

Management of Peritoneal Metastases (PM) from colorectal cancers: New Perspectives

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Declaration of interest

BOARDS	Congress and teaching	Trials	
0	Merck	0	
	Ipsen		
	Novartis		
	Sanofi		

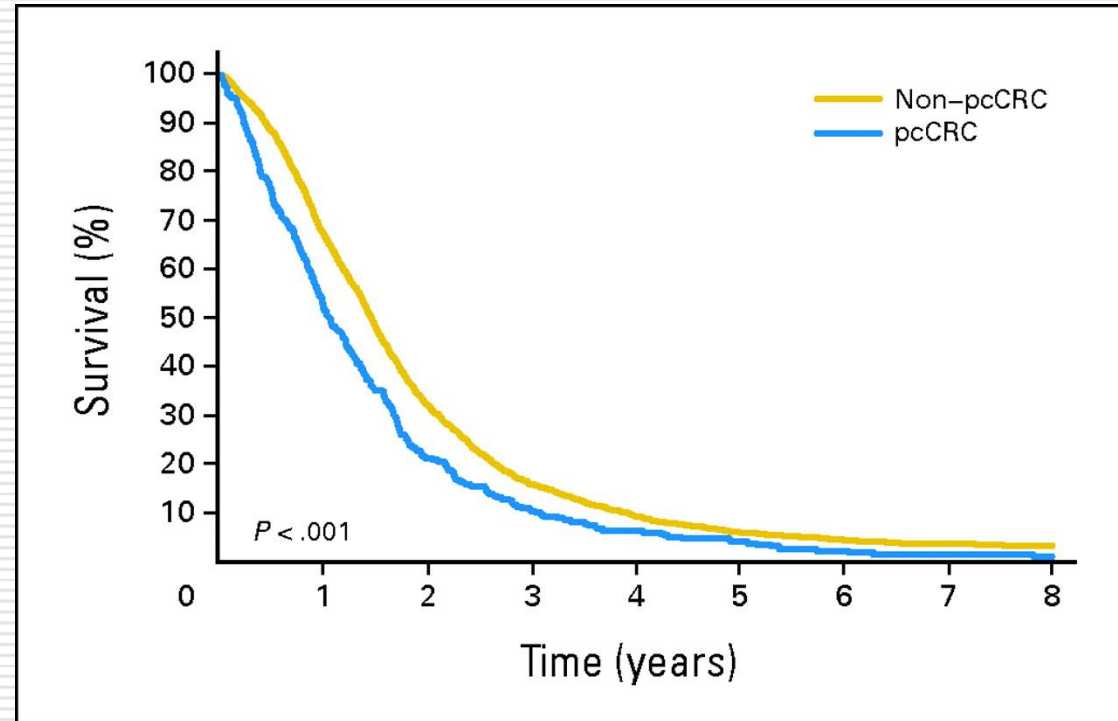
The peritoneum is an organ

- **Own histologic structure**
- **Own circulations and drainages**
- **Its surface = the body square surface**
- But, 1 tumor seeding —————> progressive diffusion in all the abdominal cavity

—————> **Like other organs, it needs an own and particular treatment.**

PM have a poorer prognosis than the other metastases

Data of 2 prospective randomized trials about chemo (oxali and Irinotecan)
2095 patients



Median survival:

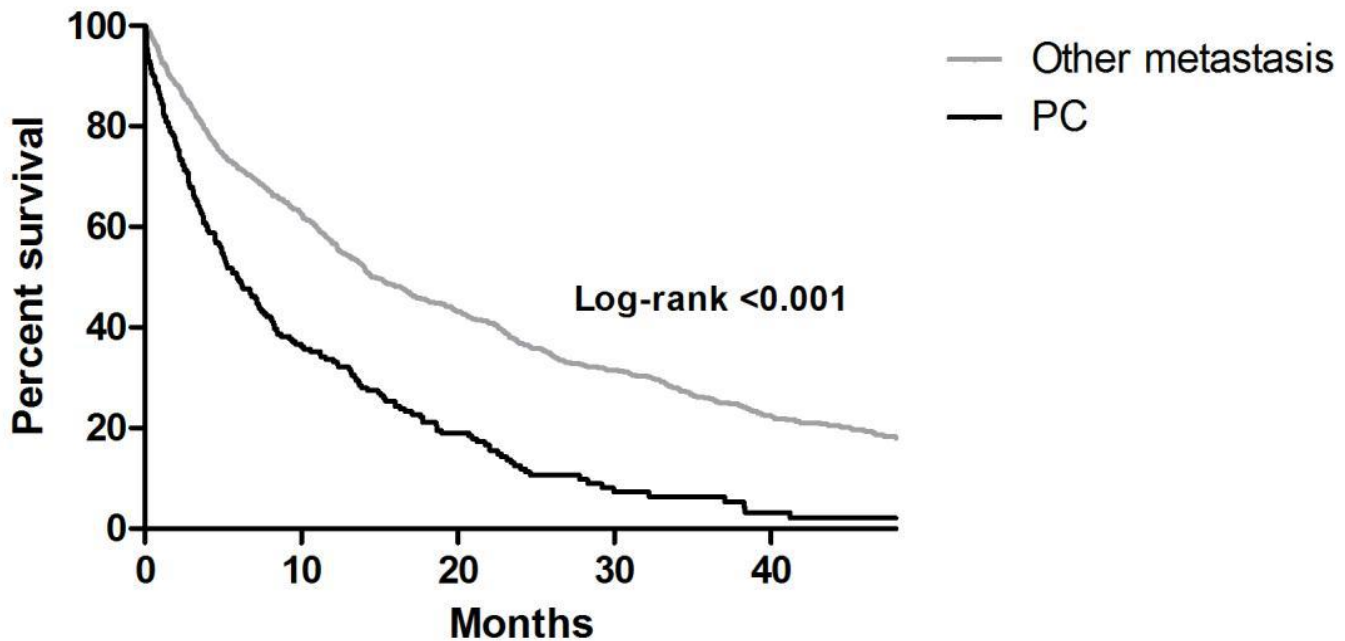
Without PC: **17.6 m**

With PC: **12.7 m**

$P < 0.01$

PM have a poorer prognosis than the other metastases

Survival after metastasis diagnosis among colorectal cancer patients diagnosed between 2003-2008



Dutch Eindhoven Cancer Registry: 1074 metastatic patients (200 with PC)

PM have a poorer prognosis than the other metastases

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

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

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

At last, appearance of PM is frequently considered as a funest event and only palliative treatments are proposed

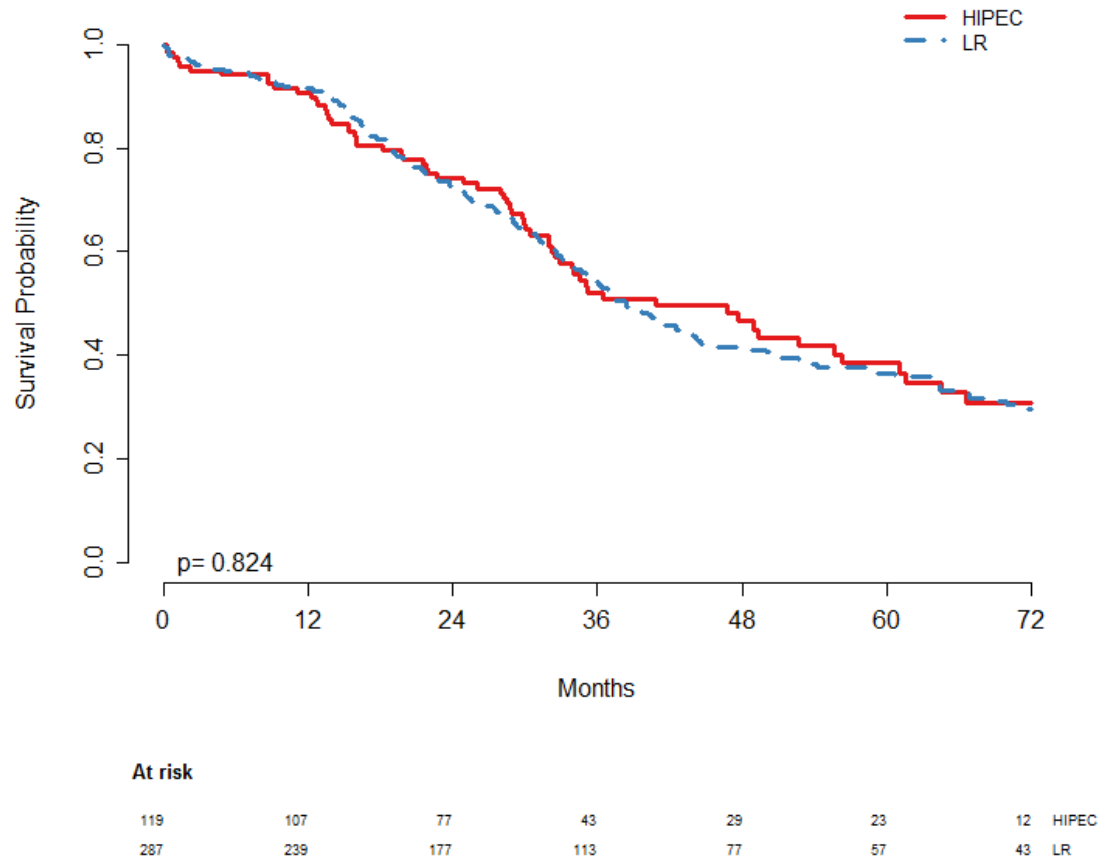
- Is it justified ?
- Is it possible to cure PM ?

In fact, the prognosis of **optimally treated** LM and PM are the same !

1993-2009

287 hepatectomy:
38.5%

119 CCRS+HIPEC:
36.5%



How to treat PC with a curative intent ?

- ☐ By using complete cytoreductive surgery (CCRS)
- ☐ Plus or minus Hyperthermic intraperitoneal chemotherapy (HIPEC)
- ☐ With the assistance of the systemic chemotherapy

Principles of CCRS + HIPEC

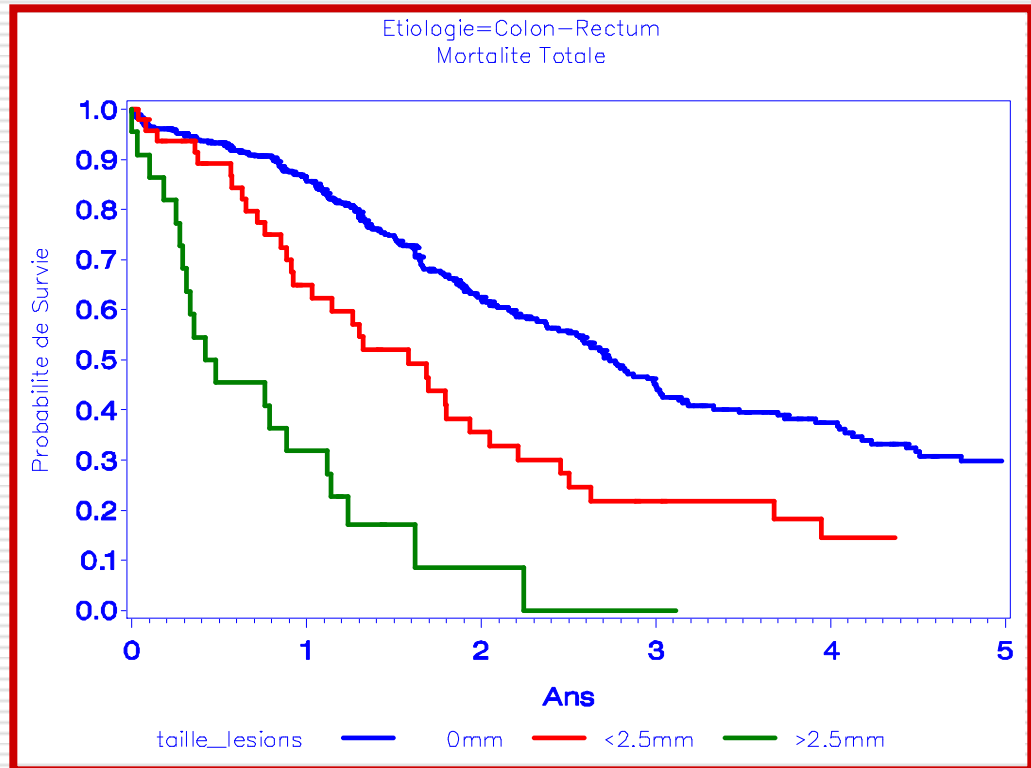
- Surgery must resect all the visible (macroscopic) disease ($> 1 \text{ mm}$ of \emptyset).
- HIPEC has the ambition to treat the remaining non visible (microscopic) disease.

Recall: with HIPEC, the penetration of drugs is limited to **1 mm** in depth.

If R2: HIPEC is contraindicated

French Registry:

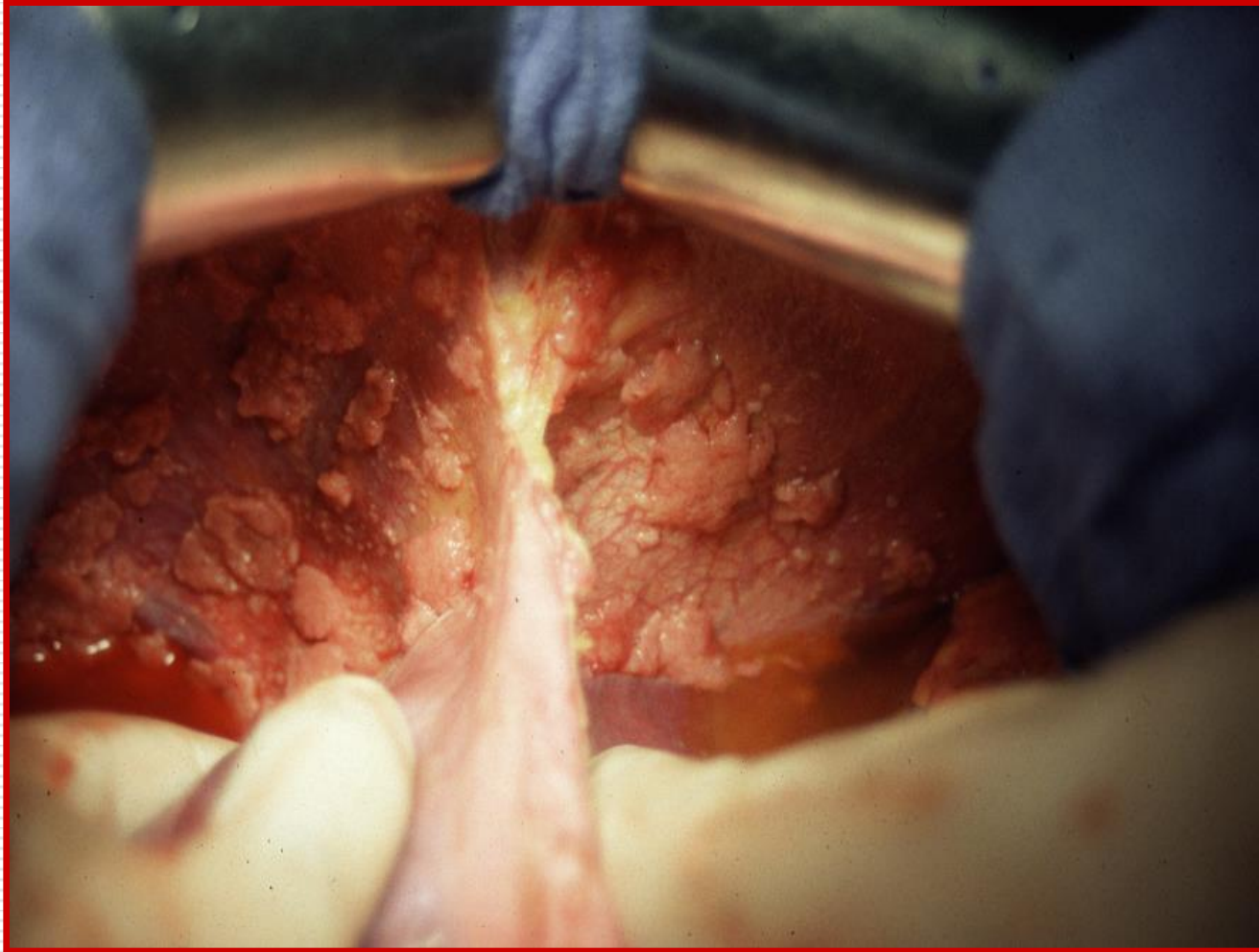
- 523 PC treated
- 1990 - 2007
- in 23 centres

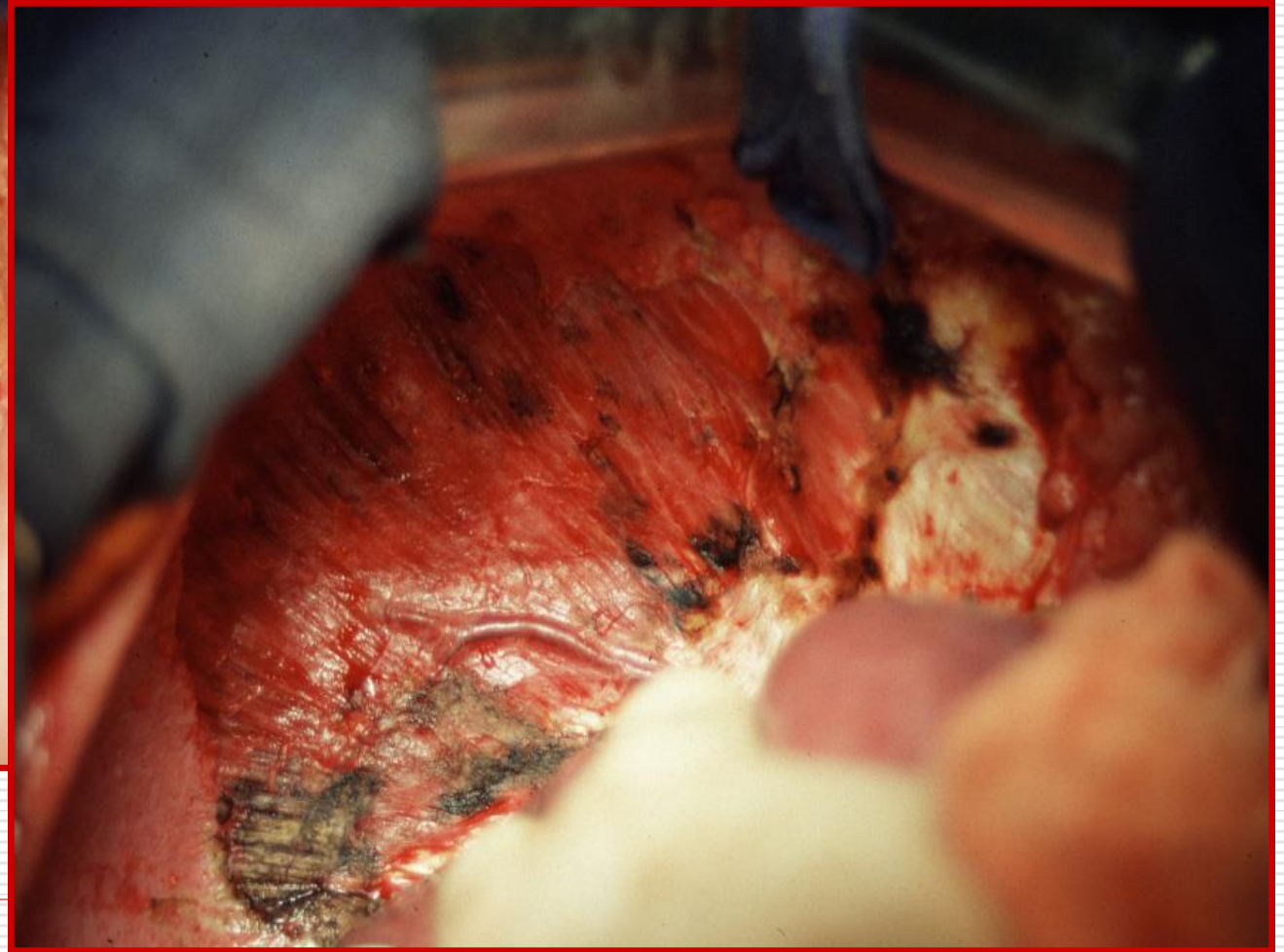
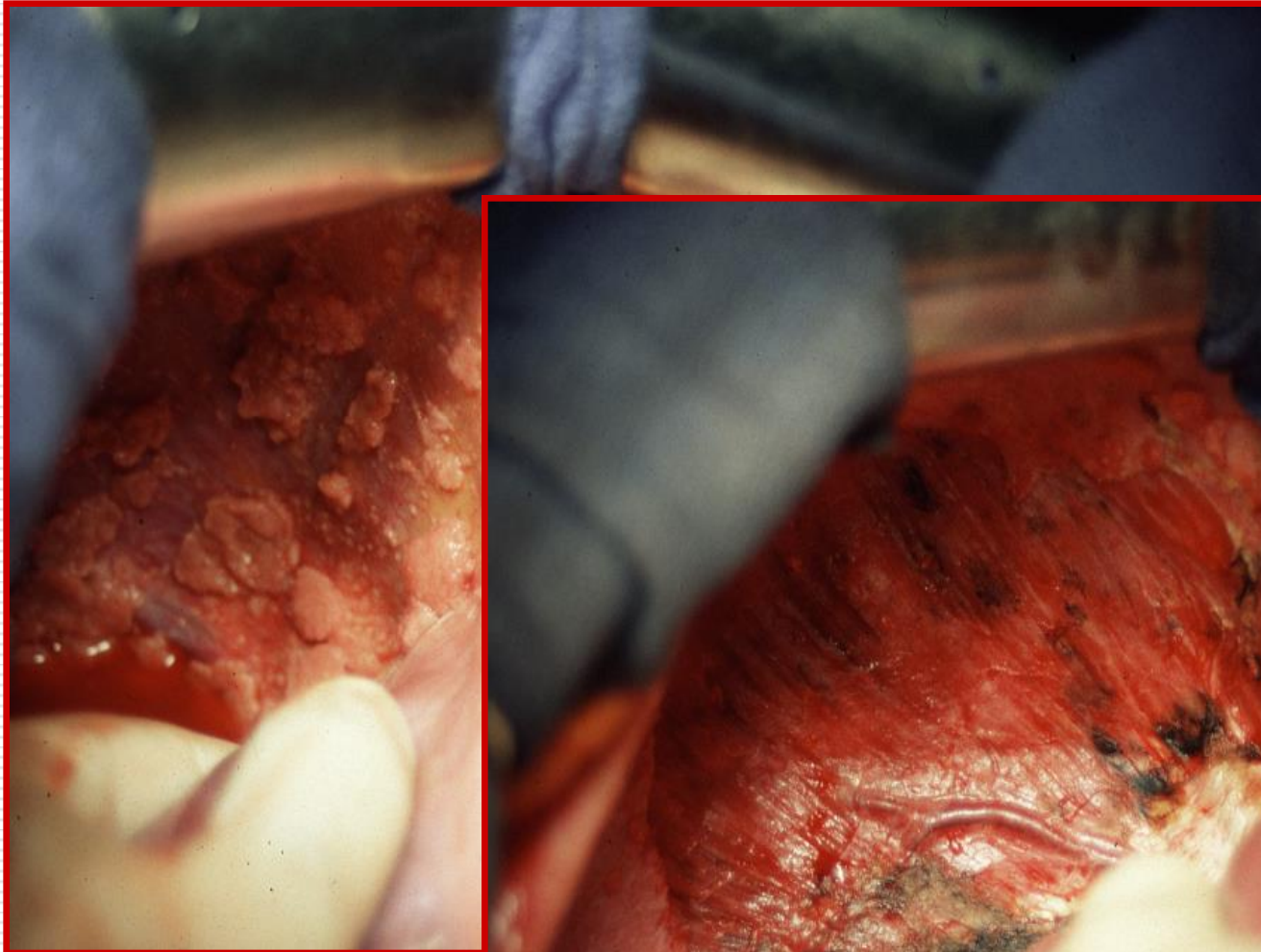


Astonishing (and illogical) !

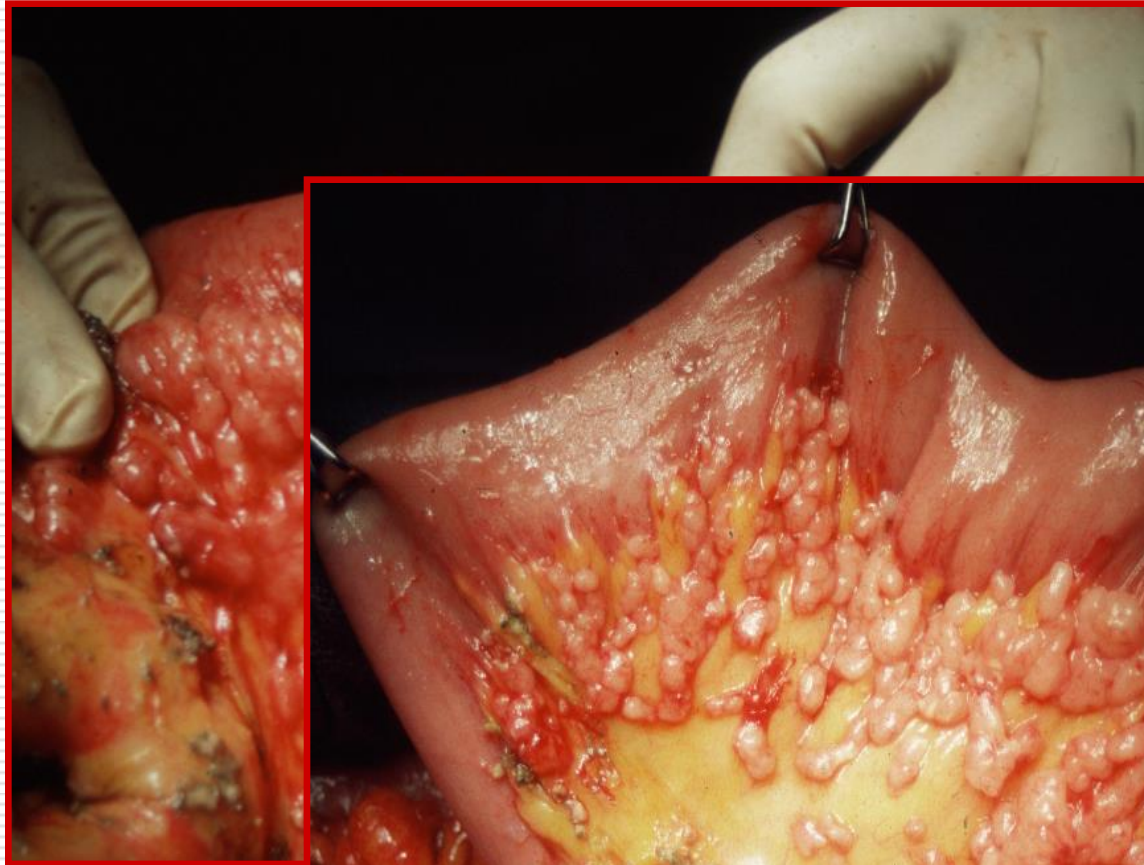
- ❑ *Levine et al. Experience of 1000 patients treated with HIPEC. (J Am Coll Surg 2014; 218: 573-87)*
- ❑ 1000 pts treated between 1991 and 2013
- ❑ Division in 5 time periods (quintiles)
- ❑ First quintile: 35% of R0/R1
- ❑ Last quartile: 53% of R0/R1

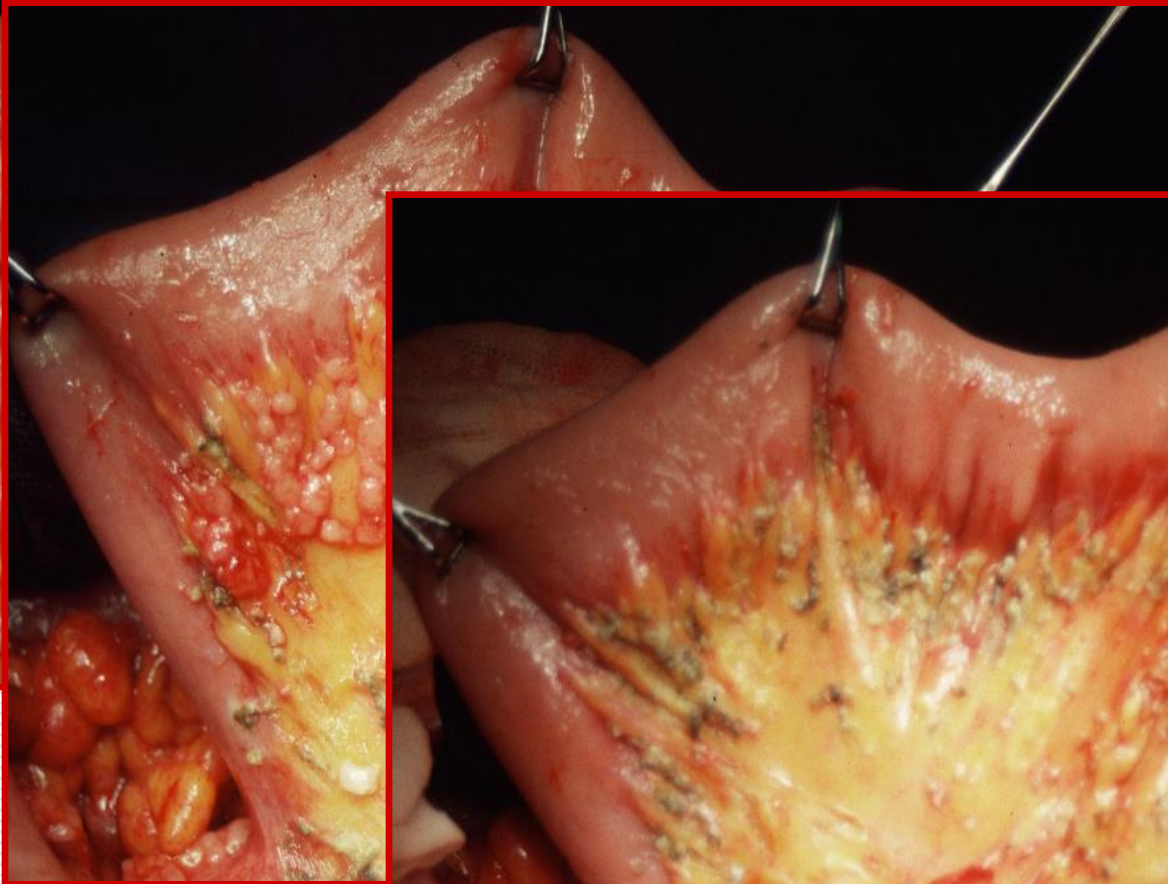
In our personnal practice: 100 % of R0/R1 !

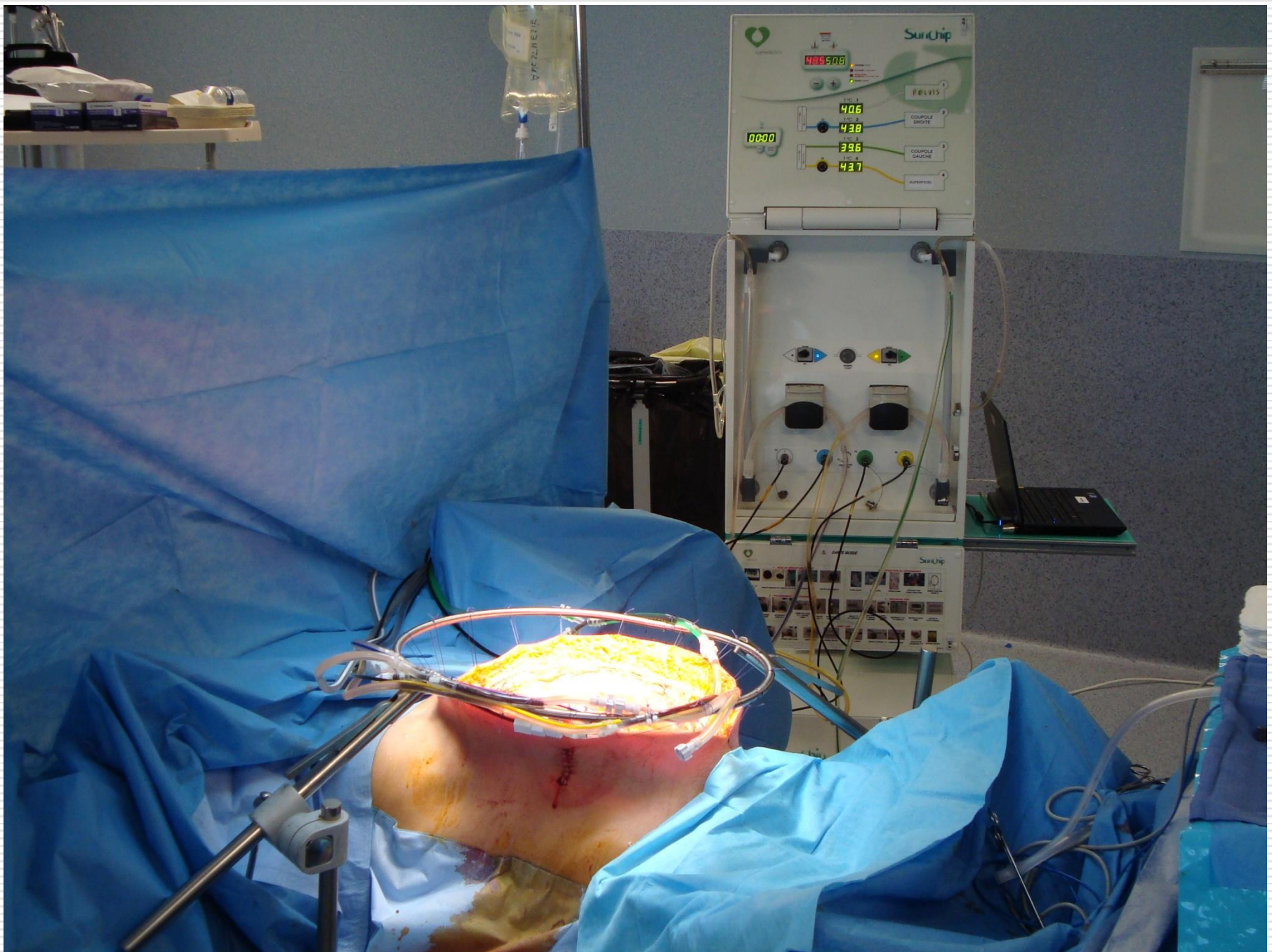


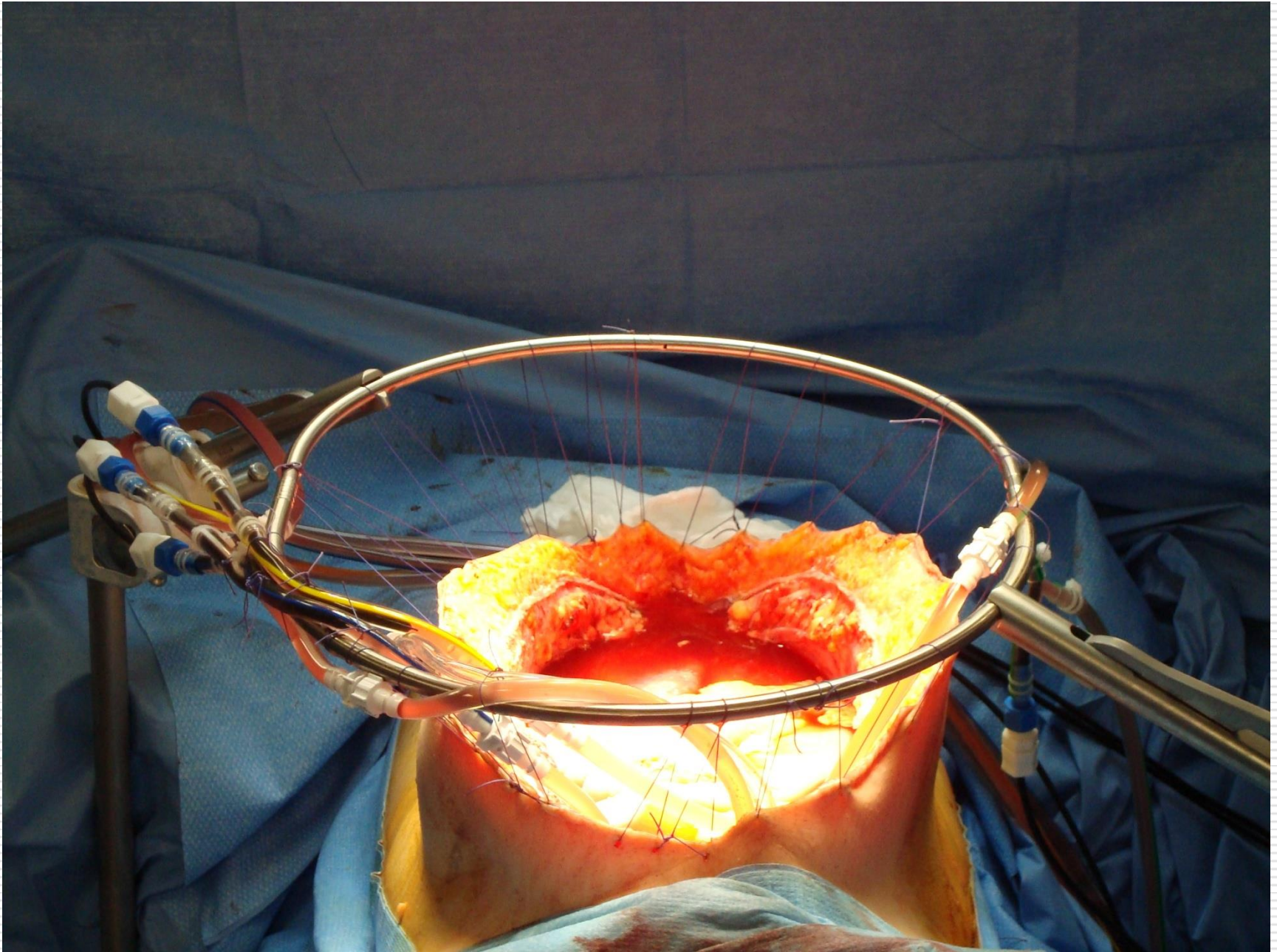












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- Surchauffe / over heat
- Niveau d'eau insuffisant / low water level
- Tension / power

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Current results of systemic chemotherapy

*Randomized Deutch trials **Cairo1** and **Cairo 2** based on Xelox: median survivals*

	Without PM	With PM	
Cairo 1 (no targeted therapy)	17 months	10 months	<0.001
Cairo 2 (with targeted therapy)	21 months	<u>15 months</u>	<0.001

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

Comparison of therapeutic results for colorectal PM: Review

- 2492 patients from 19 selected studies

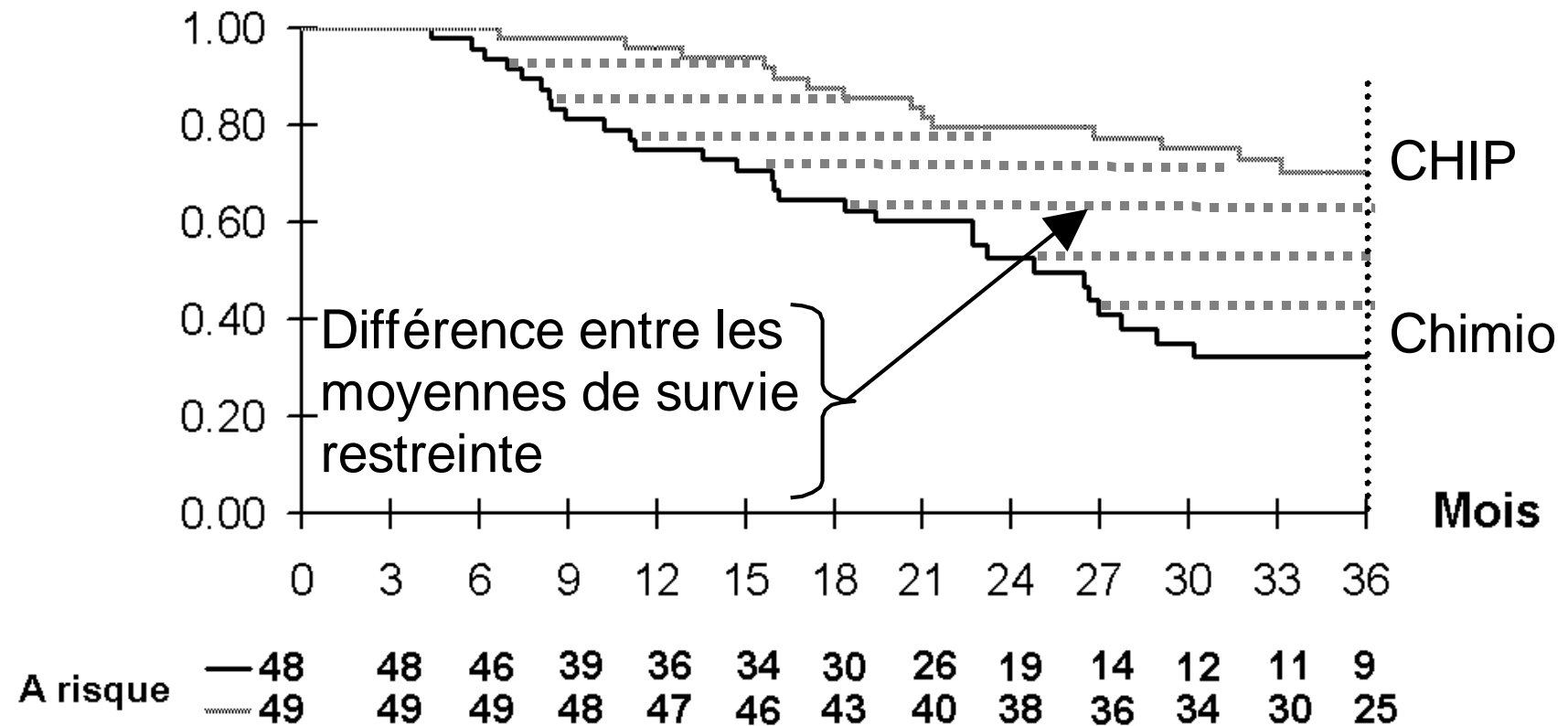
	Nb	Median S.	5-year S.
Incomplete CS + chemo.	1408	12 months	13%
CCS + HIPEC	1084	33 months	40%

Current evidence have demonstrated the efficiency of CCS+ HIPEC for which should now embraced as the standard of cure.

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)

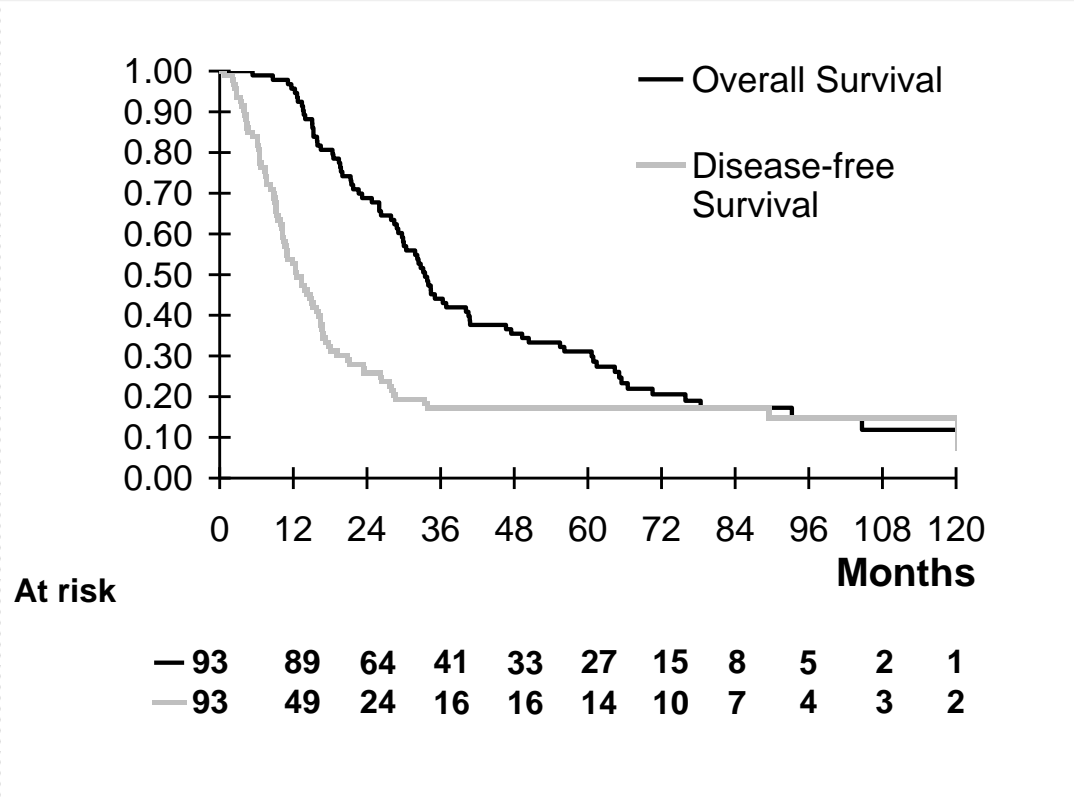
Is it possible to obtain definitive cure with CCRS + HIPEC ?

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 2013; 257: 1065-71)

- ❑ Median follow-up: 99 months
- ❑ Median Survival : **34 months** (currently: 60 months)
- ❑ Overall 5-year survival : 32% (currently: 48%)



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

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%**

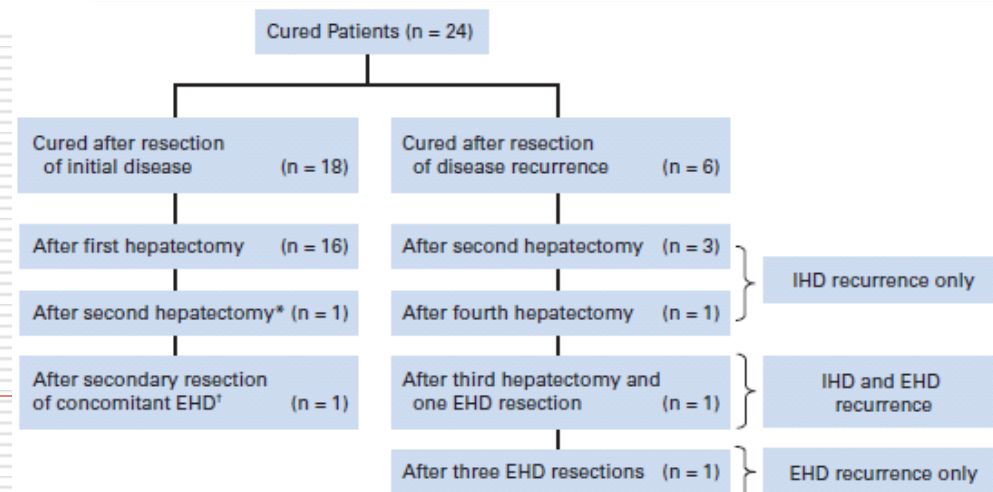
Table 1. Characteristics of 102 Actual 10-Year Survivors

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

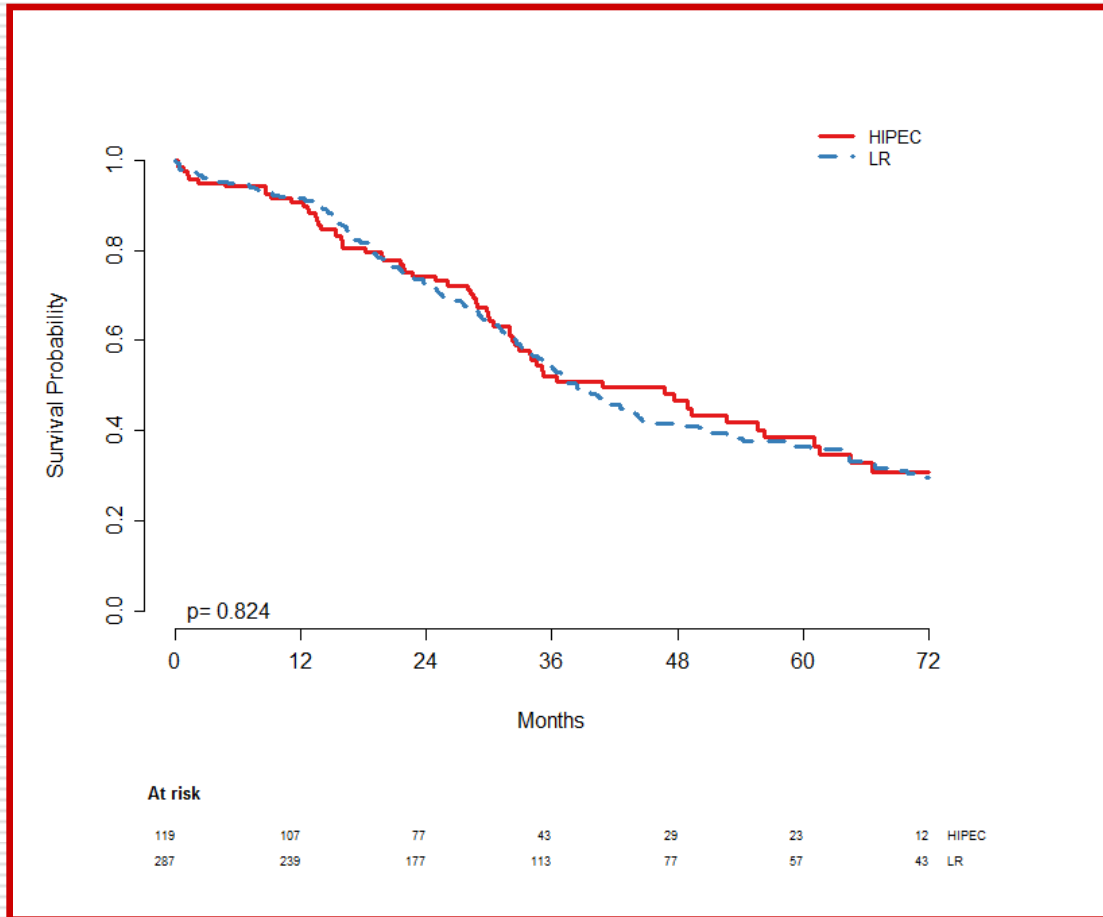
Patients With Initially Unresectable Colorectal Liver Metastases: Is There a Possibility of Cure?

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

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



Our results (comparison of LM and PM)

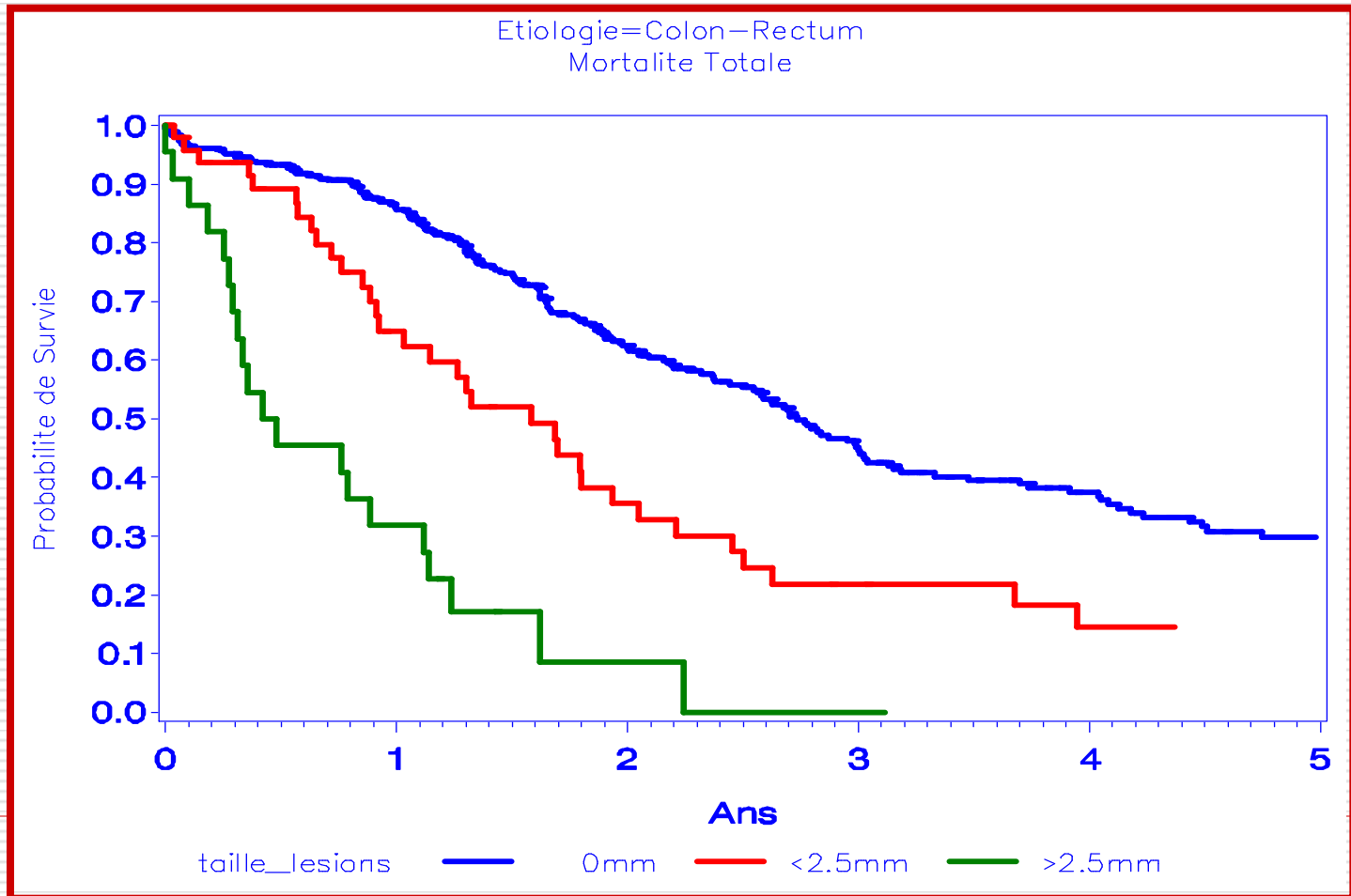


Prognostic factors (CRS+HIPEC)

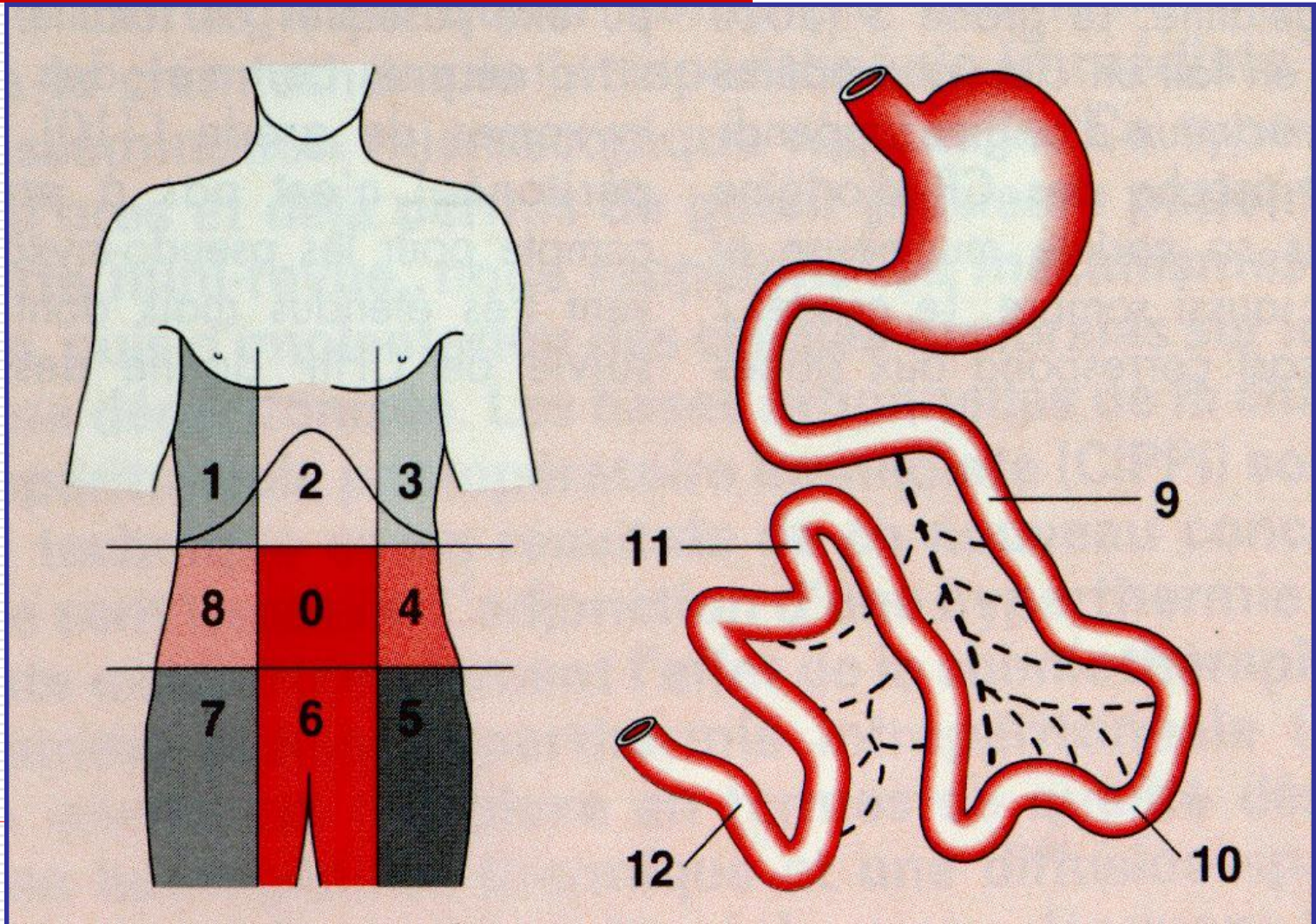
- ❑ French registry (1990 – 2007)
- ❑ 523 patients treated in 23 centres
- ❑ Mortality: 3%, grade 3-4 morbidity: 30%

- ❑ **Two major prognostic factors (+++):**
 1. The completeness of the cytoreductive surgery
 2. The extent of the peritoneal disease (PCI)

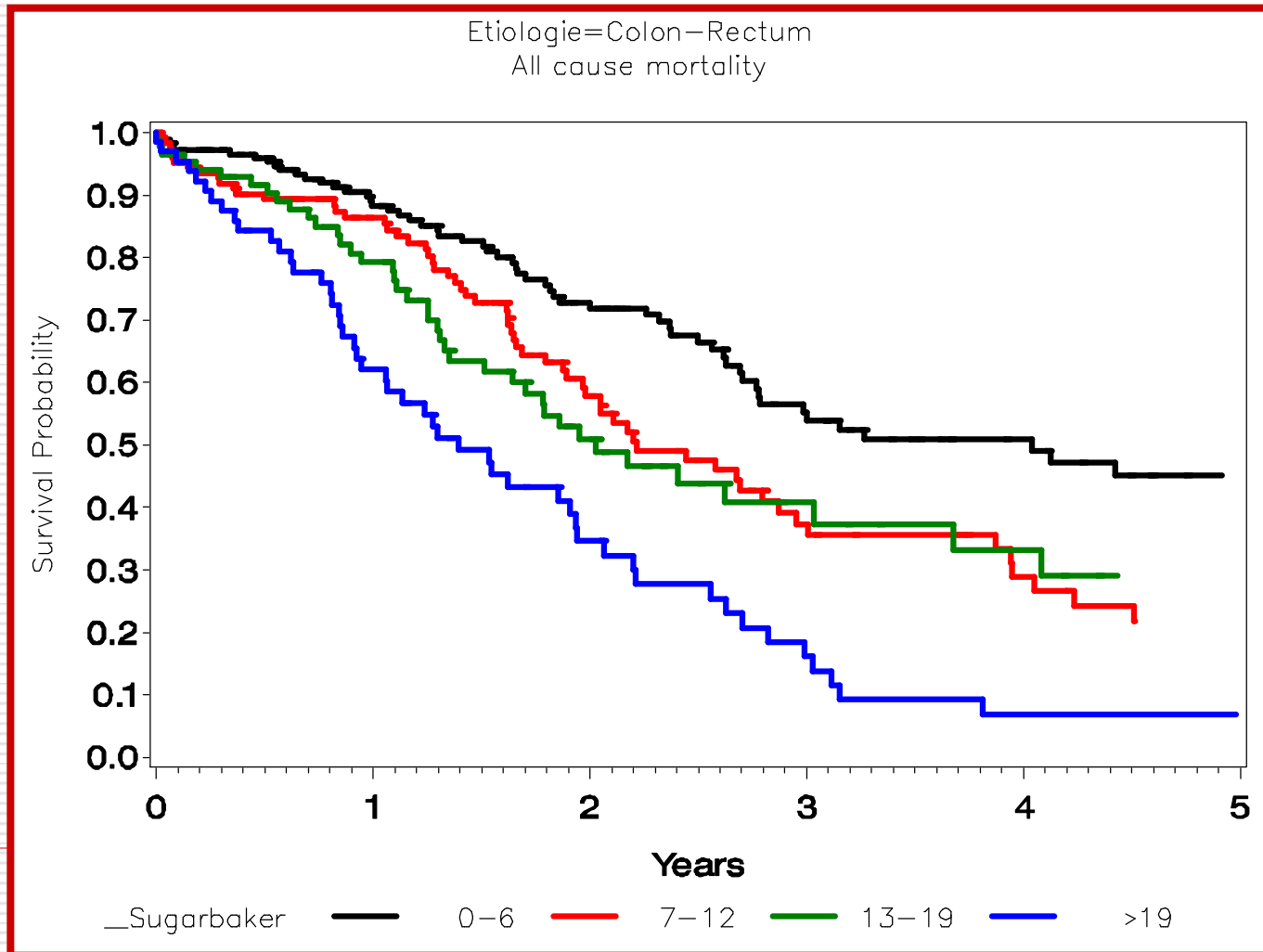
Survival according to the **Radicality** of the Surgery ($p < 0.0001$)



The Peritoneal carcinomatosis Index (PCI) (Ranging from 1 to 39)



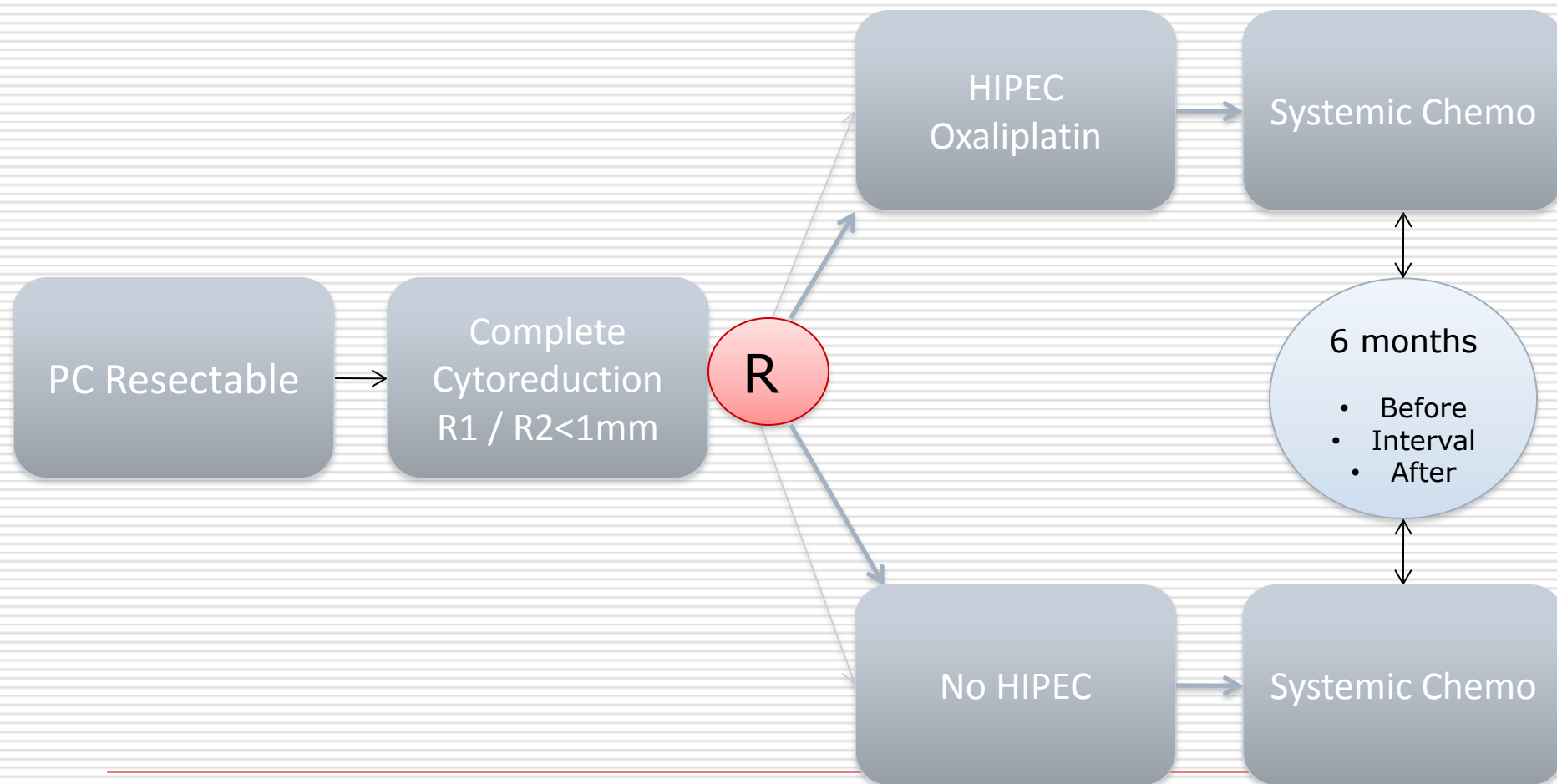
Survival according to the **Extent** of the P ritoneal Carcinomatosis ($p < 0.0001$)



What is the exact gain due to HIPEC alone ?

- We do not know in human
- There is many proofs in animal models
- Only a randomized trial will give the answer

French multicentric randomized trial « Prodiges 7 »



Current status of Prodigie 7 trial

- End-point: To improve OS from 30 months to 48 months
 - The 270 patients have already been randomized.
-

Current proposed guidelines for colorectal PM

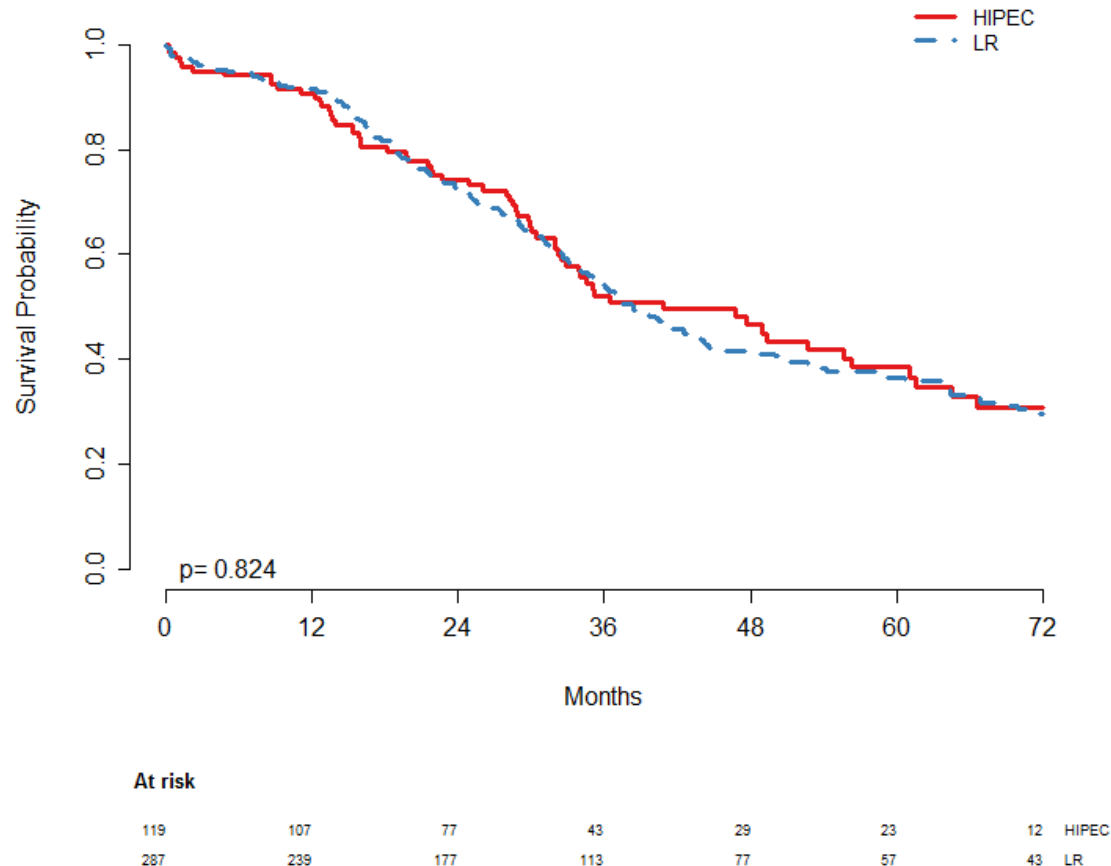
- CCRS + HIPEC is the gold standard treatment for patients:
 - With a good general status
 - With a PCI index lower than 16
 - Who are chemosensitive
 - With no other metastases (excepted ovarian metastases or 1-5 LM easily resectable or ablatable).

Equivalence between LM and PM

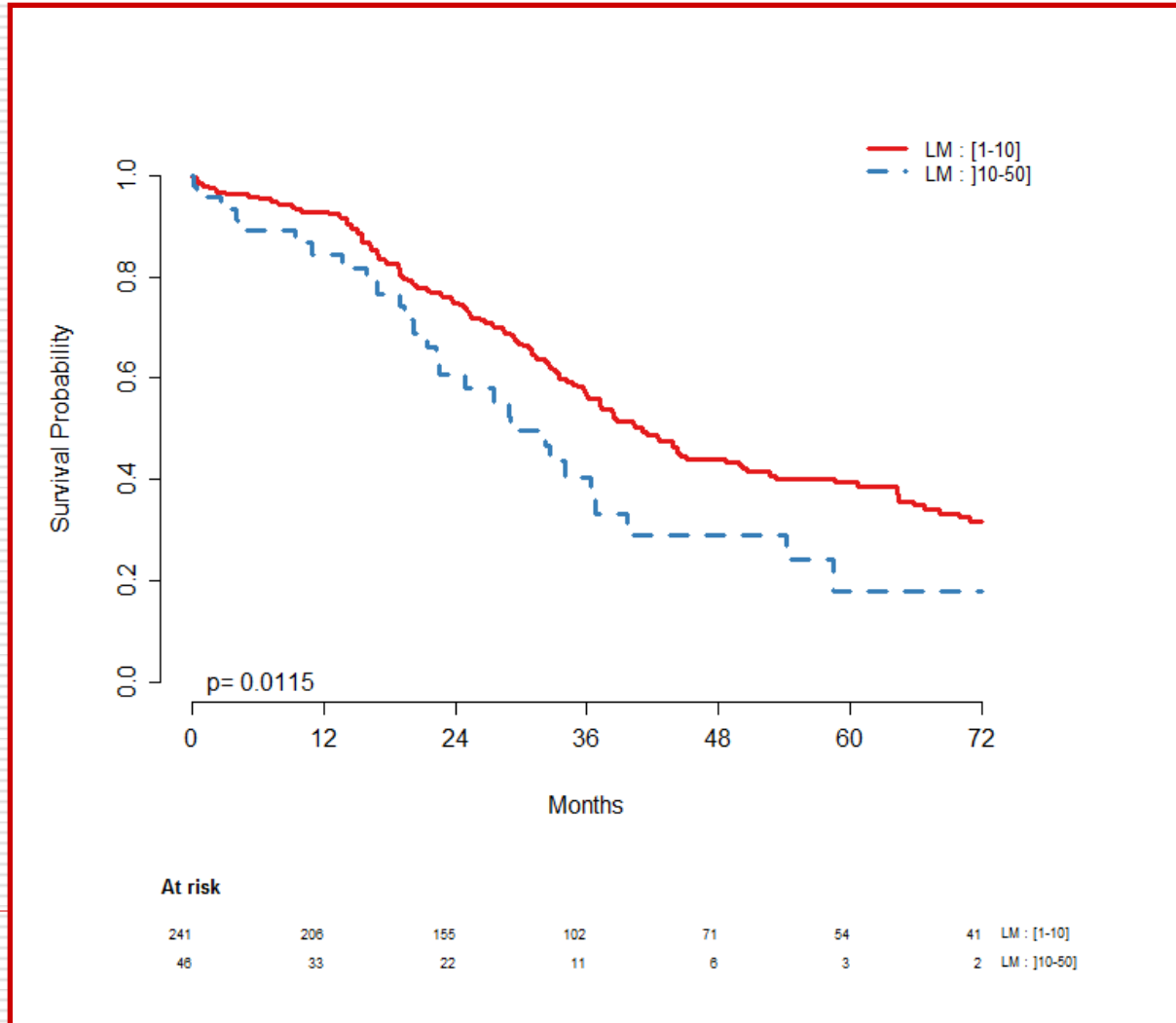
- 287 hepatectomy
- 119 CCRS+HIPEC
- Exclusion of [Hepatec + CCRS-HIPEC] (n=37)
- Follow-up > 5 years

- Subgroups according to the global tumor load:
 - LM in 2 groups: ≤ 10 LM, and > 10 LM
 - PM in 3 groups: PCI 1-5, 6-15, > 15

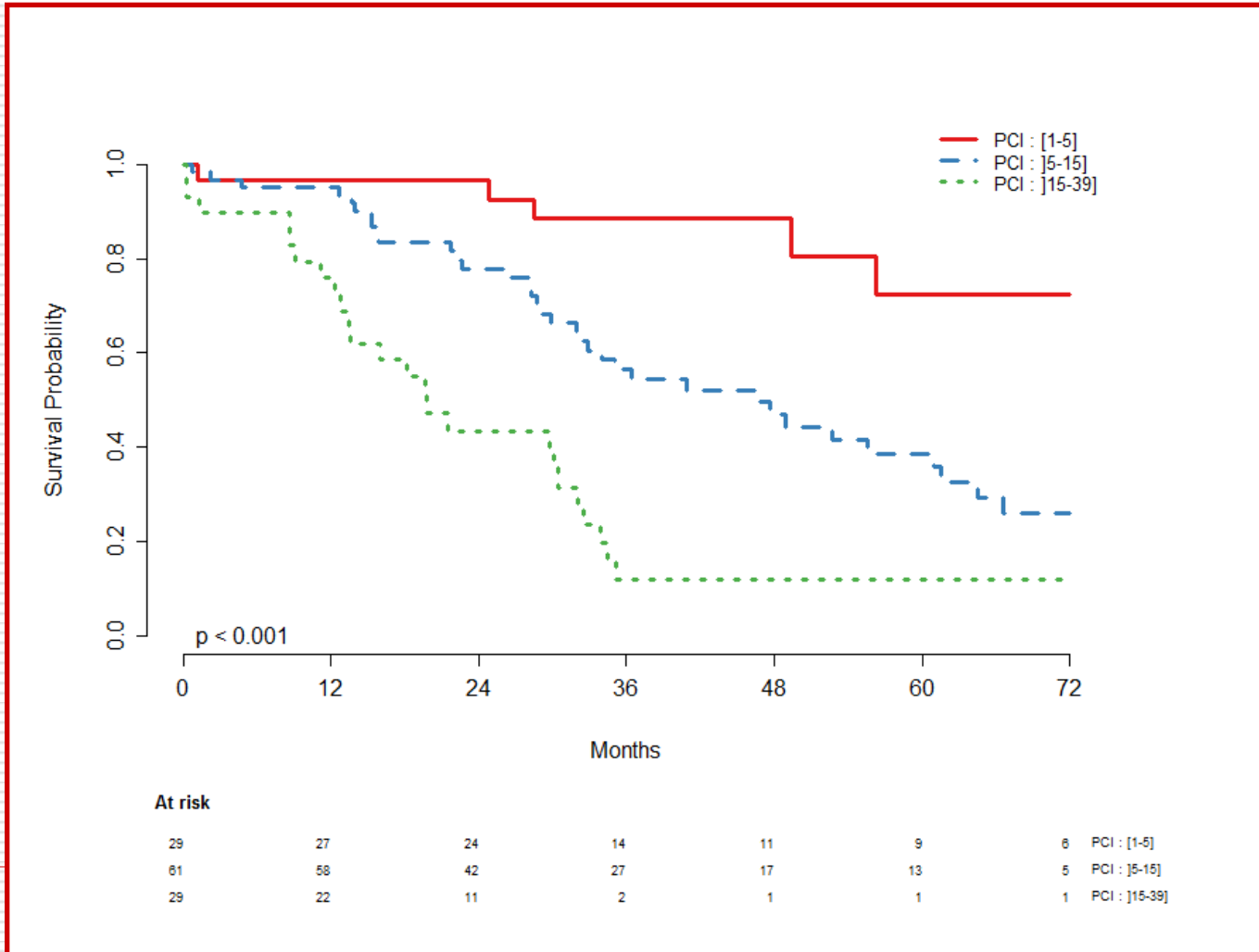
Same overall global survival



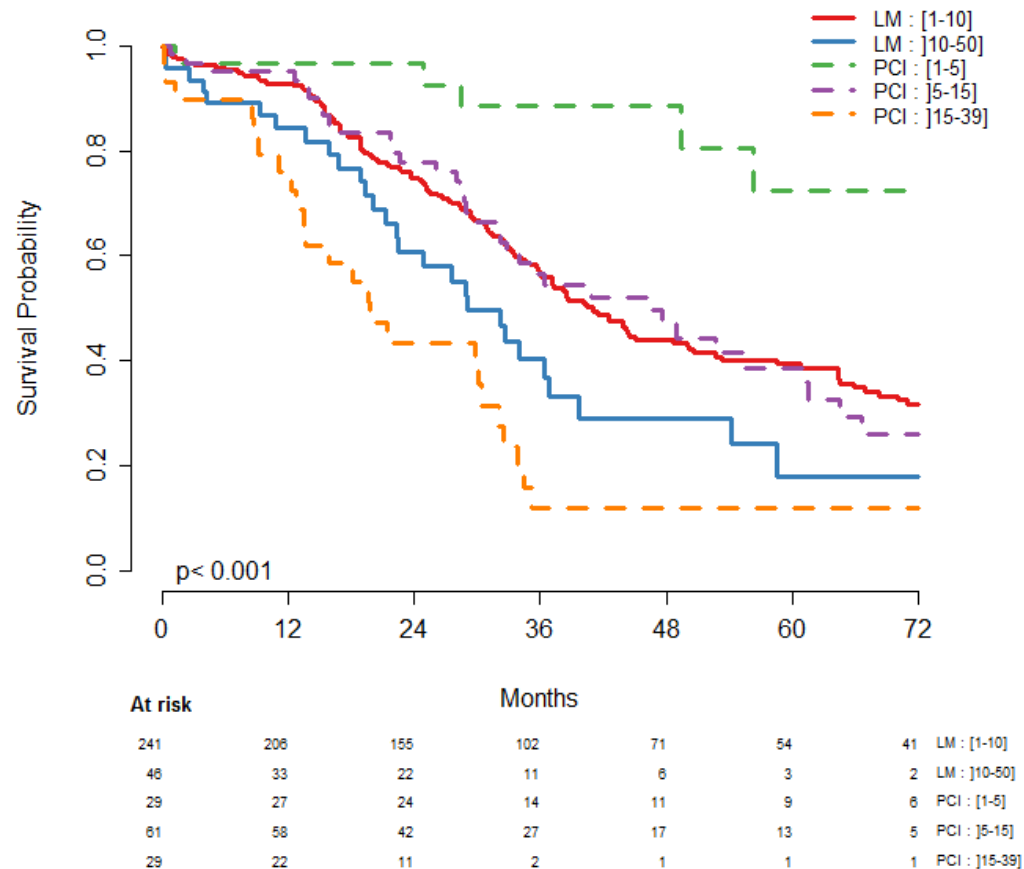
Overall survival for the 2 gps of LM



Overall Survival for the 3 gps of PM



Equivalences and difference between LM and PM



A future for this combined approach to treat early colorectal PM ?

- Survival results are very high when the PCI is low (72% when PCI from 1 to 5).
- Surgery is easier and morbidity is lower when the PCI is low

➡ PM must be detected and treated at a very early stage !

How to detect PM at an early stage ?

- ❑ No symptoma, no imaging, no biological markers
 - ❑ The only way: to propose a **second-look**
 - ❑ But, it is not possible to propose it to all patients
 - ❑ We must select a population of **high-risk patients**
 - ❑ Then to proove that effecively they present early PC, that CCRS+HIPEC is feasible and not too morbid, and at last, that this new approach improves overall survival.
-

Who are High-risk patients ?

Systematic review of the literature published from 1941-2011

□ High-risk: $\geq 40\%$

- Synchronous PM (resected): 54-75%
- Ovarian metastases: 56-62%
- Perforated primary tumor: 24-54%

□ No High-risk: $\leq 20\%$

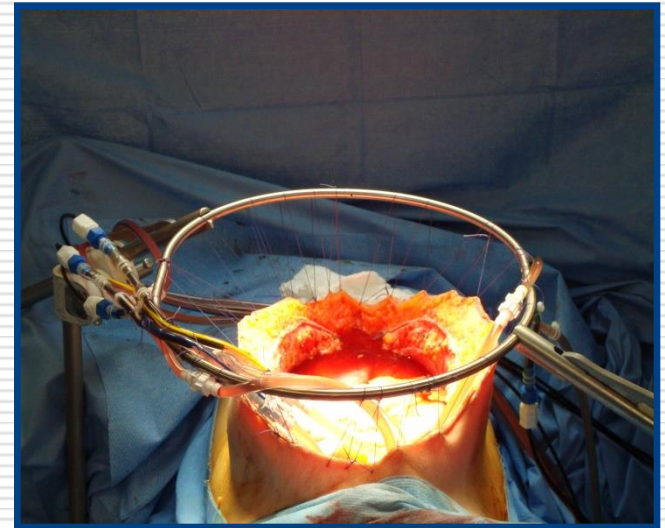
- T4 tumor: 8-17%
- Positive cytology: 9-36%
- Histologic subtype: 11-36%
- Occlusion / Bleeding: < 15%

Second-look trial: Phase 1-2

- ❑ **41 patients** included between **1999 and 2009**
- ❑ They received 6 months of chemo., then
- ❑ Second-look at 1 year

- ❑ **Macroscopic PM was present in 56%**
- ❑ **It was early cases (mean PCI = 8)**

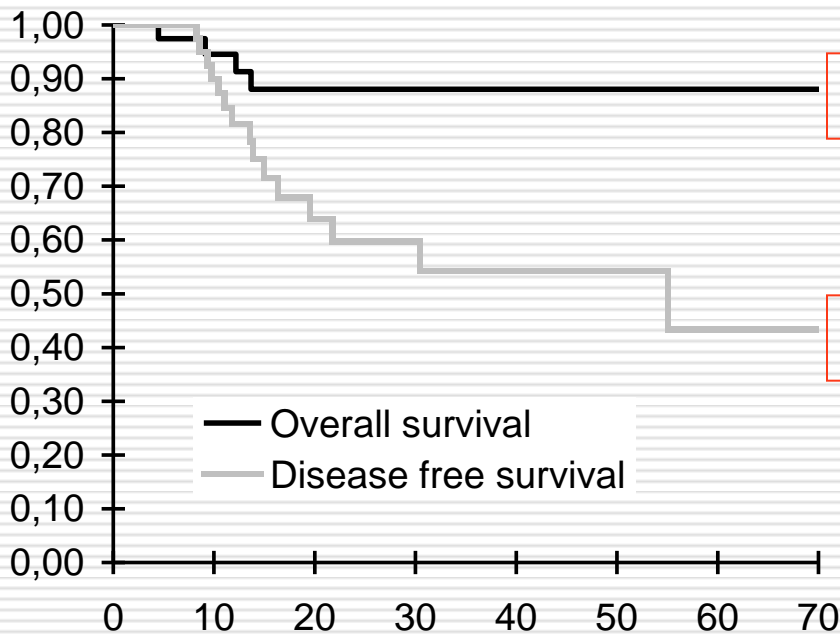
- ❑ 100% underwent HIPEC
- ❑ Mortality: 2%, morbidity: 10%



-
- Minimal synchronous PC resected with the primary tumour: PM in 60%
 - ovarian metastases resected : PM in 62%
 - Perforated primary tumour: PM in 37%
-

Survival rates

Peritoneal recurrence : 17%



5-y overall survival 90%

5-y disease free survival 44%

Patients at risk		Months							
		0	10	20	30	40	50	60	70
—	41	31	24	19	18	12	11	9	
—	41	34	15	11	8	6	4	4	

ProphyloCHIP Trial

« high risk » patients



**6 months IV Folfox IV
then:**

Work-up that must be negative

Randomization



Standard arm



Experimental arm



Surveillance



**Systematic 2nd
look plus HIPEC**

n = 130 patients

1st endpoint : 3-y Disease-free survival; to improve DFS from 40% to 65%

Conclusions

- ❑ For eligible patients, CCRS+HIPEC is currently the gold standard treatment.
 - ❑ CCRS + HIPEC is able to definitively cure many patients.
 - ❑ Its results are similar to those obtained with hepatectomy for LM.
 - ❑ It gives very high results when the PCI is low.
 - ❑ The second-look approach for high-risk patients could be the main future of CCRS+HIPEC.
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