



# Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications

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Pressurised intraperitoneal aerosol chemotherapy (PIPAC) was introduced as a new treatment for patients with peritoneal metastases in November, 2011. Reports of its feasibility, tolerance, and efficacy have encouraged centres worldwide to adopt PIPAC as a novel drug delivery technique. In this Review, we detail the technique and rationale of PIPAC and critically assess its evidence and potential indications. A systematic search was done to identify all relevant literature on PIPAC published between Jan 1, 2011, and Jan 31, 2019. A total of 106 articles or reports on PIPAC were identified, and 45 clinical studies on 1810 PIPAC procedures in 838 patients were included for analysis. Repeated PIPAC delivery was feasible in 64% of patients with few intraoperative and postoperative surgical complications (3% for each in prospective studies). Adverse events (Common Terminology Criteria for Adverse Events greater than grade 2) occurred after 12–15% of procedures, and commonly included bowel obstruction, bleeding, and abdominal pain. Repeated PIPAC did not have a negative effect on quality of life. Using PIPAC, an objective clinical response of 62–88% was reported for patients with ovarian cancer (median survival of 11–14 months), 50–91% for gastric cancer (median survival of 8–15 months), 71–86% for colorectal cancer (median survival of 16 months), and 67–75% (median survival of 27 months) for peritoneal mesothelioma. From our findings, PIPAC has been shown to be feasible and safe. Data on objective response and quality of life were encouraging. Therefore, PIPAC can be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins. However, its use in further indications needs to be validated by prospective studies.

## Introduction

Peritoneal metastasis is a heterogeneous group of primary disease or metastatic spread within the abdominal cavity. The most frequent conditions concern patients with ovarian (up to 46% at initial presentation), gastric (14%), and colorectal (5%) primary tumours, and patients with peritoneal mesothelioma.<sup>1–4</sup> A common feature of peritoneal metastasis is a reduced response to systemic chemotherapy and poor prognosis compared with other metastatic sites, at least in the recurrent setting.<sup>5–7</sup>

Intraperitoneal chemotherapy has been proposed as an alternative approach for these patients to improve tissue concentrations and to reduce systemic toxicity.<sup>8–10</sup> This approach is a valid option in several types of malignancies in the adjuvant setting, such as ovarian and gastric cancer, for which phase 3 trials have been done.<sup>8,11,12</sup> Long-term survival has been reported for different disease entities when combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC).<sup>13–17</sup> However, high morbidity and mortality and the unclear role of HIPEC have led to reduced acceptance of this technique within the medical community, despite growing but still controversial high-level evidence.<sup>18–20</sup>

Pressurised intraperitoneal aerosol chemotherapy (PIPAC) has been proposed as an alternative mode for intraperitoneal drug delivery in certain situations, claiming improved distribution, enhanced tissue uptake, better tolerance, and repeatability using minimally invasive access.<sup>21,22</sup> The intriguing concept and favourable initial reports<sup>23,24</sup> have triggered the adoption of PIPAC as a drug delivery technique, mainly within Europe (appendix p 1).

We did a systematic review with the aim of detailing the rationale and technique of PIPAC and critically assessing the available evidence of its feasibility, safety, and tolerance and its use in potential indications other than ovarian and gastric cancer.

## Data collection

### Literature search strategy and selection criteria

Medical subject heading (MeSH) terms “intraperitoneal” AND “chemotherapy” AND “pressurised” were used to search MEDLINE, Embase, the Cochrane Database of Systematic Review, and the Cochrane Central Register of Controlled Trials without language restrictions. Pertinent references and electronic links were hand-searched, and cross-referencing was done for selected articles. The search was limited to studies published between Jan 1, 2011 (the year PIPAC was first used in humans) and Jan 31, 2019. The search terms were identified first in the title, and then in the abstract or MeSH. Only reports on PIPAC were retained, and other forms of intraperitoneal chemotherapy were excluded. All studies of interest were obtained as full-text articles. All publications related to PIPAC, including preclinical and clinical reports and systematic and narrative reviews, were considered to retrieve the maximum number of publications. Owing to our focus on clinical evidence, preclinical reports, reviews, and publications not reporting on any of the clinical outcomes were excluded from the analysis. Clinical reports were further divided into prospective (phase I and II studies) and retrospective evidence. In addition, ongoing research was retrieved from the international clinical trial registries ClinicalTrials.gov and EU Clinical Trials Register. The International Standard Randomised

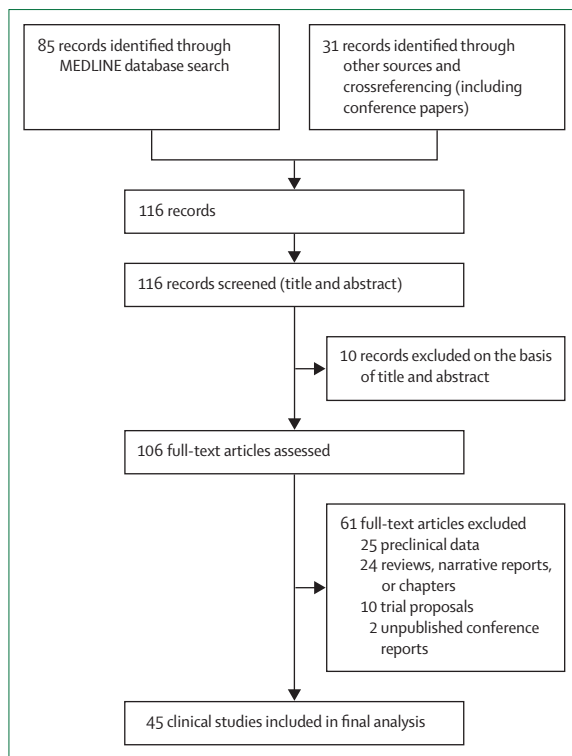
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See Online for appendix



**Figure 1: Flowchart of selected studies**  
The selection process adheres to PRIMSA guidelines.<sup>25</sup>

Controlled Trial Number was used to identify unpublished prospective trials.

### Additional information

The manufacturer of the nebuliser (until 2015 MicroPump, Reger, Villingendorf, Germany; since 2015 CapnoPen, Capnomed, Villingendorf, Germany) was contacted to obtain data on PIPAC procedures over time. For this purpose, the number of sold nebulisers (single-use device) was used as a proxy measure for the number of PIPAC procedures done.

As the authority responsible for the certification of PIPAC course training, the International Society for the Study of Pleura and Peritoneum was contacted to define the number and geographic location of active institutions using PIPAC and expert centres offering certification courses.

### Data analysis

Relevant data were extracted and documented in an a-priori structured database (figure 1). The following items were recorded for each study when available: authors, title, year of publication, primary cancer, number of patients, number of PIPAC procedures, and details on the surgical intervention (rate of non-access, repeatability, and intraoperative complications). Postoperative outcome measures included postoperative surgical complications, toxicity according to Common

Terminology Criteria for Adverse Events 4.0 (CTCAE criteria),<sup>26</sup> mortality, overall survival, and progression-free survival (prospective studies only).

Tumour response was recorded if assessed according to RECIST,<sup>27</sup> histological response (ie, objective tumour response) including peritoneal regression grading score,<sup>28</sup> tumour regression grading system according to Glaze and colleagues<sup>29</sup> and Dworak and colleagues,<sup>30</sup> or peritoneal cancer index<sup>31</sup> improvement. Across all studies reporting efficacy, tumour response was assessed in patients who received at least one cycle of the study medication. Quality of life, symptom relief, or decreased ascites were assessed in studies specifically reporting on these outcomes.

Meta-analysis of outcomes was not done owing to the heterogeneity of original data and outcome measurements. Instead, descriptive statistics were applied and the available information summarised in table form with descriptively pooled outcome data (weighted means) according to level of evidence (prospective or retrospective).

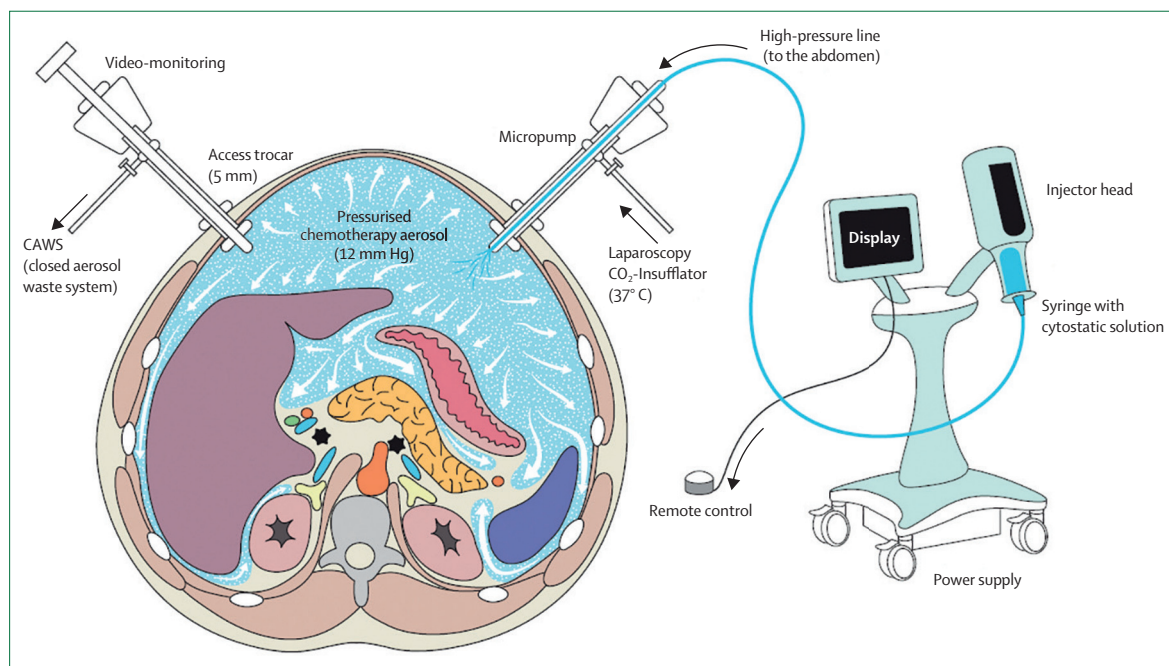
Of note, data was not pooled if assessment or reporting of specific outcomes was heterogeneous.

### Findings

Our systematic literature review identified 106 publications on PIPAC, with a substantial increase in the number of articles published since 2016 (appendix p 2). Excluding 25 preclinical studies, 24 reviews or narrative reports, 10 trial proposals, 2 unpublished conference reports, only 45 clinical studies, including case studies and occupational health studies, were identified (figure 1). Considering overlapping patient cohorts, our analysis included 1810 PIPAC procedures in 838 patients. The main disease entities were ovarian (345 [41%] of 838), gastric (185 [22%]), colorectal (104 [12%]), peritoneal mesothelioma (58 [7%]), and other (146 [17%]) cancers, including pseudomyxoma peritonei, hepatobiliary, and pancreatic origin. In the same timeframe of the literature search, 5151 PIPAC procedures were done by active PIPAC centres (appendix p 1), with a sharp increase in 2017 and 2018 (appendix p 2).

### Procedure, safety protocol, and treatment regimens

Technique, safety protocol, and treatment regimens are highly standardised among expert PIPAC centres, as highlighted by other analyses.<sup>32–35</sup> The abdomen is accessed with one 10–12-mm (nebuliser) and one 5-mm (optical) trocar (figure 2). The same incisions are used for consecutive procedures. The abdomen is insufflated with CO<sub>2</sub> under standard pressure conditions (12 mm Hg). Ascites is quantified (cytology) or, if ascites is not present, a peritoneal flushing is done, and the fluid is sampled for cytology. The abdominal cavity is then explored with documentation of the peritoneal cancer index and at least three representative biopsies are taken using biopsy forceps. Intraperitoneal chemotherapy containing



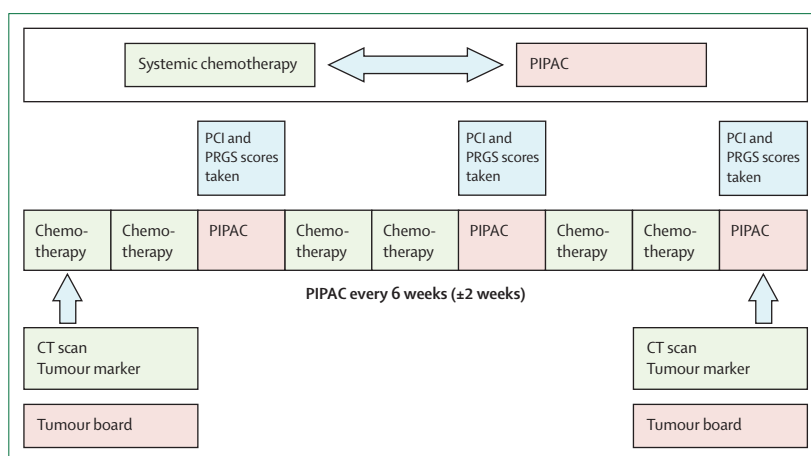
**Figure 2: Schematic of PIPAC set-up**

A hermetically sealed 10–12-mm trocar and a 5-mm balloon trocar are inserted. The liquid chemotherapy regimen is vaporised using a standard injector connected to a nebuliser. Reprinted from Hübner and colleagues<sup>38</sup> with permission from Médecine et Hygiène. PIPAC=pressurised intraperitoneal aerosol chemotherapy.

oxaliplatin alone or cisplatin followed by doxorubicin injected in sequence is then applied as an aerosol using a standard high-pressure injector (maximal upstream pressure 290 psi, flow rate 0.5–0.7 mL/s) and using the procedure-specific nebuliser (CapnoPen). After injection, the therapeutic capnoperitoneum is maintained for 30 min before the remaining aerosol is evacuated into a closed aerosol waste system through two microparticle filters in the wall outlet. Two different safety protocols have been validated by different institutions and regulatory bodies (Odense University Hospital, Denmark; Lyon Sud University Hospital, France; Ruhr University Bochum, Germany; Ghent University Hospital, Belgium; Institut National de Recherche et de Sécurité, France; and Cancer Research Institute Ghent, Belgium) and include the features of air-tight abdomen, advanced air flow in the operating room, remote administration, and checking of all items against a standardised safety checklist.<sup>21,33,35,37</sup>

Contraindications for PIPAC should be respected and include life expectancy of less than 3 months, bowel obstruction, exclusive total parenteral nutrition, decompensated ascites, simultaneous tumour debulking with gastrointestinal resection, and previous anaphylactic reaction to the chemotherapy drug used, in addition to relative contraindications of extraperitoneal metastasis, an Eastern Cooperative Oncology Group performance status of greater than two, and portal vein thrombosis.

Two intraperitoneal regimens are used for PIPAC procedures: cisplatin in combination with doxorubicin and oxaliplatin as monotherapy. At least three PIPAC



**Figure 3: Concomitant systemic and intraperitoneal treatment**

Suggested treatment schedule for PIPAC every 6 weeks ( $\pm 2$  weeks), alternating with systemic chemotherapy. PIPAC=pressurised intraperitoneal aerosol chemotherapy. PCI=peritoneal cancer index. PRGS=peritoneal regression grading score.

procedures are done at  $6\pm 2$ -week intervals, but thereafter treatment can be pursued depending on tolerance and treatment response.<sup>38,39</sup>

PIPAC has been administered alone or after systemic fluorouracil.<sup>38,40,41</sup> Concomitant systemic treatment is possible with most used regimens, including FOLFOX, FOLFIRI, FLOT, and EOX. Most centres would recommend no systemic treatment for 2 weeks before and 1 week after PIPAC procedure. Typical treatment schemes are provided in figure 3.

**Feasibility, safety, toxicity, tolerance, and quality of life**

Doses for the combined cisplatin and doxorubicin regimen were defined by a single dose-escalation study in patients with ovarian cancer.<sup>42</sup> The combined regimen (10.5 mg/m<sup>2</sup> cisplatin, 2.1 mg/m<sup>2</sup> doxorubicin) will be evaluated in a future phase III study, PIPAC OV-3 (EudraCT 2018-003664-31)<sup>43</sup> Two-dose escalation studies are ongoing (NCT03172416 and NCT03294252)<sup>44,45</sup> to define the optimal dose of oxaliplatin, which is used at the empirical dose of 20% (92 mg/m<sup>2</sup>) of the Elias regimen for HIPEC.<sup>46</sup>

The feasibility, safety, and tolerance of repeated PIPAC treatment were confirmed by four prospective and 16 retrospective cohort studies (table 1). Surgical complications were rare (3% of patients had intraoperative complications, and 3% had postoperative complications in prospective studies and 0–11% had intraoperative and 0–6% had postoperative complications in retrospective studies; table 1). Across all types of studies, adverse events (CTCAE grade >2) occurred after

12–15% of procedures. Most common events were bowel obstruction [0–5%], bleeding [0–4%], and abdominal pain [0–4%]). Whereas no mortality was observed in prospective trials, the mortality in retrospective studies was 2.7% (table 1).

Toxicity and occupational health issues were assessed by nine independent groups. Peripheral systemic drug uptake under PIPAC was minimal (venous doxorubicin concentrations of 4.0–6.2 ng/mL, half-life of 86–468 min).<sup>22</sup> Six studies evaluated renal and hepatic toxicity and inflammatory response,<sup>40,51,63–66</sup> although none observed cumulative hepatic or renal toxicity. A modest and transitory inflammatory response (eg, C-reactive protein increase or leucocytosis) was observed in two studies,<sup>40,64</sup> which was commensurate with disease extent in one study.<sup>64</sup> One report<sup>67</sup> showed severe hypersensitivity reactions in 4 (3%) of 132 patients receiving PIPAC, but all reactions were managed by immediate intraperitoneal exsufflation without further complications. Occupational health issues were

	Main primary	Number of patients	Number of PIPAC	Non-access	≥2 PIPAC	Surgical complications from first PIPAC	Adverse events (CTCAE 4.0)		
							Grade 3	Grade 4	Grade 5
<b>Prospective</b>									
PIPAC OV-1 <sup>47</sup>	Ovarian	64	130	11/64 (17%)	43/53 (81%)	4/53 (8%)	8/53 (15%)	0/53	0/53
PIPAC GA-1 <sup>48</sup>	Gastric	25	43	NA	12/25 (48%)	NA	4/25 (16%)	0/25	0/25
PIPAC GA-2 <sup>41</sup>	Gastric	31	56	0	15/31 (48%)	1/31 (3%)	4/31 (13%)	0/31	0/31
PIPAC OPC-1 <sup>49</sup>	Various	35	129	0	30/35 (86%)	2/35 (6%)	4/35 (11%)	1/35 (3%)	0/35
Subtotal, weighted means	..	155	358	8.5%	69.4%	5.9%	13.9%	0.7%	0
<b>Retrospective</b>									
Tempfer and colleagues <sup>50</sup>	Ovarian	21	34	3/21 (14%)	8/18 (44%)	3/18 (17%)	3/18 (17%)	2/18 (11%)	0/18
Tempfer and colleagues <sup>51</sup>	Ovarian	99	252	17/99 (17%)	50/82 (61%)	5/82 (6%)*	17/82 (21%)	3/82 (37%)	0/82
Nadiradze and colleagues <sup>52</sup>	Gastric	25	60	1/25 (4%)†; 3/24 (13%)‡	17/24 (71%)	3/60 procedures (5%)	6/24 (25%)	1/24 (4%)	2/24 (8%; nr)
Odendahl and colleagues <sup>53</sup>	Various	91	158	NA†; 5/91 (6%)‡	48/91 (53%)	3/91 (3%)	8/91 (9%)	1/91 (1%)	3/91 (3%; 2r, 1nr)
Robella and colleagues <sup>40</sup>	Various	14	40	0	14/14 (100%)	0	0/14	0/14	0/14
Demtröder and colleagues <sup>54</sup>	Colorectal	17	48	0†; 6/17 (35%)‡	14/17 (82%)	0	4/17 (24%)	0/17	0/17
Graversen and colleagues <sup>55</sup>	Pancreatic	5	16	0	5/5 (100%)	0	0/5	0/5	0/5
Hübner and colleagues <sup>56</sup>	Various	44	91	2/44 (4%)	30/42 (71%)	1/42 (2%)	0/42	0/42	1/42 (3%; nr)
Alyami and colleagues <sup>38</sup>	Various	73	164	NA	45/73 (62%)	NA	14/73 (19%)	0/73	5/73 (7%; 1r, 4nr)
Khosrawipour and colleagues <sup>57</sup>	Pancreatic	20	41	0†; 3/20 (15%)‡	10/20 (50%)	0	0/20	0/20	1/20 (5%; nr)
Falkenstein and colleagues <sup>58</sup>	Biliary tract	13	17	2/13 (15%)	5/11 (45%)	0	0/11	0/11	0/11
Kurtz and colleagues <sup>59</sup>	Various	71	142	8/71 (11%)	39/63 (62%)	7/142 (5%)	1/63 (16%)	0/63	1/63 (16%; nr)
Gockel and colleagues <sup>60</sup>	Gastric	28	46	3/28 (11%)†; 2/24 (8%)‡	14/24 (58%)	NA	0/24	0/24	0/24
Horvath and colleagues <sup>61</sup>	Pancreatic	12	23	0	6/12 (50%)	0	0/12	0/12	0/12
Jansen-Winkeln and colleagues <sup>52</sup>	Various	62	111	5/59 (8%)†; 4/54 (7%)‡	33/54 (61%)	7/54 (13%)	NA	NA	NA
Giger-Pabst and colleagues <sup>39</sup>	Mesothelioma	29	74	7/29 (24%)	20/22 (91%)	0	1/22 (5%)	2/22 (9%)	1/22 (5%; r)
Subtotal, weighted means	..	624	1317	10.5%†	62.6%	Not pooled (data heterogeneity)	10.4%	1.7%	r: 0.8%; nr: 1.9%

PIPAC=pressurised intraperitoneal aerosol chemotherapy. CTCAE=Common Terminology Criteria for Adverse Events. NA=not available. r=death related to PIPAC procedure. nr=death not related to PIPAC procedure. \*CTCAE grade 3 or 4. †Primary non-access (during first PIPAC), ‡Secondary non-access (during repeated intended PIPAC).

**Table 1: Feasibility, safety, and tolerance of PIPAC**

specifically and independently assessed by five groups, all of which showed a very low risk of exposure with adequate safety measures.<sup>37,62,68–70</sup>

Quality of life was studied independently by four groups, showing consistently stable or improved global quality-of-life scores.<sup>39,40,47,51,53,55,71</sup> Peritoneal metastasis-related symptoms were specifically assessed by one study,<sup>38</sup> and improvement or complete relief was observed in 34 (64%) of 57 patients.

### Oncological efficacy

Treatment response was assessed in four prospective and eleven retrospective cohort studies using different endpoints (table 2). An objective clinical response was reported in 62–88% of patients with ovarian cancer (mostly as third-line treatment), which translated into a median survival of 11.0–14.1 months. Clinical response for patients with gastric cancer (both as salvage and upfront therapy) was between 50% and 91%, with a median survival of 8.4–15.4 months. Similarly, clinical response was 71–86% for colorectal cancer (as third-line treatment; a median survival 15.7 months), and 67–75% (median survival of 27 months) for patients with peritoneal mesothelioma.

12 clinical trials of PIPAC were recorded in international registries (appendix p 3). Most of them were launched in 2018, including a phase III study of platinum-resistant ovarian cancer<sup>43</sup> and two multicentre studies for gastric and upper gastrointestinal cancer.<sup>73,74</sup>

### Discussion

PIPAC is a new treatment alternative for patients with peritoneal metastasis and has undergone initial evaluation. Based on 1810 procedures in 838 patients, PIPAC can be considered a feasible, safe, and well tolerated treatment with no negative effect on quality of life. Oncological efficacy has been documented, according to different assessment tools, in 50–88% of patients with advanced peritoneal metastasis who are refractory to standard treatment. The prospective PIPAC registry (NCT03210298) and future clinical trials, including a phase III study, should help define the most appropriate indications for PIPAC treatment.

Peritoneal metastasis is a common occurrence in intra-abdominal malignancies and is associated with a dismal prognosis in the absence of an aggressive therapeutic approach.<sup>75</sup> Peritoneal metastasis remains an unsolved challenge in modern oncology, and patients with peritoneal metastasis are often not included in randomised trials.<sup>5</sup> For unresectable peritoneal metastasis, systemic chemotherapy remains the standard of care. However, efficacy is reduced owing to a weak penetration of agents into the peritoneum (because of low blood flow, interstitial fibrosis, and the plasma-peritoneal barrier) with consecutive relative chemoresistance and non-negligible toxicity.<sup>7,76</sup> Standard intraperitoneal chemotherapy by lavage has pharmacokinetic limitations, such as unequal

distribution, poor tissue penetration, and only a single-dose of administration, such as with hyperthermic intraperitoneal chemotherapy. Thus, in early 2000, the German pioneer group introduced the idea of therapeutic capnoperitoneum under pressure by testing a device for this approach, with initial technical issues preventing it from being applicable in the clinical setting.<sup>77</sup> Ten years later, the same group created a second-generation device to resolve the issues of the previous device.<sup>78</sup> Following the principles of the IDEAL framework,<sup>79</sup> this innovative surgical technique went through multiple steps. After creating the device and resolving the initial technical difficulties, PIPAC went through several evaluations. Preclinical studies showed good penetration of PIPAC into the tumour nodules and good distribution inside the abdominal cavity.<sup>23,24,80,81</sup> Surgical techniques were standardised by the same group.<sup>22,80</sup> Thereafter, highly standardised training workshops were initiated, and the technique was adopted and confirmed by other expert groups (appendix p 1).<sup>32–35</sup> The concept of PIPAC was supported by favourable initial reports regarding the feasibility, safety, treatment regimens, tolerance, quality of life, and oncological efficacy of this delivery technique.<sup>23,24</sup> PIPAC has been broadly adopted, mainly in Europe, and has succeeded in the development and exploration part of the IDEAL framework, as confirmed by this review; it is proceeding to an assessment stage in several clinical trials, including phase I, II, and III trials in different indications (appendix p 3). The next step is to initiate more trials to evaluate the long-term outcome and follow-up phase. The level of evidence (progression-free survival) of palliative systemic chemotherapy, immunotherapy, surgery, and intraperitoneal chemotherapy for treating patients with peritoneal metastasis is low as compared with liver metastasis, for example.<sup>5</sup> Furthermore, owing to a shortage of drugs approved for intraperitoneal delivery, cisplatin, doxorubicin, and oxaliplatin are used off-label for HIPEC, PIPAC, and other catheter-based systems. PIPAC is not a defined therapy but a generic system for intraperitoneal drug delivery, which is able to aerosolise a large range of substances in a variety of diseases and indications. Evaluation of this technique is not possible by comparison with other administration routes (eg, intravenous or rectal).

For the treatment of resectable peritoneal metastasis, cytoreductive surgery and HIPEC is the gold standard for pseudomyxoma peritonei and peritoneal mesothelioma,<sup>82,83</sup> and is also an option for colorectal, ovarian, and gastric peritoneal metastasis.<sup>15,17,20,84</sup> However, because of its associated morbidity and mortality, this approach is limited to a highly select group of patients who have a favourable tumour biology and few comorbidities. For unresectable peritoneal metastasis, no role exists for such an aggressive treatment strategy, and systemic chemotherapies and targeted therapies remain the standard of care. For colorectal peritoneal metastasis, the best median survival by systemic chemotherapy was

	Number of patients	≥2 PIPAC	Peritoneal cancer index improvement	Assessment of response				Survival
				Histological	Regression score	RECIST	Other	
<b>Ovarian</b>								
PIPAC OV-1 <sup>47</sup>	64	43/53 (81%)	26/34 (76% 3rd PIPAC)	ITT: 33/53 (62%) to 28/53 (72%)*; PP: 26/34 (76%) to 30/34 (88%)*	Glaze et al <sup>49</sup>	ITT: 33/53 (62%); PP: 16/31 (52%)*	..	OS: 331 days (mean; 95% CI 291–371); PFS: 144 days (mean; 122–168)
Tempfer and colleagues <sup>50</sup>	21	8/18 (44%)	..	PP: 6/8 (75%)	Glaze et al <sup>49</sup>	..	..	442 days (mean)
Tempfer and colleagues <sup>51</sup>	99	50/82 (61%)	32/50 (64%)	PP: 38/50 (76%)	Glaze et al <sup>49</sup>	..	..	14.1 months (median)
<b>Gastric</b>								
PIPAC GA-1 <sup>48</sup>	25	12/25 (48%)	..	ITT: 9/25 (36%); PP: 9/12 (75%)	PRGS <sup>58</sup>	ITT: 10/25 (40%); PP: 10/13 (77%)	..	8.4±1.7 months (mean); PCI ≤12: 13.1±3.5
PIPAC GA-2 <sup>41</sup>	31	15/31 (48%)	..	PP: 9/15 (60%) to 21/23 (91%)	PRGS <sup>58</sup>	..	..	13 months (median), 1-year OS: 49.8%
Nadiradze and colleagues <sup>52</sup>	25	17/24 (71%)	..	ITT: 12/24 (50%); PP: 12/17 (71%)	TRGS <sup>52</sup>	..	..	15.4 months (median)
Gockel and colleagues <sup>60</sup>	24	14/24 (58%)	8/14 (57%)	PP: 11/14 (79%)	PRGS <sup>58</sup>	..	79% stable or decreased ascites	210 days (median; range 66–625; all); 450 days (median; 206–481; ≥3 PIPAC)
<b>Colorectal</b>								
Demtröder and colleagues <sup>54</sup>	17	14/17 (82%)	..	ITT: 12/17 (71%); PP: 12/14 (86%)	Dworak et al <sup>60</sup>	..	..	15.7 months (median)
<b>Pancreas</b>								
Graversen and colleagues <sup>55</sup>	5	5/5 (100%)	..	PP: 4/5 (80%)	PRGS <sup>58</sup>	..	..	14 months (median), 10–20 months (range)
Khosrawipour and colleagues <sup>57</sup>	20	10/20 (50%)	..	PP: 7/10 (70%)	TRGS <sup>52</sup>	..	..	36.6 weeks (95% CI 36.6–5.11)
<b>Biliary tract</b>								
Falkenstein and colleagues <sup>58</sup>	13	5/11 (45%)	..	PP: 4/5 (80%)	PRGS <sup>58</sup>	..	..	85 days (median; 95% CI 59.2–110.4; overall)
<b>Mesothelioma</b>								
Giger-Pabst and colleagues <sup>59</sup>	29	20/22 (91%)	..	PP: 15/20 (75%)	Dworak et al <sup>60</sup>	..	..	26.6 months (median; 95% CI 9.5–43.7)
<b>Various</b>								
PIPAC OPC-1 <sup>49</sup>	35	30/35 (86%)	..	ITT: 20/35 (57%); PP: 20/30 (67%)	PRGS <sup>58</sup>	..	..	..
Alyami and colleagues <sup>58</sup>	73	45/73 (62%)	61% (PP); 65% (3rd PIPAC)	..	..	..	46–63% with symptom relief	..
Kurtz and colleagues <sup>59</sup>	71	39/63 (62%)	..	PP: 24/36 (67%)	PRGS <sup>58</sup>	..	..	11.80 months (median; 95% CI 7.45–16.20)
<b>Total, weighted mean</b>	<b>552</b>	<b>65.0%</b>	<b>66.7%</b>	<b>PP: 73.7%; ITT: 57.1%</b>	<b>..</b>	<b>PP: 56.4% ITT: 59.0%</b>	<b>..</b>	<b>Data not pooled (different primaries)</b>

Studies that reported less than five patients were excluded. PIPAC=pressurised intraperitoneal aerosol chemotherapy. RECIST=Response Evaluation Criteria in Solid Tumors. ITT=intention to treat. PP=per protocol. OS=overall survival. PFS=progression-free survival. TRGS=tumour regression grading system; PRGS=peritoneal regression grading score. \*External blinded assessment.

**Table 2: Clinical efficacy of pressurised intraperitoneal aerosol chemotherapy**

estimated to be 16.3 months (IQR 12.9–19.2).<sup>5</sup> In patients treated using PIPAC, only one study<sup>54</sup> exclusively evaluated the survival in colorectal peritoneal metastasis. Multiple clinical trials are ongoing to assess the role of PIPAC for patients with colorectal peritoneal metastasis. For gastric peritoneal metastasis, multiple studies have estimated survival after PIPAC (table 2). For example, Alyami and colleagues<sup>58</sup> presented results from the Lyon cohort at the 38th European Society of Surgical Oncology with a median survival of 19.1 months. These preliminary

results for patients with gastric peritoneal metastasis are promising when compared with data for patients who have been treated with systematic chemotherapy alone, in whom the reported median survival did not exceed 10.7 months (95% CI 9.1–12.8).<sup>86</sup> Among patients with recurrent platinum-resistant ovarian cancer, Pujade-Lauraine and colleagues<sup>87</sup> reported 16.6 months survival as the best outcome for systemic chemotherapy. However, the available data indicated survival of 11.0–14.1 months after PIPAC. For patients with malignant peritoneal

	Colorectal cancer		Gastric cancer		Ovarian cancer		Peritoneal mesothelioma		Biliary tract cancer		Appendiceal cancer	
	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC	PIPAC	HIPEC
High risk for peritoneal metastasis after primary tumour resection	USC	USC	USC	USC	-	-	-	-	?	?	-	-
Upfront or interval situation and resectable peritoneal metastasis	USC	PCI ≤ 15	USC; PCI > 6	USC; PCI ≤ 6	USC	+	USC	+	USC	USC	-	+
Synchronous or recurrent peritoneal metastasis as sole metastatic site and unresectable disease, or patient not eligible for extensive cytoreductive surgery or HIPEC and with 2nd or 3rd line of systemic chemotherapy	+	-	+	-	+	-	+	-	+	-	+	-
Refractory ascites	+	-	+	-	+	+/-	+	-	+	-	+	-
Systemic chemotherapy intolerance	+	-	+	-	+	-	+	-	+	-	+	-
Unfavourable histology	+*§	-*	+*§	-*	+†§	+†	+‡§	+/-‡	+§	-	+*§	-*

PIPAC=pressurised intraperitoneal aerosol chemotherapy. HIPEC=hyperthermic intraperitoneal chemotherapy. USC=under study condition. PCI=peritoneal cancer index. \*Signet ring histology. †Clear cell carcinoma, undifferentiated ovarian cancer. ‡Sarcomatoid or biphasic peritoneal mesothelioma. §Unfavourable histology is an additional argument to introduce PIPAC earlier in the treatment strategy.

**Table 3: Potential indications for the use of PIPAC and HIPEC**

mesothelioma, 12 months was the best survival reported for this group of patients using systemic chemotherapy only.<sup>88</sup> Subsequent cytoreductive surgery and HIPEC after PIPAC as neoadjuvant treatment has been described by Girshally and colleagues.<sup>89</sup> They performed cytoreductive surgery and HIPEC in 21 (5%) of 406 patients with unresectable peritoneal metastases. Among these patients, more than 50% presented a low peritoneal cancer index (mean 5.8, SD 5.6). Additionally, French data<sup>90</sup> also presented at the 38th European Society of Surgical Oncology meeting indicate that 21 (14%) of 146 patients with an initial median peritoneal cancer index of 16 (IQR 1–39) had a successful secondary cytoreductive surgery and HIPEC after neoadjuvant PIPAC. These data suggest that strictly selected patients with unresectable peritoneal metastasis could be eligible for secondary cytoreductive surgery and HIPEC after repeated PIPAC sessions with palliative intent. The appendix (p 3) details ongoing clinical trials using PIPAC, which will provide more evidence on its feasibility and safety in the next few years. In palliative management, survival should not be the only and principal endpoint. Quality of life and treatment tolerance also represent other important treatment endpoints, for which the preliminary results of PIPAC appear promising.<sup>53,71</sup> The replacement of one cycle of systemic chemotherapy with PIPAC every 6 weeks ( $\pm 2$  weeks), as has been proposed by several teams (figure 3), might improve overall tolerance and quality of life by reducing adverse effects of systemic treatment.<sup>40</sup> However, future studies should evaluate whether or not this reduction in dose intensity is counterbalanced by a decrease in efficacy.

Defining indications for PIPAC is difficult without large prospective comparative studies. The potential indications for PIPAC are summarised in table 3, along with proposed indications for HIPEC according to the best available evidence. The intent and indications are

very different for HIPEC and PIPAC. HIPEC performed in conjunction with cytoreductive surgery offers the best outcomes, with potentially curative intent, but only for highly selected patients with peritoneal metastasis.<sup>15,17,20,82–84</sup> Most of these patients benefit from additional perioperative systemic chemotherapy, and the outcomes of systemic chemotherapy alone have improved considerably with the advent of multidrug combinations, including targeted therapies.<sup>5</sup> However, for patients who are not candidates for cytoreductive surgery and do not tolerate or respond (anymore) to systemic treatment, off-label PIPAC therapy appears to be legitimate, and PIPAC can be considered a treatment option in patients without a validated treatment approach. However, PIPAC should only be done within the framework of clinical studies when competing with an evidence-based therapy (table 3). Some of these questions are being investigated in prospective study protocols (appendix p 3).<sup>43,45,73,74,91</sup> The international prospective PIPAC registry (NCT03210298) should also provide regularly updated large-scale information on safety, efficacy, and quality of life outcomes for different disease entities and indications. The surgical approach and administration of PIPAC are standardised and homogeneous, indications and treatment regimens are highly standardised among treatment centres,<sup>32</sup> and dedicated training centres (appendix p 1), and the International Society for the Study of Pleura and Peritoneum-endorsed standardised PIPAC training curriculum should help maintain homogeneity and high treatment standards. The standards include respecting the contraindications to PIPAC treatment to prevent avoidable (severe) complications and futile treatment interventions.

8 years after the first PIPAC treatment in humans and 4 years after wider adoption (appendix p 2), PIPAC should still be considered a new technique. No studies have been done comparing PIPAC with other treatment options,

including systemic chemotherapy, and, as with any new treatment, no long-term results are available. Therefore, in accordance with the IDEAL framework, PIPAC should still be considered in the assessment stage. The status of PIPAC evaluation has several problems. The available studies are heterogeneous with regard to patients and indications. Additionally, patient overlap exists between studies from the same groups. For our analysis, duplicates were carefully removed. Furthermore, assessment of treatment response and efficacy, such as peritoneal regression grading score, RECIST, and peritoneal cancer index, differed considerably between studies (table 2); standardisation for future studies should be a top priority. A new method of assessing tumour response, especially for micronodular diffuse peritoneal metastasis, which is not sufficiently visible on morphological examinations, should probably be established with this new therapeutic technique. PIPAC is indicated mainly for patients receiving palliative treatment. The appropriate endpoints to evaluate or promote this technique could be one or more of the following items: overall survival, disease-free survival, quality of life, ascites control, and obstruction-free survival. No randomised trials for any treatment method are measuring these outcomes in patients with peritoneal metastasis.

Our analysis has methodological limitations. A meta-analysis of the data was not feasible owing to the heterogeneity of the data. Comparative data are not available, and selection bias is a potential problem. Because PIPAC has only been practised on a larger scale since 2015, long-term data cannot be expected before 2020. Furthermore, PIPAC is not considered superior to liquid intraperitoneal chemotherapy, and PIPAC dosing, pressure, exposure time, and time intervals are still used empirically. These limitations are inherent to all new treatments. However, the introduction and evaluation of PIPAC closely follows the IDEAL framework, including three major points: homogeneity of technique, indications, and drug regimens;<sup>32</sup> structured certification courses for safe implementation of this potentially dangerous method with endorsement by a scientific society; and, scientific evaluation from the beginning within an international academic network using a prospective registry and multiple prospective clinical studies, including dose-finding and randomised phase III studies evaluating efficacy.

### Conclusion

In summary, PIPAC can be considered a safe and promising treatment alternative for patients with advanced isolated refractory peritoneal disease. Other indications are being studied according to the IDEAL framework, such as prophylactic, neoadjuvant, or adjuvant treatment strategies including treatment combinations with systemic regimens. Reliable results should be available within the next 5–10 years.

### Contributors

MA and MH developed the idea. MA, MH, and FG drafted the review and prepared the tables and figures. All authors substantially revised the manuscript. All authors reviewed and approved the manuscript before submission. MA and MH both contributed equally to this manuscript.

### Declaration of interests

We declare no competing interests.

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