City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

KEYNOTE LECTURE

Primary & Metastatic Peritoneal Malignancies

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Department of Surgery
King Khaled University Hospital

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

Disclosures

- I do not have any relevant financial relationships.

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

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

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

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

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

- Diversity in surgery
- Addressing a diagnosis of advanced cancer for different patients with different access to healthcare

City of Hope

ISSPP


Canada
United States
Mexico
Venezuela
Brazil
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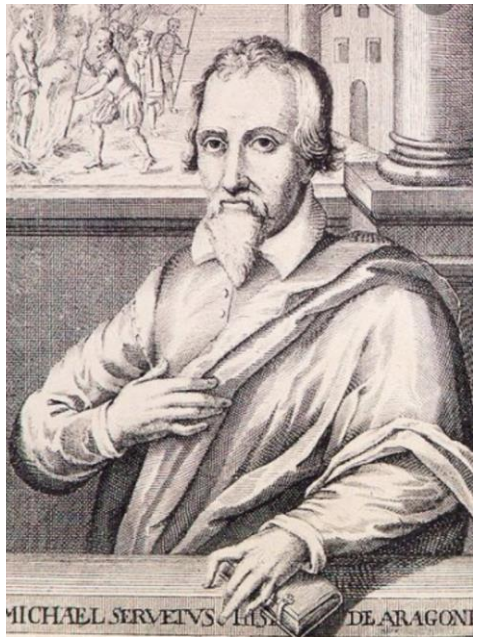
Bolivia
Chile
Argentina


KINGDOM OF HEAVEN
DIRECTOR'S CUT
キングダム・オブ・ヘブン
2枚組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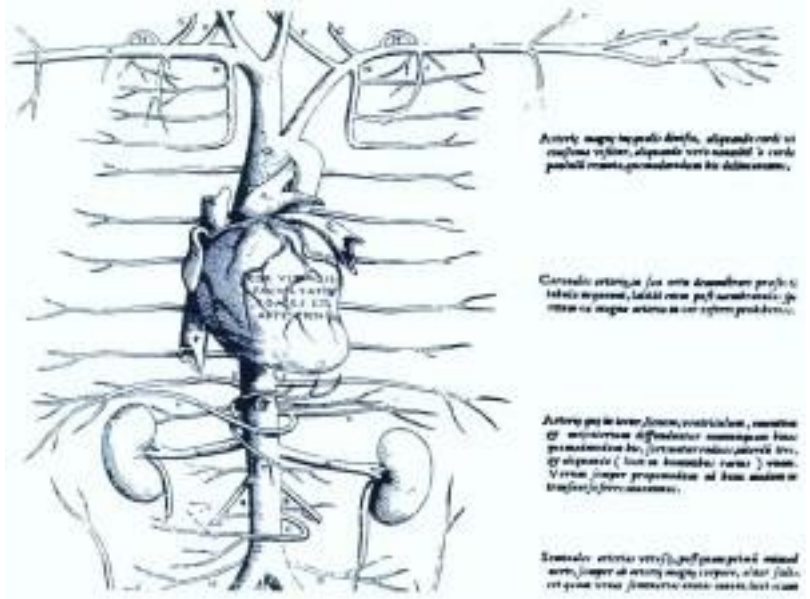

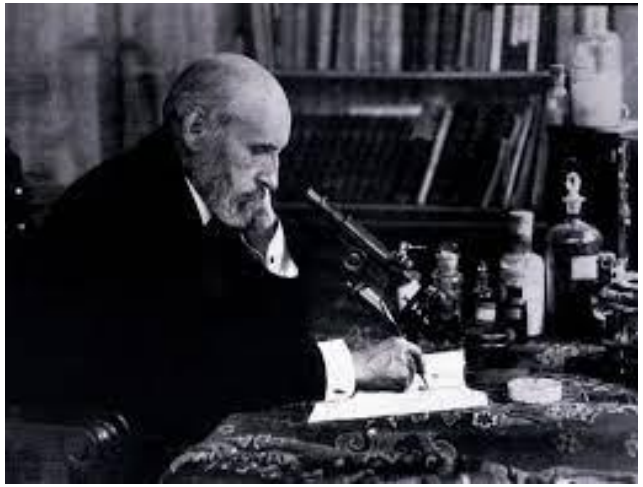

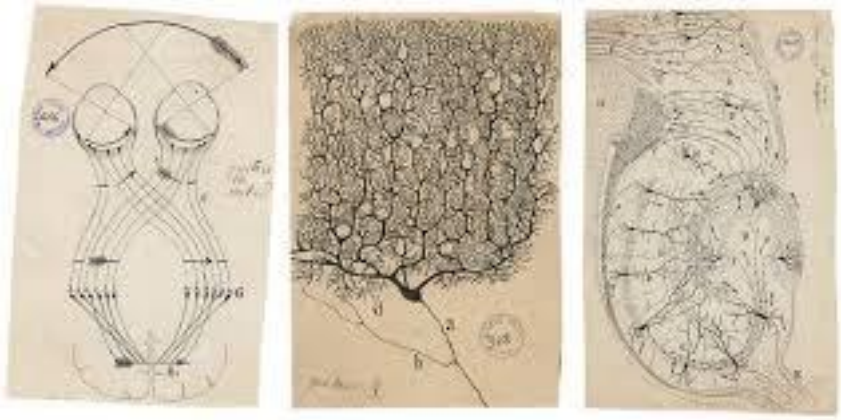

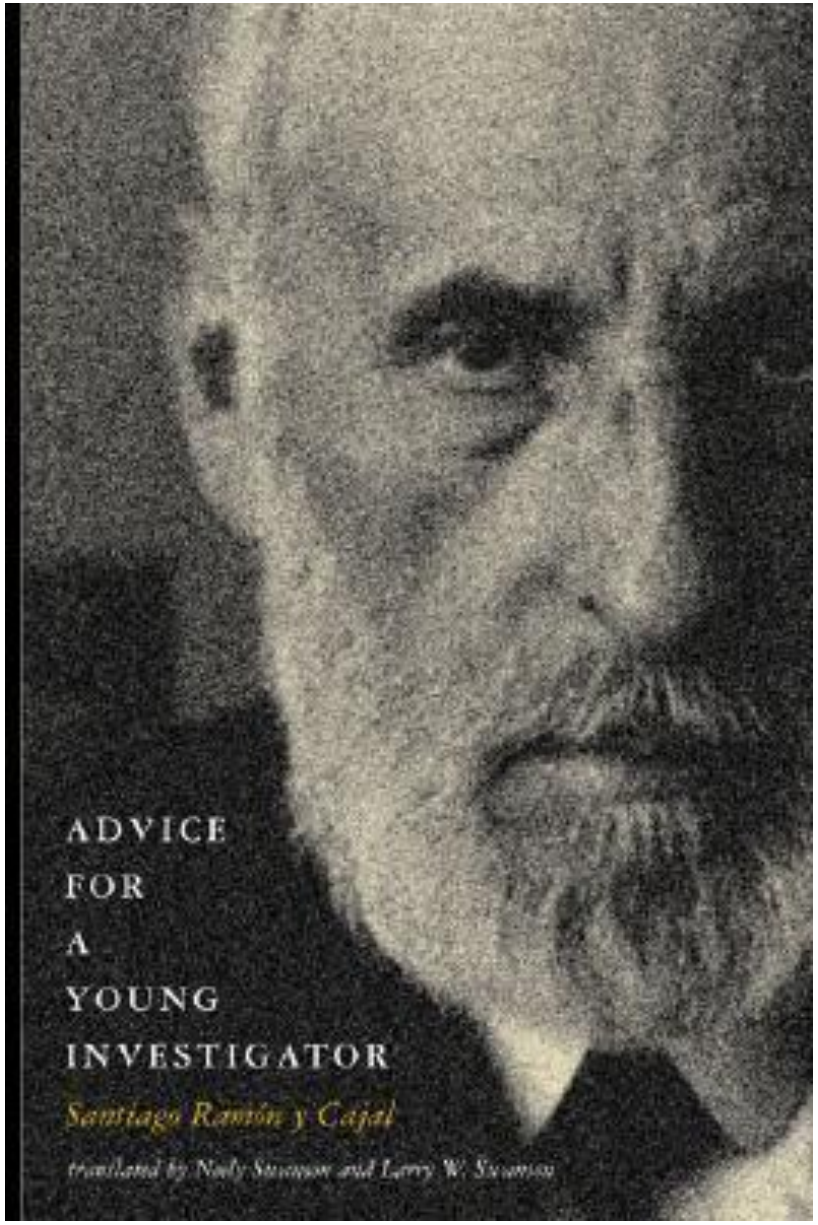
ADVICE
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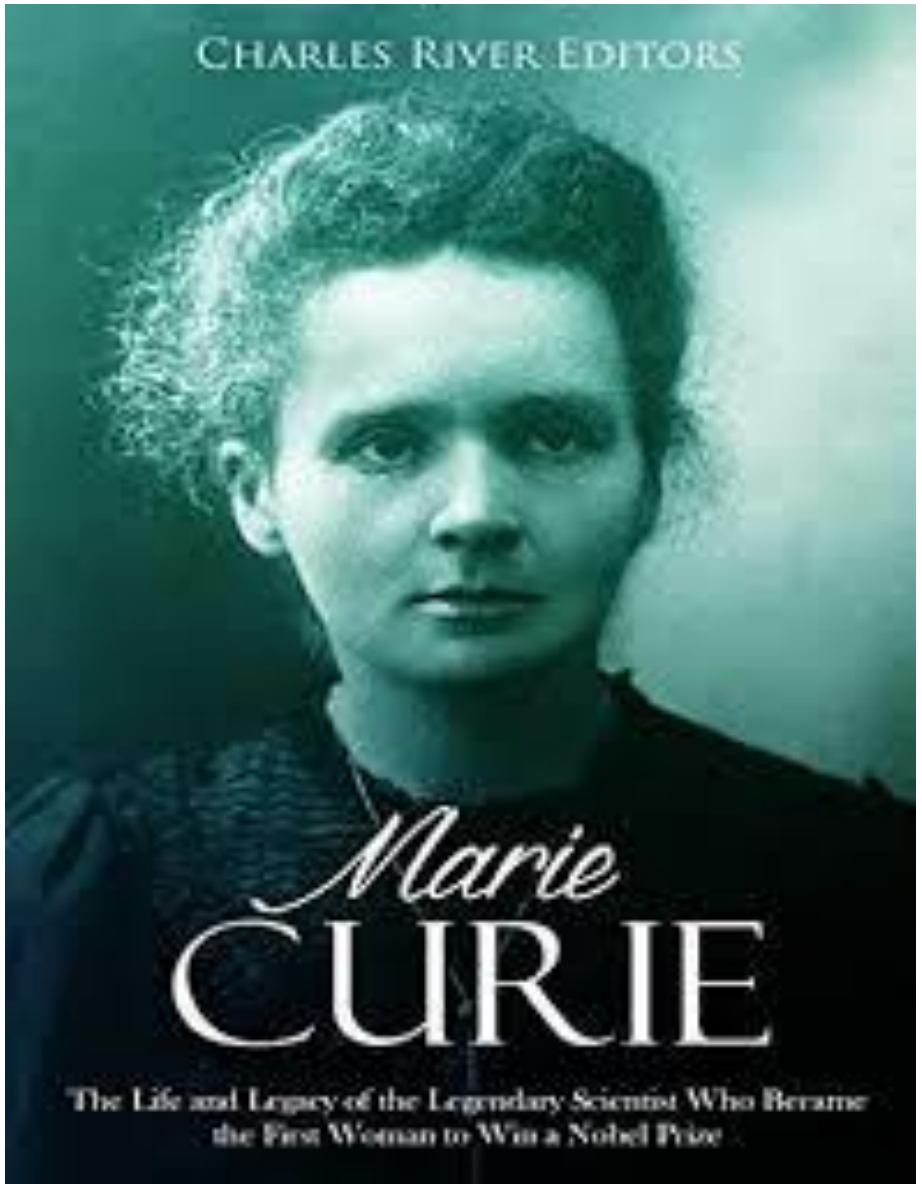
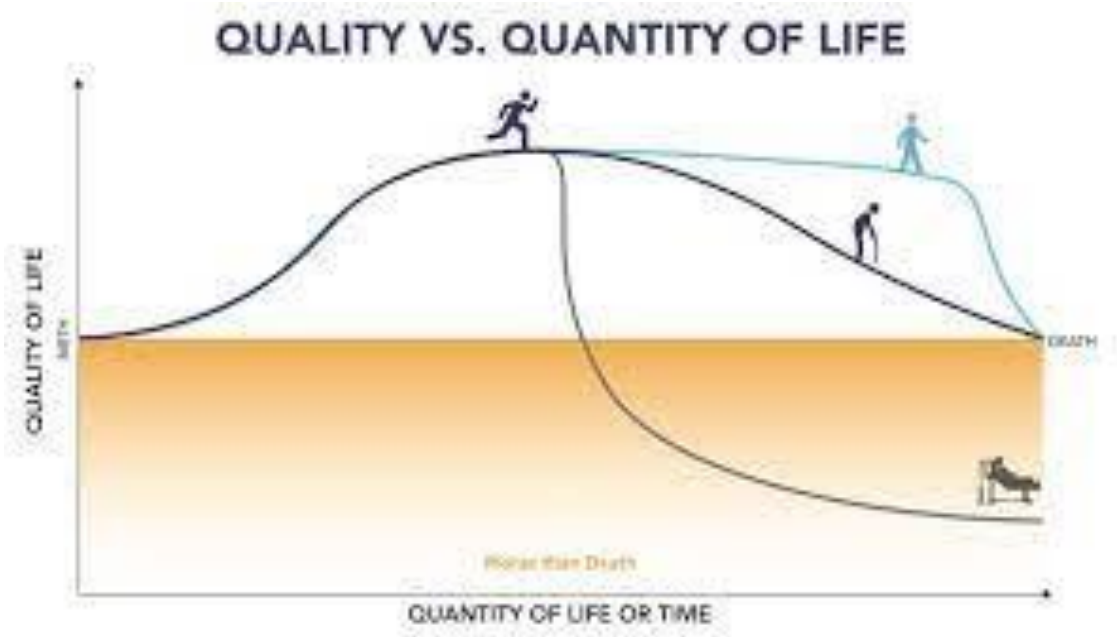
Santiago Ramón y Cajal

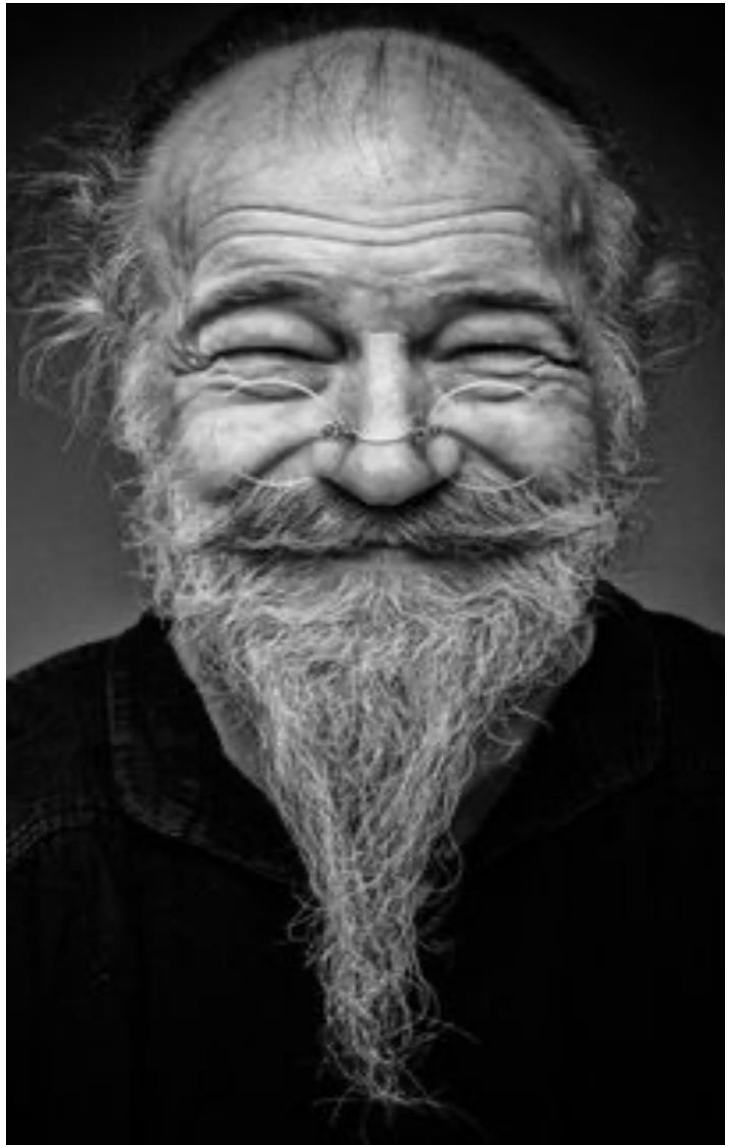

CHARLES RIVER EDITORS
Marie
CURIE
The Life and Legacy of the Legendary Scientist Who Became the First Woman to Win a Nobel Prize

Top Research Priorities

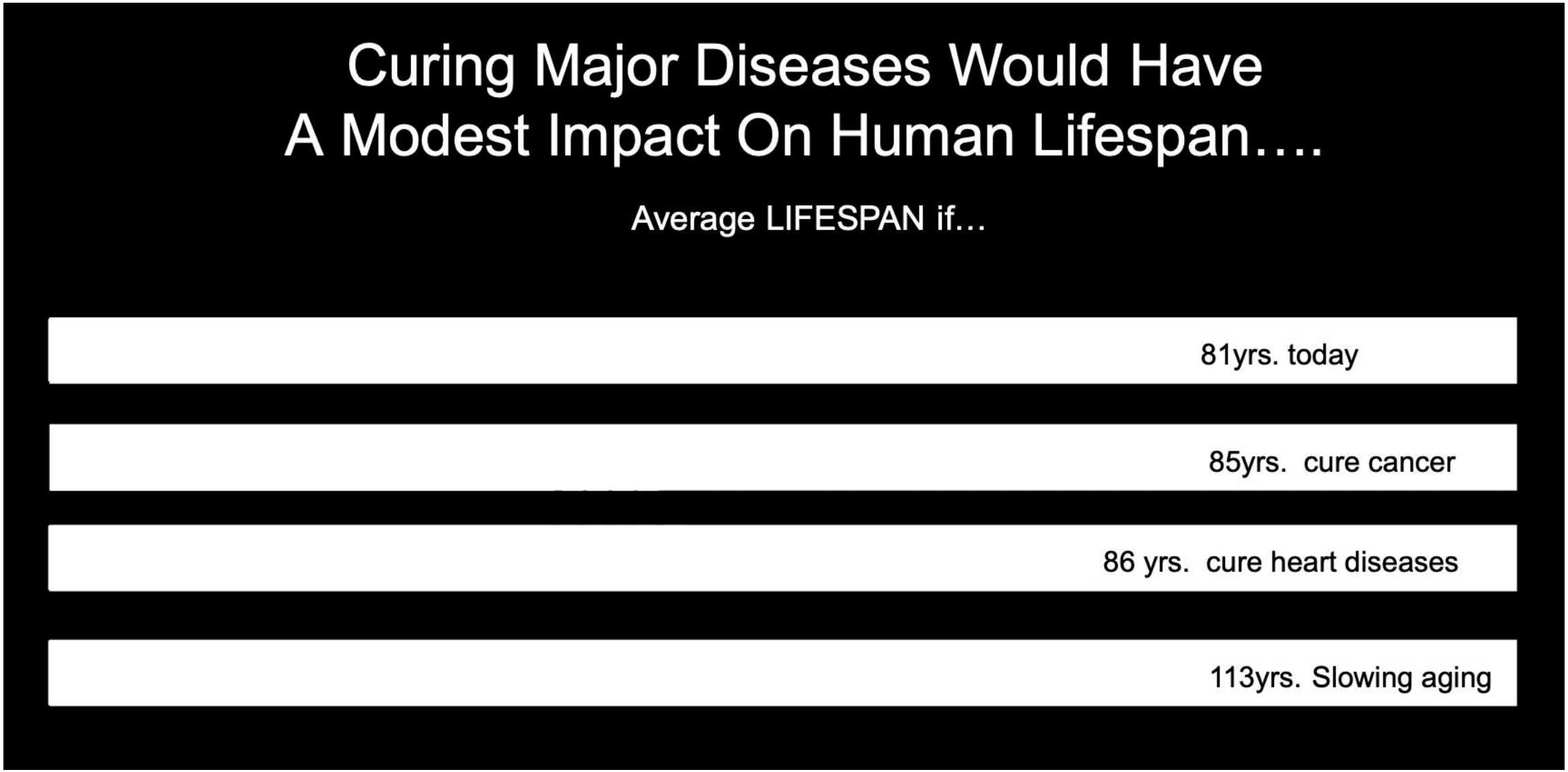
Longevity

Happiness





Curing Major Diseases Would Have A Modest Impact On Human Lifespan….



Courtesy Prof. Gonzalez-Freire

What keep us healthy and happy as we go through life?

re

ut

er

3. Good relationships protect our brains

doi: XXX; Article citation ID: _#################### For the Primer, visit doi: XXX

PrimeView
Primary and metastatic peritoneal surface malignancies

Peritoneal surface malignancies (PSM) include tumours of primary peritoneal origin, such as peritoneal mesothelioma and peritoneal cancer, and metastases of other cancers, such as digestive and reproductive tract, lung, breast and kidney cancers. Their incidence, treatment sensitivity and prognosis vary widely.

Epidemiology

The incidence of PSM seems to be highest in patients with ovarian or gastric cancer but estimating accurate values is complex, as PSM are difficult to detect on imaging and not specifically documented in registries. Overall, the incidence of PSM caused by metastasis seems to be >20 times higher than that of primary peritoneal cancers according to one study. Common risk factors for PSM include tumour stage, lymph node involvement, histological subtype and positive peritoneal fluid cytology.

Diagnosis

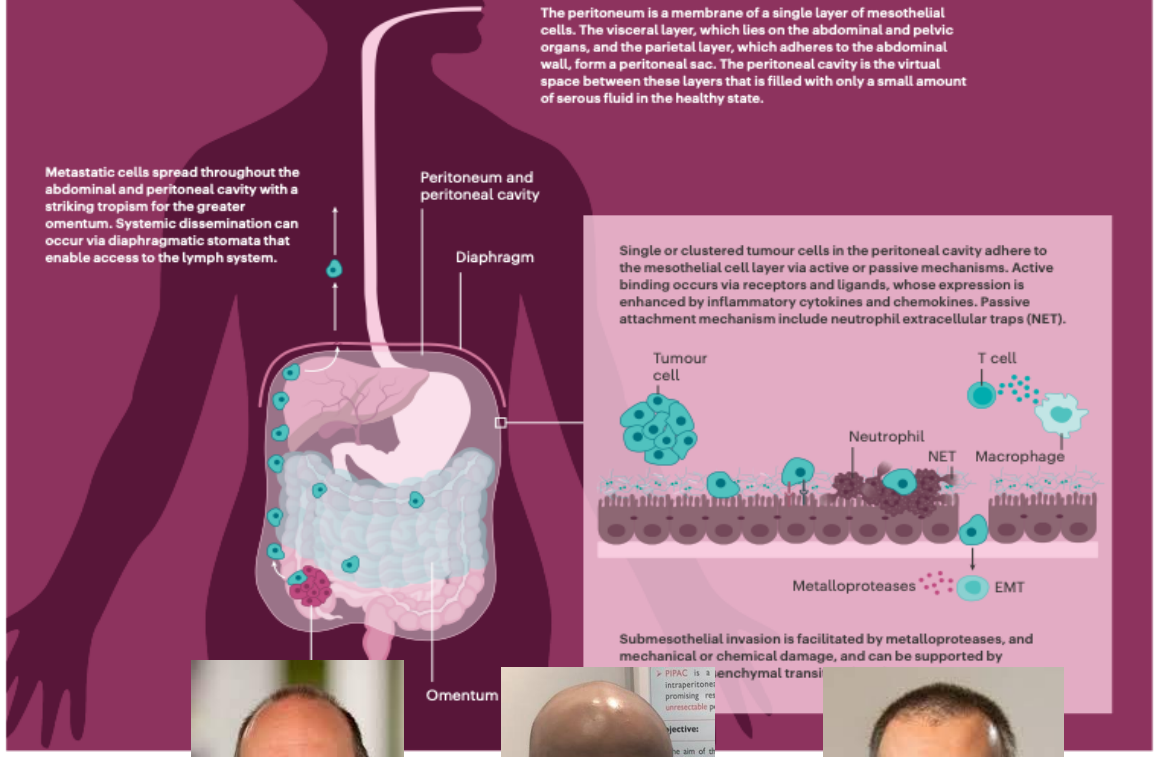
The origin and extent of disease affect the clinical presentation of PSM. Initially, abdominal pain and distension might be common in patients with gastrointestinal malignancies. Symptoms of late-stage disease include fatigue, nausea, anorexia, weight loss and constipation. A palpable mass and ascites can be signs at examination. PSM diagnosis often requires advanced technology for appropriate imaging, such as CT, PET-CT and MRI, and interventional techniques, such as surgical exploration. Tumour markers can be useful in PSM diagnosis, such as CEA and CA19-9 for gastrointestinal cancers, and CA125 for ovarian malignancies and mesothelioma.

Quality of life

Disease-related and treatment-related effects strongly influence quality of life (QOL) and change during the disease course. To define the optimal treatment and avoid misunderstandings around treatment intent and prognosis, transparent discussions between care givers, patients and relatives are crucial. For example, perioperative morbidity of cytoreductive surgery combined with intraperitoneal chemotherapy might be acceptable when used with curative intent, whereas maintenance or improvement of QOL become more important in the palliative setting.

Pathophysiology

The development of peritoneal metastases depends on mechanical forces, such as gravity and diaphragmatic excursion, and on interactions between tumour cells, mesothelial cells and the underlying extracellular matrix.



Management

Management of PSM differs according to the malignancy that caused the disease and often requires individualized treatment strategies with optimized patient selection. Typical management modalities include systemic chemotherapy therapy, loco-regional treatment (cytoreductive surgery and intraperitoneal chemotherapy) and supportive or palliative care. Evaluation in multidisciplinary tumour boards is recommended and includes selection of the treatment sequences of surgery, neoadjuvant, perioperative and/or adjuvant systemic therapy, as well as intraperitoneal chemotherapy. Several modalities of intraperitoneal chemotherapy that have different characteristics and indications and can be combined into sequences are available, including hyperthermic intraperitoneal chemotherapy, pressurized intraperitoneal aerosol chemotherapy, neoadjuvant intraperitoneal and systemic chemotherapy and early postoperative intraperitoneal chemotherapy.

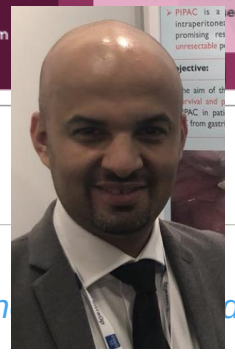
- **Strong evidence for the efficacy of systemically administered molecularly targeted drugs or immunotherapy in PSM is lacking, but enabling patients to access clinical research projects and drug therapy studies is important.**

Outlook

Several preclinical PSM models to test treatment sensitivity and resistance are in development, including 2D and 3D in vitro, xenograft and patient-derived organoid models. These organoids are a promising approach to select personalized intraperitoneal therapy but further work is needed to more accurately reproduce patient tumour characteristics. In addition, formulations of nanomedicines that improve intraperitoneal drug delivery are being researched. Fluorescence-guided surgery has the potential to increase detection of PSM and improve the success of cytoreductive surgery in the future.

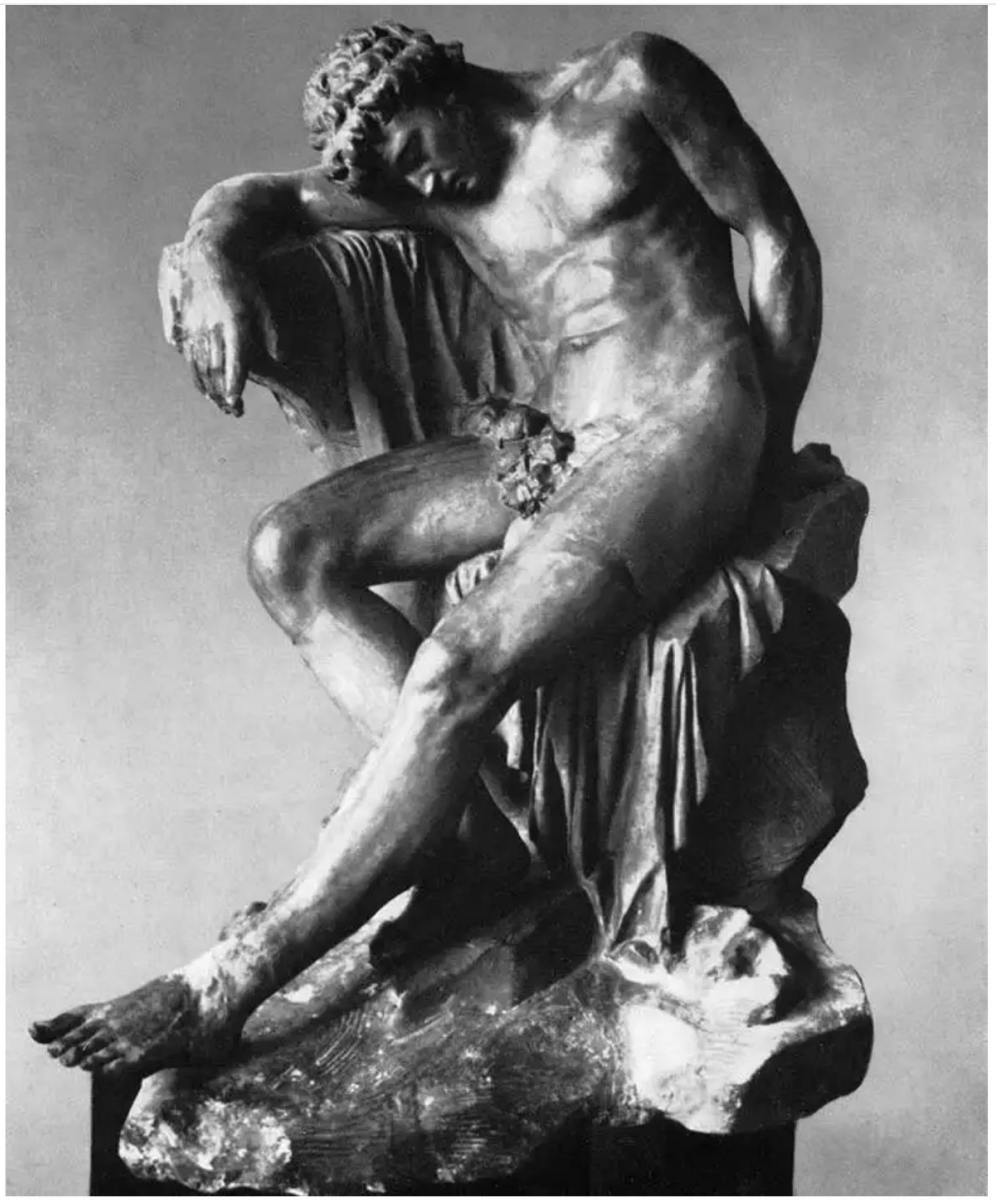
nature reviews disease primers

Written by Clemens Thoma; designed by Laura Marshall



City of Hope

Advancing Innovati or Can de the P the Pleura



Morpheus Sleeping, by Ivan Prokof'yevich Prokof'yev, 1782, via the Web Gallery of Art

Dr. Everett Sugarbaker, father of mesothelioma experts Drs. Paul and David Sugarbaker.

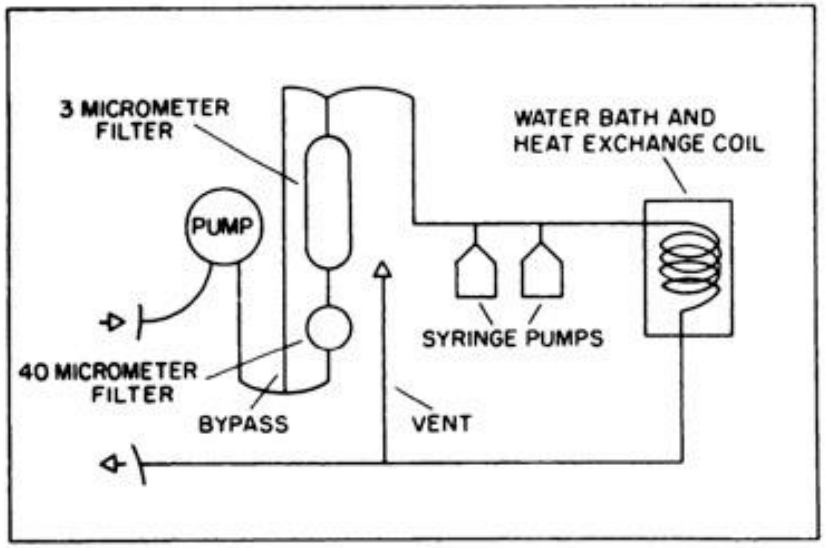
Prof. Paul Sugarbaker

[CANCER RESEARCH 40, 256–260, February 1980]
0008-5472/80/0040-0000$02.00

Clinical Delivery System for Intraperitoneal Hyperthermic Chemotherapy

John S. Spratt,[1] Robert A. Adcock, Marie Muskovin, William Sherrill, and John McKeown

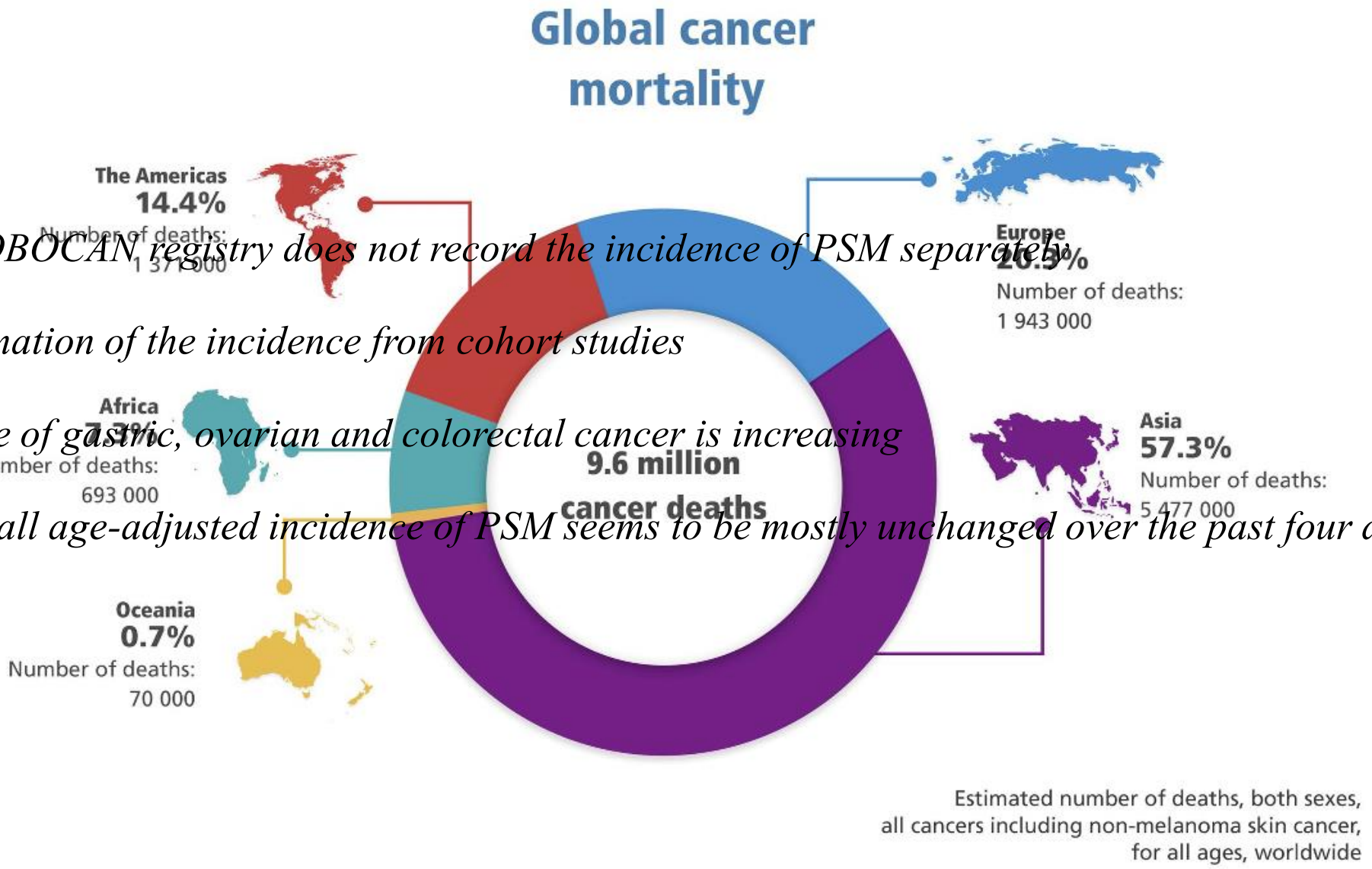
Department of Surgery, Section of Surgical Oncology [J. S. S.], Price Institute of Surgical Research [R. A. A., W. S.], The Cancer Center [M. M.], University of Louisville, Louisville, Kentucky 40202



HIPEC

We all like rare…

- *The GLOBOCAN registry does not record the incidence of PSM separately*
- *Approximation of the incidence from cohort studies*
- *Incidence of gastric, ovarian and colorectal cancer is increasing*
- *The overall age-adjusted incidence of PSM seems to be mostly unchanged over the past four decades*



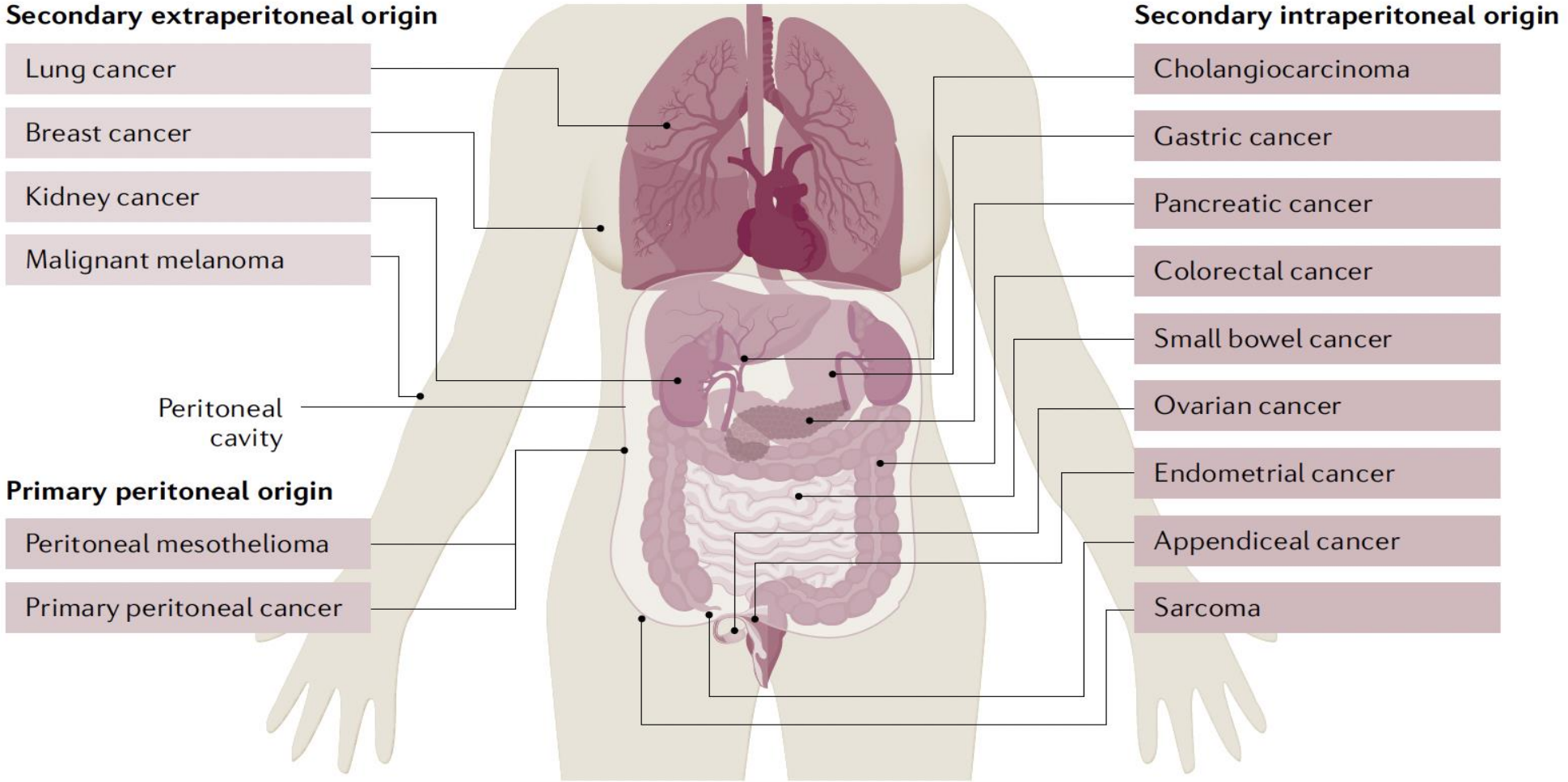
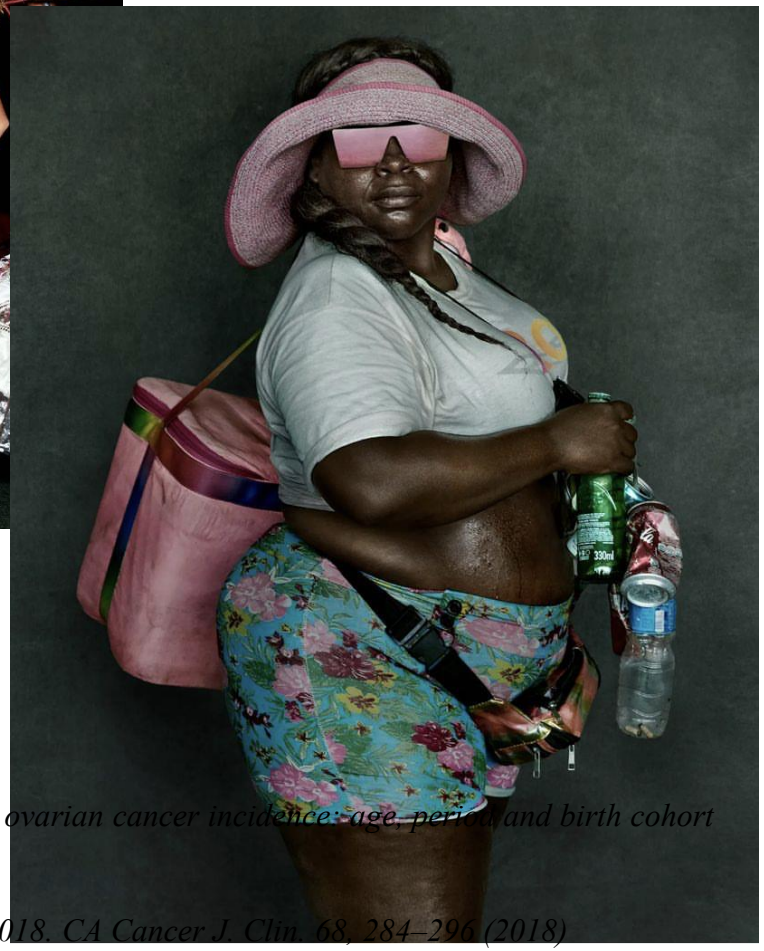


Fig. 1 | **Tumours causing peritoneal surface malignancies.** Peritoneal surface malignancies are a heterogeneous group of malignancies that can arise from primary tumours of the peritoneum or disseminate secondarily as peritoneal metastases from tumours of intraperitoneal origin and from tumours of extraperitoneal origin.

PSM secondary to intraperitoneal tumours

Incidence of PM of ovarian origin increased 4,4%



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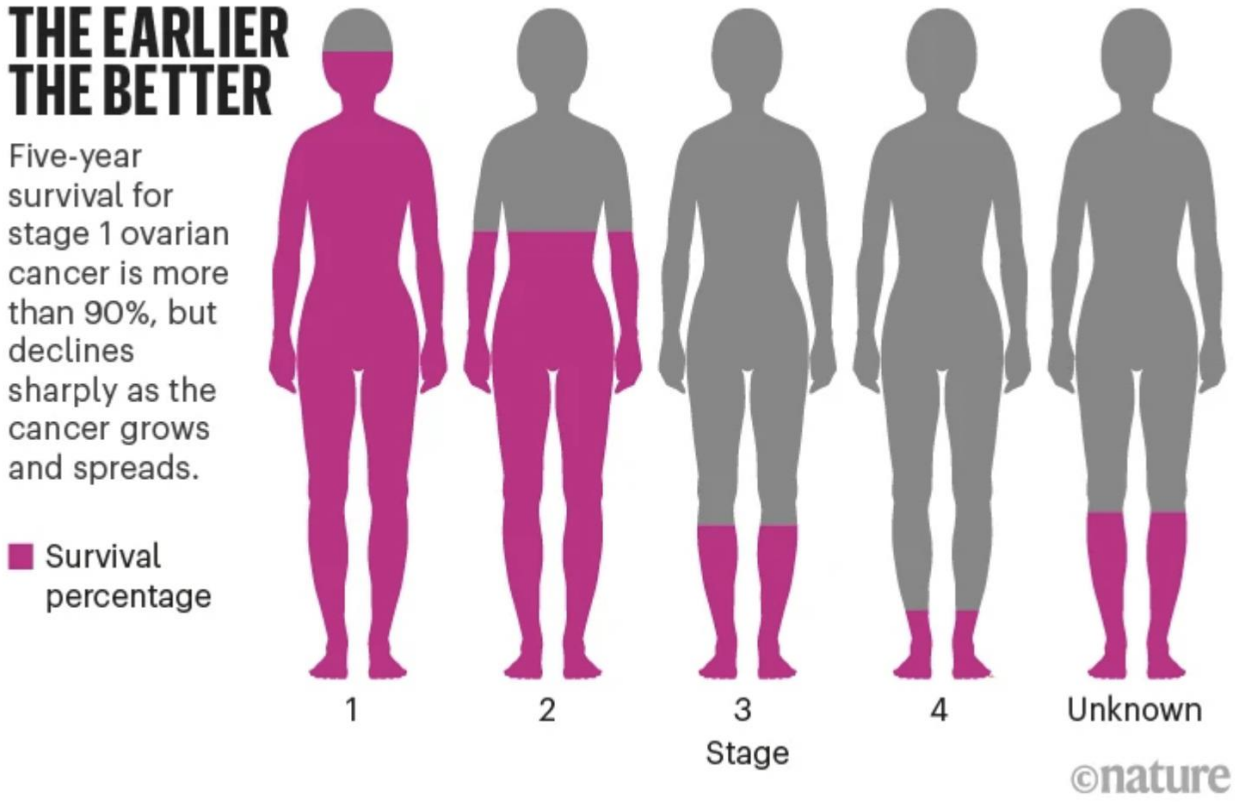

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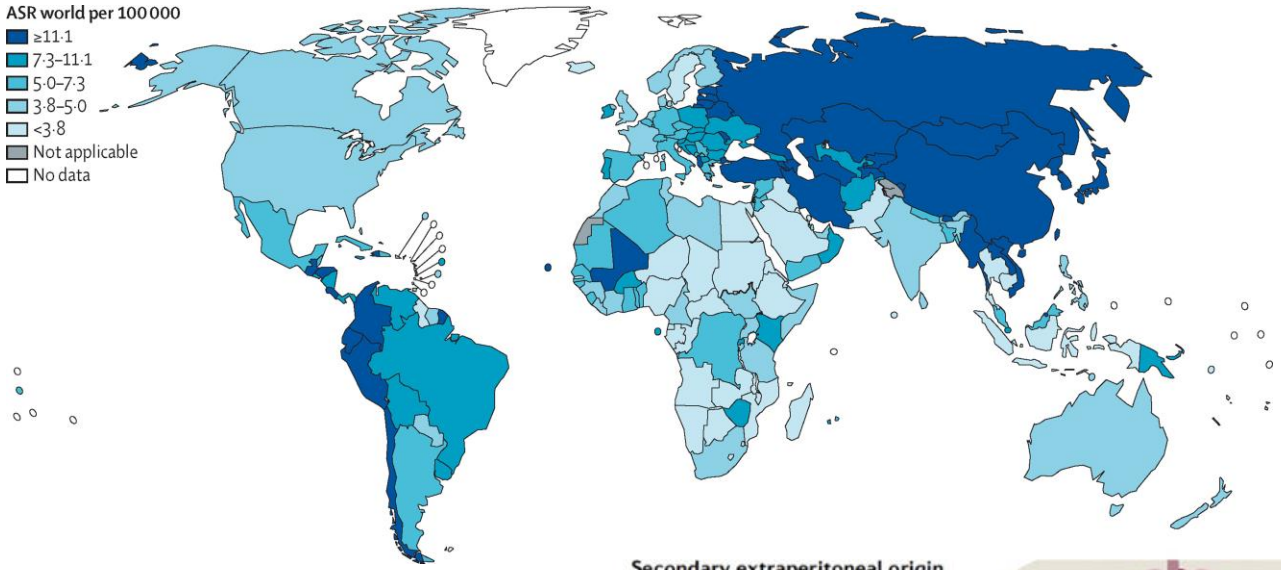

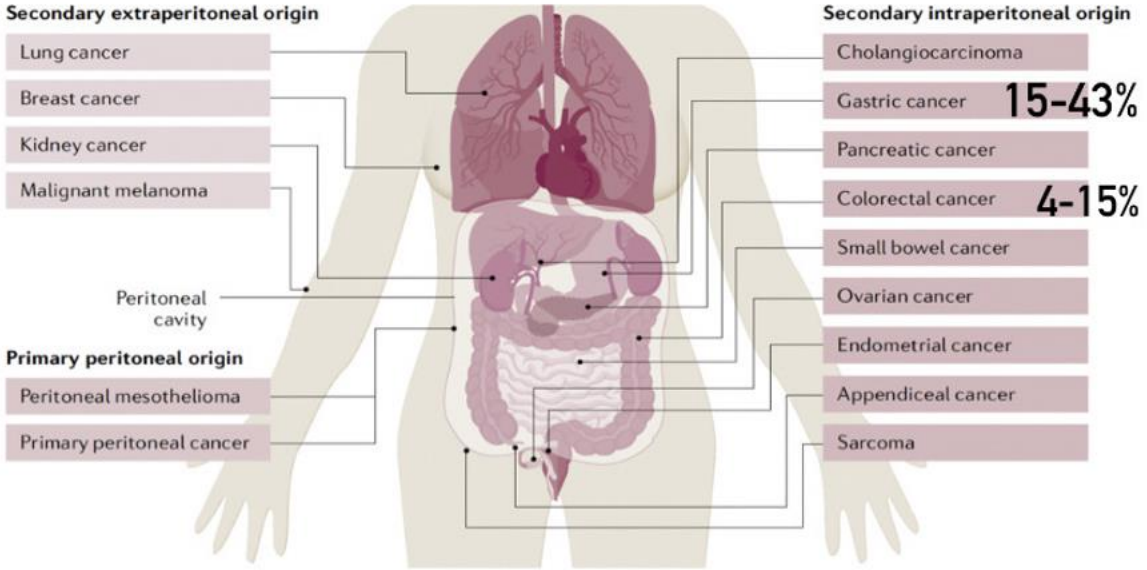

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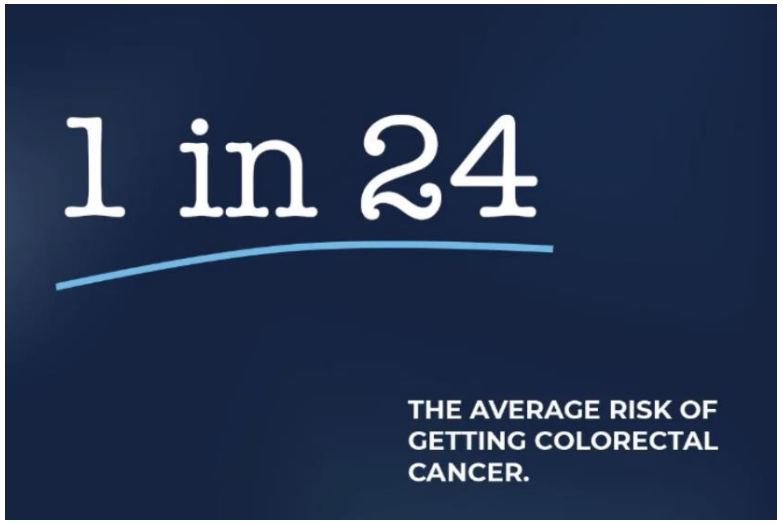

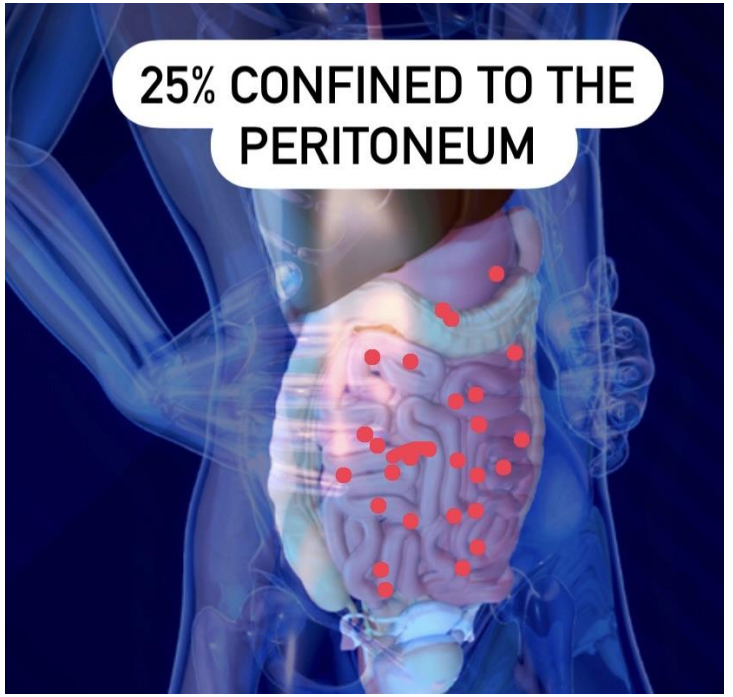

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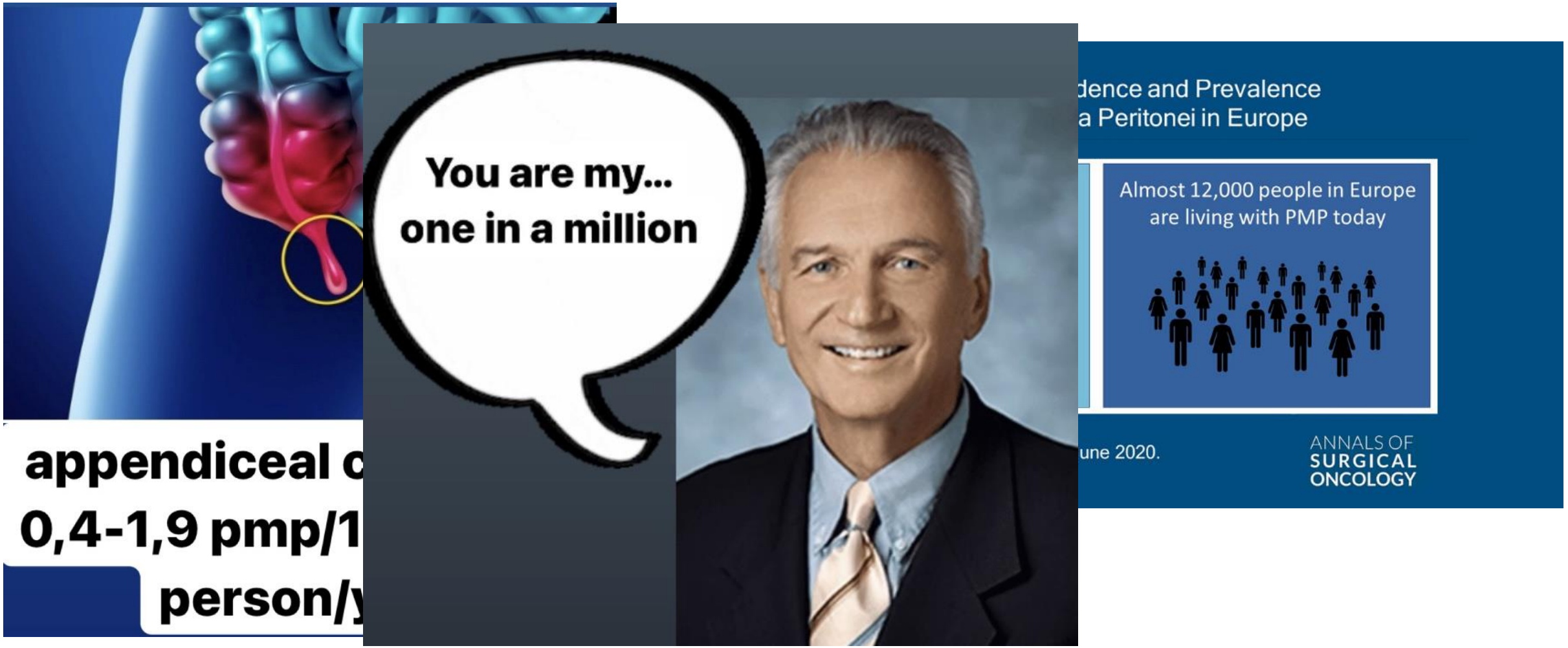

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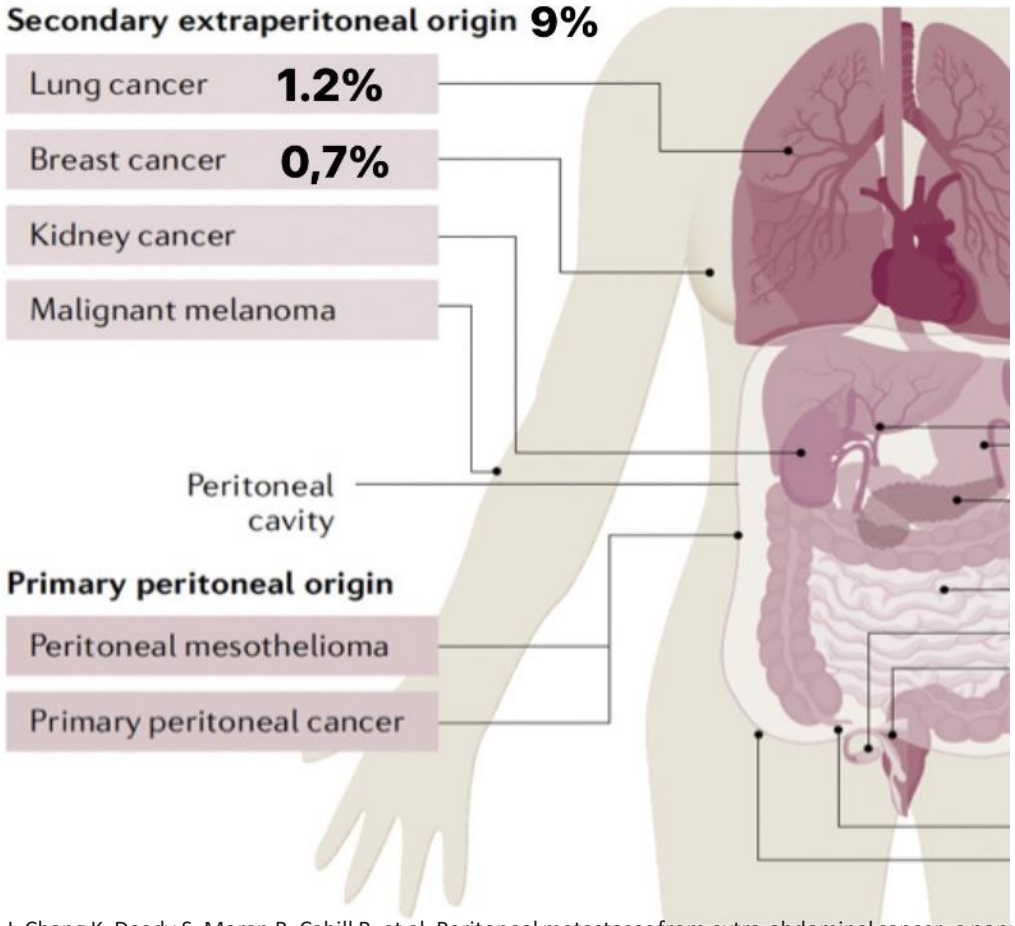
PSM secondary to extraperitoneal tumours



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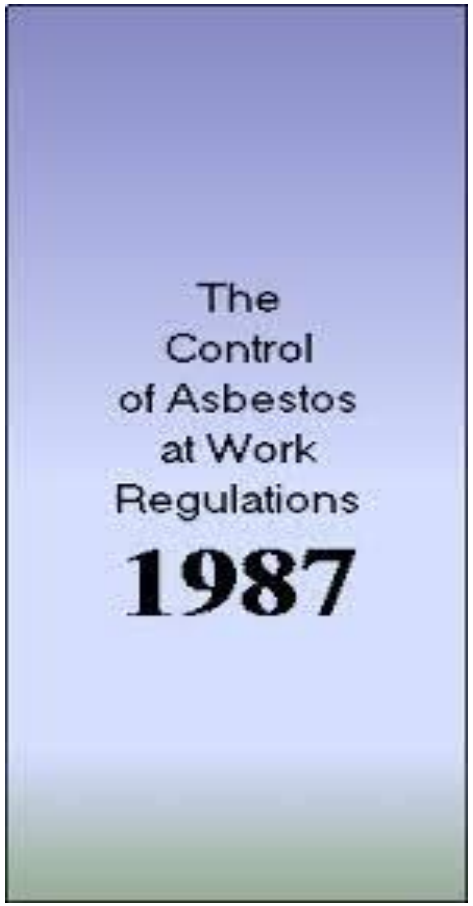
PSM of primary peritoneal tumours



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PSM of primary peritoneal tumours

Incidence per 100.000 from 2008-2012

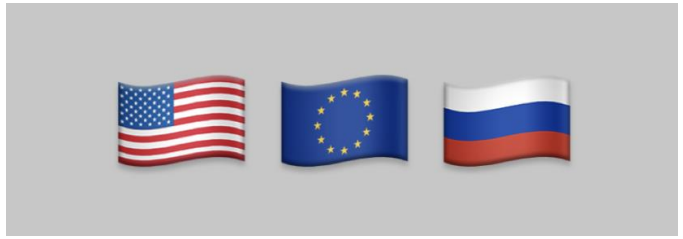
men 0.9
women 0.3

men 1.7
women 0.4

0.9 to 1.24 per million per year
2011-2015 vs
1993-2003

10-20%

since 2012
since 2016



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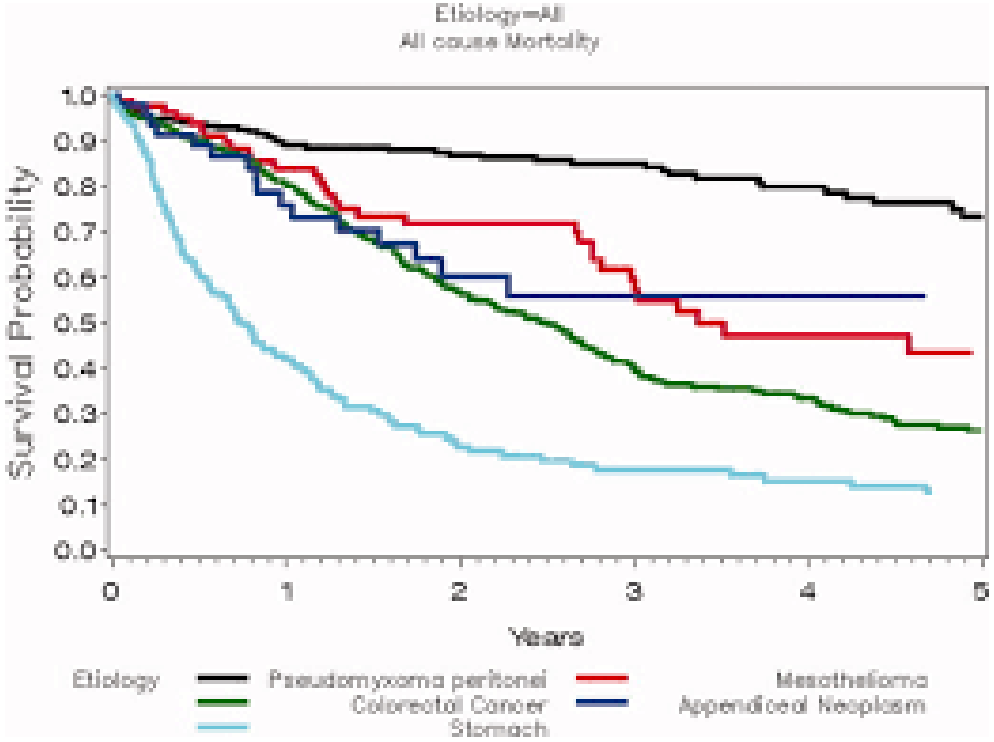
DANGER


IRON
ASBESTOS
LEAD


ASBESTOS


NOT FOR SALE

Trends in prognosis of PSM…



⬆️ number of patients undergoing CRS+HIPEC

⬆️ early diagnosis

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Risk factors

- **Advanced s**
  - T sta
  - Lymp
  - Histo
  - Posit

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Cancer Risk Genes

20-25% of **ovarian cancers** ∞ germline genetic disorders

Homologous recombination repair deficiency → *BRCA1* and/or *BRCA2* mutations

15% epithelial ovarian cancer ∞*BRCA1* and *BRCA2*

gastrointestinal cancers, such as pancreatic, colorectal and gastric

10 % of **colorectal cancers** ∞ germline genetic disorders

Mismatch repair deficiency ∞ Lynch syndrome (3%)

- *MLH1*, *MSH2*, *MSH6*, or *PMS2*
- Deletion in *EPCAM* → inactivation of MSH2

APC mutation ∞ familial adenomatous polyposis

gastrointestinal cancers, such as pancreatic, colorectal and gastric

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Sinicrope FA. Lynch syndrome–associated colorectal cancer. New England Journal of Medicine. 2018;379(8):764-73.

Rustgi SD, Ching CK, Kastrinos F. Inherited Predisposition to Gastric Cancer. Gastrointestinal Endoscopy Clinics. 2021;31(3):467-87.

Peritoneal anatomy and physiology

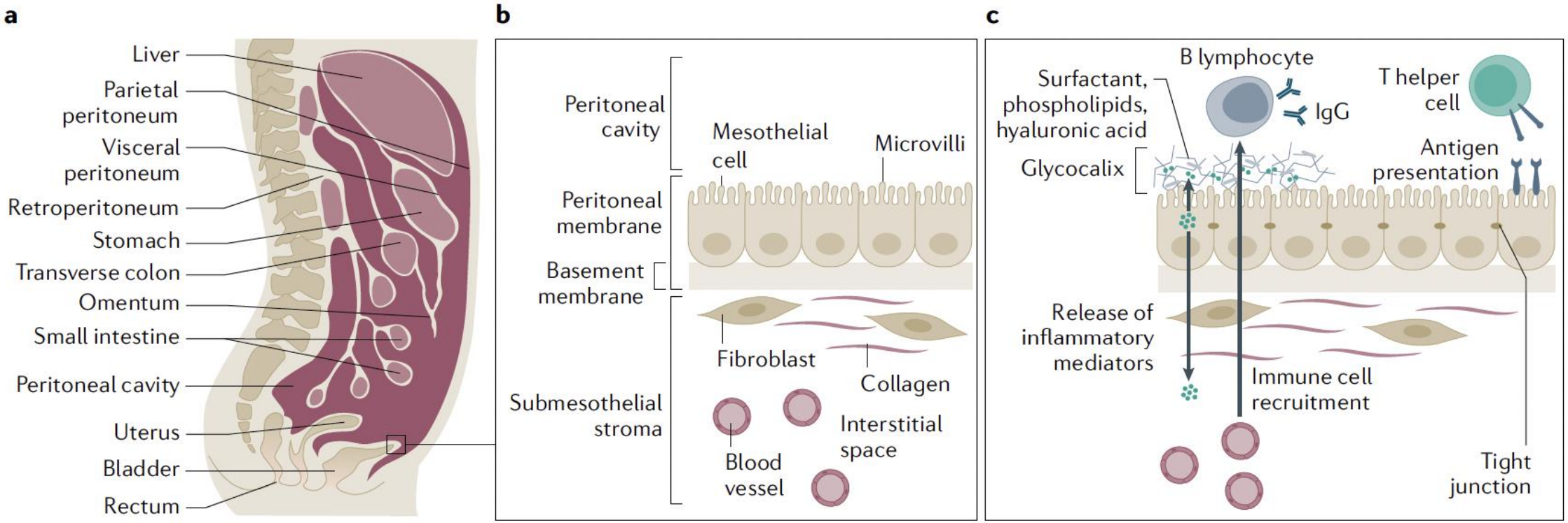
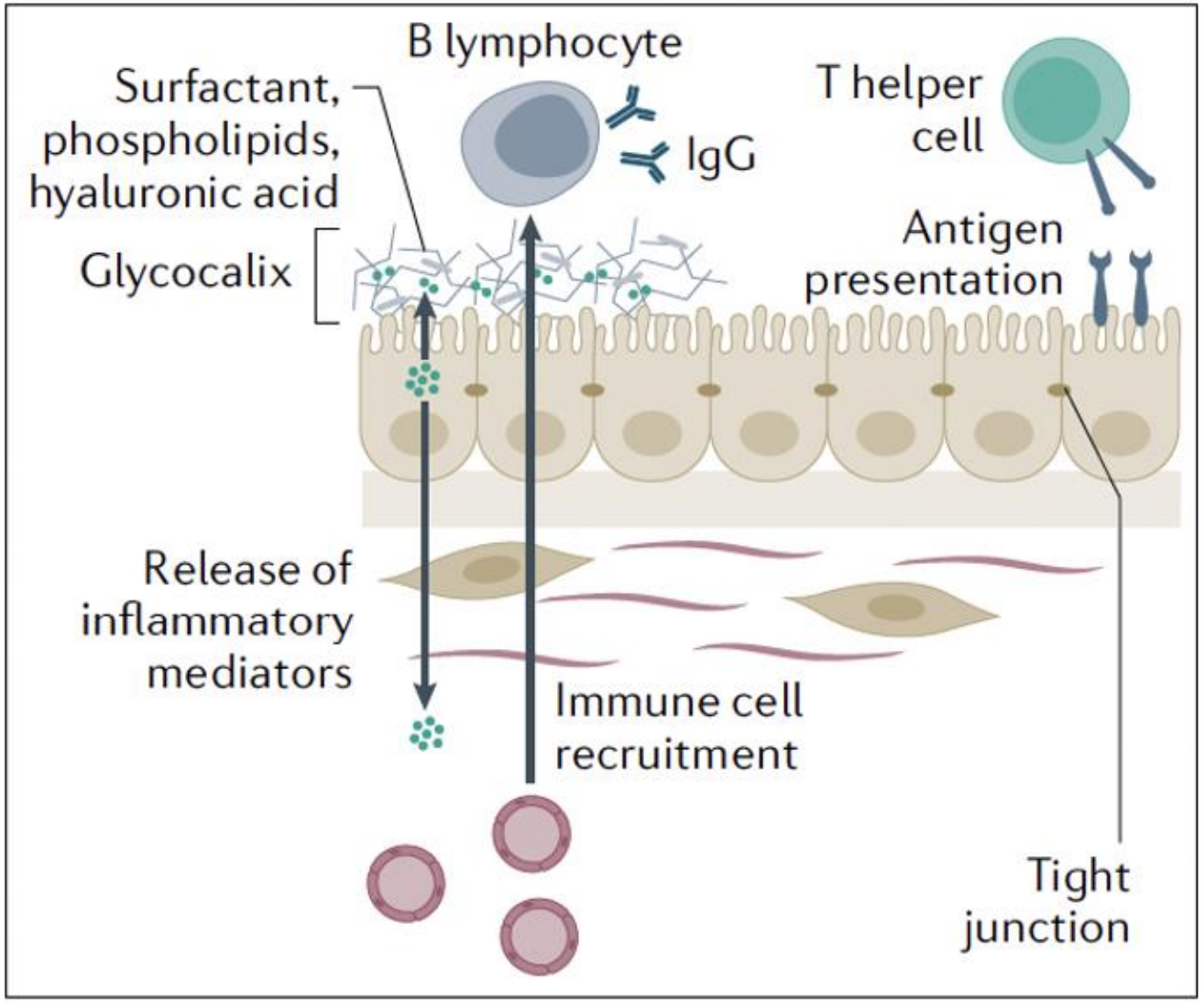
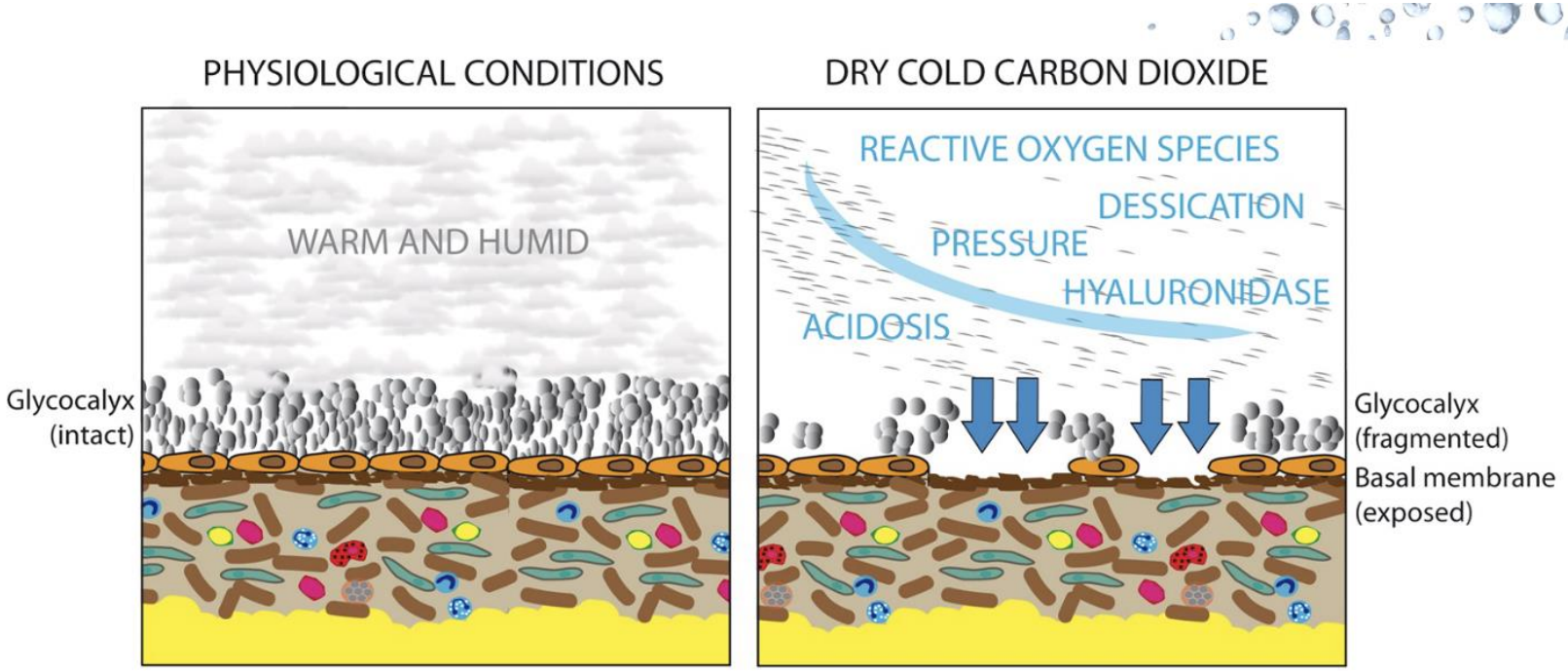


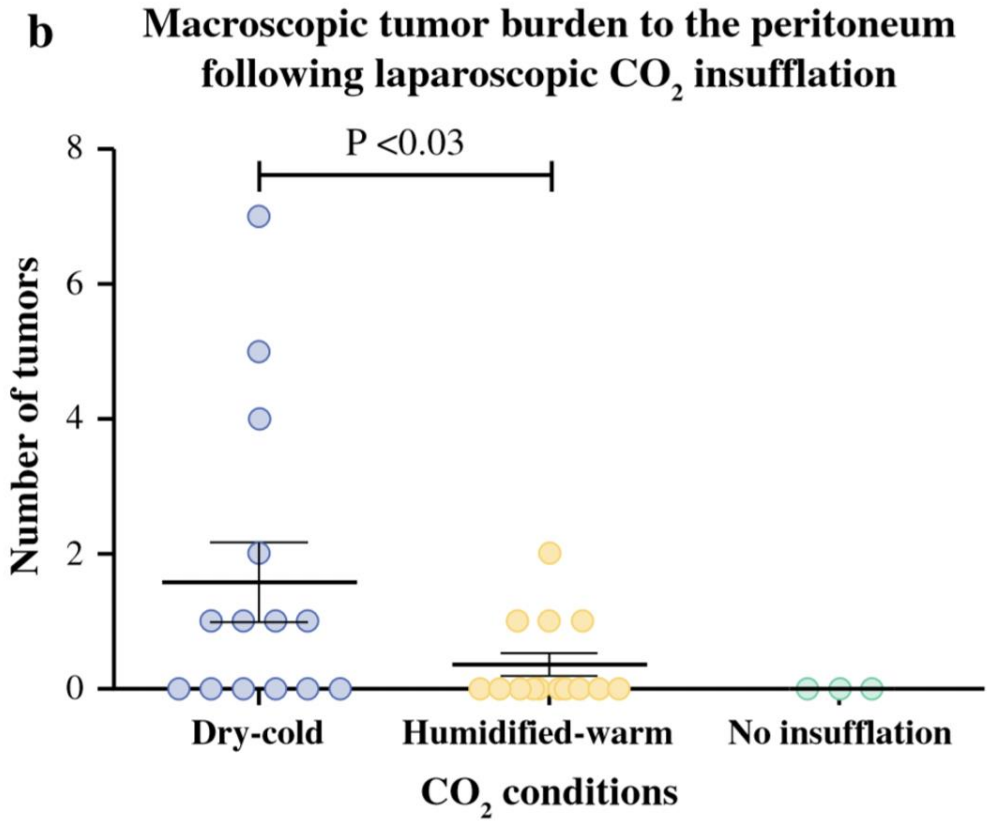
Fig. 2 | **Peritoneal anatomy and physiology. a** | The peritoneum is a serous membrane consisting of a single layer of mesothelial cells with complex apical and basal interactions. It forms a peritoneal sac that covers the abdominal organs. The visceral peritoneum describes the layer of the peritoneum adjacent to the abdominal organs, and the parietal peritoneum is the layer that adheres to the abdominal wall. The peritoneal cavity is the (virtual) space between these two layers that is filled with a small amount of serous fluid in the healthy state. **b** | The healthy peritoneal cavity is lined by mesothelial cells that express hundreds of microvilli per cell, which enable nutrient, waste and gas exchange as well as some organ mobility. The mesothelial cells are supported by a basement membrane, which consists of a laminin polymer and a collagen IV network. Numerous other cells contribute to a dynamic submesothelial stroma that responds to mechanical stress, cellular damage and infection. **c** | Immune cells may traffic to the mesenchymal apical surface, which is protected by a complex chemical mix predominated by a glycocalyx, despite close cellular connections via tight junctions. Depending on the health status of the peritoneum and the presence of antigens, various inflammatory mediators can be released in both directions. Parts **a** and **b** adapted from REF.[406], Springer Nature Limited.

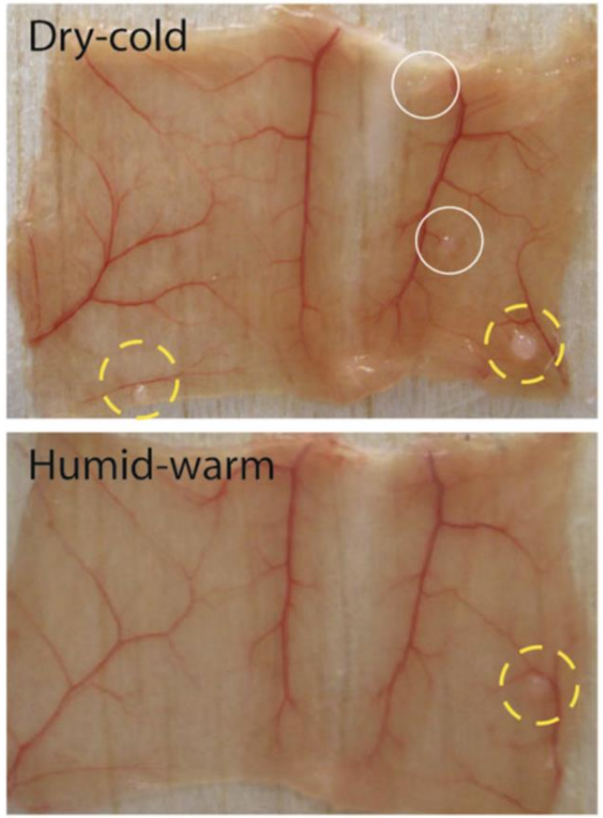

B lymphocyte
Surfactant, phospholipids, hyaluronic acid
IgG
T helper cell
Glycocalix
Antigen presentation
Release of inflammatory mediators
Immune cell recruitment
Tight junction

Peritoneal injury and repair



Wilson R, Pleura Peritoneum 2017



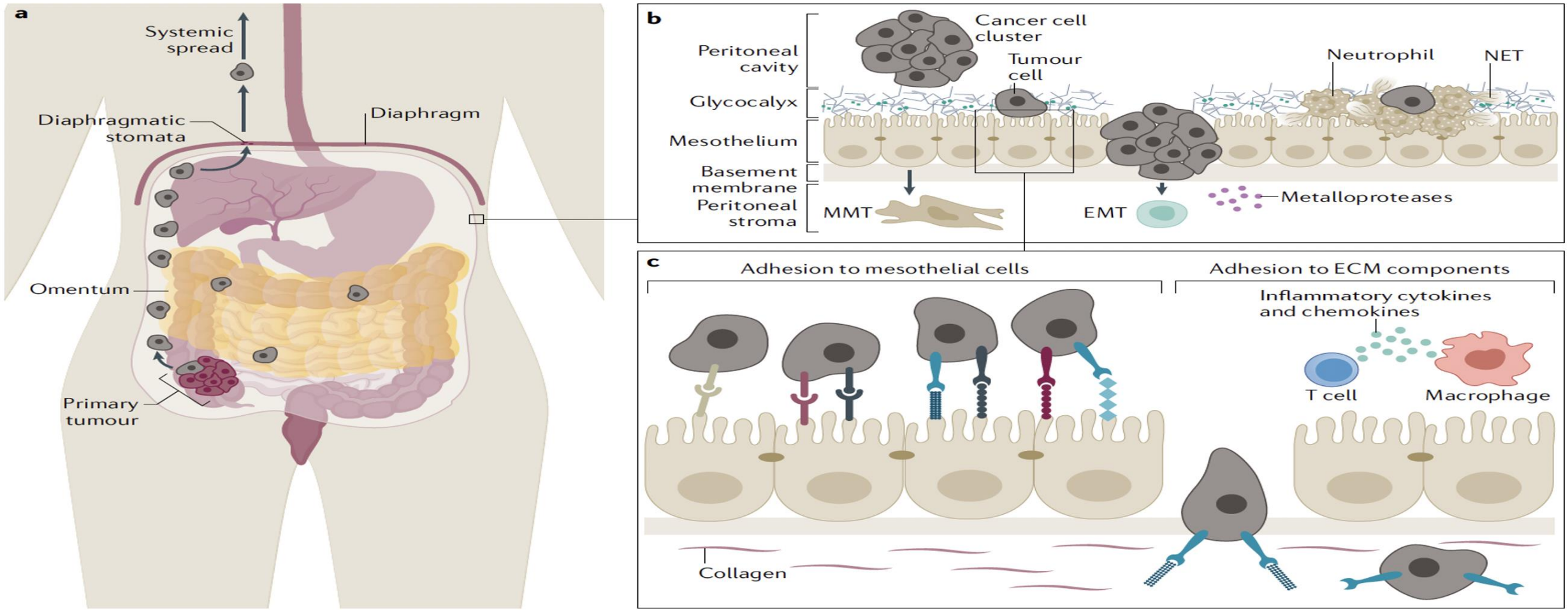


Carpinteri S, Ann Surg Oncol (2015) 22:S1540–S1547

Peritoneal metastasis and carcinomatosis

PRIMER

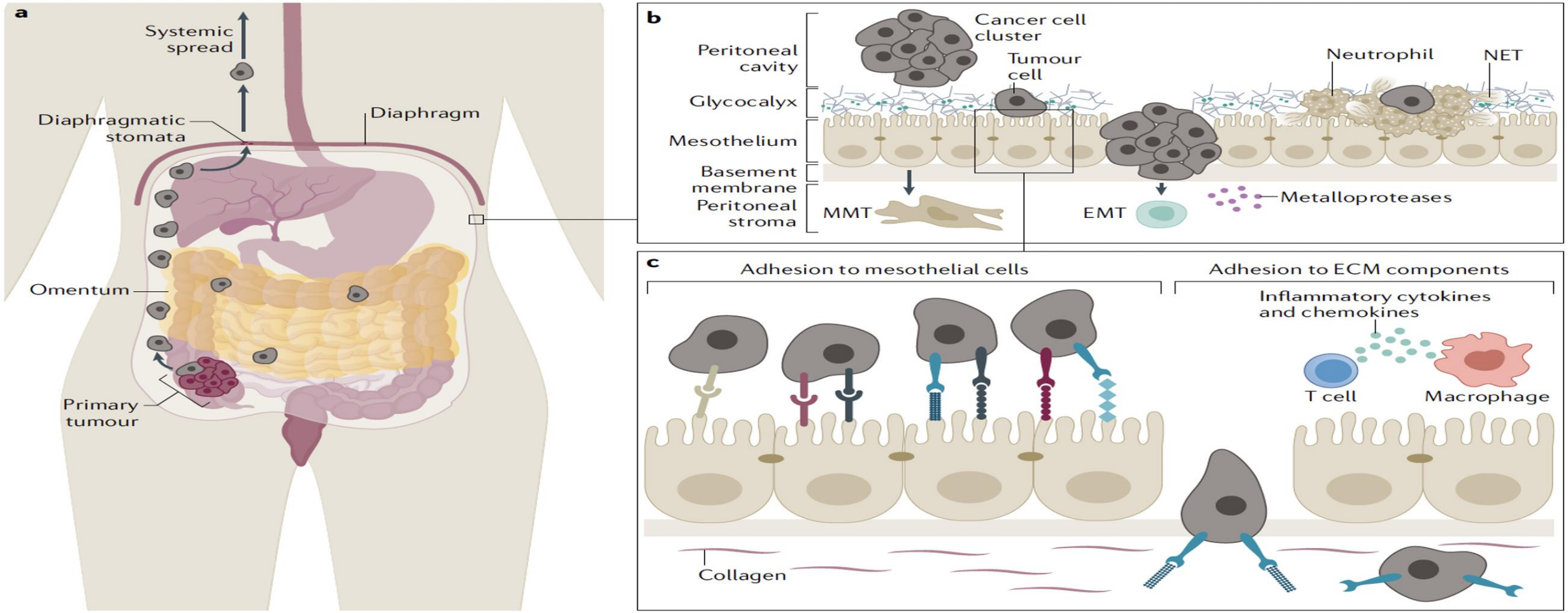
Cortés-Guiral, Delia, & Hübner, Martin et al. "Primary and metastatic peritoneal surface malignancies." *Nature Reviews Disease Primers* 7.1 (2021): 1-23.

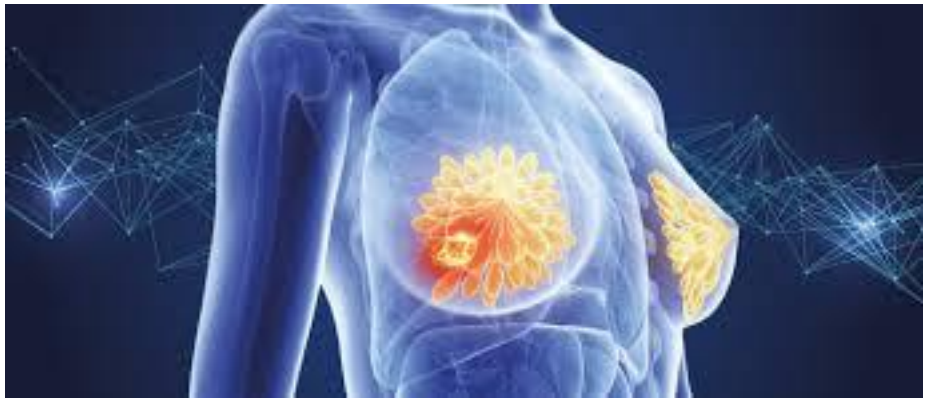


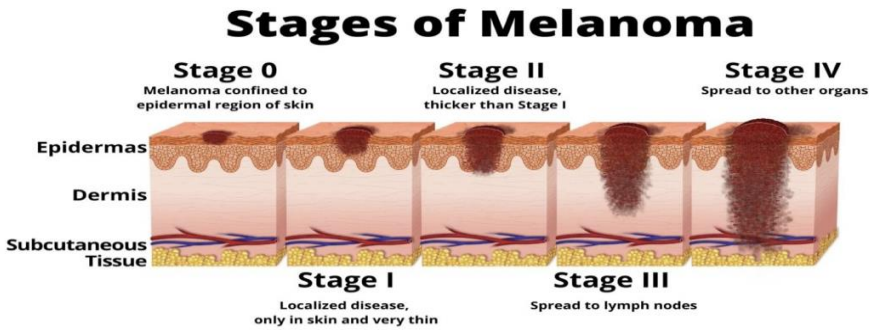
Detachment of cells from the primary tumour

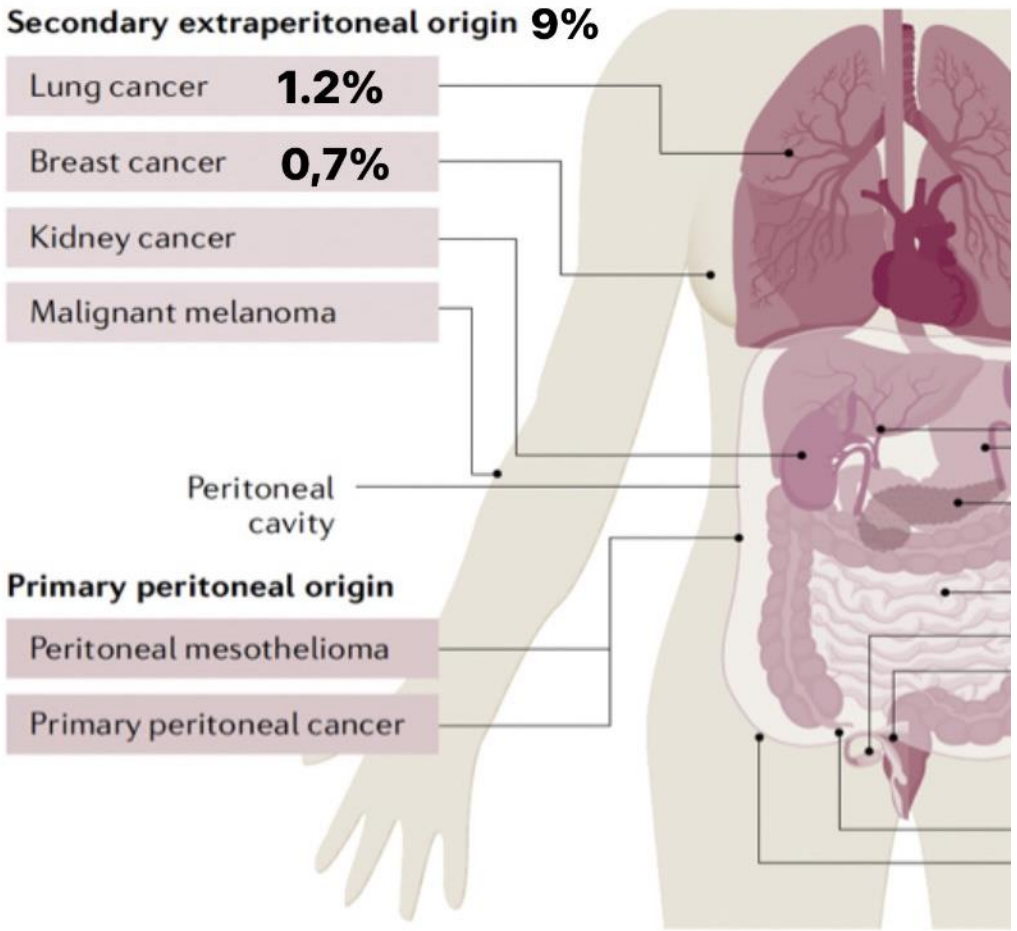
PRIMER

Cortés-Guiral, Delia, & Hübner, Martin et al. "Primary and metastatic peritoneal surface malignancies." *Nature Reviews Disease Primers* 7.1 (2021): 1-23.






Stages of Melanoma
Stage 0
Melanoma confined to epidermal region of skin
Stage II
Localized disease, thicker than Stage I
Stage IV
Spread to other organs
Epidermas
Dermis
Subcutaneous Tissue
Stage I
Localized disease, only in skin and very thin
Stage III
Spread to lymph nodes

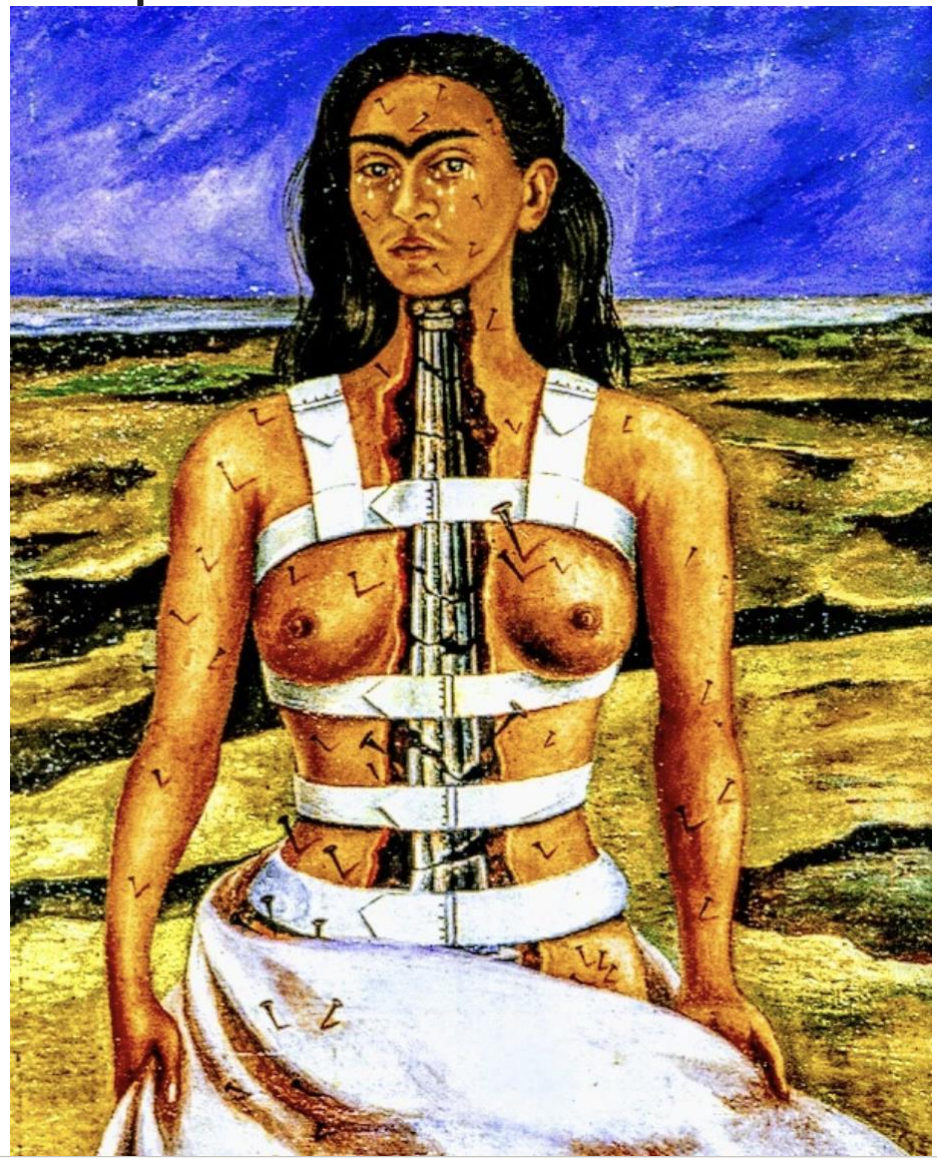

Secondary extraperitoneal origin 9%
Lung cancer 1.2%
Breast cancer 0,7%
Kidney cancer
Malignant melanoma
Peritoneal cavity
Primary peritoneal origin
Peritoneal mesothelioma
Primary peritoneal cancer

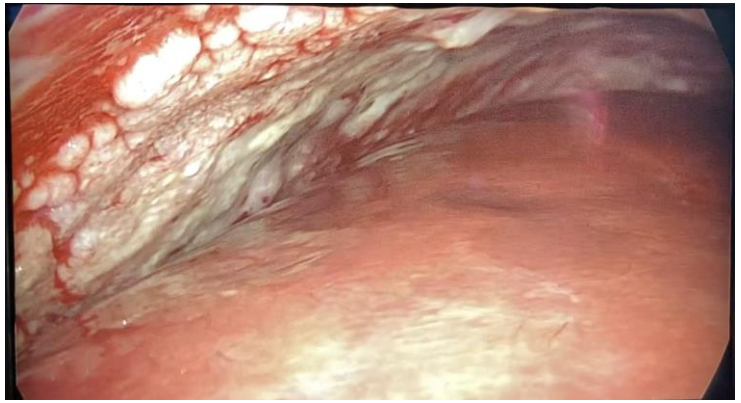
Symptoms associated with peritoneal metastases

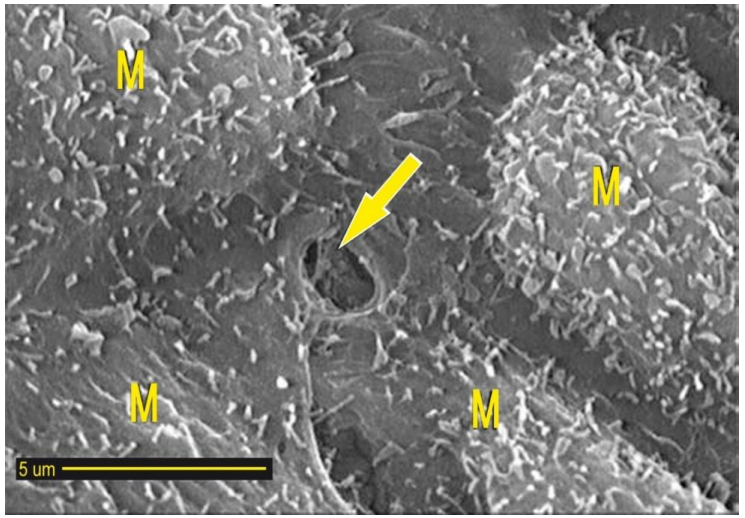
Pain

Ascites

Obstructive symptoms



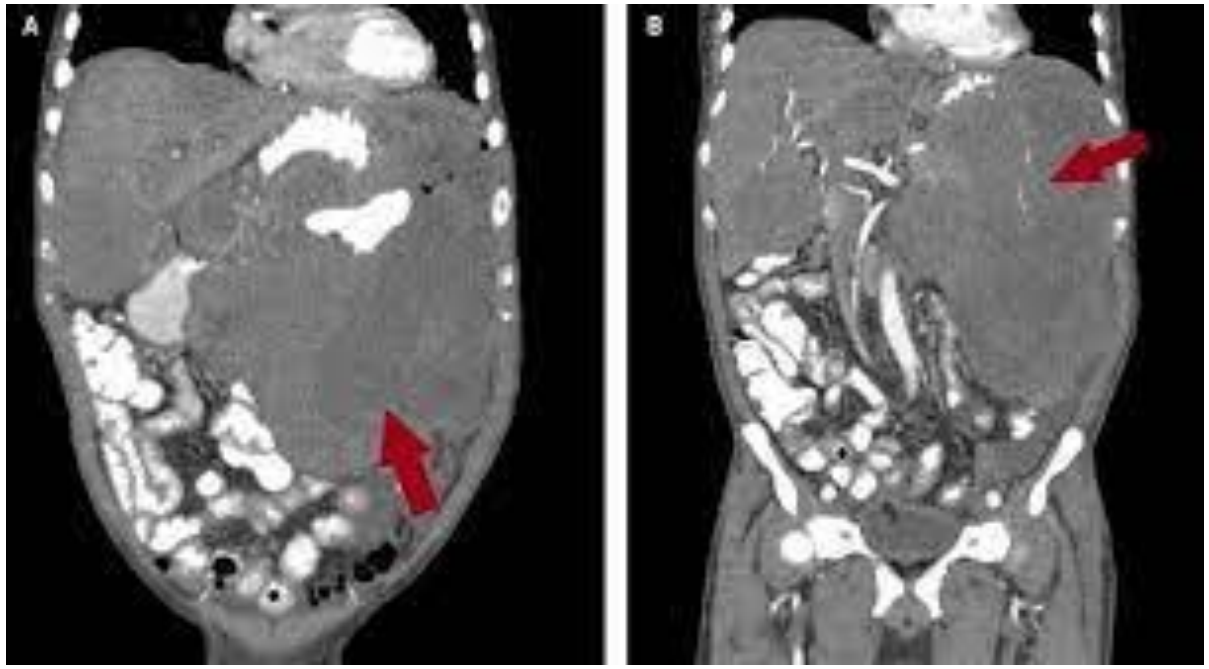




Clinical presentation

- At the onset, specific to the primary cancer-symptoms
  - Abdominal pain
  - Distension
- At late stage disease, unspecific symptoms 85%
  - Abdominal distension
  - Fatigue
  - Nausea, anorexia, weight loss and constipation
  - Clinical examination may identify palpable mass and ascites as usual signs.

Imaging modalities



CT vs PET-CT vs MRI

Table 1 | **Imaging modalities and their performance for peritoneal surface malignancies**

Imaging modality	Accuracy	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Refs
CT	0.804	0.758	0.821	0.61	0.902	154–156,160–162
PET–CT	0.76	0.905	0.652	0.656	0.908	160,162,164,165
MRI	0.875	0.877	0.873	0.895	0.851	45,155,160,168

Although differences in appreciating peritoneal metastases of different malignancies are commonly described in the literature, these have never been quantified with accuracy or compared between different primary malignancies.

Cortés-Guiral, Delia, & Hübner, Martin et al. "Primary and metastatic peritoneal surface malignancies." *Nature Reviews Disease Primers* 7.1 (2021): 1-23.

PET-CT vs Immuno-PET

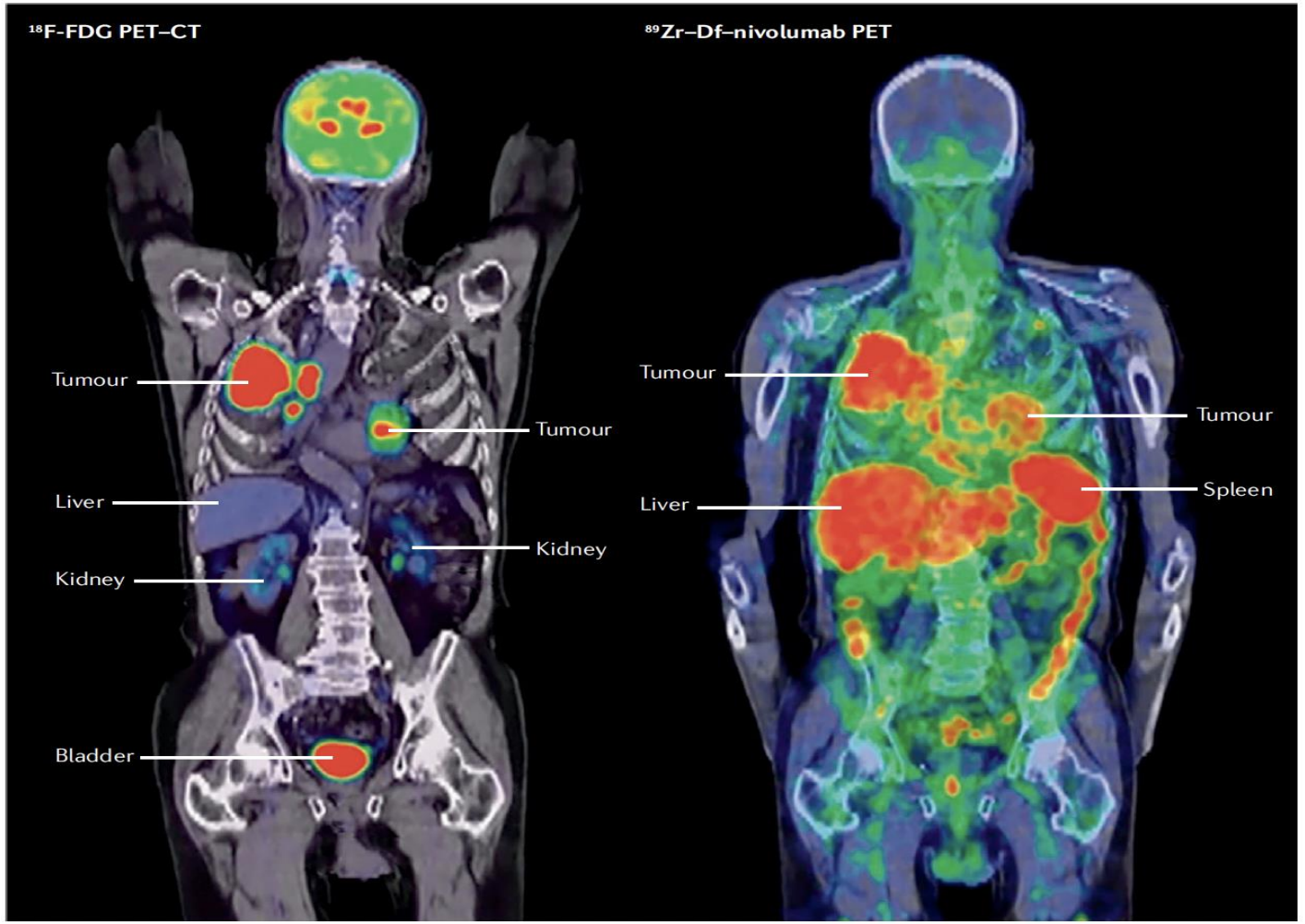
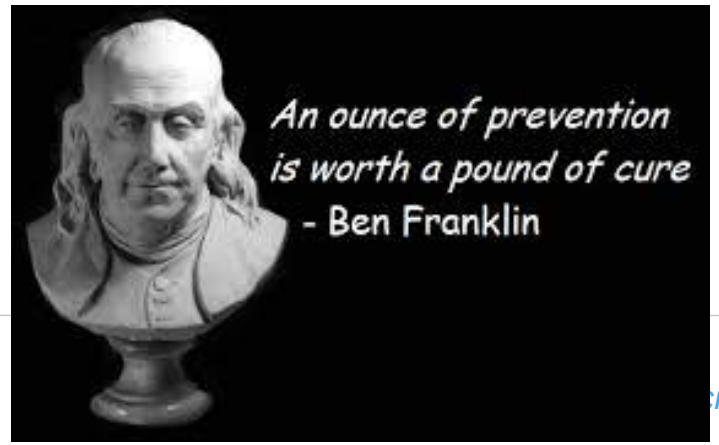


Fig. 4 | **ImmunoPET imaging.** Comparison of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET–CT (left image) with immunoPET (right image) for the same patient. Molecular imaging via immunoPET enables the combination of the precision of tissue targeting via a specific monoclonal antibody with the sensitivity of PET, resulting in better delineation of malignancy.

Cortés-Guiral, Delia, & Hübner, Martin et al. "Primary and metastatic peritoneal surface malignancies." *Nature Reviews Disease Primers* 7.1 (2021): 1-23.

Patients at high risk of PSM

Identification	Adjuvant Systemic Chemotherapy	Extensive intraoperative peritoneal lavage (EIPL)	Intrapertioneal chemotherapy	Genetic testing
CRC **Sync Ovarian Mets** **Perforated** T4 Positive cytology Mucinous Signet ring cells	CRC 56% Pancreas 13.5%	EXPEL RCT trial (800 patients with gastric cancer) gastrectomy alone or gastrectomy plus EIPL 3-year overall survival in the two groups was similar	HIPEC **CRC** COLOPEC PROPHYLOCHIP PROMENADE HIPEC-T4 **GASTRIC** 3 RCT (Japan) GASTRICHIP	PIPAC **CRC** OPC-3 **GASTRIC** OPC-4 GASPACO



Screening

- Colorectal cancer screening is widely implemented and resulted in incidence and mortality reduction
- Gastric or oeso-gastric cancer screening is common in Asia and also led to reduced mortality from these cancers
- Preventive strategies are proposed to individuals with high-risk mutations include intensive screening and/or preventive surgery
  - Bilateral salpingo-oophorectomy can reduce the risk of epithelial ovarian cancer diagnosis by up to 96%
    - Earlier for *BRCA1* mutations
  - Prophylactic total colectomy
    - Familial adenomatous polyposis, usually before 25 years of age
  - Prophylactic total gastrectomy
    - *CDH1* mutation at age 20–30 years or 5 years earlier than the age of the youngest affected family member
    - 87% of patients who undergo prophylactic gastrectomy due to *CDH1* mutation have evidence of malignancy

Zauber AG. The Impact of Screening on Colorectal Cancer Mortality and Incidence: Has It Really Made a Difference? Digestive Diseases and Sciences. 2015;60(3):681-91.

Kim J-H, Han K-D, Lee JK, Kim H-S, Cha JM, Park S, et al. Association between the National Cancer Screening Programme (NSCP) for gastric cancer and oesophageal cancer mortality. British journal of cancer. 2020;123(3):480-6.

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Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. The New England journal of medicine. 2002;346(21):1616-22.

Guillem JG, Wood WC, Moley JF, Berchuck A, Karlan BY, Mutch DG, et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(28):4642-60.

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El Rami FE, Barsoumian HB, Khneizer GW. Hereditary diffuse gastric cancer therapeutic roadmap: current and novel approaches in a nutshell. Therapeutic advances in medical oncology. 2020;12:1758835920967238.

Intraperitoneal Treatment Modalities

Comparison of main features, advantages and disadvantages

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.

HIPEC

- Applied as single administration after cytoreductive surgery (CRS) by use of a perfusion machine. Circulation of the heated chemotherapy solution can be performed using either an open (termed Coliseum) or a closed technique for a duration of 60–120 min and at a temperature of 40–43 °C.
- Indications: Curative.
- Potential other indications: Palliative, neoadjuvant and adjuvant.

PIPAC

- Applied repeatedly by laparoscopy using a two-trocar technique. PIPAC is not combined with CRS. Administration of chemotherapy is achieved via a high-pressure injector and a procedure-specific aerosolizer, creating a therapeutic aerosol with improved distribution and tissue entry.
- Indications: Palliative.
- Potential other indications: Neoadjuvant, adjuvant.

NIPS

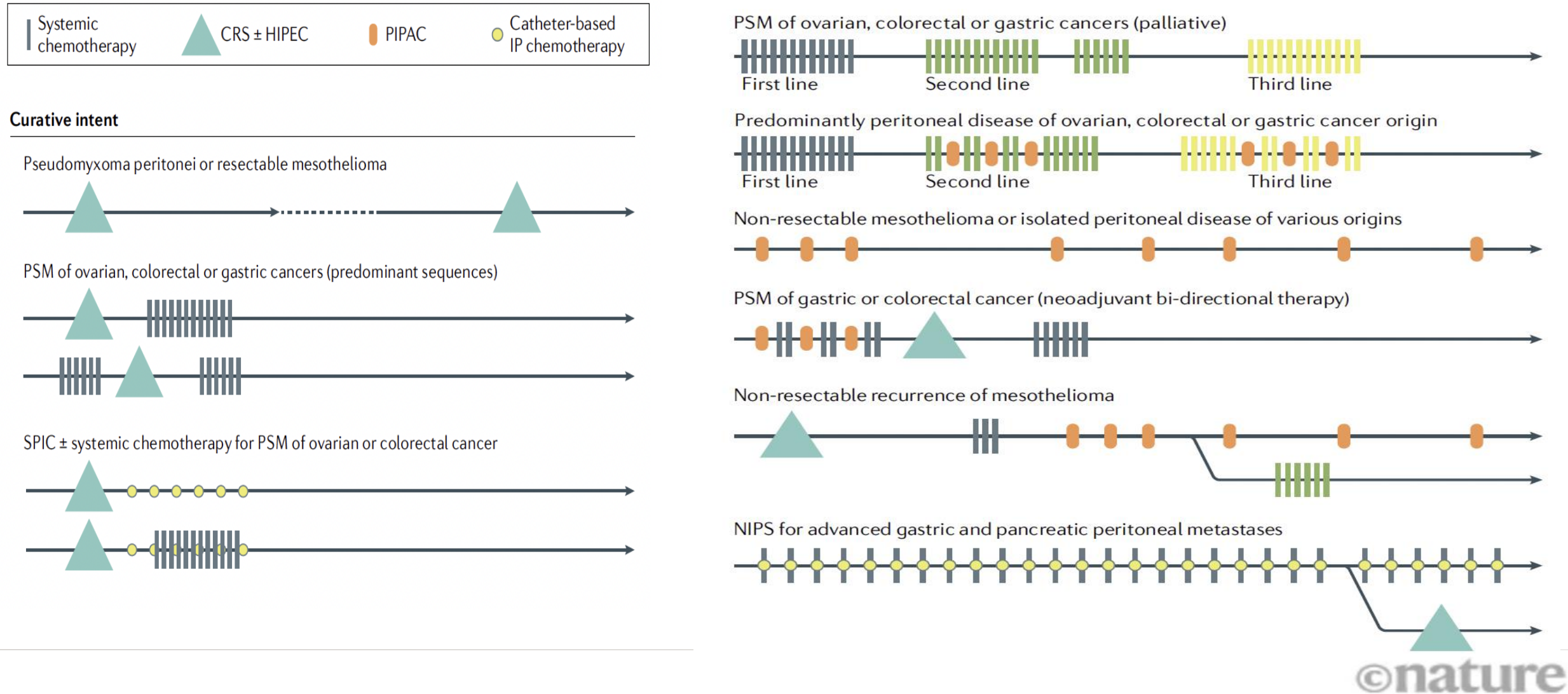
- Long-course combination treatment of intraperitoneal and intravenous chemotherapy using implanted catheter access ports.
- Indications: Neoadjuvant.

EPIC

- Administered typically after CRS and HIPEC by use of intraoperatively placed intraperitoneal catheters to extend intraperitoneal drug exposure over 5 days postoperatively.
- Indications: Adjuvant.

Cortés-Guiral, Delia, & Hübner, Martin et al. "Primary and metastatic peritoneal surface malignancies." *Nature Reviews Disease Primers* 7.1 (2021): 1-23.

Sequences of Treatment in PSM



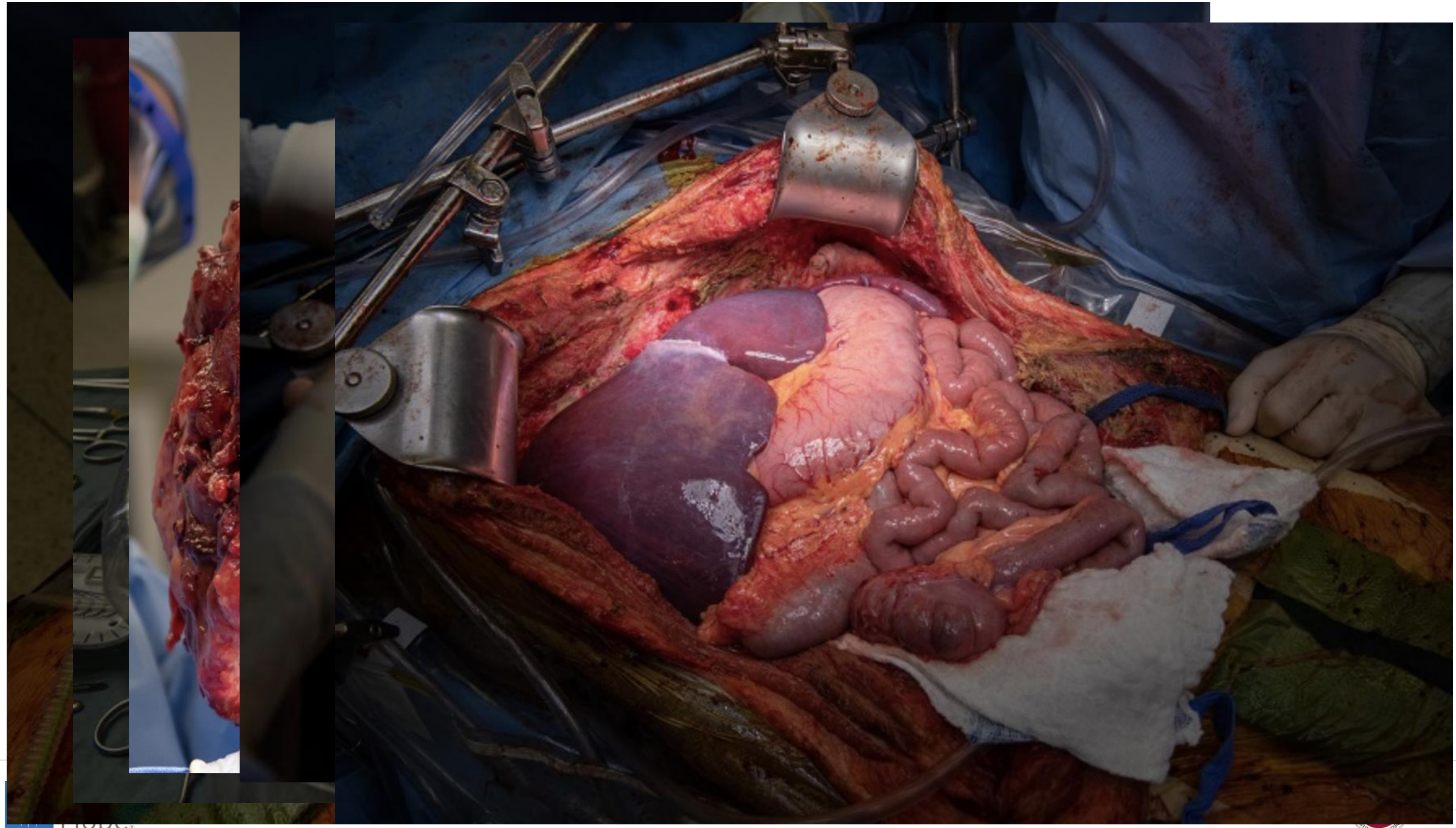
Cortés-Guiral, Delia, & Hübner, Martin et al. "Primary and metastatic peritoneal surface malignancies." *Nature Reviews Disease Primers* 7.1 (2021): 1-23.

Pseudomyxoma Peritonei and Appendiceal Cancer

CRS & HIPEC (always)

- Better than CRS alone
  - Regardless of residual disease
  - Regardless of histopath grade
- Prognosis
  - Completeness of CRS
    - Learning curve! 130 proc
  - Histopathological grade
    - Low-grade MS not reached
    - High-grade < 30 month
- HIPEC
  - cisplatin plus mitomycin C
  - oxaliplatin plus intravenous 5-FU

- Non-resectable non-metastatic low-grade PMP → bowel obstruction → TPN or Multivisceral transplantation
- Recurrence → bromelain and acetylcysteine (BroMac) for dissolution of tumor-produced mucin
- Non-resectable non-metastatic high-grade PMP → iterative intraperitoneal chemotherapy



Malignant peritoneal mesothelioma

CRS & HIPEC

- MOS 53 months
- Prognostic factors
  - Completeness of CRS
  - Histologic subtype
  - Nodal status
- HIPEC
  - cisplatin plus doxorubicin (PSOGI)

Other systemic therapies

- Systemich chemo MOS < 27 months
- Bevacizumab
- Immunotherapy
  Nivolumab (anti-PD-L1)
  Ipilimumab (anti-CLTA-4)
- Targeted therapies
  Anti-mesothelin antibody
  Pulsed dendritic cells

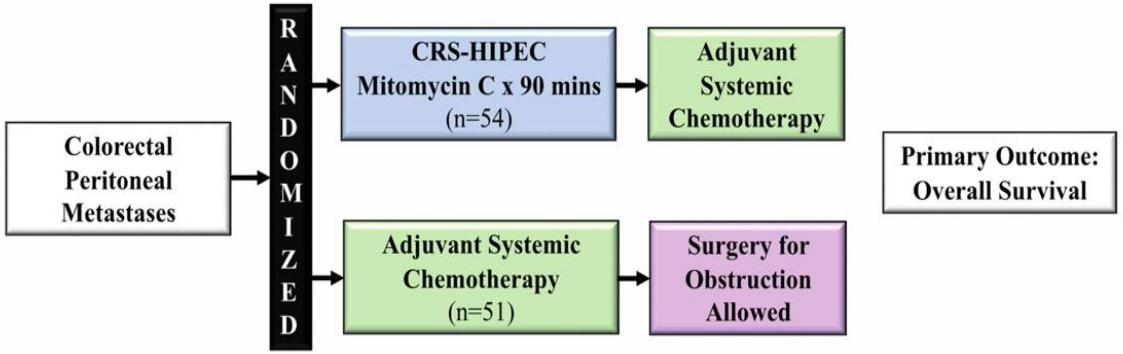
Non-resectable up-front

- PIPAC cisplatin plus doxorubicin
  - MESOTIP trial
- Intraperitoneal pemetrexed & systemic chemotherapy
  - Long-term normothermic intraperitoneal pemetrexed increased survival at 75% at 5 years
- Conversion rate > 50%

PSM of colorectal origin

CRS &…?

Netherlands Trial



Inclusion Criteria: (a) Synchronous or metachronous localized CRC PM (confirmed histologically or positive cytology); (b) Age <71; (c) Able to tolerate HIPEC; (d) medical eligibility

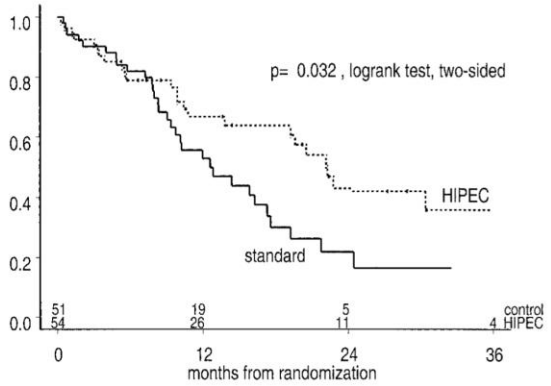


Fig 2. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC).

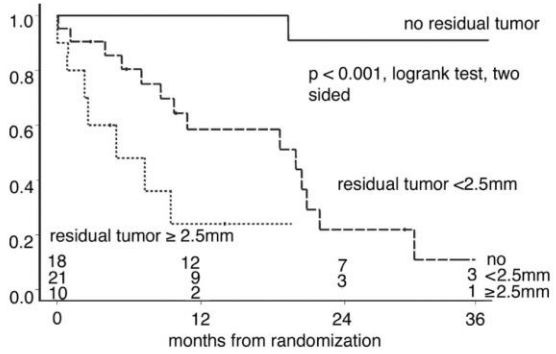
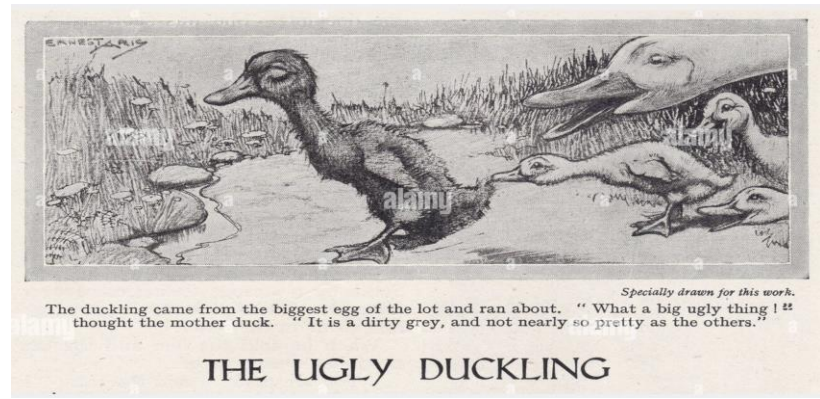


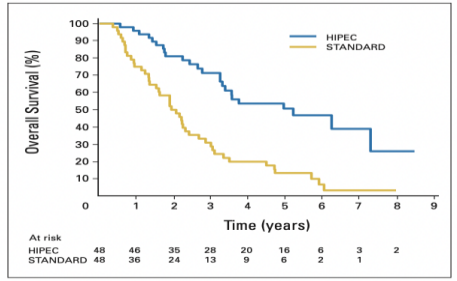
Fig 4. Kaplan-Meier survival curve of 49 patients with peritoneal Carcinomatosis (PC) treated by cytoreduction followed by hyperthermic intraperitoneal chemotherapy, comparing the number of regions affected with PC.



VOLUME 27 · NUMBER 5 · FEBRUARY 10 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Complete Cytoreductive Surgery Plus Intraperitoneal Chemohyperthermia With Oxaliplatin for Peritoneal Carcinomatosis of Colorectal Origin

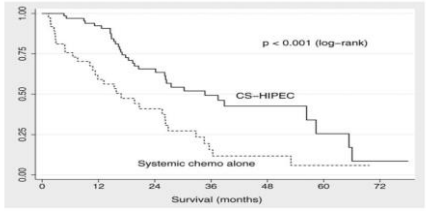
Dominique Elias, Jérémie H. Lefevre, Julie Chevalier, Antoine Brouquet, Frédéric Marchal, Jean-Marc Classe, Gwenaël Ferron, Jean-Marc Guilloit, Pierre Meeus, Diane Goéré, and Julia Bonastre



Original Article

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemoperfusion Versus Systemic Chemotherapy Alone for Colorectal Peritoneal Carcinomatosis

Jan Franko, MD, PhD; Zuhaib Ibrahim, MD; Niraj J. Gusani, MD; Matthew P. Holtzman, MD; David L. Bartlett, MD; and Herbert J. Zeh, III, MD



CLINICAL TRIAL | VOLUME 53, P155-162, JANUARY 01, 2016

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

P.H. Cashin • H. Mahteme • N. Spång • ... M. Torkzad • B. Glimelius • W. Graf • Show all authors

Published: January 02, 2016 • DOI: https://doi.org/10.1016/j.ejca.2015.09.017 • Check for updates

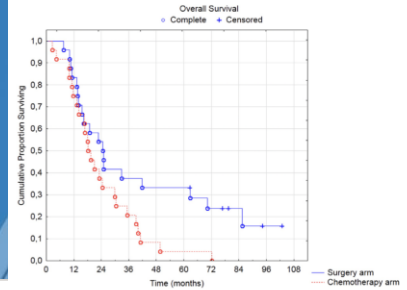
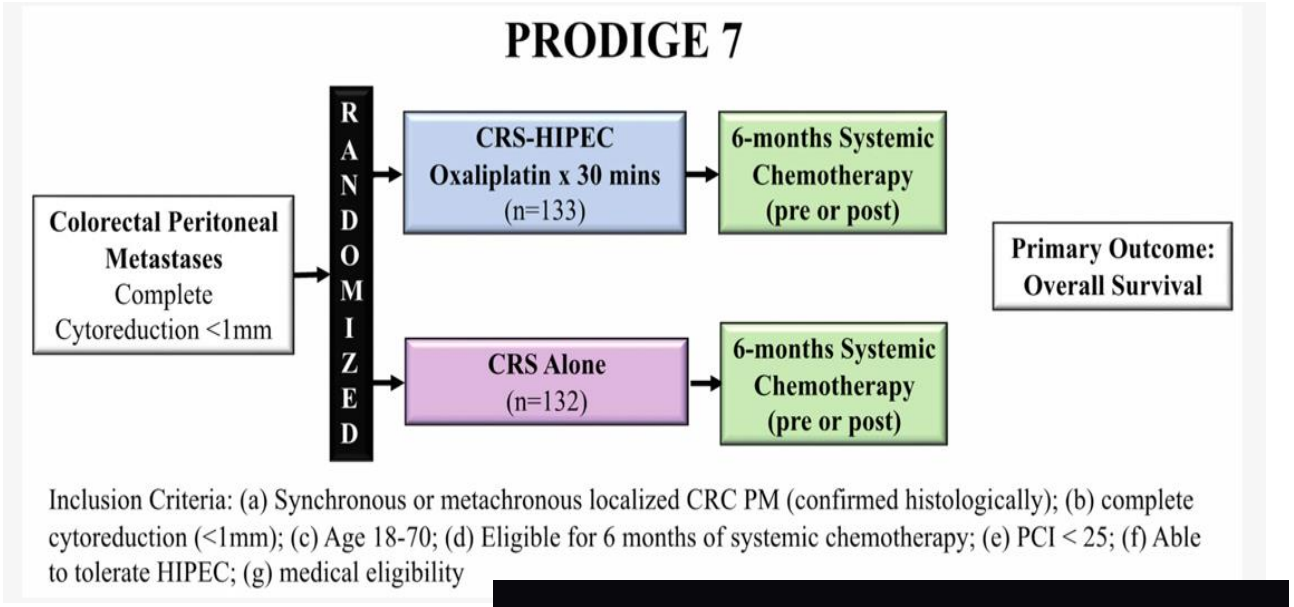
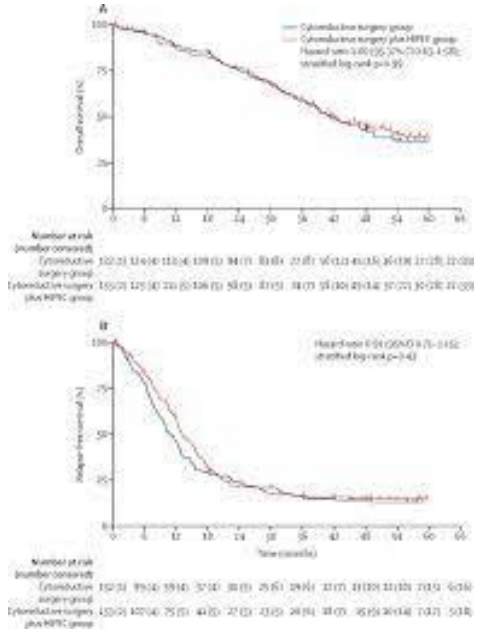


Fig. 2. Overall survival after cytoreductive surgery combined with intraperitoneal chemotherapy compared to systemic chemotherapy only in peritoneal metastases of colorectal origin, $p = 0.04$.

PSM of colorectal origin





Ann Surg Oncol (2016) 23:2315–2322
DOI 10.1245/s10434-016-5143-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

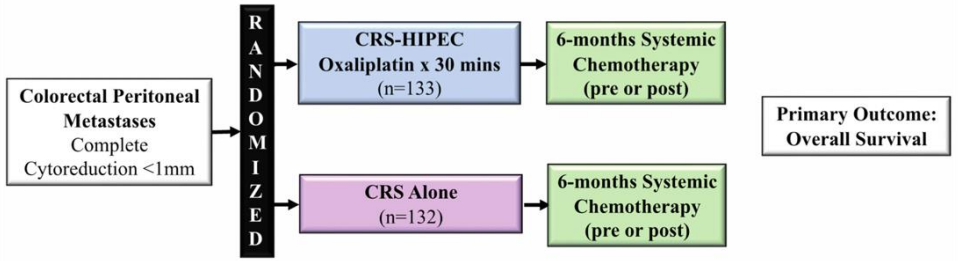
ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy with Oxaliplatin Increases the Risk of Postoperative Hemorrhagic Complications: Analysis of Predictive Factors

Thibaut Charrier, MD[1,2], Guillaume Passot, MD[1,2], Julien Peron, MD[3], Christelle Maurice, MSc[4], Sashka Gocevska, MD[5], François Quénet, MD, PhD[5], Clarisse Eveno, MD, PhD[6], Marc Pocard, MD, PhD[6], Diane Goere, MD, PhD[7], Dominique Elias, MD, PhD[7], Pablo Ortega-Deballon, MD, PhD[8], Delphine Vaudoyer, MD[1,2], Eddy Cotte, MD, PhD[1,2], and Olivier Glehen, MD, PhD[1,2]

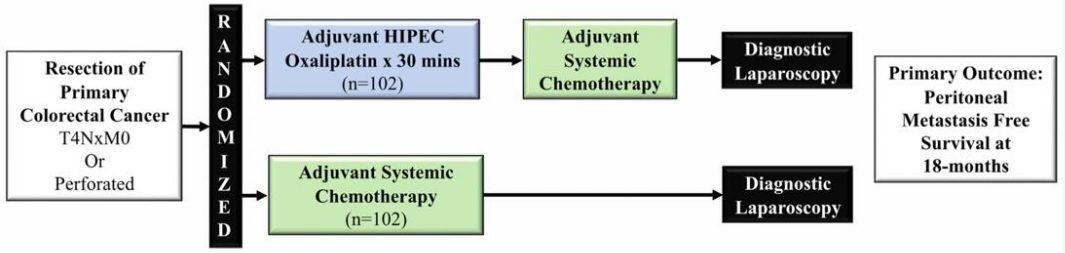
PSM of colorectal origin

PRODIGE 7



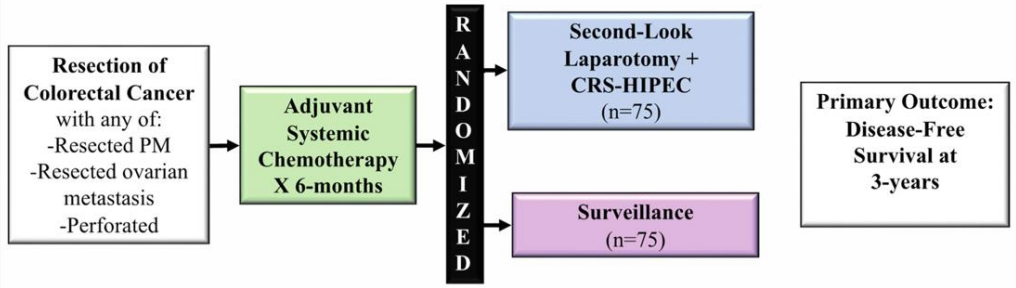
Inclusion Criteria: (a) Synchronous or metachronous localized CRC PM (confirmed histologically); (b) complete cytoreduction (<1mm); (c) Age 18-70; (d) Eligible for 6 months of systemic chemotherapy; (e) PCI < 25; (f) Able to tolerate HIPEC; (g) medical eligibility

COLOPEC



Inclusion Criteria: (a) Resectable clinical or pathologic T4NxM0 or perforated Colon Cancer (perforation= tumor, bowel, or peritumoral abscess); (b) Age 18-75; (c) Intention to start systemic chemotherapy; (d) Able to tolerate HIPEC; (e) medical eligibility

PROPHYLOCHIP-PRODIGE 15



Inclusion Criteria: (a) 'High-Risk' for peritoneal metastasis; (b) Age 18-70; (c) Received 6 months of adjuvant chemotherapy; (d) No peritoneal recurrence or metastatic spread; (e) Life expectancy > 12 weeks; (f) Able to tolerate HIPEC; (g) medical eligibility

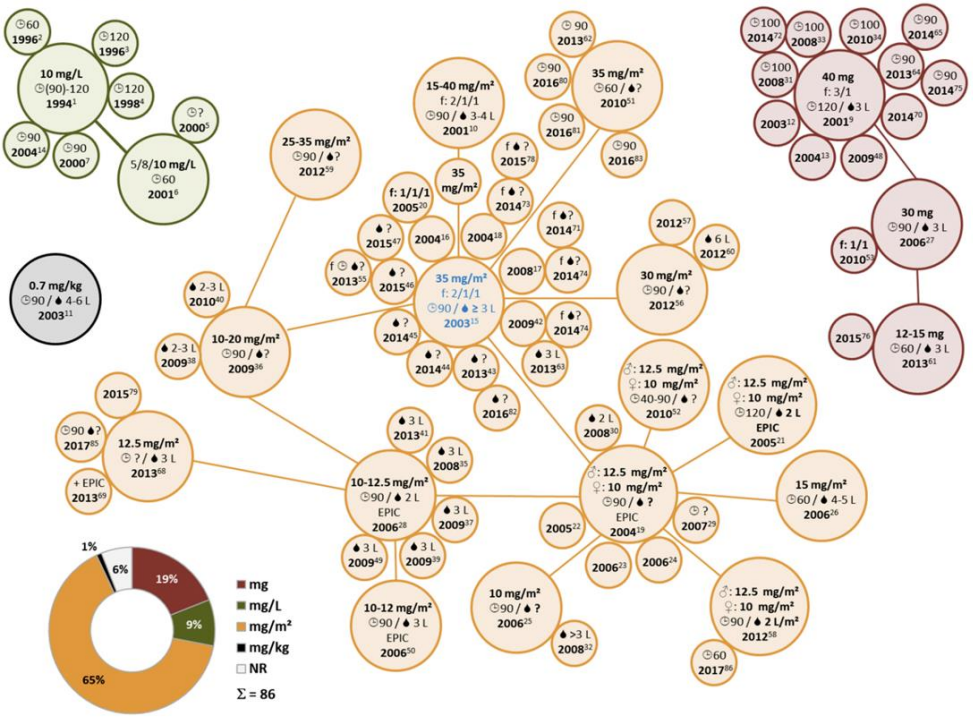
Journal of *Clinical Medicine*

MDPI

Review

Systematic Review of Variations in Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Metastasis from Colorectal Cancer

Can Yurttas [1,†], Giulia Hoffmann [1,†], Alexander Tolios [2], Sebastian P. Haen [3,4,5], Matthias Schwab [6,7,8], Ingmar Königsrainer [1,‡], Alfred Königsrainer [1,4], Stefan Beckert [1,§] and Markus W. Löffler [1,3,4,6,*]



memo (2020) 13:434–439
https://doi.org/10.1007/s12254-020-00653-6

memo
magazine of european medical oncology

Cytoreductive surgery and HIPEC in colorectal cancer—did we get hold of the wrong end of the stick?

Can Yurttas · Oliver M. Fisher · Delia Cortés-Guiral · Sebastian P. Haen · Ingmar Königsrainer · Alfred Königsrainer · Stefan Beckert · Winston Liauw · Markus W. Löffler

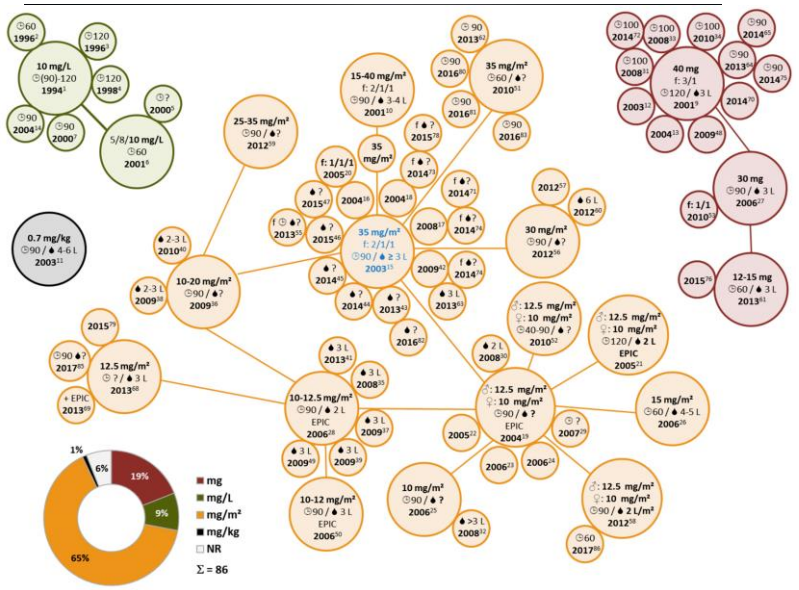
erapies for Can *nd the Pleura*

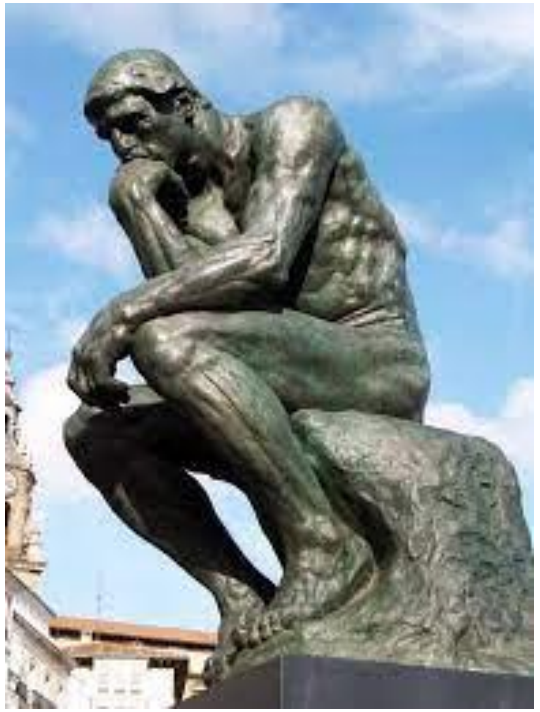
Pereira et al. BMC Cancer (2022) 22:536
https://doi.org/10.1186/s12885-022-09572-7

BMC Cancer

STUDY PROTOCOL Open Access

GECOP-MMC: phase IV randomized clinical trial to evaluate the efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) with mytomicin-C after complete surgical cytoreduction in patients with colon cancer peritoneal metastases





- Could we justify the administration of any therapy which does not improve survival over the survival of the CRS alone arm, specially outside clinical trials?
- If Mytomicin-C does not do better than Oxaliplatin, what is the rational?
- Time to base the next clinical trial on preclinical supportive evidence instead of experimental?

Should I keep on using Oxaliplating HIPEC?

www.nature.com/bjc

British Journal of Cancer

ARTICLE OPEN

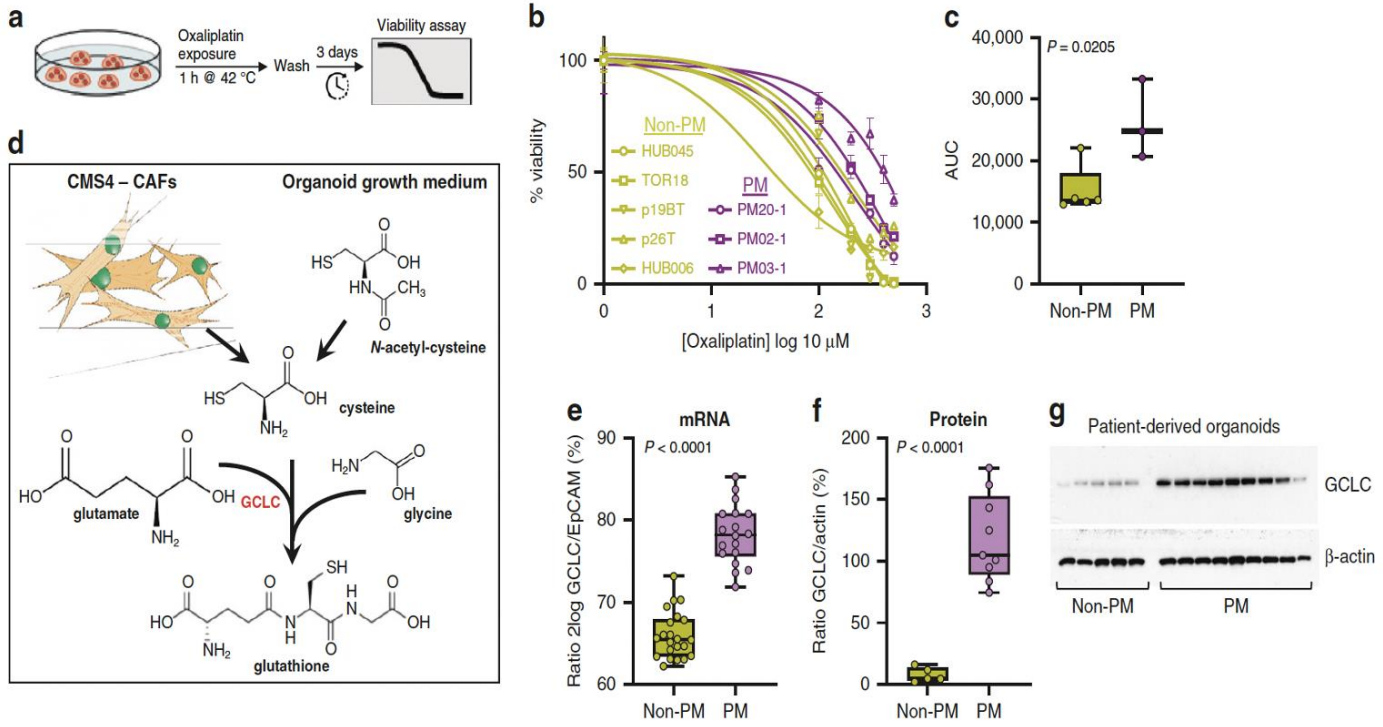
Check for updates

Translational Therapeutics

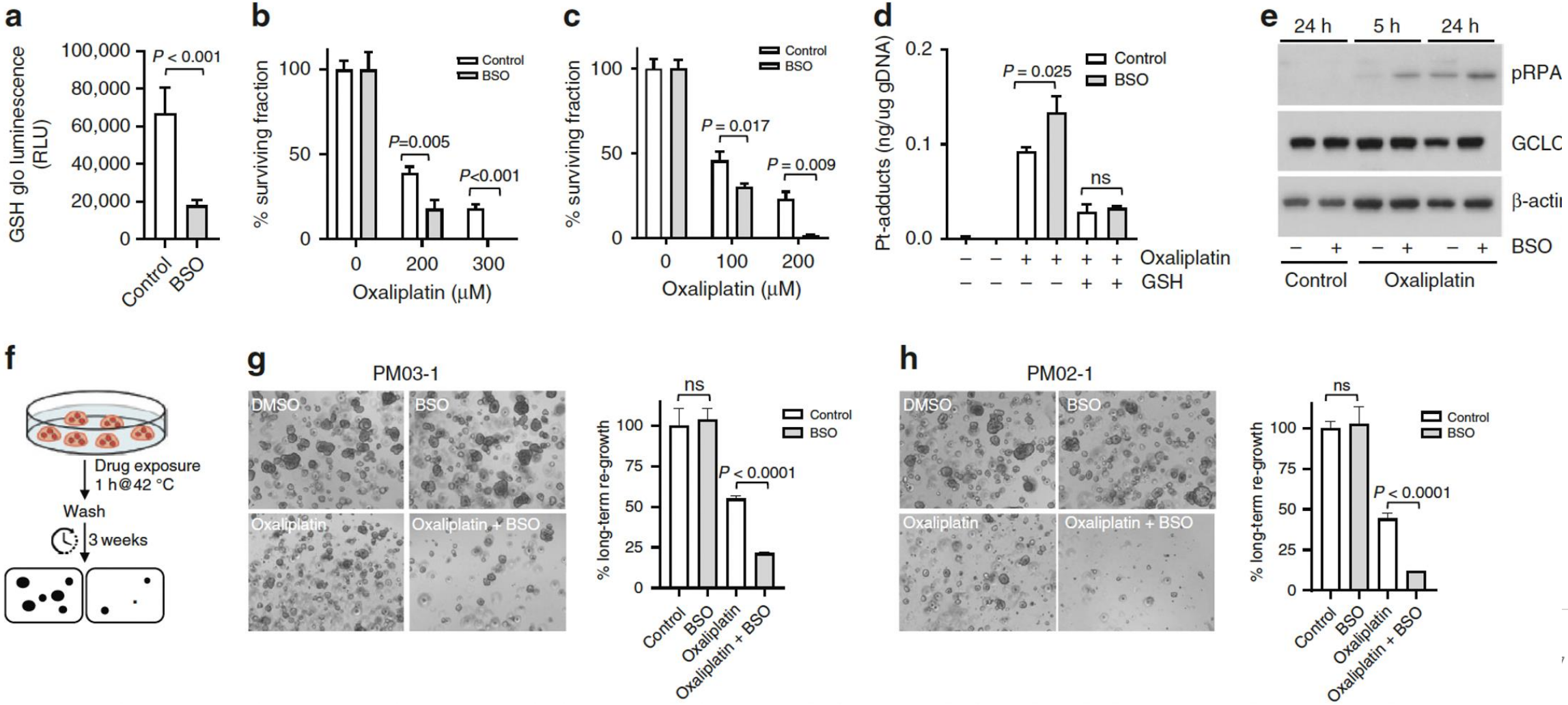
Peritoneal metastases from colorectal cancer belong to Consensus Molecular Subtype 4 and are sensitised to oxaliplatin by inhibiting reducing capacity

Jamila Laoukili[1,11], Alexander Constantinides[1,11], Emma C. E. Wassenaar[1,2,11], Sjoerd G. Elias[3], Danielle A. E. Raats[1,4], Susanne J. van Schelven[1], Jonathan van Wettum[1], Richard Volckmann[5], Jan Koster[5], Alwin D. R. Huitema[6,7,8], Simon W. Nienhuijs[9], Ignace H. J. T. de Hingh[9,10], René J. Wiezer[2], Helma M. U. van Grevenstein[1], Inne H. M. Borel Rinkes[1], Djamila Boerma[2]✉ and Onno Kranenburg[1,4]✉

- *PMDO cultures*
  - *were resistant to oxaliplatin*
  - *expressed high levels of glutamate-cysteine ligase (GCLC) causing detoxification of oxaliplatin through glutathione synthesis*
- *72 h of exposure of PMDO to oxaliplatin increases drug sensitivity markedly*
- *One-hour oxaliplatin exposure modest tumouroid killing effect*

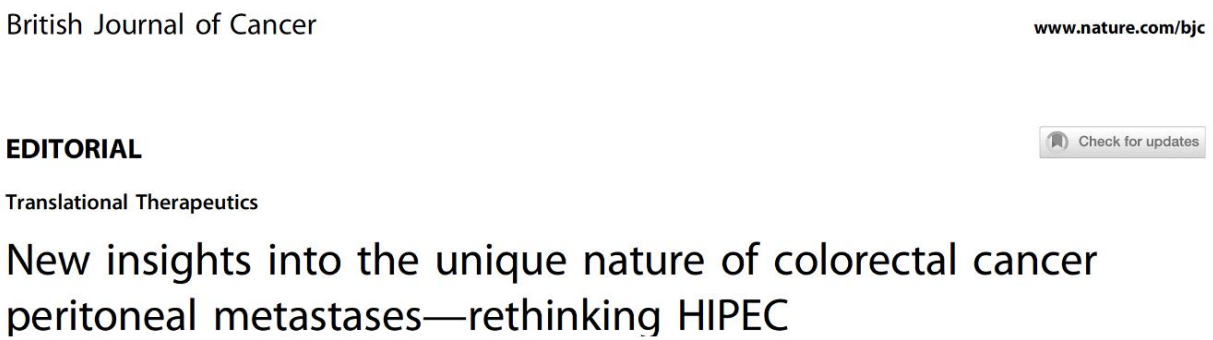


After HIPEC-OX re-growth can be observed after 3 weeks



Good news…

- ***GCLC knockout increases sensitivity to oxaliplatin!!!!***
- *GCLC inhibitors?*
  - *Buthionine sulfoximine (BSO)*
  - *APR-246*
- *BSO allows oxaliplatin to kill tumouroids effectively within the1-h treatment period and impedes long-term regrowth*



British Journal of Cancer www.nature.com/bjc

EDITORIAL

Check for updates

Translational Therapeutics

New insights into the unique nature of colorectal cancer peritoneal metastases—rethinking HIPEC

PSM of gastric origin

CRS & HIPEC

- Prognostic factors
  - Completeness of CRS CC-0
  - PCI < 6
- HIPEC
  - PERISCOPE II trial

    HIPEC vs Palliative chemo
- Repeated HIPEC

PIPAC

- Systemich chemo & PIPAC
  - 20.1 months
  - 14.3 % conversion

NIPS

- Docetaxel or Paclitaxel
  - PHOENIX-GC

PSM of ovarian, fallopian tube and primary peritoneal cancer origin

CRS

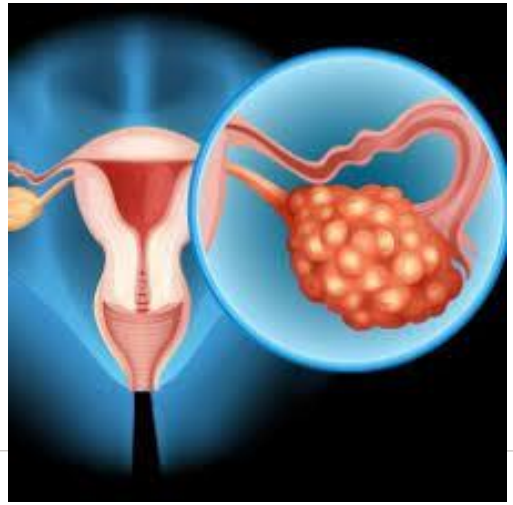
- Up-front scenario
  - CRS & systemic chemo
  - CRS vs debulking
- Interval surgery
  - CRS & HIPEC cisplatin
    - OVHIPEC
- Pelvic and para-aortic lymphadenectomy can be safely omitted in patients without evidence of node involvement

Recurrence scenario

- CRS MS 11.2 months
  - Good performance status
  - Platinum treatment-free interval of <6 montns
  - Complete resection at the primary surgery
  - Absence of large ascites volumes
- CRS & HIPEC MS 19.4 months
  - HIPOVA-01

PIPAC

- PIPAC cisplatin and doxorubicin for recurrent (phase I study)
  - 62% of patients objective tumor response
  - 76% patients histological tumor regression and PCI improvement
- Ongoing phase III trial PIPAC-OV3



PSM of rare origins

PANCREATIC PM

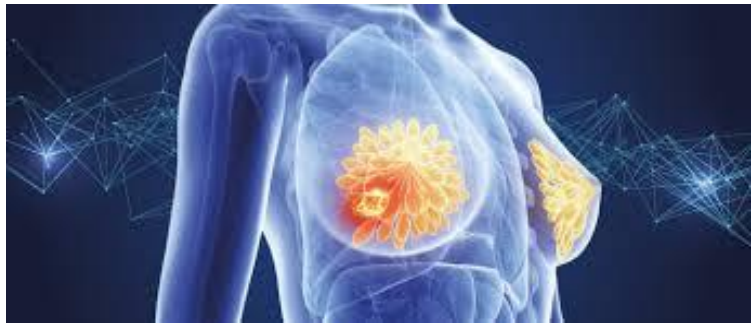
- CRS & HIPEC 16 months
  - Mytomicin-C
  - Cisplatin

CHOLANGIOCA PM

- CRS & HIPEC 21.4 months

BREAST CANCER PM

- CRS & HIPEC ?
- 82% of patients with PM also have other metastatic sites



PERITONEAL SARCOMATOSIS

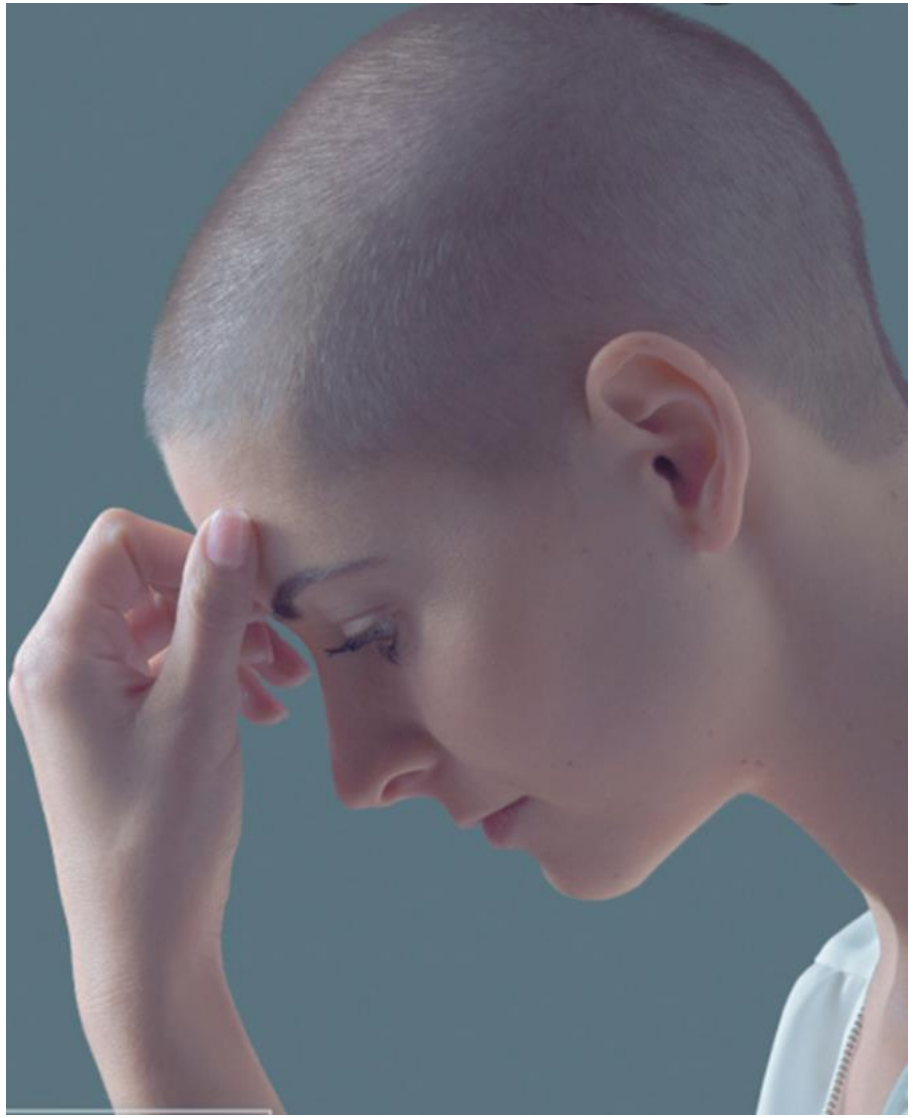
- CRS
  - OS 12-34 months
- CRS & HIPEC
  - 5-year overall survival 40%
- HIPEC ?

Quality of life

- Oncological treatments can have positive or negative effects on QoL and this balance tends to shift over time.
- QoL should, therefore, be regarded as a longitudinal measure
- Peritoneal metastases are more frequently symptomatic than metastases at other sites
- Bowel obstruction deserves particular mention, as physical and psychological suffering accompanies loss of essential functions of living as well as lack of treatment options and consequent loss of hope

Quality of life

- Systemic chemotherapy remains the standard treatment for metastatic disease
- Systemic chemotherapy can have a profound negative effect on QoL
- A close partnership between doctors, patients and their families with transparent and honest information on expected benefits, potential risks and treatment options is, therefore, of utmost importance to define the optimal treatment for the individual patient by shared decision-making.
- Misunderstanding between patients and care providers concerning the intent of treatment and prognosis is frequent
- QoL and patient-related outcome and experience measures (PROMs, PREMs) are increasingly used in routine clinical practice and as primary outcomes in research in the palliative setting.
- Several tools are available to assess these outcomes but none of them are specific for patients with PSM

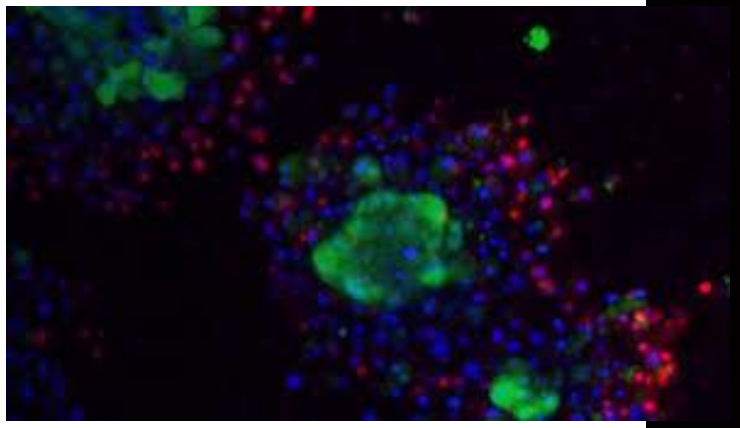


Quality of life

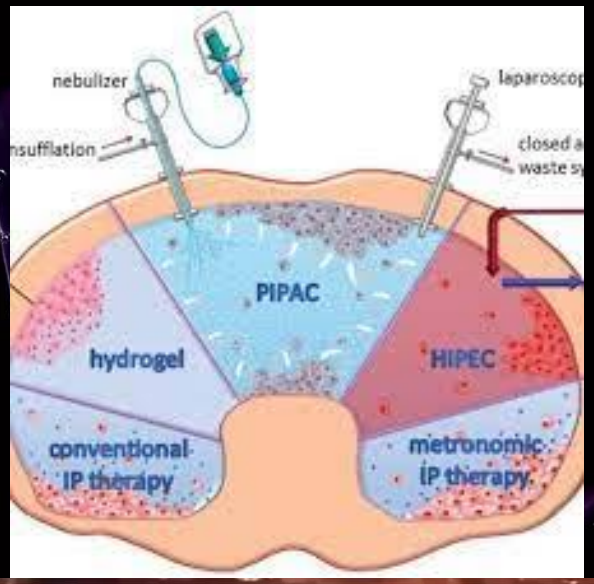
- Ongoing international efforts concentrate on the creation of dedicated tools to measure QoL and PROMs specifically for patients with PSM.
- These tools will have to be validated in different countries to account for socio-cultural diversity
- Curative setting: CRS & HIPEC
  - High risk of perioperative morbidity and mortality seems acceptable
  - Patients have to be aware of a transitory deterioration of QoL lasting ~6 months after surgery before getting back to baseline performance
- Palliative setting and in patients with limited life expectancy
  - QoL is more important
  - PIPAC has been shown to be a safe and feasible treatment option in patients with therapy-refractory disease who are not candidates for a potentially curative approach
    - 2/3 of patients objective treatment response
    - No negative effect on QoL
    - Symptoms improve in >50% of repeatedly treated patients who can gain additional quality life time and hope

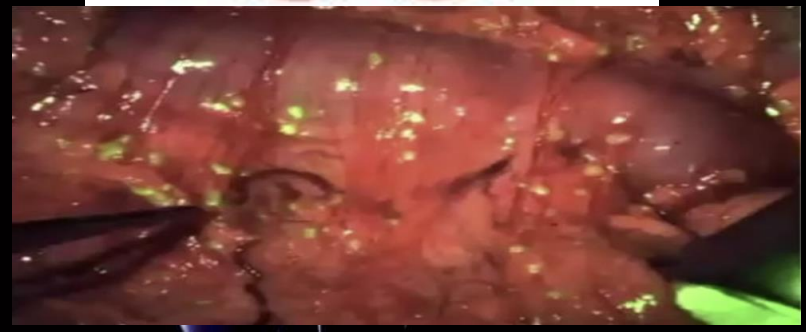
Outlook

Personalized Medicine



AI Day 2022





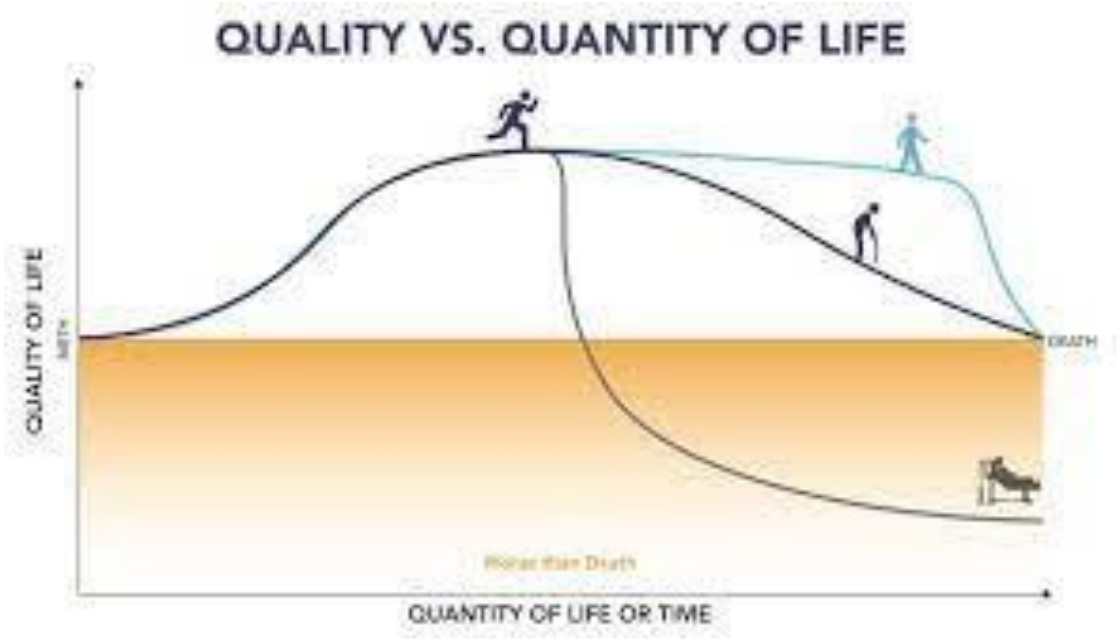
Surgical Innovations

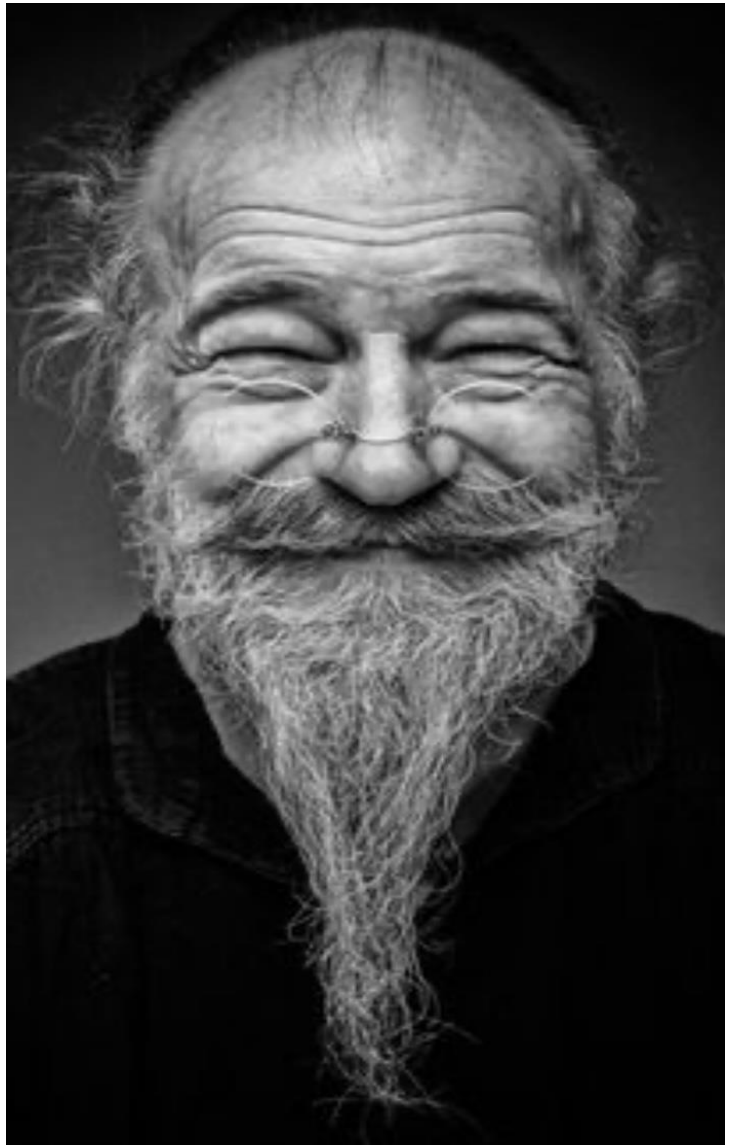
The Challenge of Clinical Trials in PSM

Top Research Priorities

Longevity

Happiness



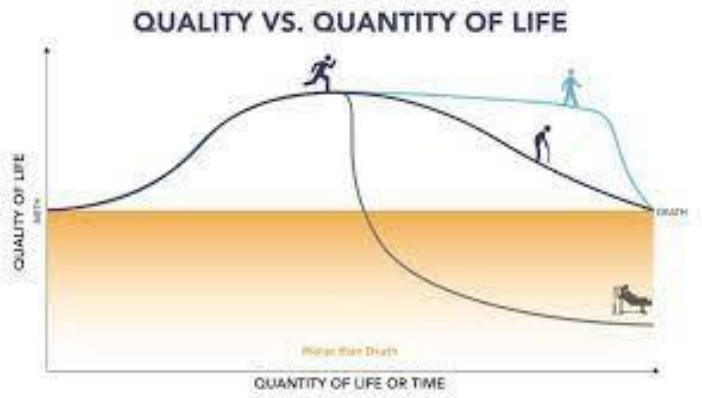


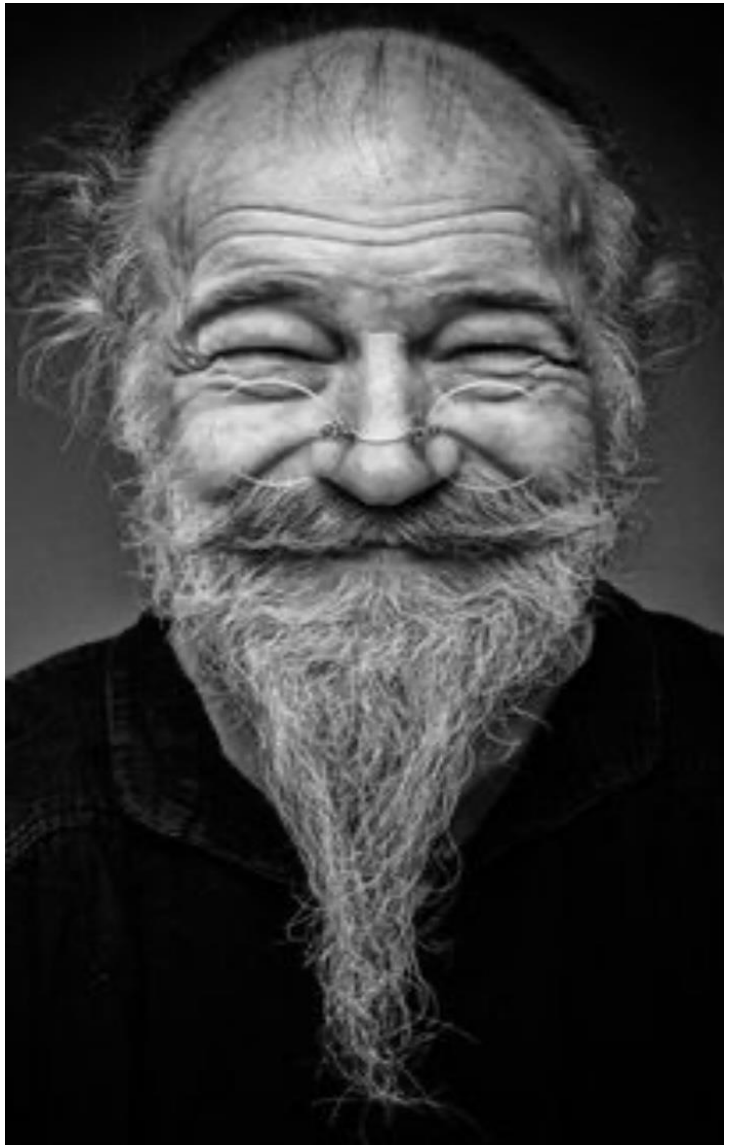
Top Research Priorities

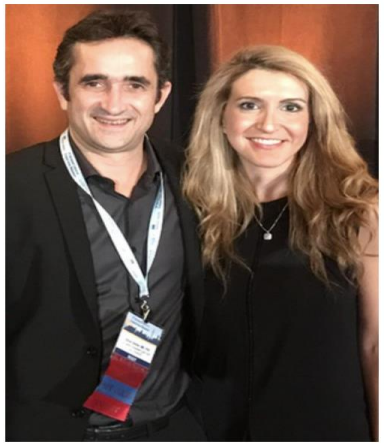
Longevity → improve survival, cure

Happiness → Patients QoL

Surgeons Number of good days







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Thank you ISSPP