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Fragmentas iš Vilniaus universiteto auklėtinio Esajo Jakobo Franko (1771–1842) Medicinos fakultete apgintos daktaro disertacijos *Tentamen inaugurale medicum super causa proxima febrium* (Vilnius, 1793), pirmojo spausdinto mokslinio darbo Lietuvoje, dedikuotos patologijos kursą dėsčiusiam VU profesoriui Jozefui Langmajeriui (1750–1810).

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Martynas Lukšta

DOCTORAL DISSERTATION
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Medical and Health Sciences
Medicine **M 001**

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VILNIAUS UNIVERSITETAS

Martynas Lukšta

Aukšto spaudimo intraperitoninė chemoterapija (PIPAC) kaip papildomas gydymas kartu su standartine sistemine pirmos eilės chemoterapija pacientams sergantiems skrandžio vėžiu išplitusiu pilvaplėvėje: pilotinis tyrimas.

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CONTENT

ABBREVIATIONS

CRS	Cytoreductive surgery
CTCAE	Common Terminology Criteria for Adverse Events
ECF	Chemotherapy regimen of epirubicin, cisplatin, fluorouracil
ECX	Chemotherapy regimen of epirubicin, cisplatin, capecitabine
FLOT	Fluorouracil, leucovorin, oxaliplatin, and docetaxel
FOLFOX	5-fluorouracil, leucovorin, and oxaliplatin
GC	Gastric cancer
GCPM	Gastric cancer peritoneal metastases
GERD	Gastroesophageal reflux disease
HIPEC	Hyperthermic intraperitoneal chemotherapy
IPC	Intraperitoneal chemotherapy
NAC	Neoadjuvant chemotherapy
ORR	Objective response rate
PIPAC	Pressurized intraperitoneal aerosol chemotherapy
PM	Peritoneal metastases
PPIs	Proton pump inhibitors
PRGS	Peritoneal Regression Grading Score
RCT	Randomized control trial
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Standard deviation

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The Ph.D. theses are submitted for defense as a set of research articles and some parts have been quoted verbatim from the previously published articles listed below:

1. Rackauskas R, Bausys A, **Luksta M**, Jurgaitis J, Paskonis M, Strupas K. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal malignancy: initial experience of the first program in the Baltic countries. World J Surg Oncol. 2021 Aug 10;19(1):236. doi: 10.1186/s12957-021-02357-5. PMID: 34376191; PMCID: PMC8356452.

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Strupas K. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in combination with FOLFOX chemotherapy as a first-line treatment for gastric cancer patients with peritoneal metastases: single-arm phase II study. BMC Cancer. 2023 Oct 25;23(1):1032. doi: 10.1186/s12885-023-11549-z. PMID: 37875869; PMCID: PMC10599063.

CHAPTER 1: GENERAL INTRODUCTION AND AIMS OF THIS THESIS

1. Gastric Cancer: epidemiology

Gastric cancer (GC) is one of the most frequently diagnosed malignancies worldwide, with over one million new cases reported annually and a high mortality rate, making it the fourth leading cause of cancer-related deaths globally (1). Despite a general decline in incidence over the past few decades, GC remains a major public health burden, especially in Eastern Asia, Eastern Europe, and parts of South America. In Lithuania, gastric cancer ranks as the fifth most common cancer, with more than 800 new cases diagnosed each year, reflecting both environmental and genetic predispositions within the population (2). GC is typically categorized based on its anatomical location within the stomach into two primary subtypes: cardia GC and noncardia GC. Cardia gastric cancer develops in the upper portion of the stomach adjacent to the esophagogastric junction, while noncardia gastric cancer arises in the lower parts of the stomach, such as the antrum and body. These subtypes are not only anatomically distinct but also differ in their pathogenesis, risk factors, and clinical behaviour. Chronic infection with *Helicobacter pylori* (*H. pylori*) is a major risk factor for noncardia GC, as the bacterium induces chronic gastritis that may progress to atrophy, intestinal metaplasia, dysplasia, and eventually carcinoma. However, it is important to note that not all individuals infected with *H. pylori* will develop cancer, as the progression is strongly influenced by host genetic factors, bacterial virulence, and environmental exposures. In addition to *H. pylori* infection, several lifestyle and dietary factors contribute to the development of gastric cancer. These include cigarette smoking, excessive alcohol consumption, high intake of salt-preserved or processed meats, and diets low in fresh fruits and vegetables, which are rich in protective antioxidants. In contrast, cardia GC is more commonly associated with obesity, central adiposity, and gastroesophageal reflux disease (GERD), suggesting a stronger link to mechanical and metabolic factors rather than chronic infection (3,4).

Epidemiologically, the global incidence of noncardia GC has declined significantly, largely due to better sanitation, widespread use of refrigeration (reducing consumption of salted and smoked foods), and public health efforts to control *H. pylori*. Meanwhile, the incidence of cardia GC has remained stable or, in some populations—particularly in high-income Western

countries—has increased, potentially linked to rising obesity and GERD prevalence (5). Notably, recent data suggest an alarming increase in gastric cancer incidence among young adults under the age of 50, a trend that contradicts the overall decline and raises concerns about new etiological factors. These may include changes in gastric microbiota, early-life antibiotic exposure, and the widespread use of proton pump inhibitors (PPIs), which alter the gastric environment and may contribute to carcinogenesis (6,7).

2. Gastric Cancer: Current Treatment Standards for Non-metastatic cancer

Surgical resection remains the cornerstone of curative treatment for non-metastatic GC and offers the best chance for long-term survival (8). Surgery alone (or endoscopic resection in specific cases) may be sufficient for early GC. The primary goal of radical surgery is the complete removal of the tumor with adequate margins and regional lymph node dissection to ensure accurate staging and minimize the risk of recurrence. The extent of resection margins is dictated by tumor characteristics, including histological type and pattern of spread (9). Lymphadenectomy is another critical component of gastric cancer surgery. It is generally classified into three levels: D1, D1+, and D2. D1 lymphadenectomy involves the removal of perigastric nodes only, while D2 dissection includes additional removal of nodes along the left gastric, common hepatic, splenic, and celiac arteries. For early-stage disease, D1 resection may be sufficient, but in more advanced cases, D2 lymphadenectomy is strongly recommended due to its association with improved disease-free and overall survival, as demonstrated in several long-term randomized trials (10).

For patients with potentially resectable but not early-stage gastric cancer, current clinical guidelines typically recommend perioperative chemotherapy over upfront surgery followed by adjuvant therapy based on the results of several large randomized clinical trials (11, 12). One of the benefits of neoadjuvant chemotherapy (NAC) is that it allows patients to receive chemotherapy before surgery, which is advantageous because postoperative complications can weaken patients physically and reduce their ability to tolerate further chemotherapy. Conversely, administering chemotherapy preoperatively often allows for better patient tolerance, higher completion rates of planned chemotherapy cycles, and more effective tumor control. Additional advantages of the neoadjuvant approach include tumor downstaging, which can convert initially borderline or unresectable tumors into surgically removable lesions, eradication of microscopic metastatic

disease, and improved rates of achieving complete microscopic tumor removal (R0 resection). Collectively, these factors contribute to improved long-term survival and clinical outcomes in GC patients (13). The pivotal MAGIC trial provided substantial evidence supporting the clinical benefit of perioperative chemotherapy combined with surgery for patients diagnosed with operable gastroesophageal adenocarcinoma. This landmark study demonstrated that patients receiving a combination chemotherapy regimen of epirubicin, cisplatin, and fluorouracil (known as the ECF regimen) both before and after surgery experienced significant improvements in survival compared to those undergoing surgery alone. Specifically, the MAGIC trial reported an increase in the five-year overall survival rate from 23% in the surgery-only group to 36% in the chemotherapy-surgery combined group (14). These promising findings were further validated by a multicenter randomized controlled trial conducted in France, known as the FNCLCC and FFCD trial. This study utilized perioperative chemotherapy with cisplatin and fluorouracil and demonstrated a notable increase in the five-year overall survival rate from 24% with surgery alone to 38% with combined perioperative chemotherapy and surgery (15). More recently, the randomized phase 2/3 FLOT4-AIO trial further advanced the role of neoadjuvant chemotherapy by investigating the modern FLOT chemotherapy regimen, comprising fluorouracil, leucovorin, oxaliplatin, and docetaxel. The FLOT regimen achieved superior clinical outcomes, significantly increasing the five-year overall survival rate to approximately 45%, compared to 36% observed in patients treated with the previously standard ECF or ECX regimens (16). Despite the clear clinical benefits demonstrated by these studies, some concerns and scepticism persist regarding the widespread adoption of neoadjuvant chemotherapy. Critics highlight that many key randomized trials assessing perioperative chemotherapy have faced methodological limitations related to surgical quality, particularly insufficient lymphadenectomy, which might influence survival outcomes. Additionally, these studies often combined patients with gastric and oesophageal adenocarcinomas, making it difficult to precisely assess whether extensive radical surgery with comprehensive D2 lymphadenectomy could diminish the perceived chemotherapy-related survival advantages. Thus, while perioperative chemotherapy has become a standard approach in Western countries, Eastern countries still emphasize traditional extensive surgical resection with standardized D2 lymphadenectomy. Furthermore, most existing research has focused predominantly on the response of the primary gastric tumor to chemotherapy,

with relatively limited data available regarding the specific impact of neoadjuvant chemotherapy on metastatic lymph node involvement (17-18).

3. Gastric Cancer: Problem of Peritoneal Metastases

GC often presents a significant clinical challenge due to the lack of effective population-based screening programs and the frequently asymptomatic nature of early-stage disease. As a result, many patients are diagnosed at more advanced stages, when curative options are limited, and prognosis is poor (19,20). At the time of diagnosis, approximately 10–30% of patients with GC already exhibit peritoneal metastases (PM), which are associated with particularly poor outcomes (21). Moreover, even after initial radical surgical treatment with curative intent, a significant proportion of patients develop metachronous PM during follow-up, underscoring the aggressive biological behaviour of GC and its tendency to disseminate within the peritoneal cavity (22). PM in gastric cancer is generally considered a terminal manifestation of the disease. Reported median overall survival in patients with PM ranges from as little as 2 to 9 months, depending on the extent of disease, performance status, and therapeutic approach (23). This short survival highlights the urgent need for more effective treatment modalities and improved patient stratification strategies. The standard treatment for GC with PM typically includes systemic chemotherapy, administered either as monotherapy or in combination with targeted therapies or immunotherapy agents. Despite advancements in systemic regimens, their efficacy in patients with PM remains markedly limited. Response rates in this subgroup are often below 14%, compared to approximately 40% in patients with hematogenous metastases such as those to the liver, lungs, or bones (24,25). The poor response of peritoneal carcinomatosis to standard systemic treatment is explained by the biological phenomenon of the "plasma–peritoneal barrier." This natural barrier prevents intravenously administered chemotherapeutic agents from adequately reaching carcinomatosis sites, and in the absence of sufficient drug concentration, the desired cytotoxic effect is not achieved (31).

4. Gastric Cancer: Intraperitoneal Therapies for Peritoneal Metastases

To overcome this above-mentioned pharmacologic limitation, various innovative drug delivery strategies have been proposed. Among these, nanoparticle-based delivery systems have shown promise in preclinical models by improving targeted drug accumulation in peritoneal tumors while

minimizing systemic toxicity (26). Another key approach is intraperitoneal chemotherapy (IPC), in which anticancer agents are directly delivered into the peritoneal cavity, allowing higher local drug concentrations, prolonged exposure of tumor nodules and free-floating cancer cells to cytotoxic agents, and reduced systemic absorption (27,28). Different methods of IPC have been developed. In several Asian countries, normothermic intraperitoneal chemotherapy via implanted intraperitoneal port systems is more frequently employed for GC patients with limited peritoneal involvement. In contrast, in Western settings, hyperthermic intraperitoneal chemotherapy (HIPEC) is more commonly used (28). HIPEC involves circulating heated chemotherapeutic agents within the peritoneal cavity after cytoreductive surgery (CRS) and has been shown to offer multiple potential benefits. First, hyperthermia itself has a direct cytotoxic effect on malignant cells. Second, elevated temperatures can enhance tissue perfusion and improve the penetration of chemotherapy agents. Third, hyperthermia increases the cytotoxicity of certain drugs—especially platinum-based compounds—through synergistic mechanisms (28). Although HIPEC can be performed as a neoadjuvant treatment before surgery, it is more commonly applied immediately after complete or near complete cytoreductive surgery, with the goal of eliminating microscopic residual disease (29). However, HIPEC is an invasive and intensive treatment modality, suitable only for highly selected patients with limited disease burden and adequate functional status. Many GC patients with PM are in poor general condition at diagnosis and may not tolerate the physiologic stress of CRS-HIPEC, thereby limiting its applicability. Despite encouraging results in certain high-volume centres, the overall clinical benefit of HIPEC remains controversial, particularly outside of specialized settings and in unselected patient cohorts (25).

A more recent and less invasive alternative is pressurized intraperitoneal aerosol chemotherapy (PIPAC), which represents a novel therapeutic strategy designed to improve drug distribution and penetration within the peritoneal cavity. First performed in Germany in 2011, PIPAC uses minimally invasive laparoscopy to deliver aerosolized chemotherapy under pressure into the abdominal cavity (22,26). This approach is thought to optimize intraperitoneal drug dispersion, increase penetration depth by elevating hydrostatic pressure, reduce vascular washout during administration, and maintain controlled intraperitoneal conditions. Moreover, PIPAC allows for repeated treatments and enables longitudinal assessment of treatment efficacy, as peritoneal biopsies can be taken during each procedure to objectively monitor tumor response over time (25).

5. PIPAC for Peritoneal Metastases in Gastric Cancer: Current Evidence and Gaps of Knowledge

Several cohort and small-scale prospective studies have suggested that PIPAC is well tolerated by patients with gastric cancer and peritoneal carcinomatosis, and that its application may be associated with tumor regression as well as improved survival and quality of life outcomes (32–36). Tumor regression during ongoing chemotherapy is assessed using the international Peritoneal Regression Grading Score (PRGS) system, which evaluates the amount of residual tumor cells in biopsies (37). Moreover, the concept of bidirectional PIPAC—where it is combined with systemic chemotherapy—has recently been proposed. One such study was published by Mohammad and colleagues (38). This retrospective study involved 42 patients who underwent 163 PIPAC procedures due to peritoneal metastases. Twenty of these patients received systemic chemotherapy prior to the PIPAC procedures. This combined treatment led to an overall survival of nearly 19 months, and disease regression in 6 patients allowed for subsequent cytoreductive surgery (38). Another study of this type was published by Ellebæk and colleagues, who retrospectively analysed 20 patients treated with systemic chemotherapy and 52 PIPAC procedures (39). This treatment resulted in an overall survival of approximately 11 months. These promising results led the authors to propose that combined treatment could become the new standard of care (39). A similar retrospective study published by Di Giorgio and colleagues indicated that the combination of standard systemic chemotherapy and PIPAC led to a median overall survival of 15.5 months in patients with peritoneally disseminated gastric cancer. However, three full PIPAC procedures could be completed in only 25% of patients (40). All these retrospective studies suggest that combining systemic chemotherapy with PIPAC may yield better outcomes than systemic chemotherapy alone in the treatment of GC peritoneal carcinomatosis. Although, despite the previous studies report encouraging results, their methodological limitations—particularly their retrospective nature—must be considered. Therefore, PIPAC remains an experimental treatment in the early stages of development and is not yet suitable for routine clinical practice. Thus, this research project was designed to address the existing knowledge gaps regarding the role of PIPAC in the treatment of peritoneal metastases from gastric cancer.

6. Structure of this thesis

6.1. Study hypotheses, tasks, and methods

This thesis aims to investigate 5 hypotheses that would facilitate improvement of care for GC patients with PM. These hypotheses are:

1) PIPAC reduces or stabilizes the peritoneal carcinomatosis index (PCI) in patients with gastric cancer.
2) In patients with cytology-positive stage IV gastric cancer, aggressive treatment approaches that combine systemic chemotherapy with radical gastrectomy and/or intraperitoneal chemotherapy lead to improved survival outcomes compared to standard palliative chemotherapy alone.
3) Conversion of cytological status following systemic chemotherapy is linked to better long-term outcomes in patients with cytology-positive stage IV gastric cancer.
4) PIPAC is a safe and feasible treatment modality for patients with gastric cancer peritoneal metastases.
5) The combination of PIPAC with cisplatin and doxorubicin, along with systemic FOLFOX chemotherapy in the first line setting, yields higher objective response rates (ORR) compared to historical ORR achieved with palliative systemic chemotherapy alone.

To test the hypotheses, address the scientific questions and fill the gaps in current knowledge a series of tasks was performed. Task and methods used to answer the scientific questions are summarized in Table 1.

Table 1. Study tasks (scientific question) and methods used to answer the scientific questions

Task (scientific question)	***Method***
1. Does PIPAC reduces or stabilizes the peritoneal carcinomatosis index (PCI) in patients with gastric cancer?	To accomplish this, a retrospective cohort study was performed, and the findings are presented in ***Part I*** of **Chapter 2.**
2. Do aggressive treatment approaches that combine systemic chemotherapy with radical gastrectomy and/or intraperitoneal chemotherapy improve survival outcomes in patients with cytology-	To address this scientific inquiry, a literature review was conducted, and the findings are presented in ***Part I,*** **Chapter 3.**

Task (scientific question)	*Method*
positive stage IV gastric cancer compared to standard palliative chemotherapy alone?	
3. Is conversion of cytological status following systemic chemotherapy associated with improved long-term outcomes in patients with cytology-positive stage IV gastric cancer?	To accomplish this, a retrospective study was performed, and the findings are presented in ***Part II*** of **Chapter 3**.
4. Is PIPAC a safe and feasible treatment modality for patients with gastric cancer peritoneal metastases?	To address this scientific inquiry, a retrospective study was performed, and the findings are presented in in ***Part II*** of **Chapter 2.**
5. Does the combination of PIPAC with cisplatin and doxorubicin, along with systemic FOLFOX chemotherapy in the first line setting, result in higher objective response rates (ORR) compared to the historical ORR of palliative systemic chemotherapy?	To accomplish this, a prospective study was performed (study protocol) and the interim results are presented in ***Part I-II*** of **Chapter 4**.

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CHAPTER 2: PIPAC FOR PERITONEAL MALIGNANCY: INITIAL EXPERIENCE OF THE FIRST PROGRAM IN THE BALTIC COUNTRIES

PART 1: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal malignancy: initial experience of the first program in the Baltic countries

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Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal malignancy: initial experience of the first program in the Baltic countries

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Abstract

Background: Peritoneal malignancies include primary and metastatic cancer of the peritoneal cavity. The most common origin for peritoneal metastasis is ovarian, gastric, and colorectal cancers. Irrespective of the origin, peritoneal metastases represent the advanced disease and are associated with poor long-term outcomes. The minimally invasive approach of pressurized intraperitoneal aerosol chemotherapy (PIPAC) allows repeated applications and objective assessment of tumor response by comparing histological samples. This study aimed to investigate the initial experience with PIPAC in the Baltic region.

Methods: All patients who underwent PIPAC at Vilnius University Hospital Santaros Klinikos between 2015 and 2020 were included in this retrospective study. The primary outcome of the study was overall survival (OS) in patients with peritoneal carcinomatosis treated by PIPAC. The secondary outcomes included postoperative morbidity; peritoneal carcinomatosis index (PCI) and ascites reduction after treatment by PIPAC.

Results: In total, 15 patients underwent 34 PIPAC procedures. PIPAC-related intraoperative and postoperative morbidity occurred in 3 (8.8%) of 34 procedures. Following PIPAC, the median PCI decreased from 8 (4; 15) to 5 (1; 16) in GC patients, although, the difference failed for significance, $p = 0.581$. In OC patients, PCI after PIPAC remained stable. Median overall survival after PIPAC procedure was 25 (95% CI 5–44) months. Ovarian cancer patients (22; 95% CI 12–44 months) had significantly higher OS, compared to gastric cancer patients (8; 95% CI 4–16 months), $p = 0.018$.

Conclusions: PIPAC is safe and feasible for patients with gastric and ovarian cancers peritoneal metastases.

Background

Peritoneal malignancies include primary and metastatic cancer of the peritoneal cavity. The most common origin for peritoneal metastasis is ovarian, gastric, and colorectal cancers [1]. Irrespective of the origin, peritoneal metastases represent the advanced disease and are associated with poor long-term outcomes [2]. Currently, systemic palliative chemotherapy remains the standard treatment for these patients, although the efficacy of such treatment is very limited. One of the limiting factors is the plasma-peritoneal barrier, which restricts the movement of the systemic chemotherapeutic drug to reach the target in the peritoneum [3]. To overcome this issue, the intraperitoneal application of chemotherapy was proposed [4]. Further, intraperitoneal

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chemotherapy is associated with reduced toxicity because of lower systemic concentrations [4]. Considering these advantages, hyperthermic intraperitoneal chemotherapy (HIPEC), usually combined with cytoreductive surgery, gained attention for peritoneal malignancies. Although, a series of recent studies (PRODIGE7, COLOPEC, CYTO-CHIP, PROFILOCHIP) failed to demonstrate the oncological benefit of the HIPEC [5–8]. Another available strategy for intraperitoneal chemotherapy application is pressurized intraperitoneal aerosol chemotherapy (PIPAC). The rationale behind PIPAC includes (1) optimization of drug distribution by applying an aerosol rather than a liquid solution; (2) applying increased intraperitoneal hydrostatic pressure to increase drug penetration to the target; and (3) limiting blood outflow during drug application [9, 10]. The minimally invasive approach of PIPAC allows repeated applications and objective assessment of tumor response by comparing histological samples [10, 11]. However, PIPAC remains an experimental treatment option for patients with peritoneal malignancy. Thus, this study aimed to investigate the initial experience with PIPAC in the Baltic region.

Materials and methods

Ethics

Vilnius Regional Biomedical Research Ethics Committee approval (No. 2020/11-1279-761) was obtained before this study was conducted. The waiver of informed consent was given by the authority. The study was conducted according to the Declaration of Helsinki.

Patients and data collection

All patients who underwent Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) at Vilnius University Hospital Santaros Klinikos between 2015 and 2020 were included in this retrospective study.

Data on patient characteristics were extracted from the prospectively collected institutional electronic database. They included clinicopathologic characteristics (age; gender; history of previous cancer treatment; origin, number, and size of metastases; peritoneal carcinomatosis index (PCI) score at every PIPAC procedure) and treatment-related characteristics (length of surgery; blood loss; chemotherapeutic drugs; postoperative complications by Clavien-Dindo classification).

Technique of procedure

Indications for the PIPAC procedure were peritoneal carcinomatosis ± refractory ascites. Potentially eligible patients willing to receive experimental treatment by PIPAC were discussed at multidisciplinary team meetings and the decision for such treatment was individual in every case.

The procedures were performed following the protocol adjusted to our infrastructure [12].

All operations were performed under general anesthesia; antibiotic prophylaxis with a single dose of cefazoline 1.0 g IV was administered at the time of induction of anesthesia. A nasogastric tube and urinary drainage were not used unless there was a specific indication for their use.

After insufflation of a 12 mmHg CO_2 open access capnoperitoneum was made, two balloon trocars measuring 5 and 10 mm were inserted into the abdominal wall. The preferred sites of insertion were the supraumbilical incision and the left iliac fossa along the same line.

An evaluation of the PCI was done. Biopsies were performed from four different regions of the peritoneal cavity, and ascitic fluid was completely drained and sent for cytological examination.

The 9-mm microinjection pump was connected to an intravenous high-pressure injector and inserted into the abdomen through the 10-mm access port.

A 5-mm camera was inserted through the other port keeping the tip of the Capnopen in view. A safety checklist was performed before the procedure ensuring there is no gas leakage.

One hundred fifty milliliters of NaCl 0.9% containing cisplatin 7.5 mg/m^2 body surface and doxorubicin 1.5 mg/m^2 body surface area was injected through the Capnopen at a pressure of 200 psi at the rate of 0.5 ml/s to generate the aerosol. The intraabdominal pressure throughout the procedure was maintained at 12 mmHg [12].

The therapeutic capnoperitoneum was then maintained for 30 min. Then, the chemotherapy aerosol was evacuated via a separate hospital air-waste system. Finally, trocars were retracted and laparoscopy was ended.

Patients were allowed oral liquids on the same day and discharged on the following day in the absence of adverse events.

Following procedures were repeated at 6 weeks intervals.

Study outcomes

The primary outcome of the study was overall survival (OS) in patients with peritoneal carcinomatosis treated by PIPAC. OS was defined as the time from the first PIPAC procedure to death. The secondary outcomes included postoperative morbidity; PCI and ascites reduction after treatment by PIPAC. Data on survival and date of death were collected from the Lithuanian National Cancer Registry.

Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 24.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as median with an

interquartile range. Categorical variables are shown as proportions. Continuous variables were compared by a Mann-Whitney *U* test, and categorical variables by the Pearson's chi-square or Fisher exact test, as appropriate. Related samples were compared by Wilcoxon signed-rank test or McNemar test, as appropriate. Overall rates were analyzed by the Kaplan–Meier method and compared by the log-rank test. Statistical significance was considered when a p value < 0.05 was achieved.

Results

Baseline characteristics

In total, 15 patients underwent 34 PIPAC procedures. The baseline clinicopathologic characteristics are shown in Table 1. All patients received systemic chemotherapy before PIPAC. Different regimens were used for ovarian cancer (OC) and gastric cancer (GC) patients. All OC patients (6/6; 100%) received platinum-based systemic chemotherapy, specifically paclitaxel, and carboplatin. In GC groups, patients received different schemes including XELOX, EOX, FOLFIRI, and FLOT.

PIPAC procedure characteristics

One, two, or three and more PIPAC procedures were performed for 5 (33.3%), 2 (13.3%), and 8 (53.4%) patients, respectively. Following PIPAC, the median PCI decreased from 8 (4; 15) to 5 (1; 16), although, the difference failed for significance, p = 0.999.PIPAC stabilized the PCI score in both—patients with GC and OC (Fig. 1). One of the indications for palliative PIPAC is refractory ascites. Among 10 patients who received at least 2 PIPACs, 7 had ascites at baseline with a median volume of 300 ml (Q1 100; Q3 2200). After PIPAC, 2 (28.6%) of these patients had no ascites and the median volume decreased to 50 ml (Q1 35; Q3 4050); however, the difference was not significant, p = 0.500. PIPAC-related intraoperative and postoperative morbidity occurred in 3 (8.8%) of 34 procedures. One patient developed severe postoperative neutropenia (2.8%) after PIPAC (Clavien-Dindo score 2); one patient (2.8%) developed intraabdominal abscess postoperatively, which was managed with ultrasound drainage (Clavien-Dindo score 3a); and in one case (2.8%) bowel was perforated during initial port placement due to extensive adhesions, it was repaired intraoperatively, and patient's further recovery was uneventful.

Long-term outcomes

The median time to follow-up after PIPAC was 10 (Q1:4; Q3: 16) months and the median survival by Kaplan–Meier analysis was 25 (95% CI 5–44) months (Fig. 2). OC patients (22; 95% CI 12–44 months) had significantly higher OScompared to GC patients (8; 95% CI 4–16 months), p = 0.018 (Fig. 3).

Discussion

The present study demonstrated the initial results of the first PIPAC program in the Baltic region country—Lithuania. PIPAC was safe and feasible for patients with gastric and ovarian cancer peritoneal metastases. The repeated PIPAC procedures were performed for 66.7% of

Table 1 Baseline clinicopathologic characteristics of patients who received PIPAC

Malignancy; *n* (%)	Gastric cancer	9 (60.0%)
	Ovarian cancer	6 (40%)
Median PCI score (Q1; Q3);	Before PIPAC	8 (4; 15)
	After PIPAC	5 (1; 16)
Sex; *n* (%)	Female (*n*; %)	11 (73.3%)
	Male (*n*; %)	4 (26.7%)
Median age (Q1; Q3); years		58 (51; 68)
Median hospitalization (Q1; Q3); days		5 (3; 6)
Median BMI (Q1; Q3)		25 (20; 30)
History of radical surgery for primary tumor; (*n*; %)	Yes	8 (53.3%)
	No	7 (46.7%)
Median CA125 level (Q1; Q3); kIU/l		103 (15; 351)
Median CEA level (Q1; Q3); ng/l		1.4 (0.5; 9.6)
Median CA19.9 level (Q1; Q3); ng/l		12.3 (6.9; 75.9)
Number of PIPAC procedures	1	5 (33.3%)
	2	2 (13.3%)
	3–4	8 (53.4%)
Median operation time (Q1; Q3); min minutes		115 (110; 133)

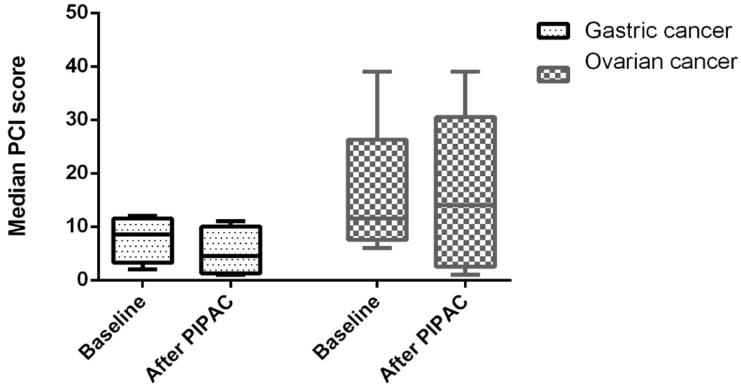

Fig. 1 Median peritoneal carcinomatosis index in patients who received PIPAC for gastric and ovarian cancer peritoneal metastases

patients, and postoperative complications occurred after 8.8% of procedures, with no postoperative mortality. PIPAC reduced the mean PCI in gastric cancer patients and stabilized the disease for ovarian cancer patients.

PIPAC is a new and emerging technique for peritoneal metastases of various cancers. Some evidence shows that it is one of the best methods to manage the burden of advanced intraperitoneal cancer by reducing or halting disease progression and improving quality of life [13]. Further, the minimally invasive approach is one of the major advantages of the PIPAC procedure, as it is associated with a low intraoperative and postoperative morbidity ranging between 0 and 11% in previous and our study [1]. A typical candidate for PIPAC suffers from miliary peritoneal carcinomatosis, which is considered an incurable disease. Although, PIPAC can stabilize the progression of peritoneal carcinomatosis and sometimes even downgrade the disease to the level, where potentially curative cytoreductive surgery with or without HIPEC is feasible [14]. In the present study, we found stabilization of the disease in ovarian cancer patients and regression of the PCI in gastric cancer patients, although

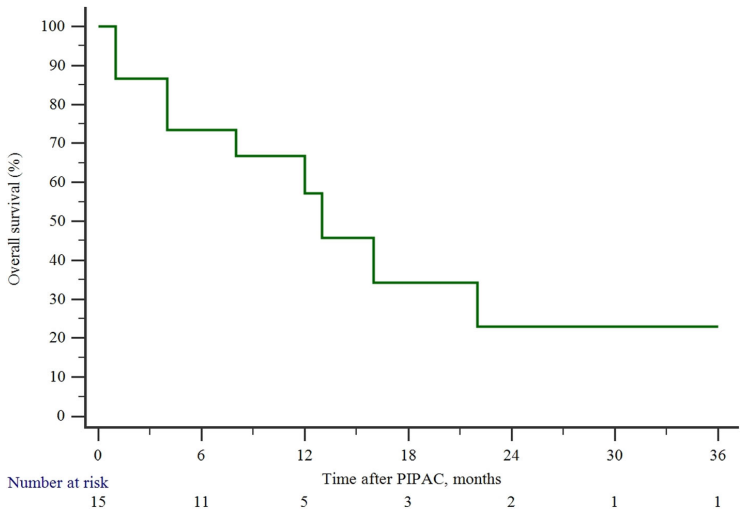

Fig. 2 Overall survival in the entire cohort of study patients who received PIPAC for peritoneal metastases

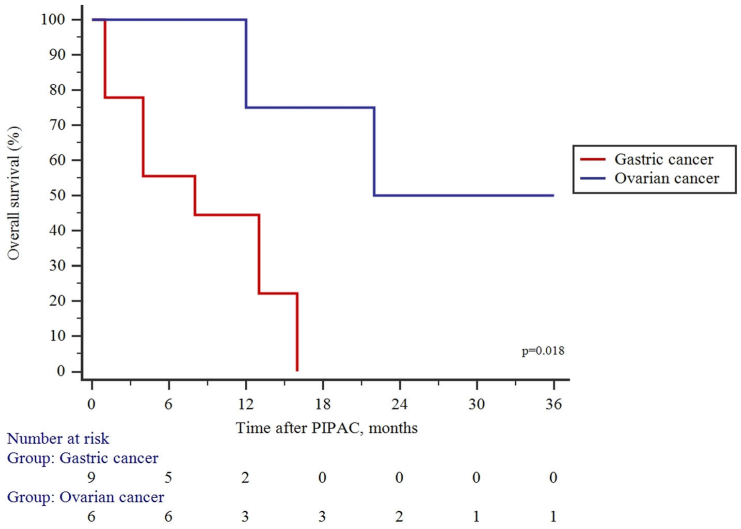

Fig. 3 Comparison of overall survival between gastric and ovarian cancer patients treated by PIPAC

the difference failed for significance. GC patients with a limited PCI may benefit from curative cytoreductive surgery + HIPEC as shown by a recent meta-analysis [15]. Thus, because of PCI score reduction after PIPAC in GC patients, it may be considered as a conversion therapy from unresectable to potentially resectable disease.

A second most common indication for PIPAC is a refractory accumulation of ascites, which impairs quality of life [16]. It has been reported that PIPAC is an excellent method to control ascites, thus it improves the quality of life at the final stages of the disease [17]. In our study, we have found that 28.6% of patients suffering ascites resolved after PIPAC. Further, the median volume of ascites decreased substantially, although the difference failed for significance.

The highest effect of PIPAC is achieved when procedures can be repeated. Alyami et al. reported a clinical response rate of 50–90%, in cases where 3 PIPACs were utilized [1]. Our results show that repeated PIPAC procedures are feasible in approximately two-thirds of patients. Although, the utilization of repeated PIPACs depends on the origin of peritoneal metastases, as three cycles were feasible for 83.3% with OC and only one-third of patients with GC. Such differences may be explained by the different severity of the disease by different origin peritoneal metastases [1]. The different origins of metastases are also, associated with different prognoses. Grass et al. reported that median survival following PIPAC ranges between 11–14.1 and 13.4–15.4 months, for OC and GC patients, respectively [11]. In contrast, our study demonstrated a longer survival for OC patients. The unclarities on the subgroup of patients who benefit the most from PIPAC have to be elucidated in future clinical studies.

A minimally invasive approach associated with low morbidity and potential therapeutic effect for incurable disease makes PIPAC an attractive novel treatment strategy for peritoneal metastases. Thus, there is a growing number of clinical studies investigating PIPAC for various types of cancers and various combinations with systemic therapy or even PIPAC as neoadjuvant therapy [17–21]. Furthermore, some novel anti-tumorigenic agents, such as taurolidine are under investigation for PIPAC [22]. These novel agents may increase the effectiveness and thus the attractiveness of PIPAC. Although to date, there is a lack of robust evidence from prospective randomized studies on the efficacy of PIPAC, thus it still has to be considered as an experimental treatment option.

Our study has some limitations. The retrospective design and small sample size are the major limitations that could lead to the selection bias and underestimation of the positive and negative effects of PIPAC for gastric and ovarian cancer patients with peritoneal metastases. Therefore, the findings of the current study must be validated with larger cohorts.

Conclusions

The present study demonstrated the initial results of the first PIPAC program in the Baltic region country—

Lithuania. PIPAC was safe and feasible for patients with gastric and ovarian cancer peritoneal metastases.

Abbreviations
OC: Ovarian cancer; GC: Gastric cancer; PIPAC: Pressurized intraperitoneal aerosol chemotherapy; PCI: Peritoneal carcinomatosis index; OS: Overall survival; HIPEC: Hyperthermic intraperitoneal chemotherapy

Acknowledgements
Not applicable

Authors' contributions
RR contributed to data collection and analysis and was a major contributor in writing the manuscript. AB contributed to analyzing the data and writing the manuscript. ML, JJ, and MP contributed to writing and reviewing the manuscript. KS contributed to data analysis, manuscript writing, and review of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Vilnius Regional Biomedical Research Ethics Committee approval (No. 2020/11-1279-761) was obtained before this study was conducted. The study was conducted according to the Declaration of Helsinki. Informed consent was waived by the Vilnius Regional Biomedical Research Ethics Committee that approved the study.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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PART 2: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Gastric Cancer Peritoneal Metastases: Results from the Lithuanian PIPAC Program

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Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Gastric Cancer Peritoneal Metastases: Results from the Lithuanian PIPAC Program

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Simple Summary: Peritoneal metastases from gastric cancer are linked to a poor prognosis, with median survival ranging from 2 to 9 months. Standard treatments, including systemic chemotherapy and targeted therapies, have demonstrated only limited effectiveness. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an experimental approach under investigation for treating these metastases, but its widespread clinical use is hindered by insufficient evidence regarding its safety and efficacy. This retrospective study presents outcomes from the first PIPAC program in Lithuania, where 32 patients underwent 71 PIPAC procedures between 2015 and 2022. Intraoperative and postoperative complications occurred in 4.2% of cases. Although reductions in peritoneal carcinomatosis index (PCI) and ascites volume were noted, they were not statistically significant. The median overall survival after PM diagnosis was 12.5 months. These findings suggest that PIPAC is a safe and feasible treatment, but further research is needed to establish its efficacy.

Abstract: Background: Peritoneal metastases (PM) of gastric cancer (GC) are considered a terminal condition, with reported median survival ranging from 2 to 9 months. Standard treatment typically involves systemic chemotherapy alone or combined with targeted therapy or immunotherapy, though efficacy is limited. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has emerged as a novel technique for treating GC PM, although it remains an experimental treatment under investigation. This study aimed to summarize the outcomes of GC PM treatment with PIPAC from the Lithuanian PIPAC program. Methods: All patients who underwent PIPAC for GC PM at Vilnius University Hospital Santaros Klinikos between 2015 and 2022 were included in this retrospective study. The safety of PIPAC was assessed by postoperative complications according to the Clavien–Dindo classification. Efficacy was evaluated based on the peritoneal carcinomatosis index (PCI), ascites dynamics throughout the treatment, and long-term outcomes. Results: In total, 32 patients underwent 71 PIPAC procedures. Intraoperative and postoperative morbidity related to PIPAC occurred after three (4.2%) procedures. Following PIPAC, there was a tendency towards a decrease in median PCI from 10 (Q1 3; Q3 13) to 7 (Q1 2; Q3 12), $p = 0.75$, and a decrease in median ascites volume from

1300 mL (Q1 500; Q3 3600) at the first PIPAC to 700 mL (Q1 250; Q3 4750) at the last PIPAC, $p = 0.56$; however, these differences were not statistically significant. The median overall survival after PM diagnosis was 12.5 months (95% CI 10–17), and the median survival after the first PIPAC procedure was 5 months (95% CI 4–10). Conclusions: PIPAC is a safe and feasible treatment option for GC PM; however, well-designed prospective studies are needed to fully assess its efficacy.

Keywords: gastric cancer; pipac; peritoneal metastasis

1. Background

Gastric cancer (GC) ranks fifth globally in incidence and fourth in mortality, affecting over one million patients annually [1]. The disease often presents a significant challenge due to the lack of effective screening programs and the frequently asymptomatic nature of its early stages, leading to diagnoses at more advanced stages [2,3]. At these stages, up to 30% of patients may present with peritoneal metastases (PM) [4]. Moreover, a significant proportion of patients develop metachronous PM despite previous radical treatment for GC [5]. PM in gastric cancer is generally considered a terminal condition, with median survival rates reported to range from 2 to 9 months [6]. The standard treatment approach for GC PM typically includes systemic chemotherapy, which may be used alone or in combination with targeted therapy or immunotherapy; however, the efficacy of these treatments is often limited [7]. A response rate of less than 14% to systemic treatment can be expected for patients with PM, compared to a response rate of approximately 40% for patients with liver, lung, or bone metastases [8]. One of the primary challenges in managing PM is overcoming the plasma–peritoneal barrier. This barrier significantly impedes the effective delivery of chemotherapeutic agents directly to the peritoneal cavity. To address this issue, various innovative approaches, including the use of nanoparticles for drug delivery [9] and intraperitoneal chemotherapy [10], have been proposed and are currently at different stages of development. One of the primary advantages of intraperitoneal chemotherapy is the minimized systemic absorption of anticancer drugs administered into the peritoneal cavity. This results in higher regional concentrations of the drugs and extended direct exposure time to PM and free cancer cells [11]. Different methods of drug delivery are utilized: normothermic intraperitoneal chemotherapy via intraperitoneal port systems is more commonly used in Asian countries, while hyperthermic intraperitoneal chemotherapy (HIPEC) is preferred in the Western world [11]. The combination of hyperthermia and chemotherapy appears to be beneficial for three main reasons: (I) hyperthermia itself has a selective cytotoxic effect on cancer cells; (II) hyperthermia enhances tissue perfusion and oxygenation, potentially increasing the penetration of cytotoxic drugs; (III) several chemotherapeutic compounds, particularly platinum derivatives, exhibit enhanced cytotoxicity when used in conjunction with hyperthermia [11]. HIPEC may be applied solely as a neoadjuvant treatment [12], but it is usually combined with complete or near-complete cytoreductive surgery. However, for this invasive treatment, patients need to be in good condition, which is often compromised in advanced GC. While the benefits of CRS and HIPEC have been demonstrated in several selected patient cohorts, their efficacy generally remains highly controversial [8]. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) represents a novel approach in this domain aimed at improving drug distribution within the peritoneal cavity [6]. PIPAC is a minimally invasive technique that utilizes physical principles to optimize the delivery of chemotherapeutic drugs. Key mechanisms of PIPAC include (I) optimizing drug dispersion through aerosol delivery, (II) enhancing drug penetration by increasing intraperitoneal hydrostatic pressure, (III) minimizing blood outflow during drug application, and (IV) controlling environmental parameters within the peritoneal cavity to target tissues more effectively [8]. Additionally, PIPAC allows for repeated drug applications and provides the ability to assess tumor responses objectively by comparing biopsies obtained at different stages of treatment [8].

The first PIPAC procedure was performed in 2011 in Germany [9], and the first and only PIPAC program in the Baltic region was established in 2015 at Vilnius University Hospital Santaros Klinikos [13]. Since then, numerous studies have examined the application of PIPAC for GC PM, as summarized in a recent systematic review [14]. These studies suggest that PIPAC holds promise as a treatment option. Nevertheless, conclusive evidence on its effectiveness remains limited, underscoring the need for further investigation. Thus, this study aims to evaluate outcomes following GC PM treatment with PIPAC at the first Baltic center.

2. Materials and Methods

2.1. Study Design and Ethics

This retrospective cohort study was carried out at Vilnius University Hospital Santaros Klinikos. Prior to its commencement, approval was obtained from the Vilnius Regional Biomedical Research Ethics Committee (No. 2020/11-1279-761), with a waiver of informed consent granted by the authority. The study adhered to the principles outlined in the Declaration of Helsinki.

2.2. Patients

All patients who underwent PIPAC for GC PM between 2015 and 2022 at Vilnius University Hospital Santaros Klinikos were included in the study. Patient data, encompassing demographic details and clinicopathologic features like gender, age, previous cancer treatment history, and the Peritoneal Carcinomatosis Index (PCI) score for each PIPAC procedure, were obtained from the institutional electronic database. Additionally, comprehensive treatment-related variables were recorded to provide a detailed overview of the clinical and surgical aspects of the procedures. These variables included the duration of surgery, intraoperative blood loss, and the specific chemotherapeutic agents used during PIPAC. Postoperative complications were documented and graded according to the Clavien–Dindo score, ensuring a standardized assessment of surgical outcomes. Furthermore, data on other oncological treatments administered alongside PIPAC were collected.

2.3. PIPAC Procedure

Our center's protocol for the PIPAC procedure has been previously published [13]. In summary, potentially eligible patients who expressed willingness to undergo experimental treatment with PIPAC were evaluated by a multidisciplinary team, and treatment decisions were made on an individual basis for each case.

All surgeries were conducted under general anesthesia, with a single 2.0 g dose of cefazolin administered intravenously for antibiotic prophylaxis before the incision. At the start of the surgery, two balloon trocars were inserted into the abdominal wall after establishing a 12 mmHg capnoperitoneum via open access. The Peritoneal Carcinomatosis Index (PCI) was then assessed, and biopsies were taken from four different regions of the peritoneal cavity. Ascitic fluid was completely drained, and its volume was recorded and sent for cytological analysis. Then, PIPAC was utilized using a 9 mm Capnopen (CapnoPharm, Tübingen, Germany) microinjection pump connected to an intravenous high-pressure injector. A solution of 150 milliliters of isotonic NaCl 0.9% containing cisplatin at a dose of 7.5 mg/m^2 body surface area and doxorubicin at 1.5 mg/m^2 body surface area was delivered through the microinjection pump at a pressure of 200 psi and a rate of 0.5 mL/s, creating an aerosol within the abdominal cavity. Intra-abdominal pressure was maintained at 12 mmHg throughout the 30 min procedure.

Subsequent PIPAC procedures were scheduled at 6-week intervals, allowing for ongoing assessment and treatment adjustments as needed. The decision to administer PIPAC bidirectionally, with systemic chemotherapy applied between PIPAC procedures or as a unimodal treatment option, was made on a case-by-case basis during multidisciplinary team meetings.

2.4. Study Outcomes

Study outcomes included (1) overall survival (OS), (2) postoperative morbidity, (3) PIPAC impact on Peritoneal Carcinomatosis Index (PCI), and (4) ascites volume.

Overall survival (OS) was defined in two ways: from the time of peritoneal metastasis (PM) diagnosis to death and from the first PIPAC procedure to death. Data on survival and date of death were collected from the Lithuanian National Cancer Registry.

Postoperative morbidity was assessed through complications arising within 30 days after the PIPAC procedures and was classified according to the Clavien–Dindo classification. The impact of PIPAC on the PCI score was evaluated to determine changes in the extent of peritoneal carcinomatosis following the treatment. Ascites volume was monitored by measuring the amount of fluid drained during each PIPAC procedure, providing insights into the treatment's effect on ascites management.

2.5. Statistical Analysis

All statistical analyses were conducted using the statistical program R studio version 2022.12.0+353 (Integrated Development for R; RStudio, PBC, Boston, MA, USA). The normality of the data was tested by using the Shapiro–Wilk normality test. Continuous variables are presented as median with an interquartile range. Related samples were compared using the Wilcoxon signed-rank test. Overall survival rates were analyzed using the Kaplan–Meier method.

3. Results

3.1. Baseline Characteristics

In total, 32 patients underwent 71 PIPAC procedures. The distribution of the number of PIPAC procedures performed per patient was as follows: nine patients (28.1%) underwent one procedure, nine patients (28.1%) had two procedures, thirteen patients (40.6%) received three procedures, and one patient (3.1%) had five procedures.

The baseline clinicopathologic characteristics of these patients are detailed in Table 1. Among the cohort, 29 patients (90.6%) received PIPAC for synchronous peritoneal metastasis (PM), while 3 patients (9.4%) were treated for metachronous PM.

Table 1. Baseline clinicopathologic characteristics of patients who received PIPAC.

Sex, n (%)	**Female**	**15 (46.9%)**
	Male	**17 (53.1%)**
Median age (Q1; Q3), years		55 (46; 66)
Median hospitalization (Q1; Q3), days		2 (1; 4.3)
Median BMI (Q1; Q3)		22.7 (20.3; 25.1)
History of radical surgery for primary tumor, n (%)	Yes	5 (15.6%)
	No	27 (84.4%)
Median CEA level (Q1; Q3) at the time of first PIPAC, ng/L		1.9 (0.98; 5)
Median CA19.9 level (Q1; Q3) at the time of first PIPAC, ng/L		12.8 (3.6; 77.1)
Number of PIPAC procedures, n (%)	1	9 (28.1%)
	2	9 (28.1%)
	3	13 (40.6%)
	5	1 (3.1%)
Median operation time (Q1; Q3), min		92.5 (85; 110)

Prior to undergoing PIPAC, 29 patients (90.6%) had received systemic chemotherapy. The chemotherapy regimens varied, with patients being treated using different schemes: FOLFOX (n = 14), XELOX (n = 7), EOX (n = 5), FOLFIRI (n = 5), and FLOT (n = 2). Specifically, 18 patients (56.3%) had been administered first-line chemotherapy, 7 patients (21.9%) received second-line treatment, and 4 patients (12.5%) were given third-line chemotherapy prior to PIPAC. Additionally, one patient (3.1%) chose to forego systemic chemotherapy and instead received adjuvant radiotherapy following gastrectomy before initiating PIPAC treatment. Notably, two patients (6.3%) received PIPAC as their first-line treatment. Twenty patients (62.5%) received PIPAC as a bidirectional treatment in combination with systemic therapy, while twelve patients (37.5%) received it as a unimodal treatment.

3.2. PIPAC Procedure Characteristics

Following PIPAC, the median PCI decreased from 10 (Q1 3; Q3 13) to 7 (Q1 2; Q3 12), $p = 0.75$ (Figure 1). At baseline, 11 patients (34.4%) had ascites. Following PIPAC, the median volume of ascites decreased from 1300 mL (Q1 500; Q3 3600) at 1st PIPAC to 700 mL (Q1 250; Q3 4750) at last PIPAC, however, the difference was not significant, $p = 0.56$. There was no need for conversion to open surgery throughout the study. In terms of morbidity, intraoperative and postoperative complications related to PIPAC occurred in 3 out of 71 procedures (4.2%). Among the patients, two experienced postoperative complications: one patient (1.4%) developed severe postoperative neutropenia (Clavien–Dindo score 2), and another (1.4%) developed an intra-abdominal abscess that required ultrasound-guided drainage (Clavien–Dindo score 3a). Additionally, one patient (1.4%) suffered an intraoperative bowel perforation during the initial port placement due to severe adhesions. However, this injury was repaired during the surgery, and the postoperative course was uneventful.

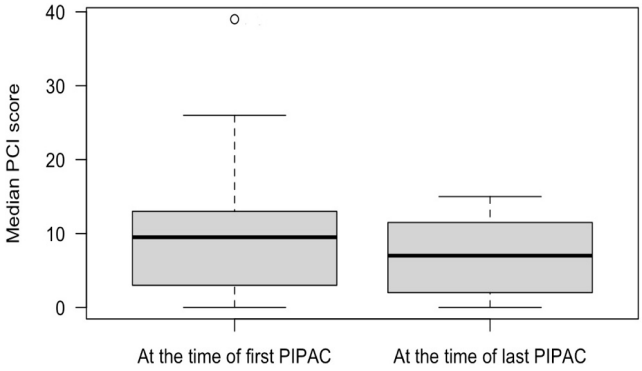

Figure 1. Median peritoneal carcinomatosis index in patients who received PIPAC procedures for gastric cancer peritoneal metastases.

3.3. Long Term Outcomes

The median time to follow-up after diagnosis of PM was 13 (Q1 9; Q3 18) months. The median OS after the PM diagnosis by Kaplan–Meier analysis was 12.5 (95% CI 10–17) months (Figure 2), and after the first PIPAC procedure, it was 5 (95% CI 4–10) months (Figure 3).

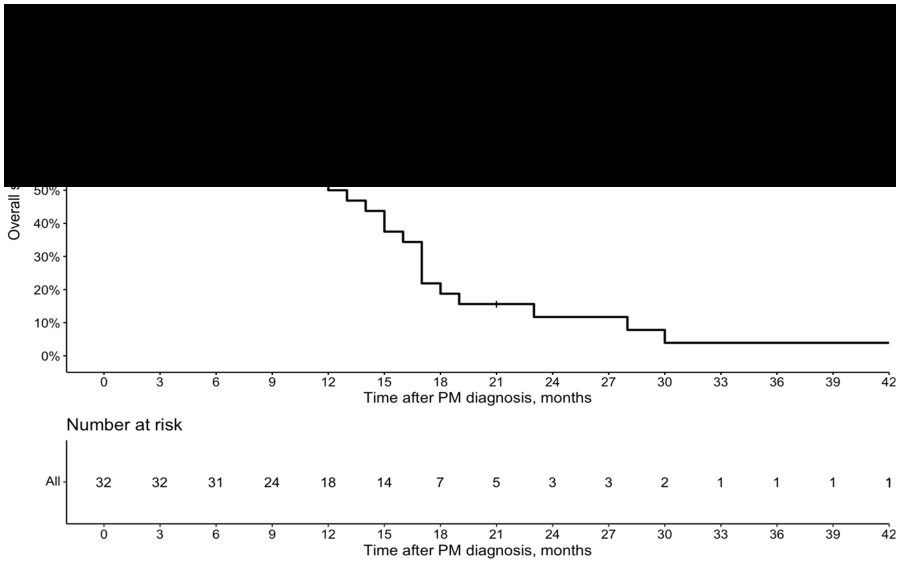

Figure 2. Overall survival from the PM diagnosis of patients who received PIPAC peritoneal metastases.

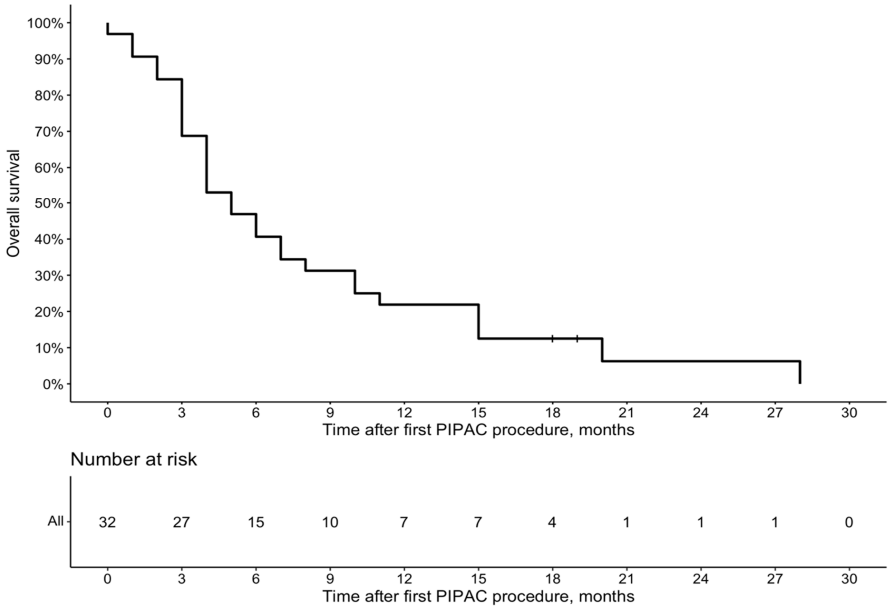

Figure 3. Overall survival from the first PIPAC procedure due to GC peritoneal metastases.

4. Discussion

This study presents the results of the first PIPAC for the GC PM program in the Baltic region. Our findings indicate that PIPAC is a safe procedure with a postoperative complication rate of less than 5% without complications threatening life. Also, we found a tendency that PIPAC may reduce the PCI and ascites volume, although these results failed to show statistical significance. Present findings contribute to the growing body of evidence supporting PIPAC as a safe, feasible, and potentially beneficial treatment option for patients with GC PM. The study provides valuable insights into the effectiveness of PIPAC in managing this challenging condition and highlights the need for further research to confirm its impact and optimize treatment protocols.

Many endpoints are utilized in existing studies to evaluate the efficacy of PIPAC. Objective assessment of therapy response is essential for evaluating new cancer treatments, but it presents difficulties for PM due to the limitations of current radiological imaging techniques, especially in patients with low-volume disease. Small peritoneal metastases are challenging to detect with imaging, and measuring changes in their volume is even more complex. Neither computed tomography nor magnetic resonance imaging reliably assesses tumor adherence or extensive involvement of the small bowel or mesentery. Consequently, peritoneal metastases are often categorized as "non-measurable disease" and excluded from response evaluations, which means patients with these metastases are frequently omitted from randomized studies [15]. Repeated laparoscopy used for PIPAC allows for direct monitoring of the efficacy of multiple cycles of intraperitoneal chemotherapy by measuring various parameters, including PCI dynamics, ascites volume, and histological response. In our cohort, we observed a trend towards a decrease in the median PCI from 10 to 7 and a reduction in ascites volume following PIPAC treatment, although these changes did not achieve statistical significance. These findings align with previous research indicating that PIPAC may help reduce ascites in patients with GC [2]. However, the evidence regarding PIPAC's impact on PCI is less clear. Several studies have suggested that PIPAC may not significantly decrease PCI [2,13,16–20], and there is no definitive evidence linking a reduction in PCI with improved patient outcomes. Such PIPAC impact on PCI is not surprising, as peritoneal metastases may not completely disappear following intraperitoneal chemotherapy but instead become non-viable and fibrotic. Tumor regression grading scores are widely used in the neoadjuvant setting for primary tumors; for instance, the Becker grading system is commonly used for GC [21]. Thus, a similar peritoneal regression grading score (PRGS) has been proposed for objective intraperitoneal chemotherapy response assessment in PM [21]. This four-tier score considers acellular mucin and infarct-like necrosis as regression features [21], and it has prognostic value, as a better response is associated with increased survival rates [22]. Unfortunately, at the time our study was conducted, PRGS was not included in our standard histological reports. As a result, we were unable to explore its potential relationship with treatment efficacy and patient outcomes in our cohort. Overall, while our study supports the potential benefits of PIPAC, especially in managing ascites, further research incorporating PRGS and other relevant endpoints is needed to fully understand the impact of PIPAC on disease progression and patient survival.

Another important aspect of PIPAC treatment is its safety and feasibility. Our results showed acceptable safety of PIPAC, with intraoperative and postoperative morbidity occurring in only 4.2% of procedures and 0% mortality. These complications included one case of neutropenia, one intra-abdominal abscess, and one bowel perforation, all of which were managed effectively. Our results are consistent with previous studies showing that the rate of severe or life-threatening complications following PIPAC ranges between 0.7% and 25% [2,16,17,20,23–26]. Such a wide range of complication rates may arise from the use of different grading systems across the studies. Most authors register and classify adverse events using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [2,16,17,23], which is the gold standard in cancer clinical trials, while others use the Clavien–Dindo scale [13,20,27,28], as we did in our study. The issue of heterogeneity in

complication reporting has recently been addressed by the PIPAC UK collaborative group in a systematic review. They proposed that CTCAE should be the standard reporting measure, along with 30-day postoperative mortality, in future prospective trials due to its comprehensive assessment, especially when PIPAC is delivered together with systemic chemotherapy [14].

Another important aspect of novel cancer treatment is its tolerability. In the present study, 71.9% of patients received more than two PIPAC procedures, and 43.8% received more than three PIPAC procedures. There were no reported failures for laparoscopic abdominal access, indicating that the discontinuation of PIPAC was due to the deterioration of general health rather than technical reasons. A higher number of PIPAC cycles has been reported to be associated with improved survival [2,16,19,20,29]. However, it remains unclear whether healthier patients survive longer and can tolerate more PIPAC cycles or if receiving more PIPAC cycles directly prolongs survival. In our cohort, the median OS after the diagnosis of PM was 12.5 months, and the median survival after the first PIPAC procedure was 5 months. These figures align with previous reports, which show a median OS ranging from 8 to 19.1 months [13,30] and survival after the first PIPAC ranging from 4.7 to 6.9 months [2,14,16,19,20,29]. Such relatively short survival after initiating PIPAC treatment must be considered carefully. In most previous studies, as well as in our cohort, the vast majority of patients received PIPAC late in the treatment pathway after the failure of several lines of systemic chemotherapy [14]. Administering PIPAC earlier, before the development of chemoresistance to systemic treatment, may increase the proportion of patients able to receive more PIPAC cycles and potentially improve treatment efficacy. Moreover, implementing PIPAC in the early stages of treatment may allow for its use in a bidirectional manner when combined with systemic chemotherapy. Although there is no clear evidence to date showing whether bidirectional therapy adds additional benefits, it has the potential to optimize both systemic and local (peritoneal) control [14].

In general, the present study suggests that PIPAC may be a valuable treatment option for selected patients with GC PM, offering a low rate of treatment-related complications and potentially promising survival outcomes.

However, several limitations must be considered when interpreting these results. The retrospective nature of the study and the relatively small sample size are significant constraints, as they may affect the robustness and generalizability of the findings. Additionally, the absence of a control group receiving standard care without PIPAC limits our ability to draw definitive conclusions about the comparative efficacy of PIPAC versus other treatment modalities. To address these limitations and provide a more comprehensive understanding of PIPAC's role in the treatment of GC PM, continued research is essential. Larger prospective studies are warranted to further elucidate PIPAC's effectiveness, optimize treatment protocols, and identify patient populations who may benefit the most from this innovative approach. Such research will help to clarify PIPAC's role within the broader context of treatment for GC PM and contribute to the development of more effective management strategies for this challenging clinical condition.

5. Conclusions

The present study suggests that PIPAC is a feasible and safe treatment option for patients with GC PM. Despite the non-significant reductions in PCI and ascites volume, PIPAC's potential to stabilize the disease and its acceptable safety profile underscores its utility as part of a multimodal treatment strategy. Continued research, including larger and prospective studies, is warranted to further elucidate the benefits and optimize the use of PIPAC in this challenging clinical context.

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Writing—Review and Editing, T.P., R.B., S.T., R.L.-L., R.S., K.B., J.B., R.R., M.P., A.R., B.B., E.B., N.L. and K.S.; Visualization, N.G.; Supervision, T.P., S.T., R.B. and K.S.; Project Administration, K.B., N.G., J.B. and M.L. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Patient consent was waived due to most patients being either deceased or not undergoing treatment at the time of the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author due to local legal regulations.

Conflicts of Interest: The authors declare that there are no conflicts of interest related to this study. This research did not receive any external funding. Some of the results presented in this manuscript have been shared with the scientific community at various national and international conferences.

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CHAPTER 3: TREATMENT STRATEGIES FOR PATIENTS WITH ONLY PERITONEAL CYTOLOGY POSITIVE STAGE IV GASTRIC CANCER

PART 1: Current treatment strategies for patients with only peritoneal cytology positive stage IV gastric cancer

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MINIREVIEWS

Current treatment strategies for patients with only peritoneal cytology positive stage IV gastric cancer

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Abstract

Gastric cancer (GC) is one of the most common malignancies worldwide and surgery remains the only potentially curative treatment option for it. Although a significant proportion of GC patients are found with distant metastases already at the initial diagnosis. Peritoneal dissemination is the most common site of metastases. Positive peritoneal cytology (Cy1) is associated with poor long-term outcomes; thus, these patients are considered as stage IV even if macroscopic carcinomatosis is absent. Currently, there is no clear evidence for the most optimal treatment for this distinct subpopulation of the stage IV cohort. Available strategies vary from palliative chemotherapy to upfront gastrectomy. This comprehensive review summarized current evidence of different treatment strategies for Cy1 GC including roles of surgery, systemic and intraperitoneal chemotherapy.

Key Words: Gastric cancer; Positive peritoneal cytology; Gastrectomy; Systemic chemotherapy; Intraperitoneal chemotherapy

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Core Tip: Positive peritoneal cytology (Cy1) is associated with poor long-term outcomes; thus, these patients are considered as stage IV even if macroscopic carcinomatosis is absent. The evidence for the most efficient treatment of these patients is conflicting. We herein review current knowledge and the outcomes of different approaches for Cy1 gastric cancers.

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INTRODUCTION

Gastric cancer (GC) remains an important health care issue as it is the fifth most common and the fourth most deadly cancer worldwide[1]. Surgery is the only potentially curative treatment option for it[2,3]. Although up to 30%-40% of GC patients already have distant metastases at the initial diagnosis and typically they are not candidates for radical surgery[4,5]. Peritoneal dissemination is the most common site of metastases[6]. Peritoneal lavage cytology at staging laparoscopy is the modern standard to detect peritoneal spread even before visible peritoneal carcinomatosis (PC) could be detected[7-9]. Positive cytology alone (Cy1) is a negative prognostic factor for recurrence and survival[10]; thus, it is defined as metastatic (M1) factor and Cy1 patients are considered as stage IV even in absence of macroscopic carcinomatosis.

Current clinical practice guidelines by the European Society for Medical Oncology (ESMO)[11] and National Comprehensive Cancer Network (NCCN) recommend palliative chemotherapy for Cy1 patients with a possibility for re-staging through treatment. Although, Japanese GC treatment guidelines distinguish Cy1 patients as a distinct subpopulation of the stage IV cohort and suggest considering neoadjuvant chemotherapy followed by D2 gastrectomy if other non-curative factors are absent [12]. Such discrepancies and a lack of standardization arise from the gap of current knowledge for the most efficient treatment of patients with only Cy1 stage IV GC. Therefore, this review aimed to summarize the current evidence for peritoneal dissemination in GC and various available treatment options for Cy1 stage IV patients.

MECHANISMS OF PERITONEAL DISSEMINATION IN GC

Patients with locally advanced [that penetrates subserosal connective tissue, serosa, or adjacent structures (T3 or T4) or more advanced N-stage] GC, unfavorable histological subtypes (diffuse type and/or signet ring cell component), or primary scirrhous type GC are at higher risk for peritoneal metastases[13,14]. The development of these metastases is a multistep process which includes: (1) Cancer cells detachment from the primary tumor; (2) Survival in the microenvironment of the peritoneal cavity; (3) Malignant cells attachment to peritoneal mesothelial cells and invasion through basement membrane; and (4) Tumor growth and the onset of neoangiogenesis[15]. However, not all free intraperitoneal cancer cells seed into the peritoneum and turn into PC nodes. Most of these cells die even after successful attachment to the peritoneum, because of the peritoneal-blood barrier[15]. Further, mesothelium, the innermost monolayer of the peritoneum, has some basic protective mechanism against the adhesion of exogenous cells[15]. PC develops only after some sub-population of free GC cells manage to penetrate the submesothelial space by producing specific growth factors and matrix metalloproteinases, which induce the contraction of mesothelial cells, exposing the submesothelial basement membrane[15]. The presence of free GC cells in the peritoneal cavity represents the initial stages of PC development, however, currently, there are no methods to determine at what exact stage this multistep process has been diagnosed. Thus, it remains unclear if the treatment concept for Cy1 patients should aim to treat the present peritoneal disease or should aim to prevent its further development. Because of such controversies, different strategies have been adopted for Cy1 GC worldwide (Figure 1).

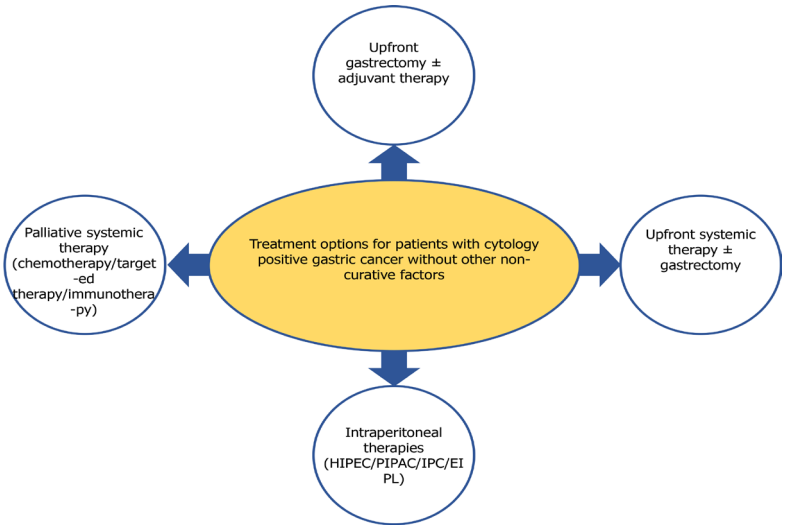

Figure 1 Different available treatment options for patients with cytology positive gastric cancer without other non-curative factors. HIPEC: Hyperthermic intraperitoneal chemotherapy; PIPAC: Pressurized intraperitoneal chemotherapy; IPC: Intraperitoneal chemotherapy; EIPL: Extensive peritoneal lavage.

UPFRONT SURGERY FOR CY1 GC PATIENTS

Surgery remains the only potentially curative treatment option for GC[3]. However, Cy1 represents stage IV disease, thus, despite it may be technically resectable, the biological rationale for surgery is controversial. The results of the randomized controlled trial (RCT) by the Japan Clinical Oncology Group (JCOG 0705) and Korea GC Association (KGCA01), comparing gastrectomy + chemotherapy *vs* chemotherapy alone in advanced GC with a single non-curable factor, showed no advantage of surgery for patients with PC[16,17]. Nonetheless, palliative chemotherapy is associated with disappointing long-term outcomes and Cy1 patients represent the distinct subpopulation of GC patients with peritoneal dissemination. Therefore, more aggressive treatment strategies including surgical resections are utilized for these patients in some centers.

Upfront radical gastrectomy followed by adjuvant S-1 monotherapy was investigated in a phase II single-arm (CCOG0301) study which enrolled 48 Cy1 GC patients across the multiple treatment centers in Japan[18]. Long-term follow-up showed 5-year overall (OS) and relapse-free survival rates were 26% and 21%, respectively. Peritoneal recurrence occurred in 62% of enrolled patients[18]. Similar results were confirmed by other groups from the East[19-21]. Kano *et al*[19] presented a retrospective study with a median follow-up of almost 10 years. Radical gastrectomy followed by adjuvant S-1 chemotherapy resulted in a 17.8% 5-year OS rate and peritoneal recurrence rate of 52.9%[19]. Further, the study documented the benefit of adjuvant S-1 monotherapy, as the median survival increased to 22.3 mo compared to 11.8 mo in the surgery alone group[19]. The benefit of adjuvant therapy was confirmed in another study from Korea by Shim *et al*[20]. Adjuvant chemotherapy by TS-1 ± cisplatin or oxaliplatin plus capecitabine (XELOX) or oxaliplatin + 5-FU (FOLFOX) improved median disease-free survival (DFS) (11.63 *vs* 6.98 mo, $P < 0.001$) and OS (25.50 *vs* 12.11 mo, $P < 0.001$)[20]. No significant differences were observed between the regimen of postoperative chemotherapy and survival[20], thus the most optimal regimen remains unclear. Another retrospective study by Komatsu *et al*[21] analyzed upfront gastrectomy followed by adjuvant S-1 based chemotherapy in 51 Cy1 GC patients, with a special focus on the impact of surgical radicality. Radical gastrectomy with ≥ D2 Lymphonodectomy was superior compared to palliative gastrectomy with the 5-year OS of 48.2% *vs* 18.2%, respectively[21]. Further, the impact of surgery for Cy1 GC treatment

was presented in another recent study from China[22]. Forty-eight Cy1 GC patients underwent upfront gastrectomy (75%; *n* = 36) or gastrectomy after neoadjuvant chemotherapy (25%; *n* = 12)[22]. The median OS and DFS were 22 and 16.5 mo, respectively[22]. However, the study did not provide a comparison of long-term outcomes between patients who received upfront surgery and neoadjuvant treatment [22]. In contrast, such a comparison was performed by Mezhir *et al*[23] In a Western cohort. Neoadjuvant therapy failed to improve DSS (1.7 *vs* 0.9, *P* = 0.76), although the relatively small sample size in the upfront surgery (*n* = 29) and neoadjuvant treatment groups (*n* = 23) should be taken into consideration[23].

Together, the current evidence indicates that radical upfront gastrectomy is feasible for Cy1 GC patients, and adjuvant chemotherapy is necessary to improve long-term outcomes. Although, most of the evidence for the upfront surgery arises from small-scale Eastern studies. Such treatment strategy needs further investigation in large-scale high-quality surgical trials, including the patients from Western parts of the world.

UPFRONT SYSTEMIC THERAPY FOR CY1 GC PATIENTS

As mentioned previously, Cy1 GC represents the stage IV disease, thus ESMO and NCCN guidelines suggest considering systemic treatment (chemotherapy) as it improves survival and quality of life compared to best supportive care[11]. Doublet or triplet platinum / fluoropyrimidine combinations ± trastuzumab is recommended as a first-line palliative treatment[11]. Although there is no evidence for the most appropriate chemotherapy regimen to treat peritoneal metastases in GC[24], therefore, different schemes are adopted in clinical practice.

Several studies investigated the rates of conversion from positive to negative cytology following initial treatment by systemic chemotherapy[23-25]. The reported rates of conversion varied between 48.9% and 72.2% after treatment by various platinum / fluoropyrimidine combinations with or without docetaxel or trastuzumab [23-25]. Such conversion from positive to negative cytology results in improved oncological outcomes. Mezhir *et al*[23] showed increased disease-specific survival (2.5 *vs* 1.4 years) in those who converted to negative cytology. Similar, Yasufuku *et al*[25] and Aizawa *et al*[24] demonstrated improved 3-year (76.9% *vs* 10.5%) and 5-year (34.6% *vs* 17.6%) OS rates, respectively.

The high rate of conversions from positive to negative cytology and the clinical benefit of it proposes to consider the initial chemotherapy not as a palliative, but as neoadjuvant treatment. Further, the study by Badgwell *et al*[26] suggested, that palliative treatment may be inferior to neoadjuvant chemotherapy, despite only 41.6% of patients treated with it underwent surgery at some point of the treatment. Neoadjuvant therapy group showed a notably higher 3-year OS rate of 12% compared to 0% in patients who were considered as having incurable stage IV disease, therefore scheduled for palliative therapy only.

The upfront systemic therapy is the most promising when the conversion of cytological status is achieved, especially if converted patients can be allocated for further surgical treatment. The most effective chemotherapy regimens and the optimal number of cycles for conversions remain unknown, thus, future studies should elucidate these unclarities.

INTRAPERITONEAL THERAPIES FOR CY1 GC PATIENTS

As shown previously, systemic chemotherapy in a neoadjuvant or adjuvant setting plays an important role to improve Cy1 GC patients' outcomes. Although, systemic chemotherapy is considered to be limited efficacy for peritoneal dissemination because of the peritoneal-plasma barrier[27]. Therefore, direct intraperitoneal therapies have been suggested as a more effective alternative for these patients.

INTRAPERITONEAL CHEMOTHERAPY AND EXTENSIVE INTRAOPERATIVE PERITONEAL LAVAGE

The rationale for intraperitoneal chemotherapy (IPC) application is the possibility to achieve high local concentration while keeping the low systemic concentration of cytotoxic drug[28]. These pharmacokinetic features of the method increase the

therapeutic efficacy and decrease systemic toxicity. The possible limitation of IPC for the PC is the limited penetration of the drug. The maximum estimated depth of drug penetration is 3 to 5 mm, although actual penetration range from a few cell layers to a few millimeters[28]. Despite this shortcoming of the method for PC, it does not preclude the eradication of free intraperitoneal cancer cells. Thus, IPC was investigated as an attractive option for Cy1 GC patients.

Imano *et al*[29] conducted a pilot clinicopathological study to investigate intraperitoneal administration of 80 mg/m^2 paclitaxel at the end of the radical D2 gastrectomy for 10 Cy1 GC patients. Pharmacokinetic analysis showed that the peak plasma concentration of paclitaxel did not reach the cytotoxic threshold level of 0.1 mol/L, while intraperitoneal drug concentration was about 6773 folds higher[29]. Such IPC cleared the peritoneal cytology as no viable cancer cells were found at 24 and 48 h after IPC[29]. Following radical surgery with IPC majority of patients received adjuvant S1 based chemotherapy[29]. Long-term outcome analysis showed a promising 3-years survival rate of 56% and the peritoneal recurrence rate of 30%[29]. Further, the authors compared these survival outcomes with a historical cohort who received gastrectomy alone and concluded that IPC significantly improves the survival of Cy1 GC patients [29]. Another study on IPC for Cy1 GC investigated the additional benefit of extensive peritoneal lavage (EIPL)[30]. Shimada *et al*[30] study included 22 Cy1 GC patients who underwent: (1) Gastrectomy; (2) Gastrectomy + IPC with 100 mg cisplatin; or (3) Gastrectomy + IPC + EIPL by peritoneal cavity washing with 10 Liters of physiologic saline solution. Postoperatively all patients received adjuvant 5-FU based chemotherapy[30]. Long-term outcomes analysis showed 2-year OS rates of 0%, 14.3%, and 57.1% in groups 1, 2 and 3, respectively. Further EIPL reduced the peritoneal recurrence rate to 42.9% compared to 85.7% and 100% in gastrectomy + IPC and gastrectomy groups, respectively. Cancer cell detection analysis in the peritoneal lavage by reverse transcriptase-polymerase chain reaction (RT-PCR) suggested 10 Liters of physiologic saline as an optimal amount to flush out the free cancer cells from the peritoneal cavity[30]. Because of the promising results in the retrospective study, the gastrectomy + EIPL + IPC strategy was tested in the subsequent multicenter RCT [31]. The study included 88 Cy1 GC patients and randomly allocated them to three previously mentioned treatment strategies[31]. This prospective study confirmed the superiority of EIPL + IPC, as the 5-year OS increased to 43.8% compared to 4.6% and 0% in IPC and gastrectomy alone groups, respectively. Further EIPL + IPC significantly reduced the peritoneal recurrence rate to 40.0% compared to 79.3% in IPC and 89.7% in gastrectomy alone groups. After the promising results of the retrospective study were confirmed in the subsequent RCT, authors recommended considering EIPL-IPC therapy as a standard prophylactic strategy for peritoneal dissemination in Cy1 GC patients[31]. However, some conflicting data on the efficacy of EIPL was presented in a recent EXPEL study. This high-quality, open-label, multicentre, phase 3 surgical RCT, conducted at 22 hospitals from South Korea, China, Japan, Malaysia, Hong Kong, and Singapore enrolled 800 patients to evaluate the potential benefit of EIPL after upfront radical gastrectomy for cT3-4 GC[32]. However, EIPL by 10 Liters of saline did not improve 3-year OS [77.0% *vs* 76.7%; HR: 1.09 (95%CI: 0.78-1.52); P = 0.62], DFS [64.8% *vs* 69.4%; HR: 1.12 (95%CI: 0.86-1.47); P = 0.40], and 3-year cumulative incidence for peritoneal recurrence [7.9% *vs* 6.6%; HR: 1.33 (95%CI: 0.73-2.42); P = 0.35]. Moreover, EPIL was associated with higher risk of adverse events (RR = 1.58, P = 0.019)[32,33].

HYPERTHERMIC IPC

Hyperthermic IPC (HIPEC) is another available method for peritoneal malignancy. It combines the benefit of IPC with the potential advantages of hyperthermia. Experimental and clinical evidence indicates that hyperthermia at a range of 41 to 43 °C destroys malignant cells by selectively increasing the number of lysosomes and lysosomal enzyme activity in malignant cells leading to increased destructive capacity [28]. Also, hyperthermia decrease blood flow in most of the malignant tumors in contrast to the opposite effect in normal tissues[28]. Such effects, together with inhibition of oxidative metabolism in malignant cells promote cell death of the more sensitive malignant cells[28]. Further, heat promotes the cytotoxic effect of the chemotherapeutical agents [28]. Thus, HIPEC was widely investigated for peritoneal disease treatment including studies in Cy1 GC patients. Meta-analysis of randomized and high-quality non-randomized trials on HIPEC for prevention and treatment of peritoneal disease in GC patients found no difference in the 3-year OS (RR = 0.99, P =

0.85) for patients with PC[34]. Although, HIPEC obtained advantages in preventing peritoneal metastases (RR = 0.63; 95%CI: 0.45-0.88; $P < 0.01$) in high-risk patients, including Cy1 GC patients[34]. Also, HIPEC might be applied in a neoadjuvant setting as showed by Badgwell *et al*[35] in a single-arm phase II study. Nineteen stage IV GC patients only by positive cytology ($n = 6$) or limited PC ($n = 13$) received up to 5 cycles of neoadjuvant laparoscopic HIPEC after initial systemic chemotherapy. In total seven (36.8%) of these converted to negative cytology and no PC and 5 of them received radical gastrectomy[35]. It is important to emphasize that the conversion rate of 66.6% (4 of 6 patients) in Cy1 patients was considerably high[35]. This aggressive treatment resulted in a 3-year OS rate of 43.5%, and the median survival of patients who received gastrectomy was 29 mo. After encouraging results of the study Badgwell *et al*[36] conducted another single-arm phase II study for an even more aggressive approach. Twenty patients with limited PC ($n = 14$) or Cy1 ($n = 6$) were treated with initial systemic chemotherapy followed by 1-2 Laparoscopic HIPEC procedures and then subsequent gastrectomy with a cytoreduction and intraoperative HIPEC[36]. Such an aggressive treatment resulted in a 28% 3-year OS[36]. However, it is important to note, that subgroup of Cy1 patients had a very promising result of such treatment, as 50% ($n = 3$) of Cy1 were alive and recurrence-free at 32-49 mo after diagnosis. Despite the encouraging initial results on HIPEC for Cy1 patients, there is a lack of data from high-quality large-scale RCTs. Currently, an ongoing phase III GASTRICHIP trial[37] is designed to evaluate the effect of HIPEC in patients with a high risk of peritoneal recurrence, including Cy1 patients after neoadjuvant chemotherapy[37]. The long-term outcomes will be available in 2023 and the results will elucidate some unclarities regarding HIPEC's role for Cy1 GC patients[34].

PRESSURIZED IPC

Another new and emerging technique for a peritoneal disease is pressurized IPC (PIPAC). During PIPAC, laparoscopic access is obtained to create a pneumoperitoneum of 12 mmHg and nebulized chemotherapy is applied to create therapeutic capnoperitoneum for 30 min[38]. The rationale for PIPAC includes: (1) Optimization of drug distribution by applying an aerosol rather than a liquid solution; (2) Applying increased intraperitoneal hydrostatic pressure to increase drug penetration to the target; and (3) Limiting blood outflow during drug application[39,40]. Further, the minimally invasive approach of PIPAC allows multiple applications of the procedure and objective reassessment of the response through laparoscopy and biopsies[39]. Similar to laparoscopic HIPEC, PIPAC may be utilized in a neoadjuvant setting and also in combination with systemic therapy. Several retrospective and prospective phase II studies suggested that PIPAC may be a safe and promising option for GC patients with PC[41-44], although, there is a lack of data for its efficacy in a specific cohort of Cy1 patients.

SYSTEMIC CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY FOR CY1 GC PATIENTS

All above-mentioned treatment strategies could be considered as experimental, as the standard treatment option for M1 GC remains palliative systemic therapy[11]. Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with M1 GC (including Cy1 patients) as standard conventional chemotherapy options [11]. Although, such treatment remains associated with poor outcomes[45], thus novel treatment options, like targeted therapy and immunotherapy, are of interest for these patients.

One of the available options, already included in a clinical practice guideline is trastuzumab - a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2). It induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated signaling, and prevents cleavage of the extracellular domain of HER2[46]. Large scale ToGA RCT showed that trastuzumab in combination with chemotherapy increases the survival of advanced or M1 HER2-positive GC patients[47]. A recent study showed trastuzumab deruxtecan, a humanized monoclonal anti-HER2 antibody attached to a cytotoxic topoisomerase I inhibitor through a cleavable linker is available and effective as a third-line treatment for HER2 positive GC patients[48]. Some other HER-2 targeting agents such as lapatinib, trastuzumab emtansine, pertuzumab are

also available, although their efficacy remains controversial[49_52]. Another available targeted therapy agent is ramucirumab, a fully humanized monoclonal antibody against vascular endothelial growth factor receptor 2[53]. This angiogenesis inhibitor was included in treatment guidelines as a second-line treatment option for patients with M1 GC after encouraging results of the REGARD and RAINBOW studies[54,55].

Another novel and promising drug class for M1 GC is immune checkpoint inhibitors. Some of these drugs improve antitumor T-cell activity by inhibiting immune checkpoints such as the programmed death-1 receptor (PD-1) and programmed death-ligand 1 (PDL1). PD1 is expressed on the surface of activated T cells that regulate their proliferation and activation and PDL1 is a major ligand for PD-1 expressed in some cancers, including GC cells[56,57]. Nivolumab is one of the available immune checkpoint inhibitors recommended in combination with fluorouracil/capecitabine and oxaliplatin for M1 HER2 negative GC, including Cy1 patients as recent RCTs demonstrated its efficacy for the first[58] and further lines treatment [59]. Pembrolizumab is another immune checkpoint inhibitor with antitumor activity in patients with PD-L1 positive GC. A phase II KEYNOTE-059 study showed promising activity and manageable safety of pembrolizumab monotherapy as a third-line treatment[60]. Although, the phase III RCT (KEYNOTE-062) failed to show improved survival with pembrolizumab or pembrolizumab plus chemotherapy compared to chemotherapy alone in previously untreated GC[61].

Despite some promising results of novel targeted therapy and immunotherapy drugs for M1 GC, the exact benefit for a distinct cohort of Cy1 GC patients remains unclear, as none of the current studies investigated this distinct subpopulation. Further studies are needed, to elucidate, the potential of novel systemic therapies for these patients.

LIMITATIONS OF THE CURRENT KNOWLEDGE AND PERSPECTIVES FOR FUTURE RESEARCH

The knowledge provided by the current evidence has some limitations. First, most of the available studies are relatively small in sample size. Second, many different treatment strategies including upfront gastrectomy, surgery after neoadjuvant systemic therapy, and IPC have been described for Cy1 GC, however, there is a lack of studies that would have compared them with each other. Thus, further large-scale international cohort studies comparing different treatments are needed to establish the most promising options. After, these should be tested in subsequent multi-center randomized control trials to provide robust evidence on the most efficient treatment for Cy1 patients.

CONCLUSION

Positive peritoneal cytology is associated with poor long-term outcomes in GC patients. Although, current evidence indicates, that this distinct subpopulation of the stage IV cohort may benefit from more aggressive treatment than palliative chemotherapy. Available strategies include upfront gastrectomy followed by adjuvant therapy, neoadjuvant chemotherapy option, and different methods of IPC utilization. Although, the most optimal treatment remains unclear because there is a lack of comparative studies. Thus, further clinical trials are needed to establish the best treatment option for Cy1 GC.

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PART 2: Neoadjuvant Chemotherapy Followed by Gastrectomy for Cytology-Positive Gastric Cancer without Any Other Non-Curative Factors in a Western Setting: An International Eastern European Cohort Study

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Neoadjuvant Chemotherapy Followed by Gastrectomy for Cytology-Positive Gastric Cancer without Any Other Non-Curative Factors in a Western Setting: An International Eastern European Cohort Study

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Simple Summary: This multicenter study delved into the outcomes of treating stage IV gastric cancer patients with positive peritoneal cytology but no other non-curative factors using chemotherapy followed by gastrectomy. The findings revealed that preoperative chemotherapy successfully eliminated peritoneal cancer cells in over 50% of patients. The median Overall and Progression-free survival stood at 20 (95% CI: 16–25) and 19 (95% CI: 11–20) months, respectively. Notably, conversion to negative cytology significantly lowered the relative risk of peritoneal progression (RR: 0.11; 95% CI: 0.03–0.47, $p = 0.002$). This study proposes that preoperative chemotherapy followed by gastrectomy shows promise as a viable treatment for stage IV gastric cancer patients with positive peritoneal cytology and no additional non-curative factors. The conversion of cytology status is associated with enhanced long-term outcomes and diminished risk of peritoneal relapse.

Abstract: The optimal approach for treating cytology-positive (Cy1) gastric cancer (GC) patients without additional non-curative factors remains uncertain. While neoadjuvant chemotherapy followed by gastrectomy shows promise, its suitability for Western patients is not well supported by existing data. To address this knowledge gap, a cohort study was conducted across four major GC treatment centers in Lithuania, Estonia, and Ukraine. Forty-three consecutive Cy1 GC patients who underwent neoadjuvant chemotherapy between 2016 and 2020 were enrolled. The study evaluated overall survival (OS), progression-free survival (PFS), cytology status conversion, and major pathological response rates, along with the factors influencing these outcomes. All patients underwent surgery post-neoadjuvant chemotherapy, with 53.5% experiencing cytological status conversion and 23.3% achieving a major pathological response. The median OS and PFS were 20 (95% CI: 16–25) and 19 (95% CI: 11–20) months, respectively. Conversion to negative cytology significantly reduced the relative risk of peritoneal progression (RR: 0.11; 95% CI: 0.03–0.47, $p = 0.002$). The study suggests that neoadjuvant chemotherapy followed by gastrectomy holds promise as a treatment option for Cy1 GC without additional non-curative factors, associating cytology status conversion with improved long-term outcomes and reduced peritoneal relapse risk.

Keywords: gastric cancer; positive cytology; neoadjuvant chemotherapy; pathological response

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1. Introduction

Gastric cancer (GC) ranks among the most prevalent malignancies globally, with over 1 million new cases and 750 thousand annual deaths [1]. Surgery remains the primary and only curative treatment option [2,3]. Unfortunately, up to 40% of patients present with distant metastases at the time of diagnosis, rendering them ineligible for radical surgery [4,5]. The peritoneum is the most frequent site of distant metastases [6,7]. Staging laparoscopy coupled with peritoneal lavage cytology stands as the diagnostic standard for detecting early peritoneal dissemination when only free cancer cells are present and peritoneal carcinomatosis (P1) has not yet formed [8–11]. Positive peritoneal cytology (Cy1), irrespective of other non-curative factors, emerges as a robust negative prognostic indicator for recurrence and survival [12]. Consequently, it is categorized as distant metastases (M1) and Cy1 patients are classified as stage IV, regardless of other non-curative factors [6].

Presently, there exists no international consensus on the optimal treatment for Cy1 GC patients. Western guidelines advocate for palliative care with potential re-staging post treatment [6,13]. In contrast, Eastern guidelines identify Cy1 patients as a distinct subset within the stage IV cohort, proposing the consideration of neoadjuvant chemotherapy followed by D2 gastrectomy if no other non-curative factors are present [14]. These disparities in recommendations and the absence of a widely accepted treatment for Cy1 patients stem from a knowledge gap. Hence, this study aims to explore the outcomes of a neoadjuvant approach for Cy1 GC within a Western cohort.

2. Material and Methods

2.1. Ethics

Local ethics committees or institutional review boards approved the study in each center before this study was conducted. All study-related procedures were performed following the Declaration of Helsinki of 1975, as revised in 1983.

2.2. Patients and Diagnostic Pathway

This cohort study screened all consecutive patients who were diagnosed with Cy1 stage IV GC without any other distant metastases between January 2016 and December 2020. The study was conducted at four major upper gastrointestinal cancer treatment centers in Lithuania, Estonia, and Ukraine: (1) National Cancer Institute, Vilnius, Lithuania; (2) Vilnius University hospital Santara Clinics, Vilnius, Lithuania; (3) National Cancer Institute, Kyiv, Ukraine; (4) North Estonia Medical Centre, Tallinn, Estonia. The standard diagnostic pathway for gastric cancer patients was consistent with current European Society for Medical Oncology (ESMO) guidelines [13] and included endoscopy with biopsy followed by chest and abdominal computed tomography (CT). If $\geq$cT2 or N+ disease and no distant metastases were detected at preoperative imaging, patients underwent diagnostic laparoscopy with peritoneal lavage for cytology. In the case of any suspicious peritoneal lesions, biopsies were taken to confirm or rule out peritoneal carcinomatosis (P1). After Cy1 GC without other non-curative factors was confirmed, all patients were discussed in multidisciplinary team meetings. Patients who were allocated to receive treatment with neoadjuvant chemotherapy followed by gastrectomy were included in the study; those who were allocated to receive best supportive care, upfront gastrectomy, or palliative chemotherapy were excluded (Figure 1).

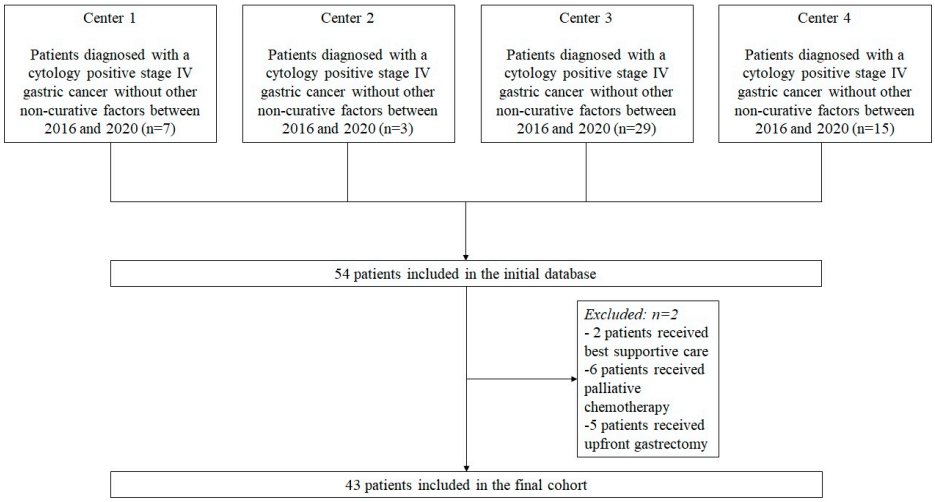

Figure 1. Flowchart of the study patients.

2.3. Treatment and Follow-Up of Study Patients

The standard neoadjuvant treatment consisted of 3–6 cycles of chemotherapy; the exact number of cycles and regimens was selected by a medical oncologist. After neoadjuvant chemotherapy was completed, patients were scheduled for chest and abdominal CT and, if no distant metastases were detected, patients were scheduled for gastrectomy. An open or laparoscopic approach was selected by a surgeon. Subtotal gastrectomy was performed if a sufficient proximal resection margin could be ensured; otherwise, total gastrectomy was performed. In the case of an unresectable primary tumor, palliative procedures were performed if necessary. The extent of lymphadenectomy depended on the individual surgeon's decision, but the standard lymphadenectomy was a D2 lymph node dissection performed as described in the 6th version of Japanese gastric cancer treatment guidelines [14]. All patients were considered for adjuvant chemotherapy after recovery from surgery. The standard follow-up protocol consisted of CT every 3 months for the first 2 years and, later, biannually. Also, esophagogastroduodenoscopy was performed 1 year after surgery.

2.4. Study Outcomes

The primary outcome of the study was overall survival (OS). Secondary end-points were progression-free (PFS) survival; conversion to negative cytology after neoadjuvant chemotherapy rates; major pathological response (mPR) after neoadjuvant chemotherapy rates; and postoperative complication rates. All postoperative complications were graded by Clavien–Dindo classification, and severe complications were defined as grade $\geq$3. OS was defined as the time between diagnosis of Cy1 stage IV GC and death. PFS was defined as the time between diagnosis of Cy1 GC and progression of the disease or death.

2.5. Statistical Analysis

All statistical analyses were conducted using the statistical program SPSS 25.0 (SPSS, Chicago, IL, USA). Continuous variables were presented as medians within the first (Q1) and third (Q3) quartiles. These variables were compared across groups using the Mann–Whitney U test or the Kruskal–Wallis test. Categorical variables were shown as proportions and were compared using the Chi-square test or Fisher's exact test. OS and PFS rates

were analyzed using the Kaplan–Meier method and were compared between the study groups using the log-rank test. To identify the factors impacting long-term outcomes in the neoadjuvant approach group, multivariable Cox proportional hazards regression analysis was used. Hazard ratios (HRs) were presented with 95% confidence intervals (CI). In all statistical analyses, two-tailed tests were used and a p-value of <0.05 was considered to be significant. The listwise deletion method was used for missing data.

3. Results

3.1. Baseline Characteristics and Neoadjuvant Chemotherapy

In total, 43 participants, with a median age of 57 (45; 65) years, were enrolled in the study. Each participant underwent a median of four (three; six) cycles of neoadjuvant chemotherapy. The most common chemotherapy regimen was fluorouracil, folinic acid, oxaliplatin, and docetaxel (FLOT), administered to 26 (60.5%) patients (Table 1).

Table 1. Baseline characteristics of study patients.

Characteristics		Patients (n = 43)
Age; median (Q1; Q3), years		57 (45; 65)
Sex; n (%)	Male	22 (51.2%)
	Female	21 (48.8%)
CCI; median (Q1; Q3)		5 (3; 7)
ECOG score; n (%)	0–1	42 (97.7%)
	≥2	1 (2.3%)
Tumor localization; n (%)	Cardia	11 (25.6%)
	Body	16 (37.2%)
	Antrum	9 (20.9%)
	Linitis Plastica	7 (16.3%)
cT; n (%)	T1-2	6 (14.0%)
	T3-4	37 (86.0%)
cN; n (%)	N0	9 (20.9%)
	N+	34 (79.1%)
Signet ring cell; n (%)	Yes	18 (42.9%)
	No	24 (57.2%)
Lymphovascular invasion; n (%)	Yes	24 (61.5%)
	No	15 (38.5%)
Lauren type; n (%)	Diffuse	18 (42.9%)
	Mix	2 (2.3%)
	Intestinal	23 (54.8%)
HER2 status; n (%)	Negative	35 (92.1%)
	Positive	3 (7.9%)
Type of chemotherapy; n (%)	FLOT	26 (60.5%)
	FOLFOX/XELOX/other platinum- and fluorouracil-based duplet	13 (30.2%)
	ECX/EOX	4 (9.3%)

Q1: quartile 1; Q3: quartile 3; CCI: Charlson Comorbidity Index; ECOG: Eastern Cooperative Oncology Group; cT: clinical tumor stage according to TNM classification; cN: clinical nodal stage according to TNM classification; FLOT: fluorouracil, folinic acid, oxaliplatin, and docetaxel; FOLFOX: fluorouracil, folinic acid, and oxaliplatin; ECX: epirubicin, cisplatin, capecitabine; EOX: epirubicin, oxaliplatin, capecitabine; XELOX: oxaliplatin and capecitabine.

3.2. Outcomes of Surgical Treatment, Cytological Status Conversion, and Major Pathological Response Rates

After completing neoadjuvant treatment, all patients underwent surgery. Palliative procedures were conducted in 3 (7.0%) patients, while another 40 (93.0%) patients underwent total or subtotal gastrectomy accompanied by D2 lymphonodectomy in 35 patients (87.5%) (Table 2). Postoperative complications occurred in 19 (45.2%) patients, including severe complications (Clavien–Dindo $\geq$ 3) in 9 (21.4%) patients.

Table 2. Surgical treatment outcomes in study patients.

Characteristics		Patients (n = 43)
Type of surgery; n (%)	Total gastrectomy	35 (81.4%)
	Subtotal gastrectomy	5 (11.6%)
	Palliative procedure	3 (7.0%)
Lymphadenectomy; n (%)	D1	5 (12.5%)
	D2	35 (87.5%)
Surgical approach	Open	39 (92.9%)
	Laparoscopic	3 (7.1%)
Multiorganic resection; n (%)	No	25 (59.5%)
	Yes	17 (40.5%)
Length of surgery, minutes (median; (Q1; Q3))		227 (163; 298)
R; n (%)	R0–1	42 (97.7%)
	R2	1 (2.3%)
Retrieved LN number (median; (Q1; Q3))		26 (20; 33)
Postoperative complications (any); n (%)		19 (45.2%)
Type of complications, n (%)	Anastomotic leakage	2 (4.6%)
	Pancreatic fistula/pancreatitis	2 (4.6%)
	Pulmonary complications	7 (16.2%)
	Wound infection or intraabdominal abscess	2 (4.6%)
	Other	6 (13.9%)
Severe postoperative complications (Clavien–Dindo $\geq$ 3); n (%)		9 (21.4%)
Intrahospital or 30 days postoperative mortality rate; n (%)		3 (7.1%)

Q1: quartile 1; Q3: quartile 3; R: residual tumor.

Post-surgery, cytological and histological examinations indicated that 23 patients (53.5%) experienced a conversion to negative cytology, and 10 patients (23.3%) achieved a major pathological response (mPR), classified as TRG1a/1b by Becker, following neoadjuvant treatment (Figure 2). Notably, there was no observed correlation between conversion to negative cytology and the achievement of a major pathological response (R = −0.302; p = 0.119). Further, there were no differences between patients who converted to negative cytology and those who maintained a positive cytology in terms of sex, age, ECOG score, tumor localization, cT, cN, presence of signet ring cells, lymphovascular invasion, and HER2 status, $p > 0.05$.

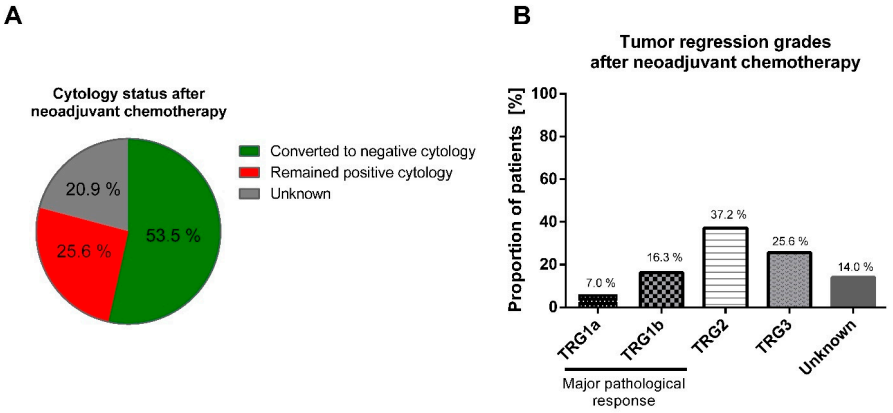

Figure 2. Neoadjuvant chemotherapy impact on the cytological status and pathological response in the primary tumor. After neoadjuvant chemotherapy, 53.5% of patients converted from positive to negative cytology (**A**); major pathological response by TRG1a/b was achieved by 23.3% of patients (**B**). TRG: tumor regression grade by Becker classification.

The type of neoadjuvant chemotherapy, along with patient and tumor characteristics, did not show associations with the rates of conversion to negative cytology or mPR (Table 3). However, clinically negative lymph nodes were associated with higher odds (OR: 29; 95% CI: 4–210) of achieving mPR. After surgical treatment, 26 (61.9%) patients underwent adjuvant chemotherapy.

Table 3. Factors associated with conversion to negative cytology and major histologic tumor regression after neoadjuvant chemotherapy.

Variable		Proportion of Patients Converting to Negative Cytology, n (%)	*p* Value	Proportion of Patients with Major Histologic Tumor Regression, n (%)	*p* Value
Sex	Male	5 (26.3%)	0.397	7 (36.8%)	0.269
	Female	6 (40.0%)		3 (16.7%)	
Age	≤60	5 (23.8%)	0.176	8 (40.0%)	0.073
	>60	6 (46.2%)		2 (11.8%)	
cT	cT1-2	3 (60%)	0.152	3 (75.0%)	0.052
	cT3-4	8 (27.6%)		7 (21.2%)	
cN	cN0	0 (0%)	0.150	7 (77.8%)	0.001
	cN+	11 (32.4%)		3 (10.7%)	
Tumor localization	Cardia	3 (33.3%)	0.195	3 (33.3%)	0.151
	Body	5 (45.5%)		5 (35.7%)	
	Antrum	3 (42.9%)		2 (25.0%)	
	Linitis plastica	0 (0%)		0 (0%)	
Type of chemotherapy	FLOT	7 (31.8%)	0.999	7 (30.4%)	0.710
	Other *	4 (33.3%)		3 (21.4%)	

Table 3. *Cont.*

Variable		Proportion of Patients Converting to Negative Cytology, n (%)	*p* Value	Proportion of Patients with Major Histologic Tumor Regression, n (%)	*p* Value
Tumor differentiation grade	G1-2	4 (20.0%)	0.217	7 (31.8%)	0.709
	G3	5 (45.5%)		3 (23.1%)	
Type by Lauren classification	Diffuse	4 (33.3%)	0.999	3 (20.0%)	0.480
	Intestinal/Mix	6 (28.6%)		7 (31.8%)	
Signet ring cell carcinoma	Yes	6 (46.2%)	0.139	4 (25.0%)	0.999
	No	4 (20%)		6 (28.6%)	
Lymphovascular invasion	Yes	4 (26.7%)	0.999	6 (26.1%)	0.999
	No	3 (20%)		4 (28.6%)	
HER2 status	Positive	1 (33.3%)	0.999	2 (66.7%)	0.201
	Negative	6 (22.2%)		8 (25.8%)	

cT: clinical tumor stage according to TNM classification; cN: clinical nodal stage according to TNM classification; FLOT: fluorouracil, folinic acid, oxaliplatin, and docetaxel; *: other types of chemotherapy; FOLFOX: fluorouracil, folinic acid, and oxaliplatin; ECX: epirubicin, cisplatin, capecitabine; EOX: epirubicin, oxaliplatin, capecitabine; XELOX: oxaliplatin and capecitabine.

3.3. Long-Term Outcomes

The median follow-up time was 16 (9; 21) months. Univariate Kaplan–Meier analysis revealed a median OS and PFS of 20 (95% CI: 16–25) and 19 (95% CI: 11–20) months, respectively. Notably, the conversion to negative cytology after neoadjuvant chemotherapy was linked to improved OS and PFS, whereas an mPR did not significantly impact long-term outcomes (Figure 3).

Throughout the follow-up period, a total of 12 patients (27.3%) were diagnosed with peritoneal metastasis, representing the most common site of progression. Peritoneal recurrence was almost exclusively observed in patients who retained positive cytology after neoadjuvant chemotherapy (72.7% vs. 8.7%, $p = 0.001$). Conversion to negative cytology significantly reduced the relative risk for peritoneal progression (RR: 0.11; 95% CI: 0.03–0.47, $p = 0.002$). Additionally, multivariable Cox regression analysis demonstrated that conversion to negative cytology after neoadjuvant chemotherapy correlated with a decreased risk of death (HR: 0.05; 95% CI: 0.01–0.58; $p = 0.017$) and recurrence (HR: 0.10; 95% CI: 0.01–0.68; $p = 0.019$) after adjusting for age, mPR, type of chemotherapy, pathologic tumor, and nodal status (Table 4).

Table 4. Multivariable Cox regression analysis for overall and disease-free survival.

Variable	Category	Overall Survival		Disease-Free Survival	
		HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age		0.89 (0.82–0.98)	0.018	0.97 (0.92–1.03)	0.371
mPR	Non-mPR	1 (Reference)		1 (Reference)	
	mPR	0.54 (0.04–6.12)	0.625	1.03 (0.11–9.56)	0.974
Cytology status after neoadjuvant chemotherapy	Positive cytology	1 (Reference)		1 (Reference)	
	Conversion to negative cytology	0.05 (0.01–0.58)	0.017	0.10 (0.01–0.68)	0.019

Table 4. *Cont.*

Variable	Category	Overall Survival		Disease-Free Survival	
		HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Type of chemotherapy	Non-FLOT	1 (Reference)		1 (Reference)	
	FLOT	0.11 (0.01–0.96)	0.046	0.48 (0.09–2.42)	0.482
ypT	ypT3-4	1 (Reference)		1 (Reference)	
	ypT1-2	0.01 (0.01–0.29)	0.007	0.04 (0.01–0.58)	0.018
ypN	ypN+	1 (Reference)		1 (Reference)	
	ypN0	0.69 (0.11–4.34)	0.694	0.41 (0.07–2.43)	0.331

HR: hazard ratio; 95% CI: 95% confidence interval; mPR: major pathological response; FLOT: fluorouracil, folinic acid, oxaliplatin, and docetaxel; ypT: pathologic tumor stage after neoadjuvant chemotherapy according to TNM classification; ypN: pathologic nodal stage after neoadjuvant chemotherapy according to TNM classification.

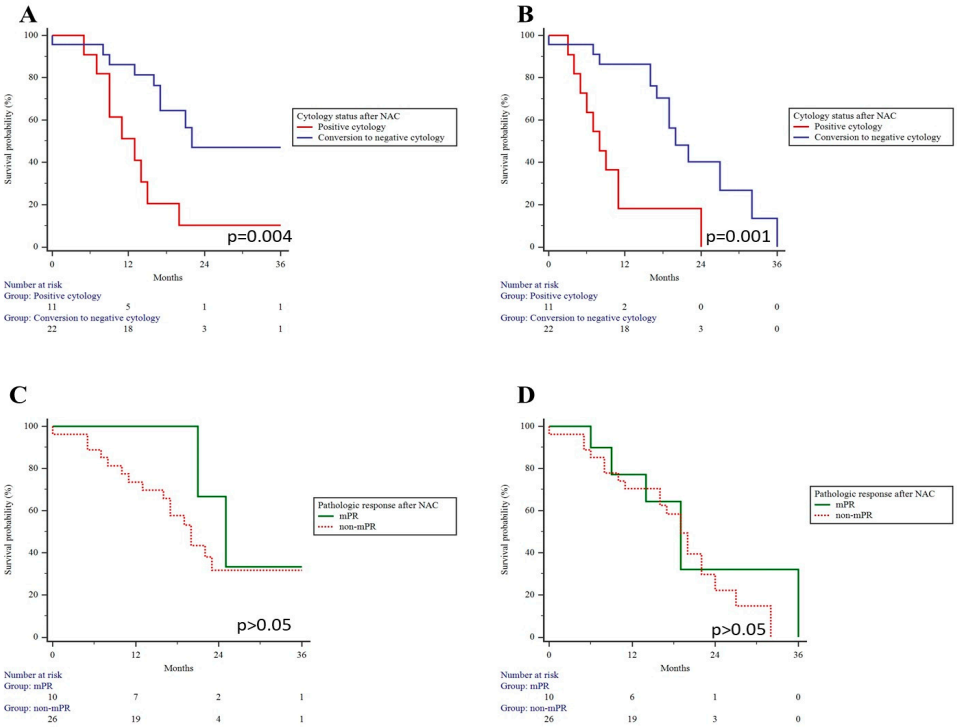

Figure 3. Overall and progression-free survival in patients who converted to negative cytology and achieved major pathological response after neoadjuvant chemotherapy. Conversion to negative cytology resulted in better overall (**A**) and progression-free survival (**B**). Major pathological response had no impact on overall (**C**) and progression-free survival (**D**) rates.

4. Discussion

This study elucidates the short- and long-term outcomes in Cy1 GC patients without additional non-curative factors following treatment with neoadjuvant chemotherapy. After

neoadjuvant chemotherapy, 53.5% of Cy1 patients experienced a conversion to negative cytology, and 23.3% achieved a major pathological response. Importantly, the conversion in cytologic status was linked to a significant reduction in the risk of death and recurrence, and particularly a lower risk for peritoneal relapse.

Treatment for Cy1 GC patients lacks standardization due to the absence of high-quality evidence. Free cancer cells detectable on cytology from peritoneal lavage signify peritoneal dissemination and metastatic disease. Consequently, akin to other GC metastases, palliative chemotherapy emerges as a standard treatment option. Unfortunately, systemic chemotherapy exhibits limited efficacy for GC peritoneal lesions [15], yielding a median survival of only 7 months [16]. Given the unsatisfactory long-term outcomes and distinct differences between Cy1 patients and GC patients with macroscopic carcinomatosis, more aggressive treatment strategies, including surgery, may be considered. Among treatments involving gastrectomy, two different options exist: upfront gastrectomy followed by adjuvant chemotherapy and gastrectomy after neoadjuvant chemotherapy. The CCOG0301 phase II single-arm study demonstrated that upfront gastrectomy followed by adjuvant S-1 monotherapy achieved 5-year OS and relapse-free survival rates of 26% and 21%, respectively. However, the peritoneal recurrence rate after such treatment is notably high at 62% [17]. Similar outcomes for upfront gastrectomy were confirmed in a retrospective study by Kano et al., revealing a 5-year OS of 17.8% and a peritoneal recurrence rate of 52.9% [18]. Further, a recent retrospective study by Bailong et al. demonstrated comparable survival outcomes for patients who underwent upfront gastrectomy and those who had gastrectomy after neoadjuvant treatment [19]. Nevertheless, the long-term outcomes achieved by preceding gastrectomy may be significantly compromised if patients do not receive adjuvant chemotherapy. Adjuvant chemotherapy after gastrectomy for Cy1 CG patients enhances OS to 22–25 months compared to 11–12 months in patients undergoing only surgical treatment [18,20]. However, the inability to tolerate cytotoxic treatment after major surgery, such as gastrectomy, is a serious issue, as 36% of patients are unable to receive adjuvant treatment due to the deterioration of their general condition after gastrectomy. This percentage can further rise to about 63% in the case of severe postoperative complications [21]. In contrast, chemotherapy applied in a neoadjuvant setting is better tolerated, with a compliance rate of more than 90% [22]. This difference may favor the neoadjuvant approach. The present study demonstrates that treatment with neoadjuvant chemotherapy followed by gastrectomy achieves acceptable long-term outcomes, with a median OS of 20 months (95% CI: 16–25). Neoadjuvant chemotherapy downsized the disease by converting to negative cytology in 53.5% of patients, and this conversion was associated with a significantly decreased risk of death (HR: 0.05; 95% CI: 0.01–0.58; $p = 0.017$) and recurrence (HR: 0.10; 95% CI: 0.01–0.68; $p = 0.019$). Our present findings align with results from previous small-scale studies, demonstrating improved long-term outcomes in 48.9–72.2% of Cy1 patients who achieve cytology status conversion [23–26]. Poor long-term outcomes in those who remain positive on cytology underscore the necessity for re-evaluation with diagnostic laparoscopy after neoadjuvant chemotherapy, because it may help to avoid almost half of the surgeries resulting in R1 resection. Furthermore, our study reveals that the vast majority of patients (72.7%) who remain positive on cytology after neoadjuvant chemotherapy will eventually develop peritoneal carcinomatosis. Considering that current systemic chemotherapy does not benefit these patients, it is crucial to explore and embrace new biomarkers. These biomarkers would play a key role in predicting the response to systemic neoadjuvant chemotherapy and allowing for personalized treatment for every patient [27]. This becomes particularly important as alternative treatment modalities, like intraperitoneal cytotoxic therapy, emerge as potential options for patients. A pilot study by Imano et al. showed that 80 mg/m^2 paclitaxel applied intraperitoneally at the end of radical D2 gastrectomy can clear peritoneal cytology. Moreover, this study showed a promising 3-year survival rate of 56% and a peritoneal recurrence rate of 30% [28]. However, conflicting data exist on the effectiveness of intraperitoneal chemotherapy. A randomized controlled study from Japan showed a poor 5-year OS of 4.6% and 0% in

patients who received gastrectomy and intraperitoneal chemotherapy with 100 mg cisplatin or gastrectomy alone. Thus, this approach remains controversial. Interestingly, the same study demonstrated promising outcomes with a 5-year OS rate of 43.8% in patients who received extensive peritoneal lavage with 10 L of a saline solution together with gastrectomy and intraperitoneal chemotherapy. Furthermore, intraperitoneal lavage reduced the peritoneal progression rate to 40.0% compared to 79.3% in the IPC group and 89.7% in the group receiving gastrectomy alone [29]. However, these techniques are rare outside of East Asia and would be considered experimental treatment in West.

Another available option for peritoneal disease, including GC, is hyperthermic intraperitoneal chemotherapy (HIPEC). A recent meta-analysis of randomized and high-quality non-randomized trials showed that HIPEC had no impact on long-term outcomes in GC patients with peritoneal carcinomatosis but may have a role in a prophylactic setting. HIPEC reduces the risk of peritoneal metastases (RR = 0.63; 95% CI: 0.45–0.88; $p < 0.01$) in high-risk patients, including Cy1 GC patients [30]. HIPEC can also find application in a neoadjuvant setting. A phase II study conducted by Badgwell et al. revealed that administering five cycles of neoadjuvant laparoscopic HIPEC after initial systemic chemotherapy resulted in cytology status conversion in 66.6% of patients [31]. However, this conversion rate does not significantly surpass the 53.5% achieved in our study with neoadjuvant chemotherapy alone. The broader acceptance of HIPEC for Cy1 GC patients is hindered by the scarcity of data from high-quality randomized controlled trials. The ongoing GASTRICHIP study, which explores the use of HIPEC in patients at high risk of peritoneal recurrence, including Cy1 patients after neoadjuvant chemotherapy, is anticipated to contribute more data to the field [32]. Another innovative technique for delivering chemotherapy intraperitoneally for GC peritoneal metastases is pressurized intraperitoneal chemotherapy (PIPAC) [33]. However, there are a lack of data regarding its efficacy, specifically in Cy1 patients.

The current study has some limitations that have to be considered. Firstly, being a retrospective study, it inherently carries typical disadvantages, including the potential for selection bias. Participants were chosen based on their eligibility for neoadjuvant chemotherapy, possibly excluding individuals with specific characteristics or conditions. Secondly, the relatively small sample size could impact the statistical power of the study, making it challenging to discern subtle differences in outcomes. Thirdly, the study's single-arm design, focusing on the neoadjuvant approach, lacks a robust comparison with alternative treatment modalities like upfront gastrectomy or palliative care. This limitation restricts the assessment of the relative effectiveness of different strategies. Notably, the low number of patients treated with alternative methods in our initial database (n = 6 palliative chemotherapy; n = 5 upfront gastrectomy) precluded their inclusion for meaningful comparison. Fourthly, the median follow-up time of 16 months might not suffice to capture long-term outcomes and evaluate the enduring efficacy of the neoadjuvant treatment strategy. Longer follow-up durations would offer a more comprehensive understanding of survival and recurrence patterns. Fifthly, our present study exclusively involved patients of the Caucasian race from Lithuania, Estonia, and Ukraine. Consequently, the generalization of our findings to other Western cohorts may be somewhat restricted. Despite these limitations, it is crucial to interpret the findings cautiously and underscore the necessity for further research to address these constraints. Notably, this study represents the largest cohort of Western patients, showcasing the efficacy of the neoadjuvant approach in Cy1 GC patients given the current knowledge landscape.

5. Conclusions

In conclusion, this study provides novel evidence that neoadjuvant chemotherapy followed by gastrectomy is a promising treatment option for cytology-positive gastric cancer patients without other non-curative factors in a Western setting. Clearance of cytology is associated with improved outcomes and a lower risk for peritoneal relapse; thus, cytological status re-evaluation should be standard before considering radical surgery.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author.

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CHAPTER 4: PIPAC WITH CISPLATIN AND DOXORUBICIN IN COMBINATION WITH FOLFOX CHEMOTHERAPY AS A FIRST-LINE TREATMENT FOR GASTRIC CANCER PATIENTS WITH PERITONEAL METASTASES

PART 1: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in combination with FOLFOX chemotherapy as a first-line treatment for gastric cancer patients with peritoneal metastases: single-arm phase II study

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Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in combination with FOLFOX chemotherapy as a first-line treatment for gastric cancer patients with peritoneal metastases: single-arm phase II study

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Abstract

Background Gastric cancer (GC) remains among the most common and most lethal cancers worldwide. Peritoneum is the most common site for distant dissemination. Standard treatment for GC peritoneal metastases (PM) is a systemic therapy, but treatment outcomes remain very poor, with median overall survival ranging between 3-9 months. Thus, novel treatment methods are necessary. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is the most novel technique for intraperitoneal chemotherapy. Some preliminary data suggest PIPAC can achieve improved long-term outcomes in patients with GC PM, especially when used in combination with systemic chemotherapy. However, there is a lack of data from well-design prospective studies that would confirm the efficacy of PIPAC and systemic therapy combination for first-line treatment.

Methods This study is an investigator-initiated single-arm, phase II trial to investigate the efficacy of PIPAC combined with systemic FOLFOX (5-fluorouracil, oxaliplatin, leucovorin) as a first-line treatment for GC PM. The study is conducted in 2 specialized GC treatment centers in Lithuania. It enrolls GC patients with histologically confirmed PM without prior treatment. The treatment protocol consists of PIPAC with cisplatin (10.5 mg/m2 body surface in 150 mL NaCl 0.9%) and doxorubicin (2.1 mg/m2 in 50 mL NaCl 0.9%) followed by 2 cycles of FOLFOX every 6–7 weeks. In total 3 PIPACs and 6 cycles of FOLFOX will be utilized. The primary outcome of the study is the objective response rate (ORR) according to RECIST v. 1.1 criteria (Eisenhauer et al., Eur J Cancer 45:228–47) in a CT scan performed 7 days after the 4th cycle of FOLFOX. Secondary outcomes include ORR after all experimental treatment, PIPAC characteristics,

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postoperative morbidity, histological and biochemical response, ascites volume, quality of life, overall survival, and toxicity.

Discussion This study aims to assess PIPAC and FOLFOX combination efficacy for previously untreated GC patients with PM.

Trial registration NCT05644249. Registered on December 9, 2022.

Keywords Gastric cancer, Peritoneal metastases, PIPAC

Background

Background and rationale

Gastric cancer (GC) is the 5th most common and 3rd most deadly cancer worldwide [1]. Peritoneal metastasis (PM), arising from GC, is the most common pattern of synchronous and metachronous dissemination and is generally associated with very poor long-term outcomes. Nowadays, the median survival of patients with GC PM ranges only between 2 and 9 months [2–6]. The standard treatment for GC PM is systemic chemotherapy alone or in combination with targeted therapy or immunotherapy. Although such treatment has very limited efficacy with only 14–25% of cases responding to it [7–9]. Several reasons are responsible for such limited efficacy. First, the plasma-peritoneal barrier isolates the peritoneum from the cytotoxic effect of intravenous chemotherapy. Second, poor intraperitoneal blood supply results in poor oxygenation of peritoneal cells, and this hypoxic state is associated with low apoptotic potential [10]. To overcome existing barriers intraperitoneal application of chemotherapy has been proposed. It offers pharmacokinetic advantages over intravenous therapy because high intraperitoneal drug concentration can be achieved while maintaining low systemic drug concentration, thus reducing treatment toxicity. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is the most novel technique for intraperitoneal chemotherapy. Through the procedure, special laparoscopic instruments are used to deliver drugs into the abdominal cavity as an aerosol under pressure. The rationale for PIPAC relies on physical and biological law which show that: (1) more homogenous drug distribution can be achieved by applying an aerosol compared to a liquid solution, (2) increased intraperitoneal hydrostatic pressure counteracts elevated interstitial fluid pressure within PM, (3) limited blood outflow at the drug application moment helps to increase intratumoral cytotoxic drug concentration and (4) the nature of the procedure allows to monitor and adjust the environmental parameters such as pH, temperature, electrostatic charge, and others for the best efficacy. Moreover, PIPAC can be applied repeatedly and biopsies can be taken during the procedure for objective assessment of tumor regression [11, 12]. PIPAC can be used as a single method for treatment ("unidirectional") or in a "bidirectional" manner when it is combined with systemic chemotherapy [13]. The bidirectional approach seems rational because intravenously applied chemotherapy may improve subperitoneal drug accumulation and also treat circulating tumor cells and systemic micrometastases [14]. Such a bidirectional approach for GC patients with PM has been reported to be safe and feasible. Also, it seems effective as pathologic response is achieved in about 60% of patients and 1-year overall survival (OS) rate exceeds 50% [15–17]. However, these studies are small and inconclusive. There is a need for a prospective study to investigate this promising treatment - bidirectional PIPAC as a first-line treatment for GC patients with PM.

Objective

This study aims to investigate PIPAC and systemic FOLFOX (5-fluorouracil, oxaliplatin, and leucovorin) chemotherapy efficacy as a first-line treatment for GC patients with PM.

Trial design

This investigator-initiated study is designed as a single-arm phase II trial to investigate the efficacy of PIPAC in combination with FOLFOX to treat GC PM.

Methods

Study setting

The study will be conducted at two major gastrointestinal cancer treatment centers in Lithuania: National Cancer Institute and Vilnius University hospital Santaros Klinikos.

Eligibility criteria criteria

The study will include GC patients with histologically confirmed PM scheduled for the first-line treatment if they meet all of the following inclusion criteria:

1. Histologically verified gastric adenocarcinoma (HER2 negative) with peritoneal metastases;
2. Age $\geq$ 18;
3. ECOG $\leq$ 1;
4. Patient willing to participate;

5. Patient is the candidate for 1st line FOLFOX palliative systemic chemotherapy.

Patients will be excluded if they meet the following criteria:

1. Extra-abdominal metastases;
2. Siewert I type gastroesophageal junction cancer;
3. Mechanical bowel obstruction;
4. Allergy to study drugs;
5. History of previous intraperitoneal chemotherapy;
6. Pregnancy of refusal for birth control at least 6 months post-study treatment.

Taking informed consent procedure

Before performing any study-related procedures, written informed consent (IC) will be obtained from the patient by the study physician. Before the screening visit, all patients will have been worked up according to standard institutional protocols for patients with GC. These include esophagogastroduodenoscopy with biopsy; chest and abdominal computed tomography (CT); diagnostic laparoscopy with peritoneal lavage and biopsy for patients with ≥ cT2 GC without extra-abdominal metastases on CT scan. At the screening visit physician will provide the patient with information and details about a study and will answer all the questions that the patient has. After the patient indicates that he/she had enough time to consider participation and clearly expresses willingness to be included in the study physician and patient will sign the IC. A copy of the signed IC will be given to the patient.

Additional consent provisions for collection and use of participant data and biological specimens

An option for permission to reuse clinical data and biological specimens collected through the study is included in the IC form.

Intervention description

PIPAC procedure description

PIPAC will be performed under general anesthesia. To prevent surgical site infections all patients will receive antibiotic prophylaxis - a single dose of cefazoline (1.0 g) will be administered intravenously during the induction of anesthesia. The surgical procedure will start by entering the abdominal cavity using an open technique described by Hasson [18] and placing a 10 mm balloon trocar. After insufflating CO_2 12mmHg capnoperitoneum will be achieved and an additional 5 mm balloon trocar will be placed under video control. Then diagnostic laparoscopy will be performed: peritoneal carcinomatosis index (PCI) will be documented, multiple biopsies from metastatic foci will be taken and ascites will be removed to measure volume and for cytological examination. In case there are no ascites peritoneal lavage will be performed. Then CAPNOPEN© (Reger Medizintechnik, GmbH, Villingendorf, Germany) is connected to an intravenous high-pressure injector and inserted into the abdomen through the 10 mm access port. A 5 mm camera will be inserted through the other port keeping the tip of the CAPNOPEN© in view. A safety checklist will be performed to ensure there is no gas leakage. Injection parameters will be adjusted to a flow rate of 0.5 mL/s and a maximum upstream pressure of 200 psi in the high-pressure injector to generate the aerosol and drug application will start. After application of cisplatin (10.5 mg/m^2 body surface in 150 mL NaCl 0.9%) and doxorubicin (2.1 mg/m^2 in 50 mL NaCl 0.9%), the therapeutic capnoperitoneum of 12 mmHg will be maintained for next 30 min at a temperature of 37 °C. Then, the chemotherapy aerosol will be evacuated via a separate hospital air-waste system, trocars will be retracted and PIPAC finishes.

Systemic chemotherapy and further treatment

Seven days after PIPAC patients will receive systemic chemotherapy. International guidelines recommend platinum-fluoropyrimidine doublet chemotherapy as a standard first-line chemotherapy for metastatic GC [19]. Thus, patients will receive FOLFOX chemotherapy which consists of intravenously administered folinic acid, 5-fluorouracil, and oxaliplatin. Within the next 4 weeks, 2 cycles of FOLFOX will be utilized. Then after 7–14 days of resting patients will again start treatment with PIPAC and the next 2 cycles of FOLFOX. In total 3 PIPACs and 6 cycles of FOLFOX will be utilized (Fig. 1).

Criteria for discontinuing or modifying allocated interventions Patients can withdraw from the trial at any time by expressing their will to the study clinician. Also, different medical conditions may force them to discontinue or modify the study interventions. These include:

1. Mechanic bowel obstruction.
2. Intraabdominal adhesions that prevent safe access to the abdominal cavity.
3. Neutropenia defined by absolute neutrophil count < $1.5 \times 10^{\wedge 9}$/L.
4. Thrombocytopenia: platelet count < $100 \times 10^{\wedge 9}$/L.
5. Renal function insufficiency: by creatinine clearance < 50 ml/min.
6. Liver function insufficiency: AST/ALT > 3× the upper limit of normal or bilirubin > 2× the upper limit of normal.

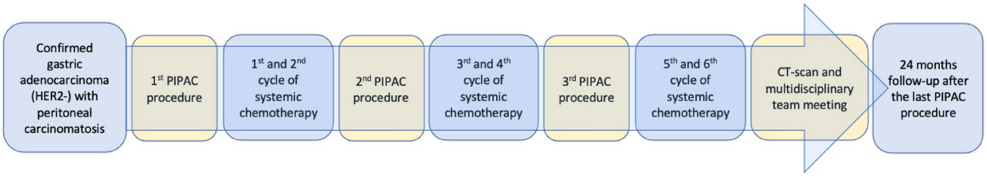

Fig. 1 Patients treatment (standard systemic chemotherapy and PIPAC) pathway

Patients will be withdrawn from the study by the individual decision of the study clinician in consultation with the principal investigator.

Provisions for ancillary and post-trial care

After experimental treatment patients will undergo CT scans and further treatment will be discussed at multidisciplinary treatment meetings to offer an individual and best available treatment option for every patient.

Outcomes

Primary outcome

The primary endpoint in this study is objective response rate (ORR) according to RECIST v. 1.1 criteria [20] in a CT scan performed 7 days after the 4th cycle of FOLFOX. ORR is the proportion of patients who have a complete response (CR), defined as the disappearance of all target lesions, or a partial response (PR), defined as ≥ 30% decrease in the sum of the diameters of target lesions.

Secondary outcomes

1. ORR according to RECIST v. 1.1 criteria in the CT-scan after all experimental treatment;
2. The median number PIPACs that can be utilized through the treatment protocol;
3. PIPAC characteristics (procedure time; intraoperative complications; length of a hospital stay after PIPAC; 30 day re-hospitalization rate);
4. Postoperative complications after PIPAC: assessed within 30 days after the PIPAC procedure and classified according to the Clavien-Dindo classification;
5. Peritoneal carcinomatosis index (PCI) measured at 2nd and 3rd PIPAC;
6. Histological regression of peritoneal metastases assessed by Peritoneal Regression Grading Score [21] measured in peritoneal biopsies at 2nd and 3rd PIPAC;
7. The volume of ascites measured at every PIPAC;
8. Biochemical tumor response: the concentration of carcinoembryonic antigen (CEA) and stomach cancer marker (Ca72-4);
9. Quality of life: it will be measured routinely using standard EORTC QLQ-C30 and EORTC QLQ-STO22 quality of life questionnaires;
10. Overall survival: defined as the time from the start of the treatment to study to death by any cause;
11. Progression-free survival: defined as the time from the start of the treatment to the progression of the disease diagnosed on CT scan or laparoscopy;
12. Toxicity according to the National Cancer Institute (NCI) Common Terminology Criteria (CTC) for adverse events v 5.0;
13. Biomarkers: gut microbiome composition, blood, and fecal biomarkers;

Participant timeline

The participant timeline can be seen in Table 1.

Sample size

In this study, we use Simon's two-stage minimax design [22] (one-sided α 5% and power 80%). The response of conventional FOLFOX chemotherapy for GC PM is about 20% [23, 24]. Considering the side effects and tolerability of PIPAC combined with systemic FOLFOX chemotherapy, we thought that ORR increase to at least 40% is necessary as a clinically meaningful anti-tumor activity to proceed to a subsequent confirmatory trial. Thus, in the first stage of this study, 18 patients have to be enrolled. If ≤ 4 responses will be observed, the study will be terminated and declared negative. If at least five responses will be observed, an additional 15 patients will be accrued to the second stage. The study will meet its primary endpoint if confirmed responses will be observed in 11 or more patients out of a total of 33 response-evaluable patients. Considering the 10% dropout rate in total this study will include 37 patients.

Recruitment

Participants will be recruited at 2 major gastrointestinal cancer treatment centers in Lithuania: National Cancer Institute and Vilnius University hospital Santaros Klinikos. The recruitment will be performed in the outpatient clinics by the clinicians who consult GC patients.

Table 1 Participant timeline

		STUDY PERIOD						
	Enrolment	**Post-allocation**						**Close-out**
TIMEPOINT**	$-t_1$	***Baseline/1st PIPAC***	***2nd PIPAC***	***3rd PIPAC***	***3 months after treatment***	***6 months after treatment***	***12 months after surgery***	***24 months after surgery***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Screening log	X							
Allocation	X							
INTERVENTIONS:								
PIPAC and FOLFOX		⟷						
ASSESSMENTS:								
Demographic and clinical questionnaire	X	X	X	X	X	X	X	X
CBC	X	X	X	X	X	X	X	X
Blood biochemistry and tumor markers	X	X	X	X	X	X	X	X
Chest, abdomen, and pelvis CT scan	X		X	X	X	X	X	X
EORTC QLQ-C30 and STO-22 questionnaires		X	X	X	X	X	X	X
PCI		X	X	X				
PRGS		X	X	X				
Ascites volume		X	X	X				
PIPAC characteristics		X	X	X				
Postoperative morbidity		X	X	X				
Serious adverse events		Throughout the study period						

All potentially eligible patients will be referred to a clinician-investigator who will screen if a patient meets the inclusion and does not meet exclusion criteria and will inform the patient about the clinical study. Patients willing to participate will be enrolled after signing written informed consent.

Data collection

The data of participants will be collected according to the study protocol. Case report forms (CRFs) will be used to ensure the appropriate collection of necessary data. Routine auditing of the study documentation will be performed to ensure the quality of the data recorded in CRFs. To ensure the timeliness of the data, the CRFs will be completed within 3 working days following every visit. All data collected in CRFs will be transferred to an electronic database for further data collection and management. The confidentiality policy is outlined in an informed consent form and will be ensured during the data collection.

Biological specimen collection

Peripheral venous blood samples and stool samples will be collected before the start of the treatment. Additionally, peritoneal metastases samples and ascites samples (100 ml) will be collected at the time of 1st PIPAC procedure.

All collected samples will be prepared according to standard laboratory protocols. Plasma and serum samples will be aliquoted in four 1ml tubes and stored at -80 C° in the laboratory at National Cancer Institute. Fresh stool samples will be split into four tubes containing at least 1 g of content and stored at -80 C° in the same laboratory. Gut microbiome analysis will be performed from stool samples by 16 S sequencing in the current trial. Also, biological specimens may be used for future studies.

Statistical analysis

Accumulated data will be processed by SPSS (version 25) statistical software. All data will be checked for normality. Continuous variables will be expressed by mean with standard deviation or median with quartiles 1 and 3. Discrete variables will be expressed as proportions and percentages. Changes in the PCI, CEA, Ca72-4, and EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires score will be assessed by using paired sample t-test, Wilcoxon rank-sum test. For statistical analysis of gut microbiome compositions, the web-based application Calypso (version 8.84) will be used. Alpha diversity will be quantified by the Shannon index. Beta diversity will be quantified by principal coordinate analysis (PCoA) based on a Bray–Curtis dissimilarity matrix with analysis of similarity (ANOSIM), as well as redundancy analysis (RDA) with one or multiple explanatory variables. Additional analyses will be performed if necessary. P values < 0.05 will be considered statistically significant in all statistical analyses.

Interim analyses

As mentioned previously this study is designed using Simon's two-stage minimax design [22] (one-sided α 5% and power 80%). Thus, interim analysis will be performed after the first stage of the study when 18 patients will be enrolled. If ORR 7 days after the 2nd PIPAC will be achieved in ≤ 4 patients, the study will be terminated and declared negative. If at least five responses will be observed, an additional 15 patients will be accrued to the second stage.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Missing data will not be imputed.

Plans to give access to the full protocol, participant-level data, and statistical code

Non-identifiable patient-level data will be available from the principal investigator upon reasonable request.

Composition of the coordinating center and trial steering committee

Vilnius University hospital Santaros Klinikos is the coordinating center of the study, and it will coordinate the trial and trial sites. Bi-monthly meetings led by the principal investigator are held to provide routine organizational support.

A trial steering committee consisting of clinicians (surgeon, medical oncologist), statistician, data manager, and research assistant are established to monitor and supervise the progress of the study. Study monitors will have full access to the data. The monitoring plan includes verification of the informed consent form, checking if patients meet inclusion and exclusion criteria, and monitoring the quality of the data recorded in the case report form. It is planned to review data of the 25% of included patients. Additionally, the steering committee will review relevant information on the topic of the research from other related studies in bi-annual meetings.

Composition of the data monitoring committee, its role, and reporting structure

Data monitoring committee (DMC) consisting of clinicians with experience to treat GC patients with PM and to conduct clinical trials will monitor the safety of the trial subjects throughout the study. Safety analyses will be held after each 13 (35%) will complete the assigned

treatment. DMC members are independent of the sponsor and will provide a recommendation to stop or continue the study. The advice of the DMC will be shared with the sponsor and principal investigator of the study, who will be responsible to inform the local research ethics committee if necessary.

Adverse event reporting and harms

All serious adverse events (SAEs), except those related to the progression of the disease, will be recorded up to 30 days after the last protocol treatment. SAEs will be reported to the principal investigator of the study within 2 working days and to the local research ethics committee that approved the study within 14 days.

Plans for communicating important protocol amendments to relevant parties

Any changes to the protocol will require formal amendment provided by Vilnius Regional Biomedical Research Ethics Committee.

Dissemination plans

The trial results will be disseminated to society at national and international conferences and publications in a peer-reviewed journal, irrespective of the study outcomes. Co-authorship will be based on the international ICMJE guidelines.

Discussion

In this study, we aim to investigate the combination of PIPAC (cisplatin and doxorubicin) and systemic FOLFOX chemotherapy efficacy for the first-line treatment of GC PM.

We designed this study, because of several reasons. First, novel treatment strategies for GC PM are urgently needed as conventional methods (systemic therapy) have only a very limited efficacy with a median OS ranging between 2 and 9 months [2–6]. Innovative drugs, especially immune-checkpoint inhibitors, hold the potential to enhance these outcomes. The phase III CheckMate 649 study demonstrated that the addition of Nivolumab to standard chemotherapy significantly extends the median overall survival from 11.6 (95% CI: 10.9–12.5) to 13.8 (12.6–14.6) months (HR 0.80 (99.3% CI: 0·68–0·94; p = 0·0002) in comparison to standard chemotherapy for treatment-naive patients with gastric, esophagogastric junction, or esophageal cancer [25]. However, it is important to note, that only 23.7% of participants had peritoneal metastases and despite some improvement long-term outcomes remained unsatisfactory.

Second, there is some evidence indicating the potency of PIPAC. A recent systematic review summarized current evidence and suggested that PIPAC can lead to improved long-term outcomes with a median OS of 8-19.1 months [13]. These results are even more encouraging, when the fact that the majority of included patients were already intensively pre-treated with sometimes several different lines of systemic chemotherapy [13], is taken into consideration. Although, current studies have many limitations, including heterogeneity of treatment protocols (PIPAC alone vs. bidirectional treatment) and measured outcomes. Also, the majority of them are retrospective [13]. Thus, there is a need for new prospective phase II studies. Our study experimental protocol consists of PIPAC with cisplatin (10.5 mg/m^2) and doxorubicin (2.1 mg/m^2) in combination with FOLFOX as a first-line treatment for GC patients with PM. There is no clear evidence showing the benefits of such bidirectional approach, although, as it is the first-line treatment, systemic control of disease by traditional FOLFOX and additional local (peritoneal) control by PIPAC seems rational and ethically acceptable. Moreover, intraperitoneally applied cytotoxic drugs have only limited penetration to peritoneal lesions of approximately up to 5 mm [26]. Therefore, an intravenously applied cytotoxic drug may have synergistic benefits for peritoneal metastases treatment by affecting tumor nodules from the site of the peritoneal surface [26]. The effectiveness of similar bidirectional approaches has been previously examined, but employing diverse methods for the application of intraperitoneal chemotherapy. In the Japanese phase III PHOENIX-GC trial, the evaluation involved adding intraperitoneal paclitaxel (20 mg/m2) through a peritoneal port or catheter to intravenous paclitaxel and oral S1 for GC patients with PM. The combined intraperitoneal and systemic chemotherapy did not demonstrate a significant improvement in median overall survival (OS) (17.7 months (95% CI: 14.3–21.3 months)) compared to standard systemic chemotherapy (14.8 months (95% CI:12.3–21.8 months)) in the overall study population, as indicated by an HR of 0.72 (95% CI: 0.49–1.04; p = 0.080). However, a post hoc sensitivity analysis, adjusted for baseline ascites, revealed significance (HR: 0.59; (95% CI: 0.39–0.87; p = 0.008)) [27]. Another bidirectional strategy involved laparoscopic hyperthermic intraperitoneal chemopetherapy (HIPEC) after systemic chemotherapy, as reported by Badgwell et al. [28]. In this phase II study, the laparoscopic HIPEC procedure could be repeated up to five times, with 5 out of 19 patients (26.3%) undergoing subsequent radical surgery due to metastasis regression. These patients achieved a median OS of 30.2 months [28]. However, it's essential to note that in these earlier studies, intraperitoneal chemotherapy was administered without the pressure and aerosolization achieved with the latest

technique for intraperitoneal chemotherapy-PIPAC. Compared to conventional methods of intraperitoneal chemotherapy application, PIPAC might offer more uniform drug distribution and improved drug penetration into peritoneal lesions, suggesting potential for enhanced treatment outcomes.

The primary outcome of the present study is objective response rate (ORR) according to RECIST v. 1.1 criteria [20] in a CT scan performed 7 days after the 4th cycle of FOLFOX. RECIST criteria may have limitations when measuring the response to therapy in peritoneal metastases, particularly when the disease burden is minimal. This is because peritoneal metastases can be challenging to determine with standard cross-sectional imaging [29]. However, it's important to note that our study investigates PIPAC and FOLFOX combination as the first-line treatment for patients with an unresected primary tumor commonly accompanied by lymph node metastases, making the identification of target lesions less problematic. Selecting ORR as the primary outcome is appropriate for a phase II study, aligning with recommendations from the European Society for Medical Oncology, as it allows for the measurement of antitumor activity before contemplating a phase III study. Additionally, several secondary endpoints, such as PCI reassessment and histological regression of peritoneal metastases following the 2nd and 3rd PIPAC, are specifically dedicated to evaluating treatment efficacy in peritoneal metastases.

To our best knowledge several other clinical studies investigating bidirectional PIPAC as a first-line treatment of GC PM are currently undergoing (NCT05318794; NCT04913662; NCT05303714). SPECTRA (NCT05318794) single-arm study is investigating the feasibility and safety of 3 cycles of standard systemic chemotherapy interposed with 3 PIPAC (Doxorubicin and Cisplatin) sessions for patients with limited peritoneal disease (PCI ≤ 3) in the United Kingdom. Another phase I study undergoing in South Korea (NCT04913662) investigates dose-limiting toxicity of PIPAC (Paclitaxel) and Systemic FOLFOX combination for GC PM. And finally, there is already a phase III randomized control trial (PIPAC_VEROne; NCT05303714) undergoing in Italy. This study randomizes patients with GC PM to 6 cycles of FOLFOX or 6 cycles of FOLFOX with 3 PIPACs (Doxorubicin and Cisplatin) performed every two cycles of chemotherapy. PIPAC_VEROne study treatment protocol is very similar to the present study. However, different from our study, the Italian trial will include only patients with the limited peritoneal disease (PCI ≤ 6).

Thus, our study will be the first to provide knowledge of PIPAC and FOLFOX efficacy for GC patients with PM, including those with higher PCI scores.

Trial status

The first patient was included in December 2022. At the time of protocol revision (October 2023) 2 centers in Lithuanian are actively recruiting patients for the study, and 17 patients have already been included.

Abbreviations

CR	Complete response
CRFs	Case report forms
CT	Computed tomography
DMC	Data monitoring committee
FOLFOX	Chemotherapy regimen of 5-fluorouracil, oxaliplatin, and leucovorin
GC	Gastric cancer
HR	Hazard ratio
IC	Written informed consent (IC)
ORR	Objective response rate
OS	Overall survival
PCI	Peritoneal carcinomatosis index
PIPAC	Pressurized intraperitoneal aerosol chemotherapy
PM	Peritoneal metastasis
SAEs	Serious adverse events

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Authors' contributions
M.L., A.B. conceived of the presented idea. M.L., A.B. developed the theory and performed the computations.A.B. verified the analytical methods. K.S., S.T., R.B., M.P., B.B. encouraged M.L., A.B. to investigate and supervised the findings of this work. All authors wrote the main manuscript text. All authors discussed and contributed to the final manuscript.

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Availability of data and materials
The data generated through this study will be available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study complies with the Declaration of Helsinki and methods were carried out in accordance with relevant guidelines and regulations. Ethical approval was obtained from Vilnius Regional Biomedical Research Ethics Committee (2022/9-1453-923) before the start of the study. Written informed consent to participate will be obtained from all study participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

PART 2: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in combination with FOLFOX chemotherapy as a first-line treatment for gastric cancer patients with peritoneal metastases: single-arm phase II study

Interim results

In this part of the thesis interim results of the single-arm, phase II clinical trial evaluating the efficacy and safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with systemic FOLFOX chemotherapy (5-fluorouracil, leucovorin, and oxaliplatin) as a first-line treatment for patients with peritoneal metastases (PM) from GC are described. The detailed protocol for this trial has been published previously and described above (23).

Baseline characteristics and primary outcome

Between November 30th, 2022, and December 31st, 2023, a total of 20 patients with histologically confirmed PM from GC were enrolled to the study after screening 86 patients (Figure 1.). Baseline and treatment characteristics are presented in Table 1.

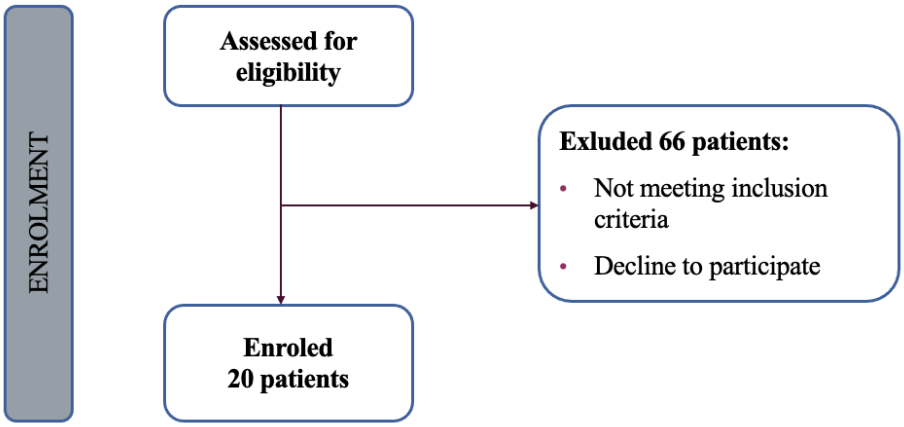

Figure 1. Patients enrolment

Table 1. Baseline and treatment characteristics of study patients.

Characteristic		
Age (years), mean (SD)		61 (9)
Male: Female		12:8
Charlson comorbidity index score, mean (SD)		8 (1)
BMI (kg/m2), mean (SD)		24 (4)
cT	1-2	0 (0)
	3-4	20 (100)
cN	0	1 (5)
	+	19 (95)
Peritoneal cytology	Negative	5 (25)
	Positive	15 (75)
Ascites at baseline	Yes	13 (65)
Proportion of patients receiving study treatment	1st PIPAC	20 (100)
	1st FOLFOX	19 (95)
	2nd FOLFOX	18 (90)
	2nd PIPAC	17 (85)
	3rd FOLFOX	17 (85)
	4th FOLFOX	17 (85)
	3rd PIPAC	17 (85)
	5th FOLFOX	17 (85)
	6th FOLFOX	16 (80)
Length of PIPAC (minutes), mean (SD)		75 (10)
Hospital stays after PIPAC (days), mean (SD)		2 (1)

Values are n (%) unless otherwise indicated.

Of the 20 enrolled patients, 3 (15%) discontinued the study treatment after the first PIPAC ± FOLFOX cycle. Seventeen patients (85%) successfully completed the full planned treatment course, consisting of 3 PIPAC procedures combined with 6 cycles of systemic FOLFOX chemotherapy. One patient (5%) completed only 5 FOLFOX cycles due to toxicity.

The primary endpoint, objective response rate (ORR) assessed after the 4th FOLFOX cycle using RECIST v1.1 criteria, was achieved in 5 out of 17 evaluable patients (29.4%).

Secondary outcomes

PIPAC impact on PCI

The median Peritoneal Carcinomatosis Index (PCI) decreased from 14 (interquartile range [IQR]: 4–23) at baseline to 8 (IQR: 2–22) after the 3rd

PIPAC; however, the change was not statistically significant ($p > 0.05$). (Figure 2.)

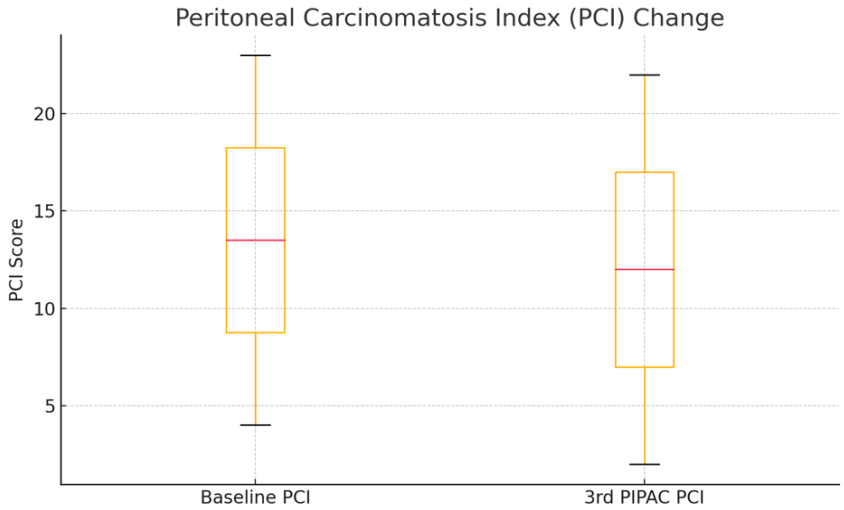

Figure 2. Peritoneal carcinomatosis index (PCI) change.

PIPAC impact on histological response grade

The complete histological response rate (PRGS score 1) significantly improved from 0% at baseline to 4 patients (23.5%) after the 2nd PIPAC and to 5 patients (29.4%) after the 3rd PIPAC ($p < 0.05$). (Table 3). Two (40%) of these 5 patients who achieved complete regression of the metastases underwent R0 cytoreductive surgery. (Figure 3.)

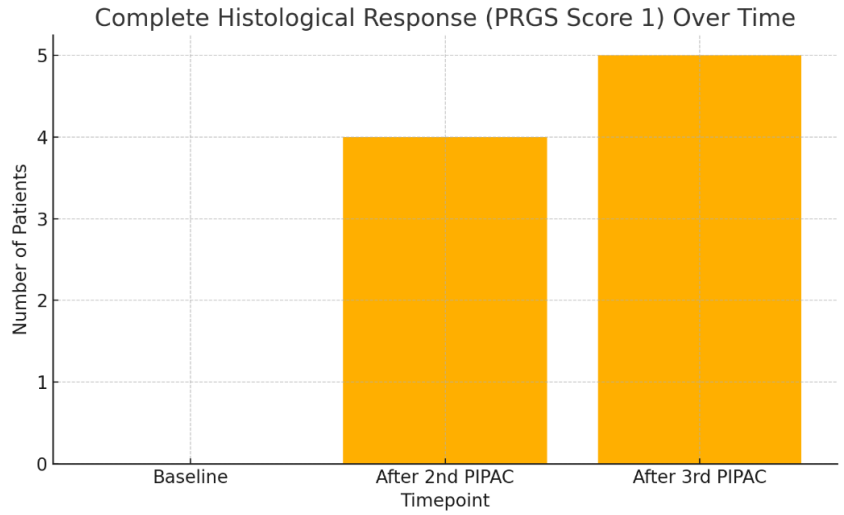

Figure 3. Complete Histological Response (PRGS Score 1) over time.

PIPAC impact on cytological status

The proportion of patients with negative peritoneal cytology increased from 5 (25%) at baseline to 6 (35.3%) after the 2nd PIPAC and to 8 (47.1%) after the 3rd PIPAC ($p > 0.05$). (Figure 4.)

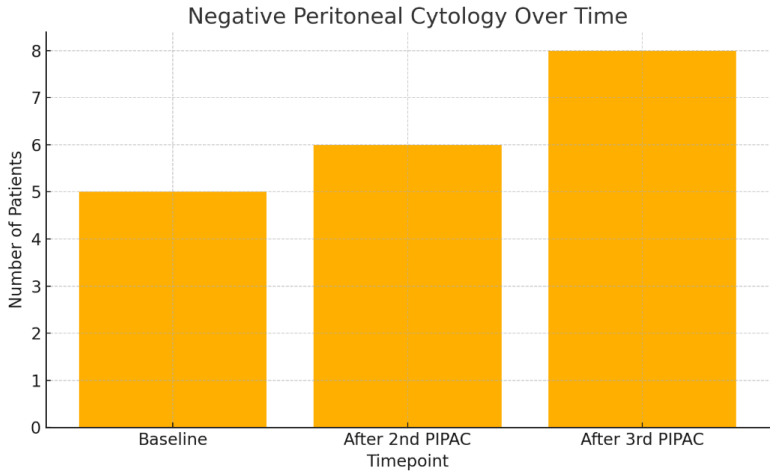

Figure 4. Negative peritoneal cytology over time.

PIPAC impact on ascites

Ascites resolution was observed, with ascites-free status increasing from 7 patients (35%) at baseline to 9 (52.9%) after the 2nd PIPAC and 12 (70.6%) after the 3rd PIPAC ($p > 0.05$). (Figure 5.)

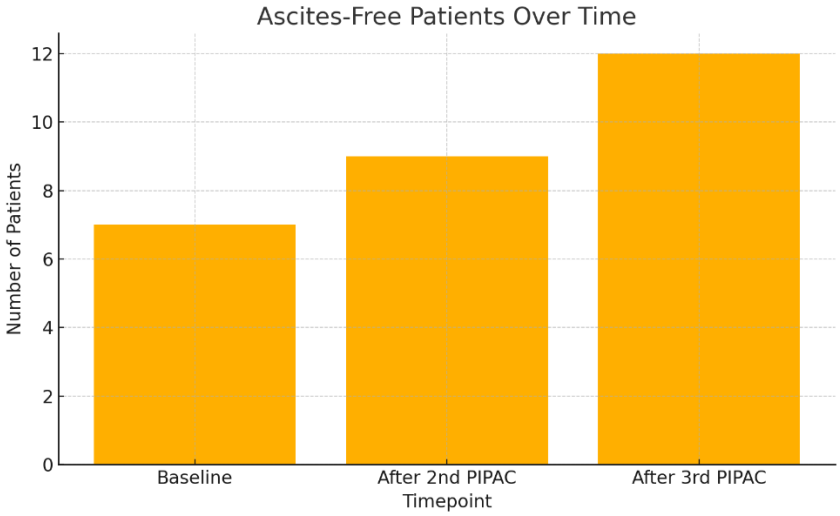

Figure 5. Ascites-free patients over time change.

Postoperative morbidity after PIPAC

Postoperative complications were minimal, with only one patient (1.8% of 54 PIPAC procedures) experiencing an ileus (Clavien-Dindo Grade II), that was managed conservatively.

Long-term outcomes

At the time of interim analysis (March 18, 2024), the mean follow-up was 7 months (±3), with 8 patients (40%) still alive. Four patients (20%) remained progression-free, including two (10%) with no evidence of disease following surgery.

Conclusions:

Interim results from the ongoing study indicate that PIPAC combined with FOLFOX as a first-line treatment is both feasible and well tolerated in patients with gastric cancer peritoneal metastases (GCPM). Some patients have demonstrated significant radiological and histological responses to the treatment. As of the time of this thesis submission, patient enrolment has been completed, with all 37 anticipated participants enrolled. The final results of the study are expected to be published in 2026.

CHAPTER 5: SUMMARY, DISCUSSION, CONCLUSIONS AND FUTURE PERSPECTIVES

SUMMARY & DISCUSSION

Chapter 1 of this thesis addresses the evolving treatment landscape for GC, a major global health concern with high mortality, particularly in Eastern Europe and Asia (1). Surgical resection remains the standard of care for localized GC, particularly with D2 lymphadenectomy, though the integration of perioperative or neoadjuvant chemotherapy has demonstrated improved outcomes. For metastatic GC, especially with peritoneal metastases (PM)—which affect up to 43% of patients—prognosis remains poor. Systemic chemotherapy is the standard but has limited efficacy due to the plasma–peritoneal barrier. Innovative local treatment strategies like hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC) are being explored. Although PIPAC has shown promise in small studies, its combination with systemic chemotherapy is still considered experimental (2,3). Hypothesis and tasks for this project are overviewed in the chapter. This thesis is structured around five main hypotheses, each tested using various methods, including a comprehensive literature review, cohort studies, and a prospective single-arm phase II study. In **Part 1 of Chapter 2** a retrospective study reports early outcomes of Lithuania's first pressurized intraperitoneal aerosol chemotherapy (PIPAC) program for patients with gastric (GC) and ovarian cancer (OC) with peritoneal metastases (PM). PIPAC was found to be safe and feasible, with no postoperative mortality and a low complication rate (8.8%). The study supports PIPAC as a potential strategy for disease stabilization, quality-of-life improvement, and possibly downstaging to facilitate curative cytoreductive surgery (CRS) + HIPEC in select GC patients. Although the regression of PCI and ascites control were not statistically significant, the trends were favourable, echoing outcomes reported in previous studies. The observation that OC patients were more likely to complete all three planned PIPAC cycles suggests disease origin influences treatment tolerance and outcome, a nuance that warrants further investigation (4). In **Part 2 of Chapter 2** another retrospective study evaluated the outcomes of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for a specific cohort of patients with only gastric cancer peritoneal metastases (GC PM). The findings suggest also that PIPAC is a safe and feasible treatment option: postoperative complication rate was low (4.2%). Within the 30-day postoperative period, there were

noreported mortality cases. Feasibility: 71.9% of patients received more than two PIPAC procedures, and 43.8% received more than three. Efficacy: Although reductions in PCI and ascites volume were observed, these changes did not reach statistical significance. Survival: Median overall survival (OS) was 12.5 months from PM diagnosis and 5 months after the first PIPAC procedure. Treatment tolerability: No laparoscopic access failures were recorded; discontinuation was due to clinical deterioration, not technical issues. The study contributes to the growing evidence supporting PIPAC as a part of multimodal therapy for peritoneal metastases but emphasizes the need for larger, prospective studies to validate these findings and refine treatment strategies. The study also sheds light on the challenge of objectively assessing PIPAC efficacy in peritoneal metastases due to imaging limitations. Small-volume disease is often non-measurable, making standard radiologic endpoints (like RECIST) inadequate. Repeated laparoscopy and emerging histologic grading systems such as Peritoneal Regression Grading Score (PRGS) offer promising alternative methods for treatment monitoring. Unfortunately, PRGS was not utilized in this cohort, limiting histologic assessment. One important observation is the potential association between the number of PIPAC cycles and survival. However, whether survival is a cause or consequence of tolerating more cycles remains unclear. This underscores the need to evaluate early integration of PIPAC into treatment protocols before systemic chemotherapy resistance develops, potentially maximizing its therapeutic benefit. Despite these encouraging outcomes, the study's retrospective nature, small sample size, and absence of a control group limit the generalizability of results. Furthermore, the lack of standardization in reporting adverse events across PIPAC studies complicates comparisons. While CTCAE v5.0 is widely recommended, varying use of grading scales (e.g., Clavien-Dindo) remains a challenge in the field. Future research should focus on larger, prospective trials with control groups, standardized outcome measures (e.g., CTCAE v5.0, PRGS), early integration of PIPAC into treatment algorithms. Such efforts will help clarify the role of PIPAC in multimodal management of peritoneal metastases and guide its adoption into routine clinical practice (5). Further, in **Part 1 of Chapter 3** article provides a comprehensive review of treatment strategies for patients with gastric cancer (GC) and positive peritoneal cytology (Cy1)—a subset of stage IV disease. Cy1 GC patients, despite lacking visible peritoneal metastases, have poor long-term outcomes due to microscopic intraperitoneal dissemination. The article highlights that positive cytology is an independent negative prognostic factor, often associated with rapid disease progression and low survival rates

if treated with standard palliative chemotherapy. The review evaluates different treatment modalities, including upfront gastrectomy with adjuvant therapy or neoadjuvant chemotherapy followed by surgery, also HIPEC (Hyperthermic Intraperitoneal Chemotherapy) or PIPAC. Although evidence from retrospective studies suggests improved outcomes with aggressive or multimodal approaches, the lack of prospective comparative trials limits strong recommendations for a single standard treatment. The article emphasizes that Cy1 patients represent a potentially treatable subgroup of stage IV GC, distinct from those with overt peritoneal carcinomatosis. Evidence suggests they may benefit from more aggressive interventions than palliative chemotherapy alone (6). Moreover, in **Part 2 of Chapter 3** multicenter retrospective cohort study evaluated outcomes of neoadjuvant chemotherapy followed by gastrectomy in 43 patients with cytology-positive (Cy1) stage IV gastric cancer, but no other non-curative factors, across centers in Lithuania, Estonia, and Ukraine. Neoadjuvant chemotherapy regimens were FLOT (60.5%), median of 4 cycles. Conversion to negative cytology occurred in 53.5% of patients and gastrectomy with D2 lymphadenectomy was performed in 93% of patients. Median overall survival (OS) was 20 months (95% CI: 16–25) and median progression-free survival (PFS) was 19 months (95% CI: 11–20). In this study postoperative complications occurred in 45.2% of patients, with 7.1% 30-day mortality. Second, cytology conversion was strongly associated with improved survival and reduced peritoneal recurrence: relative risk (RR) for peritoneal progression: 0.11 ($p = 0.002$) and hazard ratio (HR) for death was 0.05 ($p = 0.017$). This study provides novel Western data supporting an Eastern-style treatment approach: aggressive multimodal therapy (neoadjuvant chemotherapy + surgery) for select Cy1 gastric cancer patients. Conversion to negative cytology appears to be the key predictor of benefit and should guide surgical decision-making. Larger prospective trials are needed to confirm these findings and standardize care (7).

In **Part 1 of Chapter 4** the protocol of novel study aiming to evaluate the safety and efficacy of a bidirectional treatment combining PIPAC using cisplatin and doxorubicin, with systemic FOLFOX chemotherapy (5-fluorouracil, oxaliplatin, leucovorin) as a first-line treatment for gastric cancer patients with peritoneal metastases (GC PM) is described. It is phase II, single-arm, feasibility study. Conducted at two leading Lithuanian cancer centers. The treatment protocol includes 3 cycles of PIPAC, each followed by 2 cycles of FOLFOX every 6–7 weeks. Evaluation includes both radiologic (RECIST v1.1) and pathologic response (e.g., peritoneal regression grading score [PRGS]). The primary endpoint is objective response rate (ORR) after the 4th

FOLFOX cycle and secondary endpoints include ORR after full treatment, PCI reduction, PRGS histologic response, ascites volume, quality of life, overall survival, toxicity, and biomarker changes. This trial addresses a critical gap of current knowledge in the treatment of GC PM—where traditional systemic therapies demonstrate poor efficacy due to pharmacokinetic challenges such as the plasma-peritoneal barrier and poor perfusion of peritoneal metastases. The study innovatively combines localized high-concentration chemotherapy via PIPAC with systemic FOLFOX, aiming for improved drug delivery both intraperitoneally and systemically. PIPAC provides enhanced local drug distribution and repeated direct tumor monitoring via laparoscopic biopsies. Combining with FOLFOX may provide synergistic benefits by treating both visible lesions and micro metastases. Use of RECIST criteria and PRGS ensures both radiologic and histologic treatment response evaluations. The bidirectional approach has shown promise in smaller retrospective studies but lacked high-quality prospective evidence—this trial fills that void. Also, this study has some limitations. It is the single-arm design study, that lacks a direct control group, limiting comparative conclusions. As well some endpoints (e.g., PCI change) may be difficult to interpret due to inherent imaging limitations for small-volume peritoneal disease (8). Although, such study is necessary to facilitate further RCT.

In **Part 2 of Chapter 4**, interim results of the above-mentioned study are presented. Initial results provide promising evidence supporting the feasibility, safety, and preliminary efficacy of PIPAC combined with systemic FOLFOX chemotherapy as a first-line treatment for patients with gastric cancer peritoneal metastases (GCPM). With a manageable safety profile and signs of disease stabilization, this combination treatment may represent a valuable addition to the current treatment landscape for GCPM, which remains a highly challenging clinical scenario. The objective response rate (ORR) of 29.4%, as assessed by RECIST v1.1, aligns with or exceeds prior studies evaluating systemic chemotherapy alone in GCPM, where response rates typically remain under 20% for patients with peritoneal involvement. This is particularly notable considering the intrinsic difficulty of radiological assessment in patients with low-volume peritoneal disease, often classified as non-measurable. The high rate of repeated PIPAC procedures—achieved in 85% of patients—further supports the feasibility of this regimen. Although the reduction in PCI and ascites volume did not reach statistical significance, both showed favourable trends, suggesting potential disease control. Importantly,

the histological response, measured via Peritoneal Regression Grading Score (PRGS), significantly improved in nearly one-third of patients, highlighting PIPAC's local cytotoxic impact. These findings reinforce the role of PRGS as a sensitive and prognostically relevant marker, even when radiologic metrics fail to capture subtle treatment effects. The conversion of positive to negative peritoneal cytology in 47.1% of patients is particularly encouraging, as cytology status is recognized as a strong prognostic factor in GCPM. Similarly, ascites resolution in 70.6% of cases may contribute meaningfully to symptom relief and improved quality of life, an essential consideration in palliative-intent treatments. In terms of safety, the low complication rate (1.8%) and 0% mortality affirm PIPAC's minimally invasive nature and suitability for patients who may not tolerate more extensive surgical interventions. The fact that 10% of patients underwent R0 cytoreductive surgery following PIPAC + FOLFOX suggests that this approach may also serve as a conversion therapy for initially unresectable disease. At the time of this thesis submission, the enrolment phase of the study has been completed. The forthcoming results are expected to provide robust conclusions regarding the efficacy and safety of the bidirectional PIPAC approach for gastric cancer peritoneal metastases (GC PM) and will help inform the design of a future RCT comparing standard systemic chemotherapy with this novel treatment as a first line treatment for these patients.

CONCLUSIONS OF STUDY TASKS

1. Although the regression of PCI was not statistically significant, the trends were favourable, echoing outcomes reported in previous studies. The median Peritoneal Carcinomatosis Index (PCI) decreased from 14 (interquartile range [IQR]: 4–23) at baseline to 8 (IQR: 2–22) after the 3rd PIPAC; however, the change was not statistically significant ($p > 0.05$).
2. The article emphasizes that Cy1 patients represent a potentially treatable subgroup of stage IV GC, distinct from those with overt peritoneal carcinomatosis. Evidence suggests they may benefit from more aggressive interventions than palliative chemotherapy alone.
3. Conversion of cytological status following systemic chemotherapy associated with improved long-term outcomes in patients with cytology-positive stage IV gastric cancer: relative risk (RR) for peritoneal progression: 0.11 ($p = 0.002$) and hazard ratio (HR) for death was 0.05 ($p = 0.017$).

4. PIPAC is a safe and feasible treatment modality for patients with gastric cancer peritoneal metastases: postoperative complication rate was low (4.2%) with no mortality. Feasibility: 71.9% of patients received more than two PIPAC procedures, and 43.8% received more than three.
5. The combination of PIPAC with cisplatin and doxorubicin, along with systemic FOLFOX chemotherapy in the first line setting, result in higher objective response rates (ORR) compared to the historical ORR of palliative systemic chemotherapy.The objective response rate (ORR) of 29.4%, as assessed by RECIST v1.1, aligns with or exceeds prior studies evaluating systemic chemotherapy alone in GCPM, where response rates typically remain under 20% for patients with peritoneal involvement.

FUTURE PERSPECTIVES TO IMPLEMENT BIDIRECTIONAL TREATMENT FOR GASTRIC CANCER PERITONEAL METASTASES IN TO THE DAILY PRACTICE

The implementation of bidirectional treatment—combining systemic chemotherapy with intraperitoneal therapy such as PIPAC—offers a promising and evolving strategy for managing gastric cancer with peritoneal metastases (GC PM) (8). Current evidence, including findings from retrospective studies and interim results of prospective trials, suggests that this combined approach is safe, feasible, and may offer enhanced tumor control and improved quality of life in selected patients (4,5). However, several key steps are required to translate this experimental regimen into a standardized component of routine clinical practice. Firstly, larger prospective randomized controlled trials (RCTs) are essential to establish definitive evidence of efficacy. The ongoing phase II single-arm trial combining PIPAC with FOLFOX chemotherapy provides a critical foundation but must be followed by comparative studies to evaluate this strategy against standard systemic chemotherapy alone (8). In addition, timing and sequencing of therapy remain areas for exploration. Emerging evidence suggests that early implementation of PIPAC—before the development of chemoresistance or performance deterioration—may improve outcomes (9). Bidirectional therapy could potentially serve not only as palliative care but also as conversion therapy enabling R0 cytoreductive surgery in initially unresectable cases. In conclusion, the integration of bidirectional treatment into the daily practice for GC PM is a realistic goal. With promising early clinical data, improvements

in monitoring tools, and increasing global experience with PIPAC, the pathway to implementation is becoming clearer. Rigorous clinical trials, refined patient selection, and coordinated efforts across institutions will be pivotal in establishing this multimodal strategy as a new standard of care for patients with peritoneal metastases from gastric cancer.

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SANTRAUKA

Daktaro disertacijos tezės pateikiamos ginti kaip mokslinių straipsnių rinkinys. Visos disertacijos dalys yra susijusios, o kai kurios jų pažodžiui cituojamos iš žemiau pateiktų publikuotų straipsnių:

1. Rackauskas R, Bausys A, **Luksta M**, Jurgaitis J, Paskonis M, Strupas K. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal malignancy: initial experience of the first program in the Baltic countries. World J Surg Oncol. 2021 Aug 10;19(1):236. doi: 10.1186/s12957-021-02357-5. PMID: 34376191; PMCID: PMC8356452.
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Oct 25;23(1):1032. doi: 10.1186/s12885-023-11549-z. PMID: 37875869; PMCID: PMC10599063.

Skrandžio vėžys: epidemiologija

Skrandžio vėžys (SV) yra viena iš dažniausiai diagnozuojamų piktybinių ligų pasaulyje – kasmet nustatoma daugiau nei vienas milijonas naujų atvejų, o mirtingumo rodiklis išlieka aukštas, todėl ši liga yra ketvirtoji pagal dažnumą mirties nuo vėžio priežastis pasaulyje (1). Nepaisant to, kad pastaraisiais dešimtmečiais bendras sergamumas mažėjo, SV išlieka svarbi visuomenės sveikatos problema, ypač Rytų Azijoje, Rytų Europoje ir kai kuriose Pietų Amerikos dalyse. Lietuvoje skrandžio vėžys yra penkta pagal dažnumą onkologinė liga – kasmet diagnozuojama daugiau nei 800 naujų atvejų, o tai atspindi tiek aplinkos, tiek genetinius gyventojų polinkius (2). SV paprastai skirstomas pagal anatominę vietą skrandyje į du pagrindinius potipius: kardijos SV ir nekardijos SV. Kardijos skrandžio vėžys išsivysto viršutinėje skrandžio dalyje, šalia stemplės ir skrandžio jungties, o nekardijos SV atsiranda apatinėse skrandžio dalyse, tokiose kaip prievartis ir kūnas. Šie potipiai skiriasi ne tik anatomiškai, bet ir patogeneze, rizikos veiksniais bei klinikine eiga. Lėtinė infekcija Helicobacter pylori (H. pylori) yra pagrindinis nekardijos SV rizikos veiksnys – ši bakterija sukelia lėtinį gastritą, kuris gali progresuoti iki atrofijos, žarnyno metaplazijos, displazijos ir galiausiai – karcinomos. Vis dėlto svarbu pažymėti, kad ne visi asmenys, užsikrėtę H. pylori, susirgs vėžiu – progresavimas stipriai priklauso nuo šeimininko genetinių veiksnių, bakterijos virulentiškumo ir aplinkos poveikio. Be H. pylori infekcijos, keletas gyvenimo būdo ir mitybos veiksnių prisideda prie skrandžio vėžio išsivystymo. Tai apima rūkymą, per didelį alkoholio vartojimą, didelį druskos, konservuotos ar perdirbtos mėsos suvartojimą ir mažą šviežių vaisių bei daržovių (turinčių antioksidantų) vartojimą. Priešingai, kardijos SV dažniau siejamas su nutukimu, pilvo srities riebalų kaupimu ir gastroezofaginio refliukso liga (GERL), kas rodo stipresnį ryšį su mechaniniais ir medžiagų apykaitos veiksniais, o ne su lėtine infekcija (3,4). Epidemiologiškai pasaulinis nekardijos SV dažnis reikšmingai sumažėjo, daugiausia dėl

geresnės sanitarijos, plataus šaldytuvų naudojimo (sumažėjus druskuotų ir rūkytų maisto produktų vartojimo) bei visuomenės sveikatos pastangų kontroliuoti H. pylori. Tuo tarpu kardijos SV paplitimas išliko stabilus arba kai kuriose populiacijose – ypač turtingose Vakarų šalyse – padidėjo, galimai dėl augančio nutukimo ir GERL paplitimo (5). Ypač nerimą kelia nauji duomenys apie didėjantį skrandžio vėžio dažnį tarp jaunų suaugusiųjų iki 50 metų, o tai prieštarauja bendrai mažėjimo tendencijai ir kelia susirūpinimą dėl naujų etiologinių veiksnių. Jie gali būti susiję su pokyčiais skrandžio mikrobiotoje, antibiotikų vartojimu ankstyvame amžiuje ir plataus protonų siurblio inhibitorių (PSI) naudojimo, kurie keičia skrandžio terpę ir gali prisidėti prie kancerogenezės (6,7).

Skrandžio vėžys: šiuo metu taikomi gydymo standartai nemetastazavusiam vėžiui

Chirurginis naviko pašalinimas išlieka pagrindiniu nemetastazavusio skrandžio vėžio (SV) gydymo metodu ir suteikia geriausią ilgalaikio išgyvenamumo galimybę (8). Ankstyvojo SV atvejais gali pakakti vien chirurginio gydymo (arba endoskopinės rezekcijos specifiniais atvejais). Radikalaus chirurginio gydymo tikslas – visiškas naviko pašalinimas su pakankamais kraštais ir regioninių limfmazgių šalinimu, siekiant tiksliai nustatyti ligos stadiją ir sumažinti recidyvo riziką. Rezekcijos apimtį lemia naviko ypatybės, įskaitant histologinį tipą ir plitimo pobūdį (9). Limfadenektomija – dar vienas svarbus skrandžio vėžio chirurginio gydymo komponentas. Ji paprastai skirstoma į tris lygius: D1, D1+ ir D2. D1 limfadenektomijos metu pašalinami tik perigastriniai limfmazgiai, o D2 – papildomai šalinami limfmazgiai palei kairiąją skrandžio, bendrąją kepenų, blužnies ir pilvo aortos arterijas. Ankstyvųjų stadijų atvejais pakanka D1 rezekcijos, tačiau pažengusio vėžio atvejais stipriai rekomenduojama D2 limfadenektomija, nes ji susijusi su geresniu išgyvenamumu be ligos ir bendru išgyvenamumu, kaip parodyta keliuose ilgalaikiuose atsitiktinių imčių tyrimuose (10). Pacientams, kuriems SV galima pašalinti chirurginiu būdu, bet liga nėra ankstyvos stadijos, dabartinės klinikinės gairės rekomenduoja taikyti perioperacinę chemoterapiją, o ne iš karto

operuoti ir po to taikyti adjuvantinį gydymą – tai paremta kelių didelių atsitiktinių imčių klinikinių tyrimų rezultatais (11,12). Vienas iš neoadjuvantinės chemoterapijos (NAC) privalumų yra tas, kad pacientai gauna chemoterapiją prieš operaciją – tai naudinga, nes pooperacinės komplikacijos gali susilpninti pacientą ir sumažinti jo galimybes toleruoti tolesnę chemoterapiją. Priešingai, chemoterapija, taikoma prieš operaciją, dažniau geriau toleruojama, leidžia pilniau užbaigti planuotus chemoterapijos kursus ir veiksmingiau kontroliuoti naviką. Kiti neoadjuvantinės terapijos privalumai – naviko sumažinimas, dėl kurio iš pradžių riboto operabilumo arba neoperabilūs navikai tampa pašalinami chirurginiu būdu, mikroskopinių metastazių naikinimas ir didesnė tikimybė pasiekti visišką mikroskopinį naviko pašalinimą (R0 rezekcija). Visi šie veiksniai prisideda prie geresnių ilgalaikių klinikinių rezultatų SV pacientams (13). Reikšmingas MAGIC tyrimas pateikė svarbių įrodymų apie klinikinę naudą taikant perioperacinę chemoterapiją kartu su chirurginiu gydymu pacientams, kuriems diagnozuotas operabilus gastroezofaginės jungties navikas. Šis tyrimas parodė, kad pacientai, kurie prieš ir po operacijos gavo epirubicino, cisplatinos ir fluorouracilo derinį (žinomą kaip ECF režimą), turėjo žymiai geresnį išgyvenamumą nei tik chirurginiu būdu gydyti pacientai. Tiksliau, MAGIC tyrimas parodė, kad penkerių metų bendras išgyvenamumas padidėjo nuo 23 % chirurgijos grupėje iki 36 % grupėje, kurioje taikyta chemoterapija ir chirurgija (14). Šiuos rezultatus dar labiau patvirtino Prancūzijoje atliktas daugiašalis atsitiktinių imčių kontroliuojamas FNCLCC ir FFCD tyrimas. Jame taikyta perioperacinė chemoterapija su cisplatina ir fluorouracilu, ir penkerių metų išgyvenamumas padidėjo nuo 24 % (tik chirurgijos grupė) iki 38 % (kombinuota terapija) (15). Dar naujesnis FLOT4-AIO II/III fazės atsitiktinių imčių tyrimas toliau vystė neoadjuvantinės chemoterapijos vaidmenį, tirdamas šiuolaikinį FLOT režimą (fluorouracilas, leukovorinas, oksaliplatina ir docetakselis). FLOT režimas pasiekė geresnius klinikinius rezultatus – penkerių metų bendras išgyvenamumas siekė apie 45 %, palyginti su 36 % pacientų, gydytų anksčiau taikytais ECF arba ECX režimais (16). Nepaisant aiškios klinikinės naudos, kurią įrodė šie tyrimai, vis dar kyla klausimų

ir skepticizmo dėl plačios neoadjuantinės chemoterapijos taikymo. Kritikai pažymi, kad daugelis svarbiausių atsitiktinių imčių tyrimų, vertinančių perioperacinės chemoterapijos naudą, turėjo metodologinių trūkumų, ypač dėl chirurginės kokybės, įskaitant nepakankamą limfmazgių šalinimą, kas gali turėti įtakos išgyvenamumui. Be to, šiuose tyrimuose dažnai buvo tiriami tiek skrandžio, tiek stemplės adenokarcinomos atvejai, todėl sunku tiksliai įvertinti, ar radikali chirurgija su išsamia D2 limfadenektomija galėtų panaikinti chemoterapijos teikiamą išgyvenamumo pranašumą. Todėl, nors perioperacinė chemoterapija tapo standartu Vakarų šalyse, Rytų šalyse vis dar didelis dėmesys skiriamas tradicinei plačiai chirurginei rezekcijai su standartine D2 limfadenektomija. Be to, dauguma iki šiol atliktų tyrimų daugiausia vertino pagrindinio skrandžio naviko atsaką į chemoterapiją, o duomenų apie tai, kaip neoadjuvantinė chemoterapija veikia metastazavusius limfmazgius, vis dar mažai (17–18).

Skrandžio vėžys: pilvaplėvės metastazių problema

Skrandžio vėžys (SV) dažnai kelia didelį klinikinį iššūkį dėl veiksmingų populiacinių patikros programų trūkumo ir dažnai besimptomės ankstyvosios ligos stadijos. Dėl to daugelis pacientų diagnozuojami jau pažengusiose stadijose, kai gydymo galimybės yra ribotos, o prognozė – prasta (19, 20). Diagnozės metu maždaug 10–30 % pacientų su SV jau turi pilvaplėvės metastazių (PM), kurios yra susijusios su ypač blogais gydymo rezultatais (21). Be to, net ir atlikus pradinį radikalų chirurginį gydymą su išgydymo tikslu, reikšminga pacientų dalis vėliau išsivysto metachronines PM, o tai pabrėžia agresyvų SV biologinį pobūdį ir jo polinkį plisti pilvaplėvės ertmėje (22). Pilvaplėvės metastazės sergant skrandžio vėžiu dažniausiai laikomos galine ligos stadija. Literatūroje nurodomas vidutinis bendras išgyvenamumas sergant PM svyruoja nuo vos 2 iki 9 mėnesių, priklausomai nuo ligos išplitimo, paciento būklės ir taikomo gydymo metodo (23). Toks trumpas išgyvenamumas pabrėžia skubų poreikį veiksmingesniems gydymo metodams ir geresnėms pacientų stratifikacijos strategijoms. Standartinis SV su PM gydymas paprastai apima sisteminę chemoterapiją, kuri gali būti taikoma kaip

monoterapija arba kartu su taikinių terapija ar imunoterapijos preparatais. Nepaisant sisteminių gydymo režimų pažangos, jų veiksmingumas pacientams su PM išlieka labai ribotas. Atsako į gydymą dažnis šioje pacientų grupėje dažnai nesiekia 14 %, palyginti su maždaug 40 % pacientų, turinčių hematogenines metastazes, pavyzdžiui, kepenyse, plaučiuose ar kauluose (24, 25). Prastas pilvaplėvės karcinozės atsakas į standartinį sisteminį gydymą aiškinamas biologiniu reiškiniu, vadinamu „plazmos ir pilvaplėvės barjeru“. Šis natūralus barjeras neleidžia į veną leidžiamiems chemoterapiniams vaistams pakankamai prasiskverbti į karcinozės židinius, o nesant pakankamos vaisto koncentracijos, norimas citotoksinis poveikis nepasiekiamas (31).

Skrandžio vėžys: intraperitoninės terapijos pilvaplėvės metastazėms gydyti

Siekdami įveikti minėtus farmakologinius apribojimus, mokslininkai pasiūlė įvairias inovatyvias vaistų tiekimo strategijas. Tarp jų daug žadančiais pasirodė nanodalelėmis pagrįsti vaistų tiekimo metodai, kurie ikiklinikiniuose modeliuose pagerino vaisto kaupimąsi pilvaplėvės navikuose, kartu sumažindami sisteminį toksiškumą (26). Kitas svarbus metodas yra intraperitoninė chemoterapija (IPT), kai priešvėžiniai vaistai tiesiogiai suleidžiami į pilvaplėvės ertmę. Tokiu būdu pasiekiamos didesnės vietinės vaisto koncentracijos, navikiniai mazgeliai ir laisvai plūduriuojančios vėžinės ląstelės ilgiau veikiamos citotoksinių agentų, o sisteminis pasisavinimas sumažinamas (27, 28). Yra sukurta keletas IPT taikymo būdų. Kai kuriose Azijos šalyse pacientams, sergantiems SV ir turintiems ribotą pilvaplėvės išplitimą, dažniau taikoma normoterminė intraperitoninė chemoterapija per implantuotą peritoninį portą. Tuo tarpu Vakarų šalyse dažniau taikoma hiperterminė intraperitoninė chemoterapija (HIPEC) (28). HIPEC metu po citoredukcinės chirurgijos (CRS) į pilvaplėvės ertmę cirkuliuoja įkaitinti chemoterapiniai vaistai, o šis metodas pasižymi keliais potencialiais privalumais. Pirma, pati hipertermija turi tiesioginį citotoksinį poveikį piktybinėms ląstelėms. Antra, pakilusi temperatūra pagerina audinių perfuziją ir vaistų prasiskverbimą. Trečia, karštis

sustiprina kai kurių vaistų – ypač platinos junginių – toksiškumą per sinergetinius mechanizmus (28).

Nors HIPEC gali būti taikoma kaip neoadjuvantinė terapija prieš operaciją, dažniausiai ji atliekama iš karto po visiškos arba beveik visiškos citoredukcinės operacijos, siekiant pašalinti mikroskopinę likutinę ligą (29). Vis dėlto HIPEC yra invazinis ir fiziologiškai reikalaujantis gydymo būdas, tinkamas tik labai atrinktiems pacientams, turintiems ribotą ligos išplitimą ir pakankamą funkcinę būklę. Daugelis SV pacientų su PM diagnozės metu yra prastos bendros būklės ir gali netoleruoti CRS-HIPEC sukeliamo streso, todėl šio metodo taikymas yra ribotas. Nepaisant optimistinių rezultatų kai kuriuose aukštos apimties centruose, bendras HIPEC klinikinis naudingumas išlieka diskutuotinas, ypač už specializuotų centrų ribų ir nevienodose pacientų grupėse (25). Naujesnė ir mažiau invazinė alternatyva yra slėginė intraperitoninė aerozolinė chemoterapija (PIPAC). Tai nauja terapinė strategija, skirta pagerinti vaistų pasiskirstymą ir prasiskverbimą pilvaplėvės ertmėje. Pirmą kartą atlikta Vokietijoje 2011 metais, PIPAC naudoja minimaliai invazinę laparoskopiją, kad į pilvaplėvės ertmę būtų suleidžiama aerozolinė chemoterapija esant slėgiui (22, 26). Manoma, kad šis metodas optimizuoja vaistų pasiskirstymą intraperitoninėje erdvėje, padidina prasiskverbimo gylį padidindamas hidrostatinį slėgį, sumažina vaistų išplovimą per kraujagysles jų suleidimo metu ir leidžia išlaikyti kontroliuojamas sąlygas. Be to, PIPAC leidžia atlikti pakartotines procedūras bei stebėti gydymo veiksmingumą ilgalaikėje perspektyvoje, nes kiekvienos procedūros metu galima paimti pilvaplėvės biopsijas ir objektyviai vertinti naviko atsaką į gydymą (25).

PIPAC taikymas pilvaplėvės metastazėms sergant skrandžio vėžiu: dabartiniai įrodymai ir žinių spragos

Keletas kohortinių ir nedidelių perspektyvinių tyrimų parodė, kad PIPAC yra gerai toleruojama pacientų, sergančių skrandžio vėžiu ir pilvaplėvės karcinoze, ir kad šio metodo taikymas gali būti susijęs su naviko regresija, pagerėjusiu išgyvenamumu bei gyvenimo kokybe

(32–36). Chemoterapijos metu vykstanti naviko regresija vertinama naudojant tarptautinę pilvaplėvės regresijos vertinimo skalę (PRGS), kuri nustato biopsijose likusių navikinių ląstelių kiekį (37).

Pastaruoju metu buvo pasiūlyta dvi-modalė PIPAC koncepcija, kai šis metodas derinamas su sistemine chemoterapija. Vienas iš tokių tyrimų buvo paskelbtas Mohammado ir kolegų (38). Tai retrospektyvus tyrimas, kuriame dalyvavo 42 pacientai, kuriems dėl pilvaplėvės metastazių buvo atliktos 163 PIPAC procedūros. Iš jų 20 pacientų prieš PIPAC gavo sisteminę chemoterapiją. Šis kombinuotas gydymas lėmė beveik 19 mėnesių bendrą išgyvenamumą, o 6 pacientams, kuriems buvo pastebėta ligos regresija, vėliau buvo atlikta citoredukcinė chirurgija (38). Kitas analogiškas tyrimas, paskelbtas Ellebæk ir kolegų, retrospektyviai išanalizavo 20 pacientų, kuriems buvo taikyta sisteminė chemoterapija ir 52 PIPAC procedūros (39). Šis gydymas užtikrino maždaug 11 mėnesių bendrą išgyvenamumą. Šie perspektyvūs rezultatai paskatino autorius siūlyti, kad kombinuotas gydymas galėtų tapti nauju gydymo standartu (39).

Panašų retrospektyvų tyrimą paskelbė Di Giorgio ir kolegos – jie parodė, kad standartinės sisteminės chemoterapijos ir PIPAC derinys pacientams, sergantiems pilvaplėvėje išplitusiu skrandžio vėžiu, lėmė vidutinį bendrą išgyvenamumą – 15,5 mėnesio. Vis dėlto net tris pilnas PIPAC procedūras pavyko atlikti tik 25 % pacientų (40).

Visi šie retrospektyvūs tyrimai leidžia manyti, kad sisteminės chemoterapijos ir PIPAC derinys gali užtikrinti geresnius rezultatus nei vien sisteminė chemoterapija gydant skrandžio vėžio sukeltą pilvaplėvės karcinomatozę. Tačiau, nepaisant šių viltingų rezultatų, būtina atsižvelgti į metodologinius šių tyrimų ribotumus, ypač jų retrospektyvų pobūdį. Todėl PIPAC išlieka eksperimentiniu gydymo metodu ankstyvoje vystymosi stadijoje ir šiuo metu nėra tinkamas taikyti įprastoje klinikinėje praktikoje. Štai kodėl šis tyrimų projektas buvo sukurtas siekiant užpildyti esamas žinių spragas apie PIPAC vaidmenį gydant pilvaplėvės metastazes, kilusias iš skrandžio vėžio.

Šio darbo struktūra

Tyrimo hipotezės, uždaviniai ir metodai

Šio darbo tikslas – ištirti penkias hipotezes, kurios galėtų prisidėti prie skrandžio vėžiu (SV) sergančių pacientų su pilvaplėvės metastazėmis (PM) priežiūros gerinimo. Šios hipotezės yra:

1. PIPAC sumažina arba stabilizuoja pilvaplėvės karcinozės indeksą (PCI) pacientams, sergantiems skrandžio vėžiu.
2. IV stadijos skrandžio vėžiu su teigiama citologija sergantiems pacientams agresyvus gydymo būdas, derinantis sisteminę chemoterapiją su radikalia gastrektomija ir/arba intraperitonine chemoterapija, pagerina išgyvenamumo rodiklius, palyginti su vien tik paliatyvine sistemine chemoterapija.
3. Citologinės būklės pokytis po sisteminės chemoterapijos yra susijęs su geresniais ilgalaikiais rezultatais pacientams, sergantiems IV stadijos skrandžio vėžiu su teigiama citologija.
4. PIPAC yra saugus ir įgyvendinamas gydymo metodas pacientams, sergantiems skrandžio vėžio pilvaplėvės metastazėmis.
5. PIPAC su cisplatina ir doksorubicinu, kartu su pirmos eilės sistemine FOLFOX chemoterapija, užtikrina didesnį objektyvaus atsako dažnį (ORR), palyginti su istoriniu ORR, pasiektu taikant vien tik paliatyvinę sisteminę chemoterapiją.

Siekiant patikrinti šias hipotezes, atsakyti į mokslinius klausimus ir užpildyti esamas žinių spragas, buvo atlikta serija uždavinių. Uždaviniai ir taikyti metodai, skirti atsakyti į mokslinius klausimus, yra apibendrinti lentelėje nr.1.

1 lentelė.Tyrimo uždaviniai (moksliniai klausimai) ir metodai, taikyti jiems atsakyti

Tyrimo uždaviniai (moksliniai klausimai)	*Metodai*
1. Ar PIPAC sumažina arba stabilizuoja pilvaplėvės karcinozės indeksą (PCI) pacientams, sergantiems skrandžio vėžiu?	Šiam tikslui pasiekti buvo atliktas retrospektyvus kohortinis tyrimas, kurio rezultatai pateikti **2 skyriaus I dalyje.**

Tyrimo uždaviniai (moksliniai klausimai)	*Metodai*
2. Ar agresyvūs gydymo metodai, derinantys sisteminę chemoterapiją su radikalia gastrektomija ir/arba intraperitonine chemoterapija, pagerina išgyvenamumą pacientams, sergantiems IV stadijos skrandžio vėžiu su teigiama citologija, palyginti su vien paliatyvine sistemine chemoterapija?	Šiam moksliniam klausimui atsakyti buvo atlikta literatūros apžvalga, kurios rezultatai pateikti **3 skyriaus I dalyje.**
3. Ar citologinės būklės pokytis po sisteminės chemoterapijos susijęs su geresniais ilgalaikiais rezultatais pacientams, sergantiems IV stadijos skrandžio vėžiu su teigiama citologija?	Šiam tikslui pasiekti buvo atliktas retrospektyvus tyrimas, kurio rezultatai pateikti **3 skyriaus II dalyje.**
4. Ar PIPAC yra saugus ir įgyvendinamas gydymo metodas pacientams, sergantiems skrandžio vėžio pilvaplėvės metastazėmis?	Šiam moksliniam klausimui atsakyti buvo atliktas retrospektyvus tyrimas, kurio rezultatai pateikti **2 skyriaus II dalyje.**
5. Ar PIPAC kartu su cisplatina ir doksorubicinu bei sistemine FOLFOX chemoterapija kaip pirmos eilės gydymas užtikrina didesnį objektyvaus atsako dažnį (ORR) nei istorinis ORR, pasiektas taikant tik paliatyvinę sisteminę chemoterapiją?	Šiam tikslui pasiekti buvo atliktas prospektyvus tyrimas (tyrimo protokolas), o tarpiniai rezultatai pateikti **4 skyriaus I–II dalyse.**

Tyrimo rezultatų apibendrinimas

1-ame skyriuje nagrinėjama besikeičianti skrandžio vėžio (SV) gydymo panorama – tai didelė pasaulinė sveikatos problema, ypač aktuali Rytų Europoje ir Azijoje, kur išgyvenamumas išlieka mažas (1). Chirurginis gydymas su D2 limfadenektomija tebėra standartinis lokalizuoto SV gydymo metodas, tačiau perioperacinės ar neoadjuvantinės chemoterapijos įtraukimas

parodė geresnius rezultatus. Metastazavusio SV atvejais, ypač kai yra pilvaplėvės metastazių (PM), kurios pasireiškia iki 43 % pacientų, prognozė išlieka bloga. Sisteminė chemoterapija yra standartas, tačiau dėl plazmos ir pilvaplėvės barjero jos veiksmingumas yra ribotas. Dėl šios priežasties tyrinėjamos naujoviškos vietinio gydymo strategijos, tokios kaip hiperterminė intraperitoninė chemoterapija (HIPEC) ir slėginė intraperitoninė aerozolinė chemoterapija (PIPAC). Nors PIPAC mažo masto tyrimuose parodė viltingų rezultatų, jos derinys su sistemine chemoterapija vis dar laikomas eksperimentiniu (2,3). Disertacijoje iškeltos penkios pagrindinės hipotezės, kurios tiriamos taikant įvairius metodus: literatūros apžvalgą, kohortinius tyrimus ir vienos grupės II fazės prospektyvų tyrimą. 2-o skyriaus 1 dalyje pristatomas retrospektyvus tyrimas, kuriame aprašomi pirmieji Lietuvoje taikyto PIPAC gydymo rezultatai pacientams, sergantiems skrandžio ir kiaušidžių vėžiu su pilvaplėvės metastazėmis. PIPAC buvo įvertintas kaip saugus ir įmanomas metodas – pooperacinis mirtingumas nenustatytas, komplikacijų dažnis – 8,8 %. Tyrimas palaiko PIPAC kaip potencialią ligos stabilizavimo, gyvenimo kokybės gerinimo ir galimo tolimesnio gydymo CRS + HIPEC strategiją pasirinktiniems pacientams.

Nors PCI sumažėjimas ir ascito kontrolė nebuvo statistiškai reikšmingi, tendencijos buvo palankios ir atitiko ankstesnių tyrimų duomenis. Pastebėta, kad OC pacientai dažniau baigė visus tris suplanuotus PIPAC ciklus, kas leidžia manyti, jog ligos kilmė turi įtakos gydymo toleravimui – tai reikalauja tolesnio tyrimo (4). 2 skyriaus 2 dalyje kitas retrospektyvus tyrimas įvertino PIPAC rezultatus pacientams tik su SV sukelta PM. Rezultatai rodo, kad PIPAC yra saugus ir įgyvendinamas: pooperacinių komplikacijų dažnis siekė 4,2 %. Per 30 dienų pooperacinį laikotarpį mirties atvejų nestebėta. PIPAC gavo daugiau nei du ciklus 71,9 % pacientų, o daugiau nei tris – 43,8 %. Nors PCI ir ascito sumažėjimas nebuvo statistiškai reikšmingas, tendencijos buvo palankios. Vidutinė bendra išgyvenamumo trukmė nuo PM diagnozės – 12,5 mėn., o nuo pirmos PIPAC procedūros – 5 mėn. Visi pacientai buvo sėkmingai operuoti laparoskopu – gydymas nutrauktas dėl klinikinės būklės pablogėjimo, o ne techninių priežasčių.

Tyrimas pabrėžia PIPAC svarbą kaip daugiakomponentės terapijos dalį, tačiau būtini platesnio masto prospektyvūs tyrimai. Aptariama ir PIPAC efektyvumo vertinimo problema – dėl ribotų vaizdinimo galimybių mažo tūrio ligai RECIST kriterijai yra nepakankami. Kiti metodai, tokie kaip kartotinė laparoskopija ir histologinės vertinimo sistemos (pvz., PRGS), siūlo alternatyvas. Nors PRGS šiame tyrime netaikyta, ji galėtų būti naudinga objektyviai vertinant atsaką į gydymą. 3-io skyriaus 1 dalyje apžvelgiamos

gydymo strategijos pacientams, sergantiems GC su teigiama citologija (Cy1). Nors nėra matomų PM, prognozė bloga. Apžvalga rodo, kad agresyvus ar kombinuotas gydymas gali pagerinti rezultatus, tačiau trūksta prospektyvių palyginamųjų tyrimų. Cy1 pacientai gali būti tinkami aktyvesniam gydymui nei tik paliatyvinė chemoterapija (6). 3-io skyriaus 2 dalyje aprašytas daugiašalis retrospektyvus tyrimas, kuriame įvertinta neoadjuvantinės chemoterapijos ir gastrektomijos seka 43 pacientams iš Lietuvos, Estijos ir Ukrainos. 53,5 % pacientų pasiekė neigiamą citologiją, o gastrektomija su D2 limfadenektomija atlikta 93 %. Vidutinė OS – 20 mėn., PFS – 19 mėn. 7,1 % pacientų mirė per 30 dienų po operacijos. Citologijos konversija buvo stipriai susijusi su išgyvenamumu ir mažesne recidyvo rizika – RR = 0.11 (p = 0.002), HR = 0.05 (p = 0.017).

4-o skyriaus 1 dalyje aprašytas naujo tyrimo protokolas, kuriame vertinamas PIPAC (cisplatina + doksorubicinas) ir FOLFOX derinio (5-FU, oksaliplatina, leukovorinas) efektyvumas ir saugumas pirmos eilės gydyme GC pacientams su PM. Tyrimas vykdomas dviejuose Lietuvos vėžio centruose. Gydymas: 3 PIPAC ciklai, tarp jų – po 2 FOLFOX ciklus kas 6–7 savaites. Vertinami tiek radiologiniai (RECIST v1.1), tiek histologiniai (PRGS) atsakai. Pirminis tikslas – objektyvaus atsako dažnis po 4 FOLFOX ciklo; antriniai – PCI, ascitas, gyvenimo kokybė, išgyvenamumas, toksiškumas, biomarkeriai. 4-o skyriaus 2 dalyje pateikti šio tyrimo tarpiniai rezultatai. Gauti duomenys rodo, kad gydymas yra įgyvendinamas, saugus ir preliminariai efektyvus: objektyvaus atsako dažnis – 29,4 % pagal RECIST. 85 % pacientų gavo kelias PIPAC procedūras. PCI ir ascito kiekio sumažėjimas nebuvo statistiškai reikšmingas, bet tendencijos – teigiamos. PRGS reikšmingai pagerėjo beveik trečdaliui pacientų. 47,1 % pacientų pasiekė citologijos konversiją, o ascitas išnyko 70,6 %. Komplikacijų dažnis – 1,8 %, mirtingumas – 0 %. 10 % pacientų buvo atlikta R0 rezekcija. Šie duomenys patvirtina PIPAC + FOLFOX derinio perspektyvumą ir būtinybę tolesniems tyrimams.

STUDIJOS UŽDAVINIŲ IŠVADOS

1. Nors PCI regresija nebuvo statistiškai reikšminga, tendencijos buvo palankios ir atitiko ankstesnių tyrimų rezultatus. Vidutinis pilvaplėvės karcinomatozės indeksas (PCI) sumažėjo nuo 14 (tarpkvartilinis intervalas [TKI]: 4–23) pradžioje iki 8 (TKI: 2–22) po trečiosios PIPAC procedūros; tačiau šis pokytis nebuvo statistiškai reikšmingas (p > 0,05).

2. Straipsnyje pabrėžiama, kad Cy1 pacientai yra potencialiai gydytina IV stadijos skrandžio vėžio pogrupis, kuris skiriasi nuo pacientų su akivaizdžia pilvaplėvės karcinomatoze. Įrodymai rodo, kad jie gali gauti naudos iš agresyvesnio gydymo nei vien paliatyvioji chemoterapija.
3. Citologinės būklės konversija po sisteminės chemoterapijos buvo susijusi su geresniais ilgalaikiais rezultatais pacientams, sergantiems citologiškai teigiamu IV stadijos skrandžio vėžiu: pilvaplėvės progresavimo santykinė rizika (RR) – 0,11 (p = 0,002), mirties rizikos santykis (HR) – 0,05 (p = 0,017).
4. PIPAC yra saugus ir įgyvendinamas gydymo metodas pacientams, sergantiems skrandžio vėžio pilvaplėvės metastazėmis: pooperacinių komplikacijų dažnis buvo mažas (4,2 %), mirtingumo nebuvo. Įgyvendinamumas: 71,9 % pacientų gavo daugiau nei dvi PIPAC procedūras, o 43,8 % – daugiau nei tris.
5. PIPAC derinys su cisplatina ir doksorubicinu kartu su sistemine FOLFOX chemoterapija kaip pirmos eilės gydymas duoda didesnį objektyvų atsako dažnį (ORR), palyginti su istoriniu paliatyvios sisteminės chemoterapijos ORR. Objektyvus atsako dažnis (ORR) buvo 29,4 %, vertinant pagal RECIST v1.1, kas atitinka arba viršija ankstesnių tyrimų, vertinusių vien sisteminę chemoterapiją sergant GCPM, rezultatus, kuriuose atsako dažnis dažniausiai būna mažesnis nei 20 % pacientams, turintiems pilvaplėvės pažeidimą.

ATEITIES PERSPEKTYVOS: DVIEJŲ KRYPČIŲ GYDYMO INTEGRAVIMAS Į KASDIENĘ KLINIKINĘ PRAKTIKĄ SKRANDŽIO VĖŽIO SU PILVAPLĖVĖS METASTAZĖMIS ATVEJU

Dviejų krypčių gydymo – sisteminės chemoterapijos derinimo su intraperitoniniu gydymu, tokiu kaip PIPAC – įgyvendinimas siūlo daug žadantį ir nuolat tobulėjančią strategiją skrandžio vėžiui su pilvaplėvės metastazėmis (SV PM) gydyti (8). Esami įrodymai, įskaitant retrospektyvinius tyrimus ir prospektyvių tyrimų tarpinius rezultatus, rodo, kad šis derinys yra saugus, įgyvendinamas ir tam tikriems pacientams gali užtikrinti geresnę naviko kontrolę bei pagerinti gyvenimo kokybę (4,5).

Tačiau, norint šį eksperimentinį gydymo režimą paversti standartine kasdienės klinikinės praktikos dalimi, būtina atlikti keletą svarbių žingsnių. Visų pirma, būtini didesnės apimties prospektyvūs atsitiktinių imčių

kontroliuojami tyrimai (RCT), kad būtų galima galutinai įrodyti gydymo veiksmingumą. Šiuo metu vykstantis II fazės vienos grupės tyrimas, kuriame derinamas PIPAC su FOLFOX chemoterapija, suteikia svarbų pagrindą, tačiau jį privalo sekti lyginamieji tyrimai, kurie įvertintų šio metodo efektyvumą, palyginti su vien sistemine chemoterapija (8).

Be to, vis dar reikia ištirti optimalų gydymo laiko parinkimą ir seką. Naujausi duomenys rodo, kad ankstyvas PIPAC taikymas – prieš išsivystant chemoresistencijai ar paciento būklės blogėjimui – gali pagerinti rezultatus (9). Dviejų krypčių gydymas galėtų būti taikomas ne tik kaip paliatyvus gydymas, bet ir kaip konversinis gydymas, leidžiantis atlikti R0 citoredukcinę operaciją pacientams, kuriems liga iš pradžių buvo laikyta neoperabilia.

Apibendrinant galima teigti, kad dviejų krypčių gydymo integravimas į kasdienę klinikinę praktiką SV PM gydymui yra realus tikslas. Turint viltingų ankstyvųjų klinikinių duomenų, tobulinant stebėjimo priemones ir didėjant pasaulinei patirčiai taikant PIPAC, šio metodo diegimo kelias tampa vis aiškesnis. Griežti klinikiniai tyrimai, patobulintas pacientų atrankos procesas ir koordinuotos pastangos tarp skirtingų institucijų bus esminiai siekiant įtvirtinti šią daugiamodalę strategiją kaip naują priežiūros standartą pacientams, sergantiems pilvaplėvės metastazėmis, kilusiomis iš skrandžio vėžio.

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CURRICULUM VITAE

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Education

2024	**Observership in Upper Gastrointestinal Surgery.** *Oesophageal and Gastric Cancer minimal invasive surgery. Amsterdam UMC. University of Amsterdam.*
2024	**Functional OGI surgery.** *Evangelical Hospital Cologne Reflux Center. Germany.*
2021	**International PIPAC hands on course.** *University Hospital Tübingen, Germany.*
2020	**European Society of Surgical Oncology (ESSO)** *Hands on Course on Minimally Invasive Gastrectomy and Esophagectomy. Utrecht, Netherlands.*
2020	**Digestive and Endocrine Surgery Department, Hopital Nouvel Civil (NHC)** | Strasbourg, France *Minimally Invasive and Robotic Digestive and Endocrine Surgery Fellowship*
2019	*Course on Laboratory Animal Sciences (FELASA, category B)*
2013 – 2018	**Vilnius University Faculty of Medicine** | Vilnius, Lithuania *Residency of abdominal surgery*
2007 – 2013	**Vilnius University Faculty of Medicine** | Vilnius, Lithuania *Medicine*

Experience

Since 2018	*Membership:* *1. Lithuanian Association of Surgeons.* *2. Lithuanian Society of Minimally Invasive Surgery.* *3. Lithuanian Society of Endoscopy.*
Since 2018	*Vilnius University hospital "Santaros" clinics, Center of Abdominal and Oncosurgery, Abdominal surgeon*

Awards

2024	*Award of the Vilnius Medical Society and Prof. I. Balčiūnienė - for the best scientific-practical work. "High-pressure intraperitoneal chemotherapy (PIPAC) as an additional treatment in combination with standard systemic supportive care chemotherapy in patients with gastric cancer with peritoneal spread: a pilot study"*

Scientific projects

Personalized trimodal prehabilitation for gastrectomy. Since 2019. Role: investigator.

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+ various contributions to national and international scientific meetings

Personal skills
Foreign language

	UNDERSTANDING		SPEAKING	WRITING
	Listening	Reading		
English	B1	B1	B1	C1
German	A1	A1	A1	A1

PC skills	Microsoft Office™, SPSS, GraphPad, MedCalc
Professional interests	Upper GI surgery, surgical oncology, minimal invasive surgery, gastric cancer, endoscopic vacuum therapy in the upper GI tract, anti-reflux surgery, hiatal hernia surgery.

VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
sui generis darinys prie VILNIAUS UNIVERSITETO

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2022 09 13 Nr. 2022/9-1453-923

Tyrimo pavadinimas:

Aukšto spaudimo intraperitoninė chemoterapija (PIPAC) kaip papildomas gydymas kartu su standartine sistemine pirmos eilės chemoterapija pacientams sergantiems skrandžio vėžiu išplitusiu pilvaplėvėje: pilotinis tyrimas

Protokolo Nr.:	2
Versija:	2
Data:	2022 09 01
Informuoto asmens sutikimo forma:	2 2022 09 01
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Pirmininkas doc. dr. Alfredas Laurinavičius

PADĖKA

Išreiškiu nuoširdžią padėką savo darbo vadovui akad. prof. habil. dr. Kęstučiui Strupui už išskirtinę akademinę mentorystę, profesionalų patarimą, rūpestį bei visapusišką pagalbą visos doktorantūros metu. Jo įžvalgos, patirtis bei palaikymas buvo neįkainojami.

Taip pat esu labai dėkingas doc. Augustinui Baušiui už nuolatinį palaikymą, vertingas įžvalgas, tikėjimą mano darbu bei paskatinimą siekti akademinio ir profesinio tobulėjimo. Jo optimizmas, kantrybė ir konstruktyvūs patarimai buvo svarbus įkvėpimo šaltinis net sudėtingiausiais momentais.

Šio daugiadisciplininio darbo įgyvendinimas buvo įmanomas tik glaudžiai bendradarbiaujant su kompetentinga komanda. Reiškiu nuoširdžią padėką pilvo chirurgams, onkologams-chemoterapeutams, patologams, radiologams, anesteziologams, gastroenterologams bei I-o operacinio bloko darbuotojams. Kiekvieno komandos nario skirtas laikas, pastangos ir profesinė patirtis ženkliai prisidėjo prie studijos rezultatų.

Dėkoju visam I-o Pilvo ir onkochirurgijos skyriui už profesionalią pagalbą ir draugišką bendradarbiavimą visos doktorantūros studijų metu.

Ypatinga padėka skiriama mano Šeimai – Ramintai ir Motiejui Lukui – už besąlygišką palaikymą, kantrybę, supratimą sudėtingais laikotarpiais. Jų buvimas šalia suteikė stiprybės ir motyvacijos nesustoti.

Nuoširdi asmeninė padėka, itin ženkliai prisidėjusiems prie šio darbo:

- prof. habil. dr. K. Strupas
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