University of Zurich[UZH]
UniversityHospital Zurich
Visceral- and Transplantation Surgery

PERITONEAL CANCER NETWORK ZURICH

34. Zwickauer Onkologie-Symposium
18. März 2017

SÜDWESTSÄCHSISCHES TUMORZENTRUM ZWICKAU e.V.

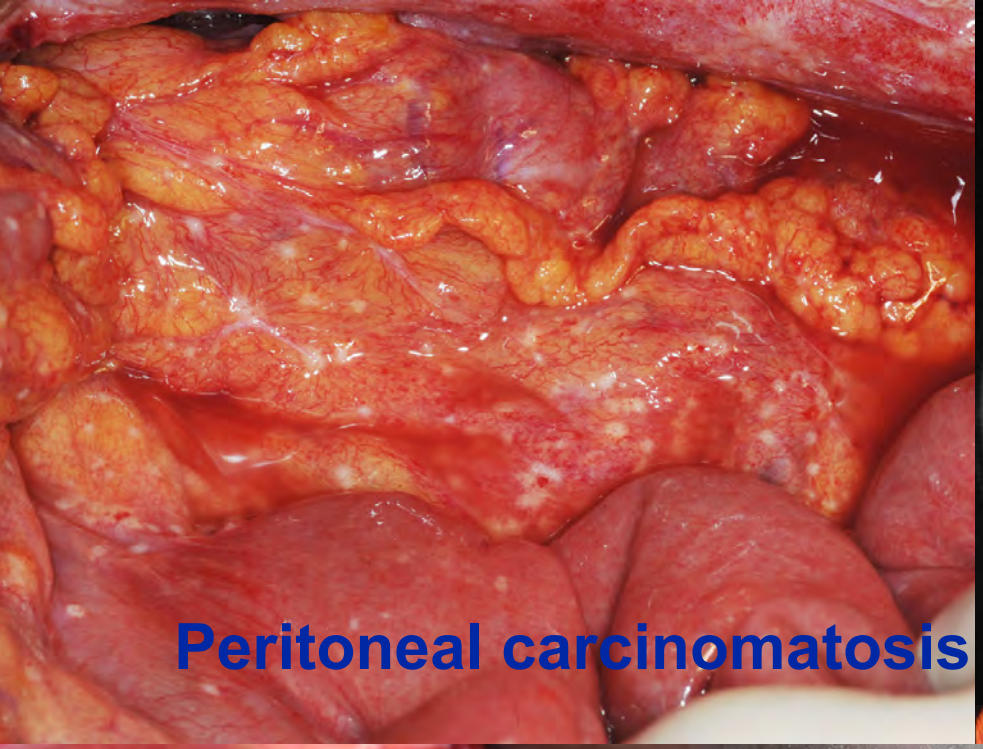
PIPAC

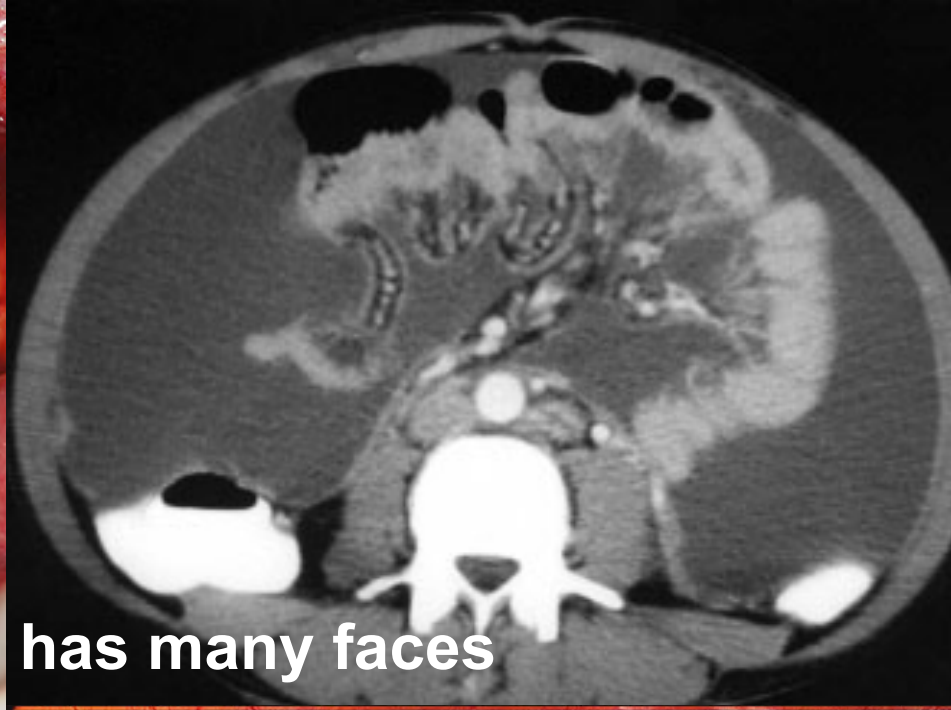
pressurized intraperitoneal aerosol chemotherapy

Kuno Lehmann

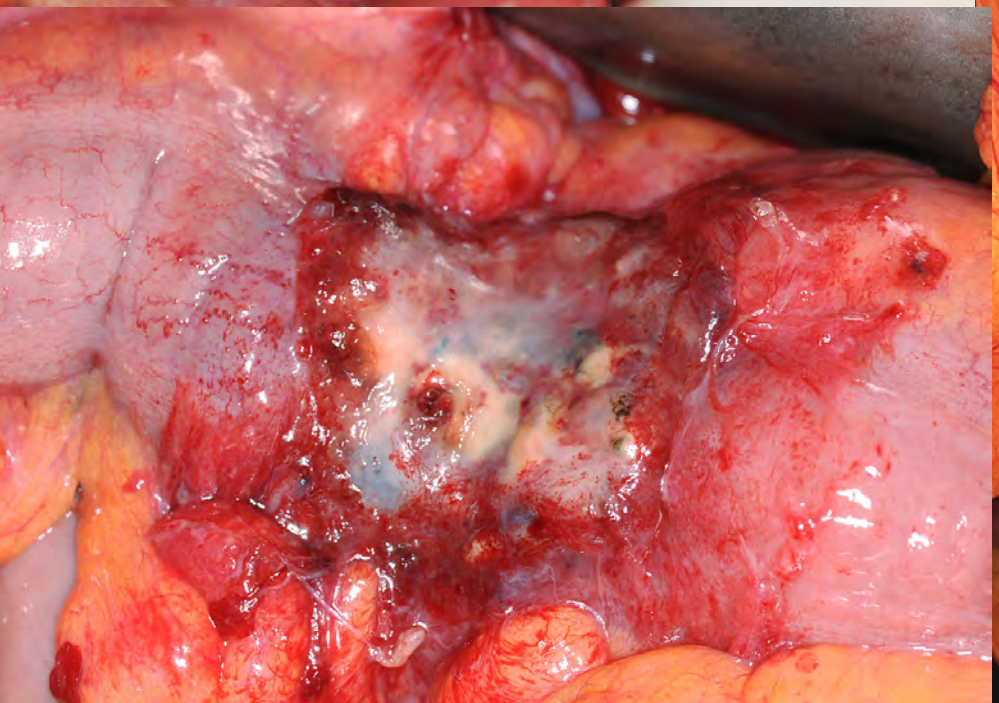
Agenda

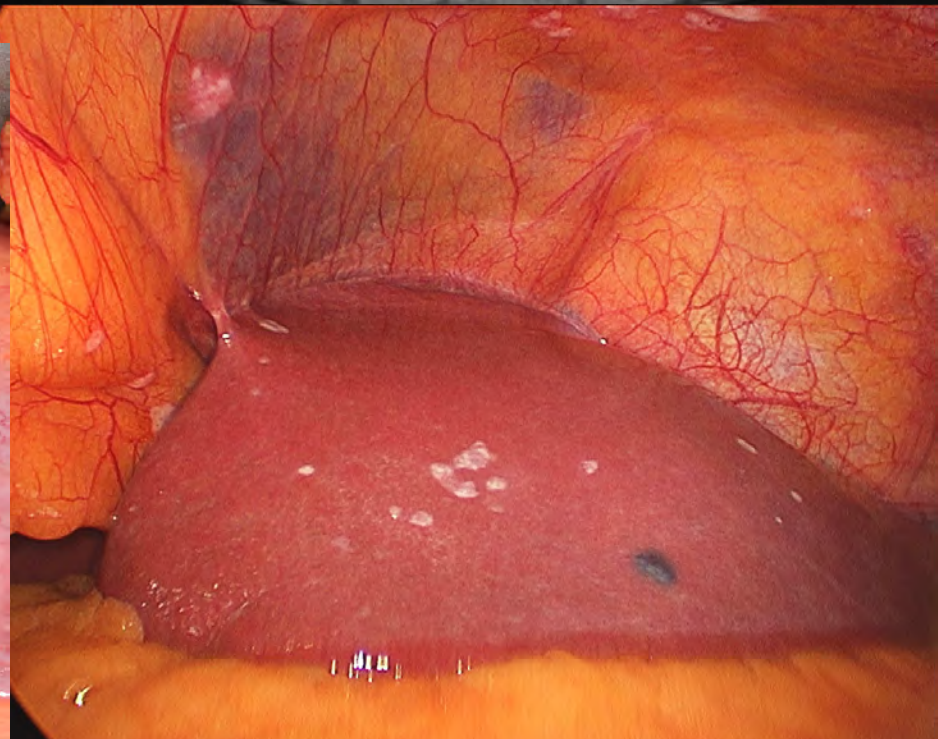
1. What is PIPAC
2. Why does a concept like PIPAC make sense
3. What is the evidence about PIPAC



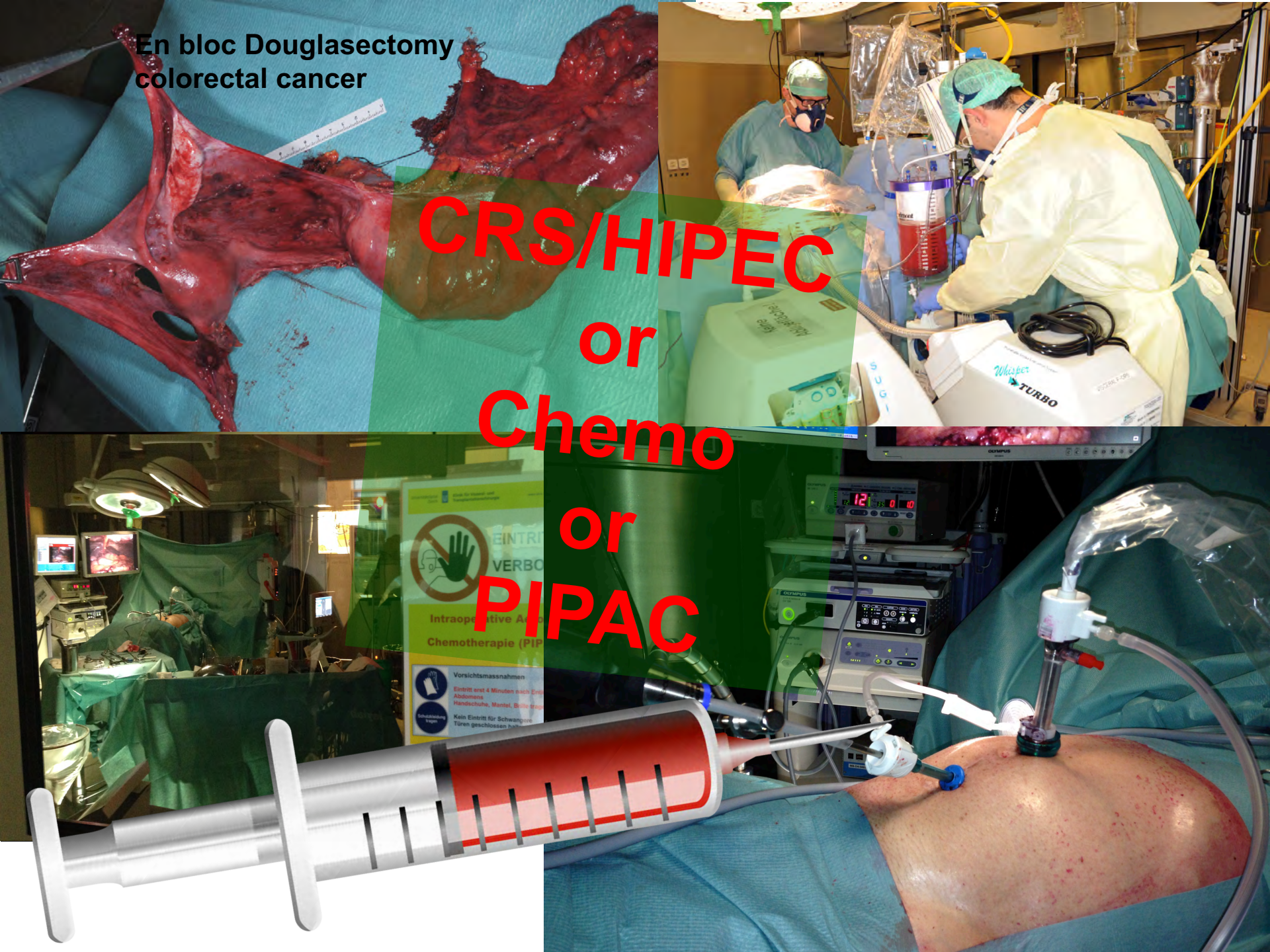


Peritoneal carcinomatosis has many faces






ONE-SIZE FITS ALL
STORE
SALE


En bloc Douglasectomy
colorectal cancer
CRS/HIPEC
or
Chemo
or
PIPAC

What is PIPAC
pressurized intraperitoneal aerosol chemotherapy

Palliative

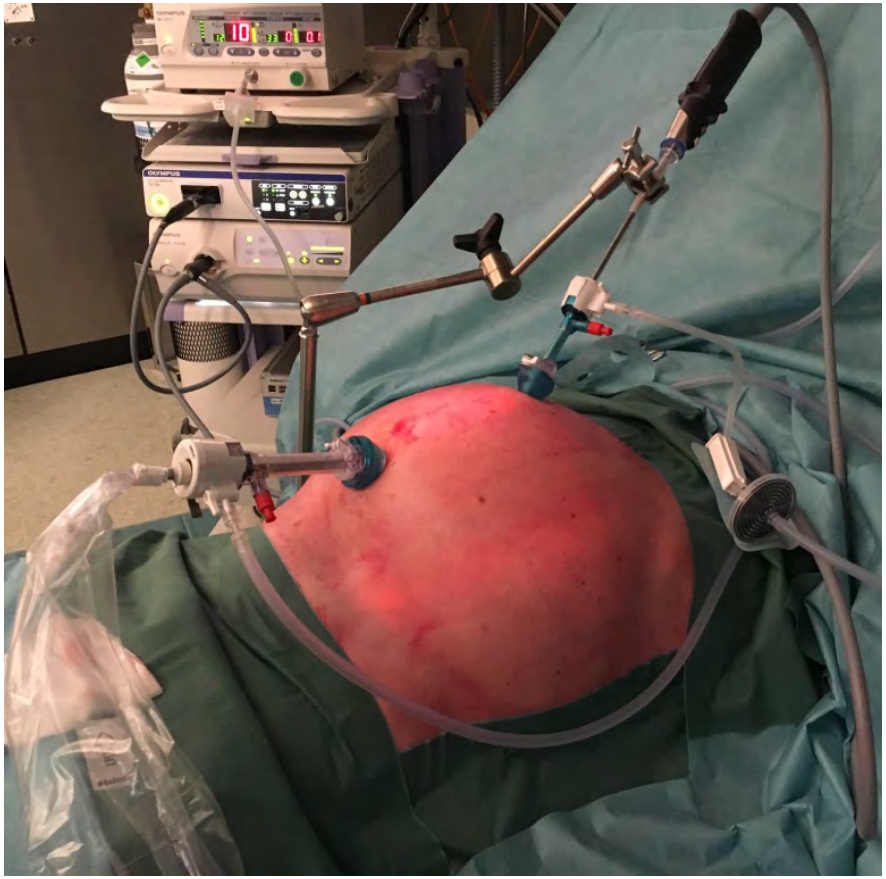
Local treatment of advanced peritoneal carcinomatosis

Laparoscopy

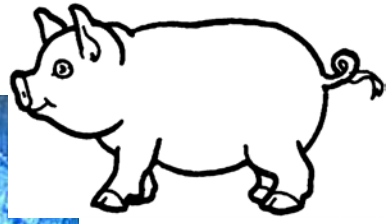
Repetition possible

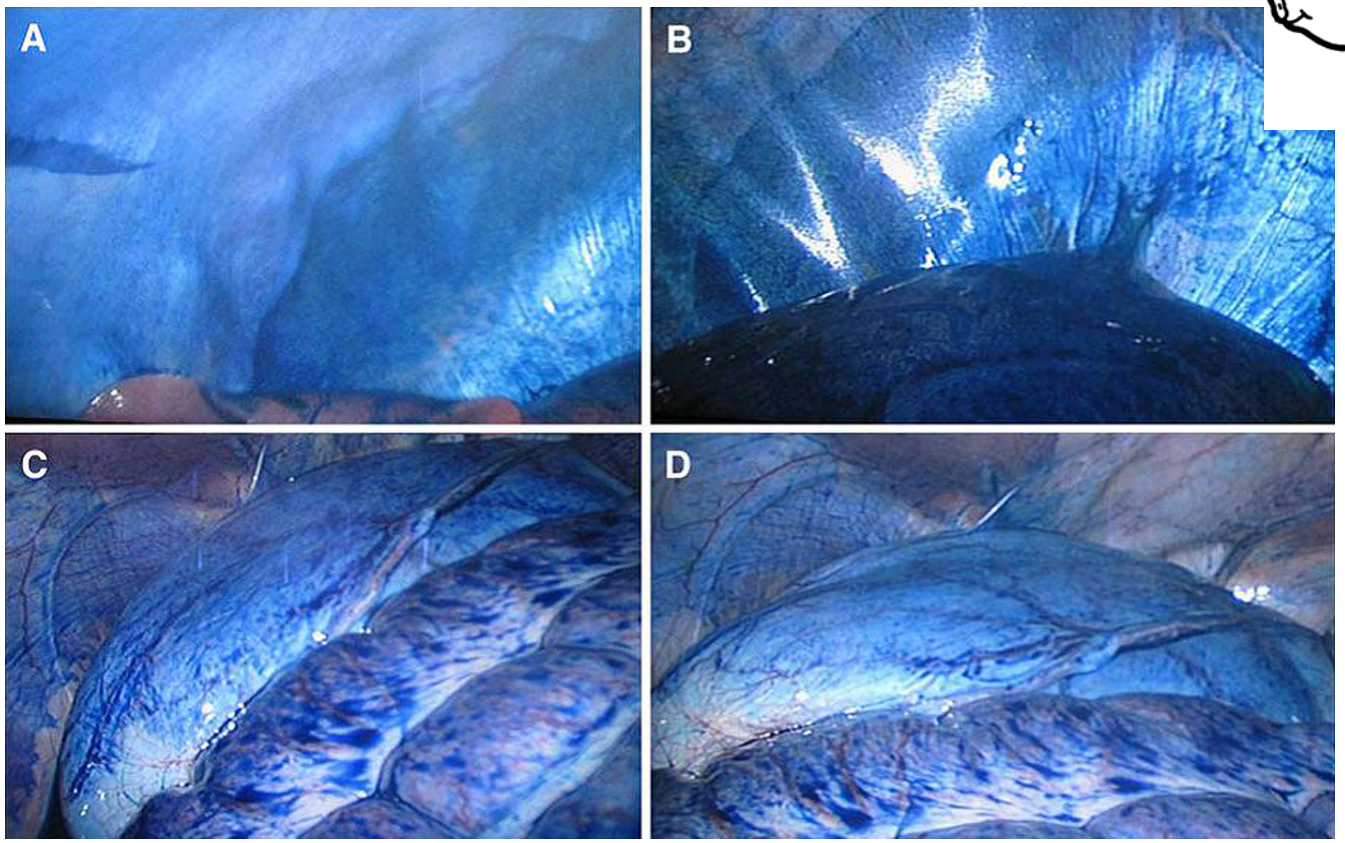
No cure

No resection



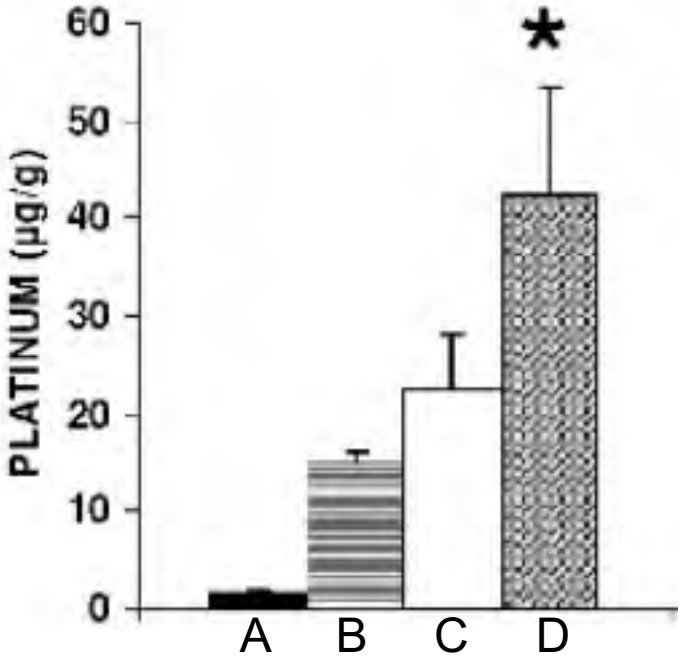
PIPAC principles: the aerosol





Marc Reymond, zur Verfügung gestellt

PIPAC principles: the pressure

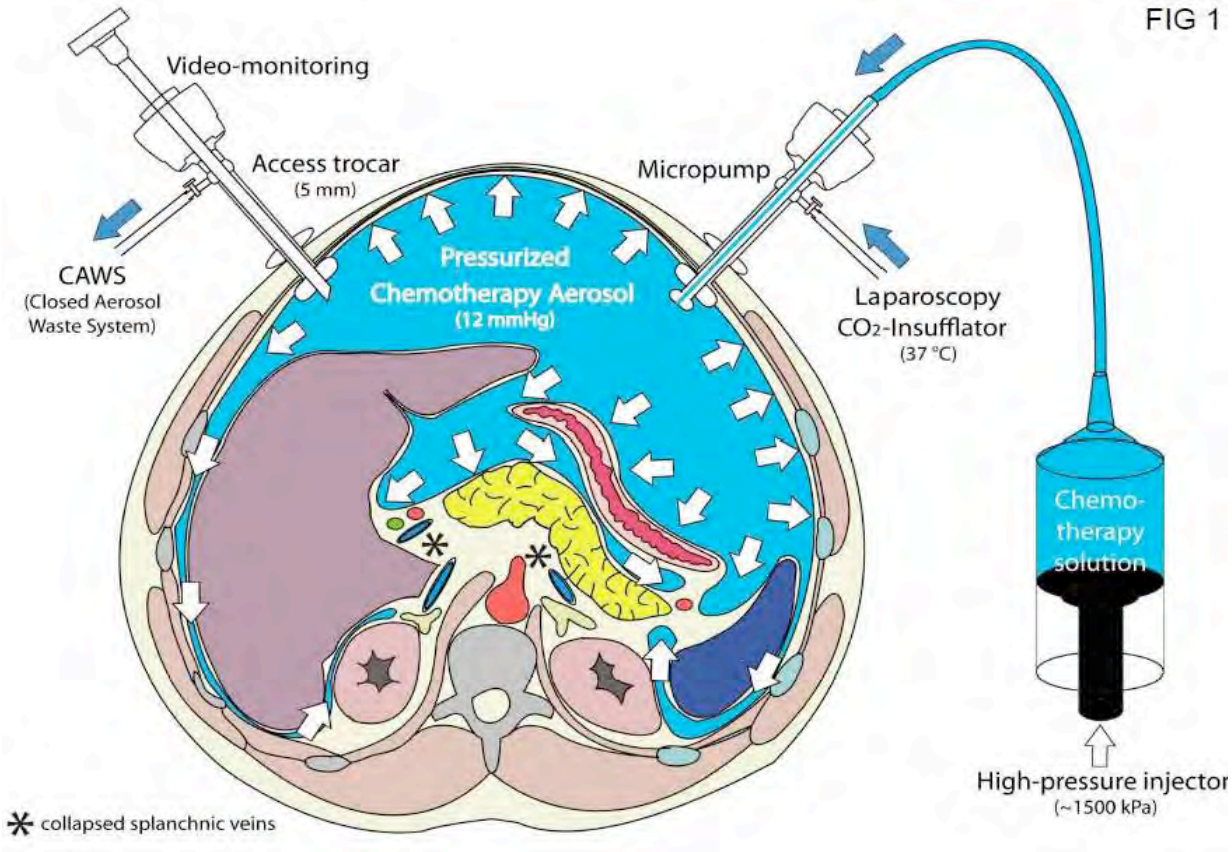


A: iv administration
B: conventional ip = same total dose as IAP
C: conventional ip = same concentration as IAP
D: pressurized ip (IAP: 22 mmHg)

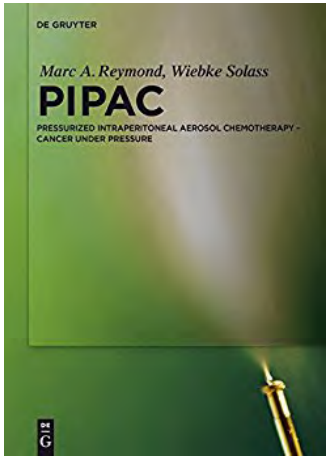
Esquis P et al, Ann Surg 2006

PIPAC (Pressurized IntraPeritoneal Aerosol Chemotherapy)

→ **10% of the systemic dose**



Marc Reymond



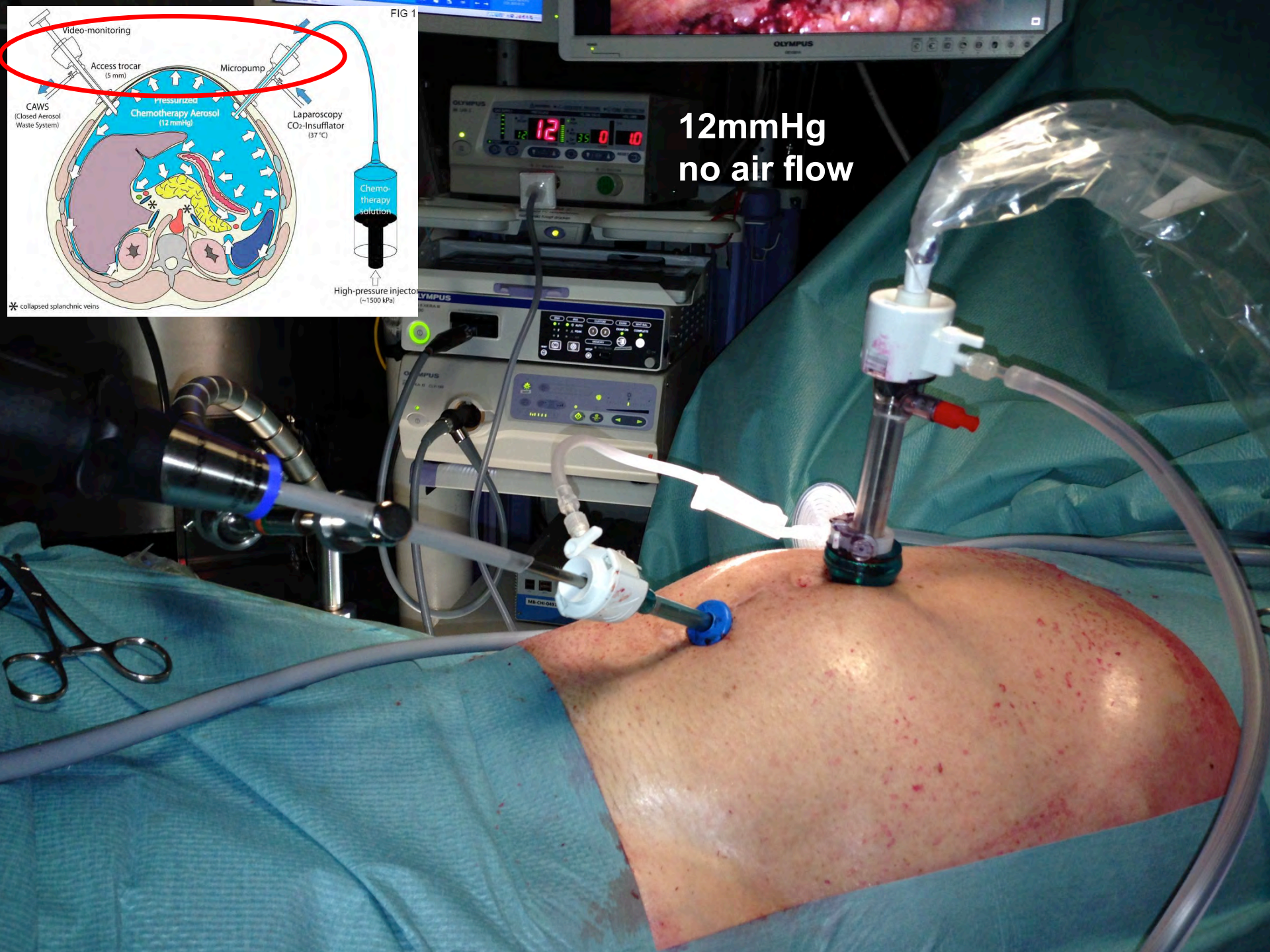
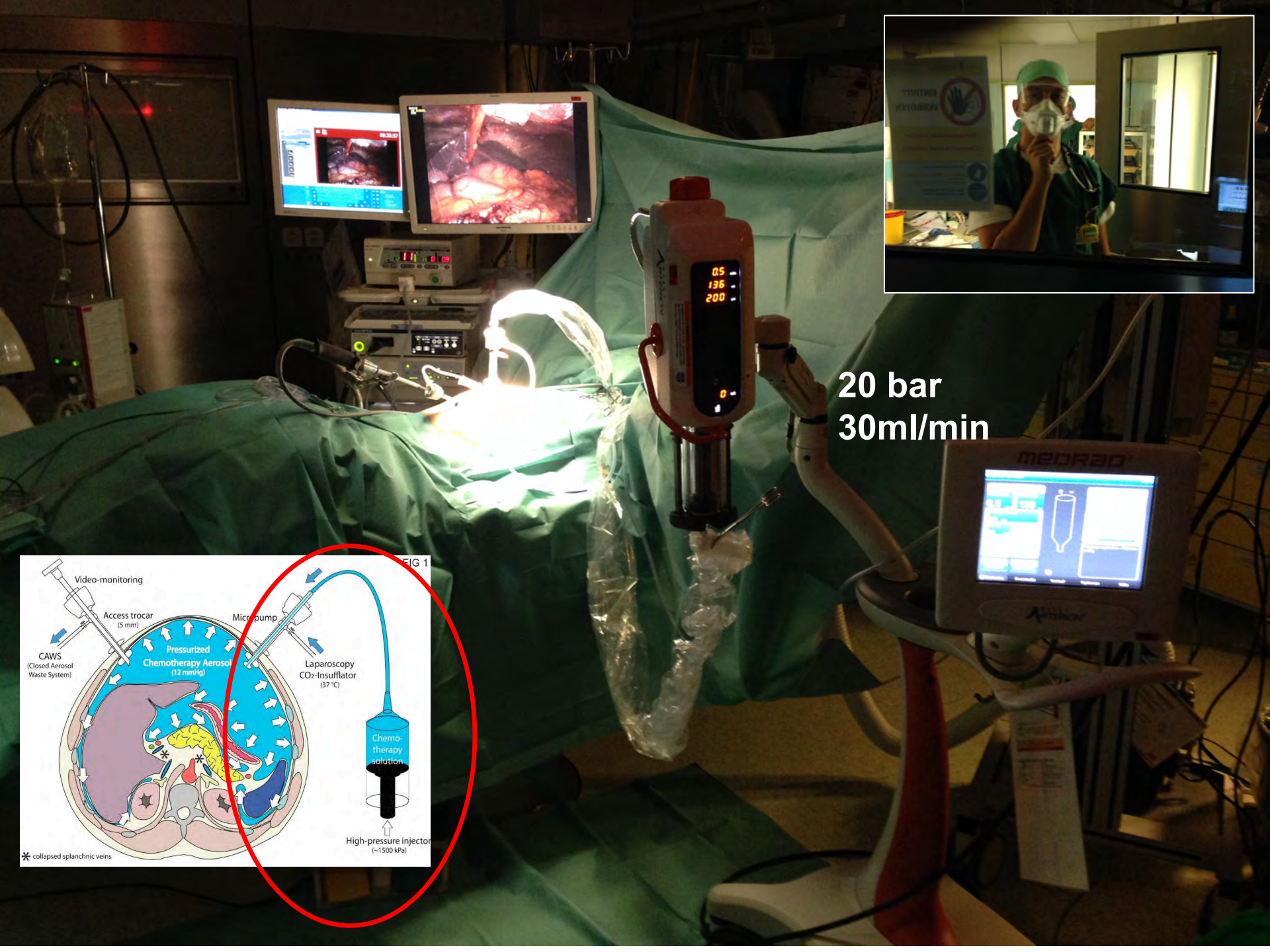


FIG 1
Video-monitoring
Access trocar
(5 mm)
Micropump
CAWS
(Closed Aerosol
Waste System)
Pressurized
Chemotherapy Aerosol
(12 mmHg)
Laparoscopy
CO2-Insufflator
(37 °C)
Chemo-
therapy
solution
High-pressure injector
(~1500 kPa)
collapsed splanchnic veins
12mmHg
no air flow


20 bar
30ml/min
FIG 1
Video-monitoring
Access trocar
(5 mm)
Micro-pump
CAWS
(Closed Aerosol
Waste System)
Pressurized
Chemotherapy Aerosol
(12 mmHg)
Laparoscopy
CO2-Insufflator
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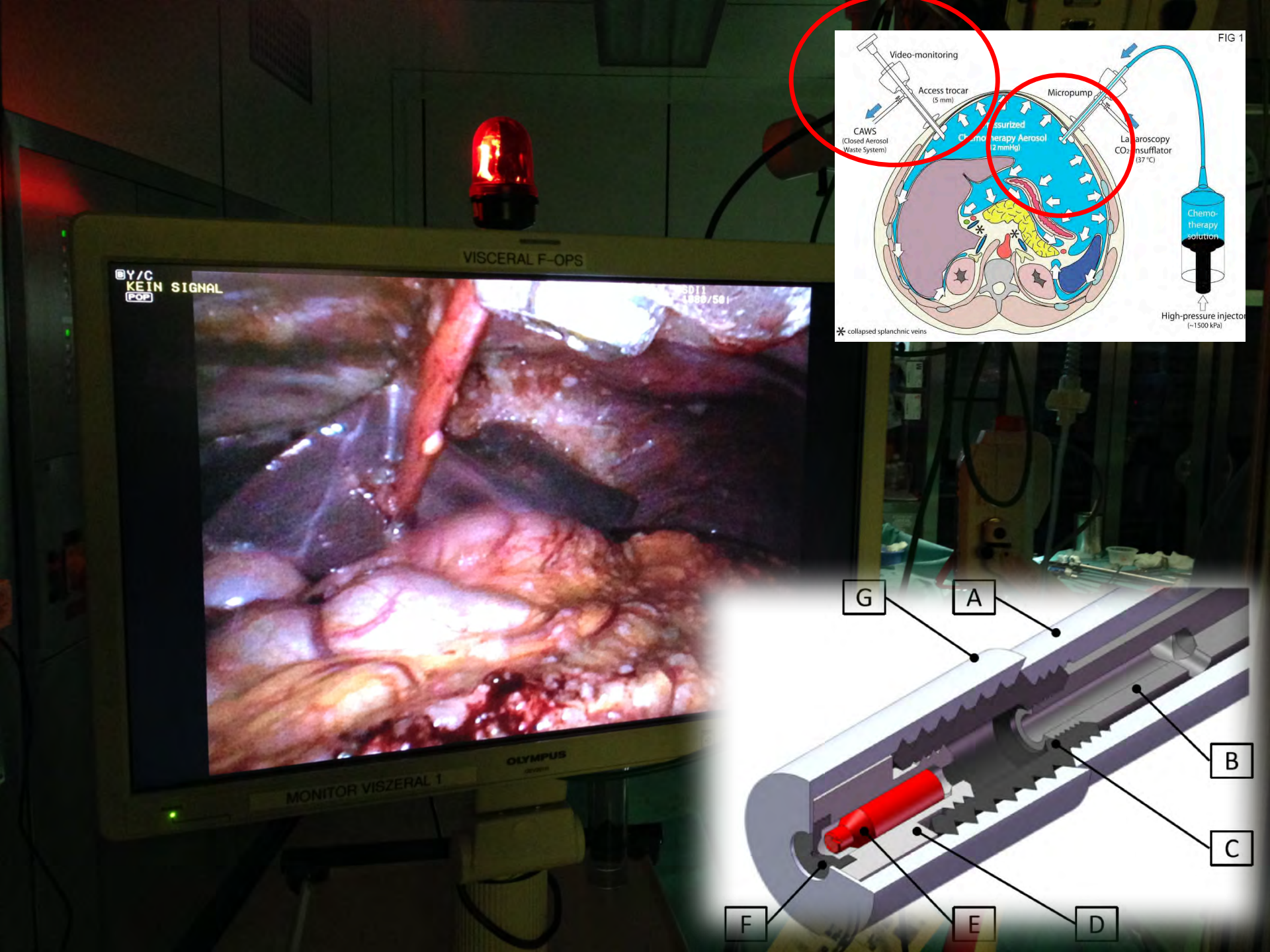
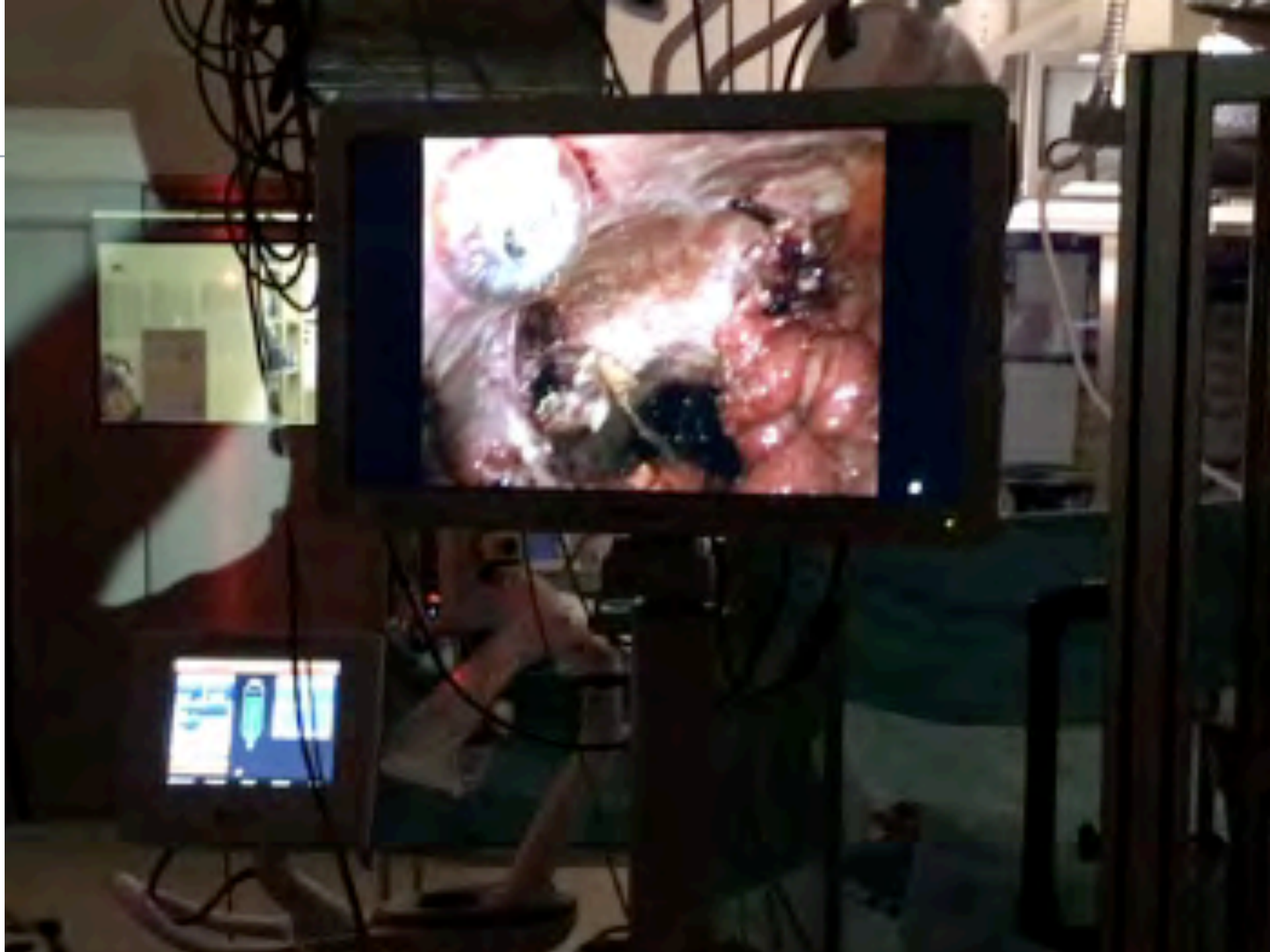
collapsed splanchnic veins

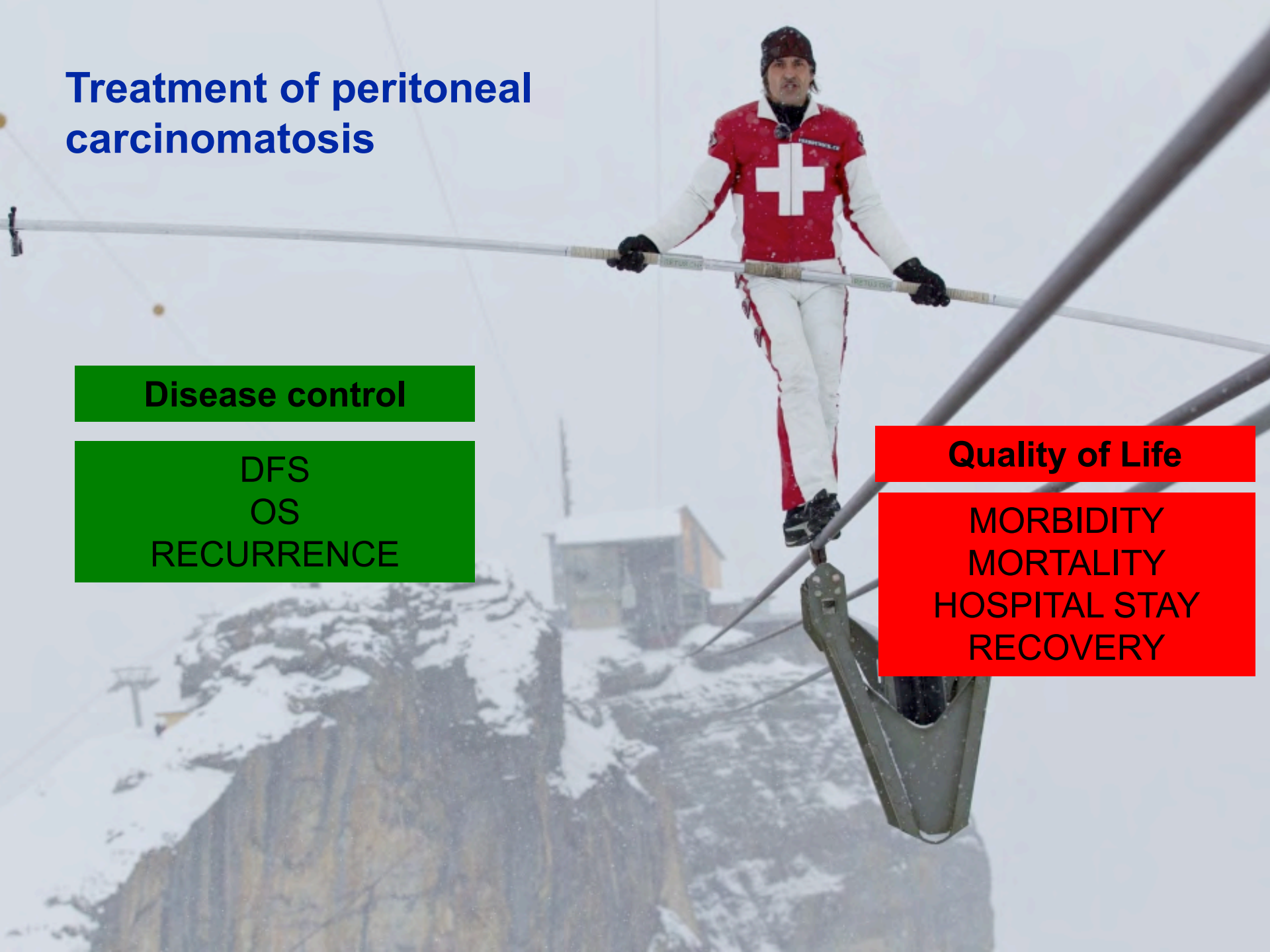

VISCERAL F-OPS
Y/C
KEIN SIGNAL
POP
OLYMPUS
MONITOR VISZERAL 1
FIG 1
Video-monitoring
Access trocar
(5 mm)
Micropump
CAWS
(Closed Aerosol
Waste System)
Chemo-
therapy
solution
High-pressure injector
(~1500 kPa)
collapsed splanchnic veins
G
A
B
C
D
E
F




Cisplatin
7.5mg/m2 BSA
Doxorubicin
1.5mg/m2 BSA
30min
12mmHg
every 6(-8) weeks
EINTRITT
VERBOTEN
Intraoperative Aerosol
Chemotherapie (PIPAC)
Vorsichtsmassnahmen
Eintritt erst 4 Minuten nach Entlüftung des Abdomens
Handschuhe, Mantel, Brille tragen
Kein Eintritt für Schwangere
Türen geschlossen halten

Why do we need a concept like PIPAC

Treatment of peritoneal carcinomatosis



Disease control

DFS
OS
RECURRENCE

Quality of Life

MORBIDITY
MORTALITY
HOSPITAL STAY
RECOVERY

Peritoneal carcinomatosis: goals & challenges

Curative approach

maximal tumor response

maximum survival

Palliation

disease control

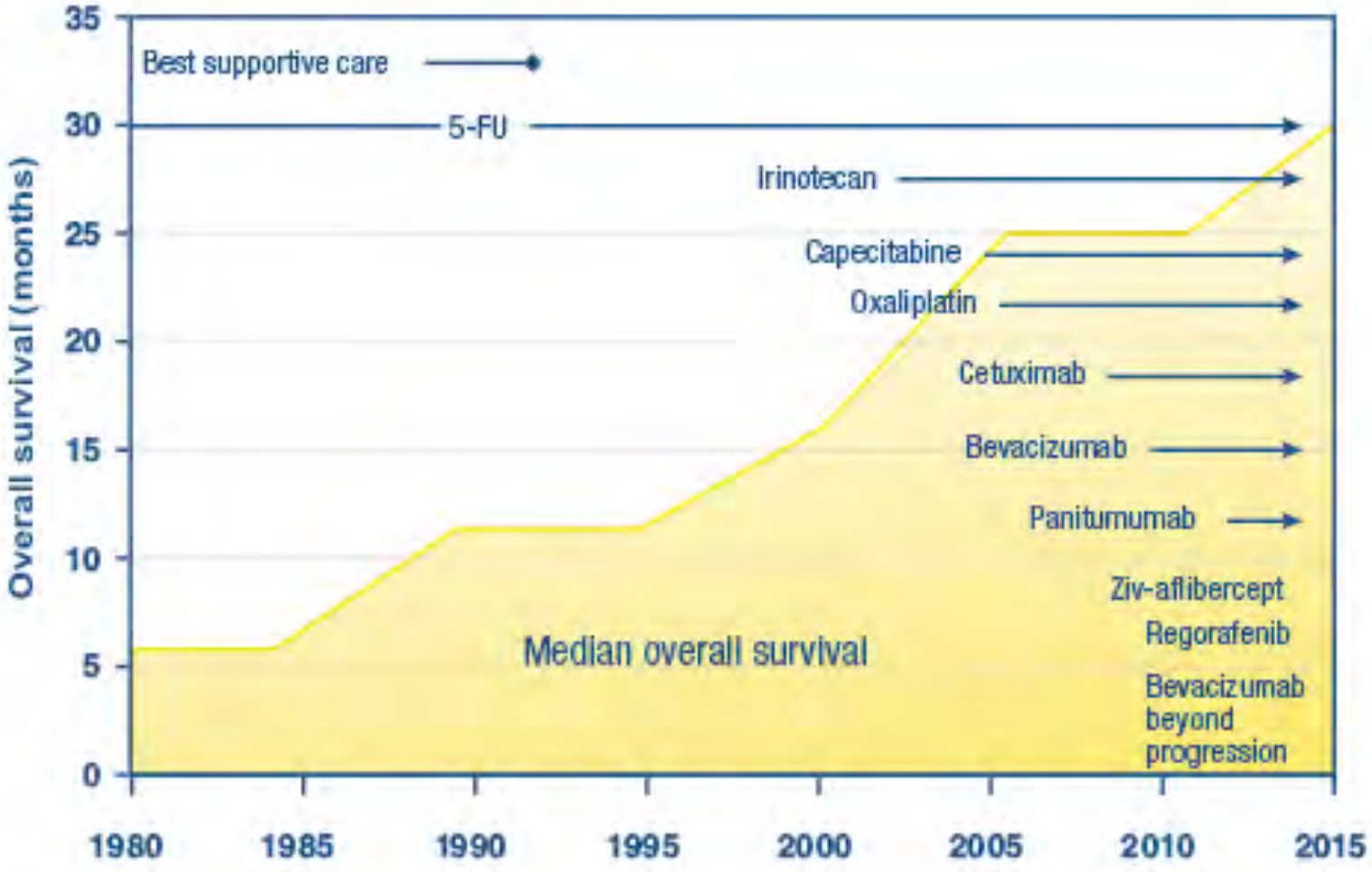
maximal quality of life

Who qualifies?

Permanent chemo? QoL?
Local response and control

Local complications frequent (ileus)
Difficult Reevaluation/response control
Diagnostic underestimation
Response to chemotherapy

CRC: Success of multimodal therapy

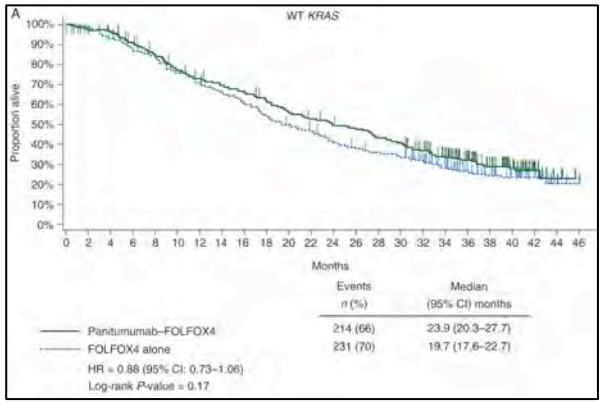


www.ascopost.com

Systemic treatment for metastatic CRC

FOLFOX / panitumumab

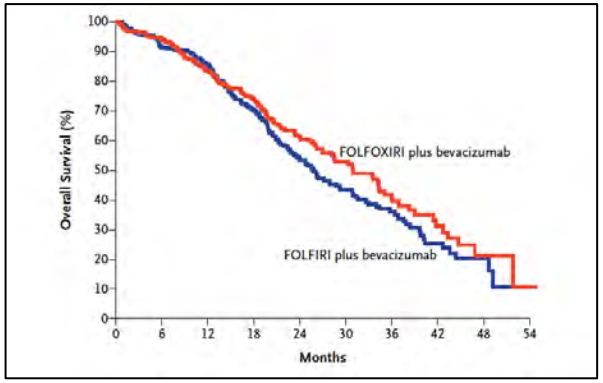
24 months mOS



Douillard et al, NEJM 2013

FOLFOXIRI / bevacizumab

31 months mOS



Loupakis et al, NEJM 2014

Response to chemotherapy (1st line)

TABLE 1. Recent Randomized Controlled Trials of Primary Chemotherapy for Metastatic Colorectal Cancer

			Response rate (%)					Outcome	
Reference	n	Regimen	CR	PR	SD	PD	Resection rate (%)	PFS	OS
PRIME, Douillard, 2010[32]	1183	PAN, FOLFOX		55			10	9.6	23.9
CRYSTAL, Van Cutsem, 2009[27]	1198	CET, FOLFIRI	0.5	46	37	NA	7	8.9	19.9
OPUS, Bokemeyer, 2009[24]	338	CET, FOLFOX	1	44	40	11	4.7	7.2	NA
N016966, Saltz, 2008[20]	1401	BEV, FOLFOX	NA				8.4	9.4	21.3
Falcone, 2007[25]	244	FOLFOXIRI	8	58	21	11	15	9.8	22.6
Hurwitz, 2004[38]	813	BEV, 5FU, IRI	4	41	NA	NA	NA	10.6	20.3

CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease; BEV, bevacizumab; CAP, capecitabine; CET, cetuximab; IRI, irinotecan, OX, oxaliplatin; PAN, panitumumab; 5FU, 5-fluorouracil; FOL, folinic acid (= leucovorin); FOLFOX, folinic acid, 5FU and oxaliplatin; FOLFIRI, folinic acid, 5FU and irinotecan; FOLOXIRI, folinic acid, 5FU and oxaliplatin and irinotecan; NA, not available; PFS, (median) progression free survival (months); OS, (median) overall survival (months).

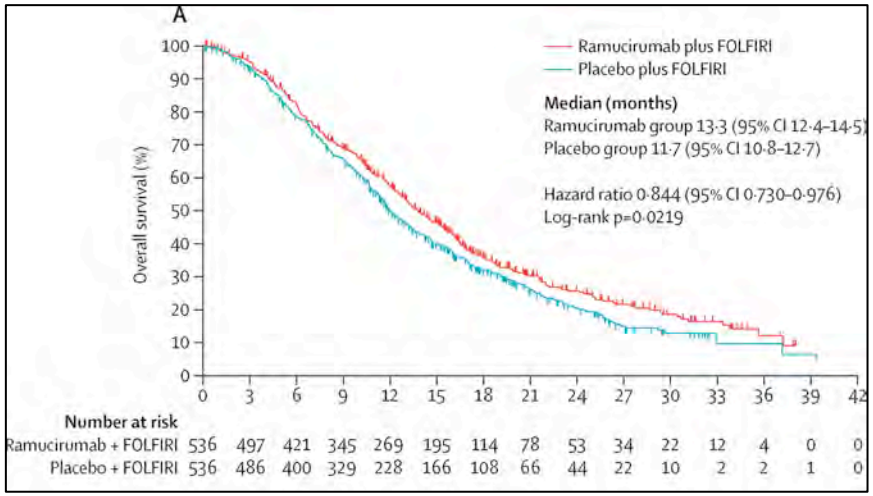
Lehmann, Ann Surg 2012

Second line treatment for metastatic CRC

FOLFIRI/ ramucirumab

13 months mOS, second line

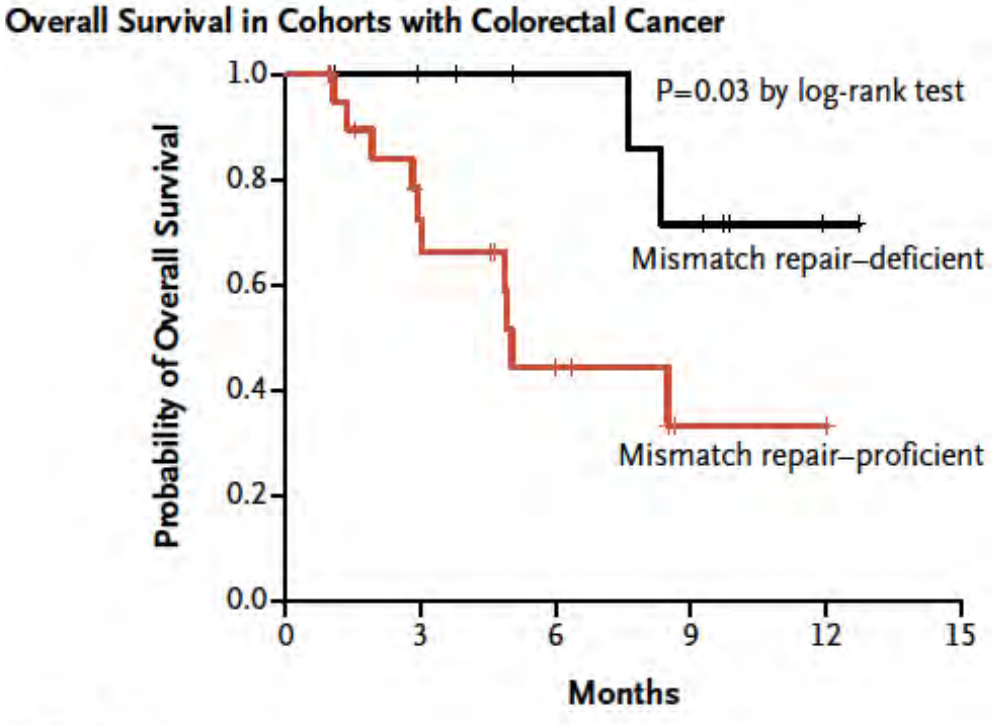
Response rate: 13.4% of patients



Taberno. Lancet Oncol 2015

? Local complications frequent (ileus)
Diagnostic underestimation
Response to chemotherapy

A giant leap for cancer therapy

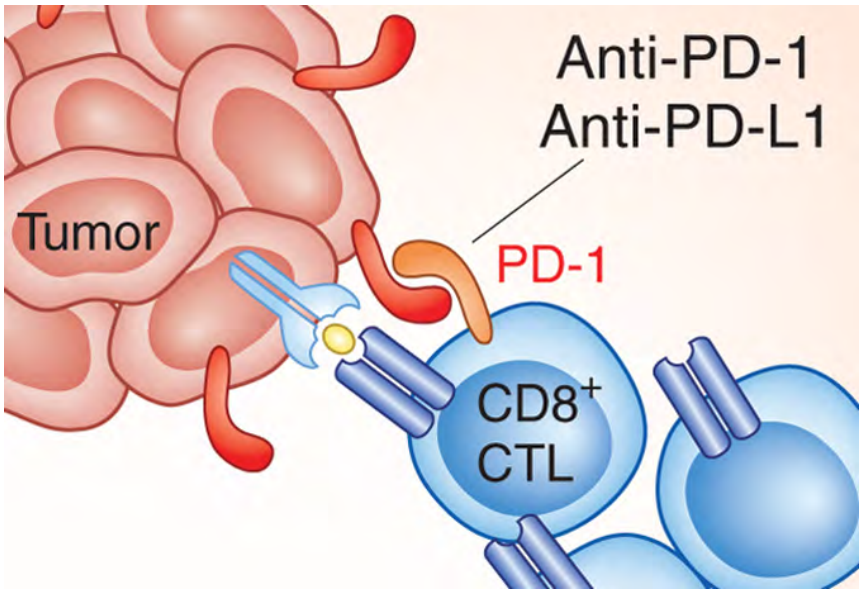


Le et al, NEJM 2015

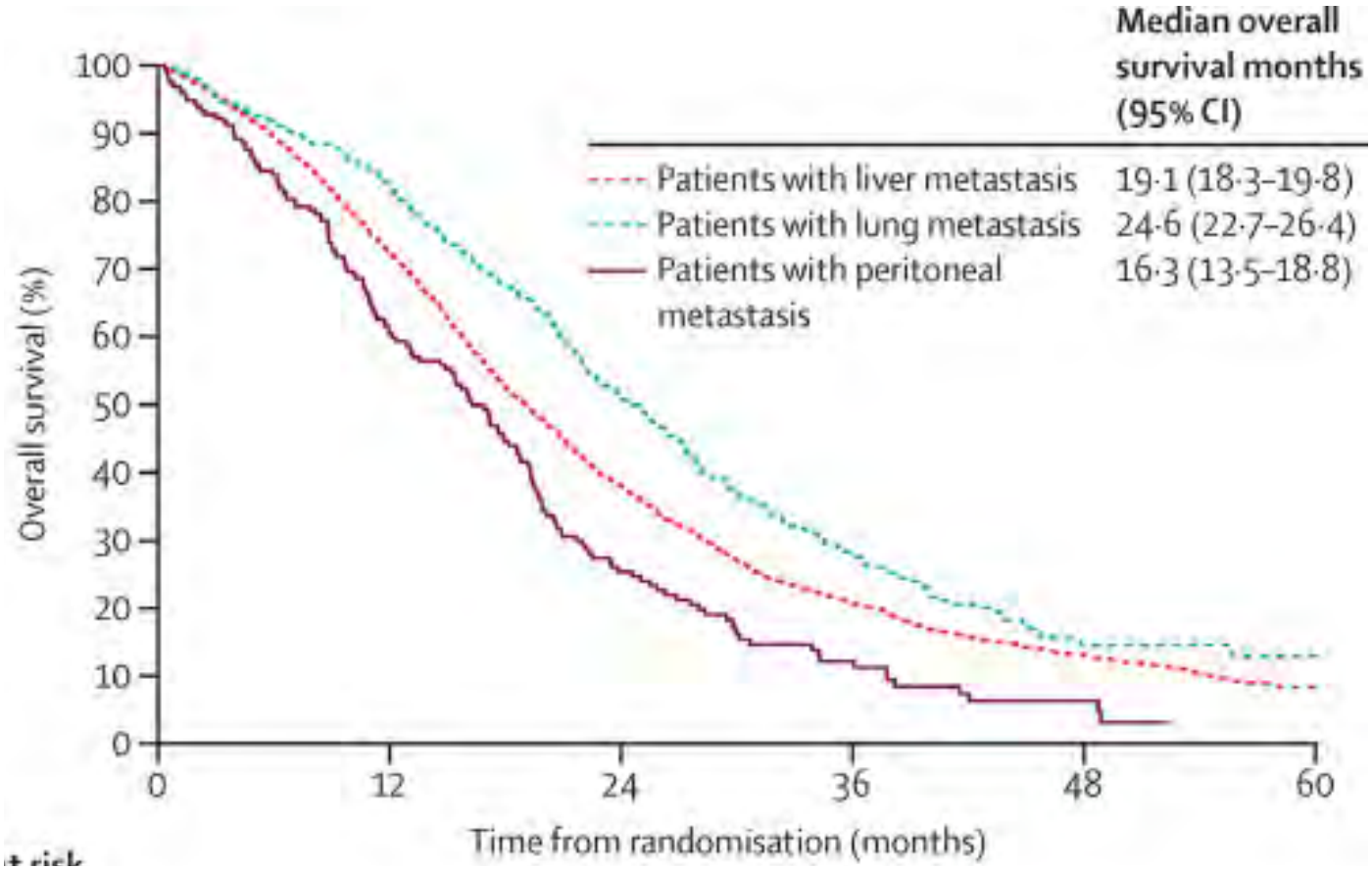
Pembrolizumab (PD-1 blockade)

3rd line

High response rates 40% (MMR-)

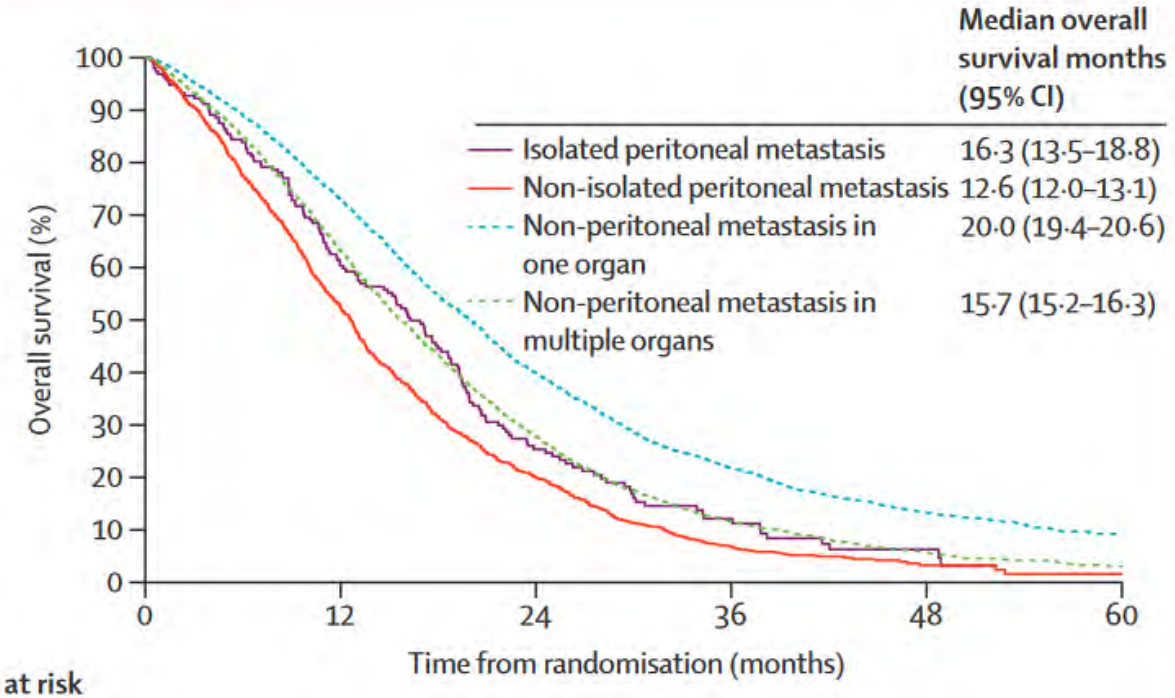


Are all mets the same



Franko J, Lancet Oncol 2016

N=10‘553



Number at risk (number censored)						
Patients with isolated peritoneal metastasis	193 (0)	110 (8)	38 (14)	13 (7)	4 (3)	0 (2)
Patients with non-isolated peritoneal metastasis	1181 (4)	583 (43)	175 (75)	35 (43)	9 (11)	2 (5)
Patients with non-peritoneal metastasis in one organ	4385 (3)	3031 (183)	1302 (499)	462 (338)	122 (208)	35 (61)
Patients with non-peritoneal metastasis in multiple organs	4790 (3)	2873 (176)	977 (468)	243 (253)	56 (98)	12 (27)

Franko et al, Lancet Oncology 2016

The benefits of systemic treatment

- ↑ Systemic control
- ↑ High response rates in first line
- Decrease tumor load
- Improve resectability
- Learn about the biology of the disease

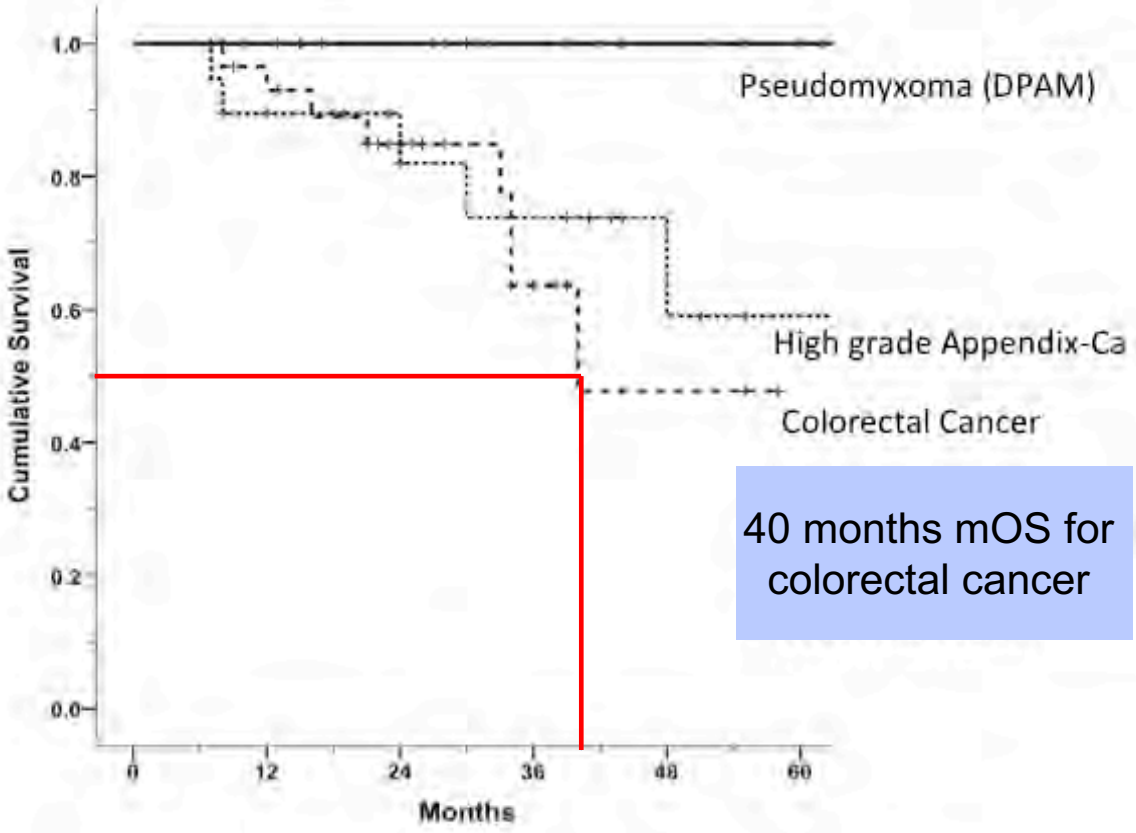
➢ **30 months OS**
➢ **60% response**

Systemic treatment is the first line therapy in PC patients (few exceptions)

? Really the only option for palliation, later lines
Isolated peritoneal carcinomatosis v.s. systemic exposure


1. Which patient qualifies for a curative approach
2. How much survival benefit is sufficient

Registry data – the surgeons selection



Schneider M, Lehmann K. Ann Surg Oncol e-version on *pubmed*

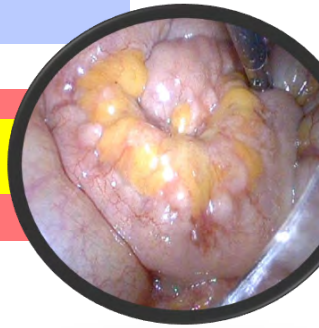
Negative risk factors for survival after CRS/HIPEC

- Histology
- Ras
- N category of the primary tumor
- Synchronous liver metastases, pulmonary nodules
- **Response to (neoadjuvant) systemic treatment**

preoperative staging

- Resectability
- PCI (peritoneal cancer index)

laparoscopy



- Postoperative morbidity
- Postoperative chemotherapy

Why do we need a concept like PIPAC

- **Palliative setting:** Systemic chemotherapy yields lower response rates in the peritoneal cavity, response rates decrease in later lines of chemotherapy

- **Curative setting:** CRS/HIPEC is not ideal for many patients Irresectable (CC-0), high PCI, tumor biology, patients wish

- **Local treatment with high response and low systemic side effects would be ideal**

Evidence about PIPAC

How To

PubMed pipac

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21. [PIPAC--Pressurized intraperitoneal aerosol chemotherapy. A novel treatment for peritoneal carcinomatosis].
Hübner M, Teixeira H, Boussaha T, Cachemaille M, Lehmann K, Demartines N.
Rev Med Suisse. 2015 Jun 17;11(479):1325-30. French.
PMID: 26255492
Similar articles

22. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC).
Odendahl K, Solass W, Demtröder C, Giger-Pabst U, Zieren J, Tempfer C, Reymond MA.
Eur J Surg Oncol. 2015 Oct;41(10):1379-85. doi: 10.1016/j.ejso.2015.06.001.
PMID: 26138283 Free Article
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23. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in a woman with pseudomyxoma peritonei: A case report.
Tempfer CB, Solass W, Buerkle B, Reymond MA.
Gynecol Oncol Rep. 2014 Oct 18;10:32-5. doi: 10.1016/j.gore.2014.10.001.
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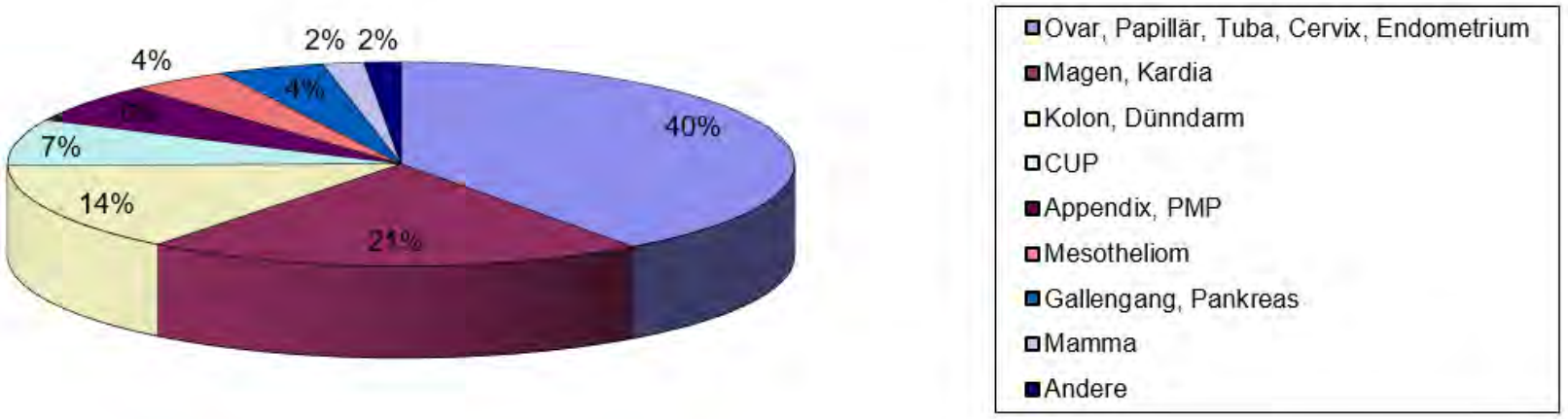
24. Low-dose pressurized intraperitoneal aerosol chemotherapy (PIPAC) as an alternative therapy for ovarian cancer in an octogenarian patient.
Giger-Pabst U, Solass W, Buerkle B, Reymond MA, Tempfer CB.
Anticancer Res. 2015 Apr;35(4):2309-14.
PMID: 25862894
Similar articles

PIPAC

1. QoL
2. Complications
3. Response rates and Outcomes

PIPAC registry: indications

5.11.2011 to 31.5.2016: 1056 PIPAC (500 patients)

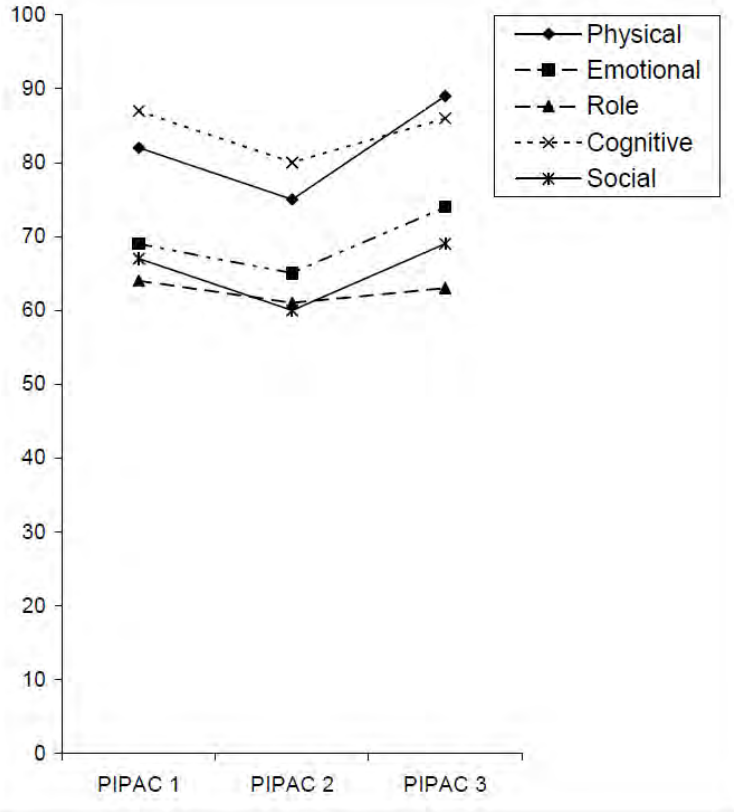


Therapy within the framework of regulatory studies PIPAC-OV1 (NCT01809379) and PIPAC-GA1 (NCT01854255) as well of as off-label use according to German AMG. All patients had previous guideline-based therapy with approval of the IRB. All patients were presented at the tumor board of the Comprehensive Cancer Center, Marien Hospital, Ruhr-University Bochum.

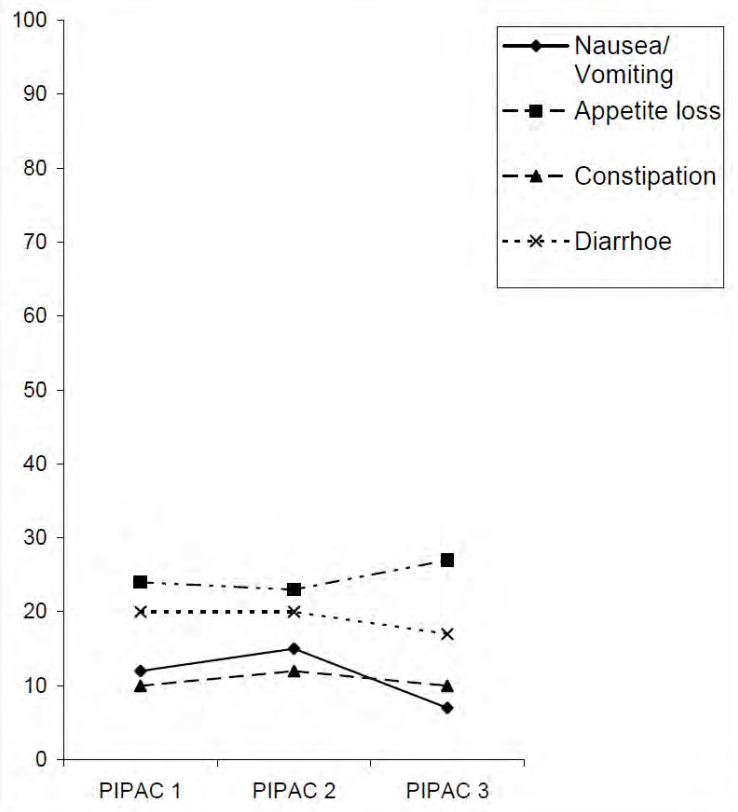
Marc Reymond, zur Verfügung gestellt

Quality of life: EORTC-QLQ30

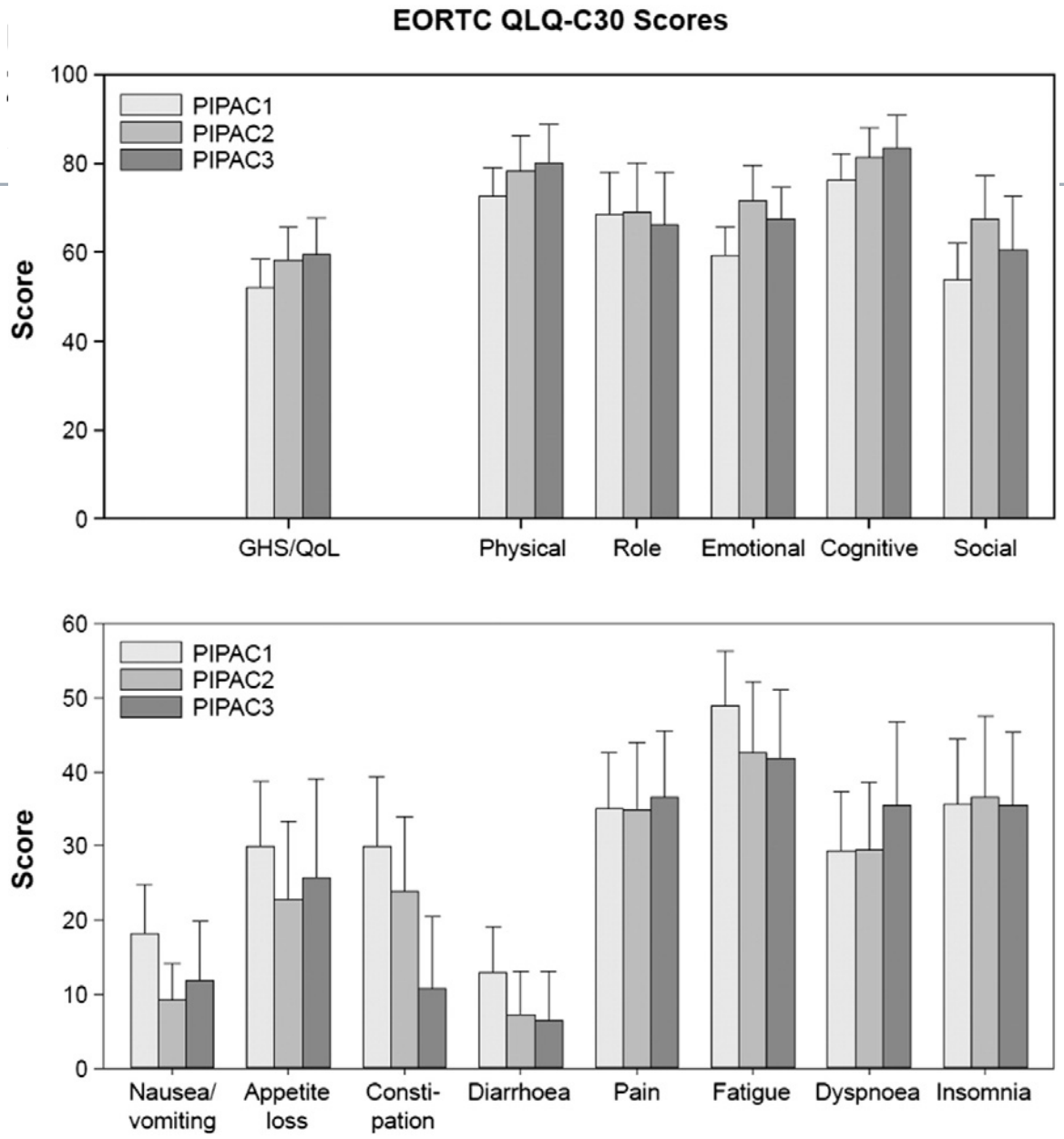
Functional scores



Symptom scores



Odendahl K et al. Eur J Surg Oncol 2015
Texeira H et al, Gastroenterol Res Pract, in press



C.B. Tempfer et al. / Gynecologic Oncology 137 (2015)

Adverse events / complications

- **non-access to the abdomen (13.0%)**

- Inflammatory syndrome (CRP)
- Abdominal pain

- nausea (41%)
- reported diarrhoea (6%)

CTCAE - Details

Acute and chronic adverse events in 53 patients undergoing pressurized intraperitoneal aerosol chemotherapy (PIPAC).

Adverse event	Grade 1	Grade 2	Grade 3
Trocar hernia	0	0	2 (4%)
Abdominal pain	53/53 (100%)	0	2 (4%)
Bowel obstruction	0	0	1 (2%)
Hemorrhage	0	0	1 (2%)
Intraoperative bleeding	0	0	1 (2%)
Cystitis	0	1 (2%)	0
Urosepsis	0	0	1 (2%)
Cardiac	6 (11%)	0	0
Neurological	1 (2%)	0	0
Renal	1 (2%)	1 (2%)	0
Pulmonary	0	5 (9%)	0
Inflammatory[a]	10 (19%)	25 (47%)	0

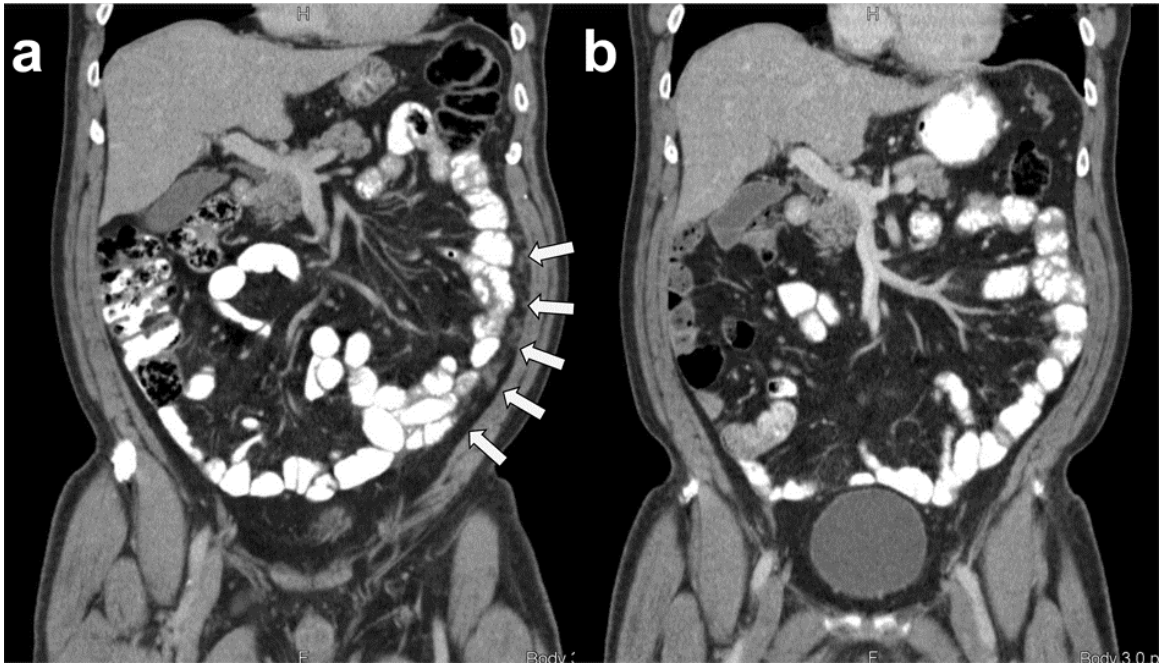
[a] Increase of C-reactive protein.

C.B. Tempfer et al. / Gynecologic Oncology 137 (2015)

(Relative) contraindications to PIPAC

- Be aware of non-access after major surgery
- Small bowel / colon injury (-> no PIPAC)
- Mechanical bowel obstruction
- Rapidly progressive ascites (response to slow)

PIPAC: colorectal cancer



PIPAC with Oxaliplatin 92mg/m2

11/17 had ≥2 lines of CX

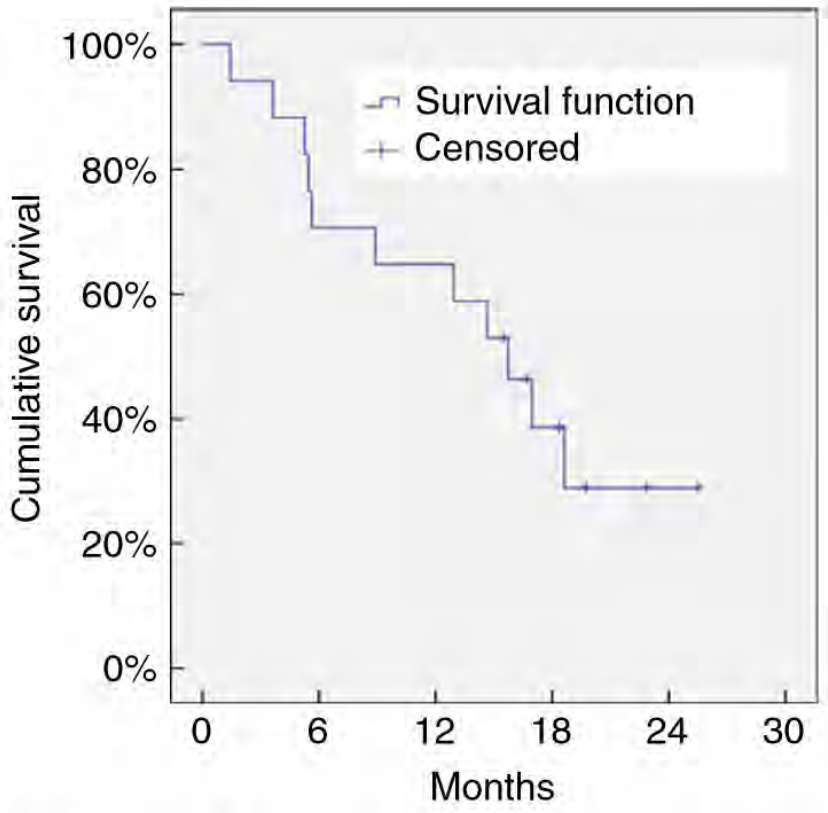
Characteristics	Value
Number of patients	17
Sex (M:F)	10:7
Age (years), mean ± SD	59 ± 12
Karnofsky index (%), mean ± SD	85 ± 13
Mean PCI (± SD)	16 (± 10)
Ascites (> 250 ml) (%)	3/17 (18)
Extraperitoneal metastasis	0/17
Status after colorectal resection (%)	17/17 (100)
Status after chemotherapy (platin-based) (%)	16/17 (94)
Previous chemotherapy	
None	1
One line	5
Two lines	10
Three lines	1
Combined chemotherapy (PIPAC + systemic)	11

PCI, peritoneal cancer index.

12/17 patients (71%) with objective response

Demtröder, Reymond. Colorectal Dis 2015

PIPAC colorectal



mean peritoneal cancer index = 16

PIPAC: oxaliplatin 92mg/m2 BSA

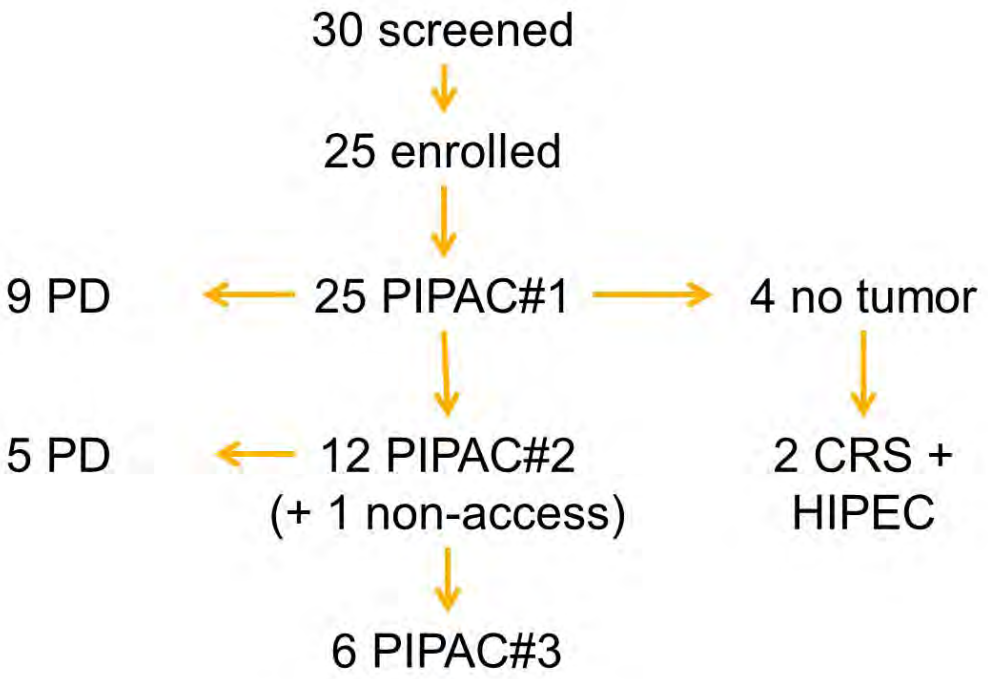
Median two lines of palliative chemotherapy

median overall survival: 15.7 months

Dentröder C et al, Colorectal Disease 2016

PIPAC: gastric cancer

PIPAC-GA1: Phase-2 study



Prospective, open, single-arm, Phase-2

Therapy : low-dose PIPAC C/D q6w, 3 cycles

PIPAC-GA1: Patients

	Value	%
Number of patients	25	
Age (years)	55.1 ± 13	
Sex (M:W)	10:15	40:60%
Karnofksy Index	81 ± 11	
Peritoneal Cancer Index ≤ 12 > 12	 8 17	 32% 68%
Histology - signet-ring - intestinal	 22 3	 88% 12%
Ascites ≤ 300 ml > 300 ml	 18 7	 72% 28%
Previous chemotherapy lines 1 2 3 4	 16 5 2 2	 64% 20% 8% 8%
Previous gastrectomy Previous radiotherapy	15 3	60% 12%

PIPAC-GA1: Histological regression

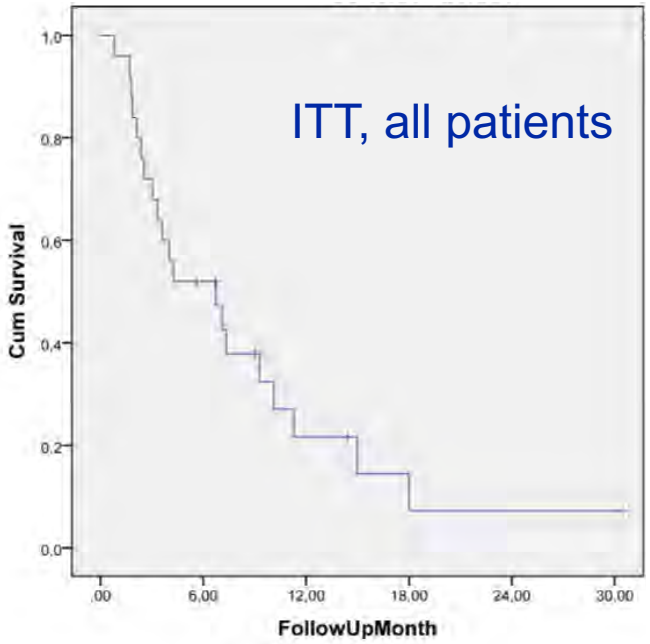
	PP	ITT
N patients	12	25
Complete response (PRGS1)	1 (8%)	1(4%)
Major response (PRGS2)	8 (67%)	8 (32%)
Minor or no response (PRGS 3 and 4)	3 (25%)	3 (12%)
Not eligible	0	13 (48%)

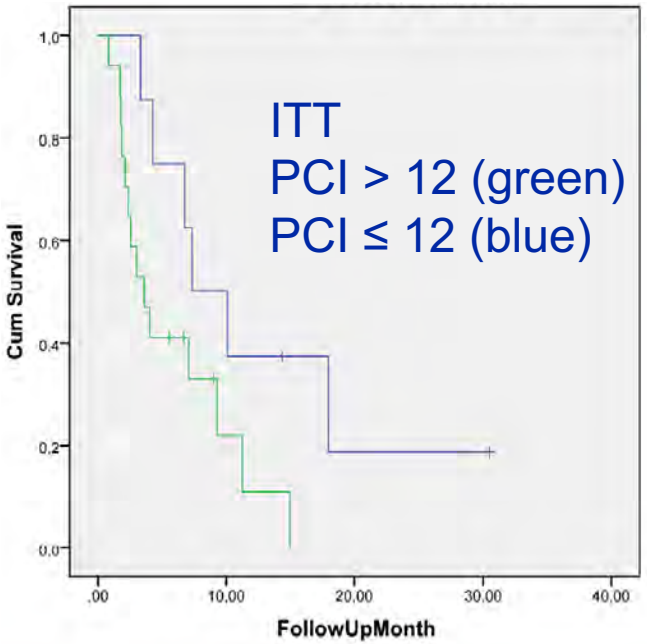
Major + complete intraperitoneal histological regression:

75% (PP)

36% (ITT)

PIPAC-GA1: overall survival





Overall survival: . Mean OS of 8.4 months after PIPAC#1 (Panel a), 13.1 months in patients with PCI ≤12 (Panel b)

PIPAC-GA2: bidirectional

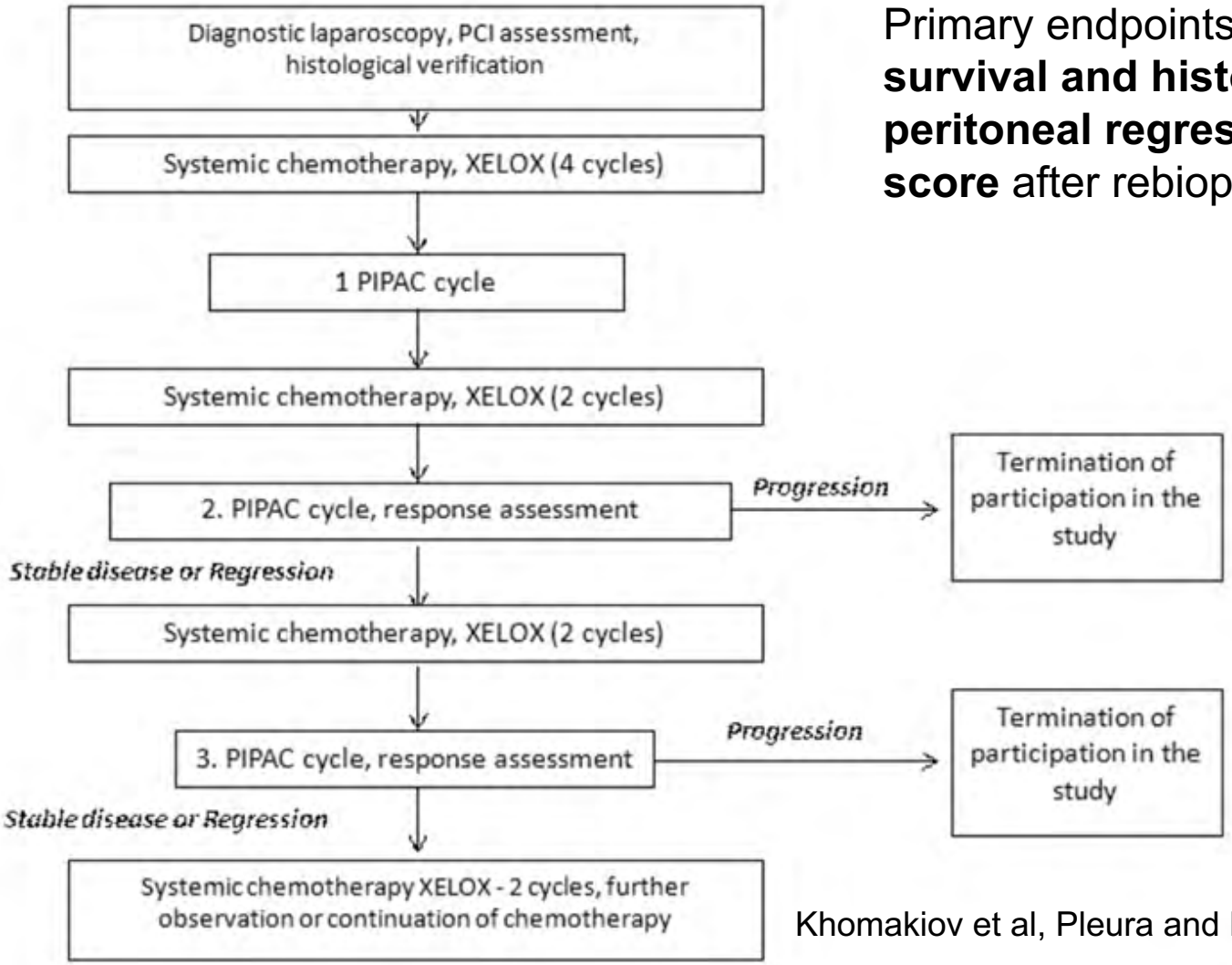
DE GRUYTER

Pleura and Peritoneum 2016; 1(3): 159–166

Vladimir Khomyakov*, Andrey Ryabov, Andrey Ivanov, Larisa Bolotina, Anna Utkina, Nadezhda Volchenko and Andrey Kaprin

Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2)

Khomakiov et al, Pleura and Peritoneum 2016



Primary endpoints were **overall survival and histological peritoneal regression grading score** after rebiopsy

Khomakiov et al, Pleura and Peritoneum 2016

PIPAC-GA2: Patients

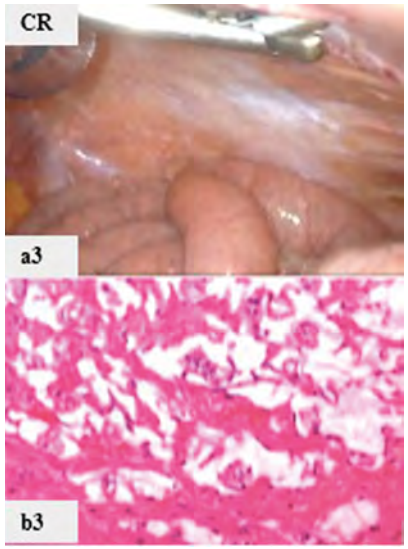
Variable	Value	Percentage
Number of patients	31	
Sex (M:F)	9:22	29 %:71 %
Mean age, years (min-max)	52 (25–70)	
Histology (Lauren classification)		
Diffuse/signet ring	30	97 %
Intestinal	1	3 %
Peritoneal Carcinomatosis Index (PCI), mean (min-max)	16 (6–34)	
Peritoneal metastasis		
Synchronous	7	23 %
Metachronous	24	77 %
Chemotherapy		
Previous	7	23 %
Synchronous	31	100 %

Khomakiov et al, Pleura and Peritoneum 2016

PIPAC-GA2: Therapy

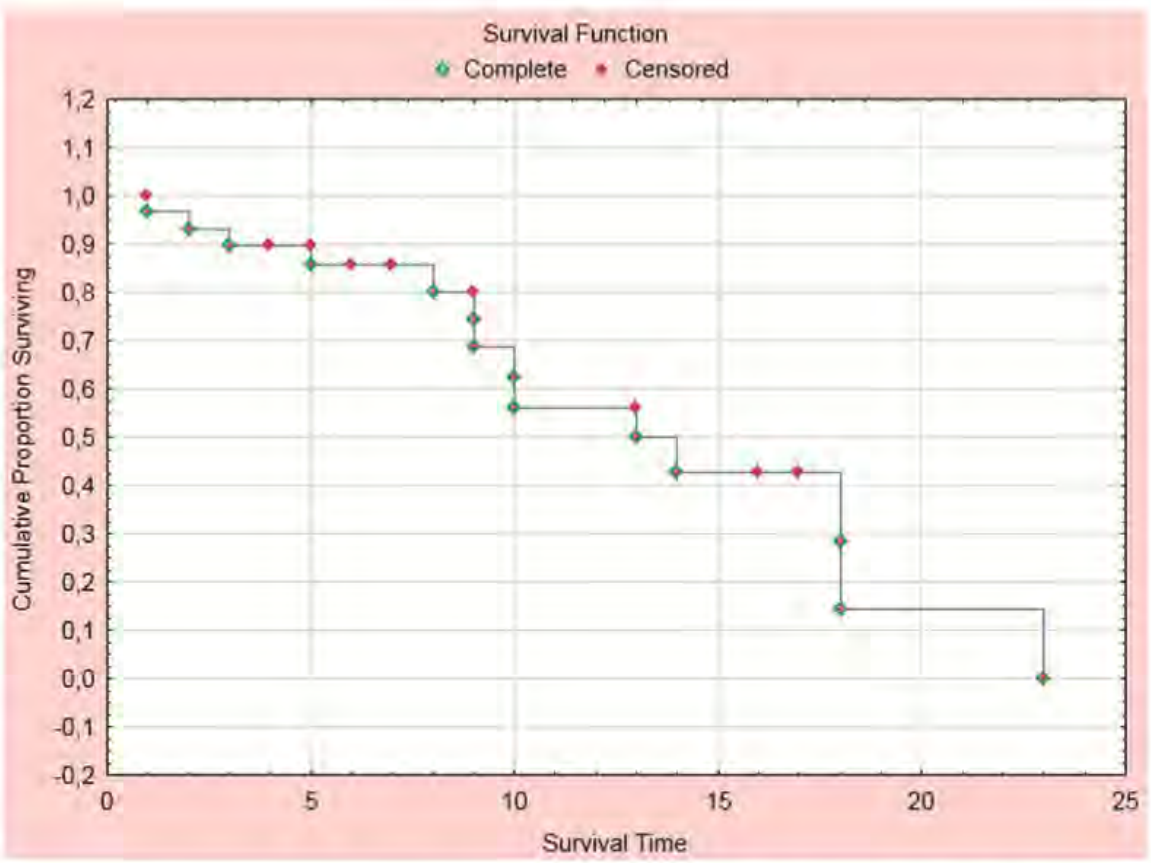
Variable	Value	Percentage
PIPAC sessions, n =56		
1	16	52 %
2	7	23 %
3	6	19 %
4	2	6 %
Histological tumor response (15 patients eligible)		
Complete response (PRGS1)	4/15	27 %
Partial response (PRGS2)	5/15	33 %
No response (PRGS 3 and 4)	6/15	40 %
Median survival (days)	390	

PRGS, Peritoneal Regression Grading Score.



Khomakiov et al, Pleura and Peritoneum 2016

PIPAC-GA02: Overall survival



Median overall survival
13 months

Khomakiov et al, Pleura and Peritoneum 2016

PIPAC-OV1

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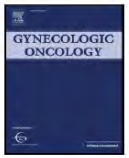


Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study

Clemens B. Tempfer [a,*], Guido Winnekendonk [b], Wiebke Solass [c], Reinhard Horvat [d], Urs Giger-Pabst [c], Juergen Zieren [c], Guenther A. Rezniczek [a], Marc-André Reymond [c]

[a] Department of Obstetrics and Gynecology, Ruhr University Bochum, Bochum, Germany
[b] Department of Radiology, Ruhr University Bochum, Bochum, Germany
[c] Department of Surgery, Ruhr University Bochum, Bochum, Germany
[d] Department of Pathology, Medical University of Vienna, Vienna, Austria

OVCA-Recurrence
60-80% of all patients

mean survival time after recurrence is 18 months

prospective, open, phase II

Cisplatin 7.5 mg/m2, Doxorubicin 1.5 mg/m2

3 x PIPAC q28-42 d; n=50

Clinical Benefit Rate (CR+PR+SD) >40% (RECIST 1.1)

Tempfer, Gynecol Oncol

Patient characteristic	Variable
Number of patients	53
Age (years; mean, ±SD)	62 (±10)
ECOG performance score	
0	32 (60%)
1	20 (38%)
2	0
3	1 (2%)
Previous chemotherapy regimens (median, range)	3 (2, 8)
Previous radiation	None
Presence of pleural effusion	5/53 (9%)
Presence of ascites	22/53 (42%)
Ascites volume (ml; median, range)	483 (0, 4500)
PCI (mean, ±SD)	16.3 (±9.9)
Serum CA 125 (U/ml; mean, ±SD)	1558 (±3964)
Site of disease	
Ovary	47 (89%)
Fallopian tube	2 (4%)
Peritoneum	4 (7%)
Cell type	
Serous papillary adenocarcinoma	48 (91%)
Mucinous adenocarcinoma	1 (2%)
Other	4 (7%)
Previous immunotherapy	
No	29 (55%)
Yes	24 (45%)
Previous surgery	
No	0
Yes	53 (100%)

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; PCI, Peritoneal Cancer Index; ml, milliliter.

n=69 enrolled; 02/13 to 02/14

non-access rate: 11/64 (17%)

ITT-population n=53
PP-population n=34 (3 x PIPAC)

Table 2
Histological assessment of tumor regression in 53 women with recurrent, platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer undergoing pressurized intraperitoneal aerosol chemotherapy (PIPAC).

Population	Moderate regression	Strong regression	Overall regression
In house pathological assessment			
ITT population (n = 53)	21	12	33/53 (62%)
PP population (n = 34)	16	10	26/34 (76%)
External blinded pathological assessment			
ITT population (n = 53)	20	18	38/53 (72%)
PP population (n = 34)	14	16	30/34 (88%)

ITT, intention to treat; PP, per protocol.

PIPAC-OV1 - Results

Median survival time:

11 (95% CI 8-13) months

Systemic CHXT, pooled analysis, various regimens, median overall survival time

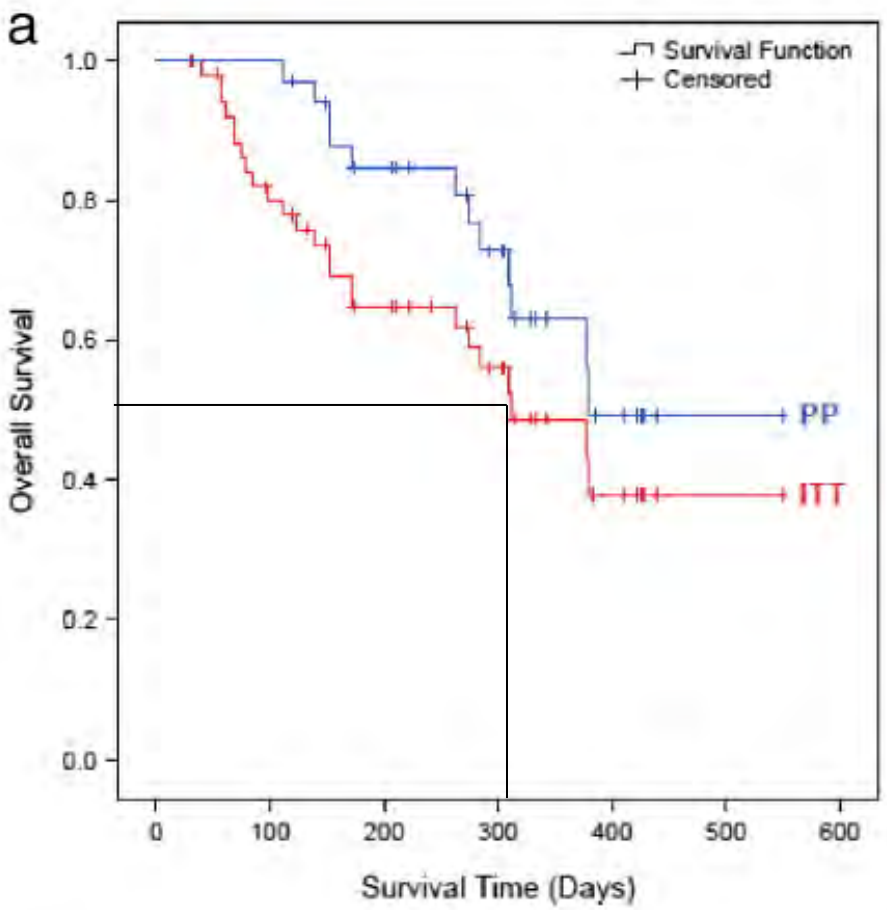
1st recurrence 18 mo (16-19)

2nd recurrence 11 mo (10-13)

3rd recurrence 9 mo (8-10)

4th recurrence 5 mo (4-10)

Hanker et al. 2012



Ongoing: PIPAC-OV2

prospective, open, phase I, dose escalation

3 x PIPAC q28-42 d; 3 x 3 design

Doxo/Cisplatin: 1.5/7.5 - 2.25/11.25 - 3/15 mg/m^2

Outcomes

- Dose-limiting toxicity (DLT)
- Maximum tolerable dose (MTD)
- Pharmacology (drugs/plasma, liver, renal)
- EORTC QLQ-C30

Status

- n=4 recruited; 1st dosage level safe

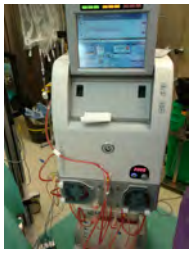
PIPAC – summary

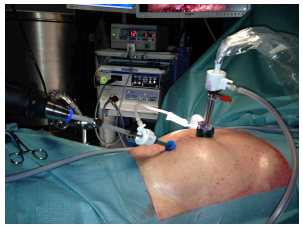
Tumor type	n	Study type	Chemo lines before	Response	mOS
CRC	17	retro	2-3	71%	15.7
GC	25	Phase II	>1	36% (75%)	8.4
OVCA	50	Phase II	3	62%	11

- Low morbidity
- High response rates despite heavy pretreatment
- More data needed

1. **INFORMED CONSENT**
2. **Systemic 1st line chemotherapy**
3. **Laparoscopy**
   - PCI
   - Resectability

Peritoneal carcinomatosis from CRC





- good risk (histology, kras) patients, defined and limited PC
- controlled disease = response to chemo
- Low PCI **(<15)**
- **CC-score 0**
- **Patient fit**
- „**Patient ready** to go the rough way“

- advanced stage (**PCI**) or **non-resectable** disease with main tumor mass in the peritoneum
- systemic treatment with high response rates received, progression after chemotherapy
- Pat wants more than chemo but no CRS

- **always first line in high grade, N+, after major surgery already performed**
- all with **advanced systemic** disease
- very advanced **(end-) stage peritoneal** disease
- (heavily operated patients)

Conclusions

- **PIPAC** has the great potential for high local response rates at low costs and complications
- **CRS/HIPEC** should be reserved for patients with limited and well resectable disease. Need for major impact on survival
- **Systemic chemotherapy** remains the golden and evolving standard

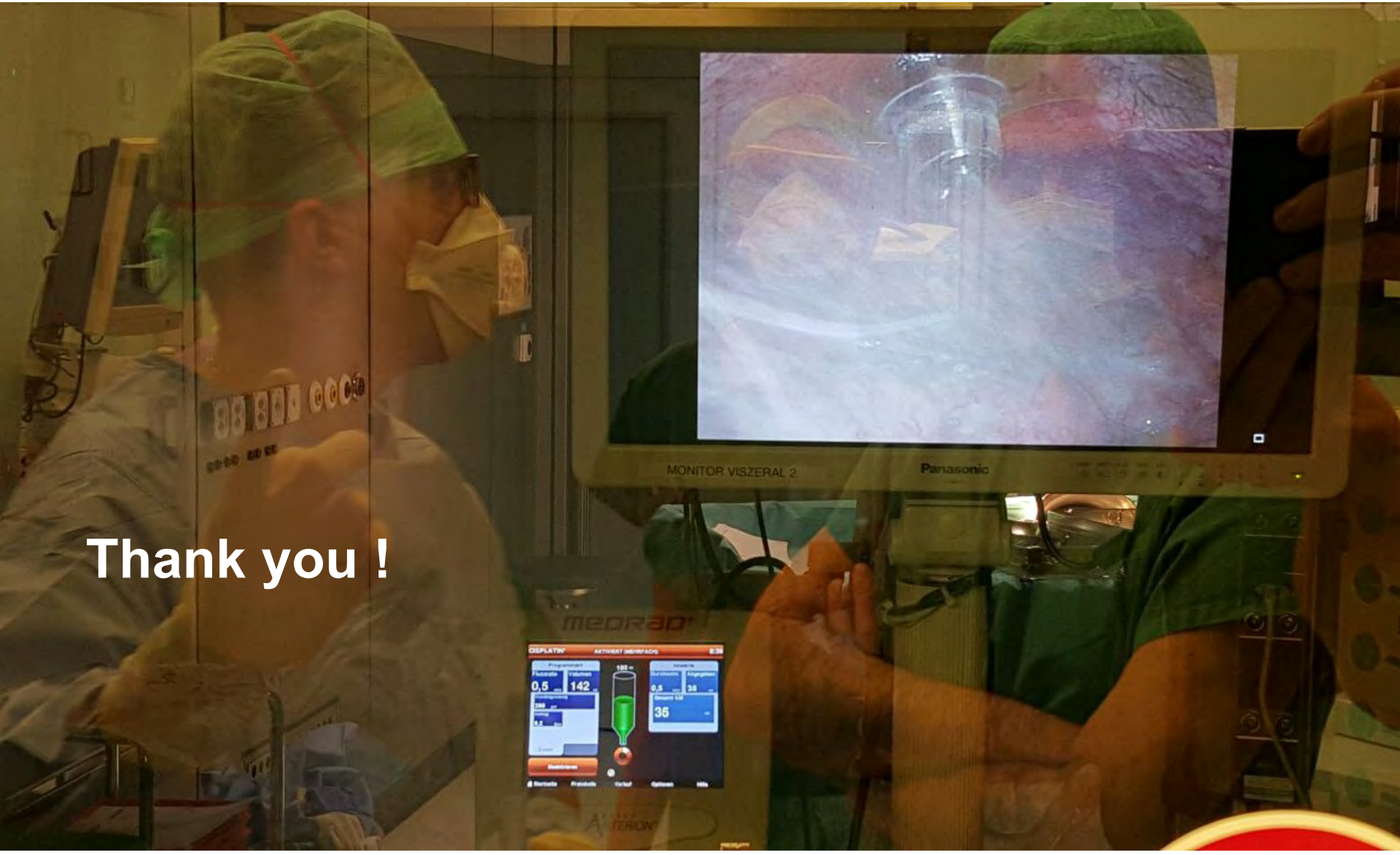
- We are far from guidelines or algorithms
- **Experience of the center** is fundamental (surgeon/oncologist)
- **Well informed patient**

University of Zurich[UZH]

UniversityHospital Zurich

Visceral- and Transplantation Surgery

ZURICH PERITONEAL ~~CANCER~~ NETWORK



Thank you !