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Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC)

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Abstract

Background: Quality of Life (QoL) plays an important role in patients with peritoneal metastasis and is deteriorating continuously until death. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) is an innovative palliative treatment of peritoneal metastasis. We present the first QoL results under PIPAC therapy.

Methods: Retrospective analysis of QLQ30 questionnaire results during repeated courses of PIPAC applications in palliative patients with pretreated peritoneal metastasis.

Results: 91 patients (M:F = 40:51, median age 64 (34–77) years) with 158 PIPAC applications were analyzed. 86% patients had previously received systemic chemotherapy. Peritoneal metastasis was advanced (Peritoneal Carcinomatosis Index I = 16 ± 10). At admission, only moderate impairment of functioning (62–83%) and symptom scores (17–47%) was observed. 48 patients received at least 2 PIPAC every 6 weeks. After PIPAC # 1, the global physical score deteriorated slightly (from 82% to 75%), but improved after PIPAC # 2 (up to 89%). Gastrointestinal symptoms (nausea/vomiting, constipation, diarrhoea, anorexia) remained stable under PIPAC therapy.

Conclusions: Quality of life was relatively high in this group of patients with advanced, pretreated peritoneal metastasis, explaining their wish for further therapy. Functioning scores and disease-related symptoms were not altered for at least 3 months in the patients able to receive repeated PIPAC. Except for a transient moderate increase of pain scores, PIPAC did not cause therapy-related QoL deterioration, especially no gastrointestinal symptoms.

Keywords: Peritoneal metastasis; Quality of life; Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC); Chemotherapy administration; Cisplatin; Doxorubicin; Oxaliplatin; Gastric cancer; Ovarian cancer; Colorectal cancer

Introduction

Peritoneal metastasis is a common pattern in advanced gynaecological and gastrointestinal cancer with about 167,940 new cases per year in Europe.[1] In Germany alone, about 60 patients are diagnosed with peritoneal metastasis every day, half of them being women with ovarian cancer. Peritoneal metastasis has a poor prognosis with a median survival under 6 months and remains an unmet medical need.[2]

Palliative systemic chemotherapy is the standard of care in this situation. However, the efficacy of systemic chemotherapy to treat peritoneal metastasis is hampered by limitations such as poor vascularisation of the peritoneum[3] and elevated intratumoral fluid pressure.[4] Intraperitoneal chemotherapy has been increasingly used in peritoneal metastasis in order to optimize local drug delivery and improve clinical outcome. Intraperitoneal chemotherapy

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has shown superior pharmacological properties on peritoneal metastasis as compared to systemic chemotherapy. However, intraperitoneal chemotherapy is also hampered by pharmacological limitations such as limited surface exposition of the peritoneum and poor tissue penetration.[5]

Side-effects reported after systemic chemotherapy for peritoneal metastasis are relatively frequent[6] and typically include renal toxicity (cisplatin), neurotoxocity (oxaliplatin), and cardiac toxicity (doxorubicin).[7–11] Intraperitoneal chemotherapy is inducing less[12] or comparable[13] systemic side-effects but is limited by local toxicity and catheter-linked complications.

Thus, there is an obvious medical need for better therapeutic options in peritoneal metastasis prolonging survival and preserving QoL by reducing both disease-related symptoms and therapy side-effects. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is an innovative drug delivery system applying chemotherapeutic drugs in gaseous form under pressure within the closed abdominal cavity during a laparoscopy. In a large animal model,[14,15] ex vivo,[16] and in vivo,[17] pharmacological properties of PIPAC have been found to be superior. Specifically, a target tissue dose of doxorubicine up to 200× higher than reported after Hyperthermic IntraPeritoneal Chemotherapy (HIPEC)[18] has been documented after PIPAC in the human patient – with 10% of the dose applied.[17]

Thus, due to the high local bioavailability during PIPAC, the chemotherapy dosage can be reduced by one order of magnitude compared to a usual systemic dose[17] which in turn largely prevents systemic side effects and organ toxicity.[19] Local toxicity is minor and well tolerated. First evidence for clinical efficacy and safety of PIPAC has recently been published[20,21] and the first prospective Phase-2 trial has been closed recently.[22] PIPAC has been shown to be safe in the occupational setting.[23,24]

Here we present the first Quality of Life (QoL) data obtained in patients with peritoneal metastasis treated with PIPAC. The aim of the present analysis was to assess QoL in patients with end-stage peritoneal metastasis. The second aim was to assess possible changes in QoL before and after repeated PIPAC applications.

Material and methods

Study design

This is an observational, retrospective analysis of QoL data collected routinely in peritoneal metastasis patients at our institution (registry data).

Patients

170 patients with advanced peritoneal metastasis were admitted for PIPAC between 7/2012 and 01/2014 at our institution (university hospital, tertiary care center). Before admission, each patient was presented in the interdisciplinary tumour board and the indication for PIPAC was decided on a case-by-case, individual basis. Bowel obstruction and/or extraperitoneal metastasis were considered contraindications for PIPAC. Eligible patients were treated with cytoreductive surgery and HIPEC. Only patients with platinum-resistant peritoneal metastasis were treated with PIPAC after application of evidence-based, guideline-recommended palliative systemic chemotherapy. The day before the PIPAC procedure, all patients were invited to fill out the QoL questionnaire, but there was no obligation to do so.

Regulatory framework

QoL is recorded routinely in all peritoneal metastasis patients at our institution. PIPAC was applied as off-label use of approved drugs, according to German legislation. All patients gave their written informed consent for the PIPAC procedure and for data collection. The Institutional Review Board (Ethical Commission of the Ruhr University Bochum) expressed no objection. Therapy, data collection, and data analysis were performed according to the Declaration of Helsinki.

PIPAC procedure

The PIPAC procedure was performed as follows at 6 weeks intervals. After insufflation of a 12 mmHg CO_2 pneumoperitoneum, two balloon safety trocars (5 and 12 mm, Applied Medical, Duesseldorf, Germany) were inserted into the abdominal wall in an operating room equipped with laminar airflow. Under video surveillance the peritoneal metastasis index (PCI) was determined based on lesion size and distribution.[25] Peritoneal biopsies were taken for histologic confirmation of malignancy during the first procedure and for ascertainment of tumour regression during all following procedures. Ascites volume was documented and ascites was removed. Then, a nebulizer (MIP®, Capnomed GmbH, Villingendorf, Germany) was connected to an intravenous high-pressure injector (Injektron 82M, MedTron, Saarbruecken, Germany) and was inserted into the abdomen. Tightness of the abdomen was documented via a zero-flow of CO_2. A pressurized aerosol containing cisplatin at a dose of 7.5 mg/m^2 body surface in a 150 ml NaCl 0.9% solution followed by doxorubicin at a dose of 1.5 mg/m^2 body surface in a 50 ml NaCl 0.9% solution were applied via nebulizer and injector. Alternatively, 14 patients with colorectal cancer received oxaliplatin 92 mg/m^2 body surface. Dosage was based on clinical experience in patients with peritoneal metastasis treated with PIPAC with documented responses.[18,19] Injection parameters were set at a flow rate of 30 ml/min and a maximum upstream pressure of 200 psi in the high-pressure injector. The injection was remote-controlled to exclude occupational exposure. The therapeutic capnoperitoneum was maintained for 30 min at a temperature of 37 °C.

Then, the chemotherapy aerosol was exsufflated via a closed line over two sequential microparticle filters into the airwaste system of the hospital. Finally, trocars were retracted and laparoscopy ended. No drainage of the abdomen was used.

Quality of life assessment

The study was conducted using the validated EORTC QLQ C-30 questionnaire[26] which was developed to assess the QoL of cancer patients. It includes 30 different items, divided into various scales. Specifically, it is split up into 6 scales, containing items for emotional (4 items), social (2 items) and physical (5 items) functioning, cognitive (2 items) and role (2 items) functioning and further global health status (2 items). Better function is represented by higher mean scores in all scales. The questionnaire also provides symptom scores, including gastrointestinal items (nausea/vomiting; constipation; diarrhoea; appetite loss) and pain. Lower scores indicate less symptoms. We choose a general questionnaire since different drugs were used and different cancers were pooled.

Karnofsky index

The Karnofsky index (KI)[27] was determined systematically in all cancer patients and was used for estimating prognosis and defining therapeutic goals. The index scale ranges from zero (death) to one hundred percent (no restriction).

Follow-up

Patients were followed-up until July 31st, 2014 or until death.

Statistical analysis

For statistical analysis, the EORTC QLQ-30 scores were linearly converted to a 0−100 scale according to EORTC recommendations.[28] Missing items were imputed for the EORTC QLQ-C30, using the method advocated by the EORTC QoL research Group. A moderate change of 10−20 points was considered clinically significant. Statistics were performed using the SPSS version 14.0 software. Descriptive statistics included mean, median, percentiles, and confidence interval. Data are presented as line charts. No comparative statistics are provided.

Results

To assess Quality of Life (QoL) in patients with advanced peritoneal metastasis, we reviewed the protocols of 114 consecutive patients having received at least 2 PIPAC within the period of time under investigation. Ninety-one patients filled out at least one QoL questionnaire and 48 patients filled out at least 2 QoL questionnaires. Patients' characteristics are summarized in Table 1.

QoL results are divided into two parts as follows: first, QoL data obtained in patients with advanced peritoneal metastasis are presented; second, evolution of QoL data under PIPAC therapy are evaluated.

QoL in patients with end-stage peritoneal metastasis

The first specific question of the present analysis was to assess QoL in patients with advanced, platinum-resistant peritoneal metastasis. 78/91 patients (86%) had received previous palliative systemic chemotherapy, and the mean time since cancer diagnosis was 23 (±26) months. Mean Karnofsky index was 86 (±14) %, with 11 patients with Karnofsky < 70%. Thus, it is apparent that patients had late-stage metastatic disease. Median survival after the first PIPAC application was 13.4 months with a mean follow-up of 12.0 months. The actuarial survival curve is given in Fig. 1.

EORTC QLQ-30 functioning and symptom scores were determined at admission and were found to be moderately altered. These scores are detailed in Table 2. For example, the physical functional (PF) score was 75% ± 28%.

In earlier studies, cancer patients were grouped according to time from first assessment to death in order to explore the association between QoL scores and survival.[29] We applied the same method in patients with peritoneal

Table 1
Characteristics of 91 patients treated by Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for advanced peritoneal carcinomatosis.

	All patients (n = 91)		Patients with ≥2 PIPAC (n = 48)	
	n	%	n	%
Gender				
Females	51	56%	25	52%
Males	40	44%	23	48%
Age				
Median (min−max)	60 (34−77)		58	(37−77)
Karnofsky Index				
Mean (±SD)	84 (±14)		86 (±13)	
Previous therapy				
Time from cancer diagnosis (months, mean ± SD)	23 (±26)		22 (±27)	
Previous systemic chemotherapy	78	86%	40	83%
Extent of peritoneal carcinomatosis				
Peritoneal carcinomatosis index (mean ± SD)	16 (±10)		15 (±9)	
Cancer origin				
Ovarian	25	27%	8	15%
Stomach	29	32%	18	38%
Colorectal	14	15%	8	19%
Appendix	6	7%	4	6%
Mesothelioma	4	4%	1	6%
CUP	6	7%	5	8%
others	7	8%	4	8%

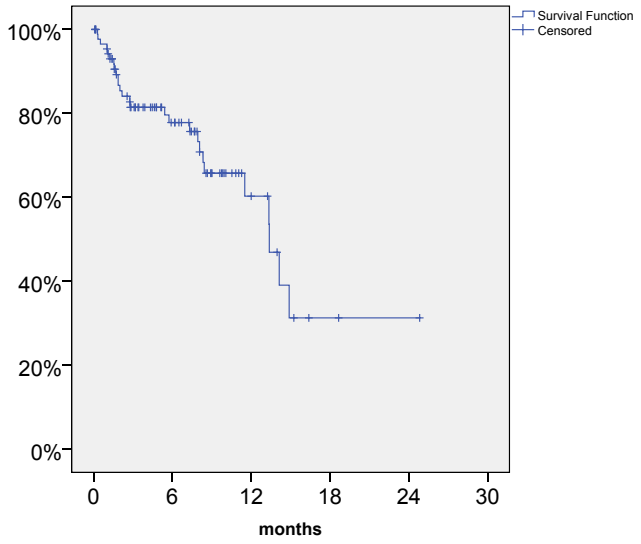

Figure 1. Survival curve of 91 patients with platin-resistant peritoneal carcinomatosis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Median survival was 13.4 months.

metastasis and found a continuous deterioration in most functional and symptom scales during the last months of life. These data are summarized in Fig. 2 (panel a) and Fig. 3 (panel a).

Complications after PIPAC

Hospital mortality was 3.3% (n = 3) of 91 end-stage patients or 1.9% of 158 PIPAC procedures. Two death were in relationship with PIPAC (2 iatrogenic bowel access lesions with following peritonitis), one because of disease progression (small bowel obstruction, refractory ascites). One (1%) adverse event CTCAE 4 (anaphylactic shock after intraoperative metamizol injection) and 8 (8.8%) adverse events CTCAE 3 were recorded (liver toxicity: n = 4; abdominal pain: n = 2; cholangitis (obstruction of a biliary stent)): n = 1: ileus = 1. Secondary access was not possible in 5 patients (5.5%) due to adhesions or disease progression.

Evolution of QoL during PIPAC

The second specific question was to assess the evolution of QoL during therapy. For this purpose, we analyzed the records of the 48 patients having received at last 2 PIPAC applications. Functional scores, including physical, emotional, cognitive, role and social scores are illustrated in Fig. 2b. There was no further deterioration of the scores in the patients receiving repeated PIPAC applications over a period of 3 months. The evolution of gastrointestinal symptom scores, including nausea/vomiting, appetite loss, obstipation, and diarrhoea is illustrated in Fig. 3b. In analogy to the functional scores, the gastrointestinal scores remained largely constant during the observation period. Pain score deteriorated slightly after PIPAC # 1 (from 28% to 37%),

Table 2
EORTC QLQ-30 functioning and symptoms scores [%] in patients with platin-resistant peritoneal carcinomatosis and in a general population of patients with advanced cancer.[25] PF: Physical functioning. EF: Emotional functioning. RF: Role functioning: CF: Cognitive functioning. SF: Social functioning. FA: Fatigue score. NV: Nausea/Vomiting score. PA: Pain score. DI: Diarrhoea score. DY: Dyspnoea score. AP: Appetite loss score. SL: Insomnia score. CO: Constipation score. FI: Financial difficulties.

	Functioning scores					Symptom scores				Symptoms – single items			
	PF mean	EF mean	RF mean	CF mean	SF mean	FA mean	NV mean	PA mean	DI mean	DY mean	AP mean	SL mean	CO mean	FI mean
Advanced cancer patients (n = 395)	46 ± 31	66 ± 26	32 ± 31	72 ± 27	48 ± 33	65 ± 27	25 ± 30	48 ± 36	26 ± 34	39 ± 36	51 ± 39	40 ± 31	43 ± 39	16 ± 27
Peritoneal cancer patients (n = 91)	75 ± 28	62 ± 27	64 ± 39	83 ± 23	56 ± 31	47 ± 28	21 ± 31	35 ± 30	19 ± 28	26 ± 30	31 ± 33	33 ± 31	17 ± 29	20 ± 30

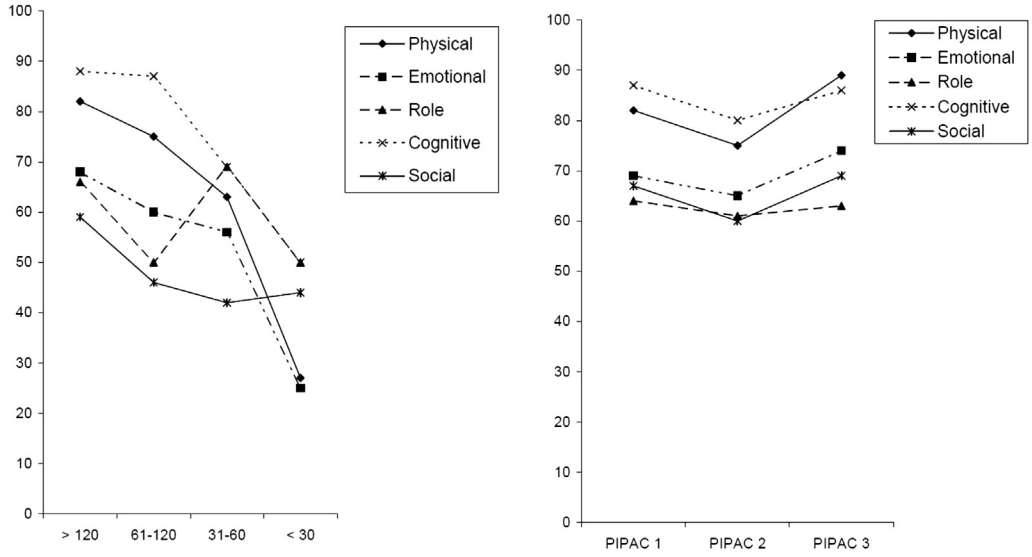

Figure 2. EORTC-QLQ30 functional scores. Left panel: in 91 peritoneal carcinomatosis patients classified according to their survival at time of assessment; right panel: in a subgroup of 48 of those patients having received at least 2 PIPAC at 6 weeks intervals. X-axis: days until death. Y-axis: score in %.

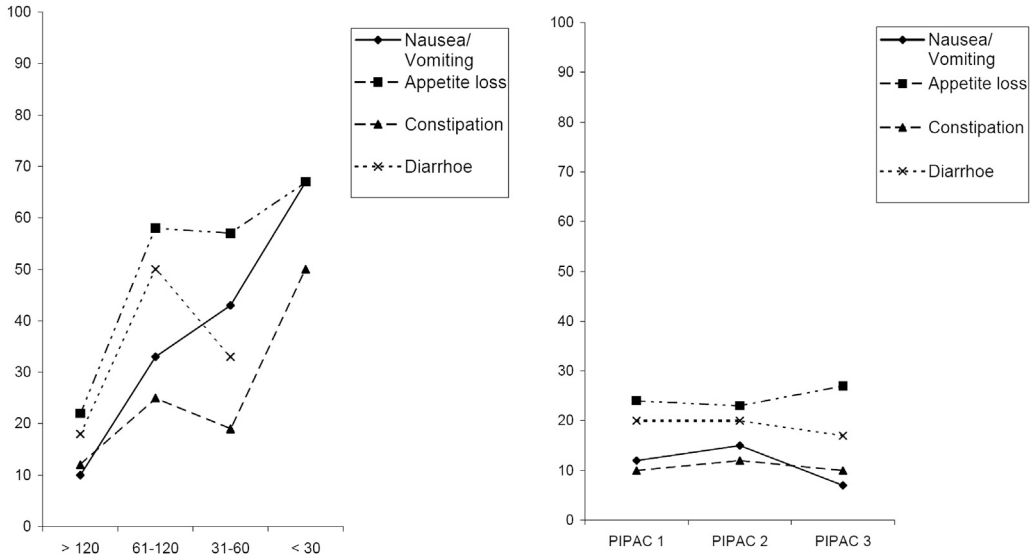

Figure 3. EORTC-QLQ30 symptom scores. Left panel: in 91 peritoneal carcinomatosis patients classified according to their survival at time of assessment; right panel: in a subgroup of 48 of those patients having received at least 2 PIPAC at 6 weeks intervals. X-axis: days until death. Y-axis: score in %.

but then improved again (32%). When contrasted with Figs. 2a and 3b, these data demonstrate a stabilization of QoL in peritoneal metastasis patients receiving repeated PIPAC applications.

Discussion

Declining quality of life scores with physical deterioration prior to death has already been documented in cancer patients.[29,30] Disease progression induces a rapid and continuous deterioration of quality of life. Response to second or subsequent lines of chemotherapy is strongly influenced by response to earlier treatment; patients with no response to up to two initial lines of treatment are less likely to respond to a third or subsequent line. For example, in gastric cancer, benefit of second-line combination chemotherapy schemas seems to be limited to patients with a good performance status, and treatment toxicity and discomfort are substantial, in particular with regimens containing cisplatin and infusional 5-FU.[6] In patients with advanced colorectal cancer under symptomatic therapy, the mean QLQ-30 physical performance deteriorated by 8.6 points at eight weeks and by 12.5 points at 16 weeks. Similarly, the global health score deteriorated by 7.1 points at eight weeks and by 15.2 points at 16 weeks.[31]

Many patients with advanced, platin-resistant peritoneal metastasis have still a relatively good performance status, and their gastrointestinal symptoms are moderate. Their hope for continued, high-quality life leads them to seek treatment beyond the standard of care, such as PIPAC.

Scores documented in our study are in good agreement with those determined in advanced cancer patients with a life expectation of >4 months[29] and with long-time survivors after cytoreductive surgery and HIPEC for peritoneal metastasis.[32]

PIPAC is a novel drug delivery system in the therapy of peritoneal metastasis in the salvage situation which optimizes physical conditions (gaseous nature and artificial hydrostatic pressure) to improve the pharmacology of drug delivery into the peritoneal tumour nodules, allowing a significant dose reduction (reviewed in[33]). The first Phase-2 trial with low-dose PIPAC with cisplatin 7.5 mg/m^2 and doxorubicin 1.5 mg/m^2 body surface in recurrent, platin-resistant ovarian cancer showed a clinical benefit rate of 60% in the third-line situation.[22] Safety data were encouraging with no CTCAE grade 4 and 5 events, grade 3 events only 15% of patients. Local toxicity of PIPAC on the bowel was well controlled (no perforation), liver and renal toxicities were minimal[19] and systemic side-effects were rare.[34]

We now report the first QoL results obtained in patients with peritoneal metastasis in the salvage situation treated with PIPAC. QoL was assessed before starting PIPAC and over a period of 3 months during the course of treatment. The most striking result that emerges from this study is the stabilisation of QoL under PIPAC. Functional scores remained stable, and gastrointestinal symptoms did not deteriorate under therapy. Only pain scores increased slightly and this negative effect was transitory. Transient abdominal pain might be explained by the chemical peritonitis induced by PIPAC. Classical side-effects of systemic chemotherapy such as mucositis, nausea/vomiting, diarrhoea, paraesthesia, cutaneous symptoms and alopecia were not reported by the patients.

To determine if a new treatment is clinically meaningful in the palliative situation, tolerability of treatment-related toxicities is of critical importance. If a therapy is less toxic than prevailing treatments, a smaller improvement in efficacy is acceptable. Conversely, a highly toxic therapy should be accompanied by an expectation of substantially greater benefit to provide a clinically meaningful outcome.[35]

In this context, the results obtained with PIPAC in this first cohort of palliative patients with platin-resistant peritoneal metastasis appear encouraging. This study provides first evidence that PIPAC does not alter quality of life of peritoneal metastasis patients in the salvage situation. However, these results should be considered with caution. First, this is a retrospective study. There was a self-selection bias because the most affected patients were excluded – patients who feel bad are lost to follow-up and do not fill out the questionnaire anymore.

Secondly, QoL remained stable under PIPAC therapy but this was only true in patients able to receive this therapy. In particular, 5 patients (5.5%) having experienced severe adverse events (CTCAE 3 to 5) after PIPAC did not receive further therapy, which might be a bias. Thus, extrapolation of these results to other patients with peritoneal metastasis is not possible. Moreover, it is unclear if the stabilization of symptoms observed was due to disease control or to the relief of side-effects previously induced by systemic chemotherapy. Finally, we could not determine how long quality of life remains stable under PIPAC therapy, and which proportion of patients truly benefit of this therapy.

QoL is difficult to measure and interpret, even when using validated instruments such as the QLQ30 questionnaire. Numbers reported here cannot be directly compared with numbers reported after systemic chemotherapy, or with patients who did not receive PIPAC in this challenging clinical setting: the patients treated with PIPAC had advanced disease, 11 of them having a Karnofsky Index lower than 70%, 24 more than 1000 ml ascites and 22 a Peritoneal Carcinomatosis Index (PCI) superior to 25. Although indication for PIPAC was decided on an individual basis by our interdisciplinary tumour board and no inclusion and exclusion criteria were predefined, there was some selection since patients with bowel obstruction or distant organ metastases were not treated.

Further work could for example include a long term longitudinal prospective study on QoL of patients with peritoneal metastasis treated with systemic chemotherapy and then with PIPAC, if possible from the time point of diagnosis of peritoneal metastasis. Such a study design would adequately describe the evolution of specific symptoms along the course of disease. It would also allow a direct comparison of the evolution of QoL under systemic chemotherapy and under PIPAC, each patient being his own control. Randomized delayed comparison with patients who do not receive PIPAC immediately in this palliative care setting may also be of use.[36] The rationale for such a prospective study is now given, since PIPAC holds promise to stabilize QoL of peritoneal metastasis patients in the salvage situation, for a period of time that remains to be determined.

Conflicts of interest

M.A.R. disclaims that he is holder of several patents on PIPAC technology and received royalties from Reger Medizintechnik, Villigendorf, Germany. The other authors have no disclaimer.

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