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Oxaliplatin use in pressurized intraperitoneal aerosol chemotherapy (PIPAC) is safe and effective: a multicenter study

Olivia Sgarbura[1, 2], MD, PhD, Martin Hübner[3], MD, PhD, Mohammad Alyami[4,5], MD, Clarisse Eveno, MD, PhD[6], Johan Gagnière, MD[7], Basile Pache, MD[3], Marc Pocard, MD, PhD[8], Naoual Bakrin, MD, PhD[4], François Quénet, MD[1, 2]

[1] Department of Surgical Oncology, Cancer Institute Montpellier (ICM), Montpellier, France ; [2] University of Montpellier, France ; [3] Department of Visceral Surgery, Lausanne University Hospital (CHUV), Lausanne, Switzerland ; [4] Department of General Surgery and Surgical Oncology, Lyon Sud University Hospital, Pierre Benite, France ; [5] Department of General Surgery and Surgical Oncology, King Khalid Hospital, Najran, Saudi Arabia ; [6] Department of General Surgery, University Hospital Lille, Lille, France ; [7] Centre Hospitalier Universitaire Clermont-Ferrand, France; [8] INSERM U1275, CAP Paris-Tech, Carcinomatosis Peritoneum Paris Technology, Lariboisière Hospital, AP-HP, Paris 7- Diderot University, Sorbonne Paris Cité, France

Corresponding author:

Olivia Sgarbura, Cancer Institute Montpellier, Surgical Oncology Department

208, Avenue des Apothicaires, 34298, Cedex 01, Montpellier, France

olivia.sgarbura@icm.unicancer.fr

Declaration of interest: none

List of abbreviations

ASA – American Society of Anesthesiology

AUC – area under the curve

BMI – body mass index

CRS – cytoreductive surgery

CTCAE – common terminology criteria for adverse events

HIPEC – heated intraperitoneal chemotherapy

IQR – interquartile range

IP - intraperitoneal

MPM – malignant peritoneal mesothelioma

OS – overall survival

PCI – peritoneal cancer index

PIPAC – pressurized intraperitoneal aerosol chemotherapy

PC – peritoneal cancer

PM – peritoneal metastases

PMP – pseudomyxoma peritonei

Abstract

Introduction:

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new drug delivery method used in patients with peritoneal cancer (PC) of primary or secondary origin. Intraperitoneal use of oxaliplatin raises concerns about toxicity, especially abdominal pain. The objective of this study was to assess the tolerance of PIPAC with oxaliplatin (PIPAC-Ox) in a large cohort of patients and to identify the risk factors for high grade toxicity, discontinuation of treatment and impaired survival.

Material and methods:

This retrospective cohort study included all consecutive patients treated with PIPAC-Ox (92mg/m²) in five centers specialized in the treatment of PC. The procedure was repeated every 6 weeks. Outcomes of interest were Common Terminology Criteria for Adverse Events (CTCAE), symptoms and survival (Kaplan-Meier). Univariate risk factors were included in a multinominal regression model to control for bias.

Results

Overall, 251 PIPAC-Ox treatments were performed in 101 patients (45 female) having unresectable PC of various origins: 66 colorectal, 15 gastric, 5 ovarian, 3 mesothelioma, 2 pseudomyxoma, 10 other malignancies (biliary, pancreatic, endocrine) respectively. The median PCI was 19 (IQR: 10-28). Postoperative abdominal pain was present in 23 patients. Out of the 9 patients with grade 3 abdominal pain, only 3 needed a change of PIPAC drug. CTCAE 4.0 toxicity grade 4 or higher was encountered in 16(15.9%) patients. The patients had a mean of 2.5 procedures/patient (SD=1.5). 50 subjects presented with symptom improvement.

Conclusions:

Oxaliplatin-based PIPAC appears to be a safe treatment that offers good symptom control and promising survival for patients with advanced peritoneal disease.

Keywords: PIPAC, oxaliplatin, peritoneal cancer, intraperitoneal chemotherapy, tolerance
Words count: abstract - 250; article – 2220

1. Introduction

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new mode of minimal-invasive intraperitoneal (IP) drug delivery for patients with peritoneal cancer (PC)(1). The current recommendations foresee at least 3 PIPAC treatments (4-6 weeks interval) as single modality or in combination with systemic chemotherapy(2).

Two regimens of IP agents are usually delivered through PIPAC: cisplatin in combination with doxorubicin (C/D) or oxaliplatin as monotherapy. A potential third agent is mitomycine C but reports are scarce for this drug(2). For any of these agents, initial doses were empirically defined in the lower range in order to avoid systemic toxicities(3). Recently, a dose-finding study allowed to safely increase C/D doses by 40% (C: 10.5mg/m2, D: 2.1mg/m2)(4). Currently, two phase I clinical trials are ongoing aiming to define the optimal dose for oxaliplatin (currently: 92mg/m2 or or 20% of the Elias regimen(5))(6;7).

PIPAC was evaluated independently by different groups confirming consistently feasibility, safety, and good tolerance of the procedure(8-10). However, PIPAC-Ox was reluctantly used for fear of toxicity (especially abdominal pain) which was encountered after IP administration of oxaliplatin by means of an intraperitoneal catheter(11) or in form of heated intraperitoneal chemotherapy (HIPEC)(12). So far, the largest experience on PIPAC-Ox included 17 patients with PM of colorectal origin having 48 PIPAC-Ox administrations (mean 2.8). CTCAE grade 3 toxicity was observed in 23% of patients but no CTCAE grade 4 was reported(13). In the French cohort analyzed at the end of the 1st year of use of PIPAC, CTCAE 4.0 grade 3 toxicities were only found in 9,7% of patients having received either cisplatin-doxorubicin, oxaliplatin or mitomycine C. While these initial studies were encouraging, they still convey limited information concerning the use of PIPAC-Ox regarding safety, tolerance and efficacy.

The aim of the present multicenter study was to assess the tolerance profile of PIPAC-Ox in a large cohort of patients and to identify risk factors for high grade toxicity, discontinuation of treatment and poor survival.

2. Material and methods

2.1 Study design

This is a multicenter retrospective cohort including all consecutive patients treated with PIPAC-Ox in five investigating centers (Montpellier Cancer Institute, Lausanne University Hospital, Lyon Sud University Hospital, Clermont Ferrand University Hospital, Lariboisière University Hospital) from January 2015 to December 2017. The study was approved by the Ethics Committee of the collecting center in accordance with the ethical standards of the Helsinki Declaration of 1975. Data was retrieved from prospectively maintained institutional data bases with permission of the respective institutional review boards and analyzed anonymously. Follow-up for survival data was performed until March 2018.

2.2 PIPAC procedure

All centers followed the structured PIPAC training program before start of the clinical program and four of them became PIPAC training centers. The procedures were performed under general anesthesia and the standard protocol was described in detail elsewhere(14). Briefly, a first trocar was placed using open technique. Two trocars were used in total: one for the endoscope and one for the aerosolizer (Capnopen©; Capnomed GmbH, Villigendorf, Germany). The latter was connected to a high-pressure injector that applied up to 20 bar and a flow of 0.5 ml/sec. A pressurized aerosol containing oxaliplatin at a dose of 92 mg/m2 body surface in a 150-ml 5% dextrose solution was applied via the injector and the aerosolizer. After the injection, therapeutical capnoperitoneum was maintained for 30 minutes at 37°C. The remaining toxic aerosol was exsufflated in a closed aerosol wasting system(15). The procedure was repeated at 6 week intervals. Patients were managed postoperatively in the surgical unit. A visual analogue scale (VAS) was used for assessment of the pain. In the immediate postoperative setting the assessment was performed four times daily. The postoperative assessment was performed at the 3 week evaluation by the surgeon in charge. All the measures were translated in the CTCAE grading system by the patient's surgeon.

2.3 Outcome measures

Demographic, clinical, disease-related and treatment-related variables were collected for all patients. Symptomatic response to treatment, evolution of the peritoneal carcinomatosis index (PCI), reasons for discontinuation of the treatment were taken into account for each PIPAC. Adverse events were graded according to CTCAE version 4.0. Survival was calculated in

months reported to the date of diagnosis of the primary disease, of the peritoneal carcinomatosis and of the first PIPAC treatment. Minimal follow-up was 3 months.

2.4 Statistical analysis

Continuous and categorical variables were collected and analyzed. Continuous data was reported as a median with an interquartile range except for the number of PIPAC procedures where the mean and the standard deviation were used for comparative purposes with previous reports. Frequencies were reported as raw numbers and percentages of the entire population of patients. Non parametric tests were used for comparison of independent variables (Mann-Whitney test, Chi-square). Regression analyses was used to test potential relationship between variables and one way ANOVA as well as multivariate analysis were performed for identifying potential prognostic factors. Regression analysis investigated the role of gender, elder age, BMI<20, primary tumor in the onset of severe abdominal pain (>grade 2) or on CTCAE complication grade 3 or higher. Univariate analysis aimed to determine if any of the following factors were potentially prognostic for the early discontinuation of the treatment (defined as the administration of <3 PIPAC) or for the impaired survival: gender, BMI<20, primary tumor, presence of abdominal pain CTCAE grade 1 to 3, presence of any grade 3 toxicities. Survival analysis was performed by use of the Kaplan Meier model. A p-value <0.05 was considered significant. All data were analyzed with the SPSS software (SPSS 17.0; SPSS Inc., Chicago, Illinois, USA) for Windows.

3. Results

Between January 2015 and December 2017, 101 patients were treated with 251 PIPAC-Ox in total. Demographics and clinical details are displayed in **Table 1**. All patients had histologically proven peritoneal metastases with a median PCI of 19 (IQR:10-28) at the start of treatment.

Patients had a mean number of 2.5 PIPAC (+/-1.5) (**Figure 1**). 64.3% and 47.5% of patients had at least 2 or 3 PIPAC procedures, respectively. Further procedural details are clarified in **Table 2**.

In 48 patients, PIPAC was associated with a type of toxicity CTCAE 4.0 grade 1 to 5 with a total of 55 adverse events. However grade 1 toxicities represented almost a half of them. Grade 4 and 5 were extremely rare (<1% each). Grade 3 toxicities were encountered in 14 cases (13.9%) (**Table 3**). Abdominal pain was present in 22.8% of all patients. 8.9% of patients had grade 3 pain, and 3% required a change of the PIPAC drug. This data was not available for 1 patient. Surgical complications grade 3 and 4 were accounted for in 4 patients (two hematomas, two surgical site infections) whereas one respiratory grade 5 toxicity was recorded in a patient with a preexistent respiratory condition

Follow-up after the first PIPAC had a median of 5 months (IQR: 5-11). 50 patients (49.5%) noted improvement of symptoms under PIPAC treatment. Median overall survival (OS) was calculated from the initial diagnosis of the primary tumor (102 months+/- 46.8), from the diagnosis of the peritoneal metastatic disease (not reached) and from the first PIPAC (not reached), respectively. The Kaplan Meier curves are presented in **Figure 2.**

There was no relationship in the binary logistic regression analysis between any of the specified factors and CTCAE complications grade 3 or higher. There was no relationship in the binary logistic regression analysis between any of the specified factors and the presence of severe abdominal pain (grade 2 or higher) except for age over 65 where p-value was as the threshold of significance (p=0.055). In linear regression, age over 65 was significantly related to abdominal pain.

Univariate analysis (ANOVA) did not identify any prognostic factors for early discontinuation of the planned treatment (3 cycles of PIPAC). Severe abdominal pain (grade 2

or higher) was one of the investigated factors and it was not retained. Univariate analysis (ANOVA) identified only a BMI lower than 20 as prognostic factor for impaired overall survival ($p=0.038$). The association of male sex and age over 65 as well as the association of BMI<20 and age>65 proved statistically significant ($p<0.05$). There were no statistically significant factors in the multivariate analysis. Cox regression analysis failed to identify significant differences in survival based on the aforementioned variables (gender, BMI<20, primary tumor, presence of abdominal pain CTCAE grade 1 to 3, presence of any grade 3 toxicities).

4. Discussions

In this multi-center study, PIPAC with oxaliplatin 92mg/m² appeared to be a safe and repeatable locoregional treatment for PC of various origins. High-grade adverse events occurred in only 15.9% of all patients, symptom response was accounted in half of the patients and encouraging survival curves call for further prospective evaluation.

Although oxaliplatin is one of the three validated drugs administered in PIPAC(9;10;16), it is still used with reluctance because of previous data showing CTCAE 4.0 grade 3 toxicities in 23% of patients(13). Furthermore, recent results from trials based on other intraperitoneal uses of oxaliplatin raised concerns with regards to the efficacy of this drug in the intraperitoneal setting(17). Unlike in hyperthermic intraperitoneal chemotherapy (HIPEC), oxaliplatin is administered repeatedly in PIPAC and under pressure conditions which enhance tissue entry(18) of a molecule with already satisfying pharmacokinetic properties (molecular weight 397.3 Da, area under the curve (AUC) peritoneum- plasma ratio 16) (19) used at five-times lower doses.

Toxicity studies on oxaliplatin-based PIPAC included reports of severe hypersensitivity(20) and peritoneal sclerosis(21). Severe hypersensitivity rates were 2.8% for oxaliplatin versus 0.6% for cisplatin-doxorubicin in a monocentric cohort of more than 300 PIPAC. In the colorectal PM cohort, CTCAE grade 3 events were observed in 4/17 patients (23%), and no CTCAE 4 side effects were documented. Postoperative pain of all grades was reported in 11 cases (64.7%)(13). In comparison, toxicity rates of systemic administration of oxaliplatin are considerably higher with a 50% rate of neuropathy under treatment which persists in 0.7% of patients beyond 18 months after treatment(22). In addition, systemic oxaliplatin administration entails a 40% risk of transient thrombocytemia of any grade and of 12-19% hypersensitivity reactions(22). None of these effects has been observed after PIPAC-Ox with the current dose regimen.

PIPAC procedures combining cisplatin-doxorubicin were also associated with CTCAE 4.0 grade 3 or higher toxicities ranging from 16-36% in phase I, phase II and cohort studies(2;4;23;24). In the feasibility phase II study, there were 16% CTCAE 4.0 grade 3 toxicities but only 4% abdominal pain grade 3(23). In the phase I study testing increasing doses of the cisplatin-doxorubicin association, only one grade 3 event (colon perforation,

surgery-related) was described and it belonged to the first dose level(4). In a cohort of patients with gastric cancer treated with PIPAC C/D, grade 3-5 toxicities were encountered in 36% of the patients (25% grade 3). The present PIPAC-Ox results are similar to that of the cisplatin-doxorubicin phase II study and superior to previous PIPAC C/D and PIPAC-Ox reports.

In the present study, 22.8% of all patients presented with abdominal pain but only 9% of them had grade 3 abdominal pain while only 3% needed a change in the PIPAC drug due to this toxicity. These figures are higher than those published for cisplatin-doxorubicin but there is no proof of significant impact on the treatment in regression analysis. Practices of pain management after the PIPAC procedure vary among the investigating centers with some centers routinely offering opioids after PIPAC-Ox which can interfere with the results. The change of the PIPAC drug was performed when grade 3 abdominal pain was persistent after 1 week use of high level analgesia (opioids or derivates). Unfortunately the quality of life data was not available for all the patients in the study. Also inflammatory response was not tested as postoperative inflammatory response was similar in a previous cohort study comparing PIPAC C/D versus PIPAC-Ox(25).

Following regression, univariate and multivariate analysis, very few prognostic factors can be identified, probably due to the heterogeneity of the patients in this cohort. The selection criteria for patients undergoing PIPAC evolved since the initial experience of some of the centers that participated in this study therefore surgical complications and the postoperative onset of bowel obstruction have diminished(2). On the other hand, the symptom improvement rate following PIPAC remains similar at 49.5%.

The survival curves following oxaliplatin-based PIPAC are very encouraging with median survival not reached for the global group or for the colorectal subgroup. Overall survival was 62% at 30 months for the entire group as well as for the colorectal patients which compares favorably with OS rates for PM patients under systemic chemotherapy(26). The other groups based on the histology of the primary tumor were scarcely represented therefore results should not be extrapolated. However these encouraging survival data, although not definitive in the absence of randomized controlled trials, demonstrate once more that advances were made in patient selection and systemic treatment association when compared to earlier studies(2;13).

Main limitations of the present study are its retrospective study design, limited patient sample, heterogeneous indications, and absence of control group. However, treatment was highly standardized as shown in a recent study(16) . Then, deliberate patient selection appears to be unlikely given the high PCI at first PIPAC, even for primary etiologies where peritoneal surgery is not a standard. Furthermore, PIPAC was utilized in larger terms in clinical practice only since 2015 and the present study provides the largest overview on PIPAC-Ox so far.

In summary, PIPAC with oxaliplatin 92mg/m^2 appears to be a feasible and safe treatment alternative for patients with advanced PC. It offers symptom improvement in half of the patients, and short-term survival data is favorable. Dose-escalation studies are underway, and ongoing and planned phase II and III comparative trials should help to define potential indications for PIPAC-Ox.

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Variable	Subtype	Value (%)
Gender	Male	56 (55.4%)
	Female	45 (44.6%)
Age	Median (IQR)	59 (50-70/5)
ASA	I	13 (12.9%)
	II	58 (57.4%)
	III	21 (20.8%)
	Missing	9 (8.9%)
BMI	Median (IQR)	23 (20.5-25.7)
	<20	22 (21.8%)
Histology	Colorectal cancer	66 (65.4%)
	Gastric cancer	15 (14.8%)
	Ovarian cancer	5 (4.9%)
	Peritoneal mesothelioma (MPM)	3 (3%)
	Peritoneal pseudomyxoma (PMP)	2 (2%)
	Other *	10 (9,9%)
Initial PCI	Median (IQR)	19 (10-28)
Synchronicity	Synchronous	46 (45,5%)
	Metachronous	53 (52,5%)
	Missing	2 (2%)
Previous chemotherapy	Yes	93 (92,1%)
	No	8 (7,9%)
Symptoms related to PM	Ascites	46 (45,5%)
	Pain	39 (38,6%)
	Impaired bowel function	23 (22,8%)

Table 1. Demographic and clinical characteristics of the patients

Legend: *other histologies represent rare indications of PIPAC such as small bowel cancer, pancreatic cancer, cholangiocarcinoma, mixed neuroendocrine and carcinoma)

Variable	Subtype	Value	
Associated chemotherapy	Yes	47 (46,5%)	
	No	6 (5,9%)	
	Missing	48 (47,6%)	
Median PCI for histological subtypes	Colorectal cancer	19 (10,5-27,5)	p=NS
	Gastric cancer	19 (10-28)	
	Ovarian cancer	18 (10-26)	
	MPM	19 (11,5-26,5)	
	PMP	16,5 (10 – 23)	
	Other	17,5(9,5-26)	
Median PCI per PIPAC cycle (IQR)	PIPAC1	19 (10-28)	
	PIPAC2	19 (14-26)	
	PIPAC 3	20 (15-27)	
	PIPAC 4	14 (8-22)	
	PIPAC 5	20 (14-30)	
	PIPAC 6	12 (10-19)	
	PIPAC 7	17,5 (-)	
	PIPAC8	17 (-)	
Mean number of PIPAC	Colorectal cancer	2,36+/-1,59	p=NS
	Gastric cancer	2,60+/-0,83	
	Ovarian cancer	2,20+/-1,1	
	MPM	2,33+/-1,53	
	PMP	3 +/-2,83	
	Other	3,2+/-2,04	
Median length of stay (IQR)		3 (2-3) days	
Secondary non-access		8 (7,9%)	
Symptom response		50 (49,5%)	
CTCAE grade 3 or higher		16 (15,9%)	
Patients presenting with any grade toxicity*		37 (36,6%)	
Post-PIPAC cytoreductive surgery		6 (5,9%)	

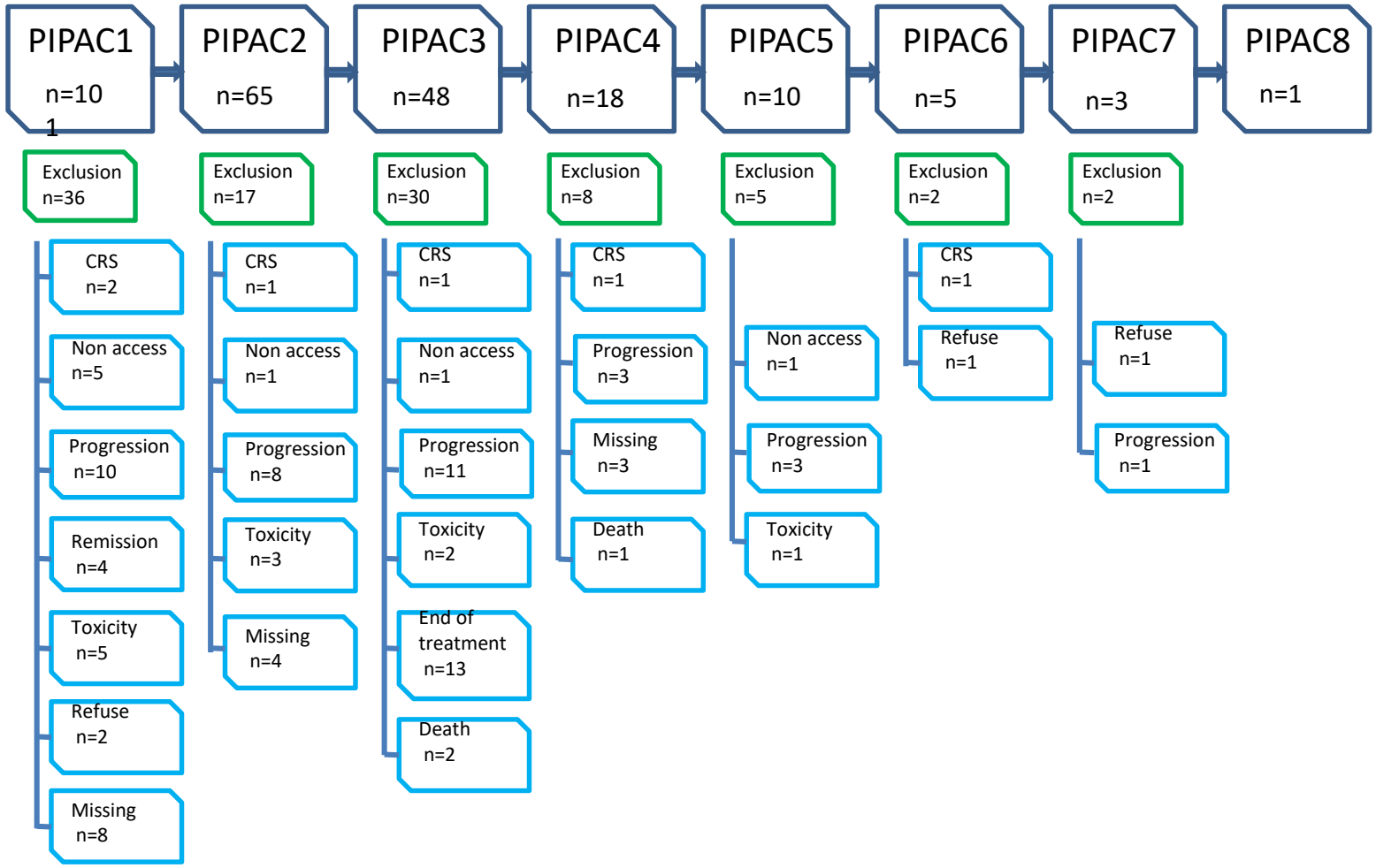
Table 2. Treatment-related characteristics of the patients in the present study (*the value is inferior to the total number of adverse events in Table 3 as several events can be described in the same patient)

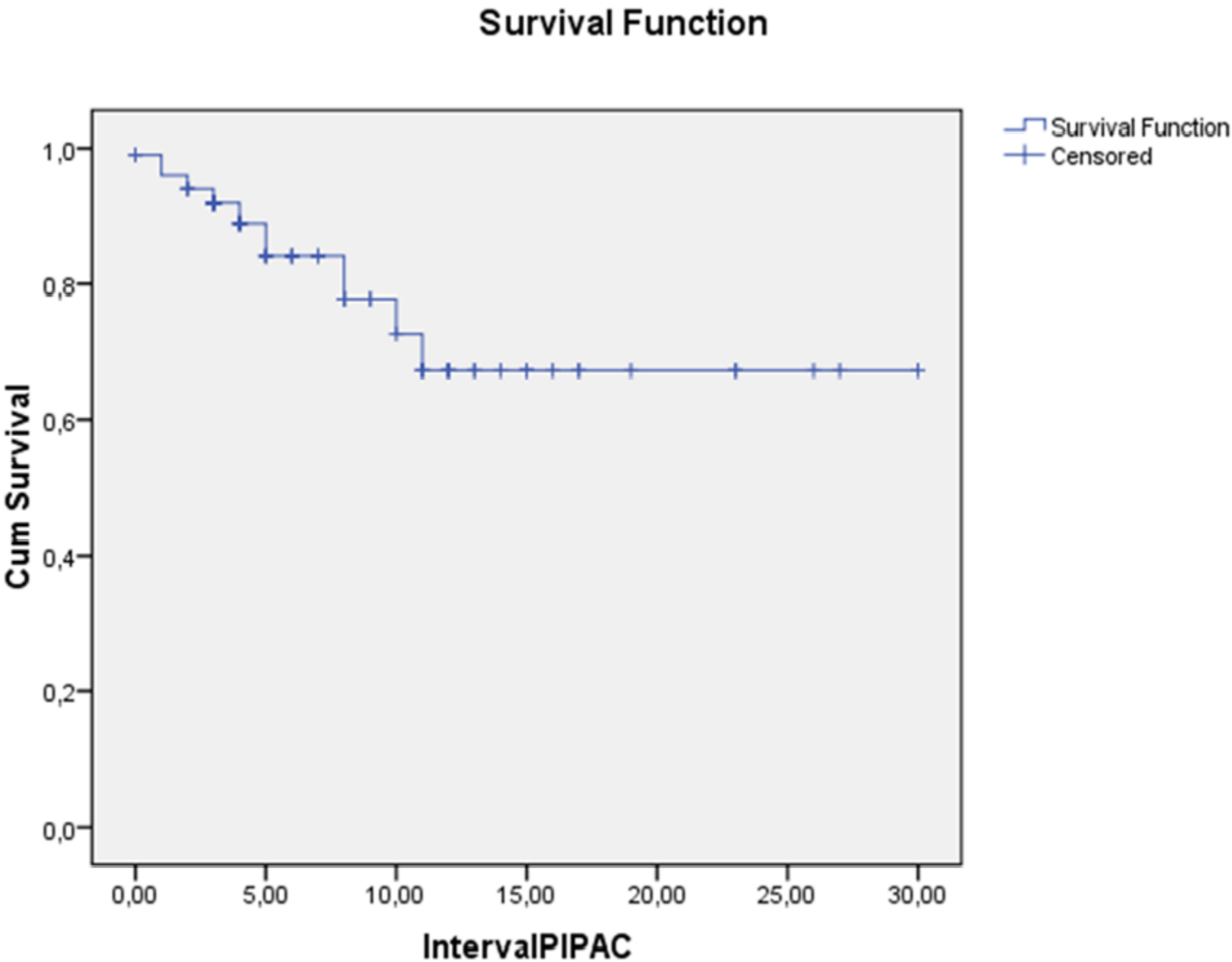
Toxicity	Grade I	Grade II	Grade III	Grade IV	Grade V	Total
Abdominal pain	11	3	9	-	-	23
Hematologic	0	2	0	0	0	2
Cardiac	0	0	0	0	0	0
Gastrointestinal	4	5	1	0	0	10
Respiratory	0	0	0	0	1	1
Renal	1	1	0	0	0	2
Hepatic	4	0	1	0	0	5
Allergic	2	0	1	1	0	4
Surgical (parietal abcess/ hematoma)	0	6	2	0	0	8
Total	22	17	14	1	1	55

Table 3. Frequency and grade of main toxicities encountered after PIPAC

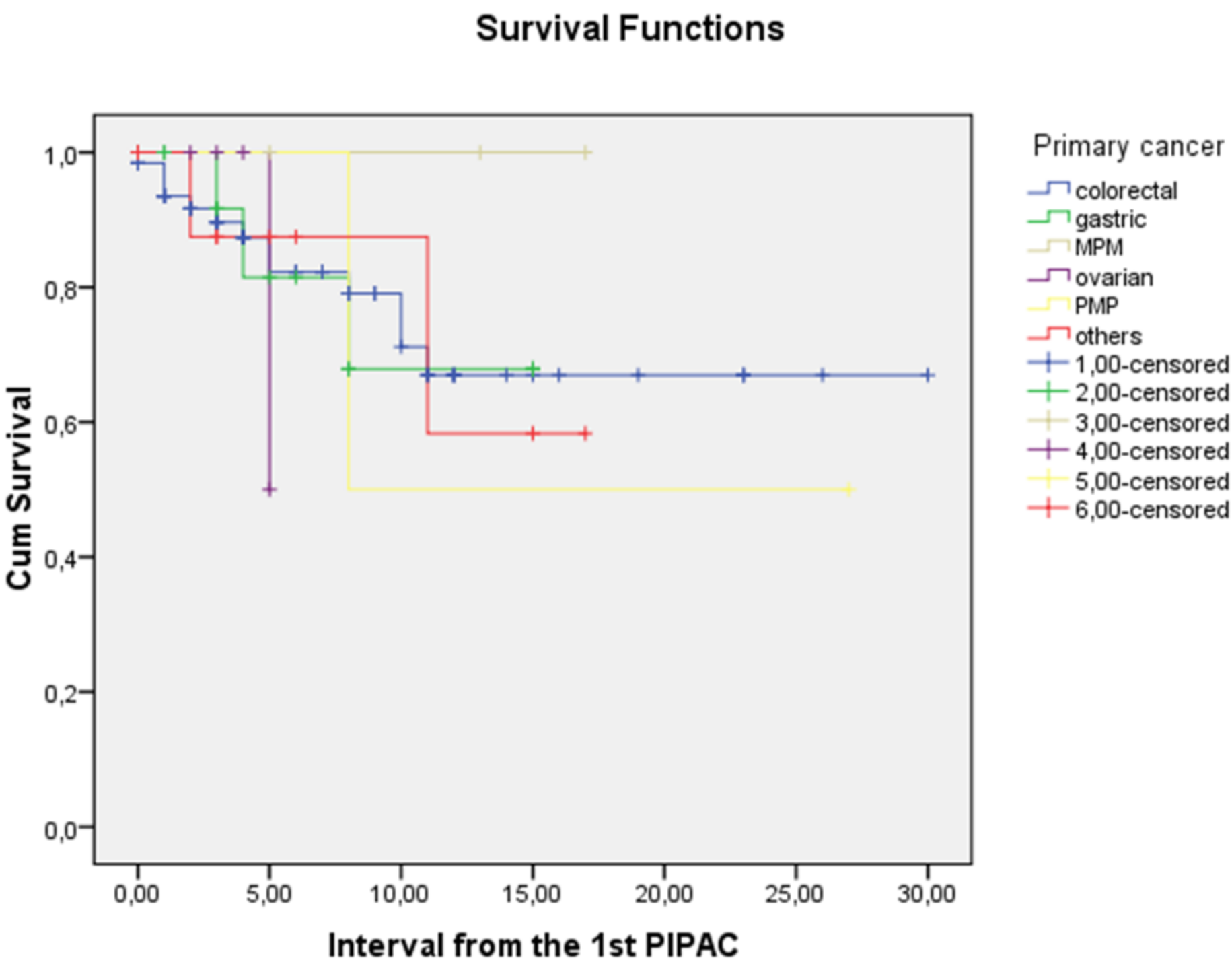
Figure1. The flow diagram of the treatment with oxaliplatin-based PIPAC. Toxicities as a reason to stop PIPAC include systemic toxicities (pain, liver failure) and local toxicities (hematoma, perforation).

Figure 2 Kaplan Meier survival curves reported to the first PIPAC administration a) for the entire group; b) for the different histological types of PC


PIPAC1
n=101
PIPAC2
n=65
PIPAC3
n=48
PIPAC4
n=18
PIPAC5
n=10
PIPAC6
n=5
PIPAC7
n=3
PIPAC8
n=1
Exclusion n=36
CRS n=2
Non access n=5
Progression n=10
Remission n=4
Toxicity n=5
Refuse n=2
Missing n=8
Exclusion n=17
CRS n=1
Non access n=1
Progression n=8
Toxicity n=3
Missing n=4
Exclusion n=30
CRS n=1
Non access n=1
Progression n=11
Toxicity n=2
End of treatment n=13
Death n=2
Exclusion n=8
CRS n=1
Progression n=3
Missing n=3
Death n=1
Exclusion n=5
Non access n=1
Progression n=3
Toxicity n=1
Exclusion n=2
CRS n=1
Refuse n=1
Exclusion n=2
Refuse n=1
Progression n=1



	3 months	6 months	12 months	18 months	24months	30 months
No at risk	101	63	43	18	7	3



No at risk	3 months	6 months	12 months	18 months	24months	30 months
Colorectal	66	32	13	5	1	1
Gastric	15	9	3	0	0	0
Ovarian	5	3	0	0	0	0
MPM	3	3	3	3	0	0
PMP	2	1	1	1	1	0
Others	10	3	2	0	0	0