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PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) FOR UNRESECTABLE PERITONEAL METASTASES. FEASIBILITY, SAFETY AND EFFICACY OUTCOMES

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Abstract

RECENTLY, a novel method for chemotherapy administration inside the abdominal cavity gained wide attention among surgical oncologists dealing with peritoneal surface malignancies. Based on laparoscopy, Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) is a drug delivery system designed to overcome the known hurdles of intraperitoneal chemotherapy. Preclinical data suggest that the aerosol drug that PIPAC creates and the increased intraabdominal pressure obtained during laparoscopy provide highly effective distribution of cytotoxic compounds into tumor nodules. Several studies have documented the favorable safety profile and promising clinical outcomes of repetitive PIPAC in different types of peritoneal malignancies.

The present research assessed the feasibility, safety, and antitumor activity of current PIPAC drug treatment schedules through a systematic review of the literature and two retrospective cohort studies on gastric cancer and pancreatic or biliary tract cancer. In addition, it includes the study protocol of the first phase II trial exploring nabpaclitaxel PIPAC in combination with gemcitabine/nabpaclitaxel systemic chemotherapy.

The systematic review of the literature of 668 patients showed an overall pathological response rate of 44% and a severe adverse events rate of 10%.

In the single-center cohort of 28 consecutive patients affected by gastric cancer peritoneal metastases undergoing cisplatin/doxorubicin PIPAC and systemic chemotherapy, the pathological response rate, in the Intention-to Treat population, was 29%, with a 7% rate of severe adverse events and 1.7 PIPAC procedures per patient.

In the 20 patients cohort of pancreatic and biliary tract cancer PM undergoing oxaliplatin or cisplatin/doxorubicin PIPAC, the pathological response rate was 42% and 62%, respectively. Concerning safety, there was just one intraoperative bowel perforation and no severe postoperative adverse events.

PIPAC was feasible and safe, with the pathological response observed suggesting a high antitumoral activity. Despite such encouraging outcomes, the present research, as well as most of the literature, is affected by several biases and the resulting evidence is controversial. More phase I and II trials might be necessary to fill this knowledge gap.

Summary

PERITONEAL metastases remain an unmet medical need. The renewed optimism for locoregional treatment of peritoneal disease brought by the successes of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) prompted the research efforts in this field. However, the achievements obtained for mucinous appendiceal neoplasms and malignant peritoneal mesothelioma were paired by small increments of benefit in other indications, at least concerning gastric and colorectal cancers. Furthermore, cytoreductive surgery can be offered only in restricted indications with limited disease extension, leaving a large number of patients without a potentially beneficial locoregional treatment on peritoneal metastases.

Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) was conceived to address this need and overcome the hurdles inherent to CRS and HIPEC. Being based on a laparoscopy, it is a minimally invasive procedure that can be repeated several times, allowing multiple locoregional chemotherapy cycles. Furthermore, laparoscopic inspection and biopsies of peritoneal disease during subsequent procedures allow a continuous response evaluation of nodules and surviving cell lines. According to preclinical evidence, the increased intraabdominal pressure obtained during laparoscopy together with the drug aerosolization provided by PIPAC should grant effective distribution of cytotoxic compounds into tumor nodules. Several trials have documented the favorable safety profile and promising clinical results in different types of peritoneal malignancies.

The present research was designed to assess the feasibility, safety, and antitumor activity of PIPAC.

First, a systematic review with a meta-analysis of 668 patients and 1480 PIPAC procedures according to the PRISMA guidelines was carried out. The search strategy led to the identification of 252 potentially relevant records plus 9 which were retrieved from cross-reference. After screening and eligibility processes, 21 studies were included in the quantitative analysis. The overall access failure rate was 5%, ranging from 0% to 14%. The rate of severe adverse events, Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher, was 10% with 7 deaths (1%) occurring in the 30 postoperative days across all studies. The overall pathological analysis provided 43.7% of

responses (95% CI: 36.29-51.26) in the Intention-To-Treat (ITT) population (Paper I).

Second, a retrospective analysis of a prospectively maintained database concerning patients affected by gastric cancer peritoneal metastases undergoing cisplatin/doxorubicin PIPAC and systemic chemotherapy was performed. Forty-six PIPAC procedures were administered to 28 consecutive patients, with a mean of 1.7 PIPAC procedures per patient. The median time to resume systemic chemotherapy after PIPAC was 6 days (range 4–7). Concerning safety, two grade 3–4 CTCAE toxicity events and one intraoperative complication were recorded. Thirteen patients (46%) repeated PIPAC. A pathological response was recorded in 28.6% of patients (ITT) (Paper II).

Third, 20 consecutive patients with pancreatic and biliary tract cancer and PM treated at two European referral centers for peritoneal surface malignancies were retrospectively analyzed. The cohorts receiving oxaliplatin or cisplatin/doxorubicin PIPAC obtained a pathological response rate of 42% and 62%, respectively. Concerning safety, there was just one intraoperative bowel perforation and no severe postoperative adverse events (Paper III).

In addition, an evaluation of the prognostic value of an immunonutritional assessment on the feasibility, safety, response, and survival of patients undergoing PIPAC was carried out. Fifty-one patients were evaluated, of which 30 (58%) underwent multiple PIPAC cycles, with a pathological response rate of 55%. Prognostic Nutritional Index (PNI) and Neutrophil-to-Lymphocytes Ratio (NLR) predicted completion of more than one PIPAC cycle, with a cut-off of 36.5 and 4.8, respectively. Based on a CT scan-derived body composition assessment, Muscle Attenuation (MA) and Body Fat Tissues (BFT) were associated with pathological response. In multivariate Cox regression analysis, only the presence of a low PNI (HR 2.41, 95% CI 1.08-5.46) was significantly associated with a worse OS (Paper IV).

Finally, a phase II open-label study to evaluate the antitumor activity of nabpaclitaxel PIPAC combined with endovenous gemcitabine-nabpaclitaxel was designed (Paper V). The primary endpoint is the Disease Control Rate (DCR), defined as the combined incidence of Complete Response (CR), Partial Response (PR), and Stable Disease for ≥ 16 weeks (SD), according to the RECIST criteria v. 1.1. The secondary outcomes include safety, pathological tumor response, time-to-progression and overall survival, QoL, nutritional status, and pharmacokinetics of nabpaclitaxel-PIPAC. The treatment schedule comprises three courses of combined chemotherapy, each consisting of II cycles of endovenous gemcitabine/nabpaclitaxel and one nabpaclitaxel-PIPAC. Hence, each patient will receive a total of VI cycles of systemic chemotherapy and three PIPAC administrations. Gemcitabine/nabpaclitaxel is administered according to the standard doses for metastatic PM (1000/125 mg/m2), while intraperitoneal nabpaclitaxel at the dosage of 112.5 mg/m2, based on a recent dose-finding trial. Simon's two-stage design is used for sample size calculation with 12 patients enrolled in the first stage and 26 in the second one if six or more patients obtain CR/PR/SD in the first stage (power 80%). The study will be positive with an alpha error =0.1, whether 19 or more patients will experience CR/PR/SD (Paper V).

PIPAC may be considered a feasible and safe procedure. The observed pathological response supports the presence of antitumor activity of current regimens on PM. Despite these encouraging results, according to current evidence, conducting late-stage trials might be premature. Several questions regarding doses, schedules, and the combination with systemic chemotherapy remain unattended and might require more phase I and II trials.

CHAPTER 1

Background, Rationale and Objectives

1.1 Background and Rationale

1.2 Objectives

1.1 Background and Rationale

Peritoneal metastasis (PM) has long been regarded as an incurable stage of tumor malignancies. Although systemic chemotherapy has achieved remarkable progress in treating several distant metastases, it has had less success in controlling PM, which may be due to a limited drug availability within the abdominal cavity[1,2].

Since the 1980s, the hypothesis emerged that PM is a locoregional disease and might require a locoregional treatment[3,4]. The peritoneal cavity can be considered as a separate compartment in which its lining, the peritoneum, offers relative protection against metastatic tumor spread [5] while providing a dose intensification due to the relative transport barrier it creates[6]. On these premises, renewed treatment options have evolved for isolated peritoneal dissemination of ovarian cancer, gastrointestinal tumors, and primary peritoneal malignancies.

Indeed, encouraging results have been obtained by using a combined therapeutic strategy based on cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)[7]. Such an approach consists of the complete removal of all peritoneal disease by multiple visceral resections and peritonectomy procedures followed by the administration of high-temperature antiblastic solution inside the abdominal cavity to address the residual microscopic disease[8].

Several studies demonstrated a pharmacokinetic advantage of the intraperitoneal delivery of chemotherapy. The peritoneal-plasma barrier and the first-pass through the liver by the portal system drainage provide high concentration gradients of antiblastic drugs between the peritoneal cavity and the systemic circulation[9]. In addition, hyperthermia has both an intrinsic antitumor activity[10] and the ability to increase the efficacy of various chemotherapeutic compounds[11,12].

However, despite considerable advances, today only a minority of PM patients can expect a significant improvement in their prognosis[13]. Indeed, CRS and HIPEC are indicated only in cases of confined PM, and many patients are excluded from potentially beneficial locoregional treatments, being offered only palliative systemic chemotherapy or best supportive care instead.

Recently, Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) has emerged as a viable method for intraperitoneal drug administration. PIPAC is a novel drug-delivery system of low-dose chemotherapy as a pressurized aerosol, inside the abdominal cavity, during a laparoscopy. It combines the theoretical pharmacokinetic advantages of intraperitoneal chemotherapy (ie, low toxicity, high intraperitoneal concentration, low systemic concentration) with the principles of the aerosol (homogeneous intraperitoneal distribution and deeper tissue penetration). Due to its minimally invasive nature and safety profile, it seems to be a promising tool for repetitive chemotherapy administration for the locoregional treatment of PM.

There is a body of evidence suggesting that PIPAC offers a superior pharmacological profile over conventional intraperitoneal lavage, based on in vitro, *in-vivo*, and *ex-vivo* studies[14–16].

According to the reports published by the same study group, the chemo-aerosol formed during the PIPAC procedure behaves in a "gaseous" manner, which, in turn, ensures a homogeneous distribution of cytotoxic compounds within the intraperitoneal space, enhancing the extent of peritoneal surfaces drug coverage[14,15,17].

A capnoperitoneum of 12 mmHg generated during PIPAC is also thought to counteract the elevated pressure within tumor nodules, resulting in a superior drug penetration depth within peritoneal nodules, as compared to peritoneal lavage[14,16].

In addition, due to its minimally invasive nature, PIPAC can be repeated several times, allowing multiple locoregional chemotherapy cycles and continuous pathological response evaluation on surviving cell lines.

The literature published so far collected some non-comparative clinical studies assessing the feasibility, safety, tolerability, and preliminary antitumor activity of PIPAC with various drugs for peritoneal metastases (PM) of various origins[18].

The unmet need of a large population of patients affected by peritoneal metastases which are not candidates for CRS and HIPEC prompted the present research aiming at the evaluation of this promising technique of intraperitoneal chemotherapy administration.

1.2 Objectives

The main objective of this thesis was to assess whether various chemotherapeutic agents administered through PIPAC would exhibit an antitumor activity on peritoneal metastases of various origins. Secondary objectives were to assess the feasibility and safety of PIPAC.

Specific objectives:

- To analyze the data published in the literature concerning anti-tumoral activity, the safety and the feasibility of PIPAC for the treatment of PM of various origins (Paper I);
- To evaluate the antitumor activity, the safety and the feasibility of cisplatin-doxorubicin PIPAC and its combination with systemic chemotherapy for the treatment of gastric cancer PM (Paper II);
- To evaluate the antitumor activity, the safety, and the feasibility of oxaliplatin or cisplatin-doxorubicin PIPAC for the treatment of pancreatic and biliary tract cancer PM (Paper III);
- To investigate the impact of body composition and immunonutritional status on PIPAC outcomes on gastrointestinal PM patients (Paper IV);
- To investigate the antitumor activity, the safety, and the feasibility of nabpaclitaxel PIPAC in combination with current systemic chemotherapy for the treatment of pancreatic PM (Paper V).

CHAPTER 2

Materials, Patients and Methods

2.1 Ethical considerations

2.2 Materials, Patients and Methods

2.1 Ethical considerations

All studies were approved by the local ethics committee and informed consent was obtained from each patient. All studies were conducted at the Fondazione Policlinico A. Gemelli - IRCCS on the basis of a formal agreement on this Ph.D. research project with the University of Palermo.

2.2 Materials, Patients and Methods

Data Collection Methods

An e-CRF was designed to collect clinical data of patients undergoing PIPAC (Paper II-IV). The software allowed direct data storage on a Microsoft Excel (Microsoft Corp, Redmond, WA; USA) database. This design allowed data to be collected prospectively in all studies and for the retrieved information to be homogeneous. Patient variables included age, gender, American Society of Anesthesiology (ASA) score, Eastern Cooperative Oncology Group Performance Status (ECOG PS), surgical history, primary tumor, date of diagnosis, date of diagnosis of PM, previous lines of chemotherapy for PM. Laboratory analysis included hematologic profile, serum chemistry profile; if possible, abdomen-CT scan images, taken within one month before the PIPAC procedure, were collected. The following perioperative data were recorded: date of the procedure, PIPAC cycle, drug used, no-entry in the abdominal cavity, the presence of adhesions, peritoneal cancer index (PCI), ascites volume, intraoperative complications, operating time, biopsies taken, date of discharge, readmission, the reason for readmission, 30-days postoperative adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events classification version 4.0 (CTCAE). The pathological response was assessed and recorded according to the Peritoneal Regression Grading Score (PRGS)[19]. Follow-up included the reason for stopping PIPAC, the date of progression, the date of death. Each patient was recalled and followed up to death whenever possible.

Study Procedures

PIPAC procedure

PIPAC is performed in a standard operating room (OR) with laminar airflow, under general anesthesia and antibiotic prophylaxis is regularly administered. Before and during each procedure, a checklist is used to ensure all materials are available and the safety protocol is strictly followed. The operating personnel wears appropriate chemotherapy-protective clothes. The Hasson technique is used to insert a 10 mm blunt tip balloon trocar through the abdominal wall. Though the preferred entry site is the left flank, this decision is variable upon evaluation of the abdomen and previous surgery scars. After obtaining a normothermic 12 mmHg capnoperitoneum, a second 5 mm blunt tip balloon trocar is inserted under direct vision and exploratory laparoscopy is performed. Only if needed, careful adhesiolysis may be performed to create sufficient working space. Ascites volume is documented, evacuated, and sent for cytology. Quadrants with adhesions are recorded, the peritoneal cancer index (PCI) is registered and photographic images are taken throughout the peritoneal cavity. Four samples of peritoneal metastases, preferably from different areas, are biopsied and sent for pathologic examination.

PIPAC setup installation is depicted in Figure 1. A nebulizer (CapnoPen, Capnomed GmbH, Villingendorf, Germany) connected to a high-pressure injector (Medrad Mark V Angiography Injection System, Medtron AG, Saarbruker, Germany) is inserted through

the 10 mm trocar and secured with its nozzle just inside the peritoneal cavity at a safe distance from visceral organs. A 5 mm laparoscopic camera, inserted through the other ancillary trocar, is secured by a laparoscope holder in a way it permanently visualizes the nebulizer. The trocar valve connected to the CO2 insufflation remains open, while the other trocar valve is connected to a closed aerosol waste system (CAWS) and it is kept closed. The CAWS consecutively consists of a smoke evacuation filter, a water seal drainage system, an infant-pediatric electrostatic microparticle filter, and the air waste system of the hospital. Hence, the chemotherapy drugs can be uploaded into the angiographic injector. The preoperatively prepared syringe containing the chemotherapy solution is vented, placed in the angiographic injector, and connected to the nebulizer with a saline-flushed high-pressure line protected by a plastic camera cover. A leak-free capnoperitoneum is ensured by zero flow of CO_2. If necessary, the external fascia may be additionally sutured and Luer lock caps may be placed on balloon valves of trocars. The angiographic injector is set at a flow rate of 30 ml/min and a maximum pressure of 200 psi. Vital parameters of the patient and a real-time laparoscopy are displayed on two screens outside the OR and general anesthesia is ensured for at least another 40 min. A checklist is used to confirm that all aforementioned steps have been adequately taken. After completion of the checklist, the entire operating personnel leaves the OR. Chemotherapy drugs are then aerosolized through the nebulizer by remote-controlled activation of the angiographic injector from outside the OR. After the complete formation of the chemotherapy-containing aerosol, the capnoperitoneum is maintained for another 30 min. During this phase, the patient and the procedure are monitored on the screens through the window of the OR.

After 30 min, the surgeon enters the OR, closes the trocar valve connected to the CO2 insufflation, and opens the trocar valve connected to the CAWS. After the complete evacuation of the aerosol, the nebulizer is removed, and the entire operating personnel enters the OR. In case no bleeding or perforations are observed, instruments are removed, and incisions are closed with absorbable sutures. All instruments and materials are directly disposed of in chemotherapy waste bins. Any procedure-related mistake or technical mishap during PIPAC is recorded directly after the occurrence.

After PIPAC, the patients are admitted to the general surgical ward. To relieve postoperative pain, they receive paracetamol (1 g, three times per day). To minimize postoperative nausea and vomiting, metoclopramide is given, upon request.

Standard postsurgical clinical evaluations are performed a few hours after the procedure and on every postoperative day. Blood is drawn for bone marrow, liver, and kidney functions, albumin, and C-reactive protein on the first postoperative day. If the postoperative period is uneventful, the patients are discharged on the second postoperative day.

PIPAC chemotherapy regimens and schedules

The PIPAC schedule in monotherapy consists of three administrations at intervals of 6 to 8 weeks.

In the case of a combination of intraperitoneal and systemic chemotherapy, the following schedule is observed: II systemic chemotherapy cycles followed by one PIPAC

administration after two weeks. Then, a one-week interval and then II systemic chemotherapy cycle followed by one PIPAC cycle, until three PIPAC cycles have been completed. Up to a one-week delay on top of scheduled intervals is considered acceptable.

The following drugs and dosage were administered through PIPAC in the studies: a combination of cisplatin 7.5 mg/m2 in 150ml NaCl solution and doxorubicin 1.5 mg/m2 in 50 ml NaCl solution (Paper II and Paper III) or oxaliplatin 92 mg/m2 in 200ml of 5% glucose solution (Paper III). Nabpaclitaxel 112.5 mg/m2 diluted in 200 ml of NaCl 0.9% solution is described in the study protocol (Paper V).

Paper I

Evidence Acquisition

Search strategy

This systematic review and meta-analysis were designed, conducted, and reported according to the PRISMA statement. A systematic search of the PubMed, Scopus, Crossref, and Google Scholar databases (up to February 2019) was conducted to identify all prospective or retrospective case series, phase I, II, or III clinical trials. Also, abstracts from the leading conference proceedings that contained the words “PIPAC” or “aerosol chemotherapy” were included.

Records were screened to exclude duplicated publications from search strategy, not pertinent papers, book chapters, and articles not in English. Publications were reviewed to assess duplication of the study population based on the participating institutions and the period of presentation of patients. Then, we performed cross-reference searches of these articles to identify further publications. Literature search, screening, study selection, and data extraction were carried out independently by two investigators on the same predefined format. Divergences were resolved by a third reviewer.

Inclusion criteria, study selection, and data extraction

Inclusion criteria for quantitative synthesis were: 1) prospective or retrospective case series, phase I, II, or III clinical trials; 2) studies that involved at least three patients treated with PIPAC; 3) reporting in English; 4) reporting of pathological response using any tumor regression grading system (including but not limited to Mandard, Dworak or the Rödel grading system or the peritoneal regression grading score system [PRGS])[19–21]. Aiming to evaluate PIPAC pathological antitumor activity, the pathological response report was an inclusion criterion. The abstracts of eligible studies were screened and articles potentially fulfilling the inclusion criteria were retrieved in full.

Extracted data included the following:

- authors, year and study design;
- sample size, comprising the number of patients treated and number of PIPAC

cycles administered;

- primitive tumor and drugs used;
- access failures;
- number of patients completing at least I, II, and III PIPAC cycles;
- toxicity events were assessed according to Common Terminology Criteria for Adverse Events (CTCAE), v. 4.014 (if reported according to other grading scales, data were adapted as appropriate);
- causes of postoperative death;
- combined systemic chemotherapy administrations;
- pathological responses including complete response and major response or partial response using the PRGS system or other pathological regression systems (TRG Mandard, etc.);
- overall survival (OS).

Statistical Methods

Descriptive statistical analysis for quantitative and qualitative data according to medians, interquartile ranges (IQR) or ranges, and rates as convenient was used. The median pathological response rate was calculated on the intention-to-treat (ITT) population (patients receiving at least one cycle of PIPAC). For pathological response outcomes included in the meta-analysis (ITT population), cumulated, and weighted data were considered by taking into account each study sample, and estimates were performed for the whole population and subgroups based on PM origin. Statistical heterogeneity between the studies was assessed using Cochran's Q statistic and inconsistency was quantified with the Higgins i2 statistics. A p-value <0.1 for a $\chi 2$ value or $i2>50$ was considered indicative of heterogeneity. However, considering the inclusion of high unbalanced data extrapolated by retrospective and non-randomized trials, it was decided to calculate the combined response rates using a derSimonian and Laird random-effects model (independently by heterogeneity tests results) to give a more conservative estimate (i.e. with wider confidence interval). Data were analyzed with the statistical package for the social sciences (SPSS) for Windows Software (v. 11.0.1; SPSS inc., Munich, Germany).

Paper II

Patients and Methods

A retrospective analysis of all consecutive patients affected by gastric cancer peritoneal metastasis undergoing PIPAC administration from September 2017 to September 2019 was performed. The indication was given by an interdisciplinary tumor board on an individual basis, taking into account the Eastern Cooperative Oncology Group Performance Status (PS-ECOG), previous chemotherapy lines and response to therapy,

number and type of previous surgeries, clinical evaluation of abdominal accessibility, disease extension on CT scan, and individual will. As a general rule, patients with unresectable peritoneal metastasis who had completed at least three months of front-line palliative chemotherapy were considered eligible. In cases of limited parenchymal and node involvement, only patients with stable extraperitoneal disease were included. Patients were enrolled to receive three PIPAC cycles.

The antitumor activity analysis was conducted in those undergoing at least two PIPAC procedures by the evaluation of variation of ascites volumes, modification of the Peritoneal Cancer Index (PCI), and pathological response based on the Peritoneal Regression Grading Score (PGRS)[19] for each PIPAC cycle. The safety analysis included intraoperative complications and post-operative toxicity according to the CTCAE v4.0 (Common Terminology Criteria for Adverse Events version 4.0).

Survival was assessed, both in the overall population and in those who underwent more than one PIPAC procedure, considering the time interval from the date of the first PIPAC procedure to the date of death or last follow-up visit. Survival was assessed in a Kaplan–Meier curve with SPSS Statistics, version 26.0 (IBM, NY, USA).

Paper III

Patients and Methods

A retrospective analysis of consecutive patients affected by PM from PDAC and CC, attempting PIPAC treatment from August 2016 to May 2019 was conducted in collaboration with Institut du Cancer de Montpellier, Montpellier, France.

Chemotherapy agents administer with PIPAC were the combination of cisplatin 7.5mg/m2 in 150ml NaCl solution and doxorubicin 1.5 mg/m2 in 50 ml NaCl solution or oxaliplatin 92mg/m2 in 200ml of 5% glucose solution. Antiblastic agents were chosen based on previous drug exposure and response to therapy. Oxaliplatin was given in the case of a response to systemic folinic acid, fluorouracil, oxaliplatin (FOLFOX) or folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) or a poor response to gemcitabine ± cisplatin. Otherwise, PIPAC cisplatin/doxorubicin was preferred if a good response was documented with gemcitabine ± cisplatin or inadequate response or severe side effects to oxaliplatin-based systemic chemotherapy.

The feasibility assessment was carried out on entry-related issues during laparoscopy, including access rate and entry complications, and the number of completed PIPAC cycles. Safety and toxicity were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The antitumor analysis was conducted by first to last procedure comparison in the population undergoing at least two PIPAC administrations. The antitumor activity was evaluated on ascites volume, peritoneal cancer index (PCI), and pathological response through the Peritoneal Regression Grading Score (PRGS)[19], considering the mean and the highest score of biopsies. The rate of pathological regression was calculated on those who underwent at least two PIPAC cycles. Overall survival (OS) was computed from the date of both first PIPAC administration and peritoneal disease diagnosis in a

Kaplan–Meier curve with SPSS Statistics, version 26.0 (IBM, NY, USA).

Paper IV

Patients and Methods

A retrospective analysis of the clinical data of patients undergoing PIPAC for PM of gastrointestinal origin between September 2018 to May 2020 was conducted. In addition, starting from laboratory data stored, the following parameters were calculated: PNI[22]: ALB [g/l] + 0.005 × LYM, NLR: NEU/LYM, and PLR: PLT/LYM. At baseline, a complete nutritional evaluation, including weight, height, Body Mass Index (BMI), was carried out. CT scans prior to the PIPAC procedure (within one month) were analyzed for body composition assessment. Concerning the pathological response the Peritoneal Regression Grading Score (PRGS) was used and any reduction of the PRGS was considered a response to treatment.

CT-derived Body Composition Parameters

A specific image analysis software (SliceOmatic v5.0, Tomovision, Montreal, Canada) was used to examine CT images, by an operator trained in musculoskeletal anatomy, to define different tissues, according to the following Hounsfield Unit (HU) thresholds: -29 to +150 for muscle, -190 to -30 for Intermuscular Adipose Tissue (IMAT), -150 to -50 for Visceral Adipose Tissue (VAT), and -190 to -30 for Subcutaneous Adipose Tissue (SAT). Skeletal muscle area (SMA) was analyzed on a single axial slice at the third vertebral level aiming to include the following muscular groups: psoas, erector spinae, quadratus lumborum, transversus abdominis, external< and internal obliques, and rectus abdominis. Muscle Attenuation (MA) was obtained by the mean HU of SMA. Tissue boundaries were manually corrected as needed. Normalizing the previously measured parameters by height squared, Skeletal Muscle Index (SMI), Visceral Adipose Tissue Index (VATI), and Subcutaneous Adipose Tissue (SATI) were obtained, while the Total Fat Area (TFA) was calculated adding all the fat tissues. According to previously published studies on PM patients[23,24], 52.4 cm2/m2 for men and 38.5 cm2/m2 for women were used as cut-off values to define low-SMI patients.

Statistical Methods

The objective of this study was to describe the immunonutritional status of patients undergoing PIPAC and to assess its relation with procedure-related, oncological, and survival outcomes. In particular, the immunonutritional variables related to the following endpoints were explored: receiving multiple PIPAC cycles, PIPAC-related adverse events, pathological response on PM biopsies, and Overall Survival (OS). Kolmogorov-Smirnov test was used to assess normal distribution. Continuous variables were expressed as median (25th and 75th percentiles), categorical ones as number (percentage). Wilcoxon rank-sum test was used to assess differences between two groups; Chi-square or Fisher Exact test was appropriately used for categorical variables. ROC curves were used to find the cut-off of the parameters statistically significant at univariate analysis, reporting area

under the curve (AUC), and cut-off, where necessary. OS was calculated using Kaplan-Meier curves and differences between them were assessed through the Log-Rank test. All significant parameters at univariate analysis ($p<0.05$) were used to construct a Cox proportional regression analysis. Statistical analysis was performed using STATA® Software (Version 14.0, Stata Corporation; College Station, TX, USA).

Paper V

Patients and Methods

This is a monocentric prospective, open-label, phase II study aiming to test the combined treatment of intraperitoneal nabpaclitaxel administered through PIPAC and endovenous nabpaclitaxel-gemcitabine chemotherapy for the treatment of pancreatic cancer peritoneal metastases. The study received the approval of the Italian drug agency (AIFA) (Approval Code: 2021-002539-51 SC 22540). The main objective is to evaluate the antitumoral activity of this combined treatment in terms of Disease Control Rate (DCR) (i.e. patients experiencing Complete Response, Partial Response, Stable Disease for ≥ 16 weeks) according to RECIST criteria v. 1.1. The secondary objectives include the evaluation of the feasibility, the safety, a further assessment of the antitumoral activity, the measurement of the overall and progression-free survival, and the evaluation of QoL through the QLQ-C30 questionnaire. Furthermore, the study aims at monitoring the patients' nutritional status during the treatment and correlating the clinical outcomes to translational research. A total of 38 patients affected by pancreatic carcinoma with peritoneal metastases undergoing first-line metastatic systemic chemotherapy will be enrolled within 24 months.

Each patient is scheduled for three combined courses of endovenous chemotherapy nabpaclitaxel-gemcitabine 125/1000 mg/m2 and nabpaclitaxel-PIPAC 112,5 mg/m2 within 27 weeks (Figure 2). Each combined course lasts 9 weeks and is constituted by two 28-day cycles of systemic chemotherapy (three administrations per cycle: days 1.8 and 15) and one cycle of PIPAC administered within 10 ± 3 days from the last administration of the second systemic cycle.

Statistical Methods

Simon's two-stage design was used to calculate the sample size for this trial 79. With a Power of 80%, P0= 40% and P1= 60%, 12 patients will be enrolled in the first stage; with 6 or more patients experiencing CR/PR/SD, at this stage, another 26 patients will be enrolled in the second stage. The study will be considered positive with an alpha error =0.1, whether 19 or more patients will experience CR/PR/SD. The planned duration of the study is 36 months.

Concerning the analysis of the primary endpoint, the DCR, all time-points responses observed while on study treatment and during the EOT visit will be included in the derivation. The ratio of the rate and its 95% CI will be presented.

Safety, feasibility, and QoL endpoints will be reported by descriptive statistics. PFS and

OS will be evaluated by survival curves using the Kaplan-Meier method. Median times and associated 95% confidence intervals will also be provided. Continuous data will be summarized using the number of available data, mean, standard deviation, median, minimum, Q1, Q3. Categorical data will be summarized using the number and percentage of patients.

CHAPTER 3

Results

Paper I

Our search strategy led to the identification of 252 potentially relevant records. Based on selection criteria, 119 publications were considered for screening, 92 papers were assessed for inclusion in the final analysis, and 21 were evaluated in the quantitative analysis. Figure 3 depicts the literature evidence acquisition and synthesis.

A total of 668 patients who underwent 1480 PIPAC cycles across the 20 studies were included in the overall analysis with a median of 26.5 patients per study (interquartile range [IQR]: 16.5-35) (Table 1). A median PCI of 16.3 (IQR: 10-26.6) resulted from the pooled analysis. Six studies reported results on a heterogeneous cohort of patients, five studies only on gastric cancer (GC), four on ovarian cancer (OC), tubal cancer (TC) or primary peritoneal cancer (PPC), two on pancreatic cancer (PAC), one on hepatobiliary cancer (HBC), one on both PAC and HBC, one on colorectal cancer (CRC), and one on malignant mesothelioma (MM).

The overall access failure rate, calculated as the proportion of access failures over the number of PIPAC administered, was 5%, ranging from 0% to 14%. The overall rate of patients completing II PIPAC cycles was 59% (IQR: 48-76%), while the overall rate of those completing at least III PIPAC cycles was 29% (IQR: 26-53%).

Data regarding treatment-related toxicity were reported by all studies but one[25]. Severe toxicities were infrequent with an overall grade 3 and 4 adverse events rate of 8% and 2% respectively. A total of seven deaths were reported across all studies within the first 30 postoperative days, which gives an overall rate of 1%. Deaths were attributed to progressive disease in three cases (two cases related to bowel obstruction), to acute renal failure in two more cases, and to cardiopulmonary decompensation consequent to ascites removal in the remaining two patients.

All trials reported details of pathological response rate as it was an inclusion criterion, which was reported according to the PRGS system in seven cases and through other systems in the remaining 14 cases. Overall pathological response rate provided a 43.70% median response to therapy (95% CI: 36.29-51.26) in the ITT population and 65.82% in those who received more than one PIPAC (95% CI: 54.40-77.21) (Figure 4)[16,25–43]. The overall pooled survival was 11.9 months, ranging from 2.8 to 26.6 months (Table 1)[16,25–43].

A subgroup analysis based on the primary tumor was performed. The pooled pathological response rate (ITT) for gastric cancer PM based on five studies and 203 patients was 38.96% (95% CI: 32.34-45.78)(Figure 5A)[25,27,36,40,43]. Concomitant systemic chemotherapy was administered to 70% of patients.

The corresponding figure for ovarian cancer PM based on 4 studies and 103 patients was 46.20% (95% CI: 36.21-56.34), without any reported combined systemic chemotherapy administration (Figure 5B)[28,32,38,39].

The pooled pathological response rate (ITT) for pancreatic cancer PM based on three studies and 31 patients was 45.54% (95% CI: 23.24-68.82) with 23% of the patients undergoing combination with systemic chemotherapy (Figure 5C)[34,35,44].

Paper II

A total of 26 patients affected by gastric cancer PM received 46 PIPAC procedures, with a mean of 1.7 PIPAC procedures per patient. All patients received the cisplatin/doxorubicin combination. The median age was 50 years old (38–79 years) and 16 patients were female (57%). Demographic characteristics and oncological data are listed in Table 2. In two cases the access to the abdominal cavity was not feasible, due to diffuse neoplastic adhesions, with one attempt being complicated by small bowel perforation. The timing of PIPAC administration and combination with systemic chemotherapy is shown in Figure 6. In detail, eight patients received PIPAC during first-line chemotherapy, nine more patients received PIPAC after first-line treatment in combination with a 5-FU-based "maintenance" regimen, four patients received PIPAC during second-line chemotherapy and seven more patients received PIPAC during third-line chemotherapy.

Thirteen patients received only one PIPAC procedure: the main reasons for not undergoing more than one procedure were clinical disease progression with bowel obstruction (five patients) (Figure 7). The median time to resume systemic chemotherapy after PIPAC was 6 days (range 4–7).

Concerning toxicity, two grade 3–4 CTCAE (Common Terminology Criteria for Adverse Events v4.0) events were recorded while grade 1–2 events occurred postoperatively to ten patients (36%). Thirteen patients (46%) received more than one PIPAC (Table 3).

The antitumor activity was assessed on the thirteen patients undergoing more than one PIPAC procedure: ascites volume evaluated during subsequent procedures increased in four patients, reduced in three patients, and did not develop in six more with or without minimal ascites at the time of first the PIPAC procedure. The PCI increased in ten patients (76.9%), remained stable in one patient (7.7%), and reduced in two patients. One of them underwent cytoreductive surgery with HIPEC (patient 23). According to the PRGS, one patient demonstrated a complete pathological regression (7.7%), seven more patients (53.8%) a partial regression, and the remaining five (38.5%) demonstrated no sign of regression. Considering the Intention-to-Treat population the pathological response rate is 28.6%. The median overall survival was 6.9 months in patients undergoing more than one PIPAC (Table 4).

Paper III

A total of 20 patients affected by pancreatic cancer or cholangiocarcinoma underwent 45 PIPAC administrations. The cohort was composed of nine male and 11 female patients with a median age of 64 years (range 42–87). ECOG PS at the time of first PIPAC was 0 in four cases, 1 in nine cases, and 2 in the remaining seven cases.

Fourteen patients suffered from peritoneal spread from pancreatic cancer and six patients from cholangiocarcinoma. Fourteen patients suffered from metachronous disease: four patients underwent a Whipple operation, two a pancreatic tail resection, three a cholecystectomy, two a hepatic resection, one a cholecystectomy combined with hepatic

resection, and two did not receive any primary tumor surgery. The remaining six patients with synchronous PM had no previous tumor-specific surgeries.

All patients underwent at least one line of metastatic systemic chemotherapy before PIPAC treatment. Chemotherapy regimens are listed in Table 5. In 11 cases, PIPAC was combined with systemic chemotherapy with a two-week interval before and 1 week after the PIPAC procedure. Consequently, there was an additional one-week delay between systemic chemotherapy administrations. The remaining nine patients underwent PIPAC as the only treatment. PIPAC Ox was administered in 12 cases and PIPAC CD in eight cases.

The median PCI at the time of the first PIPAC was 20 for pancreatic cancer and 14 for CC (Table 2). High volume ascites (>2000 ml) was evident in six patients. Two more patients had low volume ascites (less than 1000 ml), while the remaining 12 patients had minimal (less than 100ml) or no ascites at all. All six patients with high volume ascites received only one PIPAC cycle.

The median procedure time was 95 min (range 71–137 min). The abdominal cavity was accessible in all patients. On laparoscopic entry, there was one (patient 15) small bowel perforation due to adhesions, which was repaired with interrupted suture and did not prevent PIPAC administration.

Eighteen grade 1 or 2 CTCAE (nausea or mild abdominal pain) complications occurred in 45 PIPAC procedures (40%), but there were no major postoperative adverse events (grade 3–4 CTCAE). All patients were discharged on the first or second postoperative day, except for one, who left the hospital on the third postoperative day.

Eleven patients (55%) underwent more than one PIPAC and were therefore available for efficacy analysis: seven patients completed three cycles (35%), four patients four or more cycles (one patient underwent seven PIPAC administrations). The main reason for discontinuing the PIPAC treatment schedule after the first PIPAC was rapid clinical deterioration (seven cases). One patient was lost to follow-up after 3 months from the first PIPAC. The majority (6/9) of those receiving only one cycle suffered from high volume ascites and had ECOG PS of 2. Along with all PIPAC cycles, PCI decreased in four patients, increased in five patients, and remained stable in the other two patients. Concerning ascites, there were only two new-onsets at the third PIPAC cycle.

According to the PRGS score, a pathological regression was recorded in 10 patients and stable disease in one more patient. Thus, considering those who underwent at least two PIPAC cycles, the pathological response rate was 90%, in particular 83% for the oxaliplatin group and 100% for the cisplatin–doxorubicin one. Whereas in the overall population, the pathological regression rate was 50% in both the PDAC (7/14) and CC (3/6) patients. Response rates in the oxaliplatin-PIPAC and the cisplatin/doxorubicin-PIPAC cohorts were 42% and 62%, respectively.

The median OS from the first PIPAC was 9.7 months for pancreatic cancer and 10.9 months for CC (Figure 8), while the median OS from PM diagnosis was 16.2 months for pancreatic cancer and 12.3 months for cholangiocarcinoma (three patients were still alive in the CC cohort). Five patients survived up to almost 2 years from PM diagnosis. Concerning survival analysis based on drug exposure, the median OS from the first PIPAC was 10.0 months for cisplatin/doxorubicin PIPAC and 9.3 months for oxaliplatin

PIPAC.

Paper IV

The baseline characteristics of the 51 patients are summarized in Table 7. The cohort study was composed of 26 males (51%) and 25 females (49%), with a median age of 63 years (54–71), and a median BMI of 20.9 kg/m2 (18.6-24.6). 41 patients (80.4%) were malnourished according to GLIM criteria. Five patients (10%) were in the third class of the ASA score, and 6 (11%) were in the second ECOG PS class. Primary tumors were gastric (39%), colorectal (33%), and hepato-pancreatic-biliary (HPB) (24%), with a 43% rate of synchronous PM. Almost all patients had already undergone one line of systemic chemotherapy, and 31 (60%) underwent 2 or more lines of systemic chemotherapy. PIPAC-related data are presented in Table 8. The access to the abdominal cavity and the first PIPAC cycle was feasible in all cases. Thirty (58.8%) patients repeated the PIPAC procedure, and the median hospital stay was 2 days (1-3) without any readmission.

Receiving multiple PIPAC cycles

Data regarding patients receiving multiple PIPAC cycles are shown in Table 9. Median SMI was 42.3 cm2/m2 (37.6-49.7), with an incidence of low-SMI rate of 72.6%. No differences between patients who received one or more PIPAC cycles about body composition parameters were found. ALB, LYM, and PNI were lower in patients who received only one PIPAC, while NEU and NLR were higher. Cut-offs were as follows: 27.5 for ALB, 3.55 for NEU, 0.90 for LYM, 36.5 for PNI, and 4.8 for NLR. AUC was higher for PNI and ALB with the value of 0.907 (p: 0.0001) and 0.911 (p:0.0001), respectively.

PIPAC-related Adverse Events

Of 102 total PIPAC procedures performed, 18 (17.6%) adverse events were developed, of which only 1 (0.9%) was Grade 3 according to CTCAE. The only severe AE consisted of diffuse abdominal cutaneous and subcutaneous inflammation due to the infiltration of oxaliplatin from the trocar sites at the second PIPAC cycle. There were no grade four and five adverse events. Due to the very limited number of severe AE, no further analysis was performed on this issue.

Pathological Response

A pathological response according to the PRGS was documented in 28 out of 30 patients receiving more than one PIPAC and available for evaluation, which accounts for 55% of the overall cohort. Table 10 reports data correlated to the pathological response. No differences between responders and non-responders according to PRGS were found in terms of blood tests. MA was higher in responding to half of the patients, while VAT, VATI, SAT, SATI, and TFA were lower in the same population. Cut-offs were as follows: 39.5 for MA, 35.4 for VAT, 13.1 for VATI, 89 for SAT, 32.1 for SATI, and 149.8 for TFA. The highest AUC value was for SAT (0.739; p:0.005).

Overall Survival

Within the median follow-up period of 36.0 months (range: 27.6-44.4), 38 (74.5%)

patients died, with a median OS of 8.33 months (95% CI 5.90-9.47) (Figure 9 - A). Table 11 reported univariate Kaplan Meier analysis for all the tested variables and the Cox regression multivariate analysis performed. For PNI analysis the same cut-off found in Table 9 was used. In particular, ascites [HR 2.50 (95% CI 1.17-5.30); p:0.01], dysphagia [HR 2.83 (95% CI 1.11-7.19); p:0.02], and PNI less than 36.5 [HR 3.43 (95% CI 1.65-7.15); p:0.0005] resulted associated with a poor OS (Figure 9 - B, C, D). At the Cox regression model, a low PNI [HR 2.41 (95% CI 1.08-5.46); p:0.034] remained the only independent factor for OS.

CHAPTER 4

Discussion

Discussion

The studies presented here documented an antitumor activity against peritoneal metastases of gastric, pancreatic, and biliary tract cancers of oxaliplatin or the combination of cisplatin/doxorubicin administered inside the abdominal cavity through PIPAC. Indeed, 30-60% of patients demonstrated a pathological regression on subsequent biopsies taken during PIPAC procedures, considering the Intention-To-Treat population (Paper II-III). Such results are consistent with the literature and corroborate the data already published[18]. Indeed, 44% of the patients showed signs of regression, based on the pooled analysis performed on the pathological response (ITT) (Paper I). However, there is no certainty whether the observed cytotoxicity will result in a clinical benefit or a reduction in disease burden.

PIPAC is a novel method to deliver drugs inside the abdominal cavity based on a laparoscopy. Remarkably, the development of PIPAC is following the IDEAL recommendations for surgical procedures, which represents a step-by-step approach to safely and successfully implement novel techniques. In 2019, according to a systematic review, PIPAC had "succeeded in the development and exploration part of the IDEAL framework" and it was ready for RCTs aiming at comparisons with the standard of care[45].

However, PIPAC is a drug-delivery system and its activity relies on both the system that creates the aerosolized drug and the drug itself. Hence, while the PIPAC device might be ready to be tested in the "assessment stage" of the IDEAL framework, there are still several questions to be answered for the drug counterpart.

In the present cohorts and several retrospective and prospective studies[45], PIPAC exhibited high antitumor activity according to the histological examination of PM specimens taken during the procedures. However, the phase-II evidence showed a high degree of discordance between the pathological and radiological response rates. At the time of this writing, five phase-II trials have been published, one on ovarian cancer, two on gastric cancer, one on colorectal cancer, and one on various clinical entities [25,39,40,46,47]. Except for the one by Khomyakov et al., all studies used the RECIST criteria v. 1.1 to measure the antitumor activity on PM in the palliative setting. The reported rate of Complete Responses and Partial Responses are 0%, 6%, and 12% in colorectal, ovarian, and gastric cancer, respectively. The mixed clinical entities trial reported an 18% response rate, which is calculated in the Per-Protocol population, leading to potentially biased results[48]. Adjusting its response rate for the Intention-To-Treat population, which is more conservative, it would be 11%.

The resulting radiological response rate of phase-II trials ranges from 0% to 12% which is far from the 14-56% pathological one, coming from the same studies, and it is not encouraging, even considering that the setting was the palliative one. Of note, all phase II trials administered arbitrarily set doses and preceded phase I studies. Therefore, the interpretation of current phase-II antitumor activity remains challenging and it is questionable if future phase-II aims should point more towards the RECIST criteria or the Peritoneal Regression Grading Score (PRGS) which is currently largely used in PIPAC literature.

Recently, three unsuccessful randomized trials evaluating oxaliplatin-based HIPEC in the treatment or prevention of colorectal cancer PM questioned the activity of intraperitoneal oxaliplatin in this population. A possible explanation would attribute the hampered efficacy of oxaliplatin to the relative chemoresistance of the Consensus Molecular Subtype (CMS) 4 of colorectal cancer[49], which is highly frequent in patients affected by colorectal cancer PM[50]. Thereby, one could question whether the scientific community should continue testing endovenous drugs for PM treatment inside the abdominal cavity or move the research interest towards specifically designed intraperitoneal drugs. For example, albumin-bound intraperitoneal chemotherapy may be a promising option to explore, as recent preclinical and clinical trials suggest that it may result in superior efficacy in the treatment of PM compared to standard chemotherapy formulations[51], and novel compounds have already been tested[52,53].

Great efforts have been made to determine PIPAC drug doses conducting several phase I trials [38,54–56]. However, they started from arbitrary set doses and their results seem controversial and not conclusive.

More in detail, concerning the combination of cisplatin/doxorubicin, two dose-finding studies have been carried out without reaching the MTD, though concluding to have found the recommended dose for Phase II studies (RP2D) [38,57]. Yet, the doses found in the first phase-I study by Tempfer et al. are slightly higher than those arbitrarily set at 7.5/1.5 mg/m2 and nearly one-third of those coming from the 2021 trial of Robella and colleagues (12.5/2.1 against 30/6 mg/m2). Furthermore, no grade 3 drug-related adverse events were reported in both trials. Unfortunately, the study by Robella et al. was prematurely closed because of “issues relating to the insurance renewal” and only one patient was recruited in the highest cohort (50/10 mg/m2). The authors concluded that the 30/6 mg/m2 dose should be the starting point for phase-II studies on repetitive PIPAC, despite having administered (and assessed) only one PIPAC per patient.

To resume, in case one would start a phase-II trial on the combination of cisplatin/doxorubicin the alternatives would be:

- a repetitive 7.5/1.5 mg/m2 cisplatin/doxorubicin PIPAC monotherapy, which was used in a phase-II trial obtaining a 6% radiological response rate[39];

- a repetitive 12.5/2.1 mg/m2 cisplatin/doxorubicin PIPAC monotherapy, coming from a dose-finding trial not reporting any DLT[38];

- a single-shot 30/6 mg/m2 cisplatin/doxorubicin PIPAC monotherapy, coming from a dose-finding trial not reporting any DLT [56].

Three dose-finding trials have been conducted to identify the MTD for oxaliplatin administered by PIPAC. [54,55,57].

The PIPOX trial by Dumond and colleagues reached the MTD as two patients in the 140 mg/m2 cohort experienced one DLT[54]. In particular, a grade 4 allergic reaction to oxaliplatin and a grade 3 non-febrile neutropenia were reported. Still, the study methods introduced a number of variables that make outcomes hard to be used for future studies. Patients underwent repetitive oxaliplatin PIPAC plus 5-FU/leucovorin 400/20 mg/m2, 24 h before PIPAC, and concomitant systemic chemotherapy, though it was not included in the protocol[58], making it difficult to attribute the AEs to one or another. For example,

one of the two DLTs that occurred at the highest dose of 140 mg/m2 was a grade 3 non-febrile neutropenia occurring 15 days after systemic chemotherapy and 27 days after PIPAC. One would question whether this AE should be ascribed to PIPAC or systemic chemotherapy. Surprisingly, the same authors stated that “none of these toxicities were considered to be related to the IP route”, despite having classified the aforementioned AE as a DLT and having set the MTD on this basis. In addition, as the trial lacks any data regarding the systemic chemotherapy regimens administered, the identified dose of 90 mg/m2 may rather represent the starting point for a phase-II study on repetitive oxaliplatin PIPAC, plus 5-FU, plus undefined systemic chemotherapy.

The Singaporean dose-finding trial of Kim et al. was designed as a traditional 3+3 dose-escalation study with oxaliplatin dose levels planned at 45, 60, 90, 120, and 150 mg/m2[55]. A single PIPAC repetition was admitted, but their protocol did not include 5-FU or concomitant systemic chemotherapy. Unfortunately, the study was ended without proceeding to the 150 mg/m2 stage, based on the DLTs of the 140 mg/m2 cohort of the Dumont trial, which again included 5-FU and concomitant systemic chemotherapy. The authors concluded that, despite not having reached the MTD, 120 mg/m2 should be the RP2D.

The trial by Robella and colleagues was designed as a model-based study on three scheduled doses of 100, 135, 155 mg/m2 administered once [56]. As the one on cisplatin/doxorubicin, the study prematurely terminated due to administrative reasons enrolling 6 patients undergoing only one PIPAC cycle. Three patients received the 100 mg/m2 dose, and another 3 the 135 mg/m2 one. No grade 3 AE occurred, and only two patients experienced a grade 2 pain AE. Despite their study protocol providing only one PIPAC administration without systemic chemotherapy, they conclude that 135 mg/m2 “could be the starting point for future phase II studies in order to evaluate the efficacy of repeated high-doses PIPAC, possibly associated with systemic chemotherapy”. [56].

So far, we would have three options for starting a phase II trial on oxaliplatin PIPAC:

- a repetitive 90 mg/m2 oxaliplatin PIPAC + 5-FU/leucovorin 400/20 mg/m2 + undefined systemic chemotherapy;

- a one-shot 120 mg/m2 oxaliplatin PIPAC monotherapy, coming from a dose-finding trial that did not reach the MTD[55];

- a one-shot 135 mg/m2 oxaliplatin PIPAC monotherapy, coming from a dose-finding trial that did not reach the MTD[57].

Some phase II studies have already been conducted with some of the aforementioned doses obtaining the aforementioned controversial response outcomes. Other phase II studies are ongoing (NCT02735928, NCT03875144, NCT03280511), thus, depending on their results, more dose-finding studies may be necessary to identify the doses for repetitive cisplatin/doxorubicin or oxaliplatin PIPAC with or without concomitant systemic chemotherapy.

A recent preliminary abstract presented the results of a phase I trial on nabpaclitaxel PIPAC[59]. A dose of 140 mg/m2 for intraperitoneal nabpaclitaxel was already identified by Cristea et al.[60] and was considered the upper limit of a dose-finding design with a Bayesian approach. No DLTs occurred but at the MTD of 140 mg/m2, considerable

surgical site infection and liver toxicity were observed. Therefore, the authors concluded that the RP2D was 112.5 mg/m2. The protocol did not exclude concomitant systemic chemotherapy and thus the RP2D is referred to a combination of nabpaclitaxel PIPAC and an undefined systemic chemotherapy. The phase II protocol, approved by the Italian Drug Agency (AIFA) and published in form of an abstract (Paper V), will explore the administration of VI cycles of systemic gemcitabine/nabpaclitaxel 1000/115 mg/m2 combined with III cycles of nabpaclitaxel PIPAC 112.5 mg/m2 for first-line metastatic pancreatic cancer with PM. Since this dose was tested in combination with undefined systemic chemotherapy which excluded taxane-based treatments, the present combination was not previously assessed. Accordingly, safety early stopping rules and dose reductions in both locoregional and systemic treatments have been planned. Considering that the primary objective of the trial is to evaluate the antitumor activity of this combined treatment, to ease the comparison with the literature, the preferred primary endpoint was the Disease Control Rate which comprises the combined incidence of Complete Response, Partial Response, and Stable Disease for at least 16 weeks, according to the RECIST criteria.

While precise indications are still under debate[13,61], PIPAC may be employed in several settings: (i) PM prevention in high-risk cases; (ii) downstaging of peritoneal disease in the neoadjuvant setting to allow cytoreductive surgery; (iii) improving regional control in combination with systemic chemotherapy for patients not eligible to cytoreductive surgery; (iv) offering a better disease control of chemorefractory PM in the palliative setting[62]. Again, some of these indications will be addressed by phase II studies and RCTs with the aforementioned doses (NCT04410887, NCT03875144, NCT02735928, NCT04734691, NCT04475159, NCT04065139, NCT03280511). Nonetheless, conducting late-phase trials without properly defined doses might be hazardous and unsuccessful. Keeping in mind that only cytotoxic agents are under examination, the recommended dose, which depends on the MTD, is a cornerstone of successful drug development and its thorough establishment is of utmost importance since it is seldom re-evaluated at later stages [63]. In the case of PIPAC, though the compounds are already developed, their administration as aerosol, inside the abdominal cavity, and during a 12 mmHg CO2 laparoscopy corresponds to the development of new drugs. Furthermore, all compounds currently applied with PIPAC are not approved for intraperitoneal use. The fact that they are well-known does not allow skipping or postponing of this critical step, which deserves a careful and thoughtful approach to establish the recommended dose and/or schedule of an experimental drug or drug combination for efficacy testing in phase II trials [63].

As with systemic chemotherapy and unlike HIPEC, PIPAC may be repeated multiple times. Despite lacking evidence on schedules, three repetitions at 4-8 weeks intervals are currently used. If a valuable lesson was learned from the successes of systemic chemotherapy in the last 30 years, progress will be the result of multidrug as well as multicycle regimens. However, the majority of patients fail to complete the three scheduled treatment cycles [9,28], being disease progression or deterioration of clinical conditions the most frequent causes of discontinuation both in the literature and in the series presented here. While this likely reflects the current late-stage study settings, the limited repetitions might have affected the observed poor radiological responses. Indeed,

only 59%, 53%, and 24% of patients received three cycles in the colorectal, ovarian, and gastric cancer phase-II studies, respectively.

The low rate of PIPAC schedules completion prompted the research performed on the immune nutritional status and body composition analysis of patients undergoing PIPAC in Paper IV. However, despite 75% of patients showing signs of low skeletal muscle mass, according to the Skeletal Muscle Index (SMI) based on CT-scan, neither muscle quantity (SMI) nor muscle quality (Muscle Attenuation: MA) were correlated with the number of PIPAC cycles. Instead, both the Prognostic Nutritional Index (PNI) and the Neutrophil-Lymphocyte Ratio (NLR) were significantly associated with tolerating more than one PIPAC. Moreover, cut-offs of 36.5 and 4.8 were calculated for PNI and NLR, respectively, but, due to the small sample size, they need further validation on a larger and more selected population.

Of note, despite the frailty of the population under study, PIPAC was a safe and well-tolerated procedure, with a 22-40% rate of grade 2 and lower AEs and only 0-2% of patients experiencing grade 3 or higher ones (Paper II-III). Nonetheless, it should be kept in mind that performing laparoscopy in the current PIPAC setting might be challenging. Adhesions to the abdominal wall due to previous surgeries scars or peritoneal malignant implants are very frequent and represent a serious concern, as the rare but non-negligible rate of bowel perforation reported in the literature testifies. In the two retrospective series reported here, there were two laparoscopic-entry bowel perforations in 91 procedures (Paper II-III). Yet, drug-related AEs were rare, confirming that PIPAC has a limited systemic impact at the current doses.

According to the initial studies, the aerosol produced during PIPAC exhibits a “gas-like” behavior, which would guarantee a homogenous distribution of cytotoxic agents throughout the entire abdominal cavity[14–16]. However, recent insights from *ex-vivo* and *post-mortem* animal studies revealed that PIPAC did not result in such uniform distribution patterns[64,65]. Indeed, according to a granulometric analysis, 97.5% of the aerosol droplets delivered during PIPAC have a size between 3 to 200 μm, while the ideal diameter to obtain gas-like properties should be 1.2 μm[66]. The current size of PIPAC particles is subject to gravitational settling and inertial impaction which turns out in the majority of the droplets depositing beneath the PIPAC nozzle[67]. Rather than a homogenous distribution, other studies reported a remarkable variation in the drug penetration between different regions of the abdominal cavity with the highest penetration depth of 0.4 mm in the area around and opposite to the nozzle[65,68]. To overcome the hurdles associated with drug distribution, new types of PIPAC methods have been implemented. Indeed, hyperthermic PIPAC (H-PAC)[69,70], nano aerosol hyperthermic chemotherapy (HINAT)[71], and electrostatic precipitation of therapeutic aerosols in the peritoneal cavity (ePIPAC)[17] demonstrated a more uniform drug distribution pattern and deeper in-tissue drug penetration as compared to standard PIPAC. Finally, a three-dimensional nozzle PIPAC head has been announced at the second congress of the International Society for the Study of Pleura and Peritoneum. Although PIPAC is a well-established and validated technique, there is room for further improvement of the current aerosol chemotherapy delivery system.

While comparisons of PIPAC with the standard of care are largely awaited by the

scientific community[45,72,73], the current evidence on drug doses, schedules, and combination with systemic chemotherapy seems limited and controversial. Research efforts should first address these sensitive issues before proceeding to more advanced stages. The identification of drugs properly designed for PM and intraperitoneal administration is ambitious but might be the safest way to succeed and PIPAC could be the ideal test bench, due to its repetitive nature and pharmacokinetics advantage as compared to infusion. The study protocol designed on nabpaclitaxel PIPAC combined with systemic gemcitabine/nabpaclitaxel (Paper V) points in this direction. Indeed, despite being conceived for systemic chemotherapy, nano albumin drugs seem great candidates for intraperitoneal administration[51], and nabpaclitaxel PIPAC could represent an added value for the standard systemic treatment of metastatic pancreatic cancer patients.

In conclusion, the effectiveness of PIPAC has yet to be demonstrated as the available evidence mainly provided encouraging antitumor activity in the palliative setting based on pathological analysis, but the radiological response was poor. The clinical implications of the observed pathological response are still not ascertained.

PIPAC may be a promising device for intraperitoneal drug administration, but the road to face the unmet clinical needs of PM patients is still long and winding. Cutting corners will not get us anywhere but back where we started.

CHAPTER 5

Tables and Figures

Table 1. Clinical studies on pathological response of patients undergoing pressurized intraperitoneal aerosol chemotherapy (PIPAC) for various indications.

Author	Year	Study Type	Patients (n)	PIPACs (n)	Tumor entity	Access failure n/tot (%)	PIPAC I cycle n/tot (%)	PIPAC II cycle n/tot (%)	PIPAC III cycle n/tot (%)	PCI	Combined . sCT n/tot (%)	Pathological tumor response n/tot (ITT) (%)	Toxicity (CTCAE 1/2/3/4/5) n/tot (%)	OS (months)
Solass	2014	CS	3	12	OC GC AC	0/12 (0%)	3/3 (100%)	3/3 (100%)	2/3 (67%)	12	0/3 (0%)	3/3 (100%)	1/3/1/0/0	9,6
Tempfer	2014	CS	21	34	OC	3/34 (9%)	18/21 (86%)	8/21 (38%)	4/21 (19%)	17,3	0/21 (0%)	6/18 (33%)	12/0/3/2/0	8,9
Tempfer	2015	P2	64	130	OC, FTC, PMC	11/130 (8%)	53/64 (83%)	43/64 (67%)	34/64 (53%)	16,3	0/64 (0%)	26/53 (49%)	71/32/8/0/0	13,6
Tempfer	2015	RCS	99	252	OC PMP CC EC	17/252 (7%)	82/99 (83%)	50/99 (51%)	34/99 (34%)	16,6	0/99 (0%)	38/82 (46%)	67/60/17/3/0	14,1
Demtroder	2016	CS	17	48	CRC	6/48 (13%)	17/17 (100%)	14/17 (82%)	9/17 (53%)	16	11/17 (65%)	12/17 (71%)	12/0/4/0/0	15,7
Nadiradze	2016	RCS	25	60	GC	4/60 (7%)	24/25 (96%)	17/25 (68%)	10/25 (40%)	16	8/25 (32%)	12/24 (50%)	14/0/3/1/2	15,4
Khomyakov	2016	P2	31	56	GC	0/56 (0%)	31/31 (100%)	15/31 (48%)	8/31 (26%)	16	31/31 (100%)	9/31 (29%)	0/3/1/0/0	13
Graversen	2017	CS	5	16	PC	0/16 (0%)	5/5 (100%)	5/5 (100%)	3/5 (60%)	-	1/5 (20%)	4/5 (80%)	17/0/0/0/0	6,4
Struller	2017	P2*	25	43	GC	0/43 (0%)	25/25 (100%)	12/25 (48%)	6/25 (24%)	-	0/25 (0%)	9/25 (36%)	26/6/4/0/0	8,4
Khosrawipour	2017	CS	20	41	PC	3/41 (7%)	20/20 (100%)	10/20 (50%)	7/20 (35%)	26,6	6/20 (30%)	7/20 (35%)	14/1/0/0/1	8,4
Gockel	2018	CS	28	46	GC	5/46 (11%)	22/28 (79%)	13/28 (46%)	7/28 (25%)	14	10/28 (36%)	7/22 (32%)	1/0/0/0/0	3,9
Somashekhar	2018	RCS	3	9	OC	0/9 (0%)	3/3 (100%)	3/3 (100%)	3/3 (100%)	19,6	0/3 (0%)	2/3 (67%)	0/1/0/0/0	-
Falkenstein	2018	CS	13	17	HB	2/17 (12%)	11/13 (85%)	5/13 (38%)	1/13 (8%)	20	10/13 (77%)	4/11 (36%)	8/6/0/0/0	2,8
Giger-Pabst	2018	RCS	29	74	MM	10/74 (14%)	25/29 (86%)	20/29 (69%)	12/29 (41%)	19,9	7/29 (24%)	15/25 (60%)	23/7/1/2/1	26,6
Tempfer	2018	P1	15	34	OC, FTC, PMC	0/34 (0%)	15/15 (100%)	11/15 (73%)	8/15 (53%)	16,3	0/15 (0%)	7/15 (47%)	71/32/1/0/1	13,6
Kurtz	2018	RCS	71	142	GC CRC OC HB PC PMP AC	11/142 (8%)	63/71 (89%)	39/71 (55%)	21/71 (30%)	19,3	42/71 (59%)	24/63 (38%)	0/2/5/3/1	11,8
Kuchen	2018	RCS	35	68	GC CRC OC HB	0/68 (0%)	35/35 (100%)	12/35 (34%)	-	12,5	0/35 (0%)	4/35 (11%)	3/1/2/3/1	13,9
Graversen	2018	P2	35	129	GC, OC, PMP, CC, SBC, M, PC	0/129 (0%)	35/35 (100%)	30/35 (86%)	27/35 (77%)	14,1	5/35 (14%)	25/35 (71%)	9/15/4/1/0	-
Robella	2018	P2*	35	55	GC OC CRC	1/55 (2%)	34/35 (97%)	25/35 (71%)	-	-	15/35 (43%)	7/34 (21%)	3/5/0/0/0	-
Khomyakov	2019	P2*	94	214	GC	0/214 (0%)	94/94 (100%)	60/94 (64%)	-	10	94/94 (100%)	39/94 (41%)	-/-/-/-/-	16,4
Pooled Analysis			668	1480		73/1480 (5%)	615/668 (92%)	395/668 (59%)	196/668 (29%)	16,6	240/668 (36%)	260/615 (42%) (95% CI: 36,29 - 51,26)	352/668 (53%)/ 174/668 (26%)/ 54/668 (8%)/ 15/668 (2%)/ 7/668 (1%)	11,9

PCI Peritoneal Cancer Index; sCT systemic chemotherapy; ITT Intention-To-Treat population; IV CHT Intravenous Chemotherapy; CTCAE Common Terminology Criteria for Adverse Events; OS Overall Survival; CS Case series; P2 Phase II study; RCS Retrospective case series; P1 Phase I study; OC Ovarian cancer; GC Gastric cancer; AC Appendiceal cancer; TC Tubal cancer; PPC Primary peritoneal cancer; CC Cervical cancer; EC Endometrial cancer; BC Breast Cancer; CRC Colorectal cancer; HBC Hepatobiliary cancer; MM Malignant mesothelioma, PMP Pseudomyxoma peritonei; SBC Small bowel cancer.

**Abstract Conference Proceedings.*

Table 2. Preoperative characteristics of gastric cancer patients with peritoneal metastases undergoing cisplatin/doxorubicin PIPAC and systemic chemotherapy.

Variable	Value
Number of patients	28
Sex (M : F)	12:16
Age, years (±SD)	50 ± 14,1
BMI (±SD)	22,5 ± 4,9
Histology	
Signet ring/Diffuse	21 (75%)
Intestinal	2 (7%)
Mixed	5 (18%)
Synchronous : Metachronous PM	12:16
Time from primary tumor diagnosis to Metachronous PM, months (±SD)	18.4 ± 22.7
Extraperitoneal disease	6 (21%)
PCI (±SD)	20 ± 9.9
Performance Status (ECOG) (±SD)	1 ± 0.6

Values are presented as median (interquartile range) or number (%). PM = peritoneal metastases; PCI = peritoneal carcinomatosis index; ECOG = Eastern Cooperative Oncology Group.

Table 3. Preoperative characteristics of gastric cancer patients with peritoneal metastases undergoing cisplatin/doxorubicin PIPAC and systemic chemotherapy.

Variable	Value
Number of PIPAC	46
Access failures	2/46 (4%)
Number of patients undergoing PIPAC cycles	
I PIPAC	26
II PIPAC	13
III PIPAC	7
Operative time (min) (±SD)	124 ± 40,3
Surgical complications, Clavien-Dindo ≥ 3	1/46 (2%)
Overall postoperative morbidity/mortality (CTCAE v 4.0)	
Grade 1 – 2	10/46 (36%)
Grade 3 – 4	2*/46 (4%)
Post-operative stay (d) (±SD)	2 ± 0,5
30-days mortality	2[#]/46

Values are presented as median (interquartile range) or number (%). CTCAE = Common Terminology Criteria for Adverse Events v4.0; PRGS = Peritoneal Regression Grading Score.

** 2 cases of hypertransaminasemia*

[#] 2 cases of rapid disease progression

Table 4. Operative outcomes in patients with gastric cancer peritoneal metastases undergoing more than one PIPAC.

Patient	Setting	PIPAC I				PIPAC II				PIPAC III				Survival
		PS	PCI	Ascites	PRGS	PS	PCI	Ascites	PRGS	PS	PCI	Ascites	PRGS	OS (mo.)
1	First-line	0	8	0	3 (3)	0	2	0	1 (1)	0	1	0	1 (1)	22,0
3	Third-line	0	10	100	2,5 (3)	0	21	100	1.7 (2)	0	-	-	-	13,7
5	Third-line	0	21	3500	3,5 (4)	0	39	300	-	1	-	400	-	6,8
7	Third-line	0	3	0	3,7 (4)	1	12	0	2.3 (3)	1	15	50	3 (3)	8,3
11	First-line	0	7	5000	3,5 (4)	0	20	10000	2 (2)	2	29	8000	2.5 (3)	5,8
16	First-line	1	27	50	3,5 (4)	1	29	50	1.7 (2)	2	30	50	2.3 (3)	3,1
17	First-line	0	23	4500	2 (2)	0	29	3200	1 (1)	0	-	-	-	4,1
18	Second-line	0	11	50	2,3 (3)	0	15	50	2 (2)	0	Transaminase elevation			5,4
19	Second-line	0	15	1000	2 (2)	0	18	0	2 (2)	0	21	50	1.3 (2)	10,4[a]
21	Maintenance	0	12	0	2 (2)	0	15	4000	2 (2)	0	-	-	-	5,4
23	First-line	0	14	0	1,3 (2)	0	14	0	1 (1)	0	CRS+HIPEC			10,3[a]
25	Maintenance	0	22	30	1,7 (2)	0	31	3000	2.3 (3)	0	-	-	-	6,9
26	Third line	0	29	4000	2,3 (3)	0	29	6000	2.3 (3)	0	29	3000	2 (3)	7,1
														6,9 ± 5,0

PCI = peritoneal carcinomatosis index; PRGS = Peritoneal Regression Grading Score; OS = Overall survival (i.e. from first PIPAC); CRS = Cytoreductive surgery; HIPEC = Hyperthermic IntraPeritoneal Chemotherapy.

[a] *Alive*

Table 5. Demographics, surgical and oncological data of patients with pancreatic and biliary tract cancer peritoneal metastases undergoing PIPAC.

Pt. nr.	Age (years)	Primary tumor	Primary tumor site	Primary tumor to PM (months)	Primary tumor surgery	Previous chemotherapy	Combined systemic chemotherapy	PIPAC Drugs	1st PIPAC ECOG PS	OS (months)
1	73	CC	Gallbladder	2,1	Cholecystectomy	GEMOX	None	Oxa	1	19,3
2	80	CC	Gallbladder	42,3	Cholecystectomy + Hepatic resection	GEM	None	Oxa	2	10,9
3	73	PDAC	Head	2,8	None	GEM --> FOLFIRINOX -->TAXOL	TAXOL	Cis + Dox	1	16,3
4	52	PDAC	Head	34,7	Whipple OP	FOLFIRINOX --> GEM --> FOLFOX	FOLFIRI	Cis + Dox	2	10,0
5	78	PDAC	Body-Tail	Synchronous	None	GEM + ABRAXANE	GEM + ABRAXANE	Oxa	1	7,8
6	55	PDAC	Head	Synchronous	None	FOLFIRINOX	FOLFIRI	Cis + Dox	0	10,0
7	43	PDAC	Body-Tail	Synchronous	None	GEM + ABRAXANE	FOLFOX	Oxa	1	5,8
8	61	PDAC	Head	16,8	Whipple OP	GEM --> RT	FOLFIRI	Oxa	2	9,3
9	64	PDAC	Body-Tail	18,0	Pancreatic tail resection	GEM	FOLFIRI	Oxa	1	6,9
10	87	PDAC	Head	12,9	None	Xeloda	Xeloda	Oxa	1	14,9
11	55	PDAC	Body-Tail	Synchronous	None	FOLFOX	None	Oxa	1	1,7
12	70	PDAC	Body-Tail	Synchronous	None	GEM + ABRAXANE	FOLFOX	Oxa	1	9,7
13	60	PDAC	Head	11,2	Whipple OP	GEM --> FOLFOX	None	Oxa	2	16,0
14	66	PDAC	Body-Tail	8,2	Pancreatic tail resection	GEM --> RT	None	Cis + Dox	2	3,4^
15	58	PDAC	Head	14,3	Whipple OP	FOLFIRI + GEM --> RT	GEM + ABRAXANE	Cis + Dox	0	9,9
16	64	CC	Gallbladder	10,4	Cholecystectomy	GEM + Cis	None	Cis + Dox	0	8,2*
17	63	PDAC	Head	Synchronous	None	GEM	GEM	Oxa	2	1,7
18	42	CC	Biliary tract	6,0	Hepatic resection	GEM	None	Cis + Dox	0*	6,8*
19	64	CC	Biliary tract	6,0	Hepatic resection	GEM + Cis	None	Oxa	2*	6,8*
20	69	CC	Gallbladder	29,0	Cholecystectomy	GEM + Cis	None	Cis + Dox	1	1,4

PM = Peritoneal Metastases; PIPAC = Pressurized IntraPeritoneal Aerosol Chemotherapy; ECOG PS = Eastern Cooperative Oncology Group Performace Status; CC = CholangioCarcinoma; PaC = Pancreatic Cancer; GEMOX = Gemcitabine + Oxaliplatin; GEM = Gemcitabine; RT = Radiotherapy; Cis = Cisplatin; Dox = Doxorubicin; Oxa = Oxapliplatin.

^ = Lost at follow-up

** = Alive*

Table 6. Perioperative outcomes of patients with pancreatic and biliary tract cancer peritoneal metastases undergoing PIPAC.

Variable	Value
Number of PIPAC	45
Number of patients per PIPAC cycles	
I PIPAC	20
II PIPAC	11
III PIPAC	7
IV PIPAC or more	4
Access failures	0/45 (0%)
Operative time (min)	95 (71 – 137)
Intraoperative complications	1*/45 (2%)
Overall postoperative morbidity/mortality (CTCAE v 4.0)	
Grade 1-2	18/45 (40%)
Grade ≥ 3	0/45 (0%)
Post-operative stay (d) (±SD)	2 ± 0.7
Histological tumor response (PRGS)	10/20 (50%)
Oxaliplatin	5/12 (42%)
Cisplatin + Doxorubicin	5/8 (62%)

Values are presented as median (range) or number (%). CTCAE = Common Terminology Criteria for Adverse Events v4.0; PRGS = Peritoneal Regression Grading Score; PM = peritoneal metastases; PaC = pancreatic cancer; CC = cholangiocarcinoma.
** = small bowel perforation*

Table 7. Baseline characteristics of the patients undergoing PIPAC assessed on the immune-nutritional status.

Variable	n (%) *or* median (IQR)
Female	25 (49)
Age (years)	63 (54-71)
Weight (kg)	59 (52-71)
Height (cm)	168 (163-173)
BMI (kg/m^2)	20.9 (18.6-24.6)
ASA Score	
1	7 (14)
2	39 (76)
3	5 (10)
ECOG PS	
0	11 (22)
1	34 (67)
2	6 (11)
Primary neoplasm	
Colorectal	19 (37)
Gastric	20 (39)
HPB	12 (24)
Synchronous	22 (43)
Metachronous	29 (57)
Previous systemic chemotherapy	
None	1 (2)
1 line	50 (98)
≥ 2 lines	31 (60)

ASA, American Society of Anesthesiology; BMI, Body Mass Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; HPB, Hepato-Pancreatic-Biliary cancer; IQR, Interquartile range; PIPAC, Pressurized Intraperitoneal Aerosol Chemotherapy.

Table 8. Operative and postoperative outcomes of the patients undergoing PIPAC assessed on the immune-nutritional status.

Variable	**n (%) *or* median (IQR)**
Total number of PIPAC	102
Only I PIPAC cycle	21 (41)
Multiple PIPAC cycles	30 (58)
Laparoscopic entry failures	0 (0)
PCI	22 (12-30)
Ascites (ml)	500 (28-1350)
Cisplatin-Doxorubicin 7,5-1,5 mg/mq	28 (55)*
Oxaliplatin 92 mg/mq	20 (39)
Operative time (min)	98 (74–131)
Intraoperative complications	1
Hospital stay (days)	2 (1-3)
Readmission rate	0
Adverse events (CTCAE v. 5.0)	
Grade 1-2	17 (17)
Grade 3	1 (1)[#]
Grade ≥ 4	0 (0)
Pathological response (PRGS)	28 (55)

IQR, Interquartile range; PIPAC, Pressurized intraperitoneal aerosol chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; PRGS, Peritoneal Regression Grading Score

** 1 patient underwent cisplatin 7,5 mg/mq only due to previous adverse reaction to doxorubicin; 6 patients received cisplatin-doxorubicin 10,5-2,1 mg/mq after dosage update in 2020.*

[#] *skin effusion and abdominal pain due to trocar-site chemotherapy infiltration.*

Table 9. Data regarding patients receiving multiple PIPAC cycles and assessed on the immune-nutritional status.

Variable	Total (51 patients)	1 PIPAC (21 patients)	≥2 PIPAC (30 patients)	p	AUC	Cut-off	Sensitivity	Specificity
SMA (cm^2)	120.1 (102.5-136.3)	121.4 (96.3-133.5)	119.4 (106.1-141.2)	0.76	-	-	-	-
SMI (cm^2/m^2)	42.3 (37.6-49.7)	42.8 (35.2-51.2)	41.6 (38.1-49.4)	0.93	-	-	-	-
Low-SMI Rate	37 (72.6%)	14 (66.7%)	23 (76.7%)	0.52	-	-	-	-
MA (HU)	41.3 (37.5-47.8)	42.6 (35.4-48.1)	40.6 (37.5-47.1)	0.84	-	-	-	-
VAT (cm^2)	36.6 (19.7-75.8)	33.0 (16.4-75.8)	39.5 (19.7-83.7)	0.64	-	-	-	-
VATI (cm^2/m^2)	13.1 (6.5-28.9)	10.2 (6.2-32.3)	13.2 (6.5-28.9)	0.76	-	-	-	-
SAT (cm^2)	92.3 (60.3-148.4)	90.9 (45.1-186.2)	94.3 (62.3-119.6)	0.83	-	-	-	-
SATI (cm^2/m^2)	32.9 (19.8-49.6)	34.5 (16.1-59.4)	32.6 (22.2-43.4)	0.90	-	-	-	-
IMAT (cm^2)	6.4 (2.7-8.4)	6.7 (3.5-8.4)	5.6 (2.5-8.7)	0.79	-	-	-	-
TFA (cm^2)	149.8 (98.5-257.8)	160.5 (70.1-298.9)	140.1 (99.9-230.6)	0.85	-	-	-	-
Creatinine (*mg/dl*)	0.85 (0.73-1.15)	0.86 (0.78-1.53)	0.83 (0.69-1.11)	0.35	-	-	-	-
Albumin (*g/l*)	29 (22-36)	22 (20-23)	33.5 (29-37)	**<0.0001**	0.907	27.5	87	90
Neutrophils ($10^3 cells/mm^3$)	4.26 (2.60-5.32)	4.51 (4.10-7.50)	3.45 (2.43-5.00)	**0.03**	0.679	3.55	53	86
Lymphocytes (10^3 cells/mm3)	1.04 (0.76-1.48)	0.83 (0.67-1.29)	1.23 (0.86-1.57)	**0.02**	0.687	0.90	73	62
Platelets ($10^3 cells/mm^3$)	199 (135-284)	213 (123-311)	197 (141-276)	0.77	-	-	-	-
PNI	34.9 (26.2-42.1)	25.9 (24.3-28.5)	40.7 (35.5-44.6)	**<0.0001**	0.911	30.1	97	86
NLR	4.6 (2.1-6.7)	6.2 (5.1-7.4)	2.4 (1.8-4.7)	**0.001**	0.771	4.8	77	81
PLR	179.2 (128.8-276.5)	252.1 (138.2-428.8)	175.7 (108.7-275.8)	0.12	-	-	-	-

AUC, Area Under the ROC Curve; IMAT, Intermuscular Adipose Tissue; MA, Muscle Attenuation; HU, Hounsfield Unit; NLR, Neutrophil-to-Lymphocyte ratio; PIPAC, Pressurized Intraperitoneal Aerosol Chemotherapy; PLR, Platelet-to-Lymphocyte ratio; PNI, Prognostic Nutritional Index; SAT, Subcutaneous Adipose Tissue; SATI, Subcutaneous Adipose Tissue Index; SMA, Skeletal Muscle Area; SMI, Skeletal Muscle Index; TFA, Total Fat Area; VAT, Visceral Adipose Tissue; VATI, Visceral Adipose Tissue Index.

Table 10. Laboratory and body-composition data correlation to pathological response of patients assessed on the immune-nutritional status.

Variable	No Pathological Response (23 patients)	Pathological Response (28 patients)	p	AUC	Cut-off	Sensitivity	Specificity
SMA (cm^2)	119.3 (104.2-144.8)	121.3 (102.3-130.6)	0.62	-	-	-	-
SMI (cm^2/m^2)	42.4 (38.0-51.3)	42.0 (37.6-44.6)	0.73	-	-	-	-
Low-SMI Rate	15 (65.2%)	22 (78.6%)	0.35	-	-	-	-
MA (HU)	38.2 (33.7-43.7)	43.6 (40.4-48.5)	**0.02**	0.693	39.5	84	62
VAT (cm^2)	62.1 (34.8-86.9)	25.8 (15.5-57.7)	**0.02**	0.691	35.4	76	61
VATI (cm^2/m^2)	22.4 (13.2-28.9)	9.5 (5.7-21.0)	**0.03**	0.688	13.1	75	77
SAT (cm^2)	118.3 (90.9-168.6)	74.6 (50.7-102.7)	**0.005**	0.739	89.0	71	82
SATI (cm^2/m^2)	41.5 (32.6-59.4)	27.3 (17.4-38.6)	**0.007**	0.731	32.1	71	77
IMAT (cm^2)	7.1 (2.7-10.8)	5.4 (2.8-7.7)	0.24	-	-	-	-
TFA (cm^2)	194.9 (124.2-290.7)	103.9 (77.6-175.8)	**0.01**	0.703	149.8	71	73
Haemoglobin (*g/dl*)	11.8 (11.7-12.9)	12.8 (11.8-14.2)	0.39	-	-	-	-
Creatinine (*mg/dl*)	0.85 (0.76-1.07)	0.87 (0.69-1.51)	0.83	-	-	-	-
Albumin (*g/l*)	28 (20-34)	29 (22-38)	0.26	-	-	-	-
Neutrophils (*10^3 cells/mm^3*)	4.36 (2.43-7.94)	4.10 (3.08-5.02)	0.62	-	-	-	-
Lymphocytes (*10^3 cells/mm3*)	1.11 (0.76-1.57)	1.03 (0.73-1.44)	0.51	-	-	-	-
Platelets (*10^3 cells/mm^3*)	203 (129-282)	200 (152-289)	0.86	-	-	-	-
PNI	34.9 (25.6-41.5)	35.2 (27.3-43.0)	0.55	-	-	-	-
NLR	4.83 (1.92-8.37)	3.95 (2.94-5.45)	0.87	-	-	-	-
PLR	238.3 (132.6-411.8)	186.4 (110.4-285.3)	0.64	-	-	-	-

AUC, Area Under the ROC Curve; IMAT, Intermuscular Adipose Tissue; MA, Muscle Attenuation; NLR, Neutrophil-to-Lymphocyte ratio; PIPAC, Pressurized Intraperitoneal Aeroso Chemotherapy; PLR, Platelet-to-Lymphocyte ratio; PNI, Prognostic Nutritional Index; SAT, Subcutaneous Adipose Tissue; SATI, Subcutaneous Adipose Tissue Index; SMA, Skeletal Muscle Area; SMI, Skeletal Muscle Index; TFA, Total Fat Area; VAT, Visceral Adipose Tissue; VATI, Visceral Adipose Tissue Index.

Table 11. Univariate and Multivariate analysis for survival of patients undergoing PIPAC assessed on the immune-nutritional status.

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age ≥65	1.49 (0.73-3.04)	0.26	-	-
Sex	1.68 (0.86-3.28)	0.11	-	-
BMI>18.5	0.83 (0.37-1.85)	0.64	-	-
ECOG ≥2	0.81 (0.25-2.66)	0.73	-	-
ASA ≥3	0.76 (0.23-2.49)	0.64	-	-
Ascites	2.50 (1.17-5.30)	**0.01**	2.18 (0.91-5.24)	0.08
Dysphagia	2.83 (1.11-7.19)	**0.02**	3.17 (1.12-8.98)	0.03
Nausea	1.29 (0.60-2.78)	0.49	-	-
CHT Cycles ≥12	0.65 (0.33-1.25)	0.18	-	-
PNI<36.5	3.43 (1.65-7.15)	**0.0005**	2.41 (1.08-5.46)	0.034
Low-SMI Rate	1.15 (0.56-2.39)	0.69	-	-
MA	1.21 (0.61-2.43)	0.57	-	-
PRGS	0.69 (0.36-1.35)	0.29	-	-

ASA, American Society of Anesthesiology; BMI, Body Mass Index; CHT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; MA, muscle attenuation; PIPAC, Pressurized intraperitoneal aerosol chemotherapy; PNI, Prognostic Nutritional Index.

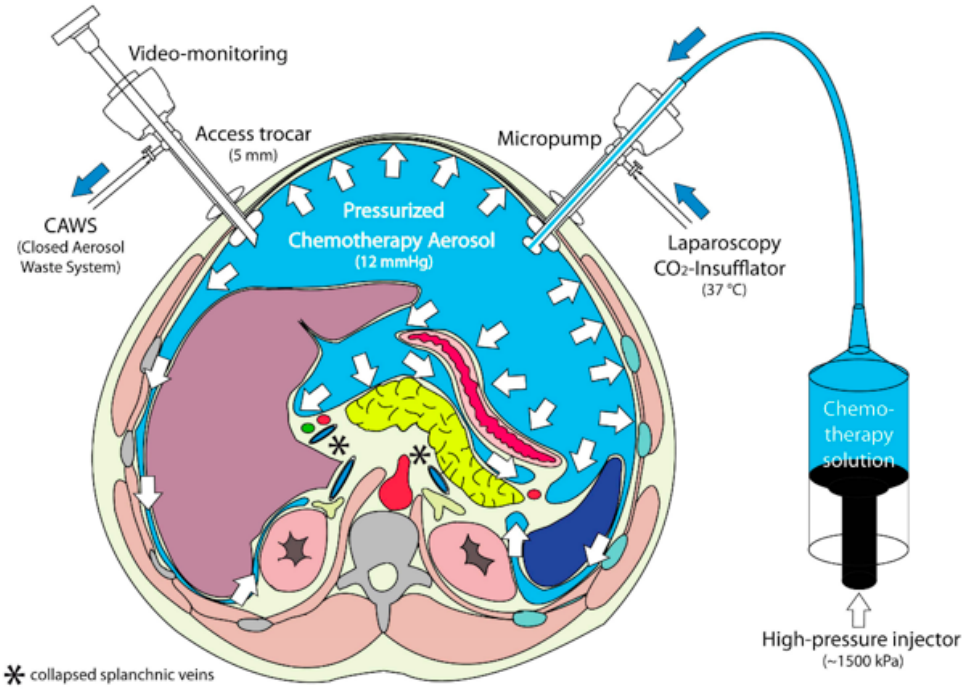


Figure 1. Schematic setup of the PIPAC procedure. The chemotherapy solution is injected by a high-pressure injector into the Micropump (CapnoPen®, Reger, Villingendorf, Germany) that is inserted inside the abdominal cavity through a 10 mm trocar. The aerosolized drug created by the Micropump diffuses into the abdominal cavity during a 12 mmHg CO2 laparoscopy and it is evacuated after 30 minutes by a 5 mm trocar into a Closed Aerosol Waste System (CAWS). The procedure is monitored through a 5 mm laparoscopic camera.

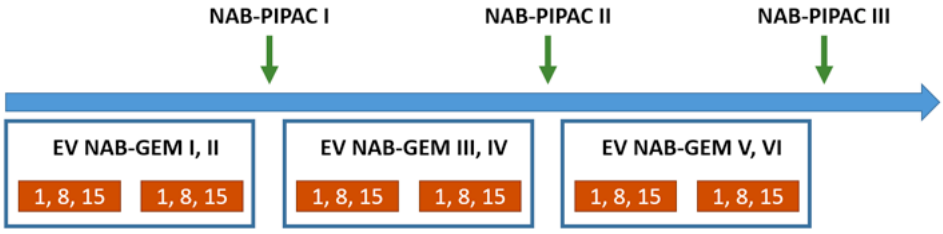


Figure 2. Schedule of combined systemic nabpaclitaxel-gemcitabine and nabpaclitaxel PIPAC. Three combined courses consisting of six cycles of endovenous Nabpaclitaxel-Gemcitabine chemotherapy and three of Nabpaclitaxel-PIPAC. Each combined course is constituted by two consecutive 28-day cycles of systemic chemotherapy (three administrations per cycle: days 1,8 and 15) and one cycle of PIPAC administered within 10-13 days from the last administration of systemic chemotherapy. Between each combined course a 7-10 days pause is observed.

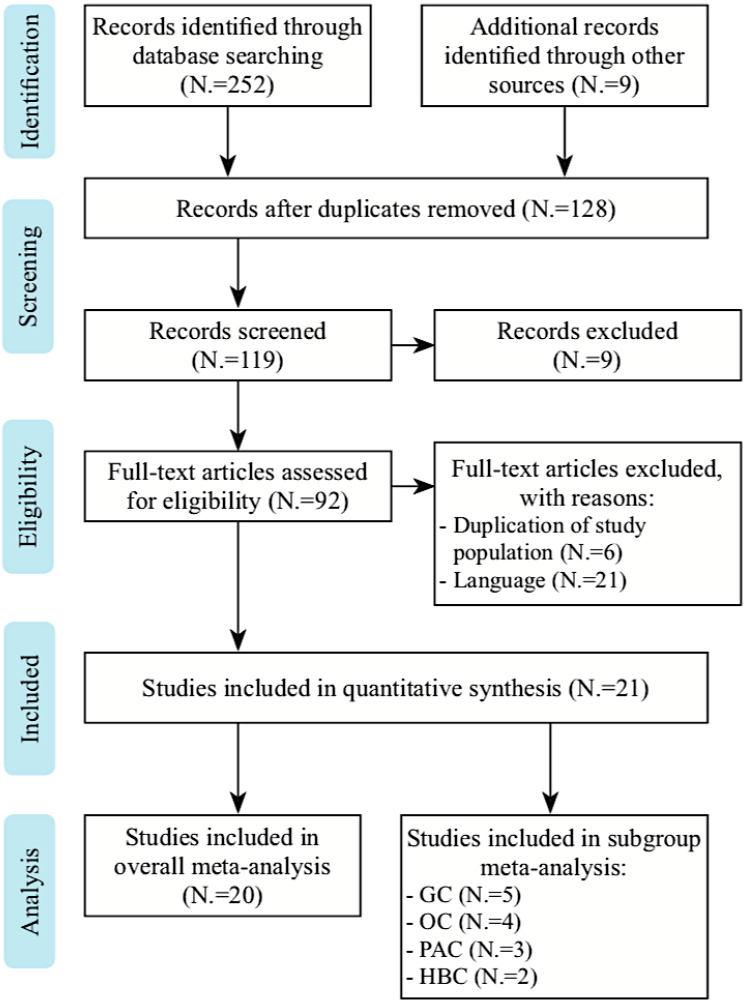


Figure 3. Flow-diagram of the literature evidence acquisition and synthesis. GC: gastric cancer; OC: ovarian cancer; PAC: pancreatic cancer; HBC: hepatobiliary cancer.

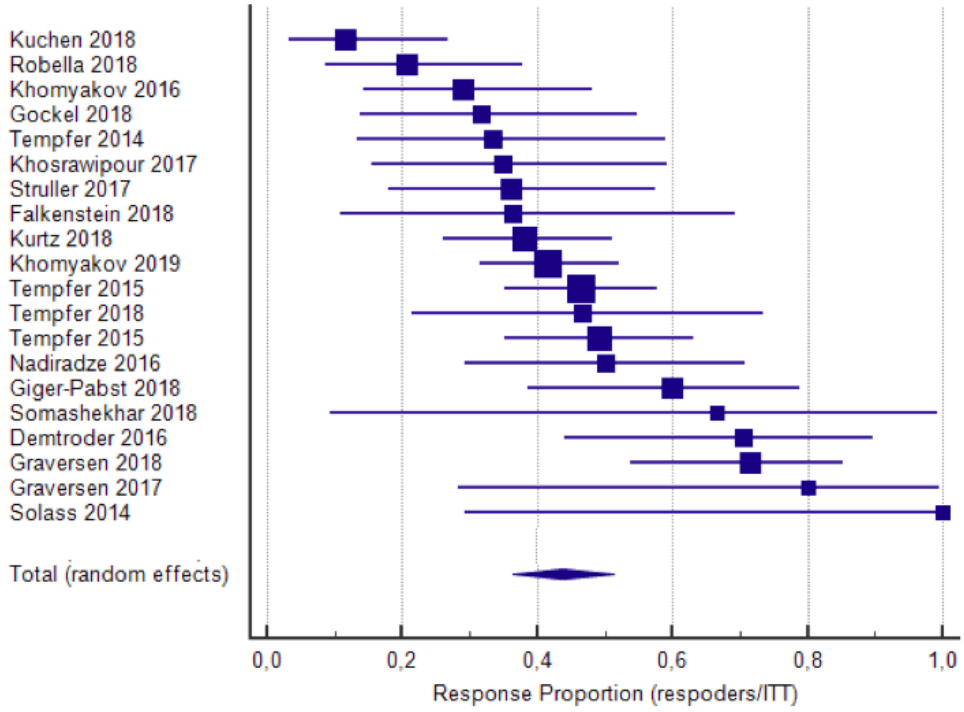


Figure 4. Overall Pathological Response meta-analysis. ITT (615 pazienti): 43,70% (95% CI: 36,29 to 51,26) Method: DerSimonian and Laird random effects model. Heterogeneity: Chi-square 62,28. DF=19 ($p < 0.0001$). I-square: 59,60%.

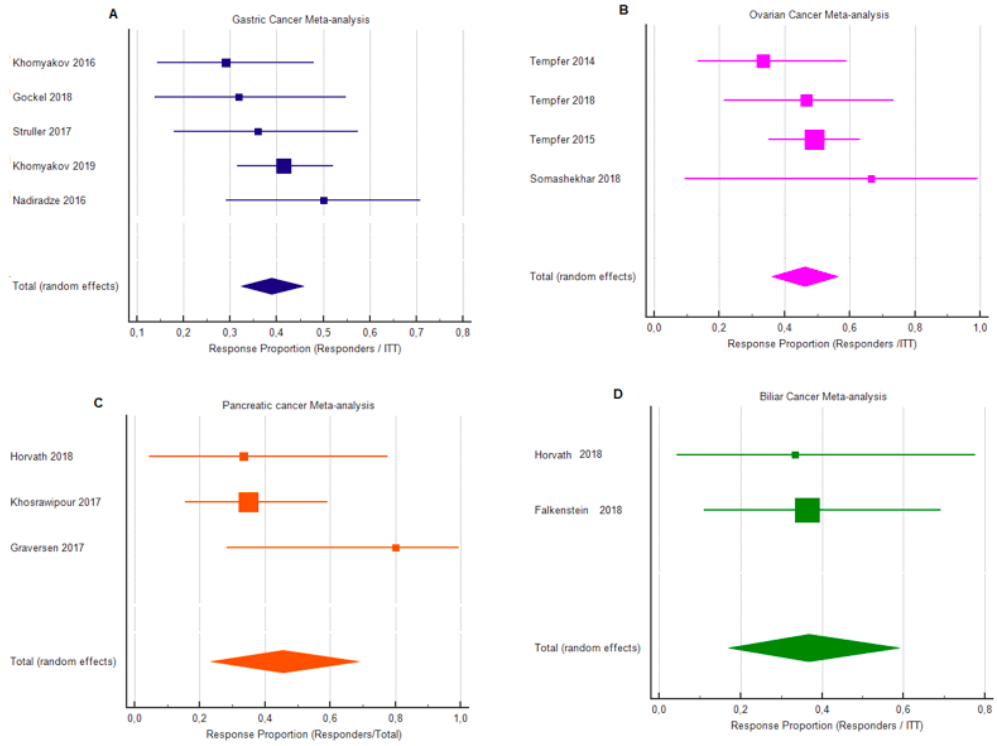
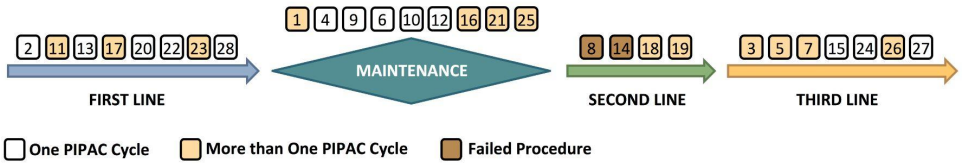


Figure 5. Pathological response by cancer type. Method: DerSimonian and Laird random effects model. A: Gastric cancer pathological response total effect (ITT: 196): 38,96% (95% CI: 32,34 to 45,78) Heterogeneity: Chi-square 3,21. DF = 4 (p 0.5231). I-square: 0%, B: Ovarian cancer pathological response total effect (ITT: 89): 46,20% (95% CI: 36,21 to 56,34) Heterogeneity: Chi-square 1,78. DF = 3 (p 0.6181). I-square: 0%; C: Pancreatic cancer pathological response total effect (sample size: 31): 45,54% (95% CI: 23,24 to 68,82) Heterogeneity: Chi-square 3,36. DF = 2 (p 0.1856). I-square: 40,63%; D: Biliary tract cancer pathological response total effect (sample size: 17): 36,75% (95% CI: 17,12 to 59,02) Heterogeneity: Chi-square 0.006. DF = 1 (p 0.9398). I-square: 0,0%.

A

B



C

SETTING	I LINE		MAINTEINANCE	II LINE		III LINE	
CHEMOTHERAPY	ECF	FOLFOX	(FOLFOX X 12) →5 FU	FOLFIRI	TAXOL	FOLFIRI	TAXOL
PATIENTS (n)	2	6	9	2	2	5	2

Figure 6. PIPAC and systemic chemotherapy combination. A: PIPAC and systemic chemotherapy combined treatment schedule; B: Timing of PIPAC administration with regards to the oncological setting; C: Systemic chemotherapy regimens.

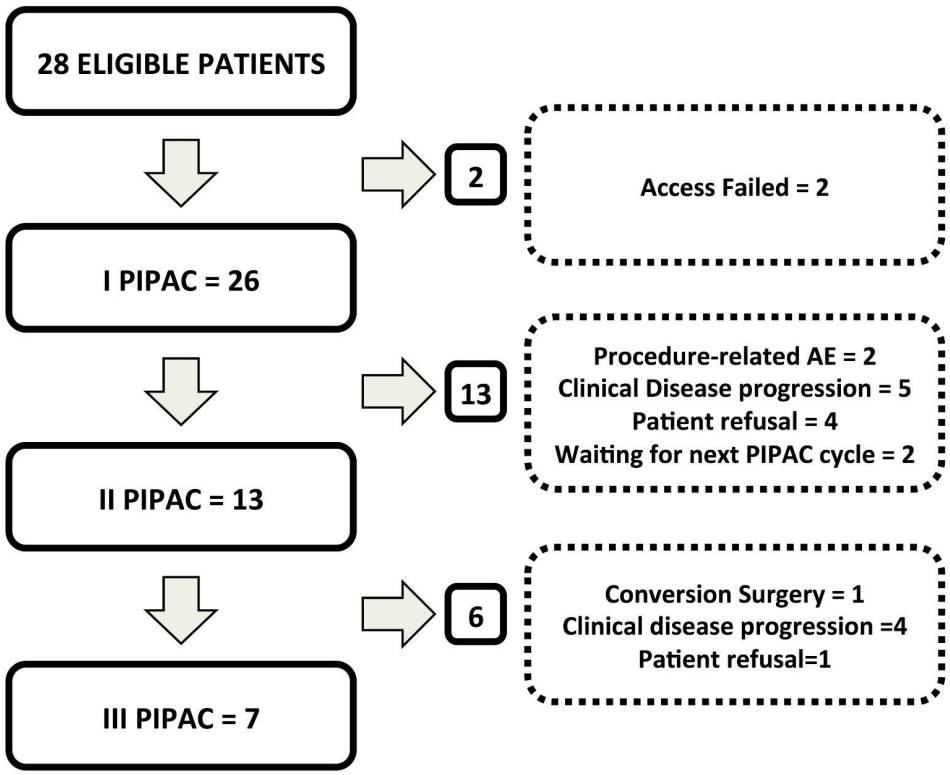


Figure 7. Flowchart of PIPAC procedures and drop-out reasons in gastric cancer peritoneal metastases treatment.

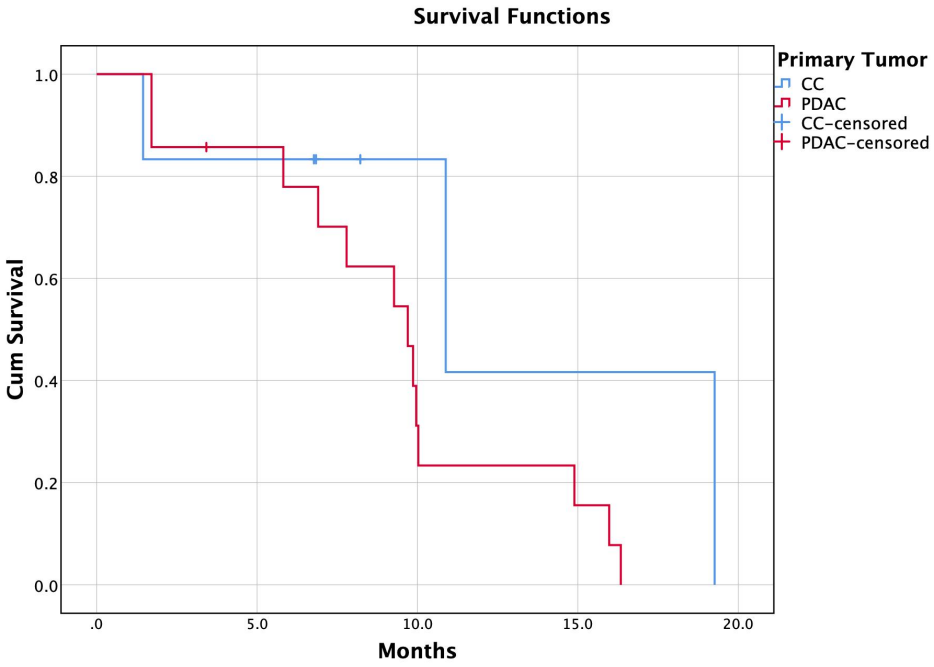


Figure 8. Kaplan–Meier survival curve from the first pressurized intraperitoneal aerosol chemotherapy. x-axis: survival in months; y-axis: cumulative survival. Red line: patients affected by pancreatic adenocarcinoma (PDAC). Blue line: patients affected by cholangiocarcinoma (CC).

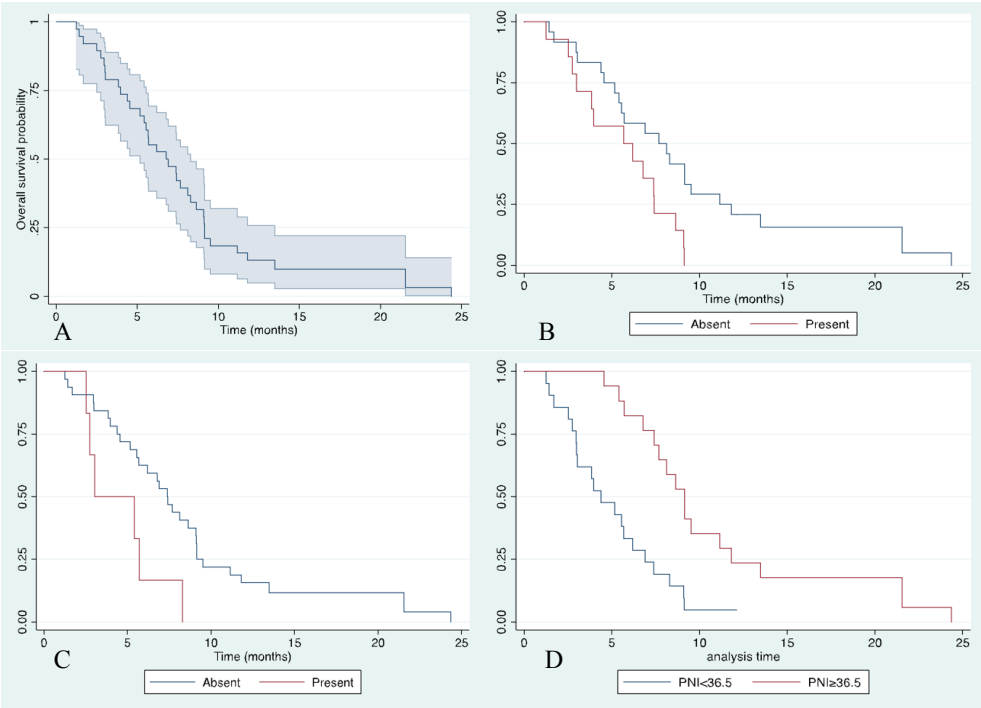


Figure 9. Overall survival analysis (A) and Kaplan Meier curves of overall survivals for ascites (B), dysphagia (C) , and PNI (D).

Bibliography

1. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst. 1997;89: 480–487.

2. Esquis P, Consolo D, Magnin G, Pointaire P, Moretto P, Ynsa MD, et al. High intra-abdominal pressure enhances the penetration and antitumor effect of intraperitoneal cisplatin on experimental peritoneal carcinomatosis. Ann Surg. 2006;244: 106–112.

3. Speyer JL, Myers CE. The use of peritoneal dialysis for delivery of chemotherapy to intraperitoneal malignancies. Recent Results Cancer Res. 1980;74: 264–269.

4. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res. 1980;40: 256–260.

5. Sugarbaker PH. Peritoneum as the first-line of defense in carcinomatosis. J Surg Oncol. 2007;95: 93–96.

6. Dedrick RL, Myers CE, Bungay PM, DeVita VT. Pharmacokinetic rationale for peritoneal drug administration. Cancer Treat Rep. 1978;62: 1–13.

7. Sugarbaker PH, Van der Speeten K. Intraperitoneal chemotherapy for peritoneal metastases: confronting diversity, maximizing benefit. J Gastrointest Oncol. 2021;12: S1–S4.

8. Sugarbaker PH. Peritonectomy procedures. Ann Surg. 1995;221: 29–42.

9. Goodman MD, McPartland S, Detelich D, Saif MW. Chemotherapy for intraperitoneal use: a review of hyperthermic intraperitoneal chemotherapy and early post-operative intraperitoneal chemotherapy. J Gastrointest Oncol. 2016;7: 45–57.

10. Overgaard J. Effect of hyperthermia on malignant cells in vivo. A review and a hypothesis. Cancer. 1977;39: 2637–2646.

11. de Bree E, Tsiftsis DD. Principles of perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. Recent Results Cancer Res. 2007;169: 39–51.

12. Takemoto M, Kuroda M, Urano M, Nishimura Y, Kawasaki S, Kato H, et al. The effect of various chemotherapeutic agents given with mild hyperthermia on different types of tumours. Int J Hyperthermia. 2003;19: 193–203.

13. Sugarbaker PH, Van der Speeten K. PIPAC may work but more data is needed. Journal of gastrointestinal oncology. ncbi.nlm.nih.gov; 2021. pp. S271–S272.

14. Solass W, Herbette A, Schwarz T, Hetzel A, Sun J-S, Dutreix M, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. Surg Endosc. 2012;26: 847–852.

15. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc. 2012;26: 1849–1855.

16. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21: 553–559.

17. 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: 592–598.

18. Grass F, Vuagniaux A, Teixeira-Farinha H, Lehmann K, Demartines N, Hübner M. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. Br J Surg. 2017;104: 669–678.

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. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis. 1997;12: 19–23.

21. Thies S, Langer R. Tumor regression grading of gastrointestinal carcinomas after neoadjuvant treatment. Front Oncol. 2013;3: 262.

22. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi. 1984;85: 1001–1005.

23. Agalar C, Sokmen S, Arslan C, Altay C, Basara I, Canda AE, et al. The impact of sarcopenia on morbidity and long-term survival among patients with peritoneal metastases of colorectal origin treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a 10-year longitudinal analysis of a single-center experience. Tech Coloproctol. 2020;24: 301–308.

24. Banaste N, Rousset P, Mercier F, Rieussec C, Valette P-J, Glehen O, et al. Preoperative nutritional risk assessment in patients undergoing cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for colorectal carcinomatosis. Int J Hyperthermia. 2018;34: 589–594.

25. Khomyakov V, Ryabov A, Ivanov A, Bolotina L, Utkina A, Volchenko N, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura Peritoneum. 2016;1: 159–166.

26. Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond M-A. Pressurized Intraperitoneal Aerosol Chemotherapy with Cisplatin and Doxorubicin in Women with Peritoneal Carcinomatosis: A Cohort Study. Anticancer Res. 2015;35: 6723–6729.

27. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond M-A. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. J Gastrointest Surg. 2016;20: 367–373.

28. Somashekhar SP, Rajagopal AK, Zaveri SS, Chandrashekhar RK, Rauthan A, Rakshit SH. First Indian Study on Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Procedure for Advanced Peritoneal Carcinomatosis Secondary to Epithelial Ovarian Cancer. Indian Journal of Gynecologic Oncology. 2018;16: 25.

29. Giger-Pabst U, Demtröder C, Falkenstein TA, Ouaissi M, Götze TO, Rezniczek GA, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for the treatment of malignant mesothelioma. BMC Cancer. 2018;18: 442.

30. Kurtz F, Struller F, Horvath P, Solass W, Bösmüller H, Königsrainer A, et al. Feasibility, Safety, and Efficacy of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastasis: A Registry Study. Gastroenterol Res Pract. 2018;2018: 2743985.

31. Kuchen N, Cereser T, Hailemariam S, Schoeb O. Safety and efficacy of pressurized intraperitoneal/intrathoracic aerosol chemotherapy (PIPAC/PITAC) in patients with peritoneal and/or pleural carcinomatosis: a preliminary experience. J Med Therap. 2018;2: 2–6.

32. 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: 307–311.

33. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond M-A. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis. 2016;18: 364–371.

34. 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: 309–314.

35. Khosrawipour T, Khosrawipour V, Giger-Pabst U. Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PLoS One. 2017;12: e0186709.

36. Gockel I, Jansen-Winkeln B, Haase L, Rhode P, Mehdorn M, Niebisch S, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in gastric cancer patients with peritoneal metastasis (PM): results of a single-center experience and register study. J Gastric Cancer. 2018;18: 379–391.

37. Falkenstein TA, Götze TO, Ouaissi M, Tempfer CB, Giger-Pabst U, Demtröder C. First Clinical Data of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) as Salvage Therapy for Peritoneal Metastatic Biliary Tract Cancer. Anticancer Res. 2018;38: 373–378.

38. Tempfer CB, Giger-Pabst U, Seebacher V, Petersen M, Dogan A, Rezniczek GA. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Gynecol Oncol. 2018;150: 23–30.

39. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study. Gynecol Oncol. 2015;137: 223–228.

40. Struller F, Horvath P, Solass W, Weinreich F-J, Strumberg D, Kokkalis MK, et al. Pressurized intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin (PIPAC C/D) in patients with gastric cancer and peritoneal metastasis: a phase II study. Ther Adv Med Oncol. 2019;11: 1758835919846402.

41. Graversen M, Detlefsen S, Bjerregaard JK, Fristrup CW, Pfeiffer P, Mortensen MB. Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. Ther Adv Med Oncol. 2018;10: 1758835918777036.

42. Robella M, Vaira M, Borsano A, De Simone M. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with oxaliplatin, cisplatin and doxorubicin in patients with peritoneal carcinomatosis: Preliminary analysis of an open-label, single-arm, phase II clinical trial. Eur J Surg Oncol. 2018;40: e5–e6.

43. Khomyakov V, Ryabov A, Utkina A, Kolobaev I, Sobolev D, Chayka A, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) combining with standard systemic chemotherapy in primary and recurrent gastric cancer (GC) with peritoneal carcinomatosis (PC): results of 214 procedures in 94 patients from case-control study. Eur J Surg Oncol. 2019;45: e77–e78.

44. Horvath P, Beckert S, Struller F, Königsrainer A, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases of pancreas and biliary tract cancer. Clin Exp Metastasis. 2018;35: 635–640.

45. Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol. 2019;20: e368–e377.

46. Rovers KP, Wassenaar ECE, Lurvink RJ, Creemers G-JM, Burger JWA, Los M, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (Oxaliplatin) for Unresectable Colorectal Peritoneal Metastases: A Multicenter, Single-Arm, Phase II Trial (CRC-PIPAC). Ann Surg Oncol. 2021;28: 5311–5326.

47. De Simone M, Vaira M, Argenziano M, Berchialla P, Pisacane A, Cinquegrana A, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Oxaliplatin, Cisplatin, and Doxorubicin in Patients with Peritoneal Carcinomatosis: An Open-Label, Single-Arm, Phase II Clinical Trial. Biomedicines. 2020;8. doi:10.3390/biomedicines8050102

48. Fortpied C, Vinches M. The Statistical Evaluation of Treatment and Outcomes in Head and Neck Squamous Cell Carcinoma Clinical Trials. Front Oncol. 2019;9: 634.

49. Song N, Pogue-Geile KL, Gavin PG, Yothers G, Kim SR, Johnson NL, et al. Clinical outcome from oxaliplatin treatment in stage II/III colon cancer according to intrinsic subtypes: Secondary analysis of NSABP C-07/NRG oncology randomized clinical trial. JAMA Oncol. 2016;2: 1162–1169.

50. Ubink I, van Eden WJ, Snaebjornsson P, Kok NFM, van Kuik J, van Grevenstein WMU, et al. Histopathological and molecular classification of colorectal cancer and corresponding peritoneal metastases. Br J Surg. 2018;105: e204–e211.

51. Van de Sande L, Cosyns S, Willaert W, Ceelen W. Albumin-based cancer therapeutics for intraperitoneal drug delivery: a review. Drug Deliv. 2020;27: 40–53.

52. Weinreich J, Struller F, Sautkin I, Giuashvili S, Reymond M, Königsrainer A, et al. Chemosensitivity of various peritoneal cancer cell lines to HIPEC and PIPAC: comparison of an experimental duplex drug to standard drug regimens in vitro. Invest New Drugs. 2019;37: 415–423.

53. Ando H, Ishida T. An RNAi therapeutic, DFP-10825, for intraperitoneal and intrapleural malignant cancers. Adv Drug Deliv Rev. 2020;154-155: 27–36.

54. Dumont F, Passot C, Raoul J-L, Kepenekian V, Lelièvre B, Boisdron-Celle M, et al. A phase I dose-escalation study of oxaliplatin delivered via a laparoscopic approach using pressurised intraperitoneal aerosol chemotherapy for advanced peritoneal metastases of gastrointestinal tract cancers. Eur J Cancer. 2020;140: 37–44.

55. Kim G, Tan HL, Sundar R, Lieske B, Chee CE, Ho J, et al. PIPAC-OX: A Phase I Study of Oxaliplatin-Based Pressurized Intraperitoneal Aerosol Chemotherapy in Patients with Peritoneal Metastases. Clin Cancer Res. 2021;27: 1875–1881.

56. Robella M, Berchialla P, Borsano A, Cinquegrana A, Ilari Civit A, De Simone M, et al. Study Protocol: Phase I Dose Escalation Study of Oxaliplatin, Cisplatin and Doxorubicin Applied as PIPAC in Patients with Peritoneal Metastases. Int J Environ Res Public Health. 2021;18. doi:10.3390/ijerph18115656

57. Robella M, De Simone M, Berchialla P, Argenziano M, Borsano A, Ansari S, et al. A Phase I Dose Escalation Study of Oxaliplatin, Cisplatin and Doxorubicin Applied as PIPAC in Patients with Peritoneal Carcinomatosis. Cancers . 2021;13. doi:10.3390/cancers13051060

58. Dumont F, Senellart H, Pein F, Campion L, Glehen O, Goere D, et al. Phase I/II study of oxaliplatin dose escalation via a laparoscopic approach using pressurized aerosol intraperitoneal chemotherapy (PIPOX trial) for nonresectable peritoneal metastases of digestive cancers (stomach, small bowel and colorectal): Rationale and design. Pleura peritoneum. 2018;3: 20180120.

59. Van de Sande L, Graversen M, Vermeulen A, Reynders D, Goetghebeur E, Cosyns S, et al. Intraperitoneal aerosolization of albumin-bound paclitaxel nanoparticles (Abraxane®) for peritoneal metastasis: a phase I first-in-human study. Eur J Surg Oncol. 2021;47: e29.

60. Cristea MC, Frankel P, Synold T, Rivkin S, Lim D, Chung V, et al. A phase I trial of intraperitoneal nab-paclitaxel in the treatment of advanced malignancies primarily confined to the peritoneal cavity. Cancer Chemother Pharmacol. 2019;83: 589–598.

61. Mortensen MB, Glehen O, Horvath P, Hübner M, Hyung-Ho K, Königsrainer A, et al. The ISSPP PIPAC database: design, process, access, and first interim analysis. Pleura Peritoneum. 2021;6: 91–97.

62. Raoof M, Malhotra G, Kohut A, O'Leary M, Frankel P, Tran T, et al. PIPAC for the Treatment of Gynecologic and Gastrointestinal Peritoneal Metastases: Technical and Logistic Considerations of a Phase 1 Trial. Ann Surg Oncol. 2021. doi:10.1245/s10434-021-10505-0

63. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst. 2009;101: 708–720.

64. Khosrawipour V, Khosrawipour T, Diaz-Carballo D, Förster E, Zieren J, Giger-Pabst U. Exploring the Spatial Drug Distribution Pattern of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). Ann Surg Oncol. 2016;23: 1220–1224.

65. Khosrawipour V, Khosrawipour T, Kern AJP, Osma A, Kabakci B, Diaz-Carballo D, et al. Distribution pattern and penetration depth of doxorubicin after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in a postmortem swine model. J Cancer Res Clin Oncol. 2016;142: 2275–2280.

66. Göhler D, Khosrawipour V, Khosrawipour T, Diaz-Carballo D, Falkenstein TA, Zieren J, et al. Technical description of the microinjection pump (MIP®) and granulometric characterization of the aerosol applied for pressurized intraperitoneal aerosol chemotherapy (PIPAC). Surg Endosc. 2017;31: 1778–1784.

67. Bellendorf A, Khosrawipour V, Khosrawipour T, Siebigteroth S, Cohnen J, Diaz-Carballo D, et al. Scintigraphic peritoneography reveals a non-uniform 99mTc-Pertechnetat aerosol distribution pattern for Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) in a swine model. Surg Endosc. 2018;32: 166–174.

68. Khosrawipour V, Khosrawipour T, Falkenstein TA, Diaz-Carballo D, Foerster E, Osma A, et al. Evaluating the effect of Micropump© position, internal pressure and doxorubicin dosage on efficacy of pressurized intra-peritoneal aerosol chemotherapy (PIPAC) in an ex vivo model. Anticancer Res. 2016;36: 4595–4600.

69. Jung DH, Son SY, Oo AM, Park YS, Shin DJ, Ahn S-H, et al. Feasibility of hyperthermic pressurized intraperitoneal aerosol chemotherapy in a porcine model. Surg Endosc. 2016;30: 4258–4264.

70. Bachmann C, Sautkin I, Nadiradze G, Archid R, Weinreich FJ, Königsrainer A, et al. Technology development of hyperthermic pressurized intraperitoneal aerosol chemotherapy (hPIPAC). Surg Endosc. 2021;35: 6358–6365.

71. Göhler D, Große S, Bellendorf A, Falkenstein TA, Ouaissi M, Zieren J, et al. Hyperthermic intracavitary nanoaerosol therapy (HINAT) as an improved approach for pressurised intraperitoneal aerosol chemotherapy (PIPAC): Technical description, experimental validation and first proof of concept. Beilstein J Nanotechnol. 2017;8: 2729–2740.

72. Badgwell B. Is PIPAC a New Summit for Peritoneal Disease Treatment or are we Lost in the Snowstorm? Ann Surg Oncol. 2021. doi:10.1245/s10434-021-10899-x

73. Lurvink RJ, Van der Speeten K, Rovers KP, de Hingh IHJT. The emergence of pressurized intraperitoneal aerosol chemotherapy as a palliative treatment option for patients with diffuse peritoneal metastases: a narrative review. J Gastrointest Oncol. 2021;12: S259–S270.

Scientific Products

THIS thesis is based on the following Papers, which are referred to in the text by their Roman numerals (I-V).

I Di Giorgio A, Abatini C, Attalla El Halabieh M, Vita E, Vizzielli G, Gallotta V, Pacelli F, Rotolo S. From palliation to cure: PIPAC for peritoneal malignancies. Minerva Medica. 2019 May 6;110(4):385-98.

II Di Giorgio A, Schena CA, El Halabieh MA, Abatini C, Vita E, Strippoli A, Inzani F, Rodolfino E, Romanò B, Pacelli F, Rotolo S. Systemic chemotherapy and pressurized intraperitoneal aerosol chemotherapy (PIPAC): A bidirectional approach for gastric cancer peritoneal metastasis. Surgical Oncology. 2020 Sep 1;34:270-5.

III Di Giorgio A, Sgarbura O, Rotolo S, Schena CA, Bagalà C, Inzani F, Russo A, Chiantera V, Pacelli F. Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin or oxaliplatin for peritoneal metastasis from pancreatic adenocarcinoma and cholangiocarcinoma. Therapeutic Advances in Medical Oncology. 2020 Jul;12:1758835920940887.

IV Rotolo S, Di Giorgio A, Cintoni M, Rinninela E, Pulcini G, Schena CA, Chiantera V, Vizzielli G, Gasbarrini A, Pacelli F, Mele MC. Body composition and immunonutritional status in patients treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for gastrointestinal peritoneal metastases: a prospective single-center analysis. Pleura and Peritoneum. 2022 *In Press*.

V Di Giorgio A, Rotolo S, Schena CA, Ferracci F, Bagalà C, Carbone C, Tortora G, Pacelli F. Combined Nabpaclitaxel Pressurized IntraPeritoneal Aerosol Chemotherapy with systemic Nabpaclitaxel-Gemcitabine chemotherapy for pancreatic cancer peritoneal metastases. A single-arm, open-label, phase II trial. Nab-PIPAC Trial (STUDY PROTOCOL). EudraCT number: 2021-002539-51. 2nd Congress of the International Society for the Study of Pleura and Peritoneum - ISSPP 2021 – October 7-8, 2021 – Rome, Italy.