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Review Article

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in patients with ovarian cancer: A systematic review

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ABSTRACT

Background: PIPAC consists in delivering normothermic chemotherapy solution directly into the peritoneal cavity as an aerosol under pressure. Currently PIPAC is considered as a palliative treatment for patients suffering from non-resectable peritoneal carcinomatosis. We performed a SR to assess tolerance and response of this novel method among patient with OC.

Methods: We searched electronic database PubMed, Embase, Web of Science, Clinical Trials.gov. We only included clinical studies reporting PIPAC with cisplatin and doxorubicin in patients with ovarian cancer.

Results: This systematic review included 4 studies. In 3 studies all patients were pretreated with cytoreductive surgery, in 1 study surgery was performed in 8/34 (23 %) patients. Mean PCI at first PIPAC procedure ranged from 16.3 to 19.6. All studies reported the proportion of patients with ascites at the first PIPAC with a pooled rate of 48,3 %. Pooled rate of CTCAE Grade 3 toxicity calculated on the total number of PIPAC was 6 % and Grade 4 was 0.9 %. One study reported two cases of small bowel perforation related or potentially related to PIPAC. On study reported a cumulative survival after 400 days of 62 % and a mean actuarial survival time of all patients who underwent PIPAC of 442 days. In another study the mean time to progression was 144 days (95 % CI 122–168 days).

Conclusion: This systematic review demonstrated that PIPAC with cisplatin and doxorubicin appear to have a good safety profile with low toxicity and encouraging trend in terms of overall survival.

1. Introduction

Peritoneal carcinomatosis (PC) is a condition usually present in advanced stages of epithelial ovarian cancer (EOC), concerning approximately 60–70 % of patients at the diagnosis [1]. The occurrence of PC has been shown to significantly decrease overall survival in patients with ovarian cancer due to poor response to systematic chemotherapy because of poor penetration of drug into the peritoneal tumor, and symptoms such as ascites and bowel occlusion, ultimately leading to death [2].

Macroscopically, it is characterized by small, white-colored nodules which are localized on the inner surface of the peritoneum. Although a multitude of adhesion molecules and microenvironmental factors have been identified in the development of PC, the exact mechanism that may contribute to dissemination of metastatic cancer cells from a primary epithelial malignancy and their growth through an epithelial cell layer

Abbreviations: PIPAC, Pressurized intraperitoneal aerosol chemotherapy; PC, peritoneal carcinomatosis; EOC, epithelial ovarian cancer; PRGS, peritoneal regression grading scale; RECIST, Response Evaluation Criteria in Solid Tumors; CTCAE, Common Terminology Criteria for Adverse Events; QoL, quality of life.

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remain to be elucidated [1,3].

Optimal cytoreductive surgery to decrease the tumor load to a minimum and platinum-based chemotherapy have been established as the most important determinants of survival in these patients. However, cytoreductive surgery is hampered by the presence of peritoneal carcinomatosis, which is often too extensive to remove completely, especially when present on the small intestine [4].

The National Comprehensive Cancer Network (NCCN) guidelines recommend carboplatin and paclitaxel as first line treatment for ovarian cancer peritoneal carcinomatosis [5]. Although chemotherapy is generally very effective with high response rates (80 %), the chance of recurrent disease in advanced-stage EOC is approximately 75 %. The prognosis is poor especially for women with Platinum resistant ovarian cancer [1,3]. The standard treatment for women with Platinum resistant ovarian cancer is chemotherapy containing taxanes, anthracyclines, gemcitabine, topotecan, and trabectedin. These drugs in various combinations and sequences provide modest survival or symptomatic benefit but with significant side effects [6].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel method implemented in many centers worldwide [7–11]. PIPAC consists in delivering normothermic chemotherapy solution directly into the peritoneal cavity as an aerosol under pressure. The theory behind PIPAC is the pharmacokinetic advantage of a pressure gradient that can overcome tumor interstitial pressure, resulting in higher concentration of chemotherapy in peritoneal lesions and lower systemic absorption. Moreover, the prolonged exposure to high concentrations of cytotoxic drugs homogeneously within the peritoneal cavity increases the local bioavailability and thus reduces local and systemic toxicity [11–13].

Although current evidence available from in vitro/in vivo/in animal studies, retrospective cohorts, phase I and II studies in humans showed that PIPAC is a feasible and safe treatment with an objective response rates and potential positive impact on quality of life, there are no results from RCTs comparing PIPAC with conventional systemic chemotherapy [13–16]. Therefore, PIPAC is currently considered as a palliative treatment for patients with peritoneal metastases [17].

In previous systematic review (SR) and meta-analysis, clinical and methodological heterogeneity among these studies was substantial, since, in general, patients with peritoneal carcinomatosis from many sites of origin were included, such as colorectal, ovarian, primary peritoneal and gastric origin [18–22].

This SR aims to provide an overview of the available literature on PIPAC and study its role in the ovarian cancer subgroup.

2. Methods

We conducted this review according to the 2020 PRISMA guidelines for SR.

2.1. Search strategy

We systematically searched electronic database PubMed, Embase, Web of Science, Clinical Trials.gov using the search terms “pressurized intraperitoneal aerosol chemotherapy” OR “PIPAC” AND “ovarian cancer” as MeSH terms.

Duplicates were identified using Rayyan.com and removed manually. No language or other restrictions were applied at the searching stage.

2.2. Eligibility criteria

We only included clinical studies reporting PIPAC with cisplatin and doxorubicin in patients with ovarian cancer. We excluded study reporting data from other type of primary tumor. Then, we did not include single case reports, animal or ex-vivo studies, on-going trials, protocol papers, books chapters and editorial letters.

2.3. Selection process

All citations were uploaded to Rayaan.com to enable systematic recording of eligibility by two independent reviewers. Titles and abstracts were screened, coded against eligibility criteria, and any publications with potential to meet the inclusion criteria were retrieved for full evaluation prior to appropriate inclusion or exclusion.

A global assessment for potential bias was made by the two reviewers, though no articles were felt to be high risk.

2.4. Quality assessment

NOS was used to assess the quality of the study included, which ranged from 3 to 9 stars.

2.5. Data collection

Eligible publications, including any available supplementary materials, underwent detailed assessment and data extraction by the principal reviewer (TC). Data was collected in an Excel database, and any ambiguity over data extraction was discussed with a second reviewer (VG). A third reviewer was available in case of disagreement but was not required. Data extracted from eligible reports included study details such as author, year and study design, study population including sample size, patient characteristics and burden of disease, technical details of the PIPAC procedure and any bidirectional chemotherapy administered, outcome data including survival data, histological response, toxicity, mortality and quality of life evaluation.

3. Results

The PRISMA flow diagram (Fig. 1) outlines the screening process. After duplicates were removed, 384 titles and accompanying abstracts underwent initial screening. Of the 33 reports that underwent full eligibility assessment, 4 studies focusing solely on ovarian cancer were included in the final analyses, representing a total of 100 patients with ovarian cancer.

Of the 4 papers included, 1 was open label, single arm, phase 2 study (Tempfer 2015), 1 was phase I, single-arm, non-randomized, open-label, dose-escalation study (Tempfer 2018), 2 were prospective, single arm studies (Tempfer 2014, Somashekhar 2018). All were single institution studies.

Studies represented multiple primary malignancies were excluded in the analysis (Giger-Pabst 2015, Hilal 2017, Rezniczek 2020, Solass 2014, Solass 2011, Nowacki 2018, Teixera 2018, Alyami 2017, Robella 2016).

The results of included studies were narratively described and grouped according to reported outcomes.

We found no RCTs, double-arm or phase III studies reported at the time of search. The characteristics of the included studies are presented in Table 1.

3.1. Patient characteristics

Somashekhar et al. enrolled patients with advanced PCI and/or unresectability because of diffuse small bowel involvement. Tempfer et al. included patients with radiological evidence of PC without extra abdominal metastatic disease, except for isolated pleural carcinomatosis/effusion. Information on previous systemic chemotherapy was available in all the 4 included studies, with 100 % of patients receiving previous treatment. In one study were enrolled patients with recurrent ovarian cancer and PC after at least two lines of previous standard cytotoxic chemotherapy (**Tempfer 2014, Tempfer 2015, Tempfer 2018**). In one study one patients was pre-treated after only one line of systematic chemotherapy (**Somashekar 2018**).

All studies reported the proportion of patients with ascites at the first

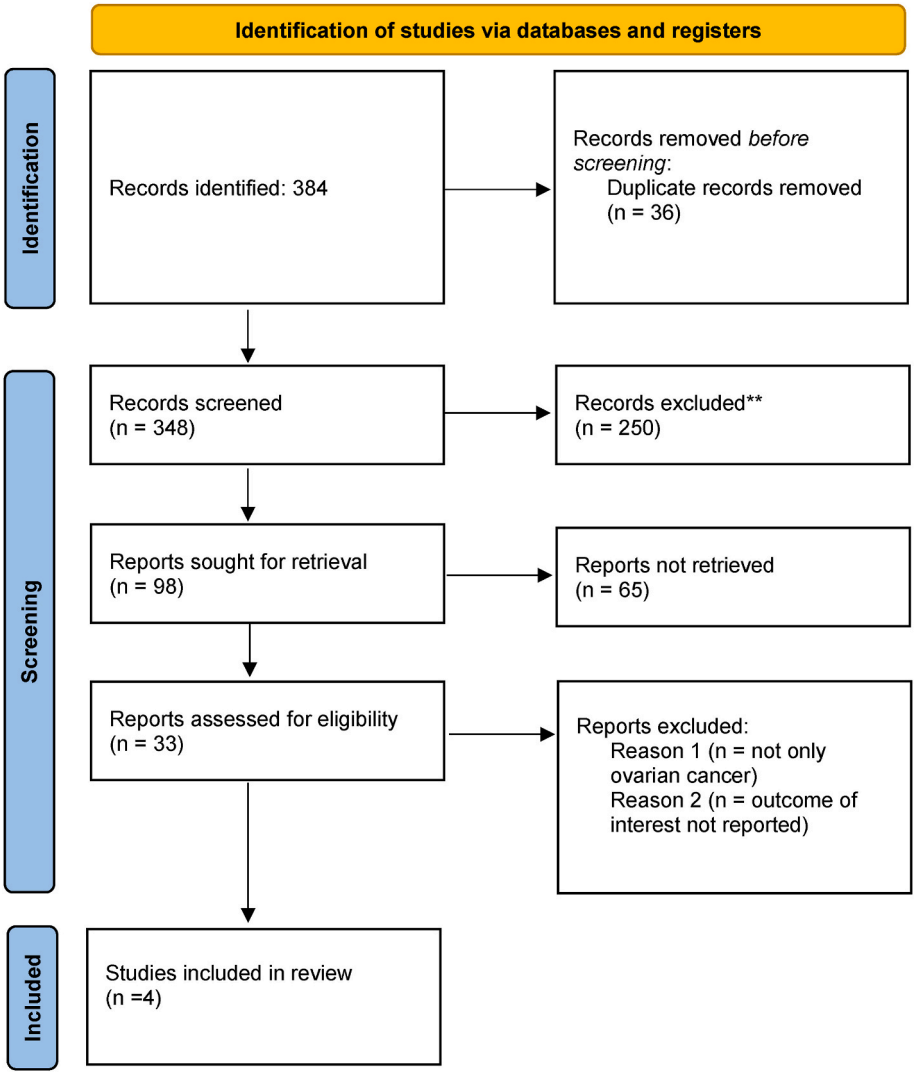

Fig. 1. PRISMA flowchart.

PIPAC with a pooled rate of 48,3 %. In 3 studies all patients were pre-treated with cytoreductive surgery, in 1 study surgery was performed in 8/34 (23 %) patients. Mean PCI at first PIPAC procedure ranged from 16.3 (**Tempfer 2015**) to 19.6 (**Somashekar 2018**) (Table 2).

3.2. Study protocol

In three studies (**Tempfer 2015**, **Tempfer 2014**, **Somashekar 2018**) the participants were treated with pressurized aereosol containing cisplatin at a dose of 7.5 mg/m2 in 150 ml NaCl 0.9 % solution followed by doxorubicin at a dose of 1.5 mg/m2 in 50 ml NaCl 0.9 % solution (Table 3).

One study was designed according a 3 + 3 dose-escalation protocol (**Tempfer 2018**). The first cohort of participants was treated with a dose of doxorubicin 1.5 mg/m2 body surface in 50 mL NaCl 0.9 % and cisplatin 7.5 mg/m2 in 150mLNaCl 0.9 % q 4–6weeks for 3 courses. The second cohort was given doxorubicin 1.8 mg/m2 and cisplatin 9.0mg/m2 and the third cohort was given doxorubicin 2.1 mg/m2 and cisplatin 10.5 mg/m2.

In all the studies the therapeutic carbon dioxide pneumoperitoneum was maintained for 30 min at a temperature of 37° Celsius.

Information on quality of life during therapy was available in 1/4 of the included studies (**Tempfer 2015**) using the EORTC QLQ-30 questionnaire.

Prevalence of PIPAC procedures >3 ranged from 27 % (Tempfer 2014) to 100 % (**Somashekar 2018**) with a pool prevalence of 50 %. To limit toxicity, the interval time between two PIPAC procedures was most commonly 4–6 weeks in all the included studies.

3.3. Tumor response assessment

Tumor response assessment was based on radiological response, histopathological tumor regression in repeat biopsies and video-laparoscopy evaluation using the Peritoneal Carcinomatosis Index (PCI) assessed during each course of PIPAC.

Three studies reported radiological response (Tempfer 2014, Tempfer 2015, Tempfer 2018) although only one (Tempfer 2015) provided the definitions for CT assessment according to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

In each study histological regression was assessed by pathological review of peritoneal samples taken during each PIPAC. In one study histological tumor regression was observed in 33/53 (62 %) patients in the intention-to- treat population (Tempfer 2015).

Somashekar et al. used the peritoneal regression grading scale (PRGS) that defined as grade 1 (complete response); grade 2 (major response); grade 3 (minor response); grade 4 (no response). In this study two patients had partial response, and one had stable disease.

In the dose-escalation study performed by Tempfer et al., in 2018

Table 1
The characteristics of the included studies.

First Author, year of publication	Country	Period	Study Design	Inclusion criteria	Exclusion criteria	EORTC QLQ-C30 questionnaire
Tempfer 2015	Germany	February 2013–February 2014	Phase II	- radiological evidence of PC. - age between 18 and 85 years. -a good performance status (Karnofsky Index N 70 %), a diagnosis of recurrent disease with disease progression. -blood, electrolyte counts, liver, and renal function parameters within 10 % of the normal range established in the laboratory of the study institution	- extra abdominal metastatic disease including retroperitoneal disease such as aortic/paraaortic lymph node recurrence except for isolated pleural carcinomatosis/effusion. - **chemotherapy or surgery within the last four weeks prior to study enrolment or a previous treatment.** - severe renal or hepatic impairment with organ-specific functional parameters N twice the upper norm. - history of severe cardiac disease. - immunocompromised status - any form of previous intraabdominal chemotherapy or intraabdominal antibody therapy.	Yes
Somashekhar 2018	India	June 2017–December 2017	Prospective study	-Patients not candidate to cytoreductive surgery or HIPEC because of poor general condition (ECOG C 2), advanced PCI, and/or unresectability because of diffuse small bowel involvement, -blood, electrolyte counts, liver, and renal function parameters within 10 % of the normal range established in the laboratory of the study institution	–	No
Tempfer 2014	Germany	December 2011–June 2013	Prospective case series	- clinical and/or radiological evidence of PC, - age between 18 and 85 years with a diagnosis of recurrent ovarian - cancer with disease progression after at least one line of previous intravenous chemotherapy with a platinum compound 3. blood and electrolyte counts, liver, and renal function parameters within 10 % of the normal range established in the respective laboratory of the study institution, - postmenopausal status.	- extra abdominal metastatic disease, except for isolated pleural carcinomatosis/effusion, - chemotherapy or surgery with in the last four weeks prior to the first PIPAC application, - previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones, - severe renal impairment or severe hepatic impairment with organ- specific functional parameters N twice the upper norm, - history of severe cardiac disease. - immunocompromised status	No
Tempfer 2018	Germany		Phase I dose-escalation study	- clinical and/or radiological evidence of PC, -age between 18 and 85 years with a previous diagnosis of EOC and disease progression after at least two lines of previous intravenous cytotoxic chemotherapy including a platinum compound, or inability or unwillingness to undergo further systemic chemotherapy after one line, - blood and electrolyte counts, liver, and renal function parameters within 50 % of the normal range	Extra abdominal metastatic disease except for isolated pleural carcinomatosis/ effusion, previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones, -severe renal impairment or severe hepatic impairment -history of severe cardiac disease. immunocompromised status	No

Table 2
The characteristics of the included studies. Study protocols.

First Author, year of publication	Sample Size	Number of PIPAC	Age	Previos systemic chemioterapy	Previous surgery	Type of chemioterapy	Mean PCI at the first PIPAC	Ascites
Tempfer 2015	53	130	62 ± 10 (mean)	100 %	53 (100 %)	cisplatin and doxorubicin	16.3 (±9.9)	22/53 (42 %)
Somashekhar 2018	3	9	43 (median)	100 %	100 %	cisplatin and doxorubicin	19.6 (range 17–23)	2/3
Tempfer 2014	18	34	63 ± 13 (mean)	100 %	8 (23 %)	cisplatin and doxorubicin	17.3 (±6.3)	16/21
Tempfer 2018	15	34	60.3 ± 12.4 (mean)	100 %	100 %	cisplatin and doxorubicin	16.3 ± (9.8)	3/15

Table 3
The characteristics of the included studies. Dose of chemotherapy. Tecnique. Temperature. Time (mins).

First Author, year of publication	Dose of chemotherapy	Tecnique	Temperature	Time (mins)
Tempfer 2015	7 · 5 mg/m2 body surface in a 150 ml NaCl 0.9 % solution followed by doxorubicin at a dose of 1 · 5 mg/m2 body surface in a 50 ml NaCl 0.9 % solution	close	37 °C	30 min
Somashekhar 2018	7 · 5 mg/m2 body surface in a 150 ml NaCl 0.9 % solution followed by doxorubicin at a dose of 1 · 5 mg/m2 body surface in a 50 ml NaCl 0.9 % solution	close	37 °C	30 min
Tempfer 2014	7 · 5 mg/m2 body surface in a 150 ml NaCl 0.9 % solution followed by doxorubicin at a dose of 1 · 5 mg/m2 body surface in a 50 ml NaCl 0.9 % solution	close	37 °C	30 min
Tempfer 2018	Cohort 1: doxorubicin 1.5 mg/m2 body surface in 50 mL NaCl 0.9 % and cisplatin 7.5 mg/m2 in 150mLNaCl 0.9 % q 4–6weeks for 3 courses. Cohort 2: doxorubicin 1.8 mg/m2 and cisplatin 9.0mg/m2 Cohort 3: doxorubicin 2.1 mg/m2 and cisplatin 10.5 mg/m2	close	37 °C	30 min

histologic tumor regression was documented in 7/11 (64 %) patients who underwent at least two PIPAC cycles: 18 % strong regression, 46 % weak/intermediate regression, 9 % no regression, 27 % indeterminate.

In the fourth study (Tempfer 2014) tumor response assessment was based on histologic tumor regression in repeat biopsies, PCI improvement, and video-laparoscopy assessment. Of the 8 women who underwent >1 PIPAC cycle, 6 patients had an objective tumor response with 1 complete response, 3 stable disease, 2 partial remission, 12 progressive disease. However, results were not separately reported for type of outcome assessment. In the same study, regression of ascites and PC was reported at repeated computed tomography (CT) scans of a patient before the first PIPAC, after the first PIPAC, and after the second PIPAC. Somashekar et al. reported symptomatic relief and ascites resolution in all the enrolled patients.

Data assessing the impact of PIPAC on symptoms and disease-free survival were insufficient.

Because of clinical heterogeneity in reporting outcomes, no meta-analysis was performed.

3.4. Survival analysis

Data to support a relationship between survival analysis and PIPAC were provided by 2 of the 4 included studies. Tempfer et al., in 2014 reported a cumulative survival after 400 days of 62 % and a mean actuarial survival time of all patients who underwent PIPAC of 442 days. The mean actuarial survival time of patients with PIPAC combined with cytoreductive surgery and patients with PIPAC alone was 486 days and 268 days, respectively. Similar results were confirmed in 2015 where the same Author reported the mean survival time after one year for the intention-to-treat population of 50 % with a mean survival time of 331 days (95 % CI 291–371 days). The mean time to progression was 144 days (95 % CI 122–168 days) (Table 4).

All manuscripts reported safety data regarding evaluation of post-operative complication and toxicity using CTCAE (Common Terminology Criteria for Adverse Events version 4 or 5)

Grading. Pooled rate of CTCAE Grade 3 toxicity calculated on the total number of PIPAC was 6 % and Grade 4 was 0.9 %. No CTCAE grade 4 toxicity was observed in three studies. Tempfer 2014 et al. reported two cases of small bowel perforation related or potentially related to PIPAC. The CTCAE grade 1–2 events were reported in Table 5.

No cases of PIPAC-related mortality, intraoperative complications or allergic reaction were reported. In one study (Tempfer 2015) quality of life was assessed using the EORTC QLQ-30 questionnaire at 3 time points (one day before PIPACs 1, 2, and 3, respectively). Specifically, global physical health scores demonstrated a continuous improvement during therapy.

4. Discussion

Current evidence on the use of PIPAC in patients with OC suggest that the safety, efficacy, and reproducibility of this method have been well established. However, PIPAC is still considered a palliative treatment providing relief from symptoms and improving patients' quality of life. To support the transition from palliative to curative intent of PIPAC in standard therapeutic course of peritoneal carcinomatosis, numerous studies have been conducted to provide insights into the value of delivering chemotherapy by taking advantage of the physical properties of gas and pressure. Consistent with existing reviews, we found an encouraging trend toward improvement in tumor response assessment, overall survival and lower morbidity rates. Since most reviews evaluated the role of PIPAC for the treatment of other primary malignancy such as gastric and colo-rectal cancer, in the present study we focused on its use for the treatment of ovarian cancer. Moreover, given the substantial heterogeneity among the available studies, we systematically reviewed only those with pressurized aerosol of cisplatin and doxorubicin. In a recent SR and meta-analysis, Di Giorgio et al. collected a wide number of patients and data by including tumor of various origin and different chemotherapy regimen [23]. Authors concluded that PIPAC may be a useful treatment option for selected patients with peritoneal metastasis with acceptable grade CTCAE 3–4 toxicity and promising survival benefit. Similarly, in another SR performed by Grass et al. 29 studies (16 preclinical and 13 clinical reports were included). PIPAC was found to be feasible, safe and well tolerated method.

Consistent with our findings, in a prospective registry study in patients with peritoneal metastasized colorectal, appendiceal and small bowel cancer, Gockel et al. reported that 86 % of repeatedly treated patients displayed decreased or stable ascites volumes, while only 1 patient displayed increased ascites [24].

However, all studies were retrospective and prospective studies and no RCTs were included [25]. In accordance with previous SR including other primary malignancy, we did not observe significant renal toxicity, myelosuppression and neurotoxicity typically documented after systematic chemotherapy.

In the present review, three of the studies used a dose of doxorubicin 1.5 mg/m2 and cisplatin 7.5 mg/m2. Only one was a dose escalation study for PIPAC-Doxorubicin/Cisplatin [9]. Results of this phase I trial showed that no dose limiting toxicities were found after 3 dose escalation steps suggesting that an increase in the dose of the chemotherapic drugs (2.1mg/m2 doxorubicin and 10.5mg/m2 cisplatin) could be recommended for further clinical trials. No other similar studies were found to compare results relating to maximum tolerated dose (MTD) for PIPAC in patients with ovarian cancer. Therefore, current evidence is not sufficient to define indications, contraindications and protocol for PIPAC in

Table 4
The characteristics of the included studies. Number of PIPAC. Tumor response assessment.PCI video-laparoscopy assessment. Overall survival.

First Author, year of publication	PIPAC > o = 3	Tumor response assessment	Histological response assessment	PCI video-laparoscopy assessment	Overall survival
Tempfer 2015	34/53 (64 %)	RECIST criteria + histopathological tumor regression + repeated video-laparoscopy assessment of PCI	Histological tumor regression in 33/53 (62 %) patients in the ITT population	PCI improvement on repeated video-laparoscopy in 26/34 (76 %) patients who underwent all 3 PIPACs	ITT population: cumulative overall survival rate of 50 % after one year. Mean survival time: 331 days (95 % CI 291–371 days. Mean time to progression: 144 days (95 % CI 122–168 days). PP population, cumulative overall survival of 63 % after one year. Mean survival time of 407 days (95 % CI 347–468). Mean time to progression: 174 days (95 % CI 150–199).
Somashekhar 2018	3/3 (100 %)	Histopathological tumor regression (Peritoneal Regression Grading Score) + repeated video-laparoscopy assessment of PCI	Peritoneal Regression Grading Score: 2 patients major response (grade 2), 1 minor response (grade 3)	PCI improvement on repeated video-laparoscopy in 3/3 (100 %) patients who underwent all 3 PIPACs	–
Tempfer 2014	5/18 (27 %)	Histologic tumor regression in repeat biopsies, PCI improvement, and video-laparoscopy assessment	1 complete response, 3 stable disease, 2 partial remission, 12 progressive disease	PCI improvement on repeated video-laparoscopy in 6/8 women who underwent >1 PIPAC	Cumulative survival after 400 days: 62 %. Mean survival time: 442 days.
Tempfer 2018	8/15 (53 %)	–	Histologic tumor regression in 7/11 (64 %) patients who underwent at least two PIPAC cycles: 2 strong regression (18 %), 5 weak/intermediate regression (46 %),1 no regression (9 %), 3 indeterminate (27 %)	–	–

Legend. ITT: intention-to treat population; ITT. PP: per-protocol population; PCI: Peritoneal Cancer Index.

patients with ovarian PC.

Moreover, efficacy outcomes depending on tumor response assessment varies sensibly. Even when declared if pathological, radiological or clinical, in most cases no detailed scores or specific criteria were provided for each method. Then, it should be noted that the characteristics of individual patients differed across treatment centers and individual trials. Although patients with poor general conditions have been excluded from all the included clinical trials, exclusion criteria differed in previous chemotherapy treatment, involvement of lymph node metastasis, other specific markers such as liver function tests and creatinine clearance. For these reasons, due to substantial heterogeneity and lack of data, no meta-analysis was performed.

Furthermore, in our SR, data to support a relationship between survival and PIPAC were limited and the authors reported the mean actuarial survival time for all patients who underwent PIPAC. Although some Authors encourage trialists to consider reporting the mean survival in cases in which a small proportion of patients are expected to achieve long-term survival, this measure cannot always adequately describe survival outcomes, especially in the presence of potential outliers or uneven distribution of survival data. In future trials, we encourage authors to add median as a supplementary measure to the trial outcomes.

As a prospect of future application in OC, since PIPAC appears feasible and not detrimental to the patients' quality of life, it can be considered as new method to administer also experimental drugs. New evidence on the therapeutic efficacy will be available with the publication of the PARROT trial whose primary objective is to determine the Clinical Benefit Rate (CBR) according to RECIST/GCOG criteria after three cycles of PIPAC with PIPAC cisplatin and doxorubicin. However, further phase I studies are needed to assess the safety profile of other drugs other than cisplatin and doxorubicin in the treatment for peritoneal carcinomatosis. Furthermore, further studies evaluating the role of PIPAC are needed to assess the proportion of tumor response and the dose-limiting toxicity also in association with systematic chemotherapy.

This also encourages prospective trials assessing oncological efficacy on platinum-sensitive patients during the era of PARP-Inhibitors.

5. Conclusion

The role of PIPAC of cisplatin and doxorubicin for patients with peritoneal carcinomatosis has evolved rapidly over the last decade, with an encouraging trend toward improvement in OS and lower toxicity rates. However, data are still insufficient to draw meaningful conclusions about survival outcomes and further studies are needed to assess the role of PIPAC not only as a palliative treatment, but also as a valid therapeutic option among patients with ovarian cancer.

Disclosure of interests

The authors report no conflict of interest.

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CRediT authorship contribution statement

Cristina Taliento: Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation. **Stefano Restaino:** Quality control of data and algorithms. **Gennaro Scutiero:** Writing – review & editing. **Martina Arcieri:** Data acquisition, Writing – review & editing. **Giulia Bernardi:** Manuscript preparation. **Ruby Martinello:** Writing – review & editing. **Lorenza Driul:** Statistical analysis. **Anna Myriam Perrone:** Data analysis and interpretation. **Anna Fagotti:** Manuscript review. **Giovanni Scambia:** Manuscript review. **Pantaleo Greco:** Manuscript review. **Giuseppe Vizzielli:** Study concepts, Study design, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation.

Table 5
CTCAE grade events.

First Author, year of publication	OC patients	CTCAE grade 1-2	CTCAE grade 3	CTCAE grade 4	Intraoperative complications/allergic reactions
Tempfer 2015	53	Abdominal pain (n = 53) Cardiac (n = 6) Neurological (n = 1) Renal (n = 1) Inflammatorya (n = 10)	trocar hernia (n = 2), bowel obstruction (n = 2), abdominal pain (n = 2), hematoma (n = 1), intraoperative bleeding (n = 1), cystitis with urosepsis (n = 1).	0	0
Somashekhar 2018	3	0	Abdominal pain (n = 1)	0	0
Tempfer 2014	18	Abdominal pain (n = 11) Nausea (n = 1)		Small bowel perforation (related or potentially related to PIPAC). (n = 2)	0
Tempfer 2018	15	Abdominal pain (n = 11) Vomiting (n = 4) Dyspnea (n = 1) Fatigue (n = 19) Appetite loss (n = 6) Nausea (n = 10) Sleep disorder(n = 8) Abdominal bulge (n = 1) Shivering (n = 1) Infection (n = 2) Obstipation (n = 2) Fever (n = 2) Night sweating (n = 2) Diarrhea (n = 5) Dizziness (n = 2) Visual problems (n = 1) Foot numbness (n = 1)	Colon perforation (n = 1)	-was observed	0

Declaration of competing interest

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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