Marco Vaira*, Manuela Robella, Alice Borsano and Michele De Simone

Single-port access for Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC): technique, feasibility and safety

DOI 10.1515/pap-2016-0021
Received November 3, 2016; accepted November 28, 2016;
previously published online December 15, 2016

Abstract

Background: Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is a drug delivery system for treatment of peritoneal metastasis (PM). A limitation of this technique is the non-access rate (10–15%) due to peritoneal adhesions. The aim of the study was to assess feasibility and safety of the single-port access technique for PIPAC.

Methods: Single-center, pilot study. Case series, retrospective analysis on 17 patients with PM of various origin treated with intraperitoneal cisplatin, doxorubicin and/or oxaliplatin administered as PIPAC. Single-port access was attempted in all patients by minilaparotomy.

Results: Twenty-nine PIPAC procedures were performed. Nine patients were subjected to 1 PIPAC, four patients to 2 PIPAC and four patients to 3 PIPAC. Access to peritoneal cavity was possible in all cases. There was no bowel access lesion. Tightness of the abdomen (CO_2-flow = 0) was achieved in all cases. No postoperative complications according to CTCAE (Common Terminology Criteria for Adverse Events) > 2 were observed, no re-laparotomies required and no postoperative mortality recorded.

Conclusions: Single port-access is feasible and safe for PIPAC. Potential advantages over multiple trocars technique are a lower non-access rate, a lower risk of bowel lesions and a better tightness of the abdomen. This has now to be confirmed in a comparative study.

Keywords: cisplatin, doxorubicin, drug delivery system, intraperitoneal chemotherapy, oxaliplatin, peritoneal metastasis, Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC), single-port laparoscopy

***Corresponding author: Marco Vaira,** Unit of Surgical Oncology, Candiolo Cancer Institute – FPO, IRCCS, Candiolo, Italy, E-mail: marco.vaira@ircc.it
Manuela Robella, Alice Borsano, Michele De Simone, Unit of Surgical Oncology, Candiolo Cancer Institute – FPO, IRCCS, Candiolo, Italy

Introduction

In patients with tumors confined to the peritoneal cavity, there is established pharmacokinetic and tumor biology-related evidence that intraperitoneal drug administration is advantageous [1]. However, there are pharmacokinetic problems linked to intraperitoneal chemotherapy (IPC), in particular poor tissue penetration and limited surface exposure [2]. The first problem is very limited penetration of the drug into tissue. Many solid tumors show an increased interstitial fluid pressure (IFP), which creates a formidable obstacle to transperitoneal transport. This elevated intratumoral pressure results into an inefficient uptake of therapeutic agents [3]. The second problem is limited exposure of the peritoneal surface to the therapeutic solution. It has been postulated that the solution of these two pharmacokinetics problems could improve, perhaps dramatically, the efficacy of IPC [2].

Against this framework, an innovative drug delivery technique for IPC might allow major progress. This technique, Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) has been developed by a Swiss surgeon over the last 20 years [4]. The principle of PIPAC is based on administration of chemotherapeutic agents into the abdominal cavity as an aerosol under pressure – during staging laparoscopy. Compared with conventional IPC using catheters or to Hyperthermic IntraPeritoneal Chemotherapy (HIPEC), PIPAC achieves a more homogeneous distribution of the drug onto the exposed peritoneal surfaces [5]. Moreover, PIPAC increases drug penetration into the peritoneal tissue by application of an artificial hydrostatic intraperitoneal pressure [6, 7].

Retrospective cases series in ovarian [8], gastric [9] can colorectal [10] cancer have shown promising preliminary results, in particular a high rate of objective histological tumor regression after repeated PIPAC application [11]. In the same indications, tolerability of PIPAC therapy was reported to be good, since only a fraction of the dose administered reaches the systemic compartment [12]. These encouraging retrospective results have recently been confirmed in two prospective

Phase-2 trials in platinum-resistant, recurrent ovarian cancer [13] and in peritoneal metastasis of gastric origin [14]. Several further clinical trials are currently ongoing for evaluating the efficacy and safety of PIPAC in various indications.

However, these studies have also shown that PIPAC has technical limitations. A first problem is a non-access rate up to 17% [15] preventing PIPAC application in a number of patients without real other therapeutic alternative. A second problem is the risk of bowel access lesions when capnoperitoneum is insufflated with a Veress needle and the first trocar is inserted blindly.

A potential solution to the problems above would be the combination of a small laparotomy with the insertion of a single-access port. In theory, single-port access PIPAC should allow abdominal access in a larger proportion of patients than blinded approach. Open-access laparoscopy has been shown to prevent intraoperative bowel and vascular lesions during laparoscopy [16, 17]. Finally, the outstanding adaptation between the ring of a single-port access and the abdominal wall should facilitate complete tightness of the abdomen and virtually exclude any contamination of the abdominal wall with the toxic aerosol [18]. Therefore, in June 2015, we started the PIPAC program in our institution with minilaparotomy and single-port approach to the abdomen.

The aim of this study was to review our experience with single-port PIPAC in order to generate first data on this access technique. Specifically, we were interested in determining the best suitable technology platform, the feasibility of the technique, the non-access rate and the incidence of bowel access lesions.

Materials and methods

Study design

This is a single-center, retrospective case series reviewing our initial experience with single-port access PIPAC.

Ethical and regulatory background

No specific inclusion and exclusion criteria were defined beforehand. Indication for IPC as PIPAC was decided case by case by the Interdisciplinary Tumor Board of our institution (IRCC). In analogy to HIPEC, PIPAC was performed as “off-label” use of approved drugs. Staging laparoscopy is performed routinely in our institution by single-port access. Our preliminary experience served as a basis for applying for a Phase-2 trial protocol (NCT02604784) [19] that has received in the meantime the formal approval of the Italian Drug Agency (A.I.F.A. – Agenzia Italiana del Farmaco).

Risk assessment and simulations

Before starting our PIPAC program, two surgeons of our institution were trained in the theoretical and practical aspects of PIPAC technology, including occupational health safety aspects, by the team of Prof. Reymond in Germany. Back home, we simulated a PIPAC procedure in four patients scheduled for staging laparoscopy by insufflating a 12 mmHg pneumoperitoneum, verifying tightness of the abdomen, inserting the instruments, exploring the abdominal cavity, positioning the camera using an a self-retaining retractor (Thompson Retractors, MI, USA) and aerosolizing a saline solution (150 mL NaCl 0.9%) into the abdomen using the CapnoPen® (Capnomed GmbH, Villingendorf, Germany), as shown in Figure 1. In a further step, we stained the saline solution with toluidine blue to verify the absence of leakage and adequate distribution of the aerosol. Finally, we performed the first PIPAC procedure using

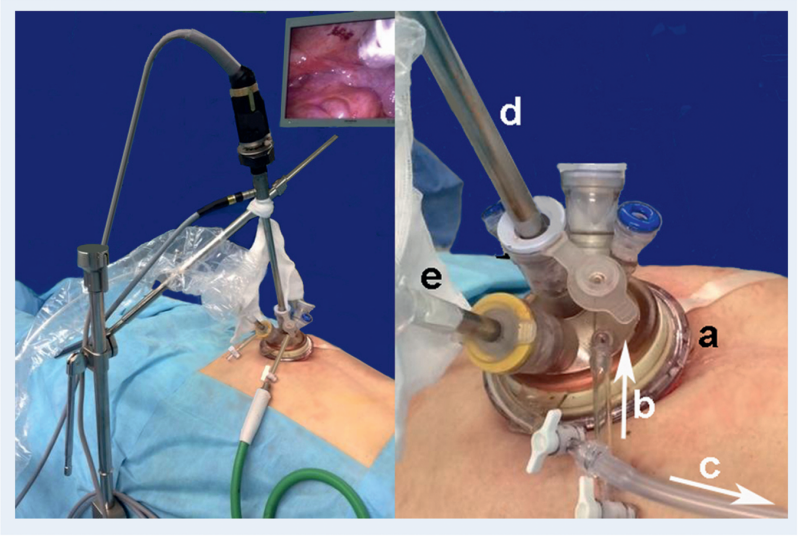

Figure 1: Technique of single-port access PIPAC. Left panel: overview showing the general setup and the self-retaining retractor (Thompson Retractors, Bisceglie, Italy). Right panel: detail of the single-port access system. (a). QuadPort+ device (Olympus Medical, Tokyo, Japan). (b) CO_2 inflow line. (c) CAWS (Closed Aerosol Waste System). (d) 10 mm Hopkins optics. (e) Nebulizer (CapnoPen®, Capnomed, Villingendorf, Germany).

chemotherapeutic drugs with strict application of the safety measures recommended by the pioneer team [18].

Technique of PIPAC

PIPAC was performed as described elsewhere [11]. Briefly, all operations were performed under general anesthesia; venous thromboembolism prophylaxis was administered the day before surgery using low molecular weight heparin (LMWHs). Antibiotics prophylaxis with a single dose of cefazolin 1 g IV was administered 30 min before surgery. An open access with a midline 5 cm incision was performed and a QuadPort + (Olympus Medical, Tokyo, Japan) was positioned. A 12 mm Hg CO_2 pneumoperitoneum was inflated. Ascites was removed if present and the amount documented. Extent of peritoneal carcinomatosis was evaluated according to Peritoneal Cancer Index (PCI) [20] and peritoneal biopsies were taken. The nebulizer (CapnoPen®, Villingendorf, Germany) was connected to a high-pressure angioinjector (Arterion 7, Medrad, Bayer, Germany) and inserted into the peritoneal cavity; the tightness of the abdomen was documented with a CO_2 zero-flow at a pressure of 12 mmHg. The laparoscopic 10 mm camera and the nebulizer were maintained in position by a self-retaining retractor (Thompson Retractors, MI, USA). Then the drugs were aerosolized into the peritoneal cavity. Injection parameters were a flow of 30 mL/min and a maximum upstream pressure of 200 psi. The injection was remote controlled in order to avoid occupational exposure. The capnoperitoneum was then maintained for 30 min at 37 °C. At the end of the procedure, the aerosol was exsufflated through two sequential micro-particle filters into the airwaste system of the hospital. Finally, the single-port platform was removed. No abdominal drain tube was placed. Nasogastric tube and urinary catheter were removed at the end of the operation.

Medication

Following drugs and doses were applied:

1) Cisplatin 7.5 mg/m^2 body surface in 150 mL NaCl 0.9 % + doxorubicin 1.5 mg/m^2 body surface in 50 mL NaCl 0.9 % in patients with epithelial ovarian cancer and diffuse malignant peritoneal mesothelioma (DMPM).
2) Oxaliplatin 92 mg/m^2 body surface in 150 mL dextrose solution in patients with colorectal cancer, appendiceal and gastric cancer.

The duration of the complete treatment was 18 weeks, with three single doses in 6-week intervals administration.

Data collection

The safety and tolerability of the procedure were assessed by collection of adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) [21] including physical examination results and daily laboratory assessments (chemistry and hematology).

Statistical analysis

This is a pilot study. Only descriptive statistics are provided.

Results

We assessed four different single-port access devices that we have employed for explorative laparoscopies. First we tested the GelPOINT Access Platform (Applied Medical Co., Milan, Italy): this system was found to be safe for preventing leakage of the toxic aerosol and sufficiently large to manipulate the ileum but the large internal ring's diameter made its placement sometimes difficult in presence of bowel adhesions. In a second step we tested the TriPort device (Olympus Medical, Tokyo, Japan). This device was also found to be able to ensure perfect tightness of the abdomen. The internal ring diameter fitted well in patients with peritoneal adhesions, but the system did not allow complete exposition of the peritoneal surfaces, and the optimal positioning of the instruments (the camera and the nebulizer) for the PIPAC procedure was difficult. In a third step we tested the QuadPort + device (Olympus Medical, Tokyo, Japan). The QuadPort + device has two 5 mm ports, as well as 10 mm, 12 mm and 15 mm instrument ports. This system in our experience, delivered the best combined results for this particular use (PIPAC procedure): easy handling, tightness of the system, adequate size of the internal ring, excellent exposition of the peritoneal surfaces and optimal positioning of the instruments. Thus, we selected the QuadPort + device for our PIPAC program.

Between June and November 2015, 17 patients with peritoneal metastasis were admitted for PIPAC therapy at our institution. PIPAC cycles were scheduled at 6-weeks interval. Patients' characteristics are presented in Table 1. Most patients had advanced peritoneal metastasis with a mean PCI of 21 (range 12–35). All patients had previous surgery, measured by Prior Surgical Score (PSS) [22] described by Sugarbaker: PSS 0: 0 patient; PSS 1: 4 patients; PSS 2: 11 patients; PSS 3: 2 patients. No patient had previous cytoreductive surgery and HIPEC. The most frequent tumor was ovarian cancer, followed by gastric cancer, colorectal cancer and malignant peritoneal mesothelioma.

During the period of time under observation, 29 PIPAC procedures were performed in these 17 patients (1.7 PIPAC/patient). Nine patients were subjected to 1 PIPAC, four patients to 2 PIPAC and four patients to 3 PIPAC. The mean operative time of the 29 procedures was 96 minutes (range 50–145 min), it was 109 (range 60–145 min) in the

Table 1: Patients' features.

Age, years	58 (range: 24–72)
ECOG score 1st PIPAC[a]	0 = 5 pts; 1 = 8 pts; 2 = 4 pts
PSS[b]	PSS 0: 0 pts PSS 1: 4 pts PSS 2: 11 pts PSS 3: 2 pts (none had CRS + HIPEC)
Number of PIPAC performed	1 PIPAC : 9 pts 2 PIPAC : 4 pts 3 PIPAC : 4 pts
PCI (median)	21 (range: 12–35)
Primary disease	Ovarian cancer: 6 pts Gastric cancer: 5 pts Colorectal cancer: 4 pts Peritoneal mesothelioma: 2 pts

[a]PIPAC, Pressurized IntraPeritoneal Aerosol Chemotherapy. [b]PSS, Prior Surgical Score; PSS 0, no prior surgery or only a biopsy; PSS 1 indicates one region with prior surgery; PSS 2 indicates 2 to 5 regions previously dissected; PSS 3 indicates more than 5 regions previously dissected. Pts, patients.

Table 2: Therapy and results (17 patients, 29 PIPACa).

Operative time	29 PIPAC: mean 96 min (range: 50–145) –First 14 PIPAC: mean = 109 min (range 60–145) –Last 15 PIPAC: mean = 87 min (range 10–110) Abdominal access: 100 % (29/29 procedures completed)
Abdominal access	100 % (29/29 procedures completed)
Hospital stay	Mean: 3.8 days (range 2–5 days)
Morbidity CTCAE[b]	Grade 1: 6 patients (abdominal pain/1 wound hematoma) Grade 2: 9 patients (nausea and vomiting) No grade 3–4 morbidity recorded No deaths recorded

[a]PIPAC, Pressurized IntraPeritoneal Aerosol Chemotherapy. [b]CTCAE, Common Terminology for Cancer Adverse Events. CTCAE Grade severity. Grade 1, mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2, moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (Activity of Daily Living). Grade 3, severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Grade 4, life-threatening consequences; urgent intervention indicated. Grade 5, death related to AE (Adverse Event).

first 14 procedures and 87 minutes (range 50–110 min) in the last 15 procedures.

Access to peritoneal cavity was possible in all cases with a minilaparotomy of 5 cm. There was no bowel access lesion. The QuadPort + device could be placed into the minilaparotomy incision in all cases. We did not register any problem in the insufflation and maintenance of the 12 mmHg capnoperitoneum. In particular, no leakage was detected. Adequate exposure of the peritoneal surface was possible in all cases.

Hospital stay was 3.8 days (range 2–5 days). There was no postoperative mortality. There was no severe postoperative morbidity (CTCAE 3 or 4). Six patients developed adverse events CTCAE grade 1 (abdominal pain; in one patient associated to wound hematoma), while in nine patients CTCAE Grade 2 events (Nausea and vomiting). C-reactive protein serum level increased significantly in all patients after the procedure. One patient had a wound hematoma that brought to a slow healing, but never required specific treatment. No infection at the minilaparotomy site was recorded. No incisional hernia was diagnosed postoperatively (Table 2).

Discussion

Over the last 15 years, we performed at our institution (tertiary reference center for peritoneal cancer) around 1,000 surgical procedures for peritoneal metastasis, and more than 400 combined procedures associating cytoreductive surgery (CRS) with HIPEC. In most patients, we have performed a staging laparoscopy for evaluating a possible indication for CRS and HIPEC. Specifically, over the last five years, we performed nearly 200 explorative laparoscopies for peritoneal metastasis by single-port access using different devices.

Clearly, only a minority of patients in good condition, with limited peritoneal disease and no aggressive tumor histology have a benefit of CRS and HIPEC [23]. For the remaining patients, there is clearly an unmet medical need since no surgical option is available and the efficacy of systemic palliative chemotherapy is limited. Therefore, together with our medical oncologists, we decided to start a PIPAC program at our institution and were one of the first centers worldwide to do so.

Earlier reports on PIPAC in peritoneal metastasis have reported about a high non-access rate [15], and also about some rare iatrogenic bowel access lesions when the first trocar is inserted blindly. Some of the PIPAC groups are preferring open access to blind puncture of the abdomen and blunt (Hasson) trocars are then usually inserted through the abdominal wall. Everyday practice shows that it is relatively difficult to obtain complete tightness of the abdomen after open access. Moreover, it has been reported that leakage of the toxic therapeutic aerosol into the abdominal wall after open

laparoscopic access can cause significant local injury, similar to extravasation of chemotherapeutic agents into the surrounding tissue after inadequate intravenous infusion. Therefore, on the basis of our previous experience, it was logical for us to modify the original PIPAC technique and to integrate single-port access in this technology.

Our first results suggest that single-port access is feasible for PIPAC application and that technique is safe. In the first 29 consecutive PIPAC procedures, the non-access rate is zero. Although this is a small cohort, it is reasonable to hope that single-port access might reduce the incidence of non-access during PIPAC, in fact, in case of omental cake, it is sometimes difficult to place trocar in upper quadrants and explore the peritoneal cavity. In those cases we observed that placing the trocar in the midline, under the umbilical scar, generally allows the access to peritoneal cavity and its exploration.

Alternatively, single-port access might be an alternative option in the patients where direct puncture was not successful.

A further potential advantage of single-port access PIPAC over conventional technique might also be to reduce the risk of bowel access lesions and therefore the incidence of such intraoperative complications.

Another important relief is that, in our experience, single-port explorative laparoscopies is useful to avoid multiple port placement, in order to reduce trocar-site cancer implants in patients with PC (and often ascites and bowel adhesions) and may permit removal of midline trocar wound in selected patients amenable for further cytoreductive surgery [24].

Single-port access technique for PIPAC might also have benefits for occupational health safety. In our experience, obtaining complete tightness of the abdomen was possible in each case and easy to achieve. We did not notice any leakage of the therapeutic aerosol into the environment, as documented by a zero-flow from the CO_2-insufflator – after taking into consideration CO_2 absorption by the patient through the peritoneal membrane.

Finally, we did not observe any infiltration of the chemotherapeutic aerosol into the abdominal wall, and there was no postoperative inflammation or tissue necrosis around the minilaparotomy. This seems a relevant observation since such complications have been reported after PIPAC, in particular after open access to the abdomen.

Single-port access PIPAC has the disadvantage to be more expensive than conventional PIPAC, due to the costs of the single-port device. However, these additional costs have to be counterbalanced with the costs of complications such as bowel access lesions, necrosis of the abdominal wall, etc. reported after PIPAC. Moreover, single-port access PIPAC might give an additional therapeutic chance to patients where conventional access was not possible, which is clearly an added value.

In theory, single-port access PIPAC might cause incisional hernia due to the minilaparotomy. However, this incidence is expected to be relatively low, according to recent literature [25]. Moreover, trocar hernia has also been reported after conventional access for PIPAC [13]. Because of the short follow-up in our patients, it is not possible to conclude on this subject at the present time point.

In summary, this pilot study provides first data suggesting that single-port access PIPAC might have several advantages over conventional PIPAC, namely a lower non-access rate, a lower risk of bowel access lesions, a lower rate of abdominal wall complications and a higher occupational health safety standard. These potential advantages have no to be confirmed in a prospective comparative trial.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Ceelen WP, Flessner MF. Intraperitoneal therapy for peritoneal tumors: biophysics and clinical evidence. Nat Rev Clin Oncol 2010;7:108–15.
2. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst 1997;89:480–7.
3. Heldin CH, Rubin K, Pietras K, Ostman A. High interstitial fluid pressure – an obstacle in cancer therapy. Nat Rev Cancer 2004;4:806–13.
4. Reymond MA, Hu B, Garcia A, Reck T, Köckerling F, Hess J, et al. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. Surg Endosc 2000;14:51–5.
5. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc 2012;26:1849–55.
6. Solass W, Herbette A, Schwarz T, Hetzel A, Sun JS, Dutreix M, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. Surg Endosc 2012;26:847–52.

7. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol 2014;21:553–9.
8. Tempfer CB, Celik I, Solass W, Buerkle B, Pabst UG, Zieren J, et al. Activity of pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. Gynecol Oncol 2014;132:307–11.
9. 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;20:367–73.
10. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectalperitoneal metastasis. Colorectal Dis 2016;18:364–71.
11. 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 J Surg Oncol 2016;29:128.
12. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). Ann Surg Oncol 2013;20:2311–16.
13. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol 2015;137:223–8.
14. Khomyakov V, Ivanov A, Ryabov A, Bolotina L, Utkina A, Volchenko N, 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;1:159–66.
15. 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;35:6723–9.
16. Köckerling F, Schneider C, Reck T. Open laparoscopy for prevention of puncture injuries. Chirurg 1996;67:183–7.
17. Ahmad G, Duffy JM, Phillips K, Watson A. Laparoscopic entry techniques. Cochrane Database Syst Rev 2008;16:CD006583.
18. Solass W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. Ann Surg Oncol 2013;20:3504–11.
19. https://clinicaltrials.gov/ct2/show/NCT02604784.
20. Esquivel J, Farinetti A, Sugarbaker PH. Elective surgery in recurrent colon cancer with peritoneal seeding: when to and when not to proceed. G Chir 1999;20:81–6.
21. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010). U.S. Department of Health and Human Services National Institutes of Health National Cancer Institute.
22. Sugarbaker PH. Cytoreductive surgery and peri-operative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. Eur J Surg Oncol 2001;27:239–43.
23. Lambert LA. Looking up: Recent advances in understanding and treating peritoneal carcinomatosis. CA Cancer J Clin 2015;65:284–98.
24. Pocard M. Exploratory laparoscopy for carcinomatosis: discard that quiver full of trocars and use just one!. J Visc Surg 2015;152:147–8.
25. Arezzo A, Passera R, Bullano A, Mintz Y, Kedar A, Boni L, Cassinotti E, Rosati R, Fumagalli Romario U, et al. Multi-port versus single-port cholecystectomy: results of a multi-centre, randomised controlled trial (MUSIC trial). Surg Endosc 2016 Oct 24. doi:10.1007/s00464-016-5298-7 [Epub ahead of print].