

First Clinical Safety and Feasibility Data of Whole-body Hyperthermia Pressurized Intraperitoneal Aerosol Chemotherapy (WBH-PIPAC) for Peritoneal Surface Malignancies

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Abstract. *Background/Aim:* This study evaluated the feasibility and safety of whole-body hyperthermia pressurized intraperitoneal aerosol chemotherapy (WBH-PIPAC) in patients with peritoneal surface malignancies. *Patients and Methods:* This study retrospectively analyzed a database of 28 patients who had received one cycle of normothermic PIPAC prior to repetitive WBH-PIPACs. WBH (39-40°C) was induced using a Water-filtered infrared A device. Doxorubicin plus cisplatin or oxaliplatin was nebulized into a constant capnoperitoneum of 20 mmHg for 30 min at doses of 6.0 mg, 30.0 mg, or 120 mg per m² body surface area, respectively. The primary outcome measures were feasibility and perioperative complications. *Results:* The median age was 62 years (range=45-78 years). Primary tumor sites included the upper gastrointestinal tract (n=9), colon/rectum (n=7), hepato-pancreato-biliary system (n=3), peritoneum (n=2), ovaries (n=2), and unknown primary (n=5). The induction of WBH failed in one patient (6 liters ascites). After a median warming period of 95 min (53-117

min), the median rectal temperature (T_{rec}) was 39.5°C (39.2-39.9°C). No hyperthermia-related side effects were observed. Twenty-seven patients received 50 WBH-PIPACs. The median time of therapeutic capnoperitoneum and treatment time with $T_{rec} \geq 39^\circ\text{C}$ was 39 min (37-43 min) and 66 min (53-69 min), respectively. The overall rate of postoperative procedure-related complications was 9/50, including seven grade I and two grade II complications. There were no grade III-V complications. *Conclusion:* In a highly selected group of patients, the feasibility and perioperative safety of WBH-PIPAC was comparable to normothermic PIPAC.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a newer technology for delivering intraperitoneal chemotherapy (IPC) that aims to overcome the limitations of liquid-intraperitoneal chemotherapy (L-IPC). During repeated staging laparoscopies, drugs are nebulized into a constant capnoperitoneum. Data from retrospective case series and a very recent phase II study on safety, feasibility, and objective tumor response rates in gynecological and non-gynecological peritoneal surface malignancies (PSM) patients are encouraging (1, 2). However, one criticism levelled at PIPAC technology is that it can currently only be carried out normothermic and the potential benefits of hyperthermia (HT) have not been exploited.

HT is recognized as an adjuvant cancer therapy in which temperatures above the physiological level, usually 39-43°C, are used to enhance the cytotoxic effect of chemotherapy and/or radiotherapy. HT affects cells and tissue in various ways. It increases blood flow, blood circulation and vascular

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permeability and simultaneously lowers the interstitial fluid pressure (IFP). This leads to an increased accumulation of low-molecular and/or macromolecular active substances in the tumor tissue. It is assumed that improved perfusion and oxygenation are the most important mechanisms by which HT improves chemo- and radiotherapeutic treatment (3, 4).

In order to combine the potential therapeutic benefits of HT with the advantages of PIPAC, prototypes for the administration of hyperthermic PIPAC (h-PIPAC/H-PAC) have been developed (5, 6). However, it is unlikely that any of these prototypes will find their way into daily clinical practice. In contrast to this, various commercially available techniques have been used to artificially increase whole body temperature [whole-body hyperthermia (WBH)] by exogenous heat application, generally aiming for core body temperatures of 41–42°C (sometimes referred to as extreme WBH) or 39–40°C (WBH in the fever range) (7).

Limited clinical data on WBH in combination with HIPEC in patients with stage IV gastric cancer show safety, feasibility and an increased 1-year survival rate of 38.5% compared to 19% in the control group (8). We raised the question whether WBH could be also a relevant adjunct to PIPAC. Therefore, we subjected a selected group of end-stage PSM patients to WBH-PIPAC. This retrospective study reports first data on the safety and feasibility of WBH-PIPAC.

Patients and Methods

Legal background. This is a retrospective analysis of a small group of patients, who received hyperthermia combined with PIPAC as a part of an individual treatment plan. All patients were informed about off-label use of the chemotherapeutic drugs. The used Medical Device “Iratherm® 1000M” is a class IIa product and complies with all requirements of the Medical Device Directive. The clinical study was performed in line with the guidelines of the Declaration of Helsinki at the Department of Surgery, Klinikum Dortmund, University Hospital of the University Witten/Herdecke, Germany. The approval of the Ethics Committee of the Medical Faculty of the University of Witten Herdecke, Germany (Nr. S-242/2023) was obtained. The study was registered in the German Clinical Trials Register under DRKS00032990.

Patient selection criteria for WBH-PIPAC. All patients had primary or metastatic PSM confirmed by histology. They were selected by a multidisciplinary tumor board accredited by the German Society for General and Visceral Surgery (DGAV). The patients were informed that PIPAC and WBH-PIPAC treatments are not part of evidence-based therapy guidelines. All patients provided their oral and written consent. Inclusion and exclusion criteria for PIPAC were already discussed previously in detail (9, 10). However, for WBH-PIPAC, only patients with an ECOG score of 0 or 1 (11) who had completed one cycle of normothermic PIPAC without perioperative complications were eligible. Additionally, contraindications for WBH-PIPAC included clinical signs of cardiac insufficiency (> NYHA grade 2) (12), current or past cardiac

arrhythmia, major lymphedemas, peripheral artery diseases, and a body weight >135 kg.

Induction of moderate whole-body hyperthermia (WBH). After completion of the “sign in” of the WHO safety checklist (13), the patients were completely undressed and placed in the pre-operative room on the Water-filtered Infrared A (wIRA) device (IRATHERM®1000, Von Ardenne Institute of Applied Medical Research GmbH, Dresden, Germany) for moderate WBH. Via a peripheral venous access, 1000 ml/h of IonoSteril® (Fresenius Kabi, Bad Homburg, Germany) was infused. The temperature was measured continuously via a rectal (T_{rec}) temperature probe. In addition, there was continuous cardio-pulmonary monitoring by heart rate (HR), non-invasive blood pressure (NIBP) and transcutaneous oxygen saturation (SpO_2). After complete preparation, the patients were covered with an insulating blanket (Figure 1).

The target temperature for moderate whole-body hyperthermia (WBH) was T_{rec} of 39.5–40°C at the end of the heating period, with a $T_{\text{rec}} \geq 39^\circ\text{C}$ during WBH-PIPAC. The output of the wIRA device was initially set to 100% for 45 min, followed by a dose reduction to 75% based on individual heat tolerance. After pre-operative hyperthermia, the patients were immediately repositioned on the operating table, transferred to the operating theatre, intubated, and prepared for WBH-PIPAC. During WBH-PIPAC, the patients were kept warm with a 43°C air blanket that had an abdominal operating window (3M™ Bair Hugger™, Model 775-57000-10, 91 cm × 213 cm, Saint Paul, MN, USA) to prevent their body temperature from dropping below 39°C. T_{rec} was monitored continuously intraoperatively. Temperature in the operating theatre as well as in pre-operative room was 23°C. After the end of the WBH-PIPAC, the T_{rec} was monitored for an additional 60 min in the recovery room using the rectal temperature probe.

WBH-PIPAC procedure and perioperative management. The time interval between PIPAC/WBH-PIPAC cycles was between four to six weeks. Systemic chemotherapy (SCTx) was discontinued one week prior and after WBH-PIPAC. All procedures were performed as previously described in detail as High Pressure/High Dose (HP/HD-PIPAC) and were performed by one senior surgeon (JZ). In order to avoid possible skin burns, all WBH-PIPACs were carried out exclusively with bipolar current devices. Oxaliplatin at a dose of 120.0 mg/m² body surface area (BSA) diluted in a total of 150 ml 5% glucose was administered in case of PSM of colorectal and appendiceal primary tumors. For all other tumor entities, doxorubicin 6.0 mg/m² BSA diluted in 50 ml 0.9% NaCl followed by cisplatin 30.0 mg/m² BSA diluted in 150 ml 0.9% NaCl. Access to the peritoneal cavity was always obtained via an infraumbilical open Hasson approach. Before starting the drug nebulization, the capnoperitoneal pressure was increased from 12 to 20 mmHg (9).

Trocar incision sites were infiltrated using 20 ml of 0.5% bupivacaine at the beginning of surgery. A standard analgesic/antiemetic therapy already started intraoperatively, usually 1 g metamizole-sodium-monohydrate and dimenhydrinate 62 mg i.v. three times a day for 24 h postoperatively, was given. A complete red and white blood count, including liver, pancreas and kidney tests, was routinely performed preoperatively and on the first and second postoperative days. Patients were usually hospitalized for a minimum of three days, as the German hospital reimbursement system requires this minimum length of hospital stay for full reimbursement of PIPAC.



Figure 1. Set-up for moderate whole-body hyperthermia (WBH). Water-filtered Infrared A (wIRA) device (IRATHERM®1000, Von Ardenne Institute of Applied Medical Research GmbH, Dresden, Germany).

Perioperative short-term outcome and data acquisition. The data of a consecutive case series of 50 delivered WBH-PIPACs were retrospectively acquired between August 2018 and August 2023. The entire staging laparoscopy, including evaluation of the Sugarbaker PCI score (14), the amount of ascites and the quality of chemotherapy nebulization, was monitored using video according to our standards for intraoperative documentation. Perioperative data are stored electronically in the patient's record. Data acquisition and database management were carried out by JZ as part of the required quality assurance as a certified center of the DGAV. Perioperative adverse events were graded according to the Clavien-Dindo Classification (15, 16). Data are expressed as absolute numbers whereas continuous data are expressed as median values followed by the range in parentheses, *i.e.*, median (range).

Results

Baseline clinical characteristics. Prior to WBH-PIPAC, all patients underwent one cycle of normothermic standard PIPAC without any perioperative complications. Twenty-eight patients (male/female ratio: 2:1) with a mean age of 62 years (45-78 years) and BMI of 21.5 kg/m² (18.5-30.7 kg/m²) were scheduled for moderate WBH-PIPAC. The patients had various types of cancer, including PSM of the upper gastrointestinal tract (UGI; n=9), colon-rectum (CRC; n=7), cancer of unknown primary (CUP; n=5), hepatopancreato-biliary (HPB; n=3), malignant epithelioid peritoneal mesothelioma (MPM; n=2), and epithelial ovarian cancer (OV; n=2). Eight patients had PSM diagnosed synchronously. In cases of metachronous PSM, the median time interval from primary tumor diagnosis to PSM diagnosis was 19.2 (range=6-198) months. Twenty patients underwent primary tumor resection and all twenty-eight

patients received a minimum of one line of SCTx prior to WBH-PIPAC. Except for eight patients, all received concomitant SCTx between PIPAC/WBH-PIPAC cycles. Table I lists the patients' preoperative baseline data.

Thermometric parameters. WBH had to be stopped prematurely in one patient with PSM of UGI origin with a BMI of 34.5 kg/m² and 6 liters of malignant ascites due to severe backpain after 60 min of warming-up with a T_{rec} of 38.1°C. As it also became clear that T_{rec} increase was delayed (0.1°C/10 min), we decided to stop the WBH treatment, and the patient subsequently underwent normothermic PIPAC treatment without complications. Therapy data of this patient are excluded from WBH-PIPAC data analyses. In a total of 27 other patients, 50 WBH-PIPACs were performed with a median T_{rec} observed at different times during the moderate WBH treatment: 37.1°C (36.8-37.7) at the beginning, 39.5°C (39.2-39.9) at the end of the warm-up period, 39.4°C (39.2-39.6) and 39.2°C (39.1-39.4) at the beginning and end of the chemotherapy nebulization, respectively. The median time for WBH-PIPAC was 61 min (52-64 min). The WBH treatment time (t_{treat}), time duration from chemotherapy nebulization with a T_{rec} ≥39°C, was 66 min (53-69 min). The thermometric parameters and the timeline of WBH-PIPAC are shown in detail in Table II.

All patients remained cardio-respiratory stable and showed no side effects of moderate WBH. The heart rate did not exceed 110/min during any treatment. Additional electrocardiographic monitoring revealed no evidence of arrhythmia or even signs of myocardial ischemia. Oxyhemoglobin (SpO₂), measured by transcutaneous peripheral pulse oximetry, was always above

Table I. Patients' preoperative baseline characteristics.

Variables	Total population (n=28)
Age at first WBH-PIPAC (years, median (range))	62 (45-78)
ECOG 0/1 (n)	7/21
Body Mass Index (kg/m ² , median (range))	21.5 (18.5-30.7)
Primary tumor origin (n)	
UGI	9
CRC	7
CUP	5
HPB	3
MPM	2
OV	2
Synchronous PSM (n)	8
Prior primary tumor resection (n)	20
Prior systemic chemotherapy (n)	28
Ongoing systemic chemotherapy between PIPAC/WBH-PIPAC procedures (n)	20
Time between tumor diagnosis and metachronous PSM [months, median (range)]	19.2 (6-189)

WBH-PIPAC: Whole-body hyperthermia pressurized intraperitoneal aerosol chemotherapy; CRC: colorectal cancer; HPB: hepato-pancreato biliary cancer; UGI: upper gastro-intestinal cancer; MPM: malignant epithelioid peritoneal mesothelioma; CUP: cancer of unknown primary; OV: epithelial ovarian cancer; PSM: peritoneal surface malignancies.

Table II. Thermometric parameters and timeline of moderate whole-body hyperthermia pressurized intraperitoneal aerosol chemotherapy (WBH-PIPAC).

Thermometric parameters	Median values (range)
Heating temperature (T _{rec} °C)	
Starting temperature	37.1 (36.8-37.7)
End of warm-up period	39.5 (39.2-39.9)
Start surgery	39.4 (39.1-39.9)
Start chemotherapy nebulization	39.4 (39.1-39.6)
End of chemotherapy nebulization	39.2 (39.1-39.4)
End of surgery	39.1 (39.0-39.4)
Heating duration (min)	
Warm-up period	94 (53-117)
End of warm-up period to the start of chemotherapy nebulization (WBH-PIPAC)	27 (23-36)
Start of chemotherapy nebulization to the end of chemotherapy aerosol exposition	39 (37-43)
Start chemotherapy nebulization to end of surgery	51 (47-55)
Duration WBH-PIPAC	61 (52-64)
Treatment time (t _{treat}); time from start chemotherapy nebulization with T _{rec} ≥39°C	66 (53-69)

Trec: Rectal temperature (°C); t_{treat}: time period from start chemotherapy treatment and Trec ≥39°C.

95% under ambient air conditions. Neither immediately after WBH-PIPAC treatment nor later in the postoperative course were any signs of skin burns observed.

WBH-PIPAC procedure details, morbidity, and mortality.

Twenty-seven patients received a total of 50 WBH-PIPACs. The median number of WBH-PIPACs administered was 2 (range=1-5). All patients received one cycle of normothermic PIPAC prior to a planned WBH-PIPAC, resulting in a median number of PIPAC/WBH-PIPAC cycles administered of 3 (range=2-5).

Sixteen patients received three PIPAC/WBH-PIPACs, while twelve, eight, six and one patient received one, two, three and four WBH-PIPACs. In two patients the access to the abdominal cavity failed to administer a third and fourth WBH-PIPAC cycle, respectively. Seven patients did not receive three consecutive PIPAC/WBH-PIPACs due to clinical deterioration and/or disease progression. Five patients underwent cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC). At the end of the study period four patients were planned to undergo further WBH-PIPAC

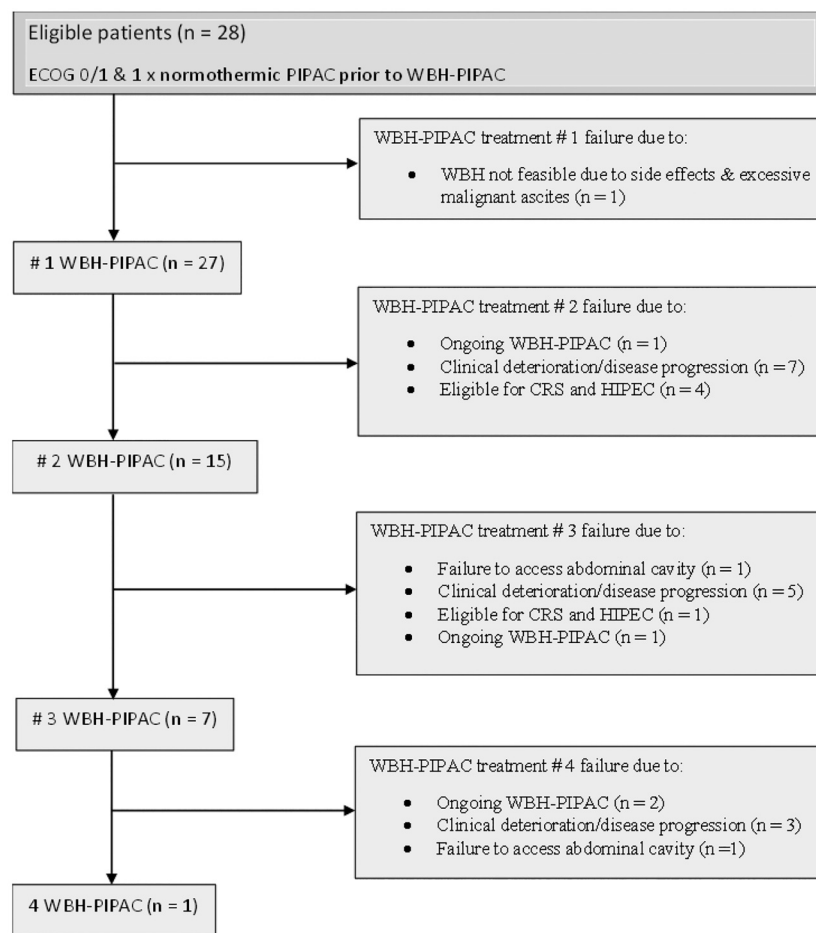


Figure 2. Patient flow chart. WBH-PIPAC: Whole-body hyperthermia pressurized intra peritoneal aerosol chemotherapy; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy.

applications. The patient flow is summarized in Figure 2.

No intraoperative technical or medical complications were observed. The gradual pressure build-up and the subsequent exposure phase to 20 mmHg capnoperitoneum over a period of 30 min was tolerated without side effects in all WBH-PIPACs, so that all applications could be carried out under intubation anesthesia without disturbances.

A total of nine postoperative complications after 50 WBH-PIPACs were observed. Minor Grade I complications occurred in seven interventions which suffered from postoperative nausea/vomiting and/or abdominal/shoulder pain. Two patients suffered from Grade II paralytic ileus. No complication > Grade III were observed. The median length of hospital stay (LOS) was 4.5 days (3-7 days). The perioperative outcome parameters for WBH-PIPAC procedures are summarized in Table III.

With a median follow-up period of 13 months (3-48 months), we observed a median overall survival of the whole WBH-PIPAC study population of 14 months (4-32 months) after the first PIPAC application.

Discussion

Whole-Body hyperthermia (WBH) could be an alternative to realize homogeneous temperatures throughout the peritoneum. WBH increases the body core temperature to 39-40°C (fever range) or 41-42°C (extreme WBH). Data from a pilot study and a phase I/II study of patients suffering from PSM of platinum resistant ovarian cancer and colorectal cancer revealed that WBH (41.8-42.1°C) could enhance the effect of SCTx but also increased the toxicity (17, 18). As most PSM patients are fragile, and to minimize the risk of toxicity and avoid deep sedation or prolonged general anesthesia, patients were scheduled for febrile WBH (39-40°C), which is generally well tolerated and requires only little or no sedation (19).

In our present case series, 28 patients with ECOG 0/1 were offered to undergo WBH-PIPAC. Finally, all patients had previously received normothermic PIPAC without complications and simple surgical access to the abdominal

Table III. Perioperative outcomes according to whole-body hyperthermia pressurized intraperitoneal aerosol chemotherapy (WBH-PIPAC).

Variables	#1 WBH-PIPAC	#2 WBH-PIPAC	#3 WBH-PIPAC	# 4 WBH-PIPAC	Total
Number of successful WBH-PIPACs	12	8	6	1	50
Number of failed PIPAC ("non-access")	0	0	1	1	2/50
Median PCI (range)	25 (17-35)	23 (17-32)	22 (18-32)	22	25 (1-35)
Operative time (min, median (range))	65.5 (55-66)	59.5 (52-63)	58.5 (53-63)	62.0	61 (54-64)
Intraoperative complications (n)	0	0	0	0	0
Total complications Clavien-Dindo (n)	4	2	3	0	9/50
Grade I	3	1	3	0	7/50
Grade II	1	1	0	0	2/50
≥Grade III	0	0	0	0	0
LOS: [days, median (range)]	4.5 (3-7)	4.5 (3-6)	3.5 (3-5)	3	4.5 (3-7)

LOS: Length of hospital stay.

cavity. This minimized the risk that patients would undergo WBH without PIPAC due to a surgical "non-access" into the peritoneal cavity and to short time interval between the end of WBH and the start of chemotherapy nebulization. In one patient, induction of WBH failed due to massive malignant ascites. The patient underwent normothermic PIPAC at the same session. Based on this experience, we conclude that patients with excessive ascites are not candidates for WBH. In the remaining 27 patients, WBH ($T_{rec} \geq 39^{\circ}\text{C}$) was achieved without complications, and subsequent WBH-PIPAC was performed after a median time interval of 94 min (53-117 min) or 27 min (23-36 min) from the end of the warm-up phase and the start of chemotherapy nebulization. The perioperative course following 50 consecutive WBH-PIPACs was found to be comparable to that of normothermic PIPAC and High-Pressure/High Dose PIPAC (HP/HD-PIPAC), as previously reported in our patients (9, 10).

Many different HIPEC strategies exist and the methodologies at different institutions are surprisingly variable. Although different cytostatic drugs and doses are used, there is agreement that the temperature in the abdominal cavity during HIPEC therapy must be uniform for 30 to 90 min, depending on the cytostatic drug used (20). The optimal temperature in the peritoneal cavity should be as evenly distributed as possible. A critical temperature threshold for HIPEC has been defined at 40°C (21). Synergy between heat and drug cytotoxicity starts at 39°C and falls off at 43°C . Temperatures above 44°C cause apoptosis in normal cells and the side effects of HT begin to outweigh possible benefits (22, 23). In our present case series of 27 patients who underwent WBH-PIPAC, the median treatment time (t_{treat}) from the start of chemotherapy nebulization and $T_{rec} \geq 39^{\circ}\text{C}$ was 66 min (53-69 min). It follows that the minimum temperature required to perform efficient HIPEC (21) was not reached in any of our patients. However, this disadvantage of WBH therapy seems to be relativized since studies of HIPEC therapy have shown that intraperitoneal

temperature distribution is inhomogeneous. Temperature measurements during HIPEC revealed that temperatures varied between sites and over time, with thermal fluctuations of up to 4°C (24, 25). Furthermore, the temperature during HIPEC was measured in the abdominal cavity and therefore it does not directly reflect the therapy-relevant tissue temperature. It is therefore likely that many HIPEC applications in everyday clinical practice do not achieve the required minimum temperatures and tissue temperatures may be even lower. However, it can be assumed that a more homogeneous temperature distribution in the abdominal cavity can be achieved with WBH (23).

Zhao *et al.* studied the effects of extreme WBH combined with HIPEC on twenty-seven patients with stage IV gastric cancer. All patients received WBH at a temperature between $41.8-42^{\circ}\text{C}$ for 120 min under propofol sedation. Intraperitoneal instillation of cisplatin (40 mg/m^2) and 5-FU (0.75 mh/2) was performed at 42°C via an indwelling catheter. They report that hyperthermia side effects were minimal, quality of life improved and the 1-year survival was 38.5% compared to the control group (8). Although these results were encouraging it is generally agreed that extreme WBH is difficult to perform and carries significant risks. Patients need to be sedated and often ventilated. Tight, invasive cardiovascular monitoring and anesthesia must be performed by experienced anesthetists. At the same time, patients with PSM often have poor general health and significant comorbidities (26). Therefore, whole body hyperthermia would not be very suitable as standard treatment option for patients with PSM. Given these facts, WBH is expensive. Additionally, calculations from France show that each PIPAC cycle is underfunded by an average of about 2,500 euros (27).

Recently, potential pharmacological effects of H-PIPAC were explored in a postmortem inverted bovine urinary bladder (IBUB). Tissue depth penetration and tissue drug concentrations between normothermic and H-PIPAC (41-

43°C) were compared. No additional pharmacological advantage was demonstrated for H-PIPAC (28). Such results should be interpreted with caution and need further evaluation in suitable in-vivo animal H-PIPAC models (29).

Conclusion

In a highly selected group of patients the repeated administration of Whole-Body Hyperthermia (WBH) and Pressurized Intraperitoneal Aerosol Chemotherapy (WBH-PIPAC) is feasible and safe. Whether the use of WBH enhances the antitumor effect remains unclear. Well-designed basic science and prospective trials are needed to explore the potential benefits of WBH-PIPAC.

Conflicts of Interest

The Authors have no conflicts of interest or financial ties to disclose in relation to this study.

Authors' Contributions

Fabian Kockelmann: Data acquisition, data analysis, data interpretation and drafting and critical revision of the manuscript. Petru Bucur, Sarah Barbey, Mehdi Ouaisi and Alexander von Ardenne: data analysis, data interpretation, drafting and critical revision of the manuscript. Jürgen Zieren and Urs Giger-Pabst: WBH-PIPAC procedures (JZ), study design, data acquisition, data analysis, drafting of the manuscript and critical revision of the manuscript.

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