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PIPAC ESSENTIALS

Principles of Capnoperitoneum and PIPAC Technology

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Disclosures

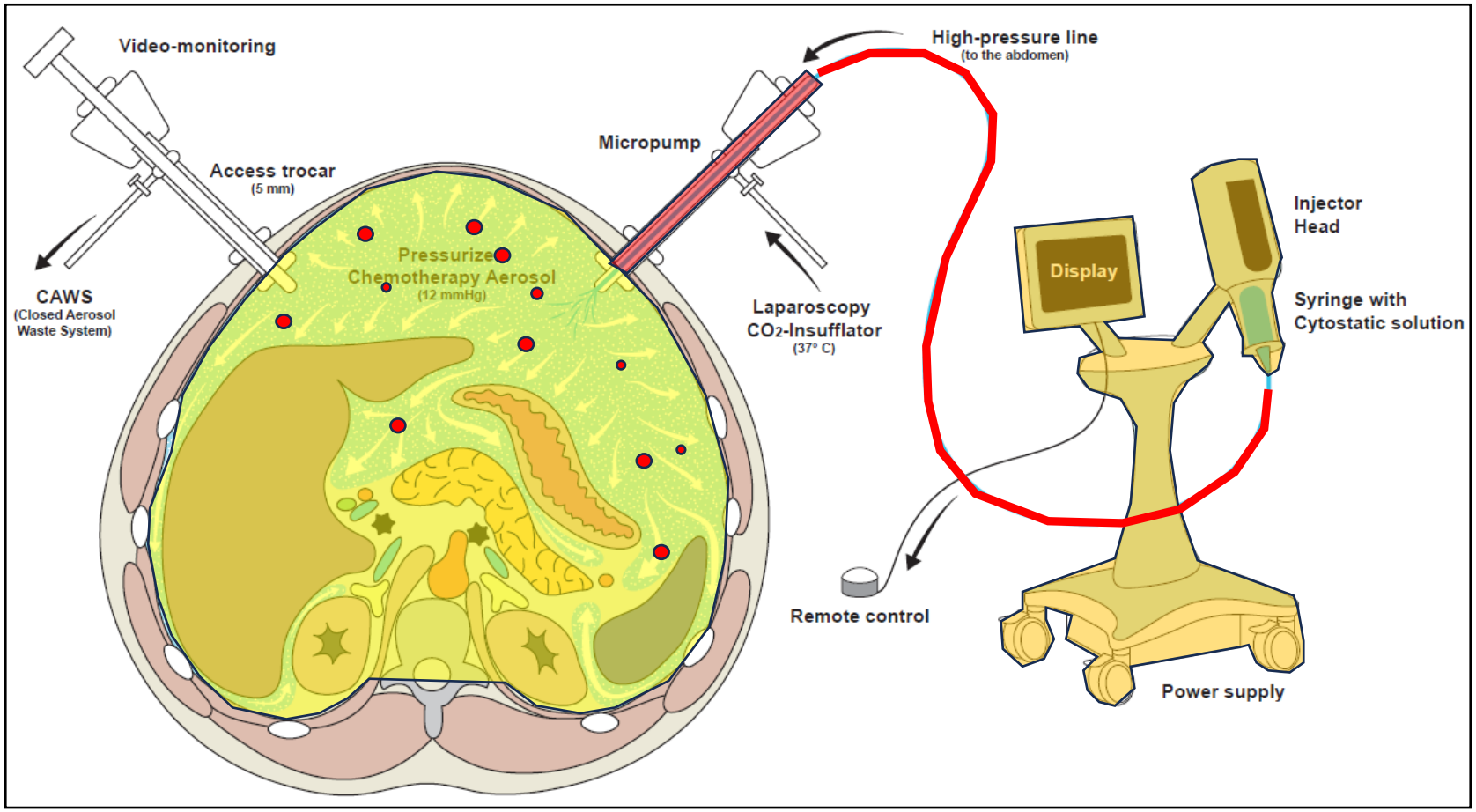
- I do not have any relevant financial relationships with any ineligible companies.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Introduction

- Aerosolization
- Spatial distribution and penetration
- Device development
- Future directions

PIPAC: Improved distribution, enhanced penetration

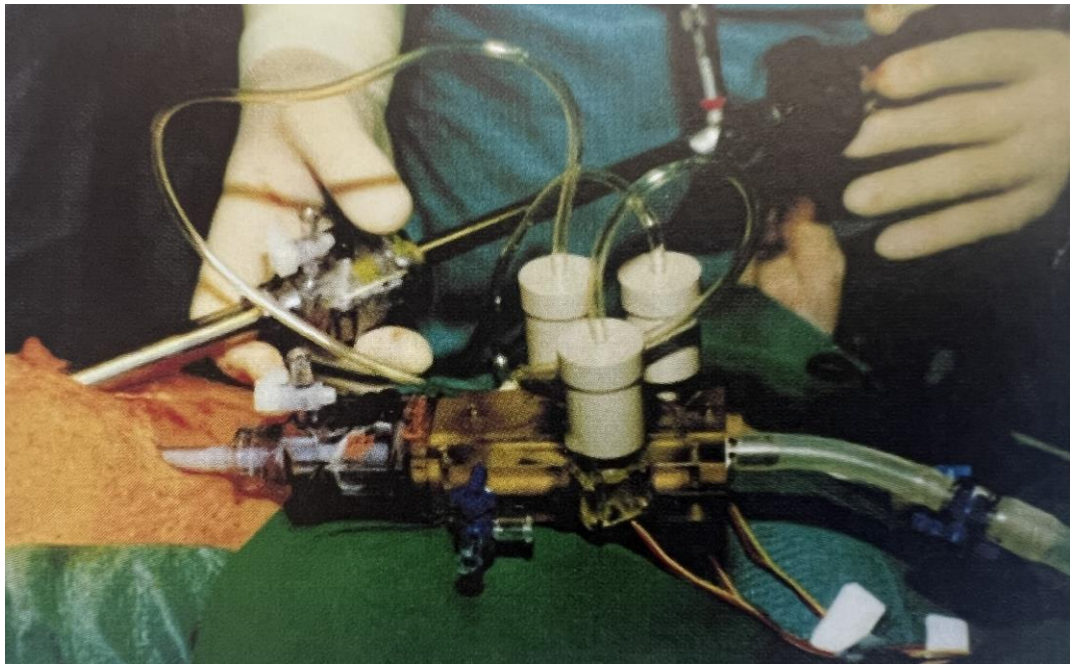


Aersolization

- Aerosol
  - Suspension of fine solid particles or liquid droplets in a gas (Carbon dioxide in case of laparoscopy)
  - Defined by size distribution of the droplets
    - Most have multiple droplet sizes, ranges between 5– 30 micrometers
    - Smaller droplets → more homogeneous distribution, not necessarily improved depth of penetration
- Mechanisms of deposition
  - Sedimentation
  - Impaction (flow dependent)

Therapeutic Capnoperitoneum

- "association of a carrier gas (CO2) with an aerosolized therapeutic substance"
  - Utilizing the CO2 pneumoperitoneum as a drug delivery mechanism*
  - Built into a 5 mm trocar
  - Concurrent with sigmoid colon resection
- Increased exposure to the peritoneal surface
- Increased hydrostatic intra-abdominal pressure



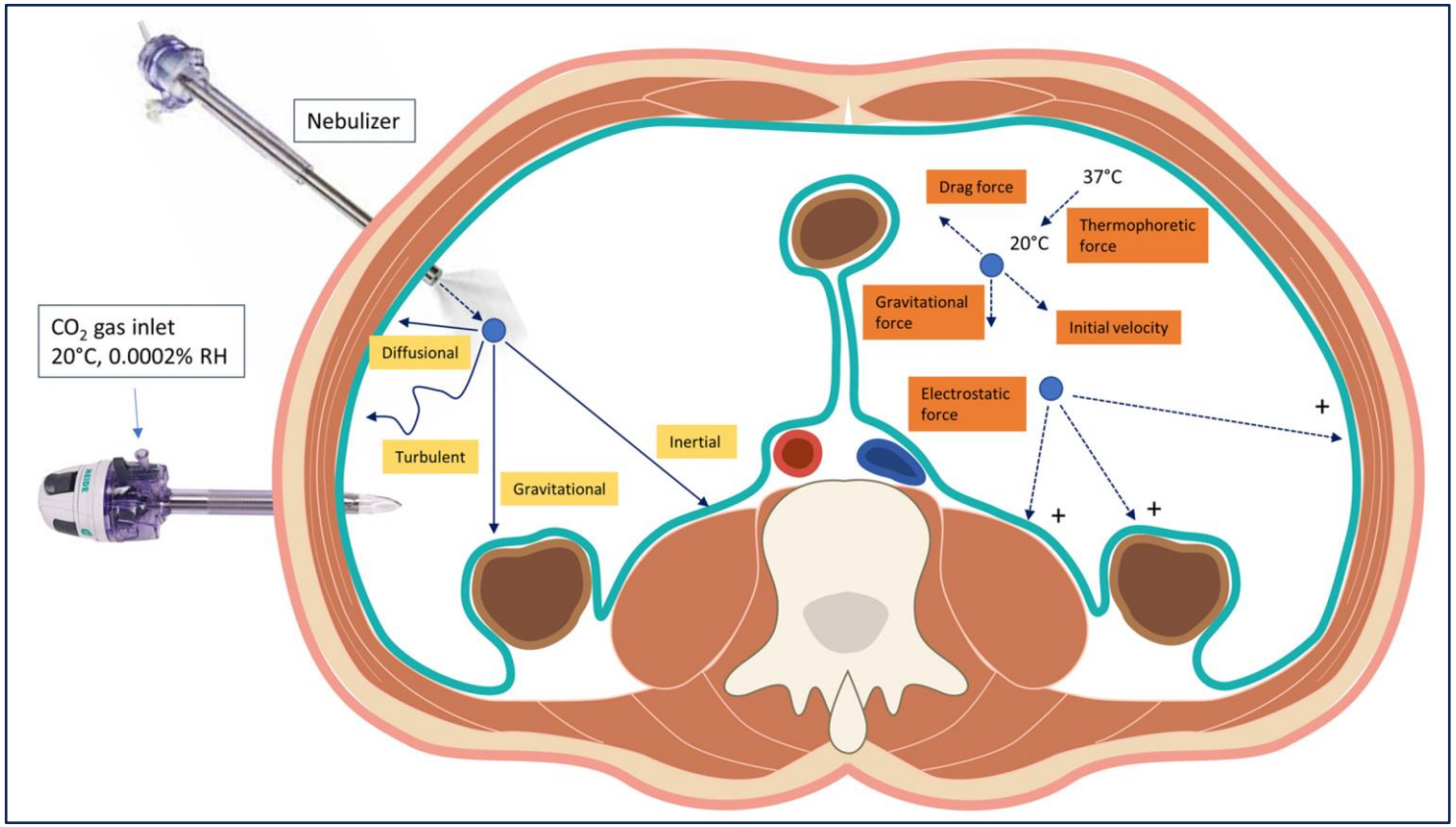
*Reymond. Surg Endo 2000.

PIPAC & Therapeutic Capnoperitoneum: Advantages

- Intraperitoneal chemotherapy delivery allows for intensification of chemotherapy exposure of peritoneal metastases
  - Peritoneal clearance is lower than plasma clearance; there exists a pharmacokinetic advantage
  - High intraperitoneal concentration with limited systemic exposure and toxicity
  - Significantly lower dose of chemotherapeutic with PIPAC when compared to HIPEC
- Penetration depth of chemotherapy in tumor tissue is limited
  - Modifiable by elevated intraperitoneal pressure
- Improved spatial distribution
  - Gas-like behavior given particle size with aerosol
- Laparoscopy allows for repeated direct administration and evaluation of response

PIPAC: Particle Transport and Deposition

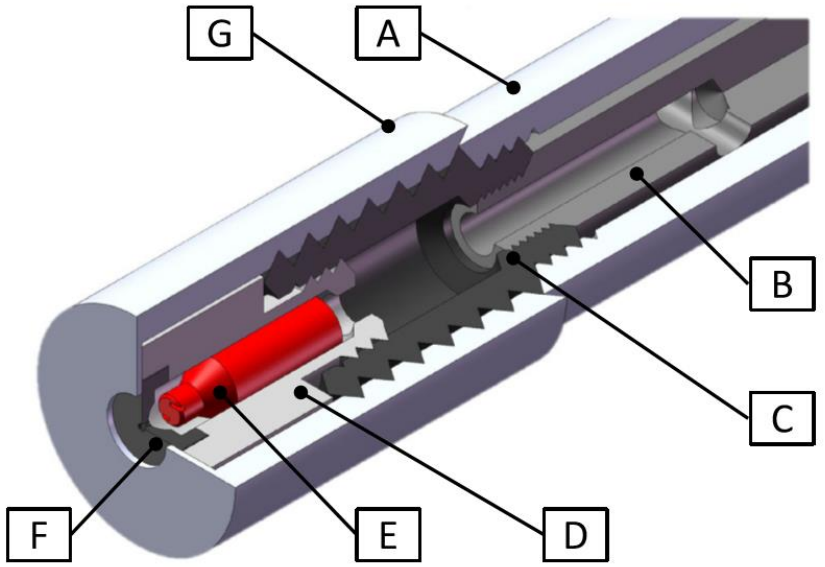
- Deposition Mechanisms
  - Inertial impaction
  - Gravity
  - Brownian diffusion
  - Turbulent (interaction with CO_2 gas)



Rahimi-Gorji. Adv Drug Delivery Reviews 2020.

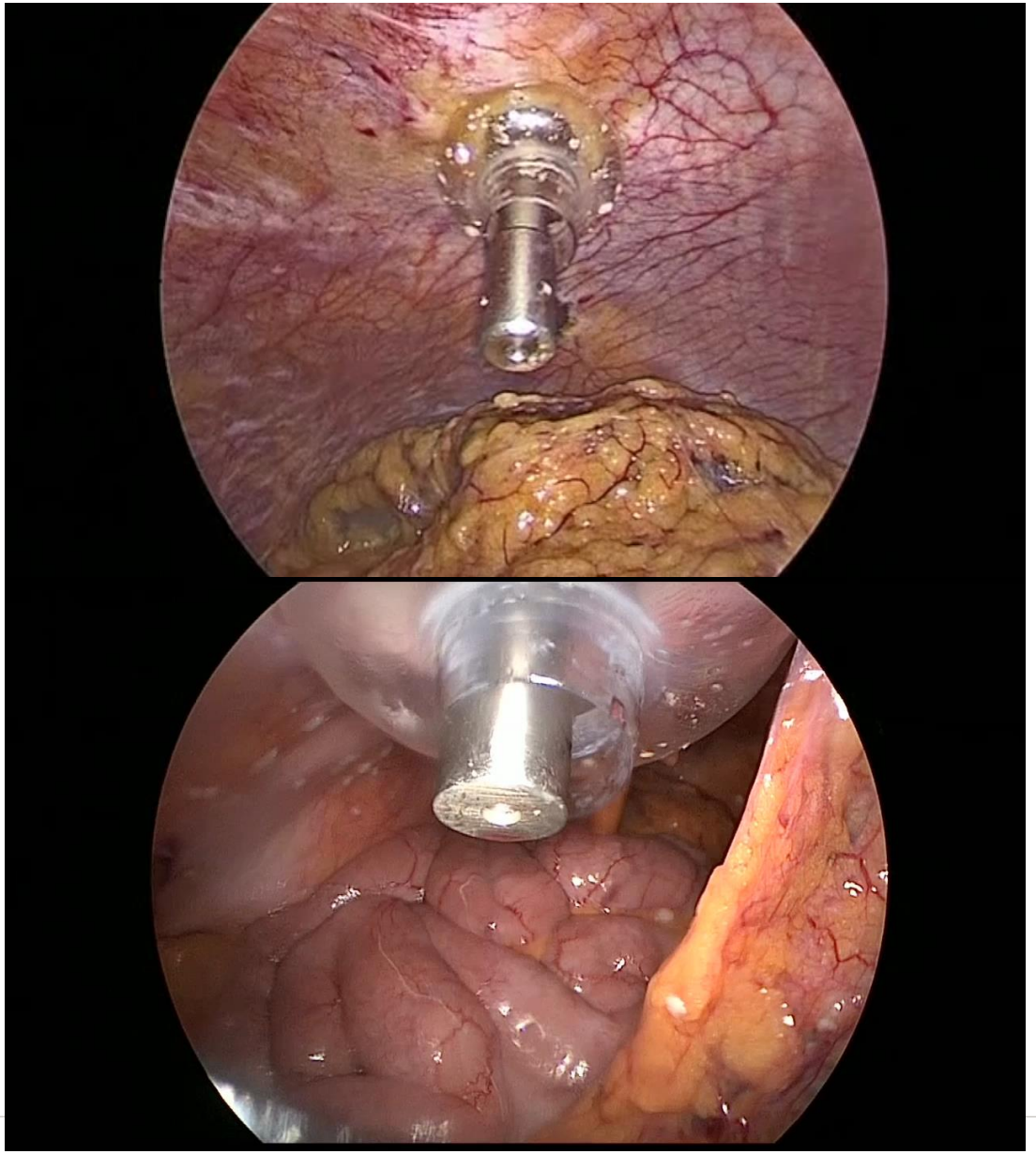
Aerosolizer

- Multiple devices now available
- Nozzle aerosolizer – 9mm diameter
  - Liquid forced through an orifice with diameter of 200 microns under pressure of 300 psi
  - Angle of distribution – 60 degrees
- Aerosolizes into existing capnoperitoneum
  - No gas flow



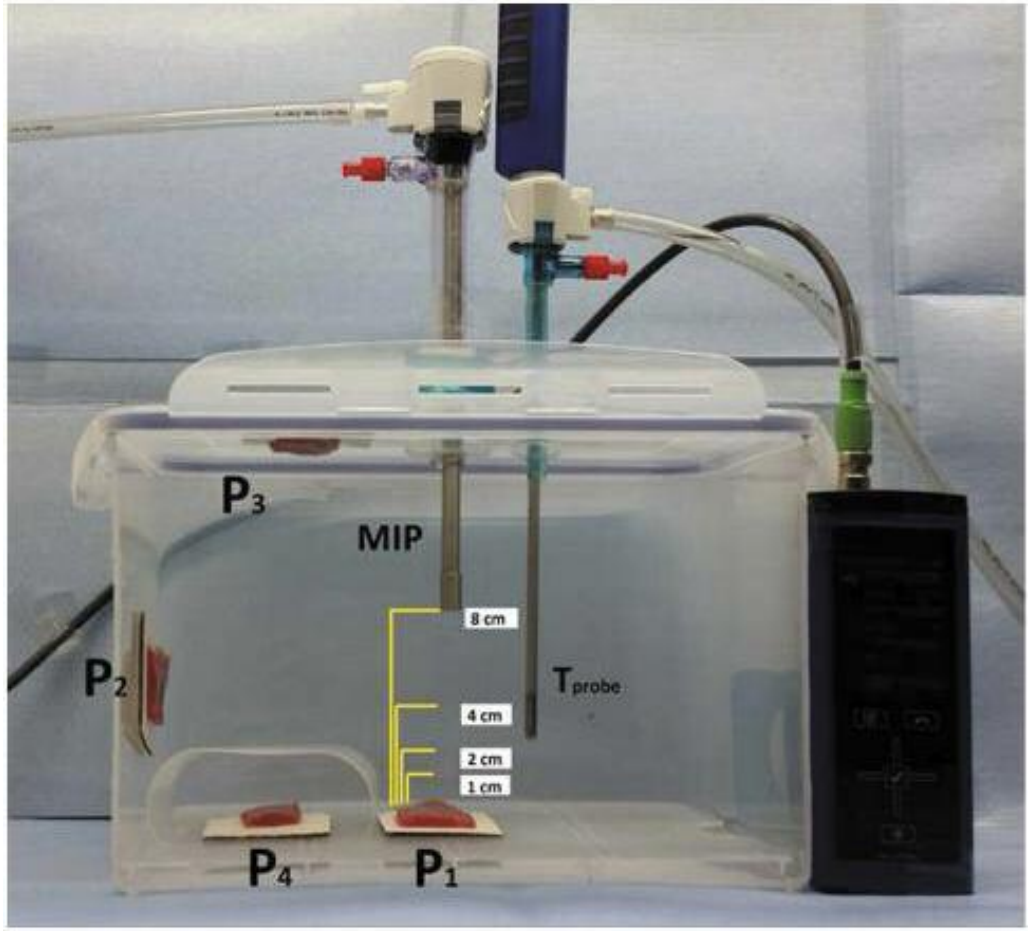
Aerosolizer

- Multiple nozzle devices
  - Up to 4 areas of dispersion with 70 degree angle each
  - Smaller size – 3mm
  - Combined device/drug combination device
  - ? more uniform droplet size and greater area of distribution



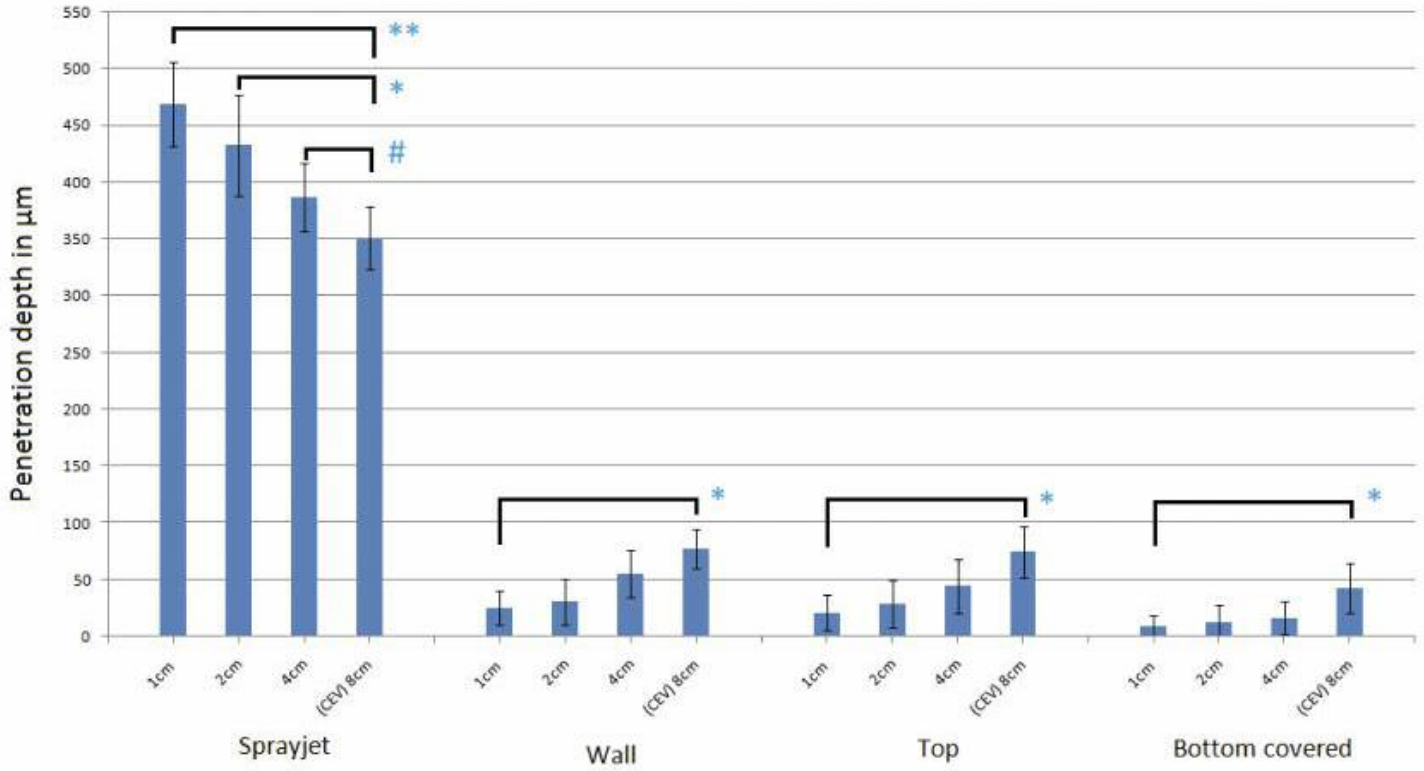
Spatial Distribution

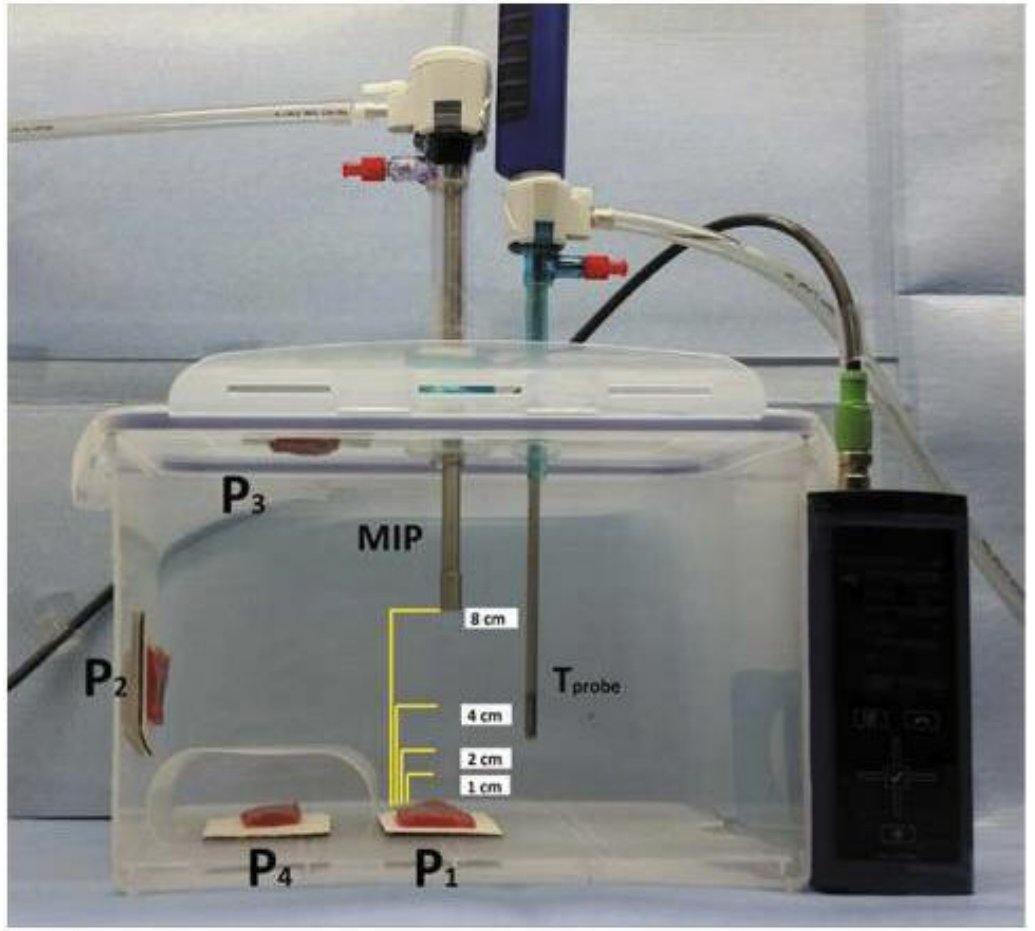
- Studied via non-anatomic, ex-vivo PIPAC model
  - Changes in internal pressure
  - Distance of device to target
  - Drug concentration on depth of penetration



Khosrawipour. AntiCancer Research 2016.

Spatial Distribution





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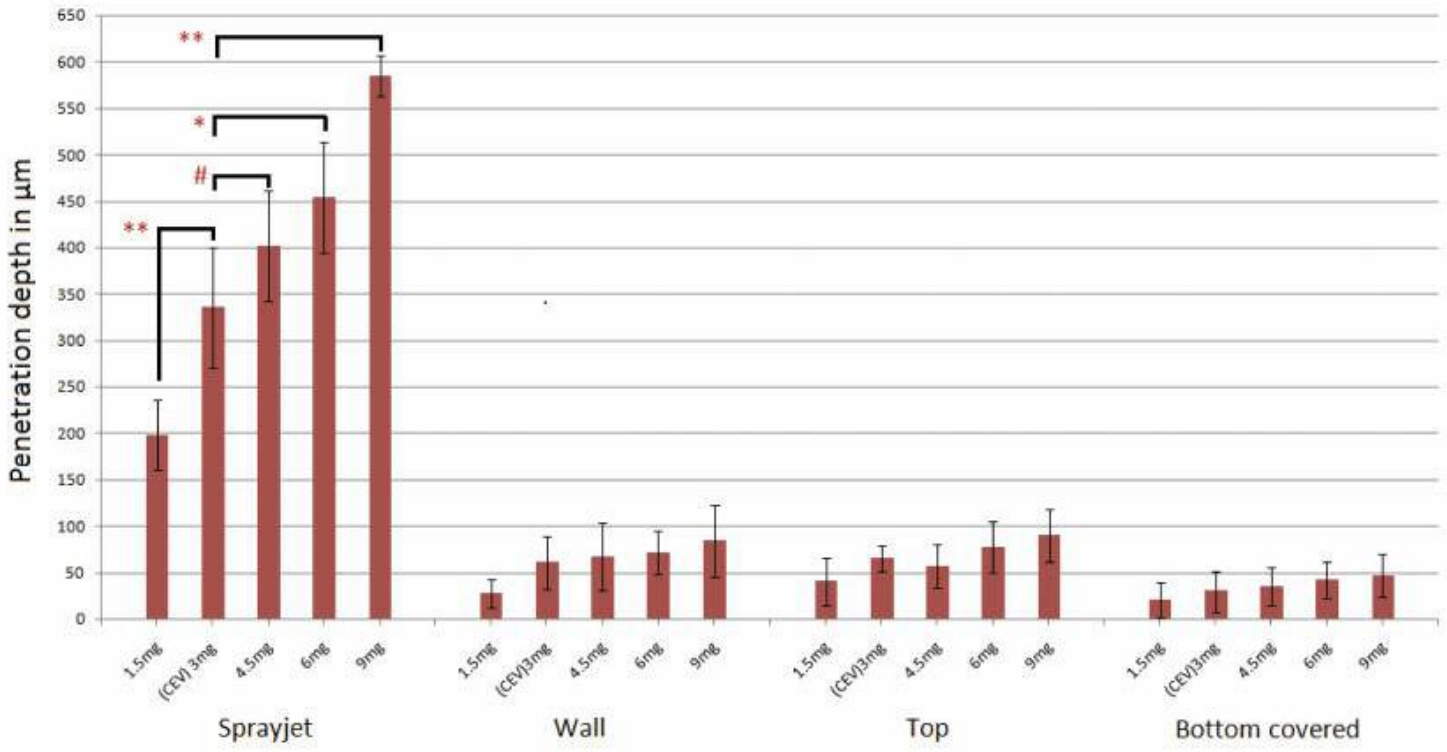

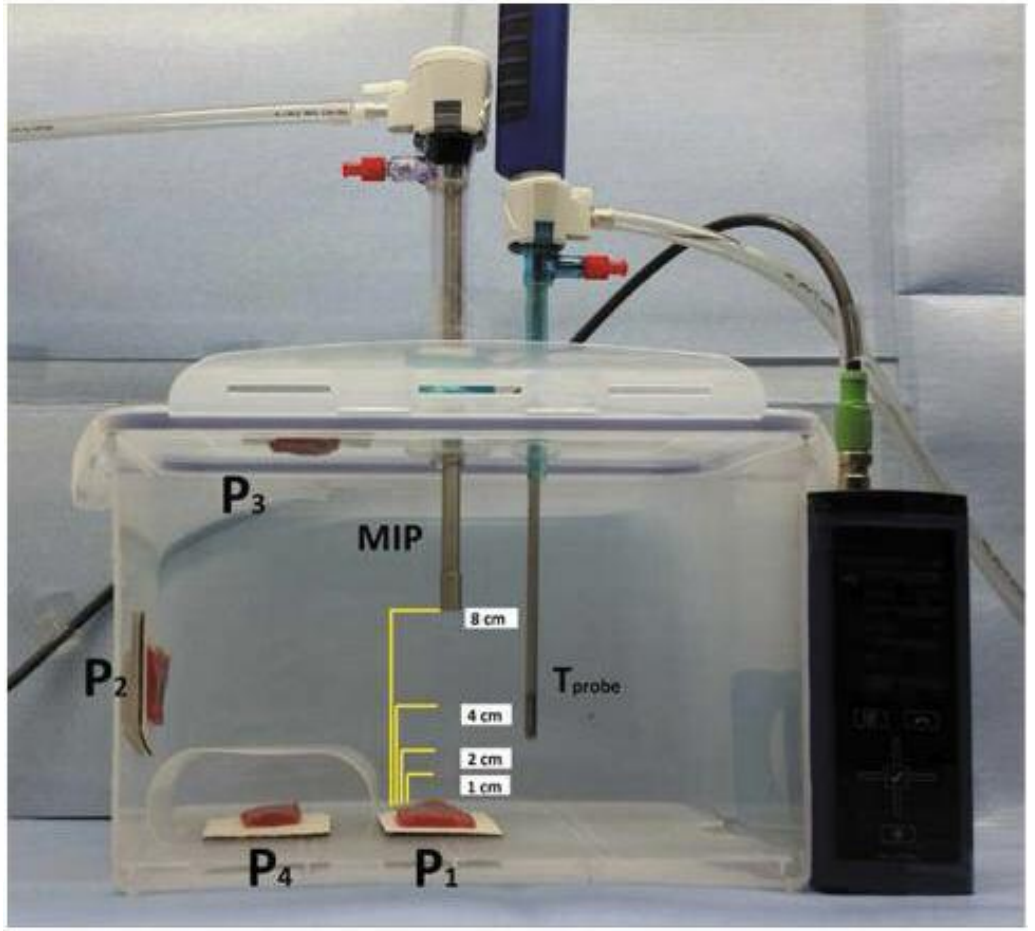

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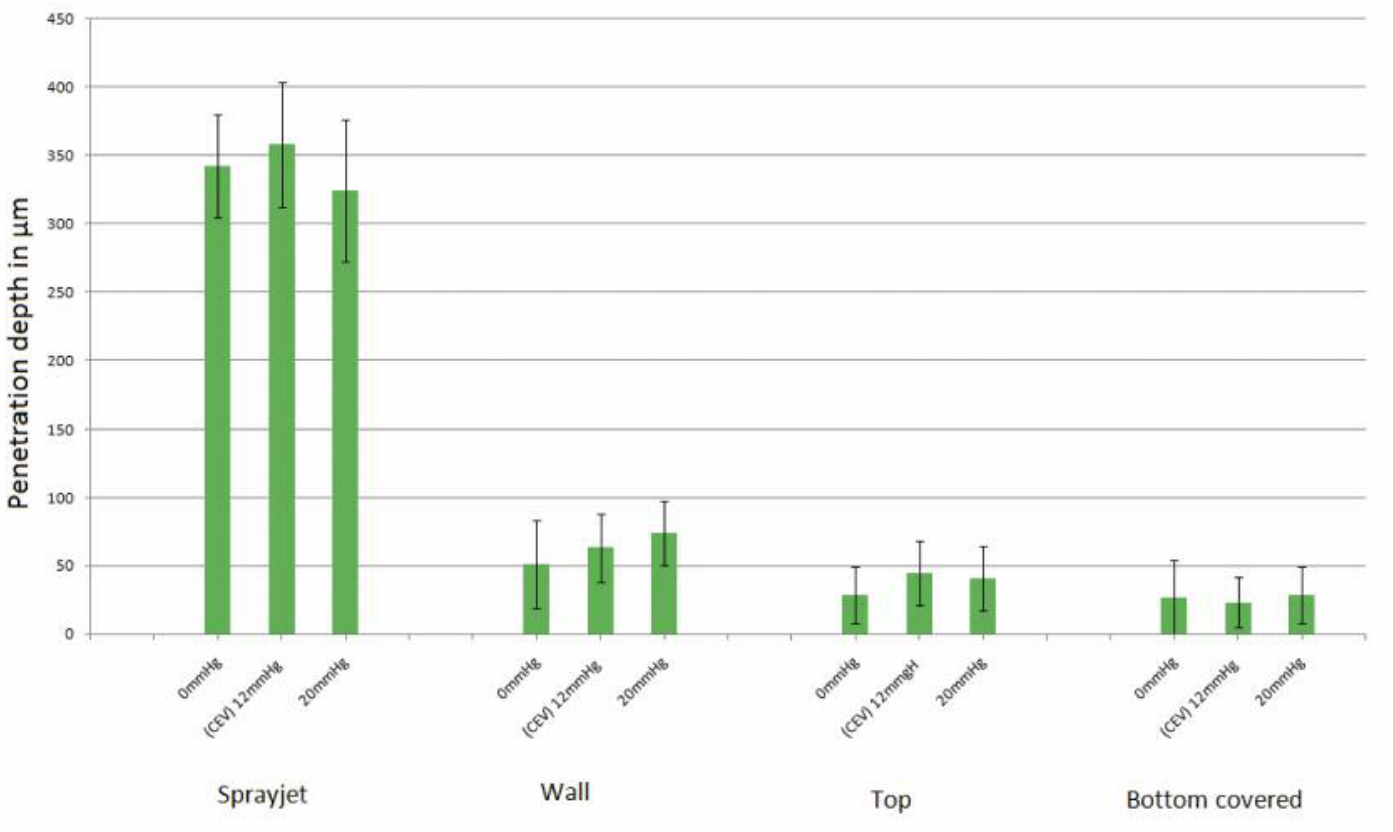
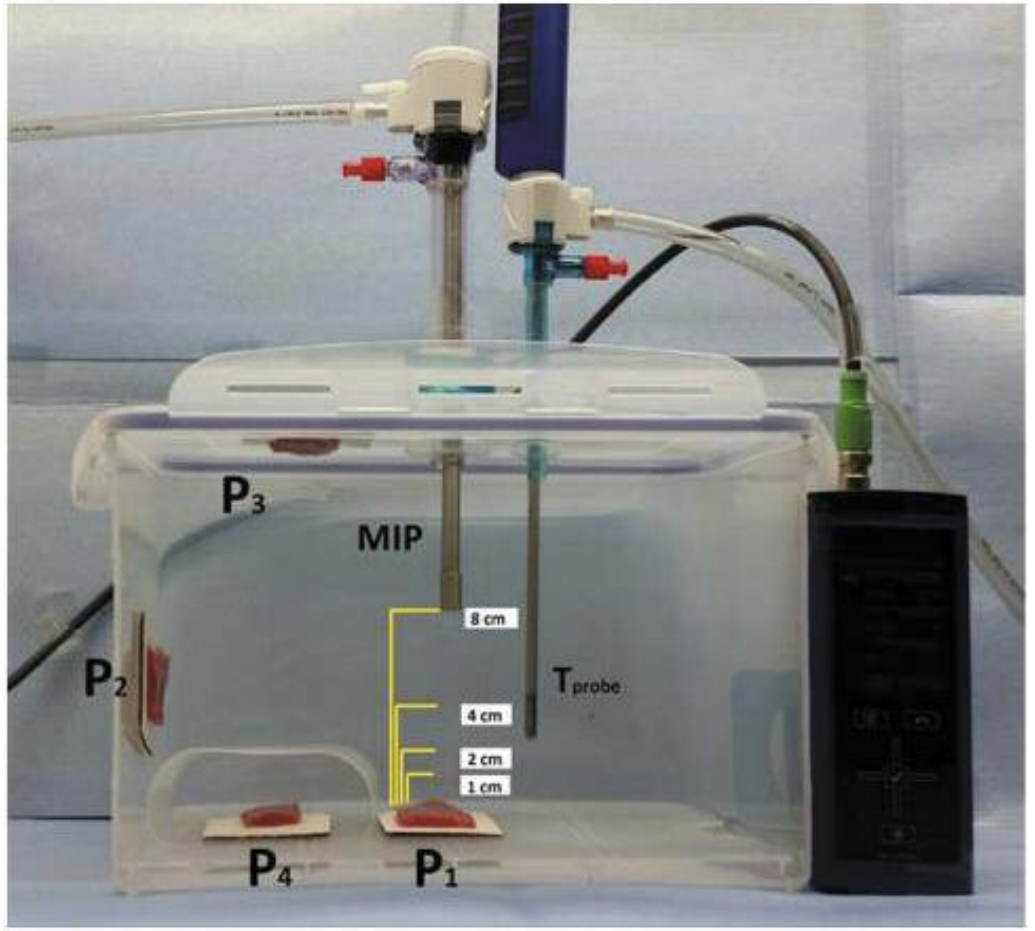
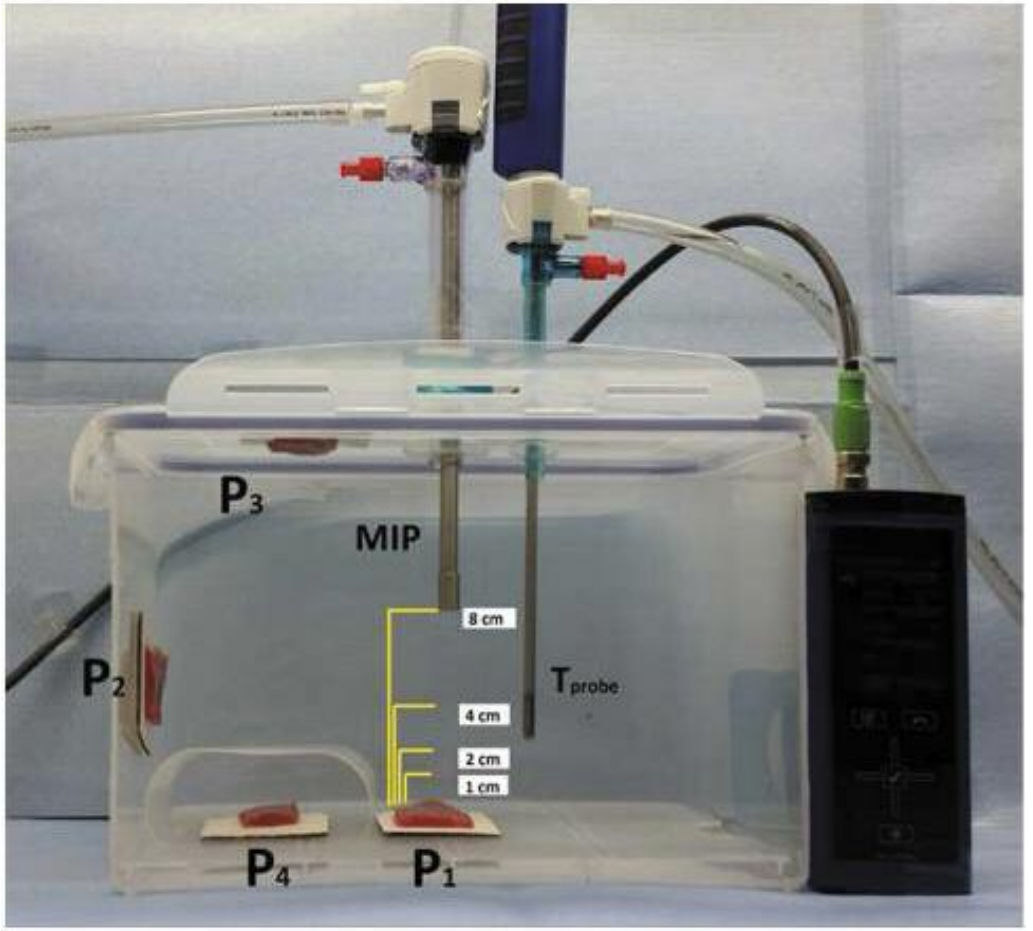




Khosrawipour. AntiCancer Research 2016.

Spatial Distribution

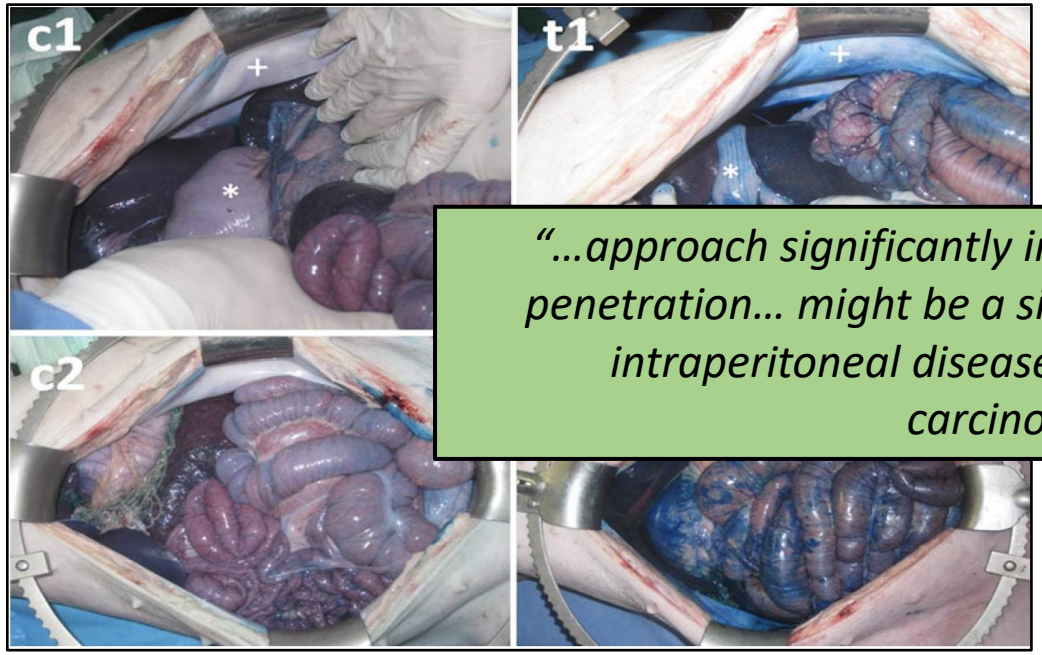
"A more homogeneous penetration within all targets at the same time cannot be achieved by changing drug concentration, position of the nozzle or pressure increase. Essential changes in the application technique of PIPAC might be necessary to optimize… the resultant clinical outcomes of the patients."

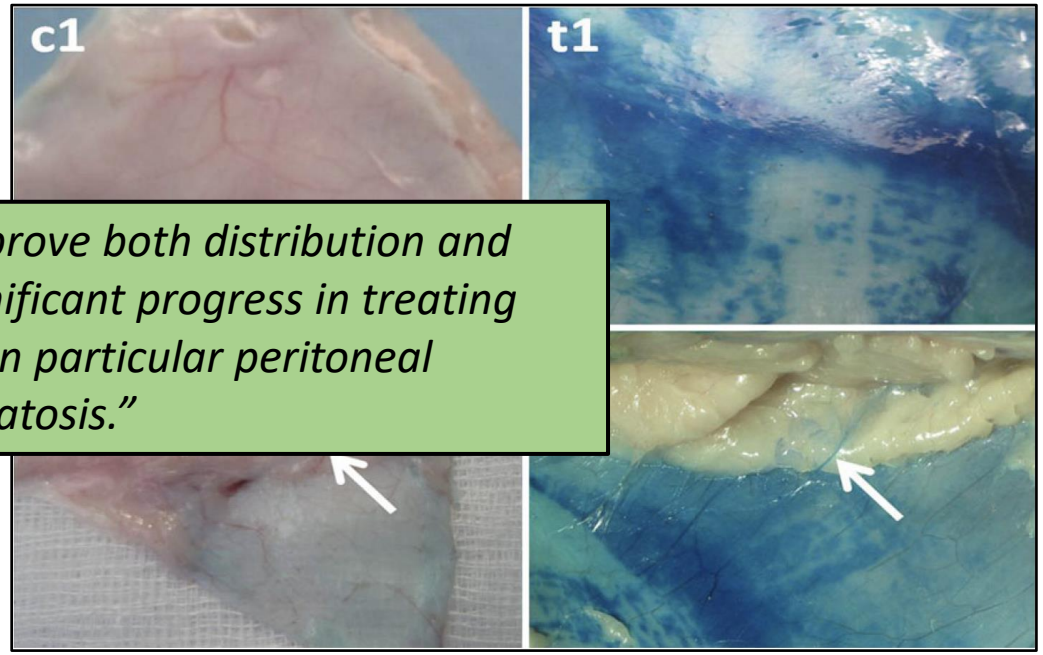


Khosrawipour. AntiCancer Research 2016.

Initial in-vivo study – Distribution and Penetration

- 5 pigs
- Methylene blue sprayed/infused for 30 minutes (4 test : 1 control)





"…approach significantly improve both distribution and penetration… might be a significant progress in treating intraperitoneal disease, in particular peritoneal carcinomatosis."

Solass. Surg Endo 2012.

Depth of Penetration

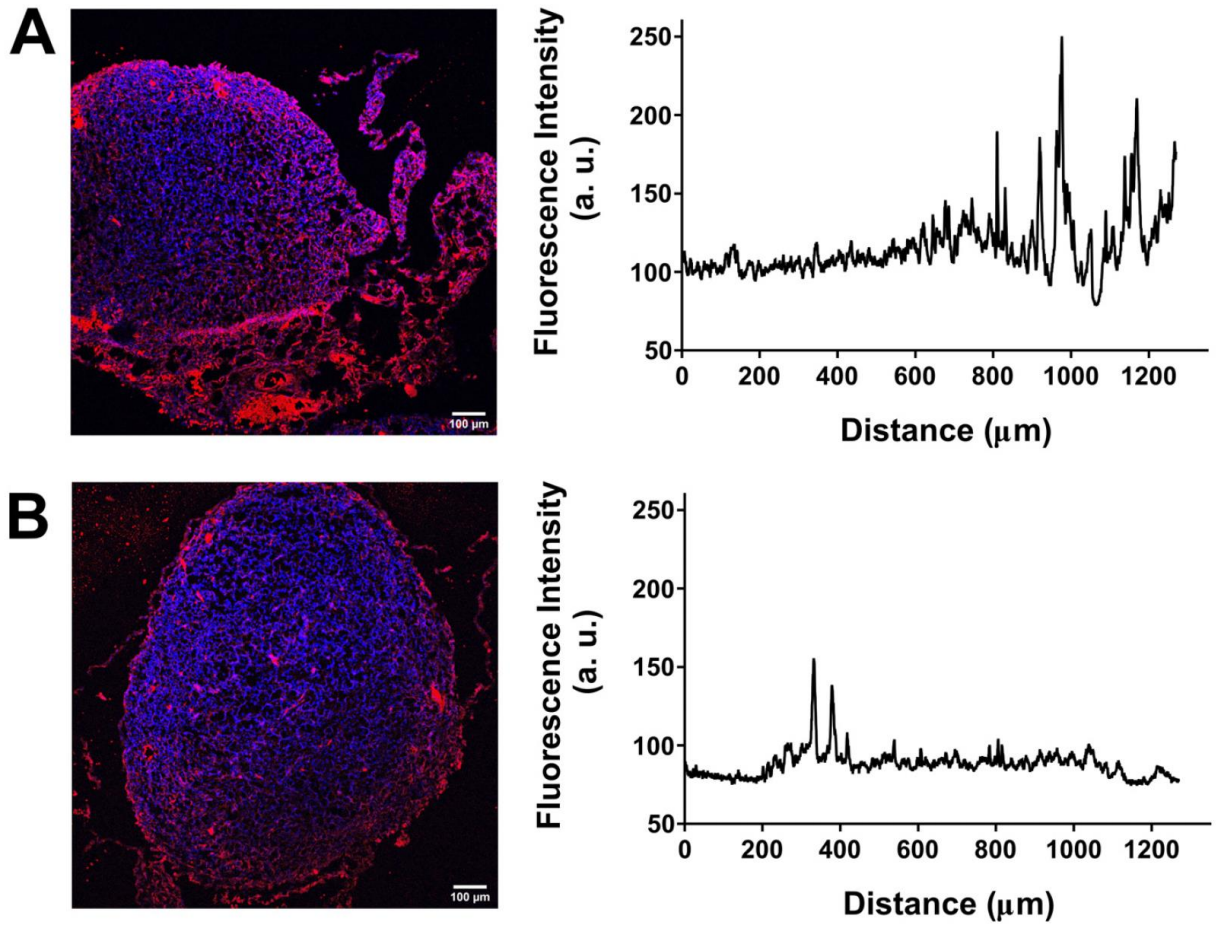
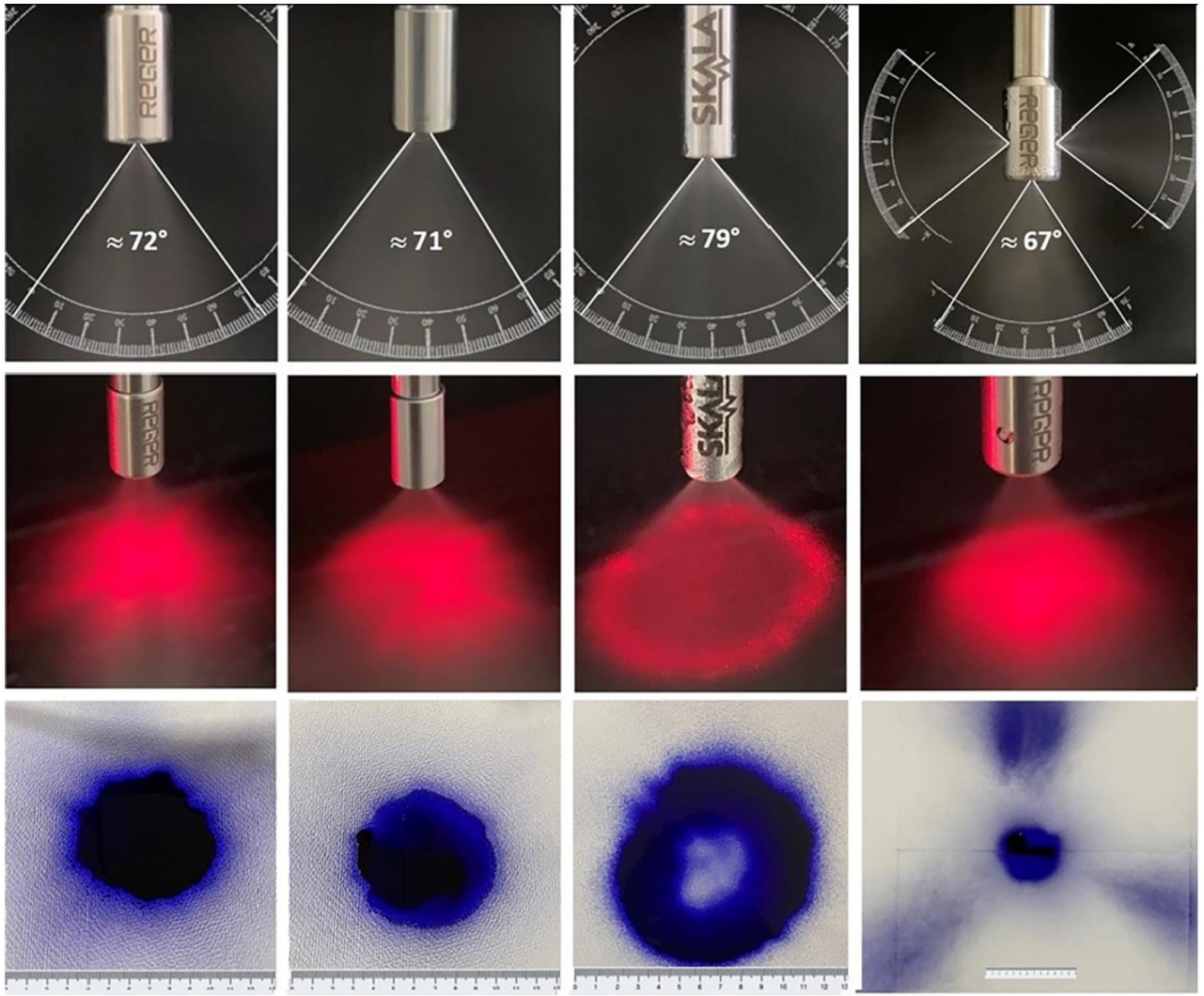


Fig. 2. Penetration of fluorescently labelled nanoparticles (red colour) in peritoneal metastases from human ovarian cancer (SKOV-3) in nude rats after laparoscopically assisted aerosol delivery (A) versus liquid instillation (B). The graphs depict the fluorescence intensity (Y axis, arbitrary units) as a function of distance, in µm, from the exposed peritoneal surface.

Evaluation of different nebulizers

- As of 2023, 4 commercially available devices
  - Nebulizer, Model 770–12, REGER Medizintechnik, Villingendorf, Germany (A),
  - HurriChem™, ThermaSolutions, White Bear Lake, MN, United States of America (B),
  - MCR-4 TOPOL1, SKALA-Medica, Soběslav, Czech Republic (C),
  - QuattroJet, Model 770–14, REGER Medizintechnik, Villingendorf, Germany (D).

Evaluation of different nebulizers



Gohler. PLOS One 2024.

Fig 4. Photographic images of spray cone angle (upper panel), of spray cone form (middle panel) and horizontal drug deposition area (lower panel, scale in cm).

Evaluation of different nebulizers

Table 1. Overview on technical and functional characteristics of the examined nozzles; * = manufacturer-recommended operational conditions.

parameter	unit	A (Nebulizer)	B (HurriChem™)	C (MCR-4 TOPOL®)	D (QuattroJet)
liquid flow rate (Q_L)	ml/s	0.5	0.5	1.3–2.0	1.5
operational pressure for *Q_L	bar	15.7	14.9	7.4–18.1	16.0
pressure initiation time for *Q_L	s	52	100	18–26	94
nozzle orifice diameter	µm	200	190	370	170
mass median diameter for 15 bar	µm	28.95	20.99	52.17	24.18
max. spray angle for *Q_L	°	≈ 72	≈ 71	≈ 79	≈ 67
number of nozzles	-	1 × axial	1 × axial	1 × axial	1 × axial, 3 × lateral
kind of spray cone	-	full cone	full cone	hollow cone	full cone
drug deposition area for *Q_L	cm^2	≈ 38.5	≈ 38.5	≈ 66	≈ 679

Gohler. PLOS One 2024.

ePIPAC: Electrostatic Precipitation

- PIPAC has improved homogeneity of IP chemotherapy distribution compared to HIPEC
  - Still limited though as seen in spatial distribution studies
- Application of an external electrostatic field counteracts gravity and drag
- Commercially available electrostatic generator (Ultravision™, Alesi Surgical)
  - High DC voltage applied to a stainless steel wand inserted into the abdomen
  - Negatively charges ions which attach to the aerosolized particles
  - These are then attracted to and accelerated toward a positively charged abdominal wall

ePIPAC: Potential Advantages

- Improved homogeneity of drug distribution
- Increased depth of penetrations
- Possible reduced operative time

Summary

- PIPAC is a drug delivery tool
  - A novel device that can deliver (novel) therapeutic agents
- Allows for increased drug concentration intraperitoneally with significantly less dose compared to systemic treatment
  - Lesser systemic toxicity
- Spatial distribution and penetration is improved compared to HIPEC
  - Ongoing improvements in devices and methods of application may further improve this