Preclinical experiments: HIPEC vs. PIPAC

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Disclosures

- CEO/Owner of Capnomed GmbH
- CEO/Owner of Capnopharm GmbH

These disclosures have been deemed as irrelevant, as this presentation is:

- Limited to basic science research, such as pre-clinical research and drug discovery, or the methodologies of research, and I will not make care recommendations.
- Intended to teach the safe and proper use of medical devices, and I will not recommend whether or when a device is used.

This presentation and/or comments will be free of any bias toward or promotion of the above-referenced companies or their products and/or other business interests.

The off-label or investigational use of Cisplatin, Doxorubicin and Oxaliplatin will be addressed.

Testing PIPAC's promises in preclinical models

1. Spatial distribution more homogeneous?
2. Increased intra-tumoral drug penetration (depth)?
3. Increased drug concentration post-procedure?
4. Decreased systemic drug uptake?
5. Increased biological activity?

Basics

1

- A solid has a volume and a shape
- A liquid has a volume but no shape
- A gas has no volume and no shape

An aerosol is an intermediary state between a liquid and a gas

2

- A gas expands within a closed space, not a liquid
- A liquid flows along the path of least resistance

3

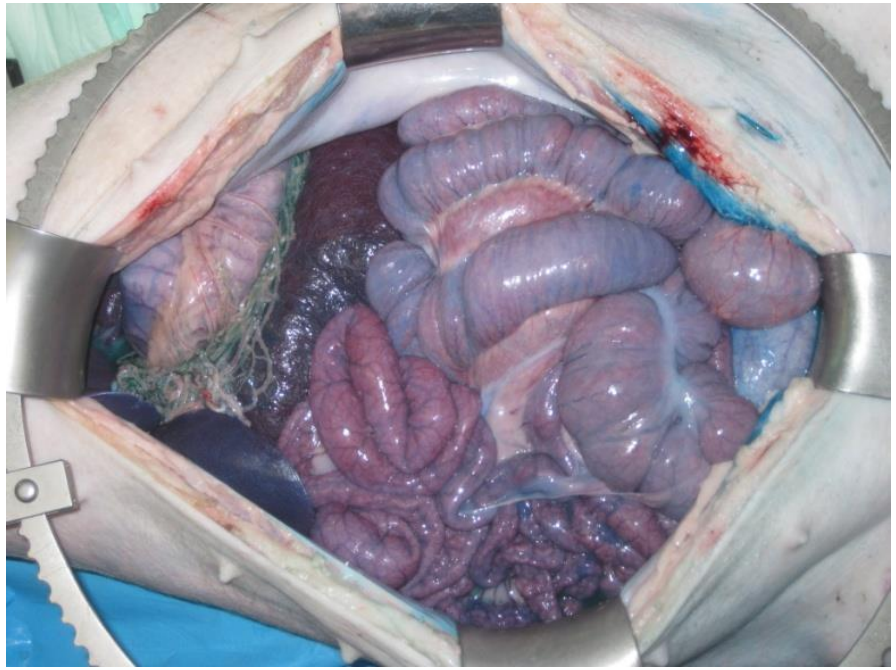
- On planet Earth, any aerosol will sediment over time

4

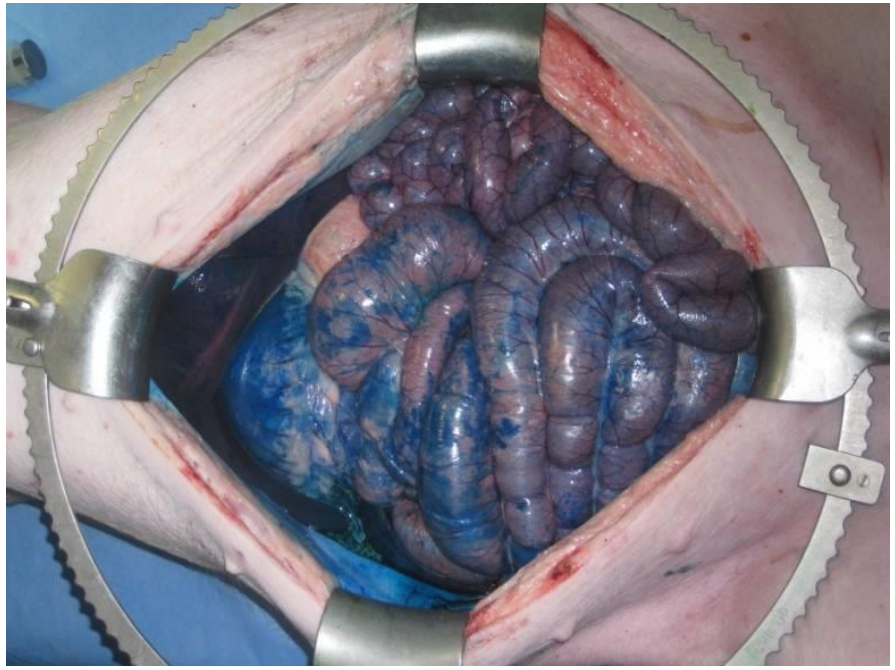
- Physical laws work even when you do not understand them

Spatial distribution: aerosol better than liquid

Liquid



PIPAC



swine model alive

Methylene blue

Solass W et al. Surg Endosc 2013

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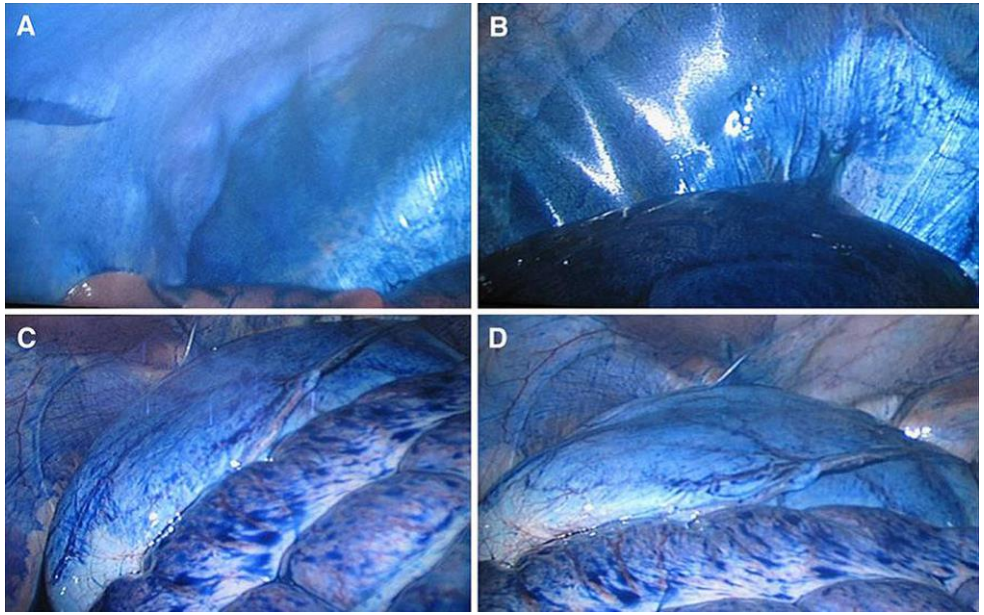
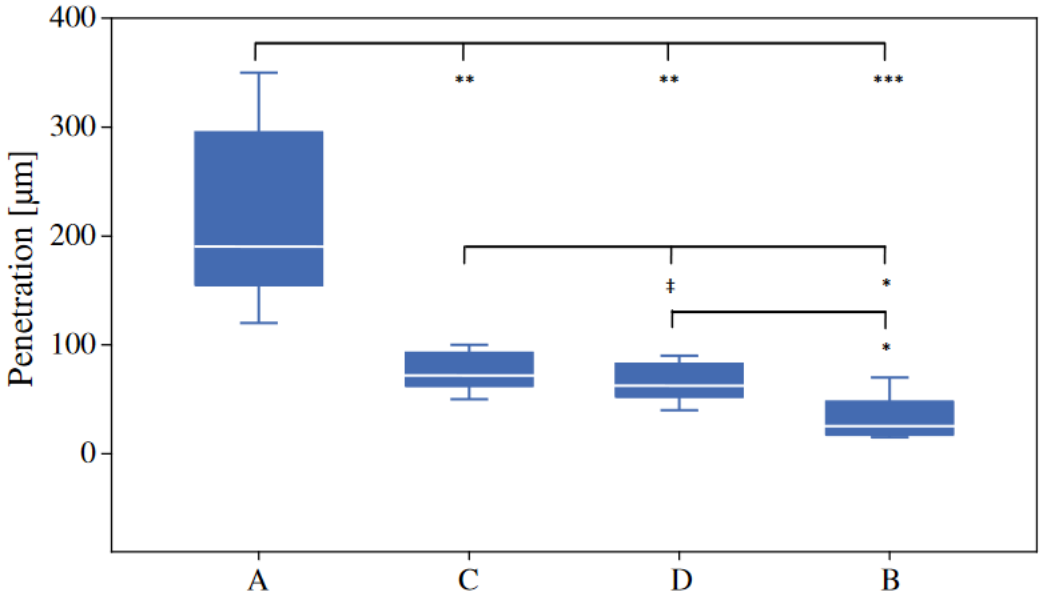
Is spatial distribution homogeneous after PIPAC ?



swine model | Methylene blue

Visually homogeneous distribution…

Solass et al Surg Endosc 2013



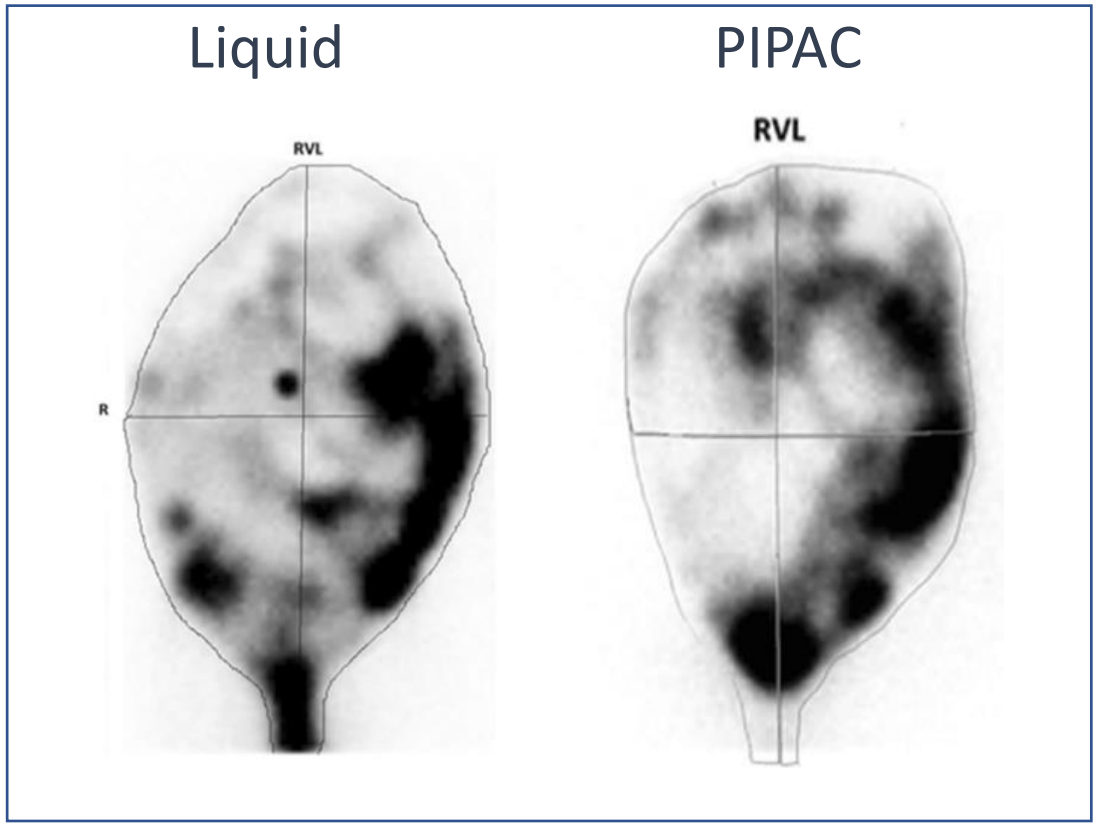
A: bottom, B: side, C: top; D: tunnel

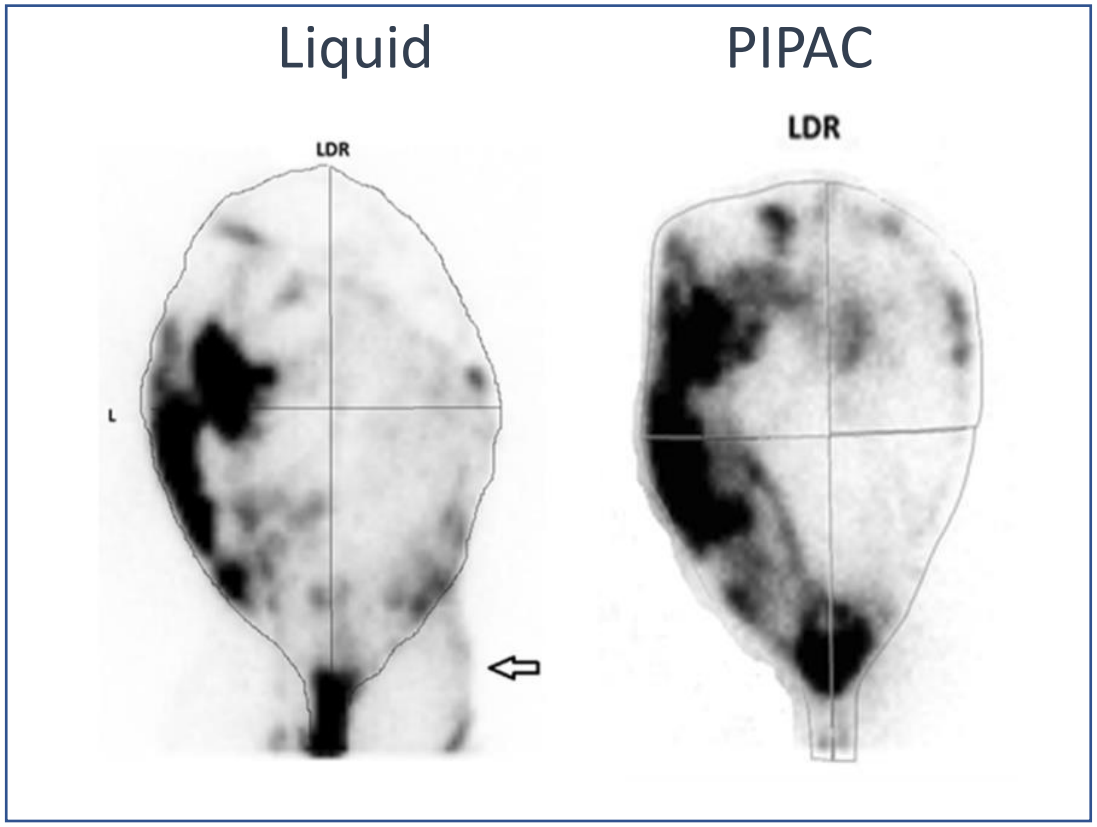
Plastic box,Tissue penetration | DOX

… but quantitatively heterogeneous

Khosrawipour et al, J Cancer Res Clin Oncol 2016

IP Liquid delivery vs PIPAC, spatial distribution





Homogeneity of spatial distribution after PIPAC is superior to IP liquid delivery but remains suboptimal. Tc99 planar scintigraphy

Swine postmortem

Bellendorf et al, Surg Endosc 2016

IP Liquid delivery vs PIPAC, spatial distribution

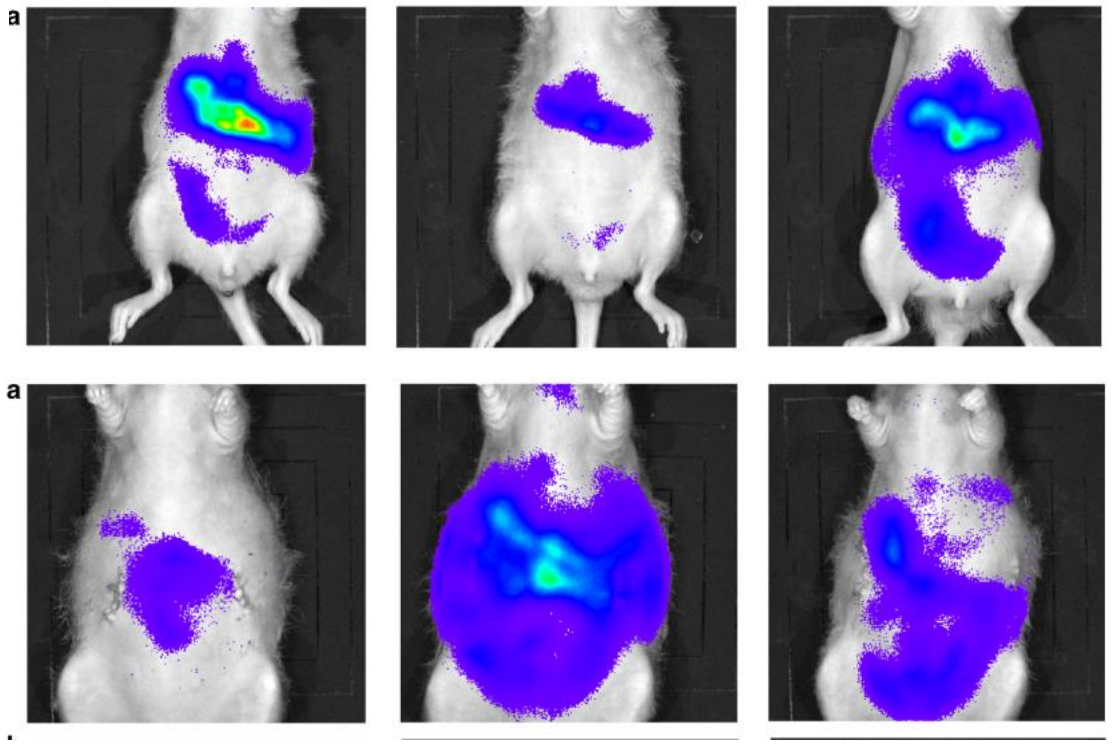
rats alive

nRNA lipoplexes

IVIS Lumina II whole body imaging system

IP liquid

PIPAC



Homogeneity of spatial distribution after PIPAC is superior to IP liquid delivery.

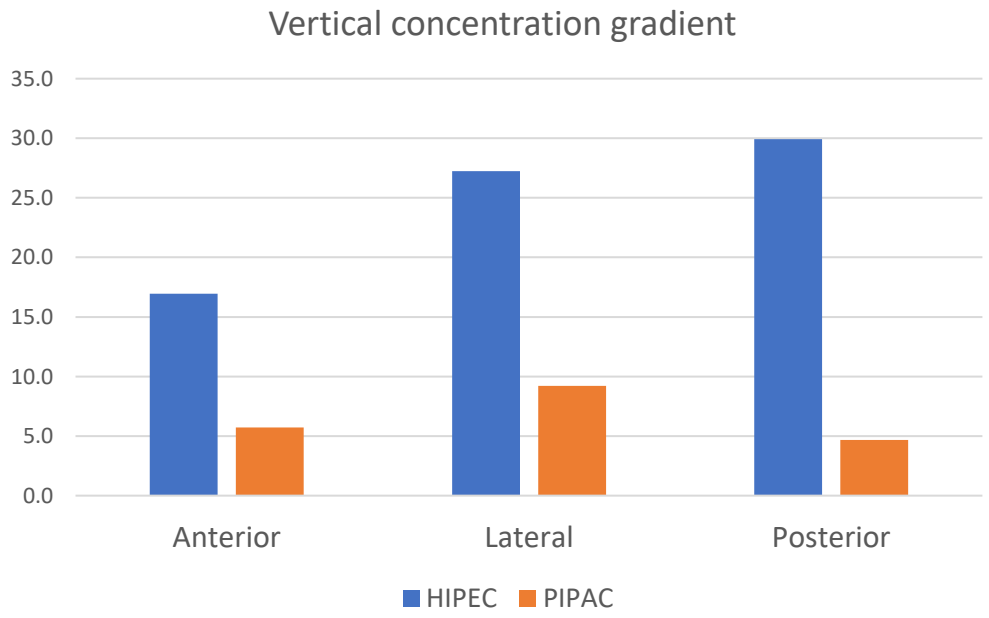
Shariati et al, Pharm Res 2019

Spatial distribution in-vivo: HIPEC versus PIPAC

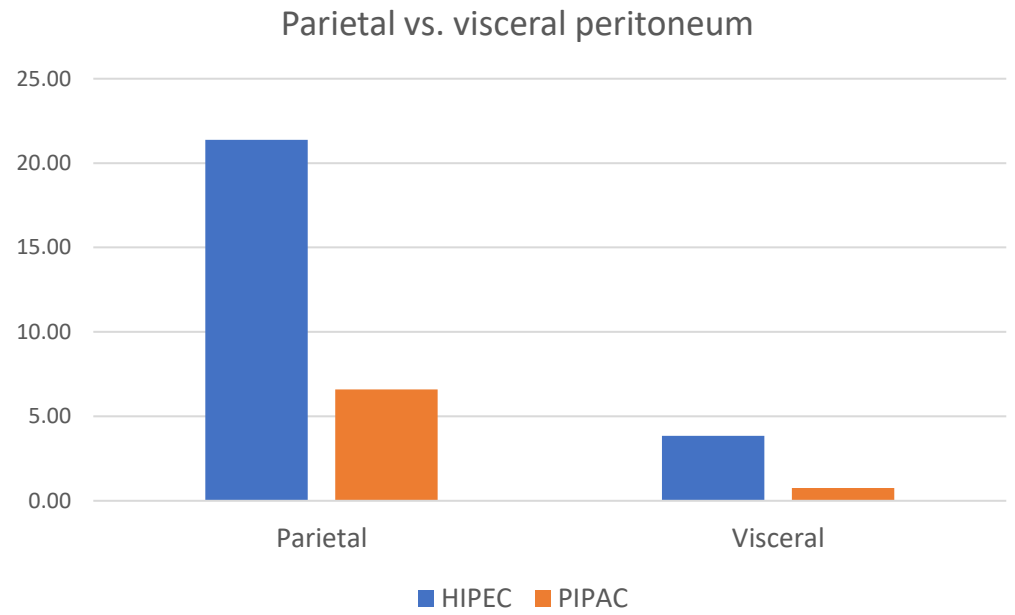
HIPEC: 70 mg/m^2@ 43° C, 60 min PIPAC: 7.5 mg/m^2 @ 37° C,30 min
9 parietal biopsies, 1 visceral biopsy (small bowel)

swine alive | cisplatin

LOCAL TISSUE CONCENTRATION



Vertical concentration gradient HIPEC > PIPAC



CIS uptake parietal > visceral peritoneum

Davigo Int J Hyperthermia 2020

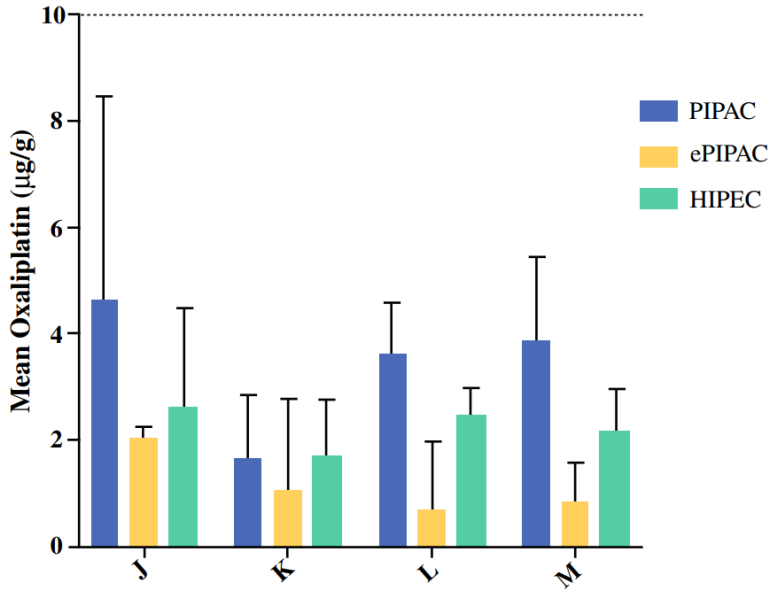
Spatial distribution: HIPEC versus PIPAC

Laparoscopic HIPEC: OX 400 mg/m^2@ 42° C, 30 min
PIPAC: OX 92 mg/m^2 @ 37° C,30 min
9 parietal biopsies, 4 visceral biopsies (small bowel)

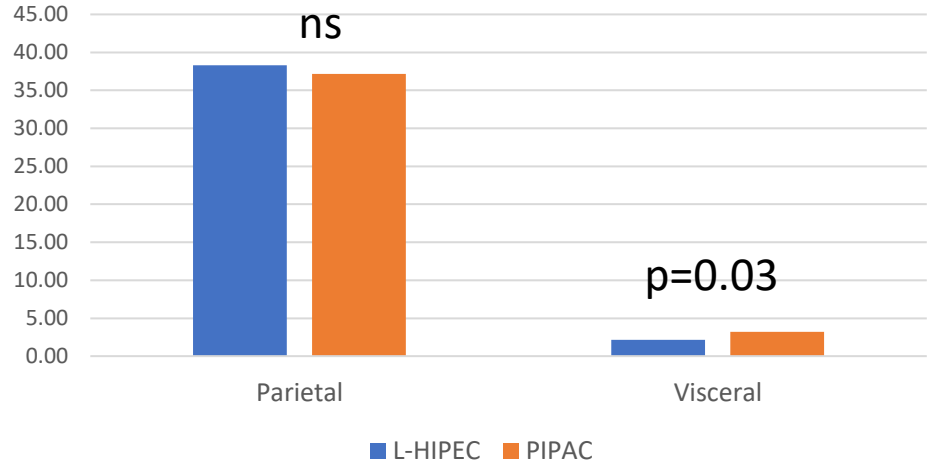
swine alive | oxaliplatin

LOCAL TISSUE CONCENTRATION

Visceral peritoneum



Parietal vs. visceral peritoneum



OX uptake parietal > visceral peritoneum
Visceral concentration 1.5x higher after PIPAC (with 20% dose)

Giger-Pabst, Ann Surg Oncol 2019

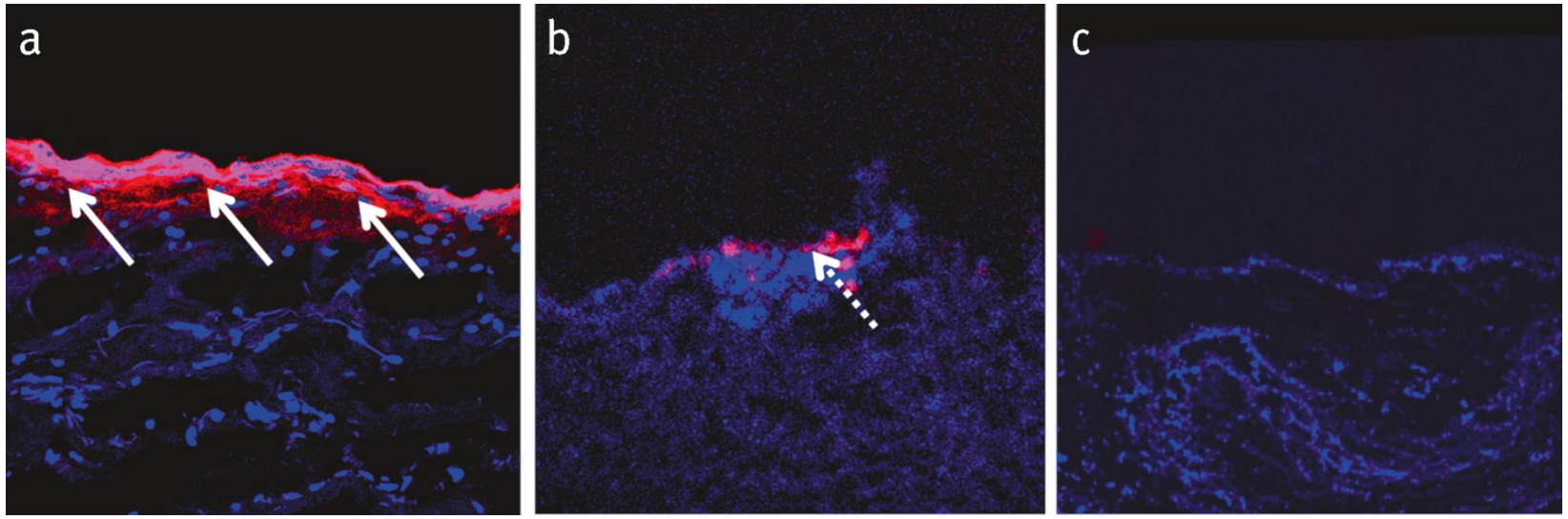
Spatial distribution after PIPAC

Drug uptake depends on the organ (omentum > ovary > caecum)
Increased IP pressure does not affect distribution patterns

Minouni et al, BMC cancer 2021

Depth of Drug Penetration

PIPAC | IP liquid | Control



Tissue fluorescence down to 1 mm depth

Minimal superficial tissue fluorescence

No tissue fluorescence

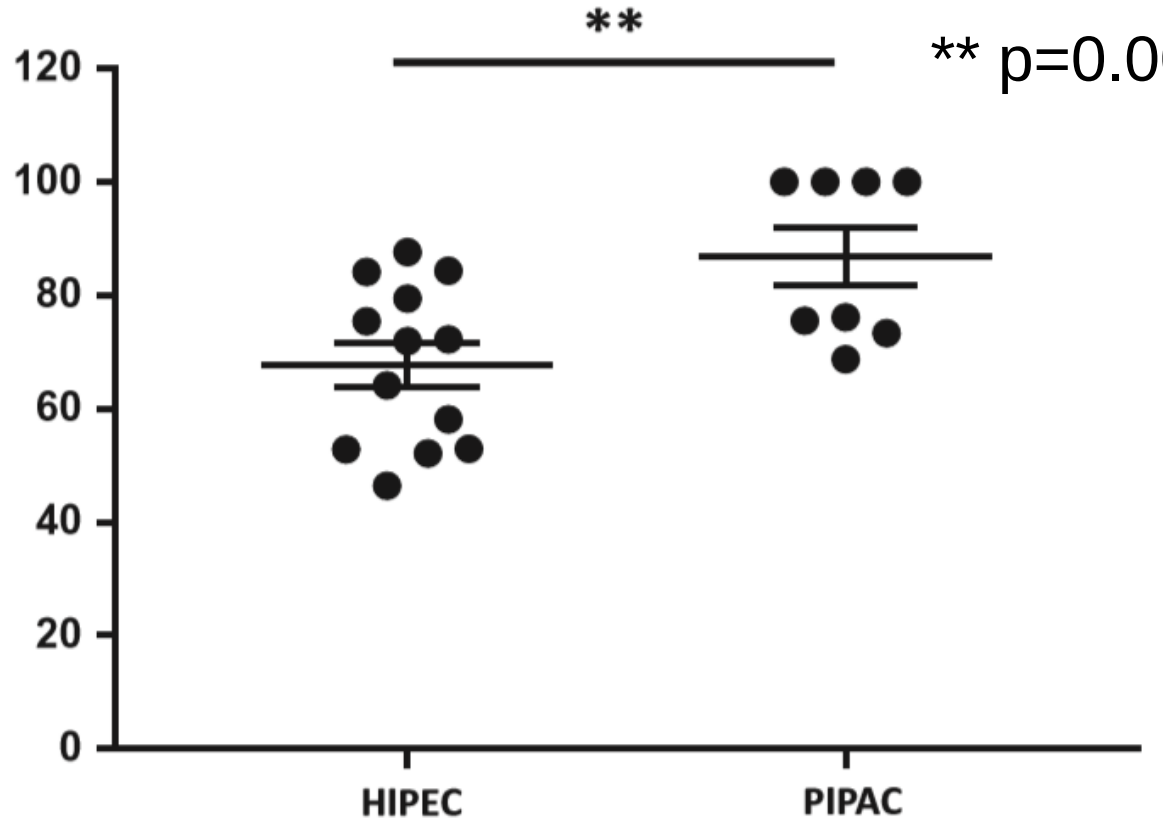
Ex vivo: human

Operation specimens

Cy5-labeled siDNA

Solass W et al. Surg Endoscopy 2012

Depth of Tissue Drug Penetration



** p=0.008

Ex-vivo xenograft model (nude mice)

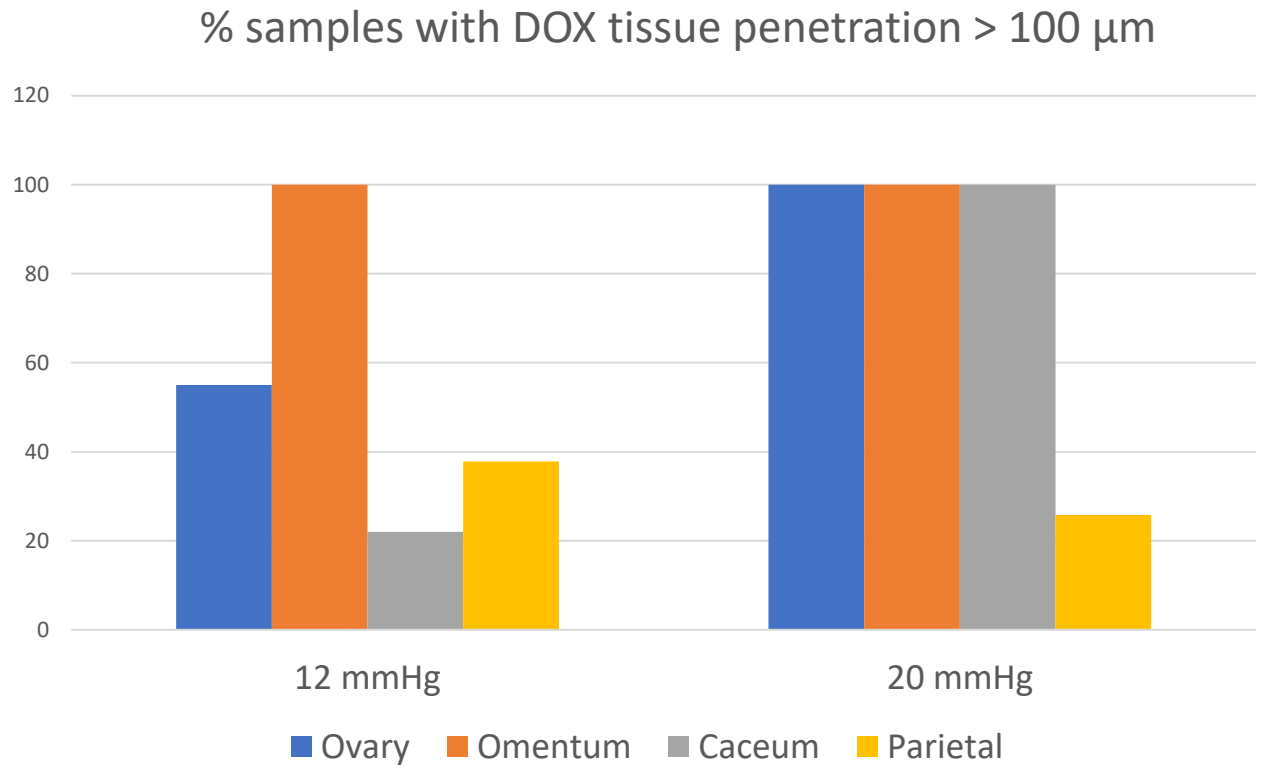
LS174 (human colon cancer cells)
CT26 (murine colon cancer cells)

oxaliplatin

Penetration depth (ratio) of oxaliplatin PIPAC > HIPEC

Eveno C et al. Pleura Peritoneum 2017

Pressure Increases depth of drug tissue penetration (PIPAC)



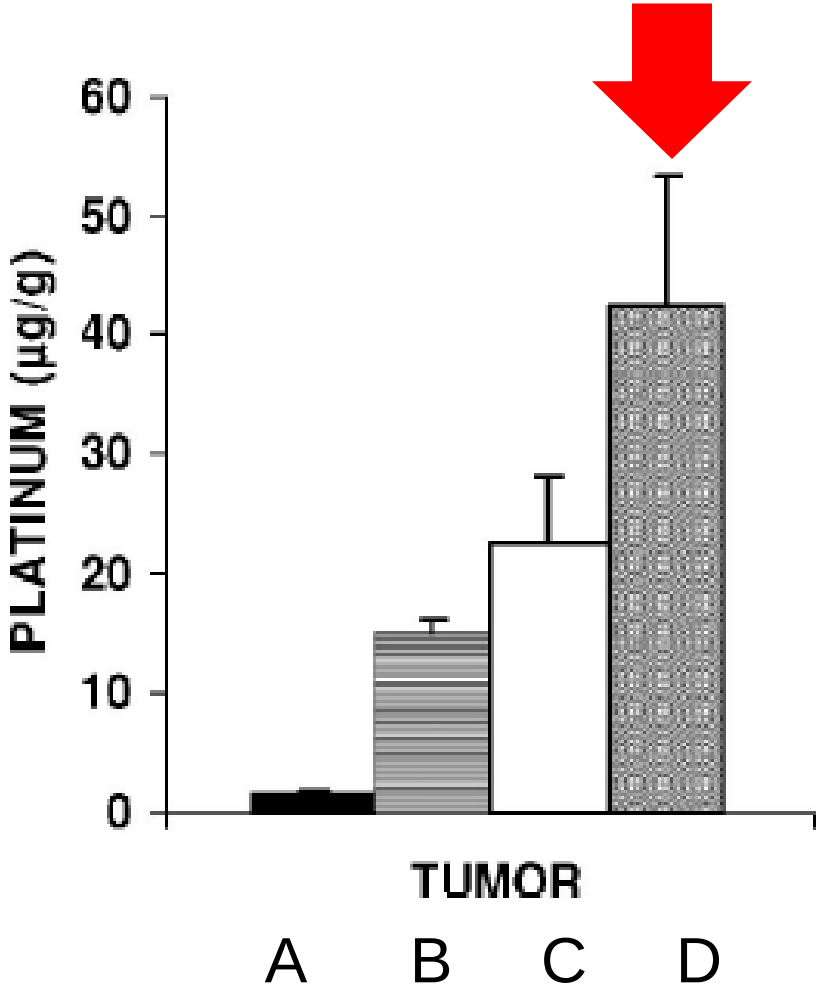
Sheep alive

doxorubicin

Pressure increases depth of tissue penetration

Minouni et al, BMC cancer 2021

Higher IP Pressure and Dose Enhance Drug Concentration



rat model

cisplatin

A: IV (3mg/kg)
B: IP (3mg/kg)
C: IP (7.5mg/kg)
D: IP (7.5mg/kg) + 22 mmHg

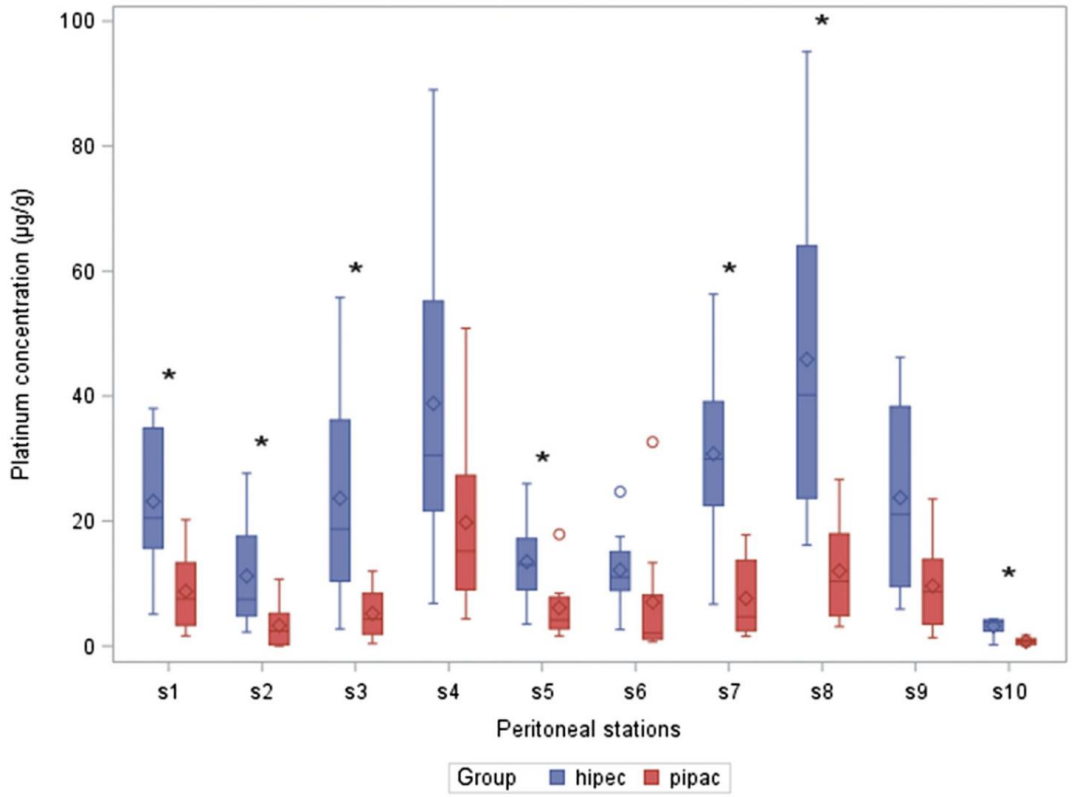
IP Liquid „HIPEC“

Esquis et al Ann Surg 2006

Tissue drug concentration: HIPEC vs. PIPAC in vivo

HIPEC: 70 mg/m^2@ 43˚ C, 60 min PIPAC: 7.5 mg/m^2 @ 37˚ C,30 min

LOCAL TISSUE CONCENTRATION



swine alive

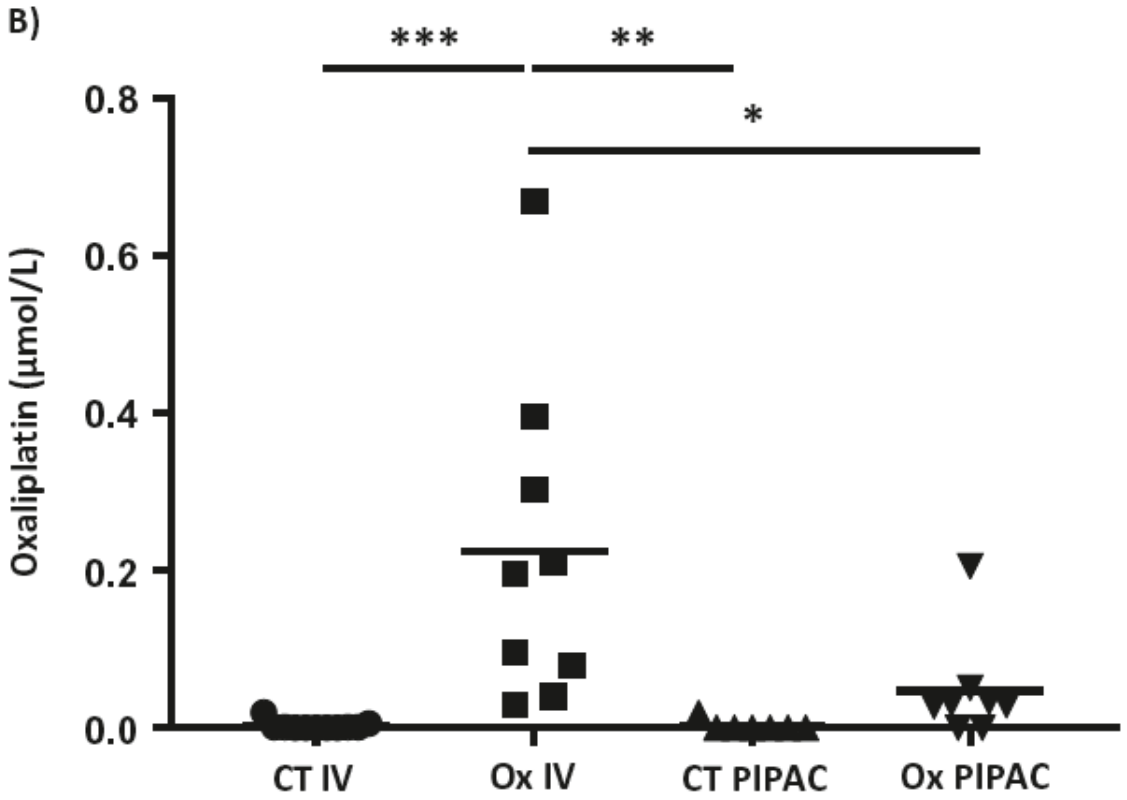
cisplatin

	Dose	Tissue concentration	Yield
HIPEC	70	18	26%
PIPAC	7,5	4,3	57%
Ratio	9,33	4,19	2,23

Higher tissue concentration after HIPEC but a better yield for PIPAC (2,2x better)

Davigo Int J Hyperthermia 2020

Systemic Drug Uptake: PIPAC vs IV



Experimental pharmacokinetic animal model (mice)

IV vs IP delivery

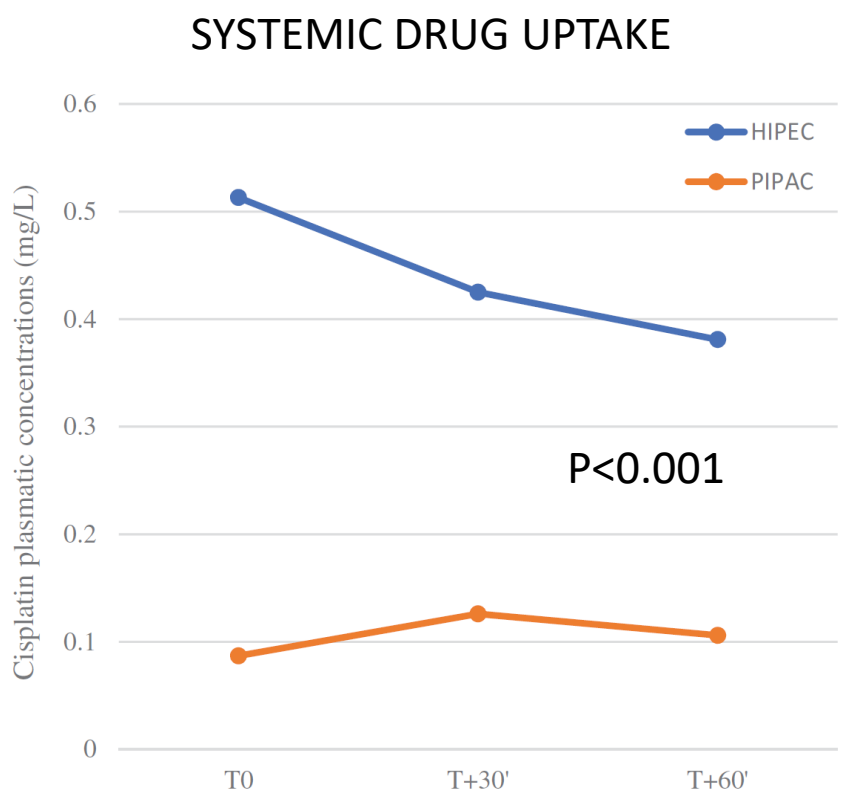
oxaliplatin

PIPAC caused minimal systemic passage of oxaliplatin. Blood concentration was higher after IV delivery (*: p=0.008)

Eveno C et al. Pleura&Peritoneum 2017

Systemic uptake: HIPEC vs. PIPAC in-vivo

HIPEC: 70 mg/m^2@ 43° C, 60 min PIPAC: 7.5 mg/m^2 @ 37° C,30 min



swine alive

cisplatin

	Dose	Blood concentration
HIPEC	70	0,425
PIPAC	7,5	0,121
Ratio	9,33	3,51

Higher systemic exposition after HIPEC vs. PIPAC

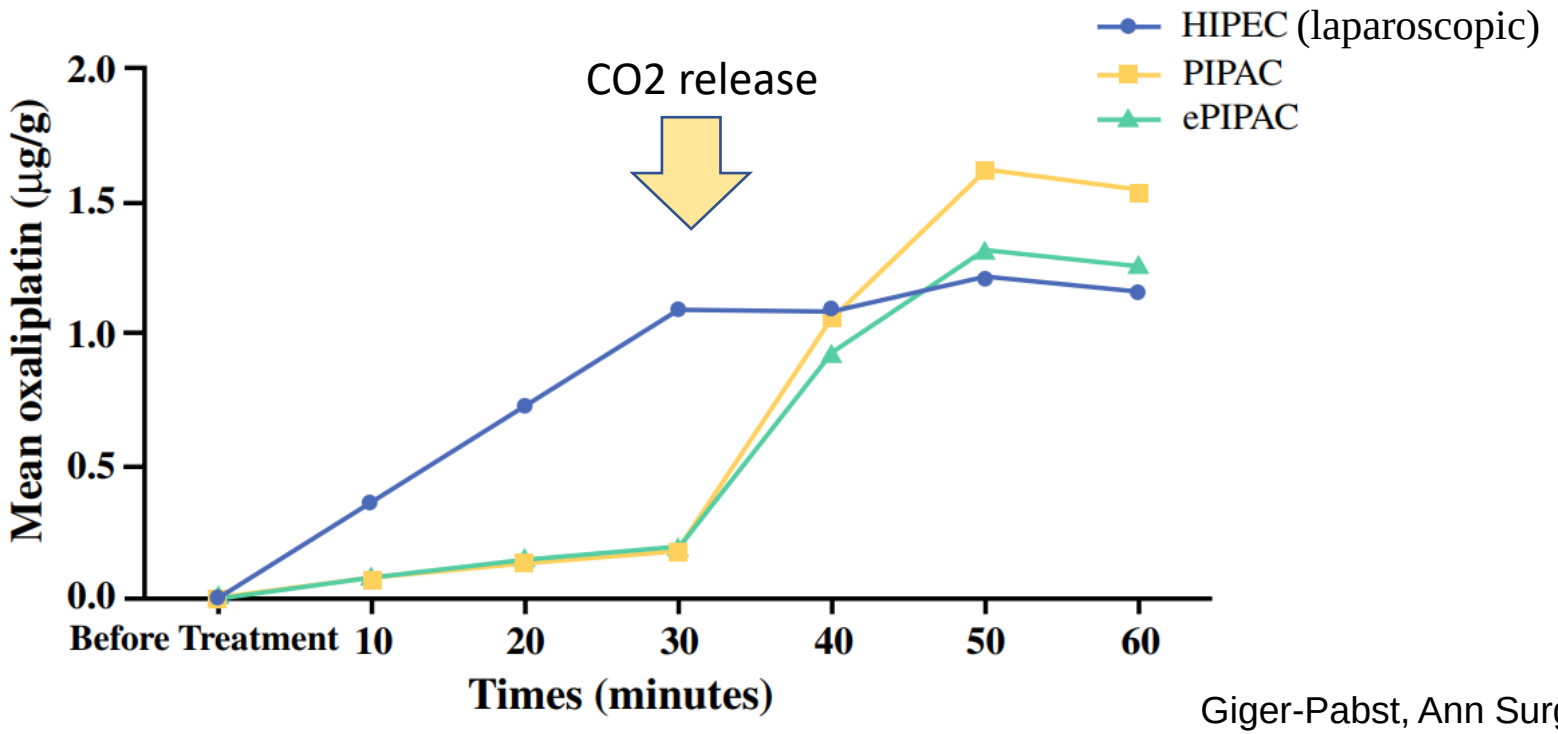
Davigo Int J Hyperthermia 2020

In-vivo comparison: L-HIPEC versus (e)PIPAC

Laparoscopic HIPEC: OX 400 mg/m^2@ 42° C, 30 min
PIPAC: OX 92 mg/m^2 @ 37° C,30 min
9 parietal biopsies, 4 visceral biopsies (small bowel)

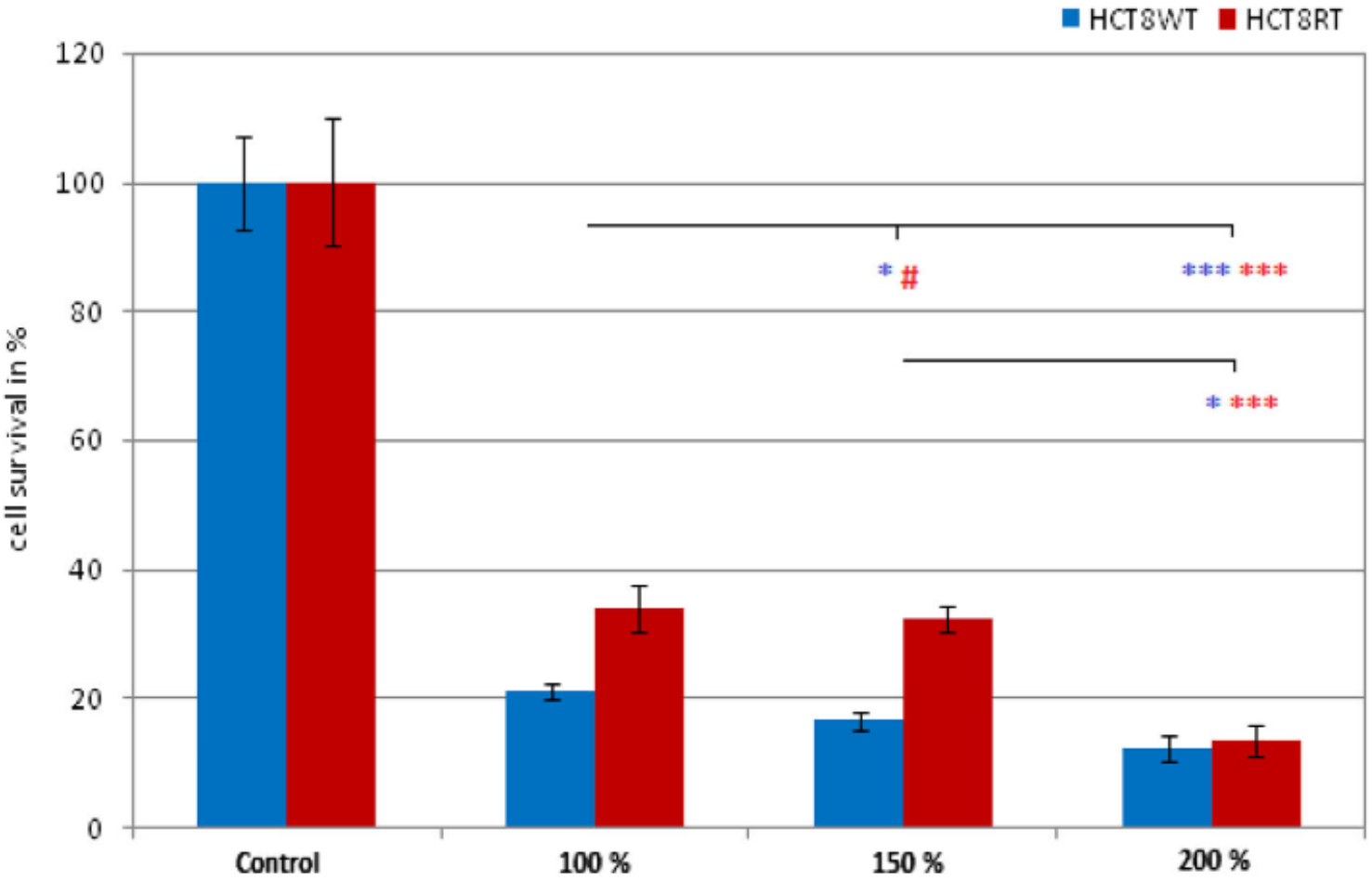
swine alive | oxaliplatin

SYSTEMIC DRUG UPTAKE



Giger-Pabst, Ann Surg Oncol 2019

Higher Dose Increases Cytotoxic Effect in vitro



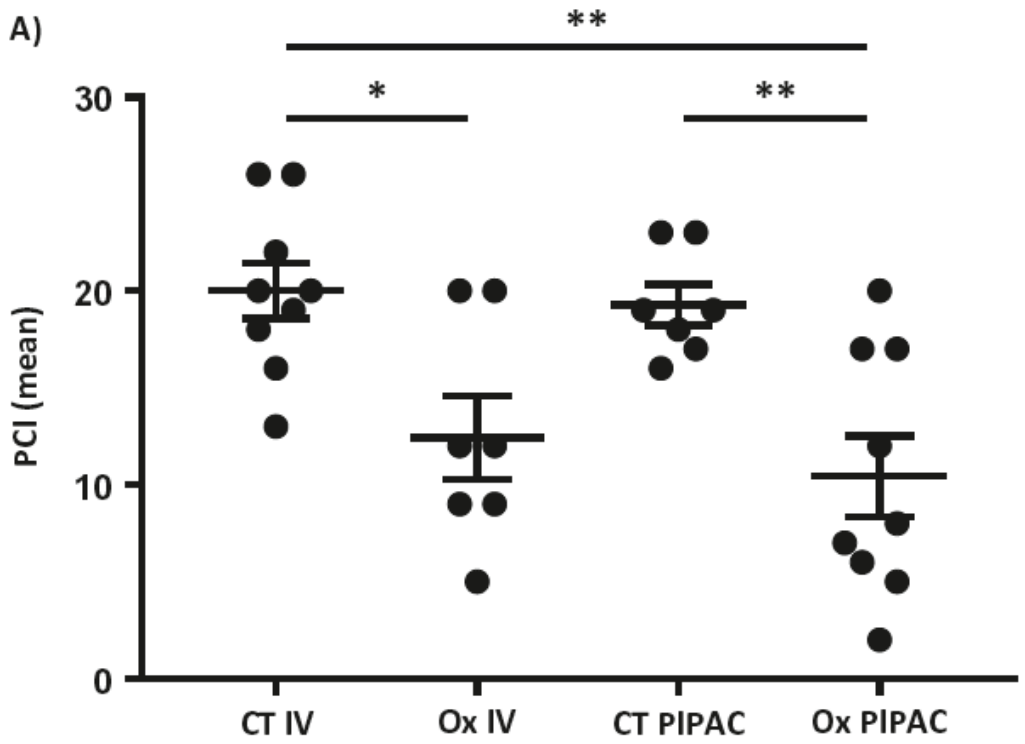
In vitro

2 cell lines

Oxaliplatin

Khosrawipour et al, WJSO 2017

Antitumoral Effect: PIPAC vs. IV



Ex-vivo xenograft model (nude mice)

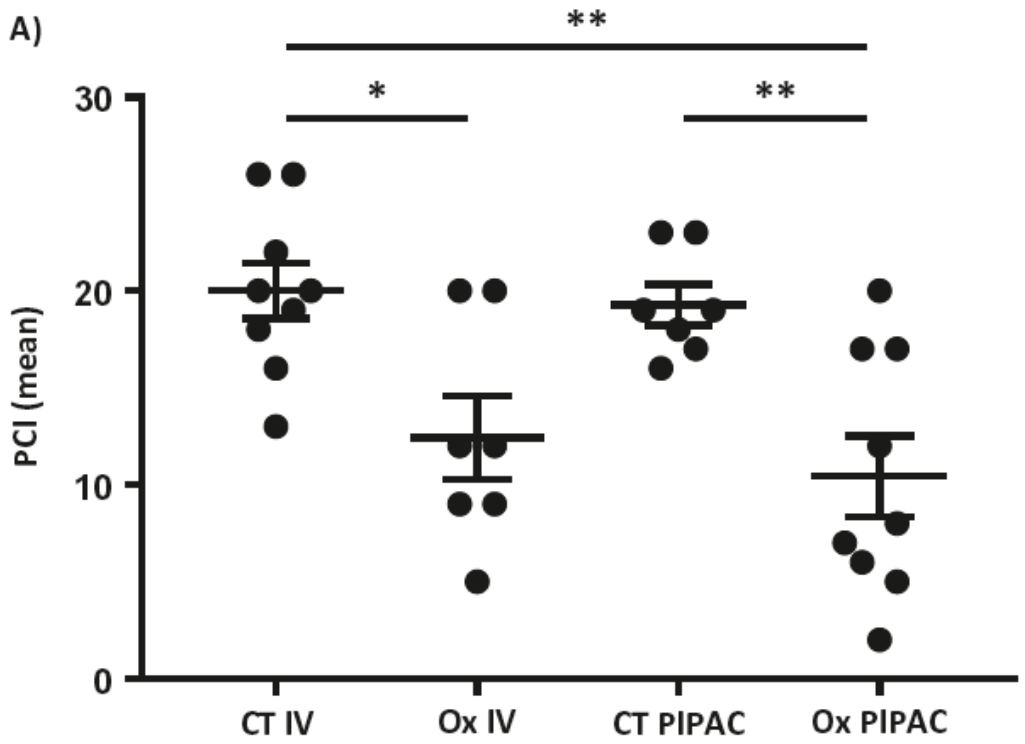
LS174 (human colon cancer cells)
CT26 (murine colon cancer cells)

Oxaliplatin

PIPAC had effect on peritoneal spread
(measured as PCI) comparable with IV - with 10% of IV dose

Eveno C et al. Pleura&Peritoneum 2017

Antitumoral Effect (PCI): PIPAC vs. IV



Ex-vivo xenograft model (nude mice)

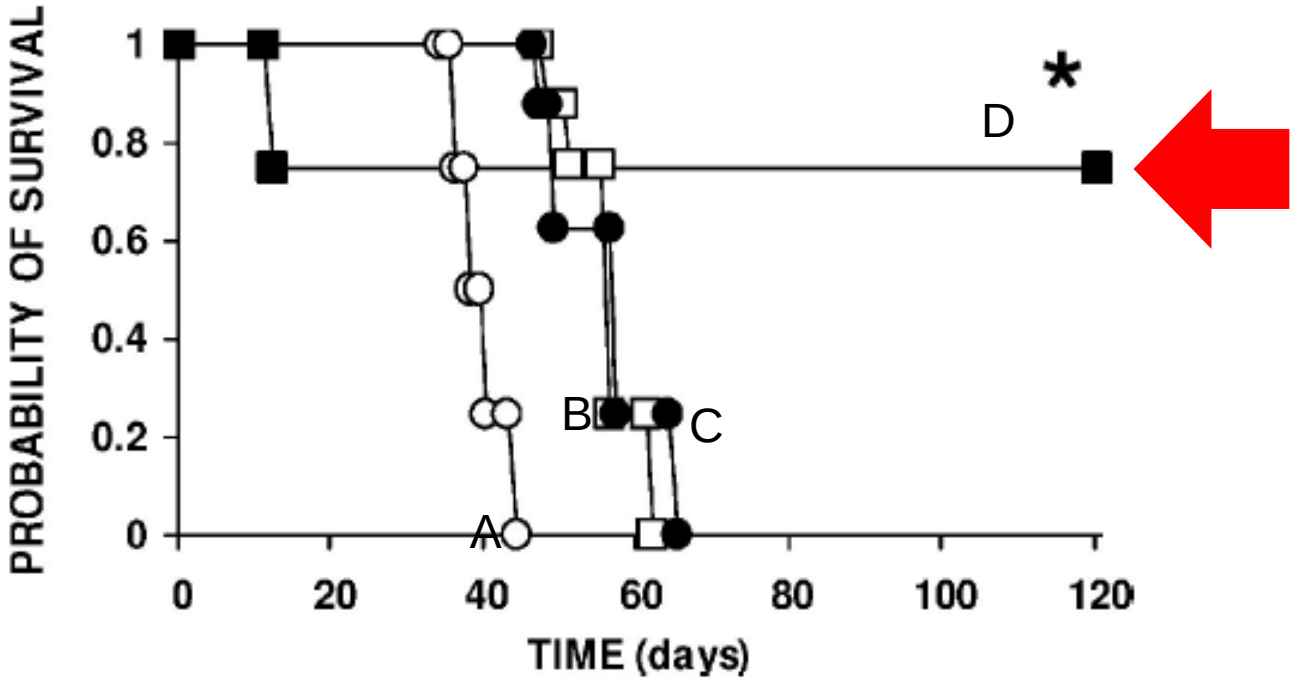
LS174 (human colon cancer cells)
CT26 (murine colon cancer cells)

Oxaliplatin

Effect of PIPAC on peritoneal spread (measured as PCI) comparable with IV - with 20% of IV dose

Eveno C et al. Pleura&Peritoneum 2017

Higher IP Pressure Enhances Antitumor Effect: HIPEC



rat model

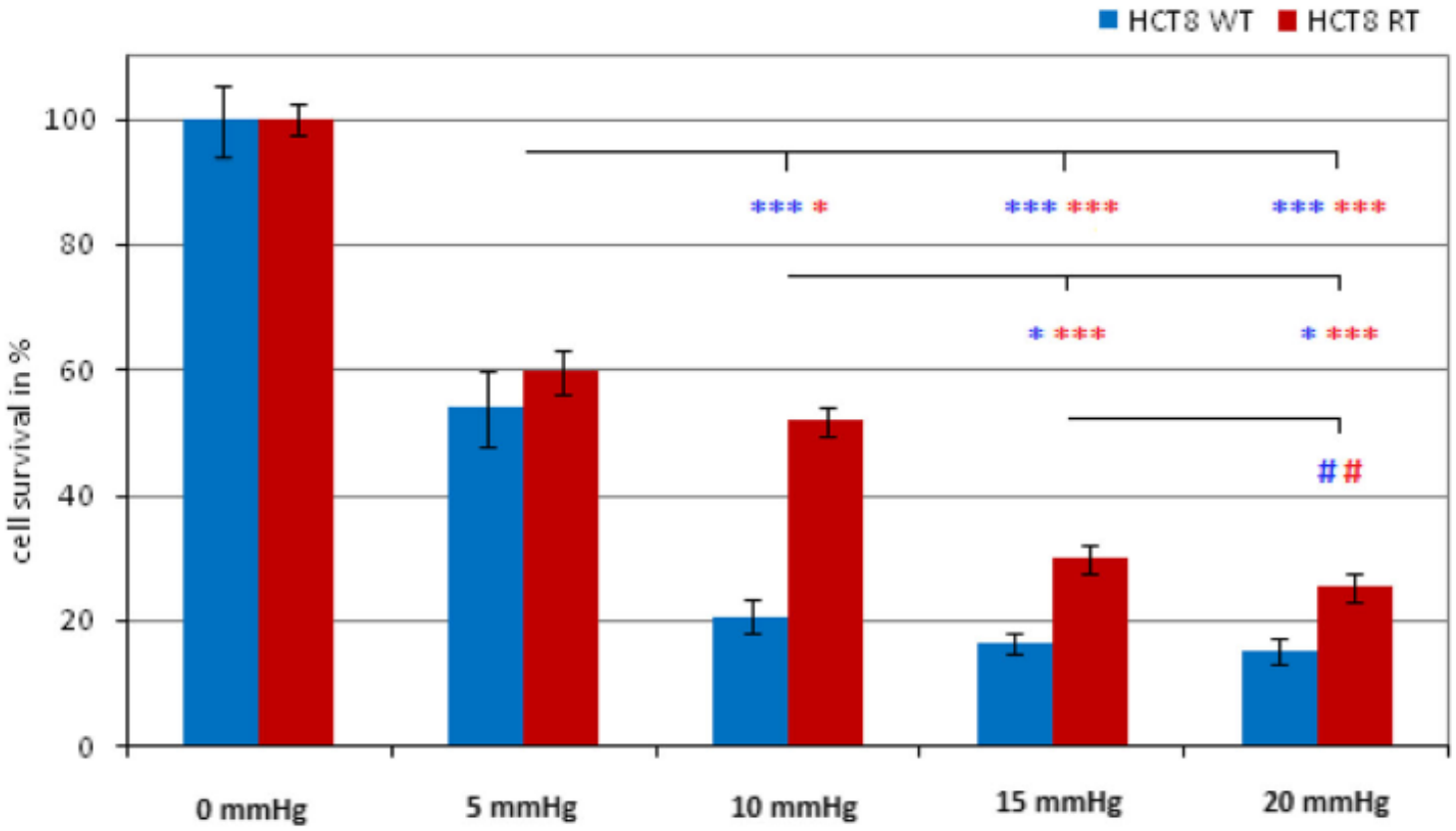
cisplatin

A: IV (3mg/kg)
B: IP (3mg/kg)
C: IP (7.5mg/kg)
D: IP (7.5mg/kg) + 22 mmHg

At same dose, animal survival after PIPAC > IV administration
Effect of increasing IP dose is marginal

Esquis et al Ann Surg 2006

Higher IP Pressure Increases Cytotoxic Effect: PIPAC



In vitro

2 cell lines

oxaliplatin

Maximal effect up to 10 mmHg, upwards only marginal effect

Khosrawipour et al, WJSO 2017

PIPAC: Promises Kept?

- ✓ Improved **distribution** within the peritoneal cavity
- ✓ Improved **penetration** of drugs into tumor / normal tissue
- ✓ Improved **concentration** of drugs into tumor / normal tissue
- ✓ Reduced **escape** into systemic circulation
- ✓ Preserved **biological activity** at reduced dose (10%)