

Original Article



Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Gastric Cancer Patients with Peritoneal Metastasis (PM): Results of a Single-Center Experience and Register Study

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ABSTRACT

Purpose: Gastric cancer (GC) patients with peritoneal metastasis (PM) have poor prognosis. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with systemic chemotherapy is a novel treatment option for patients in stage IV of the disease.






Materials and Methods: Between November 2015 and June 2018, prospective data collection was performed in 24 patients with GC and PM (median age, 57; range, 44–75 years). These patients underwent 46 PIPAC procedures with a median number of 2 interventions per patient (range, 1–6). A laparoscopic access was used and a combined therapy of cisplatin and doxorubicin aerosol was administered.

Results: The median peritoneal carcinomatosis index before the 1st PIPAC was 14 (range, 2–36), and the median ascites volume in patients before the 1st PIPAC was 100 mL (range, 0–6 mL, 300 mL). Eleven patients, who received 2 or more PIPAC procedures, had decreased and stable volumes of ascites, while only 3 patients displayed increasing volume of ascites. The median overall survival was 121 days (range, 66–625 days) after the 1st PIPAC procedure, while 8 patients who received more than 3 PIPAC procedures had a median survival of 450 days (range, 206–481 days) ($P=0.0376$).

Conclusions: Our data show that PIPAC is safe and well tolerated, and that the production of ascites can be controlled by PIPAC in GC patients. Patients, who received 2 or more PIPAC procedures, reported a stable overall quality of life. Further studies are required to document the significance of PIPAC as a palliative multimodal therapy.

Trial Registration: ClinicalTrials.gov Identifier: [NCT03100708](https://clinicaltrials.gov/ct2/show/study/NCT03100708)

Keywords: Gastric cancer; Peritoneal metastasis; PIPAC; Palliative chemotherapy

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Author Contributions

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Globally, gastric cancer (GC) is the second most common cause of cancer-related death [1] and although more prevalent in East Asia, it is one of the 5 most common cancers in Europe in terms of incidence and mortality [2]. GC frequently metastasizes hematogenously to distant organs or directly into the peritoneum. Peritoneal metastasis (PM) is the most frequent pattern of metastasis in stage IV GC. Synchronous PM was reported in 10–40% of all GC patients, even in those initially scheduled for curative surgery [3–5]. About 60% of deaths due to GC are related to metachronous PM [3,6]. Life expectancy in patients with GC-induced PM is limited to about 3–9 months [5,7,8]. The effect of systemic therapy on PM is limited, which, in part, has been explained by restricted drug distribution to the peritoneum [9].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a relatively new method used in selected patients with PM who have no indication for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC). In PIPAC, the cytotoxic agents are applied laparoscopically (usually by 2 trocars) using pressurized aerosols. The treatment objective is to alleviate symptoms, in particular to control ascites and to induce regression of PM, leading to a better quality of life (QoL). Before PIPAC can be administered, potentially curative treatment options like CRS and HIPEC have to be excluded and further tumor manifestations, such as distant hematogenous metastases, are to be ruled out.

In December 2015, we initiated a prospective single-center registry study (NCT03100708) to investigate the perioperative morbidity and mortality as well as the safety aspects of PIPAC [10]. In addition, we assessed prospectively its efficacy and patients' prognosis and QoL. The current publication is dedicated to the cohort of GC patients, comprising the largest population of our study.

MATERIALS AND METHODS

Patients

Patients with a histologically proven GC-induced PM, following a standardized diagnostic laparoscopy, were eligible for this study. The indications for PIPAC were determined in our multidisciplinary tumor board, where also the option of CRS and HIPEC had to be excluded, taking into account the peritoneal carcinomatosis index (PCI) (usually higher than 8–10), comorbidities, and patients' preferences. Patients with progressive disease during systemic chemotherapy and patients with distant metastases other than PM were not eligible for PIPAC. However, individual interviews were carried out in qualified and low-risk patients who were absolutely interested in this option for symptomatic ascites control. Precondition to undergo surgery was an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better, which was re-evaluated before each repeated procedure at intervals of about 6 weeks.

The prospective registry study started in December 2015 (NCT03100708) with the 1st GC patient recruited in January 2016, and the last in February 2018, comprising a total of 24 patients undergoing a total of 46 PIPAC procedures. As this study was also open for patients with diagnosis other than GC, this number represented 35% of PIPAC study procedures carried out (131) during the period December 2015–February 2018. Written informed consents were given by all the patients after being properly educated about the experimental nature of the treatment. The treatment involved the “off-label” use of PIPAC in addition to systematic

chemotherapy. Patients, who had undergone repeated PIPAC procedures, received systemic chemotherapy cycles between the PIPAC procedures. The information and the medical enlightenment were provided by specialized surgeons and medical oncologists. The conduct of the study was in accordance with the declaration of Helsinki and the protocol was approved by the local ethics committee of the University of Leipzig (No. of the approval: 106-16-14032016).

Methods

PIPAC procedures have recently been described in detail by our group [10] and others [11,12], and were performed laparoscopically under general anesthesia. The standardized pre-therapeutic diagnostic laparoscopy was video-documented. Both diagnostic laparoscopy and PIPAC strictly followed our internal standardized operational procedures and adhered to the respective checklists. In brief, a pneumoperitoneum of 12 mmHg was induced by an open mini-incision (1 cm) with a 12 mm-trocar inserted consecutively (Kii Fios Advanced Fixation; Applied Medical, Düsseldorf, Germany) under video-optic guidance. An additional 5 mm trocar was placed into the abdominal cavity under direct visualization. If ascites was present, it was completely evacuated by suction and quantified (in mL). First, the accessibility to the abdomen was described ("access" vs. "non-access") and especially, the adhesion score was assessed and documented if patients have had previous surgeries or adhesions due to tumor manifestation, according to the modified method of Coccolini et al. [13]. PCI according to Sugarbaker was evaluated [14,15] and verified by a second surgeon. A localized peritonectomy of the best accessible areas of the 4 abdominal quadrants was carried out according to our protocol [10], and the samples were sent for pathological analysis. The micropump (Capnomed GmbH, Villingendorf, Germany) was installed into the 12 mm-trocar and fixed under direct vision. After going through the checklist with all the persons present in the odds ratio (OR), the injection pump (Medrad Arterion Mark 7, Leverkusen, Germany) was connected and all the staff left the operating room. The chemo-distribution of aerosol was initiated and controlled from a footswitch in the preparation room, separated by a closed window from the OR. This allowed the monitoring of the laparoscopy tower, the injection pump, and the anesthesia condition of the patients by all the responsible persons. First, cisplatin at a dosage of 7.5 mg/m² in 150 mL NaCl 0.9%, then doxorubicin at 1.5 mg/m² body surface in 50 mL NaCl 0.9% were insufflated. The injection pump delivered the chemotherapy at a maximum pressure of 200 psi and a flow rate of 0.5 mL/min to the micropump. Here, the fluid was transformed to aerosol and applied to the abdomen. A constant pressure of 12 mmHg with a zero flow of CO₂ ensured that the patient was relaxed and that the aerosol did not escape from the abdomen. After this phase of application, the aerosol was kept in the abdominal cavity for 30 minutes. Finally, the situs was controlled for bleeding and the pump was removed under direct vision, while the rest of the aerosol and CO₂ were transferred into the central ventilation system of the clinic (in analogy to the vent of anesthetic gases) through a closed system. The procedure was finalized by removing the trocars (without abdominal drainage) and closing the fascia and the skin. All single-use products and the micropump were disposed, and the multiple-use instruments were cleaned and sterilized [10].

With regard to the postoperative course, complications were classified according to Clavien-Dindo [16].

Histopathological regression was examined in patients undergoing at least 2 PIPAC procedures [14]. The relative tumor cell covering areas of each biopsy were analyzed (in %) by 2 experienced gastrointestinal pathologists (C.W. and K.S.). The biopsy with the maximum

tumor cell area was used to evaluate peritoneal regression. Briefly, biopsies were fixed in 4% buffered formalin, embedded in paraffin, cut to 4 μ m sections, and stained with hematoxylin and eosin (H&E) using an automated slide stainer (Sakura Tissue Tek Prisma, Tokyo, Japan).

Clinical chemistry (COBAS C-system 8000 and E-module; Roche Diagnostics, Mannheim, Germany) and hematology laboratory values (Sysmex XN 9000 system; Sysmex Europe GmbH, Norderstedt, Germany) were analyzed routinely on day 1 and day 3 postoperatively, according to the guidelines of the German Medical Association (Berlin, Germany).

All the above mentioned intraoperative and postoperative parameters were recorded for each (new and repeated) PIPAC procedure with a special emphasis on the clinical course.

The nutritional risk score (NRS) was assessed at each pre-surgical clinical visit, the QoL was evaluated using the European Organization for Research and Treatment (EORTC) quality of life questionnaire core 30 (QLQ-C30) questionnaires before each PIPAC, and the changes in the volume of ascites were measured. The QLQ survey was introduced to our PIPAC patient cohort in March 2016. Hence, 20 out of 24 patients were interviewed on the quality of their lives before each PIPAC administration. The EORTC QLQ-C30 module was split into items which included: global health status, physical, emotional, role, cognitive, and social functioning. Higher scores represented better functioning and lower scores represented financial difficulties and symptoms of the following items: gastrointestinal tract factors (nausea/vomiting, constipation, diarrhea, and appetite loss), fatigue, pain, and insomnia. The EORTC QLQ-C30 scores were linearly converted to a 0–100 scale [17]. Of 37, 7 (18.9%) questionnaires were not completed.

Data management and statistical analyses

Demographic, clinical, oncological, intraoperative, and postoperative data of patients with GC undergoing PIPAC were recorded in a special established database in accordance with our prospective registry study (NCT03100708). Data were either expressed as median (range) or mean (\pm standard error of mean). The course of the intraoperative parameters and the histologically determined tumor cell area were presented on column-tablets (PCI/tumor cell area) and as waterfall blot (ascites). The overall survival (OS) was depicted as Kaplan-Meier curves. Data analyses were performed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA). The statistical analysis methods are displayed in the corresponding figure and table legends.

RESULTS

Twenty-eight patients presented histologically confirmed PM that were attributable to GC and were eligible for PIPAC following the criteria of our multidisciplinary tumor board (**Fig. 1**). One patient had undergone his 1st–4th PIPAC and another patient his 1st in a different institution (**Table 1**). In 5 intended procedures, “non-access” abdomens were present, and in 1 patient, aspiration occurred during initiation of intubation for anesthesia and the procedure had to be stopped. Of these 6 prematurely terminated attempts, 4 occurred in the initial, and 2 in the repeated procedure (**Fig. 1**). Other reasons for different numbers in PIPACs performed are: 2 patients received CRS and HIPEC after their 1st and 3rd PIPAC procedures, respectively, had progressive disease and therefore they were not eligible for PIAPC any more or disease related death. In total, the patients received a median of 2 (range, 1–6) PIPACs. Of 14, 10 patients

Table 1. PIPAC procedures and post-operative in-hospital stay

	1st PIPAC	2nd PIPAC	3rd PIPAC	4th PIPAC	5th PIPAC	6th PIPAC
No.	22	13*	7	2	1*	1*
OP duration mean±SEM (min)	106±4.2	107±7.9	99±3.3	97±19	124	93
Post-OP in-hospital stay (day)	4 (3–7)	4 (2–9)	4 (2–5)	4 (4)	2	4

PIPAC = pressurized intraperitoneal aerosol chemotherapy; OP = operative; SEM = standard error of mean.

*Previous PIPAC procedures N° 1–4 in a different institution.

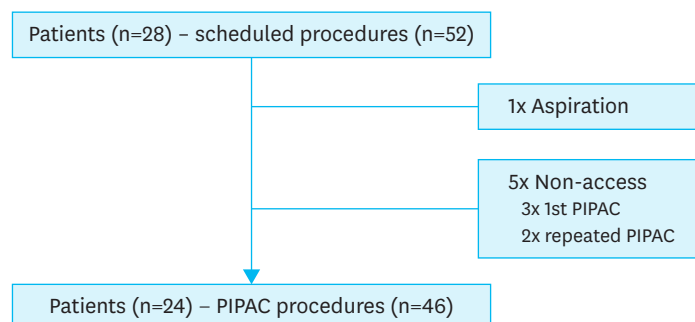


Fig. 1. Flow chart of patient inclusion and PIPAC procedures. 28 patients were eligible for PIPAC with 52 scheduled PIPAC procedures. Because of 1 aspiration and 5 “non-access” abdomens, 24 patients received 46 PIPAC procedures. PIPAC = pressurized intraperitoneal aerosol chemotherapy.

(71.4%), who received 2 or more PIPACs, received systemic chemotherapy cycle between each PIPAC procedure.

In total, 46 PIPAC procedures were performed in 24 patients (9 women and 15 men) with a median age of 57 years (range, 44–75 years). Patients had a median ECOG performance status of 1 (range, 0–2) and an NRS of 1 (range, 0–5), which did not change in the course of repeated PIPAC procedures (**Table 2**).

Table 2. Patient characteristics

Patient characteristics	Value
No. of patients	24
Gender	
Women	9 (37.5)
Men	15 (62.5)
Age (yr)	57 (44–75)
ECOG-performance status	1 (0–2)
NRS	1 (0–5)
Distant metastases except for PM	
None	19 (79.2)
Hepatic metastasis	3 (12.5)
Hepatic and adrenal gland metastasis	1 (4.2)
Pleura	1 (4.2)
Laurén's classification	
Diffuse type	19 (79)
Intestinal type	5 (21)
PM	
Synchronous	18 (75.0)
Metachronous	6 (25.0)
PCI according to Sugarbaker	14 (2–36)

Values are presented as median (interquartile range) or number (%).

ECOG = Eastern Cooperative Oncology Group; NRS = nutritional risk score; PM = peritoneal metastasis;

PCI = peritoneal carcinomatosis index.

In GC patients treated with PIPAC, synchronous PM was diagnosed in 18 (75%), while 6 (25%) had metachronous PM. The median time delay between 1st diagnosis of GC with synchronous PM and the 1st PIPAC was 5.5 months (range, 2–22 months). In GC patients with metachronous PM, the median time interval between 1st diagnosis of GC to the 1st PIPAC was 48.5 months (range, 15–84 months), and from diagnosis of PM to the 1st PIPAC was 4 months (range, 0–5 months). Patients received their last cycle of systemic chemotherapy 30 days (range, 9–210 days) before PIPAC. Patients were treated with different standard chemotherapy regimens in 1st (20), 2nd (13), and 3rd (4) line therapies before receiving the 1st PIPAC. Four patients with synchronous PM were scheduled for the 1st PIPAC before the 1st systemic chemotherapy cycle. Additionally, 12 of 24 patients had previously undergone a curative intended gastrectomy, and 1 patient underwent CRS and HIPEC before the 1st PIPAC (**Table 3**). According to Laurén's classification, 19 (79%) patients displayed a diffuse type, and 5 (21%) an intestinal type (**Table 2**).

In general, patients eligible for PIPAC were considered to have no other distant metastases apart from PM. However, in our series, 5 (20.8%) patients had other forms of systemic metastases apart from PM and were included in this study due to patients' absolute wish and/or indications of symptomatic ascites. Three of the 5 patients had regredient hepatic metastases, 1 had regredient hepatic and adrenal gland metastases, and 1 had a pleura metastasis in the course of the systemic therapy.

The duration of surgery did not increase with repeated PIPAC procedures and was 105 minutes (range, 78–150 minutes) in median. Apart from patients with “non-access-abdomen,” adhesions were observed only in a minority of the cohort with a median adhesion score of 2.5 (range, 0–23). Only 1 patient who underwent a 2nd PIPAC procedure was diagnosed with an adhesion score of 23, whereas at the 1st PIPAC, an adhesion score of 2 was detected.

Patients' median PCI according to Sugarbaker at 1st PIPAC was 14 (range, 2–36) and ascites volume was 100 mL (range, 0–6 mL, 300 mL). The patient with a PCI of 2 was offered CRS and HIPEC, but did not want to undergo this more extensive procedure. In patients who received 2 PIPAC procedures or more, the PCI and the development of ascites volume were assessed [14]. In total, 8 (57%) patients displayed a decreased or stable PCI score at repeated PIPACs (**Fig. 2A**). A median of 5 (range, 3–10) biopsies were taken and evaluated per patient and treatment. Histopathological analysis of the tumor cell portions in biopsies taken before each PIPAC showed a reduction or stabilization of the maximum tumor cell portion in 11 (79%) patients (**Fig. 2B**). Slides of representative H&E staining of biopsies are depicted in **Fig. 2C**, exemplary showing patient No. 10 and No. 13 with decreased, and patient No. 3 and

Table 3. Previous treatment before PIPAC

	Patients	Description
Systemic chemotherapy before the 1st PIPAC		
First-line	20	FLO, FLOT, EOX, ECX, FOLFOX, HER-FLOT, FLOT/ECF, capecitabin
Second-line	13	Ramucirumab/paclitaxel, FLOT, FOLFIRI, FOLFOX, capecitabine, cisplatin, trastuzumab
Third-line	4	Ramucirumab mono, ramucirumab/paclitaxel, Ramucirumab+FOLFIRI
Operative procedures before PIPAC		
Gastrectomy	12	4/5 subtotal gastrectomy and total gastrectomy with D2 lymphadenectomy, gastrectomy
CRS and HIPEC	1	-

PIPAC = pressurized intraperitoneal aerosol chemotherapy; FLO = 5-fluorouracil+folinsäure+oxaliplatin; FLOT = fluorouracil+folinsäure+oxaliplatin+docetaxel; ECF = epirubicin+cisplatin+5-fluorouracil; EOX = epirubicin+oxaliplatin+capecitabine; ECX = epirubicin+cisplatin+capecitabine; FOLFOX = leucovorin+5-fluorouracil+oxaliplatin; HER = herceptin; FOLFIRI = folinic acid+fluorouracil+irinotecan; CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemoperfusion.

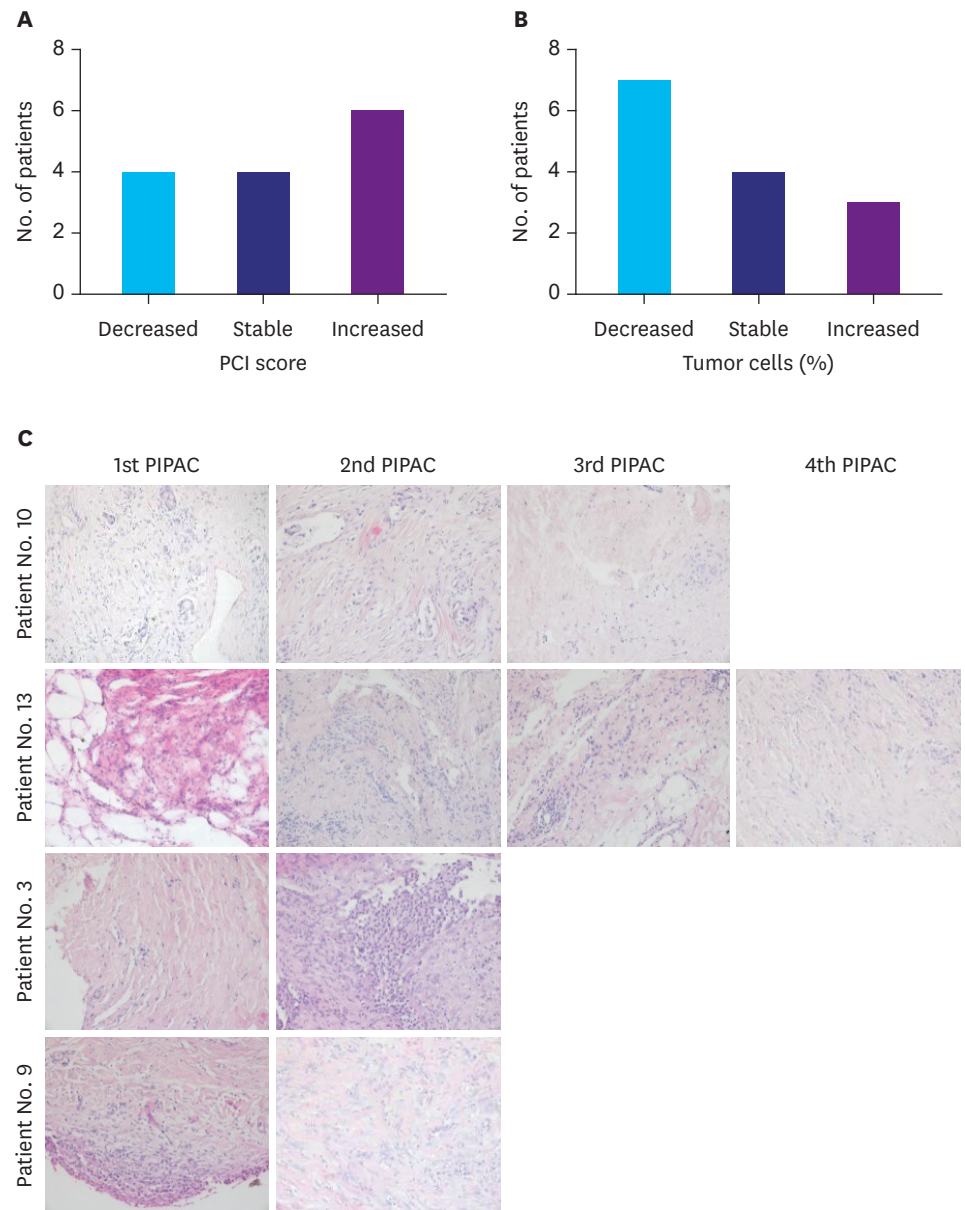


Fig. 2. PCI and tumor cell portion developments in patients with multiple PIPAC procedures. (A) Number of patients with decreased, stable, and increased PCI, (B) Number of patients with decreased, stable, and increased tumor cell portions in PM biopsies, and (C) representative H&E staining of patients with decreased tumor cell portions (patients No. 10 and No. 13) and increased tumor cell portions (patients No. 3 and No. 9). The biopsies for tumor cell evaluation were taken before each PIPAC.

PCI = peritoneal carcinomatosis index; PIPAC = pressurized intraperitoneal aerosol chemotherapy; PM = peritoneal metastasis; H&E = hematoxylin and eosin stain.

No. 9 with increased tumor cell portions. Of 14 repeatedly-treated patients, 11 displayed decreased or stable ascites volumes, while only 3 showed an increase (**Fig. 3**). In 10 (71%) patients, the PCI score development correlated with the change in the determined maximum tumor cell portion and in 10 (71%) patients, the PCI score correlated with the ascites volume development. The change in the evaluated maximum tumor cell portion correlated with ascites volume development in 10 (71%) patients. A correlation of all investigated criteria, ascites volume, PCI score, and tumor cell portion, was noted in 8 (57%) patients.

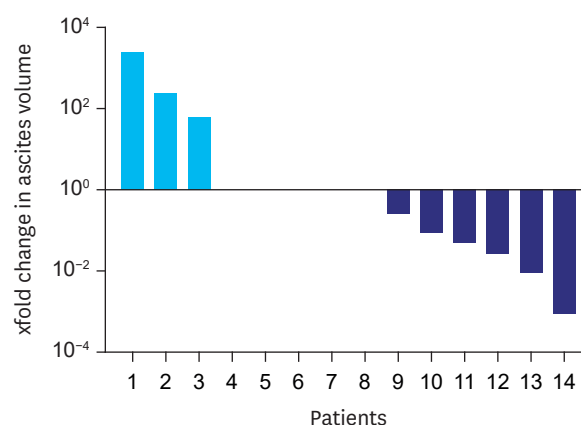


Fig. 3. Relative ascites development in patients with multiple PIPAC procedures. The fold changes of decreased (6), stable (5), and increased (3) ascites volumes during multiple PIPAC procedures are blotted as waterfall blot. PIPAC = pressurized intraperitoneal aerosol chemotherapy.

The post-operative in-hospital stay was a median of 4 days (range, 2–9 days) and did not increase with repeated treatment procedures.

We observed only 1 postoperative complication according to Clavien-Dindo (grade I: nausea and emesis). To assess postoperative chemo-toxicity, patients were monitored using 2 standardized blood controls at the 1st and the 3rd postoperative days. There was no patient with postoperative renal failure. Leucocytes and creatinine values were within the reference ranges in median. Seven and 3 patients had higher and lower values, respectively than the reference values for leucocytes ($3.5\text{--}9.8 \times 10^9/\text{L}$). A postoperative increase in C-reactive protein (CRP) was observed. No signs of liver toxicity were documented in any patients. Aspartate amino transferase/alanine amino transferase values were below the reference values at both investigated time points (**Table 4**).

The OS of the 24 investigated patients was a median of 210 days (range, 66–625 days), while the median follow-up was 159 days (range, 66–625 days) after receiving the 1st PIPAC procedure (**Fig. 4A**). Dividing the patient cohort into those who received 1 or 2 PIPACs [16] and 3 or more PIPACs [8] yielded a significant ($P=0.0376$) increase in median OS from 121 days (range, 66–625 days) to 450 days (range, 206–481 days), respectively (**Fig. 4B**). Stratification to whether patients had synchronous or metachronous PM (**Fig. 4C**) or to Laurén's classification did not result in different OS (**Fig. 4D**). QoL was assessed in 20 patients from March 2016 to February 2018 before each PIPAC procedure and a global health score of 52 ± 5.9 was reported before the 1st PIPAC procedure. Patients, who received 2 or more PIPACs, had a stable global health score and stable to slightly decreased functioning and symptom scores, e.g., the physical functioning scale decreased from 78 ± 4.8 at the 1st PIPAC to 66 ± 7.5 at the 2nd PIPAC and was 63 ± 13 at the 3rd PIPAC. No change in gastrointestinal tract item scores (nausea/vomiting, constipation, and diarrhea) was observed, except in appetite loss, which was slightly increased with repeated PIPAC procedures (**Table 5**).

Table 4. Clinical chemistry and hematology

	1-day post-OP	3-day post-OP	Reference values
Leucocytes (WBC) ($\times 10^9/\text{L}$)	7.15 ± 0.426	5.73 ± 0.396	3.5–9.8
CRP (mg/L)	36.9 ± 5.5	66.8 ± 11.05	<5
Creatinine ($\mu\text{mol/L}$)	76.8 ± 2.81	73.6 ± 2.68	45–84

WBC = white blood cells; CRP = C-reactive protein; OP = operative.

DISCUSSION

Treatment of patients with PM attributable to GC remains challenging. With the current standard of care, which is the application of systemic chemotherapy in sequential treatment lines, survival outcomes remain limited to 8–12 months (median) in European patients [18]. PM, and especially the presence of ascites, is a feature of poor prognosis for patients with stage IV GC, who receive chemotherapy [19] and even with the contemporary promising

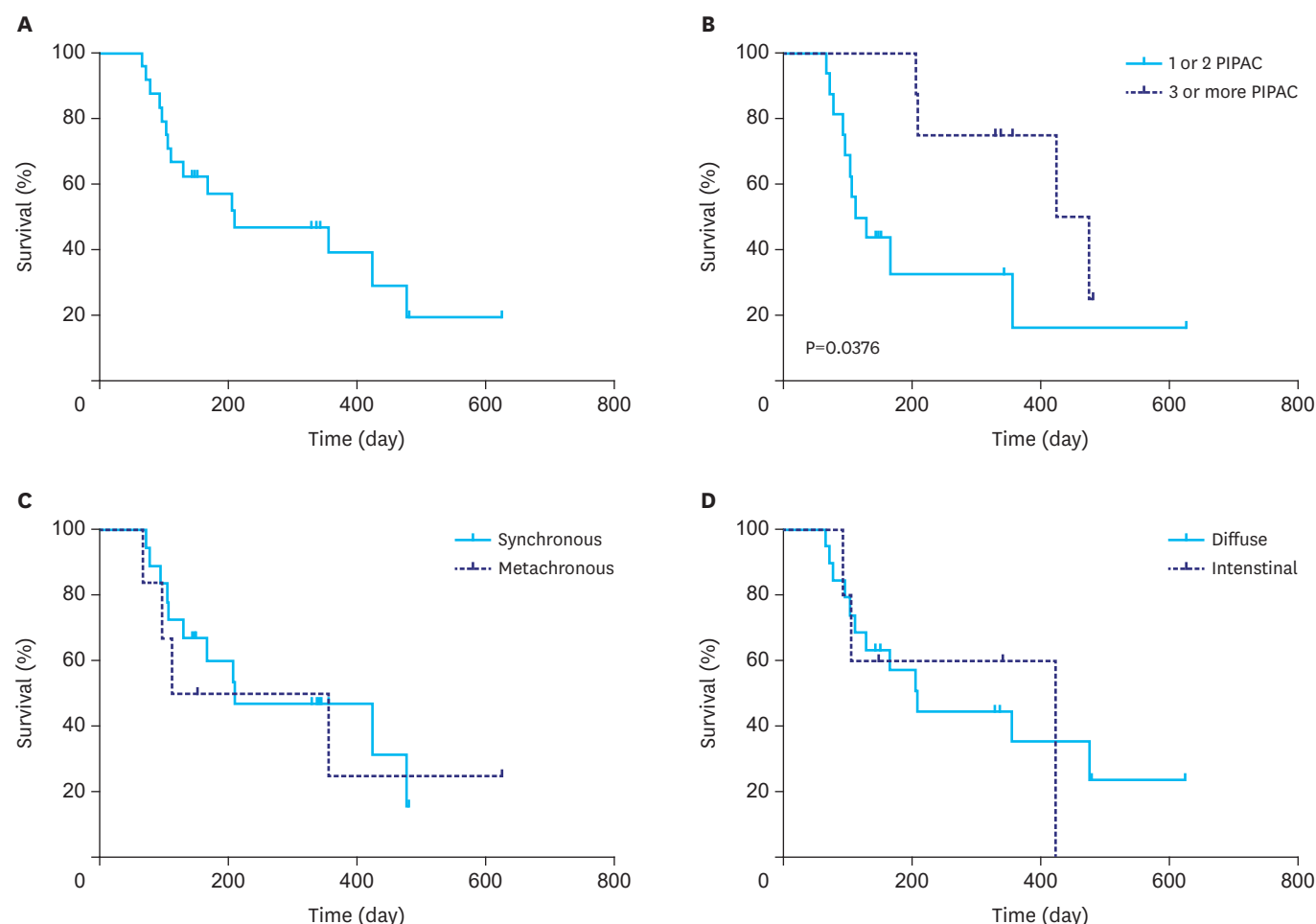


Fig. 4. Survival curves. (A) Kaplan-Meier survival curves of all 24 patients treated by PIPAC, (B) stratification of patients, who received 1 or 2 PIPACs (16) vs. 3 or more PIPACs (8; P=0.0376), (C) metachronous (6) vs. synchronous (18) PM, and (D) diffuse (19) vs. intestinal (5) type of GC according to Laurén's classification (Log-Rank [Mantel-Cox] test).

PIPAC = pressurized intraperitoneal aerosol chemotherapy; PM = peritoneal metastasis; GC = gastric cancer.

Table 5. EORTC QLQ-C30

EORTC QLQ-C30	Global health status	Functioning scores					Symptom scores				Symptoms-single items					
	QL2	PF	EF	RF	CF	SF	FA	NV	PA	DI	DY	AP	SL	CO	FI	
1st PIPAC	52±5.9	78±4.8	69±4.8	59±6.9	87±4.7	62±7.6	33±5.2	24±7.3	25±5.0	40±9.8	21±6.0	29±8.9	29±7.4	13±5.1	11±5.1	
2nd PIPAC	51±8.3	66±7.5	66±8.3	52±8.0	79±8.2	44±7.7	36±6.2	21±8.2	35±6.6	29±13	33±6.3	21±14	50±11	13±8.8	25±11	
3rd PIPAC	48±14	63±13	68±8.5	47±18	73±14	47±18	22±6.1	20±12	37±14	20±13	33±18	47±17	33±0.0	7±6.7	27±6.7	

Data are shown as mean±standard error of mean.

EORTC = European Organization for Research and Treatment; QLQ-C30 = quality of life questionnaire core 30; PIPAC = pressurized intraperitoneal aerosol chemotherapy; PF = physical functioning; EF = emotional functioning; RF = role functioning; CF = cognitive functioning; SF = social functioning; FA = fatigue score; NV = nausea/vomiting score; PA = pain score; DI = diarrhea score; DY = dyspnea score; AP = appetite loss score; SL = insomnia score; CO = constipation score; FI = financial difficulties.

developments in the treatment of GC, survival outcomes have not dramatically changed [20]. Symptom control and the maintenance of QoL remain the major treatment objectives in the management of patients with stage IV GC.

Options beyond palliative chemotherapy are limited in patients with stage IV GC and PM. Hence, PIPAC might enrich the portfolio of palliative treatment options with the overall goal of symptomatic improvement and alleviation of QoL-reducing parameters. Due to its minimal-invasive applicability, low operative risk, and short post-operative in-hospital stay with a good overall tolerability, this additional option in systemic therapy seems acceptable in critically ill patient cohort.

Our data indicate that the majority of patients developed either regredient or at least stable ascites in the course of PIPAC follow-up treatment. Ascites, especially with associated intraabdominal compression syndrome and/or the necessity of repeated paracenteses are a very decisive parameter in determining global and health-related QoL. In more than half of the repeatedly treated patients, the changes in the volume of ascites correlated with PCI and histopathological regression scores (8; 57%). However, in 6 cases (43%), this correlation was not observed. This might be explained by the potential earlier functional response of peritoneal tumor cells to pressurized aerosol chemotherapy and diminished secretion of fluids. This was possibly earlier than the visible macroscopic (PCI) or microscopic (histopathologic scores) regression with regard to repeated therapy in the investigated intervals of only 6 weeks.

Limitations of our data are:

- 1) A considerable proportion of patients was included with non-peritoneal metastases for symptomatic control of ascites or according to patients' wishes, although this was generally determined as contraindication.
- 2) Heterogeneous pre-treatment regimens and responses to systemic therapy, different biology according to Lauren's classification, and various PCI scores at 1st PIPAC, rendering evaluation of the true impact of PIPAC on changes at follow-up more difficult.
- 3) The relative small cohort and short follow-up of a non-randomized population do not allow any conclusive judgement of this new intervention option for PM in GC. In addition, volume of ascites and QoL are well known to correlate with each other, as QoL increases in the course of ascites control.
- 4) We were not able to provide associated improvement of the QoL by using validated scores, as provided by the structured interview using the EORTC QLQ-C30 questionnaire, with decreased ascites volumes. This was possibly due to the subjective and the multifactorial nature of the assessment and the lack of reliability in repeated evaluations.

To our knowledge, there are only limited data of GC patients undergoing PIPAC and documented follow-up, with similar sized patient cohorts assessed at each center [21-25]. A recently published multicenter study by Nowacki et al. [11] of 832 PIPAC procedures in 15 centers, with 280 (41.1%) cases attributable to GC, revealed that PIPAC procedures were homogeneously performed in these established centers with standardized techniques, facilitating current and future international multicenter prospective clinical trials.

In 24 patients with GC and PM and a mean PCI of 16 (± 10) with a similar chemo-aerosol regime as ours (cisplatin and doxorubicin), Nadiradze and colleagues described an objective

tumor response in 12 patients (50%), of whom 6 displayed no vital tumor cells, the same number showed major pathological response, and 3 had minor response. In this series, 17 patients underwent repeated PIPAC, of whom 3 had a “non-access” abdomen in a redo procedure. Postoperative adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade >2) were observed in a relatively high percentage (37.5%; 6 grade 3: hepatotoxicity, cholangitis; 1 grade 4: allergy, myolysis; 2 grade 5: ascites decompensation and death, progressive small bowel obstruction and death) [25]. Although the dose applied was only 10% of a usual systemic dose, most of these complications were due to a postoperative inflammatory syndrome with elevated CRP, which the authors explained as the consequence of a possible chemical peritonitis. However, acute and cumulative local toxicities of PIPAC were well controlled, and no bowel perforations or gastrointestinal side effects > CTCAE grade 2 were observed. With a follow-up of 248 days (range, 105–748 days), the median survival time was 15.4 months, although this study also included 4 patients (17%) with extraperitoneal metastases, in particular to the pleura and the liver. Simultaneous chemotherapy was administered in 33% [25].

Patients showed a relatively high QoL in a heterogeneous group of 91 patients undergoing PIPAC, including 29 with GC-induced PM except for a transient moderate increase of pain scores [22]. PIPAC did not cause therapy-related QoL deterioration and especially, there were no additional gastrointestinal symptoms associated with this palliative approach. Using the EORTC QLQ-C30 questionnaire, functioning scores and disease-related symptoms were not altered for at least 3 months in the patients able to receive repeated PIPAC [22]. Most publications available containing reasonable cohorts of GC used the 6–8 weeks interval of PIPAC, embedded in multimodal treatment [11,21,23,25,26]. PIPAC combined with associated systemic therapy showed no accelerated renal or hepatic toxicity and proved a safe and well-tolerated procedure [21,24].

Globally, 4 randomized studies are currently examining the impact of D2-gastrectomy and HIPEC [5] (Germany, HIPEC_stomach [NCT01683864]; France, GASTRICHIP [NCT01882933]; China [NCT02240524]; USA [NCT03092518]). Final results of these studies are not available yet. Patients with “high-risk cytology” and evidence of at least one of the mentioned predictors had a significantly worse survival chance than “low-risk patients” [27]. These new cytologic criteria could possibly contribute to the identification of patients who might benefit from the addition of PIPAC to the current standard of care therapy. Currently, 2 prospective-randomized studies are being conducted for HIPEC in GC. One of these, the Gastric Cancer with Peritoneal Carcinomatosis study (NCT02158988) evaluates the effect of CRS +/- HIPEC embedded in a perioperative chemotherapy regimen and a 2nd study from France investigates the role of adjuvant HIPEC following resection of GC, expecting results in 2020 and 2023, respectively. A current trial by Goetze et al. [28] is evaluating the impact of PIPAC in combination with standard chemotherapy in primarily untreated naive upper GI-adenocarcinomas with peritoneal seeding (phase II/III trial) and will hopefully clarify its oncologic efficacy (EudraCT: 2018-001035-40)

In conclusions, the oncologic and functional impact of PIPAC, in PM attributable to GC is not conclusive yet. In highly-qualified patients, critically indicated within the frame of systemic chemotherapy, PIPAC is not toxic and may lead to a symptom-oriented optimization with regard to ascites reduction, (partial) macroscopic and histopathologic regression of PM and better QoL.

PIPAC has the potential — due to its restricted invasiveness, limited surgical side-effects and risks, and its lack of systemic toxicity — to be used for symptom control in GC patients with disseminated PM, in addition to systemic therapy. However, the predictors of response and the optimum intervals of PIPAC within systemic therapy concepts are yet to be identified in on-going further studies.

Thus, we are not too optimistic that PIPAC will become standard treatment in GC patients with PM in the near future.

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