



THIRD ANNUAL
ISSPP
Congress 2022

*International Society
for the Study of Pleura
and Peritoneum*



TREATMENT MODALITIES

Current Landscape of
Peritoneal Treatments

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

Disclosures

- Grant from Capnomed.
- Consultant for Encare.

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.

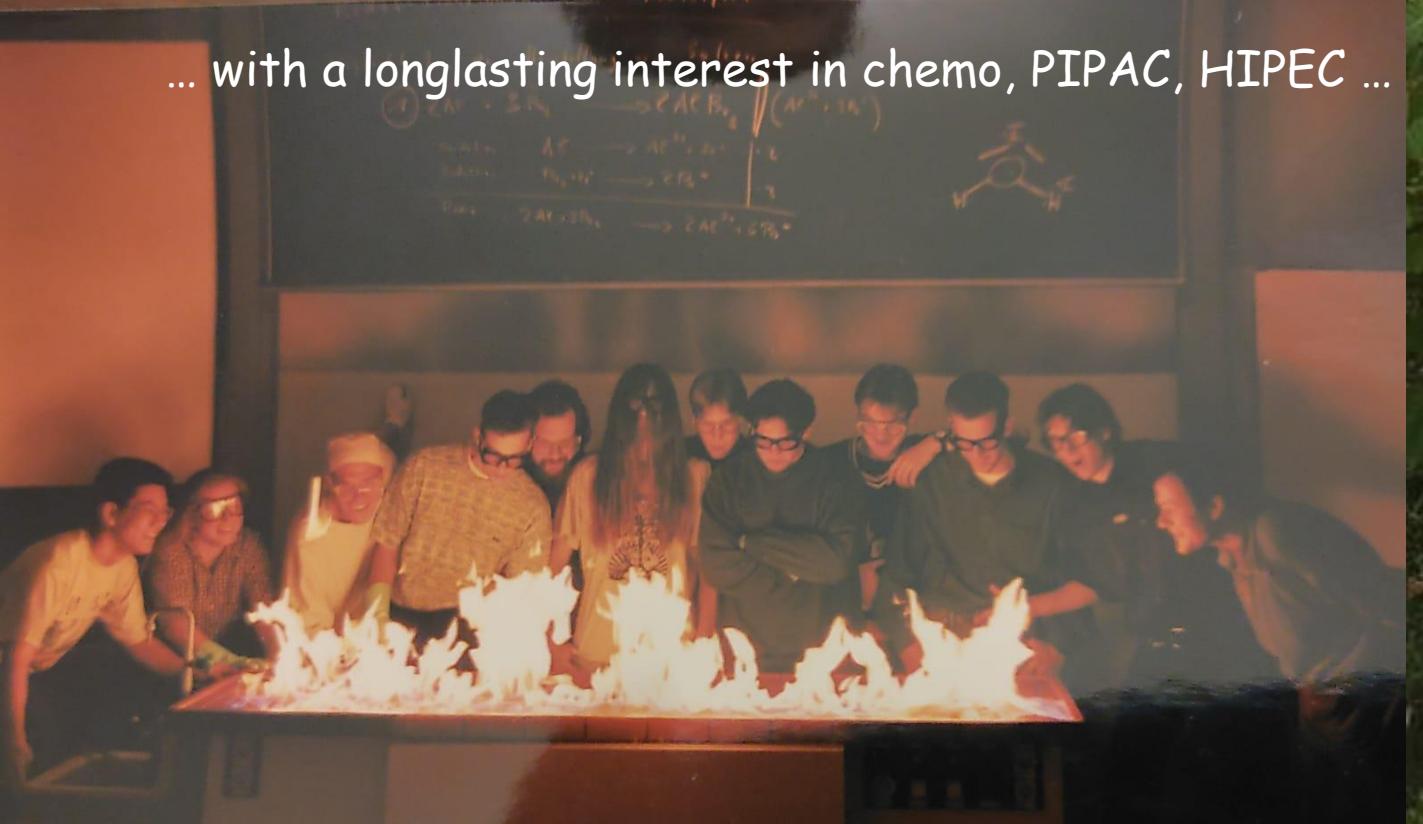
This presentation has been peer-reviewed and no conflicts were noted.

Disclosure 2: I am just a surgeon





... with a longlasting interest in chemo, PIPAC, HIPEC ...



*L*andscapes of peritoneal cancer treatment



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Roadmap

Peritoneal surface malignancies: Definition and Epidemiology

Systemic treatment

Locoregional treatment

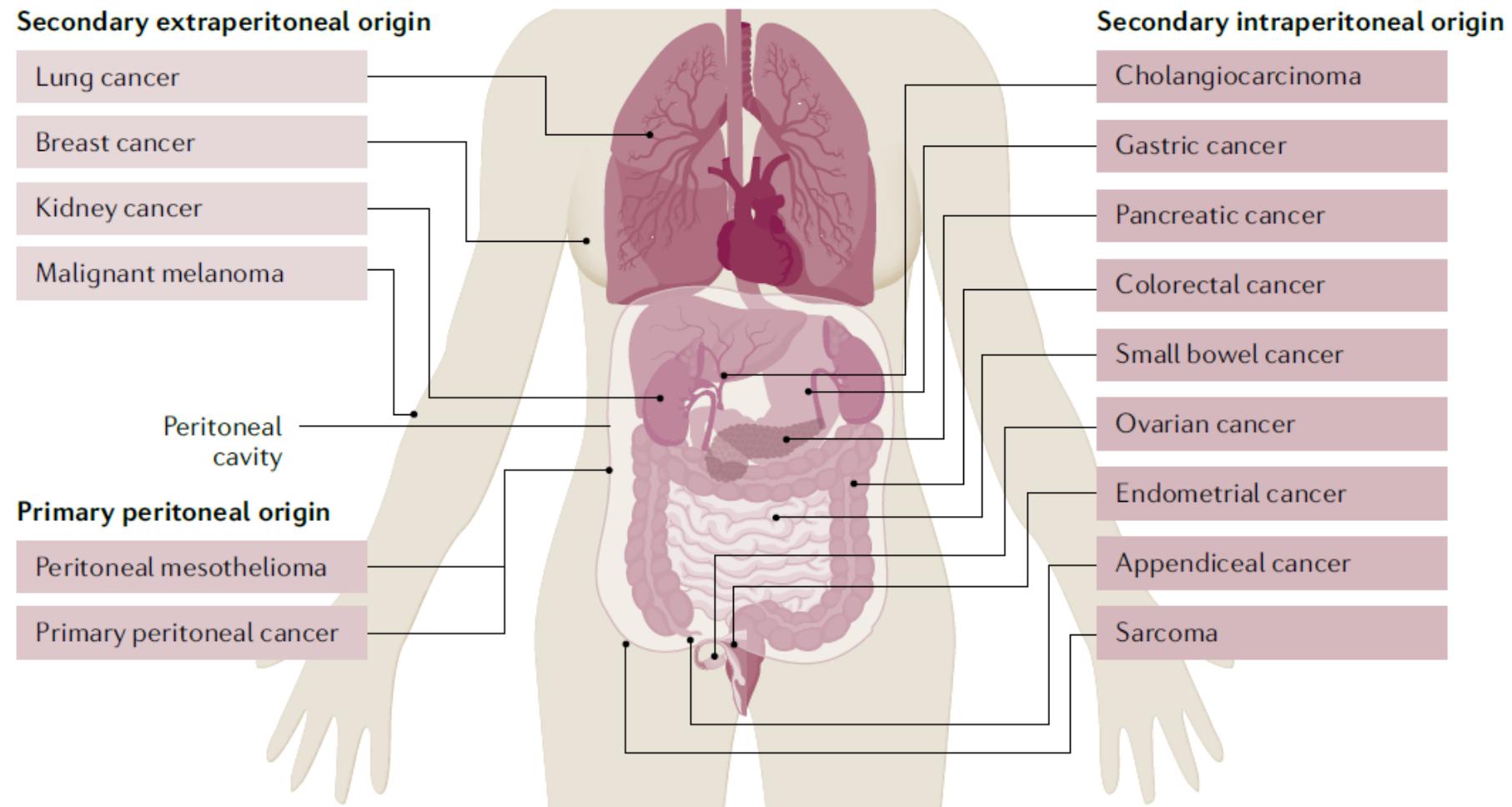
CRS±HIPEC±EPIC
NIPS
PIPAC

Comprehensive treatment strategies

India



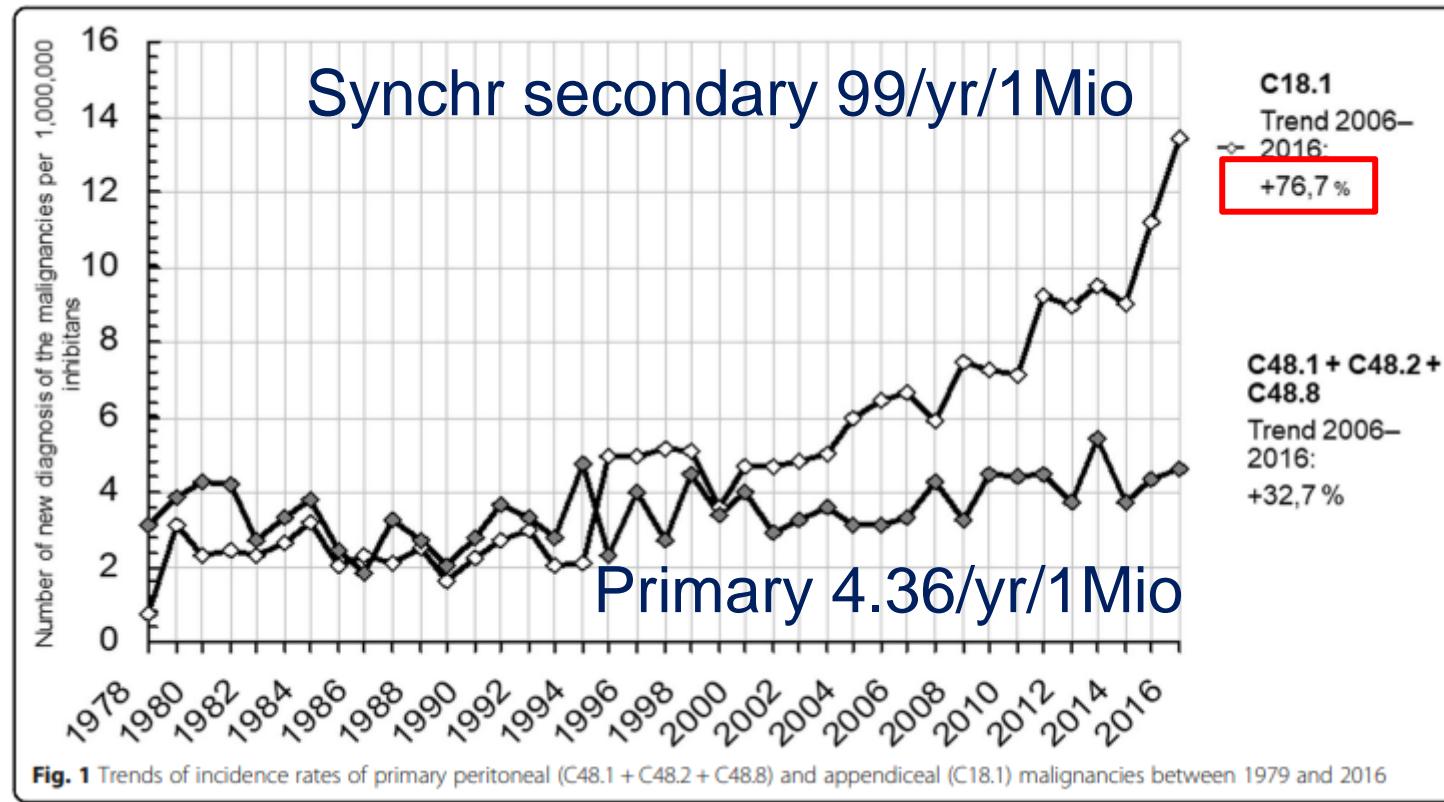
Tumours causing PSM



Incidence by entity

Tumor	Incidence of peritoneal carcinosis
Colorectal Cancer	15–20% if isolated 20–30% with other localizations e.g liver
Stomach Cancer	10–20% when first diagnosed, 30–40% for T3N + primary tumor, 40–50% with recurrence
Ovarian Cancer	60–80% at first diagnosis, 55–75% with recurrence
Pancreatic cancer, cholangiocellular carcinoma	5–10%
Cancer of unknown primary (CUP syndrome), breast cancer, renal cell carcinoma, retroperitoneal sarcoma	<5%

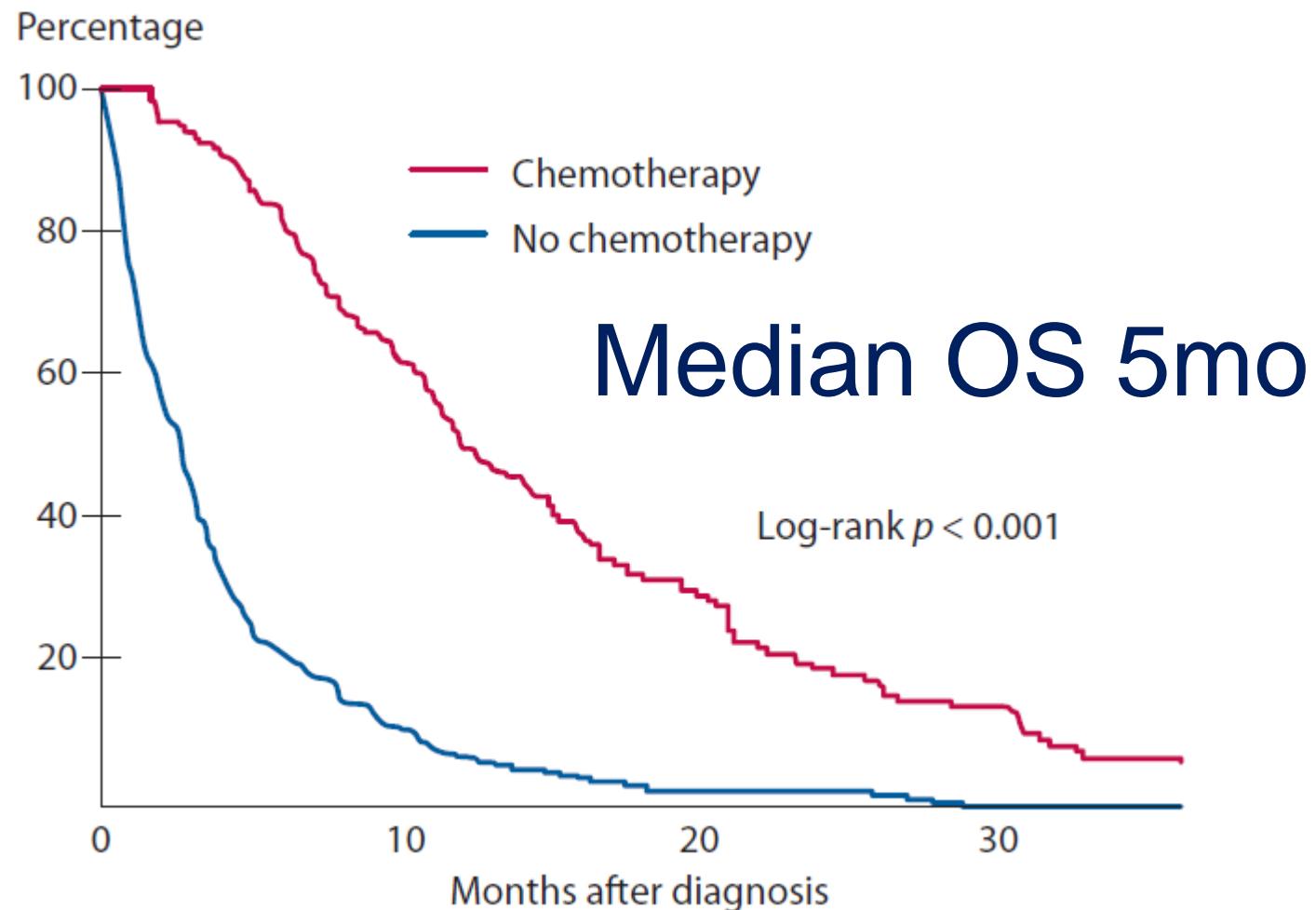
Incidence increasing?



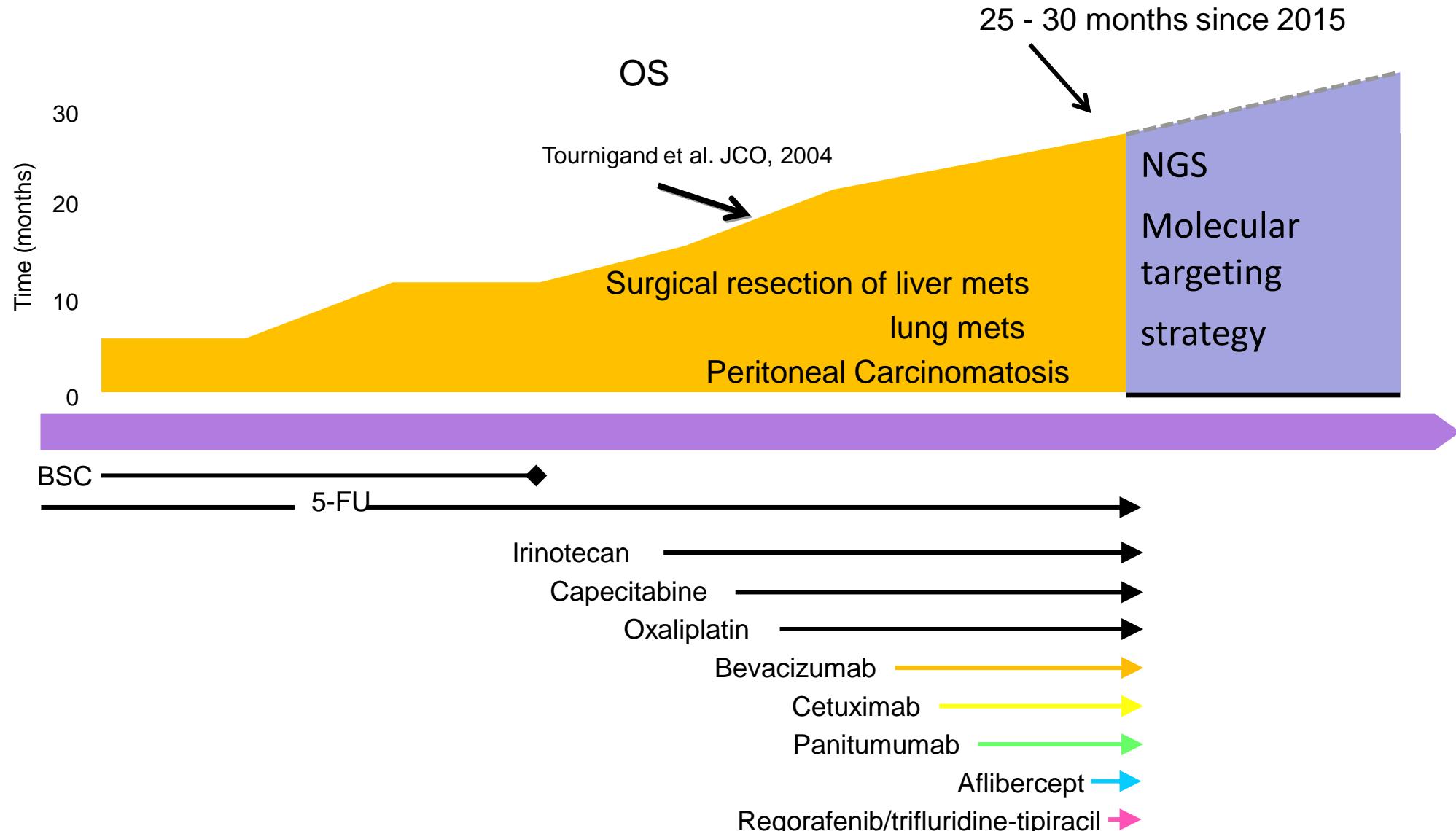
Nigeria



Standard treatment



Survival of metastatic colorectal cancer



A wide-angle photograph of a sunset or sunrise over a body of water. The sky is filled with large, dark, billowing clouds. Bright, golden-yellow rays of light pierce through these clouds, creating a dramatic and ethereal effect. The horizon line is visible at the bottom of the frame, showing a dark blue ocean. The overall mood is serene and majestic.

Israel

Immunotherapy: hope for subgroups!

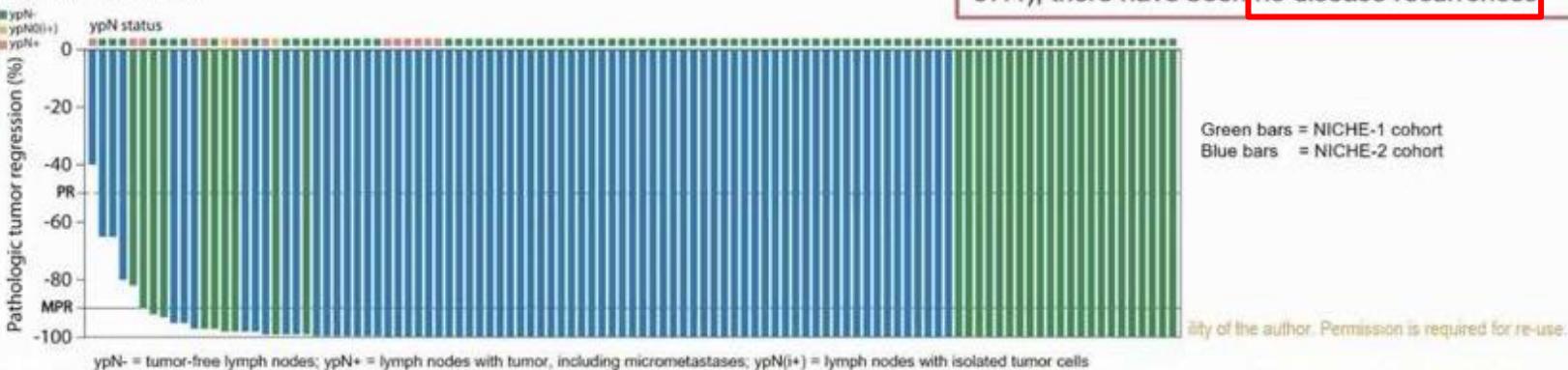
Primary tumour	Molecular alterations	Alterations that favour a response to ICIs
Peritoneal mesothelioma	Ki67 expression >9% associated with inferior prognosis ¹⁹ ; loss of <i>BAP1</i> expression associated with improved prognosis ^{23–26} ; ALK fusions seem to reflect a distinct molecular profile with different characteristics from those of <i>BAP1</i> loss ³⁴⁶ ; <i>EWSR1/FUS–CREB</i> fusions associated with an epithelial phenotype albeit of indeterminate prognostic relevance ^{347,348}	PD-L1 ^a (11–72%) ^{349–352}
PMP	Ki67 expression >15% associated with an inferior prognosis in patients with high-grade appendiceal PMP ³⁵³	PD-L1 ^a (2.2%) ³⁵⁴
Colorectal cancer	<i>KRAS</i> and <i>BRAF</i> mutations ⁵² , <i>NTRK</i> , ALK and <i>ROS1</i> fusions associated with an inferior prognosis ⁵⁴ ; implications of <i>ERBB2</i> amplifications for prognosis remain controversial ⁵³	MSI-H (5% of stage IV) ³⁵⁵
Gastric cancer	<i>HER2</i> overexpression associated with inferior prognosis; MSI-H status associated with improved prognosis ^{37–39}	PD-L1 ^a (14.5–57.1%) ^{356–358}
Ovarian cancer	Loss-of-function <i>BRCA1/2</i> mutations and mutations leading to HRD associated with increased sensitivity to both platinum-containing agents and PARP inhibitors and improved prognosis ⁵⁹	PD-L1 ^a (7.7–68.6%) ^{359,360}

HRD, homologous recombination deficiency; ICI, immune-checkpoint inhibitor; MSI-H, microsatellite instability high; PARP, poly(ADP-ribose) polymerase; PMP, pseudomyxoma peritonei. ^aProportion of tumours with PD-L1 expression on ≥1% of tumour cells.

Major pathologic response in 95% of patients; 67% pCR

Pathologic response (RVT)		Patients n= 107
Yes	(≤ 50%)	106 (99%)
Major	(≤10%)	102 (95%)
Complete	(0%)	72 (67%)
Partial	(10% - 50%)	4 (4%)
No	(≥50%)	1 (1%)

RVT = residual viable tumor



Adjuvant chemotherapy (CTx)

- 14 patients with ypN+ disease
- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences

**Myriam Chalabi**

Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study

06:01

4G



Tweet



Cesar Nevarez Graber liked



President Biden

@POTUS

United States government official

...

I believe we can end cancer as we know it and even cure cancers once and for all.

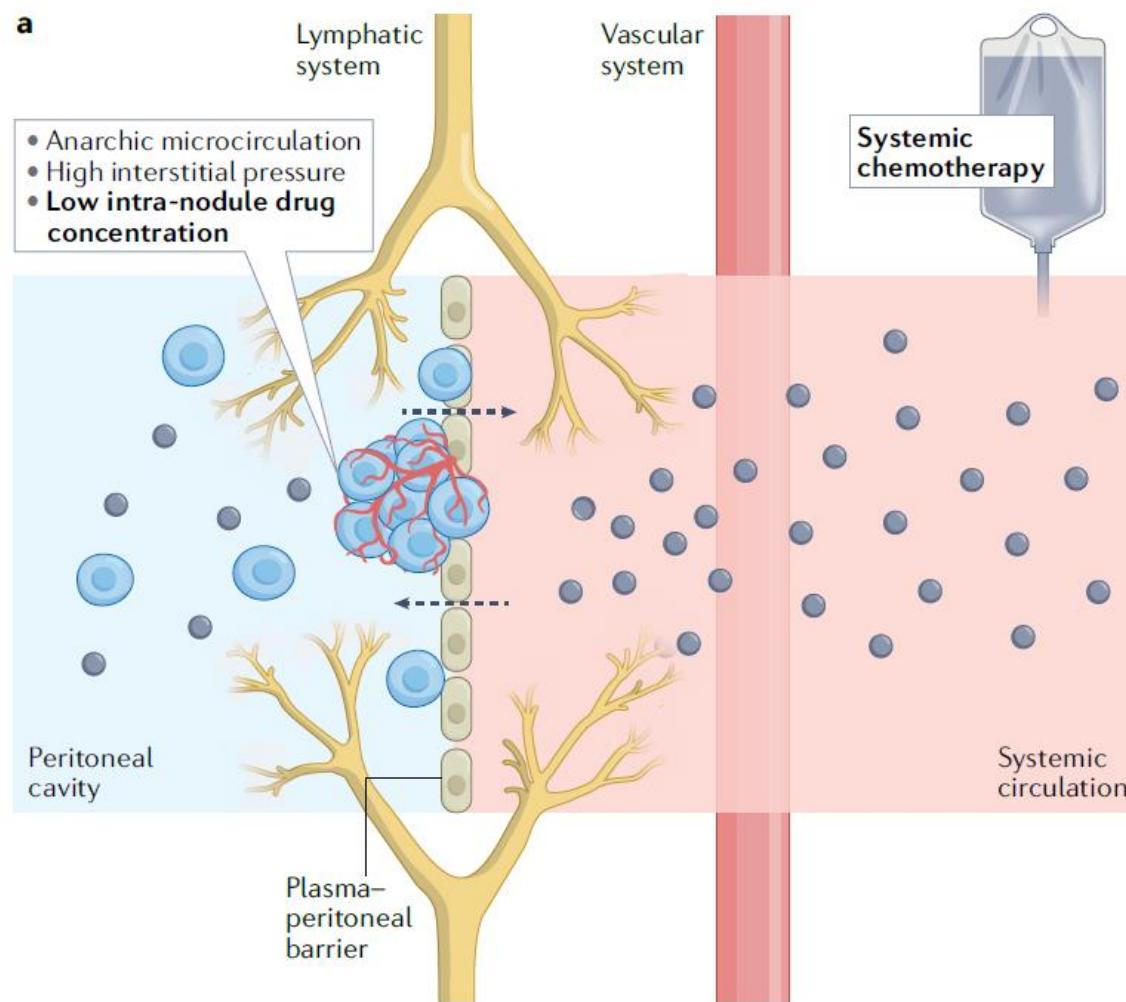
yet another ...

23:40 · 12/09/2022 · The White House

15,8K Retweets **5475** Quote Tweets **162K** Likes

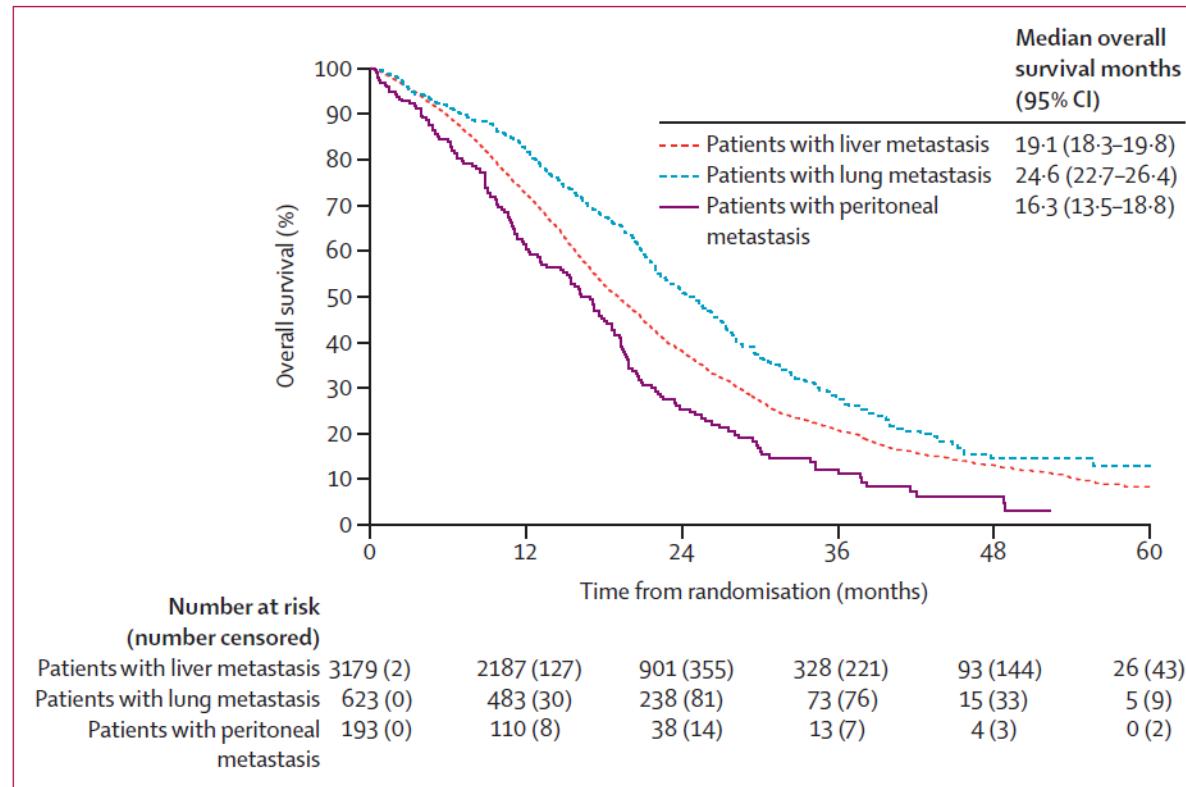


Limitations of systemic chemotherapy



Peritoneal mets: dismal prognosis

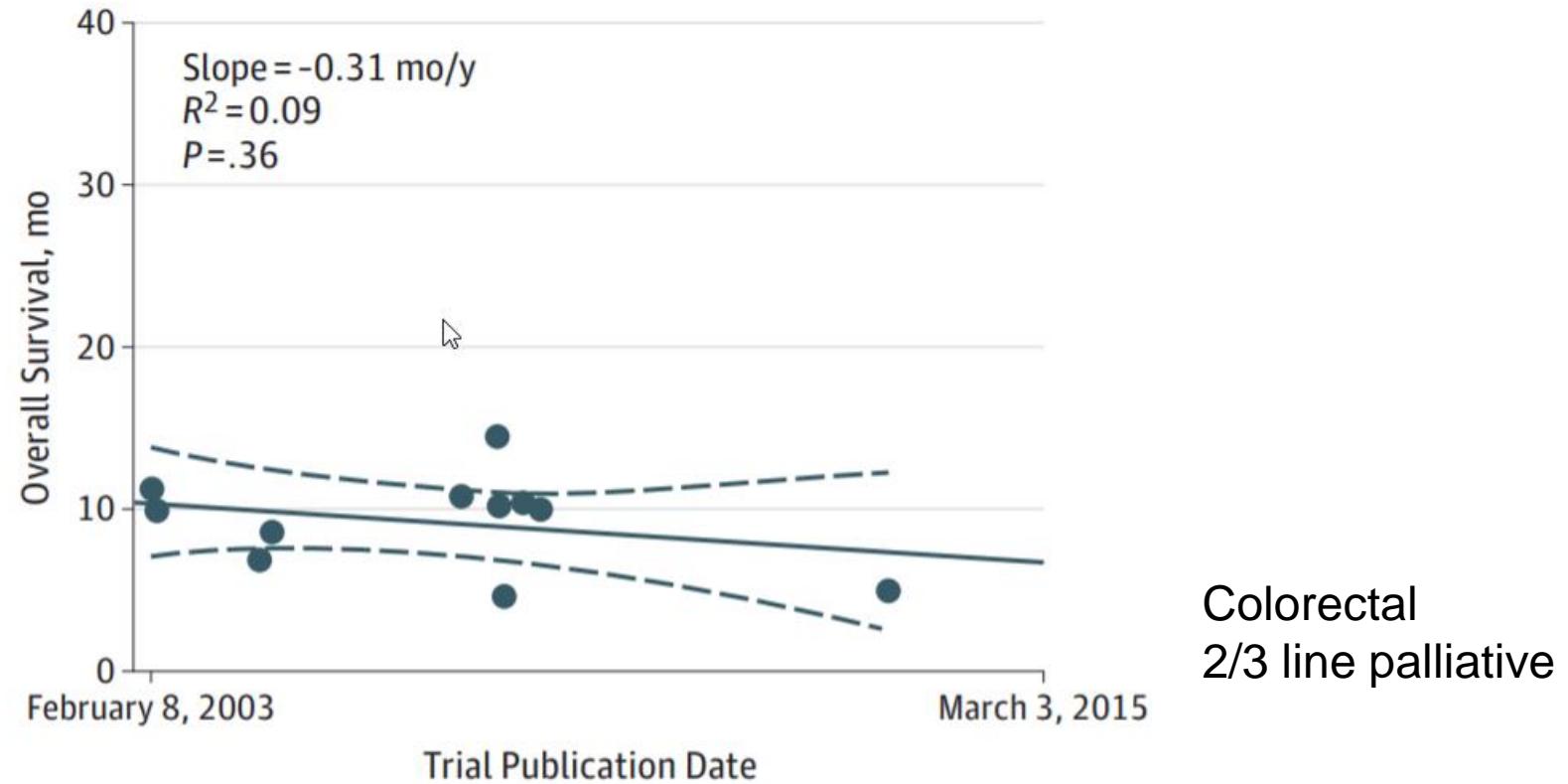
colorectal





Malaysia

Little improvements of the « gold standard »



The
biggest
room in
the
world
is ...

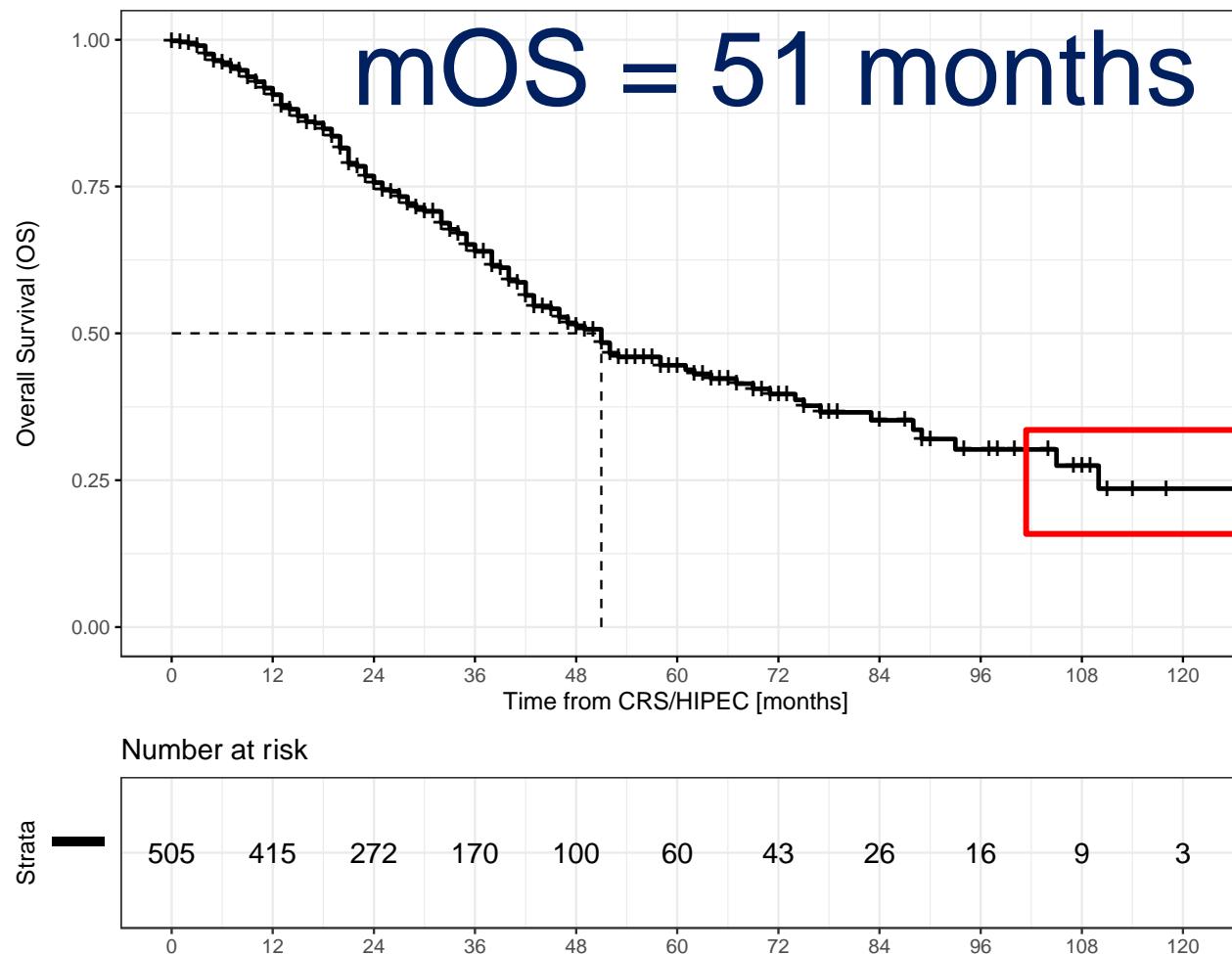
... the room
for
improvement!



A dramatic photograph capturing a large-scale forest fire. In the foreground, intense orange flames engulf several trees, casting a bright glow against the dark smoke. The smoke billows upwards and to the left, creating a dense, hazy atmosphere. In the background, tall, thin trees stand amidst the smoke, their trunks appearing as dark silhouettes. The overall scene conveys a sense of destruction and the powerful impact of the fire.

Brazil

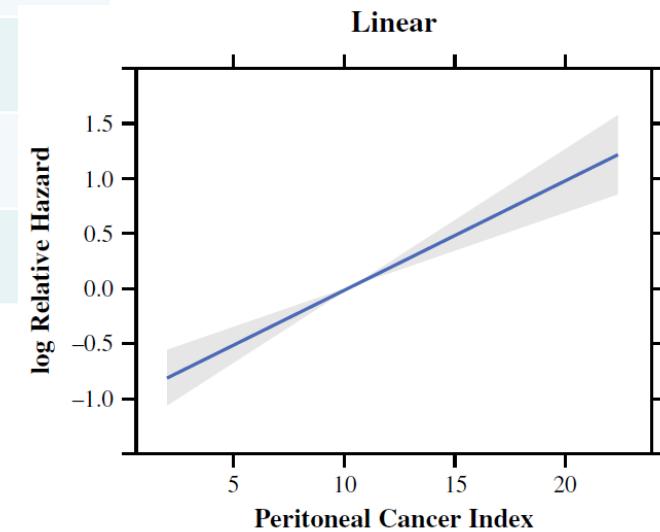
Excellent outcomes after CRS/HIPEC



Key of success: complete cytoreduction

	Complete CRS	Incomplete ...	HR
Ovarian	62mo	28 (46 none)	
CRC	>40mo		
DMPM	94mo	67mo	24
PMP	103	53	
Gastric		18.8mo	1.45

↑ 10% CRS = ↑ 5.5% OS
PCI + 1 = ↓ 5% OS



Kepenekian Nature Rev Clin Oncol 2022, Bonnot JCO 2019 and BJS 2021,
Faron Ann Surg Oncol 2016

Patient selection for CRS

Patient's condition

- Age
- Performance status
- Vital function status
- Motivation, psychology
- Comprehensive geriatric assessment

Centre

- Surgeon's skills
- Multidisciplinary peritoneal surface malignancy team
- Intensive care unit availability
- Interventional radiology
- Prehabilitation and enhanced recovery

Resectability of peritoneal surface malignancies

Tumour

- Histological features
- Response to neoadjuvant systemic or intraperitoneal chemotherapy
- Molecular factors

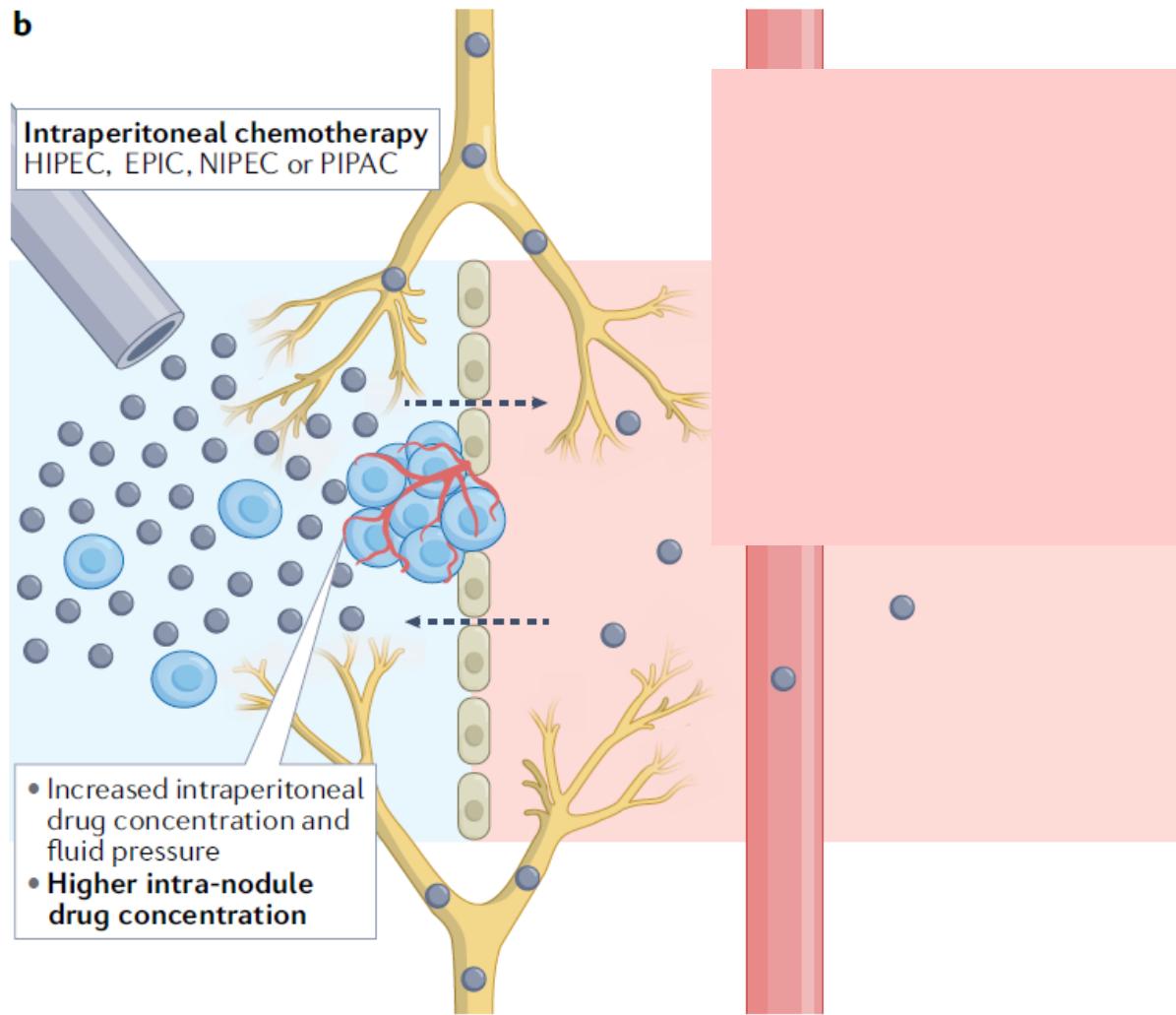
Peritoneal disease

- Disease extent (PCI)
- Possibility of complete cytoreductive surgery
- Extraperitoneal disease

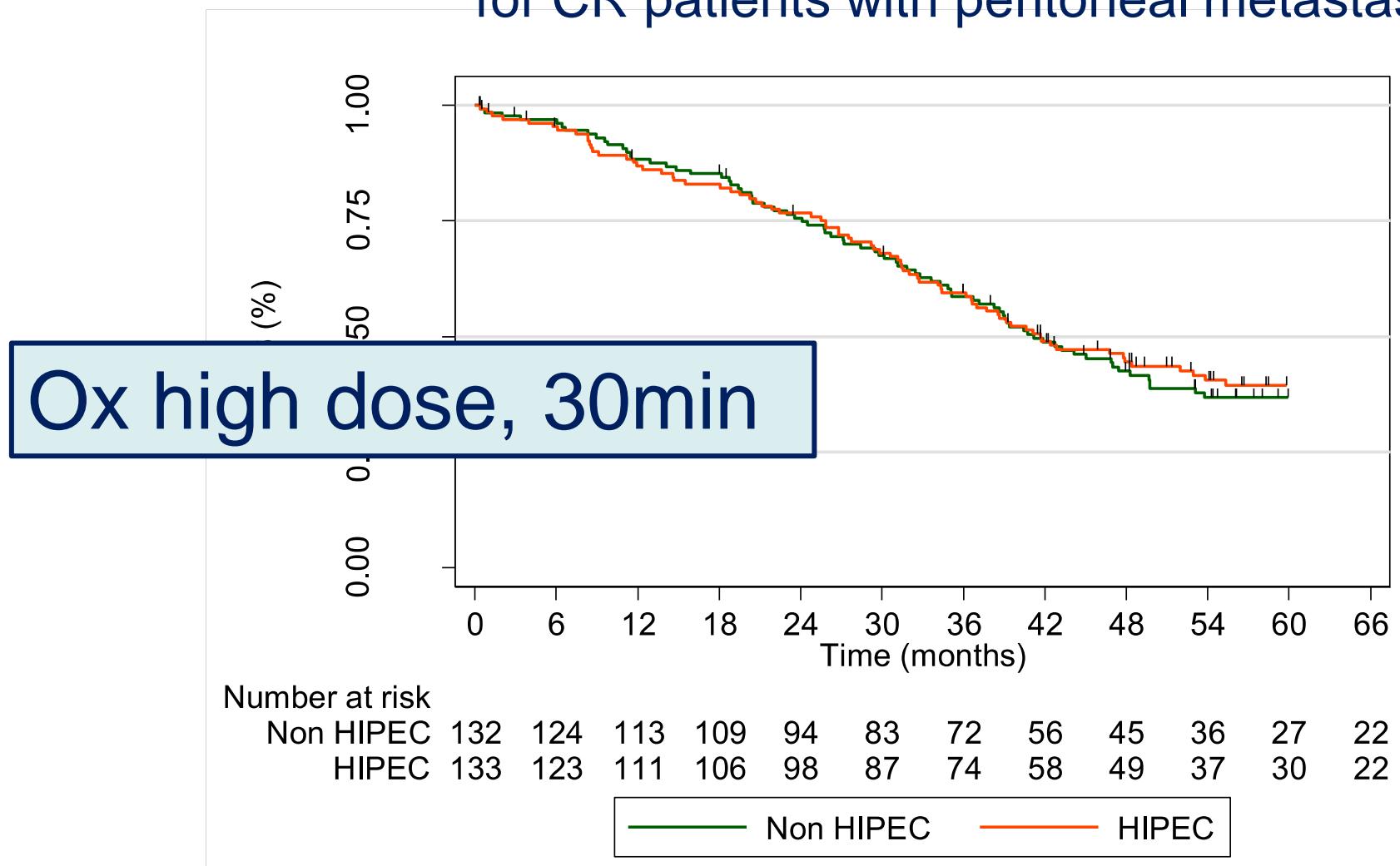


USA

Rationale for IP chemotherapy

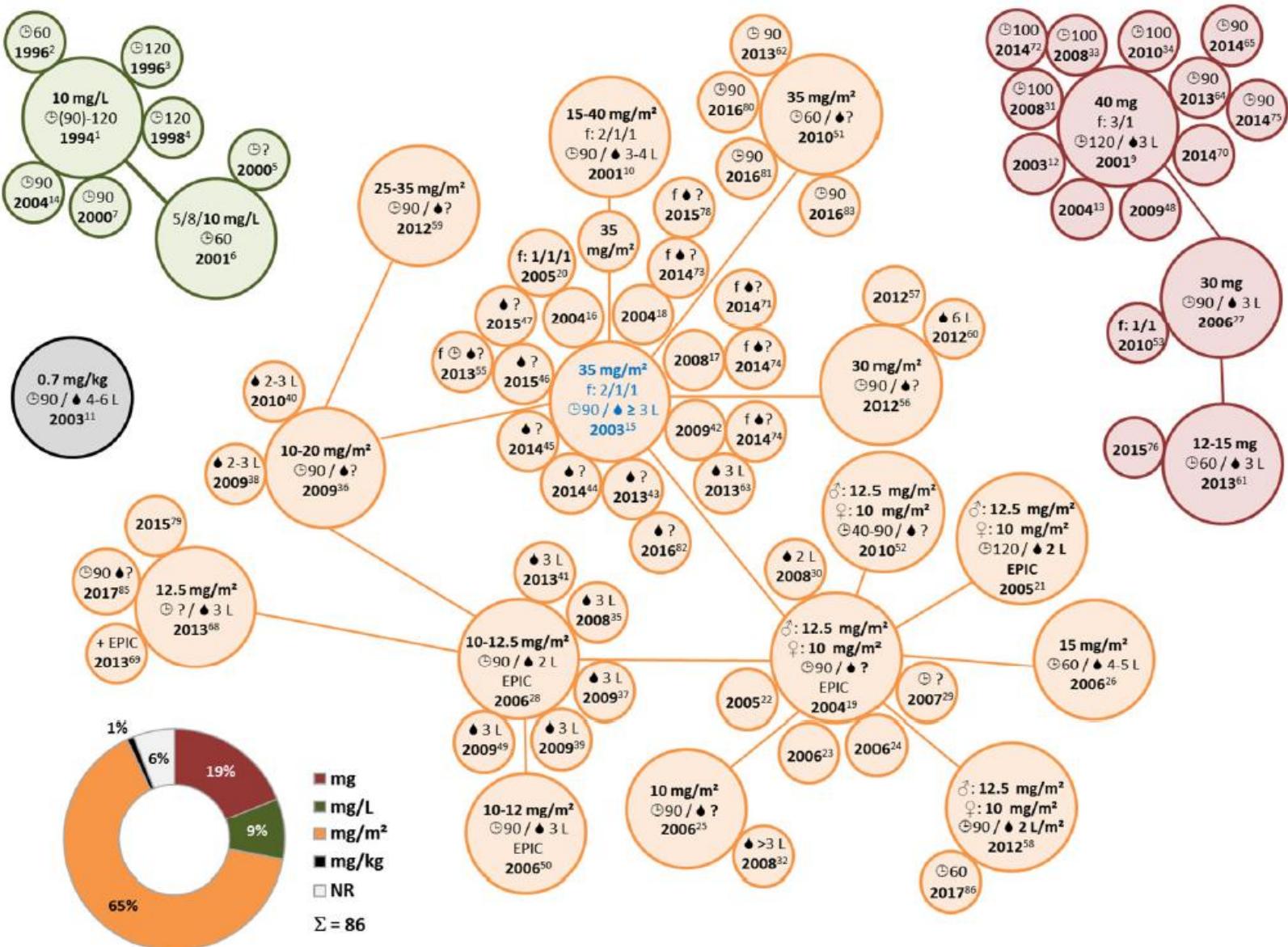


Prodige 7: HIPEC as treatment for CR patients with peritoneal metastases





France



Spain

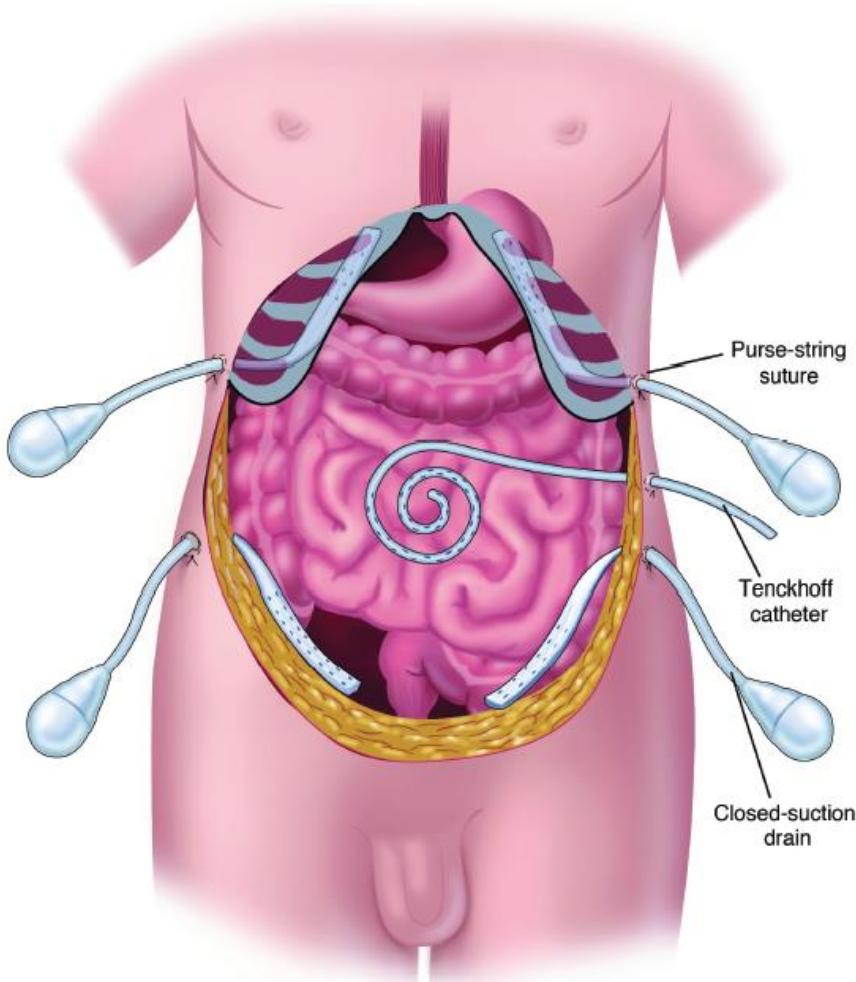






Rumania

Early Post-OP IP Chemotherapy



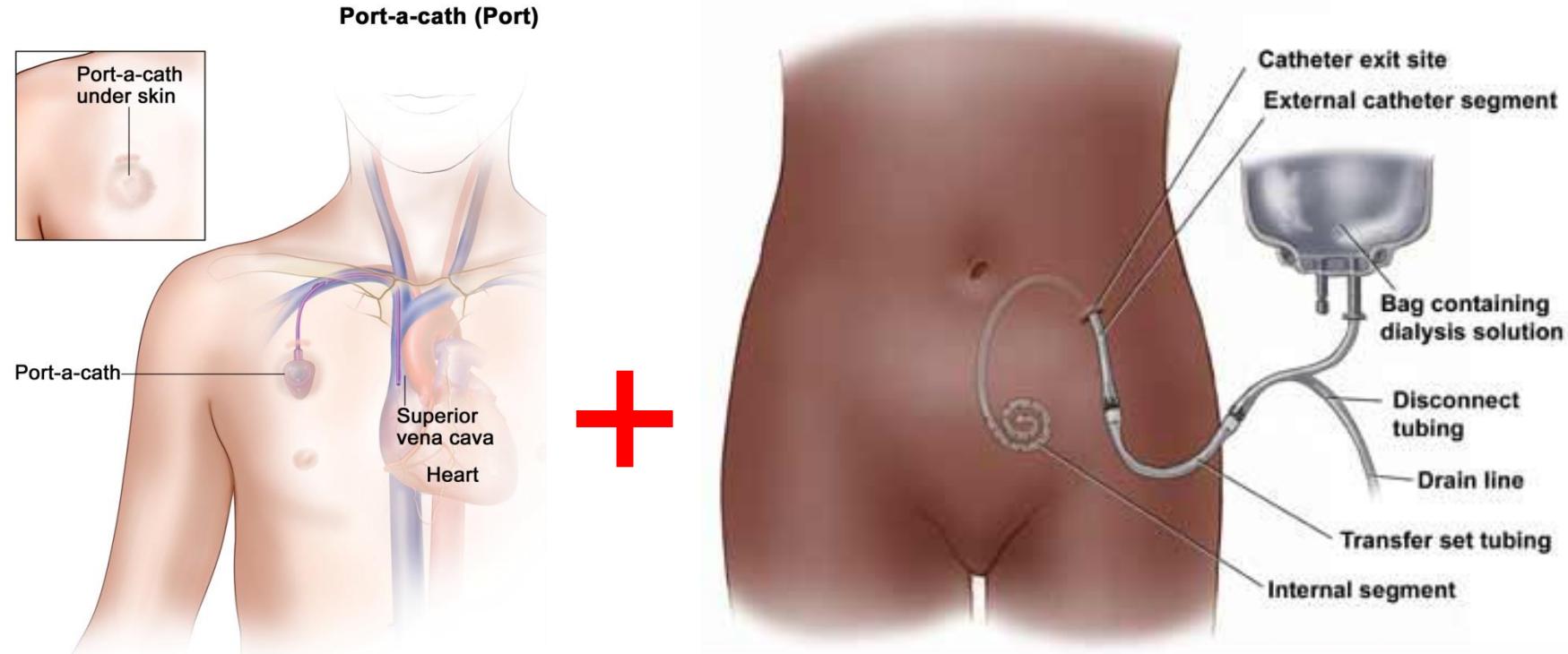
Author (Ref)	Year	n	Method	Agent for IPC
Glehen <i>et al.</i> (23)	2004	506	EPIC±HIPEC	5-FU
Kecmanovic <i>et al.</i> (51)	2005	18	HIPEC+EPIC	5-FU
Da Silva <i>et al.</i> (52)	2006	70	HIPEC+EPIC	5-FU±MMC
Fuzun <i>et al.</i> (53)	2006	29	HIPEC+EPIC	5-FU
Bijelic <i>et al.</i> (54)	2007	49	HIPEC+EPIC	5-FU±MMC
Elias <i>et al.</i> (55)	2007	23	EPIC	5-FU+MMC
Piso <i>et al.</i> (56)	2007	32	HIPEC+EPIC	5-FU
Yan <i>et al.</i> (57)	2008	50	HIPEC+EPIC	5-FU
Bretcha-Boix <i>et al.</i> (58)	2010	20	HIPEC+EPIC	5-FU
Saxena <i>et al.</i> (59)	2010	63	EPIC±HIPEC	5-FU
Cashin <i>et al.</i> (60)	2012	57	SPIC	5-FU+leucovorin
Klaver <i>et al.</i> (61)	2012	24	EPIC±HIPEC	5-FU
Chua <i>et al.</i> (62)	2013	75	HIPEC+EPIC	5-FU
Huang <i>et al.</i> (63)	2014	62	HIPEC+EPIC	Docetaxel+carboplatin

Combination: more complications
no survival benefits



Australia

Neoadjuvant IP and Systemic Chemotherapy

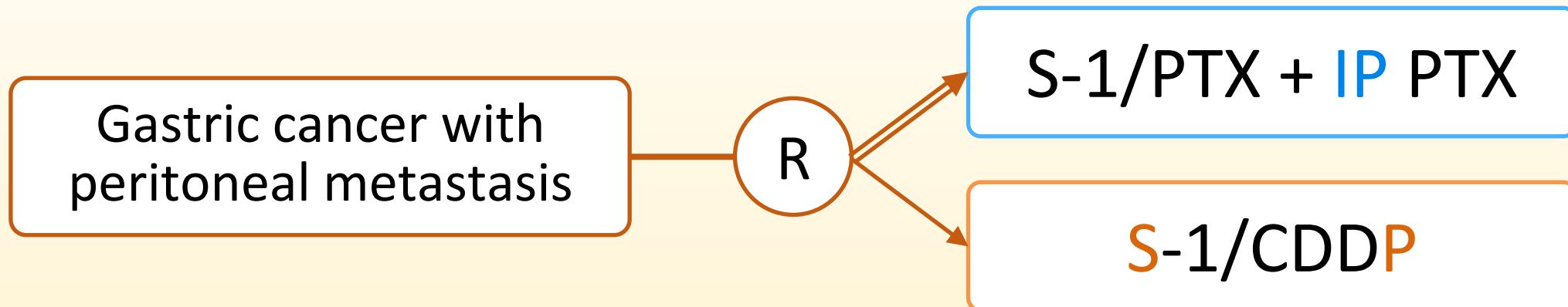


Modification: SPIC
Sequential Perioperative Intraperitoneal Chemotherapy



2011-2016

PHOENIX-GC Trial



Key Eligibility Criteria

- Peritoneal metastasis
- No or <2mo. prior chemo
- No prior gastrectomy
- No other distant metastasis
- No frequent ascites drainage

Stratification

- Institution
- Prior chemotherapy +/-
- Peritoneal meta.
 P_1/P_{2-3}

Primary Endpoint

- Overall survival

Secondary Endpoints

- Response rate
- 3-yr OS rate
- Safety

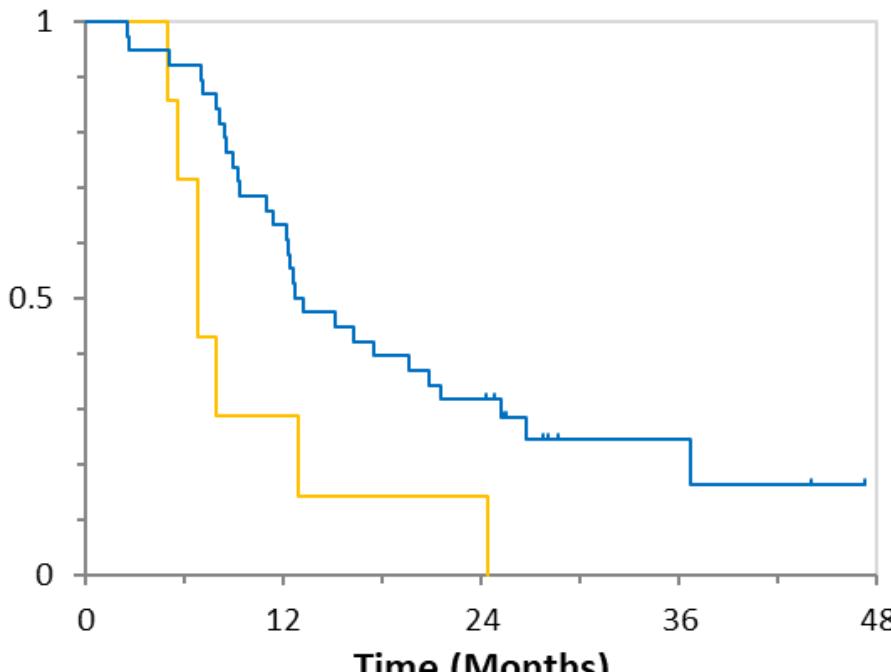
By courtesy of H. Ishigami

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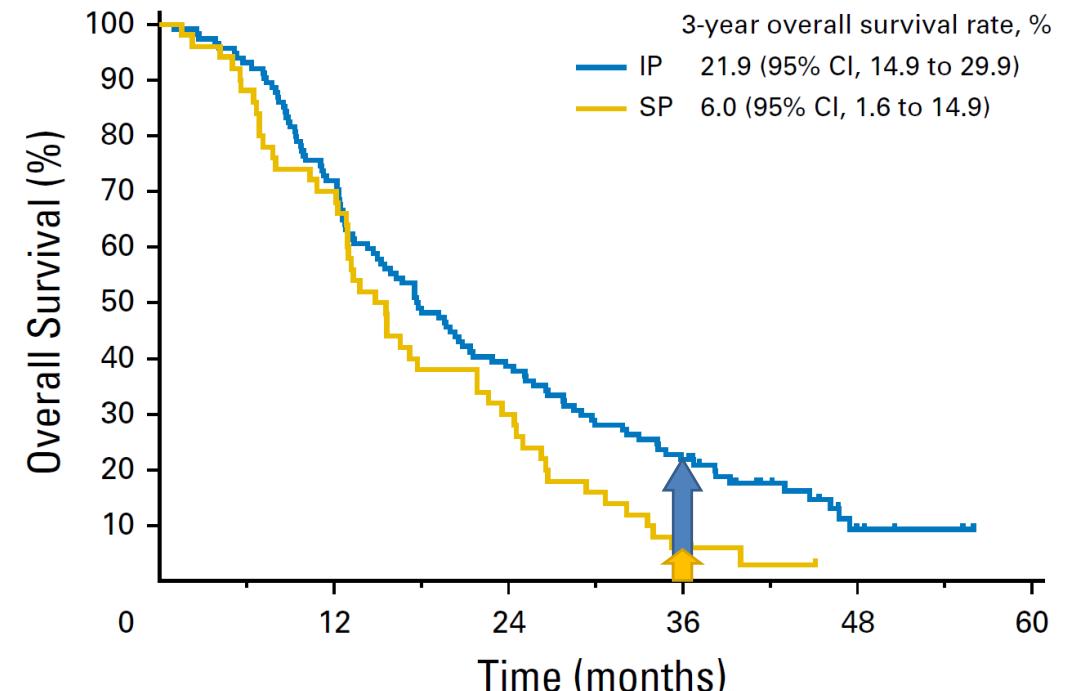
Overall Survival

Moderate amount ascites



HR 0.38 (95%CI 0.16–0.90)

B Additional 1-year follow-up analysis



No. at risk

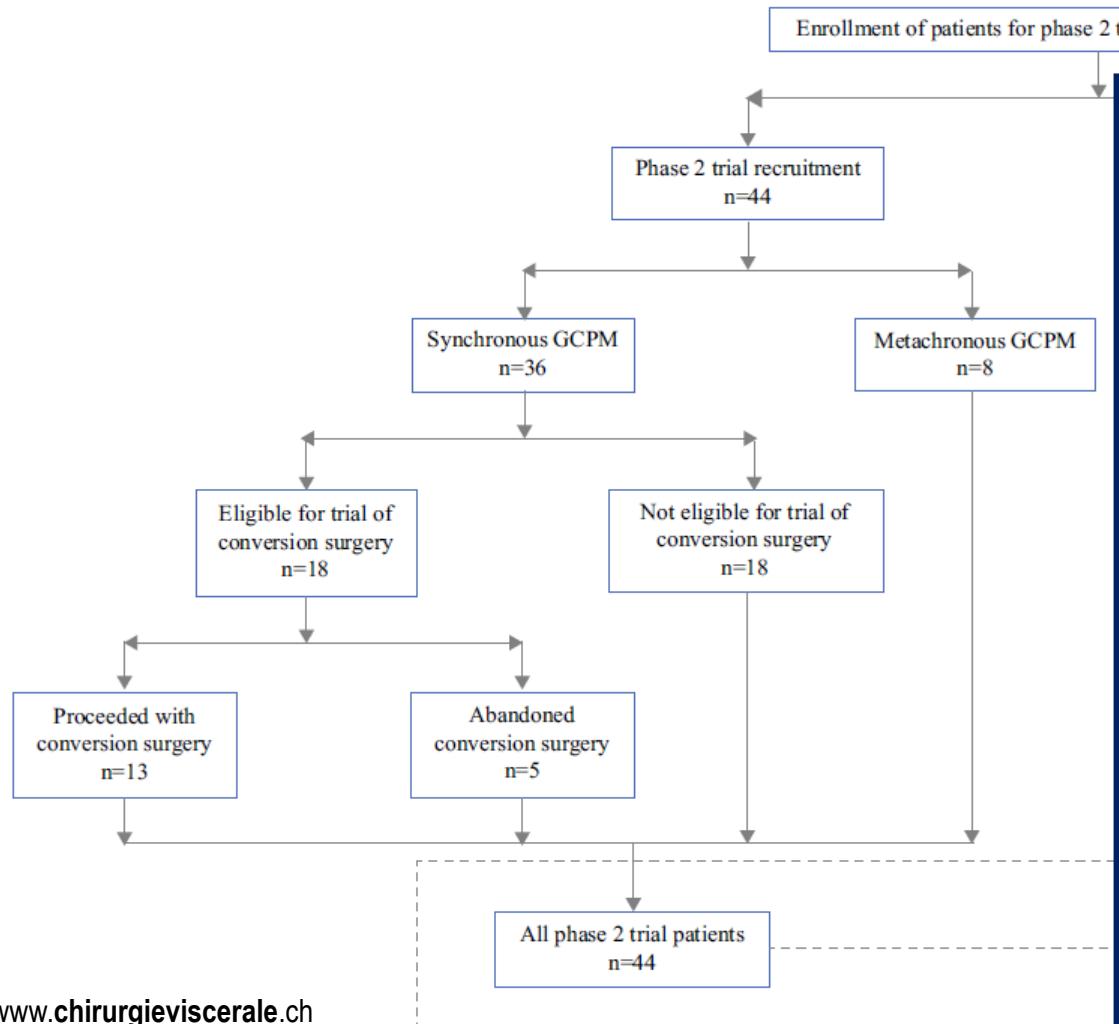
IP	114	82	44	25	4	0
SP	50	35	15	3	0	0

By courtesy of H. Ishigami

Ishigami H et al. *J Clin Oncol* 2018

39

Outcomes of a Phase II Study of Intraperitoneal Paclitaxel plus Systemic Capecitabine and Oxaliplatin (XELOX) for Gastric Cancer with Peritoneal Metastases



Σ 402 cycles of IP PTX and XELOX

AE \geq 3: neutropenia (18%) \rightarrow 2+
electrolyte derangements (14%)
diarrhea (7%)

Port-related complications in 23%
 \rightarrow 9% re-OP

Propensity score matching



Prince Charles

- Male
- Born in 1948
- Raised in the UK
- Married twice
- Lives in a castle
- Wealthy & famous

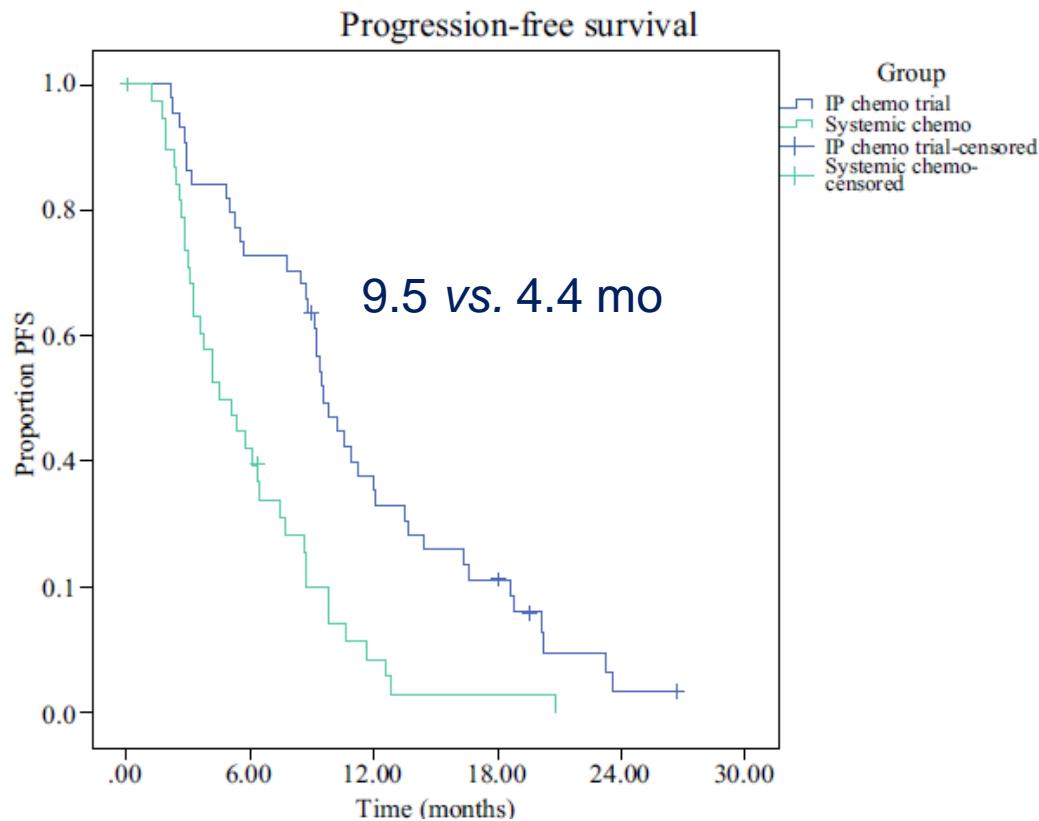
Ozzy Osbourne

- Male
- Born in 1948
- Raised in the UK
- Married twice
- Lives in a castle
- Wealthy & famous

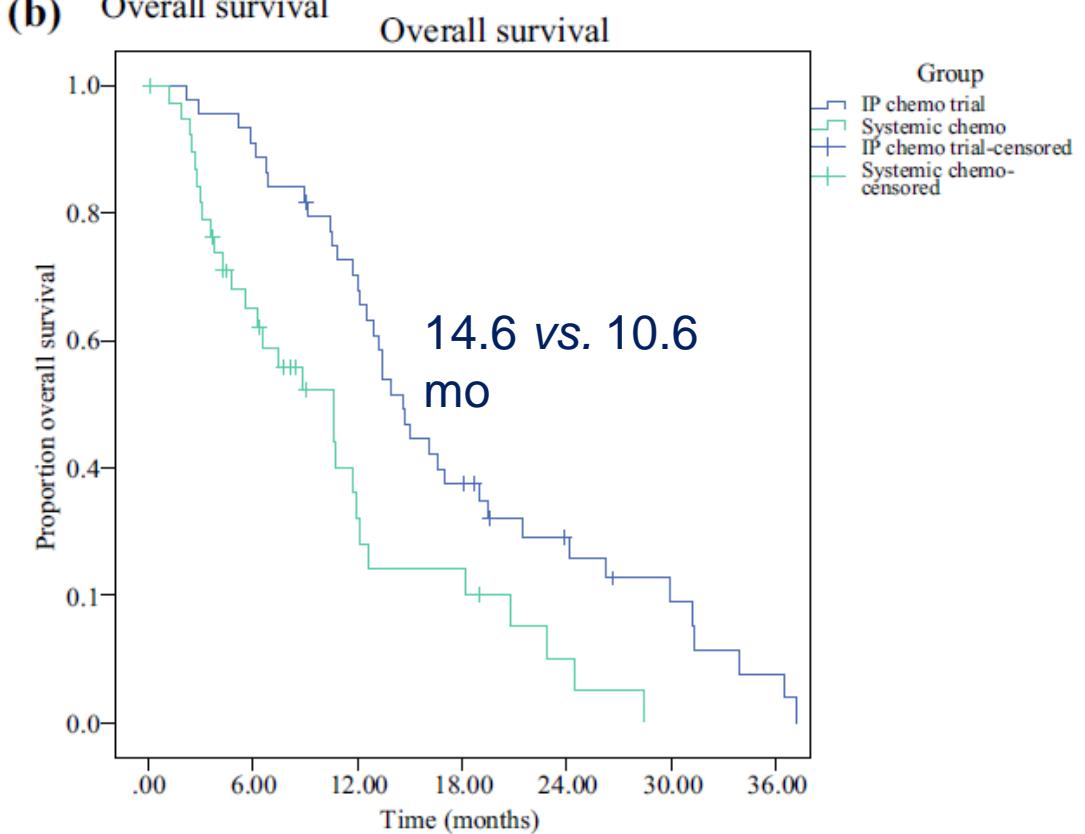


Same in Singapore ...

(a) Progression-free survival



(b) Overall survival



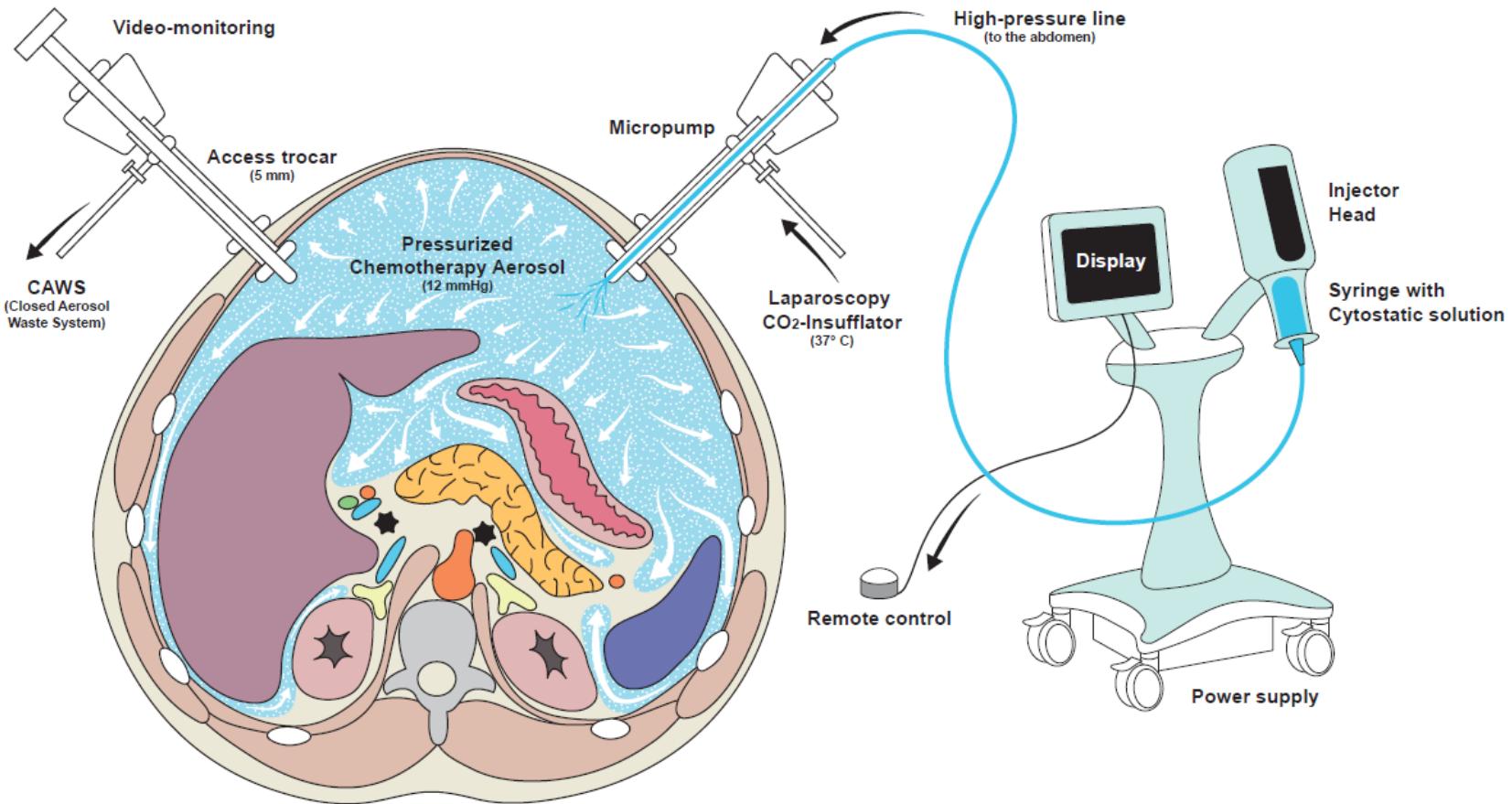
In IP group: conversion surgery in 36.1% (13/36)
→ median OS of 24.2 (95% CI 13.1–35.3) months
→ 1-year OS of 84.6%



Vietnam



PIPAC: rationale and set-up



3 applications within 3 months

Reymond *Surg Endoscopy* 2000
Solass *Ann Surg Oncol* 2014
Hübner *RMS* 2015

Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications

Mohammad Alyami*, Martin Hübner*, Fabian Grass, Naoual Bakrin, Laurent Villeneuve, Nathalie Laplace, Guillaume Passot, Olivier Glehen, Vahan Kepenekian

Main primary	Number of patients	Number of PIPAC	Non-access	≥2 PIPAC	Surgical complications [A: for ≥2 PIPAC?]	Adverse events (CTCAE 4.0)		
						Grade 3	Grade 4	Grade 5
Prospective								
PIPAC OV-1 [A: ref 57?]	Ovarian	64	130	11/64 (17%)	43/53 (81%)	4/53 (8%)	8/53 (15%)	0/53
PIPAC GA-1 (NCT01854255)	Gastric	25	43	NA	12/25 (48%)	NA	4/25 (16%)	0/25
PIPAC GA-2 [A: ref 39?]	Gastric	31	56	0	15/31 (48%)	1/31 (3%)	4/31 (13%)	0/31
PIPAC OPC-1 [A: ref 80?]	Various	35	129	0	30/35 (86%)	2/35 (6%)	4/35 (11%)	1/35 (3%)
Subtotal, weighted means	..	155	358	8.5%	69.4%	5.9%	13.9%	0.7%
Retrospective								
Tempfer and colleagues ⁵⁸	Ovarian	21	34	3/21 (14%)	8/18 (44%)	3/18 (17%)	3/18 (17%)	0/18
Tempfer and colleagues ⁵⁹	Ovarian	99	252	17/99 (17%)	50/82 (61%)	5/82 (6%)*	17/82 (21%)	3/82 (37%)
Nadiradze and collaegues ⁶²	Gastric	25	60	1/25 (4%); 3/24 (13%)‡	17/24 (71%)	3/60 procedures (5%)	6/24 (25%)	1/24 (4%)
Odenthal and colleagues ⁶⁸	Various	91	158	NA†; 5/91 (6%)‡	48/91 (53%)	3/91 (3%)	8/91 (9%)	1/91 (1%)
Robella and colleagues ⁶⁸	Various	14	40	0	14/14 (100%)	0	0/14	0/14
Demtröder and colleagues ⁷²	Colorectal	17	48	0†; 6/17 (35%)‡	14/17 (82%)	0	4/17 (24%)	0/17
Graversen and colleagues ⁷⁶	Pancreatic	5	16	0	5/5 (100%)	0	0/5	0/5
Hübner and colleagues ⁸³	Various	44	91	2/44 (4%)	30/42 (71%)	1/42 (2%)	0/42	1/42 (3%; nr)
Alyami and colleagues ¹⁰	Various	73	164	NA	45/73 (62%)	NA	14/73 (19%)	0/73
Khosrawipour and colleagues ⁸⁴	Pancreatic	20	41	0†; 3/20 (15%)‡	10/20 (50%)	0	0/20	0/20
Falkenstein and colleagues ⁸⁵	Biliary tract	13	17	2/13 (15%)	5/11 (45%)	0	0/11	0/11
Kurtz and colleagues ⁸⁶	Various	71	142	8/71 (11%)	39/63 (62%)	7/142 (5%)	1/63 (16%)	0/63
Gockel and colleagues ⁸⁷	Gastric	28	46	3/28 (11%)†; 2/24 (8%)‡	14/24 (58%)	NA	0/24	0/24
Horvath and colleagues ⁸⁸	Pancreatic	12	23	0	6/12 (50%)	0	0/12	0/12
Jansen-Winkel and colleagues ³³	Various	62	111	5/59 (8%)†; 4/54 (7%)‡	33/54 (61%)	7/54 (13%)	NA	NA
Giger-Pabst and colleagues ³⁷	Mesothelioma	29	74	7/29 (24%)	20/22 (91%)	0	1/22 (5%)	2/22 (9%)
Subtotal, weighted means	..	624	1317	10.5%†	62.6%	Not pooled (data heterogeneity)	10.4%	r: 0.8%; nr: 1.9%

- ✓ Safe and feasible
- ✓ Well-tolerated
- ✓ Encouraging clinical response

But: mixed cohorts AND
no RCTs/comparative studies yet

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input checked="" type="checkbox"/>	Unknown [†]	PIPAC for the Treatment of Colorectal Peritoneal Metastases	<ul style="list-style-type: none"> Colorectal Neoplasms Peritoneal Metastases 	<ul style="list-style-type: none"> Procedure: Pressurised Intraperitoneal Aerosol Chemotherapy (PIPAC) 	<ul style="list-style-type: none"> Imperial College Healthcare NHS Trust London, United Kingdom
2	<input checked="" type="checkbox"/>	Completed	PIPAC for Peritoneal Metastases of Colorectal Cancer	<ul style="list-style-type: none"> Colorectal Neoplasms Peritoneal Neoplasms Appendiceal Neoplasms Peritoneal Carcinomatosis 	<ul style="list-style-type: none"> Combination Product: repetitive ePIPAC-OX 	<ul style="list-style-type: none"> Catharina Hospital Eindhoven, Netherlands St. Antonius Hospital Nieuwegein, Netherlands
3	<input checked="" type="checkbox"/>	Not yet recruiting	Combined Neoadjuvant Systemic and PIPAC Therapy (NASPIT) for Patients With Colorectal Peritoneal Metastasis Eligible for CRS and HIPEC: A Prospective Phase II Trial	<ul style="list-style-type: none"> Metastatic Colorectal Cancer Peritoneal Carcinomatosis Colorectal cancer 	<ul style="list-style-type: none"> Procedure: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) 	
4	<input type="checkbox"/>	Recruiting	PIPAC for the Treatment of Peritoneal Carcinomatosis in Patients With Ovarian, Uterine, Appendiceal, Colorectal, or Gastric Cancer	<ul style="list-style-type: none"> Clir VB Clir AJC Clir AJC (an Per Per 		
5	<input checked="" type="checkbox"/>	Not yet recruiting	Second Line Oxaliplatin Based Chemotherapy Alone Versus Oxaliplatin Based PIPAC and Chemotherapy in Colorectal Peritoneal Carcinomatosis : A Phase II Randomized Multicentric Study			
6	<input type="checkbox"/>	Completed	Study of Efficacy and Safety of Laparoscopic Intra-abdominal Chemotherapy (PIPAC) Performed in Patients With Peritoneal Carcinomatosis From Colorectal, Ovarian, Gastric Cancer and Primary Peritoneal Tumors			
7	<input type="checkbox"/>	Terminated	Oxaliplatin in PIPAC for Nonresectable Peritoneal Metastases of Digestive Cancers	<ul style="list-style-type: none"> Dig 		
8	<input checked="" type="checkbox"/>	Recruiting	Adjuvant Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in Resected High Risk Colon Cancer Patients	<ul style="list-style-type: none"> Per Per Per Col 		
9	<input type="checkbox"/>	Not yet recruiting	Intrapertitoneal Aerosolized Nanoliposomal Irinotecan (Nai-IRI) in Peritoneal Carcinomatosis From Gastrointestinal Cancer	<ul style="list-style-type: none"> Per Peritoneal Metastases Colorectal Cancer (and 5 more...) 		Ghent, East-Flanders, Belgium
10	<input type="checkbox"/>	Recruiting	International Registry of Patients Treated With Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC)	<ul style="list-style-type: none"> Peritoneum Cancer Peritoneum Neoplasm Pleural Cancer (and 12 more...) 	<ul style="list-style-type: none"> Combination Product: PIPAC 	<ul style="list-style-type: none"> Rocco Cancer Institute Buenos Aires, Argentina Peter MacCallum Cancer Centre Melbourne, Australia SALK - Salzburger Landeskliniken Salzburg, Austria (and 13 more...)



all you need is
patience

Research

hospital

Closing the gap ...

Multicenter retrospective cohort study:

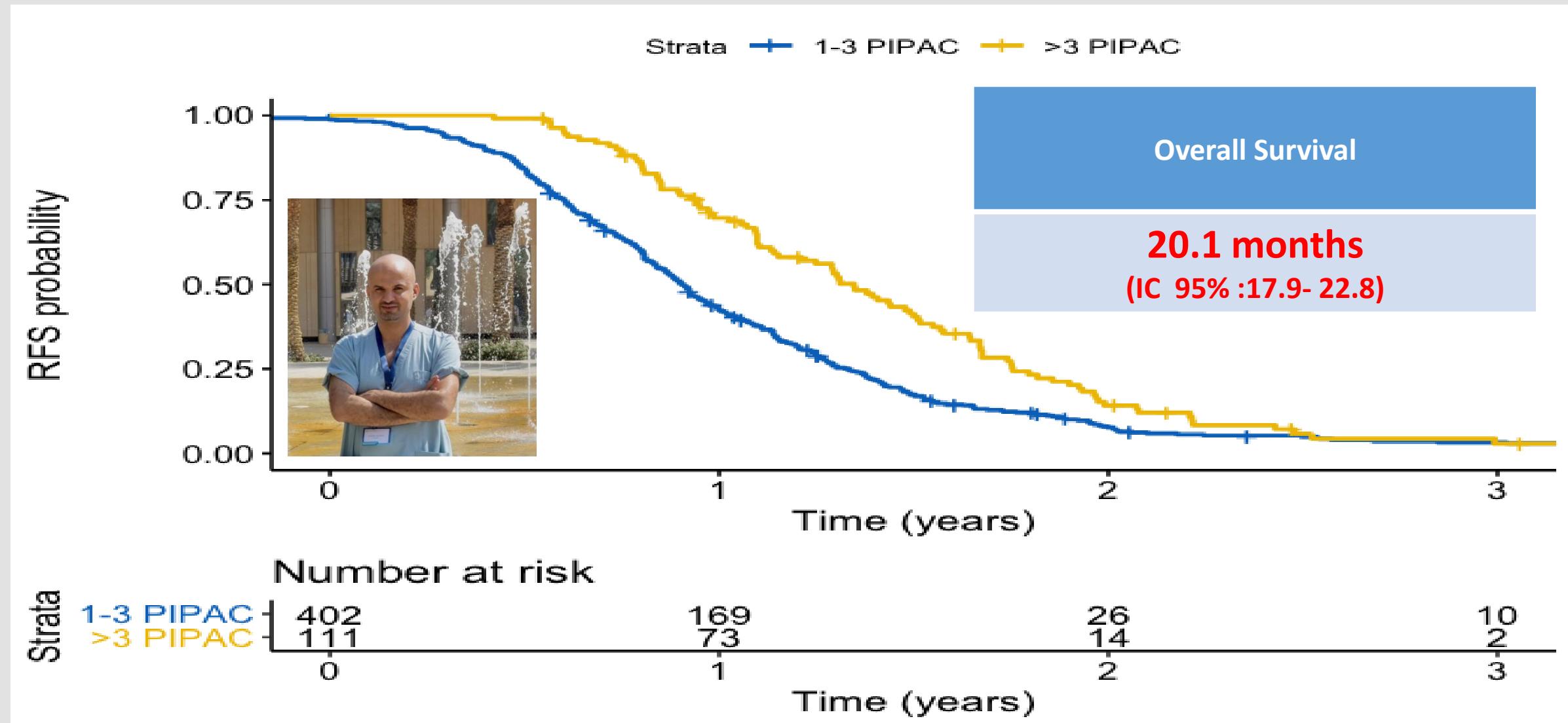
Invitation of ALL active PIPAC centers :
>60 procedures

Non-selected consecutive patients

Oncological outcomes by disease entity



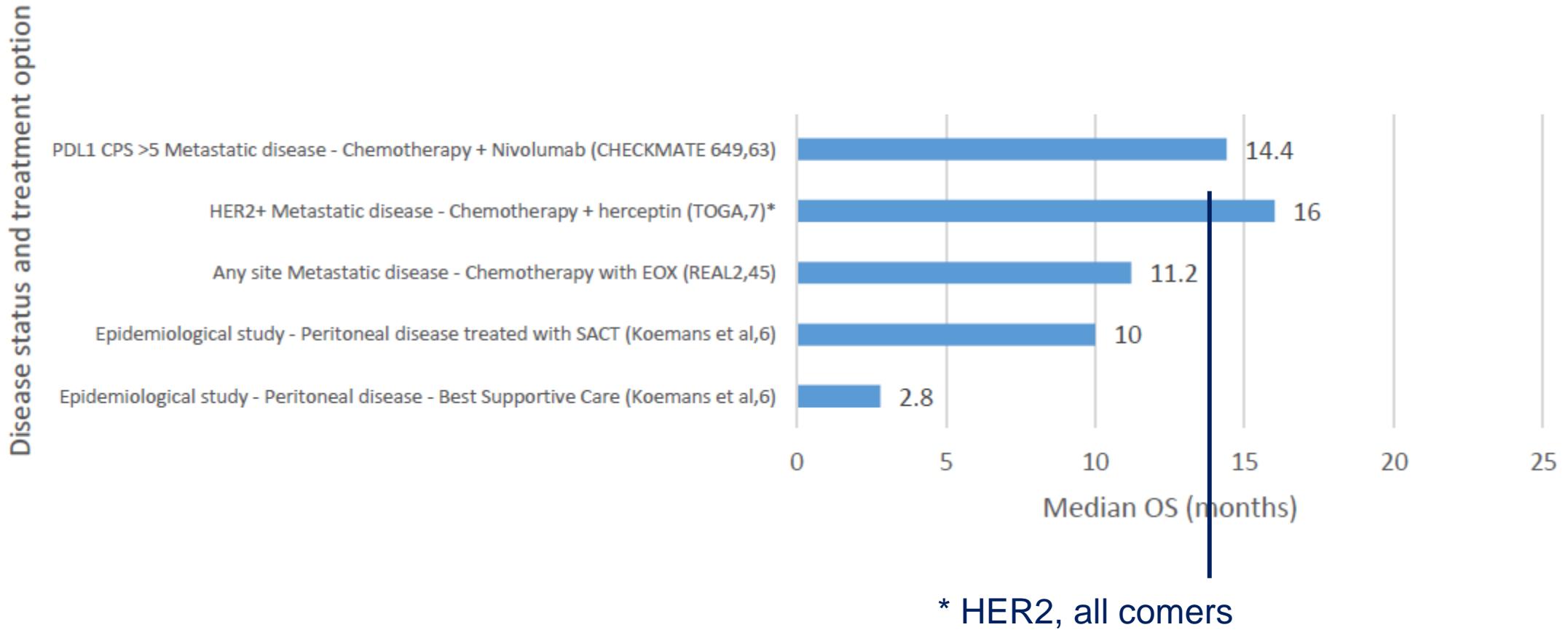
	Ovarian	Colorectal	Gastric	Mesothelioma	HPB	Total (PIPAC)
Ahmedabad	9	7	5	2	-	23 (62)
Barcelona	8	4	11	-	4	27 (60)
Dijon	15	10	5	2	5	37 (95)
Ghent	8	36	26	-	-	70 (215)
Grenoble	3	14	11	2	2	32 (96)
Lausanne	42	47	13	6	6	114 (280)
Leipzig	4	23	36	6	16	85 (175)
Lyon	41	52	105	26	12	236 (810)
Manipal	22	10	2	2	-	36 (62)
Montpellier	21	18	22	6	13	80 (240)
Moscow	10	1	191	-	-	202 (380)
Paris	2	12	29	5	-	134 (48)
Regensburg	6	9	19	-	2	36 (120)
Rome	-	17	31	2	17	67 (110)
Salzburg	8	-		6	3	17 (102)
Strasbourg	11	7	17	5	1	41 (100)
Torino	24	45	39	7	4	119 (250)
Tübingen	8	23	33	2	20	86 (150)
TOTAL	242	335	595	79	105	1356 (3441)



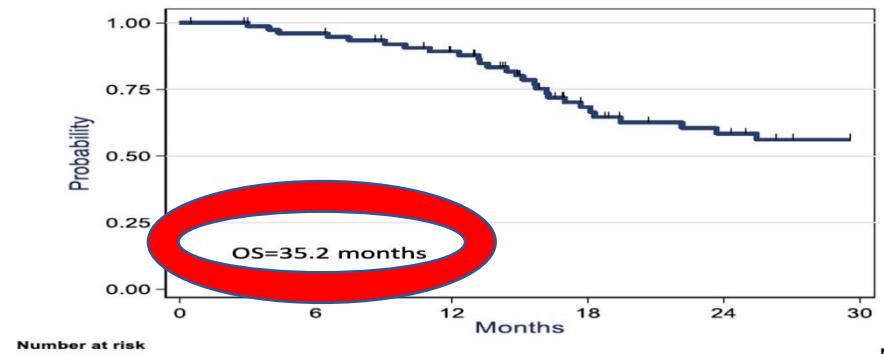
Alyami et al PSOGI 2021

Benchmark gastric M+

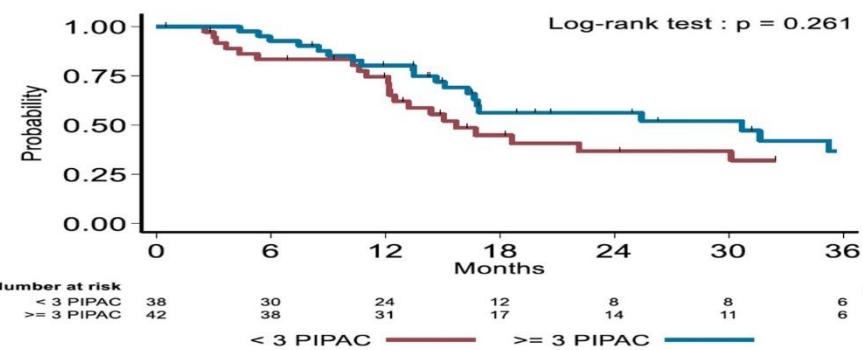
Σ 18 studies, 751 patients



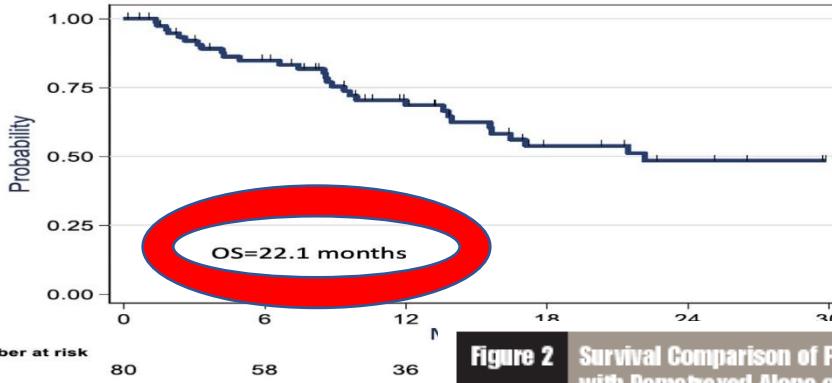
Overall survival: mesothelioma



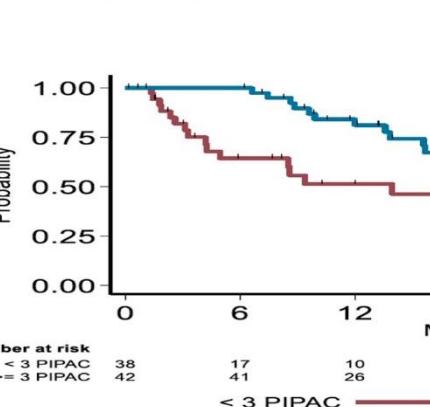
A



C

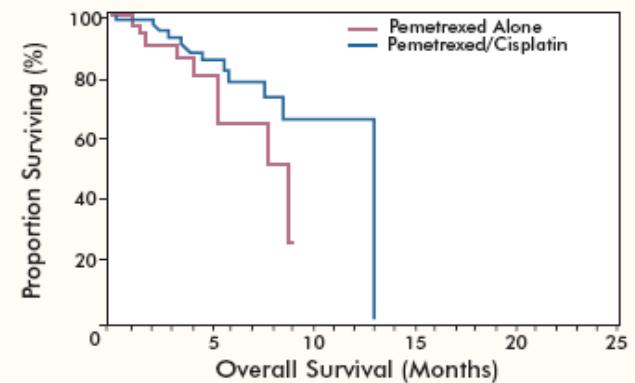


B



D

Figure 2 Survival Comparison of Peritoneal Mesothelioma Treated with Pemetrexed Alone or Pemetrexed/Cisplatin



Parameter	Pemetrexed Alone (n = 32)	Pemetrexed/Cisplatin (n = 42)
Median Survival, Months (95% CI)	8.7 (5.4-*)	13.1 (8.6-13.1)
1-Year Survival, %	0	65
Censorship, %	72	82

Median OS for resected patients: 49.6 months (CI 95% [37.6; 61.6]).



IP modalities: features and (dis)advantages

Feature	HIPEC	PIPAC	NIPS	EPIC
Potency of drug	++	+	+++	+++
Intraperitoneal concentration	++	++	++	++
Duration of tumour exposure	+	+	+++	+++
Depth of drug infiltration	+++	+++	++	++
Frequency and duration	++	++	+++	+++
Drug distribution	+++	+++	++	++
Combination with heat	+++	+	#	#
Minimally invasive surgery	+	+++	#	#
Repeated pathological evaluation of tumour response	+	+++	#	#
Cost	+++	++	+	+
Potential toxicity	+	+	++	+++

+, low; ++, medium; +++, strong; #, not applicable.



Tanzania



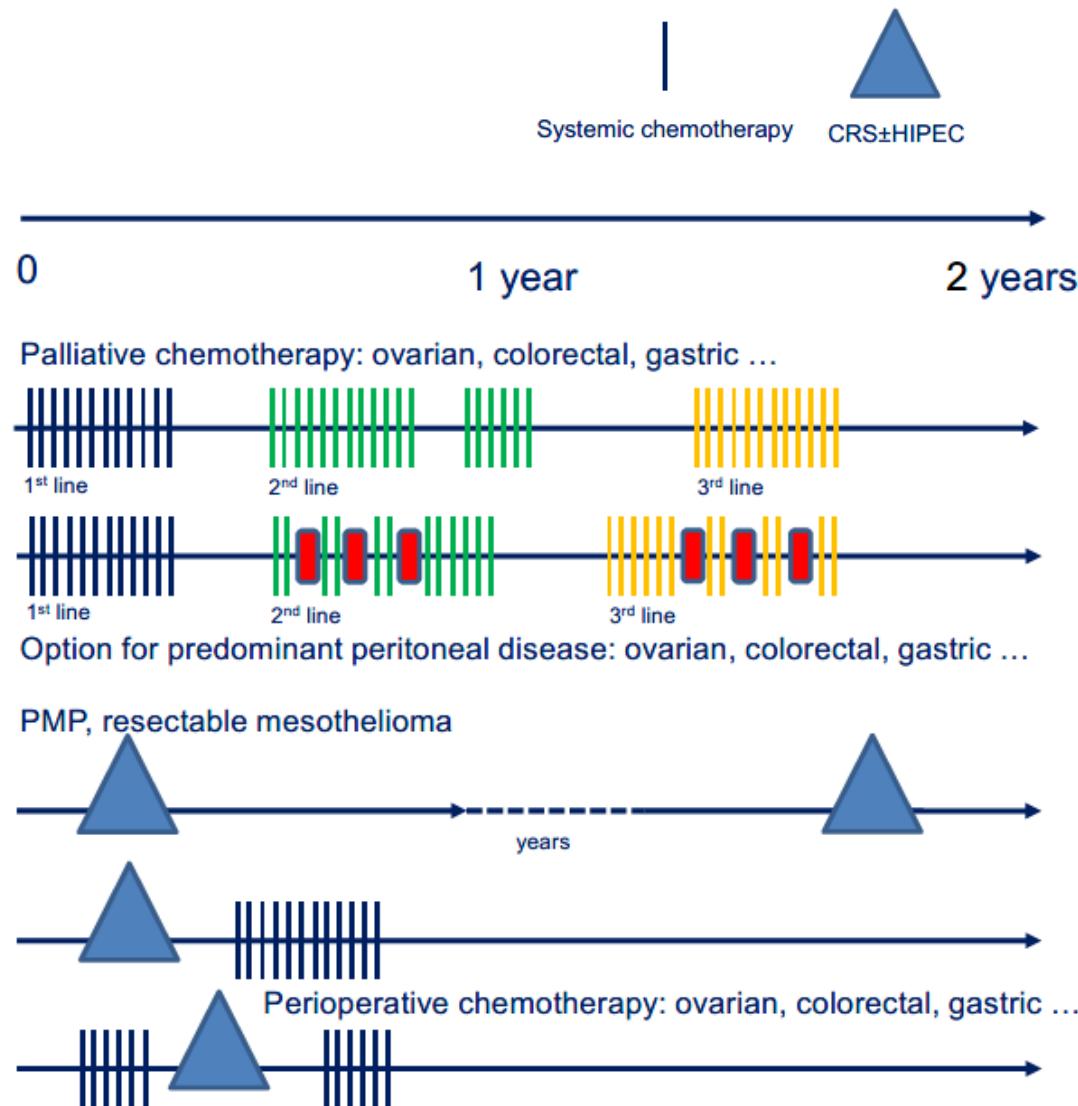


Martin with the **BIG 5**

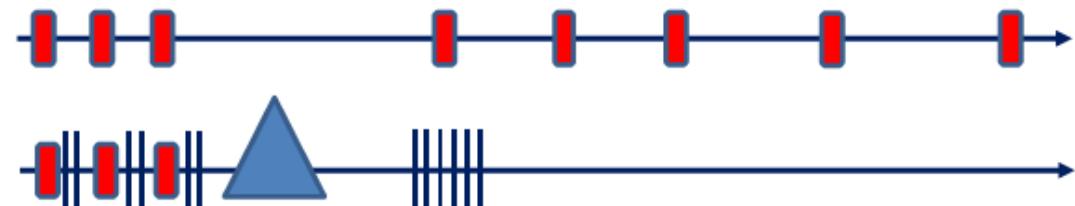
Please stop the « either .. or » or
one treatment « against » the other!!



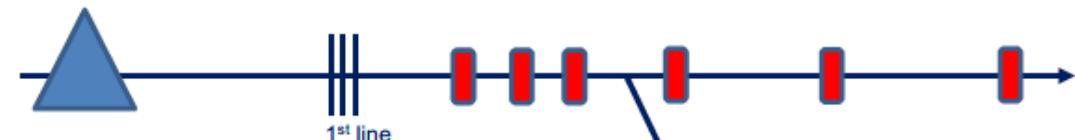
Treatment sequences for PSM: typical examples



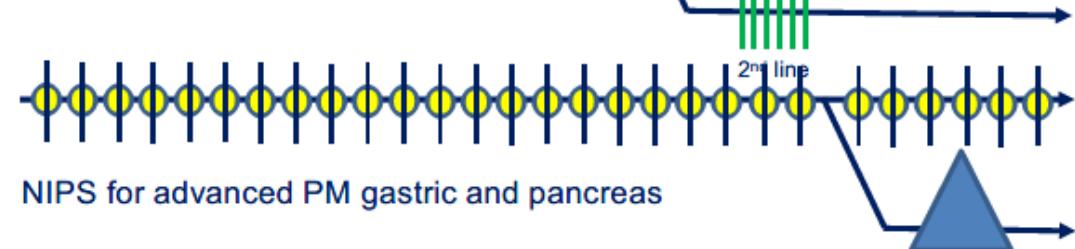
Non-resectable mesothelioma, isolated peritoneal disease (various origins)



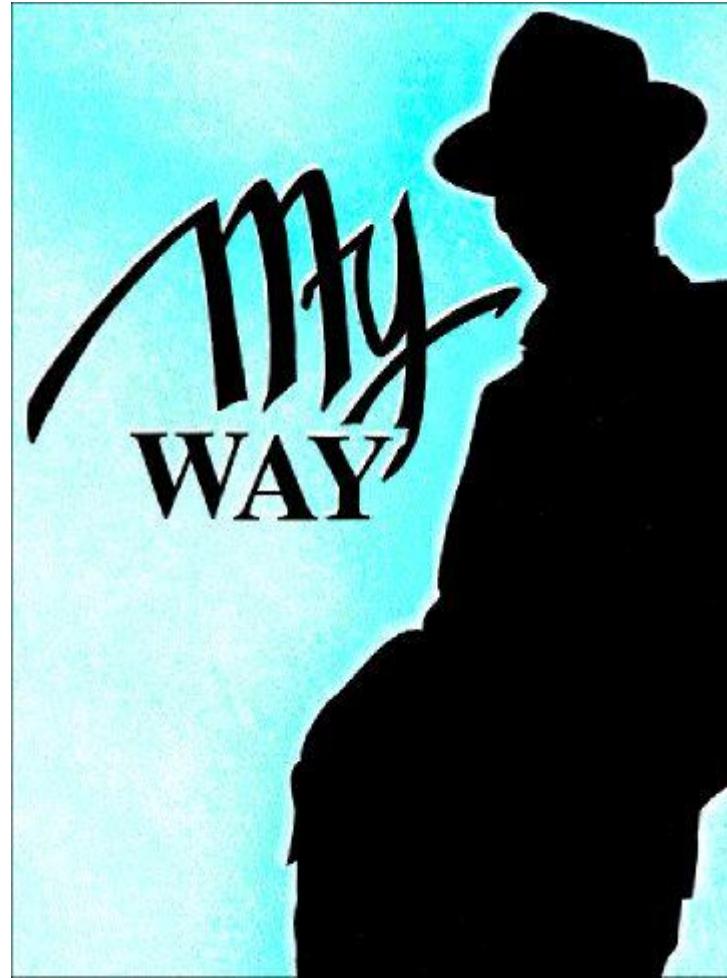
Neoadjuvant bi-directional treatment: gastric, colorectal



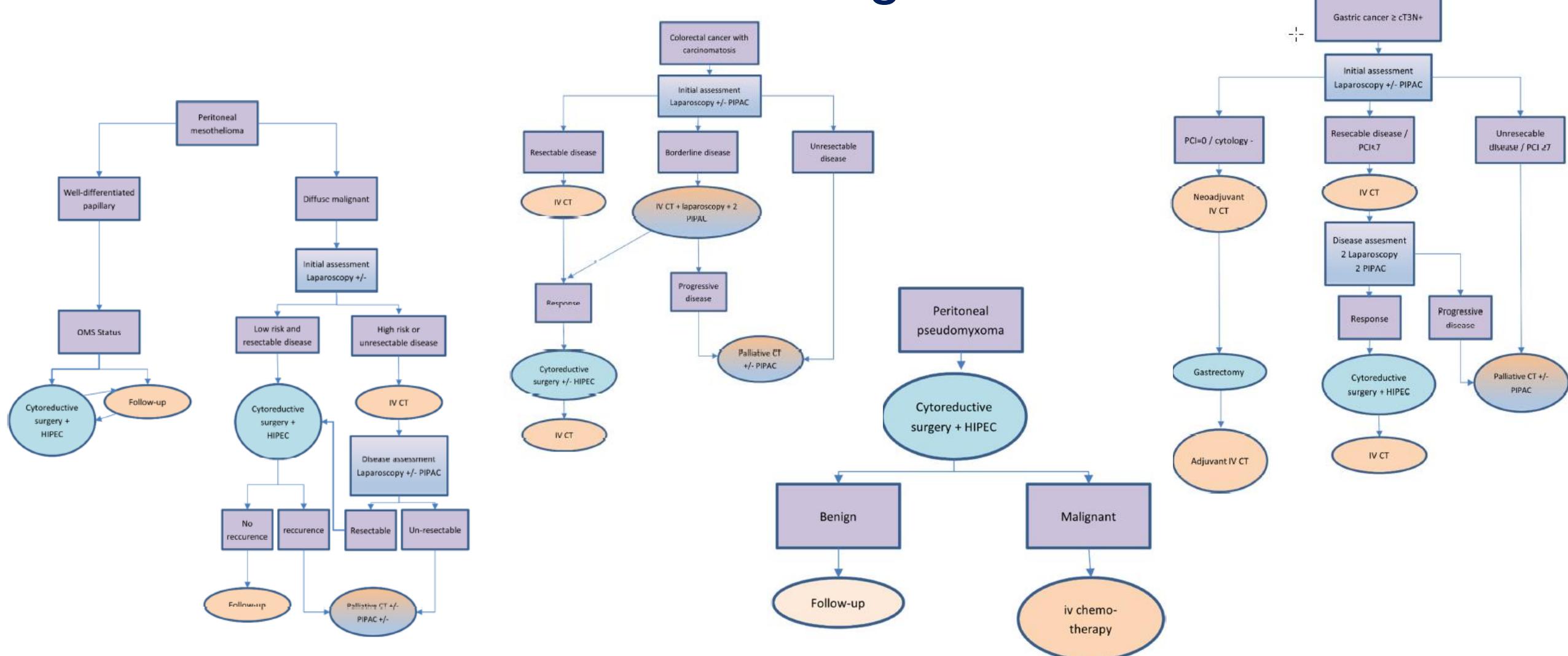
Mesothelioma, non-resectable recurrence



NIPS for advanced PM gastric and pancreas

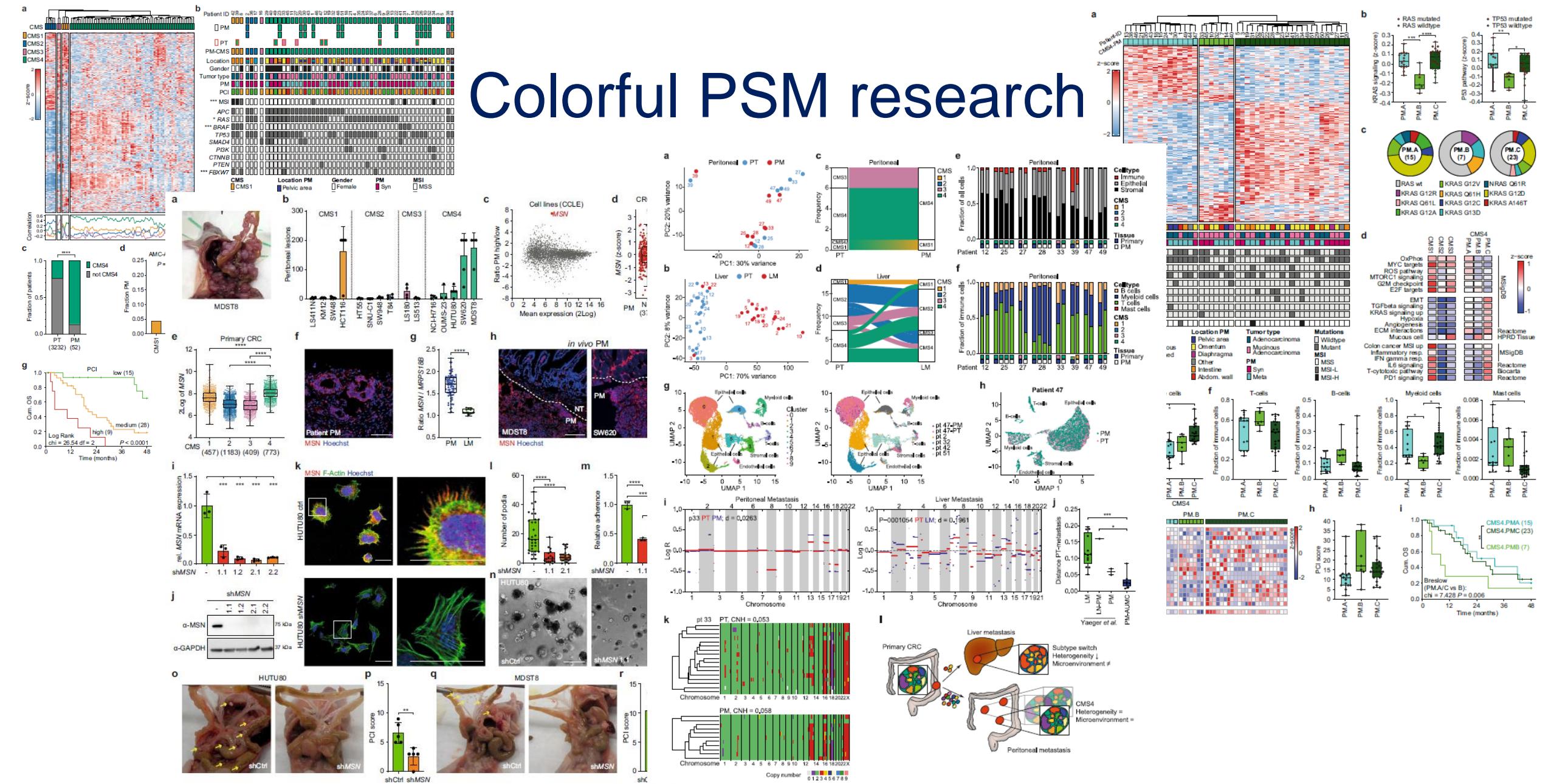


Swiss treatment algorithms: GI

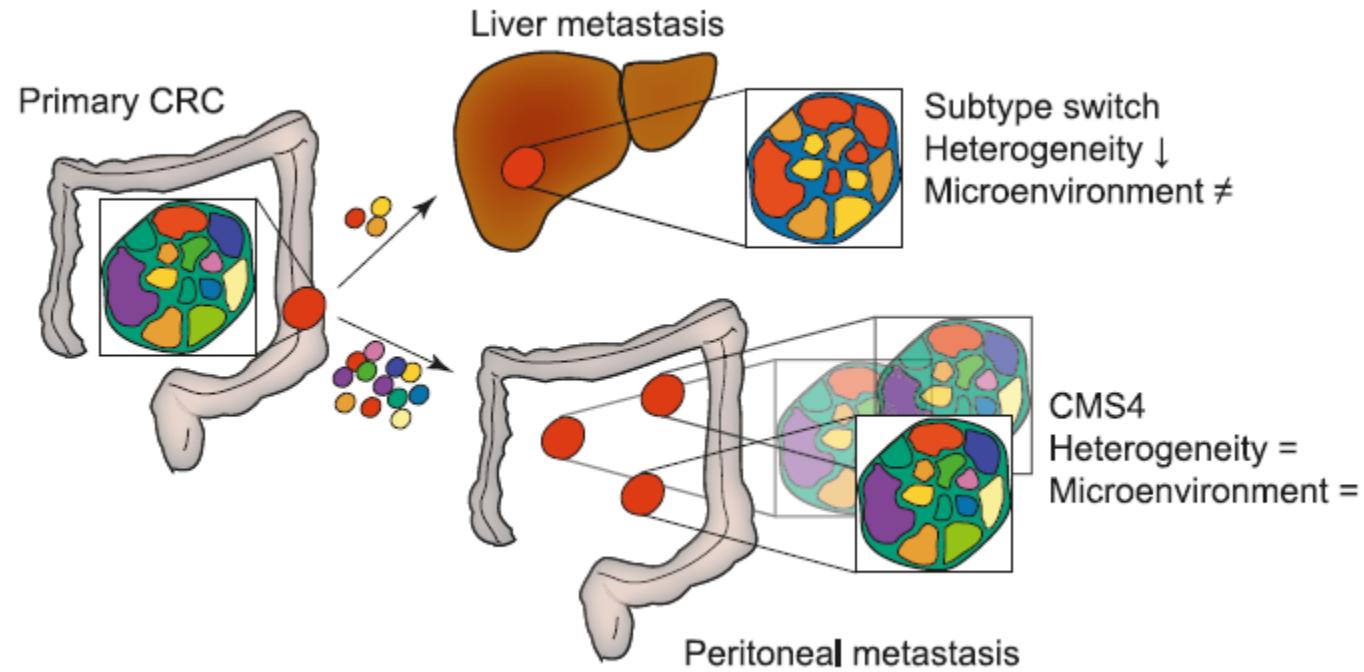




China



Colorectal PM = „distinct disease entity“?



Polyclonal metastatic seeding

CRC-PM: Molecular subtype **CMS4**, 3 categories

Important for dissemination: Structural protein **Moesin**

Conclusion I

Optimal landscape = multimodal oncological collaboration

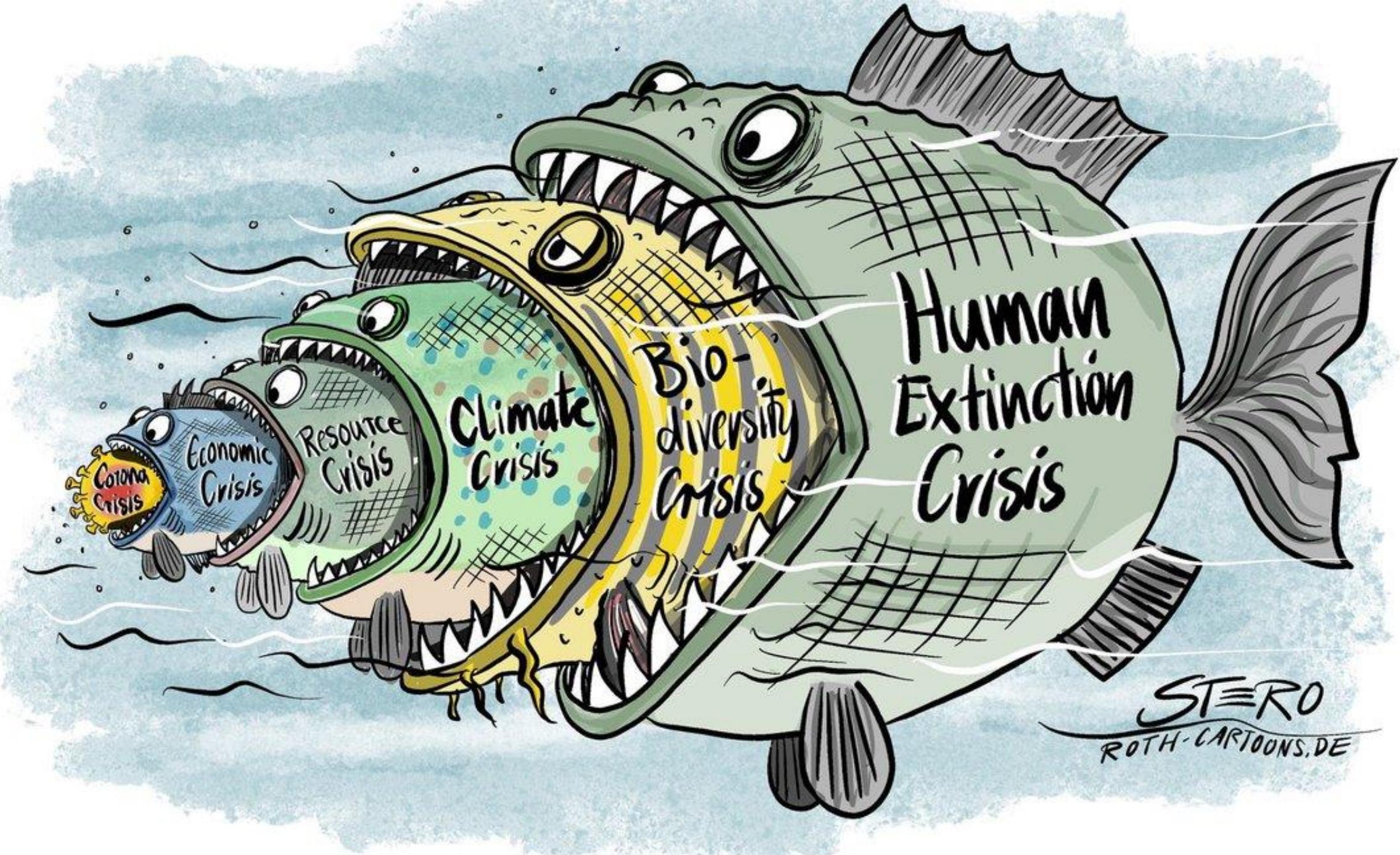
- Optimal patient selection
- Optimal treatment sequence
- Optimal surgery and perioperative care

... allows to offer safe treatments with excellent oncological outcomes and a (small) potential for cure to patients with peritoneal metastases.

Conclusion II

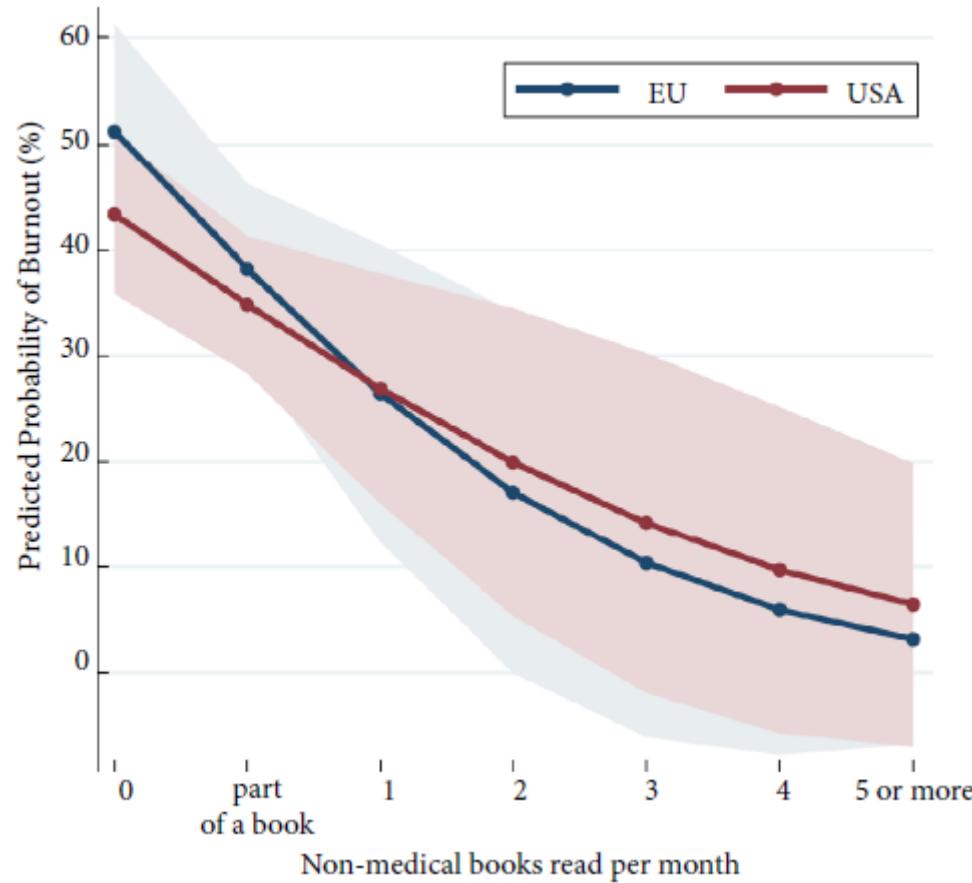


Standardization of treatments and prospective registries

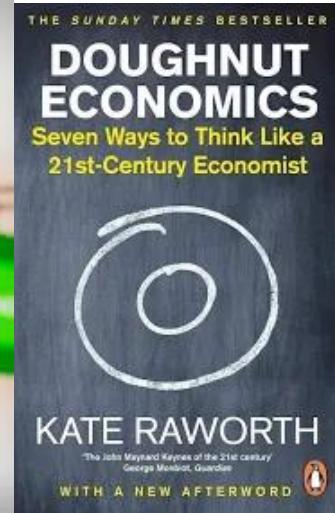


Risk for physician burn-out: 40%

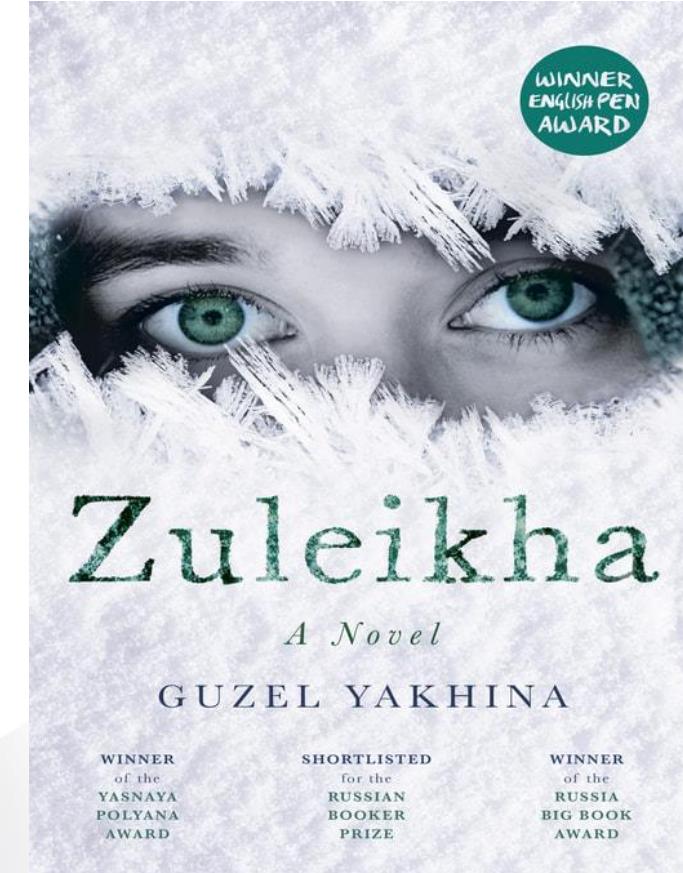
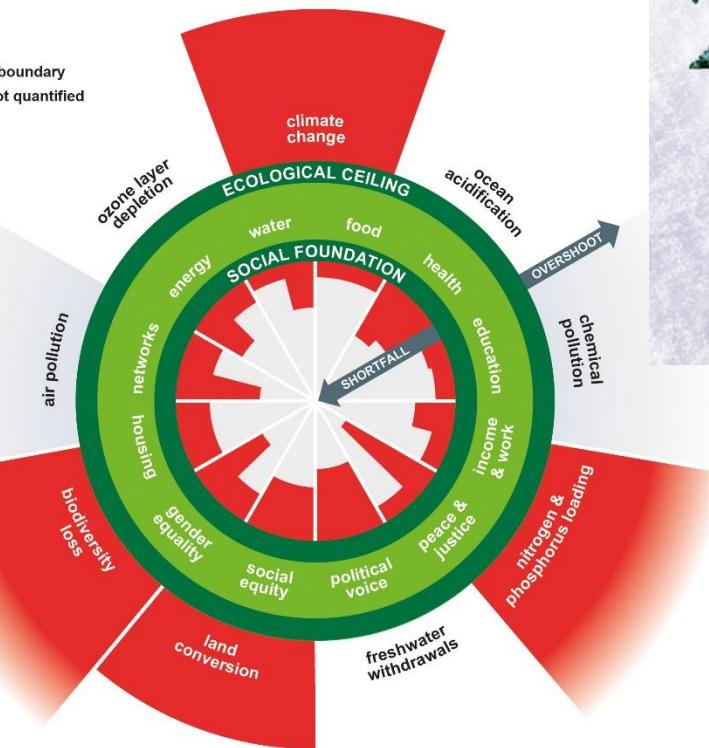
Let's read more



Suggested reading:



■ Beyond the boundary
■ Boundary not quantified

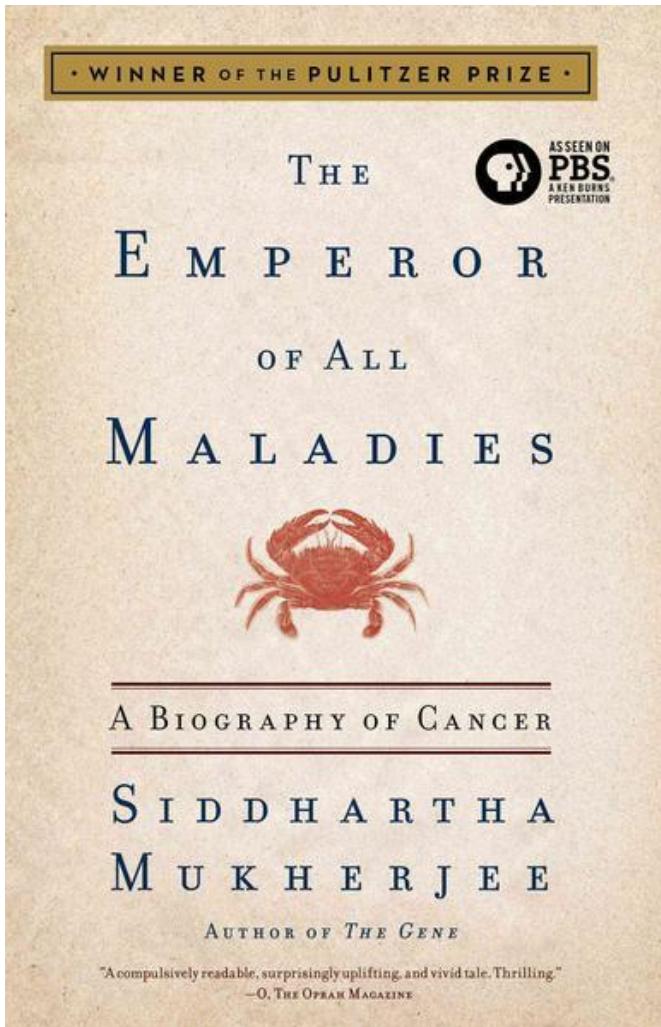


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... and one for Joe



06:01

4G



Tweet

Cesar Nevarez Gruber liked



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United States government official

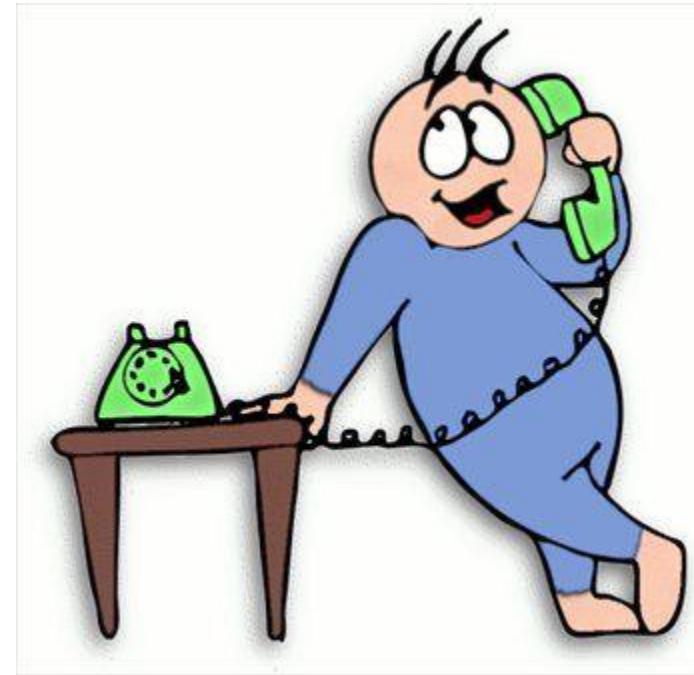
I believe we can end cancer as we know it and even cure cancers once and for all.

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