Cancer Treatment Reviews

Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases: A systematic review by the PIPAC UK Collaborative

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Corresponding Author:	Amy Nicola Case, MbBCh FRCR Swansea Bay University Health Board Swansea, Swansea UNITED KINGDOM
First Author:	Amy Nicola Case, MbBCh FRCR
Order of Authors:	Amy Nicola Case, MbBCh FRCR
	Susan Prosser
	Christopher J Peters
	Richard Adams
	Sarah Gwynne
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Suggested Reviewers:	Tim Underwood University of Southampton t.j.underwood@soton.ac.uk Professor in Upper GI Surgery with expertise in the field of gastric cancer.
	Nick Maynard Oxford University Hospitals NHS Trust: Oxford University Hospitals NHS Foundation Trust nick.maynard@ouh.nhs.uk Main interest is surgical management of oesophagogastric cancer, Cancer lead at OUH, Chair of Clinical Services and Audit for AUGIS and Surgical Lead for the

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	National Oesophagogastric Cancer Audit
	Tom Crosby Velindre University NHS Trust tom.crosby@wales.nhs.uk Professor and Consultant Clinical Oncologist in UGI malignancy, National Cancer Clinical Director for Wales, CI for SCOPE 2 trial for OG cancer

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Essential Title Page

Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases: A systematic review by the PIPAC UK Collaborative

A. Case [a, b,*], S. Prosser [a], C.J. Peters [c], R. Adams [d], S. Gwynne [a, b] On behalf of the PIPAC UK Collaborative

[a] South West Wales Cancer Centre, Singleton Hospital, Sketty Lane, Swansea, SA2 8QA, UK
[b] Swansea University Medical School, Grove Building, Singleton Park, SA2 8PP, UK
[c] Department of Surgery and Cancer, Imperial College London, St Marys Hospital, Praed Street, London, W2 1NY, UK
[d] Centre for Trials Research, Cardiff University and Velindre Cancer Centre, Velindre Road, Whitchurch, CF14 2TL, UK

*Corresponding author address: South West Wales Cancer Centre, Singleton Hospital, Sketty Lane, SA2 8QA. Email: amy.case@wales.nhs.uk

Second Title Page

Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases: A systematic review by the PIPAC UK Collaborative

Abstract

Introduction: Gastric cancer with peritoneal metastases (GCPM) carries a poor prognosis, with survival limited to approximately 2.4-10 months. Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) offers pharmacokinetic advantages resulting in higher concentrations of chemotherapy in peritoneal deposits, whilst reducing systemic absorption and potential toxicity. This systematic review aims to evaluate the efficacy, tolerability and impact on quality of life (QOL) of PIPAC for the treatment of GCPM.

Materials and Methods: The review was registered with PROSPERO (CRD42021281500) and conducted in accordance with PRISMA standards. MEDLINE, EMBASE and The Cochrane Library were searched for papers describing PIPAC in patients with peritoneal metastases. English language clinical studies reporting outcome data on ≥3 GCPM patients were eligible, including abstracts containing original data. The Clinical Trials.gov database was also searched.

Results: Eighteen reports were analysed, representing 751 patients with GCPM, consisting of 4 prospective, 11 retrospective studies and 3 abstracts. There were no randomised or phase III studies. Median overall survival (mOS) ranged from 8 – 19.1 months and 1-year OS between 49.8 - 77.9%. Reporting of histological response was heterogeneous, but complete response (PRGS1) was reported in 0-35%, and partial response (PRGS2/3) in 0-83.3%. Grade 3 and 4 toxicity was 0.7-25% and 0-4.1% respectively. Three studies assessed QOL, reporting no significant difference after PIPAC.

Conclusion: PIPAC may offer promising survival benefits, limited grade 3 and 4 toxicity, low mortality rates and maintain QOL for GCPM patients. However, phase 3, randomised trials are required to confirm this, and identify which patients are most likely to benefit.

Keywords

Pressurised intraperitoneal aerosolized chemotherapy, PIPAC, gastric cancer, peritoneal metastases

Introduction

Gastric cancer is the fifth most common cause of cancer globally, equating to over a million cases per year[1]. Despite recent advances in some other tumour types, gastric cancer continues to carry a poor prognosis, particularly in the metastatic setting where 1-year overall survival is approximately 20%[2].

Peritoneal dissemination is common, with approximately 10-21% of patients presenting with synchronous peritoneal disease at diagnosis, though surgical cohort studies report up to 40% have occult peritoneal metastases at staging laparascopy[3,4]. In addition, it is the commonest site of disease recurrence following radical treatment[5], and may be the only site of disease for up to 65% of patients[6].

The presence of peritoneal disease is usually considered incurable even in the absence of other visceral metastases. Without treatment median overall survival (mOS) is only of 2.4 months[6]. Current standard of care for metastatic gastric cancer is systemic chemotherapy, with the addition of targeted therapy or immunotherapy for selected patients increasing mOS up to 16 months[7,8]. However, peritoneal disease poses additional complexities to the treating oncologist. Reduced blood supply and high interstitial pressure, resulting in poor penetration of drug into the peritoneum can lead to poor response to traditional systemic anti-cancer therapies (SACT). Peritoneal carcinomatosis can also result in distressing sequelae including pain, refractory ascites and bowel obstruction. This underlies the urgent need for novel treatment strategies in this setting.

Pressurised intraperitoneal aerosolized chemotherapy (PIPAC)

Pressurised intraperitoneal aerosolized chemotherapy (PIPAC) was developed in 2011 as an innovative way to deliver chemotherapy directly into the peritoneum at high pressure[9]. Early phase studies have confirmed the pharmacokinetic advantages of PIPAC; the pressure gradient created can overcome tumour interstitial pressure, resulting in higher concentration of chemotherapy in peritoneal tumour nodules and improved distribution throughout the peritoneal cavity, whilst minimising systemic absorption and potential toxicity. [10]

Following its development in Germany, the procedure has been implemented across Europe via the establishment of stringent certification courses[11]. As such, the PIPAC technique is largely standardized across more than 60 centres[12,13]. However despite promise, it has not yet

become routine practice worldwide, and for example, is not currently NICE approved for routine use in the UK[14].

PIPAC is performed under general anesthesia during a laparoscopic procedure. Access to the abdomen is gained via 2 incisions (10-12mm and 5mm), through which 2 trocars are inserted. The abdomen is insufflated with CO_2 to achieve normothermic capnoperitoneum (37◦c, 12mmHg), after which the peritoneal cavity is explored, any ascitic fluid drained, peritoneal cancer index (PCI) score assessed and biopsies taken. A cytotoxic solution is nebulized and injected at high pressure using a procedure specific, patented device (CapnoPen®). For gastric cancer, cisplatin 7.5mg/m2 and doxorubicin 1.5mg/m2 are the most commonly used agents[13]. The therapeutic capnoperitoneum is maintained for 30 minutes, and then evacuated via a closed waste system. PIPAC can be repeated every 4-6 weeks, and can be given either alone (i.e. "unidirectional") or in a "bidirectional" manner alongside systemic chemotherapy, when it is given in alternating cycles (for example 1-2 cycles of chemotherapy alternating with PIPAC).

Phase I and II data has been encouraging regarding the safety and tolerability of PIPAC for the management of peritoneal metastases from many primary tumour sites including ovarian, colorectal and gastric cancer. In addition, studies have confirmed feasibility of delivering multiple PIPAC treatments, and suggest improvement in survival, whilst maintaining patient quality of life (QOL).[15]

The PIPAC UK Collaborative is a multi-disciplinary research group dedicated to establishing the role of PIPAC by developing future UK-based clinical trials to contribute to the international evidence base. This systematic review aims to evaluate the efficacy, tolerability and impact on QOL of PIPAC for the treatment of gastric cancer with peritoneal metastases (GCPM).

Methods

The review protocol was registered with PROSPERO (registration number CRD42021281500, registered 27/9/2021) and conducted in accordance with PRISMA standards (Preferred Reporting Items for Systematic Reviews and MetaAnalyses)[16].

Search strategy

The electronic databases MEDLINE (Ovid) and EMBASE (OVID) were searched using a combination of text terms and relevant controlled vocabulary to identify papers describing PIPAC in patients with peritoneal metastases. The search was not specific to gastric cancer in order to capture any publications with a mixed study population that provided gastric data, to fully reflect numbers of gastric cancer patients treated with PIPAC. See Supplementary Materials (Appendix A) for search strategies. A search on PIPAC and cancer was conducted in The Cochrane Library.

Duplicates were identified using EndNote and removed manually. No language or other restrictions were applied at the searching stage. Non English results were removed during the review process. The Clinical Trials.gov database was searched to identify on-going trials. An alert was set up on PubMed to provide weekly updates of new literature, which was ceased at the date of completion of the review (19/11/21). Reference lists of included papers were screened to identify additional studies. Web of Science (Clarivate) was used to conduct citation tracking of included studies.

Eligibility Criteria

All clinical studies, of any design including qualitative studies, reporting PIPAC in patients with GCPM were eligible for review. Where the study population was mixed (i.e. representing multiple primary malignancies) outcome data must have been reported specifically for the gastric cancer cohort. Abstracts reporting gastric specific outcome data that did not overlap with subsequent publication (either full text or later abstract), were included for analysis. In order to fully evaluate the current status of the published literature, systematic reviews that provided methodology were retained and evaluated separately from papers reporting raw data.

Exclusion criteria included studies that did not include a gastric cancer cohort, or did not define any gastric cancer specific outcomes separately, single case reports, papers reporting outcomes on ≤3 gastric cancer patients, narrative overviews (without systematic methodology), protocol papers (though these were retained for discussion), book chapters, letters, pre-clinical/animal/ex-vivo studies, studies not published in English, or any reports focussed on alternative methods of intra-peritoneal chemotherapy, such as Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

Selection process

All citations were uploaded to an Excel database to enable systematic recording of eligibility by two independent reviewers (AC and SG). 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.

Where multiple publications from the same research group were presented, articles were assessed for potential data overlap, and if confirmed, the most complete dataset was included. Where there was ambiguity over potential overlap, authors were contacted for clarification, but if overlap could not be confirmed, studies were included and this was highlighted in data tables. A global assessment for potential bias was made by the two reviewers, though no articles were felt to be high risk.

Data collection

Eligible publications, including any available supplementary materials, underwent detailed assessment and data extraction by the principal reviewer (AC). Data was collected in an Excel database, and any ambiguity over data extraction was discussed with a second reviewer (SG). 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. For a full list of data variables collected, see Supplementary Materials (Appendix B).

Results

The PRISMA flow diagram (figure 1) outlines the screening process. After duplicates were removed, 484 titles and accompanying abstracts underwent initial screening. Of the 117 reports that underwent full eligibility assessment, 18 were included in the final analyses, representing a total of 751 patients with GCPM. Seven systematic reviews were included for separate evaluation.

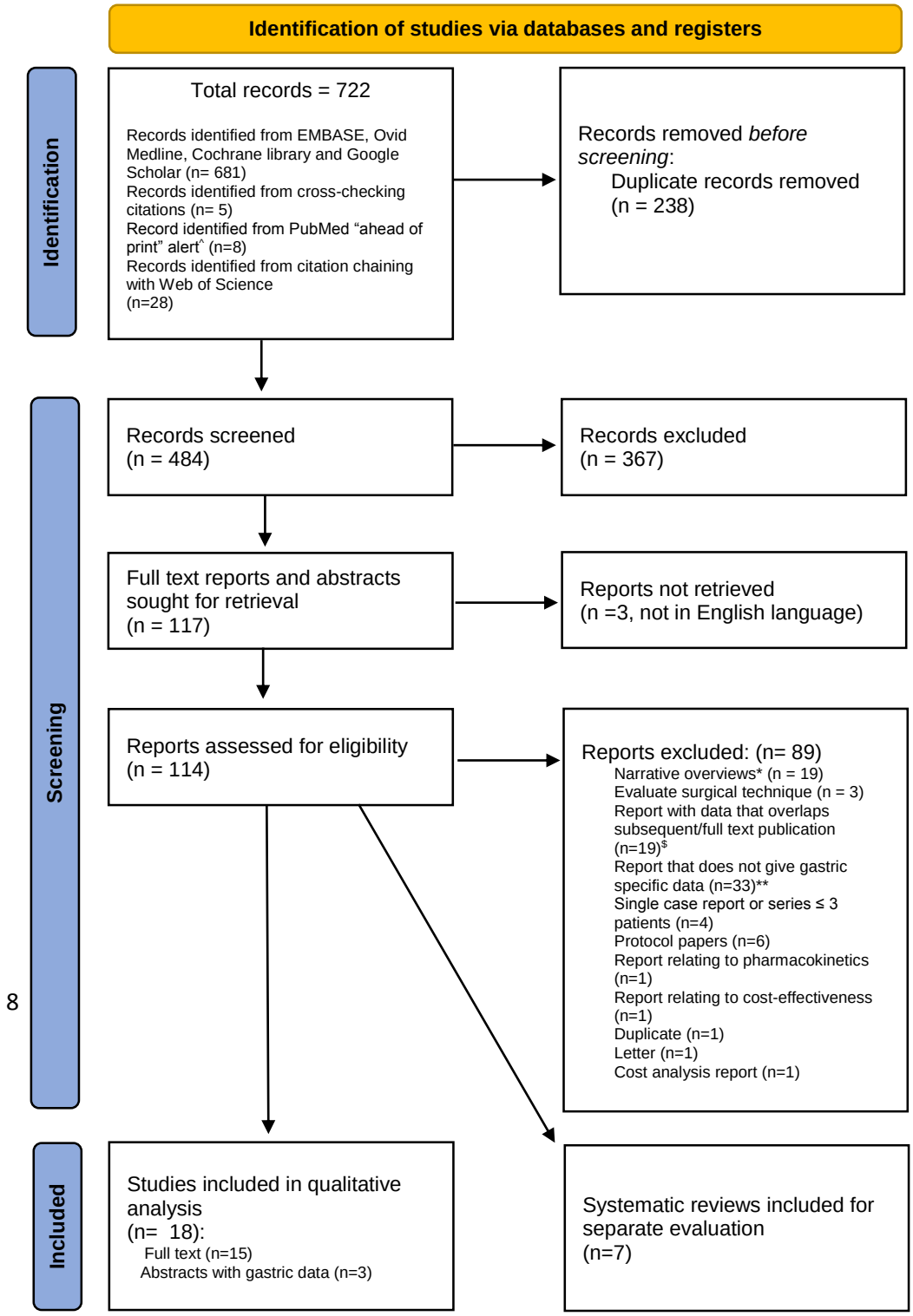


Figure 1 – PRISMA flow diagram. Publication selection process according to eligibility criteria

*Overview reports without systematic review methodology

** Publications featuring a mixed cohort of primary cancers including gastric cancer, but report pooled data rather than separate gastric specific data

$ Reports that overlap with full text paper, or subsequent abstract, confirmed by comparing research centre and dates of recruitment, or by confirmatory correspondence with report authors.

^ Weekly PubMed alert of online publications ahead of print/ PubMed indexing, set up to receive new reports between date of initial search, to 19/11/2021

Of the 18 papers included, 15 were in full text format, representing 506 GCPM patients in total. Of these, 4 were prospective, phase II, single arm, single institution studies[17-20]. Eleven were retrospective analyses of prospective databases, 10 of which were single institution[21-30] and 1 was multi-institution spanning 5 centres[31]. All were single arm, except one non-randomised, retrospective dual arm study which compared PIPAC plus SACT with SACT alone[27]. Three abstracts were included that were deemed to represent a sample of patients not included in other reports, describing a sum of 245 patients[32-34]. Reports with confirmed or potential for overlapping data are highlighted in table 1.

Studies focussed solely on a gastric cancer cohort represent 13/18 studies, and report outcomes on 680 patients in total (range 20-144). Four studies represented multiple primary malignancies but reported outcome or safety data for their gastric cohort, so were included in the analysis (n=71 patients, range 9-26).

There were no randomised trials, or phase III studies reported at the time of search. In our view, all published data represents stage 2a evidence based on the IDEAL framework of surgical development[35]. Table 1 summarises the study design, PIPAC and chemotherapy protocol of each study.

Study Design					PIPAC Protocol			Bidirectional chemotherapy		
Authors (Year)	**Study design**	**Gastric or mixed cohort**	**Time period of patient recruitment**	**No. of gastric patients ITT (total cohort if mixed)**	**Number of PIPACs performed in study**	**Chemotherapy used for PIPAC (dose mg/m^2)**	**Interval between PIPAC**	**Bidirectional with SACT? (%) ****	**Systemic Regimen**	**Timing of SACT with PIPAC**
Khomyakov et al. (2016)[19, #, a]	Prospective, open label, phase II. Single arm, single institution	Gastric only	Aug 2013- Jun 2016	31	56	Cisplatin (7.5) + Doxorubicin (1.5)	6 weeks	Yes (100%)	XELOX	4 cycles upfront, then 1 x PIPAC followed by 2 x SACT (repeat). 1 week washout between SACT and PIPAC
Struller et al. (2019)[20]	Prospective, open-label, phase II. Single arm, single institution	Gastric only	Nov 2013- Apr 2016	25	43	Cisplatin (7.5) + Doxorubicin (1.5)	6 weeks	No	N/A	N/A
Ellebæk et al (2020)[18]	Prospective, cohort study (data from PIPAC-OPC1 and PIPAC-OPC2 reported). Single arm, single institution	Gastric only	Mar 2015 - Oct 2018	20	52 (11 ePIPAC)	Cisplatin (7.5) + Doxorubicin (1.5)	4-6 weeks	Yes (n=9, 45%)	NS	NS
De Simone et al. (2020)[17]	Prospective, phase II non-randomised, open-label. Single arm, single institution	Mixed	Oct 2015 - Oct 2017	10 (63)	123*	Cisplatin (7.5) + Doxorubicin (1.5)	6-8 weeks	Yes (50%)	NS	7-10 day washout before and after PIPAC
Nadiradze et al (2016)[24, #, c]	Retrospective analysis of prospective database. Single institution	Gastric only	2011-2013	25	60	Cisplatin (7.5) + Doxorubicin (1.5)	NS	Yes (33%)	NS	NS
Gockel et al. (2018)[21]	Retrospective analysis of prospective database. Single institution	Gastric only	Dec 2015- Feb 2018	24	46	Cisplatin (7.5) + Doxorubicin (1.5)	NS	Yes (71% of those who had >1 PIPAC)	NS	NS
Kurtz et al (2018)[30, #, c]	Retrospective analysis of prospective database. Single institution	Mixed	"Since July 2016" and follow up ended Oct 2017	26 (71)	142*	Cisplatin (15) + Doxorubicin (1.5)	6 weeks (up to 3 months in selected cases)	Yes (59.1%)*	NS	Minimum delay of 2 weeks between last SACT and PIPAC (4 weeks for VEGFi). SACT could be restarted immediately after PIPAC (in practice 1 week)
Sgarbura et al. (2019)[31]	Retrospective analysis of a prospective database. Multi-institution (5 centres)	Mixed	Jan 2015- Dec 2017	15 (101)	251*	Oxaliplatin (92)	6 weeks	Yes (46.5%)*	NS	NS
Willaert et al (2019)[26]	Retrospective analysis of a prospective database. Single institution	Mixed	Sept-2015 – Apr 2018	11 (52)	135* (ePIPAC)	Cisplatin (7.5) + Doxorubicin (1.5) *or* Oxaliplatin (92) *or* Irinotecan(4.4)*	6 weeks (4 weekly if no systemic options)	Yes (72% gastric patients, 58.3% all comers)	NS	NS
Di Giorgio et al. (2020)[23]	Retrospective analysis of prospective database. Single institution	Gastric only	Sept 2017 - Sept 2019	28	46	Cisplatin (7.5) + Doxorubicin (1.5)	6-8 weeks	Yes (all)	Based on previous therapy. ECF/ FOLFOX 1st line. FOLFIRI or TAXOL 2nd /3rd line.	2 X SACT then 1 PIPAC (repeat) 2 week washout after SACT before PIPAC, and 7 days before next SACT.
Alyami et al. (2021)[22, #, b]	Retrospective analysis of prospective database. Single institution	Gastric only	Before 2018	42	163	Cisplatin (7.5) + Doxorubicin (1.5)	6-8 weeks	Yes (all)	NS	2 x SACT then 1 PIPAC (repeat) 2 week washout before and after each PIPAC
Rackauskas et al. (2021)[25]	Retrospective analysis of prospective database. Single institution	Mixed	2015-2020	9 (15)	34	Cisplatin (7.5) + Doxorubicin (1.5)	6 weeks	NS	NS	NS
Tidadini et al. (2021)[27]	Retrospective analysis of prospective database. Dual arm, non-randomised (PIPAC + SACT vs SACT alone) Single institution	Gastric only	July 2016 - Sept 2020	17 PIPAC, 29 Control	42	Cisplatin (7.5) + Doxorubicin (1.5) *or* Oxaliplatin (92)*	6-8 weeks	Yes (100% of PIPAC arm)	NS	PIPAC and SACT alternating (with PIPAC replacing a cycle of SACT)
Feldbrugge et al (2021)[28]	Retrospective analysis of prospective database Single institution	Gastric only	Mar 2017- May 2020	50	90	Cisplatin (7.5) + Doxorubicin (1.5)	NS	Yes (all)	NS	2 week interval between application of SACT and PIPAC. 2 x SACT then 1 PIPAC (repeat)
Sindayigaya et al (2021)[29, #, c]	Retrospective analysis of prospective database. Single institution	Gastric only	NS	144	296	Cisplatin (7.5) + Doxorubicin (1.5)	NS	Yes (23.8%)	NS	SACT discontinued 10-14 days before and after each PIPAC.
Bonnot et al (2020)[32, #, b] *Abstract only*	Retrospective analysis of prospective database Single institution	Gastric only	Jan 2016- Jan 2019	91	346	Cisplatin (7.5) + Doxorubicin (1.5)	NS	Yes (all)	NS	2 x SACT then 1 PIPAC (repeat)
Khomyakov, V. M., et al. (2020)[32, #, a] *Abstract only*	Not stated. Single institution	Gastric only	NS	127	310	Cisplatin (NS) + Doxorubicin (NS)	6-8 weeks	Yes (all)	XELOX or FOLFOX	4 cycles upfront, then PIPAC alternating with SACT (based on previous regimen)
Pocard et al (2020)[34] *Abstract only*	Retrospective analysis of prospective database Single institution	Gastric only	2017-2018	27	75	NS	Median 47 days	Yes	FOLFIRI	2 x SACT then 1 PIPAC (repeat)

Table 1 - Summary of each paper outlining study design and detail of PIPAC and bidirectional chemotherapy protocol in each trial.

NS = Not stated. SACT = Systemic anti-cancer therapy. XELOX q21= Oxaliplatin 130mg/M2m d1, cape 1000mg/m2 BD for d1-14, then 1 week break. *In mixed cohort studies, data with * refers to the entire reported cohort (not just the gastric patients) **Bidirectional treatment refers to IV systematic chemotherapy given in a concurrent manner, alternating with PIPAC therapy, with details of timing of systemic therapy given where stated. $Mean given (not median)

^Only abstract available in English, thus only abstract included in analysis (full text available in Russian only). [#a-c] Same trial group – possible overlap between study populations, with a-c denoting the papers where overlap may exist: [#a] - Confirmed overlap between the 2016 full text PIPAC-GA2 and 2020 abstract, but given and the latter abstract reports an additional 96 patients, both were retained and highlighted here. [#b] - Potential cross-over between Alyami et al. 2021 and an abstract from the same group in 2020 (unconfirmed by authors) [#c] - Potential for overlap between reports by Sindayigaya et al and Nadiradze et al, who acknowledge the latter paper as their first series, though it is unclear if these patients were included in their updated publication. It is uncertain whether papers by Sindayigaya et al and Kurtz et al refer to the same prospective PIPAC registry (unconfirmed by author

Patient characteristics

Patient characteristics for each study, reflecting burden of disease and prior therapy are summarised in table 2. Both synchronous and metachronous metastatic disease were included. Diffuse, or signet ring morphology was the predominant histological subtype. Median PCI ranged from 8-21.2 across studies. Extra-peritoneal metastatic disease was permitted in 8 studies, an exclusion criterion in 5, and 5 have not provided this detail. Where included, extra-peritoneal disease ranged from 8-21%, and included retroperitoneal lymphadenopathy, pleural disease, hepatic, bone, adrenal and ovarian metastases. Variation exists across studies regarding number of lines of SACT prior to PIPAC, with at least 1 prior line of treatment reported in 100% patients in 8 studies, 23- 95% in 7 studies and 8 studies reporting a proportion of patients in the ≥3rd line setting (see table 2).

Study authors (Year of publication)	Median PCI (range)	Extra-Peritoneal disease	Prior lines of systemic chemotherapy treatment received by patient cohort (%)~				
			At least 1 prior line (%)	2 lines (%)	3 lines (%)	4 lines (%)	5 lines (%)
Khomyakov et al. (2016)[19, #]	16 (6-34)	Retroperitoneal lymph nodes	23[#]	NS	NS	NS	NS
Struller et al. (2019)[20]	15.3 (±10.6)^	Isolated pleural effusions only	100	64	20	8	8
Ellebæk et al(2020)[18]	10.5 (2-39)	Not permitted	95	NS	NS	NS	NS
De Simone et al.(2020)[17,*]	NS	Not permitted	100	NS	NS	NS	NS
Nadiradze et al (2016)[24]	16 (±10.0)^	N=4 (17%) 3 pleura, 1 liver	79	36	46 *(3rd +4th line)*	NS	NS
Gockel et al. (2018)[21]	14 (2-36)	n=5 (20.8%), 3 hepatic, 1 hepatic + adrenal, 1 pleura	83.30	54.1	16	NS	NS
Kurtz et al (2018)[30, *]	19.3 (±12.5)^	Isolated pleural effusions only	84.5	23.9	14.1	21.1 *(≥4 lines)*	NS
Sgarbura et al. (2019)[31, *]	19 (10-28)	NS	92.1	NS	NS	NS	NS
Willaert et al (2019)[26, *]	21.2 (2-29)	n = 7 (13.3%) treated, stable liver/lung, n=1 (1.9%) pleural	89.6	16.7	20.8	NS	NS
Di Giorgio et al. (2020)[23]	20 (3-32)	n = 6 (21%) 2 extra-abdominal LNs, 1 liver, 1 bone, 1 ovarian, 1 pleural	100	14.2	25	NS	NS
Alyami et al .(2021)[22]	17 (1-39)	Not permitted	100	47.6	11.9	NS	NS
Rackauskas et al.(2021)[25, *]	8	NS	100	NS	NS	NS	NS
Tidadini et al. (2021)[27]	18 (12-20)	Not permitted	100	NS	NS	NS	NS
Feldbrugge et al (2021)[28]	19 (1-39)	N= 4 (8%) Krukenberg tumours only	100	NS	NS	NS	NS
Sindayigaya et al (2021)[29]	15 (1-39)	Not permitted	91	29.9	12.5	4.9 *(≥4 lines)*	NS
Bonnot et al (2020)[32]	16 (3-39)	NS	NS	NS	NS	NS	NS
Khomyakov et al. (2020)[33]	NS	NS	NS	NS	NS	NS	NS
Pocard et al(2020)[34]	NS	NS	100	NS	NS	NS	NS

Table 2 – Summarising disease burden of patient population in each study.

PCI = Peritoneal Carcinomatosis Index. #4 cycles XELOX (Oxaliplatin 130mg/m^2 d1, cape 1000mg/m^2 BD for d1-14, q21) given upfront prior to PIPAC in study (thus though only 23% pre-treated, all patients received 4 cycles of XELOX in the first line prior to PIPAC in study) NS = Not stated. LN = lymph nodes. * mixed cohort study, data presented with * reflects entire cohort, not gastric specific. ^ mean presented instead of median. ~ %, either stated directly by each report or calculated from raw data provided.

PIPAC Administration

As demonstrated in table 1, administration of PIPAC was consistent, with 15/18 studies delivering cisplatin 7.5mg/m2 and doxorubicin 1.5mg/m2 for gastric patients, with the exception of Kurtz et a[30] who administered cisplatin at a higher dose of 15mg/m2, and Sgarbura et al[31], who studied exclusively Oxaliplatin in this setting. Oxaliplatin was permitted as an option in 2 other studies, one only if cisplatin and doxorubicin was contra-indicated, and the other, a mixed cohort study. Interval between PIPAC was most commonly 6- 8 weekly (n=6), followed by 6 weekly (n=5)[26]. Most studies aimed to administer at least 3 PIPAC to study participants. Median number of PIPAC procedures per patient, ranged from 1.7 – 3, though of note, the range was wide, with small numbers of patients undergoing more, the uppermost being 18 for a single patient[32]. One study included a cohort who underwent ePIPAC, constituting 11 of 52 PIPAC procedures (a technique that utilises an electrostatic precipitation with the aim of improving distribution and absorption)[18]. Median length of stay was 3 days (range 1-5) though the reported range for each paper was wide, with outliers extending to 43 and 56 days (the former being due to bowel perforation and requirement for re-operation[22,28]). One study reported PIPAC being successfully given as an outpatient procedure in 65.2% of cases[26]. Table 3 demonstrates the proportion of patients completing 1,2 or 3 or more PIPAC in each study, and reason for not completing >1 PIPAC.

In summary, 90.1-100% underwent 1 PIPAC (excluding the Khomyakov 2016 paper, whose intention to treat data included patients in the pre-PIPAC chemotherapy phase who had not yet commenced PIPAC), but this decreased to 48-85% having ≥2 PIPAC and 24-71.4% undergoing ≥3 PIPAC, with the most common reasons for halting treatment being disease progression and deterioration in patient condition.

Study	% completing 1 PIPAC	% completing ≥2 PIPAC	% completing ≥3 PIPAC	Reasons stated for not completing >1 PIPAC
Khomyakov et al. (2016)[18, **]	51.6	22.5	25	Progression n= 8, Awaiting next PIPAC n=5, Lost-to-follow up n=3
Struller et al. (2019)[20]	100	48	24	Progression n=9, Histology negative n=4
Ellebæk et al. (2020)[18]	100	70	50	Deterioration of condition n=6
De Simone et al. (2020)[17, *]	100	63.4	31.7	Progression n=6, Deterioration of condition n=9, Palliative or rescue surgery n=8
Nadiradze et al. (2016)[24]	96	71	40	Non-access n=3, other NS
Gockel et al. (2018)[21]	91.6	54	45	NS
Kurtz et al. (2018)[30, *]	100	56.3	29.5	Progression/death n=7, Negative histology n=12, non-access n=8, Awaiting next PIPAC n=4
Sgarbura et al. (2019)[31, *]	100	64.3	47.5	Progression n=10, Remission n=4, CRS n=2, Non-access n=5, Toxicity n=5, refuse n=2
Willaert et al (2019)[26, *]	92	71	54	Progression n=5, Weakness n = 1, bowel obstruction n=2, refuse n=1, other n=2
Di Giorgio et al. (2020)[23]	93	50	27	Progression n=5, Awaiting next PIPAC n=2, refuse n=4, adverse event n=2
Alyami et al. (2021)[22]	100	80.1	71.4	NS
Rackauskas et al. (2021)[25, *]	100	66.7	53.4	NS
Feldbrugge et al. (2021)[28]	100	50	26	[#] Progression n=17, Patient/oncologist preference n=7, CRS+HIPEC N=5, non-access n=4, death n=4
Sindayigaya et al. (2021)[29]	90.1	53.4	31.2	Adhesions n=5, Deterioration of condition n=36, refuse n=1, CRS+HIPEC n=1, other n=11
Pocard et al. (2020)[34]	100	85	63	NS

Table 3 – Proportion (%, either stated directly by each report or calculated from raw data provided) of patients completing 1, 2 OR ≥3 PIPAC in each study.

NS= not stated. *Mixed cohort study, with data presented here representing entire cohort, not gastric specific. **At time of publication, all patients had received at least one cycle of study medication, which for this study included 4 cycles of SACT upfront prior to any PIPAC, so may not have entered PIPAC phase of study at point of data lock. [#] Study gives reasons for not completing 3 PIPAC

Bidirectional treatment protocol

16 studies permitted bidirectional treatment, with one excluding[20], and one not providing details. However, the proportion of patients undergoing bidirectional treatment ranged from 23.8% to 100%, and few studies provide detail of the SACT regimen, timing in relation to PIPAC or washout (see table 1). A regimen of 2 cycles of SACT to every 1 PIPAC treatment is the most common. With regards to washout period between SACT and PIPAC, only 7 papers gave this information, with recommended interval varying between 1 week-2 weeks.

Survival

Outcome measures are summarised in table 4. In the gastric only studies, median overall survival (mOS) ranged from 8 – 19.1 months, and 1-year OS between 49.8-77.9%. Five studies report survival from first PIPAC, for which gastric only results range from 4.7 – 6.9 months[18,20,21,30,36].

There is some data to support a relationship between number of PIPACs delivered and OS. A subgroup analysis by Sindayigaya et al reported mOS of 9 months with 0-2 PIPAC, compared to

16 months for ≥3 PIPAC (p=0.0003)[29]. Similarly, De Simone et al report mOS for the intention to treat (ITT) population of 15 months, compared to 18 months per protocol (PP, patients who underwent at least 2 PIPAC procedures)[17]. Gockel et al also reported a significant difference in mOS based on number of PIPAC received, increasing from 121 days for the 1-2 PIPAC group, to 450 days for ≥3 PIPAC (p=0.0376)[21]. This was echoed by the mOS reported by Di Giorgio of 9 months (95% C.I 8.2-17.1) for those who received 1 PIPAC, compared to 15 months (95% C.I 12.8-20.4) for those who underwent ≥1 PIPAC[23].

With regards to outcomes with bidirectional treatment, Sindayigaya report no statistically significant difference between those who had SACT alongside PIPAC and those who did not (15 vs 16 months, p=0.55)[29]. A subgroup analysis by De Simone et al, also found no statistically significant difference between groups who received bidirectional treatment or did not (20.6 vs 15 months, p=0.72)[17].

Efficacy

Histological response was evaluated by all 4 prospective trials[17-20], 6/11 retrospective studies[21,23,24,26,29,30] and 1 abstract[33], though marked heterogeneity in reporting of data is noted. Eight of these studies use PRGS (peritoneal regression grading score) to measure response, a tool proposed and subsequently validated by Solass et al, which requires histological assessment of multiple, repeated peritoneal biopsies taken over multiple PIPAC sessions[37,38]. As such, only a proportion of patients with adequate biopsies, who have undergone >1 PIPAC are evaluated in each study, thus histological response rates often do not represent the entire study population (even PP). In addition, there is variation around timing of response evaluation in relation the number of PIPAC treatments given. Reported results are summarised in table 4, along with PCI and RECIST response and change in ascites volume (additional comparative data available in Supplementary Information, Appendix C). A PRGS score of 1 (complete histological response) was reported in 7 studies[17,19,20,23,24,30,33], ranging from 0-35%, PRGS 2-3 (partial response), up to 83.3% and PRGS of 4 (no response) of up to 40% has been reported. Five studies provide data regarding PCI response. Of these, two report no statistical difference in PCI across PIPAC treatments[20,29], two a decreased or stable score[21,25], and one an increased PCI[23].

Three studies describe imaging response on CT (computed tomography) using RECIST criteria, with a range of overall response rate of 33.3-40% i.e. sum of complete response (CR), partial response (PR) and stable disease (SD)[17,20,26]. De Simone et al also assessed clinical response in using 18F-FDG-PET for 13 patients, reporting a PR for 7 patients, and progressive disease in 11

(PERCIST criteria), though authors note that in many cases FDG-PET was non-specific due to mucinous or signet ring histology, or the presence of inflammatory peritonitis post-PIPAC[17].

Response in terms of reduction of ascites is variable across studies. Reduction or stabilisation of volume ranges from 23 – 78% of patients, though is only reported in a small proportion of patients and at different time points across studies, making comparison difficult.

Safety

Variation exists across the 16 studies reporting safety data with regard to evaluation of post-operative complication and toxicity. CTCAE (Common Terminology Criteria for Adverse Events version 4 or 5) grading was most consistently reported, presented in 11 studies, as summarised in table 4. CTCAE Grade 3 toxicity ranges from 0.7-25%, and grade 4 from 0-4.1%. Five studies reported complications only using Clavien-Dindo classification, with major complication rates (Clavien-Dindo grade 3 or above) ranging from 1.4-11.8%[21,25,27,28,34]. Laparoscopic non-access rates range from 0 to 12%.

Similarly, differences also exist regarding PIPAC-related mortality data, with a range of time-scales and definitions reported (see Appendix D, Supplementary materials). Of the 13 papers that detail mortality, 4 specifically report post-operative mortality within 30 days[17,19,22,23]. Three papers report mortality via CTCAE, and 3 with Clavien-Dindo scales, though description of timing post-operatively varies, and is not always stated[26-29,31,34]. Three studies report "in hospital" or "treatment-related" deaths, though similarly, time-limit for reporting was unclear[20,24,30]. There were 2 additional studies that reported no post-operative mortality, but did not detail endpoint.[25,33].

Combining all post-operative mortality and grade 5 toxicity regardless of endpoint, the overall mortality rate ranges from 0-8.3% (total of 10 deaths, across a combined population of 773 patients for whom this data is reported) with 8 studies reporting no deaths or grade 5 events. Causes of death stated include cardiopulmonary decompensation explained by ascites removal in the critically unwell patient, small bowel obstruction due to disease progression[24], respiratory complications in a patient with pre-existing condition[12], 2 cases of rapid disease progression within 30 days of PIPAC[23], cardiopulmonary decompensation 12 days post procedure[30], pulmonary embolism and bowel obstruction within 30 days of PIPAC[22], paralytic ileus and cardiac failure[29]. It is therefore clear that some of these deaths appear secondary to disease progression rather than consequences of the PIPAC treatment itself.

	Survival data				Other efficacy data					Safety data	
First author (Year)	Median OS (months)	1 year OS (%)	Survival from first PIPAC	PFS	Histological response		PCI response	Ascites volume response	Imaging response (RECIST)	CTCAE Toxicity	Non-access rate
					Assessment method, population assessed	Result					
Khomyakov (2016)[18]	13.0	49.80%	NS	NS	PRGS ≥2 PIPAC, n=15	Overall response = 60% PRGS1 =4/15 (27%) PRGS2= 5/15 (33%) No response 6/15 (40%)	NS	NS	NS	G2 = 6.4% G3 = 3.2% G4 = 0 G5 = 0	0
Struller (2019)[20]	NS	NS	6.7 months ITT	NS	Histological tumour response assessment. >1 PIPAC, n=12	Total histological response = 9/25 (36% ITT, 6/6 100% PP) CR =1/12, (4% ITT,16.7%PP) Major = 8/12 (32% ITT, n=5 PP 83.3%) Minor/no response =3/12 (12%ITT)	Stable. Mean PCI: PIPAC 1 = 15.4, PIPAC 2 = 11.1 PIPAC 3 = 13.3	"Did not increase under PIPAC" Mean ascites volume: PIPAC 1 = 493ml PIPAC 2 = 642ml PIPAC 3= 83ml	Overall CBR 40%. CR = 1 (4% ITT, 16.7% PP), PR = 2 (ITT 8%, n=1 PP 16.7%), SD=7 (28% ITT, n= 4 PP 66.7%).	G1 n=25 (100%) G2 n=5 (20%) G3 n=3 (12%) G4= 0 G5= 0	1/43 (2%)
Ellebæk (2020)[18]	11.5	NS	4.7 months	NS	PRGS NS	CR = 0 *After 1 PIPAC:* Regression = 5 (36% PP, 25% ITT), Stable = 5 (36% PP, ITT 25%). *After 2 PIPACs:* Regression = 4 (40% PP, 20% ITT), Stable = 2 (20% PP, 10% ITT).	NS	Reduced from PIPAC 1 (median 25 ml, range 10-2400) to last PIPAC (median 20ml, range 10-250). Ascites prevailed in 5/8 patients	NS	G3 n=1 (%NS) G4 n=1 (%NS) G5 = NS	NS
De Simone (2020)[17, *]	15 .0 (ITT)* 18.1 (PP)*[£]	67% (ITT)* 61% (PP)*	NS	7.4 months (PP)* Not reached (ITT)	PRGS ≥2 PIPAC, n=29 ≥3 PIPAC, n=12*	*After 2 PIPAC:* PRGS 1 = 6, PRGS 2 = 1, PRGS 3 = 16, PRGS 4 = 6 *After 3 PIPAC:* PRGS 1=3, PRGS 2= 0, PRGS 3=8, PRGS 4= 1*	NS	NS	Overall DCR 35% PR= 17.5% (PP) SD= 17.5% (PP)	G3/4 = 2.40%* G5 = 0	2.9%*
Nadiradze (2016)[24]	15.4	52%	NS	NS	Histological tumour response assessment. ≥2 PIPAC, n=17	Overall response= 50% (ITT) Of those ≥2 PIPAC: CR = 6/17 PR= 6/17 SD= 3/17	NS	NS	NS	G1 n=15/24 (62.5%) G2 n= 6/24 (25%) G3 n=6/24 (25%) G4 n=1/24 (4.1%) G5 n= 2 (8.3%)	Primary n=1 (4%) Secondary n =3 (12%)
Gockel (2018)[21]	NS	NS	210 days (6.9 months)	NS	Relative tumour cell portion covering areas in%. ≥2 PIPAC, n=14	"Reduction or stabilisation of maximum tumour cell portion in 79%"	Decreased or stable n = 8 (57%). Increased PCI n = 6 (42.9%)	Decreased or stable n=11/14 (78% of repeatedly treated patients) Increased n=3	NS	NS	n=5
Kurtz (2018)[30,*#c]	NS	NS	6.8 months	NS	PRGS ≥2 PIPAC, n=36	PRGS improved or stable in n=24/36 (67%), PRGS 1= 10/39 (26%). PRGS deteriorated in n=12 (33%)*	NS	Decreased between PIPAC#1 and PIPAC #3 (p=0.03)*	NS	G2 n= 1 (0.7% procedures) * G3 n= 1 (0.7% procedures) * G5 n= 1 (1.4%)*	8/71 (11.2%)*
Sgarbura. (2019)[31, *]	Not reached * (KM given for subgroups[£])	NS *	Not reached* (KM given for subgroups[£])	NS	N/A	NS	NS	NS	NS	G1 n= 22 (21.8%)* G2 n= 17 (16.8%)* G3 n= 14 (13.9%)* G4 n= 1 (<1%)* G5 n= 1 (<1%)	n = 8 (7.9%)*
Willaert (2019)[26, *]	NS	NS	NS	NS	PRGS Reported in those >2 PIPAC, but also by cohort	*Gastric specific data, mean PRGS:* Regression = 5/11 SD= 2/11 PD= 4/11	NS	NS	PR = 1/9 SD=2/9 PD=6/9	G1 n=19 (14.1%)* G2 n= 22 (16.3%)* G3 n=17 (12.6%)* G4 n= 0* G5 n = 0	n = 3 (5.7%)*
Di Giorgio. (2020)[23]	12.3	NS	5.9 months	NS	PRGS ≥2 PIPAC, n=13	CR = 1/13 (7.7%), PR= 7/13 (53.8%). No regression =5/13 (38.5%)	Increase = 10/13 (76.9%) Stable = 1/13 (7.7%) Reduced = 2/13 (15.3%)	Increase = 4/13 (30.7%) Decrease = 3/13 (23%) No ascites = 6/13 (46.1%)	NS	G1/2 n=10 (22%) G3/4 n=2 (4%) G5 n= 2 (4%)	n = 2 (4%)
Alyami. (2021)[22]	19.1	NS	NS	NS	NA	NS	NS	50% complete resolution of ascites after 3rd PIPAC	NS	G1/2 n= 5 (3.1%) G3/4 n= 5 (3.1%) G5 n= 2 (4.7%)	NS
Rackauskas (2021)[25, *]	8	NS	NS	NS	NA	NS	Decrease in median PCI from 8 to 5 (p=0.581)*	28.6% (n=2/7) had reduction/resolution of ascites (p=0.500)*	NS	G1- G4 = NS G5 = 0	NS

Tidadini (2021)[27]	12.8 PIPAC + SACT vs 9.1 SACT alone	94.1 % PIPAC+ SACT vs 66.7% SACT alone	NS	NS	NA	NS	NS	NS	NS	*Clavien-Dindo stated – see text* G5 = 0	NS
Feldbrugge (2021)[28]	NS	NS	NS	NS	NA	NS	NS	NS	NS	*Clavien-Dindo stated – see text* G5 = 0	NS
Sindayigaya (2021)[29]	11.0	NS	NS	NS	PRGS if ≥3 PIPAC and ≥3 biopsies from each quadrant, n=37	PRGS 1/2 = 27/37 (73%) PRGS 3/4 = 9/37 (24.3%)	No statistically significant difference	No statistically significant difference	NS	G1/2 n=54 (37.5%) G3 n=7 (4.8% of patients) G4 = 0 G5 n = 2 (1.4%)	n = 12 (8.4%)
Bonnot (2020)[32, #]	15.1	NS	NS	NS	NA	NS	NS	NS	NS	NS G5 = 0	NS
Khomyakov, (2020)[32, #^]	16.0 (in n=80 >1 PIPAC)	77.9%	NS	NS	PRGS n=72	PRGS1 = 10 (13.9%) PRGS2 = 40 (55.6%)	NS	NS	NS	"No severe complications observed"	NS
Pocard et al (2020)[33]	NS	NS	NS	"Maximum duration of control 11 months"	NA	NS	NS	NS	NS	*Clavien-Dindo stated – see text*	NS

Table 4 – Efficacy and Safety data

NS = Not stated. CR = Complete response, PR = partial response, PD = progressive disease, SD = stable disease. ITT = Intention to treat. PP = Per protocol. CBR = Clinical benefit rate, measured by independent radiologist using RECIST. CBR is defined as the total number of patients with CR, PR and SD. DCR = Disease control rate. Measured as CBR. CTCAE = Common Terminology Criteria for Adverse Events (CTCAE). Histological response as measured by score such as Peritoneal Regression Grading Score (PRGS) where PRGS G1= Complete response (absence of tumour cells) G2= Major response (major regression) G3 = Minor response (sore regressive features but predominance of residual tumour cells) G4= No response. PCI = Peritoneal Carcinomatosis Index.

*For mixed cohort studies, gastric results are given, unless * when data refers to the entire reported cohort (not just the gastric patients). [£]Study included due to reporting of Kaplan Meier curve for gastric cohort which infers median OS of approximately 12 months (PP). For the purpose of this table, PIPAC related mortality reported by each study is deemed as Grade 5 toxicity, represented in the CTCAE column. For more information of mortality data, see Supplementary Information Appendix D.

Quality of Life (QOL)

Three studies report prospective QOL data. Two are gastric specific studies, evaluating a total of 34 patients using the EORTC QLQ-C30 questionnaire[20,21], and one mixed cohort study of 63 patients (of whom 10 were gastric), that used Short Form 36 Health Survey (SF-36)[17]. Struller et al. assessed 14 gastric patients before and after their first PIPAC using QLQ-C30 and reported no statistically significant differences in functional or symptom scales, though did note deterioration of >10 points for pain and diarrhoea[20]. Using the same method, in their gastric specific study of 20 patients, Gockel et al report stable global health score in patients who underwent ≥2 PIPAC, and stable to slightly decreasing functioning score (78 ±4.8 to 63±13) [21]. Similarly, De Simone et al also reported no statistically significant difference in QOL measures[17]. Importantly, no comparison exists between QOL measures for those having PIPAC alone versus bidirectional treatment.

Systematic reviews

Seven systematic reviews were included for separate review and citation tracking (summarised in Appendix D, supplementary materials)[15,39-44]. Though all include gastric studies in their review, to our knowledge there has been only one focussed solely on PIPAC for GCPM. Published in 2019 by Garg et al, this paper included 10 articles, representing 129 patients, though only 2 reports were gastric specific[39].

Discussion

We present, to our knowledge, the largest and most up to date systematic review of PIPAC for GCPM, representing 751 patients and demonstrating promising mOS between 8-19.1 months. The study populations presented here consist mainly of heavily pre-treated patients (some having received up to 5 prior lines of chemotherapy), the majority with diffuse histology, many with a heavy burden of peritoneal disease (PCI score up to 39) and a proportion with extra-peritoneal metastatic disease (8-21%). Given these poor prognostic factors, and that the median OS achieved in the first line setting with standard doublet SACT is in the region of 9-11 months[45], these results are encouraging.

Timing of PIPAC: Should we aim for earlier intervention?

Given the heterogeneous, advanced disease burden in these studies, a trial of PIPAC in the first line setting for peritoneal only disease is needed to ascertain whether better outcomes can be achieved if PIPAC is delivered prior to development of resistance to SACT. Using PIPAC as an earlier intervention may increase the proportion of patients able to receive all planned PIPAC treatments, important given the possible correlation between number of PIPAC administered and improved outcomes. Whether this is a true treatment effect, with improved efficacy when ≥2 PIPAC are delivered, or whether due to disease biology, with patients who are not responding more likely to stop PIPAC earlier, remains unclear. However, administering PIPAC earlier in the treatment pathway, when patients are potentially fitter with better performance status, may in itself result in improved ability to deliver 3 PIPAC, and possibly improve efficacy, and needs to be assessed in future trials.

There is evidence to suggest that patients with late stage, extra-peritoneal disease benefit less from PIPAC. Nadiradze et al.[24] demonstrated mOS of only 3 months in patients with extra-peritoneal metastatic disease, and subsequently established this as an exclusion criterion in their later studies. Additionally, Sindayigaya et al report that those who had ≤2 PIPAC had significantly higher PCI score, higher proportion of ascites and longer hospital stay[29], further demonstrating the importance of careful patient selection to maximize benefit.

The role of bidirectional therapy

It remains unclear whether bidirectional therapy adds additional benefit. Limited data available through subgroup analyses suggests no statistically significant benefit. However, with marked heterogeneity in the number of lines of SACT previously received in these study populations, the potential for chemo-resistant disease exists, thus making drawing conclusions difficult. Furthermore, given these trials were not designed or powered to demonstrate this, and the lack of prospective, randomised data comparing bidirectional and unidirectional treatment, these results should be interpreted with great caution. A recent attempt at meta-analysis comparing the two by Ploug et al.[42] was unsuccessful due to the heterogeneity of data presented. A bidirectional approach may be preferential to many oncologists especially in the first line setting, with aim of optimising both systemic and local (peritoneal) control, further underlying the urgent need for randomised trials.

Safety and tolerability

This review has found that PIPAC appears to be safe and well tolerated, with Common Terminology Criteria for Adverse Events (CTCAE) toxicity of ≥ grade 3 of 0-37.5% and mortality rates of 0-8.3%, though the higher rates in this range were recorded in an early series that included very high risk patients by Nadiradze et al. (described earlier)[24]. Excluding this paper, which for the purpose of this review could be considered to be an outlier given its high risk population, grade 3 toxicity is <13.9% and mortality <4.7%. This is consistent with published systematic reviews - 838 mixed cohort patients (Alyami et al 2019[15]) demonstrating CTCAE >G2 in 12-15% and mortality rate of 2.7%, and 921 patients by Winkler et al reporting CTCAE ≥3 of 13.3% and mortality of 2.2%[44]. However, we found that heterogeneity exists around recording toxicity and mortality, with some studies solely reporting Clavien-Dindo, or ambiguity regarding timing of assessments. CTCAE would be considered as integral to assessment, especially when SACT is delivered and should become a standard reporting measure, along with 30-day post-operative mortality in future prospective randomised trials. Though some authors have suggested that causality between PIPAC and death was unlikely in their series (which may indeed be the case when rapid disease progression has occurred), one must consider in addition to the intraperitoneal chemotherapy itself, the anaesthetic risk and complications relating to other integral stages of the procedure, such as large volume paracentesis, when reporting and interpreting PIPAC-related mortality.

Though not documented in this series, severe hypersensitivity reactions have been reported, with a French series of 132 patients undergoing 383 PIPAC procedures documenting severe reactions in 4 (3%), of which 2 (2.8%) followed Oxaliplatin and 2 (0.6%) cisplatin-doxorubicin, and all of which were managed successfully without complication[46]. No acute or cumulative hepatic or renal toxicity has been demonstrated post-PIPAC in any studies to date[47,48]. Though not widely used for gastric GCPM, there are case reports of peritoneal sclerosis following PIPAC with oxaliplatin[49].

This review has only identified 34 gastric cancer patients who underwent formal QOL evaluation, which though reporting encouraging results, clearly only represents a very small population. However, these findings are consistent with larger QOL focused studies, including a 2020 systemic review of QOL measures after PIPAC in 425 patients, of which 92 were gastric, also reached the same conclusion of “generally stable” global health, symptom and function scores, though did also note an increase in pain, as well as fatigue in 2 studies [43]. Randomized studies with

robust QOL evaluation are required to confirm these findings, but also to evaluate the impact of bidirectional treatment on QOL. Randomized trials are currently ongoing that will address this, including PIPAC-EstoK-01[50], and a study by Somashekhar et al, (registered trial number REF/2018/08/021225, currently recruiting) the latter comparing QLQ-C30 scores at 0, 60, 120 and 180 days in a mixed cohort of patients treated with PIPAC, with those treated with SACT alone[51].

Limitations of the evidence base

Heterogeneity in endpoints across studies makes assessing the literature challenging. Even when similar end points are defined, marked heterogeneity exists with variation in use of ITT or PP results presented (with the latter posing a risk of selection bias). As previously mentioned, similar challenges were faced by Ploug et al[42] in their attempt at meta-analysis, rendered impossible due to the heterogeneous dataset, resulting in the recommendation of a standard framework of reportable items for future PIPAC studies, which we would support based on our findings.

In contrast, there is consistency across studies in terms of PIPAC procedure technique - a result of stringent training and implementation programmes. As well as describing an almost identical procedural approach, the studies analysed by this review largely use the same chemotherapy regimens. Of note, phase 1 data suggests higher doses of cisplatin and doxorubicin are safe[52] and as such are being administered in the ongoing randomised phase 2 PIPAC-EstoK-01 trial[50]. Further phase 1 studies are being run internationally in parallel to further establish dosing and exposure (see table 5).

The optimal imaging modality to measure peritoneal response to PIPAC has yet to be defined. CT was used in all 5 studies reporting details of imaging modality used, with one study also incorporating 18F-FDG-PET. Though not evaluated in these studies, there is evidence to suggest that MRI is superior to CT in evaluating peritoneal disease, with an MRI defined PCI score specificity of 91% (compared to 50% for CT)[53]. As well as potentially a useful tool for early detection of peritoneal disease, and patient selection for PIPAC, it may have additional value in assessing treatment response. MRI is being investigated alongside CT in PIPAC-OPC2 study, for which results are awaited[54].

The potential of PIPAC as a multi-modal therapy with cytoreductive surgery (CRS) followed by HIPEC (Hyperthermic Intraperitoneal Peritoneal Chemotherapy)

GCPM is traditionally managed with palliative intent from the outset. However, emerging data suggests that for those with an excellent response to PIPAC (PCI ≤8), a more radical approach of CRS followed by HIPEC may be considered in the hope of prolonged disease control, or even cure. Though not a pre-defined end point of this review, we have observed in the literature presented here, 7 studies report small numbers proceeding to CRS+HIPEC (range 3.8-18.5%)[20,22,27,29,32].

In addition, in 2021 Alyami et al published the results of a mixed cohort study of 146 patients with unresectable peritoneal disease who underwent PIPAC, of which 60 had GCPM[55]. Twenty-six patients (17.8%) of the total cohort had a good enough response to warrant CRS+HIPEC, of which the largest cohort was gastric, consisting of 13 patients. However, CRS+HIPEC carries higher risk of morbidity than its PIPAC counterpart, with a CTCAE grade III/IV complication rate of 52.3% and mortality rate of 4% in this series. Therefore, though there may be a place for this radical approach in highly selected patients, it remains experimental and further research is required.

The growing evidence base for PIPAC

The marked increase in gastric patients (n=751) included in this review compared to previous (n=129 in the Garg et al. 2019 review[39]) reflects the steep increase in international research interest in the role of PIPAC. Furthermore, the previous review identified 5 active trials enrolling patients with GCPM in 2019, compared to at least 11 now open according to the clinicaltrials.gov registry (date of search 6/12/2021), summarised in table 5. Of these studies, 3 are exclusively focussed on PIPAC for gastric cancer, 5 are phase I, 3 are observational, 1 is a pilot study, and 2 are phase 2. Only one is a randomised dual-arm study: PIPAC-Esto-K-01 is randomising between bidirectional PIPAC with standard of care IV systemic chemotherapy, or systemic chemotherapy alone, and is currently recruiting [50]. An additional 3 studies are evaluating PIPAC in the adjuvant or neo-adjuvant setting (not detailed here).

The International Society for the Study of Pleura and Peritoneum (ISSPP) has developed an international PIPAC database to monitor worldwide PIPAC activity and outcomes, which was launched in June 2020, and endeavours to publish an annual report and will provide a homogenous data set for evaluation[56].

In addition, our search identified two more protocol papers, one the previously described QOL study[51], and the other a prospective, randomised, multi-centre, phase III study of PIPAC in combination with systemic chemotherapy versus systemic chemotherapy alone in the first line setting upper gastrointestinal adenocarcinomas with peritoneal seeding, with a primary outcome measure of PFS[57]. Once published, this expansion of evidence into larger scale, randomised studies will move PIPAC research into phase 2b/3 of the IDEAL Framework.

The evolution of PIPAC is taking place simultaneously to the expansion of immunotherapy (IO) into the armoury against metastatic gastric cancer. So far evidence surrounding the safety of PIPAC alongside systemic immunotherapy treatment is limited to a single case study[58]. However, a phase 1 trial currently assessing safety of PIPAC with Oxaliplatin has been expanded to include an arm incorporating IV Nivolumab alongside PIPAC, the results of which we await with interest[59].

Study name	Study Identifier	Sponsor	Primary Cancer site	Trial Design (Phase, sample size, primary outcome measure)	Status
Pressurised Intraperitoneal Aerosol Chemotherapy (PIPAC) with Oxaliplatin, and Oxaliplatin in combination with Nivolumab in patients with peritoneal carcinomatosis (PIPAC)	NCT03172416	National University Hospital Singapore	Gastric	• Phase 1 (21 participants) • 3+3 dose escalation study of Cohort 1 PIPAC alone, Cohort 2 PIPAC + IV Nivolumab 240mg q14 • *Primary outcomes:* Safety and tolerability. MTD of PIPAC with Oxaliplatin alone and PIPAC with Oxaliplatin and IV Nivolumab	Recruiting* Estimated completion 2022
Safety PIPAC using paclitaxel in gastric cancer patients with peritoneal metastasis	NCT04913662	Seoul National University Bundang Hospital.	Gastric	• Phase 1 (18 participants) • Safety of PIPAC using paclitaxel combined with IV FOLFOX. • *Primary outcome:* DLT within 2 weeks after 1st PIPAC Recommended dose of paclitaxel for phase II trial.	Recruiting. Last updated June 2021. Estimated completion 20221.
Pressurised Intraperitoneal aerosol chemotherapy (PIPAC) in Gastric carcinomatosis. Phase II randomized controlled study (PIPAC EstoK-01)[50]	NCT04065139	Assistance Publique - Hôpitaux de Paris	Gastric	• Phase 2 (94 participants) • Prospective, open-label, randomised, 2 arms; Control arm of standard chemotherapy (SOC) vs experimental arm of PIPAC (cisplatin + doxorubicin) + systemic chemotherapy • *Primary outcome:* 24 months PFS	Recruiting* Estimated completion 2022
PIPAC for peritoneal metastases	NCT04956068	National Cancer Centre, Singapore	Gastrointestinal, Hepatobiliary, Gynecological, Breast	• Phase 1 (15 participants) • Non-randomised, open label study of PIPAC with cisplatin and doxorubicin in 2 arms; i) Unresectable PM (palliative) and ii) Extensive PM (neoadjuvant intent) • *Primary outcome:* CTCAE toxicity; major (CTCAE ≥3), minor (CTCAE 1-2) length of hospitalization.	Recruiting. Last update July 2021. Estimated completion November 2023
Treatment of Peritoneal Carcinomatosis with Pressurised IntraPeritoneal Aerosol Chemotherapy (PIPAC-OPC2)[54]	NCT03287375, EudraCT 2016-003394-18	Odense University Hospital, Denmark	Gastrointestinal, ovarian, primary peritoneal	• Phase 2 (137 participants) • Prospective, single arm, open-label trial of PIPAC (cisplatin + doxorubicin for non-colorectal, Oxaliplatin for colorectal) • *Primary outcome*: Histological response using PRGS (number with PRGS 1/2) within a series of 3 PIPAC procedures.	Recruiting (Last update 2017) Estimated completion 2020
Evaluation of Molecular and Pathophysiological Mechanisms of Peritoneal Carcinomatosis and Monitoring of the Efficiency of PIPAC (Pressurized Intra-peritoneal Aerosol-Chemotherapy) as a Local Chemotherapeutical Treatment.	NCT03100708	University of Leipzig, Germany	Colorectal, ovarian, gastric, pancreatic and primary peritoneal.	• Observational study (500 participants) • Prospective registry of patients undergoing PIPAC with cisplatin + doxorubicin (non-colorectal) or Oxaliplatin (colorectal) • *Primary outcome:* OS	Recruiting. Last update 2019. Estimated completion 2021
A Phase Ib Trial of Intraperitoneal Cisplatin and Nab-paclitaxel Administered by Pressurised Intraperitoneal Aerosol Chemotherapy in the Treatment of Advanced Malignancies Confined to the Peritoneal Cavity	NCT04000906	University Hospital Geneva, Switzerland.	Pancreatic, oesophago-gastric, ovarian, primitive peritoneal mesothelioma.	• Phase Ib (36 patients) • Investigating combination of PIPAC with cisplatin (10.5mg/m^2) and Nab-paclitaxel (escalated doses from 7.5mg/m^2 to 70mg/m^2) • *Primary outcome:* Define MTD of nab-paclitaxel administered by PIPAC with cisplatin.	Recruiting. Last updated Sept 2021. Estimated completion 2023
International Registry of Patients Treated with Pressurised IntraPeritoneal Aerosol Chemotherapy (PIPAC) (PIPACRegis)*	NCT03210298	Ruhr University of Bochum, Germany	Colorectal, ovarian, gastric, appendiceal, pseudomyxoma peritonei, mesothelioma, pancreatic cancer, gallbladder, small bowel	• Observational (1000 participants) • Multicentre, international, web-based prospective documentation of the indications and results of PIPAC for malignant pleural and peritoneal diseases. • *Primary outcome:* OS	Completed recruitment. Results being analysed.
Study Evaluating the Bonds Between Circulating Tumoral ADN (ctDNA) and the Development of Peritoneal Carcinomatosis for Patients Treated With PIPAC	NCT04766502	Institut de Cancérologie de Lorraine, France	Any with peritoneal mets	• Pilot study (20 participants) • Single arm, open label pilot study investigating the variation of plasma ctDNA concentration between the 1st and 3rd PIPAC session by collecting blood the day before and 24 hours each PIPAC. • *Primary outcome:* ctDNA concentration change, PRGS	Not yet recruiting. Last updated Nov 2021. Estimated completion 2024.
Safety and Efficacy of Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC) in Ovarian, Uterine, Appendiceal, Colorectal, and Gastric Cancer Patients With Peritoneal Carcinomatosis (PC)[60]	NCT04329494	City of Hope Medical Center, California, USA.	Ovarian, Uterine, Appendiceal, Colorectal or Gastric Cancer	• Phase 1 (16 participants) • Dual arm safety study; i) Ovarian, uterine, appendiceal or gastric having PIPAC with cisplatin + doxorubicin ii) Colorectal having PIPAC with Oxaliplatin + IV 5FU leucovorin • *Primary outcome:* DLT assessed by CTCAE v5	Recruiting. Last updated June 2021. Estimated completion 2022
Study of Plasma Tumor-promoting Factors and Immune Function After Laparotomy, Cytoreductive Surgery and HIPEC vs. PIPAC in Patients With Peritoneal Metastasis (IMMUNOPAC)	NCT04122885	University Hospital Tübingen	Ovarian, gastric or colorectal	• Observational study (60 participants) • Prospective cohort study of CRS+HIPEC vs PIPAC to investigate the effect of treatment on serum concentrations of proteins of interest (IGFBP-3, VEGF, Ang 2, PUGF, sVCAM, CHI3L1, MMP-2, MMP-3, MCP-1) • *Primary outcome:* Serum level of the proteins of interest over time	Recruiting. Last updated 2019. Estimated completion 2022

Table 5 – PIPAC Clinical trials recruiting patients with gastric cancer and peritoneal metastases listed as active according to the clinicaltrials.gov registry summarising trial design and status (date of search 6.12.21)

*Status confirmed with Research group. OS = Overall survival. PFS = Progression Free Survival. MTD = Maximum tolerated dose. DLT = Dose limiting toxicity. CTCAE = Common Terminology Criteria for Adverse Events (CTCAE). PRGS= Peritoneal Regression Grading Score.

Future directions

Based on the body of evidence presented in this review, we propose a prospective phase II randomised controlled trial of bidirectional PIPAC for GCPM in the first line setting, to confirm potential benefit and refine optimal patient selection. The available data suggest that eligibility should be limited to those with peritoneal only metastases and good performance status. We strongly recommend standardised endpoints are reported in future PIPAC trials to allow cross-study comparison and future meta-analyses. Furthermore, areas of further research are needed with regards to optimal methods of response assessment, including radiological assessment such as MRI. Parallel translational studies would also be helpful in determining mechanism of action and informing development of future trials.

Conclusion

Peritoneal carcinomatosis due to gastric cancer carries a poor prognosis and is frequently associated with the development of distressing symptoms and rapid deterioration in QOL. PIPAC may be a useful treatment option for selected GCPM patients, with promising survival benefit, acceptable grade 3 and 4 toxicity and low mortality rates. However, phase 3, randomised trials are now required to confirm these findings, define the role of bidirectional therapy, and refine optimal choice of therapy and patient selection.

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*PIPAC UK Contributors: Amy Case, Angela Casbard, Chris Peters, David Chuter, Emma Hudson, Gina Brown, Harry Hall, Jamie Murphy, Jared Torkington, Jody Parker, Jonathan Frost, Joy Garfitt, Kitrick Perry, Leona Batten, Lisette Nixon, Peter Kyle, Richard Adams, Sarah Gwynne, Sadie Jones, Sophie Tate, Steve Kihara, Alan Parker, Alice Baggaley.

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Graphical Abstract (for review)
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Pressurised IntraPeritoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases.

Background

Peritoneal metastases from gastric cancer carries a very poor prognosis of 2.4-10 months.

PIPAC offers higher concentration of chemotherapy in peritoneal deposits, reduced systemic absorption, and may improve outcomes.

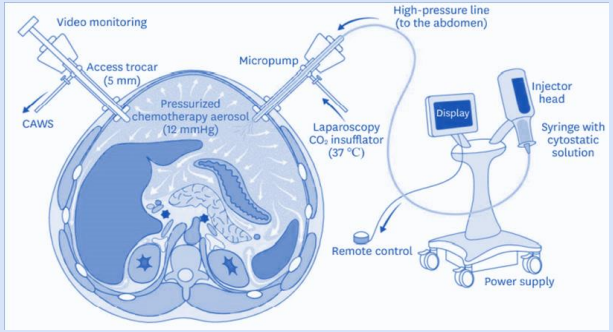


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Systematic review

Aim: To evaluate the efficacy, tolerability and impact on QOL of PIPAC for gastric cancer with peritoneal metastases

18 reports
751 patients

- 4 prospective
- 11 retrospective
- 3 abstracts

0 phase III RCTs

Findings

mOS	8.0 – 19.1 months
1 yr	49.8 - 77.9%
CTCAE	G3 toxicity 0.7- 25% G4 toxicity 0-4.1%
QOL	No statistically significant difference

Conclusion

PIPAC may offer promising survival benefits, limited toxicity and maintain QOL for gastric cancer patients, but phase 3. randomised evidence is needed.

PIPAC UK COLLABORATIVE

A. Case, S.Prosser, C.Peters, R. Adams, S.Kihara, S.Gwynne

Cancer Treatment Reviews 2022

Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases: A systematic review by the PIPAC UK Collaborative

Highlights

- PIPAC enhances absorption of chemotherapy in peritoneal metastases.
- Phase I/II overall survival data is promising for gastric peritoneal carcinomatosis
- Reported rates of PIPAC associated grade ≥3 toxicity and death are low.
- Quality of life is not impaired by PIPAC treatment.
- Phase 3 trials are needed to confirm these findings.

Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases: A systematic review by the PIPAC UK Collaborative

A. Case, S. Prosser, C.J. Peters, R. Adams, S. Gwynne, On behalf of the PIPAC UK Collaborative

CRediT Statement

A. Case: Conceptualization, Methodology, Investigation, Formal analysis, Writing (original draft and editing), Visualisation.

S. Prosser: Methodology, Investigation, Writing – review and editing.

C.J. Peters: Conceptualization, Methodology, Writing – review and editing, Supervision.

R. Adams: Conceptualization, Methodology, Writing – review and editing.

S. Gwynne: Conceptualization, Methodology, Investigation, Formal analysis, Writing (original draft and editing), Supervision

Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases: A systematic review by the PIPAC UK Collaborative

A. Case, S. Prosser, C.J. Peters, R. Adams, S. Gwynne, On behalf of the PIPAC UK Collaborative

Conflict of Interest Statement

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Declarations of Interest: None

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