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

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Pressurized Intraperitoneal Aerosol Chemotherapy: rationale, evidence and potential indications

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Abbreviations: PIPAC – Pressurized IntraPeritoneal Aerosol Chemotherapy, PM - Peritoneal Metastasis, CRS – CytoReductive Surgery, HIPEC – Hyperthermic IntraPEritoneal Chemotherapy, CTCAE - Common Terminology Criteria for Adverse Events, EORTC - European Organisation for the Research and Treatment of Cancer, GI – GastroIntestinal, OR – Operative Room, PCI – Peritoneal Cancer Index

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Abstract

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) was introduced as a new treatment for patients with peritoneal metastases. Reports of its feasibility, tolerance, and efficacy have encouraged many centres worldwide to adopt PIPAC. We aimed to detail the technique and rationale of PIPAC and to critically review its evidence and potential indications.

A systematic literature search was conducted to identify all relevant articles on PIPAC until January 31, 2019. Only clinical reports were considered, without language restrictions. Results are provided as a descriptive summary, as a meta-analysis could not be performed due to heterogeneity.

A total of 106 articles or reports on PIPAC were identified, and 45 clinical studies on 1'810 PIPAC procedures in 838 patients were retained for the present analysis. The most frequent indication was refractory isolated peritoneal disease, mainly from ovarian, gastric, and colorectal primary cancer, but also from peritoneal mesothelioma, hepatobiliary, and pancreatic cancer. Repeated PIPAC was feasible in 64% of patients with low intra- and post-operative surgical complications (3% and 3% in prospective studies, respectively). Adverse events (CTCAE >2) occurred after 12-15% of procedures, most commonly bowel obstruction, bleeding and abdominal pain. No mortality was observed in prospective studies, while it was 2·7% in retrospective reports. Repeated PIPAC did not have a negative impact on quality of life and improved symptoms in 64% of patients. An objective clinical response of 62-88% was reported for ovarian cancer (median survival 11 to 14 months), 50-91% for gastric cancer (median survival 8 to 15 months), 71-86% for colorectal cancer (median survival 16 months), and 67-75% (median survival 27 months) for peritoneal mesothelioma.

PIPAC has been shown to be feasible and safe. Objective response rates and potential positive impact on quality of life were encouraging. Therefore, PIPAC can be considered a treatment alternative for refractory, isolated peritoneal metastasis of various origins. Further indications need to be validated by ongoing prospective studies.

Introduction

Peritoneal metastasis (PM) 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.[1-4] A common feature of PM is a limited response to systemic chemotherapy and poor prognosis compared to other metastatic sites, at least in the recurrent setting.[5-7]

Intraperitoneal chemotherapy has been proposed as an alternative approach for these patients to improve tissue concentrations and to limit systemic toxicity.[8-10] This approach is a valid option in several types of malignancies in the adjuvant setting, such as ovarian and gastric cancer.[8,11,12] Long-term survival has been reported for different disease entities when combining cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).[13-17] However, high morbi-mortality and the unclear role of HIPEC have led to limited acceptance, despite growing but still controversial high-level evidence.[18-20]

Pressurized 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 (Figure 1).[21,22] The intriguing concept and favourable initial reports[23,24] triggered wide adoption of PIPAC, mainly in Europe (appendix p 1).

This systematic review aims to detail the rationale and technique of PIPAC and to critically review the available evidence and potential indications.

Data Collection

Systematic review

Medical subject heading (MeSH) terms “Intraperitoneal AND chemotherapy AND pressurized” were used to scrutinize the main electronic databases, including Medline (searched through PubMed), Embase, the Cochrane Database of Systematic Review, and the Cochrane Central Register of Controlled Trials. Pertinent references and electronic links were hand-searched, and cross-referencing was performed for selected articles. The search was limited to studies published between January 1, 2011 (year of first PIPAC in human) and January 31, 2019. The search terms were identified first in the title, and then in the abstract or MeSH. Only reports on pressurized intraperitoneal application of chemotherapy 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/clinical reports and systematic/narrative reviews, were considered to retrieve the maximum number of publications, without language restrictions. Due to the focus of the present study on clinical evidence, preclinical reports, reviews, and publications not reporting on any of the clinical outcomes mentioned below were subsequently excluded from the analysis. Clinical reports were further divided into prospective (phase I/II studies) and retrospective evidence.

Searching clinical trial registries

Ongoing research was retrieved from the international clinical trial registries ClinicalTrials.gov (https://clinicaltrials.gov) and EU clinical trials register (https://www.clinicaltrialsregister.eu). The International Standard Randomised Controlled Trial Number (www.isrctn.com) was used to identify unpublished prospective trials.

Spread of PIPAC technology

The manufacturer of the nebulizer (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 nebulizers (single use device) was equalized to the number of PIPAC procedures performed.

The International Society for the Study of Pleura and Peritoneum (ISSPP) has been contacted as the authority responsible for the certification of PIPAC course training in order to define the number and geographic location of active institutions performing PIPAC, and expert centres offering certification courses.

Outcome assessment

Relevant data were extracted and documented in an *a priori* structured database. 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 intra-operative complications). Post-operative outcome measures included post-operative surgical complications, toxicity according to Common Terminology Criteria for Adverse Events 4.0 (CTCAE criteria),[25] mortality, overall survival, and progression-free survival. (prospective studies).

Tumour response was recorded if assessed according to RECIST criteria,[26] histological response (i.e., objective tumour response) including peritoneal regression grading score (PRGS),[27], (TRG) according to Glaze et al[28] and according to Dworak et al[29] or peritoneal cancer index (PCI)[30] improvement. Consistently across all studies reporting efficacy, tumour response was assessed in patients who received at least

one cycle of the study medication. Quality of life (QoL), symptom relief, or decreased ascites were assessed in studies specifically reporting on these outcomes. Data are presented in accordance with the PRISMA statement (Figure 2).[31]

Statistical analysis

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

Of note, pooling of data was not performed if assessment or reporting of specific outcomes was heterogeneous, as specified in Table 2.

Findings

The systematic literature review identified 106 publications on PIPAC, with an exponential increase since 2016 (appendix p 2). Excluding 25 preclinical studies, 24 reviews or narrative reports, 10 trial proposals, and 2 unpublished conference reports, 45 clinical studies, including case studies and occupational health studies, were retained (Figure 2). Considering overlapping patient cohorts, the analysis included 1'810 PIPAC procedures in 838 patients. The main disease entities were ovarian (41·2%), gastric (22·1%), colorectal (12·4%), peritoneal mesothelioma (6·9%), and other (17·4%) cancers, including pseudomyxoma peritonei, hepatobiliary, and pancreatic origin. In the same timeframe, 5151 PIPAC procedures were performed by active PIPAC centres (appendix p 1), with a sharp increase in 2017 and 2018 (appendix p 2).

PIPAC: procedure, safety protocol, treatment regimens

Technique, safety protocol, and treatment regimens are highly standardized among expert centres, as highlighted by recent analyses.[32-35] The abdomen is accessed with one 10/12-mm (nebulizer) and one 5-mm (optical) trocar (Figure 1). The same incisions are used for consecutive procedures. The abdomen is insufflated with CO_2 under standard pressure conditions (12 mmHg). Ascites is quantified (cytology) and in case there was no ascites, a peritoneal flushing is performed, and the fluid is sampled for cytology. The abdominal cavity is then explored with documentation of the Peritoneal Cancer Index (PCI) and at least three representative biopsies are taken using biopsy forceps. Intraperitoneal chemotherapy containing 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 the procedure-specific nebulizer (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 and include the features of air-tight abdomen, advanced air flow in the OR, remote administration, and checking of all items against a standardized safety check-list.[21,33] Contraindications for PIPAC should be respected and include life expectancy <3 months, bowel obstruction, exclusive total parenteral nutrition (TPN), decompensated ascites, simultaneous tumor debulking with gastro-intestinal resection, and previous anaphylactic reaction to the drug used, in addition to the relative contraindications of extraperitoneal metastasis, ECOG > 2, and portal vein thrombosis.

Two intraperitoneal regimens are currently used for PIPAC procedures: cisplatin in combination with doxorubicin, and oxaliplatin as monotherapy. Doses are detailed below. At least three PIPAC procedures are foreseen at 6±2 week intervals, but thereafter treatment can be pursued depending on tolerance and treatment response.[36,37]

PIPAC has been administered alone or after systemic 5-FU.[36,38,39] Concomitant systemic treatment is possible with most currently used regimens, including FOLOFOX, FOLFIRI, FLOT, and EOX. Most centres would recommend no systemic treatment for 2 weeks before and 1 week after the PIPAC procedure. Typical treatment schemes are provided in Figure 3.

Evidence: feasibility, safety, toxicity, tolerance, QoL

Doses for the combined cisplatin and doxorubicin regimen were defined by a dose-escalation study in patients with ovarian cancer.[40] The combined regimen (10·5

mg/m^2 cisplatin, 2·1 mg/m^2 doxorubicin) will be evaluated in a future phase III study, PIPAC OV-3.[41] Two-dose escalation studies are ongoing[42,43] (NCT03172416 - NCT03294252) to define the optimal dose of oxaliplatin, which is currently used at the empirical dose of 20% (92 mg/m^2) of the Elias regimen for HIPEC.[44]

The feasibility, safety, and tolerance of repeated PIPAC treatment were confirmed by four prospective and 16 retrospective cohort studies. Surgical complications were rare (prospective studies: 3% intra-operative and 3% post-operative; retrospective studies: 0-11% intra-operative and 0-6% post-operative). Across all studies, adverse events (CTCAE >2) occurred after 12-15% of procedures (most common: bowel obstruction, 0-5%; bleeding, 0-4%; abdominal pain, 0-4%). Whereas no mortality was observed in prospective trials, the mortality rate in retrospective studies was 2·7%. Feasibility (non-access), repeatability and tolerance (adverse events) are given in detail in Table 1.

Toxicity and occupational health issues were assessed by nine independent groups. Peripheral systemic drug uptake under PIPAC was minimal (venous doxorubicin concentrations: 4·0-6·2 ng/ml; half-life 86 to 468 minutes).[22] Six studies evaluated renal and hepatic toxicity and inflammatory response.[38,45-49] Consistently, no cumulative hepatic or renal toxicity was observed. A modest and transitory inflammatory response (C-reactive protein increase, leucocytosis) was observed,[38,47] commensurate with disease extent.[47] A recent report demonstrated severe hypersensitivity reactions in 3% of patients, but all were managed without further complications.[50] Occupational health issues were specifically and independently assessed by five groups, demonstrating very low risk of exposure with adequate safety measures.[51-55]

QoL was studied independently by four groups, showing consistently stable or improved global QoL scores and symptom improvement in 64% of patients.[36-38,46,56-59]

Evidence: 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 ovarian cancer patients (mostly third line) translating into a median survival of 11 to 14·1 months. The clinical response for gastric cancer patients (salvage and upfront) was between 50 and 91%, with a median survival of 8·4-15·4 months, 71-86% for colorectal cancer (third line; median survival 15·7 months), and 67-75% (median survival 27 months) for peritoneal mesothelioma.

Outlook: ongoing and planned clinical studies on PIPAC

Twelve clinical trials of PIPAC are currently recorded in international registries (appendix p 3). Most of them were launched within the last year, including a phase III study of platinum-resistant ovarian cancer[41] and two multicentre studies for gastric and upper gastrointestinal cancer.[60,61]

Discussion

PIPAC is a new treatment alternative for patients with PM and has undergone thorough initial evaluation. Based on 1'810 procedures in 838 patients, PIPAC is a feasible, safe, and well-tolerated treatment with no negative impact on QoL. Oncological efficacy has been documented, according to different assessment tools, in 50 to 88% of patients with advanced PM refractory to standard treatment. A prospective registry and multiple prospective clinical trials, including a phase III study, should help define the most appropriate indications for PIPAC treatment.

PM is a common occurrence in intra-abdominal malignancies and is associated with a dismal prognosis in the absence of an aggressive therapeutic approach.[62] PM remains an unsolved challenge in modern oncology, and patients with PM have been barely included in randomized trials.[5] For unresectable PM, systemic chemotherapy remains the standard of care. However, efficacy is limited due to a weak penetration of agents into the peritoneum (low blood flow, interstitial fibrosis, plasma-peritoneal barrier) with consecutive relative chemoresistance and non-negligible toxicity.[7,63] Standard intraperitoneal chemotherapy by lavage still has important pharmacokinetic limitations, such as unequal distribution, poor tissue penetration, and single-dose administration for HIPEC. 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 sitting.[64] The same group created a second generation device 10 years later to resolve the issues of the previous device.[65] Following the principles of the IDEAL framework,[66] this innovative surgical technique went through multiple steps. After creating the device and resolving the initial technical difficulties (stage 1: innovation), PIPAC went through multiple evaluations. Preclinical studies demonstrated good

penetration of PIPAC into the tumour nodules and good distribution inside the abdominal cavity (stage 2a: development).[23,24,67,68] Surgical techniques were standardized by the same group.[22,67] Thereafter, highly standardized training workshops were initiated by the same group, and the technique was adopted and confirmed by other expert groups in recent studies (appendix p 1).[32-35] The concept of PIPAC was supported by favourable initial reports regarding the feasibility, safety, treatment regimens, tolerance, QoL, and oncological efficacy (stage 2b: exploration).[23,24] 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 stage 3 (assessment) 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 (stage 4: long-term study). The level of evidence (PFS) of palliative systemic chemotherapy, immunotherapy, surgery and intraperitoneal chemotherapy for treating patients with PM is low as compared to liver metastasis, for example.[5] Furthermore, due to a shortage of drugs approved for intraperitoneal delivery, cisplatin, doxorubicin and oxaliplatin are currently used off-label for HIPEC, PIPAC and other catheter-based systems. PIPAC is not a defined therapy but a generic system for IP drug delivery able to aerosolize a large range of substances in a variety of diseases and indications. It is not possible to evaluate this system by comparing it to other administration routes (intravenous, rectal, etc..).

For the treatment of resectable PM, CRS and HIPEC is the gold standard for pseudomyxoma peritonei and peritoneal mesothelioma,[69,70] and also an option for colorectal, ovarian, and gastric PM in selected patients.[15,17,20,71] However, because of its morbidity and mortality, this curative approach is limited to highly select patients with favourable tumour biology and few co-morbidities. For unresectable PM, there is

no role for such aggressive treatment, and the systemic chemotherapies and targeted therapies remain the standard of care. For colorectal PM, the best median survival by systemic chemotherapy was estimated to be 16·3 months.[5] In patients treated by PIPAC, only one study exclusively evaluated the survival in colorectal PM, and it reached 15·7 months in a total of 17 patients.[72] Multiple clinical trials are ongoing to assess the role of PIPAC in this indication. For gastric PM, multiple studies have estimated a survival of 8·4 to 15·4 months after PIPAC (Table 2). In addition, Alyami et al[73] recently presented results from the Lyon cohort in ESSO38 with an excellent median survival of 19·1 months. These preliminary results in gastric PM are promising compared to current data for patients treated with systematic chemotherapy alone, in whom the reported median survival did not exceed 10·7 months.[74] Among patients with recurrent platinum-resistant ovarian cancer, Pujade-Lauraine et al reported 16·6 months survival as the best outcome for systemic chemotherapy.[75] On the other hand, the available data indicated survival ranging between 11 and 14·1 months after PIPAC (Table 2). Giger-Pabst et al reported 26·1 months of survival (Table 2) after PIPAC in 26 patients with malignant peritoneal mesothelioma.[37] Twelve months was the best survival reported for this indication using systemic chemotherapy only.[76] Finally, subsequent CRS and HIPEC after PIPAC as neoadjuvant treatment was described by Girshally et al.[77] They performed CRS and HIPEC in 21 of 406 patients (5·2%) with unresectable PM. Among these patients, more than 50% presented a low PCI (mean 5·8 ± 5·6). In addition, the French data presented recently at ESSO38 indicates that 21 of 146 patients (14·4%) with an initial median PCI of 16 had a successful secondary CRS and HIPEC.[78] These data suggest that strictly selected patients with unresectable PM could be eligible for secondary CRS and HIPEC after repeated PIPAC sessions with palliative intent. The online (appendix p 3) details the ongoing clinical trials to date regarding

PIPAC, which will provide us more evidence in the next few years. In palliative management, the survival should not be the only and principal endpoint. QoL and treatment tolerance represent a major issue for which the preliminary results of PIPAC appear promising.[58,59] The replacement of one cycle of systemic chemotherapy with PIPAC every 6±2 weeks, as has been proposed by several teams (Figure 3), may improve the overall tolerance and QoL by reducing the adverse effects of systemic treatment.[38] Future studies should evaluate whether this reduction in dose intensity is not counterbalanced by a decrease in efficiency.

To date, it is difficult to define indications for PIPAC without large prospective comparative studies. The potential indications for PIPAC are summarized in Table 3, along with proposed indications for HIPEC according to the best available evidence. Currently, the intent and indications are very different for HIPEC and PIPAC. HIPEC performed in conjunction with CRS offers the best outcomes, with potentially curative intent, but only for highly selected patients with PM.[15,17,20,69-71] Most of these patients benefit from additional peri-operative systemic chemotherapy, and the outcomes of systemic chemotherapy alone have improved considerably with the advent of multi-drug combinations, including targeted therapies.[5] However, for patients who are not candidates for CRS and do not tolerate or respond (anymore) to systemic treatment, off-label PIPAC therapy appears to be legitimate, and PIPAC can currently be considered a treatment option in patients without a validated treatment approach. However, PIPAC should only be performed within the framework of clinical studies when competing with an evidence-based therapy (Table 3). Some of these questions are currently being investigated in prospective study protocols (appendix p 3), including a phase II trial evaluating PIPAC with oxaliplatin as an adjuvant therapy in resected high-risk colon cancer (NCT03280511),[79] a phase I/II study of oxaliplatin

dose escalation for non-resectable PMs of digestive cancers (stomach, small bowel, and colorectal; NCT03294252),[43] PIPAC EstoK 01, a randomized and multicentre phase II study of PIPAC with cisplatin and doxorubicin in gastric PM,[60] PIPAC-OV3, a multicentre, open-label, randomized, two-arm phase III trial of the effect of cisplatin and doxorubicin on progression-free survival as PIPAC vs. chemotherapy alone in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (EudraCT number 2018-003664-31),[41] and a phase III, prospective, open, randomized multicentre clinical study with two arms that aim to evaluate the effects of PIPAC combined with systemic chemotherapy vs. intravenous systemic chemotherapy alone in patients with metastatic upper GI tumours and PM (EudraCT: 2018-001035-40).[61] Finally, the international prospective PIPAC registry (NCT03210298) should provide regularly updated large-scale information on safety, efficacy, and QoL for different disease entities and indications. Currently, the surgical approach and administration of PIPAC are standardized and homogenous, indications and treatment regimens are highly standardized among treatment centres[32] and dedicated training centres (appendix p 1), and the ISSPP-endorsed standardized PIPAC training curriculum should help maintain homogeneity and high treatment standards. The standards include respecting the contraindications to PIPAC treatment in order to prevent avoidable (severe) complications and futile treatment.

Eight 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. So far, no comparative studies have been performed and, as with any new treatment, no long-term results are available yet. Therefore, in accordance with the IDEAL framework, PIPAC is still in the assessment stage. The current status of PIPAC evaluation has several problems. The available studies are heterogeneous with

regards to patients and indications. In addition, there is patient overlap between studies from the same groups. For the present analysis, duplicates were carefully removed. Furthermore, assessment of treatment response and efficacy, such as PRGS, RECIST, and PCI, differed considerably between studies (Table 2); standardization for future studies is a top priority. A new method of assessing the tumour response, especially for micronodular diffuse PM, which is not sufficiently visible on morphological exams, should probably be established with this new therapeutic technique. Currently, PIPAC is indicated mainly for palliative patients. The appropriate endpoints to evaluate or promote this innovative technique could be one or more of the following items: OS, DFS, QoL, ascites control, and obstruction-free survival. Finally, there are no randomized trials yet for any treatment modality measuring these outcomes in patients with PM.

The current analysis has methodological limitations. A meta-analysis of the data was not feasible due to heterogeneity. Comparative data are not available yet, and selection bias is a potential problem. Practiced on a larger scale only since 2015, long-term data cannot be expected before 2020. Furthermore, PIPAC is currently not considered as superior to liquid intraperitoneal chemotherapy and PIPAC dosing, pressure, exposure time, and time intervals are still empiric.These are all inherent limitations of new treatments. However, the introduction and evaluation of PIPAC closely follows the IDEAL framework, including three major points: (I) homogeneity of technique, indications, and drug regimens,[32] (II) structured certification courses for safe implementation of this potentially dangerous method with endorsement by a scientific society (ISSPP), and (III) scientific evaluation from the beginning within an international academic network using a prospective registry and multiple prospective clinical studies, including dose-finding and randomized phase III studies evaluating efficacy.

Conclusion

PIPAC can be considered a safe and promising treatment alternative for patients with advanced isolated refractory peritoneal disease. Other indications are currently 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.

Conflicts of interest

We declare that we have no conflicts of interest.

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 prior to submission. MA and MH both contributed equally to this manuscript.

References

1. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *International journal of cancer* 2011; **128**(11): 2717-25.

2. Thomassen I, van Gestel YR, van Ramshorst B, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. *International journal of cancer* 2014; **134**(3): 622-8.

3. Henderson JT, Webber EM, Sawaya GF. Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2018; **319**(6): 595-606.

4. Raza A, Huang WC, Takabe K. Advances in the management of peritoneal mesothelioma. *World journal of gastroenterology* 2014; **20**(33): 11700-12.

5. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *The Lancet Oncology* 2016; **17**(12): 1709-19.

6. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. *Journal of the National Cancer Institute* 1997; **89**(7): 480-7.

7. Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. *The Lancet Oncology* 2003; **4**(5): 277-83.

8. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *The New England journal of medicine* 2006; **354**(1): 34-43.

9. Glehen O, Mohamed F, Gilly FN. Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia. *The Lancet Oncology* 2004; **5**(4): 219-28.

10. Glehen O, Cotte E, Schreiber V, Sayag-Beaujard AC, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. *The British journal of surgery* 2004; **91**(6): 747-54.

11. Markman M, Bundy BN, Alberts DS, et al. Phase III Trial of Standard-Dose Intravenous Cisplatin Plus Paclitaxel Versus Moderately High-Dose Carboplatin Followed by Intravenous Paclitaxel and Intraperitoneal Cisplatin in Small-Volume Stage III Ovarian Carcinoma: An Intergroup Study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *Journal of Clinical Oncology* 2001; **19**(4): 1001-7.

12. Yonemura Y, Bandou E, Sawa T, et al. Neoadjuvant treatment of gastric cancer with peritoneal dissemination. *European Journal of Surgical Oncology (EJSO)* 2006; **32**(6): 661-5.

13. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010; **28**(1): 63-8.

14. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer* 2010; **116**(24): 5608-18.

15. Chia CS, You B, Decullier E, et al. Patients with Peritoneal Carcinomatosis from Gastric Cancer Treated with Cytoreductive Surgery and Hyperthermic

Intraperitoneal Chemotherapy: Is Cure a Possibility? *Annals of surgical oncology* 2016.

16. Jafari MD, Halabi WJ, Stamos MJ, et al. Surgical outcomes of hyperthermic intraperitoneal chemotherapy: analysis of the american college of surgeons national surgical quality improvement program. *JAMA surgery* 2014; **149**(2): 170-5.

17. Le Saux O, Decullier E, Freyer G, Glehen O, Bakrin N. Long-term survival in patients with epithelial ovarian cancer following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group* 2018: 1-6.

18. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *The New England journal of medicine* 2018; **378**(3): 230-40.

19. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2003; **21**(20): 3737-43.

20. Bonnot PE, Piessen G, Kepenekian V, et al. Cytoreductive Surgery with and without Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer with Peritoneal Metastasis (CYTO-CHIP study): A Propensity-Score Analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2019; **In press**.

21. Solass W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. *Annals of surgical oncology* 2013; **20**(11): 3504-11.

22. Solass W, Kerb R, Murdter T, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. *Annals of surgical oncology* 2014; **21**(2): 553-9.

23. Grass F, Vuagniaux A, Teixeira-Farinha H, Lehmann K, Demartines N, Hubner M. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. *The British journal of surgery* 2017; **104**(6): 669-78.

24. Tempfer C, Giger-Pabst U, Hilal Z, Dogan A, Rezniczek GA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal carcinomatosis: systematic review of clinical and experimental evidence with special emphasis on ovarian cancer. *Archives of gynecology and obstetrics* 2018; **298**(2): 243-57.

25. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute: Bethesda, 2009.

26. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer (Oxford, England : 1990)* 2009; **45**(2): 228-47.

27. Solass W SC, Detlefsen S , Carr NJ, Bibeau F Peritoneal sampling and histological assessment of therapeutic response in peritoneal metastasis: proposal of the Peritoneal Regression Grading Score (PRGS). *Pleura and Peritoneum* 2016; **1**(2): 99 -107.

28. Glaze S, Nation J, Kobel M. Type-specific response to neoadjuvant chemotherapy: ovarian high-grade serous carcinoma versus colorectal mucinous

carcinoma. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC* 2012; **34**(7): 678-82.

29. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *International journal of colorectal disease* 1997; **12**(1): 19-23.

30. Jacquet P, Sugarbaker P. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker P, ed. Peritoneal Carcinomatosis: Principles of Management: Springer US; 1996: 359-74.

31. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical research ed)* 2009; **339**: b2535.

32. Nowacki M, Alyami M, Villeneuve L, et al. Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: An international survey study. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2018; **44**(7): 991-6.

33. Hubner M, Grass F, Teixeira-Farinha H, Pache B, Mathevet P, Demartines N. Pressurized IntraPeritoneal Aerosol Chemotherapy - Practical aspects. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2017; **43**(6): 1102-9.

34. Giger-Pabst U, Tempfer CB. How to Perform Safe and Technically Optimized Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Experience After a Consecutive Series of 1200 Procedures. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2018; **22**(12): 2187-93.

35. Cazauran JB, Alyami M, Lasseur A, Gybels I, Glehen O, Bakrin N. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Procedure for Non-resectable Peritoneal Carcinomatosis (with Video). *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2017.

36. Alyami M, Gagniere J, Sgarbura O, et al. Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. *Eur J Surg Oncol* 2017; **43**(11): 2178-83.

37. Giger-Pabst U, Demtroder C, Falkenstein TA, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for the treatment of malignant mesothelioma. *BMC cancer* 2018; **18**(1): 442.

38. Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. *World journal of surgical oncology* 2016; **14**: 128.

39. Khomyakov V, Ryabov A, Ivanov A, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura and Peritoneum; 2016. p. 159.

40. Tempfer CB, Giger-Pabst U, Seebacher V, Petersen M, Dogan A, Rezniczek GA. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. *Gynecologic oncology* 2018; **150**(1): 23-30.

41. Bakrin N, Tempfer C, Scambia G, et al. PIPAC-OV3: A multicenter, open-label, randomized, two-arm phase III trial of the effect on progression-free survival of

cisplatin and doxorubicin as Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) vs. chemotherapy alone in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. Pleura and Peritoneum; 2018.

42. Kim G, Tan Hon L, Chen E, et al. Study protocol: phase 1 dose escalating study of Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) with oxaliplatin in peritoneal metastasis. Pleura and Peritoneum; 2018.

43. Dumont F, Senellart H, Pein F, et al. Phase I/II study of oxaliplatin dose escalation via a laparoscopic approach using pressurized aerosol intraperitoneal chemotherapy (PIPOX trial) for nonresectable peritoneal metastases of digestive cancers (stomach, small bowel and colorectal): Rationale and design. Pleura and Peritoneum; 2018.

44. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(5): 681-5.

45. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Annals of surgical oncology* 2013; **20**(7): 2311-6.

46. Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy with Cisplatin and Doxorubicin in Women with Peritoneal Carcinomatosis: A Cohort Study. *Anticancer Res* 2015; **35**(12): 6723-9.

47. Teixeira Farinha H, Grass F, Labgaa I, Pache B, Demartines N, Hubner M. Inflammatory Response and Toxicity After Pressurized IntraPeritoneal Aerosol Chemotherapy. *Journal of Cancer* 2018; **9**(1): 13-20.

48. Tempfer CB, Hartmann F, Hilal Z, Rezniczek GA. Intraperitoneal cisplatin and doxorubicin as maintenance chemotherapy for unresectable ovarian cancer: a case report. *BMC cancer* 2017; **17**(1): 26.

49. Larbre V, Alyami M, Mercier F, et al. No Renal Toxicity After Repeated Treatment with Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Patients with Unresectable Peritoneal Metastasis. *Anticancer research* 2018; **38**(12): 6869-75.

50. Siebert M, Alyami M, Mercier F, et al. Severe hypersensitivity reactions to platinum compounds post-pressurized intraperitoneal aerosol chemotherapy (PIPAC): first literature report. *Cancer chemotherapy and pharmacology* 2018.

51. Willaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). Pleura and Peritoneum; 2017. p. 121.

52. Ndaw S, Hanser O, Kenepekian V, et al. Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination. *Toxicology letters* 2018; **298**: 171-6.

53. Graversen M, Pedersen Peter B, Mortensen Michael B. Environmental safety during the administration of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Pleura and Peritoneum; 2016. p. 203.

54. Ametsbichler P, Bohlandt A, Nowak D, Schierl R. Occupational exposure to cisplatin/oxaliplatin during Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)? *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2018; **44**(11): 1793-9.

55. Jansen-Winkeln B, Thieme R, Haase L, et al. [Perioperative safety of intraperitoneal aerosol chemotherapy : Analysis of our first 111 pressurized

intraperitoneal aerosol chemotherapy (PIPAC) procedures]. *Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen* 2019; **90**(2): 137-45.

56. Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Clinical & experimental metastasis* 2017; **34**(5): 309-14.

57. Tempfer CB, Winnekendonk G, Solass W, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study. *Gynecol Oncol* 2015; **137**(2): 223-8.

58. Odendahl K, Solass W, Demtroder C, et al. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2015; **41**(10): 1379-85.

59. Teixeira Farinha H, Grass F, Kefleyesus A, et al. Impact of Pressurized Intraperitoneal Aerosol Chemotherapy on Quality of Life and Symptoms in Patients with Peritoneal Carcinomatosis: A Retrospective Cohort Study. *Gastroenterology research and practice* 2017; **2017**: 4596176.

60. Eveno C, Jouvin I, Pocard M. PIPAC EstoK 01: Pressurized IntraPeritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized and multicenter phase II study. Pleura and Peritoneum; 2018.

61. Oliver Goetze T, Al-Batran S-E, Pabst U, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with standard of care chemotherapy in primarily untreated chemo naïve upper gi-adenocarcinomas with peritoneal seeding – a phase II/III trial of the AIO/CAOGI/ACO. Pleura and Peritoneum; 2018.

62. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; **88**(2): 358-63.

63. Minchinton AI, Tannock IF. Drug penetration in solid tumours. *Nature reviews Cancer* 2006; **6**(8): 583-92.

64. Reymond MA, Hu B, Garcia A, et al. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. *Surgical endoscopy* 2000; **14**(1): 51-5.

65. Solass W, Herbette A, Schwarz T, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. *Surgical endoscopy* 2012; **26**(3): 847-52.

66. McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet* 2009; **374**(9695): 1105-12.

67. Solass W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. *Surgical endoscopy* 2012; **26**(7): 1849-55.

68. Khosrawipour V, Khosrawipour T, Kern AJ, et al. Distribution pattern and penetration depth of doxorubicin after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in a postmortem swine model. *Journal of cancer research and clinical oncology* 2016; **142**(11): 2275-80.

69. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30**(20): 2449-56.

70. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(36): 6237-42.

71. Goere D, Malka D, Tzanis D, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? *Annals of surgery* 2013; **257**(6): 1065-71.

72. Demtroder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2016; **18**(4): 364-71.

73. Alyami M, Bonnot PE, Mercier F, et al. pressurized intraperitoneal aerosol chemotherapy (pipac) for nonresectable peritoneal metastasis from gastric cancer. *European Journal of Surgical Oncology* 2019; **45**(2): e149.

74. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. *JAMA Oncol* 2017; **3**(9): 1237-44.

75. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014; **32**(13): 1302-8.

76. Miura JT, Johnston FM, Gamblin TC, Turaga KK. Current trends in the management of malignant peritoneal mesothelioma. *Annals of surgical oncology* 2014; **21**(12): 3947-53.

77. Girshally R, Demtroder C, Albayrak N, Zieren J, Tempfer C, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as a neoadjuvant therapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World journal of surgical oncology* 2016; **14**(1): 253.

78. Alyami M, Mercier F, Siebert M, et al. Pressurized intraperitoneal aerosol chemotherapy (pipac) before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for nonresectable peritoneal metastasis. *European Journal of Surgical Oncology* 2019; **45**(2): e16-e7.

79. Graversen M, Detlefsen S, Fristrup C, Pfeiffer P, Mortensen Michael B. Adjuvant Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in resected high-risk colon cancer patients – study protocol for the PIPAC-OPC3 Trial. A prospective, controlled phase 2 Study. Pleura and Peritoneum; 2018.

80. Graversen M, Detlefsen S, Bjerregaard JK, Fristrup CW, Pfeiffer P, Mortensen MB. Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. *Therapeutic advances in medical oncology* 2018; **10**: 1758835918777036.

81. Tempfer CB, Celik I, Solass W, et al. Activity of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. *Gynecologic oncology* 2014; **132**(2): 307-11.

82. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. *J Gastrointest Surg* 2016; **20**(2): 367-73.

83. Hubner M, Teixeira Farinha H, Grass F, et al. Feasibility and Safety of Pressurized Intraperitoneal Aerosol Chemotherapy for Peritoneal Carcinomatosis: A Retrospective Cohort Study. *Gastroenterol Res Pract* 2017; **2017**: 6852749.

84. Khosrawipour T, Khosrawipour V, Giger-Pabst U. Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. *PloS one* 2017; **12**(10): e0186709.

85. Falkenstein TA, Gotze TO, Ouaissi M, Tempfer CB, Giger-Pabst U, Demtroder C. First Clinical Data of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) as Salvage Therapy for Peritoneal Metastatic Biliary Tract Cancer. *Anticancer Res* 2018; **38**(1): 373-8.

86. Kurtz F, Struller F, Horvath P, et al. Feasibility, Safety, and Efficacy of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastasis: A Registry Study. *Gastroenterol Res Pract* 2018; **2018**: 2743985.

87. Gockel I, Jansen-Winkeln B, Haase L, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Gastric Cancer Patients with Peritoneal Metastasis (PM): Results of a Single-Center Experience and Register Study. *J Gastric Cancer* 2018; **18**(4): 379-91.

88. Horvath P, Beckert S, Struller F, Konigsrainer A, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases of pancreas and biliary tract cancer. *Clin Exp Metastasis* 2018; **35**(7): 635-40.

89. Hubner M, Teixeira H, Boussaha T, Cachemaille M, Lehmann K, Demartines N. [PIPAC--Pressurized intraperitoneal aerosol chemotherapy. A novel treatment for peritoneal carcinomatosis]. *Revue medicale suisse* 2015; **11**(479): 1325-30.

Figure legend:

Figure 1 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 vaporized using a standard injector connected to a nebulizer. Reprinted from *Rev Med Suisse* with permission from *Médicine et Hygiène*.[89]

Figure 2 Flow chart of selected studies

The selection process adheres to the guidelines outlined in the PRISMA statement.

Figure 3 Concomitant systemic and intraperitoneal treatment

Suggested treatment schedule for PIPAC every 6±2 weeks, alternating with systemic chemotherapy.

PCI – Peritoneal Cancer Index, PRGS – Peritoneal Regression Grading Score, chemo –

chemotherapy, CT – computed tomography.

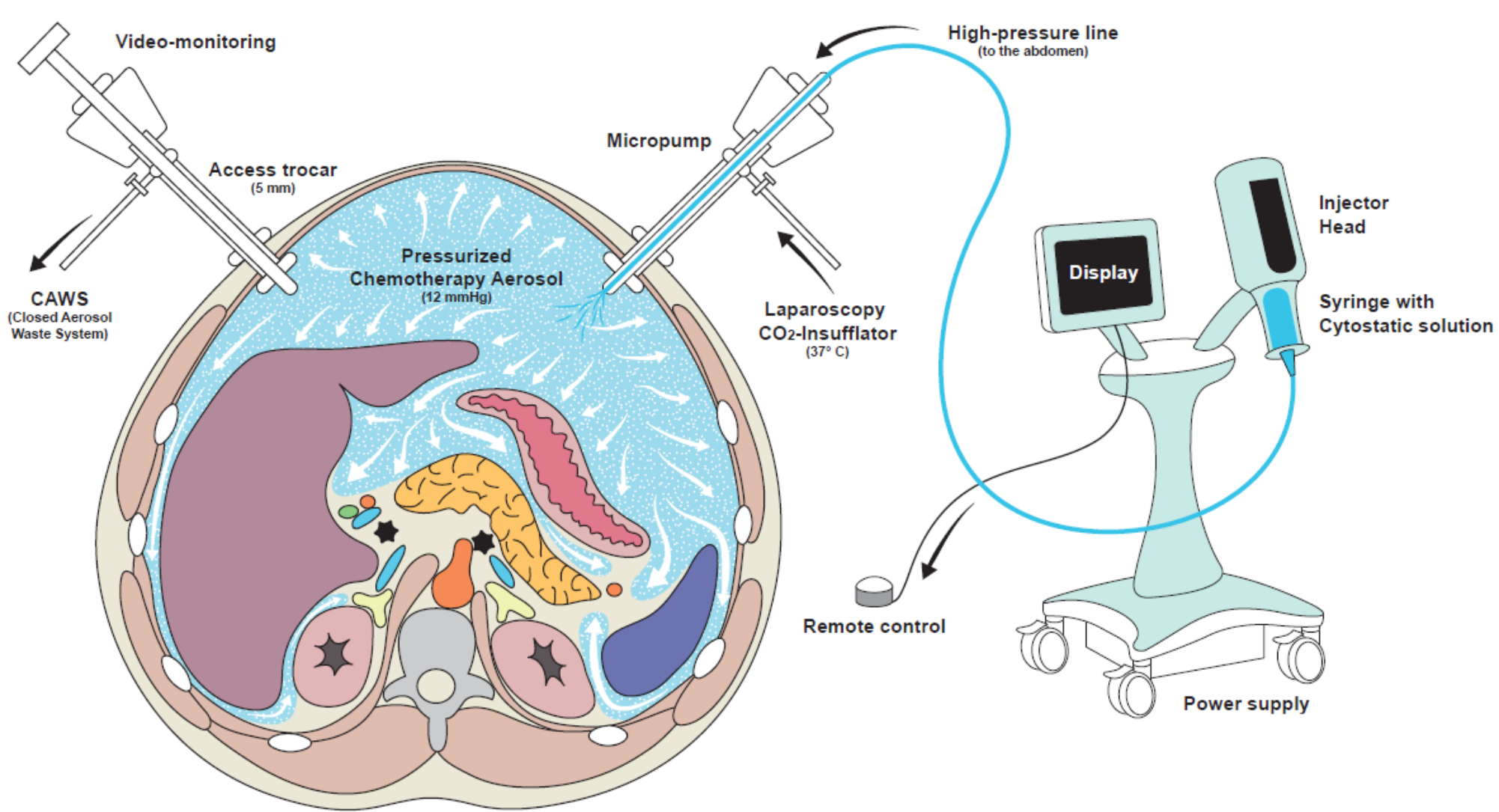
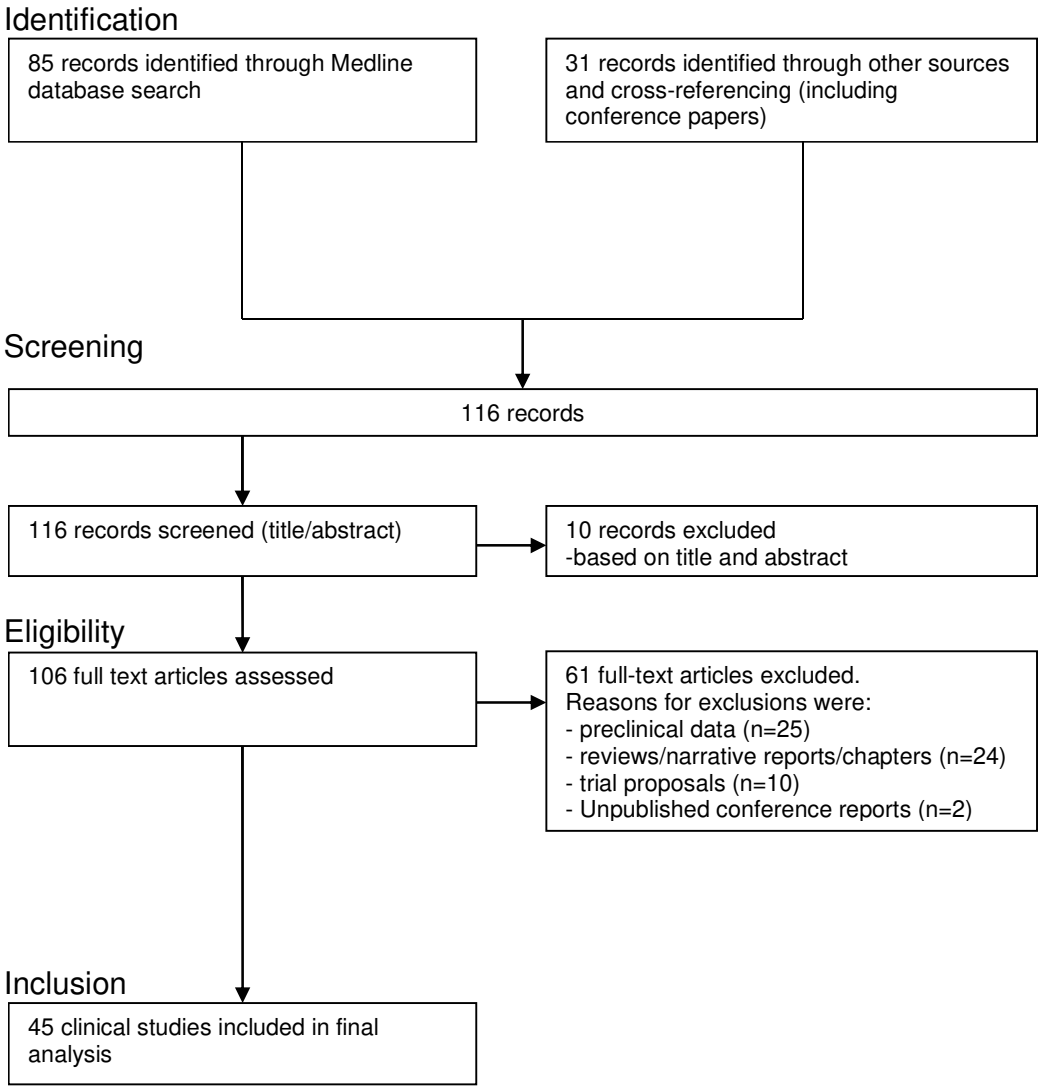
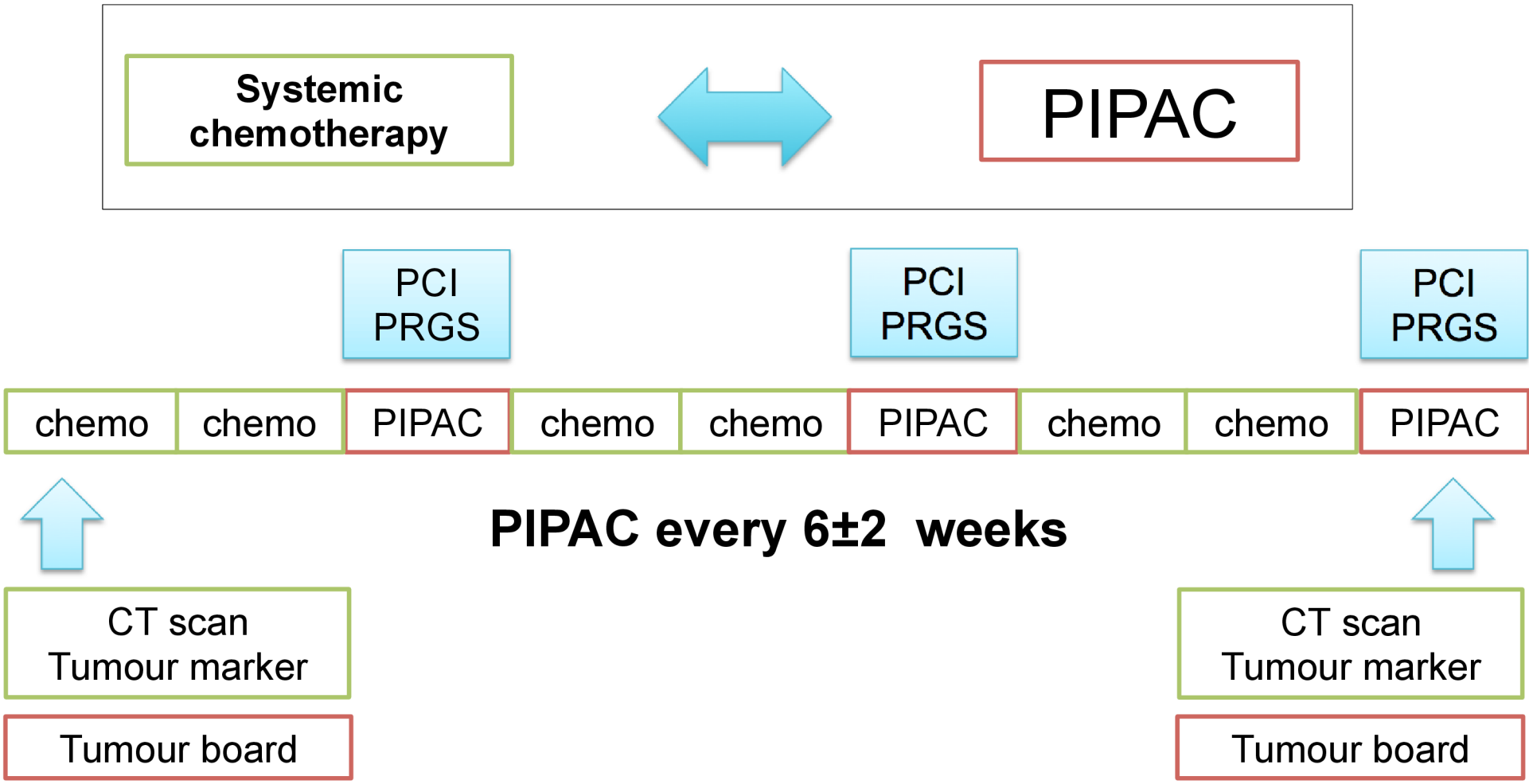

Video-monitoring
Access trocar
(5 mm)
CAWS
(Closed Aerosol
Waste System)
Pressurized
Chemotherapy Aerosol
(12 mmHg)
Micropump
High-pressure line
(to the abdomen)
Laparoscopy
CO2-Insufflator
(37° C)
Remote control
Display
Injector
Head
Syringe with
Cytostatic solution
Power supply

Figure 2 Flow chart of selected studies



The selection process adheres to the guidelines outlined in the PRISMA statement.


Systemic chemotherapy
PIPAC
PCI PRGS
PCI PRGS
PCI PRGS
chemo
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PIPAC
PIPAC every 6±2 weeks
CT scan Tumour marker
Tumour board
CT scan Tumour marker
Tumour board

Table 1 Feasibility, safety, and tolerance of pressurized intraperitoneal aerosol chemotherapy (PIPAC)

Prospective	Main primary	N	n PIPAC	Non-access	≥2 PIPAC	Surgical complications	Adverse events (CTCAE 4·0)		
							3	4	5
PIPAC OV-1[55]	ovarian	64	130	17% (11/64)	81% (43/53)	8% (4/53)	8/53	0/53	0/53
PIPAC GA-1	gastric	25	43	N/A	48% (12/25)	N/A	4/25	0/25	0/25
PIPAC GA-2[37]	gastric	31	56	0	48% (15/31)	3% (1/31)	4/31	0/31	0/31
PIPAC OPC-1[78]	various	35	129	0	86% (30/35)	6% (2/35)	4/35	1/35	0/35
SUBTOTAL/ Weighted means		**155**	**358**	**8·5%**	**69·4%**	**5.9%**	**13·9%**	**0·7%**	**0**
Retrospective									
Tempfer 14[79]	ovarian	21	34	14% (3/21)	44% (8/18)	17% (3/18)	3/18	2/18	0/18
Tempfer 15[44]	ovarian	99	252	17% (17/99)	61% (50/82)	6%* (5/82)	17/82	3/82	0/82
Nadiradze 15[80]	gastric	25	60	4%** (1/25) 13%*** (3/24)	71% (17/24)	5% (3/60 pr.)	6/24	1/24	2/24 (nr)
Odendahl 15[56]	various	91	158	N/A** 6%*** (5/91)	53% (48/91)	3% (3/91)	8/91	1/91	3/91 (2r, 1nr)
Robella 16[36]	various	14	40	0	100% (14/14)	0	0/14	0/14	0/14
Demtröder 16[70]	colorectal	17	48	0**, 35%*** (6/17)	82% (14/17)	0	4/17	0/17	0/17
Graversen 17[54]	pancreatic	5	16	0	100% (5/5)	0	0/5	0/5	0/5
Hübner 17[81]	various	44	91	4% (2/44)	71% (30/42)	2% (1/42)	0/42	0/42	1/42 (nr)
Alyami 17[34]	various	73	164	N/A	62% (45/73)	N/A	14/73	0/73	5/73 (1r, 4nr)
Khosrawipour 17[82]	pancreatic	20	41	0**, 15%*** (3/20)	50% (10/20)	0	0/20	0/20	1/20 (nr)
Falkenstein 18[83]	biliary tract	13	17	15% (2/13)	45% (5/11)	0	0/11	0/11	0/11
Kurtz 18[84]	various	71	142	11% (8/71)	62% (39/63)	5% (7/142 pr.)	1/63	0/63	1/63 (nr)
Gockel 18[85]	gastric	28	46	11%** (3/28) 8%*** (2/24)	58% (14/24)	N/A	0/24	0/24	0/24
Horvath 18[86]	pancreatic	12	23	0	50% (6/12)	0	0/12	0/12	0/12
Jansen-Winkeln 18[53]	various	62	111	8%** (5/59) 7%*** (4/54)	61% (33/54)	13% (7/54)	N/A	N/A	N/A
Giger-Pabst 18[35]	mesothelioma	29	74	24% (7/29)	91% (20/22)	0	1/22	2/22	1/22 (r)
SUBTOTAL/ Weighted means		**624**	**1317**	**10·5%****	**62·6%**	*not pooled (data heterogeneity)*	***10·4%***	***1·7%***	**r: 0·8%** **nr: 1·9%**

CTCAE – Common Terminology Criteria for Adverse Events, N/A – not available, r – death related to PIPAC procedure, nr –death not related to PIPAC procedure, pr. – procedures, N – number of patients, PIPAC GA-1 (NCT01854255) – doi : 10.1200/JCO.2017.35.4_suppl.99
*CTCAE grade ¾, **primary non-access (during 1st PIPAC), ***secondary non-access (during repeated intended PIPAC), ****presented at SSO meeting 2/18/2018, Jacksonville, FL

Table 2: Clinical efficacy of pressurized intraperitoneal aerosol chemotherapy (PIPAC)

Primary	Study/author	N	≥ 2 PIPAC	Assessment of response					Survival
				PCI improvement	**Histological**	Regression score	**RECIST**	**Other**	
Ovarian	PIPAC OV-1[57]	64	81% (43/53)	76% (26/34 3rd PIPAC)	ITT: 62% (33/53)-72% (38/53)* PP: 76% (26/34)-88% (30/34)*	Glaze et al.	ITT: 62% (33/53) PP: 52% (16/31)*		OS: 331 d (mean) PFS: 144 d (mean)
	Tempfer 14[81]	21	44% (8/18)		PP: 75% (6/8)	TRGS			442 d (mean)
	Tempfer 15[46]	99	61% (50/82)	64% (32/50)	PP: 76% (38/50)	Glaze et al.			14·1 m (median)
Gastric	PIPAC GA-1	25	48% (12/25)		ITT: 36% (9/25) PP: 75% (9/12)	PRGS	ITT:40% (10/25) PP: 77% (10/13)		8·4±1·7 m (mean) PCI ≤ 12: 13·1±3·5
	PIPAC GA-2[39]	31	48% (15/31)		PP: 60% (9/15)-91% (21/23)	PRGS			13 m (median), 1-year OS: 49.8%
	Nadiradze 15[82]	25	71% (17/24)		ITT: 50% (12/24) PP: 71% (12/17)	TRGS			15·4 m (median)
	Gockel 18[87]	24	58% (14/24)	57% (8/14)	PP:79% (11/14)	PRGS		79% stable or decreased ascites	210 days (median, all) 450 days (median, ≥3 PIPAC)
Colorectal	Demtröder 16[72]	17	82% (14/17)		ITT: 71% (12/17) PP: 86% (12/14)	TRGS			15·7 m (mean)
Pancreas	Graversen 17[56]	5	100% (5/5)		PP: 80% (4/5)	PRGS			14 m (median), 10-20 m (range)
	Khosrawipour 17[84]	20	50% (10/20)		PP: 70% (7/10)	TRGS			36·6 w
Biliary tract	Falkenstein 18[85]	13	45% (5/11)		PP: 80% (4/5)	PRGS			85 d (median, overall)
Mesothelioma	Giger-Pabst 18[37]	29	91% (20/22)		PP: 75% (15/20)	Dworak et al.			26·6 m (median)
Various	PIPAC OPC-1[80]	35	86% (30/35)		ITT: 57% (20/35) PP: 67% (20/30)	PRGS			
	Alyami 17[36]	73	62% (45/73)	61% (PP) 65% (3rd PIPAC)				46-63% with symptom relief	
	Kurtz 18[86]	71	62% (39/63)		PP: 67% (24/36)	PRGS			11.8 m (median)
TOTAL/ Weighted mean		**552**	**65·0%**	**66·7%**	**PP: 73.7%** **ITT: 57.1%**		**PP: 56.4%** **ITT: 59%**		*Not pooled (different primaries)*

Studies reporting on < 5 patients excluded. PCI – Peritoneal Cancer Index, RECIST – Response Evaluation Criteria in Solid Tumours, PP – per protocol, ITT – intention to treat, OS – overall survival, PFS – progression-free survival, d – days, w – weeks, m – months, N – number of patients, TRGS – tumor regression grading system, PRGS – peritoneal regression grading score, PIPAC GA-1 (NCT01854255) – doi : 10.1200/JCO.2017.35.4_suppl.99

*external blinded assessment.

	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 PM after primary tumour resection	USC	USC	USC	USC	-	-	-	-	?	?	-	-
Upfront or interval situation and resectable PM	USC	PCI≤ 15	USC PCI> 6	USC PCI ≤ 6	USC	+	USC	+	USC	USC	-	+
Synchronous or recurrent PM as : - sole metastatic site - and unresectable disease, - or patient not eligible to extensive CRS and/or HIPEC - and with 2nd or 3rd line of systemic chemotherapy-	+	-	+	-	+	-	+	-	+	-	+	-
Refractory ascites	+	-	+	-	+	+/-	+	-	+	-	+	-
Systemic chemotherapy intolerance	+	-	+	-	+	-	+	-	+	-	+	-
Unfavourable histology	+*	-*	+*	-*	+°	+°	+¨	+/-¨	+	-	+*	-*

Table 3. Potential indication for Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

PM, peritoneal metastasis; CRS, cytoreductive surgery; USC, under study condition; PCI, peritoneal carncer index

- unfavorable histology is an additional argument to introduce PIPAC earlier in the treatment strategy in this situation
* signet ring histology
° clear-cell carcinoma, undifferentiated ovarian cancer
¨ sarcomatoid or biphasic peritoneal mesothelioma