

# When to think of Surgery plus or minus HIPEC for Peritoneal Carcinomatosis ?

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# **For colorectal PC**

- 1. When to think to surgery ?**
- 1. Plus or minus Peritoneal Chemo ?**

# Stages IV treated with Chemo: **PC have a poorer prognosis than other sites**

From the phase III trials N9741 and N9841 (Folfox / Folfiri)

	Nb	Median OS
Without PC	1731	<b>17.6 months</b>
With PC	364	<b>12.7 months</b>

p < 0.01

**Conclusion:**

- Shorter OS and PFS when PC
- **5-y survival with Folfox: 4%**

(Franko J et al. ASCO 2011)

## PC have a poorer prognosis than other sites

*Randomized Deutch trials **Cairo1** and **Cairo 2** based on Xelox*

	<b>Without PC</b>		<b>With PC</b>		
	Nb	Median S.	Nb	Median S.	p
<b>Cairo 1</b> (no targeted therapy)	739	<b>17</b>	34	<b>10</b>	<0.001
<b>Cairo 2</b> (with targeted therapy)	689	<b>21</b>	47	<b>15</b>	<0.001

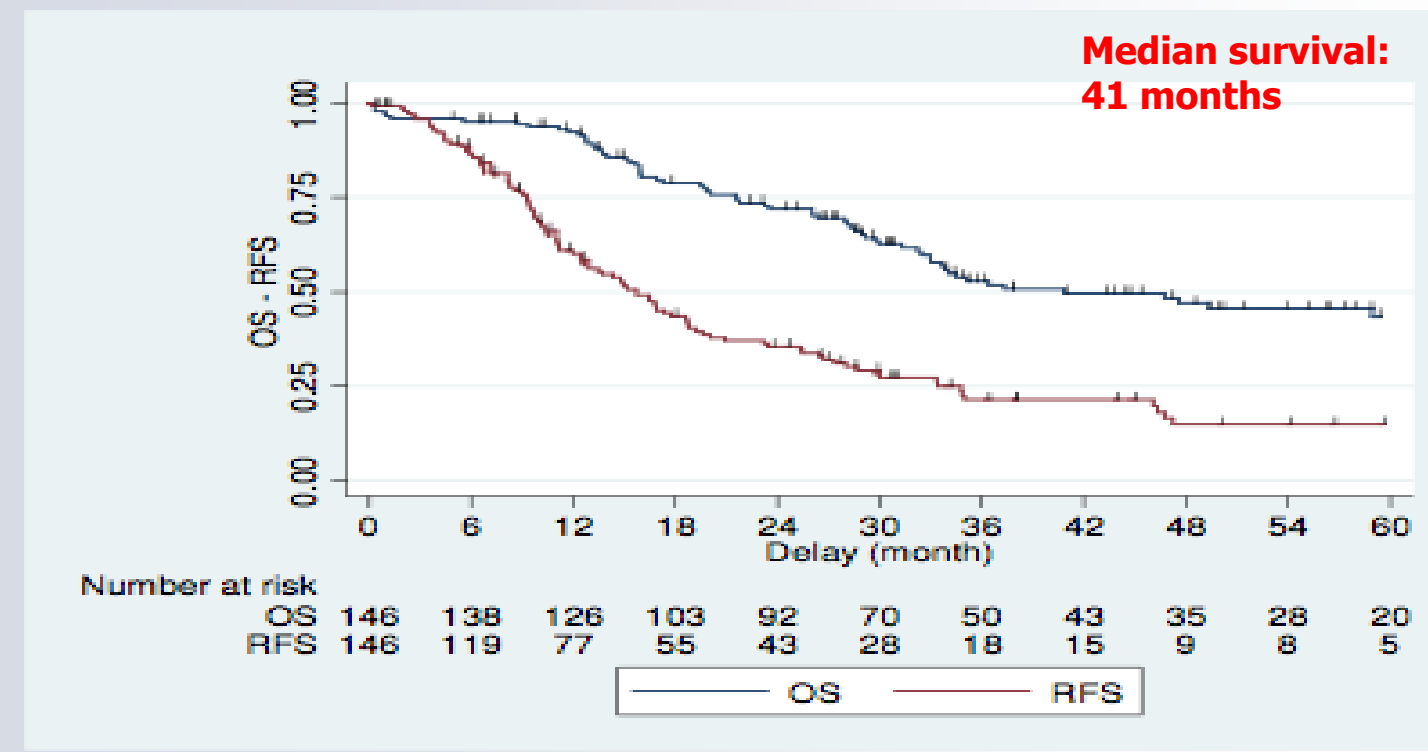
**Conclusion:** PC is a factor of severity, and resistance to chemotherapy

*(Klaver Y. et al. **EJSO** 2012; 38: 617-623)*



# Current survival rate of 146 colorectal PC treated with CCRS + HIPEC: Prospective bi-centric study (Paris/ Montpellier)

Fig.1 a The RFS and the OS of the whole patient population



(Quenet, Elias et al, Ann Surg 2011; 254: 294-301)

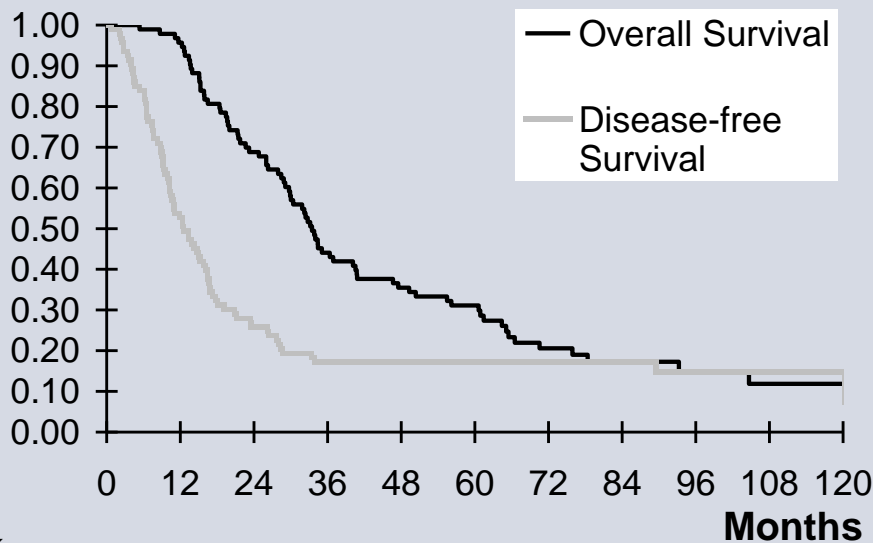
# **Is it possible to obtain definitive cure with CCRS + HIPEC ?**

- Prospective study of our patients treated between January 1995 and December 2005 (n=93). Learning curve = worst results.

**The Cure = no recurrence during a minimal delay of 5 years**

*(Goéré et al. Ann Surg 2012, in press)*

- **Median follow-up: 99 months**
- **Median Survival : 34 months**
- **Overall 5-year survival : 32%**



**Absolute cure at 5 years: 17/107 pts = 16%**

At risk

— 93	89	64	41	33	27	15	8	5	2	1
— 93	49	24	16	16	14	10	7	4	3	2

## Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure

James S. Tomlinson, William R. Jarnagin, Ronald P. DeMatteo, Yuman Fong, Peter Kornprat, Mithat Gonen, Nancy Kemeny, Murray F. Brennan, Leslie H. Blumgart, and Michael D'Angelica

**At 10 years:  
102/612 pts = 16,7%**

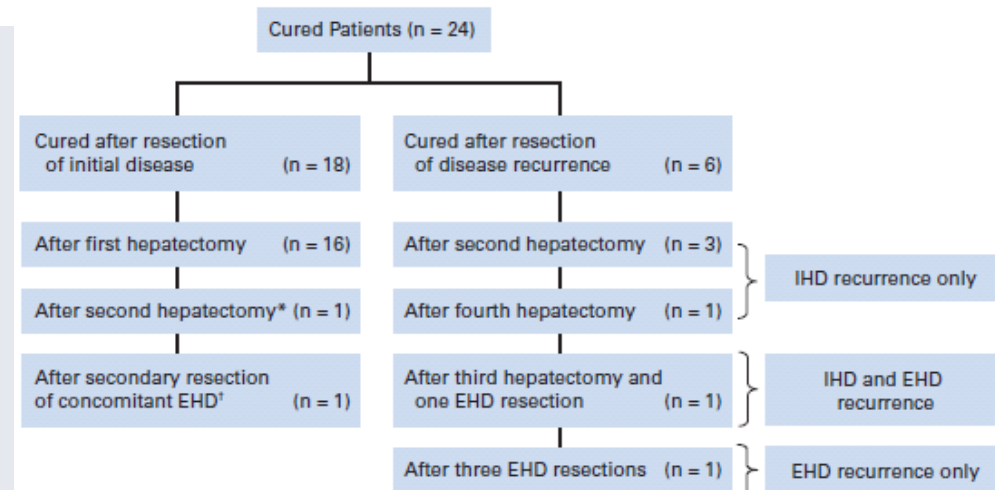
**Table 1.** Characteristics of 102 Actual 10-Year Survivors

Characteristic	No. of Patients
Disease status	
NED	99*
AWD	2
DOD	1
Median follow-up, months	146
Disease recurrence	16
Liver	7
Lung	6
Liver/lung	2
Peritoneum	1

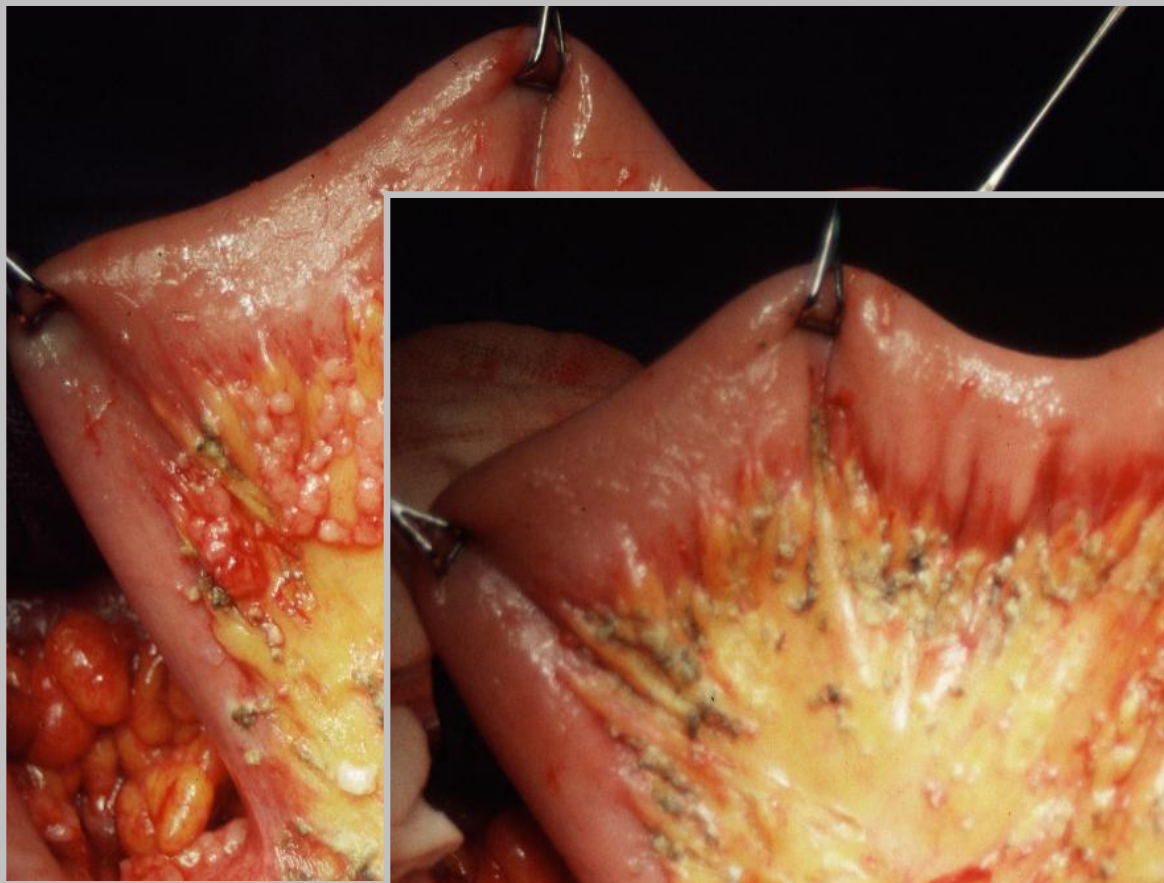
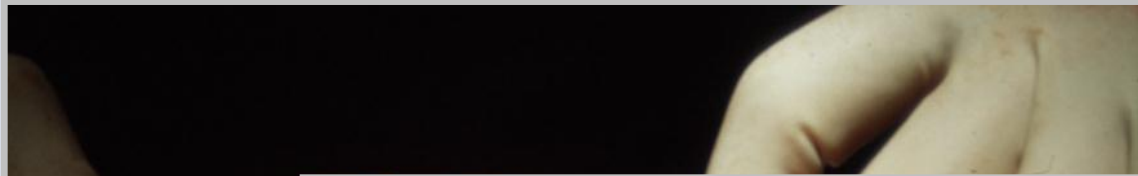
## Patients With Initially Unresectable Colorectal Liver Metastases: Is There a Possibility of Cure?

René Adam, Dennis A. Wicherts, Robbert J. de Haas, Oriana Ciacio, Francis Lévi, Bernard Paule, Michel Ducreux, Daniel Azoulay, Henri Bismuth, and Denis Castaing

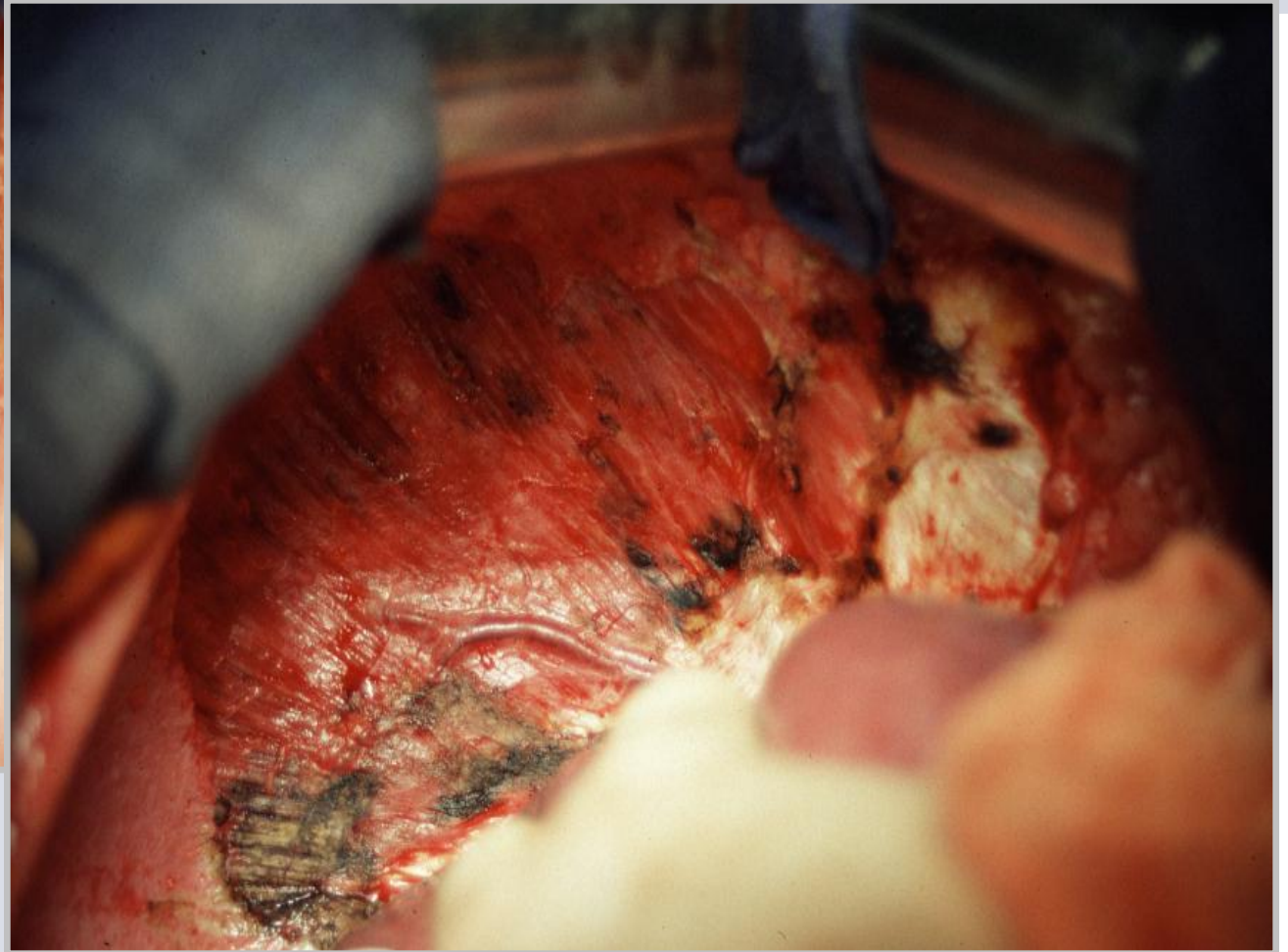
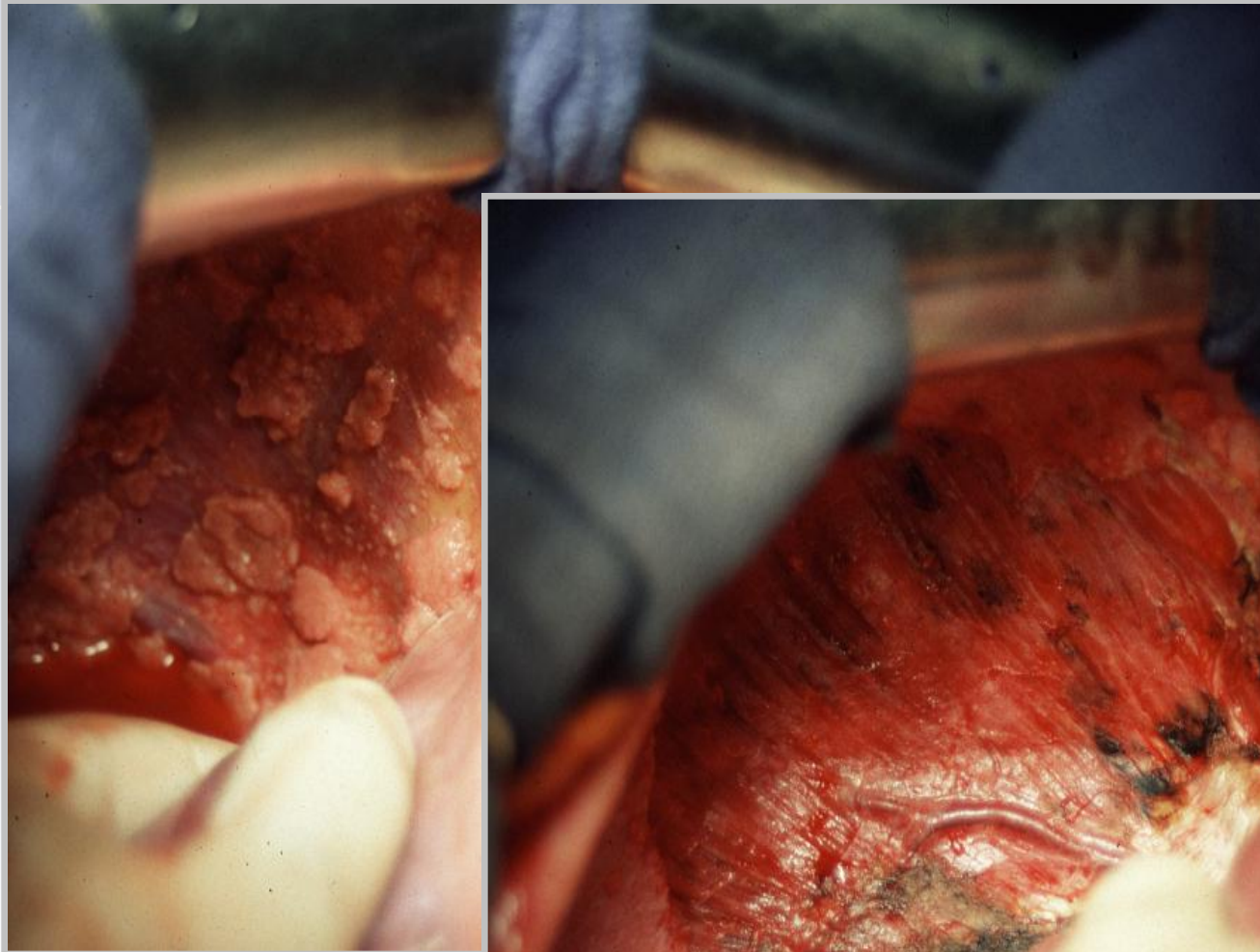
**At 5 years without rec.  
24/148 pts = 16%**

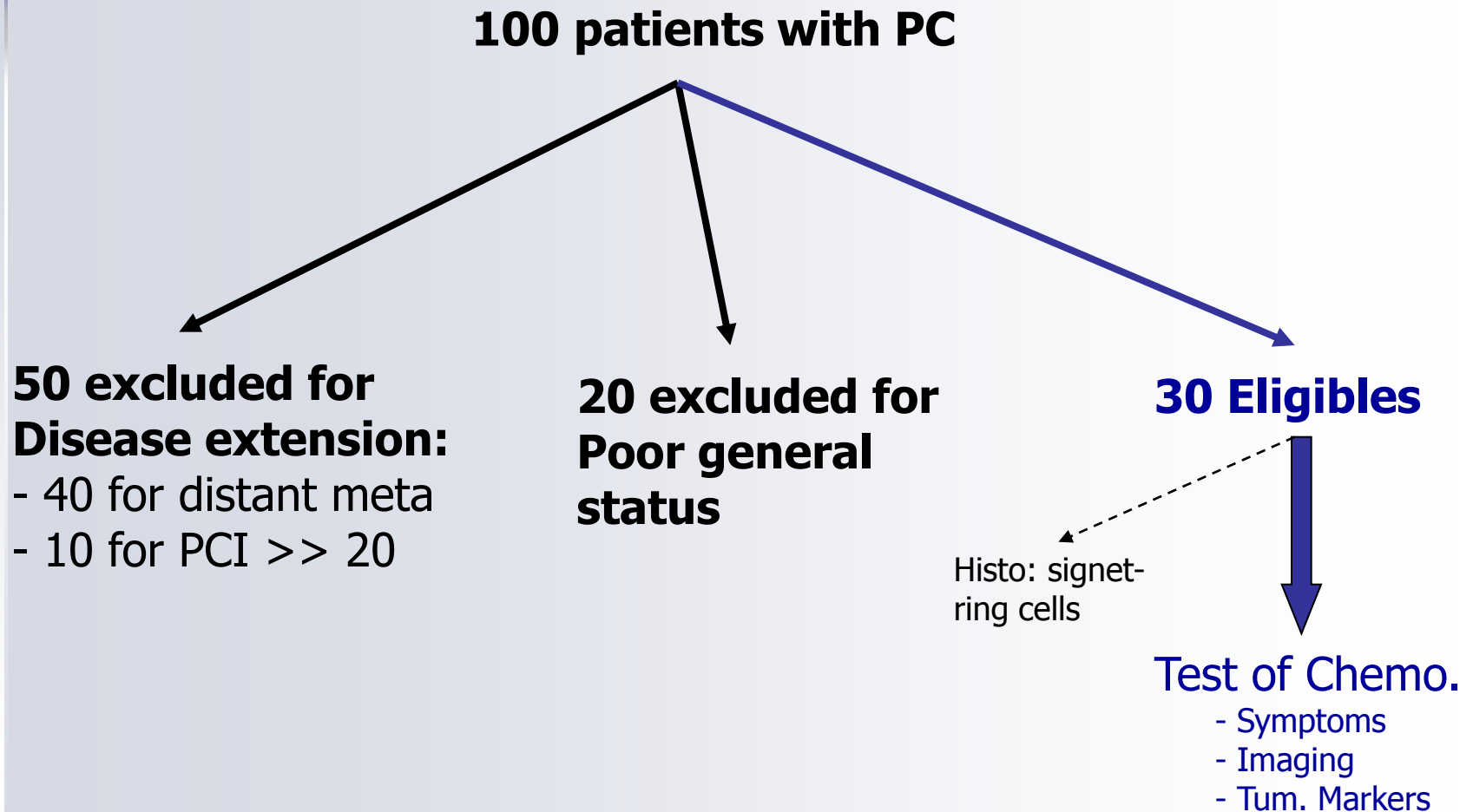


# **1) Who is resectable ?**











# Outcome of patients with PC progressing under chemo.

- Those who progress under chemo have an hazard ratio X 5 to be non resectable

*(Cashin P et al. EJSO 2012)*

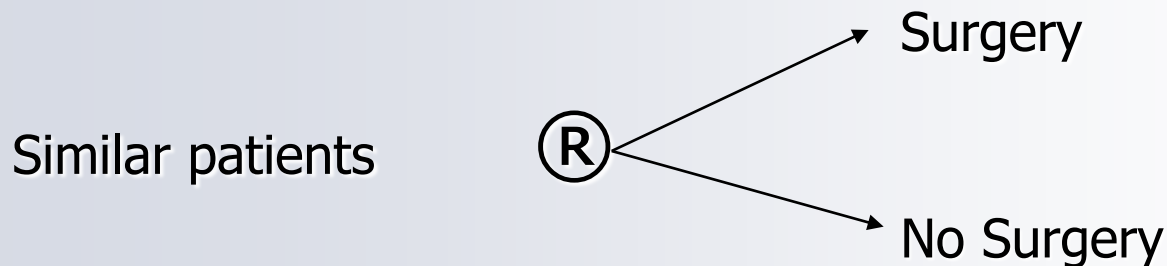
# 1st Conclusion:

- 20-25% of patients with PC are eligible for surgery
  - Without distant metastases
  - With a minimal or moderate PC
  - With a good general status
  - Who did not progress under chemo.

## **2) Is there a benefit to use surgery alone ?**

# Surgery *versus* No Surgery

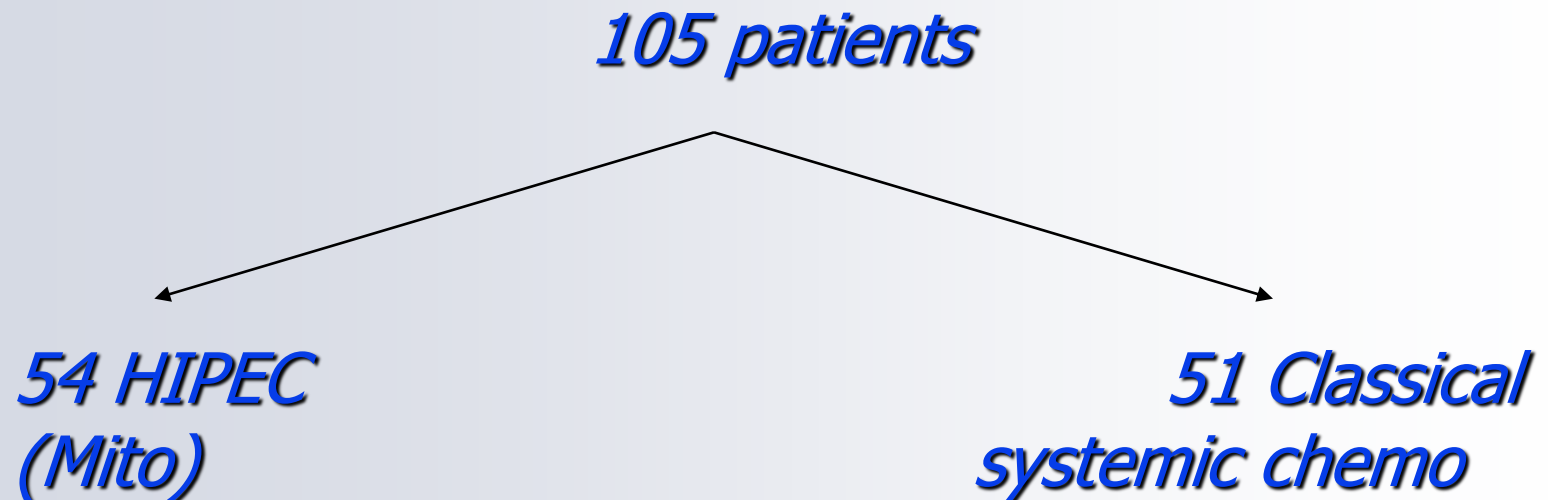
- Is there a trial comparing ?



- Answer is: NO

but 2 trials give non direct arguments in favor of surgery

# Randomized study (Amsterdam)



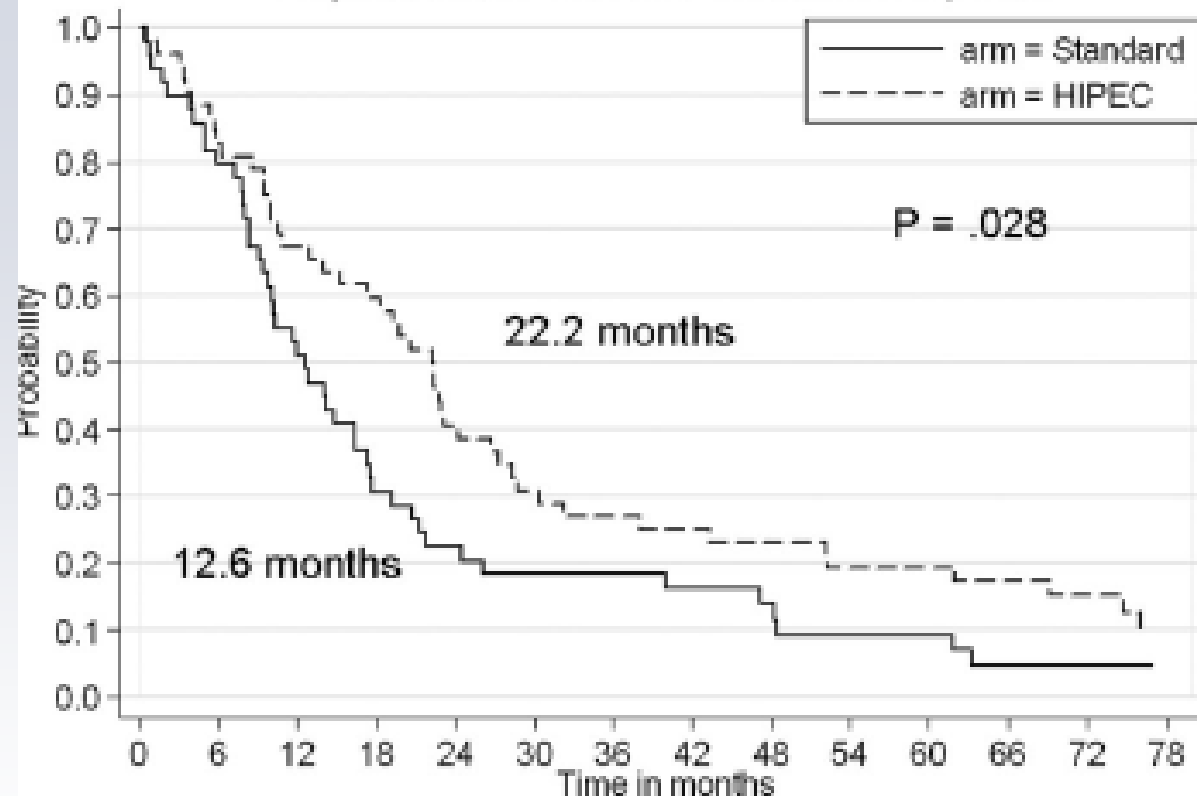
***Verwaal et al. J Clin Oncol 2003; 21: 3737***

# Cytoreduction in the HIPEC-group

	Number
no macroscopic tumour ( R1 )	18 (38%)
macroscopic tumour < 2 mm (R2 <sup>a</sup> )	21 (43%)
macroscopic tumour > 2 mm (R2 <sup>b</sup> )	9 (19%)

# Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer

By Vic J. Verwaal, Serge van Ruth, Esko de Bree, Goutie W. van Slooten, Harm van Tinteren, Henk Boot, and Frans A.N. Zoelmulder

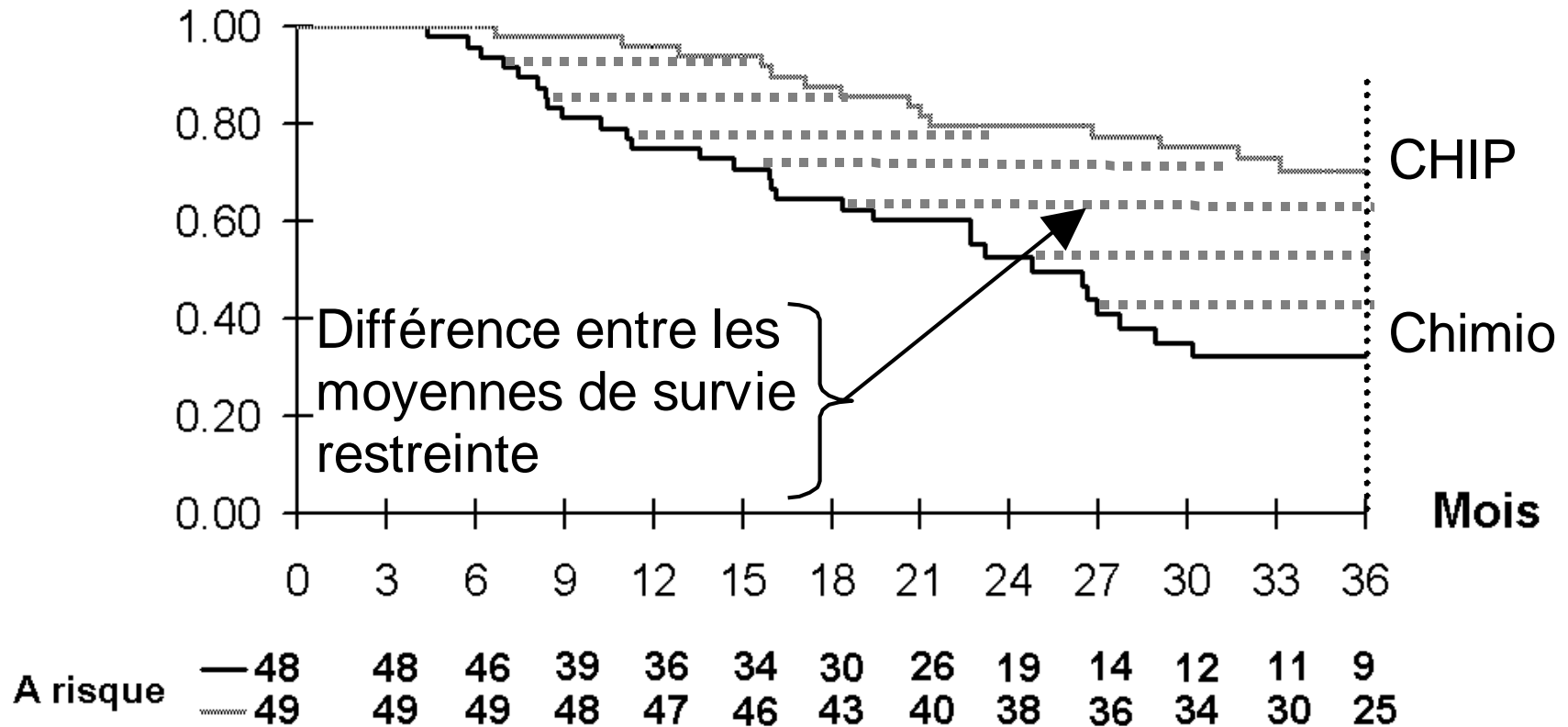


Median survival  
for surgical pts:  
**22 months**

# Retrospective comparative study

In the control group: 3.4 lines of chemo

Median survivals: 25 months vs 60 months



(Elias et al. J Clin Oncol 2009; 27:681-5)



# Complete resection alone of PC ?

	Nb	Selection	Median OS	5-Y Survival
Mulsaw 2011 (Erlangen)	31	IP <10	25 months	22%
Cashin 2012 (Uppsala)	57	+ SPIC*	25 months	18%
Evrard 2012 (Bordeaux)	30	IP <20	31 months	28%

\*SPIC = Sequential postop. intraperitoneal chemo.

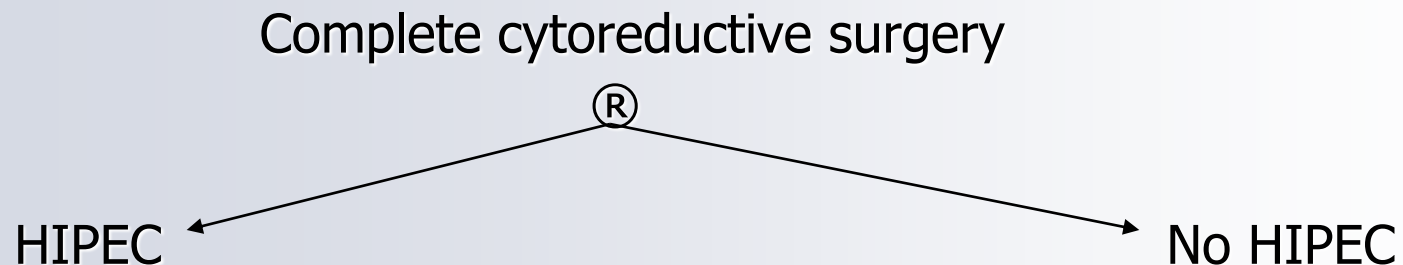
## **2<sup>nd</sup> Conclusion:**

- **When it is possible to resect the PC: it is useful for the patient.**
- **A complete cytoreductive surgery is far better than an uncomplete surgery: do your best to obtain it !**
- **If you succeed, median survival will be 25 months at least.**

### **3) Is it useful to add HIPEC ?**

# Complete surgery (CS) alone *versus* CS plus HIPEC ?

- We have not yet the answer
- French **Prodige 7** trial is on going  
(Already 310 eligible and 210 randomized patients among the 280...)



# Principle of HIPEC:

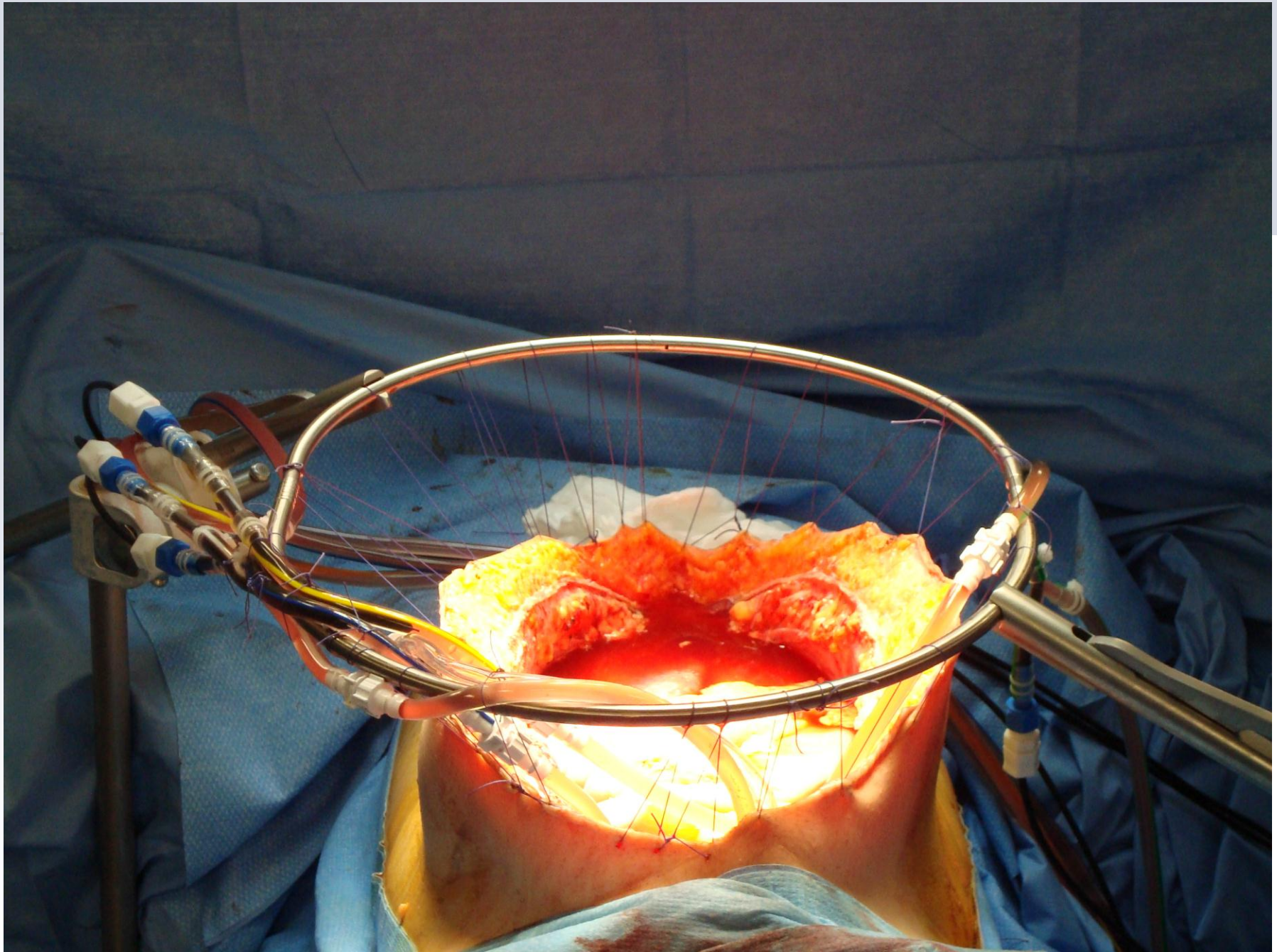
## A combined treatment

1. Surgery to treat the visible disease ( $> 1$  mm)
  2. HIPEC to treat the remaining non visible disease.
- The strong **belief** of surgeons in the efficacy of this « package » encourage them to devote a lot of time and a lot of energy to resecting all visible disease (+++).
  - This allows to underline the major prognostic impact of the **completeness** of cytoreductive surgery.















# Impact of HIPEC alone: experimental data

60 rats with colorectal PC were randomized in 3 arms.

Hipec: 90 min, close procedure, inflow temperature at **42°C**.

	CRS	CRS + HIPEC Mito <b>15 mg/m<sup>2</sup></b>	CRS + HIPEC Mito <b>35 mg/m<sup>2</sup></b>
Nb	20	20	20
R2	6	4	4
<b>Med. Surv</b>	<b>43d</b>	<b>75d</b>	<b>97d</b>
P		0.003	< 0.001

Conclusion: Efficacy of HIPEC and efficacy of increasing dosage.

*(Klaver Y et al. Br J Surg 2010; 97: 1874-80)*

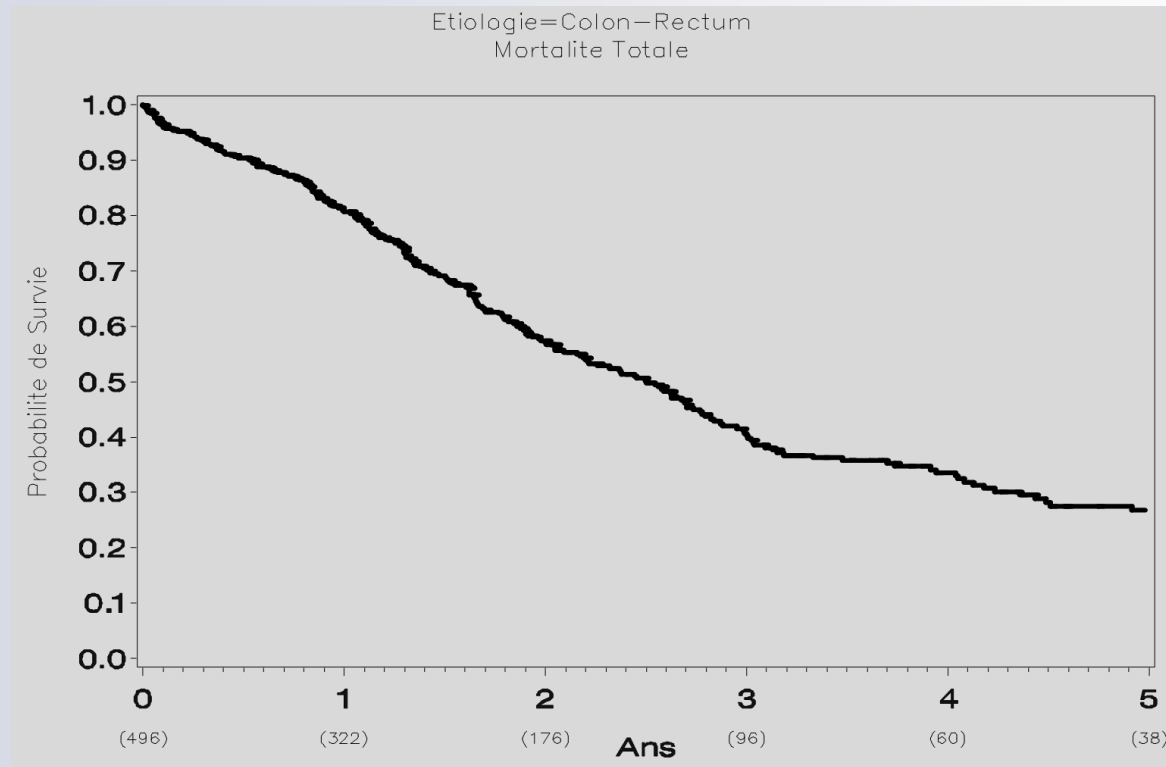
# French registry: 523 colorectal PC treated with cytoreductive surgery + intraperitoneal chemo treated in 23 centres.



- Multicentric retrospective study (15 years),
  - Including the leaning curves of all the centres = the worst results
  - Complete cytoreductive surgery (CC0) in 85% of the cases
- 
- Postoperative deaths: **3%**
  - Morbidity (grade 3-4): **30%**
  - Mean hospital staying: **22,5 days**

*(Elias et al. J Clin Oncol 2009; 27: 681-685)*

# Overall Survival of the 523 patients

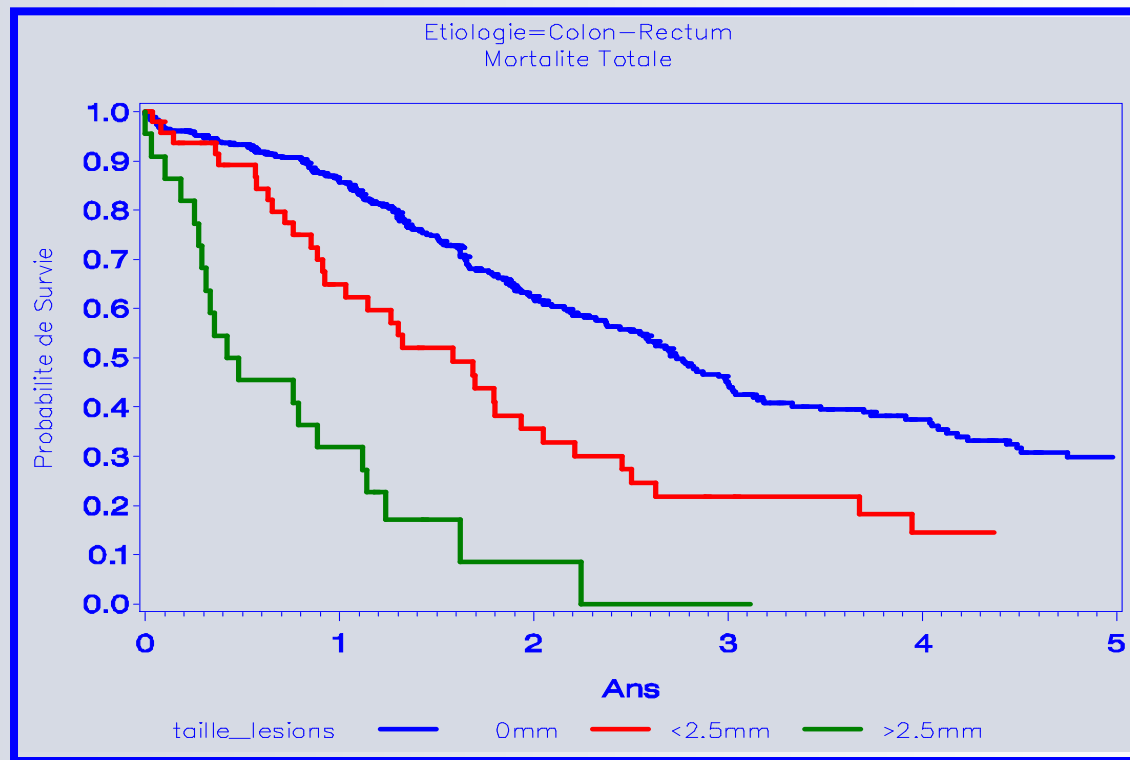


**Median survival: 30 months**

**5-years survival: 27%**

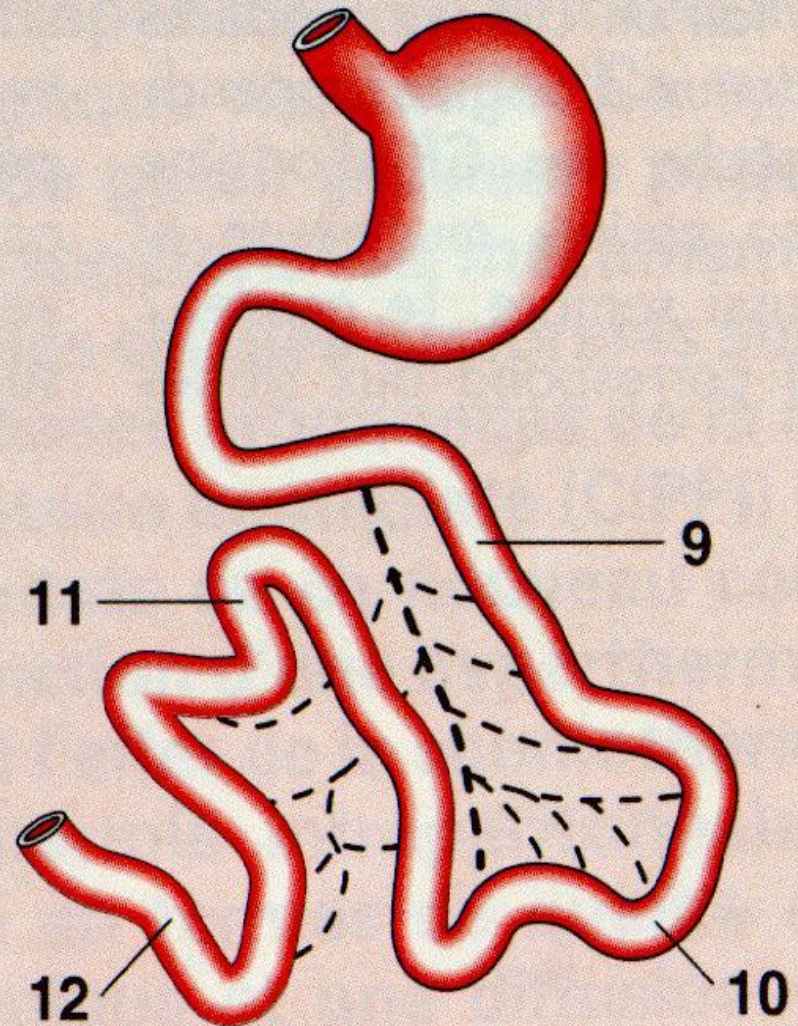
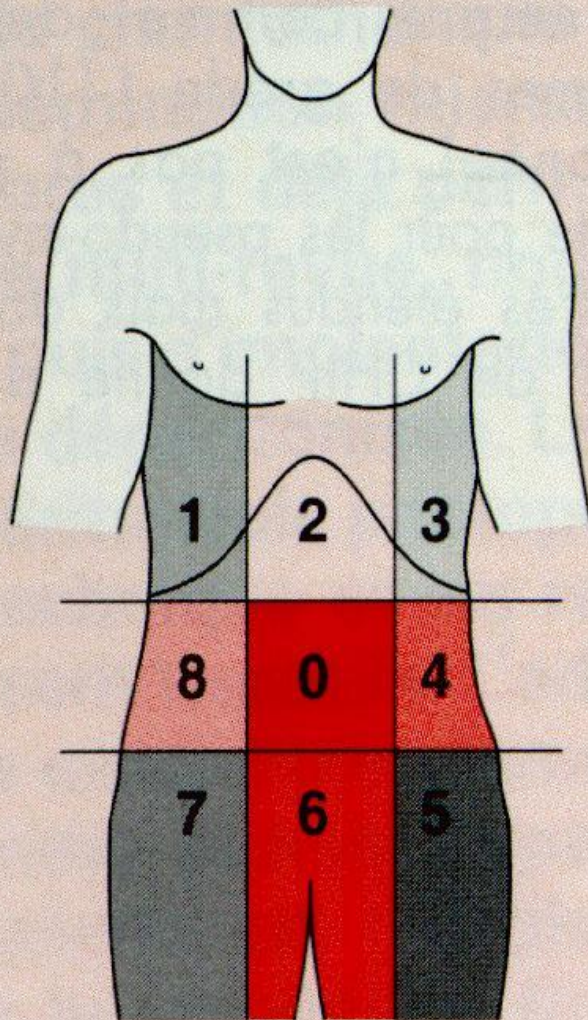
# Survival according to the **Radicality** of the Surgery ( $p < 0.0001$ )

## Look at the median survivals....

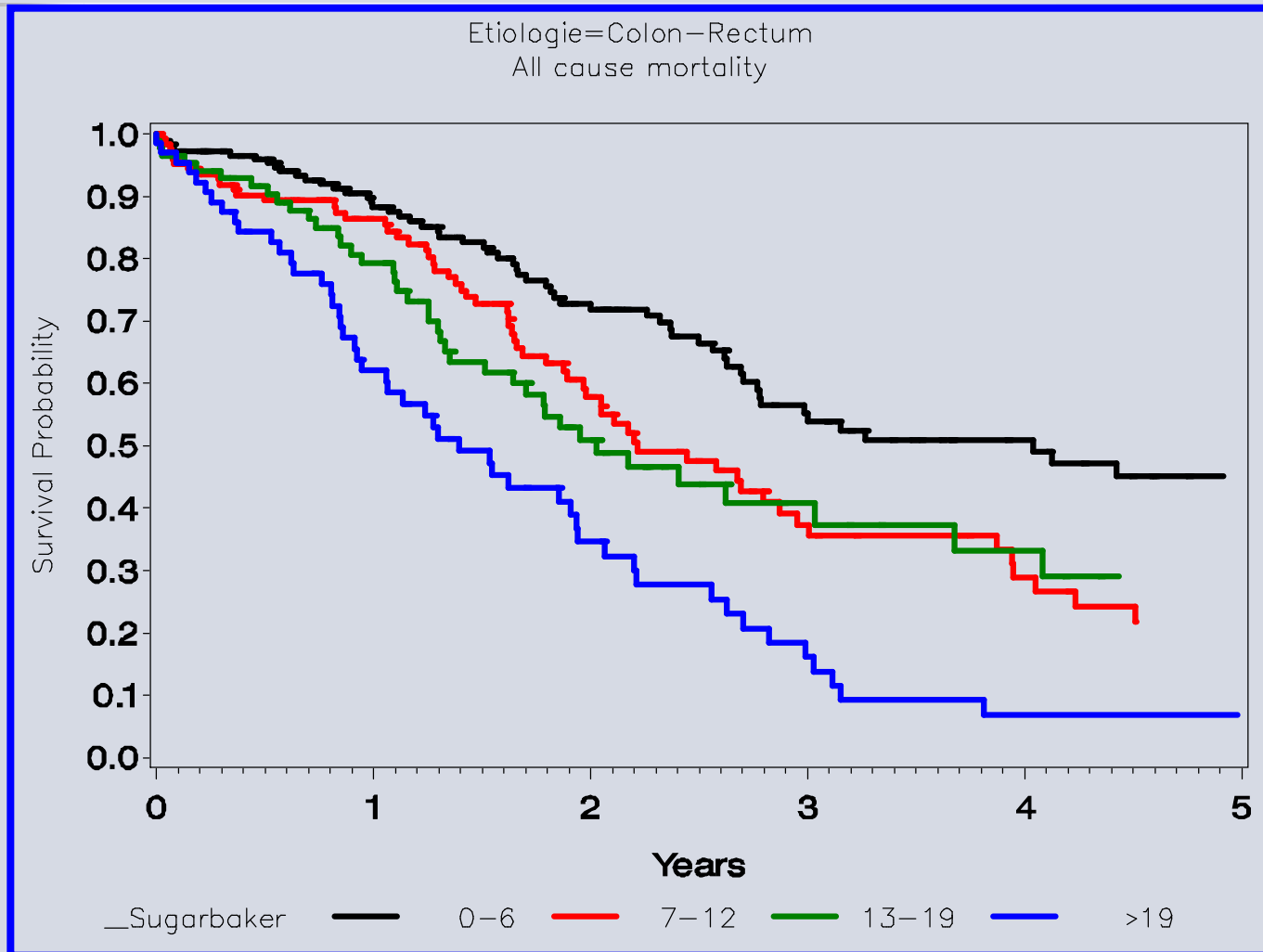




# The Peritoneal carcinomatosis Index (PCI)

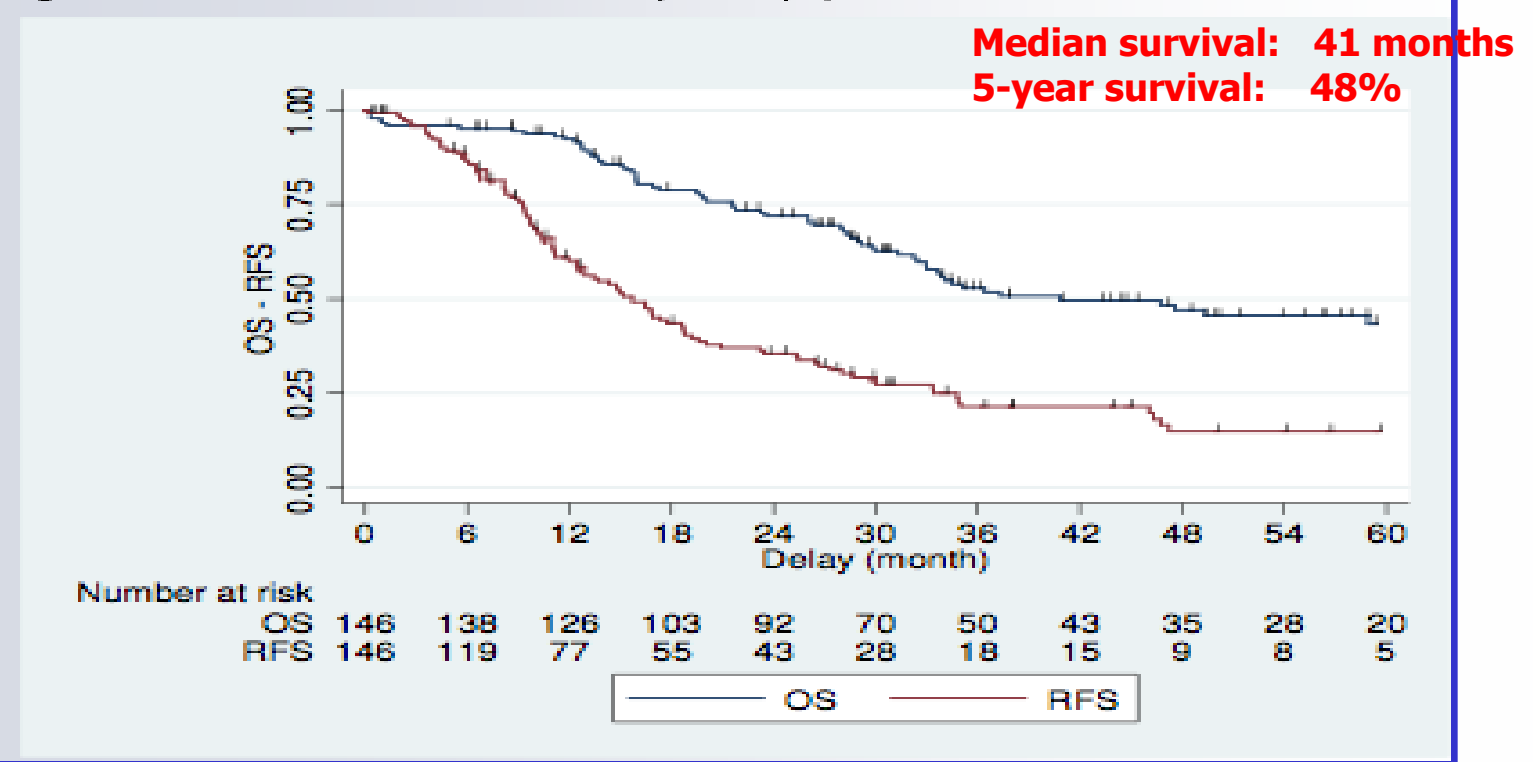


# Survival according to the **Extent** of the P ritoneal Carcinomatosis ( $p < 0.0001$ )



# Current survival rate of 146 colorectal PC treated with CCRS + HIPEC: Prospective bi-centric study (Paris/ Montpellier)

Fig.1 a The RFS and the OS of the whole patient population



(Quenet, Elias et al, Ann Surg 2011; 254: 294-301)



# At last.....

After a **complete** cytoreductive surgery followed with HIPEC, overall survival and definitive cure rates **are the same** than those obtained after **partial** hepatectomy for liver metastases.

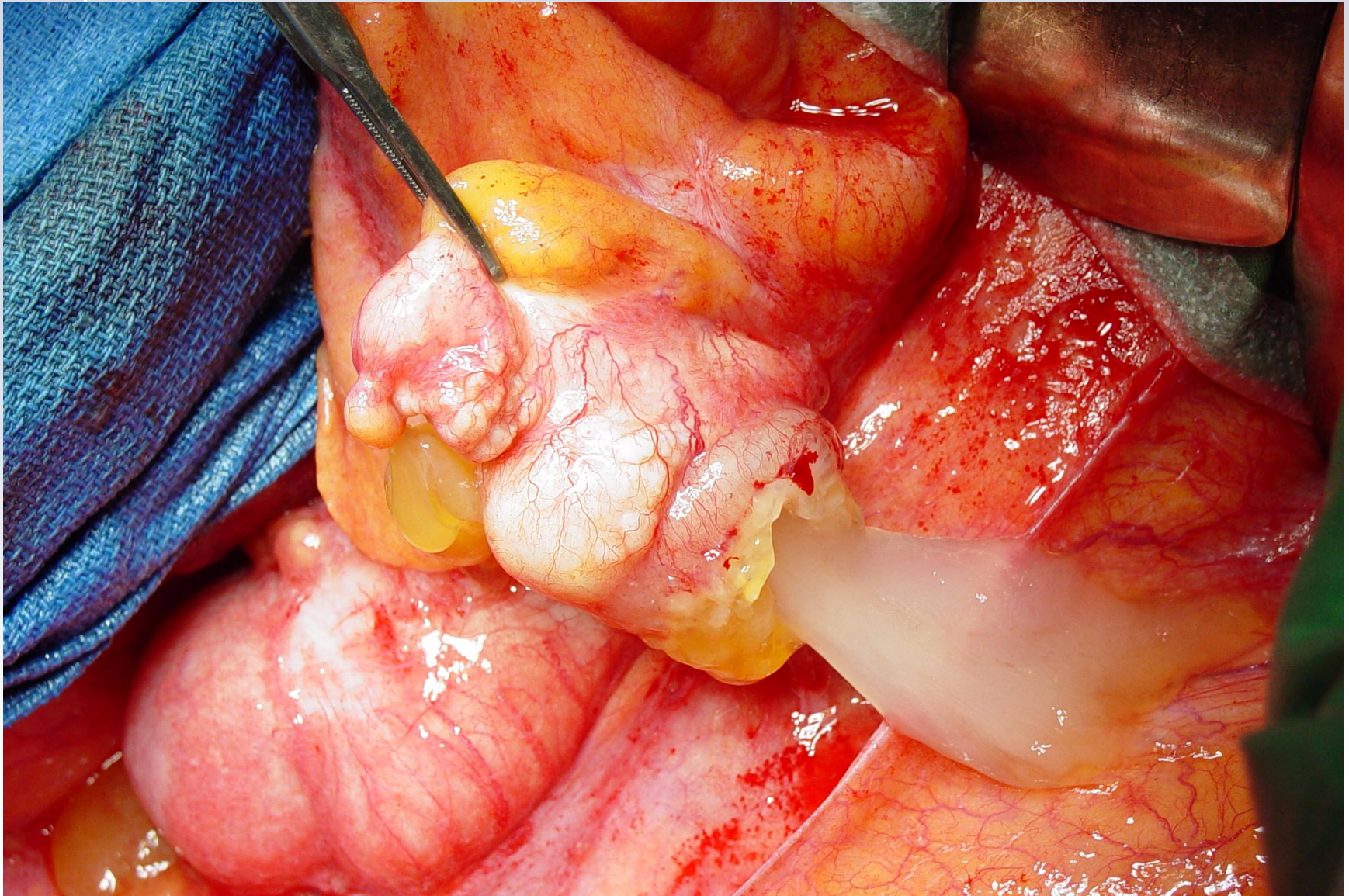


# **For non colorectal PC**

- 1. When to think to surgery ?**
- 2. Plus or minus Peritoneal Chemo ?**

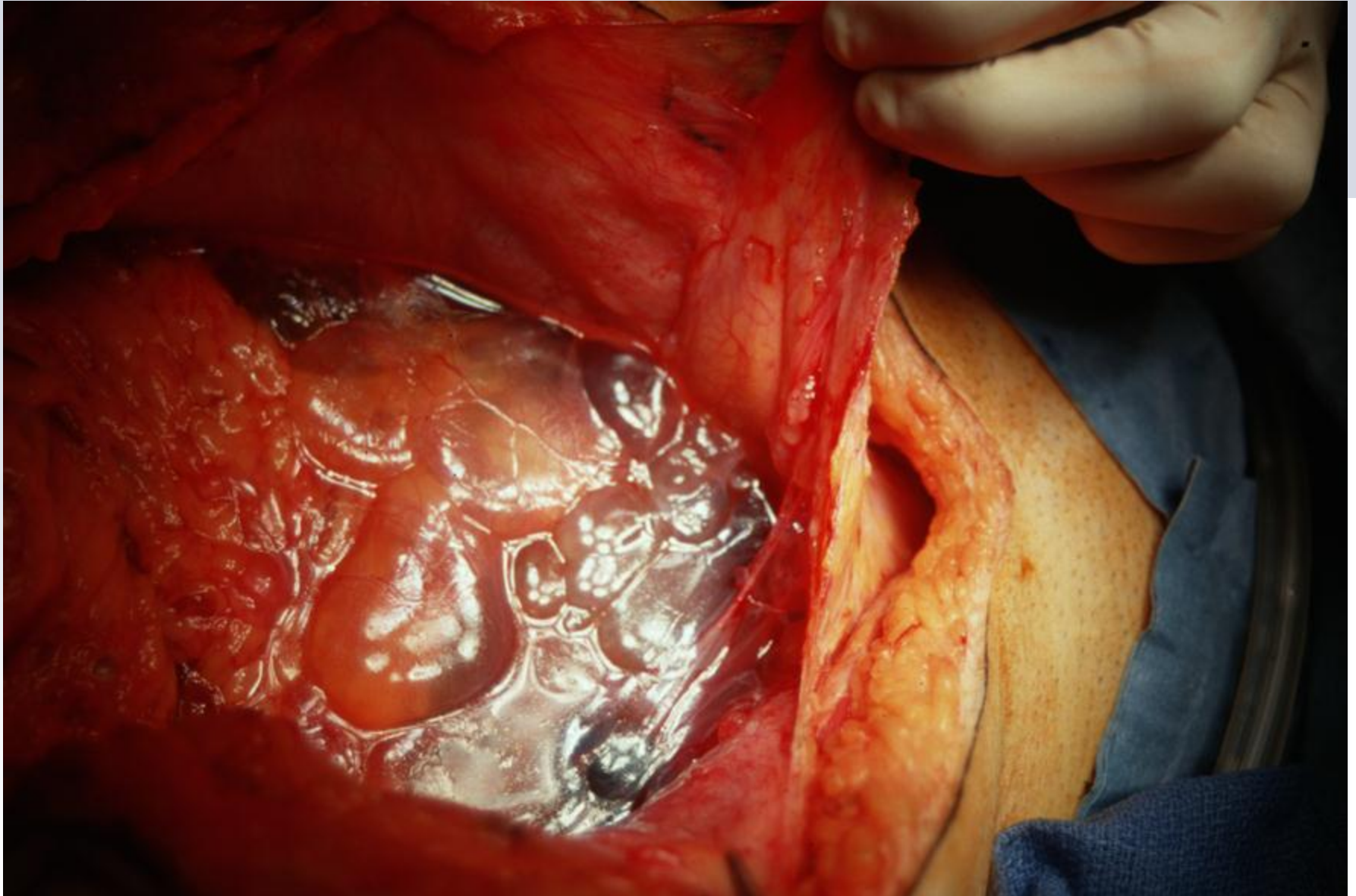
# Peritoneal Pseudomyxomas

- Low grades
- High grades

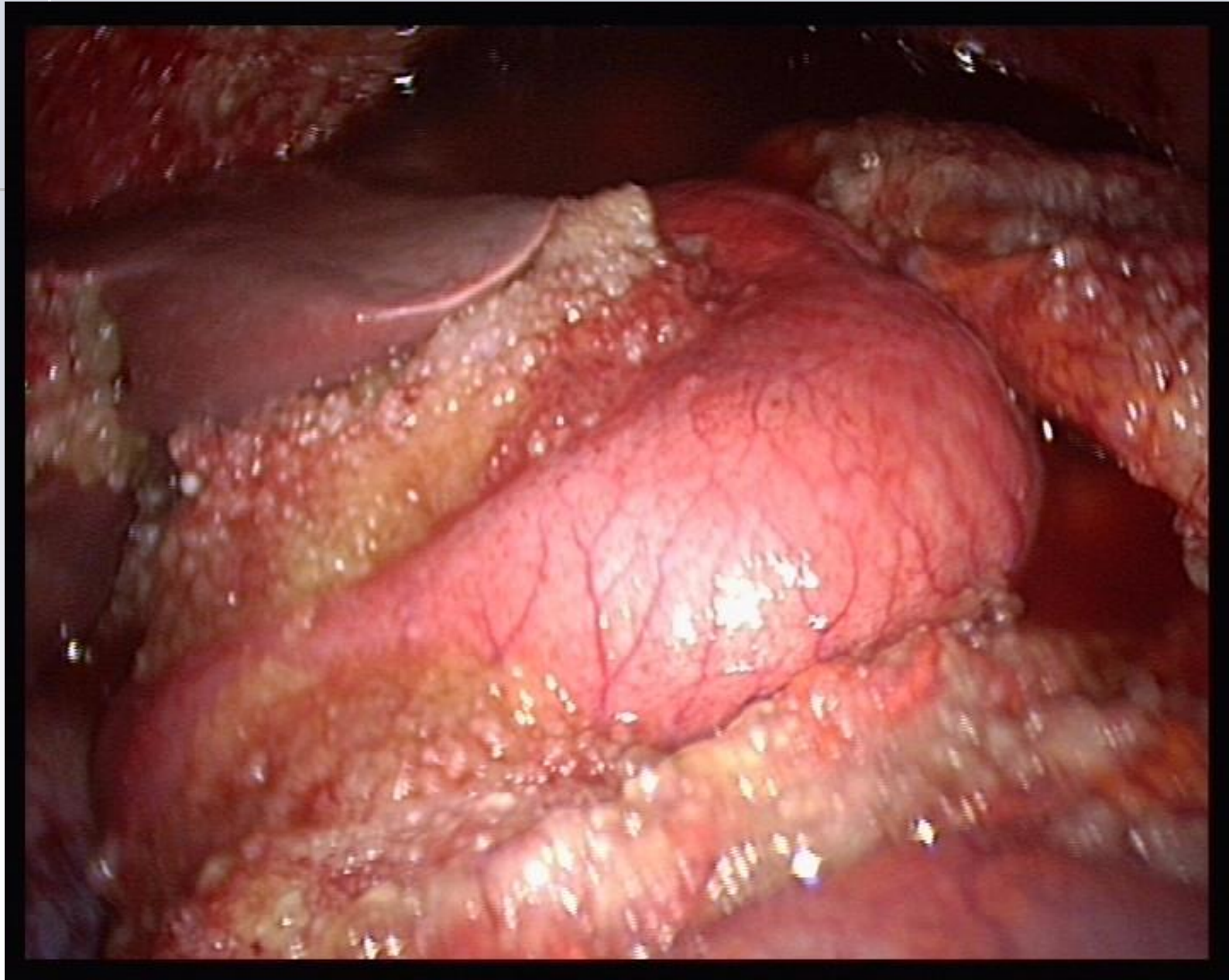


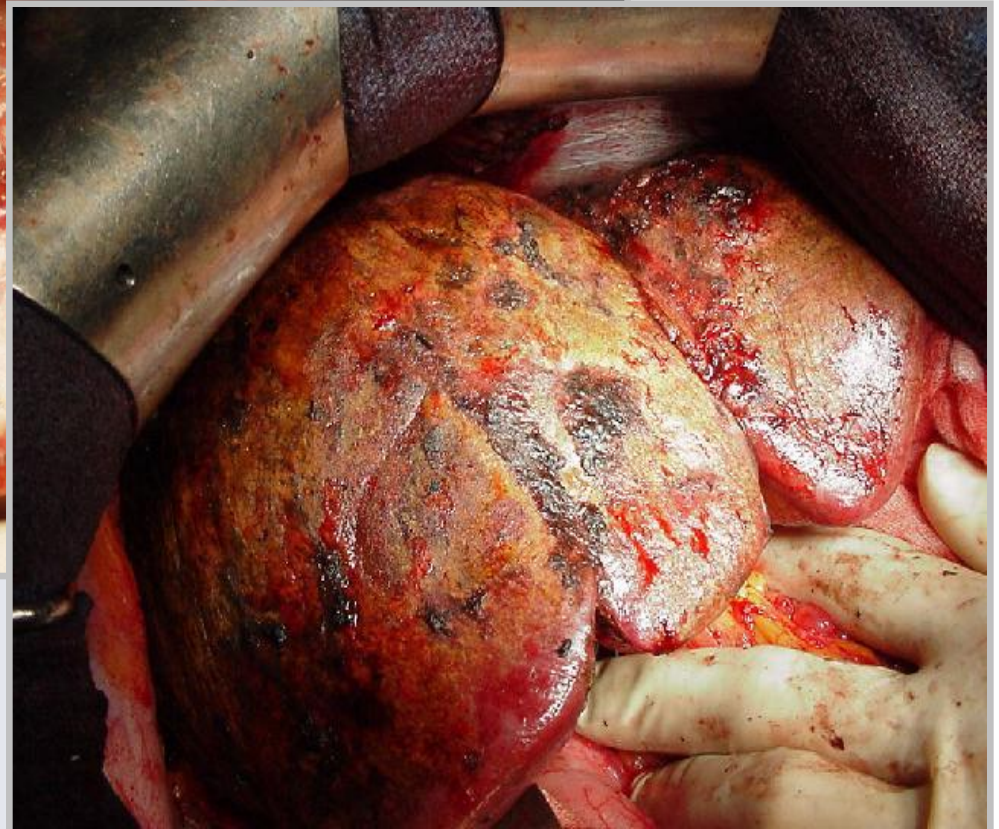
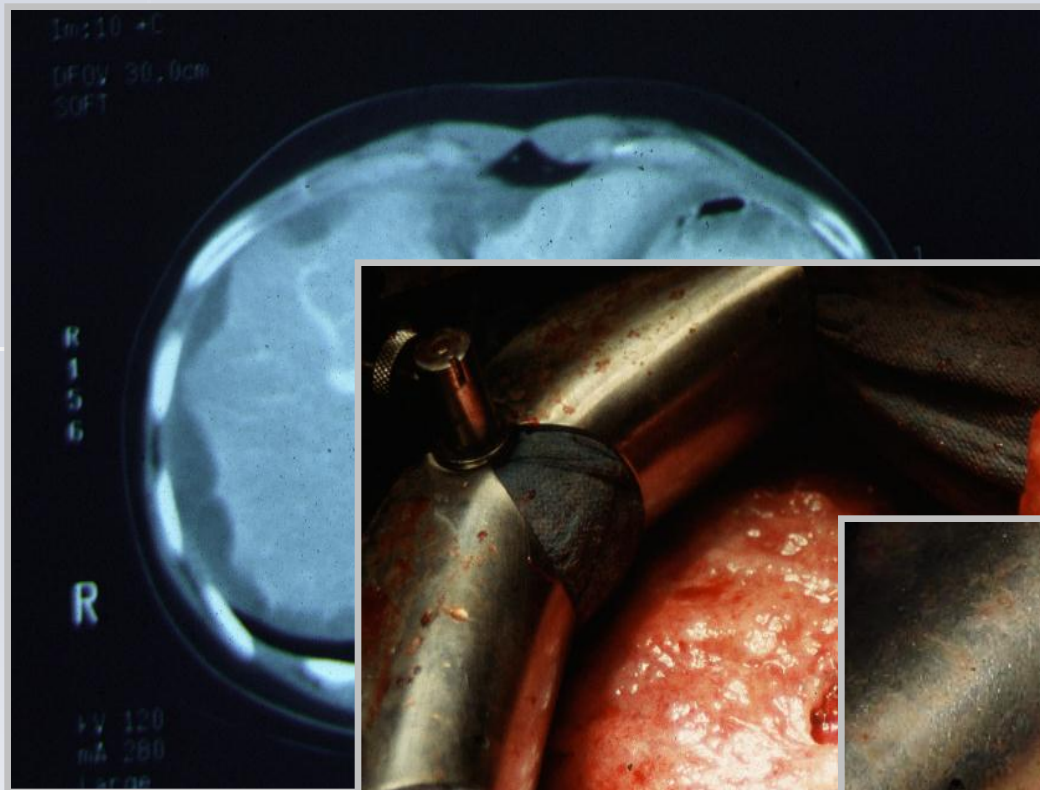












# 2298 pts treated with CRS + HIPEC

*(Multi-institutional registry. Chua T. et al. New Eng J Med 2012)*

- 16 specialized centres (1993 to 2011)
- Mortality: 2%, major morbidity: 24%
  
- **Median survival: 196 months (16 years)**
- **10-year overall survival: 63%**
  
- Prognostic factors (multivariate):
  - Histologic subtype
  - Completeness of cytoreductive surgery
  - High peritoneal index
  - Older age (> 53y)
  - Use of HIPEC

**Versus 21% at 10 years** with usual treatment.

97 pts of the MSK

*(Miner et al. Ann Surg 2005)*



# **Malignant Peritoneal Mesotheliomas**

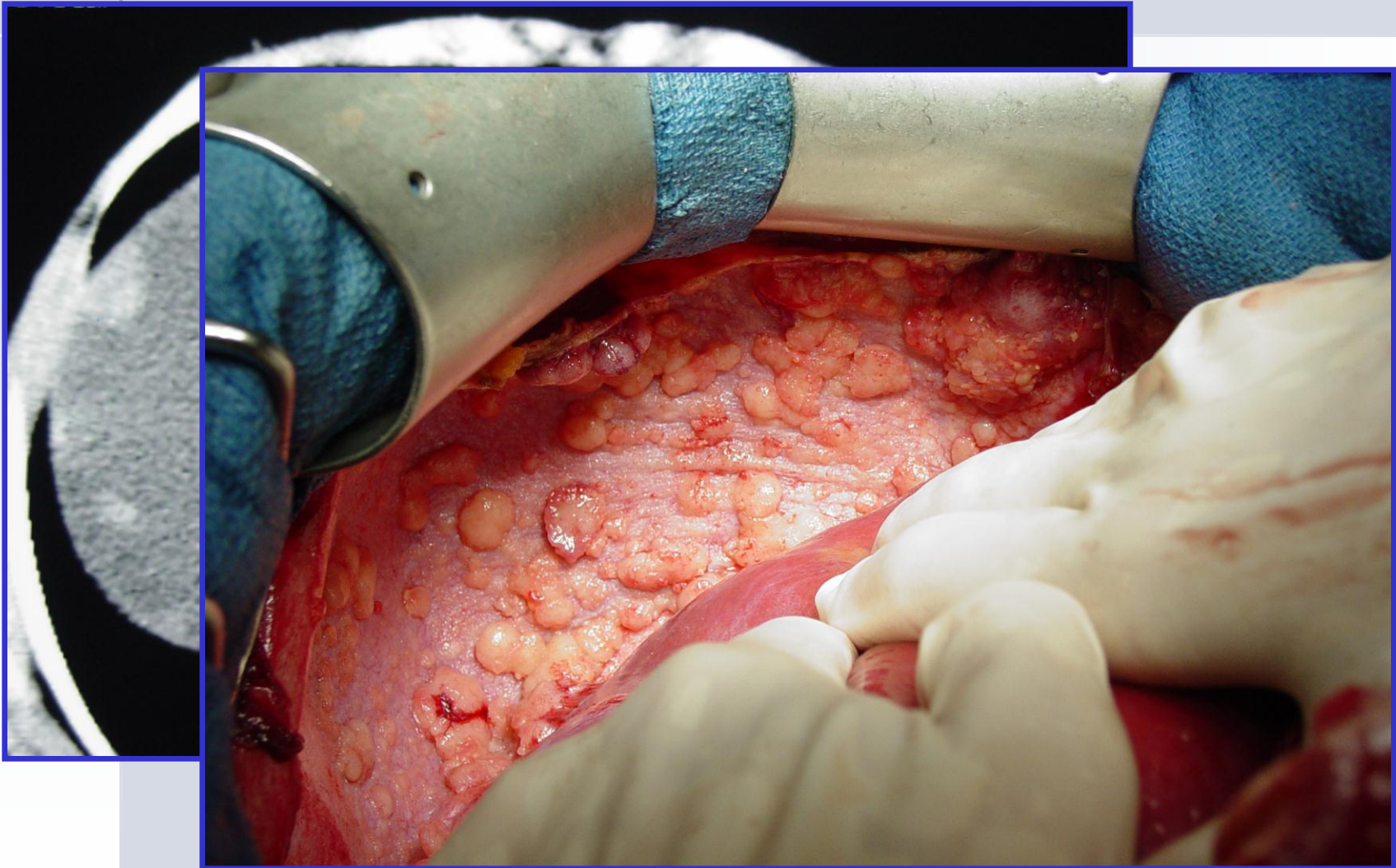
- Different subtypes

# Papillary Type

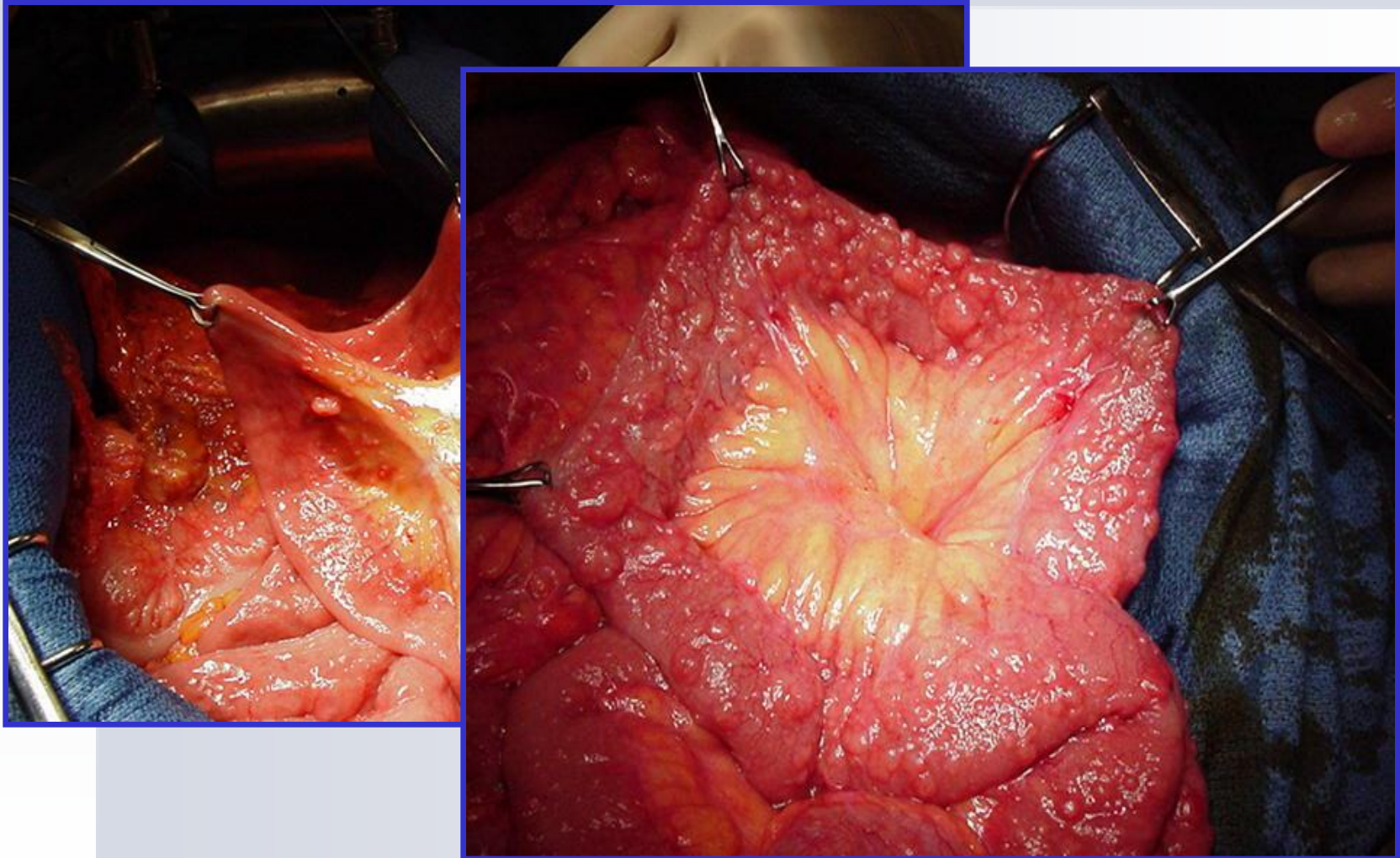




# Epithelioid Type



# Epithelioid Type





# Epithelioid (girl of 14 years)





# Cystic Type



# 405 pts treated with CRS + HIPEC

*(Multi-institutional registry, Yan T et al. J Clin Oncol 2009)*

- 8 specialized centres, 1989-2009
- 80% of epithelial tumors
- 46% of complete cytoreductive surgery, HIPEC=92%
- Postop mortality: 2%
  
- **Median survival: 53 months**
- **5-year survival : 47%**
- Prognostic factors (multivariate):
  - Epithelial subtype, and absence of lymph node metastasis
  - Completeness of cytoreduction
  - HIPEC

**Versus , with usual treatment:**

**- Median: 15 months**

**- 5 year survival : 20%**

# For PC of other origins ?

## ■ Probably NO for gastric cancers:

- 159 pts in the French registry (*Glehen O, Ann Surg Oncol 2010*)
- 5-year overall survival: only 13% !

## ■ Probably YES for ovarian cancers:

- Preliminary results are promising
- Even at the moment of the first surgery or even when recurrence
- Numerous trials are on going

## ■ YES for small bowel adenocarcinomas



# For PC of other origins ?

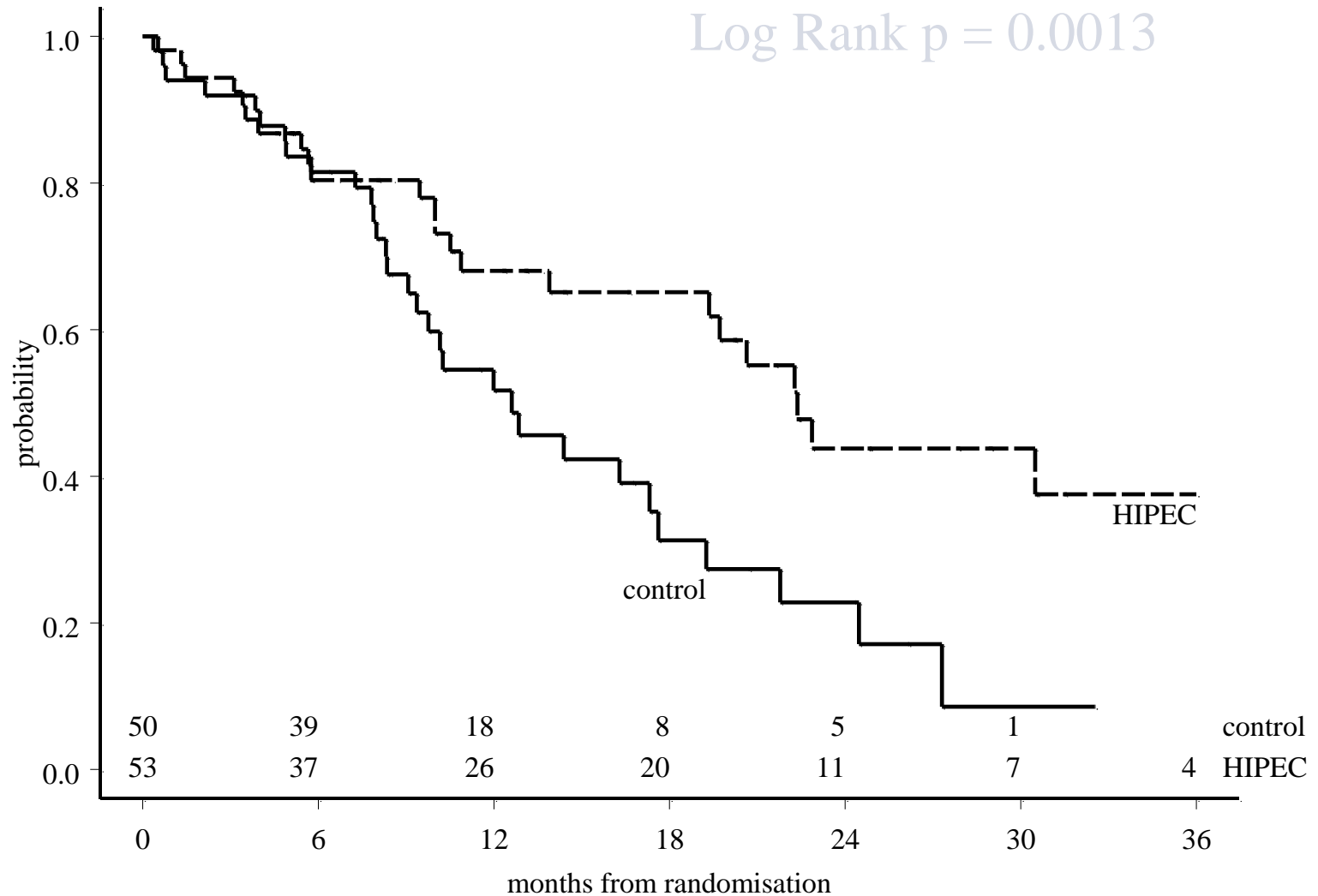
- Cytoreductive surgery **alone** for neuro-endocrine tumors ?
- Complete CRS + HIPEC for **selected** non usual cases:
  - Pseudopapillary pancreatic tumors (Franz's tumors)
  - Hepatocellular carcinomas
  - Gallbladder cancers

# Conclusion

- The treatment of PC has dramatically changed during the last 10 years.
- Now it is possible to definitely cure some PC (like liver metastasis)
- The impact of a complete surgery is major (+++).
- The impact of HIPEC is not clear enough.
- The indications of this combined treatment according the origins and according the extent of the disease are in progress.
- To progress more rapidly: include your patients in trials !

**Thank you**

At 3 years: 36% vs 10% ( $p < 0.01$ )



# Verwaal 2005: 117 patients with Colorectal

**PC:** Look at the median survival of R2a-R2b groups

