Review Article on New Technologies

The emergence of pressurized intraperitoneal aerosol chemotherapy as a palliative treatment option for patients with diffuse peritoneal metastases: a narrative review

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Abstract: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an emerging palliative treatment for patients with unresectable peritoneal metastases. Potential advantages of PIPAC over current treatment options are a homogeneous intraperitoneal distribution, low local and systemic toxicity, and enhanced tumour penetration. Given these possible benefits, PIPAC is increasingly implemented in many centres worldwide. Scientific research into PIPAC is currently available from *in vitro*/*in vivo*/in animal studies, retrospective cohorts in humans, and phase I and II studies in humans. There are no results from randomised trials comparing PIPAC with conventional treatment, such as palliative systemic therapy. This narrative review aimed to provide an overview of the currently available literature on PIPAC. In general, repetitive PIPAC was feasible and safe for patients and operating room personnel. Primary and secondary non-access rates varied from 0–17% and 0–15%, respectively. Iatrogenic bowel injury was observed in 0–3% of PIPAC procedures. CTCAE grade 1–2 complications were common, mostly consisting of abdominal pain, nausea, vomiting, and fatigue. CTCAE grade 3–4 complications were uncommon, occurring on 0–15% of PIPAC procedures. Post-operative mortality rates of 0–2% were reported. The risk of occupational exposure to cytotoxic drugs was very low when strict safety guidelines were followed. Clinical heterogeneity was high in most studies, since, in general, patients with unresectable peritoneal metastases from a variety of primary tumours were included. Also, patients received either PIPAC monotherapy or PIPAC combined with concomitant systemic therapy, and were able to receive PIPAC in any line of palliative treatment. Since the results were generally not stratified for these three important factors, this severely complicates the interpretation of results. Based on the current literature, PIPAC may be regarded as a promising palliative treatment option in patients with diffuse peritoneal metastases. Initial results show that it is feasible and safe. However, well designed and (ideally) randomized controlled trials are urgently needed to determine the additional value of PIPAC in this setting. Until then, PIPAC should preferably be performed in the setting of clinical trials.

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

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Introduction

Peritoneal metastases are frequently encountered in patients with intra-abdominal malignancies (1-4). Unfortunately, most patients are not eligible for curative-intent treatment and are treated with palliative systemic therapy or receive no treatment at all. Despite treatment with palliative systemic therapy, the prognosis of patients with peritoneal metastases is poor. This might be due to the presence of the plasma-peritoneal barrier, which is hypothesized to limit chemotherapy concentrations in peritoneal metastases, yielding poorer response rates than in the treatment of systemic (e.g., liver, lung) metastases. Therefore, the direct intraperitoneal delivery of chemotherapy could be an interesting alternative, aiming to increase intraperitoneal chemotherapy concentrations (5). However, the results with conventional intraperitoneal chemotherapy lavage have not been convincing in this setting, probably explained by poor tumour penetration, dose-limiting local toxicity, and an inhomogeneous intraperitoneal drug distribution (6,7).

This has led to the development of new methods for intraperitoneal drug delivery. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a laparoscopic method for the repetitive administration of intraperitoneal chemotherapy as a pressurized aerosol, claiming to overcome the limitations of conventional peritoneal lavage by achieving an enhanced tumour penetration, low local and systemic toxicity, and a homogeneous intraperitoneal drug distribution.

Over the past decade, PIPAC has been increasingly practiced for the treatment of peritoneal metastases of various primary tumours in many centres worldwide (8,9). Currently, the most common indications are peritoneal metastases from gastric cancer, ovarian cancer, and colorectal cancer. Also, the use of PIPAC was also infrequently reported for unresectable peritoneal metastases from other primary tumours, such as hepatobiliary and pancreatic tumours, pseudomyxoma peritonei and mesothelioma. In humans, most patients receive PIPAC with cisplatin (7.5 mg/m^2) and doxorubicin (1.5 mg/m^2). An exception are colorectal cancer patients, who receive PIPAC with oxaliplatin (92 mg/m^2). This narrative review aims to provide an overview of the studies currently available.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-497).

Experimental and in-animal studies

In 2012, a first animal-study using macroscopic assessment showed that PIPAC resulted in more intense staining and superior distribution of methylene blue throughout the entire peritoneal cavity than conventional peritoneal lavage (10). However, other studies (both ex-vivo and in-animal studies) found that PIPAC resulted in an inhomogeneous distribution pattern of the pressurized aerosol, with maximum macroscopic staining and microscopic tissue penetration depth in the area around and opposite to the microinjection pump (11-13). As a result, the degree of macroscopic staining and microscopic tissue penetration depth was very low in other areas. Changing the position of the microinjection pump, increasing the drug concentration, or increasing the pressure of the therapeutic capnoperitoneum did not overcome this problem (14).

The inhomogeneous distribution and tissue penetration depth could be related to the relatively large size of the PIPAC aerosol droplets, resulting in the deposition of the aerosolized liquid within a 15 cm circular area beneath the microinjection pump, mainly due to gravitational settling and inertial impaction (15). Increasing the flow rate of the aerosol might be able to decrease the droplet size and increase the homogeneous distribution of the aerosol (16).

In an effort to increase tissue depth of penetration, several ex-vivo and in-animal experiments were performed with tissue irradiation, liposomal coating of cytotoxic agents, and electrostatic precipitation of the pressurized aerosol. An inhibitory effect on the tissue penetration depth of the cytotoxic agents was found after tissue irradiation and liposomal coating (17-20). However, two studies suggested superior aerosol distribution and tissue uptake after electrostatic PIPAC as compared to regular PIPAC (21,22).

Pharmacokinetics

An in-animal study showed that the systemic exposure to oxaliplatin was comparable after HIPEC (400 mg/m^2), PIPAC (92 mg/m^2) and electrostatic PIPAC (92 mg/m^2), despite a much higher oxaliplatin dose that was used during HIPEC (23). Remarkably, (electrostatic) PIPAC resulted in a biphasic pattern of systemic uptake, with limited systemic uptake during the first thirty minutes followed by a rapid increase during the next thirty minutes. This biphasic pattern could be caused by the high intra-

abdominal pressure during the first thirty minutes, reducing intraperitoneal blood flow and lowering systemic uptake (24). However, in another in-animal study, HIPEC with cisplatin (70 mg/m^2) resulted in higher systemic exposure to cisplatin than PIPAC with cisplatin (7.5 mg/m^2) (25). Nevertheless, PIPAC resulted in relatively higher systemic concentrations of cisplatin, reaching a two-fold greater yield. This might suggest that PIPAC can achieve similar exposure of chemotherapeutic agents as HIPEC by using a lower dosage.

Finally, two in-animal studies showed that the systemic exposure to and maximum concentrations of oxaliplatin (26) and paclitaxel (27) were higher after intravenous administration than after PIPAC, even though the same dosages were used. This suggests that a significant amount of the cytotoxic agent is not entering the systemic circulation but remains in the peritoneal cavity at the end of a PIPAC procedure.

Cytotoxicity

Three *in vitro* studies were performed investigating the cytotoxicity of several PIPAC drugs. PIPAC with oxaliplatin showed a more potent cytotoxic effect than PIPAC with mitomycin C or taurolidine (28). Furthermore, PIPAC with oxaliplatin showed a similar cytotoxic effect as HIPEC with oxaliplatin (26), despite the five-fold higher dosage used during HIPEC. The cytotoxic effect of PIPAC with oxaliplatin was more pronounced, dose-, and pressure-dependent in wild-type colon cells than in chemotherapy resistant colon cells (29). Both exposure time and temperature of the pressurized aerosol did not affect cytotoxicity.

In human studies

Studies currently available in patients are, without exception, retrospective cohort studies or prospective phase I or II studies (*Table 1*). Furthermore, the majority of the available studies included patients with unresectable peritoneal metastases from a variety of primary tumours, who received PIPAC either as a monotherapy or combined with concomitant systemic therapy, and who received PIPAC either as first-line palliative therapy or as later line of palliative therapy. Since most studies did not provide stratified results based on primary tumour, PIPAC monotherapy versus PIPAC with concomitant systemic therapy, and line of palliative treatment (first versus later line), there is a high degree of clinical heterogeneity in most studies. This seriously hampers the interpretation of these results, in particular with regards to tumour response and survival.

Occupational exposure

One of the initial concerns of PIPAC was the potential exposure of operating room staff to aerosolized cytotoxic agents. To minimize the risk of exposure, PIPAC is performed in an operating room with laminar airflow with a closed abdomen. Protective curtains cover the patient and the connection to the high-pressure injection pump, and a closed aerosol waste system is used to remove the toxic aerosol. To investigate the risk of exposure with these safety measures, several studies examined air and surface-wipe samples, as well as blood and urine from operating room staff, after PIPAC with cisplatin-doxorubicin (30-36) or oxaliplatin (30-32) for contamination with cytotoxic agents. Although no or negligible traces of the cytotoxic agents were reported by three studies, four studies did find significant contamination of several operating room surfaces (e.g., floor, high pressure injection pump) and the exterior surface of sterile gloves (32-35). In one study PIPAC was performed in an operating room without laminar airflow, and no traces of cisplatin-doxorubicin in air or surface-wipe samples were found, except for the surgeon's outer gloves, suggesting that PIPAC could be performed in an operating room without laminar airflow (37). These findings show that with the adherence to very strict safety guidelines during PIPAC, the risk of exposure of operating room staff to cytotoxic agents is very low.

Inflammatory response and organ toxicity

The administration of cytotoxic agents by PIPAC is thought to induce a chemical peritonitis, explaining the abdominal pain and transient inflammatory response often reported during the first post-operative days (34,38-44). Interestingly, one study found that the inflammatory response was greater after PIPAC with oxaliplatin than after PIPAC with cisplatin-doxorubicin (44). Both PIPAC with cisplatin-doxorubicin and PIPAC with oxaliplatin did not result in clinically relevant liver or renal dysfunction during the first post-operative days (34,40-49), nor did it appear to result in cumulative toxicity (45).

Table 1 An overview of the studies discussed in this narrative review

Experimental studies	In-animal studies	In-human studies
Khosrawipour (2016) (11)	Solaß (2012) (10)	Graversen (2016) (30)
Khosrawipour (2016) (14)	Khosrawipour (2016) (12)	Willaert (2017) (31)
Göhler (2017) (15)	Bellendorf (2018) (13)	Ametsbichler (2018) (32)
Khosrawipour (2016) (17)	Van de Sande (2019) (16)	Ndaw (2018) (33)
Khosrawipour (2016) (18)	Khosrawipour (2017) (19)	Jansen-Winkeln (2019) (34)
Van de Sande (2020) (22)	Mikolajczyk (2018) (20)	Graversen (2018) (35)
Eveno (2017) (26)	Kakchekeeva (2016) (21)	Solass (2013) (36)
Schubert (2019) (28)	Giger-Pabst (2019) (23)	Delhorme (2019) (37)
Khosrawipour (2017) (29)	Davigo (2020) (25)	Tempfer (2014) (38)
	Eveno (2017) (26)	Nadiradze (2016) (39)
	Tan (2020) (27)	Robella (2016) (40)
		Demtröder (2016) (41)
		Gockel (2018) (42)
		Reymond (2016) (43)
		Teixeira Farinha (2018) (44)
		Blanco (2013) (45)
		Larbre (2018) (46)
		Tempfer (2018) (47)
		Falkenstein (2018) (48)
		Giger-Pabst (2018) (49)
		Hübner (2017) (50)
		Alyami (2017) (51)
		Graversen (2020) (52)
		Sabaila (2015) (53)
		Hübner (2017) (54)
		Sgarbura (2019) (55)
		Somashekhar (2019) (56)
		Katdare (2019) (57)
		Tempfer (2015) (58)
		Gockel (2020) (59)
		Struller (2019) (60)
		Khosrawipour (2017) (61)
		Horvath (2018) (62)
		Kurtz (2018) (63)
		Willaert (2019) (64)
		Tempfer (2015) (65)
		Di Giorgio (2020) (66)
		Graversen (2017) (67)
		Di Giorgio (2020) (68)
		Odendahl (2015) (69)
		Solass (2014) (70)
		Graversen (2018) (71)
		Siebert (2021) (72)
		Dumont (2020) (73)
		Ellebaek (2020) (74)
		Alyami (2021) (75)
		Siebert (2019) (76)
		Khomyakov (2016) (77)
		Teixeira Farinha (2017) (78)

Feasibility and safety

Laparoscopic access to the peritoneal cavity is required to perform PIPAC. However, due to previous abdominal surgeries, the peritoneal cavity may become inaccessible. This may result in primary non-access, meaning that a first PIPAC is not feasible to perform in a patient. Secondary non-access occurs if a first PIPAC can be performed in a patient but the formation of new adhesions prevent a subsequent PIPAC procedure. Generally, other treatments (e.g., systemic therapy) are paused several days to weeks before and after the administration of PIPAC, aiming to reduce the risk of morbidity due to cumulative toxicity. Thus, both primary and secondary non-access should be prevented as much as possible to prevent unnecessary interruptions of treatment.

Both primary (34,35,38,39,42,48-54,56-59,62-66) and secondary (34,35,39-42,47,49-51,54-57,59-63,66) non-access rates widely varied among studies. Primary non-access was observed in 0–17% of patients, although two studies reported a primary non-access rate of 24% and 28%. Secondary non-access was observed in 0–15% of patients, although one study reported a secondary non-access rate of 35%. This suggests that the chemical peritonitis induced by PIPAC can result in the formation of adhesions. Risk factors for primary and secondary non-access should be determined to further enhance patient selection criteria and minimize non-access rates.

Reported complications during the PIPAC-procedure were scarce. The most common intraoperative complication was an iatrogenic bowel injury (0–3% of total PIPAC procedures, except for one study reporting an iatrogenic bowel injury in 6% of total PIPAC procedures) (34,35,38-42,47,48,54,63-69). Post-operatively, most adverse events consisted of grade 1 and 2 abdominal pain, nausea, vomiting, and fatigue, according to the Common Terminology Criteria for Adverse Events (CTCAE). CTCAE grade 3 and 4 post-operative complications were observed in 0–15% of total PIPAC procedures, mostly consisting of abdominal pain, intestinal obstruction or ileus, or an anaphylactic reaction to the chemotherapeutic agent (0% as reported by references 40,42,43,48,50,53,54,56,59,61,62,67,68,70,77; >0% as reported by references 34,35,38,39,41,47,51,55,57,58,60,63-66,69,71-76). Post-operative mortality varied from 0–2% of total PIPAC procedures, except for one study reporting a mortality rate of 6%. Mortality was mainly caused by unrecognised bowel injury or bowel obstruction (0% as reported by references 35,38,40-43,48,56,58-60,62,64,65,67,68,70; >0% as reported by references 34,39,49-51,55,57,61,63,66,69,71,72,75). There is currently no evidence suggesting that electrostatic precipitation of the pressurized aerosol or concomitant systemic therapy with bevacizumab results in increased complication rates (43,52,64,72).

It should be noted that in most studies, adverse event rates were not stratified by PIPAC monotherapy and PIPAC with concomitant systemic therapy (i.e., bidirectional therapy), even though patients treated with bidirectional therapy might be at a greater risk of adverse events due to the more intensive treatment.

Tumour response

Several studies reported on tumour response. However, these results are difficult to interpret due to the presence of clinical heterogeneity (i.e., primary tumour, line of palliative treatment, PIPAC monotherapy versus PIPAC with concomitant systemic therapy) and the criteria used to assess response. The peritoneal regression grading scale was used in most studies and histological regression was defined as complete or partial response (79,80). The majority of studies reporting histopathological regression focused on patients with peritoneal metastases from one primary origin, except for six studies. The latter reported on an overall histopathological regression rate (intention to treat) of 12–71% (35,52,56,63-65). Four other studies reported on gastric cancer patients, and histopathological regression (intention to treat) varied from 25–50% (39,60,66,74). In ovarian cancer patients, histopathological regression (intention to treat) varied from 6–17% (38,53,58). In hepatobiliary-pancreatic cancer patients, histopathological regression (intention to treat) varied from 35–100% (43,48,61,62,67). Also, one study reported higher histopathological regression rates in hepatobiliary-pancreatic cancer patients treated with PIPAC with cisplatin-doxorubicin than in those treated with PIPAC with oxaliplatin (68). Finally, two studies reported on histopathological regression (intention to treat) in either colorectal (41) or malignant mesothelioma (49) patients treated with repetitive PIPAC, and found a response rate of 71% and 26%, respectively. The above mentioned histopathological regression rates were all recalculated by the authors according to the intention-to-treat principle (number of patients with histological response/total number of patients treated with PIPAC), since histopathological regression was only reported in patients receiving repetitive

PIPAC. This may introduce a bias as most patients who are ineligible to receive repetitive PIPAC have experienced progressive disease during treatment with PIPAC. Ideally, in future clinical studies histopathological regression should also be interpreted according to the intention-to-treat principle.

Patient reported outcomes (PROs)

Few studies reported PROs in patients treated with PIPAC. The EORTC-QLQ-C30 was used in all these studies. PROs were not reported separately for patients treated with PIPAC monotherapy and PIPAC with concomitant systemic therapy, again resulting in clinical heterogeneity. Furthermore, PROs were measured at different time intervals after treatment with PIPAC, which also varied greatly among studies. Several studies did not provide information on when PROs were measured (49,58,69), whereas others measured PROs before each PIPAC (42,60,65,78), after each PIPAC (40,78), or at fixed intervals regardless of treatment with PIPAC (35). Naturally, timing of PRO measurement affects these results – measuring directly after PIPAC will provide insight into the short-term effects of PIPAC on PROs, whereas measuring before the next PIPAC will provide insight into the long-term effects of PIPAC on PROs.

Six out of eight studies did not provide a statistical analysis of PROs, but merely a narrative description. Of the two studies that did provide a statistical analysis, the first analysis only found a significant increase in nausea and vomiting after the first PIPAC, but otherwise stable PROs (78). The second analysis did not find a significant change in any PRO, reporting a stabilization of PROs during treatment with PIPAC (60).

In the narrative others, some described a stabilization of PROs during treatment with PIPAC (35,40,69), an improvement of all functional and symptom scales (49), or mixed results (42,58,65). In studies reporting mixed results, most function scales improved but several symptom scales deteriorated (e.g., dyspnoea, diarrhoea, pain, appetite loss).

Survival

Several studies reported on overall survival, and all reported stratified results based on primary tumour location. However, no stratified results were reported based on the line of palliative treatment and/or PIPAC monotherapy versus PIPAC with concomitant systemic therapy, which complicates the interpretation.

Median overall survival (OS), as calculated from first PIPAC, varied widely based on primary tumour. In patients with gastric cancer, an OS of 5 to 7 months was reported (42,63,66,74). However, one study reported an OS of 19 months for gastric cancer patients treated with PIPAC, although the interval was not mentioned (75). In ovarian cancer patients, OS varied from 7 to 15 months (53,58,63,65). In hepatobiliary-pancreatic cancer patients, OS ranged from 3 to 12 months (48,61,63,68). In colorectal cancer patients, one study reported an OS of 16 months, and median OS was not reached in a second study (41,63).

Dose escalation studies of PIPAC drugs

To date, the results of two PIPAC dose-escalation studies have been published that investigated the maximum tolerated dose of cisplatin-doxorubicin (47) and oxaliplatin (73). The first study did not reach the maximum tolerated dose of cisplatin-doxorubicin, suggesting that PIPAC with cisplatin-doxorubicin can be safely performed at doses of 10.5 and 2.1 mg/m^2, respectively. The second study did not observe dose-limiting toxicity at oxaliplatin 90 mg/m^2 but observed two dose-limiting toxicities (allergic reaction, n=1; neutropenia, n=1) at the next dose of oxaliplatin 140 mg/m^2. Although these results discourage the administration of oxaliplatin 140 mg/m^2 by PIPAC, it is possible that PIPAC with oxaliplatin at a dose between 90 and 140 mg/m^2 (e.g., 115 mg/m^2) would be well-tolerated by patients. A second dose-escalation study, of which the results are not yet available, might elaborate on this in-between dose (81).

Ongoing studies

In colorectal cancer, one dose-escalation study investigates the maximum-tolerated dose of PIPAC with oxaliplatin, starting at a dose level of 45 mg/m^2 and escalating to 60, 90, 120 and 150 mg/m^2 (81). Furthermore, three prospective phase II studies are ongoing, treating colorectal cancer patients with PIPAC monotherapy (82), PIPAC with concomitant systemic therapy (Netherlands Trial Register; NL8303), or both (Clinicaltrials.gov; NCT03868228). To the best knowledge of the authors, there are currently no ongoing randomized controlled trials focusing on PIPAC with oxaliplatin in patients with colorectal cancer.

Two studies specifically focus on PIPAC in patients with gastric cancer. One is a phase II study in which PIPAC monotherapy with oxaliplatin and nivolumab is performed

(Clinicaltrials.gov; NCT03172416). The other is a phase III study which randomizes between systemic therapy alone versus PIPAC with cisplatin-doxorubicin with concomitant systemic therapy (83).

One phase II study and two phase III studies focus on PIPAC in patients with ovarian cancer. The phase II study performs PIPAC monotherapy with cisplatin-doxorubicin (Clinicaltrials.gov; NCT02735928). The two phase III studies both have a similar study design, both randomizing between PIPAC monotherapy with cisplatin-doxorubicin versus systemic therapy (84,85).

Also, one phase III study randomizes between PIPAC with cisplatin-doxorubicin with concomitant systemic therapy versus systemic therapy alone in patients with a malignant peritoneal mesothelioma (86).

Finally, five prospective studies are currently recruiting patients with peritoneal metastases from various primary tumours. One is a dose-escalation study for PIPAC with nab-paclitaxel and cisplatin in patients with oesophageal, gastric, ovarian or pancreatic tumours, or with a malignant peritoneal mesothelioma (Clinicaltrials.gov; NCT04000906). Two phase II studies treat patients with PIPAC monotherapy with cisplatin-doxorubicin or oxaliplatin (Clinicaltrials.gov; NCT04329494) (87). Furthermore, two phase III studies are randomizing patients between systemic therapy alone versus PIPAC with cisplatin-doxorubicin and concomitant systemic therapy (88); or versus PIPAC monotherapy with cisplatin-doxorubicin or oxaliplatin (89).

Discussion and conclusions

Currently available data from phase I and II studies suggest that repetitive PIPAC is feasible and safe for both patients and operating room personnel. Occupational exposure to cytotoxic drugs during and after PIPAC is very low when PIPAC is performed according to strict safety guidelines (e.g., closed aerosol waste system, laminar airflow). Although repetitive PIPAC is feasible in most patients, some studies reported high secondary non-access rates (>15%). Risk factors for secondary non-access should be investigated to improve patient selection and counselling. Minor postoperative adverse events (CTCAE grade 1–2), such as abdominal pain, nausea, vomiting and fatigue, occurred in the majority of patients. Major adverse events (CTCAE grade 3–4) and post-operative mortality were low, being reported in <15% and <2% of PIPAC procedures, respectively.

Unfortunately, based on currently available results it remains impossible to draw reliable conclusions with regards to tumour response and survival after PIPAC. This is caused by the high degree of clinical heterogeneity (i.e., various primary tumours, various lines of palliative treatment, mixed cohorts with both PIPAC monotherapy and PIPAC with concomitant systemic therapy) and the lack of stratified results in the majority of studies. Furthermore, the few studies who did provide stratified results to reduce clinical heterogeneity are hampered by small study populations.

Thus, well-designed randomized controlled trials are required to determine the potential additional role of PIPAC. Such trials are currently ongoing for patients with peritoneal metastases from gastric cancer (83), mesothelioma (86), and ovarian cancer (84,85), as well as for patients with peritoneal metastases from any primary tumour (88,89). Investigators are urgently encouraged to provide stratified results based on primary tumour, line of palliative treatment, and PIPAC monotherapy versus PIPAC with concomitant systemic therapy, which will facilitate an adequate interpretation of the results. While awaiting these results, treatment with PIPAC should preferably be performed in the setting of a clinical trial.

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Footnote

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