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Scintigraphic peritoneography reveals a non-uniform ^{99m}Tc-Pertechnetat aerosol distribution pattern for Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) in a swine model

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Abstract

Background Although recent data are contradictory, it is still claimed that Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) would deliver an aerosol which distributes homogeneously throughout the entire abdominal cavity.

Methods ^{99m}Tc-Pertechnetat was administered in four postmortem swine using either PIPAC or liquid intraperitoneal chemotherapy (IPC). The animals were examined by planar scintigraphy and SPECT/CT. Planar distribution images were divided into four regions of interest (ROIs: right/left upper and lower abdominal quadrant). SPECT/CT slices were scanned for areas of intense nuclide accumulation ("hot spots"). The percentage of relative distribution for planar scintigraphy was calculated by dividing the summed individual counts of each ROI by total counts measured in the entire abdominal cavity. The relative distribution of the "hot spots" was analyzed by dividing the counts of the local volume of interest (VOI) by the summed volume counts measured in the entire abdominal cavity.

Results In all four animals, planar scintigraphy showed inhomogeneous nuclide distribution. After PIPAC only 8–10% of the delivered nuclide was detected in one ROI with a mean deviation of 40% and 74% from a uniform nuclide distribution pattern. In all animals, SPECT/CT revealed "hot spots" beneath the PIPAC Micropump, catheter tip, and in the cul-de-sac region which comprise about 25% of the total amount of delivered nuclide in 2.5% of the volume of the entire abdominal cavity.

Conclusions Our present data indicate that the intra-abdominal aerosol distribution pattern of PIPAC therapy is non-homogeneous and that the currently applied technology has still not overcome the problem of inhomogeneous drug distribution of IPC.

Keywords MIP® · Aerosol · Distribution · Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) · ^{99m}Tc-Pertechnetat · Peritoneography

Abbreviations

CO_2	Carbon dioxide
CT	Computed tomography
IAP	Intra-abdominal pressure
IPC	Intra-peritoneal chemotherapy
LDR	Left side–dorsal–right side
PM	Peritoneal metastasis
PIPAC	Pressurized Intra-Peritoneal Aerosol Chemotherapy
MBq	Mega Becquerel
MIP®	Micropump (Reger Medizintechnik, Rottweil, Germany)
ROI	Region of interest
RVL	Right side–ventral–left side

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SPECT	Single-photon emission computed tomography
^{99m}Tc	^{99m}Tc-Pertechnetat
VOI	Volume of interest

Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) is a new technology to deliver intra-peritoneal chemotherapy (IPC) to treat patients suffering from advanced peritoneal metastasis (PM) [1, 2]. The liquid chemotherapy drug is delivered by means of a high pressure injector and a high pressure line to a patented mono-component nozzle (PIPAC Micropump/MIP®). With a working pressure of 8.3 bars, sheering forces at the MIP® nozzle orifice generate droplets with a mean size of 25 µm which are then injected with a velocity of 60 km/h in a capnoperitoneum of 12 mmHg pressure [3]. This therapeutic approach to PC has been assumed to have the potential to overcome two major limitations of conventional liquid IPC—incomplete irrigation of the peritoneal surface by the drug containing solution and poor drug penetration into tumor tissue [4].

The increased intra-abdominal pressure during PIPAC by means of the capnoperitoneum is assumed to counteract the pathological increased intra-tumoral pressure and therefore amplify the influx of the chemotherapeutic drugs into tumoral tissue. First data obtained in human patients assume a higher local drug biodisponibility and a better therapeutic index [2] compared to antecedent data reported of liquid IPC. Furthermore, delivering IPC as an aerosol has been reported to result in a homogenous intra-abdominal drug distribution pattern because the aerosol supposedly behaves "gas-like" [1, 2, 5].

However, very recent data obtained of a non-anatomic ex vivo and anatomic postmortem PIPAC model, as well as granulometric, technical, and calculated data of the MIP® strongly support the assumption that local aerosol impactation beneath the nozzle of the MIP® is the main mechanism of drug deposition leading to a non-uniform spatial drug distribution pattern [3, 6, 7].

Therefore, the aim of this study was to objectively elucidate the spatial aerosol distribution pattern of the MIP® by means of ^{99m}Tc-Pertechnetat scintigraphic peritoneography in a postmortem swine model.

Material and methods

PIPAC procedure with ^{99m}Tc-Pertechnetat

For all experiments, the German landrace pigs (35–40 kg) were obtained from the Aesculap medical training center (Aesculap Akademie, Gesundheitscampus Bochum, Germany) where the animals were euthanized for a laparoscopic surgery training course. Both the training course at the Aesculap Akademie as well as our experiments were approved by the local authorities and the local board on animal welfare. All applicable international, national, and/or institutional guidelines for the use, handling, and disposal of animal cadavers and radioactive materials were followed.

The fresh postmortem swine cadavers were placed in a supine position and fixed in a stable position at all four extremities. An infraumbilical mini-laparotomy was performed, and a 12 mm trocar (Kii®Balloon Blunt Tip System, Applied Medical, Rancho Santa Margarita, CA, USA) was inserted in the abdominal cavity. A constant capnoperitoneum was then established throughout the whole PIPAC experiment (Olympus UHI-3 insufflator, Olympus medical life science and industrial divisions, Olympus Australia, Notting Hill, Australia). A five mm camera (Karl Storz GmbH & Co KG, Tuttlingen, Germany) was introduced into the 12 mm trocar. A 5 mm trocar (Kii®Balloon Blunt Tip System, Applied Medical, Rancho Santa Margarita, CA, USA) was then placed in the right-lateral hemi-abdomen under visual control. The PIPAC Micropump (MIP®, Reger Medizintechnik, Rottweil, Germany) was connected to a high pressure injection line (High Pressure Injection Line with Male/Female Luer lock 120 cm, 1200 psi, Smith Medical, Hranice, Czech Republic). An aqueous solution of 150 MBq of ^{99m}Tc-Pertechnetat in a total volume of 150 ml 0.9% NaCl was filled in a syringe which was then tightly connected to the high pressure line and finally brought into the injector head of the high pressure injector (Injektron 82 M, MedTron, Saarbrücken, Germany). The MIP® was then inserted into the 12 mm trocar in a perpendicular position with a maximum distance of the MIP® nozzle orifice to the small bowel serosal surface. The camera was placed and fixed in the 5 mm trocar to monitor adequate nebulization of the MIP®. After the tightness of the abdominal cavity (no CO_2 flow) was confirmed, PIPAC was delivered with a flow rate of 30 ml/min (max. pressure 200 psi upstream) in the abdominal cavity (28 °C) with a constant capnoperitoneum of 12 mmHg. The abdominal cavity was exposed after the aerosol phase another 30 min to the ^{99m}Tc-Pertechnetat aerosol. The capnoperitoneum was then evacuated via a HEPA (High Efficiency Particulate Arrestance) filter system. All PIPAC procedures were performed by a senior surgeon (GPU) with a personal experience of more than 600 PIPAC procedures performed since 2012.

Liquid intra-peritoneal ^{99m}Tc-Pertechnetat delivery via indwelling catheter

Liquid intra-peritoneal ^{99m}Tc-Pertechnetat was delivered via a standard pigtail catheter (Plus Drain drainage

catheter, Peter Pflugbeil GmbH, Zorneding, Germany) placed into the abdominal cavity through infraumbilical puncture. The catheter was secured and sealed at the skin with a purse string suture. An aqueous solution of 150 MBq of ^{99m}Tc-Pertechnetat in a total volume of 150 ml NaCl 0.9% was filled in a syringe which was then connected to the catheter and manually injected into the swine. The animal was brought then in Trendelenburg, anti-Trendelenburg, left-, and right-lateral position for one minute in each position prior to scintigraphic analysis.

^{99m}Tc-Pertechnetat scintigraphic peritoneography in planar & SPECT/CT technique

After the procedures, planar scintigraphy and SPECT/CT imaging were performed on a double-head gamma camera (Siemens Symbia T2, Siemens Medical Systems, Hofmann Estates, IL, USA) equipped with low-energy high-resolution collimators. A 360° acquisition in supine position with 32 projections, 8 s per projection, and a matrix of 128 × 128 was used. Additionally, anterior–posterior (LDR and RVL) planar images (acquisition time: 3 min) were acquired. Finally, a low-dose CT was performed (5 mm slice thickness; 130 kV). Images were reconstructed using 3D iterative reconstruction (Flash 3D, 4 iterations and 8 subsets) and were then transferred into Siemens Syngo for further processing using via software with MM Oncology and mMR General application software (Siemens Medical).

Quantification of ^{99m}Tc-Pertechnetat distribution

The planar distribution images were divided into four regions of interest (ROI: upper right/left and lower right/left abdominal quadrants) for both anterior and posterior views. The abdominal cavity was visually identified in scintigraphy imaging and ROI contours were manually drawn in MM Oncology application. Counts derived from anterior and posterior views were assessed for each ROI. The deviation from uniform (homogenous) distribution was defined as difference between measured counts for each region and expected area proportional counts for each region: area proportional deviation from

$$\text{uniform distribution} = (\text{region area}/\text{total abdominal area}) \times \text{total abdominal counts} - \text{measured regional counts}.$$

Relative deviation from uniform nuclide distribution was calculated by dividing the regional count deviation individually for each abdominal region by the expected area proportional counts for each abdominal region: relative deviation from uniform distribution = area proportional deviation from uniform distribution/[(regional area/total abdominal area) × total abdominal counts]. For each swine, the quality of nuclide distribution was given as mean of the regional relative deviation from uniform distribution of the four ROIs.

SPECT and co-acquired low-dose CT data were transferred to Siemens syngo.via quantification software (mMR General application). In the low-dose CT, ROIs were manually drawn on each CT slice delineating the abdominal cavity to the individual anatomical shape. All ROIs were combined to a VOI (Volume of Interest) containing the complete abdominal cavity. This VOI was transferred to the co-registered distribution SPECT, and counts were measured. SPECT/CT slices then were scanned for areas with intense focal deposition of ^{99m}Tc nuclide ("hot spots"). VOIs were drawn around detectable representative reference "hot spots" in the SPECT datasets, and the total counts were calculated. The percentage of relative distribution in the "hot spots" was calculated by dividing the counts of each VOI by the summed counts of the whole abdominal cavity.

Results

Planar scintigraphic analysis of the intra-abdominal ^{99m}Tc-Pertechnetat distribution

The two PIPAC procedures were delivered without any technical difficulties. The distance of the nozzle orifice of the PIPAC Micropump (MIP®) to the peritoneum of the underlying small bowel peritoneum was adjusted at the maximum possible distance of 6 cm (swine 1) and 7 cm (swine 2), respectively.

In both animals, planar scintigraphy showed an inhomogeneous ^{99m}Tc-Pertechnetat distribution pattern where in the right upper abdominal quadrant only between 8.5 and 9.8% of the regional delivered ^{99m}Tc-Pertechnetat counts were measured. In contrast, in animal one, a maximum of 61.9% of the regional relative nuclide deposition was found to be localized in the left upper abdominal quadrant. The distribution in animal two was more homogeneous compared to animal one yet 42.9% of the regional relative nuclide distribution was detected solely in the left lower abdominal quadrant. A high relative deviation from an assumed uniform aerosol/drug distribution of 40.3 and 74.2% was observed in both animals. Representative pictures on planar scintigraphic analyses and details on scintigraphic quantification of ^{99m}Tc-Pertechnetat PIPAC experiments are shown in Fig. 1 and Table 1, respectively.

Liquid ^{99m}Tc-Pertechnetat experiments via indwelling catheters were performed without major difficulties. However, in one animal, a vaginal leak with a minimal

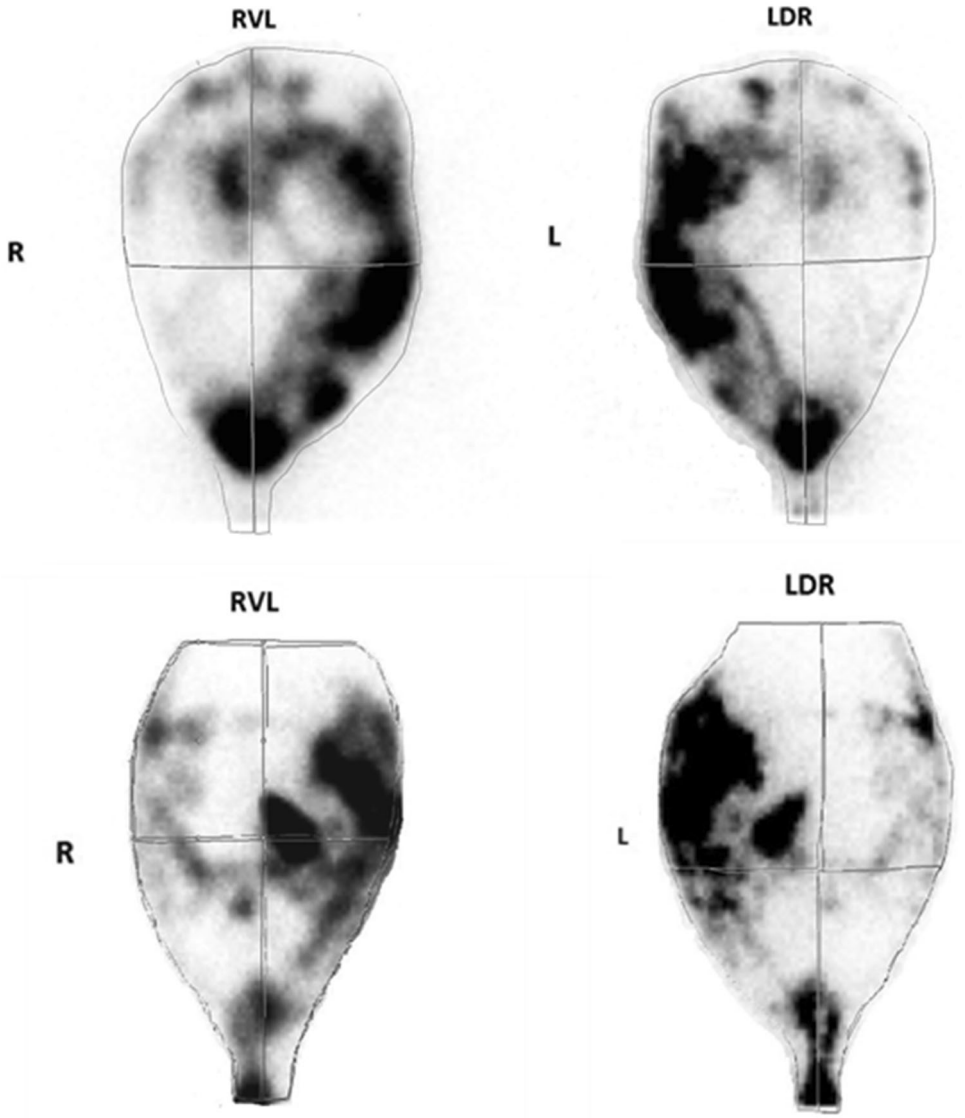

Fig. 1 Planar scintigraphic analysis after ^{99m}Tc-Pertechnetat PIPAC. *Upper panel* PIPAC animal N° 1, *lower panel* PIPAC animal N° 2, *RVL* right–ventral–left, *LDR* left–dorsal–right. The *fine black line* delineates the outer borders of the abdominal cavity as well as the four regions of interest (ROIs); *L* left, *R* right

^{99m}Tc-Pertechnetat contamination of the right inguinal skin region occurred. Nevertheless, scintigraphic analysis showed an almost similar distribution pattern compared to the PIPAC experiments. In some abdominal quadrants, only 8.8–13% of delivered nucleotide could be found with an overall relative deviation from uniform nuclide distribution of 23.6 and 34.0%, respectively. Details on planar scintigraphic analyses are shown in Fig. 2 and Table 1.

SPECT/CT analysis of the intra-abdominal ^{99m}Tc-Pertechnetat distribution

In all four animals, SPECT/CT analysis revealed intense ^{99m}Tc-Pertechnetat deposition ("hot spots") below the MIP® nozzle, the catheter tip, and in the small pelvis (cul-de-sac). In the two animals which underwent PIPAC, the "hot spots" beneath the PIPAC Micropump (MIP®) and in the cul-de-sac comprise together 20.8–65.5% of the total nuclide counts in 2.4 and 8.2% of the total intra-abdominal volume, respectively (Fig. 3). Similar findings were observed for liquid intra-peritoneal ^{99m}Tc-Pertechnetat delivered via an indwelling catheter. The two "hot spots" contained 20.8 and 25.1% in 2.4 and 4.8% of the total abdominal cavity volume (Fig. 4). Regardless of the application technique used, the combination of both "hot spots" comprises approximately 20–30% of the total intra-abdominal delivered ^{99m}Tc-Pertechnetat aerosol in a volume of about 2–3% of the entire abdominal cavity volume. Details on SPECT/CT quantification of all four animals are given in Table 2.

Discussion

Peritoneal metastasis (PM) is an advanced condition of gastrointestinal and gynecologic malignancies, leaving the majority of patients with only palliative therapeutic options

Table 1 Quantification of nuclide distribution using planar scintigraphy

Abdominal regions (ROIs)	LDR Regional counts [k_{counts}]	RVL Regional counts [k_{counts}]	Geometric mean [k_{counts}]	Regional relative nuclide distribution [%]	Relative deviation from uniform distribution [%]
PIPAC: N° 1					
Upper right	26.1	46.7	31.1	8.6	65.8
Upper left	230.7	271.4	225.5	61.9	147.8
Lower right	26.8	54.9	38.4	10.5	57.8
Lower left	51.7	92.4	69.1	19.0	25.2
Abdominal cavity	335.3	465.4	364.1	100	Ø 74.2
PIPAC: N° 2					
Upper right	33.9	100.9	58.5	9.8	60.7
Upper left	155.2	169.4	162.1	27.2	8.9
Lower right	79.5	179.1	119.3	20.1	19.8
Lower left	234.3	278.4	278.4	42.9	71.6
Abdominal cavity	502.1	727.8	595.3	100	Ø 40.3
Lavage: N° 3					
Upper right	62.5	119.9	86.6	8.8	64.9
Upper left	294.4	318.3	306.1	31.1	24.2
Lower right	208.5	273.7	238.9	24.2	3.0
Lower left	338.7	369.6	353.8	35.9	43.6
Abdominal cavity	904.1	1081.5	985.4	100	Ø 33.9
Lavage: N° 4					
Upper right	270.3	92.4	158.0	26.0	3.9
Upper left	92.7	66.5	78.5	12.9	48.4
Lower right	284.6	151.2	207.4	34.1	36.4
Lower left	202.7	125.3	159.4	26.2	5.8
Abdominal cavity	850.3	435.4	608.4	100	Ø 23.6

LDR left–dorsal–right, *RVL* right–ventral–left, *Ø* arithmetic mean of relative deviation from uniform distribution of the four regions of interest (ROIs)

such as systemic palliative chemotherapy. Even in the area of modern poly chemotherapeutic treatment, the prognosis remains poor. For PM from non-gynecological malignancies such as gastric, colorectal, and pancreatic cancer, the median survival is in average less than 6 months [8]. Failure of chemotherapy, irrespective to the various underlying mechanisms, is due to inadequate drug delivery to the cancer cells [9]. Several strategies to increase the anti-tumoral effect of systemic chemotherapy have been investigated, including dose escalation and treatment intensification. However, the benefit appears to be marginal whereas toxicity increases with no significant extension of overall survival in advanced cancer stages [10, 11]. One apparent solution to the problem is to localize high concentrations of drugs within the tumor. Such a loco-regional treatment approach has been pioneered by Dedrick et al. who suggested that tumor within the peritoneal cavity could be exposed to cytotoxic drugs logs greater than those that may be safely applied during systemic drug administration [12].

Although the clinical benefit of liquid intra-peritoneal chemotherapy (IPC) in the management of PM has been well demonstrated for decades [13–15], IPC regiments are associated with significant local and systemic toxic complications. Furthermore, if IPC is delivered via indwelling catheters, high incidences of catheter associated complications of up to 20% have been reported [16] while exhibiting major limitations of liquid IPC such as poor drug penetration into tumoral tissue, as well as inhomogeneous drug distribution in the abdominal cavity resulting in under- or untreated tumor [4].

Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) is a novel approach to deliver IPC in patients suffering from end-stage PM. The chemotherapeutic drugs are delivered as a therapeutic aerosol by means of a high pressure injector and a connected mono-component nozzle into a constant capnoperitoneum of 12 mmHg in the abdominal cavity during a standard laparoscopy. Since the PIPAC approach has a far higher surface/volume ratio of the delivered chemotherapeutic drugs compared with

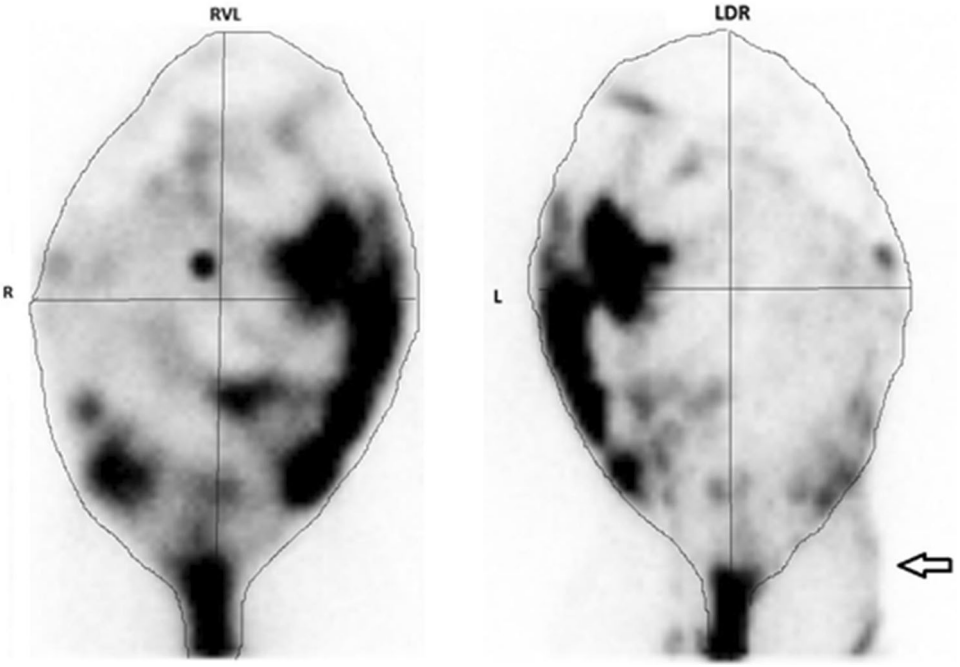

Fig. 2 Planar scintigraphic analysis of ^{99m}Tc-Pertechnetat delivered as liquid solution. Animal N° 3; *Left panel* ventral projection (*RVL* right–ventral–left), *Right panel* dorsal projection (*LDR* left–dorsal–right). *Right panel* arrow marks ^{99m}Tc-Pertechnetat contamination in the right inguinal region. The *fine black line* delineates the outer borders of the abdominal cavity as well as the four regions of interest (ROIs)

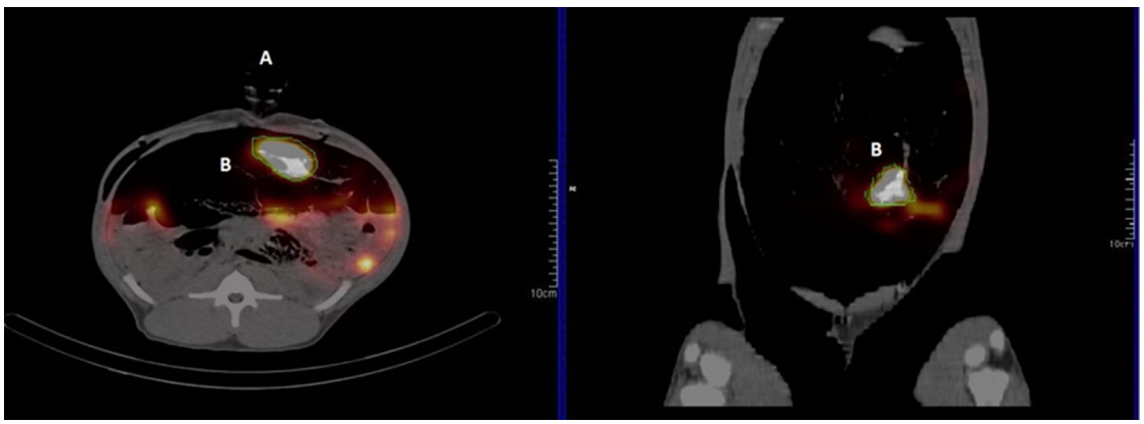

Fig. 3 SPECT/CT of PIPAC animal N° 1. *Left panel A* subumbilical placed 12 mm trocar where the PIPAC Micropump (MIP®) was formerly placed to deliver the ^{99m}Tc-Pertechnetat "aerosol and then removed for scintigraphic analysis. *Right panel B* "hot spot" on the small bowel peritoneum beneath the PIPAC Micropump (MIP®)

standard liquid IPC, this technology only requires 10% of a standard liquid IPC dose, while chemotherapy concentration itself is eight to ten times higher. So PIPAC technology is taking advantage of physical properties. First, according to Fick's law, drug diffusion into tissue depends on the drug concentration [17] and second, increased pressure additionally enhances the in-tissue drug influx [18–20]. Furthermore, the delivered aerosol during PIPAC therapy is assumed to behave "gas-like" and the drug distribution pattern during this approach has been described as homogeneous throughout the entire abdominal cavity [1, 2, 5].

Our present data obtained by ^{99m}Tc-Pertechnetat scintigraphic peritoneography demonstrate that the aerosol distribution pattern is inhomogeneous. In both PIPAC animals, aerosol deposition in certain abdominal regions was found to be very poor with only between 8 and 9% of the total ^{99m}Tc-Pertechnetat counts detected. In contrast, other areas showed a strong accumulation of activity with up to 62.0% of the regional relative aerosol distribution located within only one abdominal region. Moreover, planar scintigraphic analysis showed a relative deviation from a uniform aerosol distribution pattern of 40 and 74%, respectively. The main reason for this non-uniform distribution pattern was identified by SPECT/CT scans. Extensive local ^{99m}Tc-Pertechnetat aerosol deposition ("hot spots") was found beneath the MIP® on the peritoneum of the central small bowel portion, the paracolic gutter, and in

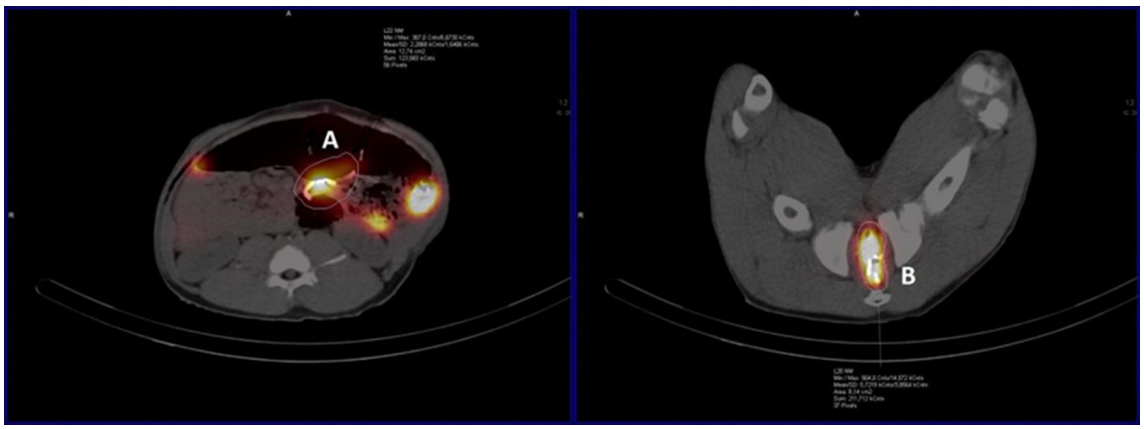

Fig. 4 SPECT/CT after liquid ^{99m}Tc delivered via indwelling catheter in animal N° 3. *Left panel A* "hot spot" at the tip of the indwelling catheter; *Right panel B* "hot spot" in the cul-de-sac

Table 2 Localization and quantification of ^{99m}Tc-Pertechnetat "hot spots" with SPECT/CT

	Application technique	Localisation of "hot spot"	Relative intra-abdominal volume [%]	Relative intra-abdominal counts [%]
1	PIPAC	beneath MIP®	1.2	17.1
1	PIPAC	cul-de-sac	1.4	11.6
2	PIPAC	beneath MIP®	5.0	43.1
2	PIPAC	cul-de-sac	3.2	22.4
3	Lavage	beneath catheter tip	1.1	4.9
3	Lavage	cul-de-sac	1.3	15.8
4	Lavage	beneath catheter tip	2.2	8.9
4	Lavage	cul-de-sac	2.6	16.2

MIP® = PIPAC micropump, PIPAC = Pressurized Intra-Peritoneal Aerosol Chemotherapy

the cul-de-sac. This distribution pattern was similar in all examined animals, irrespective if PIPAC or liquid IPC were applied. These "hot spots" together comprise about 20–30% of the total amount of delivered aerosol in only 2–3% of the total intra-abdominal volume.

Our findings are consistent with recent data on a state-of-the-art technical analysis of the MIP®. It has been reported that more than 97.5 vol.% of the aerosolized liquid is delivered as droplets with sizes >3 µm which are primarily deposited on the surface beneath the MIP® by gravitational settling and inertial impaction. These findings were furthermore confirmed by ex vivo gravimetric analyses, where more than 86.0 vol.% of the aerosolized liquid was deposited within a circular area with a diameter of 10 cm beneath the MIP® nozzle [3]. Moreover, the aerosol droplet characteristics of PIPAC technology as well as the mechanism of aerosol delivery into the abdominal cavity by injecting the droplets with a velocity of 60 km/h are comparable to the ones determined for common propellant spray cans [3, 21]. The objective of operating spray cans is to deposit as much material as possible on a target surface by inertial impactation. Since the currently used PIPAC technology has similar granulometric and operational parameters as reported for common propellant spray cans, inertial impactation of the aerosol droplets with the peritoneum beneath the MIP® nozzle is the major mechanism of local drug deposition in PIPAC technology. The aerosol droplets generated by the MIP® immediately impact with the underlying peritoneum where the droplets accumulate and form liquid accumulation ("hot spot 1") which, due to gravitational force, follows along the paracolic gutter to the cul-de-sac where another main depot of liquid is formed ("hot spot 2"). Briefly, the MIP® only delivers a small amount of the aerosolized liquid (2.0 vol.%) in the shape of small aerosol droplets (<1.2 µm) which can follow the curved stream line and have the ability to distribute in the entire abdominal cavity [3]. Therefore, the amount of drug which is deposited outside the spray jet of the MIP® is much poorer in certain abdominal quadrants where only minimal amounts of ^{99m}Tc-Pertechnetat were detected. Therefore, the scintigraphic distribution pattern observed in our present study showed similar findings irrespective

whether PIPAC or liquid IPC via an indwelling catheter were delivered.

Our data are in strong contrast to previous reports on the drug distribution pattern of PIPAC technology. Solass et al. delivered methylene blue during PIPAC therapy in ventilated pigs or liquid solution as continuous lavage via indwelling catheters. They reported that following PIPAC procedures, methylene blue staining of the abdominal cavity was homogeneous throughout the entire abdominal cavity and, thus, far superior to that observed for peritoneal lavage in a control animal [1]. However, these findings must be interpreted with caution. The concentration of the methylene blue solution delivered during the PIPAC experiments was much higher than that used for intraperitoneal lavage. Therefore, the quality of intra-abdominal methylene blue distribution of PIPAC and intra-peritoneal lavage cannot be determined and accurately compared by sole simple visual inspection and therefore, these observations are biased.

Furthermore, these staining experiments are in strong contrast to recently published data obtained in non-anatomic ex vivo and anatomic postmortem animal PIPAC model which report an inhomogeneous spatial distribution pattern of aerosolized doxorubicin. The highest in-tissue penetration depth of aerosolized doxorubicin has been observed in tissue samples located in the vicinity of the MIP® nozzle compared to tissue samples located outside the MIP® nozzle aerosol spray jet. These differences of in-tissue doxorubicin penetration depth are very likely the consequence of poor drug exposure of those samples localized outside the MIP® nozzle aerosol spray jet [3, 6, 7].

Nevertheless, since PIPAC is a safe and probably effective treatment option in the management of patients suffering from end-stage PM [22–24] it would be of great value if technical innovations could improve the current spatial drug aerosol distribution pattern. Such an innovation may have the potential to furthermore reduce the total amount of chemotherapy used for intra-abdominal aerosol chemotherapy while enhancing the efficacy and improving the clinical outcome of such an approach. Size reduction of the delivered aerosol droplets is a major step toward optimization of the drug distribution pattern in the abdominal cavity. However, due to technical limitations of any mono-component nozzle—such as the MIP® [3]—new technical approaches of aerosol generation and aerosol delivery for PIPAC therapy must be explored. Current aerosol generators which are routinely used for inhalation therapy in lung medicine are capable to generate significantly smaller aerosol particles. However, such nebulizer systems, due to technical conditions, can only generate the therapeutic aerosol outside the abdominal cavity whereas the aerosol has to be brought into the abdominal cavity in a closed flow-through technique—similar to that of liquid heated intra-peritoneal chemotherapy (HIPEC). We observed first encouraging results with such an approach in the in vivo swine.

In summary, our data demonstrate that the currently used PIPAC technology does not achieve homogeneous intra-abdominal aerosol distribution. This is an important limiting factor in the delivery of IPC. However, since PIPAC therapy is a promising new therapeutic approach to PM, technical innovations to further optimize intra-abdominal aerosol therapy are much needed.

Authors Contribution Alexander Bellendorf: Study design, laboratory analysis, data acquisition and drafting, and critical revision for important intellectual content of the manuscript. Veria Khosrawipour: Study design, laboratory analysis, data acquisition. Tanja Khosrawipour: Drafting of the manuscript. Simon Siebigteroth: Laboratory analysis and data acquisition. Joseph Cohnen: Laboratory analysis and data acquisition. David Diaz-Carballo: Drafting and critical revision for important intellectual content of the manuscript. Jürgen Zieren: Drafting and critical revision for important intellectual content of the manuscript. Andreas Bockisch: Drafting and critical revision for important intellectual content of the manuscript. Urs Giger-Pabst: Study design, labor analysis, data acquisition and drafting, and critical revision for important intellectual content of the manuscript.

Compliance with ethical standards

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