THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

FIRST GREAT DEBATE

Is There a Role of Regional Therapy in Colorectal Cancer? (CON)

Marwan G. Fakih, MD

Professor, Medical Oncology and Therapeutics Research
Judy and Bernard Briskin Distinguished Director of Clinical Research
Associate Director for Clinical Sciences
Medical Director, Briskin Center for Clinical Research
Co-Director, Gastrointestinal Cancer Program
Section Head, GI Medical Oncology
City of Hope

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- Consultant/Advisory for Amgen, AstraZeneca, Bayer, GlaxoSmithKline, Mirati Therapeutics, Pfizer, PsiOxus Therapeutics, Roche/Genentech, and Taiho Oncology.

- On the Speakers Bureau for Guardant 360.

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.

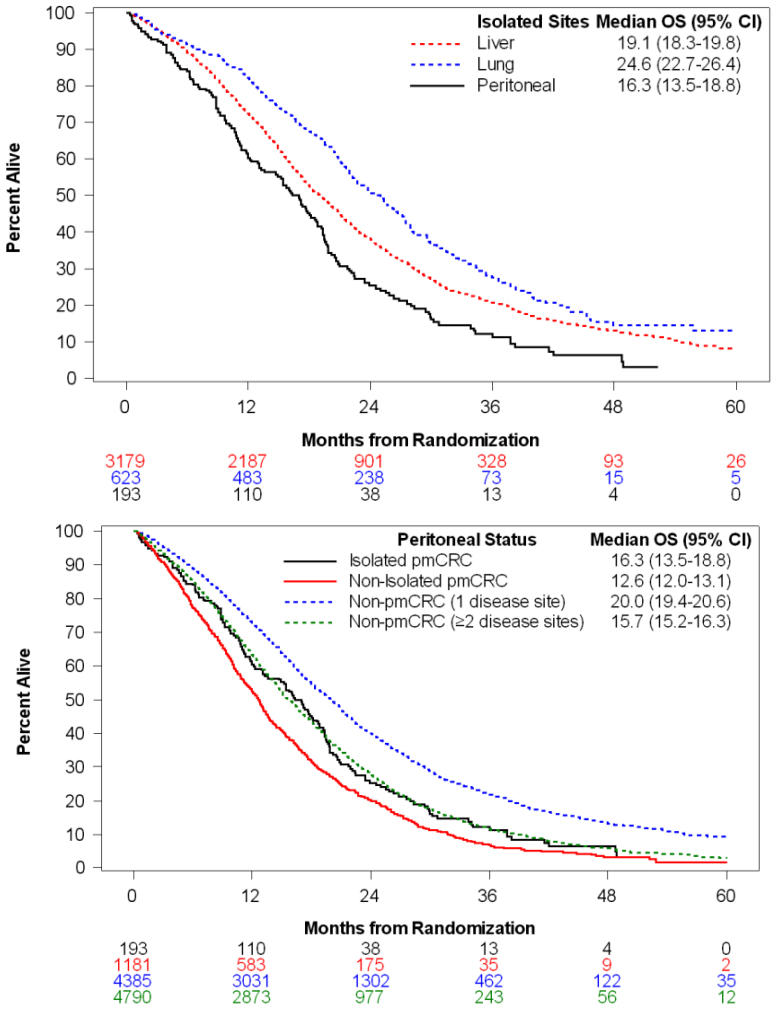
This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Systemic Chemotherapy has Activity in Peritoneal Carcinomatosis: ARCAD 1st Line Experience

Study	Accrual Period
N016966	02/2004-02/2005
OPTIMOX1	01/2000-06/2002
OPTIMOX2	12/2002-06/2003
C97-3	12/1997-12/1999
CAIRO	01/2003-12/2004
CAIRO2	06/2005-12/2006
COIN	03/2005-05/2008
FOCUS	05/2000-12/2003
FOCUS2	01/2004-07/2006
03-TTD-01	04/2002-08/2004
AGITG MAX	07/2005-06/2007
HORG 99.30	10/2000-12/2004
GONO	11/2001-04/2005
FIRE II	09/2004-12/2006

	Events/Total	Median OS [months] (95% CI)†	Hazard Ratio (95% CI)‡	P-value
All patients with isolated organ/disease site Disease Sites				<.0001#
Liver-only	2269/3179	19.1 (18.3-19.8)	0.75 (0.63-0.88)	0.0004+
Lung-only	391/623	24.6 (22.7-26.4)	0.53 (0.44-0.64)	<.0001+
Peritoneal-only	159/193$	16.3 (13.5-18.8)	Reference	--
Distant Lymph Nodes-only	281/405	19.4 (17.0-21.9)	0.69 (0.57-0.84)	0.0003+
Other Isolated Organ/Site	127/178	18.0 (14.4-20.5)	0.85 (0.67-1.07)	0.1707+
Multiple Organs/Sites‡	4757/5971	15.0 (14.6-15.3)	1.02 (0.87-1.20)	0.8058+
All Arms with Only Cytotoxic Agents Disease Sites				<.0001#
Liver-only	1907/2543	18.3 (17.7-19.2)	0.78 (0.65-0.93)	0.0047+
Lung-only	332/511	23.8 (22.0-26.0)	0.55 (0.45-0.67)	<.0001+
Peritoneal-only	137/163	16.3 (12.9-19.2)	Reference	--
Distant Lymph Nodes-only	228/320	18.2 (16.5-21.3)	0.72 (0.58-0.89)	0.0025+
Other Isolated Organ/Site	107/147	18.4 (13.6-20.7)	0.84 (0.65-1.08)	0.1705+
Multiple Organs/Sites‡	3719/4498	14.5 (14.1-15.0)	1.04 (0.87-1.23)	0.6856+
All Arms with at Least One Targeted Agent Disease Sites				<.0001#
Liver-only	362/636	22.2 (20.5-25.7)	0.58 (0.38-0.90)	0.0157+
Lung-only	59/112	27.4 (23.8-33.5)	0.42 (0.26-0.69)	0.0006+
Peritoneal-only	22/30	17.1 (13.0-22.1)	Reference	--



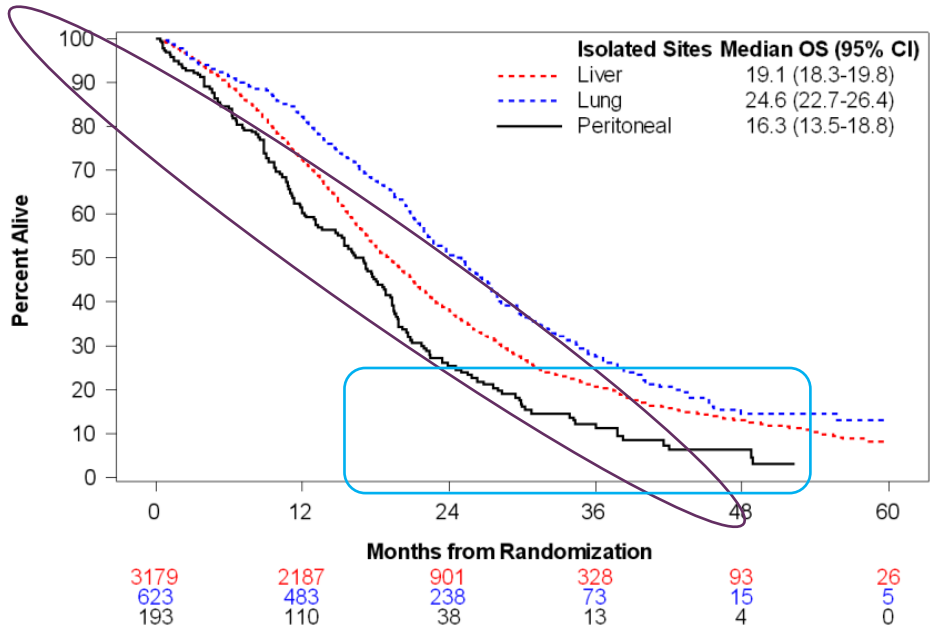
Franko J. Lancet Oncol. 2016 Dec;17(12):1709-1719

Flaws of Historical Control Comparison and CRS+/- HIPEC

- Chemotherapy historical outcomes include many patients who are NOT CRS candidate
    - Cannot compare outcome of predominantly non-CRS candidates to lower burden of disease CRS patients
- Many centers incorporate neoadjuvant therapy prior to CRS, therefore excluding poor biology that is less likely to benefit, and therefore further enriching with better prognosis peritoneal only disease
- CRS/HIPEC series do not capture accurately Time Off Chemotherapy following CRS and therefore practically discounting the impact of systemic therapy in this population
- There is no data on impact of burden of disease on systemic therapy response and outcome (lower burden undergo CRS).
- **<u>Up to 10% -24% of patients with PC and neoadj therapy have cPR at CRS; path response is the most important predictive factor of outcome</u>**
- Prospective clinical trials with CRS have recently reported a mOS of 41.7 months in the setting of perioperative systemic therapy (PRODIGE7).

It is hard to argue against the role of CRS , especially given the potentially curative outcome in some patients (albeit rare).

<u>I will argue that there is NO ROLE FOR HIPEC or PIPEC in the management of metastatic colorectal cancer to the peritoneum</u>

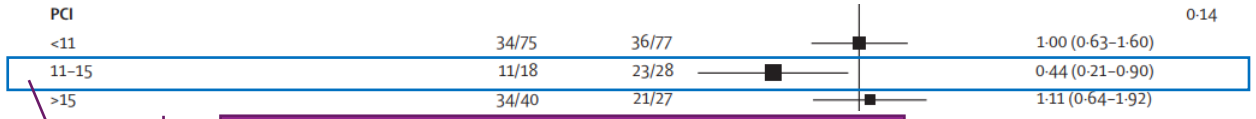


Franko J. Lancet Oncol. 2016 Dec;17(12):1709-1719
Quenet F. Lancet Oncol 2021. Feb; 22: 256-66
Passot G. Ann Surg Oncol 2014; 8: 2608-14
Rovers, KP. JAMA. Surg 2021; 156: 710-20

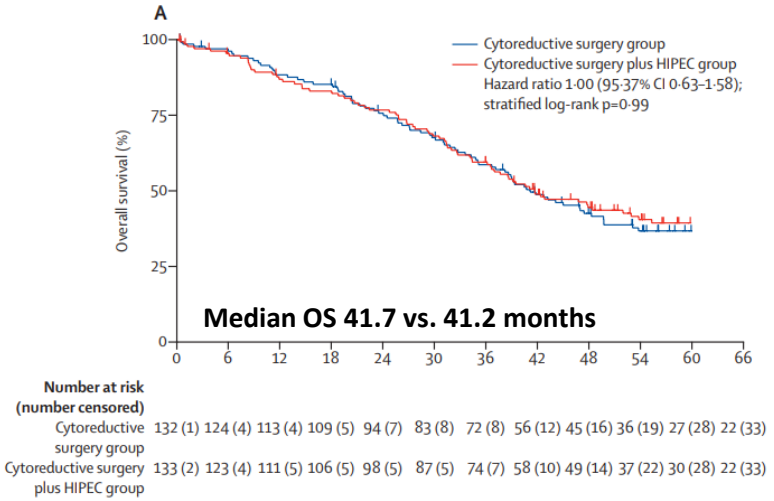
PRODIGE7: CRS + HIPEC vs. CRS for CRC Peritoneal Metastases

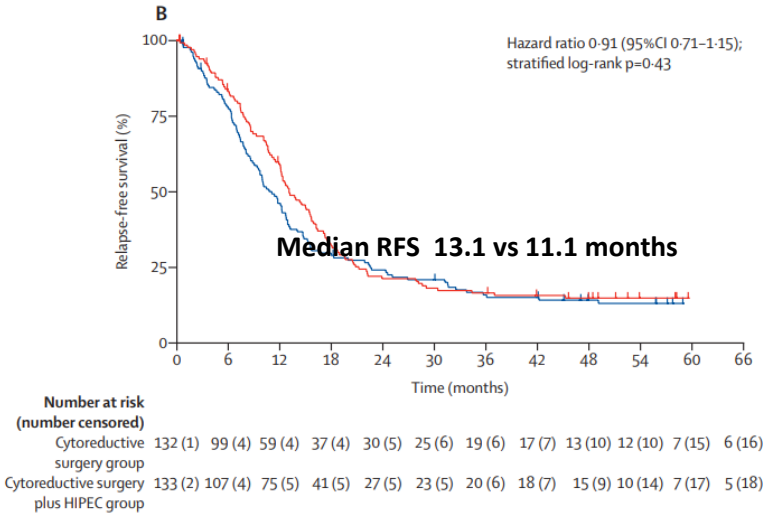
- Prior therapy allowed
- Peritoneal-only disease
- Peri-operative therapy mandated (95% receive pre or/plus post CRS systemic Rx)
- ECOG 0-1
- PCI ≤ 25
- Pts expected to have a full cytoreduction (no visible or < 1mm residual disease)
- Closed (Ox 360mg/m^2) or open (460mg/m^2) abdominal techniques + pre-op 5-FU/LV
- Primary outcome OS

- No difference in OS by adding HIPEC
- No difference in peritoneal DFS by adding HIPEC
- Severe complications at 30 days 42% HIPEC vs 32% CRS
- Severe complications at 60 days 26% HIPEC vs 15% CRS



- Not a primary or secondary endpoint
- Hypothesis generating
- Does not set SOC



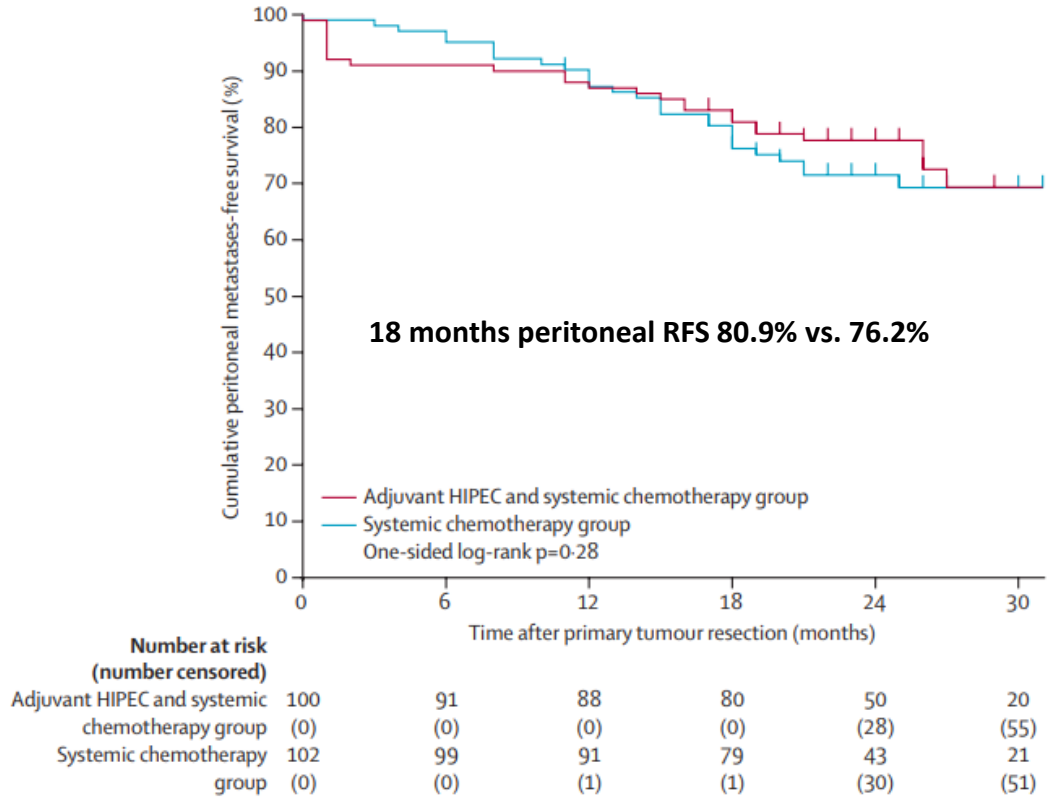


Quenet F. Lancet Oncol 2021. Feb; 22: 256-66

Adjuvant HIPEC in Pts with Locally Advanced Colon Cancer (COLOPEC)

- HIPEC therapy would be expected to be mostly effective in eradicating micrometastatic disease
- COLOPEC evaluated the role of adjuvant HIPEC in T4N0-2 patients at the time of surgery vs. surgery with both arms receiving post-op adj chemotherapy
- Adj oxaliplatin 460mg/m^2 HIPEC (30 min, 42C) + FU/LV at time of surgery or 5-8 w post surgery
- Laparoscopy at 18 months in pts without recurrence
- Primary Endpoint: Peritoneal Metastases Free interval at 18 months

- No difference in peritoneal RFS (but more noted on laparotomy in control arm)
- More delay in systemic adjuvant therapy in the experimental arm (10 weeks vs. 6 weeks)
- 18-month DFS 69% experimental arm vs. 69.3% control
- 18-months OS 93% experimental arm vs. 94.1% control

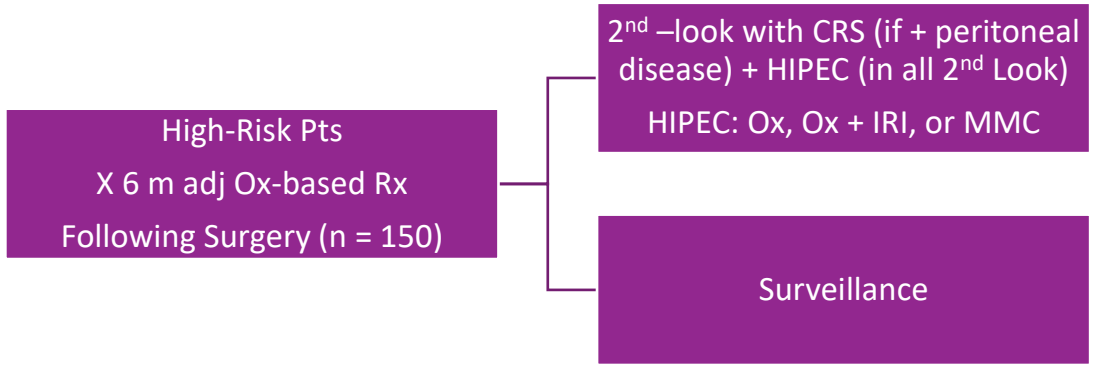


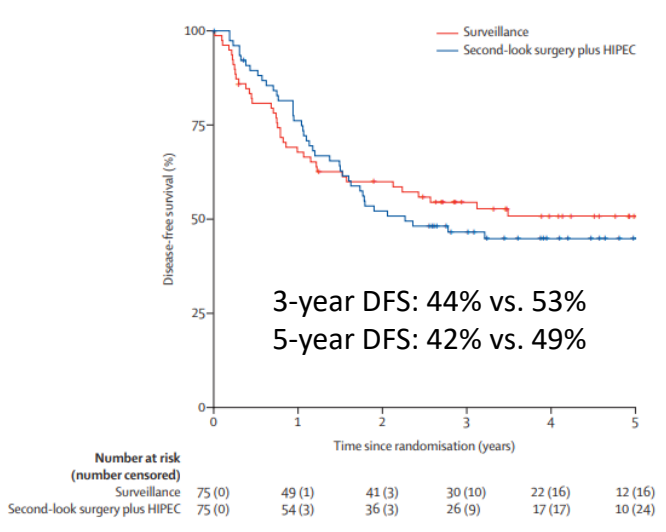
Claver C, Lancet Oncol. 2019; 4:761-70

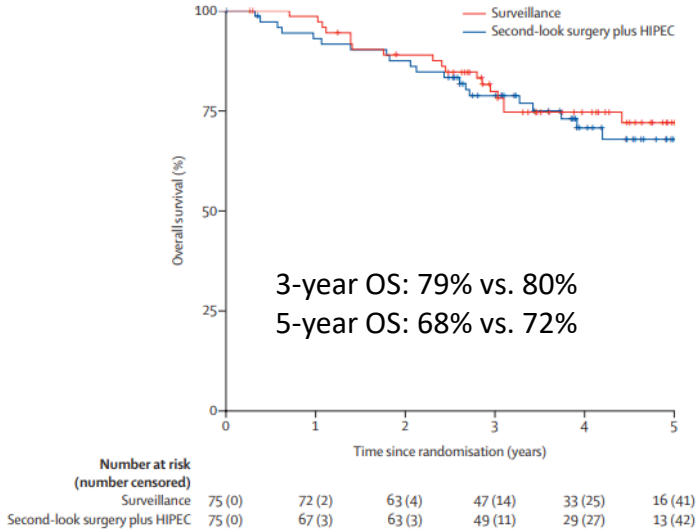
PROPHYLCOP-PRODIGE15: Second-Look Surgery vs. Surveillance in Patients at High-Risk for Carcinomatosis

- Patients with resected peritoneal CRC, resected ovarian CRC mets, and perforated CRC were enrolled
- Primary end point was 3 years DFS
- HIPEC: Ox (460mg/m^2), (Ox/IRI 300/200/m^2), MMC (35m/m^2)

- No difference in DFS (numerically better in surveillance)
- No difference in OS
- Major post-op complications post-second look were seen in 41% of patients







Goere D, Lancet Oncol. 21: 1147-54

HIPEC Should Only be Investigated in Prospective Clinical Trials

- 3 prospective trials failed to show benefit
- 3 clinical trials confirm increased morbidity (First Do No Harm!)
- MMC is NOT the answer outside of a clinical trial setting
  - Multiple retrospective comparative trials show no benefit for MMC vs. Oxaliplatin[1,2,3]
  - Comparative retrospective analysis of pre-op chemotherapy followed by CRS with or without MMC HIPEC showed no benefit to HIPEC[4]
  - MMC has minimal to no systemic activity in MCRC (first line and refractory trials)
- The failure of oxaliplatin 30 min infusion does not justify a 90 min infusion
  - No clinical evidence of the superiority of 90 min infusion over 30 min
  - 30 min infusion of systemic oxaliplatin (XELOX30) has shown similar clinical outcome to 90 min (granted difference in admin mode than HIPEC)[5]

1. Bakkers, C. Eur J Surg Onc. 2020; 49: 1902-07
2. Woeste, M. J Surg Oncol. 2020; 121: 1298-1305
3. Prada-Villaverde A. J Surg Oncol. 2014; 110: 779-785
4. Baratti D. Anna Surg Oncol. 2020; 27: 98-106
5. Qvortrup C. 2010. Annal Oncol. 2010; 21: 87-91

Is there a role for PIPAC in MCRC with PC?

- Pressurized intraperitoneal aerosol chemotherapy (PIPAC)
  - Potential improved distribution
  - enhanced tissue uptake
  - better tolerance
  - can be given repeatedly
- To date, NO randomized clinical trials have reported on a benefit from PIPEC in colorectal cancer PM
- PIPAC-OPC3 phase 2 trial in resected peritoneal carcinomatosis (60-patient single arm- not reported)

Colorectal								
Demtröder and colleagues[54]	17	14/17 (82%)	..	ITT: 12/17 (71%); PP: 12/14 (86%)	Dworak et al[30]	..	..	15·7 months (median)

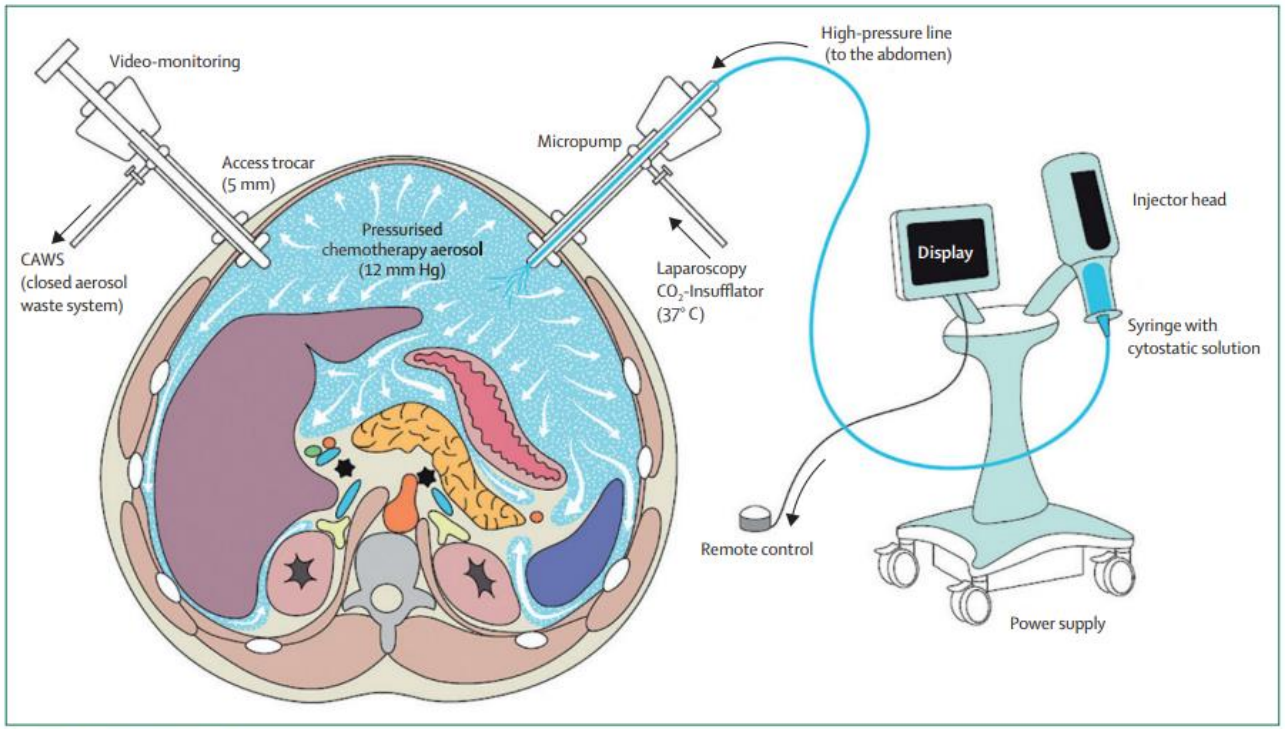


Figure 2: **Schematic of PIPAC set-up**
A hermetically sealed 10–12-mm trocar and a 5-mm balloon trocar are inserted. The liquid chemotherapy regimen is vaporised using a standard injector connected to a nebuliser. Reprinted from Hübner and colleagues[36] with permission from Médicine et Hygiène. PIPAC=pressurised intraperitoneal aerosol chemotherapy.

Alyami M, Lancet Oncol 2019; 2368-77

Demtroder Trial: 17 Pts with Pre-Treated CRC with PM

only patients without further treatment options, patients whose disease had not responded to or relapsed after available treatments and those for whom other treatments were contraindicated

all but one patient received prior palliative combination systemic chemotherapy including FOLFOX or FOLFIRI and/or cetuximab and/or bevacuzimab. The last patient specifically requested a combined protocol that included PIPAC and systemic chemotherapy to maximize the therapeutic potential.

pressurized aerosol con-taining oxaliplatin at a dose of 92 mg/m2body surfacein a 150-ml dextrose solution was applied via the nebu-lizer and injector

At least 3 treatments were planned with histological response assessment

TRG0: indicated a tumor without regression

TRG1 : dominant tumor mass with obvious fibrosis and/or vasculopathy

TRG2: dominantly fibrotic changes with few tumor cells

TRG3: very few tumor cells difficult to locate in the fibrotic tissue

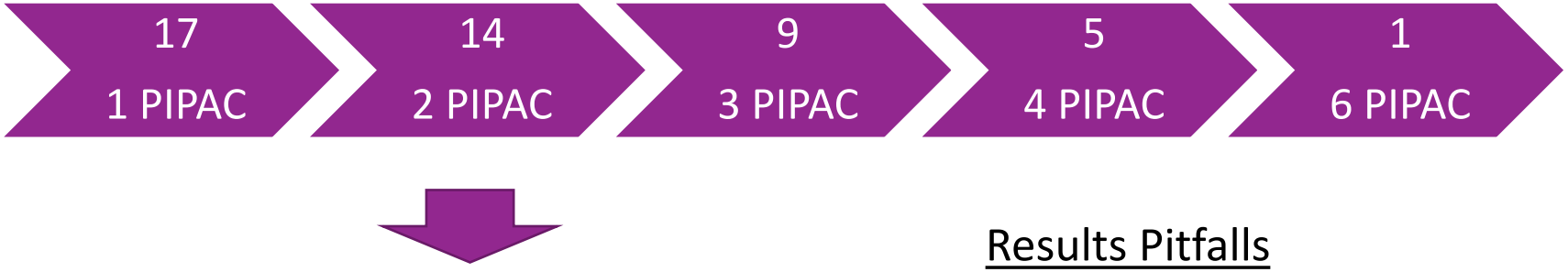
TRG4 : only a fibrotic mass without tumor cells

Demtroder C, Colorectal Disease; 18: 364–371

Demtroder Trial: Design and Results Flaws

Design Pitfalls

- **Small sample size**
- **Retrospective**
- **Heterogenous population**
- **Systemic chemo "on demand" with 1 patient chemo-naïve and receiving 1st line IV Chemo + PIPAC**
- **11/17 patients received systemic chemo along with PIPAC (no details on the systemic treatment)**
- **6/17 patients had 1 or less prior systemic treatment**
- **Median Peritoneal Cancer Index was 16 (+/-10), yet not considered as CRS candidate (better prognosis population)**



Evaluable for histological response:

- 7/14 complete (1 had CRS and was not a complete path response)
- 4/14 major
- 2/ 14 partial
- 2/14 no response

Mean OS = 15.7 m

Results Pitfalls

- 86% histological response does not reflect overall population
- No correlation between histological response and overall outcome provided
- No results on RADIOGRAPHIC response
- No data on TTP (radiographic)
- No data on post-progression therapy

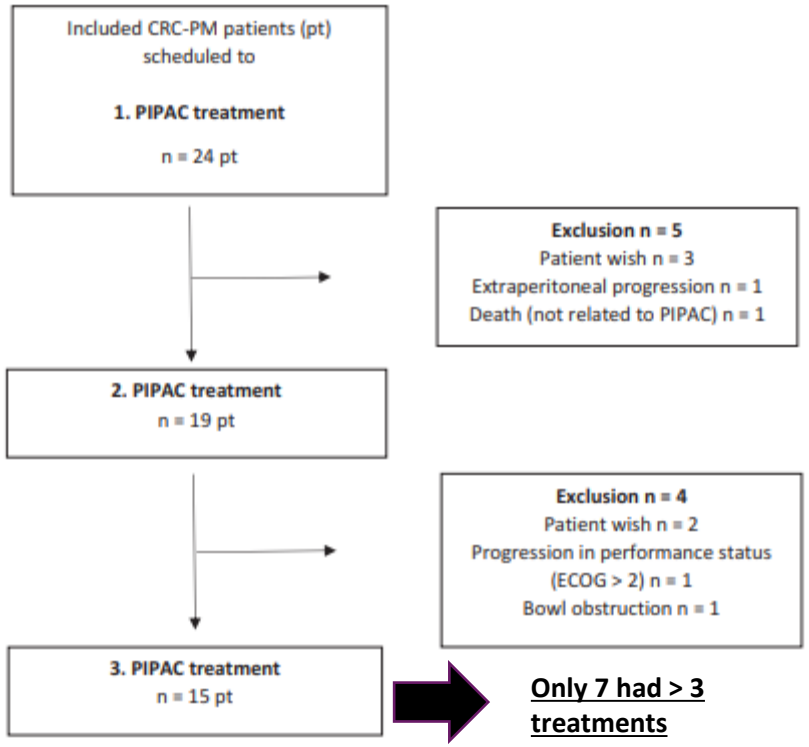
Leads me to conclude that this study does not provide evidence of substantial efficacy

Demtroder C, Colorectal Disease; 18: 364–371

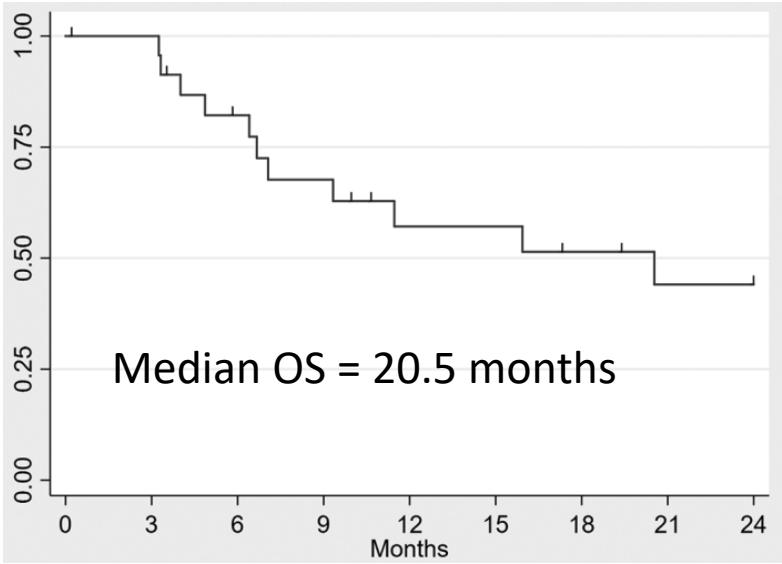
PIPAC-OPC1/OPC2 Experience with Ox-based PIPAC

Number of patients	24
Number of procedures	75
Age: years, median (range)	64 (40–80)
Performance status	
0	7 (29%)
1	14 (58%)
2	3 (13%)
Gender	
M/F	13/11
Chemotherapy	
Neoadjuvant[a]	4 (17%)
Adjuvant[b]	10 (42%)
Palliative[c]	22 (91%)
Bidirectional treatment[d]	3 (12.5%)
PCI score (median, range)	
PCI when ≥ 11 regions evaluated ($n = 16$)	14.8 (1–30)
PCI when < 11 regions evaluated ($n = 8$)	2.6 (1–8)
PCI total	10.7 (1–30)
Ascites	
Yes (%)	7 (29%)
Median, range (mL)	50 (10–2700)

[a]Four patients received neoadjuvant chemotherapy prior to primary colorectal cancer surgery. [b]Ten patients received adjuvant chemotherapy after primary colorectal cancer surgery. [c]Two patients did not want to receive systemic chemotherapy. [d]Tree patients received bidirectional treatment (PIPAC and systemic palliative chemotherapy).



Histological regression seen in 54% if ITT population



- No PFS reported
- No Post-Progression Treatment Reported
- No Chemo-free interval data post progression reported

Bremholm Ellebaek S. Pleura and Peritoneum; 2020; 20200109

Systematic Review of PIPAC Trials in CRC

- **Only one study reported on PFS (median was only 3 months!!)**
- **If a modality of treatment is associated with a robust mPFS, why is it not reported?**
- **What happened to the other 9 studies that did not report OS?**
- **Are we dealing with a reporting bias?**
  - **Studies with good OS will report OS**
  - **Those with bad OS will not report it**
  - **PFS not reported since it is poor**
  - **Lack of transparency regarding associated systemic therapy given with PIPAC and its potential impact on outcome?**
- **If histological response is so good across several studies, how come conversion to CRS is so poor?**

Table 9 Progression-free and overall survival

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	Median (months)	1 year	Calculated from	Follow-up (months)
A. Progression-free survival							
De Simone [2020] (20)	23	16 (b)	32 (b)	3	ns	ns	ns
B. Overall survival							
Demtröder [2016] (15)	17	17	42	15	65% (c)	First PIPAC	22±4 (d)
Ellebæk [2020] (17)	24	24	75	21	60% (c)	First PIPAC	29 [?–?] (e)
De Simone [2020] (20)	23	16 (b)	32 (b)	27	ns	ns	ns
Kurtz [2018] (21)	17	17	ns	Not reached	60% (c)	First PIPAC	10±4 (d)
Sgarbura [2019] (22)	66	66	ns	Not reached	67% (c)	First PIPAC	5 [5–11] (e)

(b) Reported in patients that underwent at least 2 PIPAC; (c) as estimated from Kaplan-Meier survival curve; (d) mean ± standard deviation; (e) median [interquartile range]. CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin; ns, not shown.

Table 10 Eligibility for secondary cytoreductive surgery

Studies	CRC patients	Evaluated patients	Total PIPAC-OX	CRS performed
Demtröder [2016] (15)	17	17	42	2
Ellebæk [2020] (17)	24	24	75	0
Alyami [2019] (25)	31	31	ns	0
Girshally [2016] (26)	ns	ns	ns	6

CRS, cytoreductive surgery; CRC, colorectal cancer; PIPAC-OX, pressurized intraperitoneal aerosol chemotherapy with oxaliplatin; ns, not shown.

Lurvink, R. J Gastrointest Oncol 2021;12(Suppl 1):S242-S258

Concerns with PIPEC Trials

- Minimal data on PFS
- No details on pre-PIPAC therapy and refractoriness vs. exposure to prior chemotherapy
- Confounded by the administration of systemic therapy in many patients
- No details on Peritoneal DFS vs non-peritoneal DFS
- Histological response not adequately validated as a surrogate marker of response
- Low conversion rate to CRS
- No details on post-PIPAC systemic therapy
- Conclusion: NOT prime for Off-Study administration!!