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► To cite this version:

Abdelkader Taibi, Sophie Geyl, Henri Salle, Laurence Salle, Muriel Mathonnet, et al.. Systematic review of patient reported outcomes (PROs) and quality of life measures after pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Surgical Oncology*, 2020, 35, pp.97 - 105. 10.1016/j.suronc.2020.08.012 . hal-03491388

HAL Id: hal-03491388

<https://hal.science/hal-03491388>

Submitted on 30 Aug 2022

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Title:

Systematic review of patient reported outcomes (PROs) and quality of life measures after pressurized intraperitoneal aerosol chemotherapy (PIPAC).

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Author Contributions: *All authors conceived the study concept, design and drafted the manuscript. All authors have read and approved the final version of the manuscript.*

Abstract

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) constitutes a recently described surgical technique to administer chemotherapy directly to the peritoneum, under pressure, for patients with peritoneal metastasis (PM). The purpose of an oncological treatment is to improve survival but without altering the patient's quality of life. The aim of this review was to evaluate patient-reported outcomes (PRO) after PIPAC for patients with PM.

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Between January 1, 2013, and January 1, 2020, studies were selected according to the following criteria: “pressurized intraperitoneal aerosol chemotherapy” OR “PIPAC” AND “patient-reported outcomes” OR “PRO” OR “Quality of life”.

In this review, 959 PIPAC and five PITAC (Pressurized IntraThoracic Aerosol Chemotherapy) were performed in 425 patients. We highlight the prominent application of generic EORTC QLQ-C30 followed by SF-36 in this review. The PROs according to the EORTC-QLQ-C30 global health score and based on symptom and function scores were stable across most studies. Moreover, PIPAC has improved the PRO of altered patients in two studies. Among 425 patients, the mortality rate was 0.7% and adverse events of Common Terminology Criteria of Adverse Events grade 3 and grade 4 were 9.6% and 1.6%, respectively. We synthesised current research on PROs among patients with PM. This review increases our understanding of the PIPAC strategy from the patient perspective. The implementation of PROs can be complex but will be essential in delivering quality care.

Keywords

PIPAC, peritoneal metastasis, quality of life, PRO, patient reported outcome

Introduction

Ovarian and digestive cancers often spread throughout the entire peritoneal cavity, which worsens patient prognosis. Regardless of the origin of peritoneal metastasis, the main approach for a curative treatment is complete cytoreductive surgery (CRS), and only used in highly selected patients (1). Systemic chemotherapy is the cornerstone of liver and lung metastasis management (2), but it is known to have low drug penetration into PM.

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) constitutes a recently described surgical technique to administer chemotherapy directly to the peritoneum, under pressure, for patients with peritoneal metastasis of various origins and who are not suitable candidates for -CRS +/- Hyperthermic Intraperitoneal Chemotherapy (HIPEC) (3,4). This novel palliative treatment is based on the observation that intraperitoneal chemotherapy under pressure and as an aerosol may enhance the drug diffusion within the peritoneal area and enhance drug penetration into PM (5).

Moreover, the principal advantage of PIPAC is that it can be associated with systemic chemotherapy and can be applied repeatedly, thus increasing its potential to achieve local control.

Although systemic chemotherapy may provide survival benefit, Quality of Life (QoL) plays an important role in patients who are likely to have a poor and deteriorating QoL due to associated pain, ascites, bowel obstruction, and fistulae.

Nevertheless, high-quality oncological care requires patients to provide information regarding how they are feeling, their symptoms, and any effects of chemotherapy or surgery. The medical community recognized the importance of considering these patient-reported outcomes (PROs) along side patients' quality of life (6). PROs are any clinical outcome reported directly by the patient and captured either through self-reporting or interview. QoL is a type of PRO, because it can only be reported by the patient him or herself but is often

analysed using questionnaires. Other PROs differ from QoL have been developed to perceive and analyse patient's expectations.

While trials have traditionally focused on clinical outcomes, patient-reported outcomes (PROs) are increasingly considered equally important (7,8). PROs are of particular interest in oncology due to the limited survival after morbid and complex treatments requiring careful appraisal and shared decision-making (9,10). In their recently published article, Marino *et al.* show increasing interest in routine patient-reported-outcome implementation (11).

The aim of this review was to evaluate patient-reported outcomes in patients with PM of various origins treated using PIPAC.

Materials and methods

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (12).

Eligibility Criteria

Studies were selected according to the following criteria: “Patient reported outcomes” AND “pressurized intraperitoneal aerosol chemotherapy” OR “PIPAC” OR “Quality of life”. We also examined references of selected papers (cross-referencing) for additional cases. Exclusion criteria included studies of PM treated by PIPAC that did not discuss the quality of life.

Search Strategy

To identify relevant papers, we searched Pubmed/Medline using keywords and MESH terms between January 1, 2013, and January 1, 2020. Only English language original articles were included in this study. However, editorials, letters, and meeting abstracts were excluded.

All potentially relevant articles from the initial search strategies were screened for relevance by scanning the titles and abstracts in relation to the eligibility criteria. The full-text versions of potentially eligible articles were retrieved. The reference lists of retrieved articles were manually searched to identify additional relevant studies. Study selection was performed independently by two reviewers (AT and SDF). In case of disagreement, a third reviewer was consulted (HS).

Data Extraction

Data extraction included origin of PM, PIPAC data, histological response, peritoneal cancer index, ascites volumes after PIPAC, and type of questionnaire used for measuring the patient-reported outcomes.

Statistical analysis

The PRISMA flow chart was formulated using Cochrane RevMan version 5.2 software. Proportions (%) were used for some categorical data.

Results of literature review

Literature search (Figure 1)

A total of 10 articles were identified from the literature search (13–22). The PRISMA flow chart outlining the study selection process is shown in Figure 1.

Indication for PIPAC (Table 1)

Ten studies were identified based on inclusion/exclusion criteria, and published prior to January 1st, 2020, in the literature. In this review, 959 PIPAC and five PITAC (Pressurized IntraThoracic Aerosol Chemotherapy) were performed in 425 patients. A total of 186 patients had ovarian cancer, 10 patients had other gynecological cancers, 92 patients had gastric cancer, 42 patients had colorectal cancer, seven had others digestive cancers, 37 had

pseudomyxoma or appendix cancer, 32 patients had peritoneal mesothelioma, five had pleural mesothelioma, and seven patients had carcinoma of unknown primary (CUP). For seven patients, we could not obtain the necessary information. The use of cisplatin and doxorubicin were preferred for PIPAC in patients with gynecological and gastric cancer. Oxaliplatin was used for PIPAC in PM related to colorectal, small bowel cancer, and pseudomyxoma.

Response after PIPAC (Table 1)

The surgeon performed multiple biopsies of peritoneal metastasis to evaluate the histological response after each PIPAC. In this review, the rate of tumour regression on histology was 38% to 100%. This rate is less than 60% in only one study (20). Tumour Grade Regression (TRG) or Peritoneal regression grading score (PRGS) were the two classifications used by the authors.

Peritoneal cancer index (PCI) improvement was noted in four studies and the mean PCI seemed to be stable under PIPAC therapy in two studies. Consecutive ascites volume measurements did not show any significant changes in two studies and increased in two studies.

Outcomes reporting (Table 2 and 3)

Two questionnaires were used: EORTC QLQ C-30 in all studies (13–22) and SF-36 (23) in two studies. The questionnaire was performed during every patient encounter: in outpatient consultation or before each PIPAC, in all studies. For four studies, the questionnaire was performed after the surgery (16,19–21). The PRO was described in eight studies. Global physical health scores showed a continuous improvement during therapy in two studies (13,15) (PIPAC #1= 47.1 vs PIPAC #6 = 60.4 and PIPAC #1 = 52 vs PIPAC #3 = 59.5). Global physical health was stable in six studies. There was no further deterioration of

functional scores, including physical, emotional, cognitive, role, and social scores in patients receiving repeated PIPAC applications. The gastrointestinal scores remained constant and two studies confirmed an improvement in appetite during the observation period (14,22). Nevertheless, PIPAC produced pain and fatigue in two studies (14,20).

Among 425 patients, the mortality rate was 0.7%. Two patients had iatrogenic bowel perforation and one had a renal failure. A total of seven (1.6%) adverse events of Common Terminology Criteria of Adverse Events (CTCAE) 4 (six digestive perforations and one anaphylactic shock) and 41 (9.6%) adverse events of CTCAE 3 were recorded in this review. Abdominal pain was the principal symptom reported by patients after PIPAC.

Discussion

PIPAC is a relatively new technology for delivering intraperitoneal chemotherapy to patients suffering from end-stage peritoneal metastasis. PIPAC is feasible, safe and well-tolerated for patients. For these patients, palliative therapy needs to integrate patient-reported outcomes (PRO) as a therapeutic aim, similar to survival. However, primary outcomes of these studies are typically the peritoneal cancer index, histological response, overall survival and progression free survival. PRO represent a novel and interesting concept that could bring significant insight into the response to treatment for patients with PM. Marandino *et al.* confirmed a lack of patient reported outcomes in major clinical trials on novel therapies (24).

In this systematic literature review, we identified 959 PIPAC and five PITAC in 425 patients with peritoneal metastasis. In this review, we highlight the preferential utilisation of generic "European Organization for Research and Treatment of Cancer" (EORTC) QLQ-C30 followed by SF-36 by the peritoneal surgeons to evaluate the patients reported outcomes after PIPAC. According to the EORTC-QLQ-C30 scoring manual, the global health, symptom and

function scores were generally stable after PIPAC treatment. Moreover, PIPAC has improved the physical and emotional criterias of fragile patients in two studies (15,18). Physical symptoms commonly included fatigue, sleep disturbances, nausea, vomiting, or cognitive problems. These data seems relevant because screening for mental health and emotional is just as important as physical health among patients with cancer (25). Although, PIPAC may potentially be similarly effective against peritoneal metastases than systemic chemotherapy (26), it may causes very mild side-effects, as pain and diarrhea (15,18). But, Oxaliplatin drug might produce more abdominal pain than Cisplatin-Doxorubin. For Dumont et al, 25% of patients experienced abdominal pain after PIPAC with Oxaliplatin (27). For patients with PM, with a shorter survival, our results are important to validate the use of PIPAC therapy, and may be considered as a palliative therapy option. We confirmed the results of another review conducted 3 years earlier including only 5 studies (28).

The majority of PIPAC studies analysed the toxicity of this novel therapy according to CTCAE. In this review, the mortality rate was 0.7% and adverse events of CTCAE 3 and 4 were 9.6% and 1.6%, respectively. Although this classification is simple to use in medical practice to evaluate postoperative complications, it does not consider totally the patient perspective. There is a lack of concordance between toxicity recording by clinicians using the CTCAEs and symptom recording by patients using PROs. Nevertheless, the CTCAE such as other classifications has enabled medical teams to analyse the toxicity of chemotherapy. Some reports on PIPAC-induced toxicities according to CTCAE 4.0 (such as pain, nausea, etc) are self-reported and could represent a PRO-CTCAE as suggested by these authors (29). Recently, the results of these study had suggested that PRO-CTCAE could be used to provide comprehensive data on symptomatic adverse events and integrate the patient experience (29). In conclusion, because the PROs include an extensive range of reports that can be unidimensional or multidimensional, the authors in majority of the studies, used the

classifications, such as EORTC or SF-36 to evaluate the “patients reported outcomes” (30–33).

Others studies have shown that the collection and integration of PROs in clinical practice have been associated with reduced emergency department visits, quality of care, and communication between patients and clinicians (9,34,35). Moreover, the measurement of patient-reported outcomes seems to improve the management of oncology patients and survival. Basch *et al.* showed that the integration of PROs into routine care for advanced cancer patients receiving chemotherapy was associated with improved survival compared to patients following a standard scheme (9). Another study from Denis *et al.* confirmed this result in patients with non-progressive lung cancer, which also showed improved overall survival (36).

In digestive cancers, majority of authors used existing questionnaires in order to evaluate PROs in theirs studies, as EORTC QLQ-C30, EORTC QLQ-LMC21, or FACT-Hep (37,38). To the best of our knowledge, there is no specific PRO for patients with PM. This is important, to develop a specific PRO questionnaire according to a Delphi study for these patients in the coming years. For example, ascites is a very important factor for the patients’ wellbeing (pain, nausea, vomiting, etc.), will play an important role for the QoL and need to be included in this future specific PRO.

Previous work has been done by groups concerned with PROs in different fields including digestive malignancies. For pancreatic cancer, the “COPRA study” established a core set of PROs, which should facilitate the design of future trials for pancreatic disease (33). Among 56 PROs, 8 PROs were analysed in this multicenter Delphi study (33), and some PROs were

less expected, as such as ability to work/do usual activities, fear of recurrence, satisfaction with services/care organization and relationship with partner/family. The International Consortium for Health Outcomes Measurement developed a standardized set of PROs to inform value-based health care in colorectal cancer (39). Among 40 outcomes, 30 were considered in the final voting, in the following categories (39): survival and disease control (overall survival, disease-specific survival, recurrence, and progression-free survival), disutility of care (Clavien-Dindo classification and the Common Terminology Criteria for Adverse Events), degree of health (EORTC QLQ C30, CR29, LM21), and quality of end-of-life care. Our study confirmed that PROs selected by peritoneal surgeons to evaluate the toxicities after PIPAC must be discussed in regard with these previously published proposals on other cancers.

In clinical practice, clinicians require objective criteria to evaluate the efficacy of a new therapy for patients with PM. Although, peritoneal cancer index (PCI) is an important prognostic factor, it is difficult to analyse it after PIPAC. During coelioscopy, the surgeon cannot distinguish between scar tissue and residual PM after PIPAC. The macroscopic aspect of PM with tumour regression is different: glassy aspect with a hard consistency and the spread of tumour neo-vessels. In this review, improvement was observed in three studies, but the majority of the authors supported the stability of PCI. Histological response was the criteria most commonly used in the literature and was a prognostic factor (40). In this review, PIPAC induced a significant histological response in patients with PM from different origin, and an objective tumour response with reduction was observed in a minimum of 62% of patients in nine studies. Histological response after chemotherapy is a prognostic factor for many cancers, such as liver metastasis from colorectal cancer (41,42). For MP from CRC, we concluded in previous studies that PRGS can be used in medical practice to evaluate histological response after chemotherapy (43,44). But, although pathological response is, of

course, of great interest in malignancies undergoing systemic or local treatment (40), this study cannot establish a strong connection between PROs and histological regression scores.

Although the major strengths of this systematic review include an overall rigorous approach guided by the PRISMA criteria, the above findings should be interpreted with caution. PIPAC procedure is still in its infancy and this systematic review of the literature has highlighted the urgent need to improve the evaluation of PROs after PIPAC. The only methodological complex point is the fact that in case of tumour progression, the PIPAC program is over and patient trough away from the clinical report of the PIPAC study. In more, subjective expectations might influence the PROs because all patients in this review knew they were treated with PIPAC. One solution is to analyse a group of patient until dead, including when the PIPAC treatment solution will be stop. A second solution is to include the PROs during a fixed time (3 months) whatever the clinical evolution and PIPAC complete cycle realization will bee. The encouraging result of this review and of studies performed in recent years in other cancers support the prognostic impact of these PROs among patients in a palliative context. Nevertheless, it will be necessary to compare the PROs according to the primary tumor because the effect of PIPAC may be different depending on this primary tumor, even if all patients have PM.

Also, it was not possible in this study to compare the PROs according to the intraperitoneal chemotherapy used, the number of PIPAC or the protocol (Exclusive PIPAC or associated with venous chemotherapy). PIPAC procedure is still in its infancy and this systematic review of the literature has highlighted the urgent need to improve the evaluation of PROs after PIPAC. The encouraging result of this review and of studies performed in recent years in other cancers support the prognostic impact of these PROs among patients in a palliative context.

Conclusion

This review increases our understanding of the PIPAC strategy from the patient perspective. PRO represents a novel and interesting concept that could bring significant insight into the response to treatment for patients with PM. Thus, in a palliative context, the challenge remains how best to evaluate to PROs in futures studies.

Acknowledgements :

None

Disclosure :

The authors declare no conflict of interest

Funding:

None

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Legends :

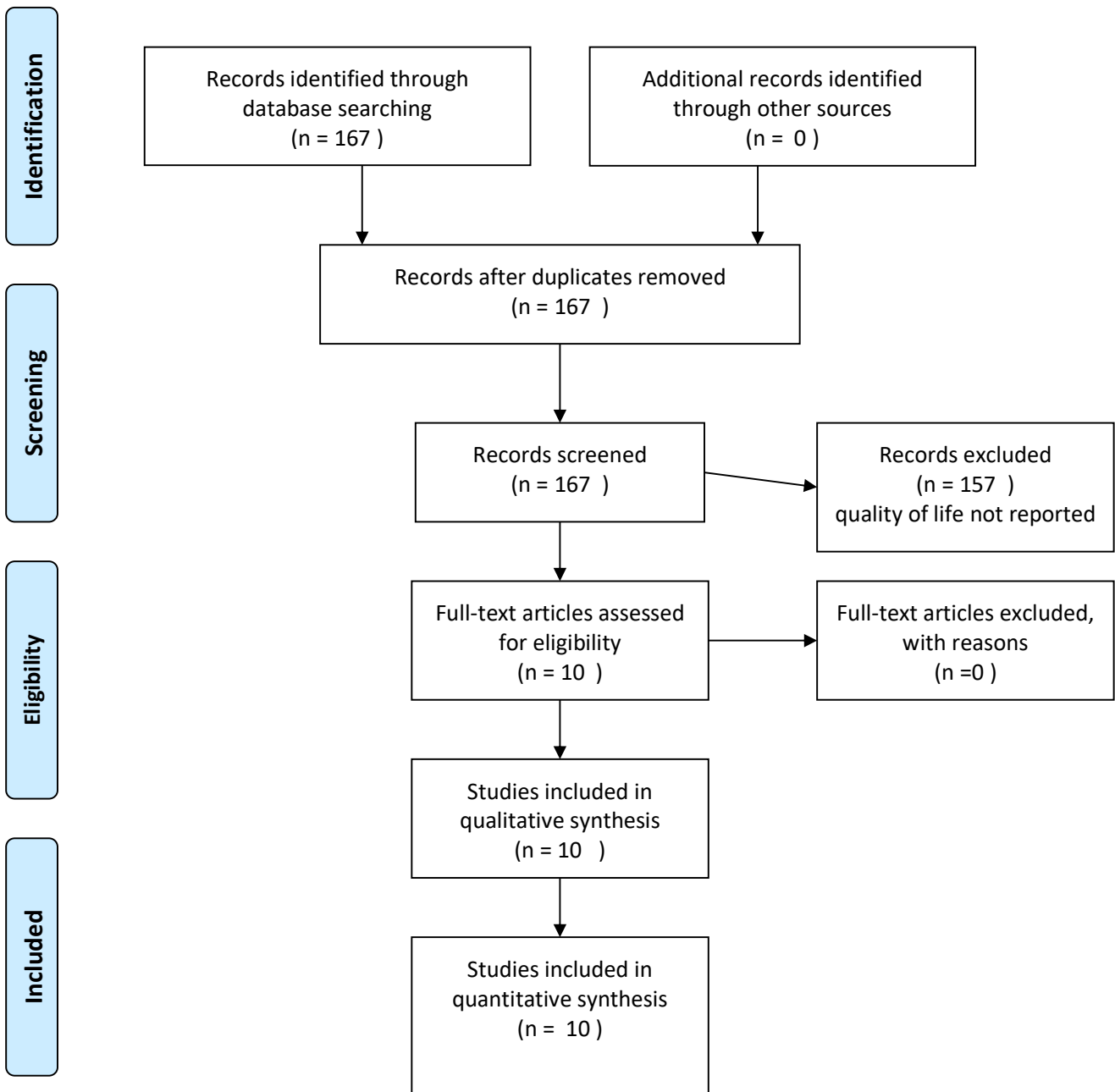
Table 1 : Patients informations, response after PIPAC and patients reported outcomes

Table 2 : Complications after PIPAC / PITAC

Table 3 : Patients reported outcomes after PIPAC / PITAC

Figure 1 : Prisma Flow diagram

Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Author	N	N of Pipac	N by each pipac	Site of disease (n)	Patients reported outcomes	Histological response	Ascites	PCI improvement
Tempfer	99	252	Pipac #1: 49 Pipac #2: 16 Pipac #3: 22 Pipac #4: 4 Pipac > 4: 8	Ovarian cancer (n=84), Fallopian tube cancer (n=1), Primary peritoneal cancer (n=6), Pseudomyxoma peritoneal (n=1), Cervical cancer (n=3), Endometrial cancer (n=3), Breast cancer (n=1).	EORTC QLQ-30+3 questionnaire one day before every pipac	76% (38/50)	Median ascites volume (ml) decreased 762±1170 to 167±456 (p=0.02).	64%, 32/50
Tempfer	64 53 eligible	202	Pipac #1: 10 Pipac #2: 9 Pipac #3: 34	Ovarian cancer (n=47) Fallopian tube cancer (n=2) Peritoneal cancer (n=4)	EORTC QLQ-30+3 questionnaire one day before every pipac	62%, 33/53, In an external blinded histological assessment 72%, 38/53,	NR	76%, 26/34
Tempfer	1	13	Pipac #13: 1	Unresectable ovarian cancer (n=1)	EORTC QLQ-30+3 questionnaire two day before every pipac	100%	NR	100% Pipac #1: PCI = 25 Pipac#13: PCI = 12
Graversen	35	129	Pipac #1: 35 Pipac #2: 30 Pipac #3: 27 Pipac #4: 14 Pipac #5: 9 Pipac #6: 8 Pipac >6: 3	Stomach (n=5) Small bowel (n=2) Cholangiocarcinoma (n=2) Pancreas (n=3) Appendix included PMP (n=4) Colorectal (n=12) Malignant peritoneal mesothelioma (n=1) Ovarian (n=5) Metastasis of unknown primary (n=1) Primary tumor in situ (n=14)	EORTC-QLQC30 at baseline, day 60, day 120 and day 180.	67%, 18/27 On an intention to treat basis 51,4%, 18/29	NR	NR
Teixeira	42	91	Pipac #1: 12 Pipac #2: 2 Pipac >2: 18	Gynaecological origin (n=21) Colorectal origin (n=14) Gastric origin (n=3) Small bowel origin (n=1) Appendicular origin (n=1) Pseudomyxoma (n=1) Mesothelioma (n=1)	EORTC QLQ-C30: during every patient encounter: in outpatient consultation, before surgery, and at discharge.	NR	NR	NR
Giger-Pabst	29	- 74 PIPAC - 5 PIPAT	Pipa #1: 5 Pipa #2: 8 Pipa#3: 5 Pipa #4: 4 Pipa #5: 1 Pipa #7 : 1 Pipa #10: 1	Abdominal malignant Mesothelioma: (n=24) Thoracic malignant mesothelioma: (n=5)	EORTC QLQ-C30 questionnaire during PIPAC treatment	N=20 75%, 15/20 On an intention to treat basis 15/29, 51.7%	Consecutive ascites volume measurements did not show any significant changes	Any significant changes.
Gockel	24	46	Pipac >1: 11	Gastric cancer	EORTC QLQ-C30 Before each PIPAC	N=14 7 Decreased	N=14 11: decreased	N=14 4: Decreased

						4 Stable 3 Increased	or stable 3 : increased	4 Stable 6 Increased
Odentahl	91	158	Pipac >2: 48	Ovarian (n=25) Stomach (n=29) Colorectal (n=14) Appendix (n=6) Mesothelioma (n=4) CUP (n=6)	EORTC QLQ C-30	NR	NR	NR
Robella	14	40	Pipac #1: 14 Pipac #2: 14 Pipac >2: 10	Diffuse malignant peritoneal Mesothelioma (n=2) Epithelial ovarian cancer (n=3) Colorectal cancer (n=2) Pseudomyxoma peritoneal (n=1) Gastric cancer (n=6)	SF-36 + EORTC QLQ-30. Before the enrolment and after each PIPAC procedure	NR	NR	NR
Struller	25	43	Pipac #1: 25 Pipac #2: 12 Pipac >2: 6	Gastric cancer	EORTC-QLQ-C30 before each PIPAC C/D cycle and then every 8 weeks.	Tumor regression on histology On an intention to treat basis (n=25) 9/25, 38% per protocol (n=6) 6/6 100%,	Mean ascites (ml) volume did not increase under Pipac therapy Pipac#1: 493 Pipac#2: 642 Pipac #3: 83	Mean PCI seemed to be stable under Pipac therapy: Pipac#1: 15.4 Pipac#2: 11.1 Pipac#3: 13.3

Table 1 : Patients informations, response after PIPAC and patients reported outcomes

PIPAC Pressurized IntraPeritoneal Aerosol Chemotherapy

PITAP : Pressurized IntraThoracic Aerosol Chemotherapy

PCI: peritoneal carcinomatosis index

Author	N of Pipac	N of patients	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3	CTCAE grade 4	CTCAE grade 5
Tempfer	252	99	N=57 Abdominal pain n=55 (56%) Bowel obstruction n=1 (1%) Anaemia n=1 (1%) Hypocalcaemia n=1 (1%) Fever n=10 (10%)	N=60 Bowel obstruction n=1 (1%) Anaemia n=8 (8%) Vomiting n=1 (1%) Infection n=4 (4%)	N=17 Bowel obstruction n=1 (1%) Small bowel perforation n=1 (1%) Colon perforation n=1 (1%) Anaemia n=4 (4%) Sepsis n=2 (2%) Trocar metastasis n=1 (1%) Breast cancer n=1 (1%) Hypertension n=1 (1%) Bile duct stenosis n=1 (1%) Respiratory insufficiency n=4 (4%)	N=3 Small bowel fistula 1 (1%) Colon perforation 1 (1%) Bowel anastomosis insufficiency 1 (1%)	0
Tempfer	202	64	Inflammatory n=10 (19%) Renal n=1 (2%) Neurological n=1 (2%) Cardiac n=6 (11%) Abdominal pain n=53 (100%)	Inflammatory n=25 (47%) Pulmonary n=5 (9%) Renal n=1 (2%) Cystitis n=1 (2%)	Uro-sepsis n=1 (2%) Bowel obstruction n=1 (2%) Haemorrhage n=1 (2%) Intraoperative bleeding n=1 (2%) Abdominal pain n=2 (4%) Trocar hernia n=2 (4%)	0	0
Tempfer	13	1	Abdominal pain 1 (100%) Fever 1 (100%)	0	0	0	0
Graversen	129	35	N=9	N=15 Urinary retention	N=4 diarrhea n =1 (2%) Small bowel obstruction n=1 (2%) Duodenal obstruction n=1 (2%) Cholestasis n=1 (2%)	N=1 Iatrogenic perforation of the jejunum (2%)	0
Teixeira	91	42	NR	NR	NR	NR	NR
Giger-Pabst	- 74 PIPAC - 5 PIPAT (Pressurized IntraThoracal Aerosol Chemotherapy)	29	N=23 Abdominal pain n=12 (15%), Pronounced wound pain n=8 (10%) Nausea/vomiting n=2 (2%) Temporary ascites leaking out n=1(1%)	N=7 Transient prerenal kidney injury	N=1 A subcutaneous chemotherapy paravasation	N=2 Postoperative small bowel anastomotic leakage	N=1 Kidney Insufficiency
Gockel	46	24	N=1 Nausea and emesis	0	0	0	0
Odentahl	158	91			N=8 Liver toxicity: n =4; Abdominal pain: n= 2; Obstruction of a biliary stent: n =1 Ileus =1.	N=1 Anaphylactic shock after intraoperative metamizol injection	N=2 Iatrogenic bowel access Lesions with following peritonitis n= 2 Disease progression n= 1
Robella	40	14	N=6 Abdominal pain	N=8 Nausea	0	0	0
Struller	43	25	N=25 Abdominal pain, nausea	N=5 Hypoalbuminemia: n = 1,	N=3 Subileus: n = 2	0	0

				Abdominal pain : n = 1, Vomiting : n = 1, Liver toxicity, n = 1, Subcutaneous toxic Emphysema, n = 1	Abdominal pain, readmission, n = 1		
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Table 2 : Complications after PIPAC / PITAC

PIPAC Pressurized IntraPeritoneal Aerosol Chemotherapy
PITAP : Pressurized IntraThoracic Aerosol Chemotherapy

Author	Global physical health scores	Physical	Role	Emotional	Cognitive	Social	Nausea/ vomiting	Appetite loss	Constipation	Diarrhea	Fatigue	Pain	Dyspnea	Insomnia
Tempfer	Global physical health scores demonstrated a continuous improvement during therapy : Pipac #1: 47.1 (95% CI=40.2 to 53.9), Pipac #2: 62.4 (95% CI=52.8 to 72.0), Pipac #3: 53.0 (95% CI=40.5 to 65.6), Pipac #4: 52.8 (95% CI=34.4 to 71.2), Pipac #5: 66.7 (95% CI=41.3 to 92.0), Pipac #6: 60.4 (95% CI=18.0 to 102.9)	±	±	±	±	±	±	±	±	±	±	±	±	±
Tempfer	Global physical health scores demonstrated a continuous improvement during therapy : Pipac #1: 52 · 0 (95% CI 45 · 8–58 · 3), Pipac #2: 58 · 1 (95% CI 50 · 7–65 · 6), Pipac #3: 59 · 5 (95% CI 51 · 3–67 · 6)	++	++	±	++	++	±	±	-	-	±	-	+	±
Tempfer	EORTC QLQ-C30 quality of life measurements were stable throughout the therapy.	+	±	±	±	±	±	-	±	±	+	+	±	++
Graversen	the EORTCQLQC30 global health score was stable between baseline and day 60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gockel	Global health score : Before the first Pipac : 52±5.9. Patients, who received 2 or more PIPACs, had a stable global health score	+	±	±	±	±	±	-	±	±	±	±	±	±
Odendahl	Stabilization of QoL in peritoneal metastasis patients receiving repeated PIPAC applications.	+	±	+	±	±	±	±	±	-	NR	NR	NR	NR
Robella	No further deterioration of physical, emotional, and cognitive scores during therapy were recorded.	NR	±	NR	±	±	NR	±	NR	NR	NR	NR	NR	NR
Struller	No statistically significant changes were observed	±	±	±	±	±	±	±	±	+	±	+	+	±

Table 3 : Patients reported outcomes after PIPAC / PITAC