PIPAC ESSENTIALS

PIPAC: Local and Systemic Toxicities, Risks and Dangers

Mustafa Raoof, MD, MS

Assistant Professor

Division of Surgical Oncology

Department of Surgery

Department of Cancer Genetics and Epigenetics

City of Hope

Disclosures

- I do not have any relevant disclosures.

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

The off-label or investigational use of Mitomycin C, Abraxane (Nab-Paclitaxel), Oxaliplatin, 5-FU, Cisplatin, and Doxorubicin will be discussed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Inclusion of patients in PIPAC trial should ensure racial and ethnic representation.
- Patients with peritoneal metastases are often considered end-stage with prognosis. There is implicit bias against treatment that points to nihilism.

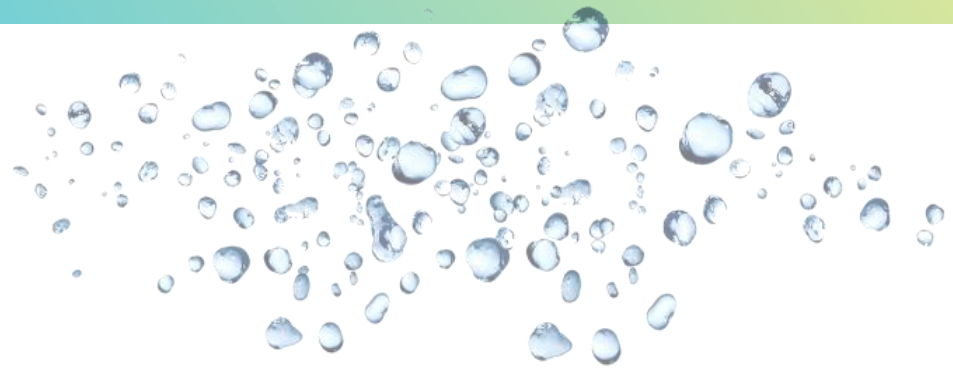
Potential Complications of PIPAC

1. Local / systemic

2. Related to surgical procedure / chemotherapy related

Time of occurrence	Potential complications
Anesthesia	allergy, aspiration
Access	bowel access lesions, bleeding
Biopsy	diaphragmatic perforation, bleeding
Exposure	allergy, subcutaneous emphysema
Postoperative period	bowel perforation, bleeding, hernia, chemical peritonitis, ileus, etc

Anaesthesia



- Allergy, including anaphylactic shock
- Aspiration of stomach contents
    - Massive ascites

- Consequence
    - Paracentesis before induction of anesthesia
    - US evaluation of the gastric emptying

Local Surgical Complications

Small injury (access injury)

- Rare complication (0.3%[1]- 0.8%[2])
- No problem when recognized and immediately sutured
- High risk of mortality if not recognized
- Trocar hernia → delayed perforation

- Consequence:
  - Use atraumatic trocars, open access technique
  - Always check visually the first trocar to exclude a bowel lesion during the „blind“ abdominal access
  - Bowel perforation → consider to postpone PIPAC

1 Giger-Pabst U et al JGIS 2018
2 International PIPAC registry 09/2018

Local Surgical Complications

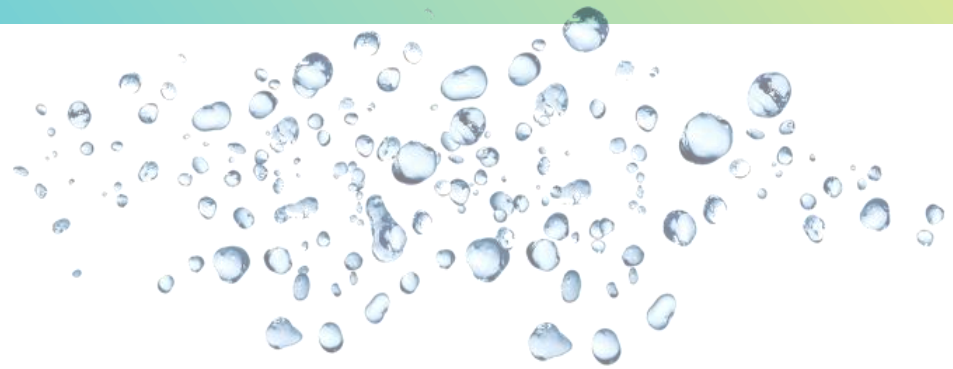
Bleeding

- Rare complication (Incidence 1-2%[1-3])

- Consequence:
  - Can be prevented by proper indication and surgical technique
  - Caution in indicating PIPAC in anticoagulated patients
  - Avoid injury of a. epigastric vessels by choosing distant access point/ transillumination of the abdominal wall
  - Hemostasis at biopsy sites if necessary

1 Grass F et al, Br J Surg, 2017
2 Tempfer CB et al, Gynecol Oncol 2015
3 Kurtz et al, Gastroenterol Res Pract 2018

Local Surgical Complications



Diaphragmatic perforation:

- Rare event
- Iatrogenic lesion (by intraoperative biopsy)
- Remains usually undiagnosed
- Results in intrapleural distribution of an aerosol
- Possible explanation for intraoperative ventilation problems
- Postoperative „Pneumothorax“ on chest X-ray

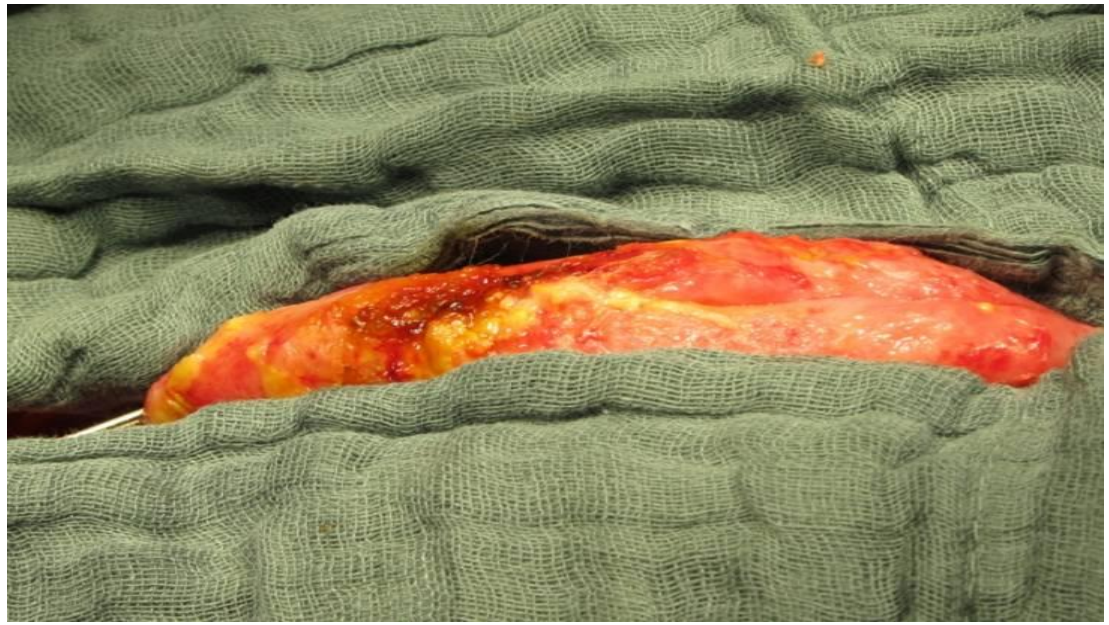
- Consequence:
  - avoid biopsy cranial to the 12th rib, if possible
  - suture and pleural drainage

Khomyakov V. et al, Pleura Peritoneum 2016

Local Surgical & Chemical Complications

Simultaneous CRS & PIPAC

- Current data does NOT support the use of simultaneous CRS + PIPAC
- Major risk of postoperative complications[1]
  - Anastomotic leakage[2]
- Difficult management if occurs
- High mortality rate

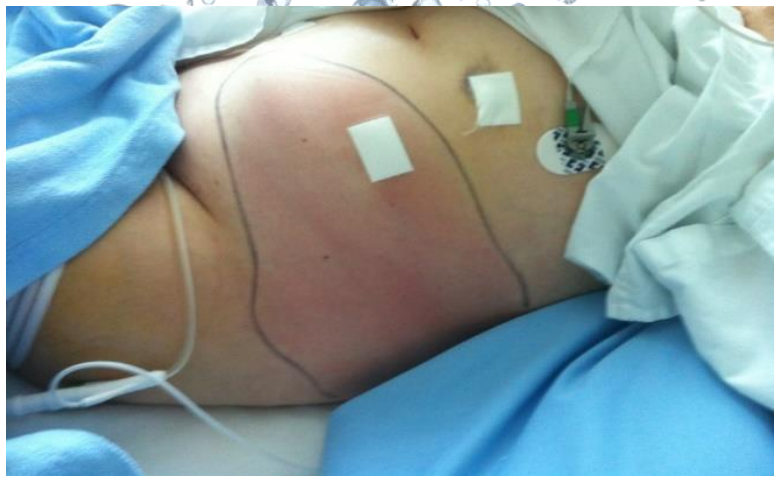


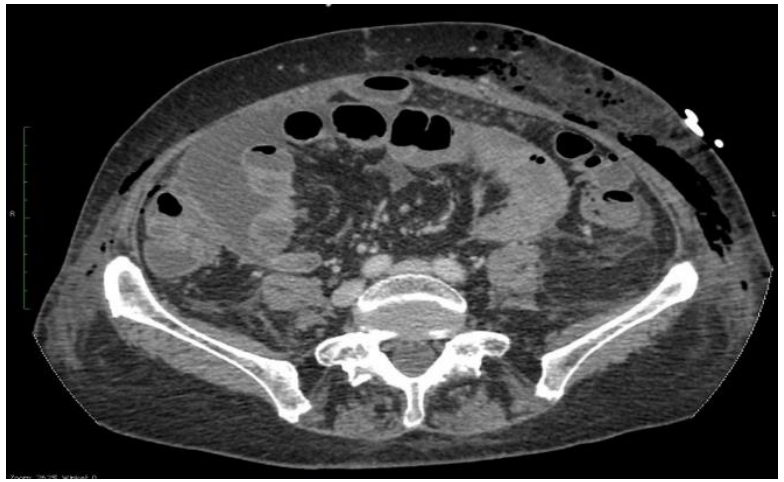
[1] Tempfer et al, Gynecol Oncol, 2014
[2] Tavernier et al., Surg End, 2019

Local Surgical & Chemical Complications

Subcutaneous toxic emphysema

- Relatively rare and usually benign evolution
- More frequent after open abdominal access
- Appears ~2 weeks postoperative and vanishes after 1 week
- Possible causes:
  - Lesion of the fascia (Biopsy/local peritonecomy)
  - Open access and leakage
  - Skin has been closed but not the fascia
  - Malignant, toxic ascites
- One case with necrosis of the abdominal wall reported.





Local Chemical Complications

Abdominal pain

- Abdominal pain CTCAE > 2 is unusual after PIPAC C/D
- Abdominal pain CTCAE 3 has been reported after PIPAC with Oxaliplatin
  - Incidence 9-16%[1,2,3]

[1]Tabchouri et al, ASO, 2021
[2] Sgarbura O et al, EJSO 2019
[3] Demtröder C et al, Colorectal Dis 2016

Local Chemical Complications

Prolonged postoperative ileus

- Incidence 3.8%[1] - 8.4%[2]
- Local toxicity of PIPAC on small bowel can induce temporary bowel paralysis

Consequence:

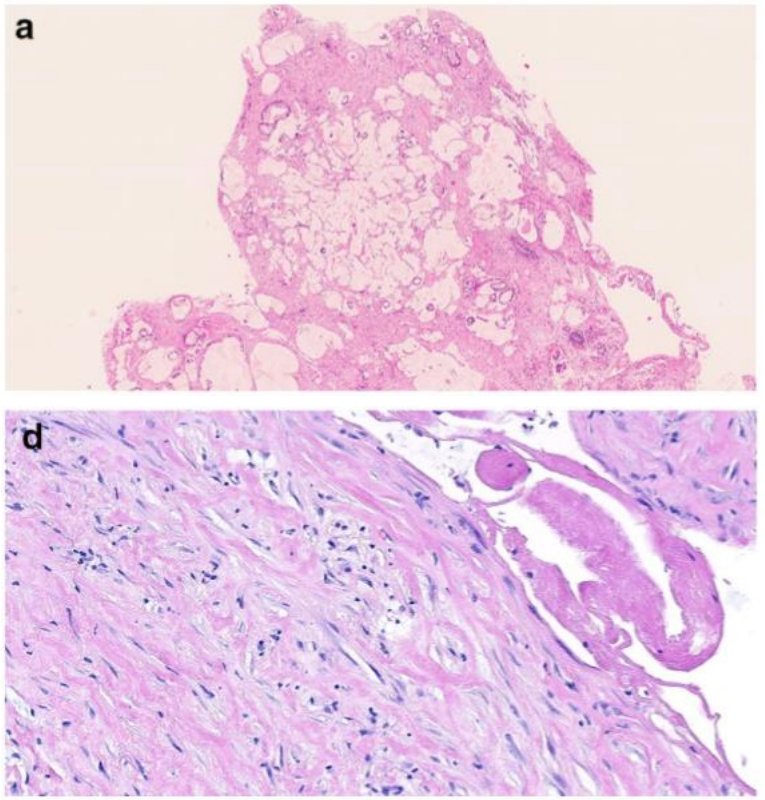
- Expected survival in PM patients with small bowel obstruction and total parenteral nutrition is estimated in weeks
- Radiological examination before procedure if symptoms of ileus are observed
- Careful patient selection reduces incidence of this complication[3]

[1] Alyami M et al, EJSO, 2017
[2] International PIPAC registry 9/2018
[3] Giger-Pabst et al J Gastroint Surg 2018

Local Chemical Complications

Severe peritoneal sclerosis (SPS)

- SPS reported in 2/24 patients after repeated PIPAC with oxaliplatin 92 mg/m^2 body surface[1]
- SPS not reported so far after PIPAC C/D
- Tumor itself (EMT) & systemic chemotherapy also causes peritoneal fibrosis
- Toxicity if IP chemotherapy is dose – dependent[2]



1 Graversen M, Clin Exp Metastasis, 2018
2 Markman M, Lancet Oncol 2003

Local Chemical Complications

Postoperative bowel perforation after PIPAC

- 3 large bowel perforations in patients with colonic stent (PIPAC OX)
- 1 small bowel perforation in a patient treated with PIPAC OX and bevacizumab[1].
- Lyon experience: 26 pts BEVA + PIPAC – 2 obstructions, 1 perforation [3]
- German experience: 50 pts Ramucirumab +PIPAC – 6% severe complications[4]
- Consequence:
  - Caution with colonic stent
  - Caution with combined PIPAC + anti-VEGF therapies

1 International PIPAC registry 9.2018
2 KCE report 285Cs , BEVACIZUMAB IN THE TREATMENT OF OVARIAN CANCER, Belgian Health Knowledge Center
3 Siebert M et al. EJSO 2019
4 Feldbrügge L et al, Front Oncol 2021

Systemic Chemical Toxicities

Intraoperative allergic reactions reported after PIPAC

- platin-based compounds[1,2] and other agents[2]: metamizol, latex, etc.
- Can be severe (anaphylactic shock)[3]

Incidence

- PIPAC OX: 2,8%
- PIPAC C/D: 0,6%
- OX intravenous: hypersensitivity reaction in 13% patients[4]

Consequence: no PIPAC with CIS or OX in patients with platin hypersensitivity unless previously tested[3]

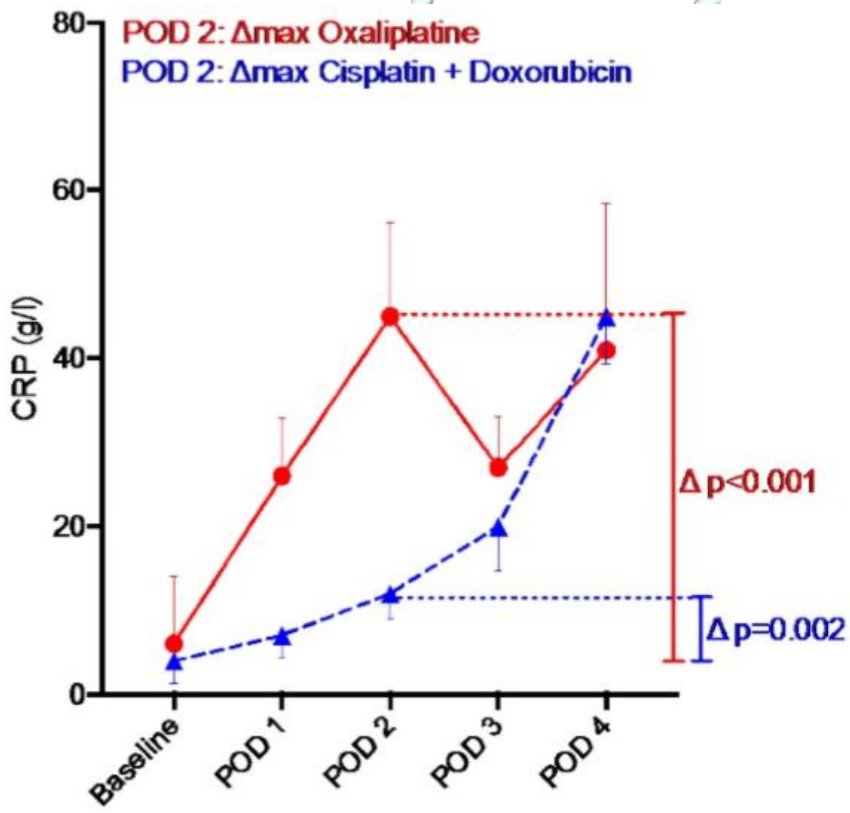
[1] Siebert M et al, Cancer Chem Pharma, 2018
[2] International PIPAC registry
[3] Gauthier A et al, Allergy, 2021
[4] Brandi G et al, Br J Cancer 2003

Systemic Surgical & Chemical Toxicities

Postoperative inflammatory response

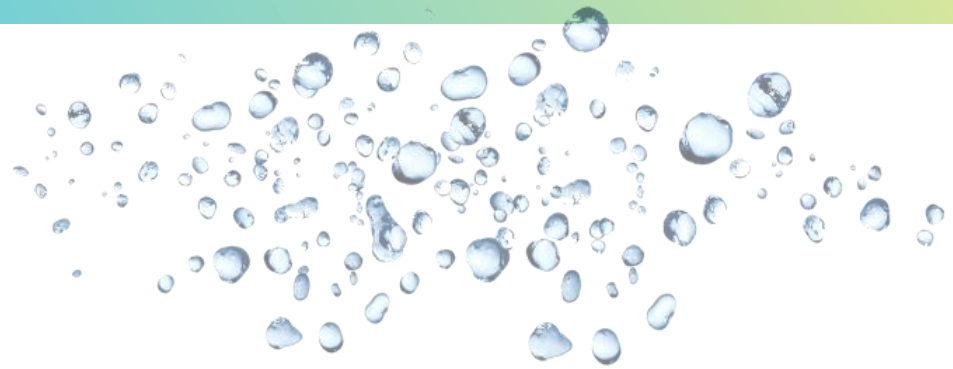
- CRP and procalcitonin (PCT) increase on POD 2
- Modest and transitory increase
- No cumulative inflammation after repeated PIPAC

Consequence: it is difficult to diagnose a postoperative peritonitis after PIPAC. In case of postoperative problems, indication for emergency CT-scan must be very liberal[2].



[1] Teixeira Farinha et al, J Cancer, 2018
2 Giger-Pabst U et al, J Gastroint Surg 2018

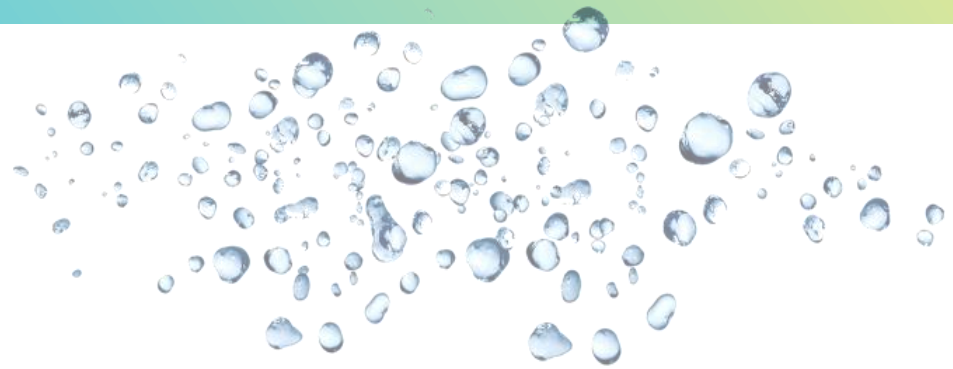
PIPAC C/D: Dose-Escalation (Phase I)



- No acute liver or renal toxicity[1,2];
- No cumulative toxicity after repeated PIPAC[1]

[1]Tempfer et al, Gynec Oncol 2018
[2]Robella et al, Cancers, 2021

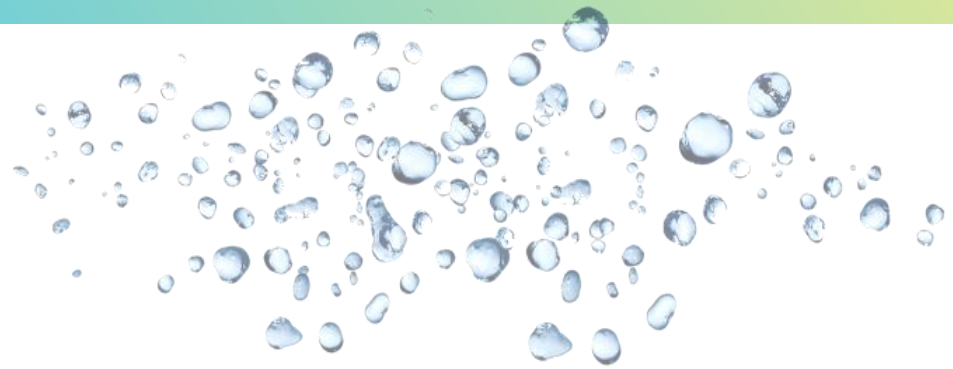
PIPAC OX



- Acute pancreatitis – phase I study – exceptional outcome not yet confirmed[1]

[1]Kim G et al, Clin Cancer Res, 2020

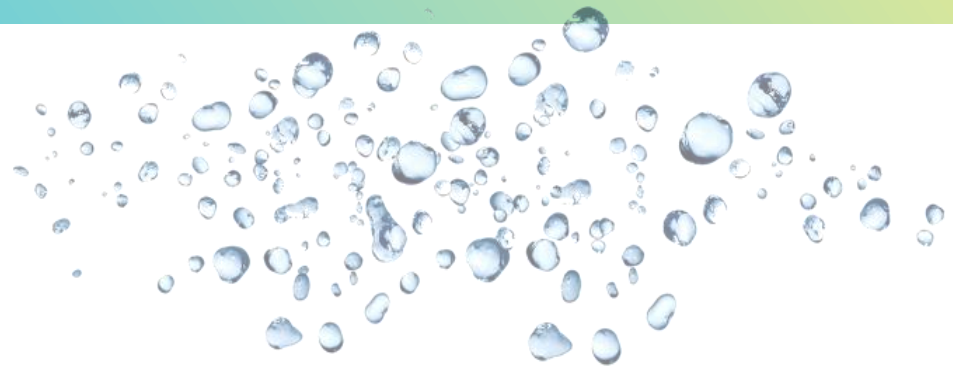
Systemic Toxicities: PIPAC vs. IV



- Toxicity of PIPAC C/D & PIPAC OX is modest compared to systemic therapy
- Example: toxicities of intravenous Oxaliplatin[1]:
  - Neuropathy
    - During treatment: 50% (any grade)
    - After 18 months: persistant in 0.7%
  - Transient thrombocytemia 40% (any grade)
  - Hypersensitivity of any grade 12-19%

[1]Hoff PM et al, Clin Colorectal Cancer, 2012

Mortality



- No procedure-related mortality was reported in 5 ICH-GCP phase I and phase II trials (207 patients)
- Anecdotical cases of hospital mortality after PIPAC were reported in some of the published series (< 1% in cumulative series)[1,2,3]
- Mortality may be (much ?) higher if patient selection criteria are not respected

1 Grass F et al Br J Surg 2017
2 Tempfer CB et al Arch Gynec Oncol 2018
3 Giger-Pabst U et al, J Gastroint Surg 2018

Bonus Slide: ePIPAC

TABLE 2 ePIPAC procedures

	ePIPAC < 3		ePIPAC ≥ 3		Total	
	n	% or min–max	*n*	% or min–max	*n*	% or min–max
No. of ePIPACs	110	100	37	100	147	100
No. ePIPACs alone	26	23.6	9	24.3	35	23.8
No. ePIPACs associated with systemic chemotherapy	84	76.4	28	75.7	112	76.2
Mean delay between ePIPAC and systemic chemotherapy (weeks)	3.9	(0–6)	4	(0–6)	3.92	(0–6)
Type of IP chemotherapy						
Oxaliplatin (90 mg/m^2)	2	1.8	0	0	2	1.4
Oxaliplatin (92 mg/m^2)	49	44.5	10	27.0	59	40.1
Cisplatin (7.5 mg/m^2)–doxorubicin (1.5 mg/m^2)	25	22.7	13	35.1	38	25.9
Cisplatin (10.5 mg/m^2)–doxorubicin (2.1 mg/m^2)	34	30.9	14	37.8	48	32.7
Duration of chemotherapy nebulization (min)						
5	56	50.9	12	32.4	68	46.3
6	31	28.2	12	32.4	43	29.3
8	23	20.9	13	35.1	36	24.5
Activation of electrostatic monitor						
Before chemotherapy nebulization	20	18.2	9	24.3	29	19.7
After chemotherapy nebulization	90	81.8	28	75.7	118	80.3
Delay of electrostatic therapy						
Minutes reported	1	0.9	0	0	1	0.7
6	64	58.2	19	51.4	83	56.5
10	4	3.6	1	2.7	5	3.4
12	6	5.5	3	8.1	9	6.1
15	14	12.7	10	27.0	24	16.3
20	1	0.9	0	0	1	0.7
30	20	18.2	4	10.8	24	16.3

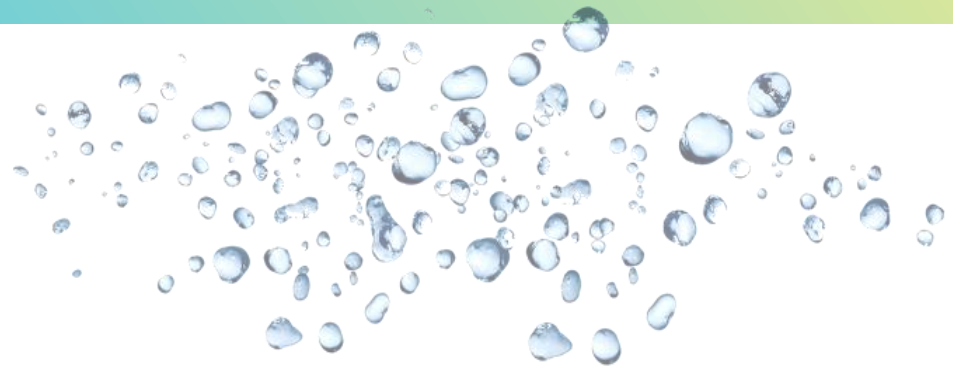
ePIPAC, electrostatic precipitation pressurized intraperitoneal aerosol chemotherapy

	ePIPAC < 3		ePIPAC ≥ 3		Total	
	n	%	*n*	%	*n*	%
No. of ePIPACs	110	100	37	100	147	100
Intraoperative complications	0	0	0	0	0	0
ePIPAC incidents	2	1.8	1	2.7	3	2.0
Postoperative complications						
Toxicities (CTCAE grade)	16	14.5	0	0	16	10.8
Nausea (2)	2	1.8	0	0	2	1.4
Acute urinary retention (2)	2	1.8	0	0	2	1.4
Asthenia (2)	2	1.8	0	0	2	1.4
Pain (3)	5	4.5	0	0	5	3.4
Postoperative occlusion (3)	2	1.8	0	0	2	1.4
Ascites (3)	3	2.7	0	0	3	2
Anaphylactic shock (4)	0	0	1	2.7	1	0.7
Postoperative complications (Clavien grade)	4	3.6	0	0	4	2.7
Subcutaneous hematoma (2)	2	1.8	0	0	2	1.4
Cholecystisis (3)	1	0.9	0	0	1	0.7
Gas embolism (4)	1	0.9	0	0	1	0.7

ePIPAC, electrostatic precipitation pressurized intraperitoneal aerosol chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events

Taibi et al, ASO 2021

Take Home



- PIPAC is feasible, **safe** and associated with few systemic toxicities
- The majority of potential adverse events are related to **surgical procedure** (laparoscopy)
- Postoperative complications can be reduced to a minimum by proper **patient selection**
- With correct training, adherence to standard operating procedures (SOPs) and to established safety protocols, there is **no learning curve** for PIPAC