

SAMO Interdisciplinary Workshop on Upper Gastrointestinal Tumors
15th and 16th November 2019, Hotel Hermitage, Lucerne

Gastric cancer

Peritoneal disease : What now ?

Pr Marc Pocard

- INSERM U.1275 : CAP Paris Tech : Carcinomatosis Peritoneum Paris Technology
- Oncological surgical unit = Lariboisière and Bégin Hospitals, Paris, France
- International Society for Study of Pleura and Peritoneum

Links of interest – Marc Pocard

- 2014 – 2019:

- **Advisory Board or Honoraria:**

Fisher & Payler, Gamida, Léo-Pharm, Novartis, Sanofi, Roche

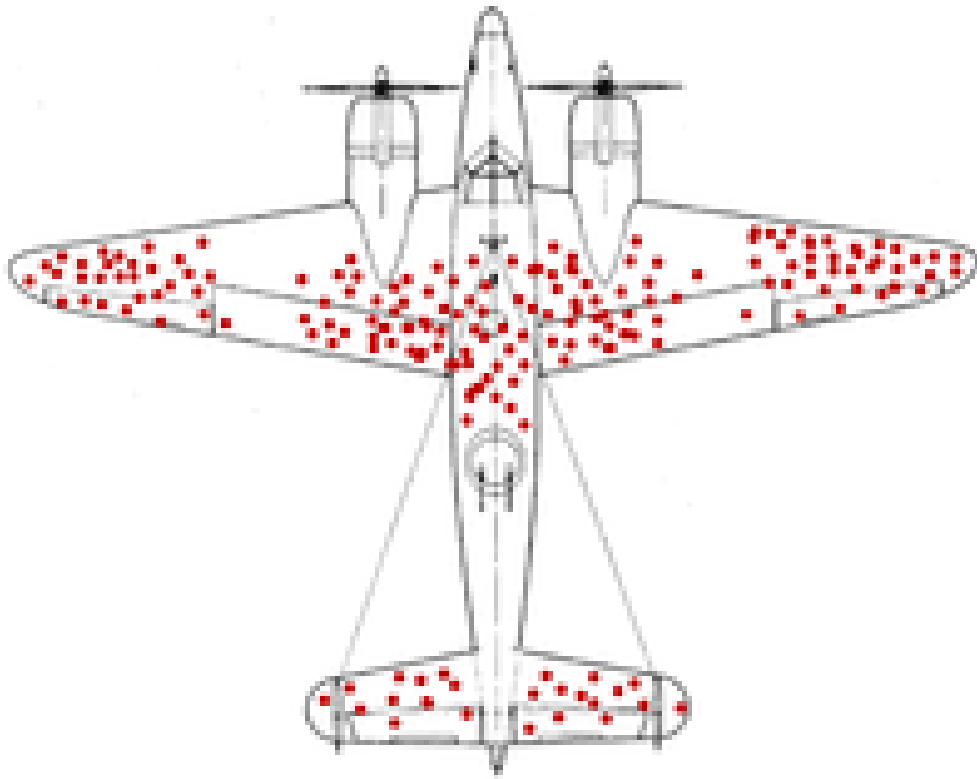
- **Award – congress – laboratory research grant:**

Capnomed, Clerad, Ethicon, Fujinon, Gamida, INSERMTransfert, Plasma-jet,
Roche, Sanofi, Sofra-médical, STAGO, Storz, Rand

Peritoneal metastasis – gastric cancer

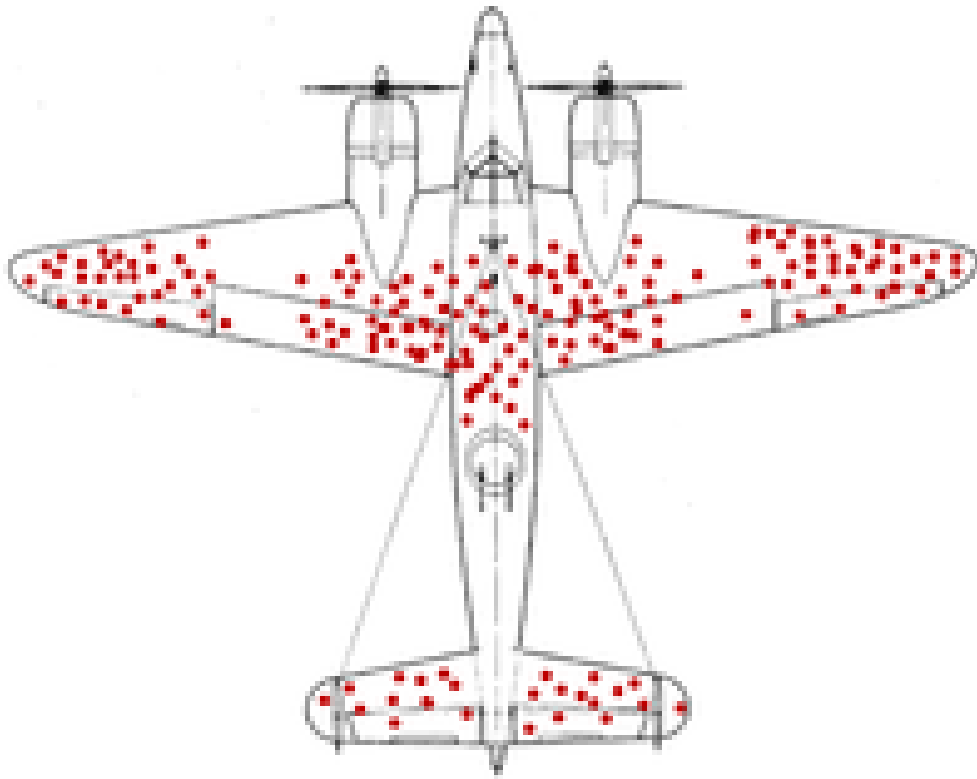
1. The survivorship bias: Hope change quality of life
2. Understand the spelling process: decrease the risk ?
3. Result of systemic chemotherapy: think about biology
4. The Hallmarks of oligometastatic disease: Application
5. The PIPAC innovation: Include in strategy

1. The survivorship bias



During World War II, Researchers from the Center for Naval Analyses had conducted a study of the damage done to aircraft that had returned from missions, and had recommended that armor be added to the areas that showed the most damage.

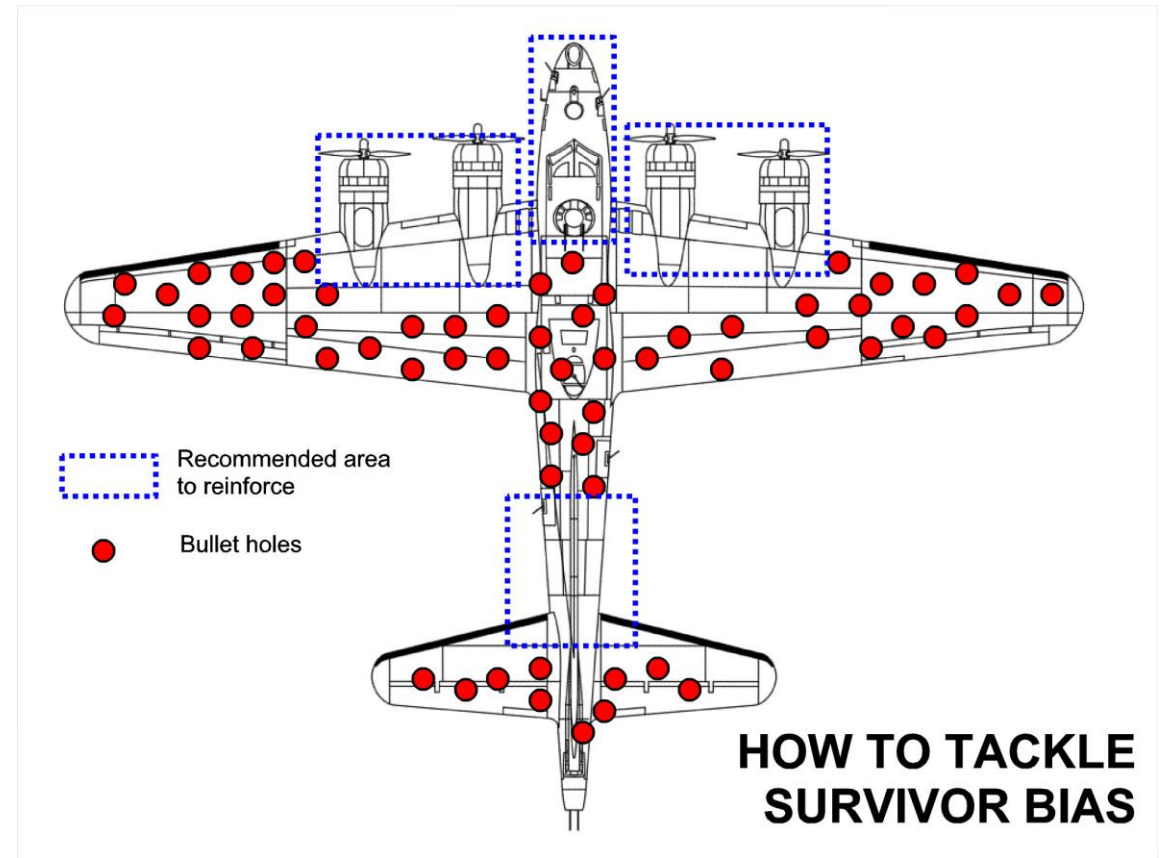
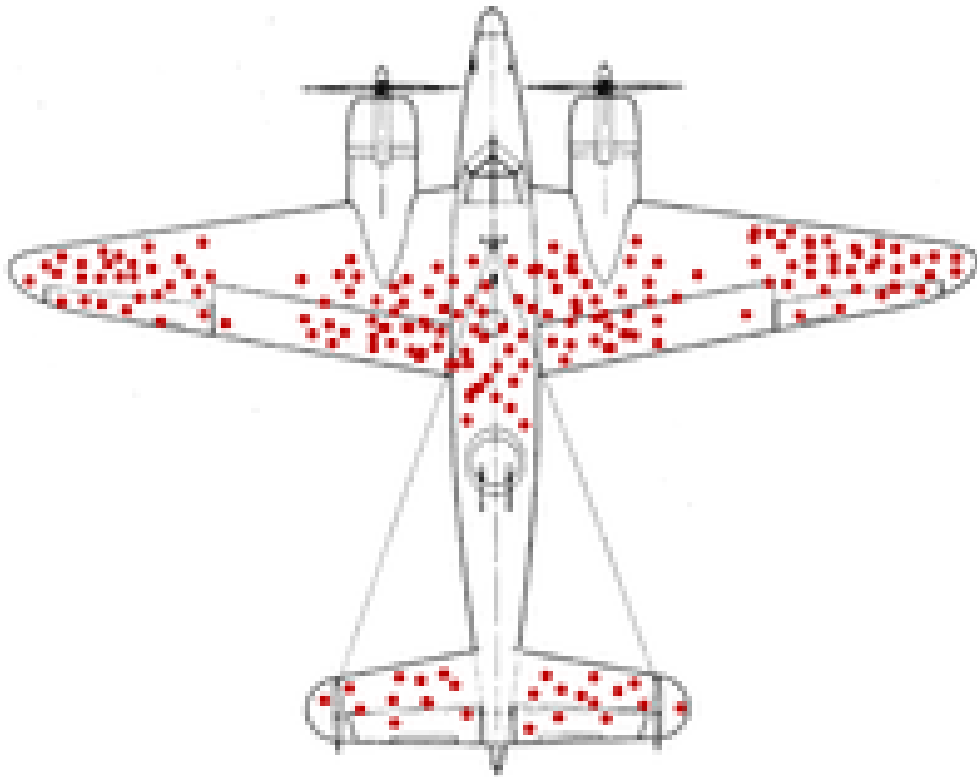
1. The survivorship bias



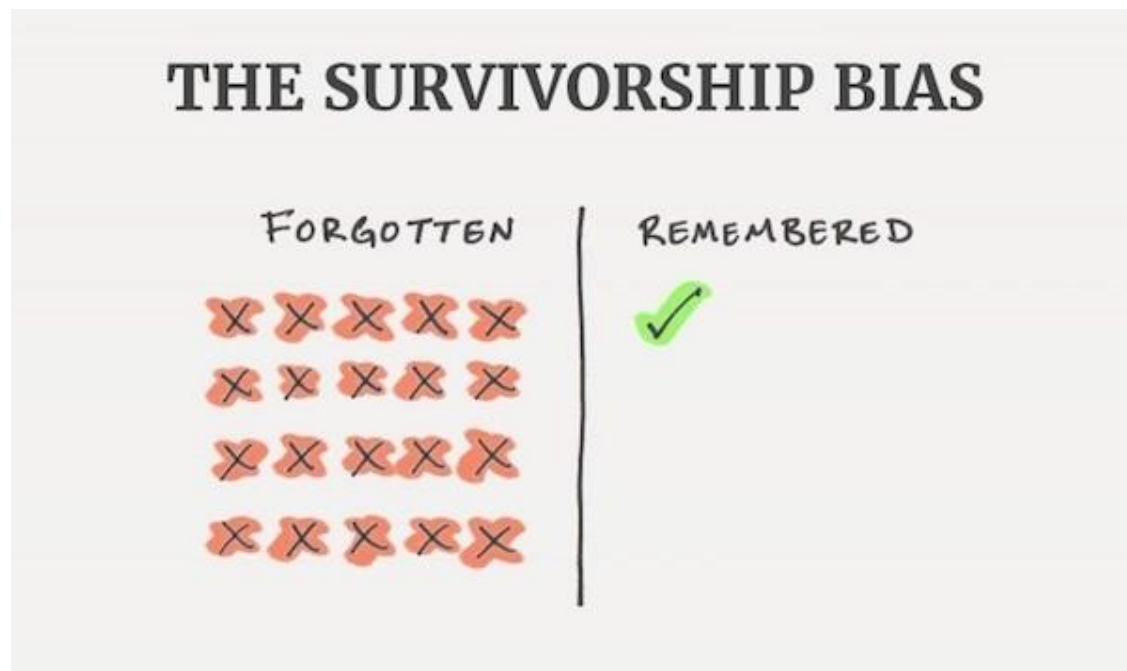
During World War II, Researchers from the Center for Naval Analyses had conducted a study of the damage done to aircraft that had returned from missions, and had recommended that armor be added to the areas that showed the most damage.

The statistician A Wald took survivorship bias
Wald noted that the study only considered the aircraft that had *survived* their missions

1. The survivorship bias



The survivorship bias.



Hope and Quality of life

Patient Education and Counseling 101 (2018) 59–66

Let's talk about empathy!

Léonore Robieux^{a,b,c,*}, Lucille Karsenti^a, Marc Pocard^{c,d}, Cécile Flahault^{a,e}

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2. Understand the spelling process

No touch technique is a surgical oncologic rule, but whatever the effort tissues have to be cut or sectioned resulting probably in a cells liberation because of lymphatic section. This situation was tested in a paper describing cell detection on peritoneum fluid during gastrectomy for gastric cancer.

More than half of the cases were no cell could be identified at the beginning of the surgery, cells are detected at the end of the gastrectomy. Therese cells have been studied and are able to growth on culture and to create a tumor if injected on nude mice.

Surgery-induced peritoneal cancer cells in patients who have undergone curative gastrectomy for gastric cancer. Takebayashi K, et al. Ann Surg Oncol. 2014;21:1991-7.

2. Understand the spelling process

However, cells detection on peritoneal fluid did not implicated that all patient presented a carcinomatosis during the follow up.

To create a carcinomatosis , peritoneum barrier had to be altered and local condition to be favourable.

But on the study, the 24 patients with viable cancer cells in the peritoneal cavity after gastrectomy showed higher peritoneal recurrence rate than those without them ($p=0.033$), 45% ($n=11/24$) versus 9% ($n=1/33$).

Surgery-induced peritoneal cancer cells in patients who have undergone curative gastrectomy for gastric cancer. Takebayashi K, et al. Ann Surg Oncol. 2014;21:1991-7.



Reduction of carcinomatosis risk using icodextrin as a carrier solution of intraperitoneal oxaliplatin chemotherapy

I. Jouvin ^{a,b}, H. Najah ^{a,b}, C. Pimpie ^b, C. Canet Jourdan ^b, R. Kaci ^c,
M. Mirshahi ^b, C. Eveno ^{a,b}, M. Pocard ^{a,b,*}

^a Department of Oncologic & Digestive Surgery, Hôpital Lariboisière – AP-HP, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France

^b Université Paris Diderot, Sorbonne Paris Cité, CART, Carcinomatosis Angiogenesis Translational Research, INSERM U965, F-75575 Paris, France

^c Department of Anatomopathology, Hôpital Lariboisière – AP-HP, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France

molecular
pharmaceutics

Article

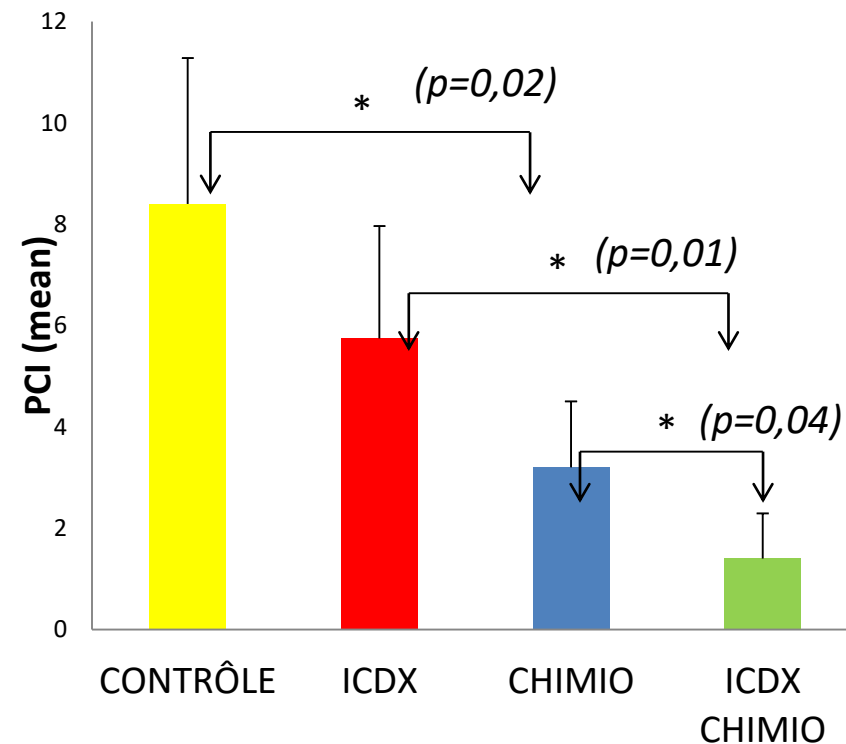
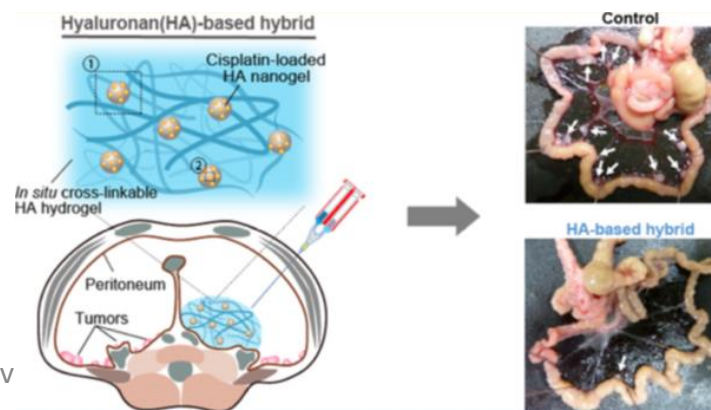
pubs.acs.org/molecularpharmaceutics

Intraperitoneal Delivery of Cisplatin via a Hyaluronan-Based Nanogel/*in Situ* Cross-Linkable Hydrogel Hybrid System for Peritoneal Dissemination of Gastric Cancer

Seiichi Ohta,[†] Shota Hiramoto,[‡] Yuki Amano,[§] Shigenobu Emoto,[¶] Hironori Yamaguchi,^{||}
Hironori Ishigami,[¶] Joji Kitayama,^{||} and Taichi Ito^{*,†,‡,§,||}

DOI: [10.1021/acs.molpharmaceut.7b00349](https://doi.org/10.1021/acs.molpharmaceut.7b00349)

Mol. Pharmaceutics 2017, 14, 3105–3113





GASTRICHIP

GASTRICHIP TRIAL

**D2 RESECTION AND HIPEC (HYPERTHERMIC INTRAPERITONEAL
CHEMOPERFUSION) IN LOCALLY ADVANCED GASTRIC CARCINOMA.
A RANDOMIZED AND MULTICENTRIC PHASE III STUDY**

Glehen et al. *BMC Cancer* 2014, **14**:183
<http://www.biomedcentral.com/1471-2407/14/183>



STUDY PROTOCOL

Open Access

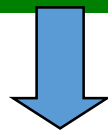
GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study

Olivier Glehen^{1,2*}, Guillaume Passot^{1,2}, Laurent Villeneuve^{3,4,5}, Delphine Vaudoyer^{1,2}, Sylvie Bin-Dorel^{3,4,5}, Gilles Boschetti⁶, Eric Piaton⁷ and Alfredo Garofalo⁸

GASTRICHIP

Randomized Multicentric Phase III

Gastric adenocarcinoma T3-T4 and/or
N+ and/or cyto + (laparoscopy and endoscopic
ultrasound)



Preoperative systemic
chemotherapy warranted

Indication of curative gastrectomy

Inclusion

RANDOMIZED



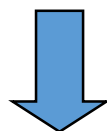
RANDOMIZED



Curative gastrectomy +
HIPEC oxaliplatin

Oxaliplatin 250 mg/m²

Curative gastrectomy



Postoperative adjuvant treatment

With courtesy O Glehen

Peritoneal metastasis – gastric cancer

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3. Result of systemic chemotherapy:

VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

- 9 months Survival
- 60% of non responder
- 70% of severe toxicity

Prospective, Randomized, Multicenter, Phase III Study of Fluorouracil, Leucovorin, and Irinotecan Versus Epirubicin, Cisplatin, and Capecitabine in Advanced Gastric Adenocarcinoma: A French Intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study

Rosine Guimbaud, Christophe Louvet, Pauline Ries, Marc Ychou, Emilie Maillard, Thierry André, Jean-Marc Gornet, Thomas Aparicio, Suzanne Nguyen, Ahmed Azzedine, Pierre-Luc Etienne, Eveline Boucher, Christine Rebischung, Pascal Hammel, Philippe Rougier, Laurent Bedenne, and Olivier Bouché

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VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

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Prospective Randomized Phase III Study of Fluorouracil, Irinotecan, and Cisplatin Versus Fluorouracil and Cisplatin in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: A French Intergroup (FFCD 99-03, EORTC 25952, and NCIC CTG N01-BT) Study

• MSI

• BRCA1 BRCA2

• HER2 +++++ Estrogen Receptor + + +

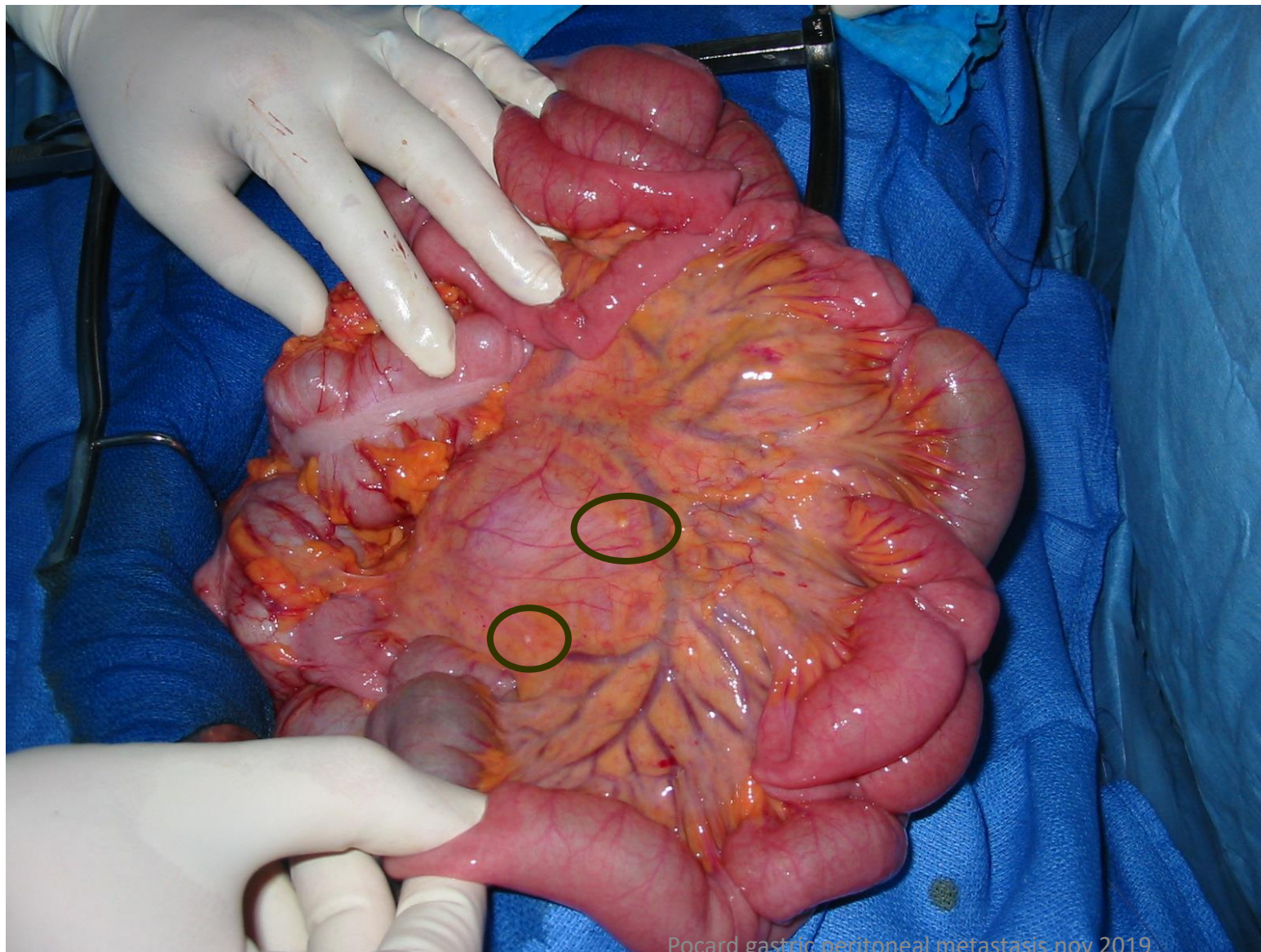
Groupe Coopérateur Multidisciplinaire en Oncologie) Study

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Patients and stories are so different

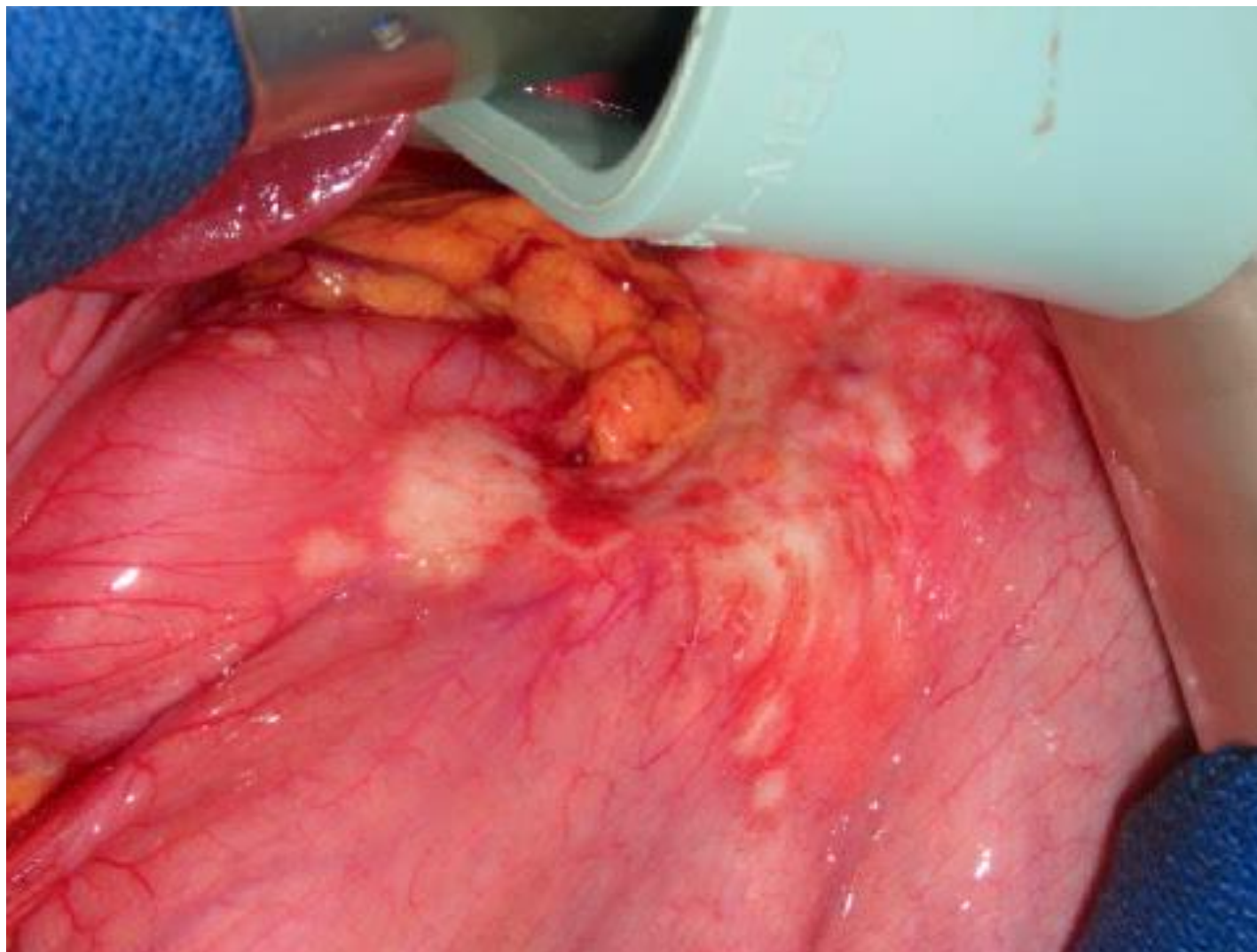


Very limited lesion PCI : 8

No CT detection

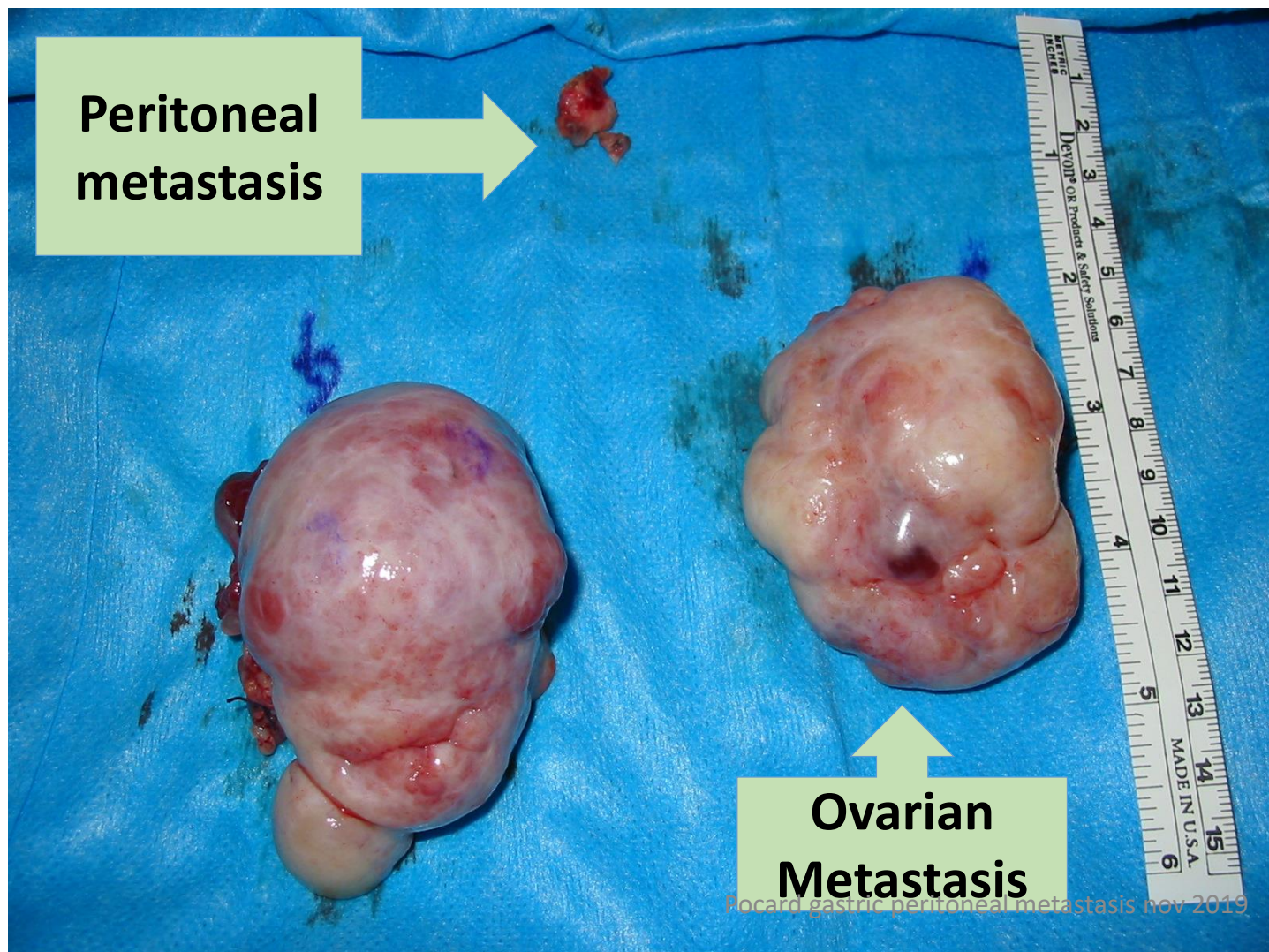
Only during laparotomy

Patients and stories are so different



Not extended disease
but
Gastric tumor is
shrinkable
and
Only palpation and
visual aspect
during laparotomy
Is an
Aggressive disease

Specific situation : ovarian metastasis did not exist
This is peritoneal metastatic process



Not extended disease
But

Associated with easy
diagnosis using CT and
clinical difficulty with big
ovarian lesion

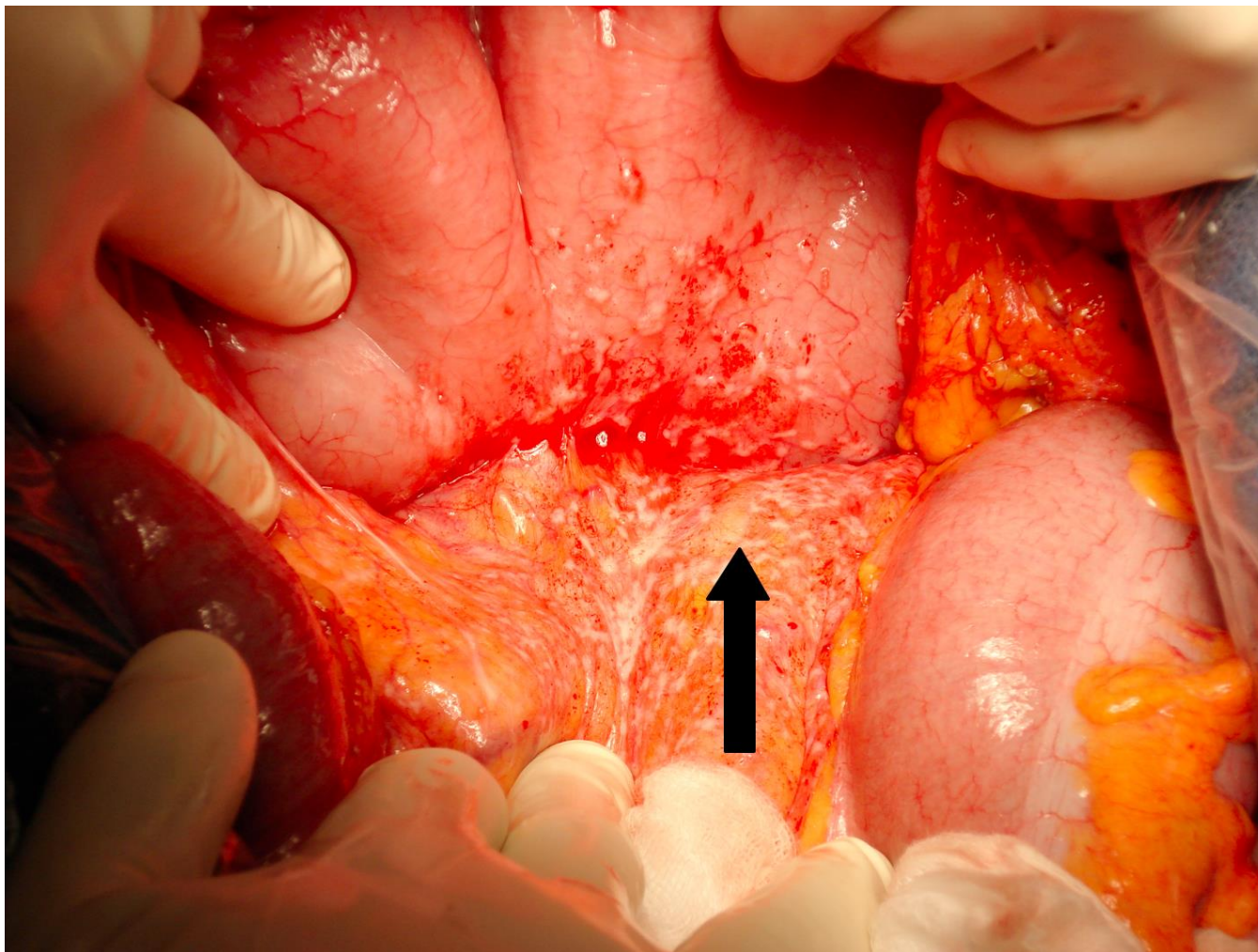
Specific situation : gastric occlusion requiring a stent



Clinical course

are always stronger and better prognosis marker than CT

Specific situation : gastric occlusion requiring a stent



Clinical course

are always stronger and better prognosis marker than CT

Extended peritoneal metastasis with no surgical resection possible CC2

CCO and PCI : nothing better ?

Ann Surg Oncol (2016) 23:1971–1979
DOI 10.1245/s10434-015-5081-3

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

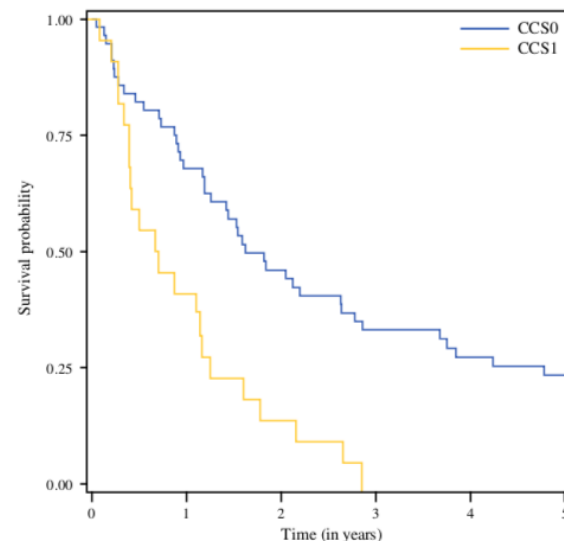
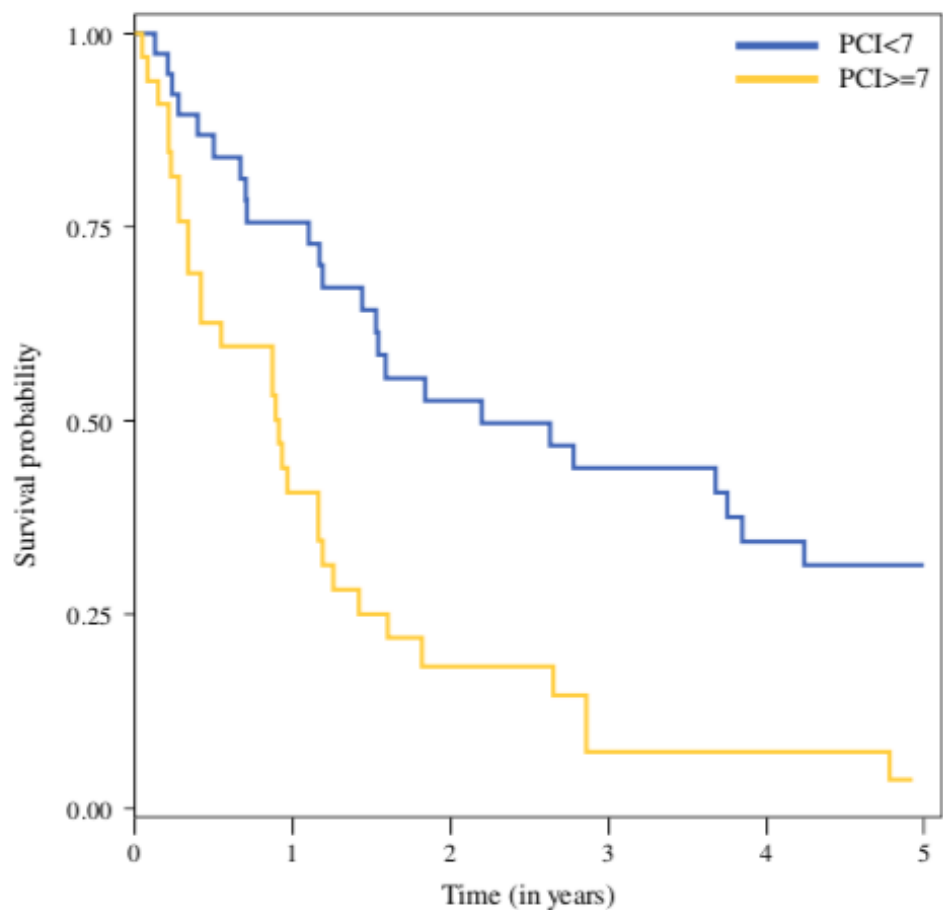


ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Patients with Peritoneal Carcinomatosis from Gastric Cancer Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is Cure a Possibility?

C. S. Chia, MBBS, MMed, FRCS¹, B. You, MD, PhD^{2,11}, E. Decullier, PhD^{3,4,5}, D. Vaudoyer, MD¹, G. Lorimier, MD⁶, K. Abboud, MD^{7,11}, J.-M. Bereder, MD⁸, C. Arvieux, MD, PhD^{9,11}, G. Boschetti, MD¹⁰, O. Glehen, MD, PhD^{1,11,12} and the BIG RENAPE Group

CCO and PCI : nothing better ?



PCI < 7

CRS complet CC0

(88 %). The 5-year overall survival (OS) rate was 18 %, with nine patients still disease-free at 5 years, for a cure rate of 11 %. All ‘cured’ patients had a PCI score below 7 and a CCS of 0. Factors associated with improved OS on multivariate analysis were synchronous resection ($p = 0.02$), a lower PCI score ($p = 0.12$), and the CCS ($p = 0.09$).

4. The hallmarks of Oligometastatic disease : how to make a choice

Patient P Status

Surgical Complexity

Clinical course

Biology

4. The hallmarks of Oligometastatic disease : how to make a choice

Patient P Status

Surgical Complexity

Clinical course

Biology

No indication

Discussion

Indication

4. The hallmarks of Oligometastatic disease : how to make a choice

Patient P Status

Clinical course

Surgical Complexity

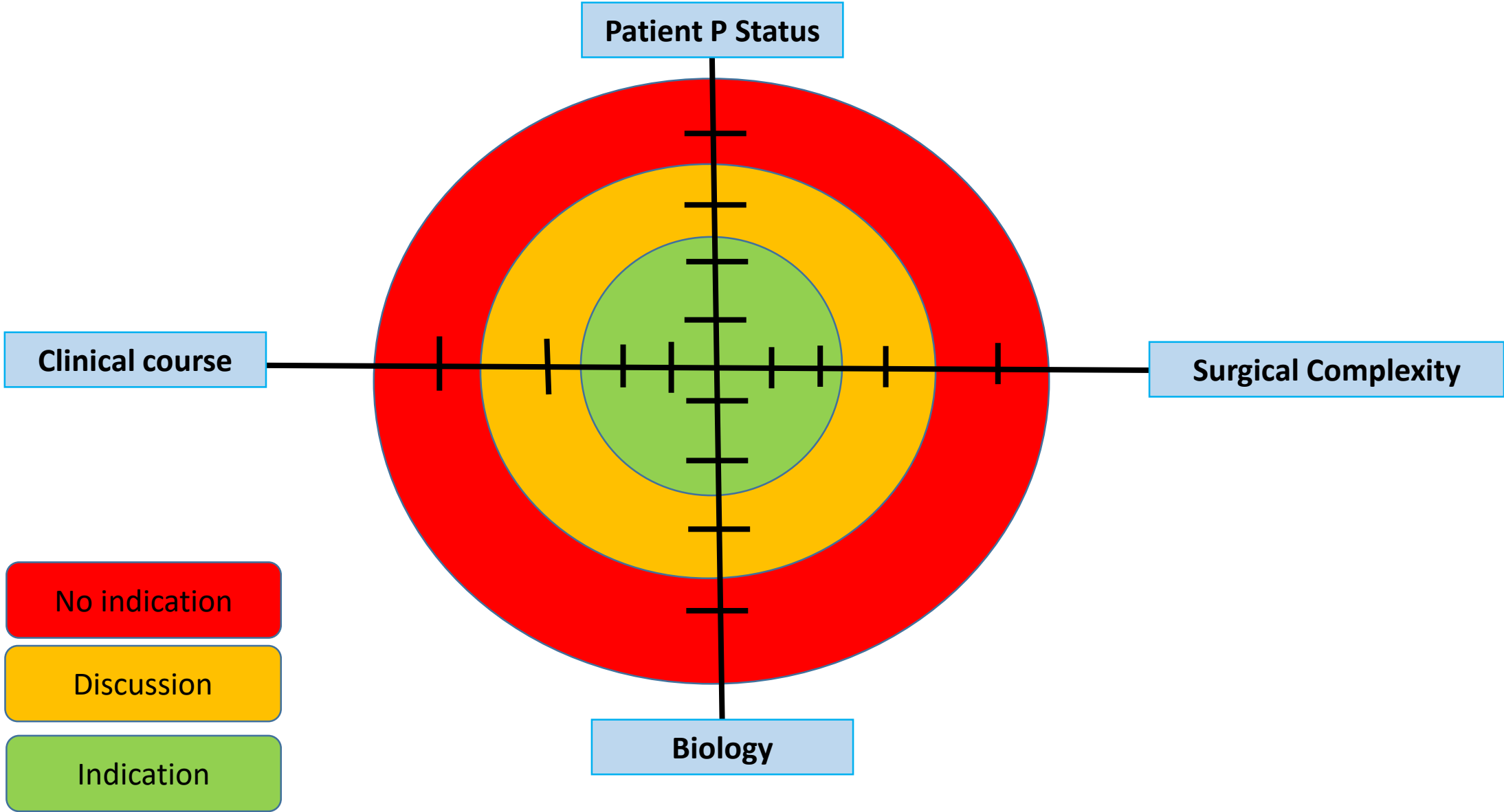
No indication

Discussion

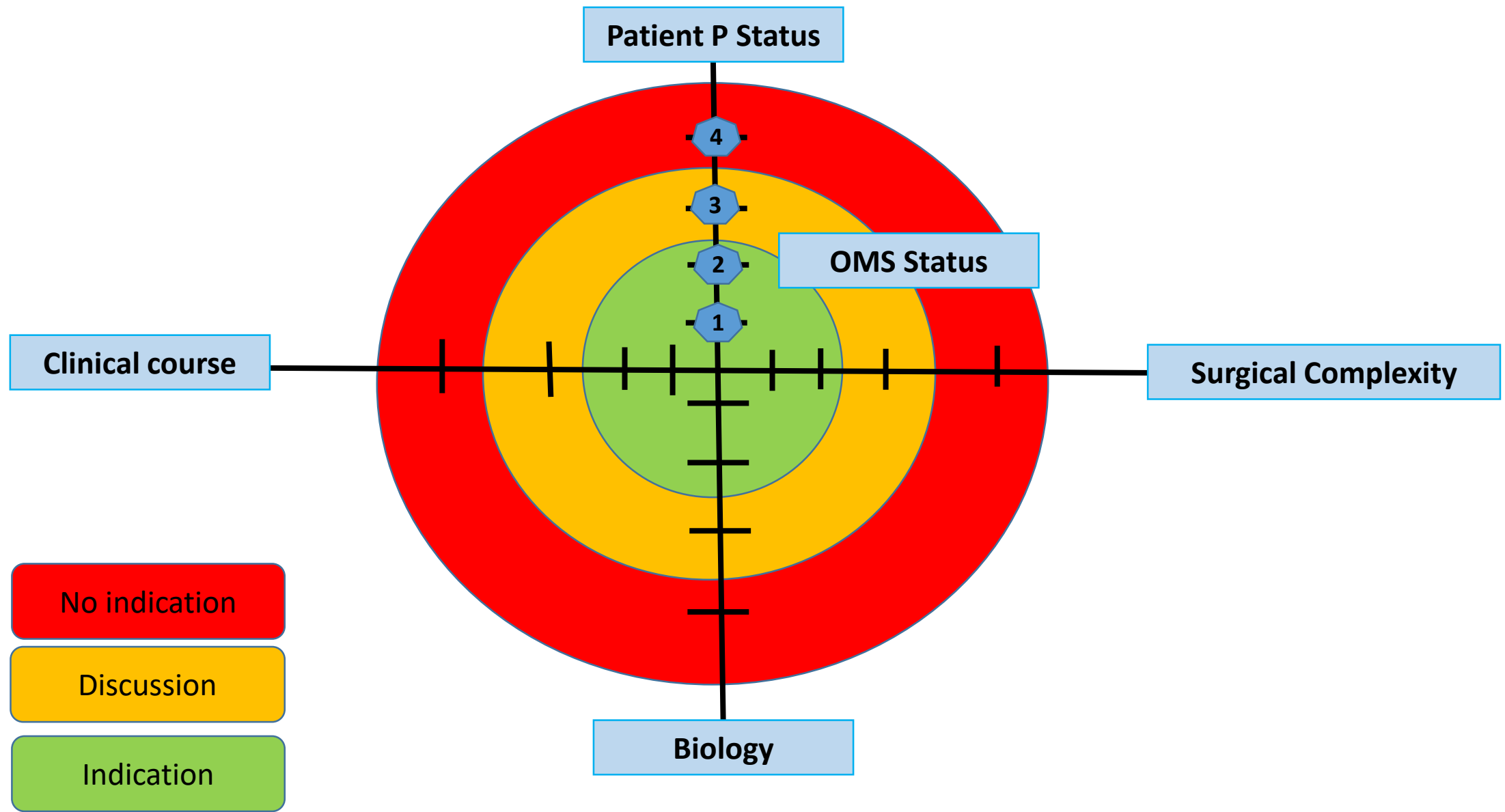
Indication

Biology

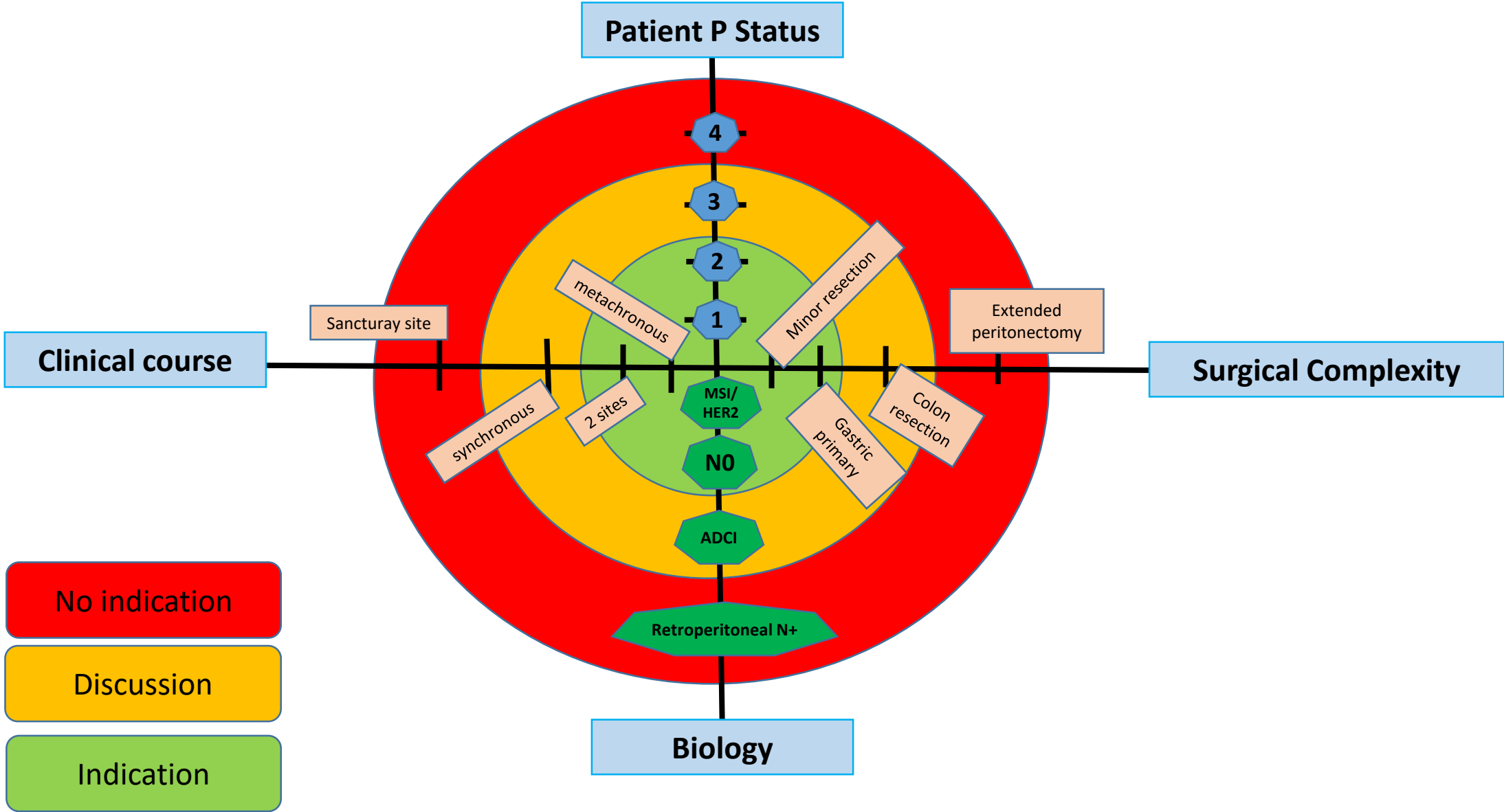
4. The hallmarks of Oligometastatic disease : how to make a choice



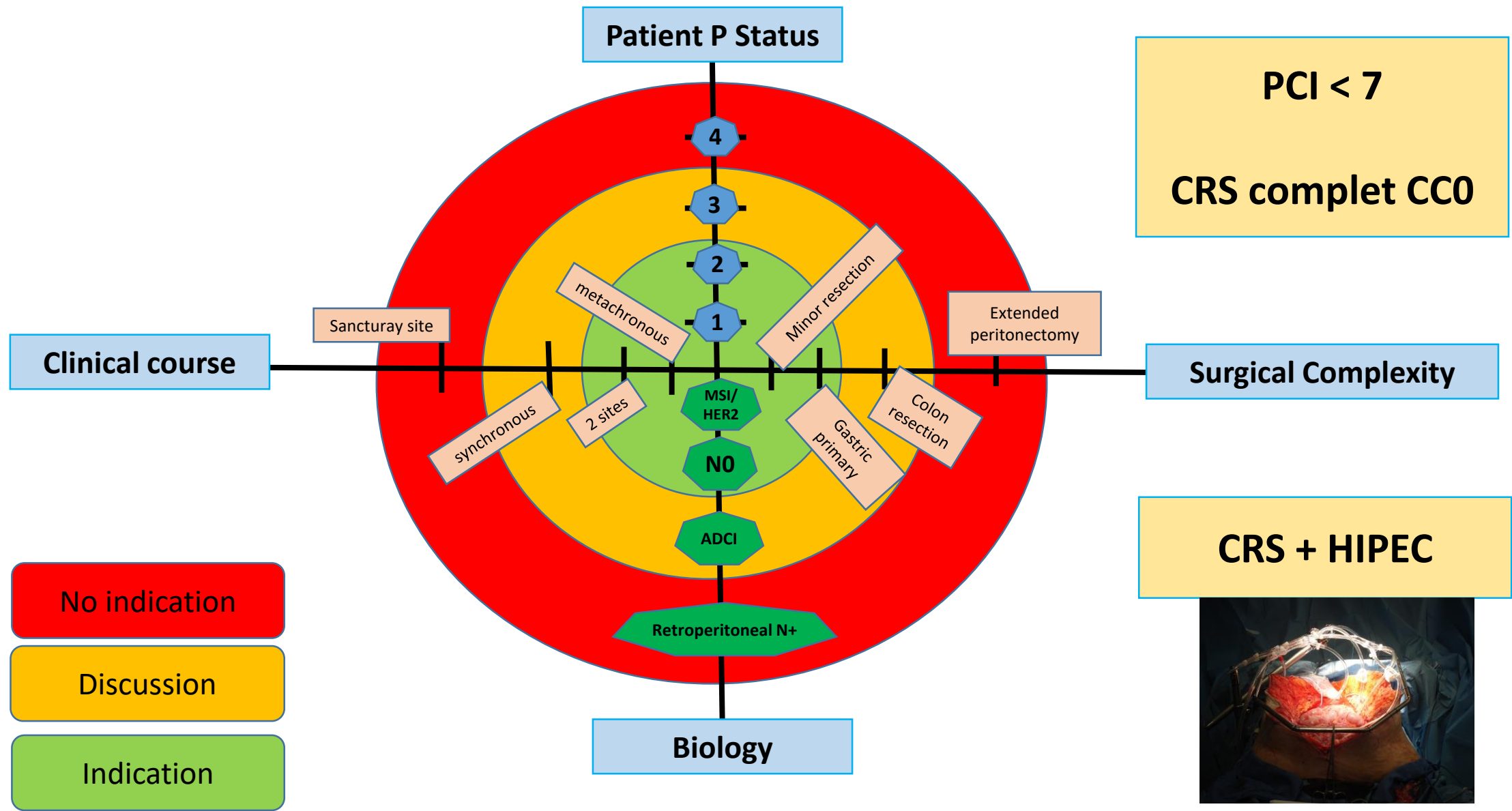
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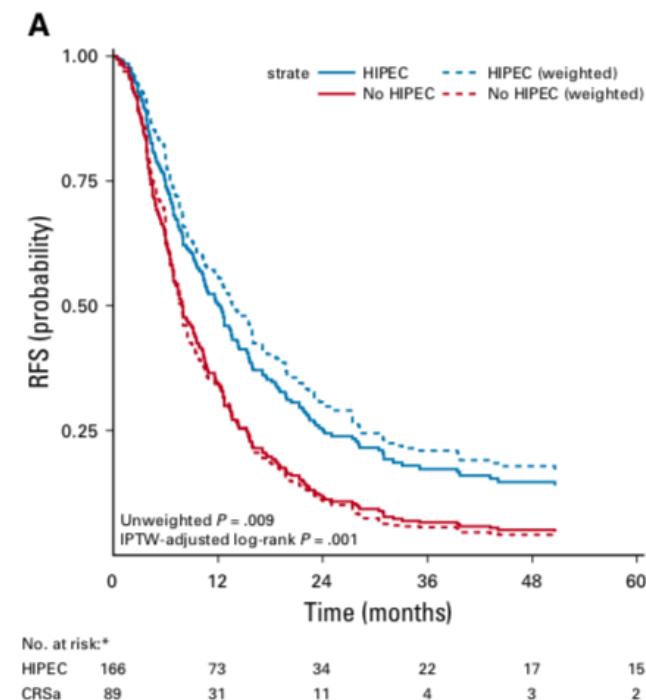
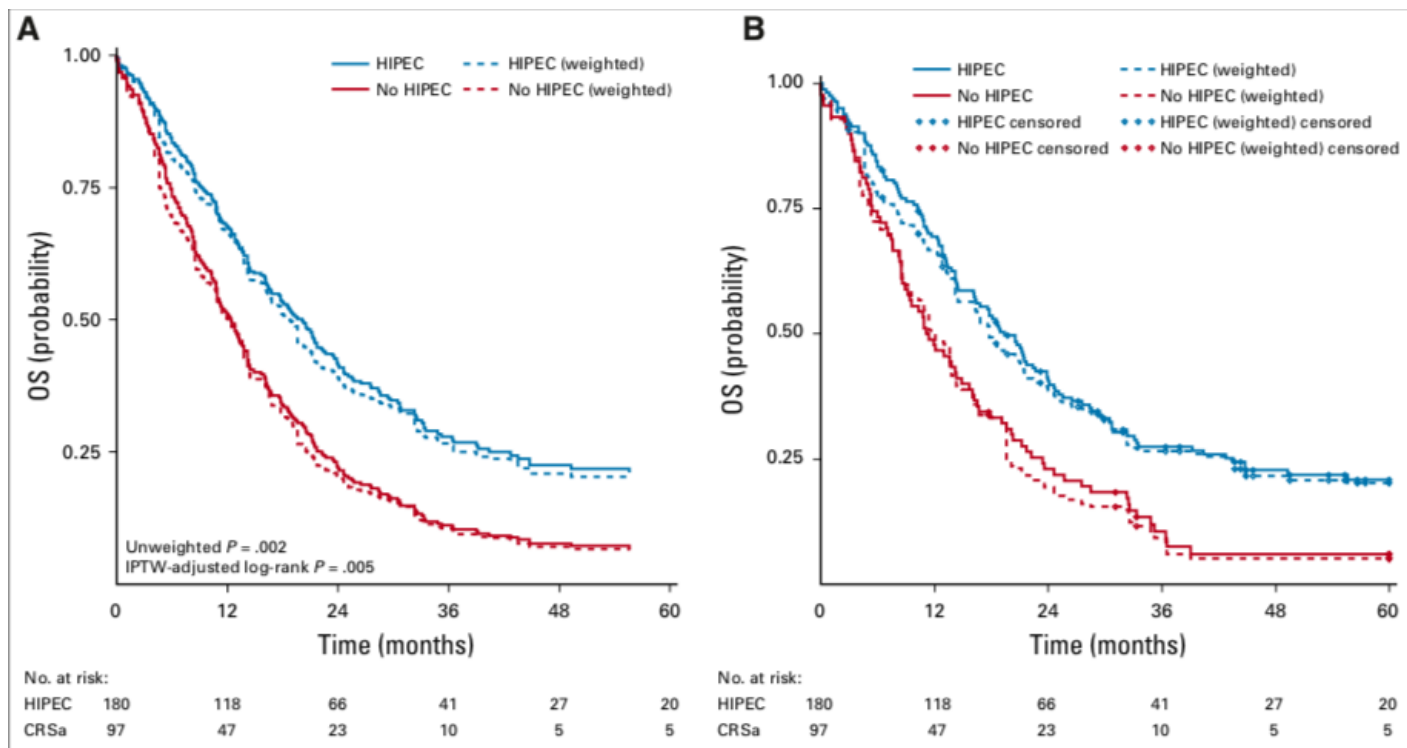
4. The hallmarks of Oligometastatic disease :

Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer With Peritoneal Metastases (CYTO-CHIP study): A Propensity Score Analysis

Pierre-Emmanuel Bonnot, MD^{1,2}; Guillaume Piessen, MD, PhD³; Vahan Kepenekian, MD^{1,2}; Evelyne Decullier, PhD⁴;
Marc Pocard, MD, PhD⁵; Bernard Meunier, PhD⁶; Jean-Marc Bereder, MD⁷; Karine Abboud, MD⁸; Frédéric Marchal, MD, PhD⁹;
François Quenet, MD¹⁰; Diane Goere, MD, PhD¹¹; Simon Msika, MD, PhD¹²; Catherine Arvieux, MD, PhD¹³; Nicolas Pirro, MD, PhD¹⁴;
Romuald Wernert, MD¹⁵; Patrick Rat, MD, PhD¹⁶; Johan Gagnière, MD, PhD¹⁷; Jeremie H. Lefevre, MD, PhD¹⁸; Thomas Courvoisier, MD¹⁹;
Reza Kianmanesh, MD, PhD²⁰; Delphine Vaudoyer, MD^{1,2}; Michel Rivoire, MD, PhD²¹; Pierre Meeus, MD²¹;
Guillaume Passot, MD, PhD^{1,2}; and Olivier Glehen, MD, PhD^{1,2}; on behalf of the FREGAT and BIG-RENAPE Networks

Journal of Clinical Oncology®

2019 Aug 10;37(23):2028-2040.

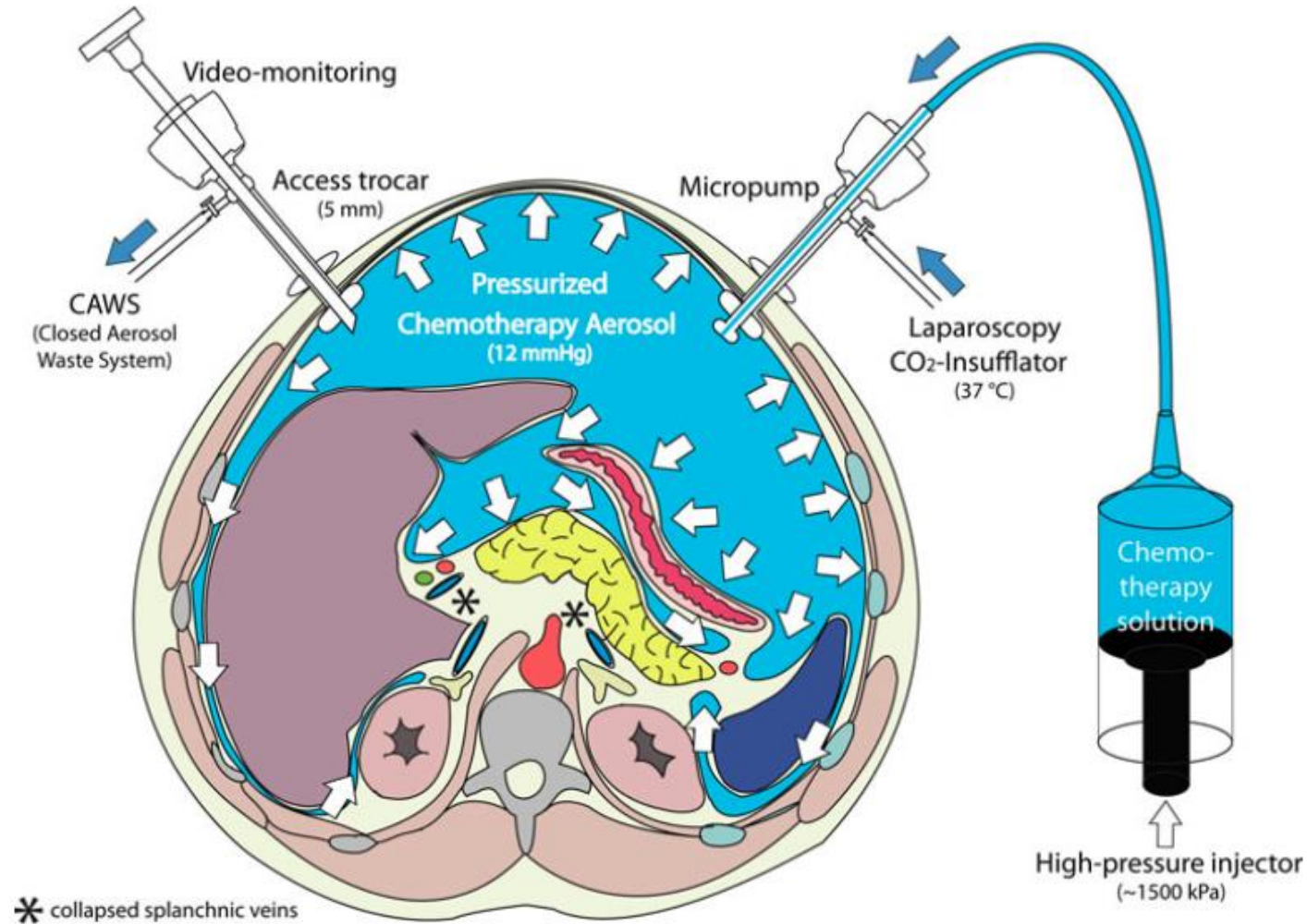


RESULTS After IPTW adjustment, the groups were similar, except that median peritoneal cancer index remained higher in the CRS-HIPEC group (6 v 2; $P = .003$). CRS-HIPEC improved overall survival (OS) in both crude and IPTW models. Upon IPTW analysis, in CRS-HIPEC and CRSa groups, median OS was 18.8 versus 12.1 months, 3- and 5-year OS rates were 26.21% and 19.87% versus 10.82% and 6.43% (adjusted hazard ratio, 0.60; 95% CI, 0.42 to 0.86; $P = .005$), and 3- and 5-year recurrence-free survival rates were 20.40% and 17.05% versus 5.87% and 3.76% ($P = .001$), respectively; the groups did not differ regarding 90-day mortality (7.4% v 10.1%, respectively; $P = .820$) or major complication rate (53.7% v 55.3%, respectively; $P = .496$).

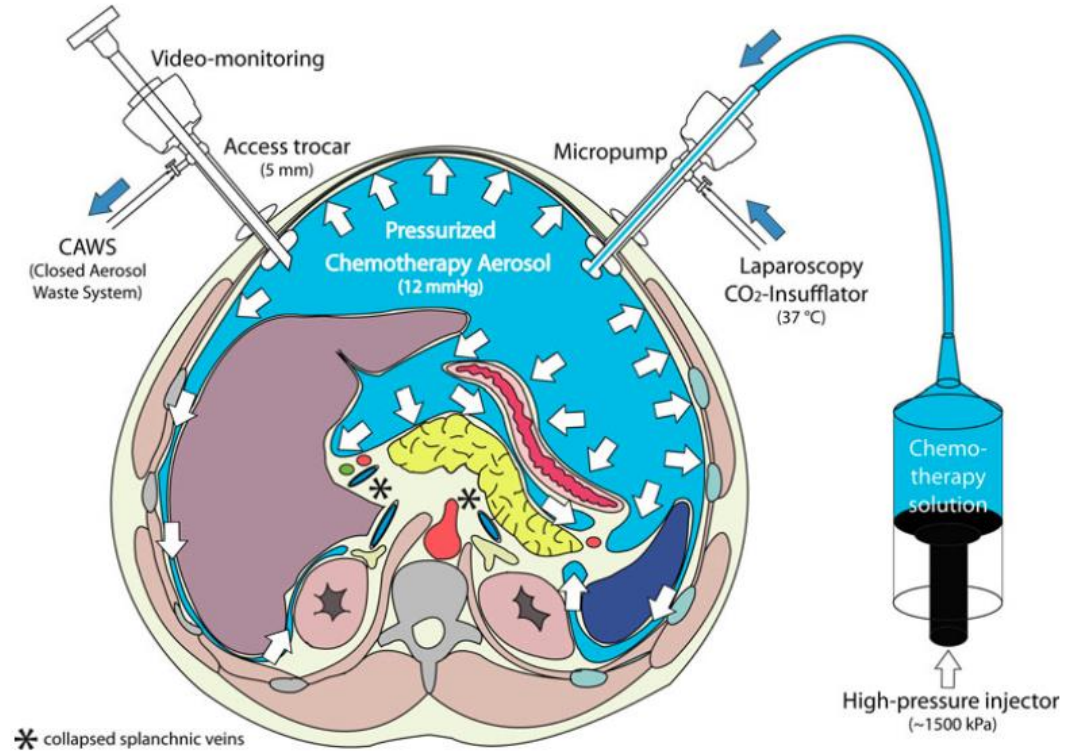
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Pressurized Intra Peritoneal Aerosol Chemotherapy: PIPAC



Pressurized Intra Peritoneal Aerosol Chemotherapy: PIPAC



1st PIPAC Nov 5th, 2011
Bielefeld Deutschland



Pressurized Intra Peritoneal Aerosol Chemotherapy: PIPAC

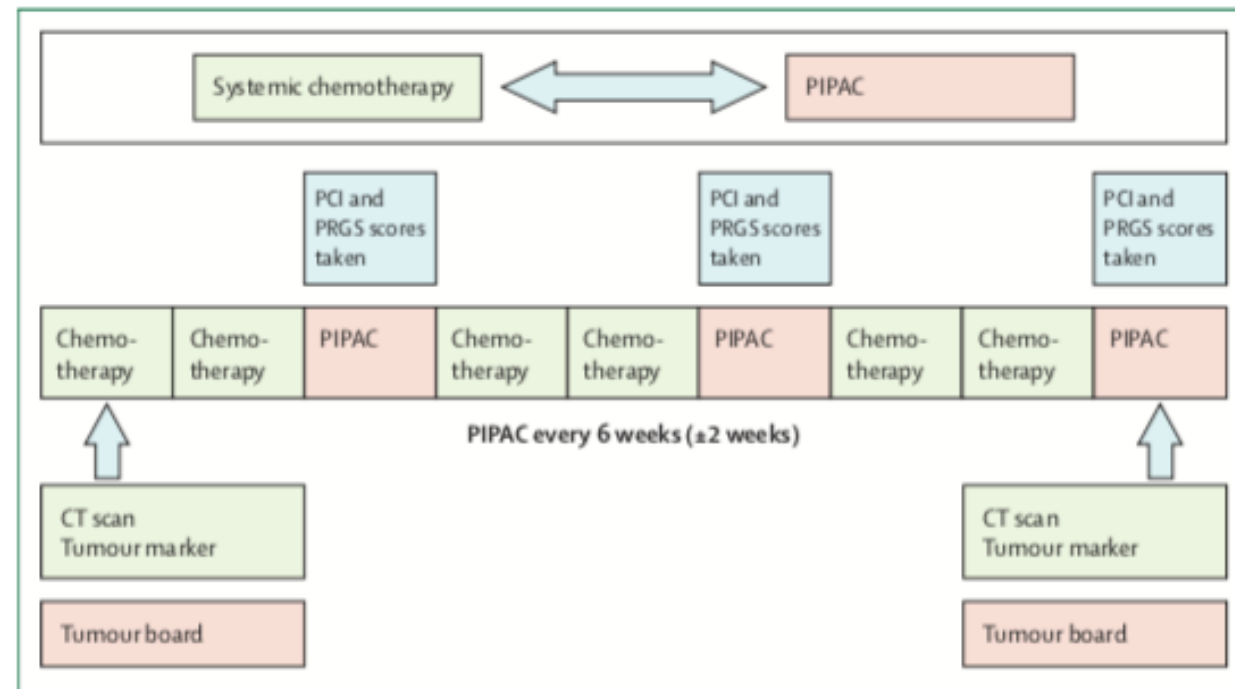
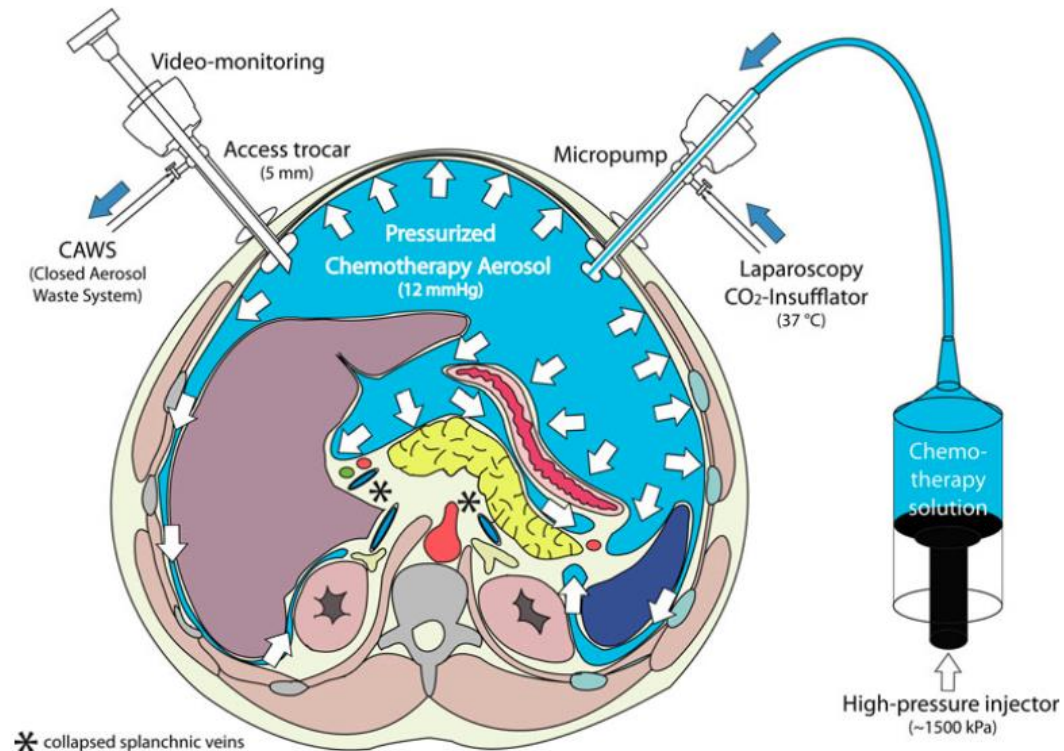
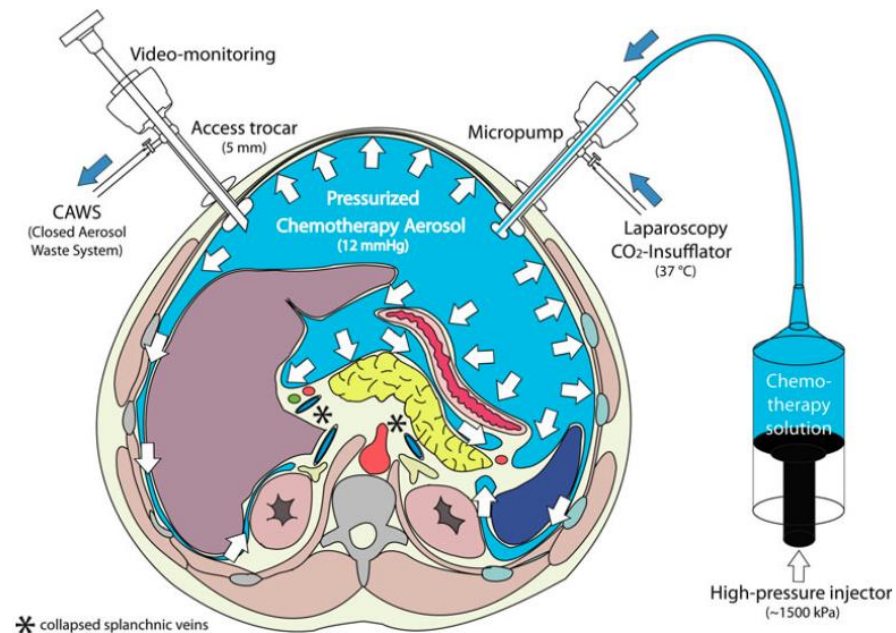


Figure 3: Concomitant systemic and intraperitoneal treatment

Suggested treatment schedule for PIPAC every 6 weeks (±2 weeks), alternating with systemic chemotherapy. PIPAC=pressurised intraperitoneal aerosol chemotherapy. PCI=peritoneal cancer index. PRGS=peritoneal regression grading score.

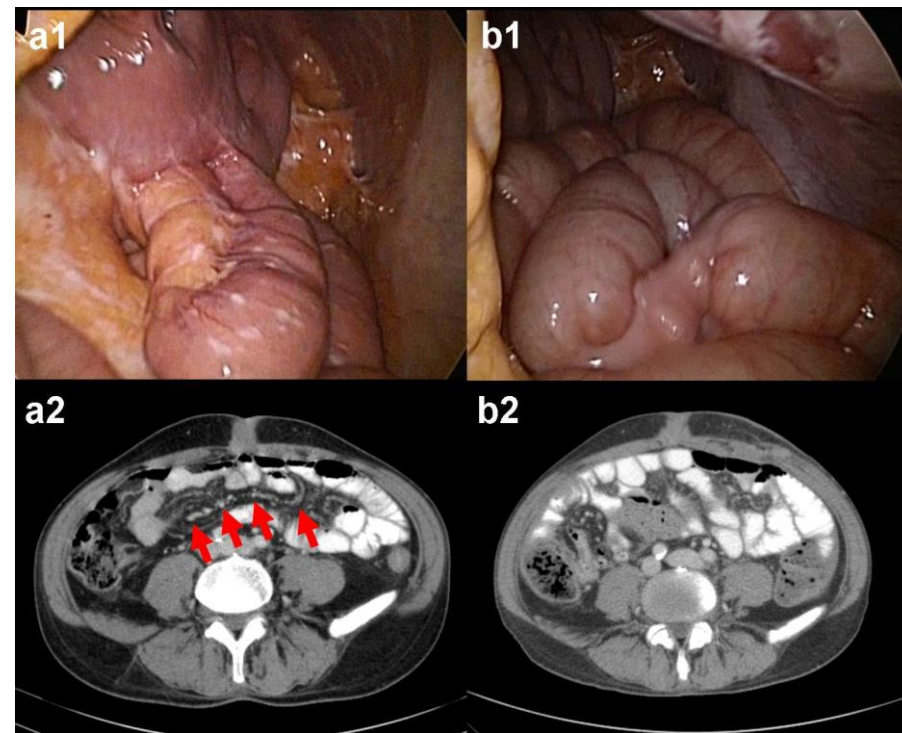
Alyami M, et al. Lancet Oncol 2019 Jul;20(7):e368-e377.

Pressurized Intra Peritoneal Aerosol Chemotherapy: PIPAC



PIPAC # 1

PIPAC # 4



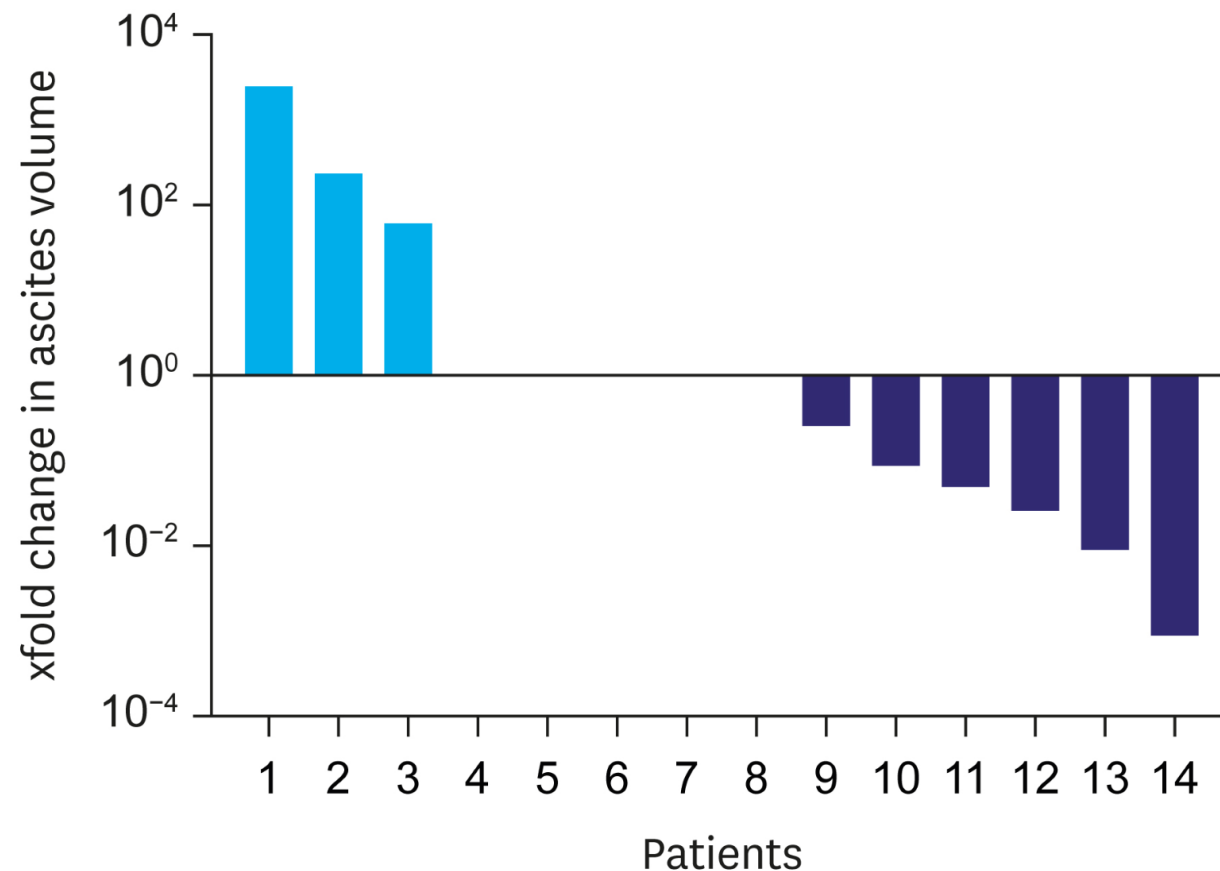
53 y.o. patient with signet ring gastric cancer,



Pressurized Intraperitoneal Aerosol Chemotherapy (**PIPAC**) in **Gastric** Cancer Patients with Peritoneal Metastasis (PM): Results of a Single-Center Experience and Register Study.

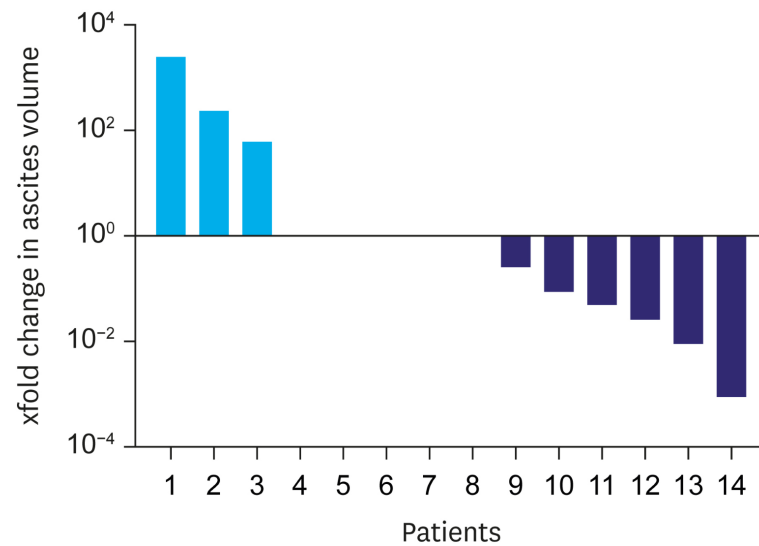
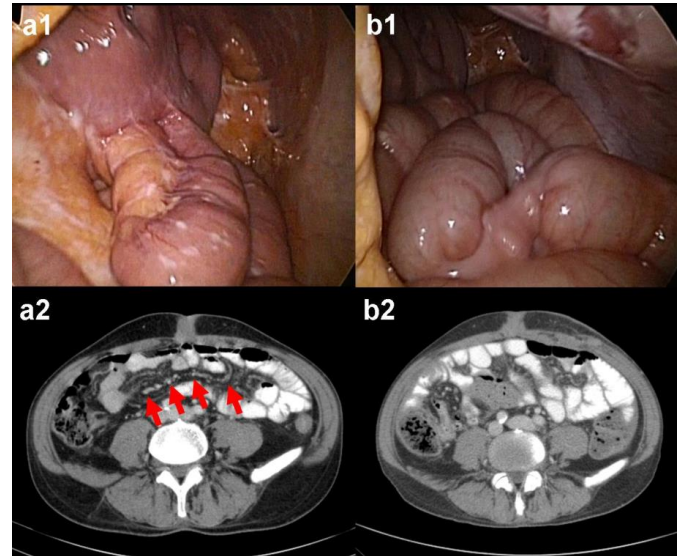
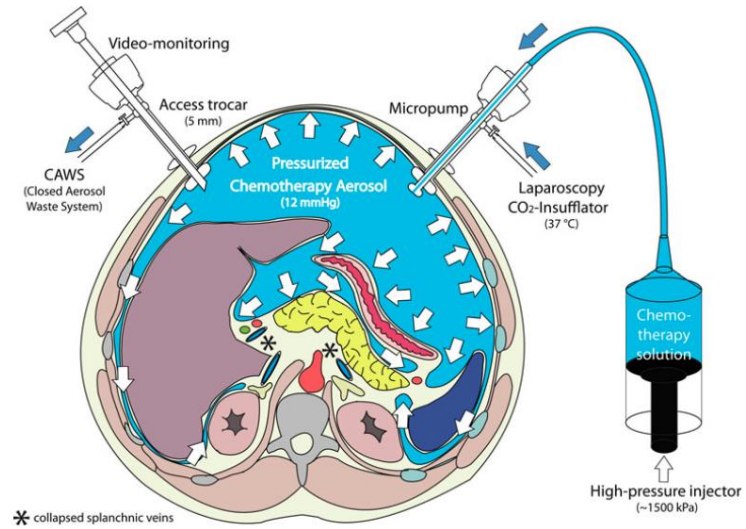
Gockel I, Jansen-Winkel B, Haase L, Rhode P, Mehdorn M, Niebisch S, Moulla Y, Lyros O, Lordick F, Schierle K, Wittekind C, Thieme R.

J Gastric Cancer. 2018;18:379-91.



Relative ascites development in patients with multiple PIPAC procedures.

Pressurized Intra Peritoneal Aerosol Chemotherapy: PIPAC



Pressurized Intra Peritoneal Aerosol Chemotherapy: PIPAC

Paris experience / Lariboisière Hospital : 2016 - 2018

- 75 PIPACs were performed for 27 patients with a median age of 58 years (28 - 72).
- All had at least one PIPAC, 85% at least 2 (n=23), 63% at least 3 (n=17) (1 - 6).
- The maximum duration of the control was 11 months, with one patient waiting for her seventh PIPACs.
- The major morbidity was 1.4% (1 evisceration), no mortality.
- The median duration between the 2 PIPACs was 47 days (extr 31 - 67).
- For two patients, disease control authorized a proposal for secondary cytoreduction surgery with HIPEC.



P.A. Hertsen Moscow Research Oncological Institute – branch
of the National Medical Research Center of Radiology,
Moscow, Russia



PIPAC

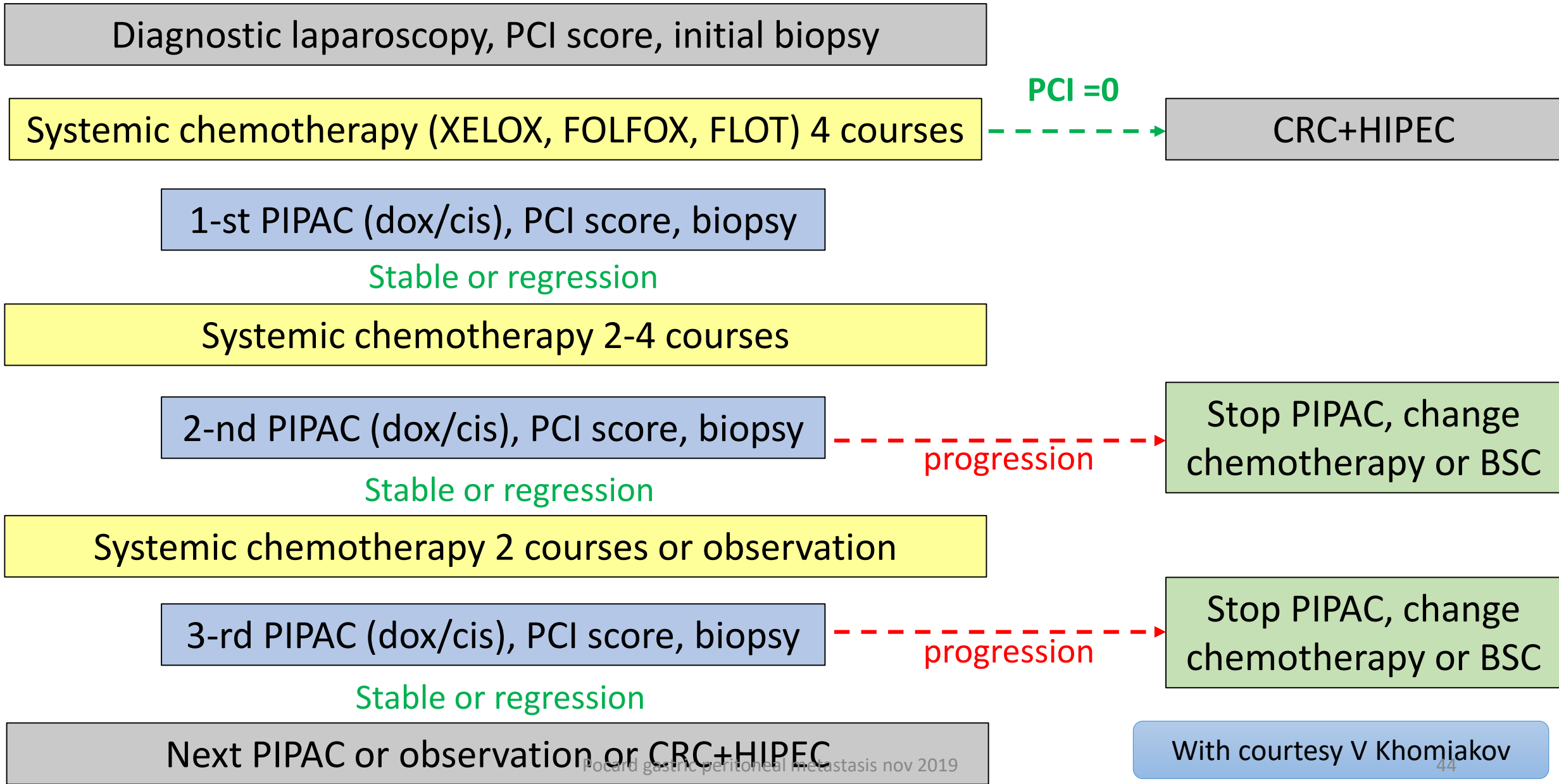
a novel approach for treatment
of peritoneal carcinomatosis

Vladimir Khomiakov

Head of Thoracoabdominal Surgical Department
Head of the National Centre for Treatment of Patients with
Peritoneal Carcinomatosis

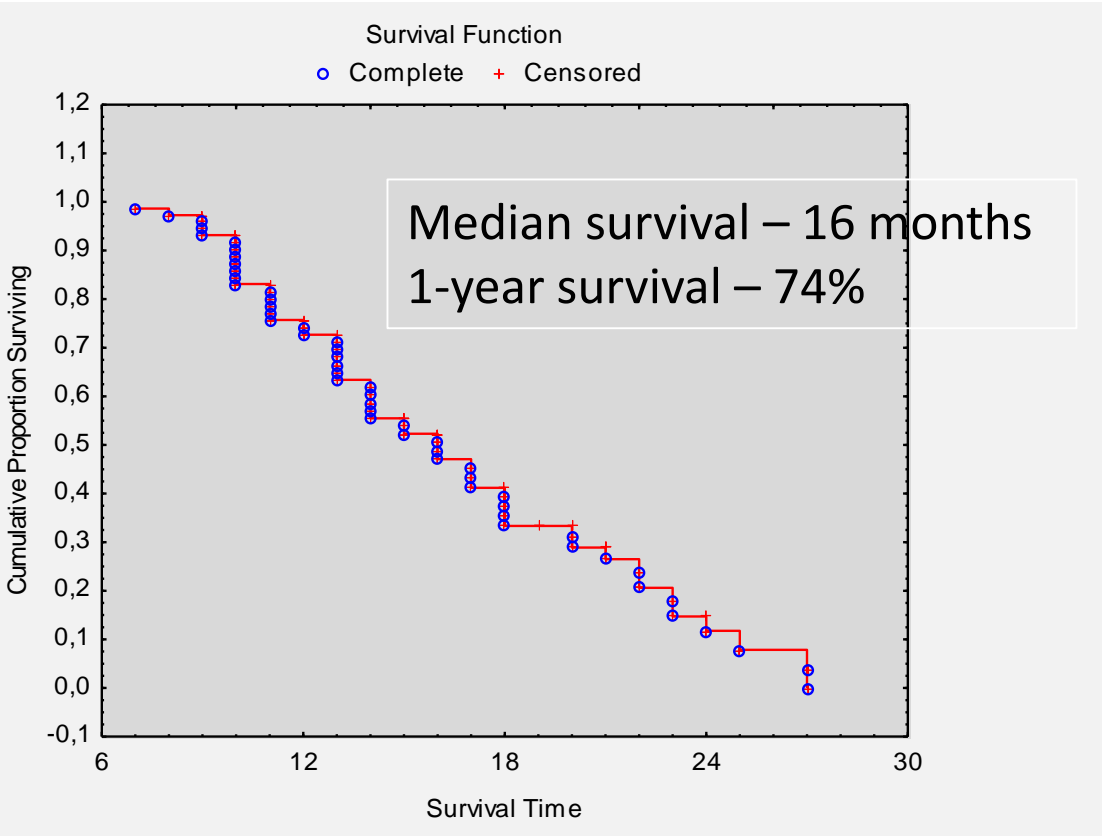


Treatment protocol for Gastric Cancer with PC



Chemotherapy before PIPAC		
4 XELOX/FOLFOX (treatment protocol 1)	83	57.6
4 FLOT/DCF (treatment protocol 1 new)	25	17.4
Other regimens (treatment protocol 2)	36	25
≥2 lines chemotherapy	49	34.1
Number of PIPAC sessions per patient (1-8)		
1	58	39.4
2	27	18.4
3	34	23.1
4	15	10.2
5	7	4.8
6	2	1.4
7	2	1.4
8	1	0.7

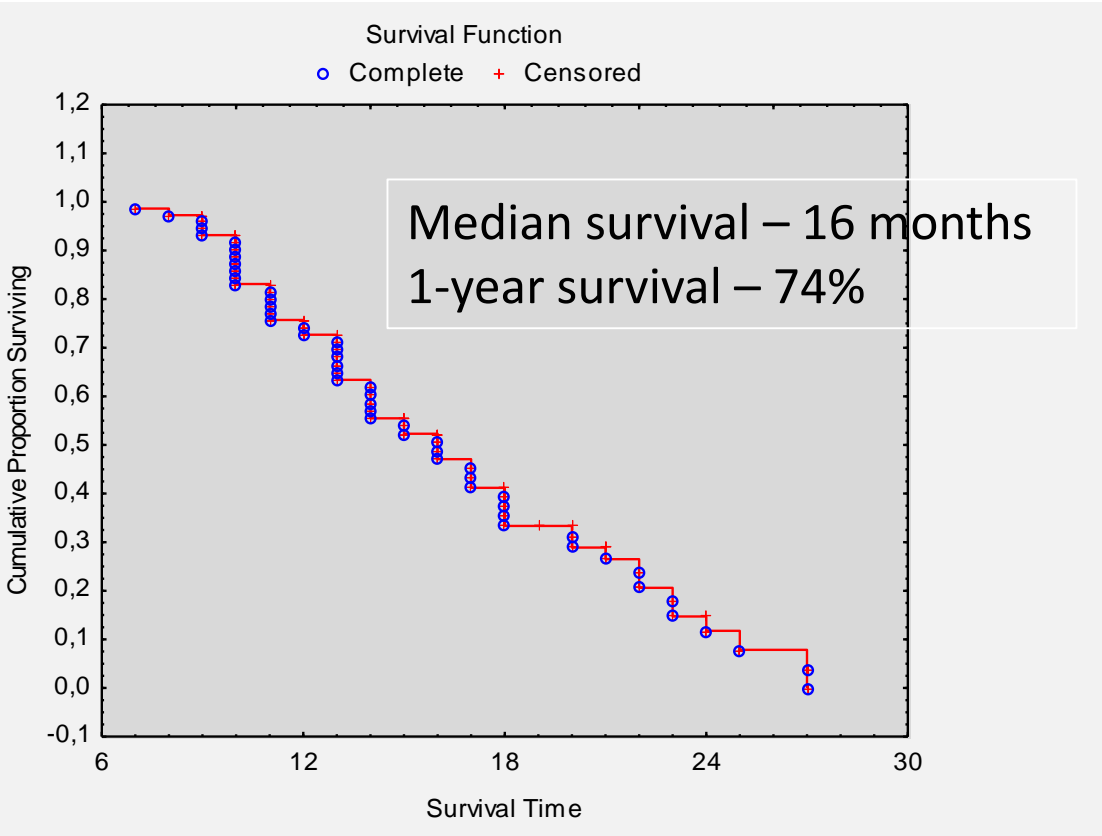
Survival data



More than one PIPAC (n=89)

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Survival data

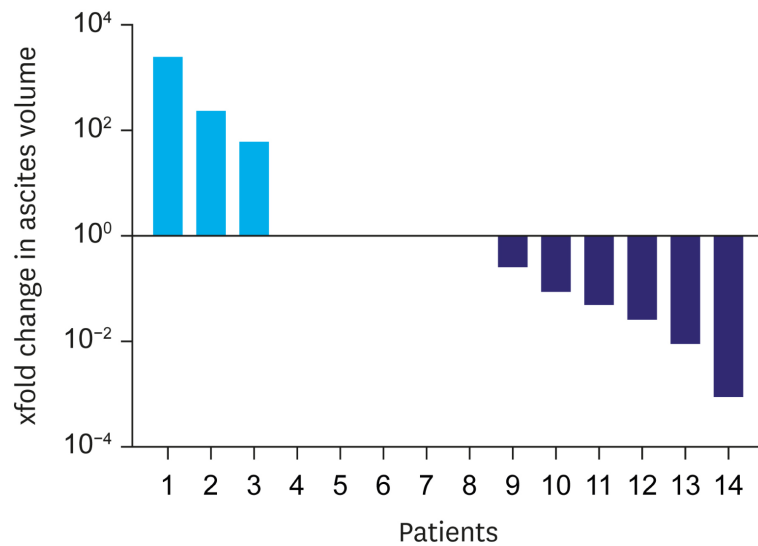
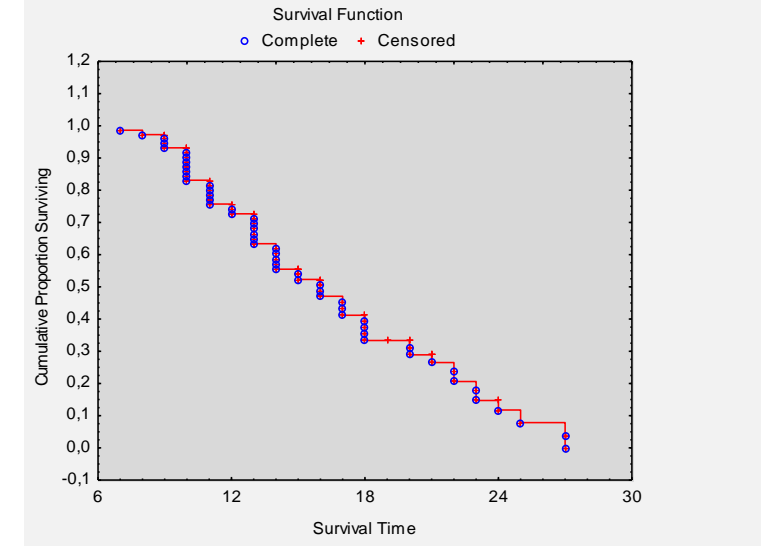
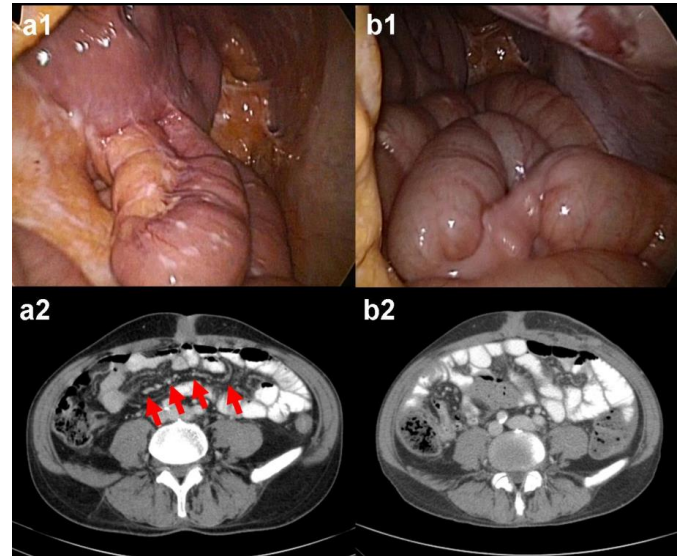
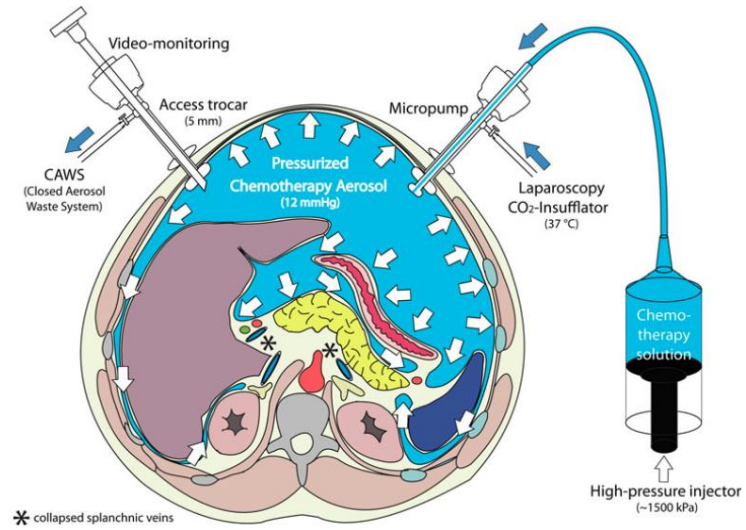


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2	27	18.4
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4	15	10.2
5	7	4.8
6	2	1.4
7	2	1.4
8	1	0.7

Pressurized Intra Peritoneal Aerosol Chemotherapy: PIPAC



Unresectable peritoneal metastasis treated by pressurized intraperitoneal aerosol chemotherapy (PIPAC) leading to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Table 4
 Follow-up for patients after Cytoreductive surgery and HIPEC.

Patient	Primary Malignancy	CC score	HIPEC drug used	Follow up (Month)	Status (Dead, Alive with recurrence, Alive free of disease)	Site of recurrence (comment)
1	Gastric	1	Mitomycin C	5	Dead	Peritoneal
2	Gastric	0	Mitomycin C	18	Alive with recurrence	Peritoneal/Bone
3	Gastric	0	Cisplatine	6	Dead	Peritoneal
4	Gastric	0	Oxaliplatin	21	Alive free of disease	N/A
5	Gastric	0	Mitomycin C	14	Alive with recurrence	Breast
6	Gastric	0	Cisplatine	9	Alive free of disease	N/A
7	Gastric	0	Cisplatine	7	Alive free of disease	N/A
8	Gastric	0	Cisplatine	9	Alive free of disease	N/A
9	Gastric	0	Mitomycin C	1	Dead	(Bowel ischemia)
10	Gastric	0	Cisplatin + Doxo	7	Alive free of disease	N/A

Clarisse Eveno*, Ingrid Jouvin and Marc Pocard

PIPAC EstoK 01: Pressurized IntraPeritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized and multicenter phase II study

Titre du projet :	
PIPAC EstoK 01: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) dans les carcinoses d'origine gastrique non résécables. Etude randomisée de phase II.	
Project title :	
PIPAC EstoK 01: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in gastric carcinomatosis. Phase II randomized study.	
Mots clés <i>Keys words</i> :	PIPAC, carcinose gastrique <i>PIPAC, gastric carcinomatosis</i>
Discipline, spécialité du projet <i>Project area</i> :	Chirurgie Oncologique, carcinose gastrique <i>Surgical Oncology, gastric carcinomatosis</i>
Organe, localisation anatomique de la tumeur <i>Organ, tumor location</i> :	Estomac, carcinose péritonéale <i>Stomach, peritoneal carcinomatosis</i>
Nombre de patients	94

Pankaj Kumar Garg, Maximilian Jara, Miguel Alberto and Beate Rau*

The role of Pressurized IntraPeritoneal Aerosol Chemotherapy in the management of gastric cancer: A systematic review

Pleura and Peritoneum 2019; 20180127

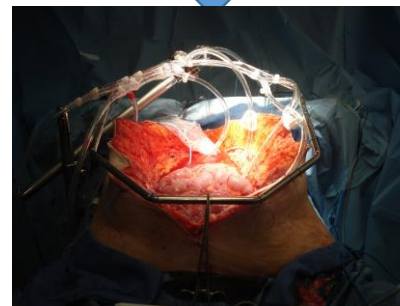
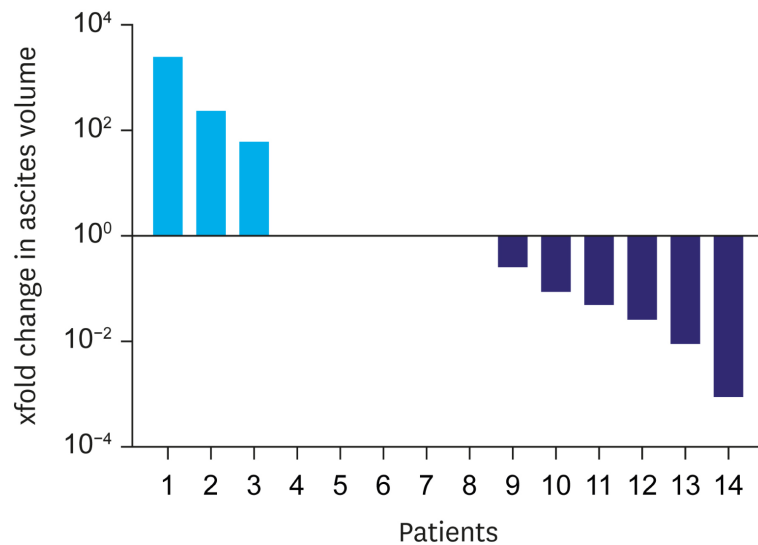
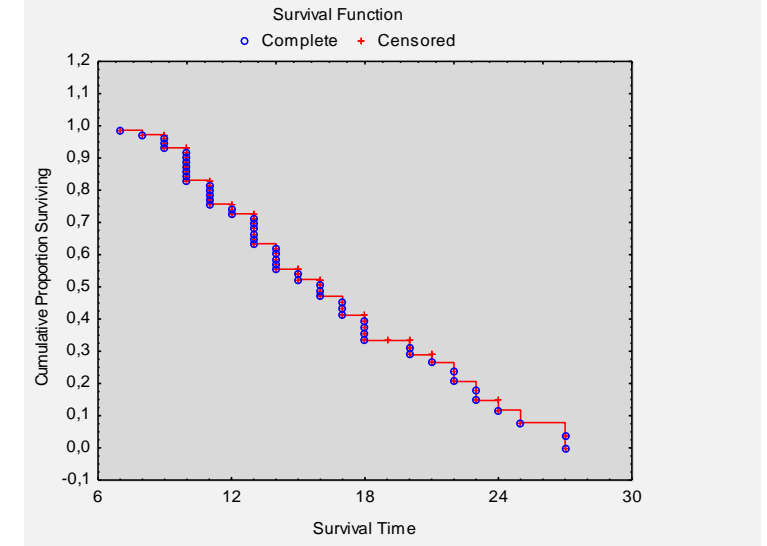
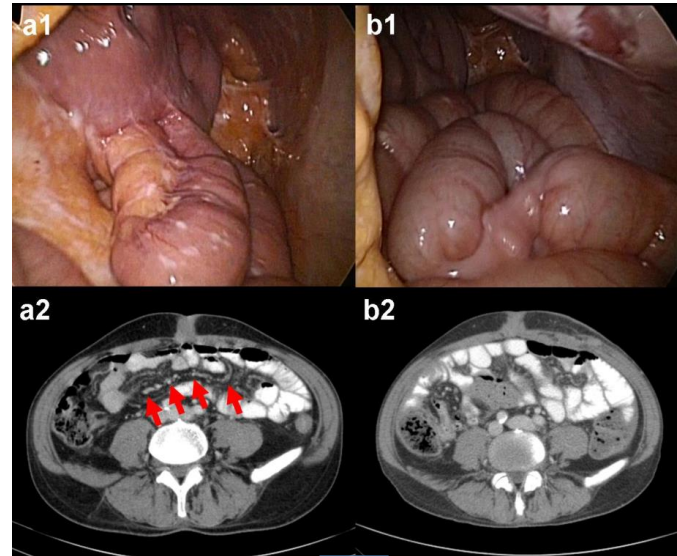
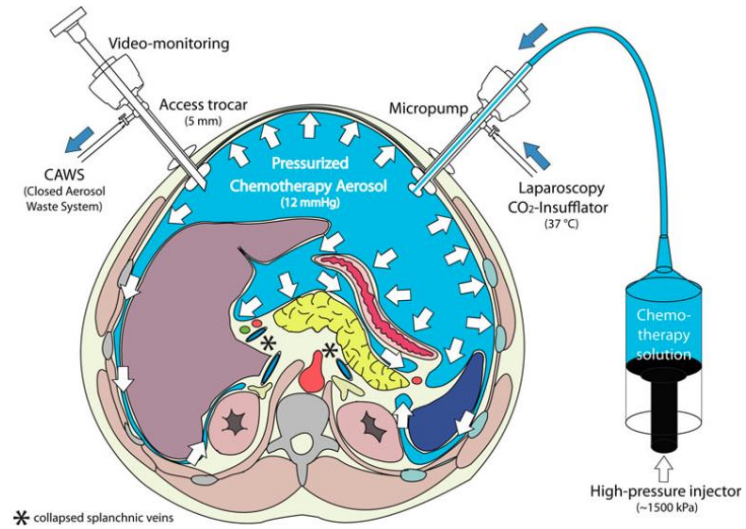


Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications

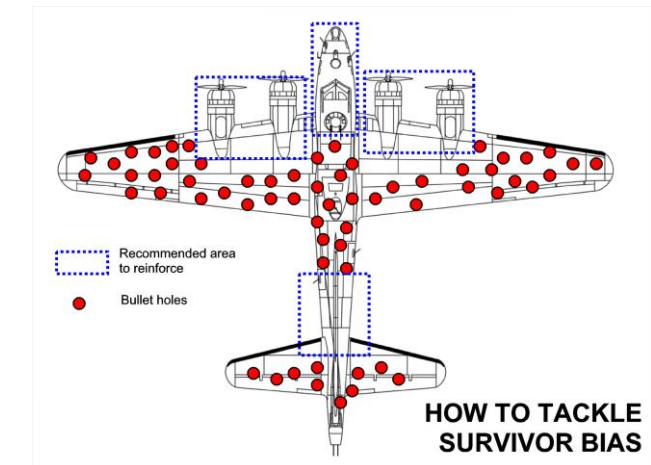
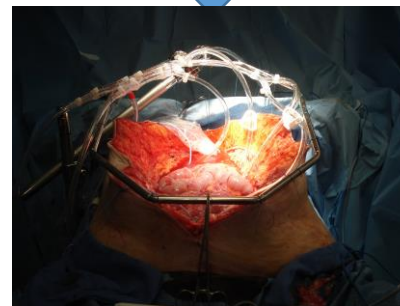
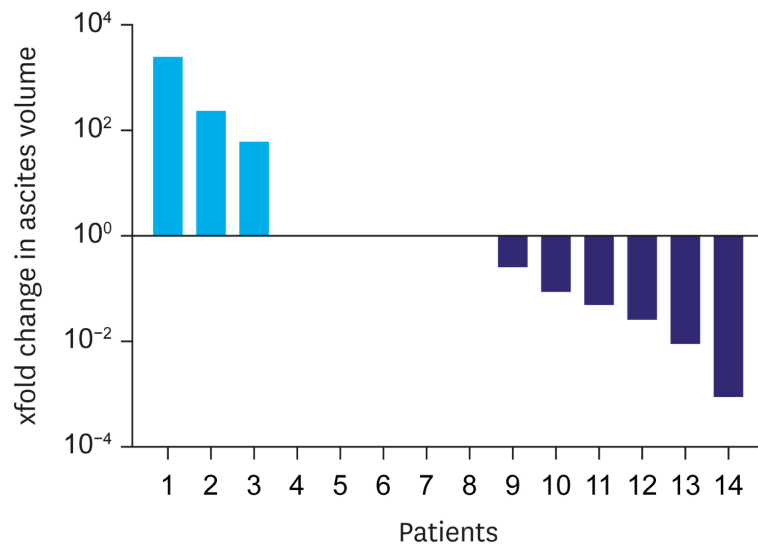
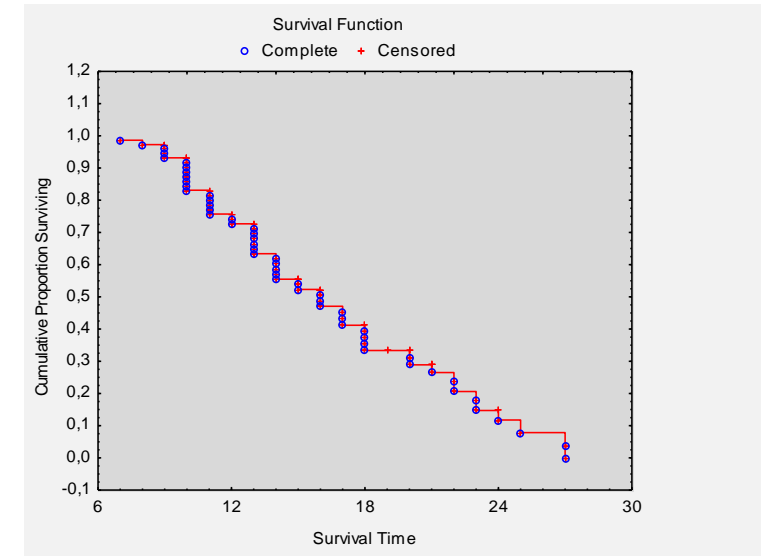
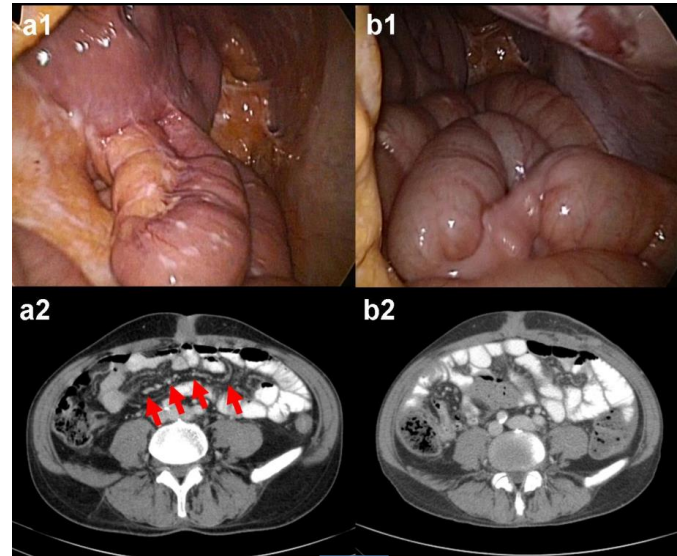
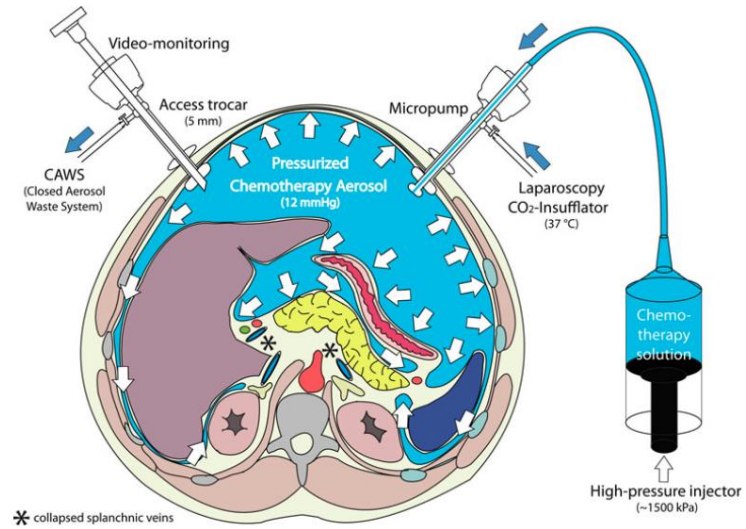
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Vahan Kepenekian*

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Gastric cancer peritoneal metastasis

- Prophylaxis is for tomorrow.
- Today offer a complete solution
 - Histologic and Genomic analysis
 - Systemic Chemo and laparoscopy
 - Cytoreductive surgery + HIPEC
 - PCI < 7 and CCO
 - PIPAC with systemic chemo

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