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Feasibility and safety of PIPAC combined with additional surgical procedures: PLUS study

Manuela Robella [a, *], Martin Hubner [b], Olivia Sgarbura [c, d], Marc Reymond [e], Vladimir Khomiakov [f], Andrea di Giorgio [g], Aditi Bhatt [h], Naoual Bakrin [i], Wouter Willaert [j], Mohammad Alyami [i, k], Hugo Teixeira [b], Andrey Kaprin [f], Federica Ferracci [g], Guillaume De Meeus [c], Paola Berchialla [l], Marco Vaira [a], ISSPP PIPAC study group

[a] Candiolo Cancer Institute, FPO – IRCCS, Candiolo, Turin, Italy
[b] Department of Visceral Surgery, Lausanne University Hospital CHUV, University of Lausanne (UNIL), Switzerland
[c] Department of Surgical Oncology, Cancer Institute Montpellier (ICM), University of Montpellier, Montpellier, France
[d] IRCM, Institut de Recherche en Cancérologie de Montpellier, INSERM U1194, Université de Montpellier, Institut régional du Cancer de Montpellier, Montpellier, F-34298, France
[e] Department of General & Transplant Surgery, University Hospital Tübingen, D-72076, Tübingen, Germany
[f] Department of Thoracoabdominal Cancer Surgery, P.A. Hertzen Moscow Research Oncological Institute – Branch of the National Medical Research Center of Radiology, Moscow, Russia
[g] Surgical Unit of Peritoneum and Retroperitoneum, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[h] Department of Surgical Oncology, Zydus Hospital, Ahmedabad, India
[i] Department of General Surgery and Surgical Oncology, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France
[j] Department of GI Surgery, Ghent University Hospital, Ghent, Belgium
[k] Department of General Surgery and Surgical Oncology, Oncology Center, King Khalid Hospital, Najran, Saudi Arabia
[l] Department of Clinical and Biological Sciences, University of Turin, Turin, 10124, Italy

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ABSTRACT

Background: PIPAC (Pressurized IntraPeritoneal Aerosol Chemotherapy) is a minimally invasive approach relying on physical principles for improving intraperitoneal drug delivery, including optimizing the homogeneity of drug distribution through an aerosol. Feasibility and safety of the new approach are now consolidated and data on its effectiveness are continuously increasing. Although any surgical procedure associated with PIPAC had always been discouraged due to the high risk of complications, surgical practice is constantly changing: with growing expertise, more and more surgical teams associate PIPAC with surgery.

Methods: PLUS study is part of the retrospective international cohort studies including 10 centers around the world (India, Italy, France, Germany, Belgium, Russia, Saudi Arabia, Switzerland) and 96 cases of combined approaches evaluated through a propensity score analysis.

Results: the procedures most frequently associated with PIPAC were not only adhesiolysis, omentectomy, adnexectomy, umbilical/inguinal hernia repairs, but also more demanding procedures such as intestinal resections, gastrectomy, splenectomy, bowel repair/stoma creation. Although the evidence is currently limited, PLUS study demonstrated that PIPAC associated with additional surgical procedures is linked to an increase of surgical time ($p < 0.001$), length of stay ($p < 0.001$) and medical complication rate ($p < 0.001$); the most frequently reported medical complications were mild or moderate in severity, such as abdominal pain, nausea, ileus and hyperthermia. No difference in terms of surgical complications was registered; neither reoperation or postoperative deaths were reported.

Conclusions: these results suggest that PIPAC can be safely combined in expert centers with additional surgeries. Widespread change of practice should be discouraged before the results of ongoing prospective studies are available.

* Corresponding author.
E-mail address: manuela.robella@gmail.com (M. Robella).

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Abbreviations

PIPAC	Pressurized IntraPeritoneal Aerosol Chemotherapy
PCI	Peritoneal Cancer Index
IPTW	Inverse Probability of Treatment Weighting
NCI	National Cancer Institute
CTCAE	Common Terminology Criteria for Adverse Events
CD	Cisplatin + Doxorubicin
OX	oxaliplatin
PLD	pegylated liposomal doxorubicin
MMC	mitomycin C
IQR	interquartile range
OR	odds ratio
CI	Confidence Interval
PM	Peritoneal Metastases
HIPEC	Hyperthermic IntraPEritoneal Chemotherapy
SMD	Standardized Mean Difference

1. Introduction

In the last decade, Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) has emerged as new palliative treatment option for patients with peritoneal metastases. It is based on the use of aerosolized chemotherapy at an elevated intra-abdominal pressure to take advantage of the following physical properties: the aerosol allows a homogeneous repartition of the substance within the abdominal cavity; the artificial pressure gradient counterbalances tumoral interstitial fluid pressure that represents an obstacle in cancer therapy [1].

Feasibility and safety of the new approach are now consolidated; the data on its effectiveness are continuously increasing: improvement in quality of life, diminishment of pain, ascites, abdominal distension and gastrointestinal symptoms. Despite its originally palliative intent, some patients had very good results in terms of histopathological/radiological response which allow the option for secondary curative surgery [2–5].

Currently any surgical procedure (including adhesiolysis or bowel sutures) is considered contra-indicated in combination with PIPAC due to the high rate of complications in the initial experience of PIPAC treatment [6,7].

Surgical practice is constantly changing and more and more surgical teams with the growth of expertise started to associate surgical procedures with PIPAC (although data have not yet been published); in this setting, two trials are investigating the combination of radical surgery for locally advanced gastric cancer in terms of postoperative adverse events and complications in one study (PIPAC-OPC 2 - ClinicalTrials.gov Identifier: NCT03287375) and overall and disease free survival in the other (GASPACCO - ClinicalTrials.gov Identifier: NCT04595929).

The aim of this multicenter retrospective cohort study (PLUS study) was to analyze feasibility and safety of PIPAC in combination with additional surgical procedures.

2. Material and methods

2.1. Participating centers and patient population

This retrospective analysis is part of the multi-center PIPAC cohort studiy aimed at evaluating oncological efficacy of PIPAC treatment by disease entity. Study centers were certified to perform PIPAC and had a minimal experience of 60 procedures. All 19 study centers were invited to contribute patients to this analysis: 10 centers with known experience in performing PIPAC associated with surgical procedures submitted the data (details are reported in section 3.1).The analysis included patients with histologically/cytologically confirmed advanced solid tumors with documented peritoneal metastases treated with PIPAC associated with any surgical procedure; as control group data about one PIPAC procedure not associated with surgery performed in the same patients were collected. In case of patients submitted to only one PIPAC and surgical procedure, a "matched" patient according to pathology and PCI (Peritoneal Cancer Index) has been included in the analysis.

2.2. Research methodology

Retrospective cases of surgery associated with PIPAC performed in all the centers authorized to carry out the procedure were collected with minimal case load according to the inclusion criteria of PIPAC cohort study. Collected information included demographic data, cancer-specific data, descriptive variables relating to the intervention (duration, surgical procedures performed, intraperitoneal drugs used, drugs doses etc.) and the postoperative period (length of stay, postoperative complications, reoperation rate, etc.).

This retrospective study received institutional review board approval by all participating centers. Considering the observational nature of the study and the use of pseudo-anonymized data, no informed consent from the patients was required.

2.3. Study end-points and statistical analysis

Primary objective of the study was postoperative morbidity rate within 30 days; secondary objectives were 30-days postoperative mortality, length of stay and reoperation rate.

To adjust for potential patient selection bias, attributable to non-randomized assignment, a propensity score analysis based on the inverse probability of treatment weighting (IPTW) was carried out to account for time-varying confounders. A standardized mean difference (SMD) of less than 0.2 between the groups post-weighting was considered an adequate balance.

The propensity score was estimated using logistic regression model, with the treatment strategies as the dependent variable and the following variables as covariates: age, tumor location, PCI, lines of chemotherapy and ascites.

A logistic regression weighted analysis was carried out on postoperative morbidity rate within 30 days, 30-days postoperative mortality and reoperation rate, whereas a weighted linear regression analysis was carried out on length of stay.

2.4. Treatment

Technique, safety protocol and treatment regimens were standardized among expert centers [5–7]. The abdomen was accessed with a single port access or one 10/12-mm (nebulizer) and one 5-mm (optical) trocar [8]. The abdomen was insufflated with CO_2 (12 mmHg). Ascites was removed and the amount quantified; in case there was no ascites, a peritoneal washing was performed for cytology examination. The abdominal cavity was explored and the disease evaluated with PCI.

If surgical procedures have been performed, these have always preceded drug nebulization; this for two reasons: in order not to manipulate specimens that have been in contact with the drug and to allow all the cytostatic to remain inside the abdominal cavity without possible dispersions.

In case of single port access, the incision was always made in the site of the previous scar with its removal; similarly, also in case of

multiple accesses with induction of pneumoperitoneum through a Verres needle or an open access, an attempt was made, also in consideration of possible adhesions, to maintain the same trocars locations in all PIPACs. In order to extract the specimen, a midline trocar incision or the median mini-laparotomy in case of single port access was enlarged.

The chemotherapy injections were remote-controlled; the flow rate was 30 ml/min and the maximal upstream pressure was 290 psi. The aerosol was maintained for 30 min at 37 °C and then exsufflated via a closed line over two sequential micro-particle filters into the air waste system of the hospital.

Perioperative morbidity was classified according to Clavien-Dindo classification for surgical complications and the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for medical complications.

3. Results

3.1. Patient's characteristics and treatment

This multicentric, retrospective study was conducted in Italian (Turin n = 50; Rome n = 16), Swiss (n = 34), Belgian (n = 8), French (Lyon n = 16; Montpellier n = 10), Russian (n = 21), German (n = 34), Indian (n = 16) and Saudi (n = 4) hospitals. Patients were treated between January 2018 and December 2020.

Of the 209 patients selected from the dataset, 196 were included in the analysis (13 cases were excluded due to missing data): 96 underwent PIPAC + additional surgical procedures (PIPAC + SP) and 100 PIPAC alone. Table 1 lists patients' demographic and clinical features before and after IPTW adjustment. Before propensity adjustment, compared with patients submitted to PIPAC alone, the PIPAC + SP group consisted of more females (68.8% vs 58%, p = 0.158) and had more frequently received concomitant systemic chemotherapy (58.2% vs 51.7%, p = 0.470): on the whole, the two groups are in any case homogeneous.

Symptoms reported by the patients before the procedure were evaluated: the details are listed in Table 2.

The most frequent surgical procedures performed were adhesiolysis, oophorectomy, omentectomy; adhesiolysis was considered not simply the set of maneuvers designed to allow the trocars positioning, but the adhesion lysis procedures aimed at creating an abdominal chamber for effective nebulization or for additional surgical procedures. The detailed description of surgical actions is reported in Fig. 1. The most frequent PIPAC drug regimens included cisplatin and doxorubicin (CD), 7.5–30 mg/m^2 and 1.5–6 mg/m^2, respectively; oxaliplatin (OX) 92–135 mg/m^2. In rare cases abraxane, pegylated liposomal doxorubicin (PLD) and mitomycin C (MMC) were used. Specifics about drug type and dose are listed in Table 3.

3.2. Outcome analysis

Compared with the PIPAC-alone group, the PIPAC + SP group had longer median surgical times (120 min [90–159 IQR] vs 90 min [75–105 IQR]; p < 0.001) and longer median hospital stay (3 days [3–5 IQR] vs 3 days [2–3 IQR]; p < 0.001). A mean increase of 52.23 min and 1.82 days was reported, respectively (CI 36.22–68.23; CI 1.05–2.59).

Neither reoperations nor deaths were registered in either group.

Surgical complication rate was similar between PIPAC + SP and PIPAC alone (5.2% vs 2%, respectively; OR = 2.52.95% CI, 0.47–13.55). The surgical complications were essentially wound infections (n = 3) and bleeding (n = 2), in all cases Clavien – Dindo grade 2.

Within the whole cohort, medical complication rate was significantly different between the two groups: 3% in PIPAC group

Table 1
Demographic and clinical features of patients before and after IPTW.

	Study group, unweighted			Study group, weighted			
Factors	PIPAC 100	PIPAC + SP 96	p	PIPAC 99.4	PIPAC + SP 96.2	p	SMD
Sex, male (%)	42 (42.0)	30 (31.2)	0.158	41 (41.0)	31 (31.8)	0.186	0.194
Age, mean (SD)	57.7 (12.3)	56.2 (12.8)	0.391	57.08 (12.26)	57.1 (13.02)	0.989	0.002
BMI, mean (SD)	23.9 (3.9)	24.2 (3.7)	0.728	24.05 (3.97)	24.15 (3.76)	0.857	0.026
ASA Score (%)			0.345			0.535	0.214
1	13 (13.0)	21 (22.3)		14 (14.0)	20 (20.8)		
2	56 (56.0)	50 (53.2)		55 (55.0)	51 (53.1)		
3	29 (29.0)	21(22.3)		28 (28.0)	21 (21.8)		
4	2 (2.0)	2 (2.1)		2 (2.0)	2 (2.1)		
ECOG Score (%)			0.454			0.848	0.088
0	46 (51.1)	52 (60.5)		48 (53.3)	49 (57.7)		
1	33 (36.7)	25 (29.1)		31 (34.7)	27 (30.9)		
2	11 (12.2)	9 (10.5)		11 (11.8)	10 (11.4)		
Karnofsky Index, mean (%)	90.2 (10.6)	91.4 (11.1)	0.510	90.56 (10.63)	91.07 (11.12)	0.769	0.046
Primary Cancer (%)			0.996			1.000	0.123
Adrenal gland	0 (0.0)	1 (1.0)		0 (0.0)	1 (0.7)		
PMP	12 (12.0)	12 (12.5)		12 (12.5)	12 (12.5)		
Cholangiocarcinoma	2 (2.0)	3 (3.1)		2 (2.5)	2 (2.6)		
Colorectal cancer	16 (16.0)	15 (15.6)		16 (16.0)	15 (16.0)		
DMPM	11 (11.0)	11 (11.5)		11 (11.3)	11 (11.3)		
Endometrial cancer	1 (1.0)	1 (1.0)		1 (1.0)	1 (1.0)		
Gastric cancer	45 (45.0)	39 (40.6)		42 (42.4)	40 (41.8)		
Ovarian cancer	10 (10.0)	11 (11.5)		11 (11.0)	10 (10.8)		
Pancreatic cancer	2 (2.0)	2 (2.1)		2 (2.2)	2 (2.2)		
Primary peritoneal cancer	1 (1.0)	1 (1.0)		1 (1.0)	1 (1.0)		
PCI, median (IQR)	18.0 (7.7–28.2)	15.0 (7.0–25.0)	0.313	15.9 (7.0–26.0)	15.7 (7.0–25.4)	0.985	0.010
IV chemotherapy, yes (%)	45 (51.7)	53 (58.2)	0.470	44 (51.3)	54 (59.0)	0.314	0.154
sCT cycles, median (IQR)	9 (6–12)	8 (5–11.2)	0.875	9 (4.97)	8 (5.12)	0.320	0.145
Symptoms, yes (%)	49 (49.0)	52 (54.2)	0.562	47 (47.2)	54 (56.3)	0.209	0.183

SMD: standardized mean difference.

Table 2
Symptoms' details before the procedure.

	PIPAC 100	PIPAC + SP 96	p
Pain, yes (%)	25 (25.0)	29 (30.2)	0.512
Ascites, yes (%)	32 (32.0)	27 (28.1)	0.663
Dysphagia, yes (%)	3 (3.0)	7 (7.3)	0.298
Obstructive symptoms/stool alterations, yes (%)	4 (4.0)	12 (12.5)	0.056
Nausea, yes (%)	5 (5.0)	5 (5.2)	1.000

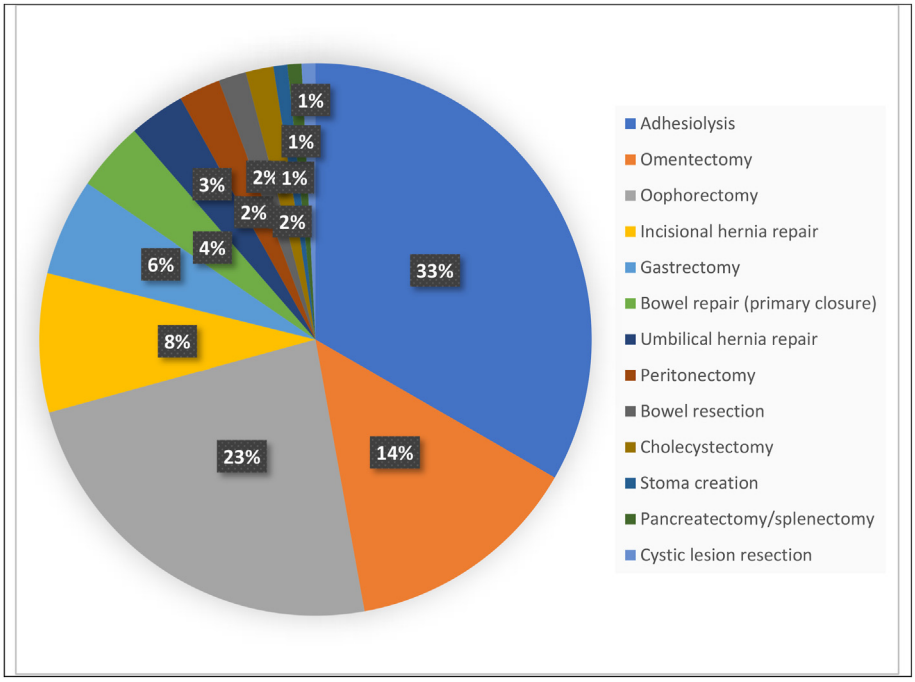

Fig. 1. Surgical procedures.

Table 3
Drug type and dose.

	PIPAC 100	PIPAC + SP 96	p
Abraxane 140 mg/m^2 (%)	1 (1.0)	0 (0.0)	0.007
CDDP 7.5 mg/m^2 + DXR 1.5 mg/m^2 (%)	57 (57.0)	41 (42.7)	
CDDP 10.5 mg/m^2 + DXR 2.1 mg/m^2 (%)	8 (8.0)	28 (29.2)	
CDDP 15 mg/m^2 + DXR 3 mg/m^2 (%)	6 (6.0)	1 (1.0)	
CDDP 30 mg/m^2 + DXR 6 mg/m^2 (%)	2 (2.0)	0 (0.0)	
CDDP 7.5 mg/m^2 + PLD 1.5 mg/m^2 (%)	3 (3.0)	0 (0.0)	
CDDP 7.5 mg/m^2 (%)	2 (2.0)	1 (1.0)	
MMC 10 mg/m^2 (%)	0 (0.0)	1 (1.0)	
OXA 92 mg/m^2 (%)	21 (21.0)	20 (20.8)	
OXA 135 mg/m^2 (%)	1 (1.0)	2 (2.1)	
OXA 92 mg/m^2 + MMC 1.5 mg/m^2 (%)	0.(0.0)	1 (1.0)	

CDDP = cisplatin; DXR = doxorubicin; PLD = pegylated liposomal doxorubicin; MMC = mytomicin C; OXA = oxaliplatin.

and 30.2% in PIPAC + SP group (odds ratio 15.62, 95% CI 4.54–53.73; p < 0.001). Analyzing in detail the medical complications, the most frequently reported were abdominal pain (24%), nausea (3.1%), ileus (6.2%) and hyperthermia (2.1%).

The relationship between the number of PIPAC associated with surgery (the first or any subsequent PIPACs) and the other outcomes was investigated: 43 patients were submitted to surgery during the first PIPAC procedure, 34 during a subsequent PIPAC. No difference in terms of surgical complications (7.0% vs 5.9%, odds ratio 0.83, 95% CI 0.10–5.32; p = 0.847), medical complications (16.3% vs 8.8%, odds ratio 0.50, 95% CI 0.10–1.96; p = 0.341), hospital stay (4 days vs 3 days, mean difference −0.60, 95% CI -2.11 – 0.90; p = 0.433) and surgical time (120 min vs 132 min, mean difference 17.14, 95% CI -11.46–46.75; p = 0.244) were reported.

4. Discussion

Born essentially with the palliative aim of alleviating symptoms, in particular to control ascites leading to a better quality of life, the histological evidence of tumor regression in patients with PM (Peritoneal Metastases) of gastric, appendiceal, and ovarian origin submitted to PIPAC dates back in 2014 [1]. Feasibility and safety of PIPAC are now consolidated and data on its effectiveness are continuously increasing. Multiple studies showed that about 75% of patients with unresectable PM develop major or complete intraperitoneal response assessed by histology after repeated PIPAC treatment [9–14].

In this international cohort, the addition of surgical procedures to PIPAC led to longer surgery time, higher rate of minor medical complications and longer hospital stay, while no difference in major surgical complications was detected. Most of the associated surgical procedures were of limited complexity: hernia repairs, omentectomy, adnexectomy; however, we must notice that even more complex procedures (intestinal resections, full-thickness intestinal repairs and gastrectomies) combined with PIPAC did not led to any

surgical complications. Furthermore, the medical complications recorded were all mild or moderate. Anyway, safety of combined gastrointestinal resection + PIPAC needs to be confirmed through ongoing prospective studies before this practice can be recommended.

To support this recommendation, an animal study used a healthy swine model to compare the postoperative anastomotic leakage rate between PIPAC and HIPEC with digestive resection and to analyze macro- and microcirculation parameters: PIPAC might have increased anastomotic leakage incidence compared to HIPEC (37.5% vs 0%). Conclusion of the authors was the warning to use PIPAC with digestive resection and the recommendation to avoid PIPAC in cases of perioperative serosal injury [15].

If good results in terms of survival have been obtained with PIPAC alone, possibly associated with systemic chemotherapy, in a palliative setting, the chance of combining PIPAC with surgical procedures (in case of safety profile confirmation) can open up new perspectives for use for this innovative approach. In this regard, the Odense group recently published promising results in PM from gastric cancer: objective tumor response was documented in 40% of the patients after PIPAC, including complete histological regression in some, whereas an additional 20% had no further tumor progression [16]. Based on these observations, they started a study (PIPAC-OPC 2 - NCT03287375) about PIPAC delivered immediately after a laparoscopic gastrectomy for gastric cancer, in order to evaluate, as primary outcomes, medical adverse events and surgical complications. Similarly, a Russian group is conducting a prospective randomized study in which patients undergoing radical surgery for locally advanced gastric cancer and a high risk of developing peritoneal carcinomatosis can receive as adjuvant treatment systemic chemotherapy with or without PIPAC (GASPACCO - NCT04595929): aim of the study is overall and progression free survival evaluation in the two groups.

Considering the known complications of cytoreductive surgery associated with HIPEC, the possibility in the future of replacing it with PIPAC, with lower dosages and equal efficacy, would open new scenarios for this method. Large series studying cytoreductive surgery + HIPEC have shown a complication rate (Clavien-Dindo classification grade III – IV) between 22 and 34% and a 30-day mortality rate between 1 and 4% [17–19]. Extent of the peritoneal metastases and hereby extent of the surgical procedures are main factors in predicting the risk of complications [20]. For this reason, given the type of procedures performed within this study and their extent, the results need confirmation by trials in which PIPAC is combined with major surgery.

The good results in terms of surgical postoperative morbidity could be explained by the high quality and experience of the participating centers that are a strength of this study. Therefore, despite the promising and reassuring results obtained, it is recommended not to use the PIPAC possibly associated with surgical procedures, in the absence of adequate experience not only in peritoneal carcinomatosis treatment, but also in PIPAC administration.

Overall the quality of the study data is good: patients were not included if data about the extent of peritoneal carcinomatosis, surgery, PIPAC and postoperative morbidity were missing. The propensity score based on IPTW adjustment significantly reduces confounding bias potentially offering estimation of treatment effect similar to randomized trials.

The limitations of the study are related to its retrospective nature and the presence of multiple variables regarding drug type and drug dose. This aspect is in line with what has been published in a recent survey: PIPAC procedure is being performed with a uniform concern for safety but with an increasing variability related to surgical aspects, chemotherapy regimens and response evaluation [21]. In this scenario, numerous phase 1 studies have been published to date about PIPAC-CD [22,23] and PIPAC-OX [22,24,25] and are ongoing for Abraxane [26]. A retrospective study reported data on the use of PLD [27], while there is little information on the use of mitomycin C [28]. A potential explanation of this heterogeneity would be the lack of any other treatment options for this patient's setting in combination with the need to make the most of a treatment that is generally well tolerated. This flourishing of studies testifies to the rapid evolution of the method, but further diversification of protocols in the absence of new evidence should be prevent: to this end, recent consensus guidelines has been published to facilitate benchmarking and analysis of outcomes [29].

5. Conclusions

This cohort study found that the association of surgical procedures and PIPAC was safe and feasible. This combination may represent a valuable treatment option for selected patients submitted to radical surgery with a high risk of developing peritoneal carcinomatosis. Confirmation by the ongoing clinical trials is warranted and could open new perspective for PIPAC application.

CRediT authorship contribution statement

Manuela Robella: Conceptualization, Funding acquisition, Formal analysis, Writing – original draft, Writing – review & editing, Study concepts, Data acquisition, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review. **Martin Hubner:** Funding acquisition, Formal analysis, Writing – review & editing, Data acquisition, Quality control of data . **Olivia Sgarbura:** Funding acquisition, Formal analysis, Writing – review & editing, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript editing, Manuscript review. **Marc Reymond:** Funding acquisition, Data acquisition. **Vladimir Khomiakov:** Funding acquisition, Data acquisition. **Andrea di Giorgio:** Funding acquisition, Data acquisition. **Aditi Bhatt:** Funding acquisition, Data acquisition. **Naoual Bakrin:** Funding acquisition, Data acquisition. **Wouter Willaert:** Funding acquisition, Data acquisition. **Mohammad Alyami:** Funding acquisition, Data acquisition. **Hugo Teixeira:** Funding acquisition, Data acquisition. **Andrey Kaprin:** Funding acquisition, Data acquisition. **Federica Ferracci:** Funding acquisition, Data acquisition. **Guillaume De Meeus:** Funding acquisition, Data acquisition. **Paola Berchialla:** Formal analysis, Study design, Quality control of data and algorithms, Statistical analysis. **Marco Vaira:** Writing – review & editing, Manuscript editing, Manuscript review. **Adnane Afifi:** , Data analysis and interpretation, Manuscript editing, Manuscript review.

Declaration of competing interest

We have no financial interest in the products presented in this work.

My coauthors and I do not have any conflicts of interests to disclose.

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