Peritoneal Carcinomatosis in CRC

Finding the Diamond in the Rough

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No Disclosure

Focus on

Appendicular neoplasms

Decision making rationale

Predictive Factors for Successful CRS & HIPEC in PC of CRC.

Historical view

Concept

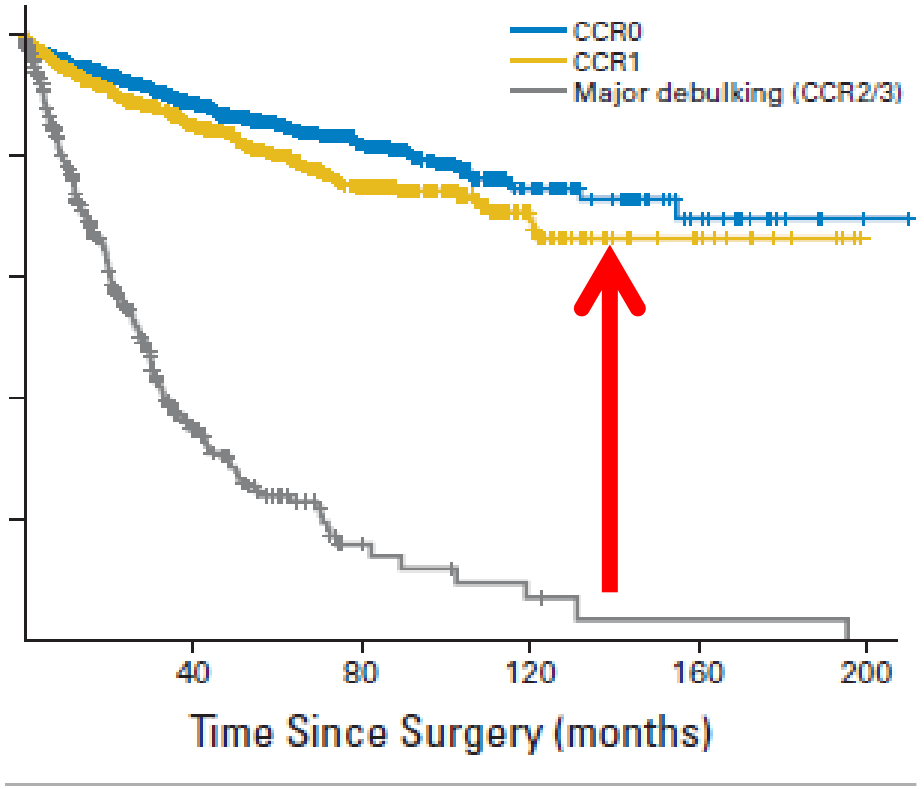
- For a long time, peritoneal neoplasms were **considered beyond surgical intervention and beyond cure.**

Options

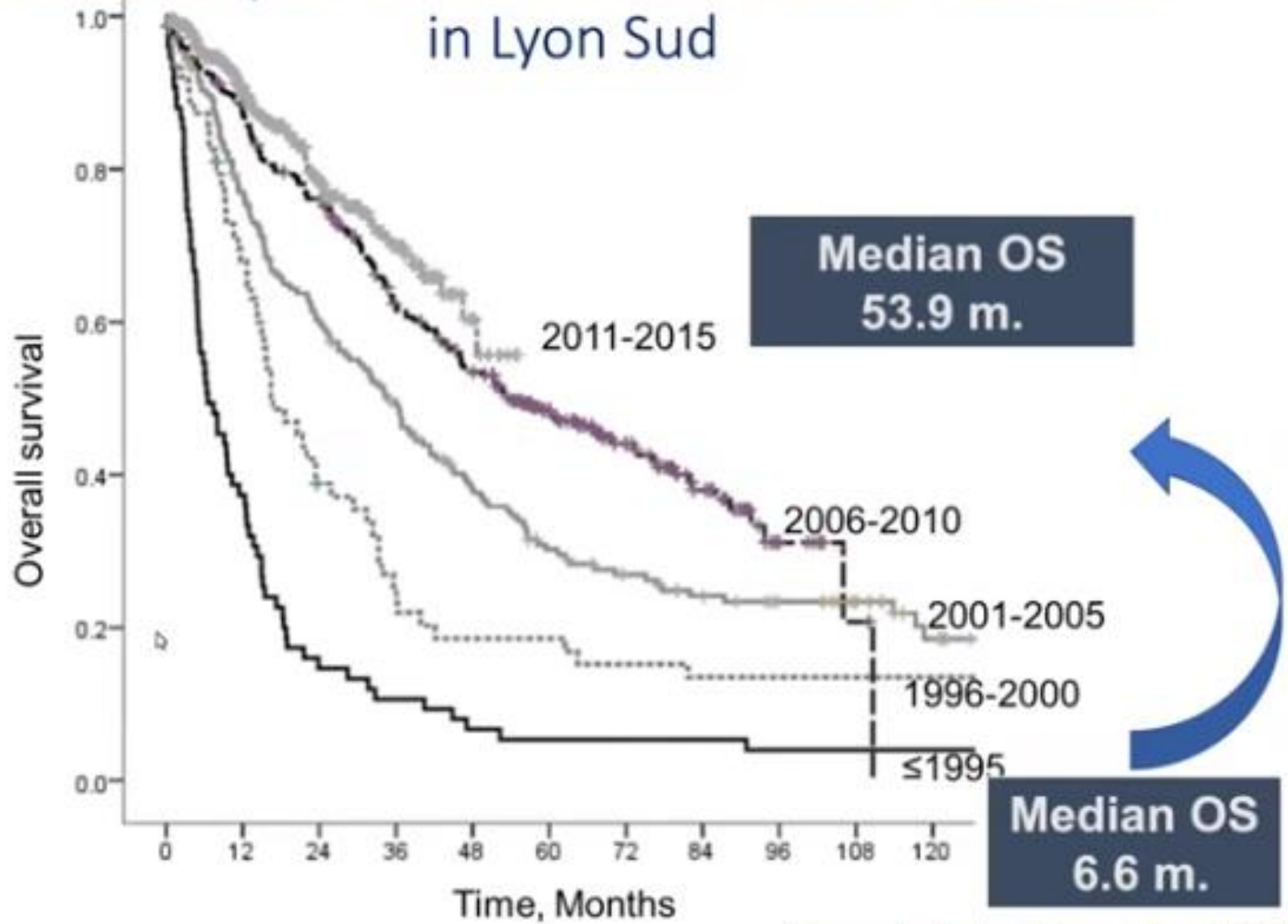
- Best Supportive Care
- Surgical Treatment to improve Quality of Life

Dramatic Change in Survival

- The concept of **(CRS-HIPEC)** was introduced and changed survival rates from **zero to approximately 80%** for all patients.
- Median overall survival has improved from **few months** to **several years**

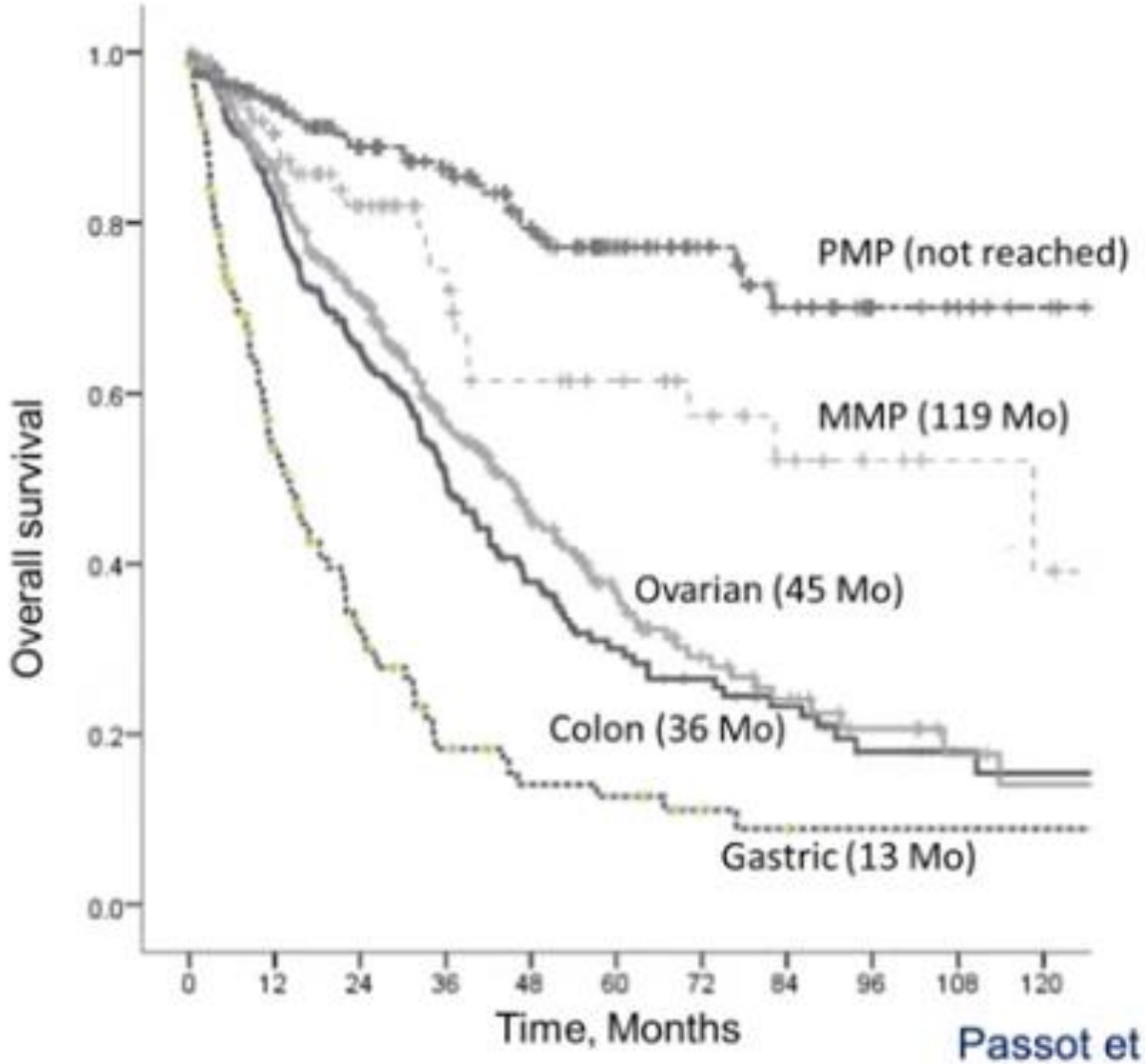


Survival of peritoneal carcinomatosis over time in Lyon Sud



Passot et al. *J Surg Onc*, 2016

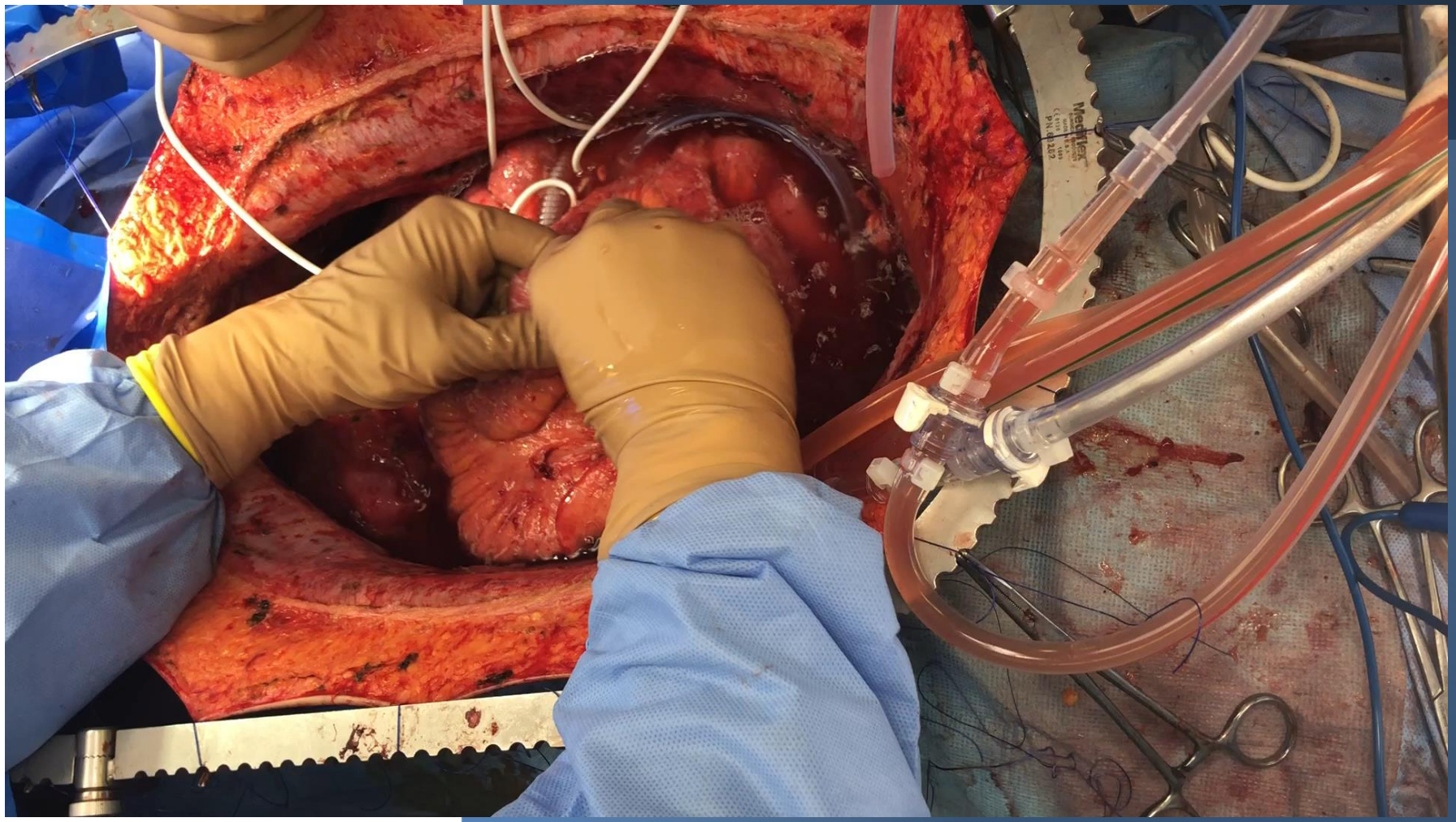
Survival Regarding Origin of PC



Passot et al. *J Surg Onc*, 2016

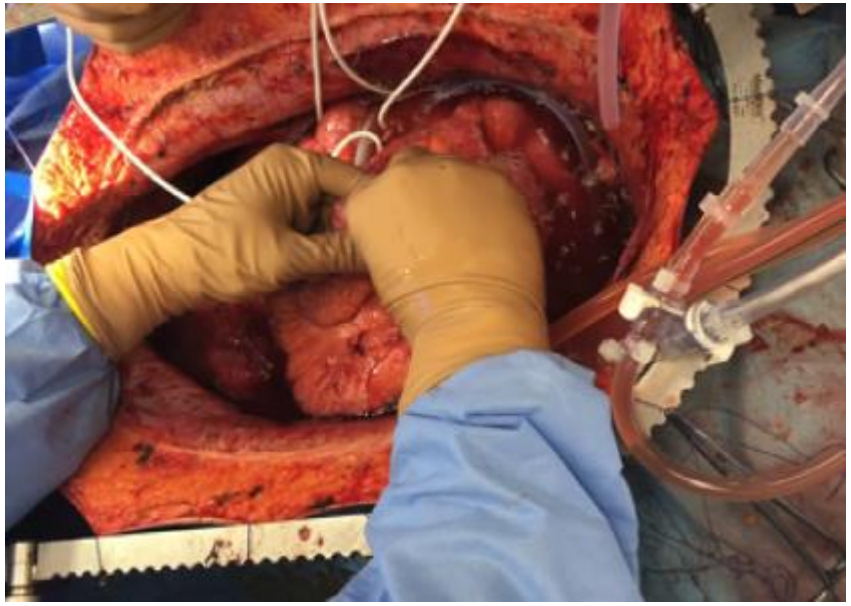
CRS

HIPEC



HIPEC effects

- Can be from cytotoxicity of **chemotherapy**.
- Can be from cytotoxicity of **heat**
- Can be **synergistic** effect of both heat and chemotherapy
- Can be from **mechanical** disruption of tumor cells.



Paul Sugarbaker

What can we reliably expect from HIPEC?

- Eradicate **Free cancer cells** present within peritoneal spaces bathed by heated chemotherapy solution (patients with positive cytology)
- Eradicate **cancer cells layered out** on normal and traumatized abdominal and pelvic surfaces during the CRS
- Eradicate **very very small volume residual disease** present at narrow margins of resection.

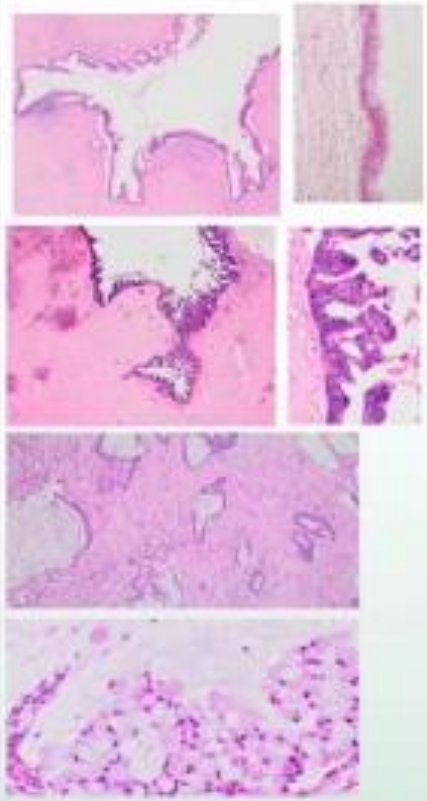
What is it that HIPEC cannot do?

- Eradicate tumor **cells trapped within scar tissue** (adhesions)
- Eradicate **vascularized tumor nodules**
- Eradicate tumor **not bathed** by the heated chemotherapy solution
- Eradicate tumor **made drug-resistant by NAC**

Appendicular neoplasm decision making rationale.

Classification of appendiceal neoplasia

	Type of invasion	Cytology	WHO Grade
LAMN Low grade appendiceal mucinous neoplasm	Pushing	Low grade	G1
HAMN High grade appendiceal mucinous neoplasm	Pushing	High grade	G2
Mucinous adenocarcinoma	Infiltrative	Any grade	G2
Mucinous adenocarcinoma with signet ring cells	Infiltrative	Signet ring cells ≥10%	G3



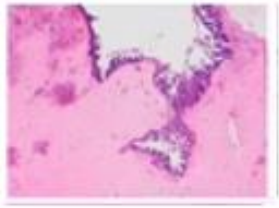
Risk of **PMP** with appendiceal primary

	If confined to appendix:	If evidence of appendiceal rupture or extra-appendiceal spread:
LAMN	Risk of pseudomyxoma minimal	Risk of pseudomyxoma if acellular mucin 3% if cellular mucin 30-40%
HAMN (scanty data)	Probably similar to LAMN	Peritoneal disease more likely to be high grade
Mucinous adenocarcinoma	Pseudomyxoma, lymphatic and haematogenous metastases possible	Peritoneal disease likely to be high grade
Mucinous adenocarcinoma with signet ring cells	Pseudomyxoma, lymphatic and haematogenous metastases likely	Prognosis is worse than mucinous adenocarcinoma without signet ring cells

LAMN

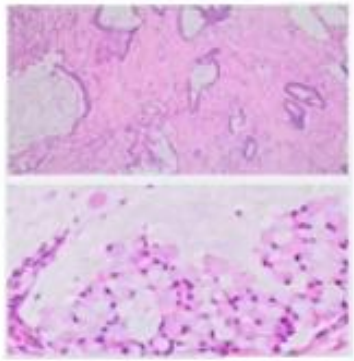
Not perforated : Appendectomy
Perforated with acellular mucin: Appendectomy
Perforated with cellular mucin: CRS/HIPEC

HAMN



Not perforated: Right hemicolectomy ?
Perforated: Rigt Hemicolectomy + CRS/HIPEC

Mucinous adenocarcinoma



Not perforated: Right hemicolectomy
Perforated: Right hemicolectomy + CRS/ HIPEC

Peritoneal Surface Oncology
PS GI
Group International

Two patterns of natural spread

Redistributed tumor in Non-invasive mucinous tumors.

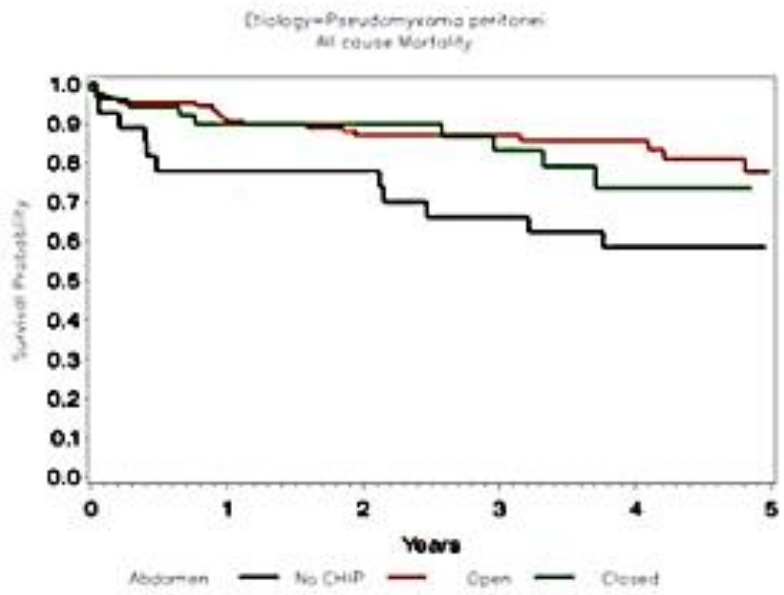
A random and proximal distribution in Aggressive tumors.

Large volume of implants within the greater omentum, beneath hemidiaphragms, and within the pelvis.

Implants are in close proximity to the perforation site and are randomly distributes on nearby surfaces.

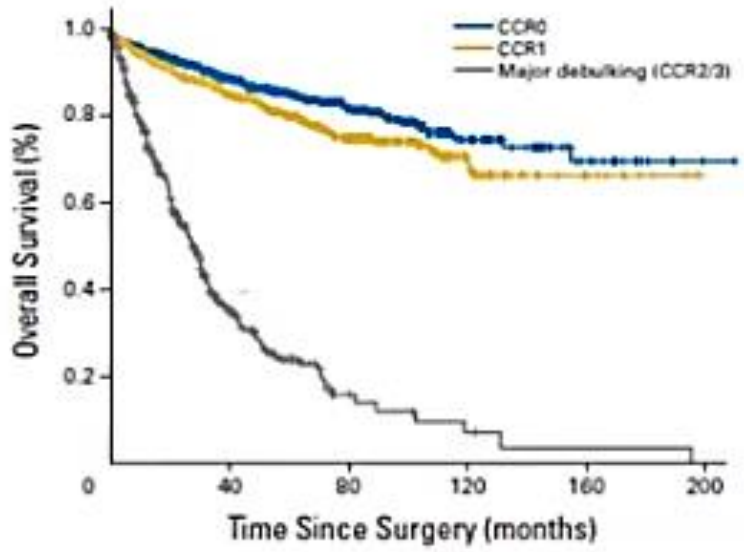
Cytoreductive surgery and HIPEC

Pseudomyxoma peritonei



French registry
Open and closed procedures

JOURNAL OF CLINICAL ONCOLOGY



2 117 patients
International Registry

Technical issues

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ac.els-cdn.com

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www.sciencedirect.com

Full Length Article

Outcome and surgical strategy in critical sites in cases of psuedomyxoma peritonei

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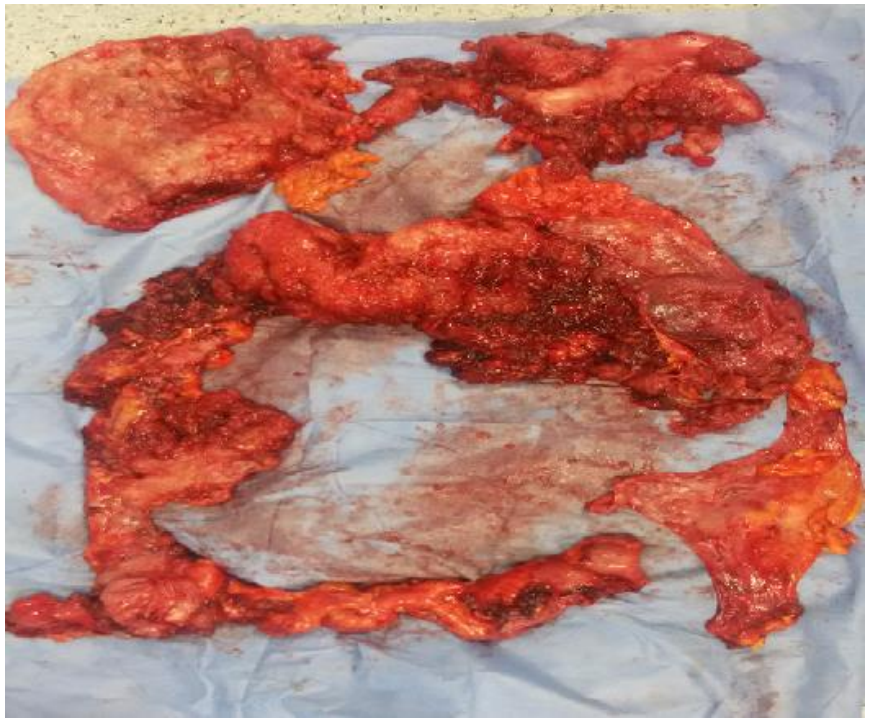
KEYWORDS
Pseudomyxoma peritonei;
Cytoreductive surgery;
HIPEC

Abstract *Background:* For a long time peritoneal neoplasms were consid
intervention and beyond cure, till the concept of cytoreductive surgery (CRS)
thermic intraperitoneal chemotherapy (HIPEC) was introduced. However this
is technically demanding and associated with considerable postoperative mor
Objective: To describe the surgical strategy in resection of critical sites loa
deposits and to evaluate short and long term results of CRS and HIPEC, in
patients with pseudomyxoma peritonei (PMP) from appendiceal origin.
Patients and methods: 21 patients with PMP, age ranged from 40 to 63 y
females. All were recruited from the department of surgery at the Natio
(NCI), Cairo University over the period from February 2011 to February 2016
to CRS and HIPEC with mitomycin-C.
Results: The median peritoneal carcinoma index (PCI) was 22 (range: 10–39)
tion (CCR-0/1) was achieved in 19 patients (90.4%) of whom 17 patients (80
cytoreduction (CCR-0). The median follow up period was 51.5 months (rang
The cumulative overall survival was 85.7% while the cumulative disease free
Conclusion: To the best of our knowledge, this is the first study reporting fiv
outcome of CRS and HIPEC in Egyptian patients with PMP from appendice
support that although technically demanding this treatment modality is safe
favorable outcome.

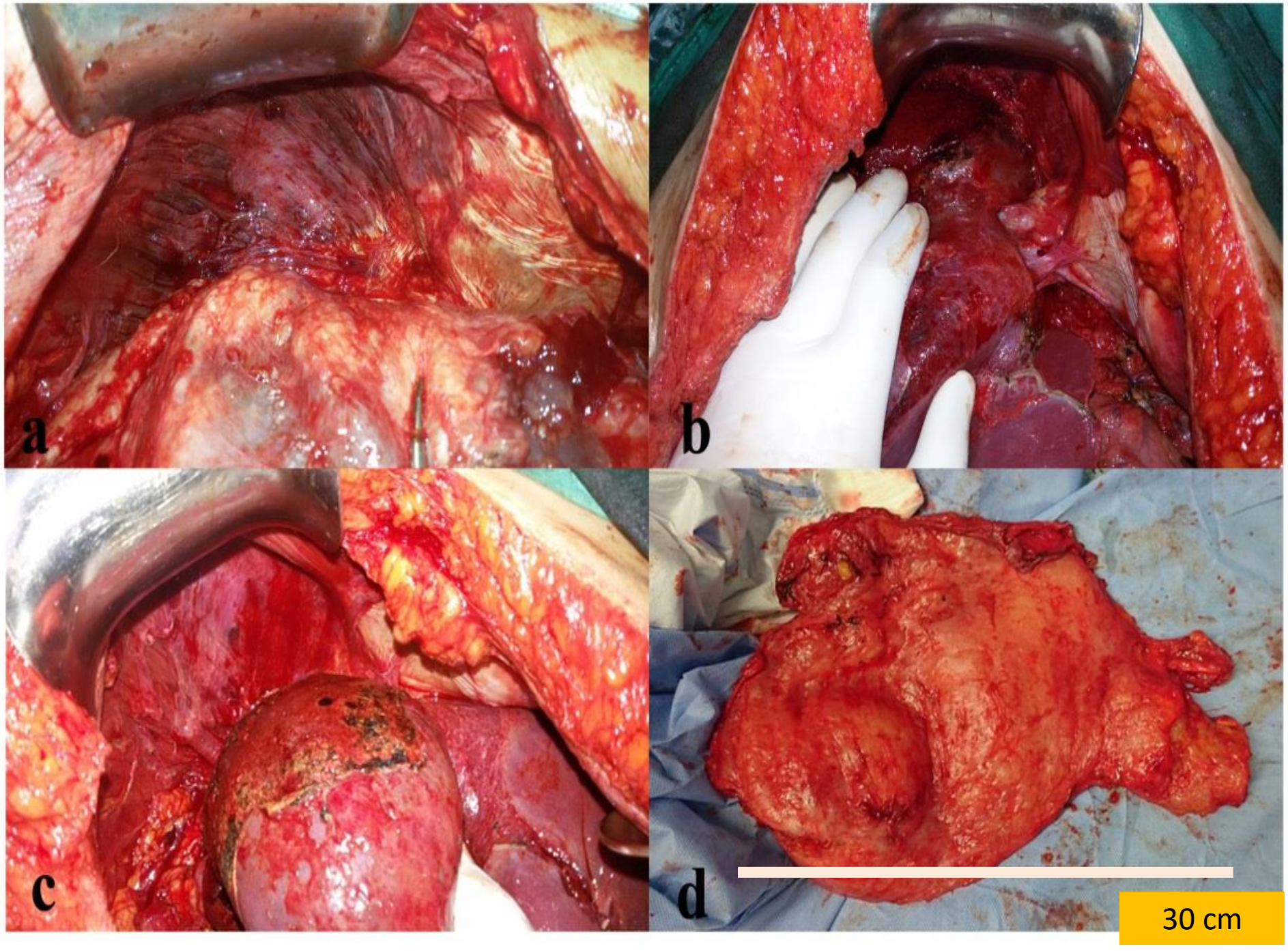
* Corresponding author.

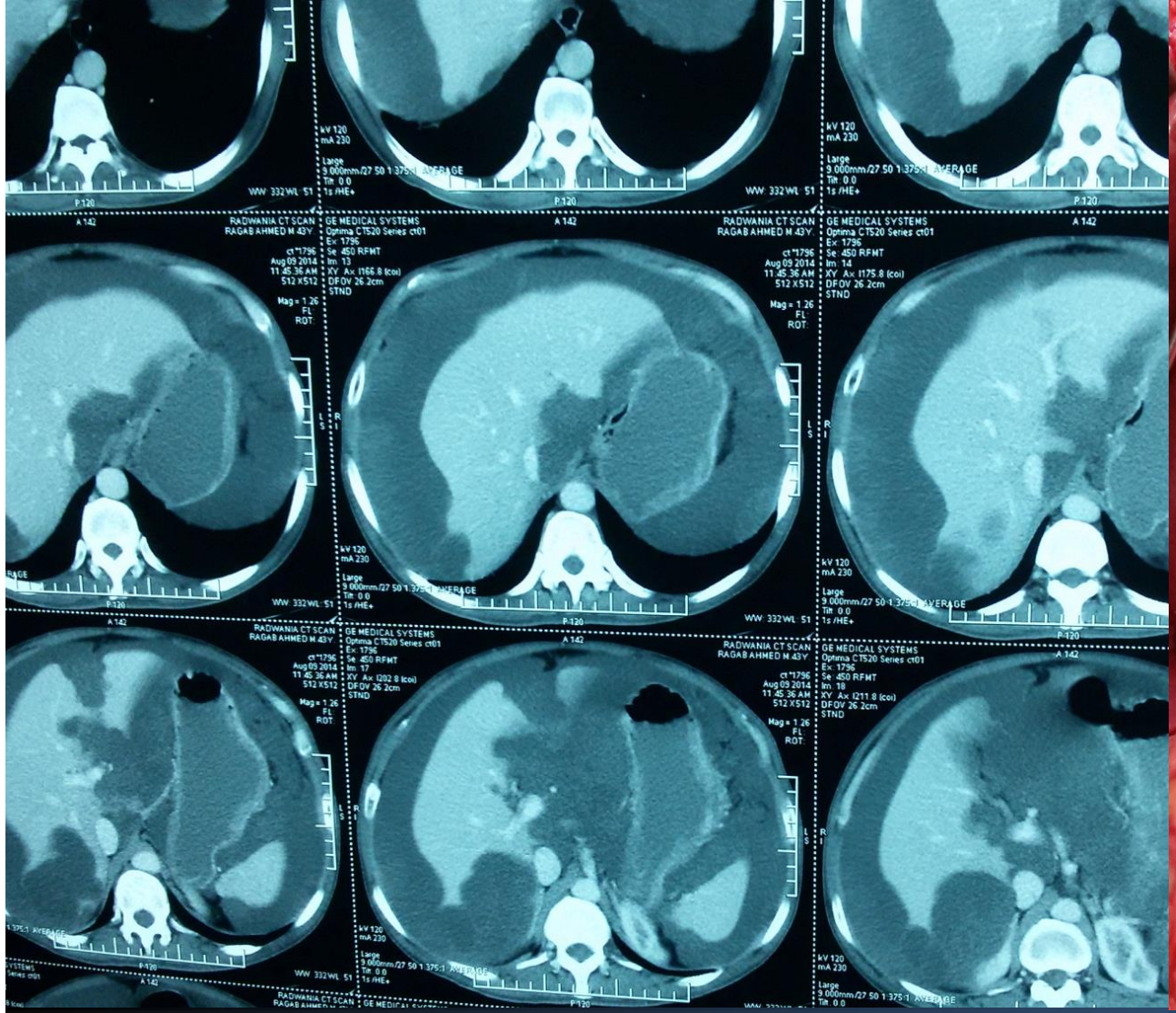
Introduction

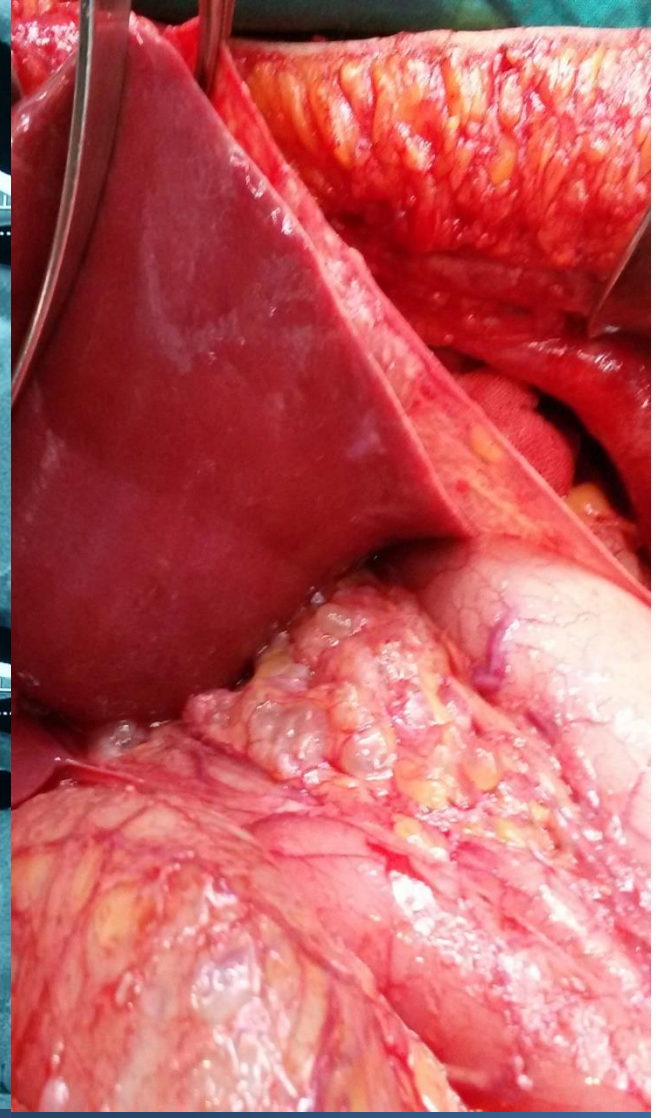
For a long time peritoneal neoplasms were



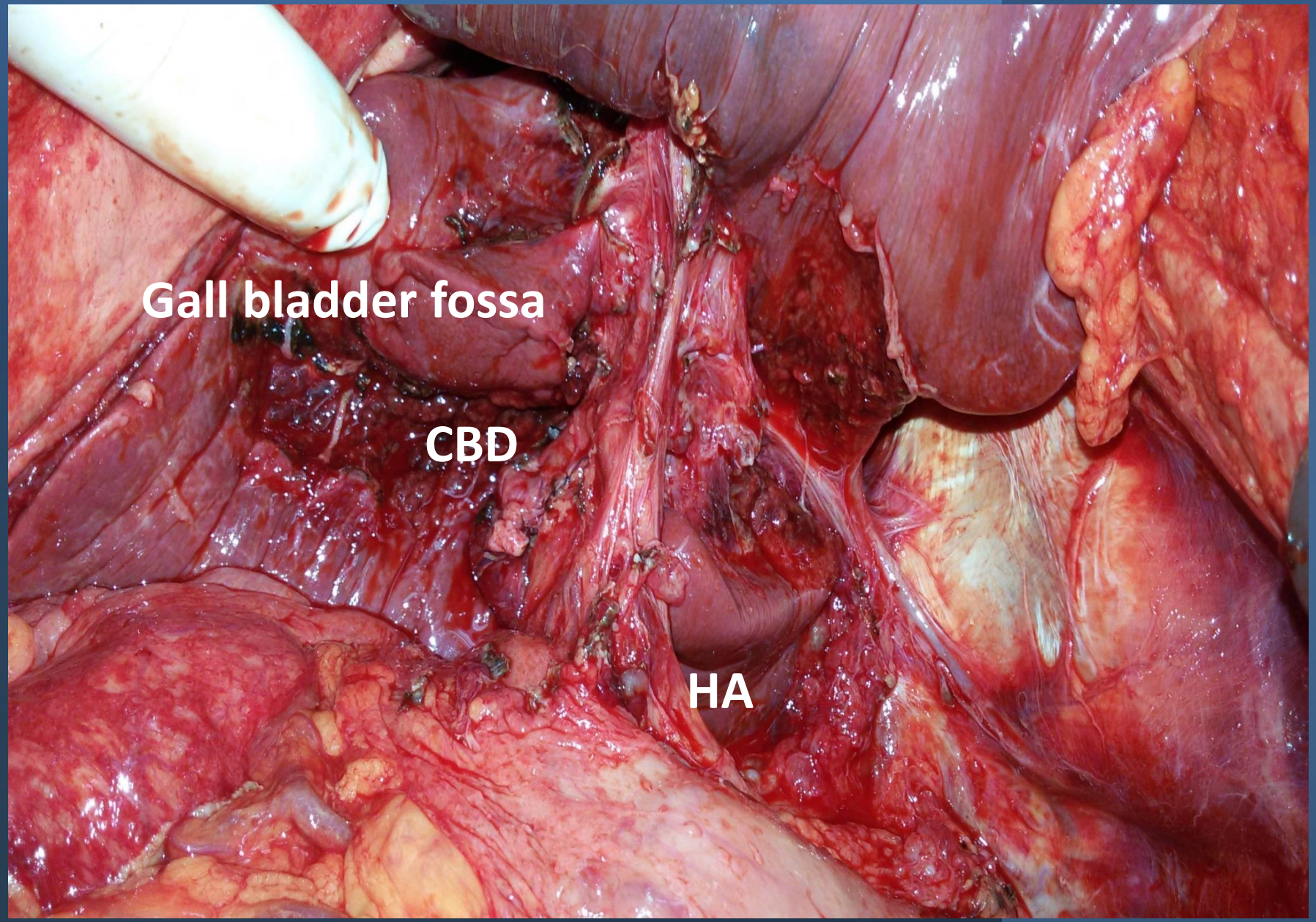
1-Tumor wrapping the liver


a
b
c
d
30 cm

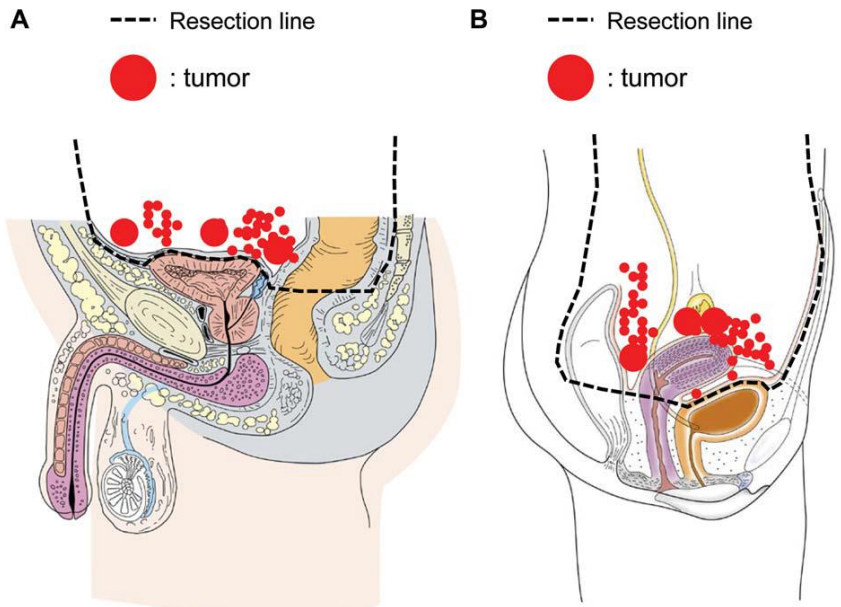


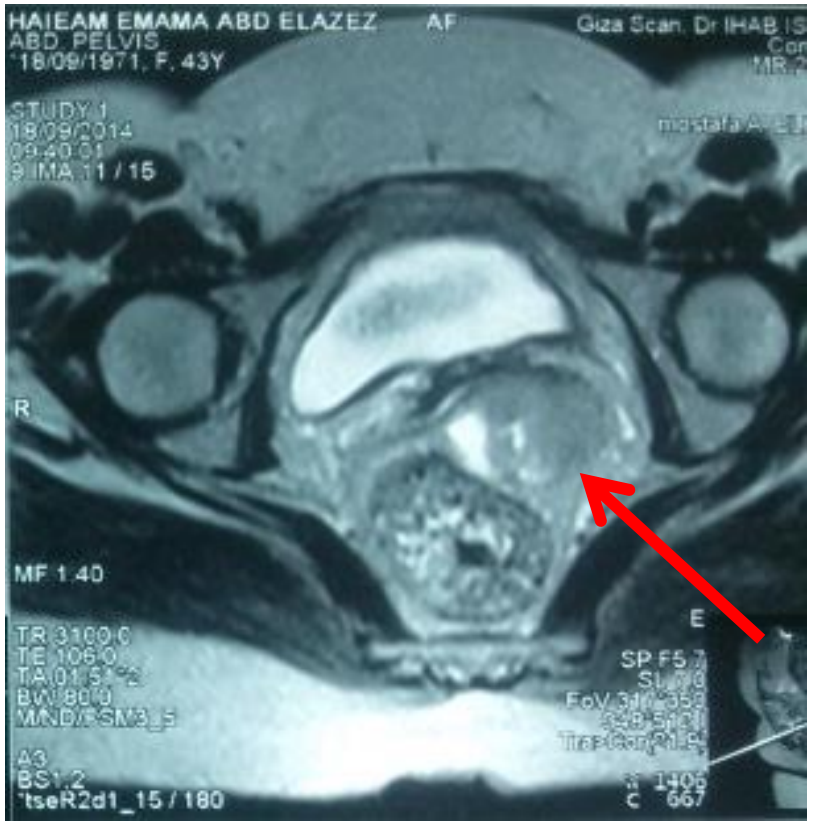


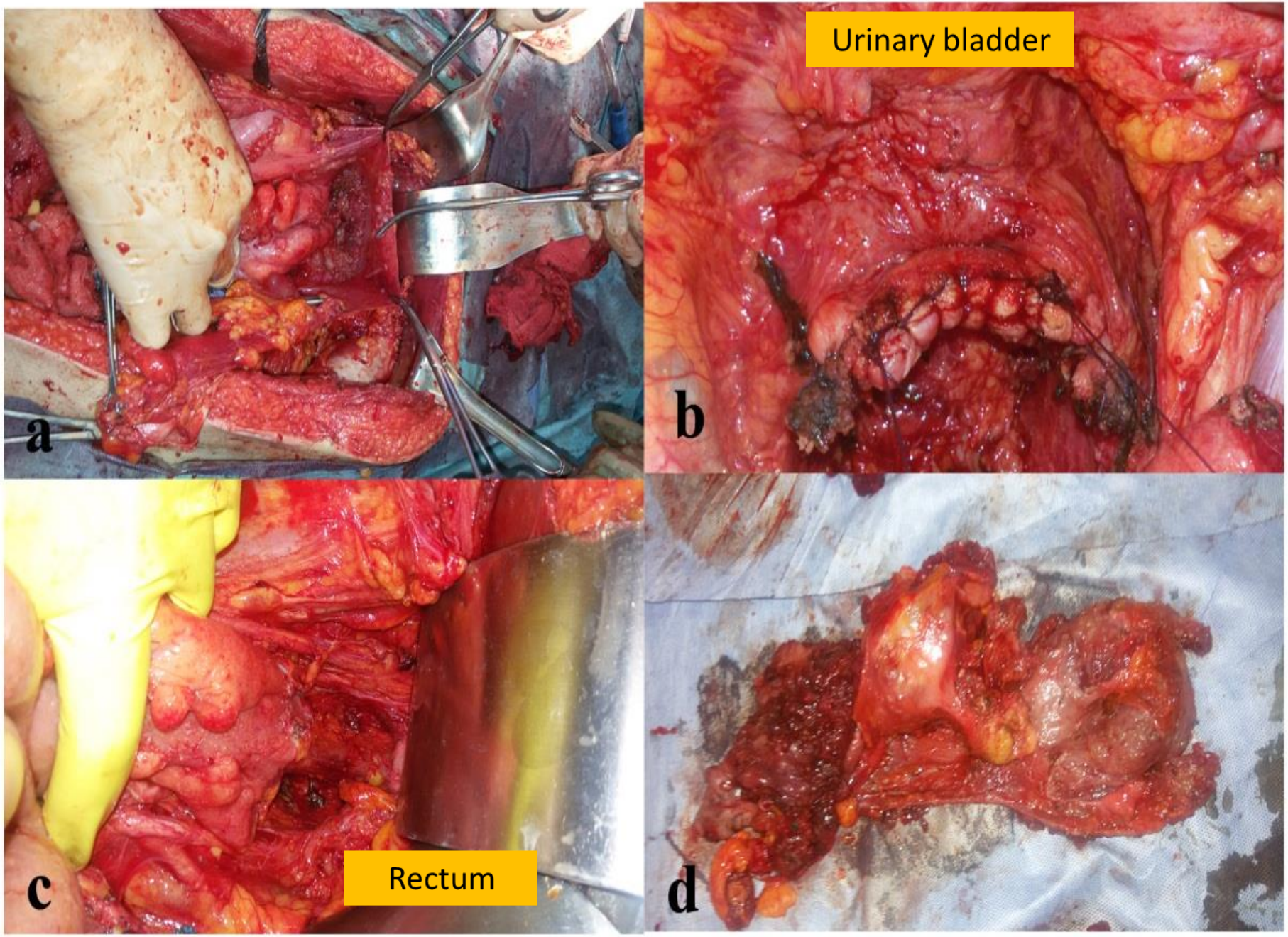
2-Tumor in the hilum of the liver


Gall bladder fossa
CBD
HA

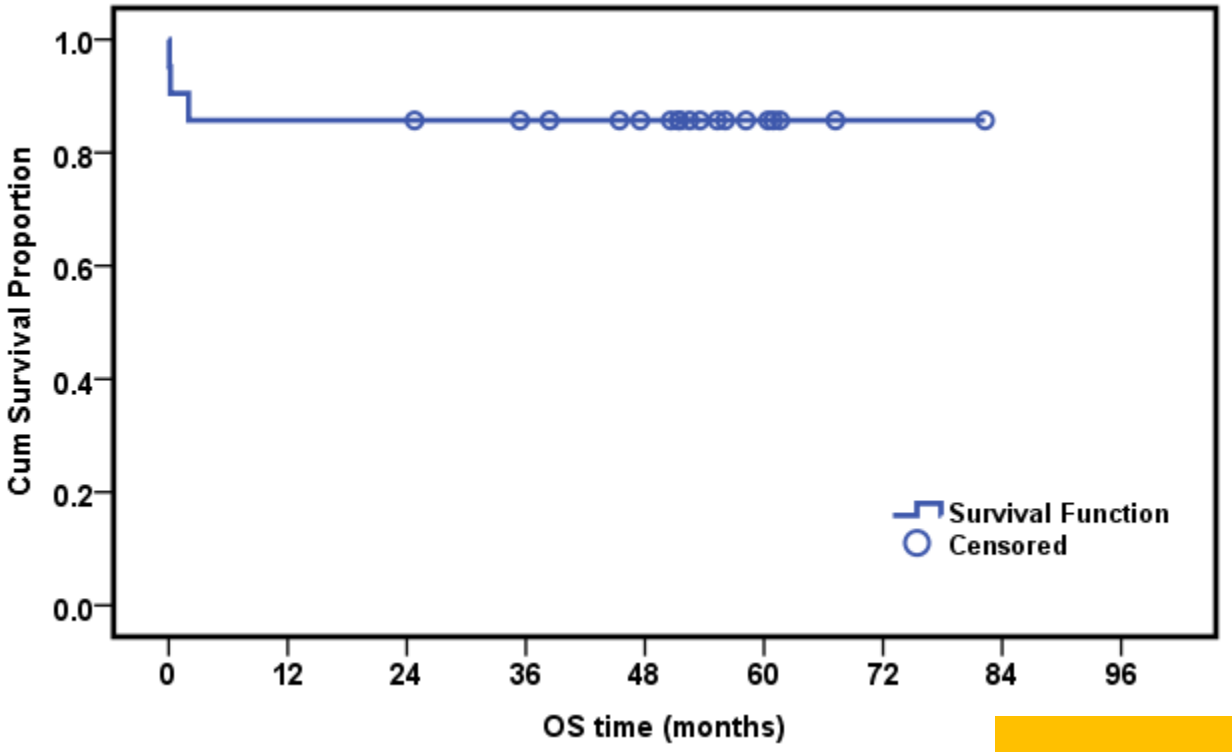
3- Tumor wedged in the pelvis





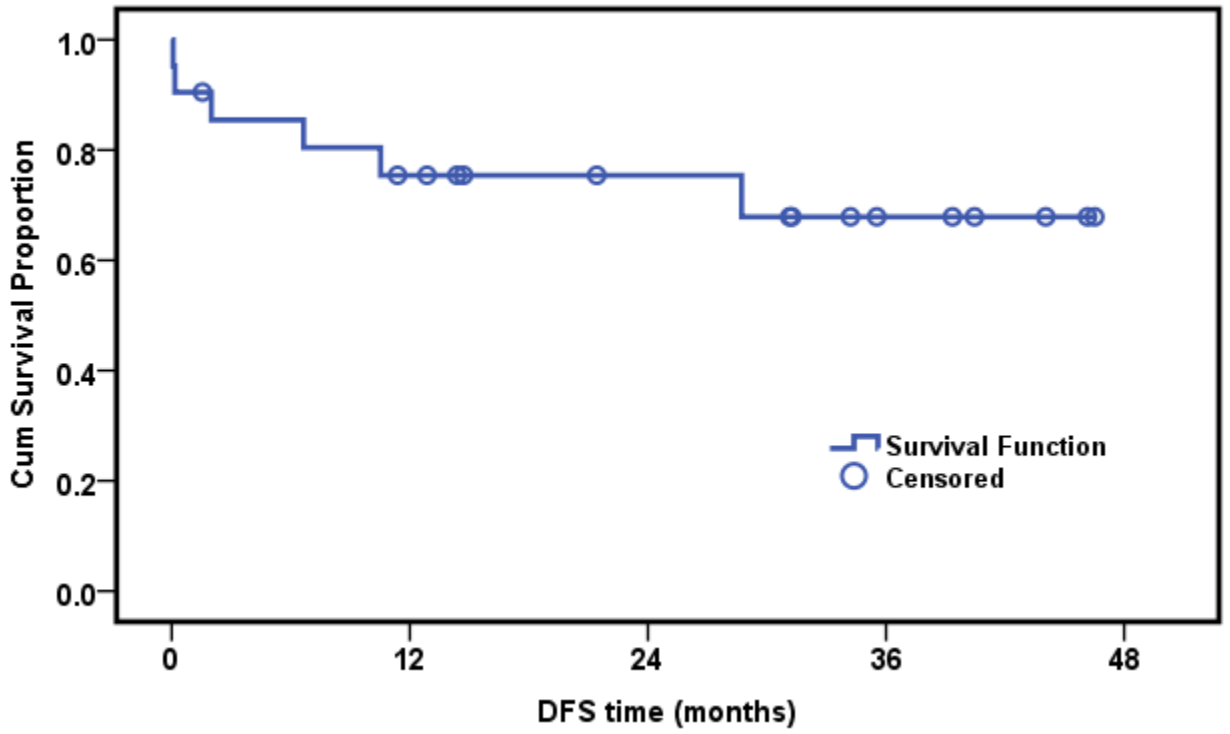

a
Urinary bladder
b
c
Rectum
d

The cumulative over all (OS) for the PMP group



85 %

The cumulative diseases free survival (DFS) for the PMP group.



77 %

Predictive factors for successful CRS & HIPEC in CRC PC.

Magnitude of the problem

15 % of cases present with synchronous carcinomatosis.

20 % of patients will develop metachronous disease at follow up.

5 % PC is the sole pattern of recurrence.

Solution of the problem

Median survival of 6 months in untreated cases

Modern chemotherapy and targeted agents the median overall survival has dramatically improved up to 24 months.

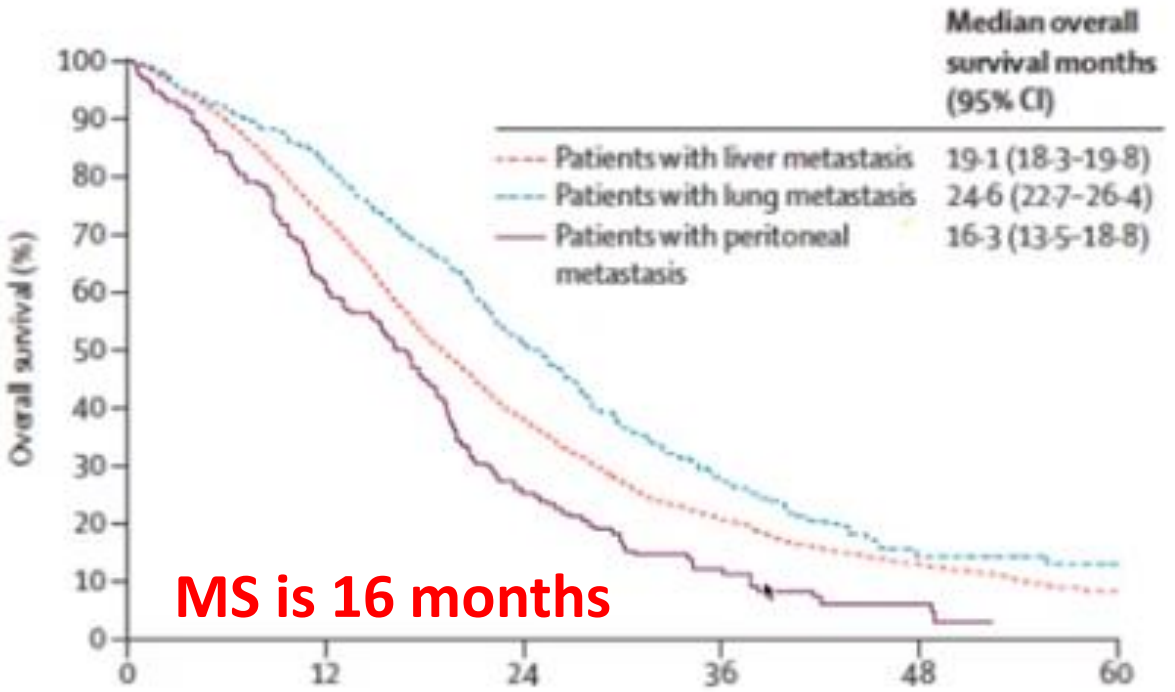
CRS and HIPEC improved median survival up to 40-60 months.

Evolution of median survival PC of CRC

		Median survival
Before 1990	**Systemic chemotherapy**	**6 months** *16 months with modern chemotherapy*
1990-2000	**Verwal 2003 Glehan 2004**	**20 months**
2000-2010	**Elias 2010**	**30 months**
2010-2020	**Quenet ASCO 2018**	**40 months**

Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database

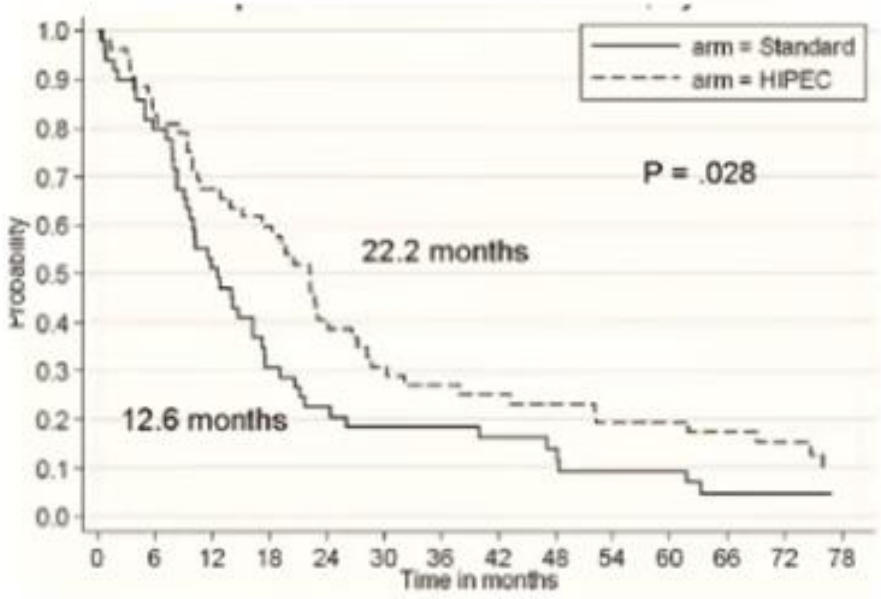
Jan Franko, Qian Shi, Jeffrey P Meyers, Timothy S Maughan, Richard A Adams, Matthew T Seymour, Leonard Saltz, Cornelis J A Punt, Miriam Koopman, Christophe Tournigand, Niall C Tebbutt, Eduardo Diaz-Rubio, John Souglakos, Alfredo Falcone, Benoist Chibaudel, Volker Heinemann, Joseph Moen, Aimery De Gramont, Daniel J Sargent, Axel Grothey, for the Analysis and Research in Cancers of the Digestive System (ARCAD) Group



Lancet Oncol 2016

(CRS & HIPEC) vs Systemic

A randomized study

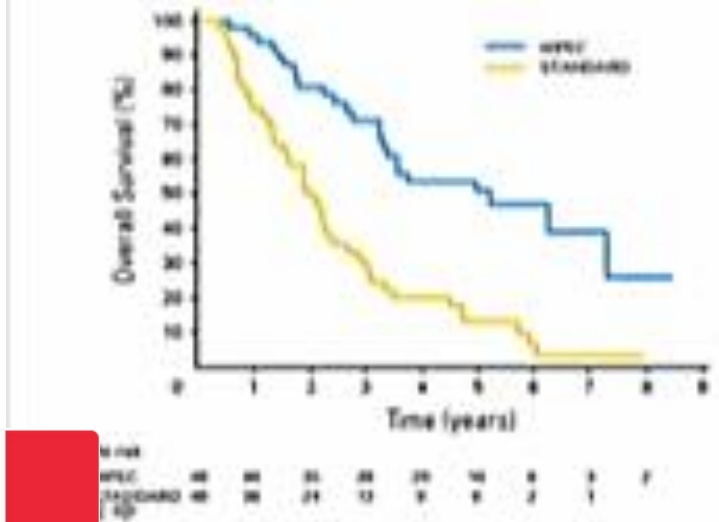


Surgery + HIPEC > Systemic chemotherapy

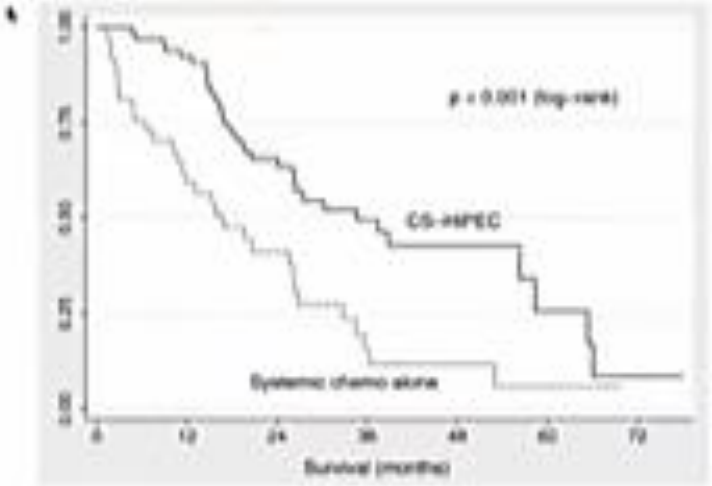
Verwall et al. J Clin Oncol 2003, Ann Surg 2008

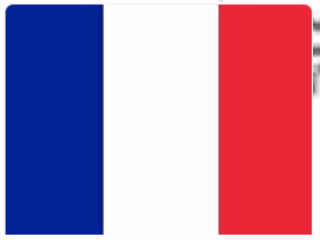
(CRS & HIPEC) vs Systemic chemptherapy

- Elias et al.(*J Clin Oncol 2008)*
  - -Cytoreduction + HIPEC vs Modern systemic chemotherapy
  - -Limited PM
  - -Median survival of 62 vs 24 months



- Franco et al.(*Cancer 2010)*
  - -Cytoreduction + HIPEC vs Modern systemic chemotherapy
  - - Morte extended PM
  - -Median survival of 35 vs 17 months





PSDSS in **1000** patient

Peritoneal Surface Disease Severity Score (PSDSS)

American Society of Peritoneal Surface Malignancies

1 013 patients

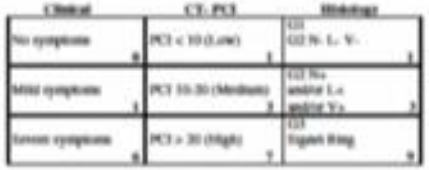
Median Survival (months)

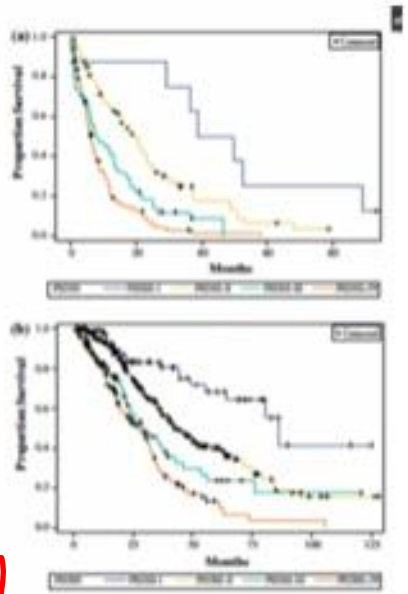
PSDSS	Chemotherapy alone	Cytoreductive surgery and HIPEC
PSDSS 1	45	86
PSDSS 2	19	43
PSDSS 3	8	29
PSDSS 4	6	28

Ann Surg Oncol 2014

American Society of Peritoneal Surface Malignancies

1 013 patients





Median survival > 60 months

Ann Surg Oncol 2014

Cure 16%

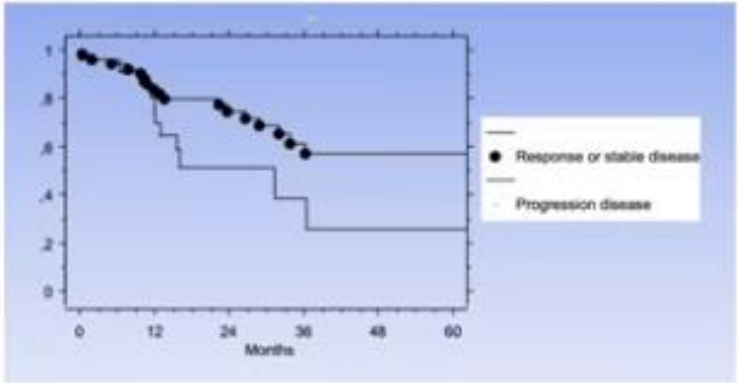
Peritoneal metastasis from colorectal cancer

- **Survival at 5 years withour recurrence : 16%**
  - **We can cure PM from colorectal cancer**

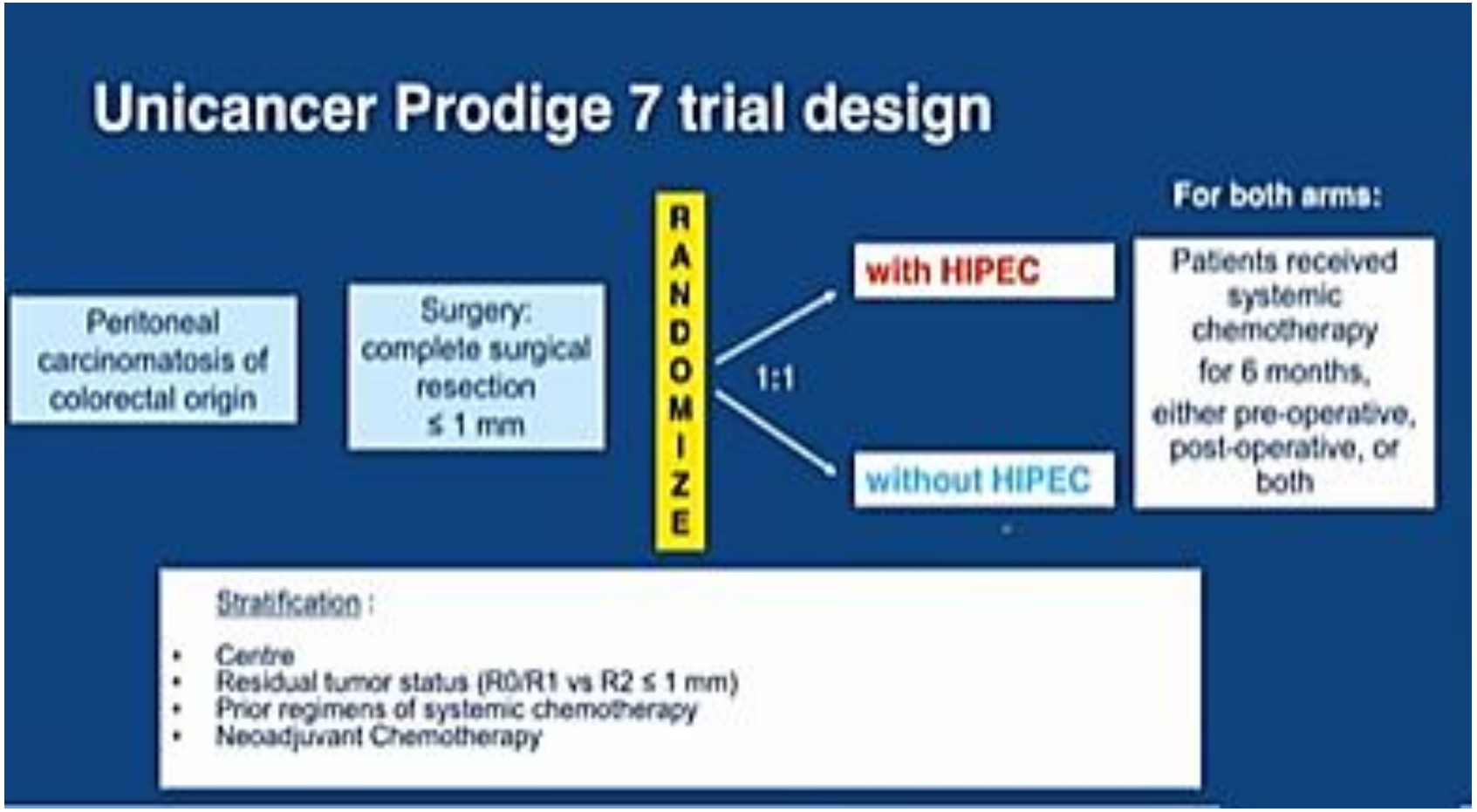
Goere et al Ann Surg 2012

- **Median survival > 60 months**
  - Strict selection of patients
  - Systemic chemotherapy

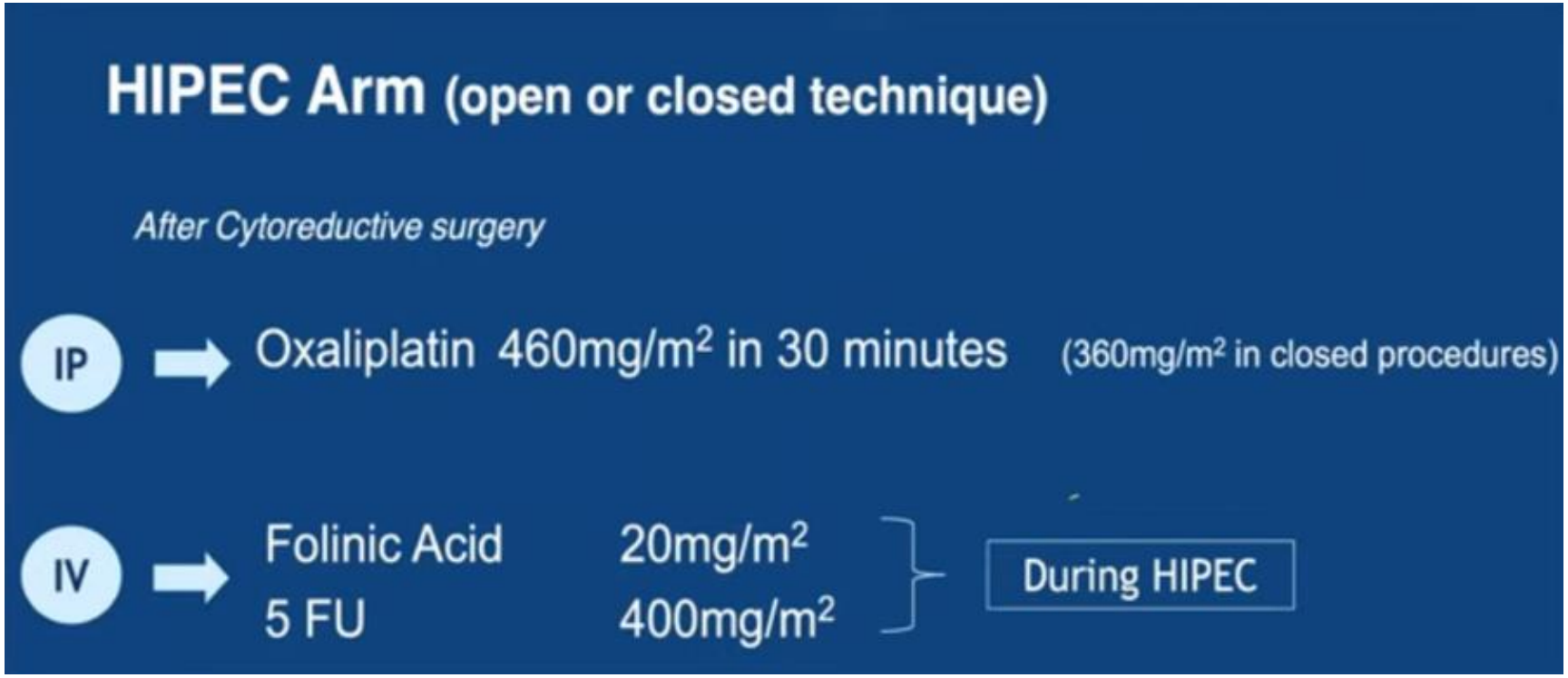
Passot et al. Ann Surg 2012

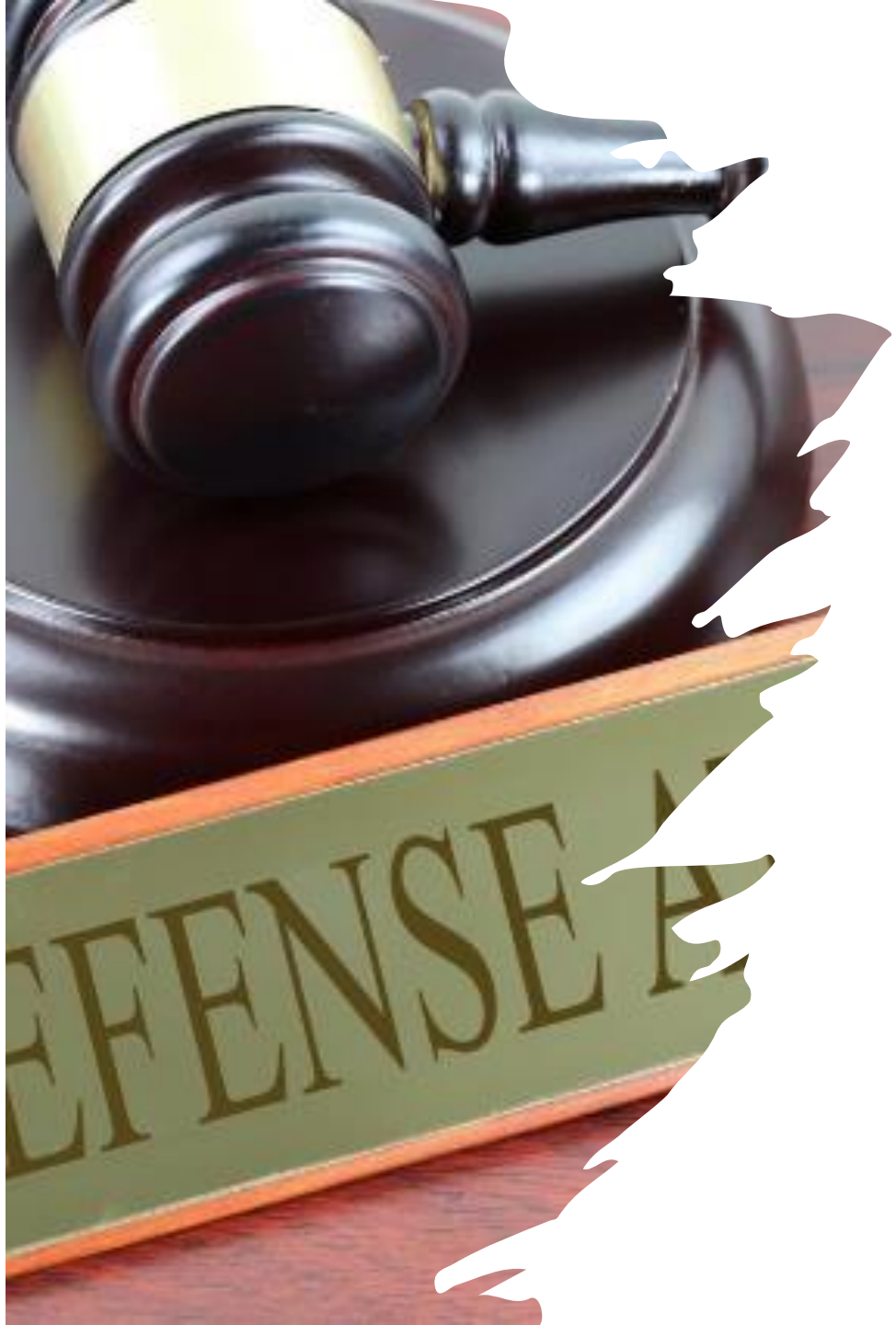


Is it CRS or HIPEC



HIPEC Arm


HIPEC Arm (open or closed technique)
After Cytoreductive surgery
IP
Oxaliplatin 460mg/m² in 30 minutes
(360mg/m² in closed procedures)
IV
Folinic Acid 20mg/m²
5 FU 400mg/m²
During HIPEC

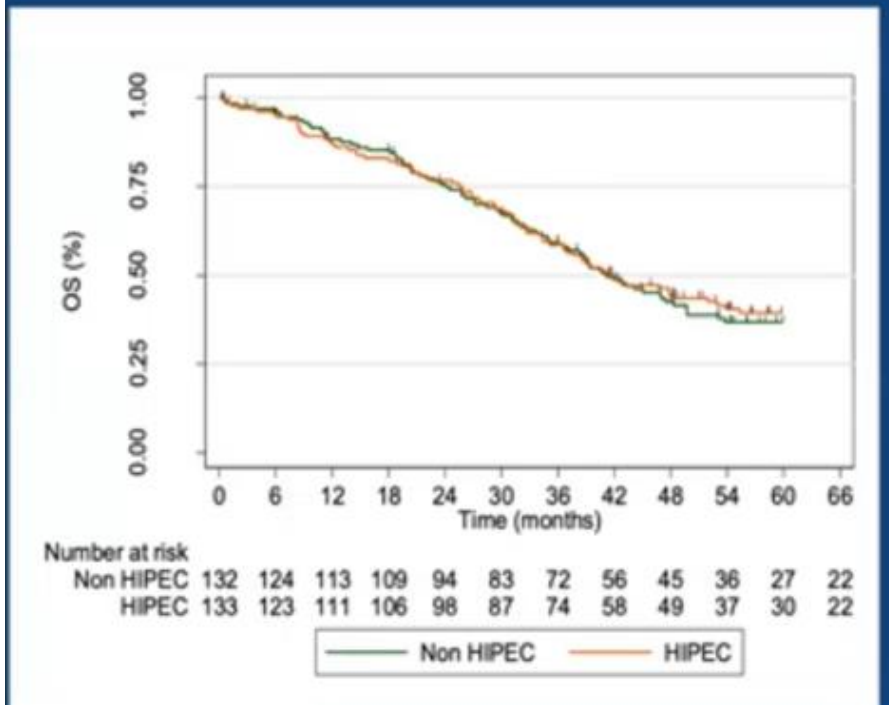


(*Sugarbaker and Chang, JSO 2021*)

- **Oxaliplatin** alone is NOT an effective agent for colorectal cancer with **a 20% response rate**
- The dose of **5-fluorouracil** by continuous infusion to achieve a maximal tolerable effectis 2400 mg/m2 over 48 hours, The dose of 5-fluorouracil in the PRODIGE 7 is only 400 mg/m2
- 58% of patients with **PCI ≤11** were likely to be NAC complete or near complete responders and are expected to have a favorable outcome with CRS alone
- **30 minutes** HIPEC is too short

Positive Lessons from Negative trial

Overall survival (ITT)



Median Follow Up: 64 months [95% CI:58.9-69.8]

	HIPEC	Non-HIPEC	P-value
Median Survival (months) [95% CI]	41.7 [36.2-52.8]	41.2 [35.1-49.7]	0.995
1-year Survival	86.9%	88.3%	
5-year Survival	39.4%	36.7%	

HR=1.00: 95%CI [0.73 - 1.37] p=0.995

HIPEC in Egypt 2010-2022

Great Enthusiasm and high Expectations from both oncologists and helpless hopeless patients.

We soon realized

- CRS and HIPEC **do not fit** all patients .
- There should be a **criteria to select** a subgroup of patients who carry good biological, pathological and clinical parameters

Decision making process is hard and complicated **(MDT)**

1. **Age**
2. **PS**
3. **DFI**
4. **PCI**
5. **Signet ring /non signet ring**
6. **Associated resectable metastases**
7. **Patient motivation**
8. **Expert center**

Selection..
Decisions Not Incisions

Contents lists available at ScienceDirect

Journal of the Egyptian National Cancer Institute

journal homepage: www.sciencedirect.com

Full length article

Peritoneal carcinomatosis in colorectal cancer: Defining predictive factors for successful cytoreductive surgery and hyperthermic intraperitoneal chemotherapy – A pilot study

Ahmed Mostafa Mahmoud [a,*], Yahia M. Ismail [b], Alaadin Hussien [a], Yasser Debaky [a], Ihab S. Ahmed [a], Hisham S. Wahba Mikhael [c], Manar Moneer [d]

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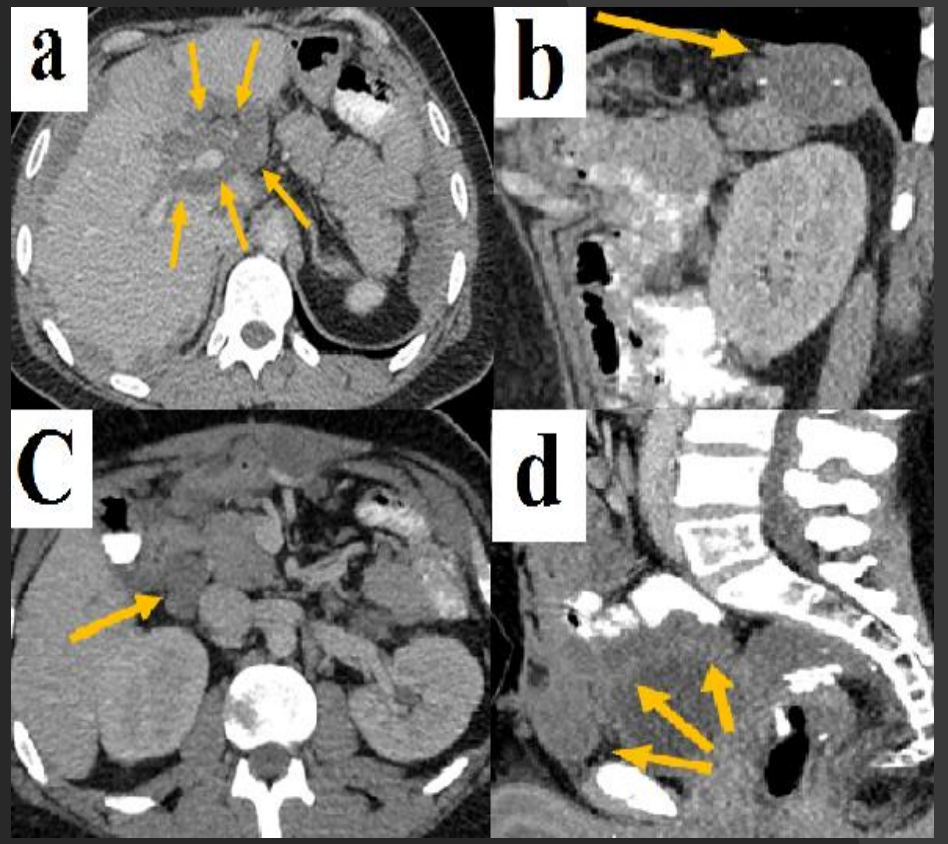
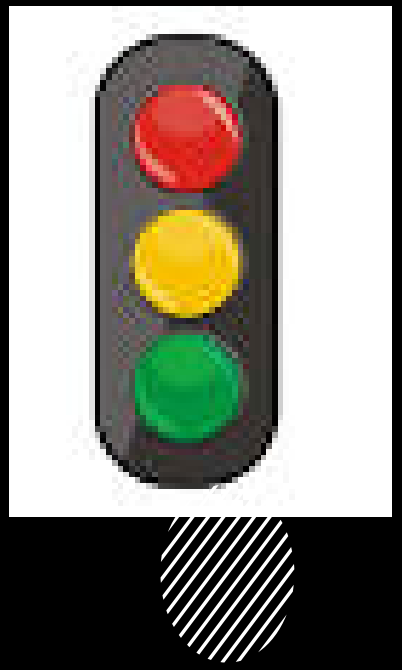
[b] Department of Medical Oncology, National Cancer Institute, Cairo University, Egypt
[c] Department of Radio diagnosis, National Cancer Institute, Cairo University, Egypt
[d] Department of Cancer Epidemiology and Biostatistics, National Cancer Institute, Cairo University, Egypt

Special Radiological Focus to **Critical Sites:**

- Hilum of the liver
- Duodenum
- Dudenojejunal junction
- Root of mesentery
- Base of the bladder

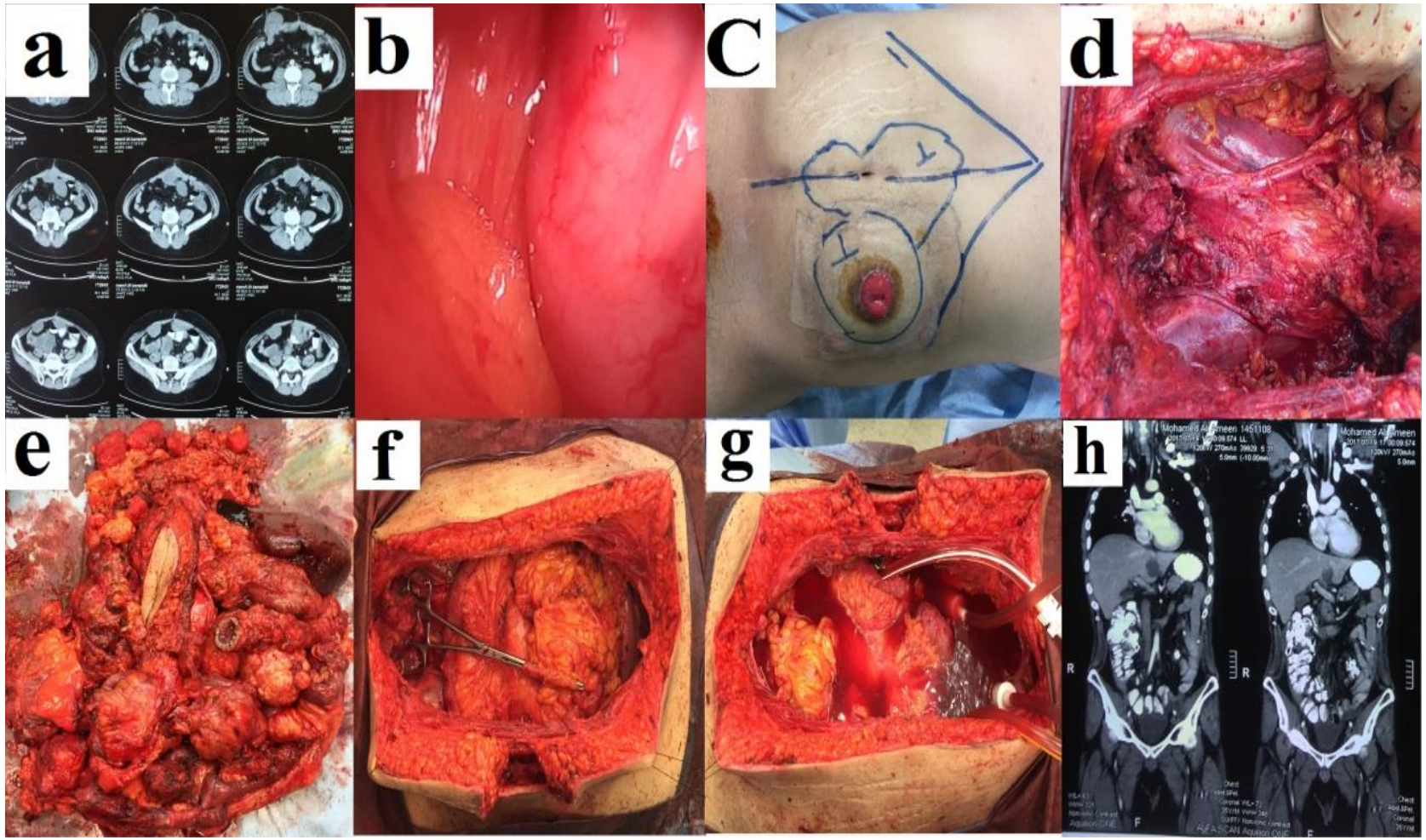


Diagnostic **Laparoscopy**



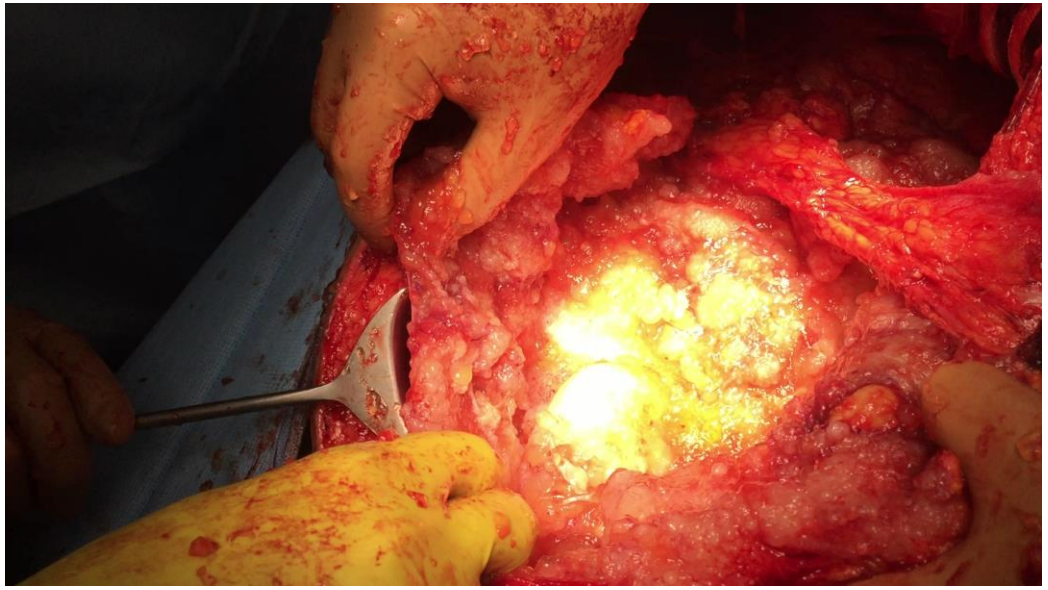
- Prior surgical scars and bulky tumor recurrence are avoided
- Midline trocars or Left upper or right upper quadrants
- Special focus to exclude extensive PCI with extensive mesenteric root involvement and/or extensive small bowel serosal involvement.

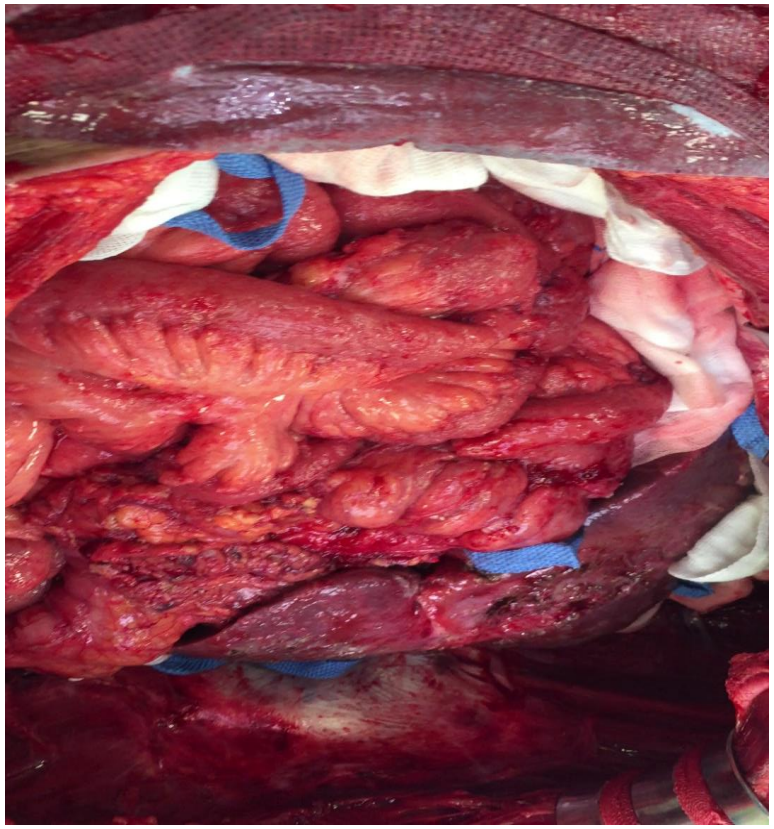
Diagnostic Laparoscopy



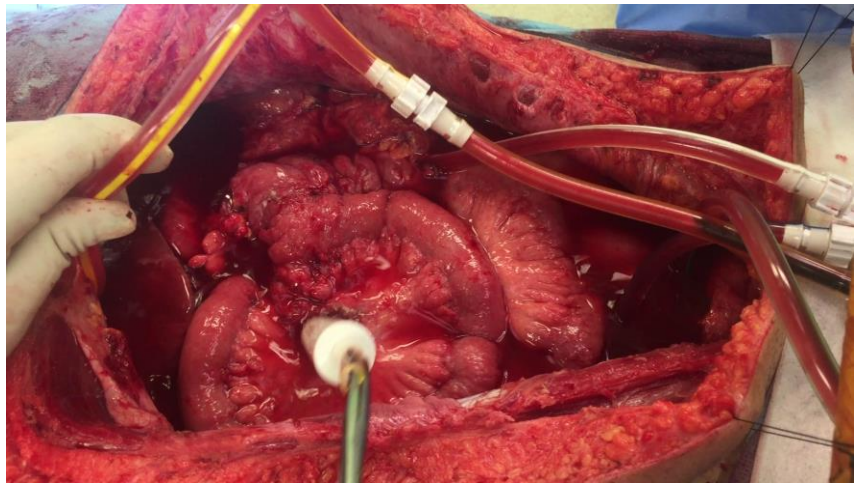
Very extensive cytoreduction in 65 years old male patient with recurrent mucinous carcinoma of right colon.

Before/After





- After CRS, HIPEC was performed using either the closed or open coliseum technique
- The abdominal cavity was perfused for one and half hour with isotonic dialysis fluid containing mitomycin C (20 mg/m2) at 42 °C



Factors affecting resectability

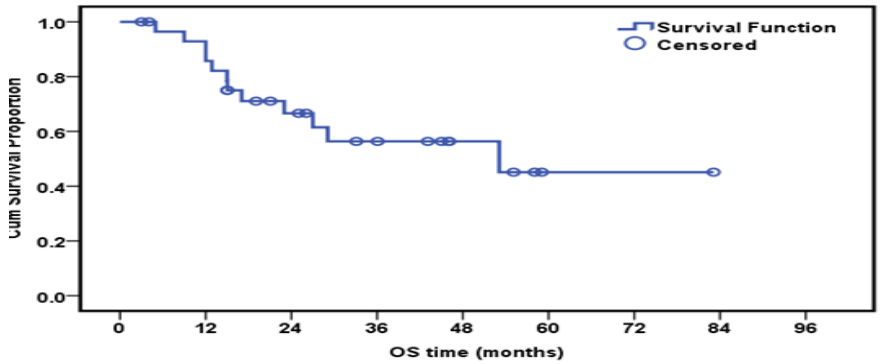
Variable	Not resectable	resectable	P value
Age			0.36
Less than 40 years	4 (33.3%)	8 (66.7%)	
More than 40 years	9 (50%)	9 (50%)	
Sex			0.17
male	6 (33.3%)	12 (66.7%)	
female	7 (58.3%)	5 (41.7%)	
Site			0.08
Ascending colon and Transverse colon	5 (41.7%)	7 (58.3%)	
Descending colon and sigmoid colon	3(25%)	9 (75%)	
Rectum	5 (83.3)	1 (16.7%)	
Pathology			0.43
*AC	5 (35.7%)	9 (64.3%)	
**SC and MC	8 (50%)	8 (50%)	
Ascites			<0.001
absent	5 (22.7%)	17 (77.3%)	
Present	8 (100%)	0 (0 %)	
Intestinal obstruction			0.13
absent	8 (33.3%)	16 (66.7%)	
present	4 (66.6 %)	2 (33.3%)	
Ureteric obstruction			***
Absent	11 (40.7%)	16 (59.3%)	
Present	2 (66.7%)	1 (33.3%)	
Retroperitoneal LNs			***
Negative	11 (42.3%)	15 (57.7%)	
Positive	2 (50%)	2 (50%)	
PCI			<0.001
≤ 20	1 (7.1%)	13 (92.9%)	
> 20	12 (75%)	4 (25%)	

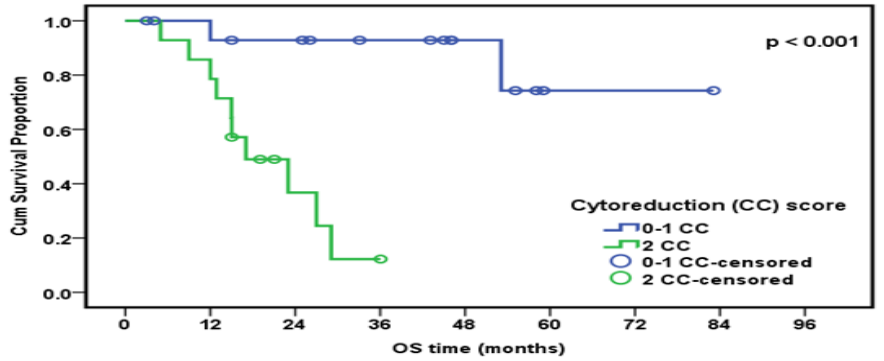
- The presences of **ascites**, extensive peritoneal disease (**PCI > 20**) were significantly correlated with failure to achieve CRS and HIPEC ($p<0.001$), also primary **rectal site** showed a trend towards significance ($p = 0.08$)

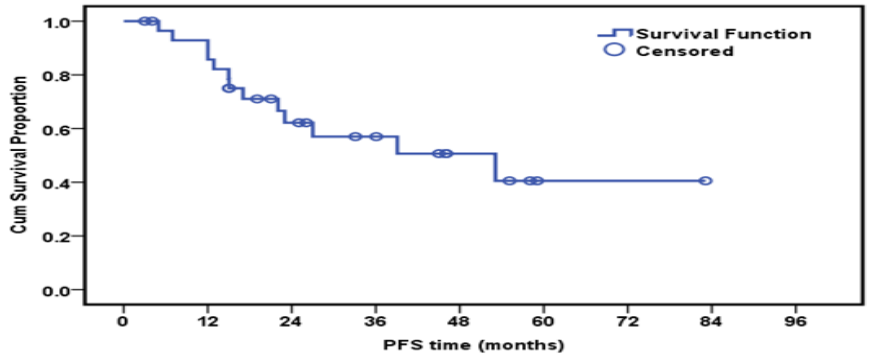
OS in relation to different prognostic factors

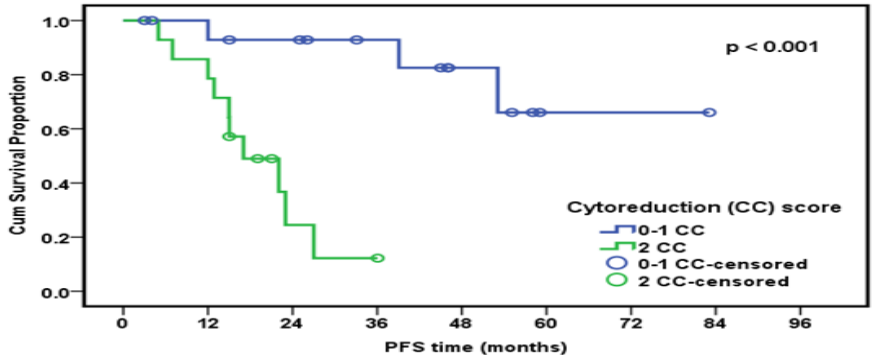
	No.	No. of events	Cumulative survival at 24 months (%)	Median survival(Months)	P- value
Whole group	30	12	66.6	53	NA
Age:					
<40	12	3	71.6	*	0.180
≥40	18	9	63.5	29	
Gender:					
Male	18	8	61.4	53	0.519
Female	12	4	75.0	*	
Ascites:					
Yes	8	7	37.5	17	0.006
No	22	5	80.0	*	
Anatomical site:					
Rectum	6	6	0.0	12	
Left colon+sigmoid	12	3	80.0	53.09	<0.001
Right colon+transverse	12	3	91.7	*	
I.O.					
Yes	5	4	40.0	22.99	0.035
No	25	8	76.7	*	
PCI					
≤20	14	2	100	*	0.002
>20	16	10	39.4	17	
CC					
0/1	17	2	92.9	*	<0.001
2	13	10	36.7	17	
Pathology					
Adenocarcinoma(NOS)	14	7	46.7	17	0.117
Mucinous/signet ring	16	5	80.2	*	
Grade					
II	24	8	72.1	*	0.275
III	6	4	50.0	23	
T Stage					
II/III	24	10	65.3	53.09	0.488
IV	6	2	75.0	27	
Presentation					
Synchronous	10	4	75.0	53	0.746
Metachronous	20	8	62.9	*	

- Patients presented with malignant ascites ,PCI>20 ,intestinal obstruction and primary rectal origin had significantly worse OS









- The cumulative overall survival (OS) and progression-free survival (PFS) **66.6 & 62.6%** respectively.
- Patients achieved **CC-0/1 had significantly prolonged OS compared to CC-2** (p<0.001)

Conclusion

- **CRS and HIPEC** as a loco-regional treatment strategy **provide longer survival** for PMP and PC-CRC patients when proper selection is carried out preoperatively.
- For CRC, patients with extensive peritoneal disease **(PCI>20), malignant ascites and IO** are poor candidates for the procedure.
- Overall, the prognosis of PC-CRC cases is still dismal, so applying **strict selection criteria** is a must to avoid unprofitable exploration.
- **Diagnostic laparoscopy** is an integral part of assessment of patients with PSM.

Paul Sugarbaker

Criticism of current HIPEC methodology

1. Limited chemotherapy penetration into tumor is by simple diffusion.
2. Chemotherapy that enters the tumor cell is rapidly cleared by blood and lymph flow into the body compartment.
3. Chemotherapy that enters the tumor cell is eluted back into the peritoneal space immediately after HIPEC ceases.

(HIPEC deficiencies because of limited penetration, rapid clearance and rapid elution are corrected by meticulous cytoreduction until no visible peritoneal metastases remain. The visceral peritoneal surfaces must be targeted by HIPEC)

Criticism of current HIPEC methodology

4. Heat and chemotherapy distribution may not be uniform even in the open method. It is not uniform in the closed method.

(The closed technique does not distribute heat and chemotherapy uniformly)

Criticism of current HIPEC pharmacology

5. Chemotherapy cytotoxicity is limited to 30-50% of patients with current chemotherapy agents.

- The cytotoxicity of HIPEC can be improved by the use of two drugs and systemic plus intravenous administration.

6. A single application of chemotherapy is unlikely to be effective in the eradication of minimal residual disease.

- Multiple HIPECs have given promising results.

Thank You For Your Kind Attention