Cytoreductive Surgery and HIPEC for CRCPM

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NO DISCLOSURES

Outline

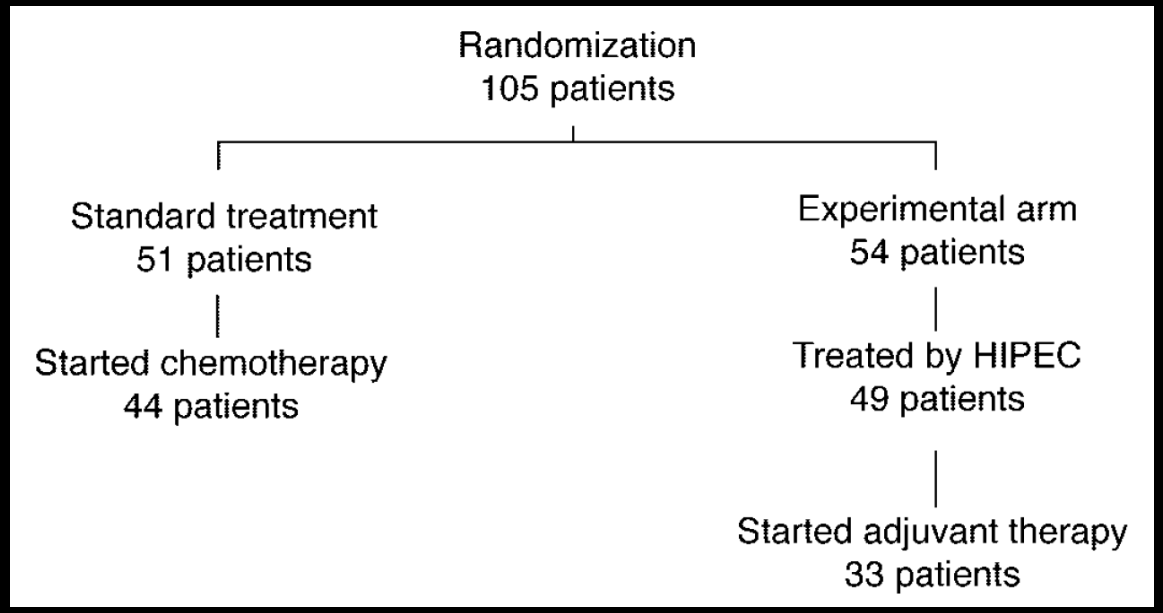
Current Evidence for CRS HIPEC in CRC

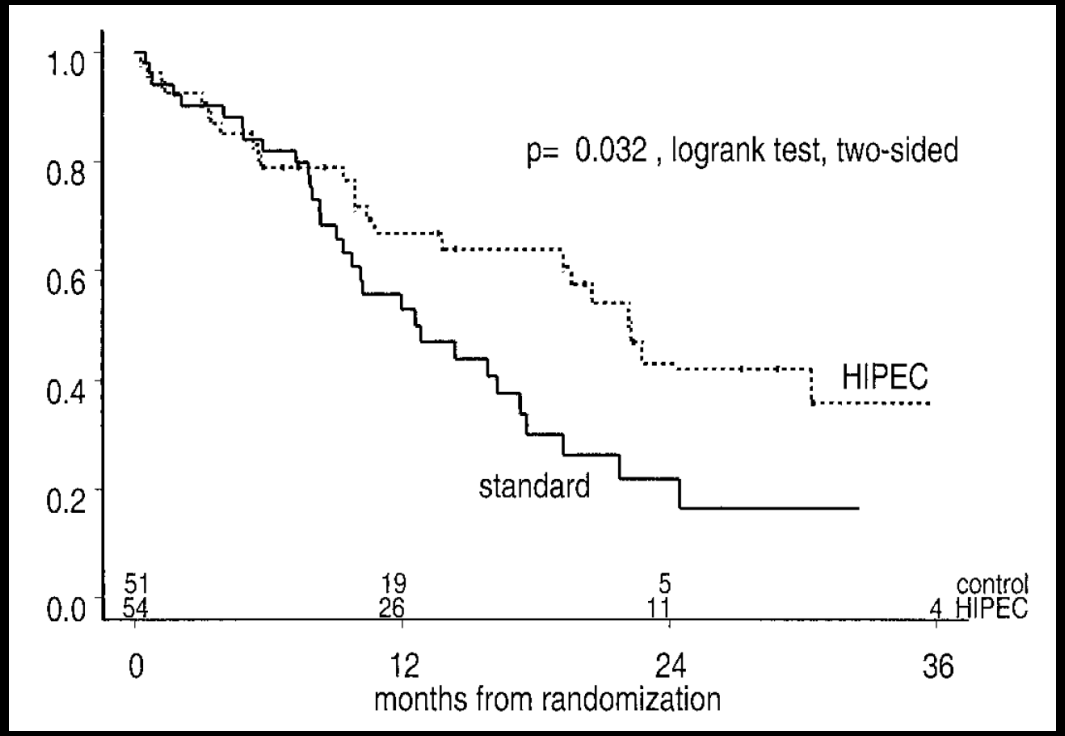
New knowledge in the science of CRC PM

Prevention of PM in CRC

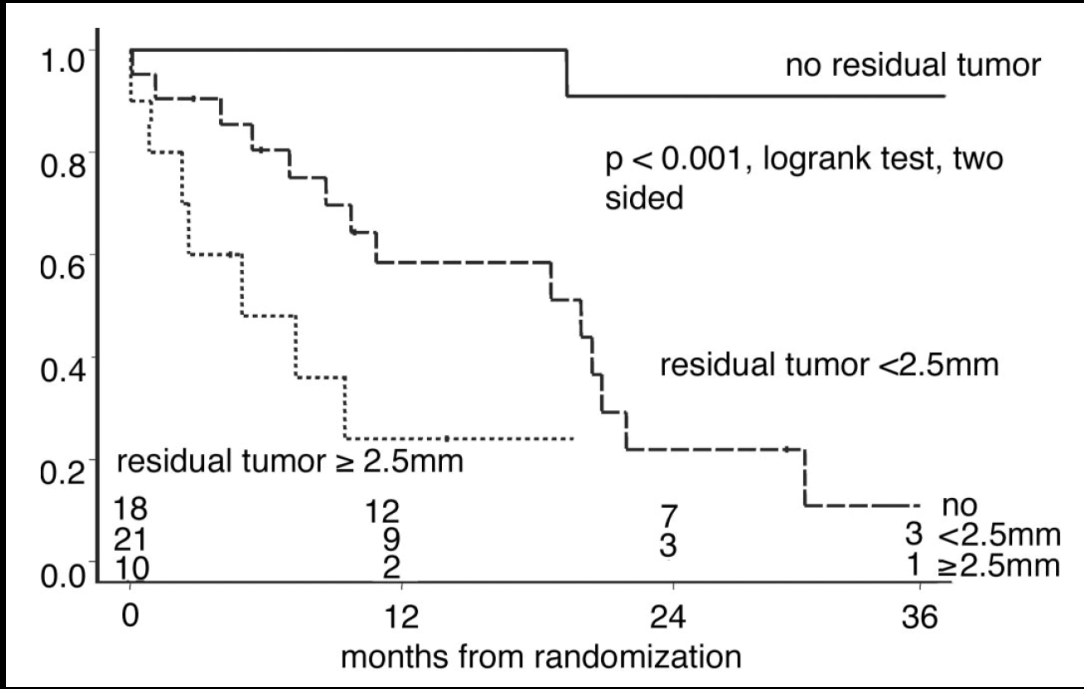
Future outlook

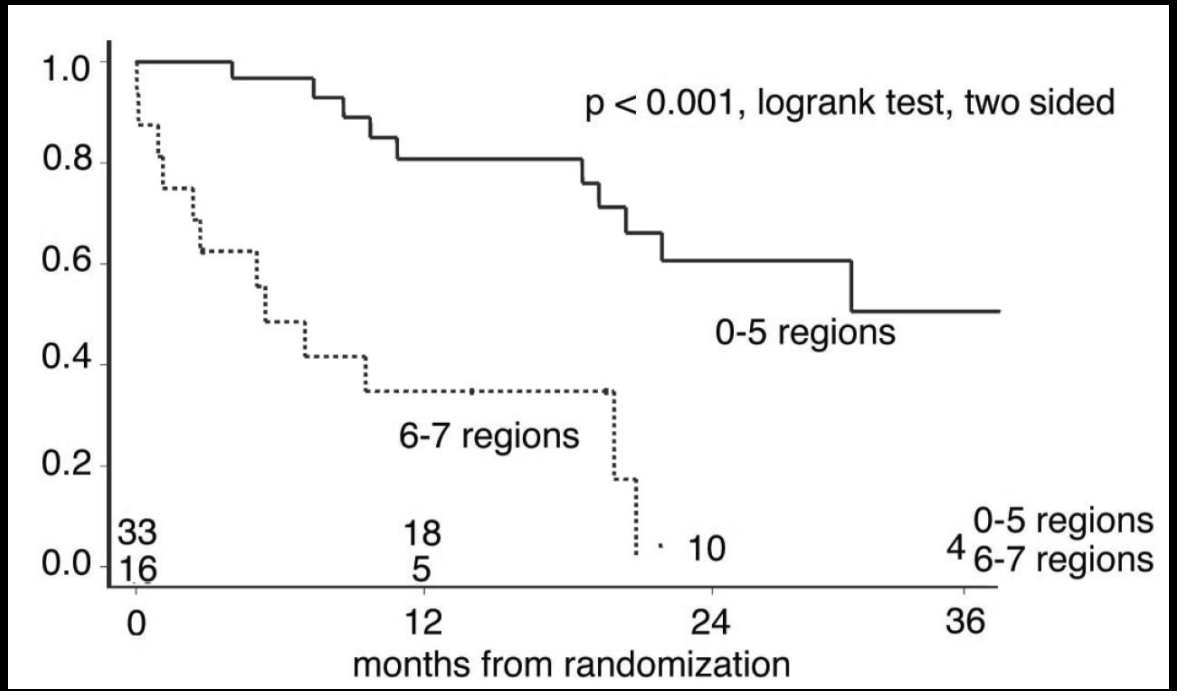
CRS HIPEC versus systemic therapy and palliative surgery



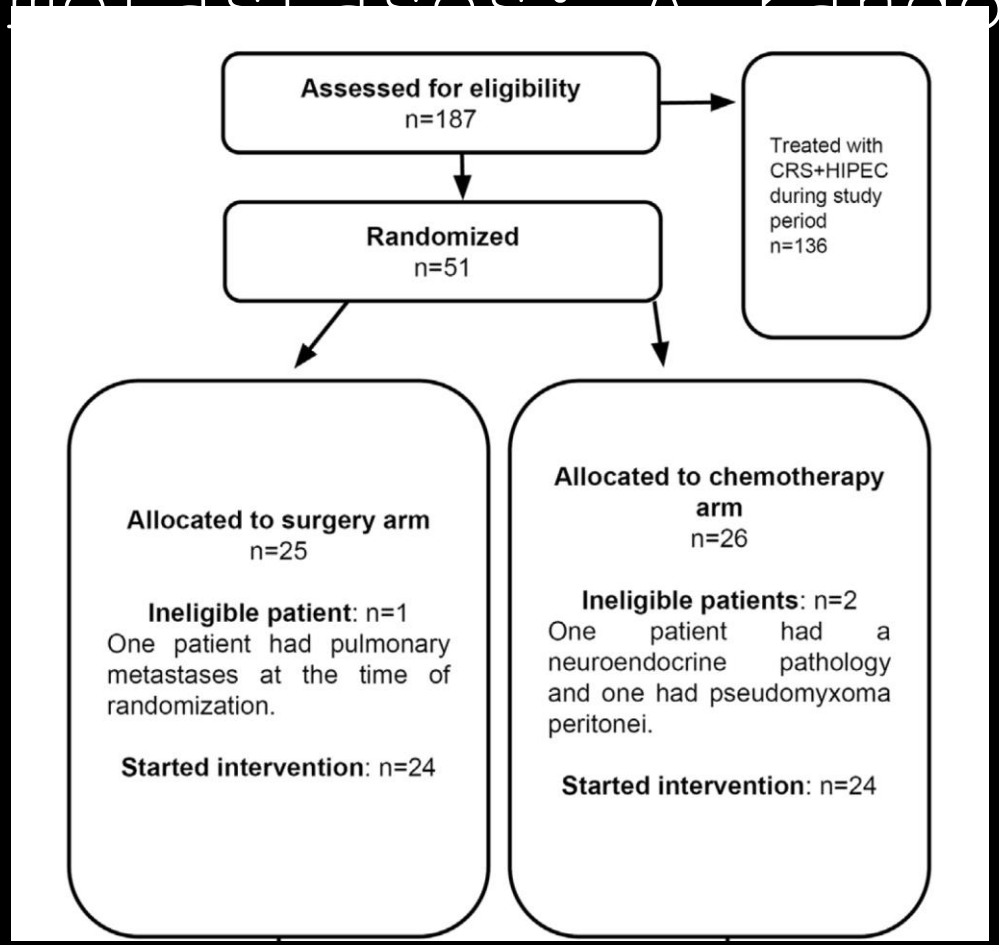


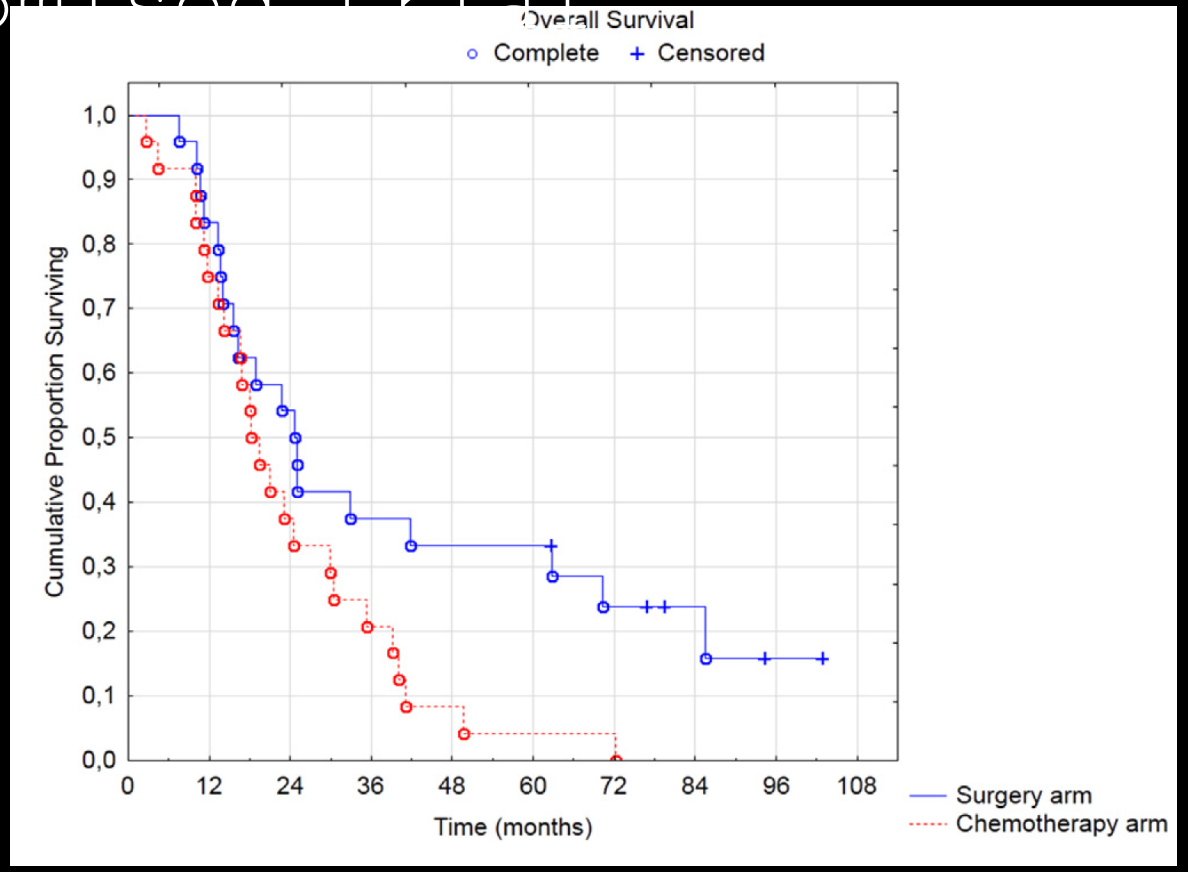
CRS HIPEC versus systemic therapy and palliative surgery





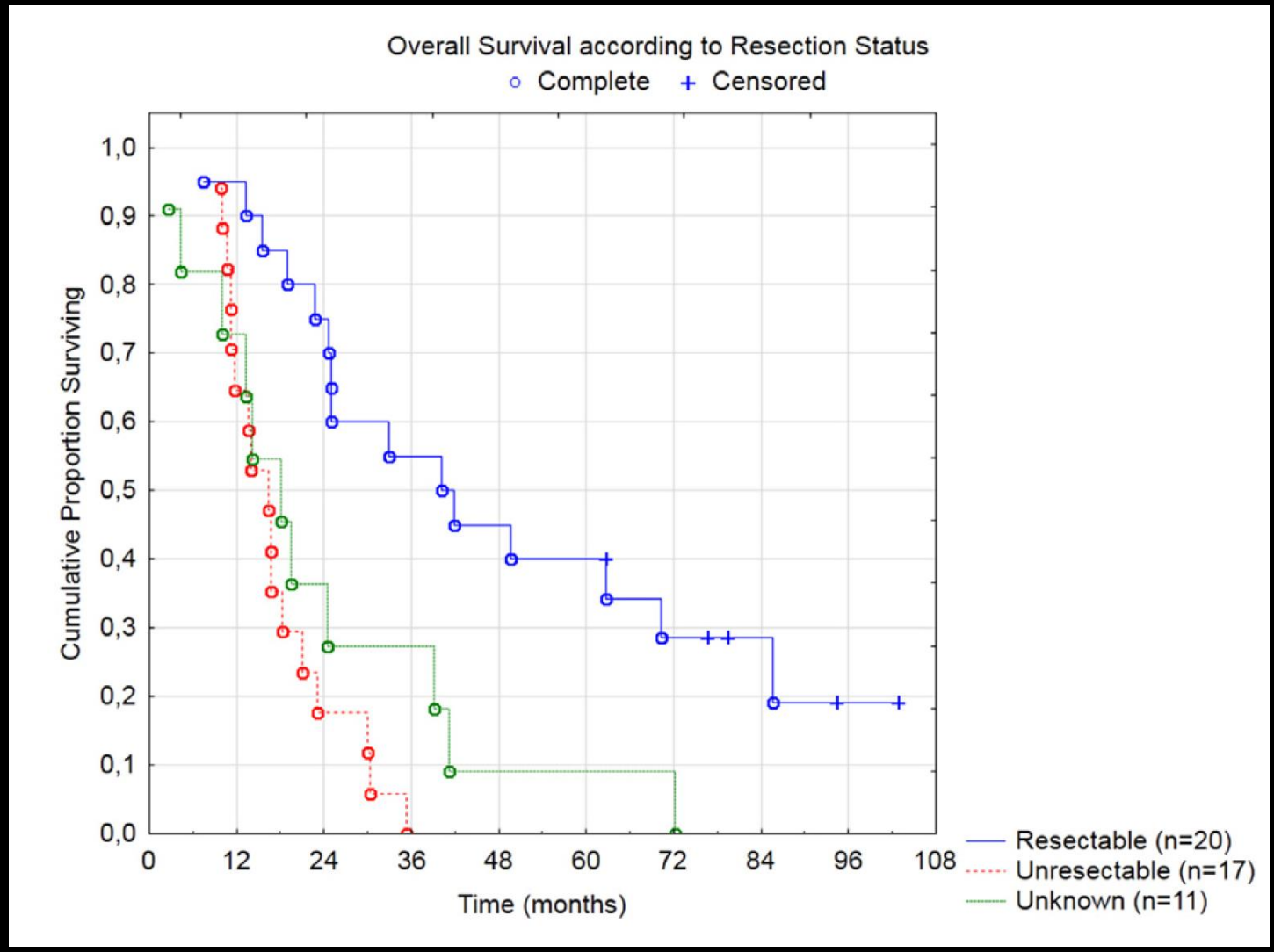
cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: A randomised trial





European Journal of Cancer 53 (2016) 155–162

Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: A randomised trial

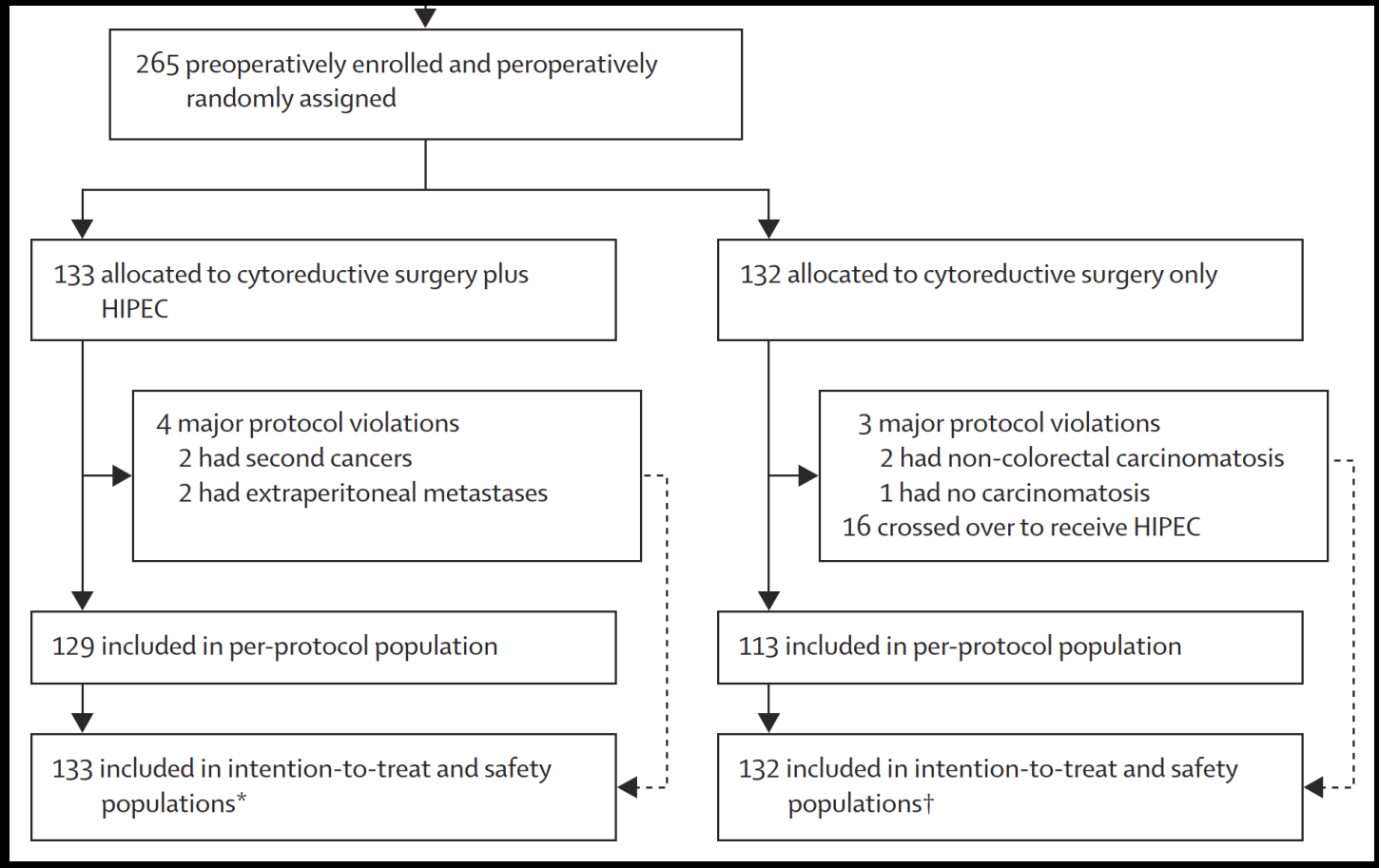


European Journal of Cancer 53 (2016) 155–162

Upfront Cytoreductive Surgery

followed by

surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label,



Lancet Oncol 2021; 22: 256–66

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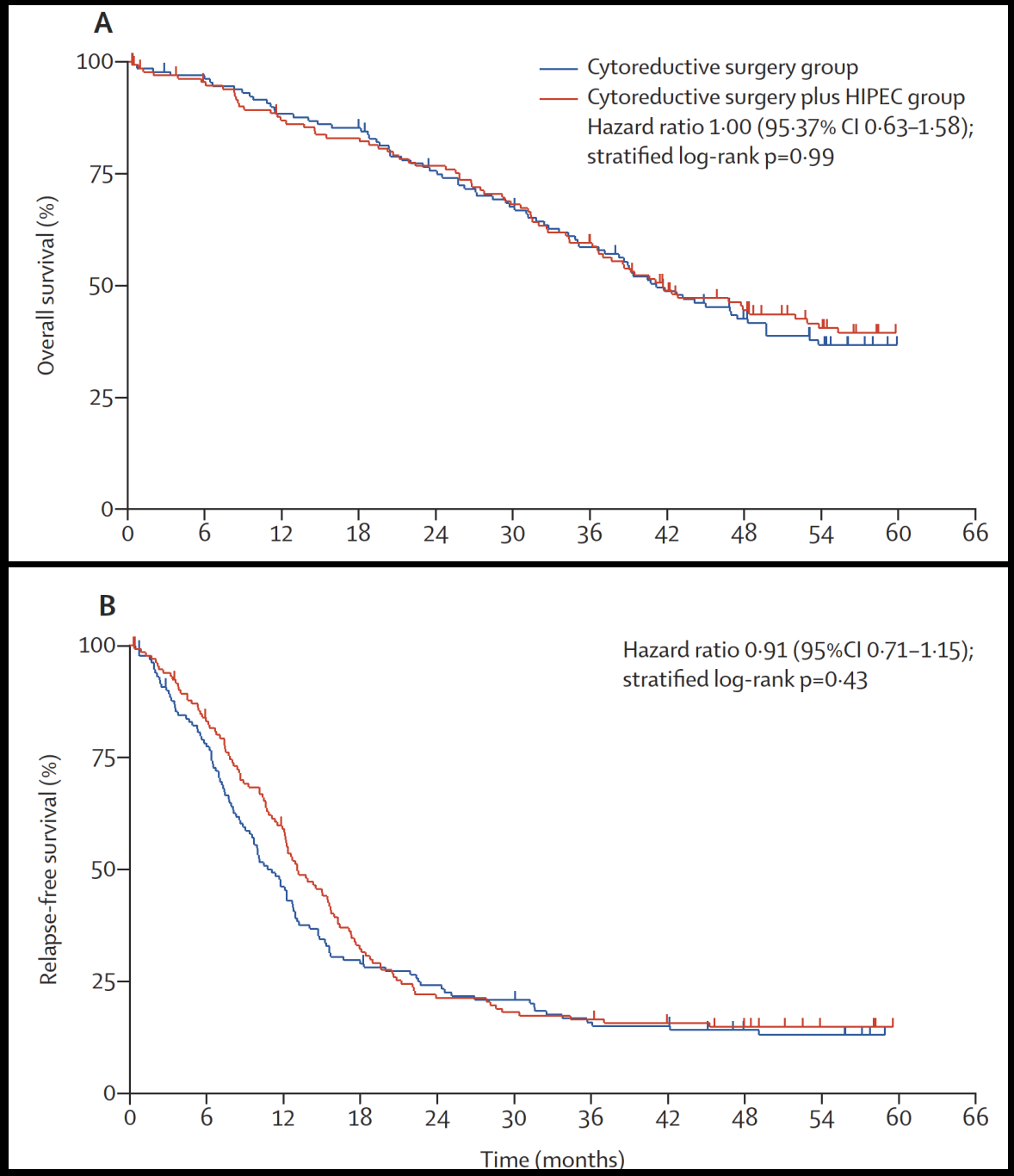
Lancet Oncol 2021; 22: 256–66



intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial

	HIPEC	CRS only	P value
Median Survival	41.7	41.2	0.995
1-year Survival	86.9%	88.3%	
5-year Survival	39.4	36.7	

xcellent results of CRS + Systemic Chemothera

Upfront Systemic Therapy

Followed by

Cytoreductive Surgery +/- HIPEC

30:00

Should HIPEC still be the standard of care after neoadjuvant systemic therapy and optimal CRS ?

cancers

MDPI

Systematic Review

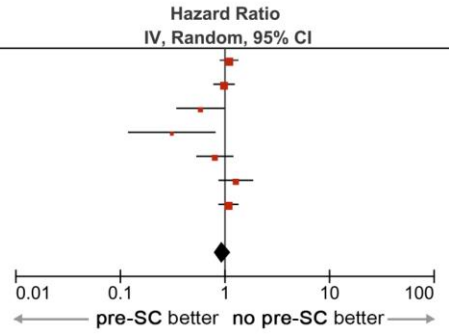
Systemic Chemotherapy in Colorectal Peritoneal Metastases Treated with Cytoreductive Surgery: Systematic Review and Meta-Analysis

Marco Tonello [1], Carola Cenzi [2], Elisa Pizzolato [1], Riccardo Fiscon [1], Paola Del Bianco [2], Pierluigi Pilati [1] and Antonio Sommariva [1,*]

(B) Preoperative Systemic Chemotherapy vs. No Preoperative Systemic Chemotherapy

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Glehen 2004	0.0905	0.0968	21.7%	1.09 [0.91, 1.32]
Elias 2010	-0.0213	0.1125	20.0%	0.98 [0.79, 1.22]
Passot 2012	-0.5405	0.2632	8.7%	0.58 [0.35, 0.98]
Ceelen 2014	-1.1712	0.4842	3.3%	0.31 [0.12, 0.80]
Beal 2020	-0.2231	0.2005	12.3%	0.80 [0.54, 1.19]
Tonello 2023	0.239	0.1872	13.2%	1.27 [0.88, 1.83]
Cashin 2023	0.077	0.1045	20.8%	1.08 [0.88, 1.33]
Total (95% CI)			**100.0%**	**0.95 [0.79, 1.14]**

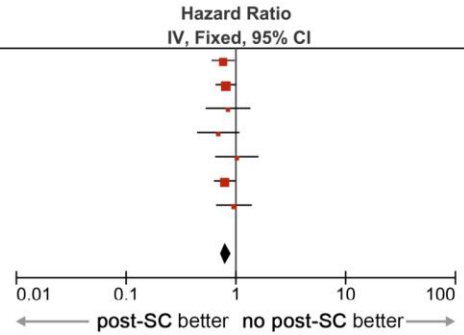
Heterogeneity: Tau² = 0.03; Chi² = 14.35, df = 6 (P = 0.03); I² = 58%
Test for overall effect: Z = 0.53 (P = 0.59)



(C) Postoperative Systemic Chemotherapy vs. No Postoperative Systemic Chemotherapy

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Glehen 2004	-0.2681	0.1162	21.5%	0.76 [0.61, 0.96]
Elias 2010	-0.2109	0.1028	27.5%	0.81 [0.66, 0.99]
Passot 2012	-0.1655	0.2317	5.4%	0.85 [0.54, 1.33]
Ceelen 2014	-0.3711	0.2181	6.1%	0.69 [0.45, 1.06]
Maillet 2016	0.0197	0.2241	5.8%	1.02 [0.66, 1.58]
Cashin 2023	-0.2357	0.1074	25.2%	0.79 [0.64, 0.98]
Tonello 2023	-0.0408	0.1835	8.6%	0.96 [0.67, 1.38]
Total (95% CI)			**100.0%**	**0.81 [0.73, 0.90]**

Heterogeneity: Chi² = 2.79, df = 6 (P = 0.83); I² = 0%
Test for overall effect: Z = 3.88 (P = 0.0001)



Cancers **2024**, *16*, 1182. https://doi.org/10.3390/cancers16061182

Received: 13 May 2024 | Accepted: 1 July 2024

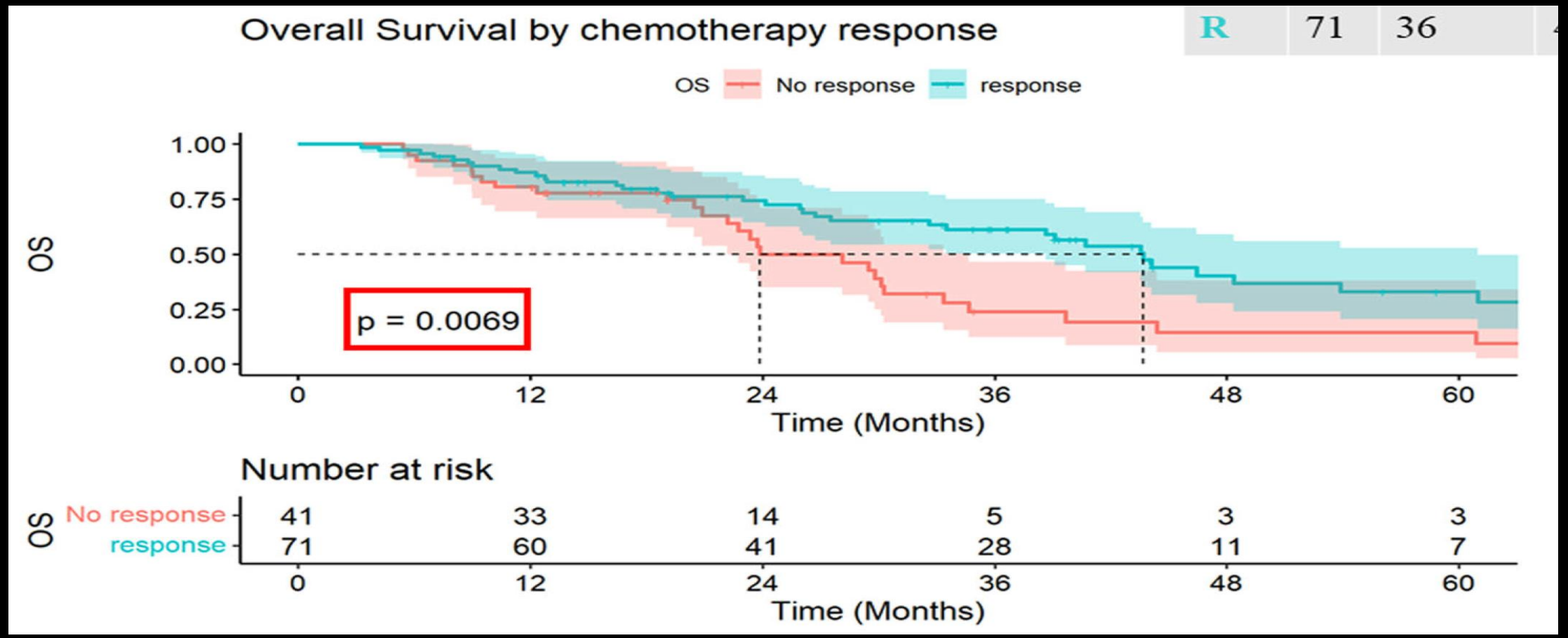
DOI: 10.1002/jso.27776

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Preoperative chemotherapy response and survival in patients with colorectal cancer peritoneal metastases

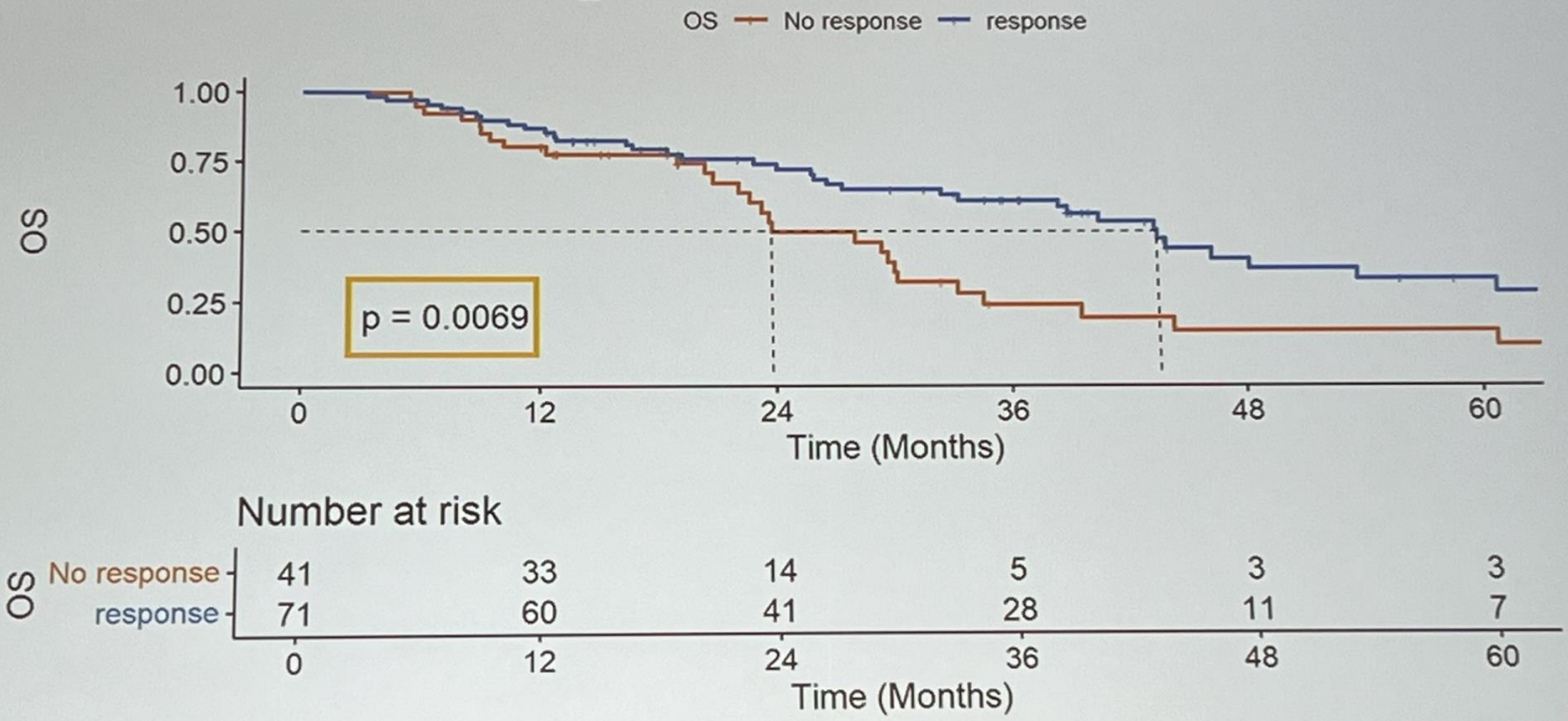
J Surg Oncol. 2024;1–11.



PSOGI VENICE 2023

OS by chemo response

	n	events	median	95% CI	HR (95% CI)
NR	41	28	23.9	22.2-34.7	
R	71	36	43.7	38.6-61.0	**0.51** (0.31-0.84)



Tinsley et al, 2023
Unpublished

MANCHESTER 1824
The University of Manchester

The Christie NHS
NHS Foundation Trust

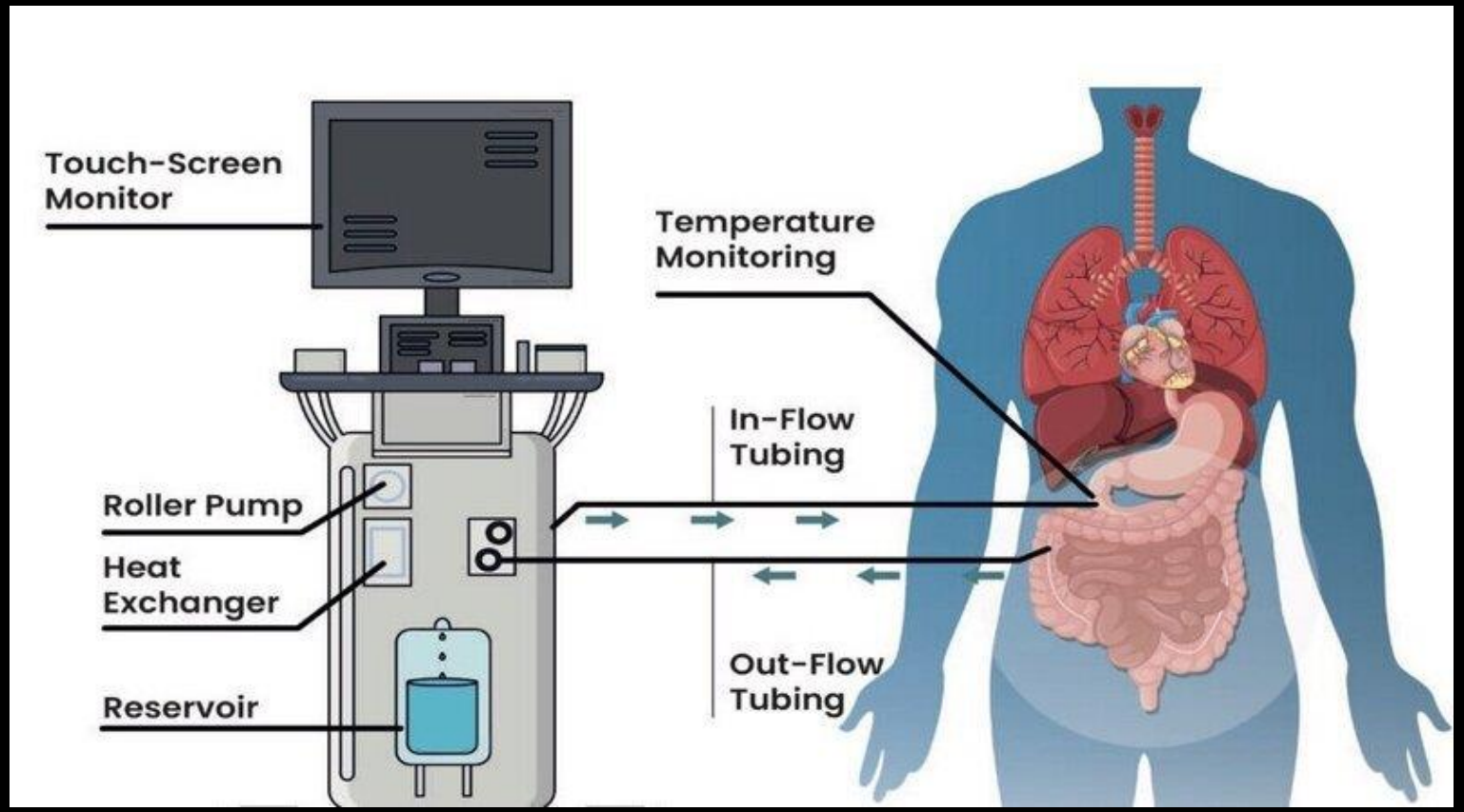
MANCHESTER CANC
RESEARCH CENTRE

STUDY PROTOCOL Open Access

Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone for isolated resectable colorectal peritoneal metastases: protocol of a multicentre, open-label, parralel-group, phase II-III, randomised, superiority study (CAIRO6)

Rovers *et al. BMC Cancer* (2019) 19:390
https://doi.org/10.1186/s12885-019-5545-0

CAIRO 6 RCT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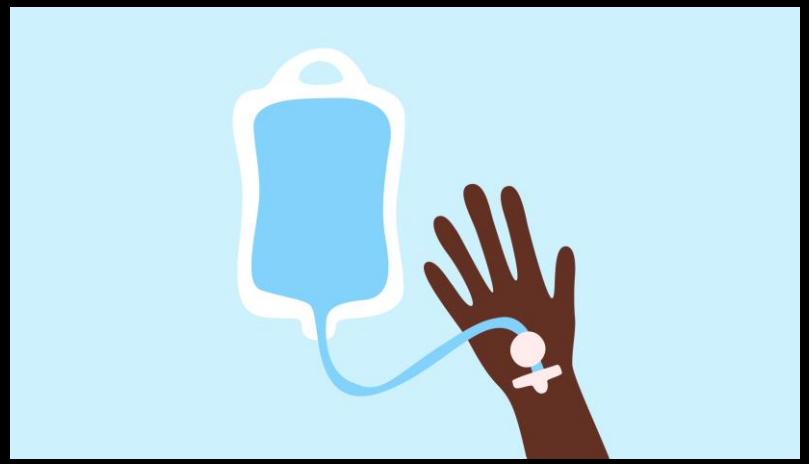
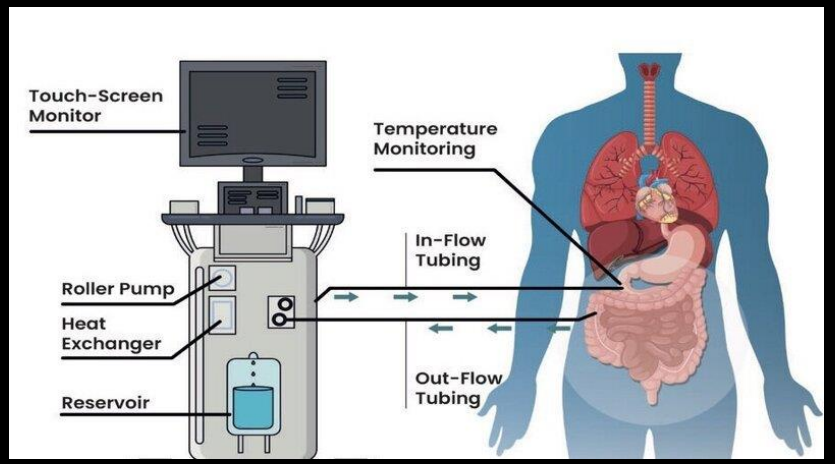
Temperature Monitoring
In-Flow Tubing
Roller Pump
Heat Exchanger
Out-Flow Tubing
Reservoir

CAIRO 6 RCT

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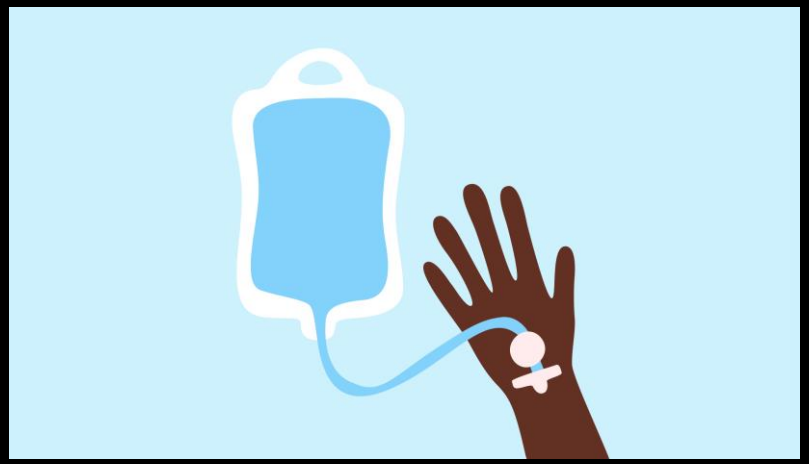
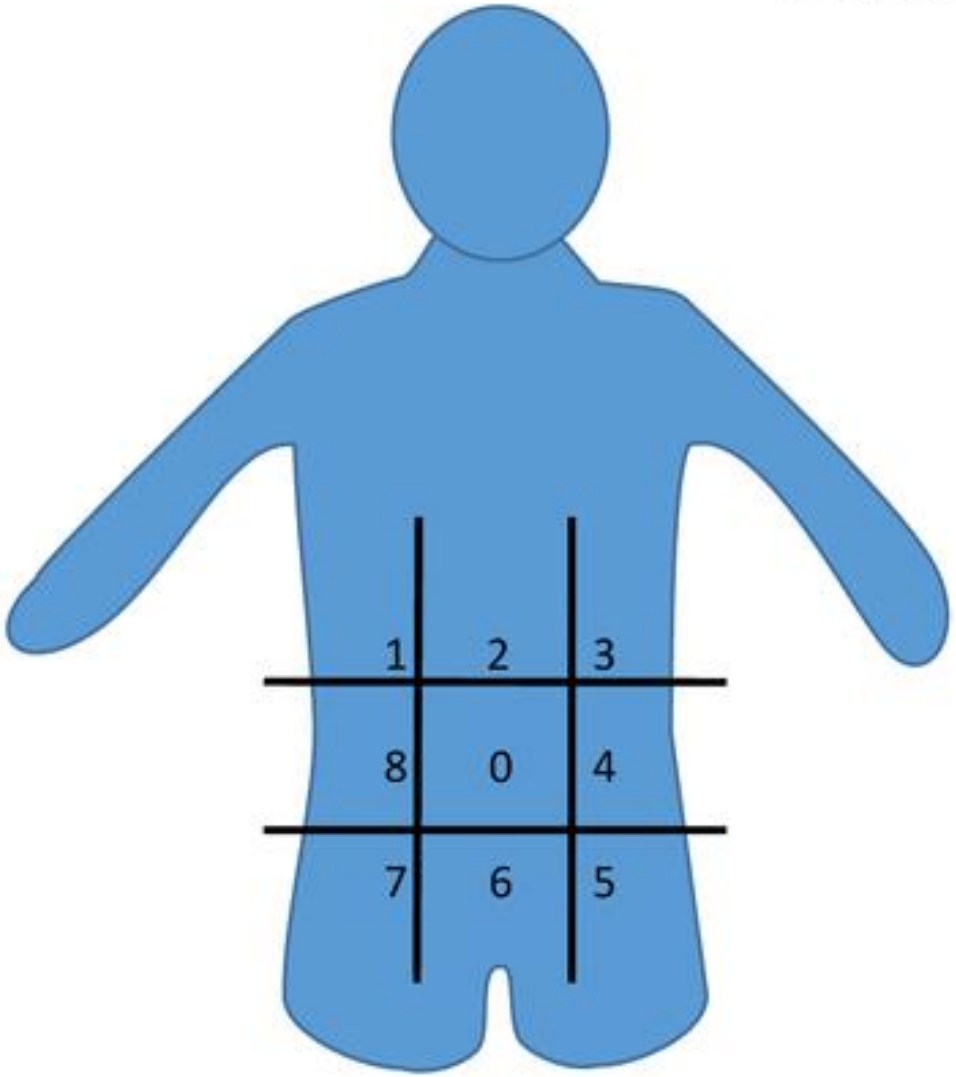


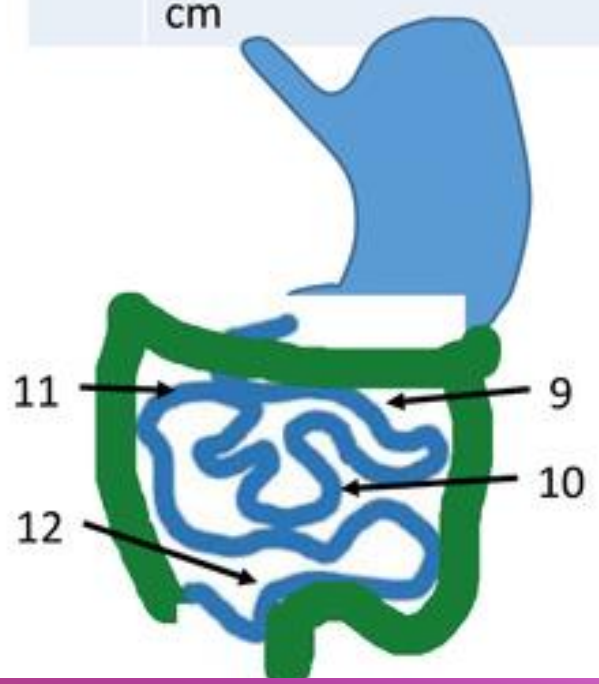
Patient Selection

Peritoneal Cancer Index



Regions
0 Central
1 Right Upper
2 Epigastrium
3 Left Upper
4 Left Flank
5 Left Lower
6 Pelvis
7 Right Lower
8 Right Flank
9 Upper Jejunum
10 Lower Jejunum
11 Upper Ileum
12 Lower Ileum

Lesion Size Score	
0	No Tumor
1	Tumors up to 0.5 cm
2	Tumors up to 5 cm
3	Tumors greater than 5 cm



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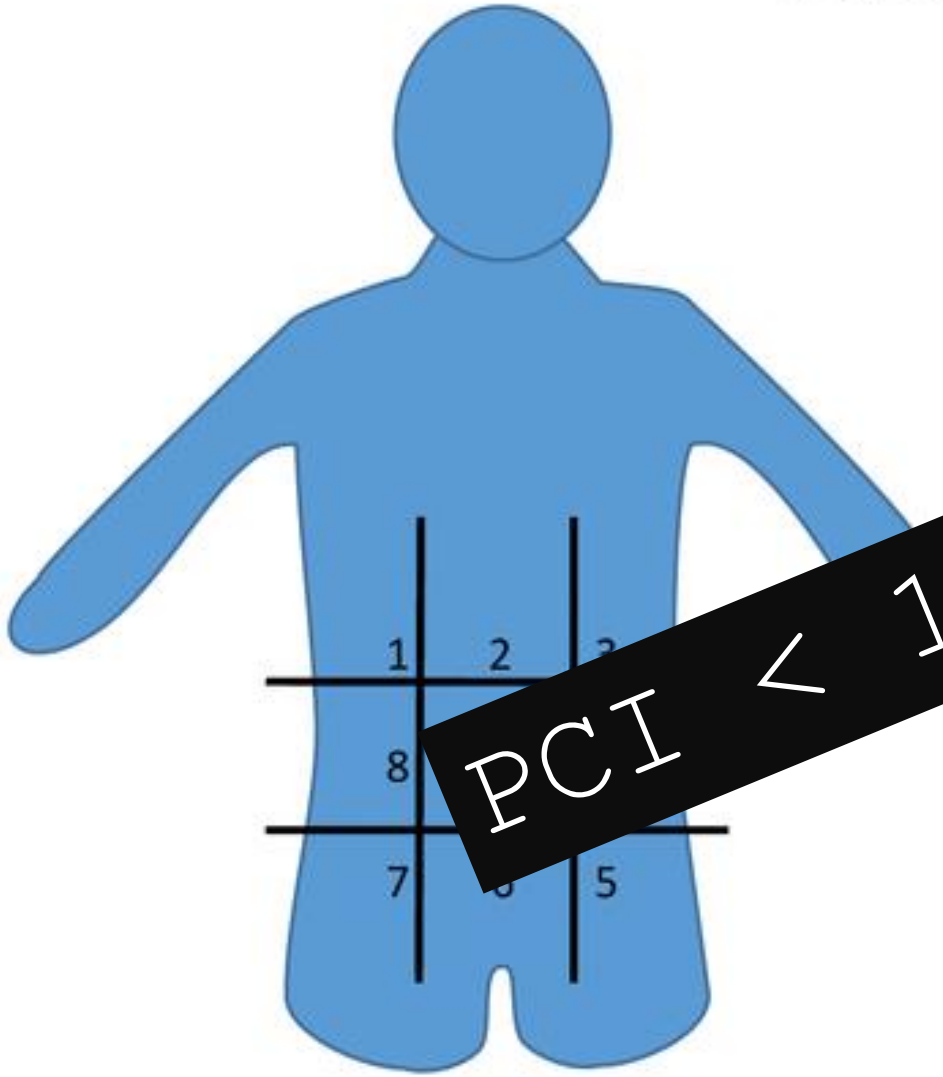

Regions
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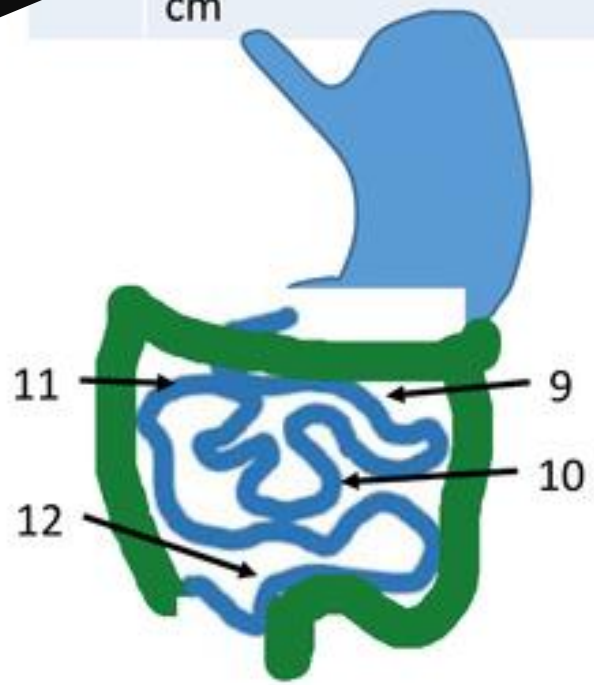
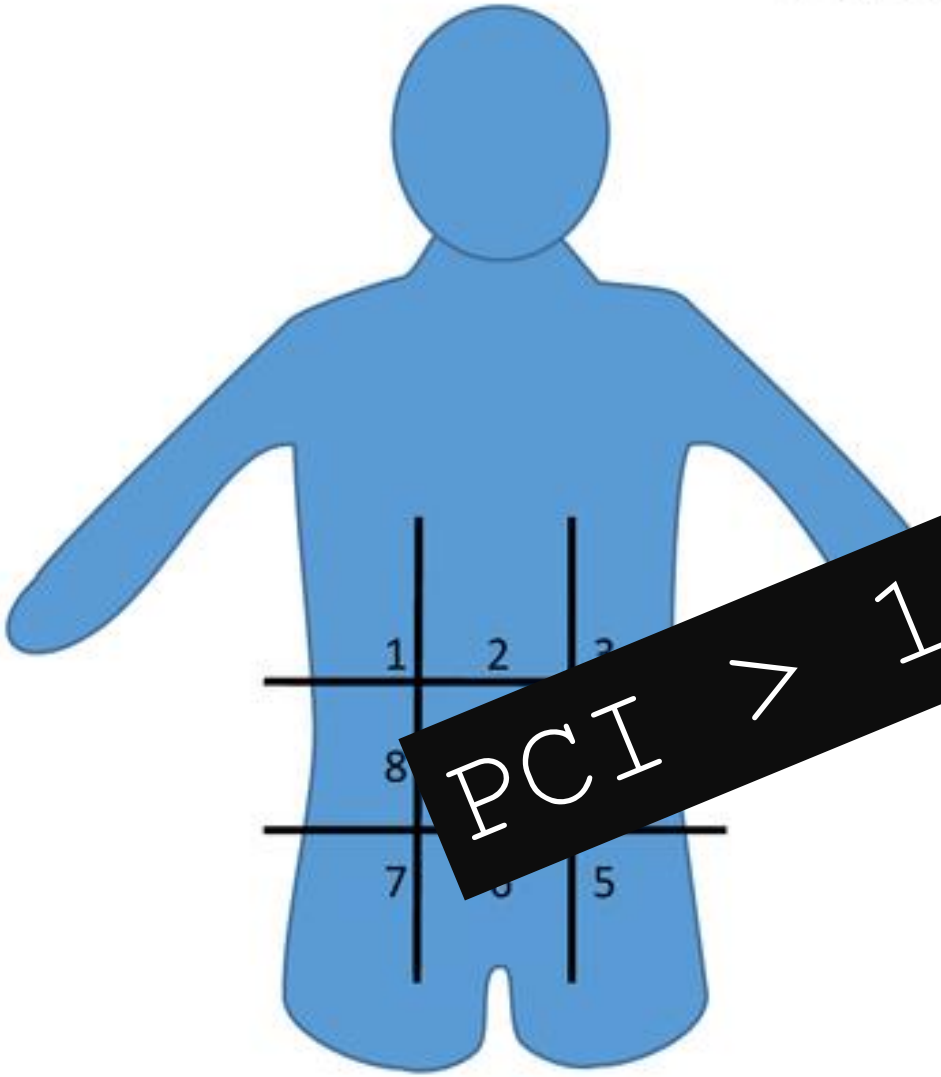


PCI < 17-20: Curative intent

Peritoneal Cancer Index



Regions
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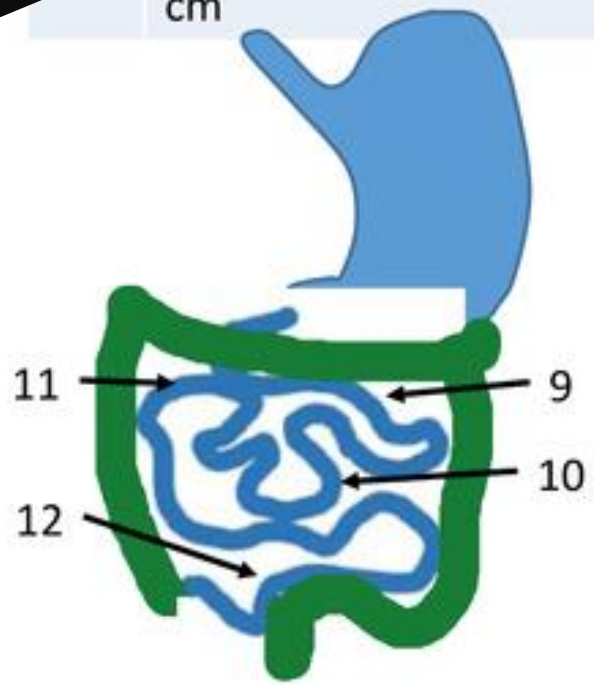
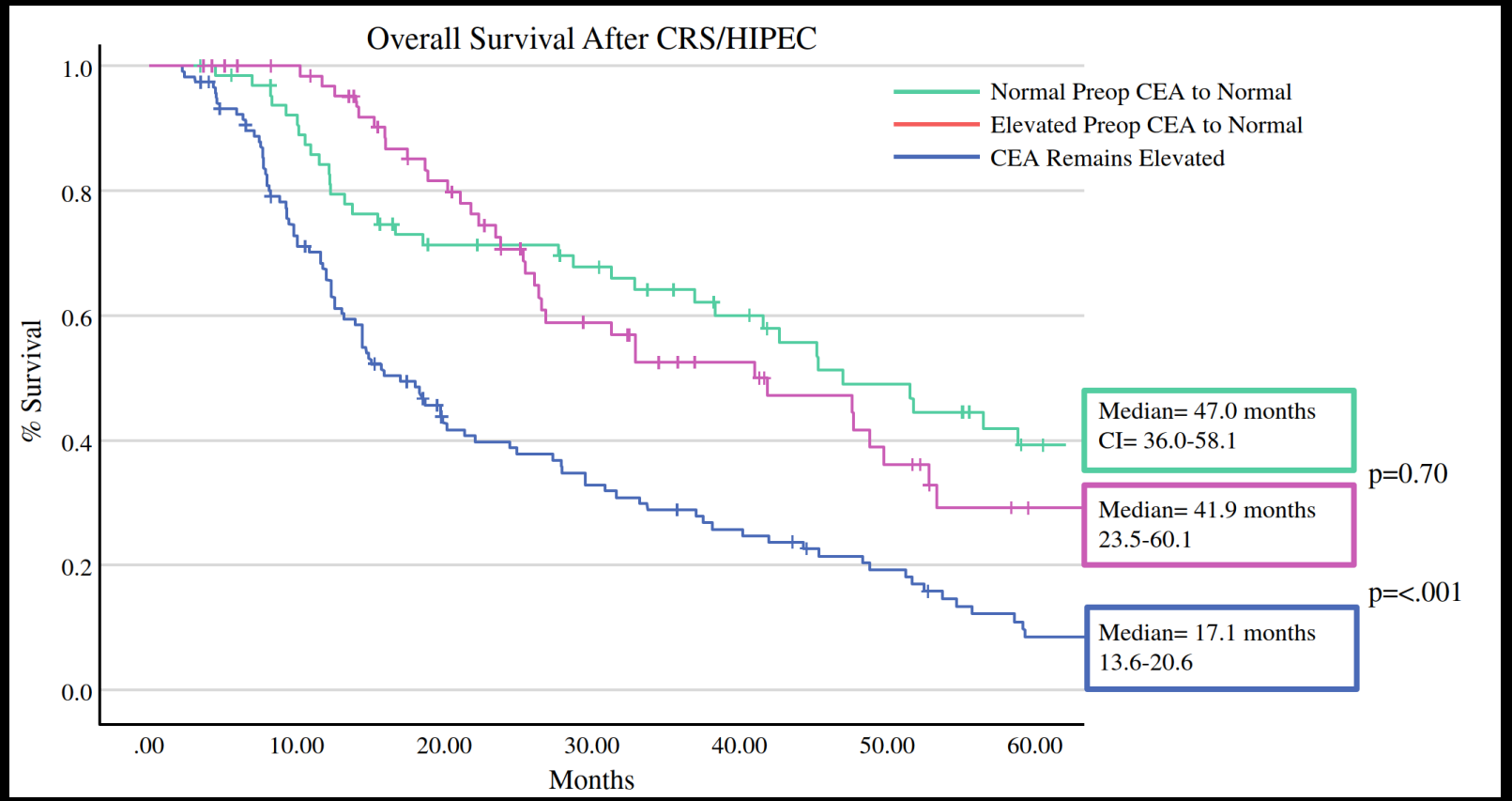


PCI > 17-20: Palliative inte

Levels After Neoadjuvant Chemotherapy and Cytoreduction with Hyperthermic Intraperitoneal Chemoperfusion Predict Improved Survival from Colorectal Peritoneal



- Ann Surg Oncol (2024) 31:2391–2400
- https://doi.org/10.1245/s10434-024-14901-0

Patient Selection

- PCI < 17 – 20
  - Ideally <10

- Response to NACT ?
- Normalization of CEA

Outline

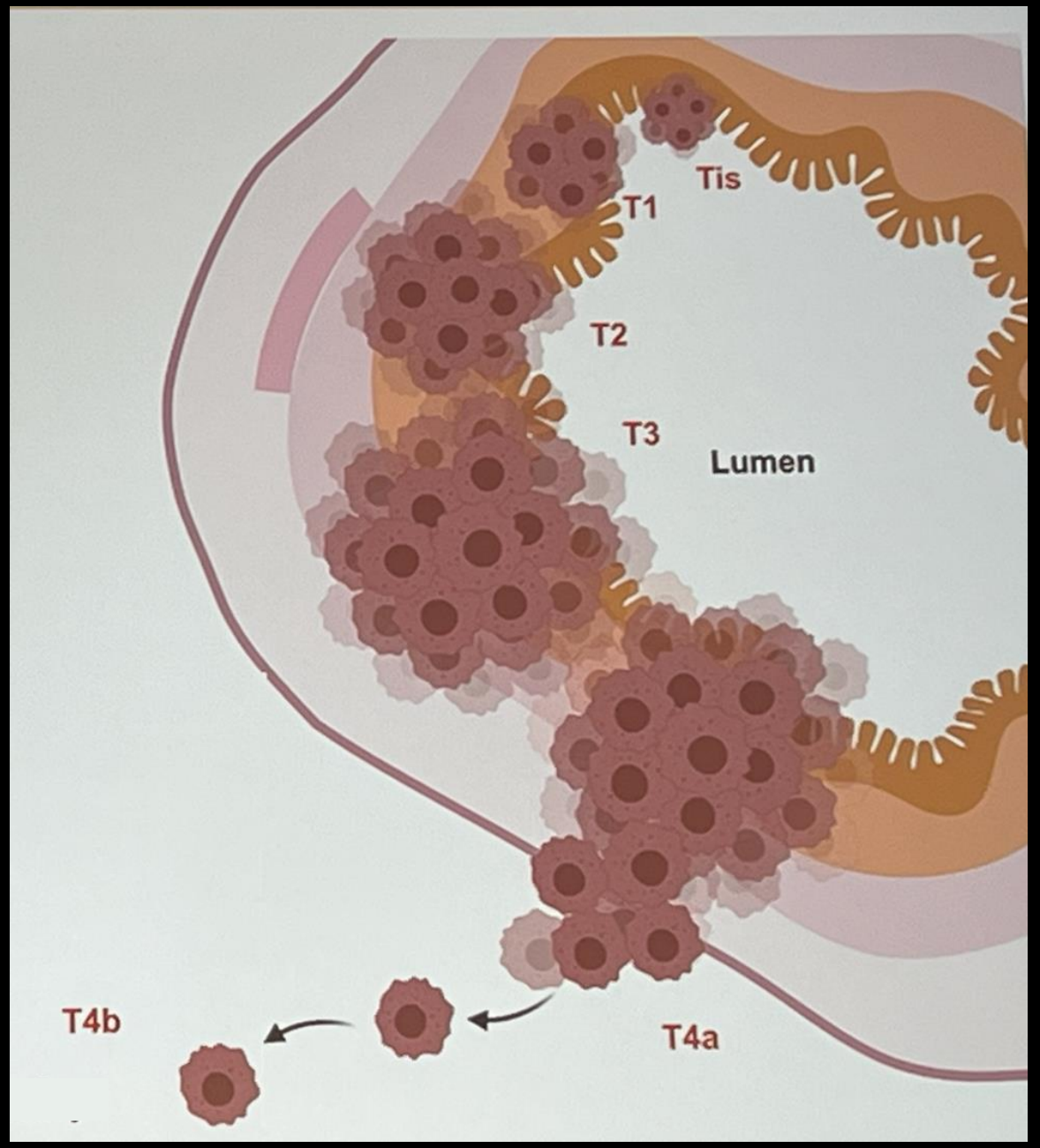
Current Evidence for CRS HIPEC in CRC

New knowledge in the science of CRC PM

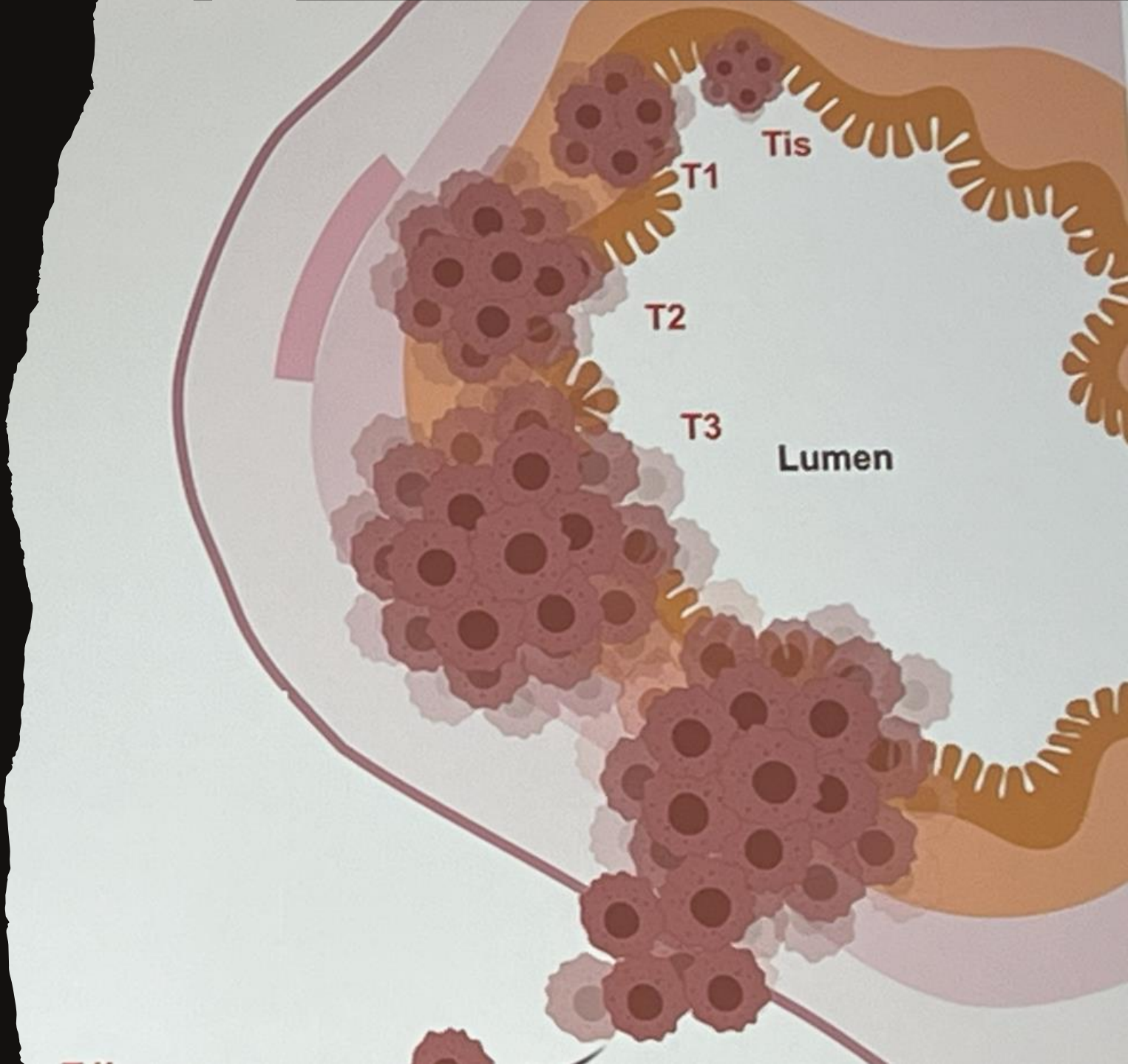
Prevention of PM in CRC

Future outlook

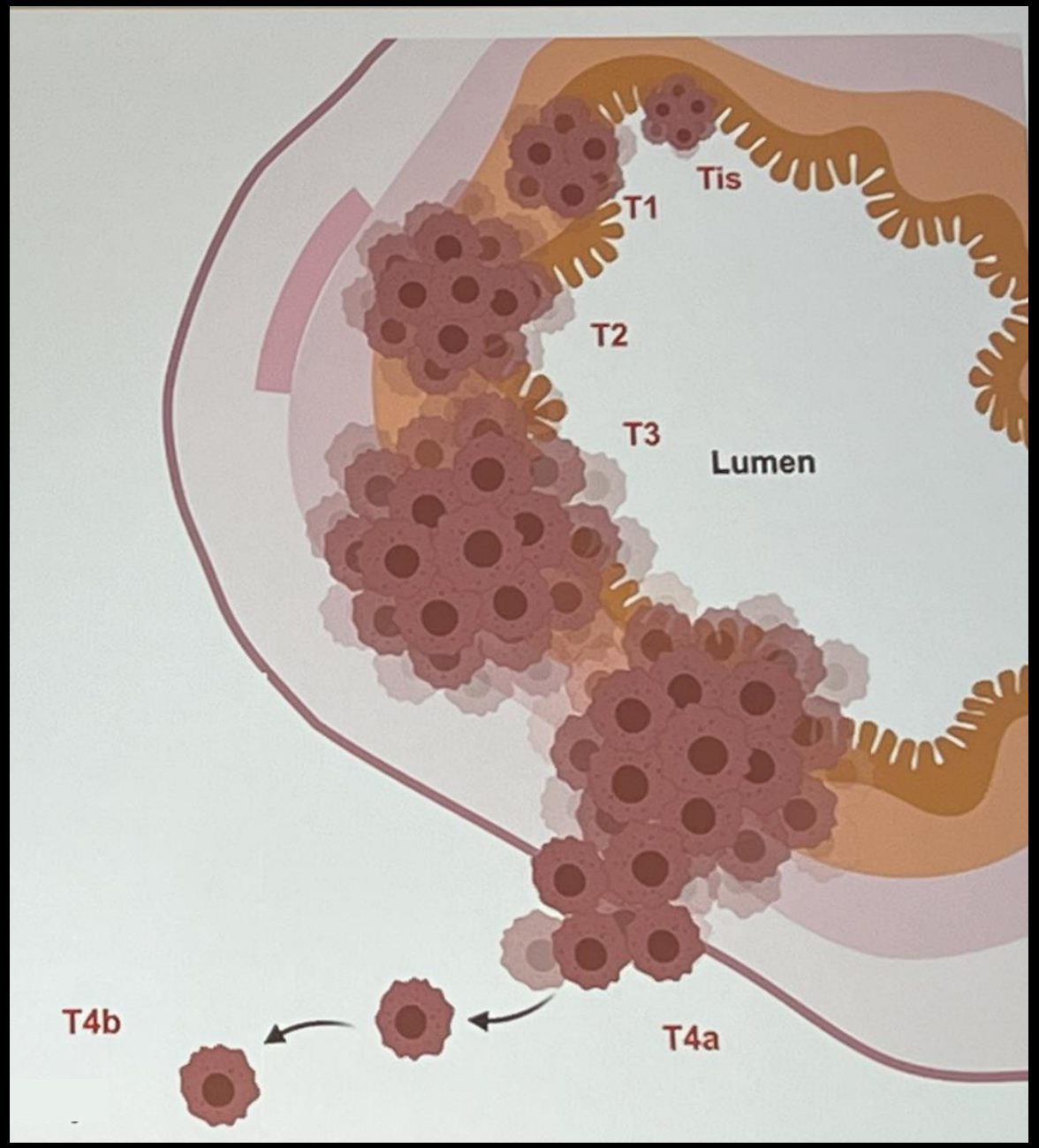
T4



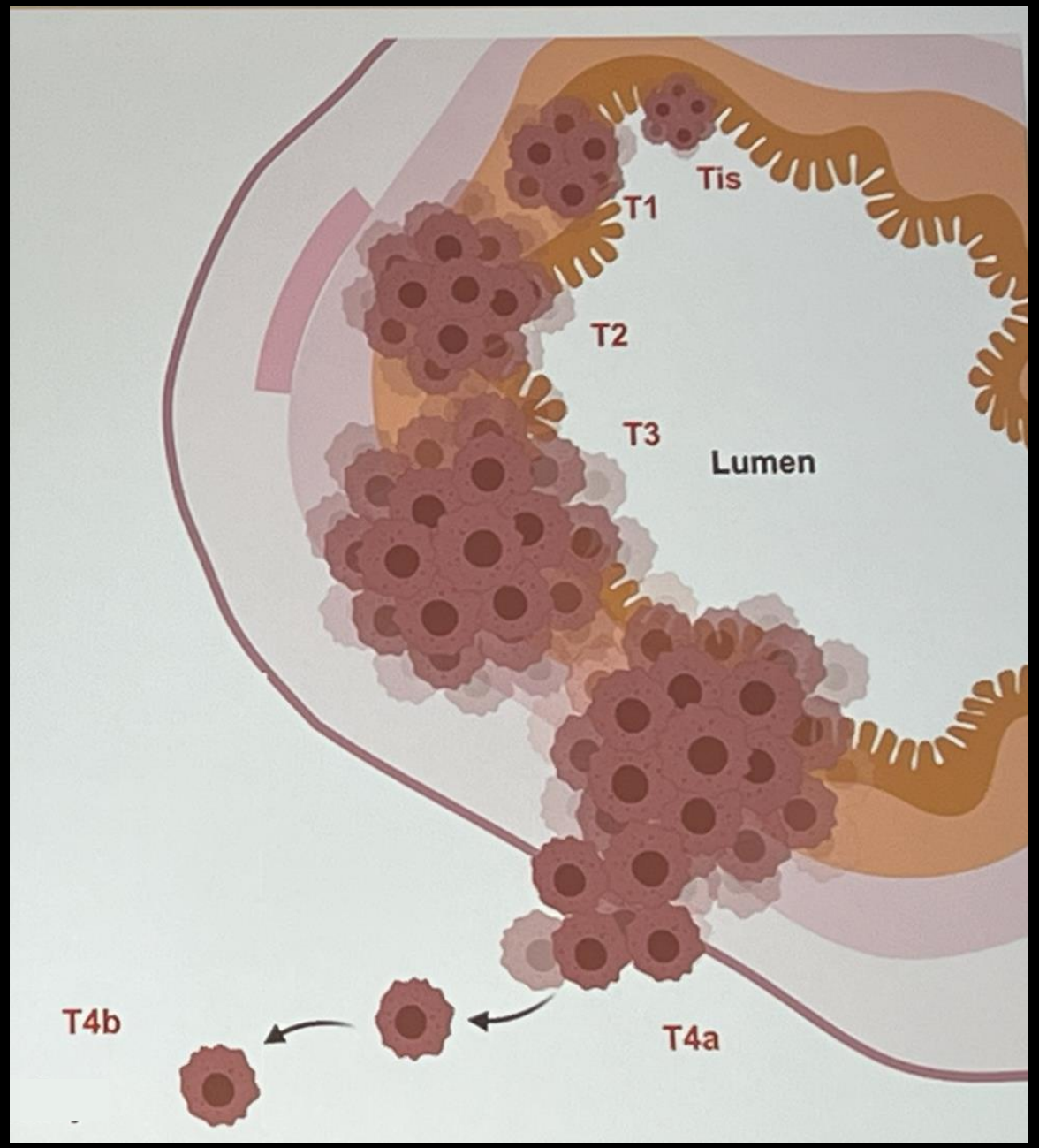
However the development of Metastases is NOT a “ random process” occurring in any T4 tumor



- Tumor cells require unique skills to survive, to adhere, to infiltrate and to proliferate in the hostile hypoxic peritoneal cavity



- Can the tumors that cause peritoneal metastases be identified ?



nature medicine

Analysis | Published: 12 October 2015

The consensus molecular subtypes of colorectal cancer

Justin Guinney, Rodrigo Dienstmann, Xin Wang, Aurélien de Reyniès, Andreas Schlicker, Charlotte Soneson, Laetitia Marisa, Paul Roepman, Gift Nyamundanda, Paolo Angelino, Brian M Bot, Jeffrey S Morris, Iris M Simon, Sarah Gerster, Evelyn Fessler, Felipe De Sousa E Melo, Edoardo Missiaglia, Hena Ramay, David Barras, Krisztian Homicsko, Dipen Maru, Ganiraju C Manyam, Bradley Broom, Valerie Boige, ... Sabine Tejpar + Show authors

Nature Medicine **21**, 1350–1356 (2015) | Cite this article

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFβ activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

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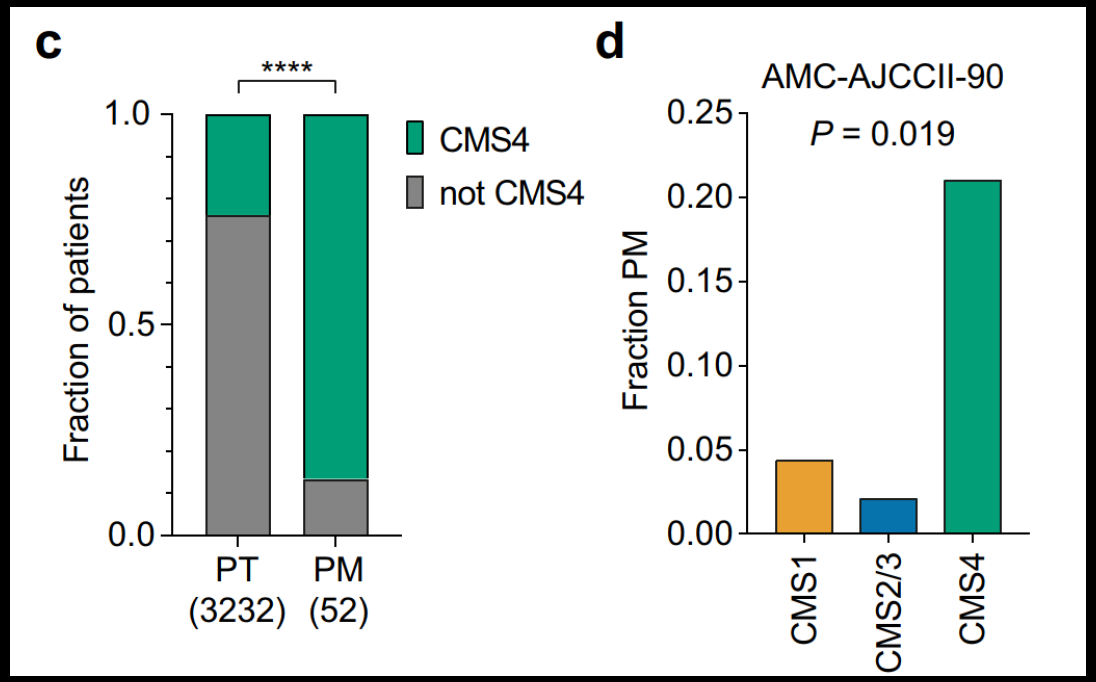
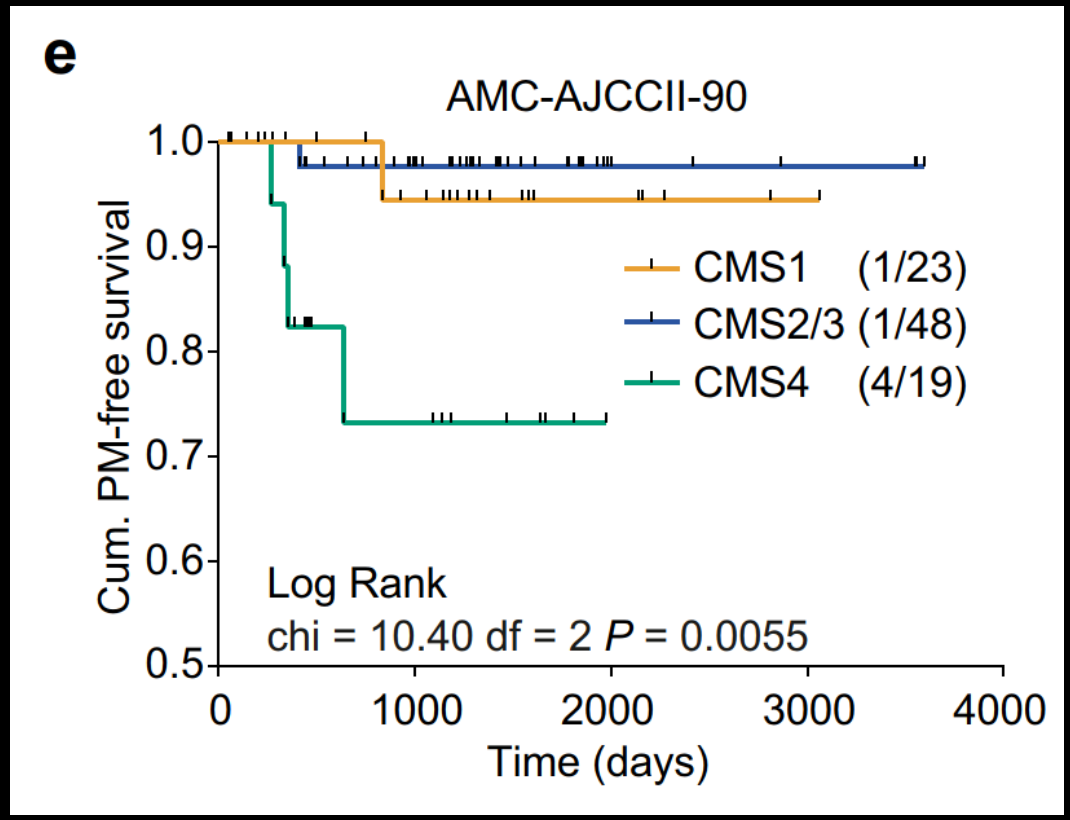
nature communications

Article

https://doi.org/10.1038/s41467-022-32198-z

Molecular characterization of colorectal cancer related peritoneal metastatic disease





nature communications

Article

https://doi.org/10.1038/s41467-022-32198-z

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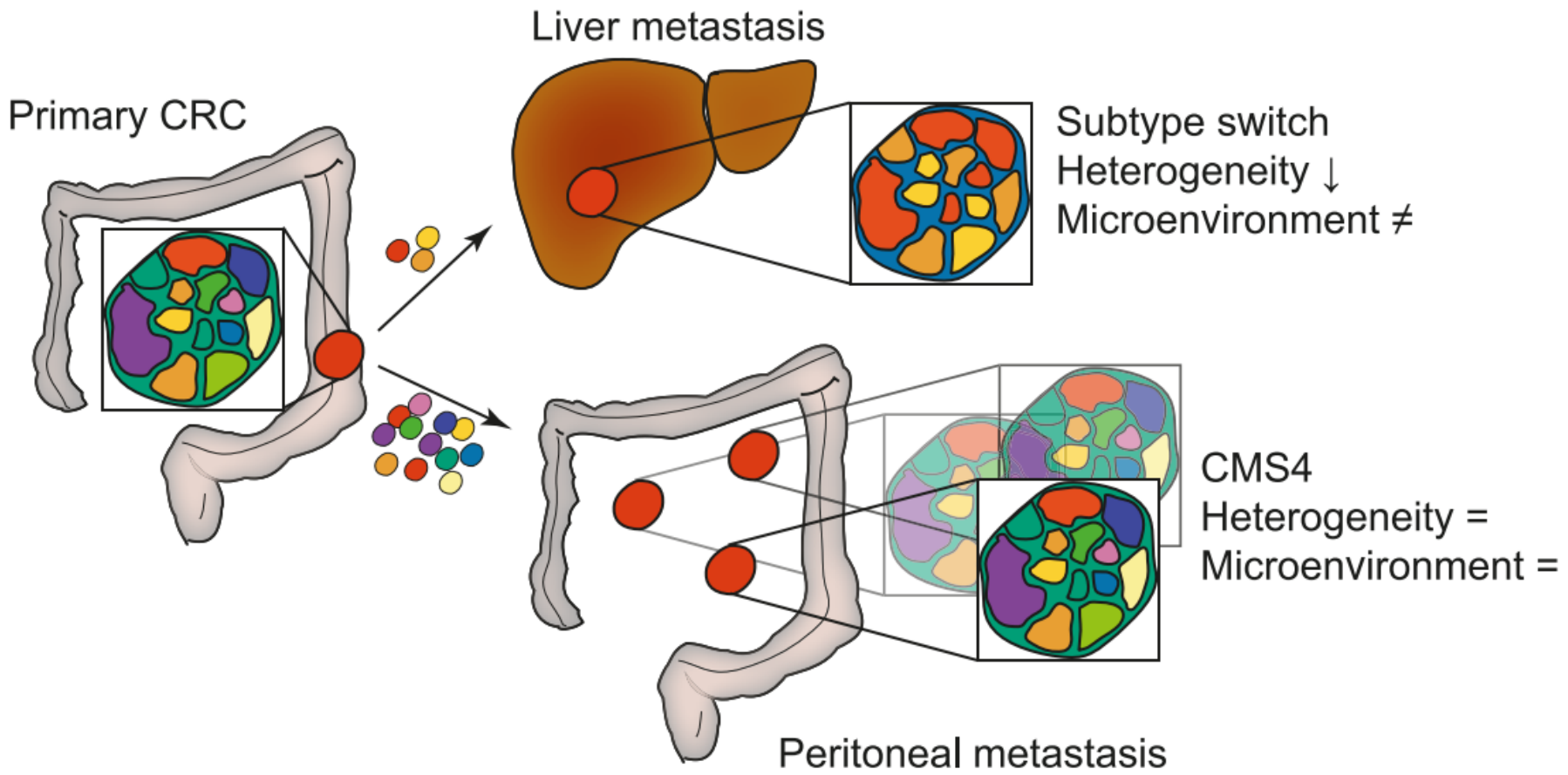
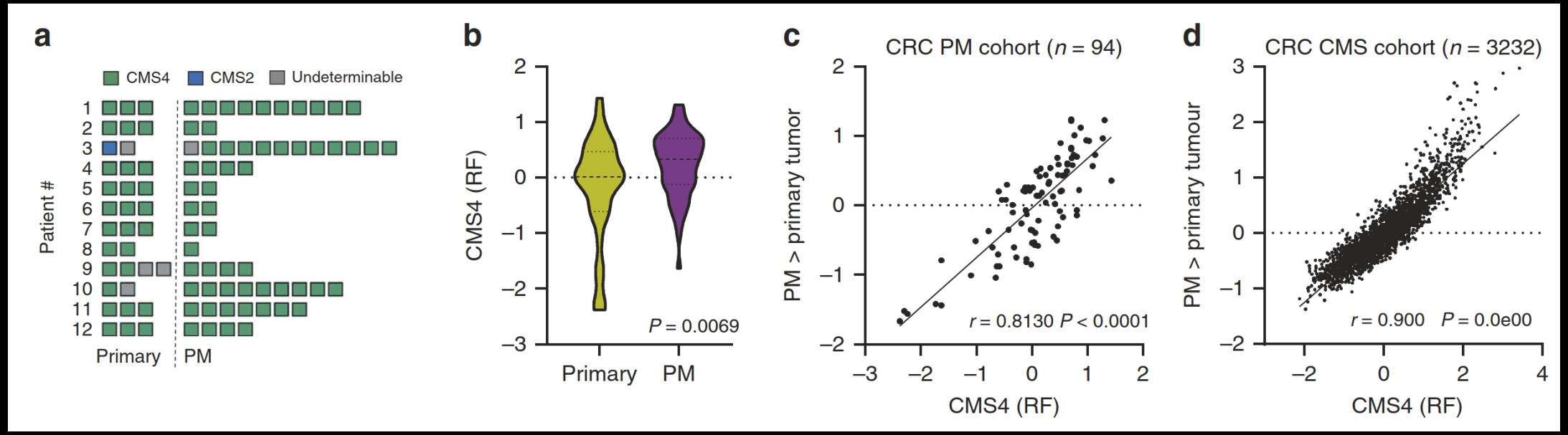
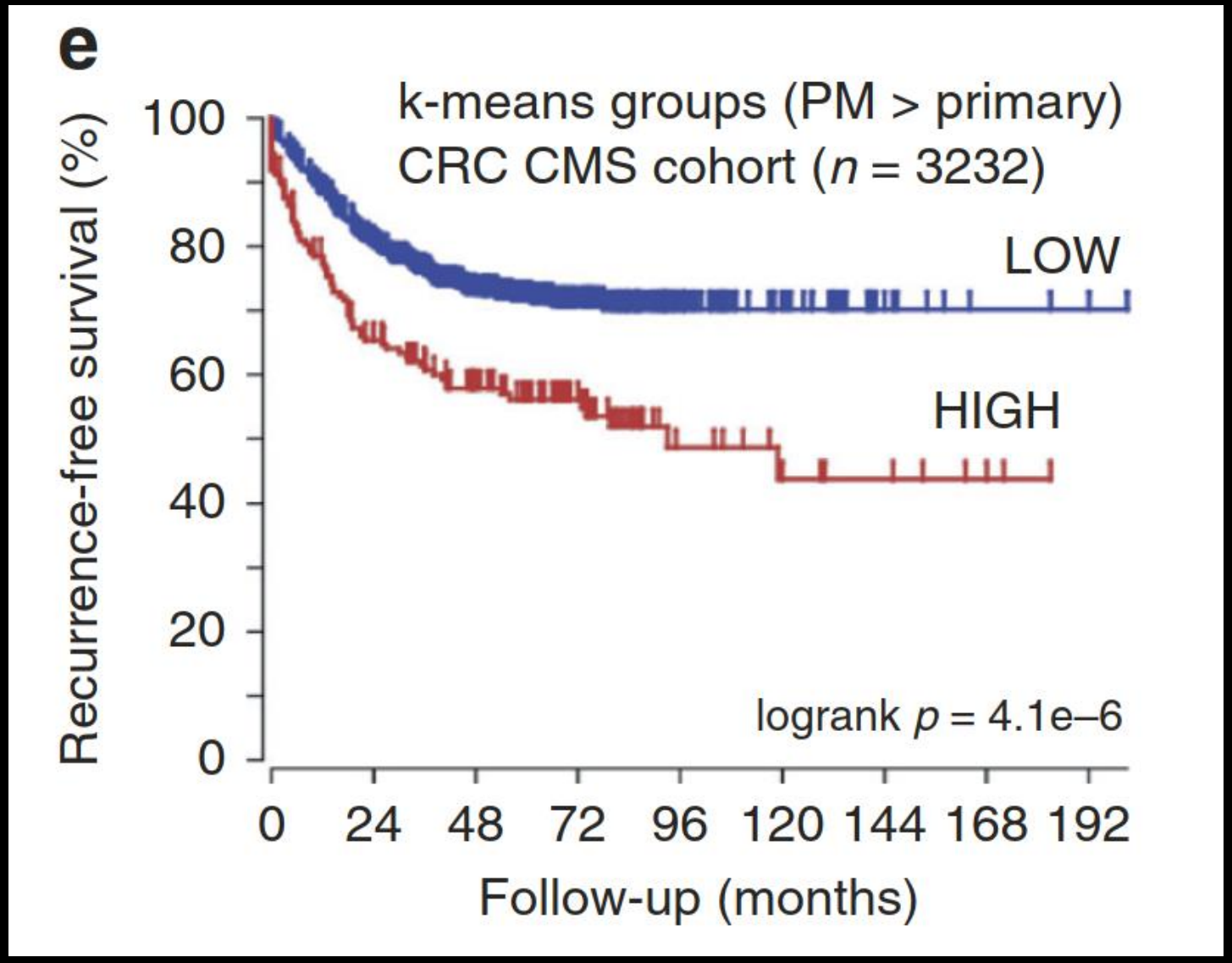


Peritoneal metastases from CRC belong to Consensus Molecular Subtype 4 are most similar to original Tumor



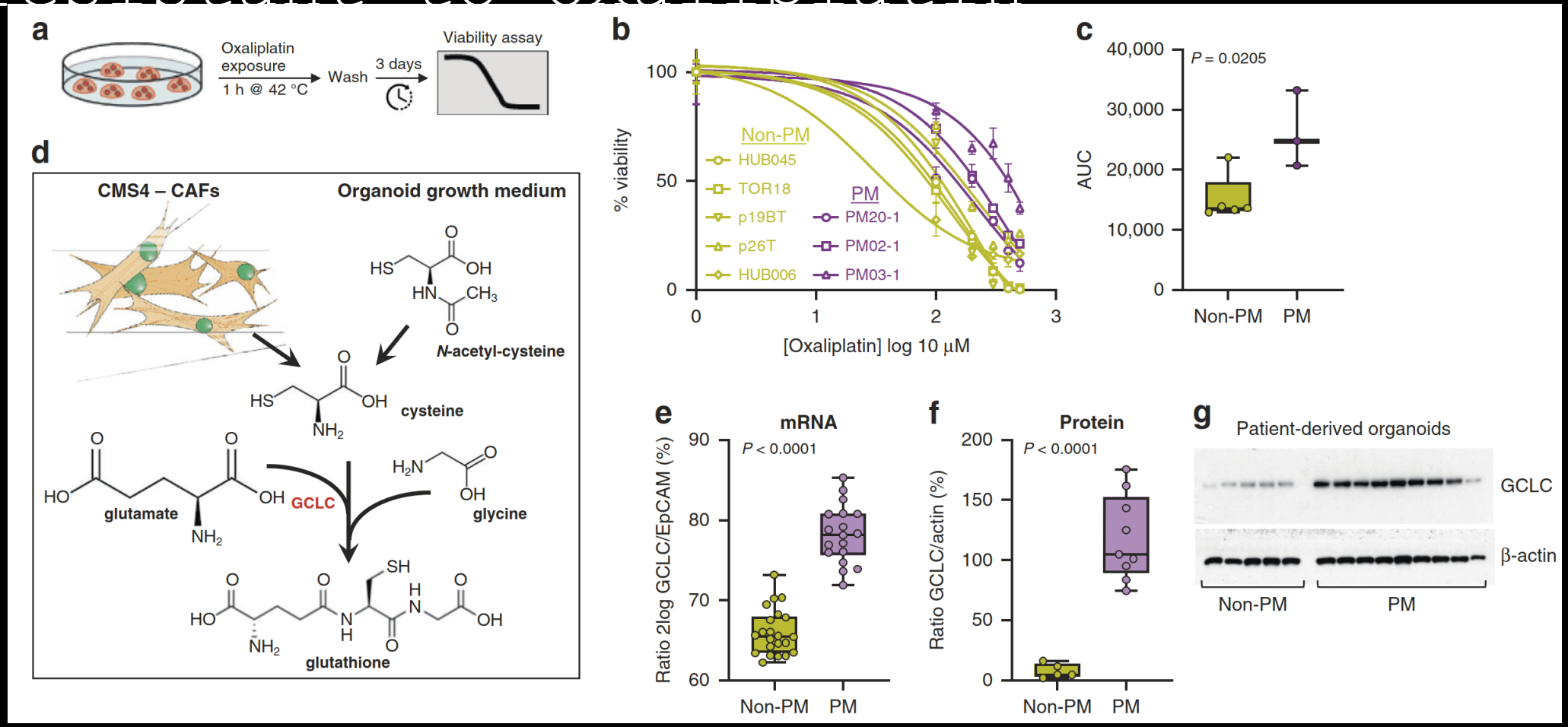
British Journal of Cancer (2022) 126:1824–1833; https://doi.org/10.1038/s41416-022-01742-5

Peritoneal metastases from CRC belong to Consensus Molecular Subtype 4 have a worse prognosis



British Journal of Cancer (2022) 126:1824–1833; https://doi.org/10.1038/s41416-022-01742-5

Peritoneal metastases from CRC belong to Consensus Molecular Subtype 4 are resistant to Oxaliplatin



British Journal of Cancer (2022) 126:1824–1833; https://doi.org/10.1038/s41416-022-01742-5

New Knowledge

85-95% of PM occur in patients with CMS4 tumors

CMS 1-2-3 tumors are less likely to develop PM

CMS-4 tumors are resistant to systemic oxaliplatin

Outline

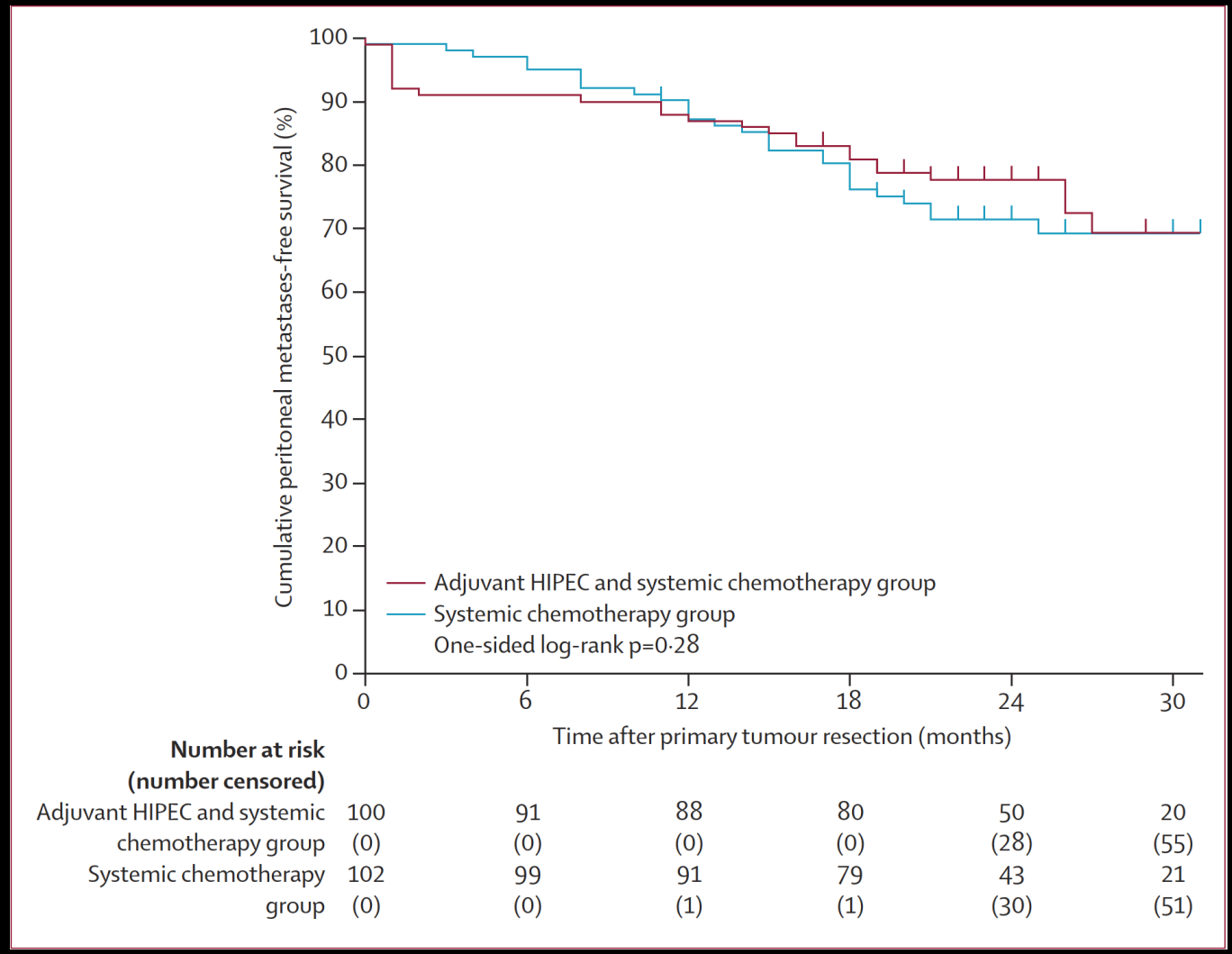
Current Evidence for CRS HIPEC in CRC

New knowledge in the science of CRC PM

Prevention of PM in CRC

Future outlook

Adjuvant Hyperthermic Intraperitoneal Chemotherapy in patients with locally advanced colon cancer (Colopec), a multicenter open label randomized trial

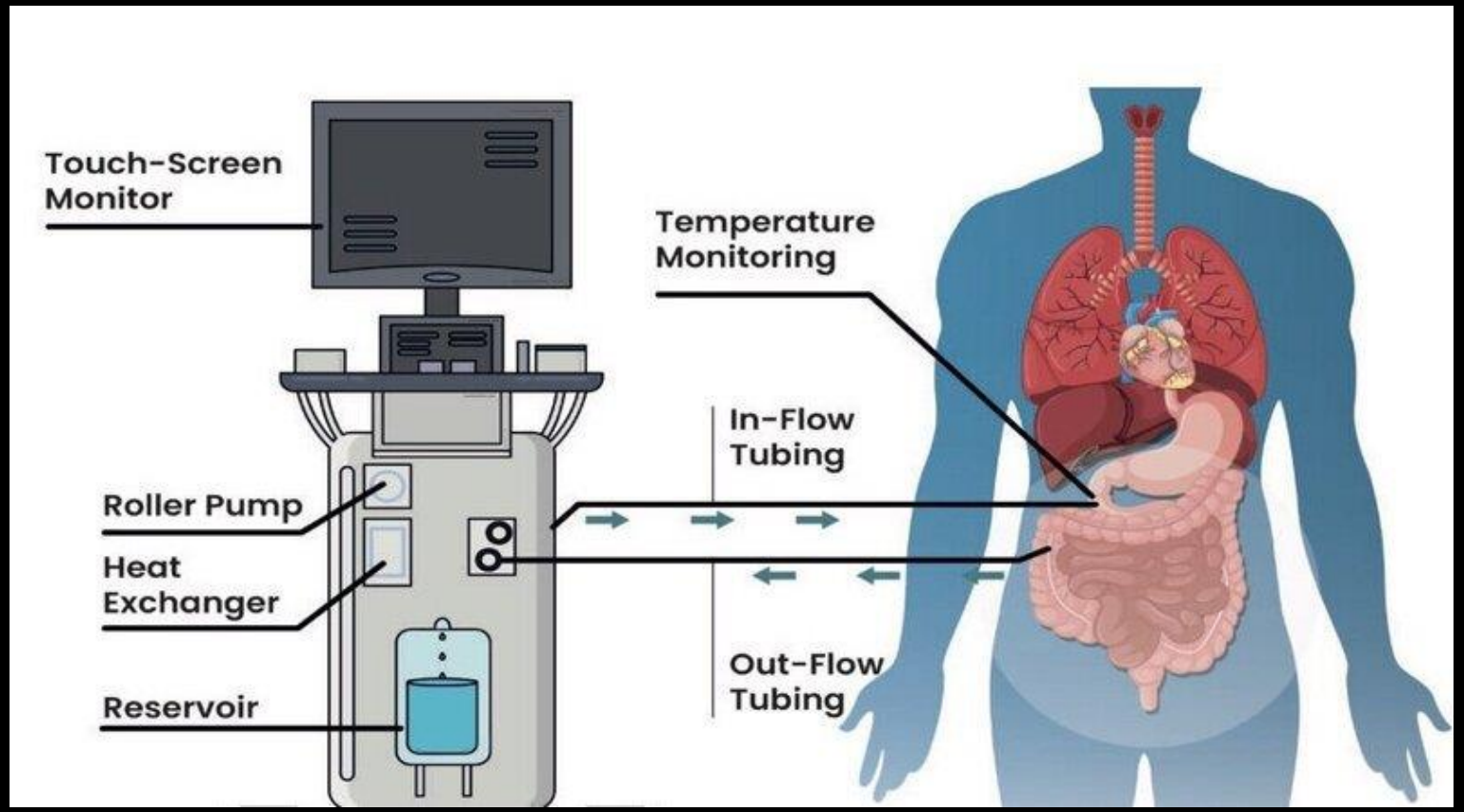


Number at risk (number censored)						
Adjuvant HIPEC and systemic chemotherapy group	100 (0)	91 (0)	88 (0)	80 (0)	50 (28)	20 (55)
Systemic chemotherapy group	102 (0)	99 (0)	91 (1)	79 (1)	43 (30)	21 (51)

Lancet Gastroenterol Hepatol

2019

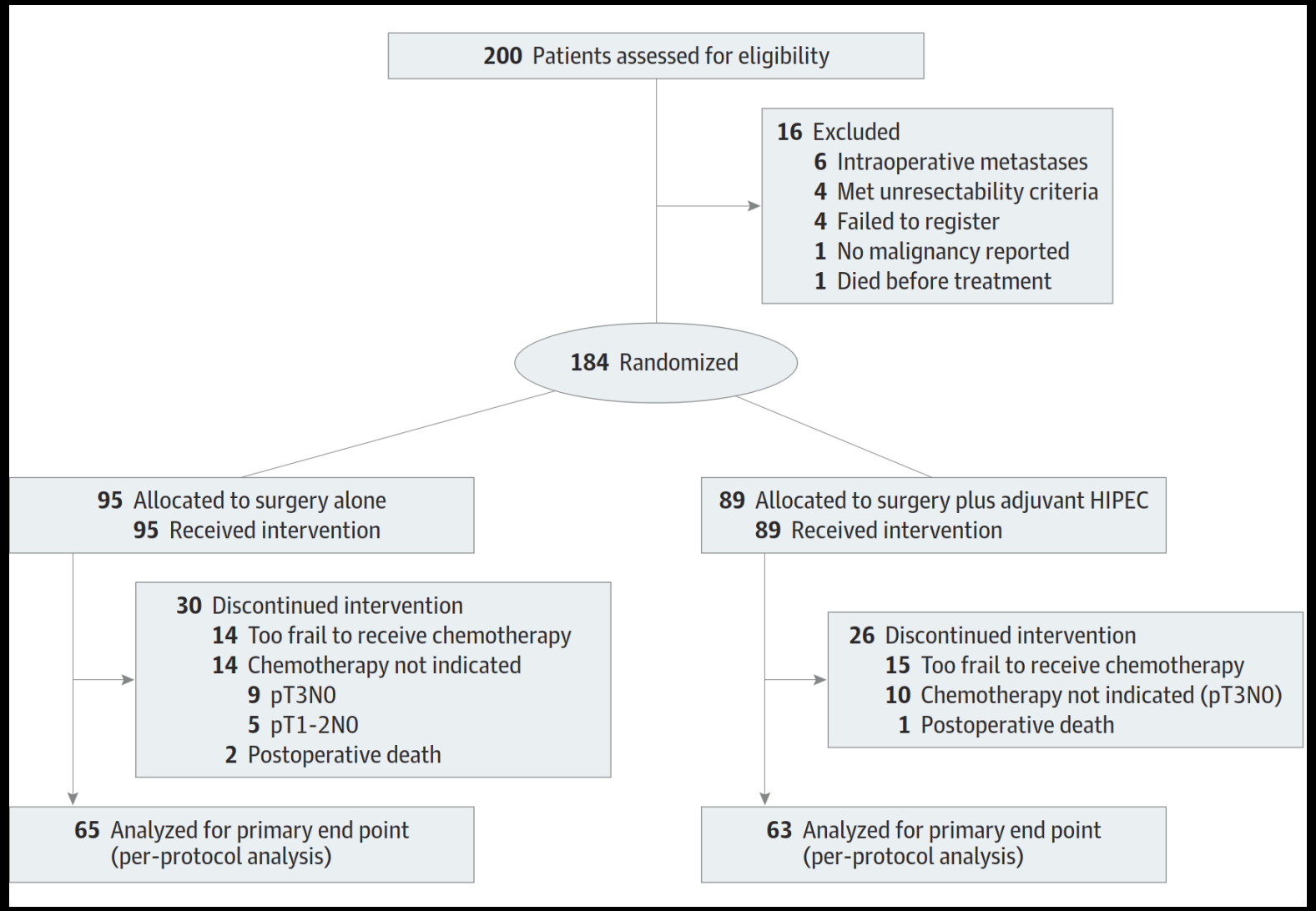
Oxaliplatin 30 minutes perfusion



Efficacy and safety of intraoperative hyperthermic intraperitoneal chemotherapy for locally advanced colon cancer.

A phase 3 randomized clinical trial

JAMA Surg. 2023;158(7):683-691. doi:10.1001/jamasurg.2023.0662



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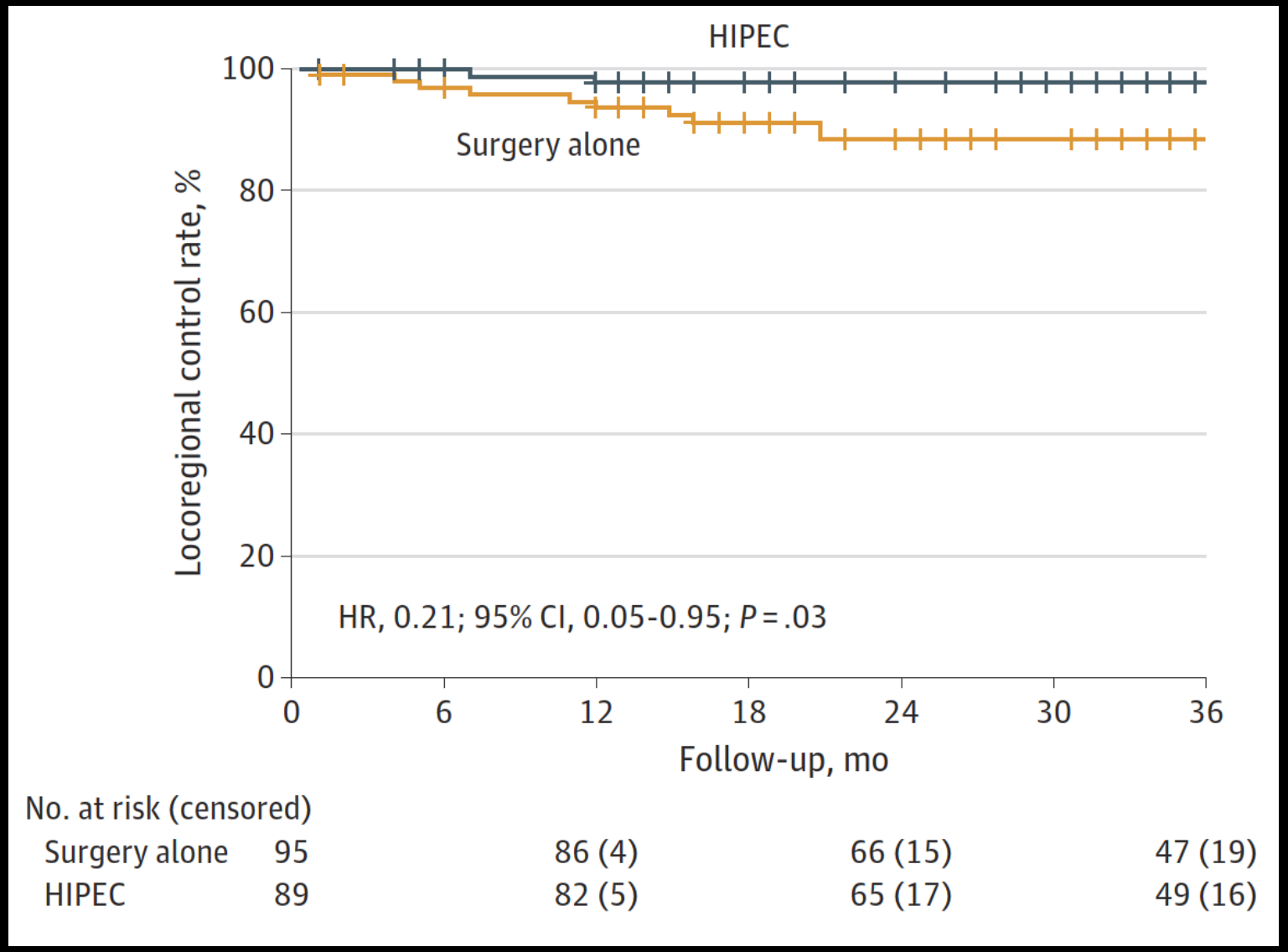
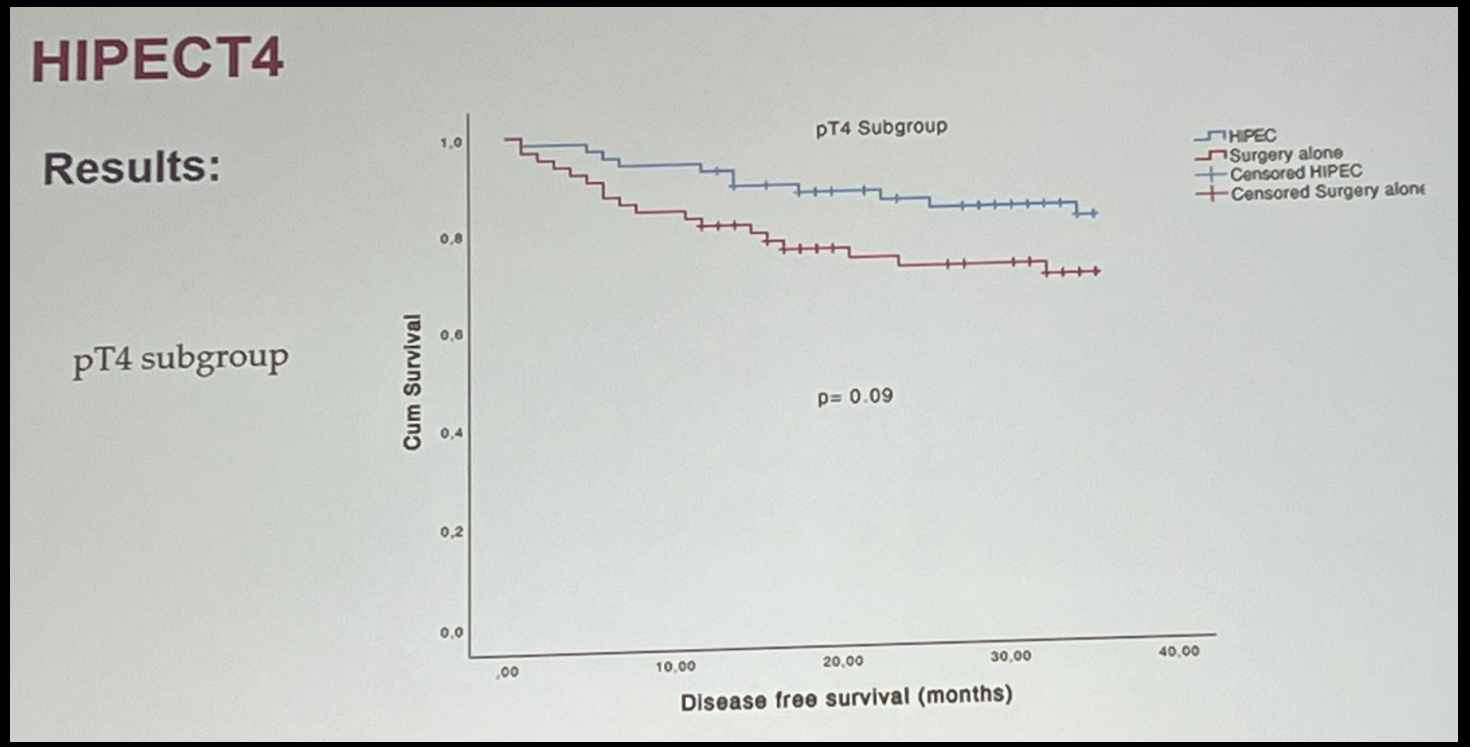
A phase 3 randomized clinical trial

JAMA Surg. 2023;158(7):683-691. doi:10.1001/jamasurg.2023.0662



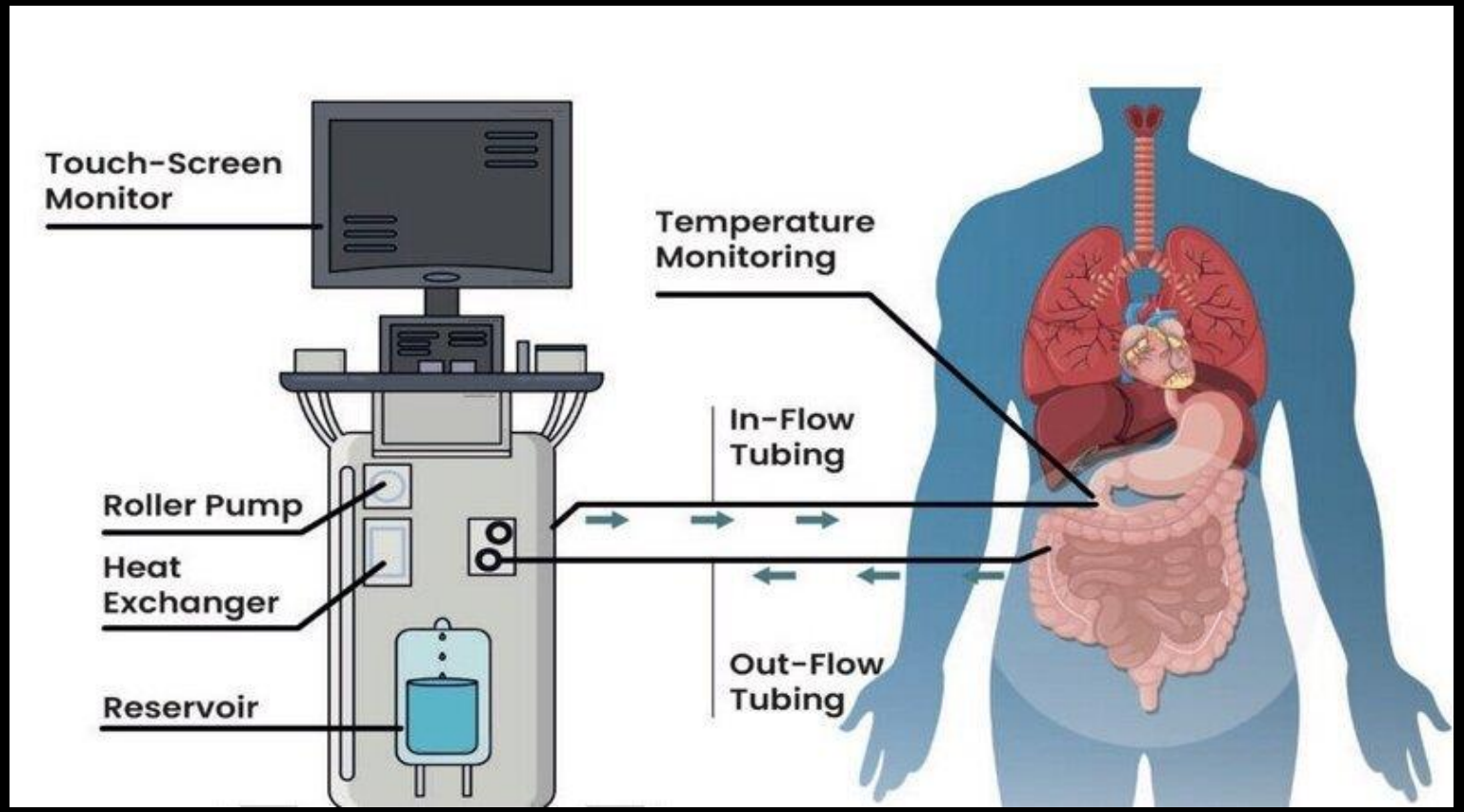
Efficacy and safety of intraoperative hyperthermic intraperitoneal chemotherapy for locally advanced colon cancer.

A phase 3 randomized clinical trial



- *JAMA Surg.* 2023;158(7):683-691. doi:10.1001/jamasurg.2023.0662

Mitomycin C 60 minutes perfusion



trial justify adjuvant HIPEC after resection of high risk CRC as standard of care ?

Volume 110, Issue 11

November 2023

JOURNAL ARTICLE

In favour of prophylactic hyperthermic intraperitoneal chemotherapy for colorectal cancer

Get access >

Alvaro Arjona-Sánchez ✉

British Journal of Surgery, Volume 110, Issue 11, November 2023, Pages 1428–1430,

JOURNAL ARTICLE

Opposed to prophylactic hyperthermic intraperitoneal chemotherapy for colorectal cancer

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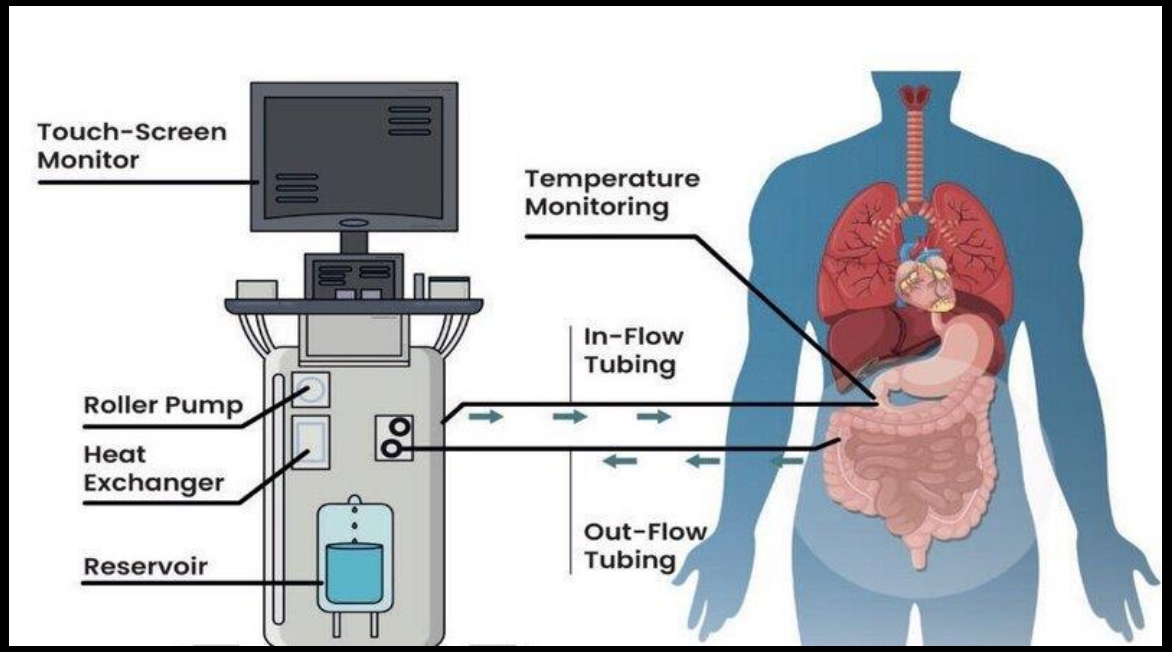
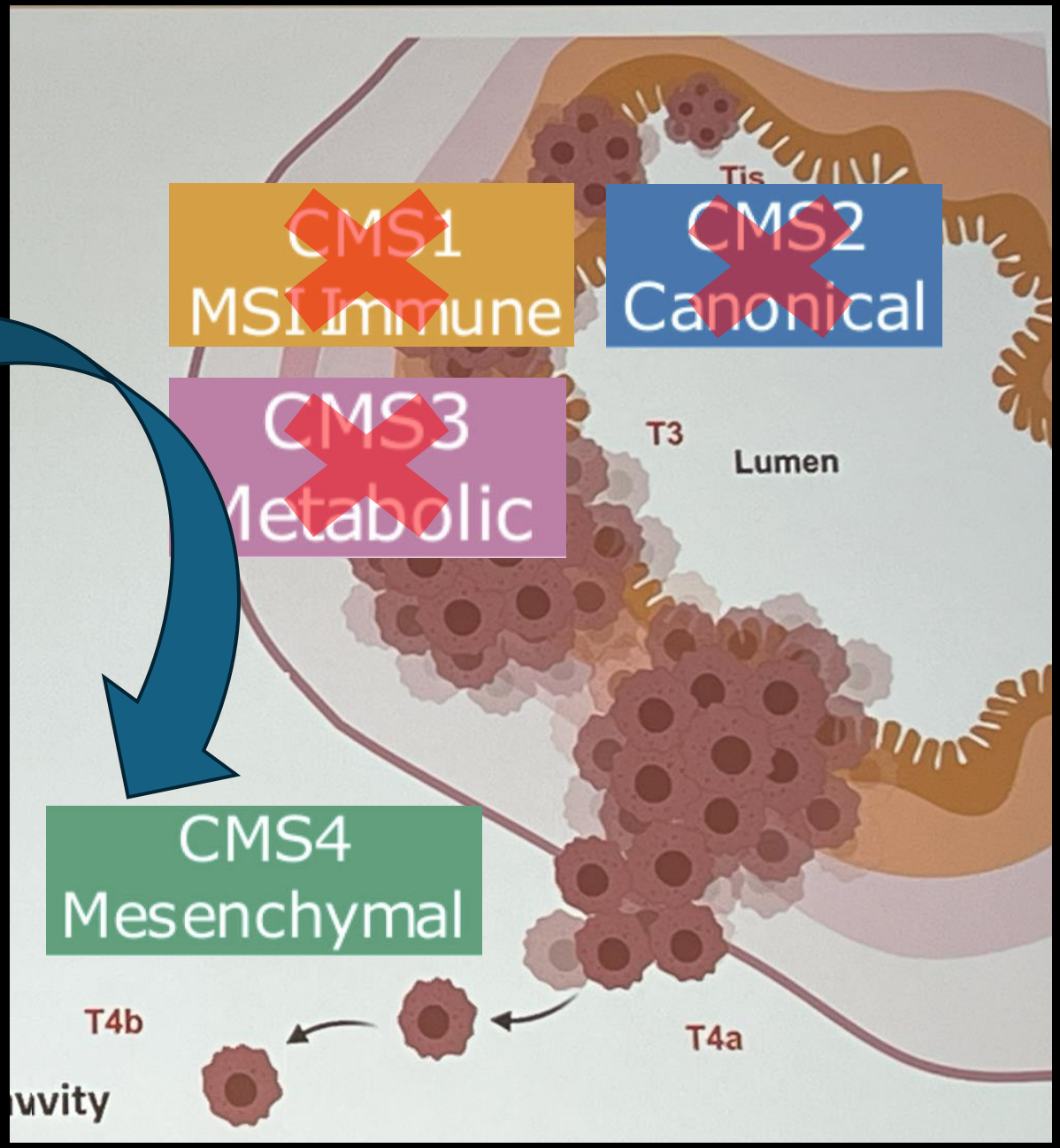
Pieter J Tanis ✉

British Journal of Surgery, Volume 110, Issue 11, November 2023, Pages 1431–1432,

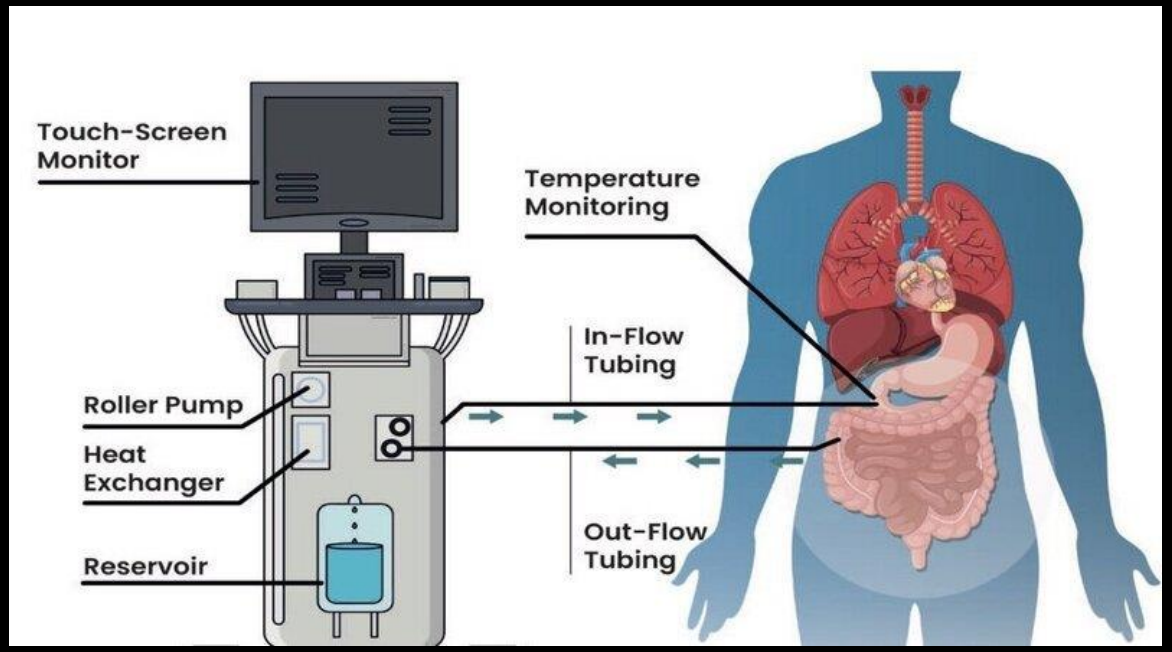
Adjuvant HIPEC Selection

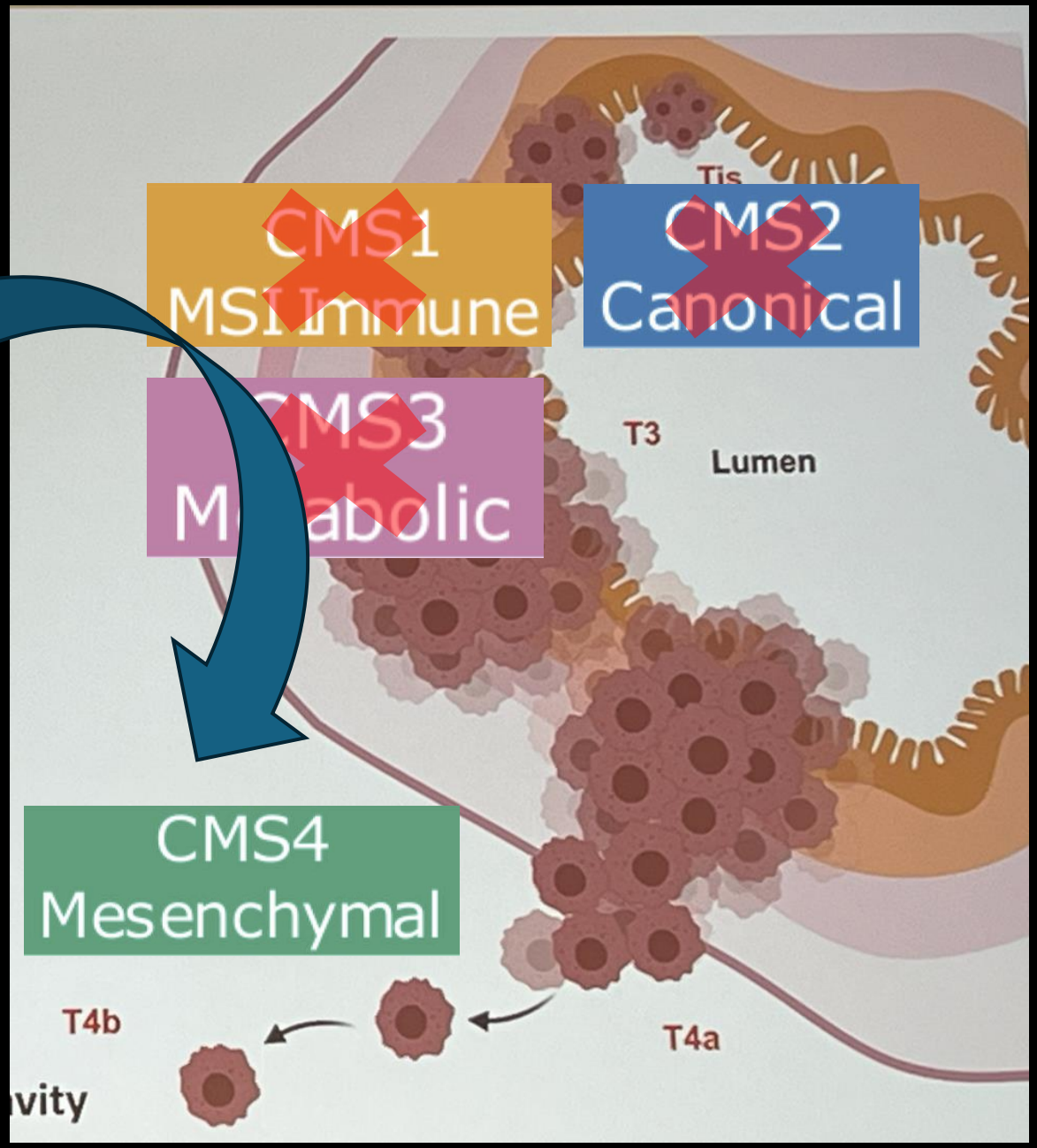




Adjuvant HIPEC

Agents that specifically Targ
CMS-4





Outline

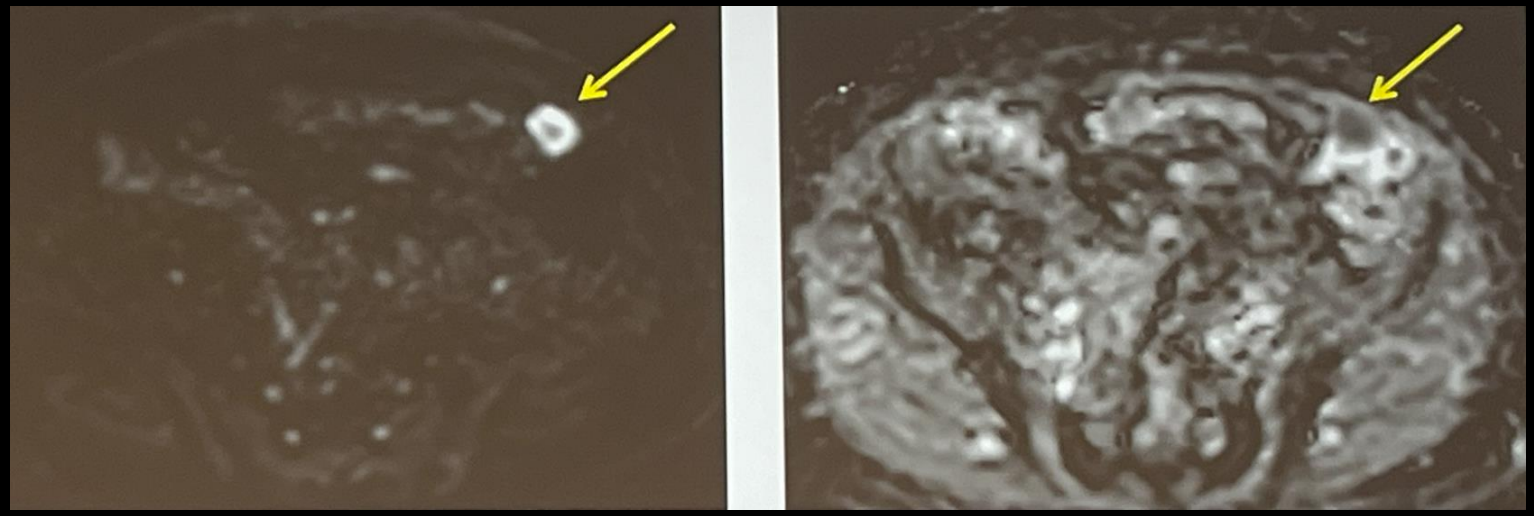
Current Evidence for CRS HIPEC in CRC

New knowledge in the science of CRC PM

Prevention of PM in CRC

Future outlook

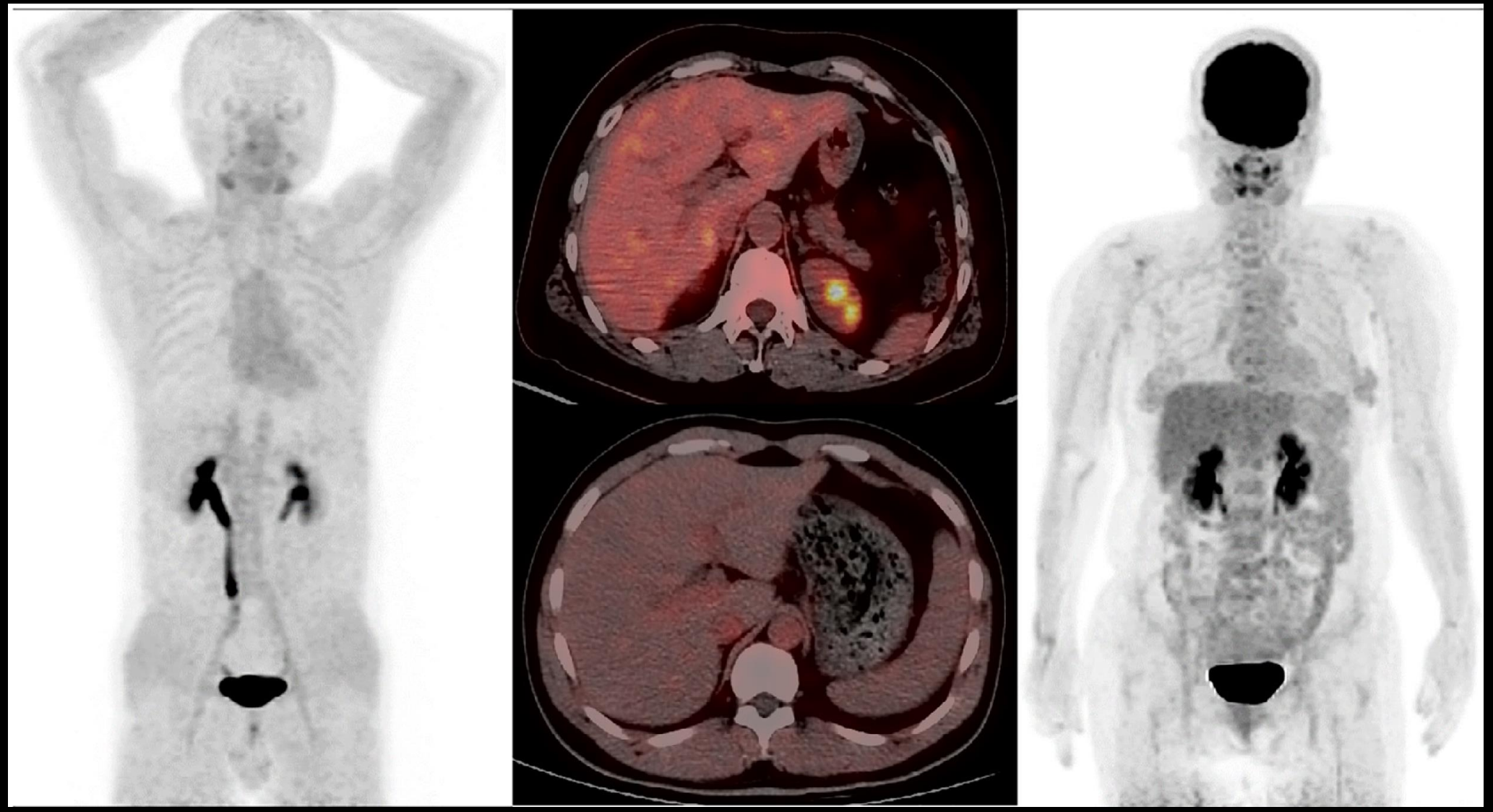
DW MRI



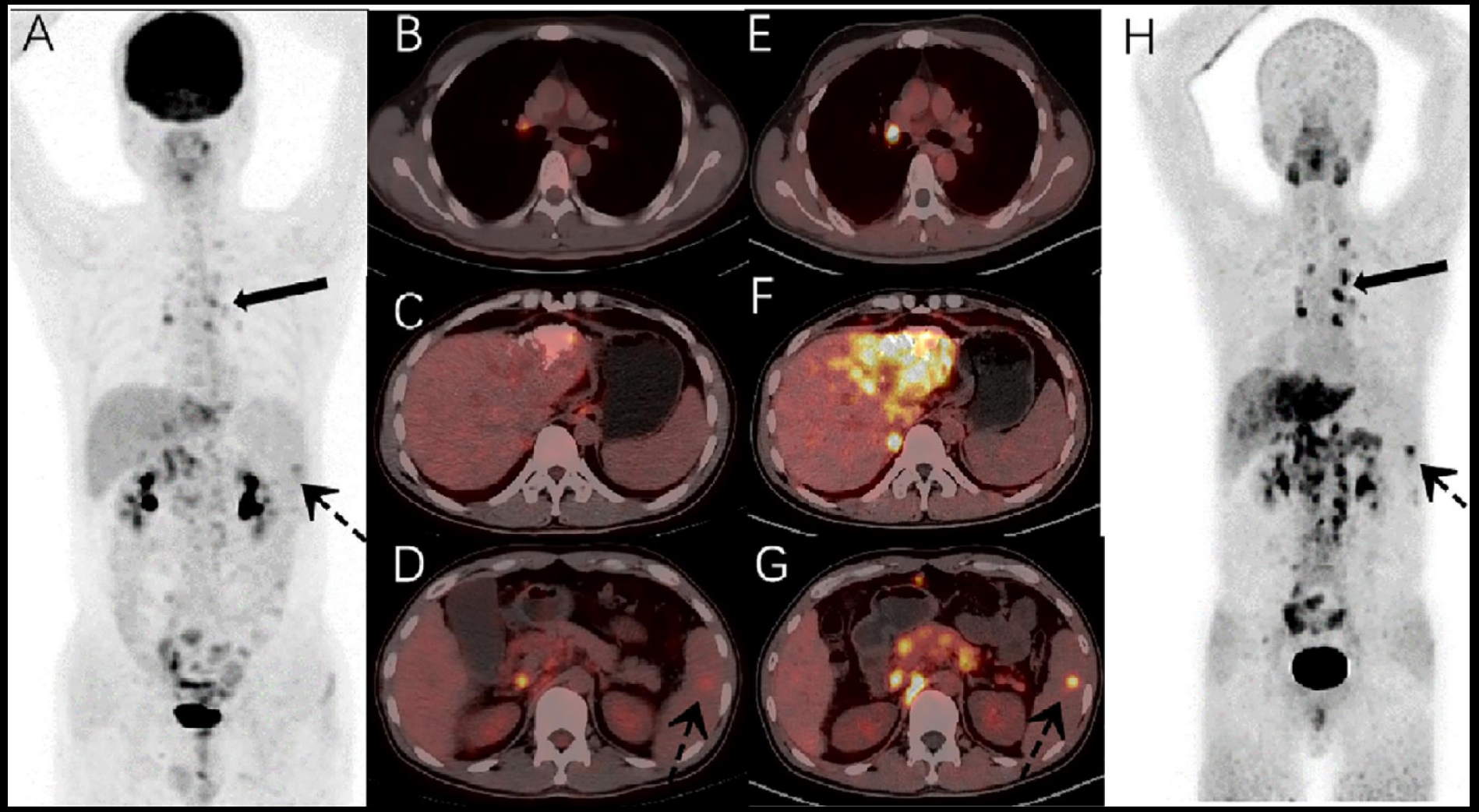
FAPI PET CT

- Fibroblast activation protein (FAP) is a membrane-bound type 2 serine protease, which is overexpressed in activated fibroblasts.
- Through the specific binding to the enzymatic domain of FAP, FAPI-PET is able to visualize the tumor stroma formation as small as 2-3 mm
- High image contrast, resulting from the low background signal in the normal organs, due to the low expression or FAP in the normal, quiescent fibroblasts
  - Targeting the activated cancer associated fibroblasts (CAFs).
  - Cancer stroma (tumor microenvironement)
- Provides a new method for imaging and treating

FAPI PET CT



FAPI PET CT



FAPI PET CT in Peritoneal Metastases

Head-To-Head Comparison of ^{68}Ga-FAPI PET/CT and FDG PET/CT for the Detection of Peritoneal Metastases: Systematic Review and Meta-Analysis

Zhao Gege, MD[1], Wang Xueju, MD[2], Ji Bin, MD, PhD[1]

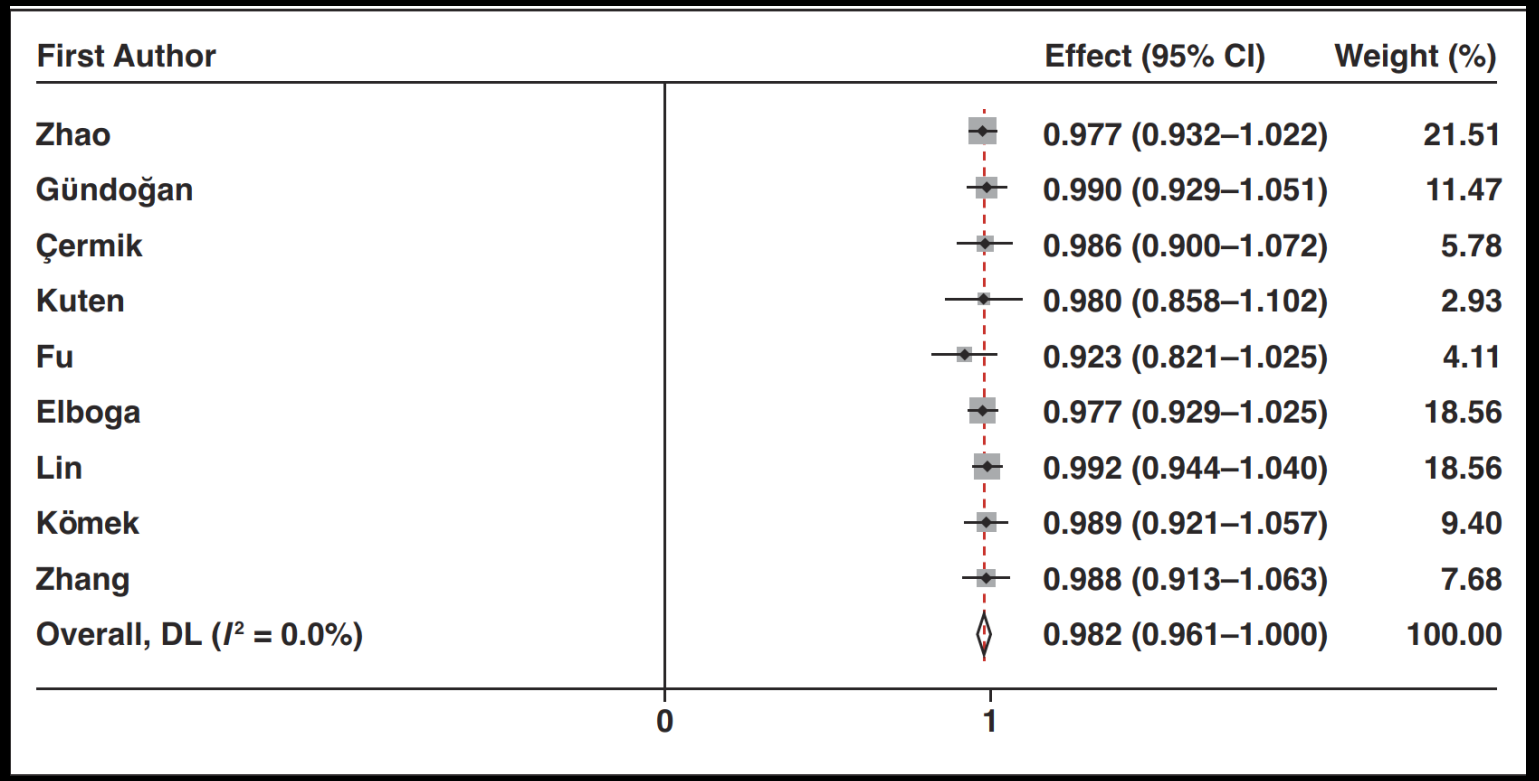
Evidence Synthesis and Decision Analysis · Systematic Review/Meta-Analysis

American Journal of Roentgenology
Volume 220, Issue 4
April 2023
Pages 461-614

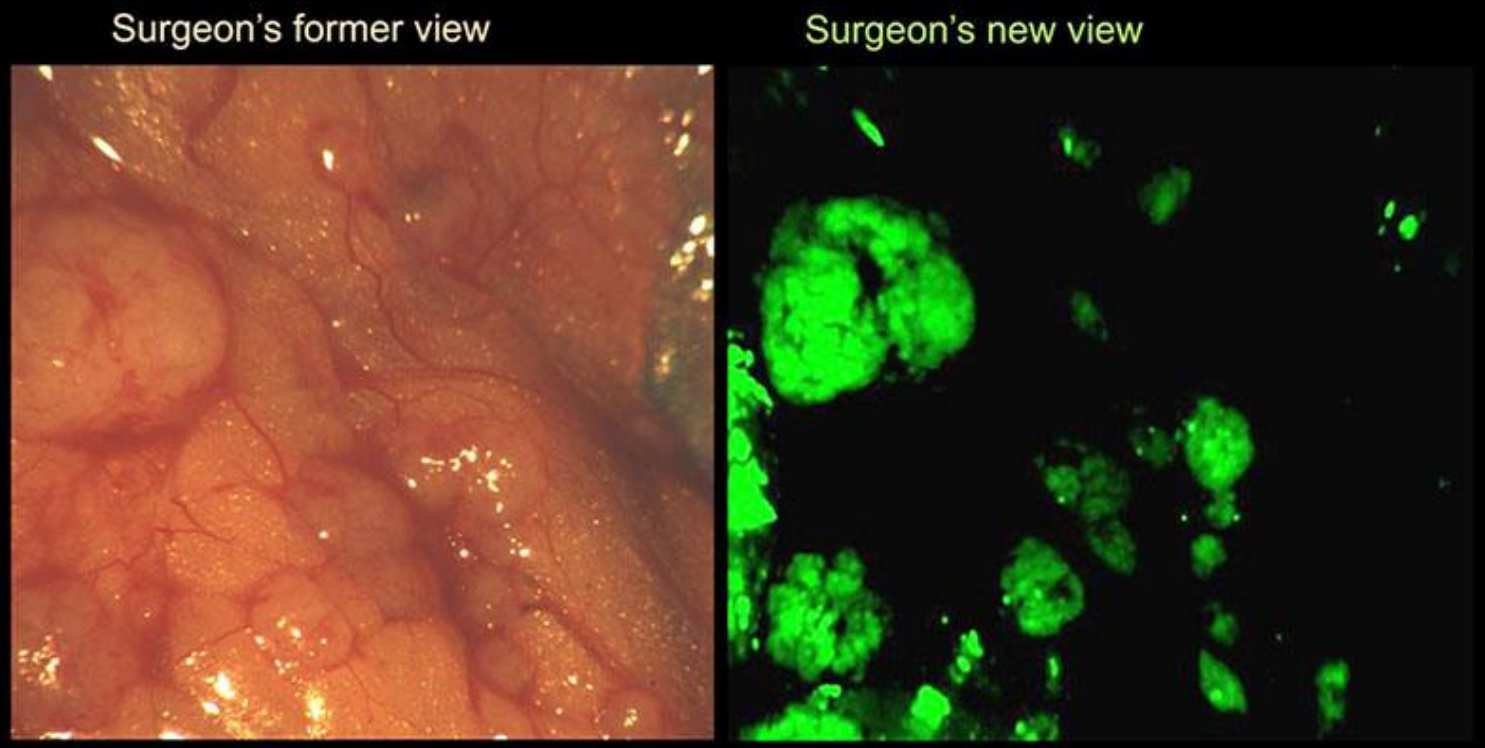
FAPI PET CT in PM

First Author	Year	Country	Study Design	Study Period	Interval Between Imaging Tests	Clinical Indication	Reference Standard[a]
Zhao [11]	2021	China	Retrospective	October 2019–August 2020	< 1 wk	Initial staging ($n = 21$) Recurrence detection ($n = 25$)	Multidisciplinary
Lan [31][b]	2021	China	Prospective	July 2020–February 2021	< 3 d	Initial staging ($n = 80$); Recurrence detection ($n = 20$)	Multidisciplinary
Gündoğan [27]	2022	Turkey	Prospective	NA	< 1 wk	Initial staging ($n = 15$); Recurrence detection ($n = 6$)	Histopathology
Çermik [25]	2022	Turkey	Prospective	NA	< 1 wk	Initial staging ($n = 33$) Recurrence detection ($n = 8$ Treatment response evaluation ($n = 1$)	Multidisciplinary
Kuten [29]	2022	Israel	Prospective	July 2020–December 2020	6 d (1–23 d)[c]	Initial staging ($n = 10$) Recurrence detection ($n = 3$)	Multidisciplinary
Fu [10]	2022	China	Retrospective	September 2020–March 2021	< 1 wk	Initial staging ($n = 61$)	Histopathology
Elboga [26]	2022	Turkey	Retrospective	September 2020–June 2021	3.2 ± 1.3 d (2–6 d)[d]	Initial staging ($n = 17$) Recurrence detection ($n = 20$)	Multidisciplinary
Lin [30]	2022	China	Prospective	August 2020–August 2021	< 1 wk	Initial staging ($n = 45$) Recurrence detection ($n = 11$)	Multidisciplinary
Kömek [28]	2022	Turkey	Prospective	June 2021–December 2021	< 1 wk	Initial staging ($n = 34$) Recurrence detection ($n = 5$)	Histopathology
Lan [24]	2022	China	Prospective	June 2020–June 2021	< 3 d	Initial staging ($n = 13$) Recurrence detection ($n = 5$)	Multidisciplinary
Zhang [23]	2022	China	Retrospective	June 2021–December 2021	< 1 wk	Initial staging ($n = 17$) Recurrence detection ($n = 8$)	Multidisciplinary

FAPI PET CT in PM

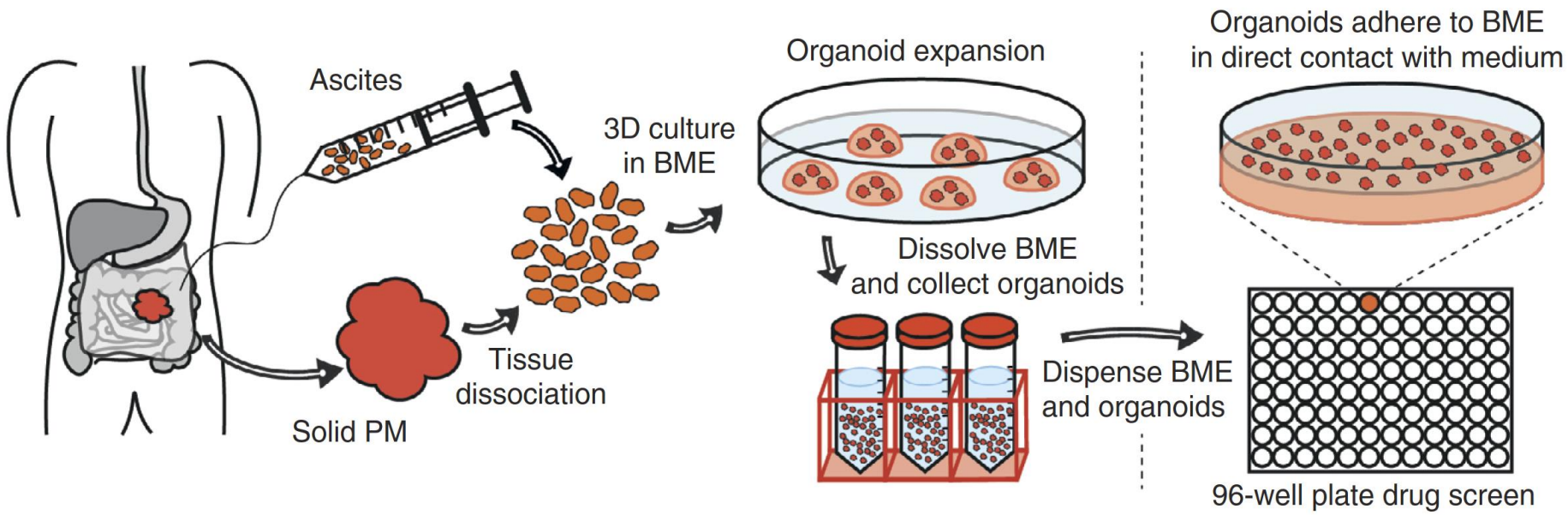


Fluorescence Guided Surgery



Organoid Technology

Fig. 1 Organoid generation and testing



Organoid Technology

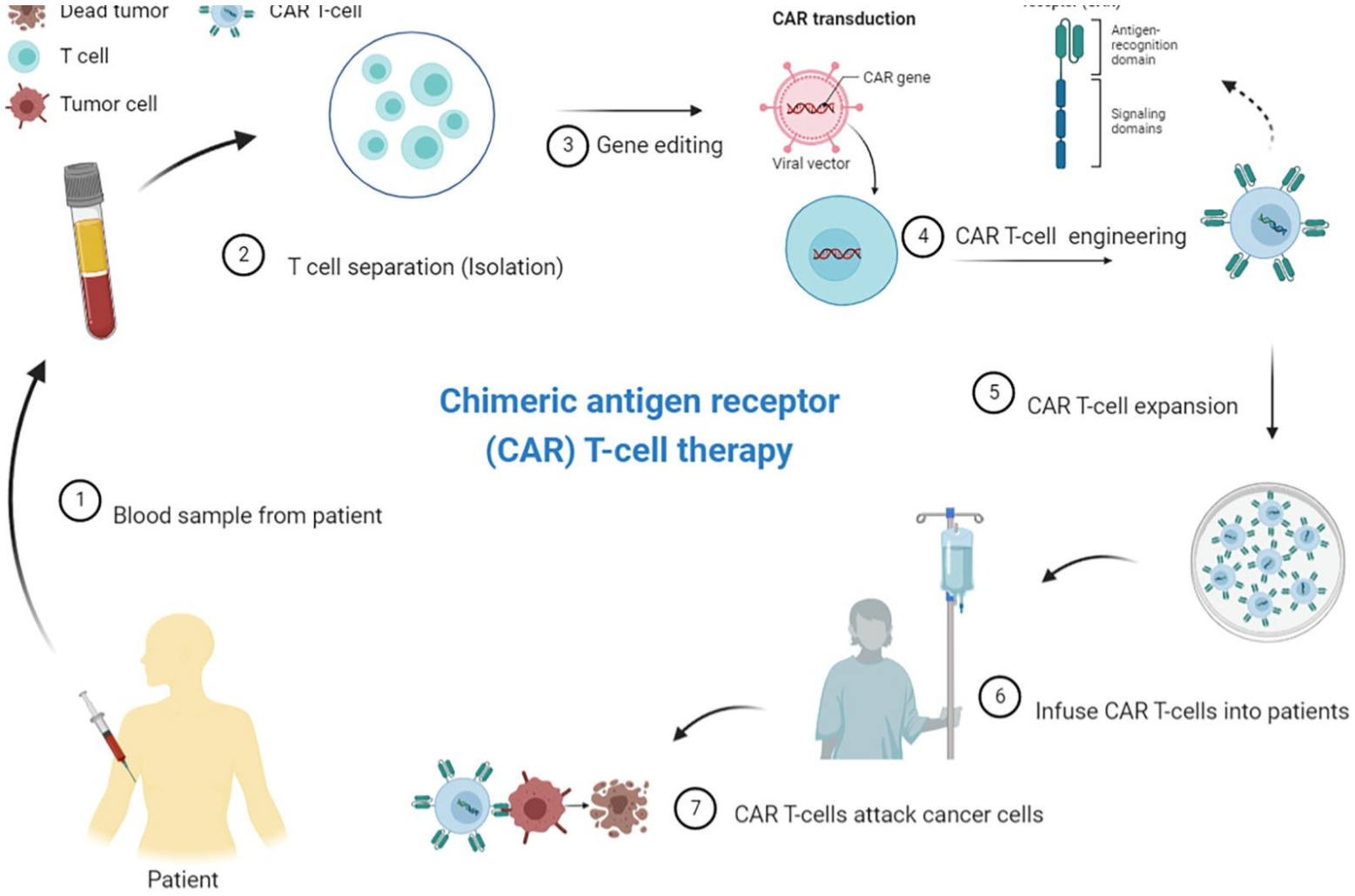
J Gastrointest Oncol 2023;14(1):442-449 | https://dx.doi.org/10.21037/jgo-22-599

Case Report

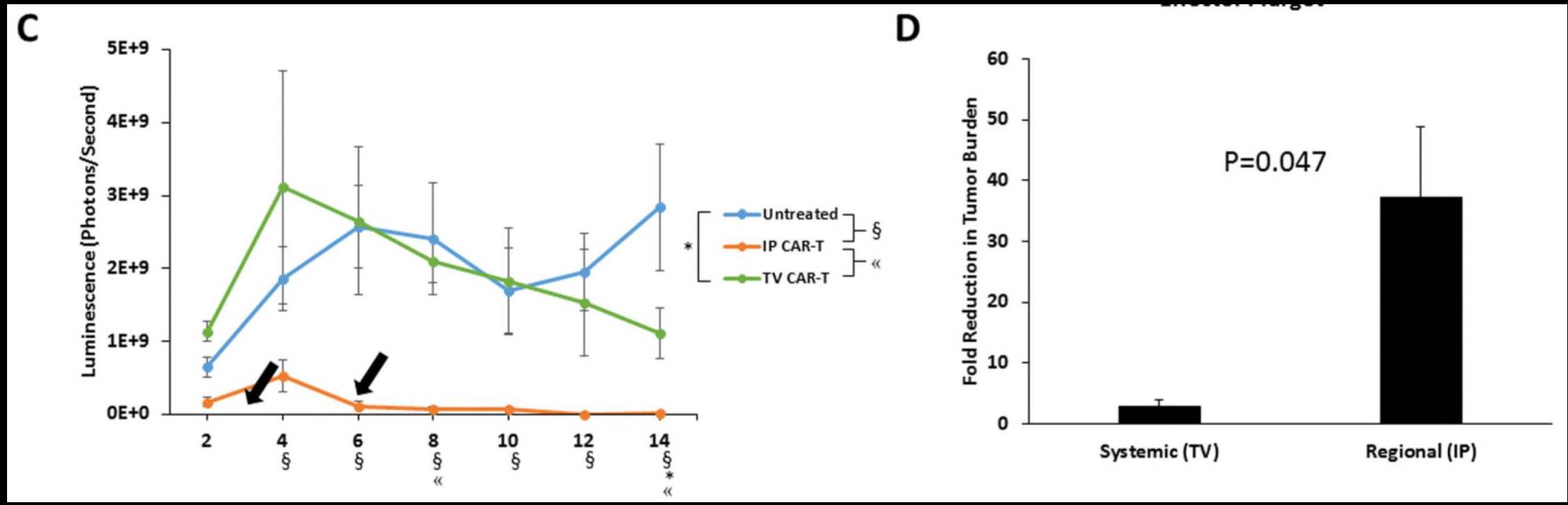
Tailored chemotherapy for colorectal cancer peritoneal metastases based on a drug-screening platform in patient-derived organoids: a case report

Isabel Prieto[1], Antonio Barbáchano[2,3,4]^, Nuria Rodríguez-Salas[3,4,5], David Viñal[5], Delia Cortés-Guiral[6], Alberto Muñoz[2,3,4]^, Asunción Fernández-Barral[2,3,4]^

CAR-T Therapy



Regional CAR-T cell infusions for peritoneal carcinomatosis are superior to systemic delivery



Cancer Gene Ther. 2016 May ; 23(5): 142–148. doi:10.1038/cgt.2016.14.

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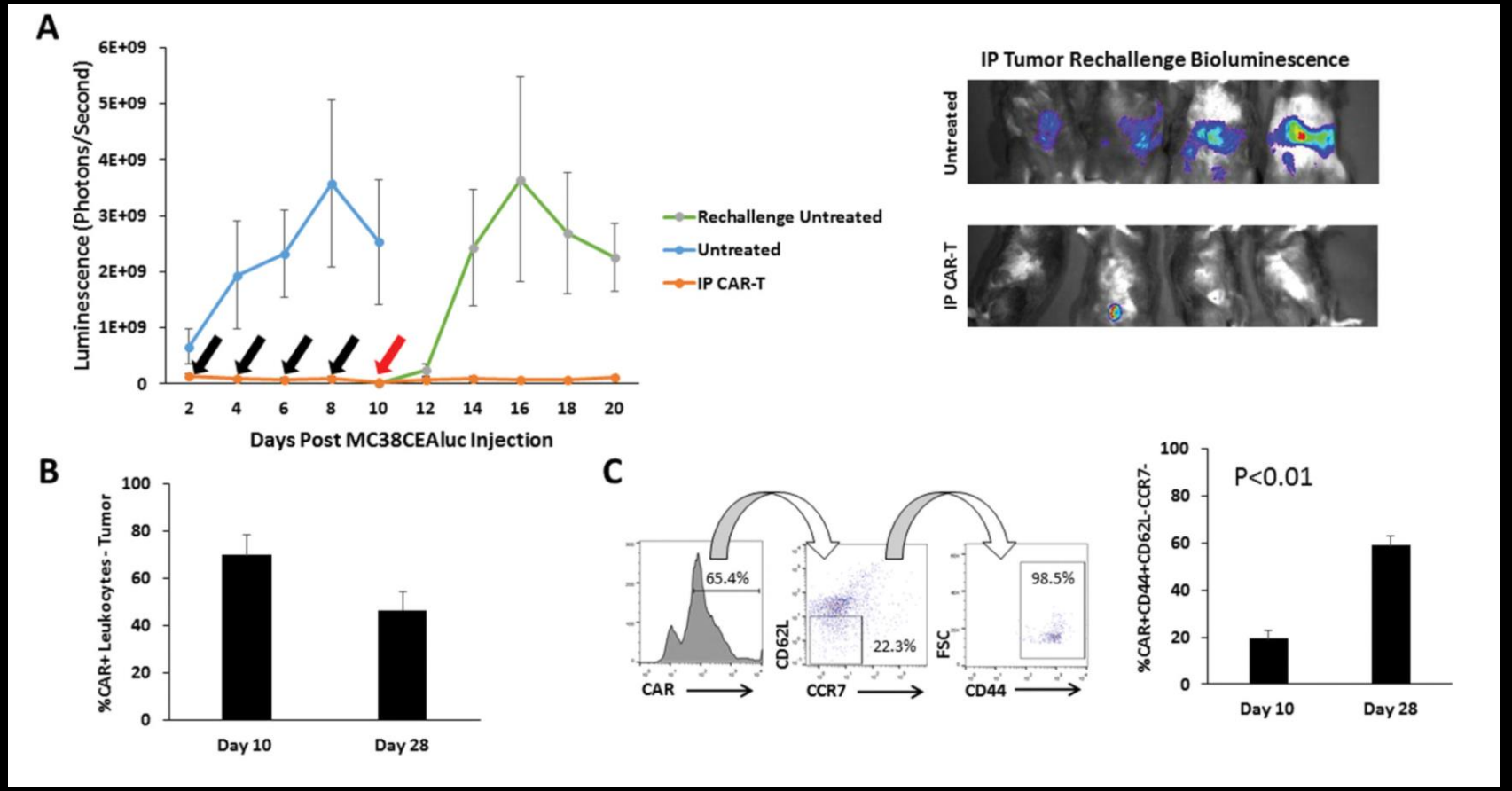

Cancer Gene Ther. 2016 May ; 23(5): 142–148. doi:10.1038/cgt.2016.14.

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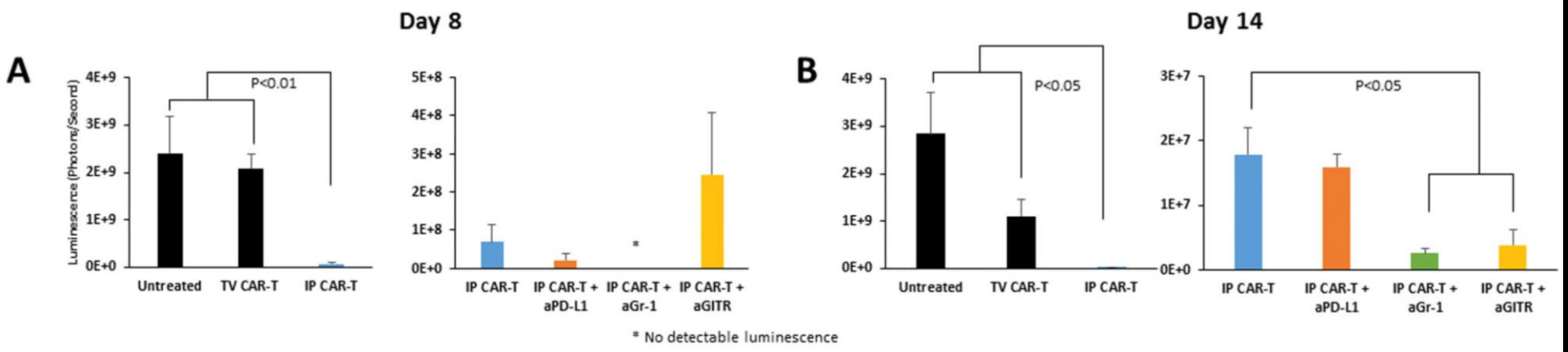
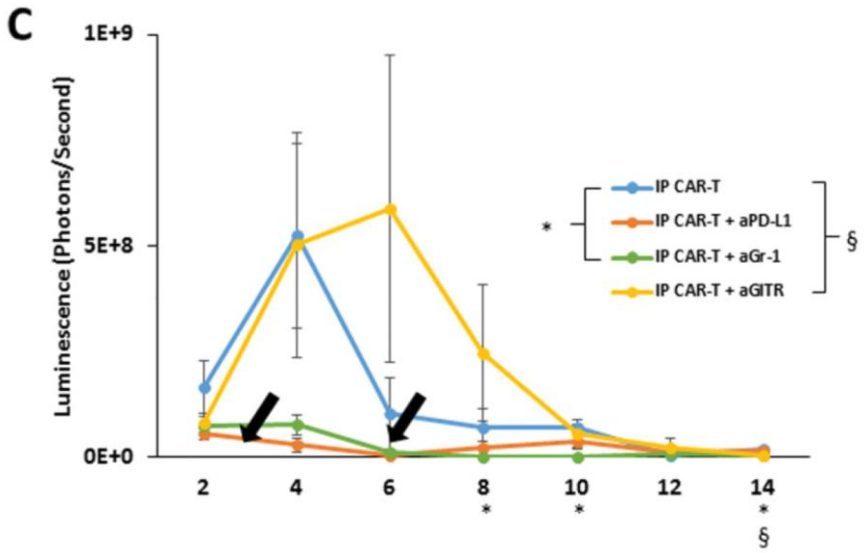
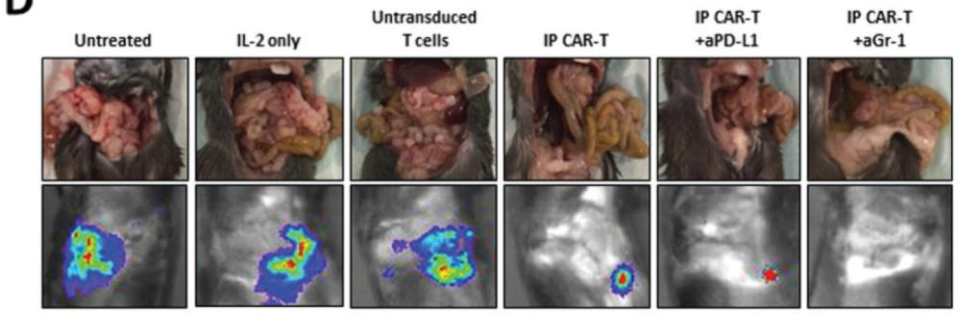


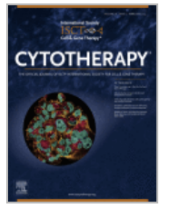




Cancer Gene Ther. 2016 May ; 23(5): 142–148. doi:10.1038/cgt.2016.14.

IP CAR-T

Cytotherapy
Volume 26, Issue 2, February 2024, Pages 113-125



FULL-LENGTH ARTICLE

Immunotherapy

Intraperitoneal administration of carcinoembryonic antigen-directed chimeric antigen receptor T cells is a robust delivery route for effective treatment of peritoneal carcinomatosis from colorectal cancer in pre-clinical study

2024 ASCO ANNUAL MEETING

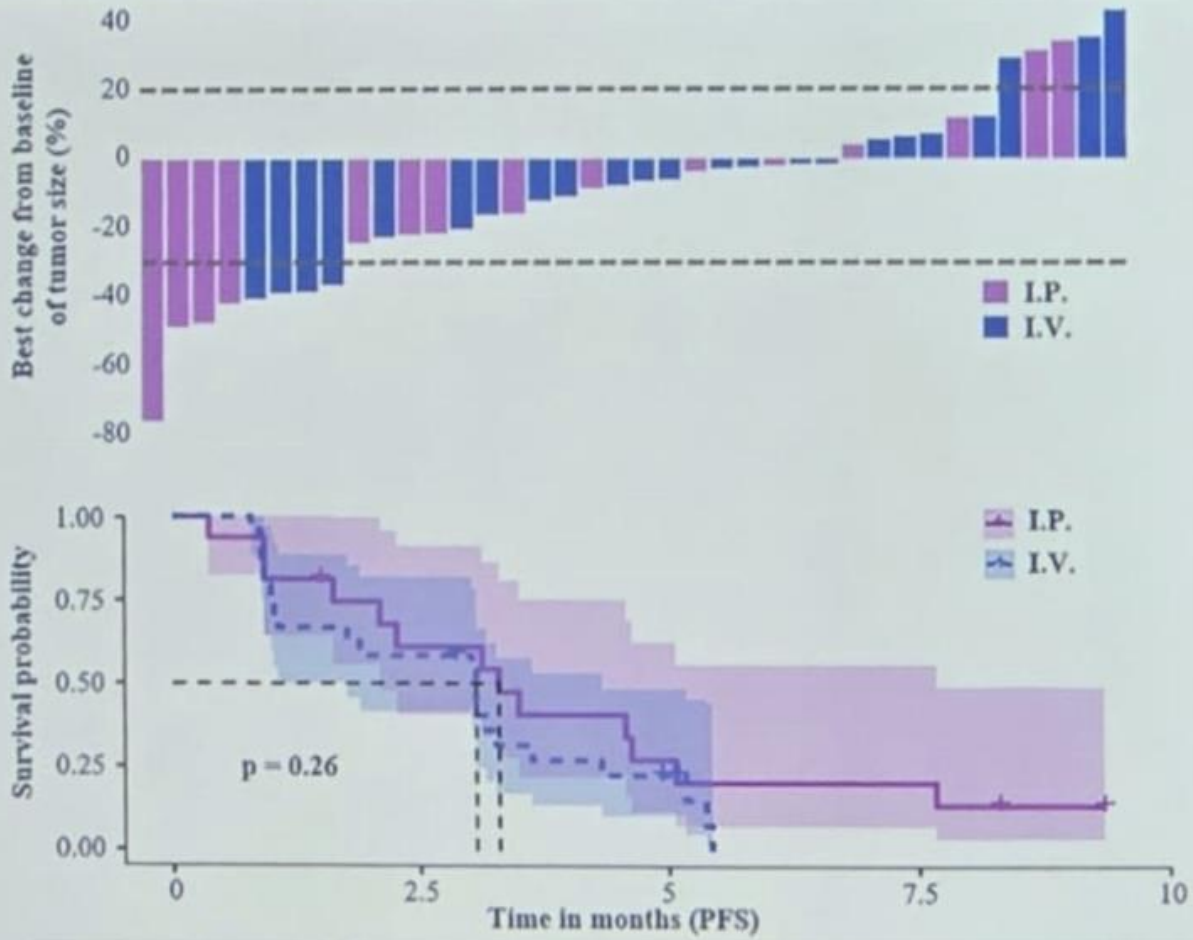
精准生物 PRECISION BIOTECH

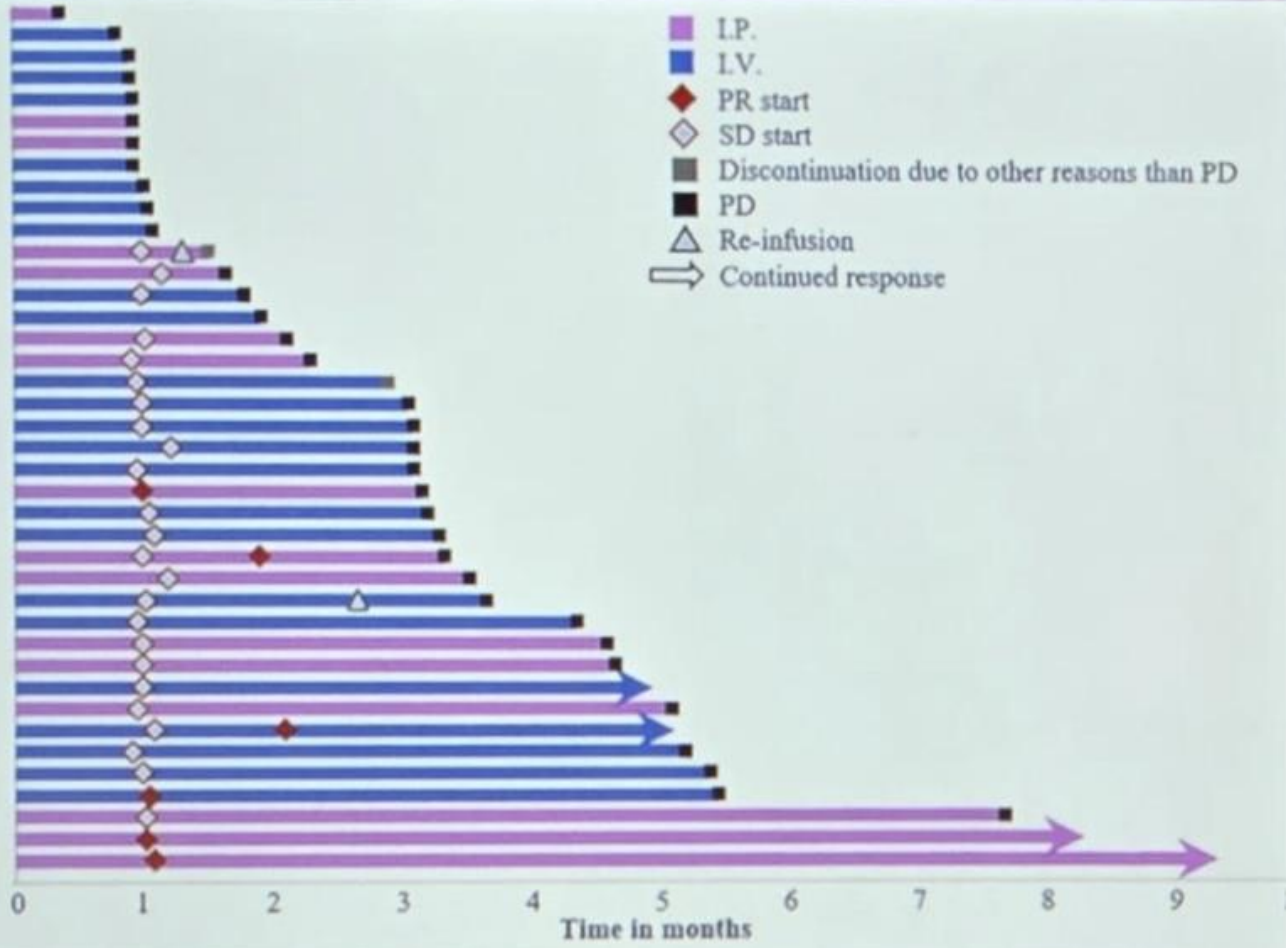
Phase l trial of hypoxia-responsive CEA CAR-T cell therapy in patients with heavily pretreated solid tumor via intraperitoneal or intravenous transfusion

Hangyu Zhang, Zhi Yang, Xudong Zhu, Jie Li, Yang Gao, Yingzi Zhang, Zhou Tong, Qihan Fu, Xuanwen Bao, Bin Li, Qianzhen Zhang, Junjie Shen, Yi Zheng, Lulu Liu, Peng Zhao, Cheng Qian, Weijia Fang

Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine(FAHZU), Hangzhou, China; Chongqing Precision Biotech Co., Ltd., Chongqing, China

I.P. group displayed a higher ORR and DCR



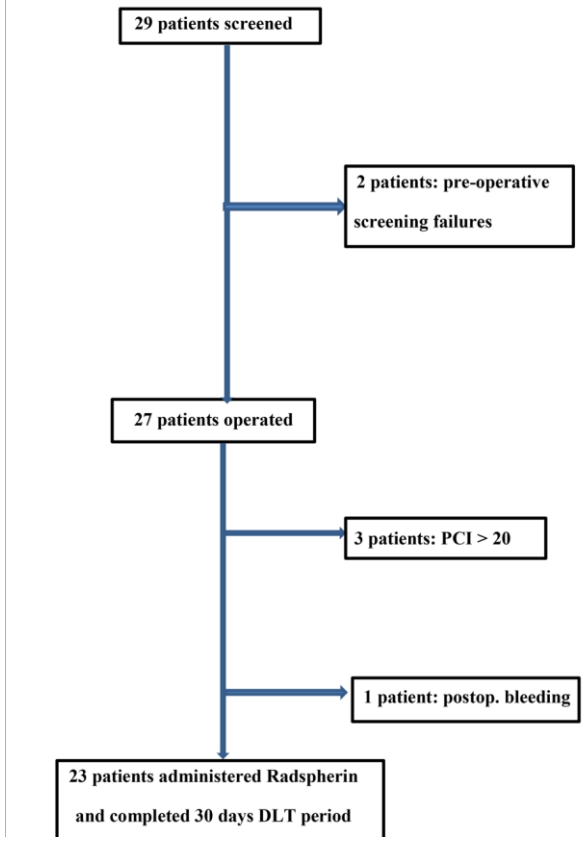


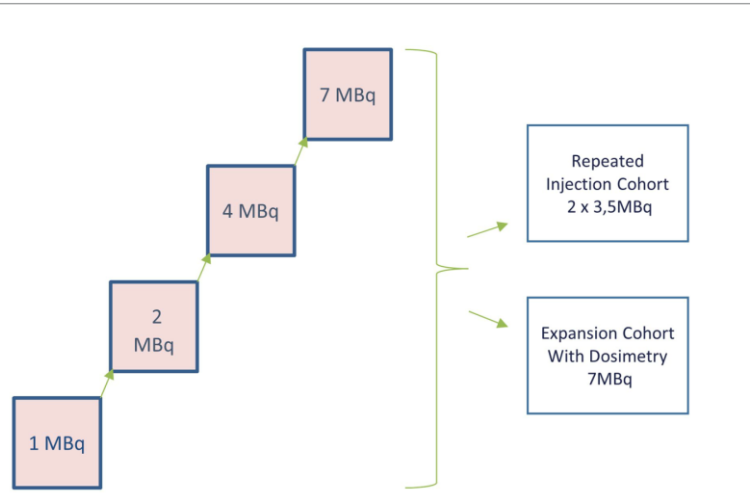
- ORR and DCR in **I.P.** group reached **25.0%** (4/16) and **87.5%** (14/16): 4 PR, 10 SD， mPFS (95% CI): **3.30** (2.10-7.67) months
- ORR and DCR in **I.V.** group reached **8.3%** (2/24) and **66.7%** (16/24): 2 PR, 14 SD， mPFS (95% CI): **3.07** (1.77-4.33) months

frontiers | Frontiers in Medicine

First experience with ^{224}Radium-labeled microparticles (Radspherin®) after CRS-HIPEC for peritoneal metastasis in colorectal cancer (a phase 1 study)

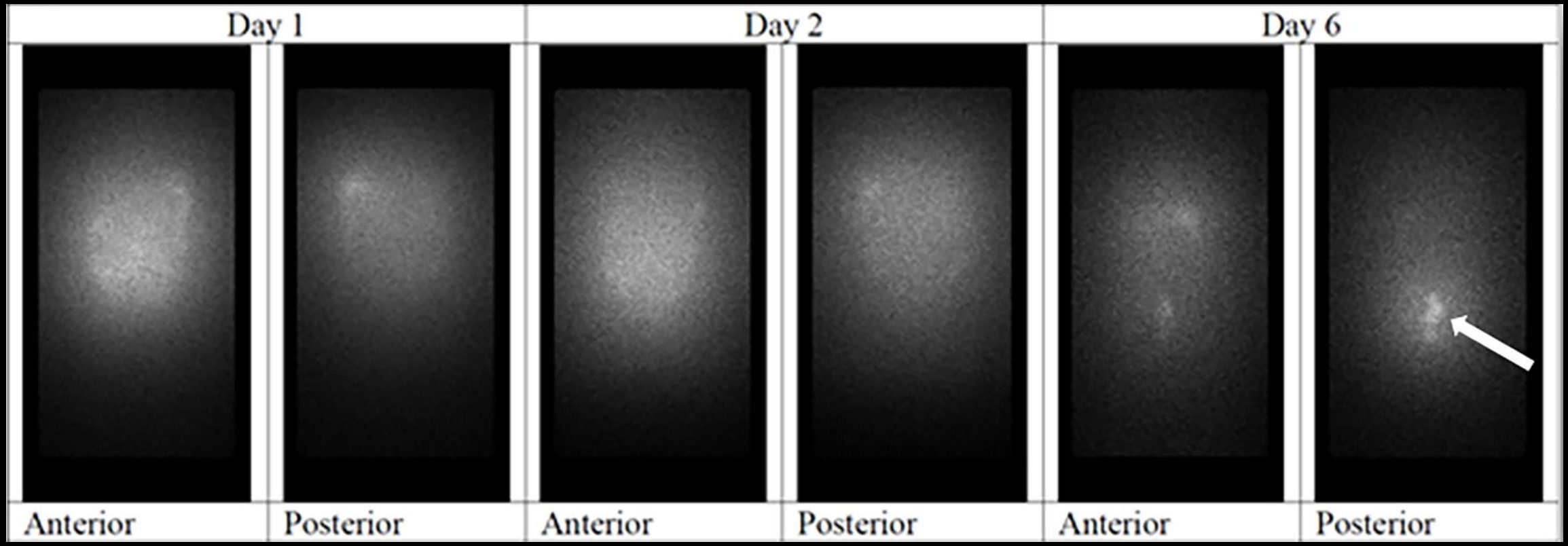
TYPE Clinical Trial
PUBLISHED 01 March 2023
DOI 10.3389/fmed.2023.1070362



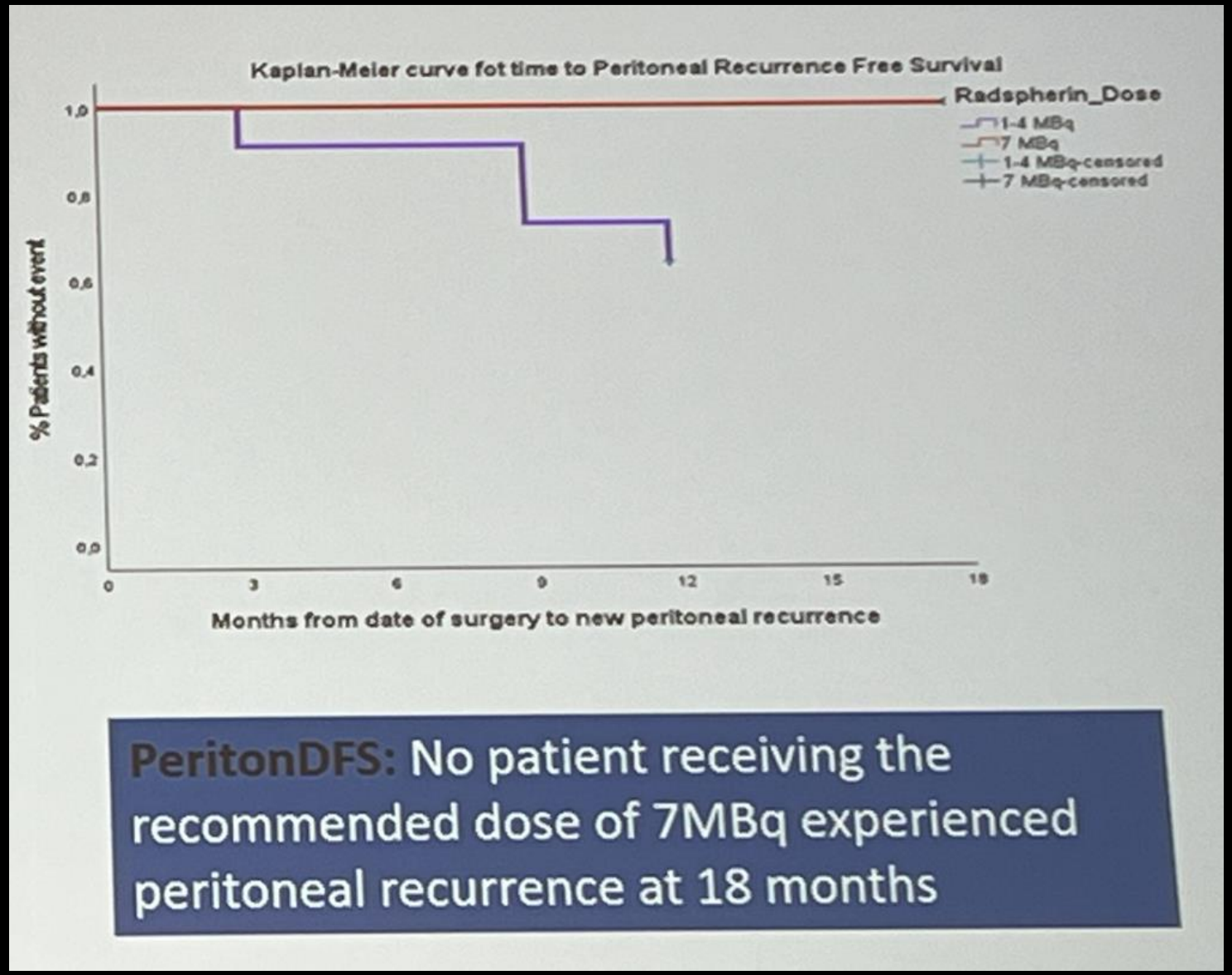


Radium Labelled Microparticles

Adjuvant 224-Radium Labelled Microparticles



Adjuvant 224-Radium Labelled Microparticles



PeritonDFS: No patient receiving the recommended dose of 7MBq experienced peritoneal recurrence at 18 months

Conclusions

CRS and HIPEC is a valuable and proven treatment modality for CRPM

Prevention

Treatment

Rapid progress in Technology is poised to help propel the treatment of this difficult condition forward

Thank you