, treatment for metastatic disease of the upper GI tract has only been studied in GC. The current indication for PIPAC in GC is for patients in a palliative situation, namely, synchronous, or recurrent

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**Table 3.** Trials registered at the NIH of the United States National Library of Medicine

| Trial number | Acronym | Design | Research question | Characteristics | | |
|---|---|---|---|---|---|---|
| | | | | main primary | drug and dose | status |
| NCT03304210 | PIPAC-Nabpac | Single-arm, phase I<br>Single center | Dose escalation, safety | Gastric, pancreas, breast, and ovarian | Paclitaxel (35–140 mg/m$^2$) BSA* | Completed |
| NCT01854255 | PIPAC-GA01 | Single-arm, phase II<br>Single center | Safety, efficacy | Gastric | Doxorubicin: 1.5 mg/m$^2$ BSA<br>Cisplatin: 7.5 mg/m$^2$ BSA | Completed |
| NCT03294252 | PIPOX-01 | Single-arm, phase I/II<br>Single center | Safety, efficacy, dose escalation | Gastric, colorectal | Oxaliplatin: 90–300 mg/m$^2$ BSA | Completed |
| NCT02604784 | PI-CaP | Single-arm, phase I/II<br>Single center | Feasibility, safety and efficacy, dose escalation | Gastric, colorectal, ovarian, peritoneal | Cisplatin: 7.5 mg/m$^2$ BSA + doxorubicin: 1.5 mg/m$^2$ BSA or oxaliplatin: 92 mg/m$^2$ BSA | Recruiting |
| NCT04000906 | Nab-PIPAC | Single-arm, phase Ib<br>Single center | Dose escalation, safety, efficacy | Pancreatic, GEJ, ovarian, peritoneal | Paclitaxel (7.5–70 mg/m$^2$) BSA$^+$<br>Cisplatin: 10.5 mg/m$^2$ BSA | Recruiting |
| NCT04047004 | PIPAC-OPC4 | Single-arm, phase I<br>Multicenter | Safety | Gastric | Cisplatin: 10.5 mg/m$^2$ BSA<br>Doxorubicin: 2.1 mg/m$^2$ BSA | Recruiting |
| NCT03172416 | – | Single-arm, phase I<br>Single center | Safety, dose escalation | Gastric | Oxaliplatin (45–150 mg/m$^2$) BSA$^‡$ [nivolumab: 240 mg IV] | Recruiting |
| NCT04329494 | – | Single-arm, phase I<br>Single center | Dose escalation, efficacy, safety | Ovarian, uterine, appendiceal, colorectal, and gastric | Cisplatin and doxorubicin. Dose not provided$^±$ | Recruiting |
| NCT04913662 | SNUBH_PIPAC_PTX | Single-arm, phase I<br>Single center | Dose escalation | Gastric | Paclitaxel: dose not provided | Recruiting |
| NCT04410887 | PISOXO | Single-arm, phase I<br>Single center | Efficacy | Gastric | Docetaxel: dose not provided | Not yet recruiting |
| NCT03100708 | PIPAC_01 | Prospective observational<br>Single center | Efficacy, QoL | Gastric, colorectal, pancreatic, ovarian, peritoneal | Cisplatin: 7.5 mg/m$^2$ BSA + doxorubicin: 1.5 mg/m$^2$ BSA or oxaliplatin: 92 mg/m$^2$ BSA | Recruiting |
| NCT04065139 | PIPAC EstoK 01 | Randomized, phase II<br>Multicenter | Efficacy, safety, QoL | Gastric | Cisplatin: 10.5 mg/m$^2$ BSA<br>Doxorubicin: 2.1 mg/m$^2$ BSA | Not yet recruiting |
| NCT04595929 | GASPACCO | Randomized control trial<br>Single center | Efficacy, safety, QoL | Gastric | Cisplatin: 7.5 mg/m$^2$ BSA + doxorubicin: 1.5 mg/m$^2$ BSA | Recruiting |

Information under http://clinicaltrials.gov. Doses provided are for intraperitoneal administration unless otherwise noted. GEJ, gastro-esophageal junction; IV, intravenous; NIH, National Institute of Health; MTD, maximal tolerated dose. * The PIPAC nab-pac study is designed to examine the MTD of albumin bound nanoparticle paclitaxel (nab-pac) administered with repeated PIPAC. Dosages: 35, 70, 90, 112.5, and 140 mg/m$^2$ BSA. $^+$ The Nab-PIPAC study is designed to determine the MTD of paclitaxel administered IP by PIPAC in concomitance with cisplatin. Dosages: 7.5, 15, 25, 37.5, 52.5, and 70 mg/m$^2$ BSA. $^‡$ The study registered under the number NCT03172416 is designed to evaluate the safety and tolerability of PIPAC using oxaliplatin. Dosages: 45, 60, 90, 120, and 150 mg/m$^2$ BSA. $^±$ In combination with other administered chemotherapeutics depending on main primary.

**Table 4.** Overview of ongoing and potential areas of basic and translational research related to aerosolized intraperitoneal drug delivery

| Research area | Potential applications | Literature examples |
|---|---|---|
| Pharmacokinetics and pharmacodynamics | Tissue penetration<br>Biodistribution | |
| Drug development | Novel anticancer drugs specifically designed for IP aerosol delivery<br>Nanoparticles<br>Lymphatic targeting | [42, 43] |
| Aerosol science | Aerosol transport, distribution, deposition | [44] |
| | Aerosol generation methods, device development | [45] |
| Physiology | Effects of peritoneal physical environment (pressure, humidity, pH, temperature) | [41] |
| Enhanced drug delivery | Electrostatic precipitation | [35] |
| | Hyperthermic aerosol delivery | [46] |
| | High intensity ultrasound | [47] |
| | Radiotherapy | [13] |
| Cancer research | Drug resistance mechanisms<br>Peritoneal and tumor microenvironment | |

PM as a sole metastatic site in the context of an unresectable disease. pmGC was the most common indication for PIPAC, namely 41.1% of interventions carried out in 9 centers [14]. According to Alyami et al. [23], an unfavorable histology (e.g., signet ring cell) would be a reason to suggest PIPAC earlier on in the treatment strategy and is currently under validation.

*Treatment Regimen and Ongoing Trials*

A widely accepted and therefore carried out treatment regimen for GC consists of a combination of cisplatin at a dosage of 7.5 mg/m$^2$ body surface area (BSA) and doxorubicin at 1.5 mg/m$^2$ BSA. There are currently three trials recruiting, where intraperitoneal administration of paclitaxel is to be studied (Table 3). An ongoing trial worth mentioning is evaluating PIPAC in an immediate postoperative adjuvant setting administering cisplatin and doxorubicin directly after carrying out a radical gastrectomy with D2-lymph node dissection. Patients will have received four cycles of neoadjuvant chemotherapy with FLOT (Docetaxel, Oxaliplatin, Leucovorin, and 5-FU) previously. Another trial by Reid et al. [36] examines the usage of PIPAC in the standard neoadjuvant protocol for patients with GC prior gastric resection using oxaliplatin at 92 mg/m$^2$ BSA.

*Oncologic Outcome*

A true oncologic outcome due to PIPAC alone is, under the current regulations and permissions, difficult to assert. PIPAC's value is best appreciated under these circumstances, as it can be administered alternating with systemic chemotherapy. Ellebæk et al. [37] recently published a study where histological Reg was seen in 36% of the patients, which showed stable disease right after the first PIPAC procedure with a significantly reduced amount of ascites. The reported median OS was 11.5 months from the time of PM diagnosis, while the Lyon group recently published OS rates of up to 19.1 months [37, 38]. Repetitive PIPACs, specifically 3 or more, with low-dose cisplatin/doxorubicin is an independent prognostic factor for prolonged OS (from 9 to 16 months) according to Sindayigaya et al. [39].

## Translational Research and Future Perspectives

As a novel locoregional drug delivery method, PIPAC offers multiple opportunities for basic and translational research (Table 4). In contrast to pulmonary aerosolized drug delivery, very little is currently known on the physiology and basic mechanisms of PIPAC. Worldwide, several centers have developed tools for the preclinical study of intraperitoneal aerosolized drug delivery. These include computational models, in vitro models, isolated organ models such as the inverted bladder, and animal models (mouse, rat, pig, sheep) [40–52].

In addition, PIPAC offers some exciting opportunities for exploring novel synergies between systemic treatment and IP aerosol delivery. Examples include the use of IP aerosolized oxaliplatin, which is known to induce immunogenic cell death, in conjunction with systemic immune checkpoint inhibitors [53]. Also, PIPAC could allow to engineer the tumor microenvironment of peritoneal cancers by using immune modulators or targeted therapies against angiogenesis, epithelial to mesenchymal transition, or cancer-associated fibroblasts [54].

## Conclusion

The evidence for PIPAC as a component of the multimodal treatment in patients with PM of GI cancer is growing. The main advantages are the low treatment-associated morbidity, and the increased pathologic Reg even in patients with several lines of chemotherapy. Currently, multiple translational and clinical studies are evaluating the oncologic benefit as a palliative, neoadjuvant, or adjuvant treatment.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

S.G.-K., M.E.A.V., W.C., B.R., and A.B.: Concept and design; analysis; drafting and revising the manuscript; and final approval.

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