Review Article on New Technologies

Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC-OX) in patients with colorectal peritoneal metastases—a systematic review

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Abstract: Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC-OX) is increasingly used as a palliative treatment option for patients with colorectal peritoneal metastases (CPM). The present study aimed to systematically review all clinical studies reporting safety and efficacy outcomes of PIPAC-OX in patients with CPM. PubMed, EMBASE, The Cochrane Library, and CINAHL were systematically searched to identify all clinical studies that included at least one patient with CPM treated with PIPAC-OX and reported one of the following outcomes: adverse events, tumor response, quality of life, secondary cytoreductive surgery, progression-free survival, overall survival, and environmental safety of PIPAC-OX. Results were narratively described. Of 28 included studies, only 14 non-comparative studies separately reported at least one outcome of PIPAC-OX for CPM, of which only two studies specifically focused on this group. These 14 studies reported adverse events (5 studies), tumor response (5 studies), secondary cytoreductive surgery (4 studies), progression-free survival (1 study), overall survival (5 studies), and environmental safety (2 studies). Except for 5 studies (describing 26 patients), none of the included studies stratified their results for PIPAC-OX monotherapy and PIPAC-OX with concomitant systemic therapy, and none of the studies reporting survival outcomes stratified results for line of palliative treatment, complicating interpretation. No PIPAC-OX related deaths were reported. No occupational platinum was detected during PIPAC-OX. The available evidence regarding PIPAC-OX for CPM is limited and difficult to interpret. Despite these limitations, PIPAC-OX appears safe in patients with CPM and safe for operating personnel. To increase insight in the role of PIPAC-OX in this setting, investigators of ongoing and future studies are encouraged to report separate outcomes of PIPAC-OX for CPM, to stratify their results for PIPAC-OX monotherapy and PIPAC-OX with concomitant systemic therapy, and to stratify survival results for line of palliative treatment.

Keywords: Pressurized intraperitoneal aerosol chemotherapy (PIPAC); colorectal cancer; peritoneal metastases; oxaliplatin

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Introduction

Peritoneal metastases are common in colorectal cancer patients (1). Most patients are treated with palliative systemic therapy, since they do not qualify for curative intent treatment with cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) (2). However, patients with colorectal peritoneal metastases (CPM) gain less survival-benefit from systemic therapy than patients with colorectal liver or lung metastases, possibly related to a phenomenon called the "peritoneum-plasma barrier", which results in lower chemotherapeutic concentrations in peritoneal metastases (3-5).

Intraperitoneal therapies have been developed to overcome this phenomenon. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is one of those new therapies. PIPAC is a laparoscopic method for repetitive delivery of low-dose intraperitoneal chemotherapy as a pressurized aerosol, claiming enhanced tumor penetration, homogeneous intraperitoneal drug distribution, and limited local and systemic toxicity (6-9). Due to these promising initial results, PIPAC is currently increasingly implemented in multiple centers worldwide (10,11). In these centers, patients with CPM are treated with PIPAC with oxaliplatin (PIPAC-OX) in an empirically chosen dosage of 92 mg/m^2 every 6–8 weeks with or without concomitant palliative systemic therapy.

To evaluate the available evidence regarding PIPAC-OX in patients with CPM, this study aims to systematically review all clinical studies that reported adverse events, tumor response, quality of life, progression-free (PFS) and overall (OS) survival, secondary cytoreductive surgery, and occupational safety in this subgroup. We present the following article in accordance with the PRISMA checklist (available at http://dx.doi.org/10.21037/jgo-20-257).

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (12). Two researchers (KPR and RJL) independently performed the literature search, study selection, data collection, and data synthesis. In case of disagreement, a third investigator (IHJH) made the final decision.

Eligibility criteria

Original research papers were eligible if they included at least one patient with non-appendiceal CPM treated with PIPAC-OX and investigated at least one of the following outcomes: adverse events, radiological response, histopathological response, cytological response, macroscopic response, biochemical response, quality of life, PFS, OS, possibility for secondary cytoreductive surgery, or environmental safety. Studies that performed *in vitro* or in animal research were not considered eligible. Studies were not excluded based on language or publication date or publication status.

Search

On 1 July 2020, PubMed, EMBASE, CINAHL, and the Cochrane Library were systematically searched with the following search ("PIPAC" or "Pressurized Intraperitoneal Aerosol Chemotherapy"). No additional terms were added to the search to increase its sensitivity. The references of all eligible manuscripts were searched for additional eligible studies.

Data collection and synthesis

A standardized form was used for data collection and contained the following items: publication year, enrolment years, study setting, the total number of patients, the total number of patients with CPM treated with PIPAC-OX, the number of patients with CPM treated with PIPAC-OX who received previous palliative therapy, the total number of PIPAC-OX in patients with CPM, the number of patients with CPM treated with PIPAC-OX with concomitant systemic therapy, reported outcomes, outcome assessment, and whether outcomes were separately reported for patients with CPM receiving PIPAC-OX.

Further data extraction and synthesis was performed for all studies that separately reported at least one outcome in ≥1 patient with CPM treated with PIPAC-OX. The following items were extracted from these studies for each outcome: the total number of patients with CPM treated with PIPAC-OX, the total number of patients with CPM treated with PIPAC-OX that were evaluable for outcome assessment, and the total number of PIPAC-OX that these patients received.

The results of included studies were narratively described and grouped according to reported outcomes. No meta-analyses were performed due to the high degree of clinical heterogeneity.

Results

The study flowchart is shown in *Figure 1*. This review included 28 studies [14 studies proceeded to data synthesis (13-26), 14 studies excluded from data synthesis (27-40)]. An overview of the study characteristics, the CPM population within each study, the reported outcomes, outcome assessment, and whether the reported outcomes were stratified for patients with CPM, is shown in *Table 1*.

All included studies were retrospective observational studies or prospective cohort studies and were all published between 2015 and 2020. All studies included patients with unresectable peritoneal metastases. Among the included studies, the degree of clinical heterogeneity was very high - most studies included patients with peritoneal metastases from any primary tumor who were treated with PIPAC with various drugs, either as monotherapy or with concomitant systemic therapy, and either as first line or as later line of palliative treatment.

Out of 28 included studies, only 14 studies separately reported at least one outcome for ≥1 patient with CPM treated with PIPAC-OX. Further data extraction and synthesis was performed in these 14 studies. In these 14 studies, the number of patients with CPM treated with PIPAC-OX ranged from 1 to 66 patients (median 13).

Adverse events

Adverse events were reported in 24 original manuscripts (13-22,27,28,31-39). Only five studies provided separate results for patients with CPM treated with PIPAC-OX (13-17), of which one study (17) did not provide the exact numbers of adverse events and was therefore not included in the data synthesis (*Table 2*).

Three manuscripts reported adverse events [Common Terminology Criteria for Adverse Events (CTCAE), v.4] from in total 21 patients with CPM who received 48 PIPAC-OX (14-16). Four patients experienced CTCAE grade 3 abdominal pain (19%), and no CTCAE grade 4 or 5 events occurred in these three studies. The following CTCAE grade 1–2 events were reported: pain (n=7, 33%), nausea/vomiting (n=7, 33%), infection (n=1, 5%), diarrhea (n=1, 5%), fever (n=4, 19%), liver/renal toxicity (n=6, 29%). However, adverse events were not separately reported for patients treated with PIPAC-OX monotherapy and patients treated with PIPAC-OX with concomitant systemic therapy.

Also, one report provided a sub-analysis of their cohort, focusing on the occurrence of severe hypersensitivity reactions after repeated PIPAC-OX (13). Two CTCAE grade 4 severe hypersensitivity reactions occurred in 2/71 (3%) PIPAC-OX, which occurred during the second and third procedure. Both patients had received an oxaliplatin-containing regimen as part of previous palliative systemic therapy. Also, both patients received PIPAC-OX with concomitant systemic therapy, although not an oxaliplatin-based regimen.

Radiological response

Two original manuscripts reported radiological response (18,20). Only one provided separate results for 15 patients with CPM, who in total received 45 PIPAC-OX (*Table 3*). All but one patient received two or more procedures, and a response evaluation was performed in these 14 patients by computed tomography (CT), although the definitions for CT assessment (e.g., Response Evaluation Criteria in Solid Tumors) were not provided. The study reported 5 (36%) patients with progressive disease, 5 (36%) patients with stable disease, and four patients (28%) showed regression of disease. Twelve out of 14 (86%) patients received PIPAC-OX with concomitant systemic therapy. The two patients that received PIPAC-OX monotherapy both had progressive disease on CT.

Histopathological response

Although histopathological response was reported in twelve studies (15-21,27-31), only five provided separate results for patients with CPM treated with PIPAC-OX (*Table 4*).

Four studies used the peritoneal regression grading scale (PRGS) to evaluate subsequent biopsies in 33/45 patients with CPM (16-19). Regressive disease was found in 19 (58%) patients, stable disease in 10 (30%) patients and progressive disease in 4 (12%) patients. In three studies, 4 of 18 patients received PIPAC-OX monotherapy. In these four patients, regressive, stable, and progressive disease was found in one, two, and one patient, respectively. In the fourth study, it was unclear whether these 15 patients received PIPAC-OX monotherapy or PIPAC-OX with concomitant systemic therapy (17).

Finally, one study used the tumor response grading

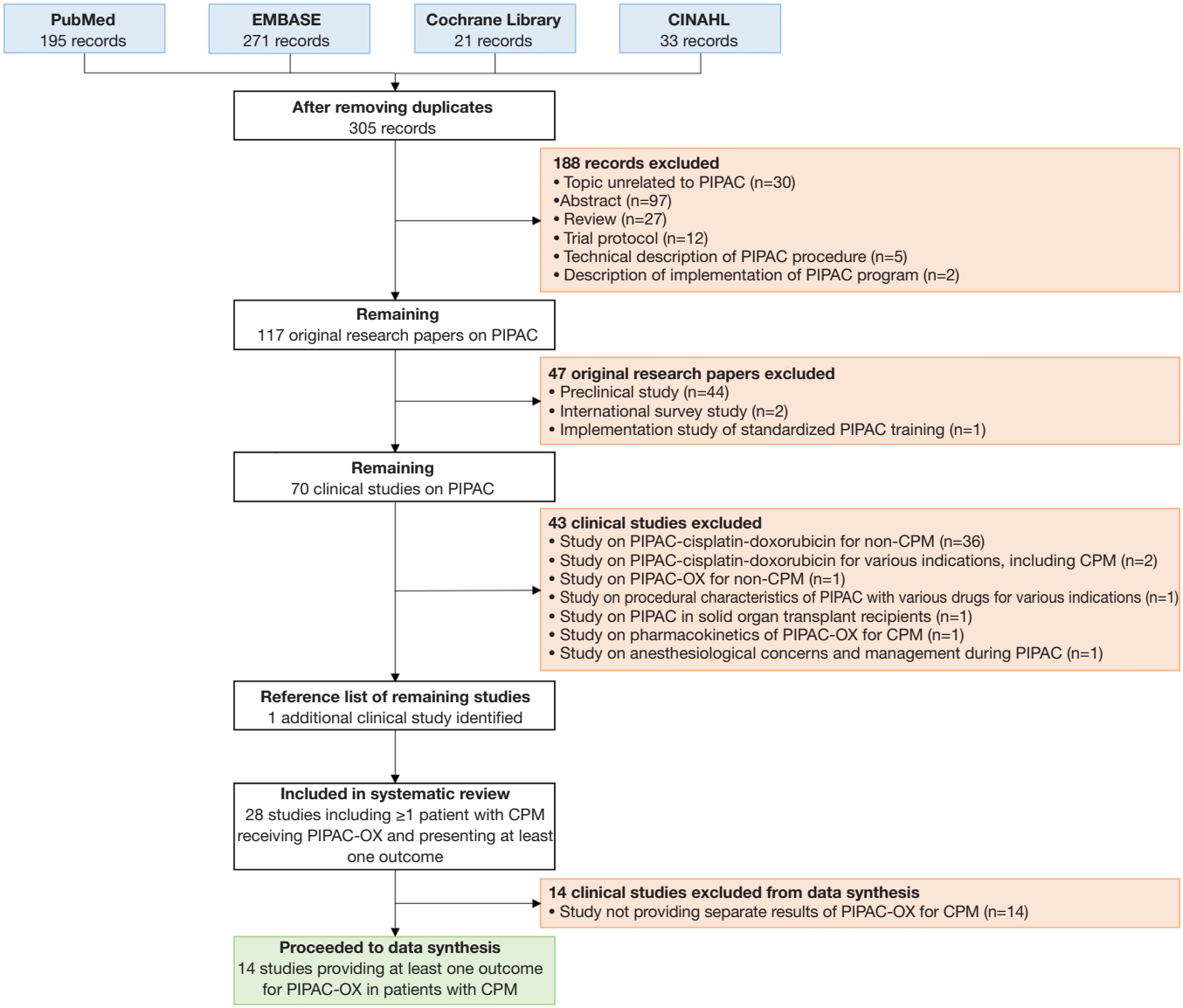

Figure 1 Literature search and study selection. CPM, Colorectal peritoneal metastases; PIPAC, pressurized intraperitoneal aerosol chemotherapy. Details of the literature search and study selection are presented in the Appendix.

system (15) (*Table 5*); 14 out of 17 patients with CPM were evaluable, and complete, major, partial, and no response was found in 7 (50%), 4 (29%), 1 (7%), and 2 (14%) patients, respectively. However, results were not separately reported for patients receiving PIPAC-OX monotherapy and patients receiving PIPAC-OX with concomitant systemic therapy.

Cytological response

Five studies reported on cytological response in ascites or peritoneal lavage, of which three studies did not provide separate results for patients with CPM treated with PIPAC-OX (*Table 6*) (17,19,28-30). The remaining two studies treated 27 patients with CPM with a total of 84 PIPAC-OX procedures (17,19). Eighteen patients were evaluable for cytological response, which showed that 6 (33%) patients converted from positive to negative cytology, cytology remained stable in 10 (56%) patients, and 2 (11%) patients converted from negative to positive cytology. However, one study did not separately report whether these patients were

Table 1 Study characteristics

First author [publication year]	Study design			CPM patients							Outcomes		Stratified for CPM
	Enrolment years	Setting	Total patients (n)	Patients		Previous palliative systemic therapy		Total PIPAC-OX (n)	Concomitant systemic therapy		Reported outcomes	Outcome assessment	
				N	%	N	%		N	%			
Siebert [2019] (13)	2015–2017	Single center	4	2	50	2	100	5	2	100	Adverse events	CTCAE v.4	Yes
Katdare [2019] (14)	2017	Single center	16	3	19	2	67	3	0	0	Adverse events	CTCAE v.4	Yes
Demtröder [2016] (15)	2012–2014	Single center	17	17	100	16	94	42	11	65	Adverse events	CTCAE v.4	Yes
											Histopathological response	TRGS	Yes
											Overall survival	From first PIPAC-OX	Yes
											CRS	N (%)	Yes
Somashekar [2019] (16)	2017	Single center	7	1	14	1	100	3	0	0	Adverse events	CTCAE	Yes
											Histopathological response	PRGS	Yes
Ellebæk [2020] (17)	2015–2019	Multi center	24	24	100	22	92	75	3	13	Adverse events	Clavien-Dindo, CTCAE v.4	Yes
											Histopathological response	PRGS	Yes
											Cytological response	Ascites	Yes
											Macroscopic response	Ascites volume	Yes
											OS	(I) From diagnosis PM	Yes
												(II) From first PIPAC-OX	Yes
											CRS	N (%)	Yes

Table 1 (*continued*)

Table 1 (*continued*)

First author [publication year]	Study design			CPM patients							Outcomes		Stratified for CPM
	Enrolment years	Setting	Total patients (n)	Patients		Previous palliative systemic therapy		Total PIPAC-OX (n)	Concomitant systemic therapy		Reported outcomes	Outcome assessment	
				N	%	N	%		N	%			
Willaert [2019] (18)	2015–2018	Single center	48	15	31	ns	–	45	12 (a)	86 (a)	Adverse events	CTCAE v.5	No
											Radiological response	Unclear	Yes
											Histopathological response	PRGS	Yes
											Macroscopic response	Ascites volume	Yes
											Biochemical response	Unclear	Yes
Graversen [2020] (19)	2018–2019	Single center	33	5	15	ns	–	9 (b)	2 (b)	67 (b)	Adverse events	Clavien-Dindo	No
											Histopathological response	PRGS	Yes
											Cytological response	Ascites	Yes
De Simone [2020] (20)	2015–2017	Single center	63	23	37	23	100	ns	ns	–	Adverse events	CTCAE v.4	No
											Radiological response	RECIST	No
											Histopathological response	PRGS	No
											Biochemical response	CEA	No
											PFS	Unclear from when	Yes
											OS	Unclear from when	Yes
											QoL	SF-36	No

Table 1 (*continued*)

Table 1 (*continued*)

First author [publication year]	Study design			CPM patients							Outcomes		Stratified for CPM
	Enrolment years	Setting	Total patients (n)	Patients		Previous palliative systemic therapy		Total PIPAC-OX (n)	Concomitant systemic therapy		Reported outcomes	Outcome assessment	
				N	%	N	%		N	%			
Kurtz [2018] (21)	2016–2017	Single center	71	17	24	ns	–	ns	ns	–	Adverse events	Clavien-Dindo, CTCAE v.4	No
											Histopathological response	PRGS	No
											Macroscopic response	Ascites volume	No
											OS	From first PIPAC-OX	Yes
Kuchen [2018] (27)	2014–2018	Single center	35	6	17	6	100	ns	ns	–	Adverse events	Clavien-Dindo	No
											Macroscopic response	Ascites volume, PCI	No
											OS	Unclear from when	No
Graversen [2018] (28)	2015–2016	Single center	35	12	34	ns	–	ns	ns	–	Adverse events	CTCAE v.4	No
											Histopathological response	PRGS	No
											Cytological response	Ascites	No
											Quality of life	EORTC QLQ C30	No
Benzerdjeb [2020] (29)	2016–2019	Single center	112	15	13	ns	–	ns	15	100	Histopathological response	PRGS	No
											Cytological response	Ascites	No
											PFS	Unclear from when	No
											OS	Unclear from when	No

Table 1 (*continued*)

Table 1 (*continued*)

First author [publication year]	Study design			CPM patients							Outcomes		Stratified for CPM
	Enrolment years	Setting	Total patients (n)	Patients		Previous palliative systemic therapy		Total PIPAC-OX (n)	Concomitant systemic therapy		Reported outcomes	Outcome assessment	
				N	%	N	%		N	%			
Graversen [2019] (30)	2015–2016	Single center	35	13	37	ns	–	ns	ns	–	Cytological response	Ascites	No
Ceribelli [2020] (31)	2016–2019	Single center	43	6	14	6	100	ns	ns	–	Adverse events	CTCAE/ Clavien-Dindo	No
											Histopathological response	PRGS	No
											CRS	n (%)	No
Sgarbura [2019] (22)	2015–2017	Multi center	101	66	66	ns	–	ns	ns	–	Adverse events	CTCAE v.4	No
											OS	(I) From diagnosis primary tumor	No
												(II) From diagnosis PM	No
												(III) From first PIPAC-OX	Yes
Teixeira Farinha [2018] (32	2015–2016	Single center	42	15	36	ns	–	ns	ns	–	Adverse events	Toxicity	No
Odendahl [2015] (33)	2012–2014	Single center	91	14	15	ns	–	ns	ns	–	Adverse events	CTCAE	No
											Quality of life	EORTC QLQ C30	No
											Overall survival	From first PIPAC-OX	No
Vaira [2016] (34)	2015	Single center	17	4	24	ns	–	ns	ns	–	Adverse events	CTCAE v.4	No
Robella [2016] (35)	2015–2016	Single center	14	2	14	2	100	6	2	100	Adverse events	Toxicity, CTCAE v.2	No
											Quality of life	SF-36, EORTC QLQ C30	No

Table 1 (*continued*)

Table 1 (*continued*)

First author [publication year]	Study design			CPM patients							Outcomes		Stratified for CPM
	Enrolment years	Setting	Total patients (n)	Patients		Previous palliative systemic therapy		Total PIPAC-OX (n)	Concomitant systemic therapy		Reported outcomes	Outcome assessment	
				N	%	N	%		N	%			
Alyami [2017] (36)	2015–2016	Multi center	73	20	27	ns	–	ns	ns	–	Adverse events	CTCAE v.4	No
											Macroscopic response	PCI	No
											CRS	N (%)	No
Hübner [2017] (37)	2015–2016	Single center	42	15	36	ns	–	ns	ns	–	Adverse events	Clavien-Dindo	No
Graversen [2018] (38)	2016–2018	Single center	41	8	20	ns	–	ns	ns	–	Adverse events	CTCAE v.4	No
Siebert [2019] (39)	2015–2018	Single center	134	26	19	ns	–	ns	26	100	Adverse events	CTCAE v.4	No
Teixeira Farinha [2017] (40)	2015–2016	Single center	42	15	36	ns	–	ns	ns	–	Quality of life	EORTC QLQ C30	No
Graversen [2016] (23)	2015	Single center	2	1	50	ns	–	1	ns	–	Environmental safety	Platinum concentrations	– (c)
Willaert [2017] (24)	2015	Single center	2	1	50	ns	–	1	ns	–	Environmental safety	Platinum concentrations	– (c)
Alyami [2019] (25)	2015–2018	Single center	146	31	21	ns	–	ns	ns	–	CRS	N (%)	Yes
Girshally [2016] (26)	2010–2016	Single center	21	11	52	ns	–	ns	ns	–	CRS	N (%)	Yes

(a) Reported only for patients that received ≥2 PIPAC; (b) reported only for patients that received ≥3 PIPAC; (c) irrelevant for platinum concentration measurement. CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRS, cytoreductive surgery; CTCAE, Common Terminology Criteria for Adverse Events; ns, not shown; OS, overall survival; PCI, Peritoneal Carcinomatosis Index; PFS, progression-free survival; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PRGS, Peritoneal Regression Grading Scale; RECIST, Response Evaluation Criteria in Solid Tumors; TRGS, Tumor Response Grading System.

Table 2 Adverse events

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	CTCAE			
				1–2	3	4	5
Siebert [2019] (13)	2	2	5	ns	ns	2	ns
Katdare [2019] (14)	3	3	3	1	0	0	0
Demtröder [2016] (15)	17	17	42	25	4	0	0
Somashekhar [2019] (16)	1	1	3	0	0	0	0

CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin; CTCAE, Common Terminology Criteria for Adverse Events; ns, not shown.

Table 3 Radiologic response

Study	CRC patients	Evaluated patients	Total PIPAC-OX	Response assessment		
				Progressive	Stable	Regressive
Willaert [2019] (18)	15	14	45	5	5	4

CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin.

Table 4 Histopathological response—Peritoneal Regression Grading Score

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	Response assessment		
				Progressive	Stable	Regressive
Somashekhar [2019] (16)	1	1	3	0	1	0
Ellebæk [2020] (17)	24	15	75	1	5	9
Willaert [2019] (18)	15	14	45	2	3	9
Graversen [2020] (19)	5	3	9 (a)	1	1	1

(a) Reported for the 3 evaluated patients. CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin.

Table 5 Histopathological response—Tumor Response Grading Scale

Study	CRC patients	Evaluated patients	Total PIPAC-OX	Response assessment			
				None	Partial	Major	Complete
Demtröder [2016] (15)	17	14	42	2	1	4	7

CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin.

Table 6 Cytological response

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	Response assessment		
				Progressive	Stable	Regressive
Ellebæk [2020] (17)	24	15	75	2	8	5
Graversen [2020] (19)	3	3	9	0	2	1

CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin.

Table 7 Macroscopic response

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	Response assessment		
				Progressive	Stable	Regressive
Ellebæk [2020] (17)	24	7	75	ns	ns	3
Willaert [2019] (18)	15	7	45	3	0	4

CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin; ns, not shown.

Table 8 Biochemical response

Study	CRC patients	Evaluated patients	Total PIPAC-OX	Response assessment		
				Progressive	Stable	Regressive
Willaert [2019] (18)	15	14	45	2	2	6

CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin.

treated with PIPAC-OX monotherapy or PIPAC-OX with concomitant systemic therapy.

The other study reported that 2 of 3 patients were treated with PIPAC-OX with concomitant systemic therapy. However, the patient treated with PIPAC-OX monotherapy converted from positive to negative cytology, whereas the cytology of two patients treated with PIPAC-OX with concomitant systemic therapy remained stable in one patient and converted from negative to positive cytology in the other patient.

Macroscopic response

Macroscopic response was reported in five studies, but only two studies reported separate results for patients with CPM treated with PIPAC-OX (*Table 7*) (17,18,21,27,36). The first study reported a decrease of ascites volume in 3 out of 7 (43%) patients, but did not report on the other four patients (17). However, macroscopic response was not separately reported for patients receiving PIPAC-OX monotherapy and patients receiving PIPAC-OX with concomitant systemic therapy. The second study evaluated ascites volume in seven patients who had all been treated with PIPAC-OX with concomitant systemic therapy, and found a decrease in ascites volume in 4 (57%) patients but an increase in 3 (43%) patients (18).

Biochemical response

The biochemical response during treatment with PIPAC-OX was reported in two studies (18,20), but was only separately reported for patients with CPM in one study (*Table 8*) (18). Fourteen of 15 patients with CPM received at least two PIPAC-OX and underwent response evaluation. Tumor markers were not determined in four patients. In the other ten patients, tumor markers increased in 2 (20%) patients, decreased in 6 (60%) patients, and remained stable in 2 (20%) patients. Out of two evaluable patients that did not receive PIPAC-OX with concomitant systemic therapy, tumor markers were not available in one patient and increased in the other patient. However, it was not mentioned how biochemical response and progression were defined and which tumor marker was used.

Quality of life

Although five studies reported quality of life results, none provided separate results for patients with CPM treated with PIPAC-OX (20,28,33,35,40).

PFS

PFS was reported in two studies (20,29), but only one reported separate outcomes for patients with CPM treated with PIPAC-OX (*Table 9*, A) (20). They reported a median PFS of 3 months in 16 patients with CPM that all received two or more PIPAC-OX. It was not reported from which time-point PFS was calculated. However, PFS was not separately reported for patients receiving PIPAC-OX monotherapy and patients receiving PIPAC-OX with

Table 9 Progression-free and overall survival

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	Median (months)	1 year	Calculated from	Follow-up (months)
A. Progression-free survival							
De Simone [2020] (20)	23	16 (b)	32 (b)	3	ns	ns	ns
B. Overall survival							
Demtröder [2016] (15)	17	17	42	15	65% (c)	First PIPAC	22±4 (d)
Ellebæk [2020] (17)	24	24	75	21	60% (c)	First PIPAC	29 [?–?] (e)
De Simone [2020] (20)	23	16 (b)	32 (b)	27	ns	ns	ns
Kurtz [2018] (21)	17	17	ns	Not reached	60% (c)	First PIPAC	10±4 (d)
Sgarbura [2019] (22)	66	66	ns	Not reached	67% (c)	First PIPAC	5 [5–11] (e)

(b) Reported in patients that underwent at least 2 PIPAC; (c) as estimated from Kaplan-Meier survival curve; (d) mean ± standard deviation; (e) median [interquartile range]. CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin; ns, not shown.

Table 10 Eligibility for secondary cytoreductive surgery

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	CRS performed
Demtröder [2016] (15)	17	17	42	2
Ellebæk [2020] (17)	24	24	75	0
Alyami [2019] (25)	31	31	ns	0
Girshally [2016] (26)	ns	ns	ns	6

CRS, cytoreductive surgery; CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin; ns, not shown.

concomitant systemic therapy.

OS

OS was reported in eight studies (15,17,20-22,27,29,33), and separately for patients with CPM treated with PIPAC-OX in five studies (*Table 9*, B). All five studies reported a median OS, which ranged from 15 to 27 months. OS was calculated from the first PIPAC-OX in four studies but the baseline time-point was not specified in one study. A median OS was not reached in two studies due to short follow-up. Four studies also showed Kaplan-Meier figures, of which a 1-year survival could be estimated, ranging from 60% to 67%. However, none of these five studies separately reported survival outcomes for patients receiving PIPAC-OX monotherapy and PIPAC-OX with concomitant systemic therapy.

Eligibility for cytoreductive surgery

Six studies provided results of a subgroup of patients that were able to undergo cytoreductive surgery after treatment with PIPAC (15,17,25,26,31,36), but two did not provide separate results for patients with CPM treated with PIPAC-OX (*Table 10*).

Two studies reported that no secondary cytoreductive surgery could be performed after repetitive PIPAC-OX in 54 patients with CPM (17,25). In one study, 3 of 24 patients were treated with PIPAC-OX with concomitant systemic therapy, but the number of patients treated with PIPAC-OX monotherapy and PIPAC-OX with concomitant systemic therapy was not reported in the second study.

The third study performed secondary cytoreductive surgery in 2/17 (12%) patients with CPM after treatment with PIPAC-OX (15). However, it was not described whether these patients had received PIPAC-OX

monotherapy or PIPAC-OX with concomitant systemic therapy.

The fourth study reported that six patients with CPM received secondary cytoreductive surgery after repetitive treatment with PIPAC-OX (26). However, the total amount of patients with CPM treated with PIPAC-OX was not reported, thus it was not possible to extract a proportion of patients undergoing secondary cytoreductive surgery.

Environmental safety

Two studies investigated occupational exposure to oxaliplatin during PIPAC-OX for CPM (23,24). Several samples were taken during two PIPAC-OX procedures. All samples showed undetectable concentrations of oxaliplatin in the air, surface wipes, or in surgeon's blood.

Discussion

This is the first systematic review providing an overview of the available evidence for the use of PIPAC-OX in patients with unresectable CPM. We found 28 clinical studies that included at least one patient with CPM treated with PIPAC-OX. Of these, 26 studies included patients receiving PIPAC with various drugs for various tumors, and only two solely focused on patients with CPM treated with PIPAC-OX. Of all 28 included studies, 14 studies provided at least one separate outcome for patients with CPM treated with PIPAC-OX. Limitations of these 14 studies were small colorectal cancer sample sizes, heterogeneous treatment regimens (PIPAC-OX monotherapy versus PIPAC-OX with concomitant systemic therapy) and heterogeneous outcome reporting (not stratifying for treatment regimen). Moreover, the majority of these studies reporting on survival did not stratify their results for patients receiving PIPAC-OX as first-line versus later-line treatment, and some studies reporting tumor response did not provide definitions of response and progression. Despite these limitations, the present systematic review shows that PIPAC-OX appears safe in patients with CPM and that no environmental exposure of oxaliplatin was detected during PIPAC-OX.

Five other studies have performed a systematic review of clinical studies on PIPAC for the treatment of peritoneal metastases (10,41-44). However, none of these systematic reviews specifically focused on PIPAC-OX in patients with CPM alone and reported on the interpretability of the results of included studies. Although these systematic reviews suggest that PIPAC is generally well tolerated, the present systematic review showed that the quality of life of patients with CPM treated with PIPAC-OX has never been reported. It is also generally assumed that PIPAC-OX is associated with low rates of systemic toxicity, whereas the present systematic review showed that the reporting of adverse events was not stratified for PIPAC-OX monotherapy and for PIPAC-OX with concomitant systemic therapy, which impedes the interpretation of these results. The lack of stratification for PIPAC-OX monotherapy and PIPAC-OX with concomitant systemic therapy also impedes the interpretation of other outcomes, such as tumor response, secondary curative intent surgery, and survival. Moreover, survival results were not stratified for line of palliative treatment, impeding comparison with survival results of trials on systemic therapy. Altogether, based on the available evidence consisting of non-comparative studies only, the (additional) benefit of PIPAC-OX for patients with CPM remains uncertain. Nevertheless, PIPAC-OX for colorectal cancer is currently increasingly practiced in multiple centers worldwide.

Thus, results from prospective cohorts or randomized controlled trials that provide outcomes stratified for primary tumor location, administration of PIPAC-OX monotherapy or PIPAC-OX with concomitant systemic therapy, and previous palliative systemic treatment are urgently required to gain more insight into these outcomes and to determine the exact role of PIPAC-OX in patients with CPM.

To the knowledge of the authors, there are currently two ongoing phase I dose escalation studies for PIPAC-OX (45,46) and there are six ongoing phase II–III clinical studies investigating PIPAC-OX in patients with CPM (47-49) (Netherlands Trial Register, NL8303; ClinicalTrials.gov, NCT04329494; NCT03868228). Three studies solely include patients with CPM and treat patients with PIPAC-OX monotherapy (47), PIPAC-OX with concomitant first-line systemic therapy (NL8303), or either PIPAC-OX monotherapy or PIPAC-OX with concomitant systemic therapy in any line of palliative treatment (NCT03868228). The other three studies include patients receiving PIPAC with various drugs for various origins, including PIPAC-OX for CPM. One of these studies is a randomized controlled trial, randomizing patients between PIPAC monotherapy and palliative systemic therapy (48). The other two studies treat patients with PIPAC monotherapy or PIPAC with concomitant systemic therapy (49) (NCT04329494). The investigators of the latter three studies are encouraged to report separate results for patients with CPM treated with PIPAC-OX to provide insights into the value of PIPAC-OX

in this particular group.

Conclusions

Despite the increasing practice of PIPAC worldwide and the growing amount of available manuscripts on PIPAC, only very few studies focus on PIPAC-OX in patients with CPM or provide separate results for this subgroup. Therefore, the currently available evidence for the use of PIPAC-OX in patients with CPM is limited and difficult to interpret, mainly since the majority of studies did not stratify their results for PIPAC-OX monotherapy versus PIPAC-OX with concomitant systemic therapy. Investigators of future studies including patients receiving PIPAC-OX for CPM are encouraged to report separate outcomes for this particular group, to stratify their results for PIPAC-OX monotherapy versus PIPAC-OX with concomitant systemic therapy, and to stratify survival outcomes for line of palliative treatment. These results may help designing future randomized trials which are required to determine the exact role of PIPAC-OX in patients with CPM.

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Footnote

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Supplementary

Appendix A—Search

Pubmed search

((PIPAC) or (Pressurized Intraperitoneal Aerosol Chemotherapy) OR (Pressurised Intraperitoneal Aerosol Chemotherapy))

Appendix B—Details of excluded clinical studies

Study on PIPAC-cisplatin-doxorubicin for non-CPM

1. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). Ann Surg Oncol 2013;20:2311-6.
2. Solass W, Kerb R, Mürdter T, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol 2014;21:553-9.
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Study on PIPAC-cisplatin-doxorubicin for various indications, including CPM (n=2)

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2. Gockel I, Jansen-Winkeln B, Haase L, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in patients with peritoneal metastasized colorectal, appendiceal and small bowel cancer. Tumori 2020;106:70-8.

Study on PIPAC-oxaliplatin for non-CPM (n=1)

1. Graversen M, Detlefsen S, Pfeiffer P, et al. Severe

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peritoneal sclerosis after repeated pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC OX): report of two cases and literature survey. Clin Exp Metastasis 2018;35:103-8.

Study on procedural characteristics of PIPAC with various drugs for various indications (n=1)

1. Hübner M, Grass F, Teixeira-Farinha H, et a;. Pressurized intraperitoneal aerosol chemotherapy – practical aspects. Eur J Surg Oncol 2017;43:1102-9.

Study on PIPAC in solid organ transplant recipients (n=1)

1. Horvath P, Yurttas C, Struller F, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases in solid organ graft recipients: first experience. Ann Transplant 2019;24:30-5.

Study on pharmacokinetics of PIPAC-oxaliplatin for CPM (n=1)

1. Lurvink RJ, Tajzai R, Rovers KP, et al. Systemic Pharmacokinetics of Oxaliplatin After Intraperitoneal Administration by Electrostatic Pressurized Intraperitoneal Aerosol Chemotherapy (ePIPAC) in Patients with Unresectable Colorectal Peritoneal Metastases in the CRC-PIPAC Trial. Ann Surg Oncol 2020. [Epub ahead of print]. doi:10.1245/s10434-020-08743-9.

Study on anesthesiological concerns and management during PIPAC (n=1)

1. Solanki SL, Kumar PP, DeSouza A, Salkani AP. Perioperative concerns and management of pressurised intraperitoneal aerosolised chemotherapy: report of two cases. Indian J Anaesth 2018;62:225-8.

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