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Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for pancreatic cancer peritoneal metastases: A retrospective multicentric study from the ISSPP PIPAC Database

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is among the most aggressive malignancies, and peritoneal metastases (PM) represent the second most common site of dissemination, carrying a particularly poor prognosis. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an emerging locoregional approach for intraperitoneal drug delivery. However, its role in PDAC-related PM remains poorly defined.

Methods: This retrospective, multicentric study based on the ISSPP registry included patients with PM from PDAC treated with PIPAC from the International Society for the Study of Pleura and Peritoneum (ISSPP) registry. Outcome measures were safety, reason for stopping PIPAC, overall survival (OS), treatment response and prognostic factors for suvival at the time of the first PIPAC.

Results: One hundred fifty six patients were treated with 350 PIPAC procedures in 6 centers. Three or more PIPAC were completed in 55 (35.2%) patients. No major surgical complications (Clavien-Dindo $\geq$3) occurred; grade 3–4 adverse events (CTCAE v5.0) were recorded in 10 of 350 procedures (2.9%), and 30-day mortality was 3.8% per patient (6/156), in all cases due to disease progression. The main reason for discontinuation were disease progression and poor general conditions in 77 (49.35%) and 10 (6.41%) patients respectively. Median OS was 19 months from diagnosis and 9 months from PIPAC1. Survival analysis from PM diagnosis based on intraperitoneal drug choice showed a median OS of 15 months in patients with cisplatin and doxorubicin and 23 months with nab-paclitaxel ($p = 0.027$). Multivariable ananlysis showed that an higher Peritoneal Cancer Index (PCI) at PIPAC1 ($p = 0.008$) was associated with worse survival, whereas the use of intraperitoneal nabpaclitaxel ($p = 0.004$). After a 120 days landmark analysis accounting for immortal-time bias, completion of $\geq$3 PIPAC procedures remained independently associated with survival (adjusted $p = 0.005$)

Conclusion: PIPAC appears to be a safe treatment option for patients with PM from PDAC, with a low rate of major complications, however its feasibility is limited, as only about one third completed $\geq$3 procedures. In this multicentric cohort a hypothesis generating survival signal and histological response were observed, particularly with nab-paclitaxel–based regimens. Prospective studies are needed to validate PIPAC for palliative treatment of PM of pancreatic origin.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies, representing a major cause of cancer-related mortality despite its relatively low incidence with 140,116 new cases reported in the European Union in 2020 and approximately 132,134 deaths [1]. Recent epidemiological modeling predicts that the incidence of PDAC will continue to rise in the coming decades, with estimated annual increases of 1.2% to 2.4% worldwide [2]. Unlike other cancers, where early detection and systemic therapies have transformed prognosis, PDAC outcomes have remained largely unchanged. Five-year survival following diagnosis remains below 12%, and only 3% in a metastatic setting, emphasizing the critical need for novel approaches [3].

Surgical resection remains the only potentially curative treatment for patients with localized disease [4]. However, approximately 70–80% of patients present with locally advanced or metastatic disease at diagnosis, precluding surgical approaches. In this setting, systemic chemotherapy represents the standard of care. Although modern combination regimens have led to modest improvements in survival, treatment remains largely palliative and is primarily aimed at prolonging survival and alleviating disease-related symptoms.

The peritoneum is the second most frequent metastatic site following the liver. Peritoneal metastases (PM) are present in about 50% of patients with PDAC at the time of death, yet its involvement carries a particularly poor prognosis. PM often result in debilitating complications including: ascites, bowel obstruction, and malnutrition, that further compromise survival and quality of life [5]. The efficacy of systemic chemotherapy against peritoneal disease is constrained by the blood-peritoneal barrier, which limits drug penetration into the peritoneal cavity and results in subtherapeutic intratumoral concentrations. Locoregional intraperitoneal delivery circumvents this barrier, achieving higher local drug exposure while minimizing systemic toxicity [6,7].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has emerged as an innovative locoregional therapy designed to overcome the limitations of conventional chemotherapy. By delivering chemotherapeutic agents as a pressurized aerosol, PIPAC ensures improved distribution, enhanced tumor penetration, and reduced systemic toxicity [8–10]. Importantly, PIPAC can be integrated into a bidirectional approach, combining intraperitoneal therapy with systemic chemotherapy [11]. This strategy simultaneously addresses peritoneal and distant disease, representing a promising avenue to improve outcomes in patients with peritoneal metastases.

While evidence supporting PIPAC efficacy in other gastrointestinal primaries is gradually increasing, data on its use in pancreatic PM remains limited [12–14]. To date, no large-scale multicentric analysis has specifically examined the feasability, safety and therapeutic effect on PM from PDAC. This study addresses this gap through a retrospective multicenter cohort analysis of patients with pancreatic PM treated with PIPAC, utilizing data from the International Society for the Study of Pleura and Peritoneum (ISSPP) PIPAC registry [15].

2. Materials and methods

2.1. Population

The target population of the study are patients with PM from PDAC treated with PIPAC included in the ISSPP PIPAC Registry. For this purpose, all active PIPAC centers (>5 PDAC PM patients) were invited to participate and to enter all eligible patients in the online registry. Six european centers contributed to the study: Fondazione Policlinico A. Gemelli IRCSS (IT), Odense PIPAC center (DK), Centre Hospitalier Lyon Sud (FR), University of Tübingen (DE), University of Lausanne (CH) and Paracelsus Medical University Salzburg (AT). All eligible patients received PIPAC treatment in line with the currently recommended indications [16]. The ISSPP PIPAC Database has been approved by the Danish Authorities to collect international data on patients treated with PIPAC. The Database is located in Odense Denmark, and complies with the *General Data Protection Regulation* (GDPR) of the European Union.

2.2. PIPAC procedure

The PIPAC procedure has been extensively described in the literature and is currently performed according to standardized technical and safety protocols [17,18]. During each procedure, a systematic exploration of the abdominal cavity was performed whenever feasible, and the extent of peritoneal disease was assessed using the Peritoneal Cancer Index (PCI). Ascitic fluid, when present, was aspirated and its volume recorded in milliliters. Peritoneal biopsies were obtained from suspected lesions to allow evaluation of histological response to treatment through Peritoneal Regression Grading Score (PRGS) [19].

The chemotherapeutic regimens used for PIPAC included: cisplatin (7.5 mg/m^2) plus doxorubicin (1.2 mg/m^2), cisplatin (10.5 mg/m^2) plus doxorubicin (2.1 mg/m^2), oxaliplatin (92 mg/m^2), and nab-paclitaxel (112.5 mg/m^2) [20,21]. The choice among regimens reflected era and centre preferences, the higher-dose cisplatin–doxorubicin schedule being adopted after the pharmacokinetic data reported by Tempfer et al. [20]. Additional surgical procedures were performed at surgical discretion and if clinical indicated [22].

2.3. Outcome

The primary objective of the study was to evaluate feasibility and safety of PIPAC in patients with PM from PDAC. Feasibility was defined as the number of patients able to undergo at least three PIPAC cycles and reasons for discontinuation. Factors associated with the completion of at least three PIPAC procedures were also evaluated. Safety was characterized by the number of patients with major surgical complications, defined as ≥3 grade according to Clavien-Dindo, or major toxicity expressed as ≥3 grade according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Secondary objectives were survival outcomes, histological response after treatment (Peritoneal Regression Grading Score, PRGS), and prognostic factors for survival at the time of first PIPAC procedure (PIPAC1). Median overall survival (mOS) was calculated both from the diagnosis of PM and from PIPAC1 [23].

Histological response was graded with the four-tier PRGS proposed by Solass et al. [24]. Treatment response was assessed in patients who completed at least three PIPAC procedures, using two predefined variables: the change in mean PRGS between PIPAC1 and PIPAC3, with response defined as a PRGS ≤2 at PIPAC3 or a reduction of at least one point in mean PRGS between the two procedures. Treament response was also evaluated by the number of patients with a reduction of the PCI of at least three points between PIPAC1 and PIPAC3.

Several variables were investigated as potential prognostic factors for survival from PIPAC1. Patient-related factors included age, sex and Eastern Cooperative Oncology Group (ECOG) performance status. Tumor-related features as the timing of the onset of PM (synchronous or metachronous) and the PCI at the time of PIPAC1 were analyzed. The analysis also considered systemic chemotherapy, intraperitoneal drug, presence of ascites and histological response to treatment at PIPAC1 through PRGS.

2.4. Statistical analysis

Continuous variables were summarized as median (interquartile range, IQR) or mean, and categorical variables as frequency (percentage, %). Overall survival was assessed using two predefined reference points: the date of diagnosis of peritoneal metastases and the date of the first PIPAC procedure. Survival probabilities were calculated with the Kaplan–Meier estimator, and differences between survival curves were

evaluated using the log-rank test. The median duration of follow-up was estimated through the reverse Kaplan–Meier method. Comparisons between groups were performed using the χ^2 or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables, as appropriate. The impact of predictive factors on mOS from PIPAC1 were assessed using a Cox proportional hazards regression model. Results were expressed as hazard ratios (HR) with corresponding 95% confidence intervals (CI). Variables with a p-value <0.100 at univariable analysis were entered into the multivariable model to identify independent prognostic factors.

To address time-dependent (immortal time) bias, treatment-exposure variables that inherently accrue over time (completion of ≥3 PIPAC procedures) were handled through a landmark approach that was performed at a prespecified time point after PIPAC1 (120 days), including only patients alive and under observation at the landmark and classifying exposures according to status at that time. The 120 days landmark was chosen to reflect the approximate time needed for patients to complete at least three PIPAC cycles. All statistical analyses and graphical outputs were performed using Jamovi version2.6.44. and R software.

3. Results

This study included data from 156 patients undergoing 350 PIPAC procedures from 2016 to 2025. Fifty five patients (35.25%) received three or more PIPAC procedures. Twenty-nine patients completed at least 4 and 13 patients completed 5 PIPAC procedures and one patient completed 9 PIPAC cycles. The group who completed three or more PIPAC was characterized by a better performance status (p = 0.003), a lower number of patients presented with ascites (p = 0.024) a lower PCI at PIPAC1 (p = 0.007). Table 1.

The most frequent reason for discontinuation of PIPAC was disease progression (49.4%), followed by poor general condition (10, 6.4%) and death (6, 3.8%). Together, these disease-driven reasons accounted for 93 patients (59.6%), indicating that discontinuation was primarily governed by tumour biology rather than by procedural factors. Eight patients (5.1%) discontinued PIPAC because of a complete response, defined as the absence of macroscopic peritoneal disease together with negative peritoneal biopsies (complete histological regression). Laparoscopic access could not be established in 5 patients (3.2%) because of extensive adhesions or carcinomatosis. The reason for discontinuation was missing in 22 patients (14.1%); in a sensitivity analysis, disease-driven reasons remained predominant under both extreme assumptions for these missing data (59.6% if none were disease-related, up to 73.7% if all were), confirming that causes of discontinuation in this population is chiefly limited by tumour biology (Table 2).

PIPAC showed a favourable peri-procedural safety profile: no major surgical complications (Clavien-Dindo ≥3) were recorded, and grade 3–4 adverse events (CTCAE v5.0) occurred in 10 of 350 procedures (2.9% per procedure). Early recurrent ascites was reported in 6 procedures (1.7%) and severe anaemia in 4 (1.1%); one procedure reported both thrombocytopenia and anaemia, and constipation, intense vomiting, hyperglycaemia and cholangitis were each reported in one procedure. Six patients died within 30 days of a PIPAC procedure, corresponding to a per-patient 30-day mortality of 3.8% (6/156); all six deaths were attributable to disease progression rather than to the procedure complications.

3.1. Survival analysis

Survival analyses were performed in 140 of the 156 patients. Sixteen patients were exluded for the time-to-event analysis due to missing data. The median follow up was 39 (range 0-58) months from PM diagnosis. Forty-four (28.21%) patients are still alive to date.

From PM diagnosis the median OS was 19 months (range 2-58). Estimated survival rates were 73% at 12 months, 18% at 36 months. (Fig. 1).

From PIPAC1 the median OS was 9 (range 1-57) months, and survival rates of 38.4% at 12 months, 6.8% at 36 months.

Two subgroup analyses were performed.

The first analysis compared patients treated with the standard PIPAC regimen (cisplatin–doxorubicin) versus those receiving nab-paclitaxel. Patients in the standard treatment group showed a mOS from PM diagnosis of 15 months, whereas those treated with nab-paclitaxel demonstrated a longer mOS of 23 months (p = 0.027) (Fig. 2A). From PIPAC1 mOS was 8 months when patients were treated with cisplatin-doxorubicin and 14 months when treated with nab-paclitaxel (p < 0.001). The baseline characteristics of these groups are shown in Table 3.

The second analysis evaluated outcomes according to the number of

Table 1
Patients charateristics and association with the completion of ≥ 3PIPAC. ECOG, eastern cooperative oncolopy group, Bimodal treatment, PIPAC along systemic chemotherapy course, ePIPAC, electrostatic Pressurized Intraperitoneal Aerosol Chemotherapy, PCI, peritoneal cancer index.

Variables	Study population 156 patients	≥3 PIPAC 55 patients	<3 PIPAC 101 patients	p-value
Gender male n (%)	73 (46.79)	21 (38.18)	52 (51.49)	0.112
Age median (range)	68 (48-85)	68.5 (48-85)	67 (49-82)	0.723
ECOG >1 n (%)	24 (15.38)	2 (3.64)	22 (21.78)	0.003
Time from primary tumor diagnosis to peritoneal metastasis n (%):				
- 0-2 months	79 (50.64)	29 (52.72)	50 (49.50)	0.701
- 3-5 months	13 (8.33)	5 (9.09)	8 (7.92)	0.801
- ≥6 months	61 (39.10)	20 (36.36)	41 (40.59)	0.605
Ascites >500 ml at PIPAC1 n (%):	77 (49.35)	16 (29.09)	61 (60.39)	0.024
Other metastases n (%):	21 (13.46)	6 (10.91)	15 (14.85)	0.491
Previous treatment n (%):	93 (59.62)	35 (63.64)	58 (57.43)	0.450
Time between diagnosis of PM and PIPAC1, months, median (range):	6 (0-55)	5 (0-34)	6 (0-55)	0.464
Bimodal Treatment n (%):	63 (40.38)	18 (32.73)	45 (44.55)	0.394
ePIPAC n (%):	10 (6.41)	2 (3.64)	8 (7.92)	0.297
Intraperitoneal drug n (%):				
- Cisplatin-doxorubicin, low dose	36 (23.08)	16 (29.09)	20 (19.80)	0.188
- Cisplatin-doxorubicin, high dose	52 (33.33)	19 (34.55)	33 (32.67)	0.813
- Oxaliplatin	10 (6.41)	0	10 (9.90)	0.015
- Nab paclitaxel	58 (37.18)	20 (36.36)	38 (37.62)	0.876
PCI at PIPAC1 median (range)	10 (0-39)	7 (0-32)	12 (0-39)	0.007

Table 2
Causes of interruption, CRS, cytoreductive surgery.

Causes of discontinuation	Study population 156 patients
Disease progression (%):	77 (49.35)
Poor general conditions (%):	10 (6.41)
Patient refusal (%):	6 (3.85)
No microscopic or macroscopic disease (%):	8 (5.13)
Death (%):	6 (3.85)
End of study (%):	8 (5.13)
Curative intended CRS (%):	1 (0.64)
No laparoscopic access (%):	5 (3.21)
Other (%):	13 (8.33)
Missing data (%):	22 (14.10)

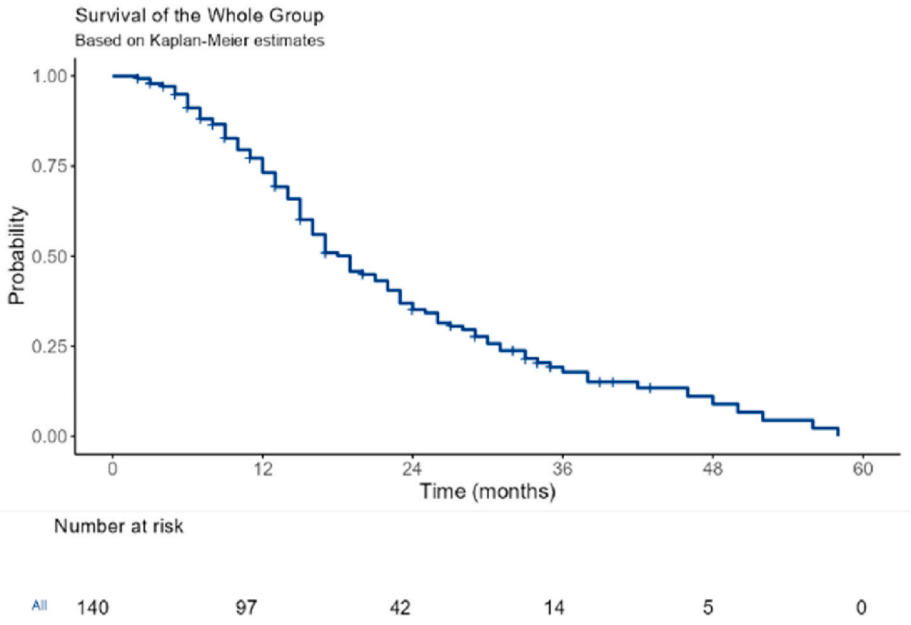

Fig. 1. Overall survival of the study from PM diagnosis.

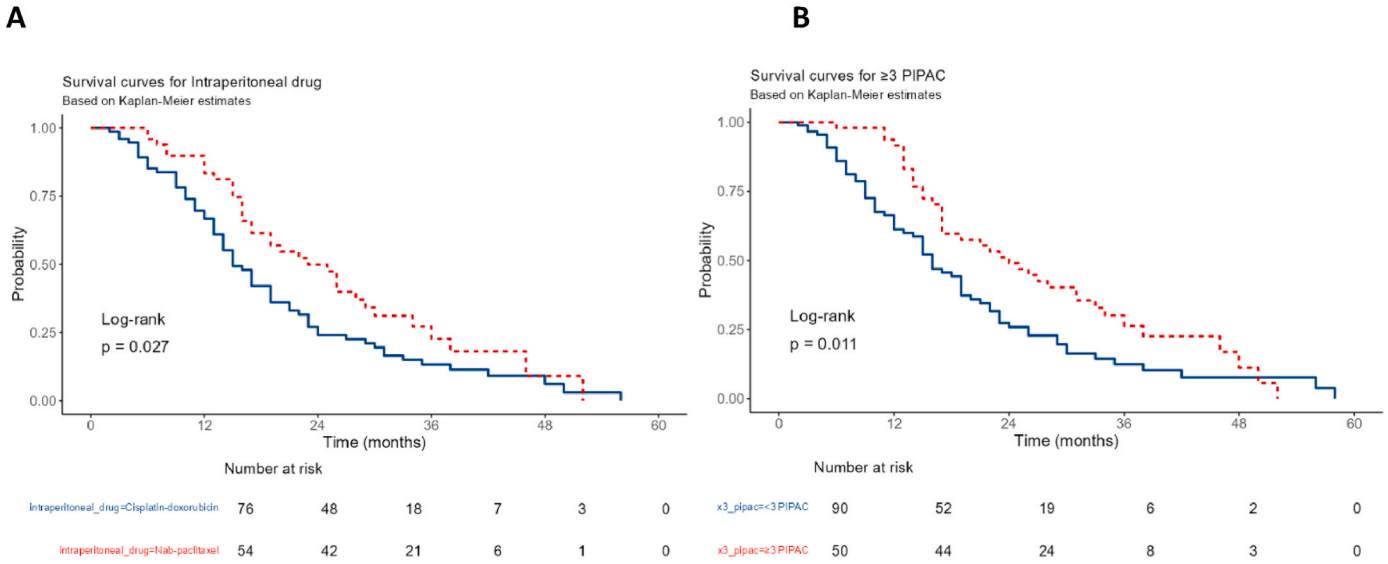

Fig. 2. A) survival from PM diagnosis based on intraperitoneal drug. B) survival from PM diagnosis based on the completion of ≥3 PIPAC.

PIPAC procedures (≥3 vs < 3). Patients who underwent ≥3 PIPACs had a significantly improved mOS of 24 months compared with 16 months in those receiving fewer than three procedures (p = 0.011) (Fig. 2B). From PIPAC1 mOS was 15 months in the group who completed ≥3 PIPAC procedures and 6 months in the group who completed <3PIPAC (p < 0.001).

3.2. Treatment response

Treatment response was assessed in the 55 patients who completed at least 3 PIPAC procedures. The assessment was made by evaluating the changes of PRGS between PIPAC1 and PIPAC3 and PCI reduction.

PRGS was evaluated in 182 (52%) PIPAC procedures. Overall mean PRGS was 2.16 ± 1.01 at PIPAC1 and 1.82 ± 0.86 at PIPAC3. A PRGS ≤2 at PIPAC3 or a reduction of the mean PRGS of at least 1 between PIPAC 1 and 3 was observed 23 (41.81%) patients.

A PCI reduction of at least 3 points was observed in 8 (14.54%) patients.

3.3. Prognostic factors for survival

We further assessed prognostic factors for survival at the time of PIPAC1. At multivariable analysis, a higher PCI at PIPAC1 independently predicted poorer survival (HR = 1.03; p = 0.008). Whereas the receipt of ≥3 PIPAC procedures (HR = 0.35; p < 0.001), and the use of intraperitoneal nab-paclitaxel (HR = 0.45; p = 0.004) were associated with improved survival. The results are shown in Table 4.

To address immortal-time bias, a landmark analysis at 120 days (patients alive at the landmark, n = 106) was performed: completion of ≥3 PIPAC procedures remained independently associated with longer survival (adjusted HR 0.58, 95% CI 0.26-0.79, p = 0.005), although the effect was attenuated compared with the uncorrected estimate (Supplementary Material 1).

Table 3
Baseline characteristhics of patients based on intraperitoneal treatment. ECOG, Eastern Cooperative Oncology Group. PIPAC, Presseurized Intraperitoneal Aerosol Chemotherapy. PM, Peritoneal Metastases. Bimodal Treatment, PIPAC plus sy.

Variables	Cisplatin doxorubicin 88 patients	Nab-Paclitaxel 58 patients	p-value
Gender male n (%)	45 (51.1)	25 (43.1)	0.342
Age median (range)	66 (48-85)	67 (49-82)	0.791
ECOG >1 n (%)	13 (14.8)	7 (12.1)	0.642
Synchronous PM	48 (54.5)	39 (67.2)	0.126
Ascites >500 ml at PIPAC 1 n (%):	44 (50.0)	30 (51.7)	0.838
Other metastases n (%):	11 (12.5)	7 (12.1)	0.938
Previous treatment n (%):	73 (82.9)	13 (22.4)	<0.001
Time between diagnosis of PM and PIPAC1 median (range):	6 (0-55)	5 (1-38)	0.183
Bimodal Treatment n (%):	14 (15.9)	44 (75.9)	<0.001
PCI at PIPAC1 median (range)	9 (0-36)	8.5 (1-39)	0.126

Table 4
Prognostic factors for survival from PIPAC1. †this estimate is subject to immortal-time bias; the corrected estimate is reported in Supplementary Material 1. ECOG, eastern cooperative oncolopy group, PCI, peritoneal cancer index, PRGS, peritoneal regression grading score.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender Male	1.05	CI 95% (0.72-1.53)	0.794			
Age	1.01	CI 95% (0.99-1.01)	0.878			
ECOG>1	2.23	CI 95% (1.32-3.77)	0.003	1.36	CI 95% (0.71-2.63)	0.356
Synchronous PM	0.80	CI 95% (0.54-1.17)	0.251			
Other metastases	1.13	CI 95% (0.65-1.96)	0.655			
Previous treatment	1.51	CI 95% (1.02-1.51)	0.040	1.13	CI 95% (0.61-1.90)	0.641
PCI at PIPAC1	1.05	CI 95% (1.03-1.07)	<0.001	1.03	CI 95% (1.01-1.06)	0.008
Ascites >500 ml at PIPAC1	1.58	CI 95% (1.08-2.29)	0.017	0.94	CI 95% (0.58-1.52)	0.786
Intraperitoneal drug: - Cisplatin-doxorubicin (reference) - Oxaliplatin - Nab paclitaxel	1.18 0.45	CI 95% (0.72-1.98) CI 95% (0.29-0.68)	0.581 0.027	0.45	CI 95% (0.26-0.77)	0.004
Bimodal Treatment	0.89	CI 95% (0.35-1.81)	0.790			
3 or more PIPAC†	0.41	CI 95% (0.28-0.61)	0.011	0.35	CI 95% (0.21-0.57)	<0.001
PRGS at PIPAC1 ≤2	0.74	CI 95% (0.42-1.30)	0.294			

4. Discussion

This study represents the first large multicentric analysis evaluating the use of PIPAC in patients with PDAC. Feasibility, defined as completion of ≥3 PIPAC procedures, was achieved in 35.25% of patients, a rate lower than that reported in the literature for other malignancies treated with PIPAC [25–27]. This difference is likely explained by the aggressive biology of pancreatic cancer, which is frequently associated with rapid disease progression, cachexia, and early clinical deterioration, ultimately limiting the ability to deliver repeated treatments [28,29]. Consistently, the principal reason for treatment discontinuation in our cohort were biological reasons such as disease progression, poor general conditions and death affecting nearly sixty percent of patients [30]. Patients who were able to complete ≥3 procedures had more favourable baseline characteristics, including lower ECOG performance status ($p = 0.003$), less patients presenting ascites at PIPAC1($p = 0.024$) and lower PCI at PIPAC1 ($p = 0.007$), highlighting that feasibility is primarily driven by patient selection and disease burden rather than procedural factors. In contrast with reports in other malignancies, baseline performance status emerged as a key determinant of treatment completion, reflecting the cachexia-prone and aggressive nature of pancreatic cancer and its substantial influence on patients' capability to tolerate repeated PIPAC therapy. The low rate of grade 3–4 adverse events (2.9% per procedure) observed in this cohort aligns with previous PIPAC series, further confirming the peri-procedural safety and tolerability of the procedure in this high-risk population.

In our cohort, the mOS was 19 months from the diagnosis of PM, in line with outcomes reported for catheter based intraperitoneal chemotherapy in PDAC with PM. In this setting, intraperitoneal paclitaxel combined with systemic chemotherapy has achieved a mOS of approximately 14.5 to 15 months from the diagnosis of peritoneal disease, with survival at one year of around 60% in phase I/II experience, and the approach is currently being evaluated in a randomised phase III trial (SP study) [31–33]. The slightly higher survival observed in our series most likely reflects patient, since only patients fit enough to undergo repeated laparoscopic PIPAC were included, and it should be interpreted with caution given the retrospective, single arm design.

Regarding intraperitoneal chemotherapy, while cisplatin and doxorubicin remain the current standard for PIPAC, nab-paclitaxel is still under clinical investigation. In our cohort, patients treated with nab-paclitaxel demonstrated a significantly longer mOS from diagnosis compared with those receiving cisplatin and doxorubicin (23 vs 15 months, $p = 0.027$). In line with our findings, systeming nab-paclitaxel seems to be one of the most active drug in the treatment of PDAC. Furthermore intraperitoneal pharmacokinetic data from Ceelen et al., showing high intratumoral drug concentrations with limited systemic exposure and a progressive increase in tissue levels over repeated administrations, suggesting a potential cumulative effect of nab-paclitaxel [34,35]. However this finding should be regarded as hypothesis-generating, as the nab-paclitaxel group more frequently received concurrent systemic chemotherapy, was less heavily pretreated and the comparator arm comprised both low dose and high dose cisplatin doxorubicin regimens.

Response to treatment remains challenging to assess in this setting, as intraoperative evaluation is inherently limited in capturing disease dynamics during PIPAC. PCI is difficult to interpret over time and likely plays a more relevant role at baseline rather than as a dynamic marker. From a histological perspective, a reduction in PRGS was observed, indicating a measurable treatment response; however, this did not translate into a survival benefit, possibly due to the limited number of patients in whom PRGS was available.

The prognostic factors identified in our multivariable model are likely to reflect both disease biology and treatment variables. A higher PCI at PIPAC1 retained a strong adverse prognostic impact, supporting the central role of peritoneal tumour burden in shaping outcomes.

Intraperitoneal nab-paclitaxel was retained a survival benefit at multivariable analysis; in light of the confounding described above, this finding is hypothesis-generating and requires prospective validation. The association between receipt of more than three PIPAC procedures and improved survival was confirmeed by the 120-days landmark analysis suggesting the need to repeat intraperitoneal treatment [35, 36]'.

This study has several limitations. Its retrospective design inherently exposes the analysis to selection bias and limits causal inference. In particular, the cohort was substantially selected: only centers with more than five PDAC PM cases contributed, patients had to be referred and fit enough to undergo repeated laparoscopic PIPAC, and those with rapidly progressive disease were rarely considered, all of which inflates the survival estimates and limits external validity. Moreover, although patients were identified through the international ISSPP PIPAC registry, registry-based studies remain dependent on data completeness and consistency across centers, with potential heterogeneity in patient selection, treatment strategies, and follow-up[37]. In particular treatment protocols were heterogeneous across the six participating centers, systemic chemotherapy strategies were variable. Only 40% of patients receiving a bimodal approach, this reflects the early-era use when PIPAC was not strictly integrated into chemotherapy course. The absence of a centralized pathology review for PRGS further weakens internal validity. Despite these limitations, this study has important strengths. To our knowledge, this is the first and largest multicentric study specifically focused on PIPAC in PM from PDAC. By leveraging an international registry-based cohort, it provides a meaningful real-world insight into this rare and clinically challenging disease setting. Overall, our findings support the feasibility and safety of PIPAC in selected patients with PM from PDAC and show encouraging signals in terms of survival outcomes. Nab-paclitaxel seems a promising intraperitoneal drug in this setting. These results provide a rationale for future prospective collaborative studies.

5. Conclusion

In conclusion, PIPAC may represent a feasible and safe locoregional treatment option for patients with PDAC associated PM, although only about one third of patients able to complete three or more procedures. The aggressive biology of the disease represents the main reason for treatment interruption. Completing three or more PIPAC and carefully patients selection for repeated procedure seems to be a favourable prognostic marker of outcome in this population. As the first multicenter study specifically addressing this indication, our analysis provides encouraging real-world signals in terms of feasibility and survival. Further prospective collaborative studies are warranted to better define patient selection, treatment timing, and the optimal integration of PIPAC within multimodal therapeutic pathways.

CRediT authorship contribution statement

Andrea Di Giorgio: study concepts, Study design. Paolo Catania: Study design, Statistical analysis, Manuscript preparation. Federica Ferracci: Data Analysis and interpretation. Michael Bau Mortensen: Manuscript review. Claus Wilki Fristrup: Data acquisition. Sönke Detlefsen: Data acquisition. Olivier Glehen: Manuscript review. Mark Raymond: Data analysis and interpretation. Yaroslaw Sautkin: Manuscript editing. Jäger Tarkan:Quality control of data and algorithms. Fabio Pacelli: Study concepts.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2026.112078.

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