Phase III trial evaluating the role of intraperitoneal chemohyperthermia (HIPEC) after maximal cytoreductive surgery of peritoneal carcinomatosis of colorectal origin

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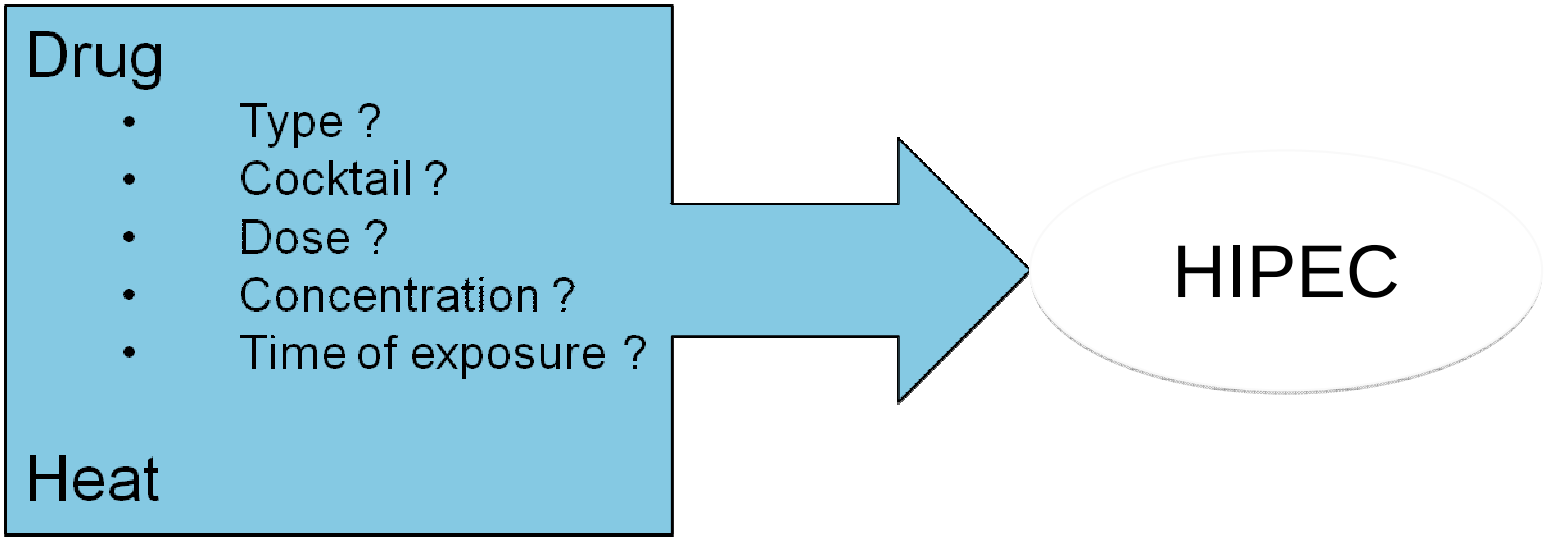
- Co-Investigators: D.Elias
  O.Glehen

Overall Median Survival with HIPEC Phase II studies (colorectal)

Sugarbaker (Dis col rectum 2000)	24
Cavaliere (J Surg Oncol 2000)	30
Beaujard (Cancer 2000)	26
Elias (Cancer 2001)	35.9
Glehen (Br J Sur 2004)	32.9
Verwaal (Br J Sur 2004)	39
Glehen (JCO 2004)	21
Shen (Ann Surg Oncol 2004)	28

in HIPEC procedures, which is the determining factor in improving survival ?



Completeness of cytoreduction

Drug…
Mitomycin C : The Dutch Trial

- 1998-2001 105 patients

- The median survival was 21.8 months
- The 3 and 5 year survival rates were 28% and 19%.

- Complete cytoreduction : median survival : 42.9 months
- Minimal residual disease : median survival : 17.4 months

- When a gross macroscopic tumor was left behind, the median survival was 5 months

- After an 8 years follow up : The 5-year survival was 45% for those patients in whom a R1 resection was achieved.

(Ann Surg Oncol. 2005 Jan;12(1):65-71 / Ann. Surg. Oncol. Vol. 15, No. 9, 2008)

Drug…
Oxaliplatin : Phase 2 Study
Survival

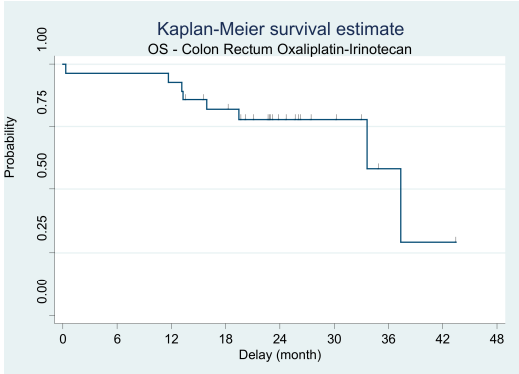
- 30 patients, median follow up 55 months
- At 3 & 5 years, global survival
  - 53 %
  - 48,5 %
- At 3 & 5 years, desease free survival was
  - 41,5 %
  - 34 %
- Médian survival was 60,1 months

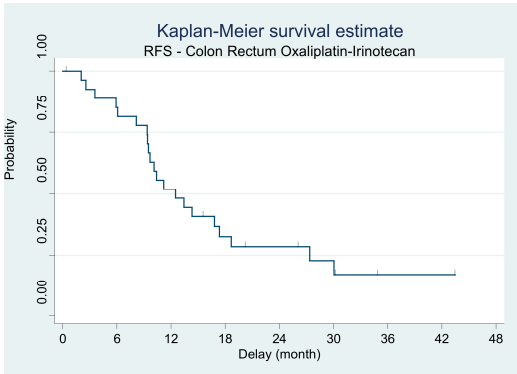
Elias D Gastroenterol Clin Biol 2006;30:1200-1204

Cocktail…
Oxaliplatin Irinotecan

37 patients

Median follow up	**24.6 months**		
- MEDIAN SURVIVAL TIME -			
Overall Survival (OS)	37.4 months		
Relapse Free Survival (RFS)	13.0 months		
- SURVIVAL RATE [95%CI] -			
	1-year	2-year	3-year
OS	93 % - [74 - 98]	78 % - [57 - 89]	58 % - [19 - 84]
RFS	52% - [32 -69]	29 % - [13 - 46]	17 % - [5 - 35]





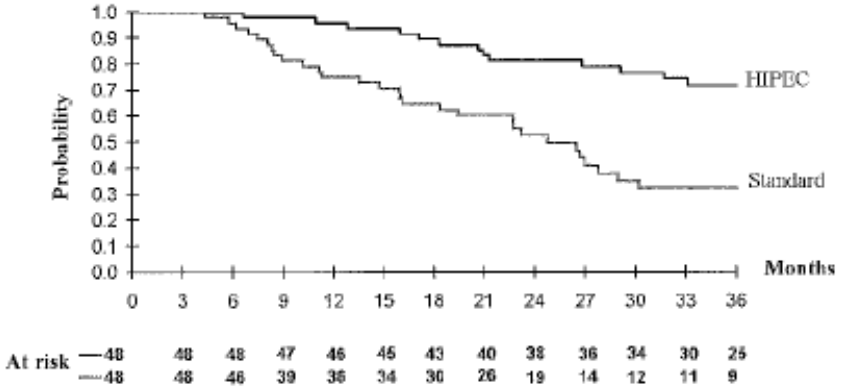
F.Quénet, Abstract ASCO 2008, ♯4084

Metastatic colorectal cancer
Systemic Chemotherapy

Author	Year	Journal	Chemo	PFS	MS
DeGramont	2000	JCO	FOLFOX	9.0	16.2
Saltz	2000	NEJM	IFL	7.0	14.8
Douillard	2000	Lancet	FOLFIRI	6.7	17.4
Tournigand	2003	JCO	FOLFOX/FOLFIRI	14.2	**21.5**
Hurwitz	2004	NEJM	IFL Beva.	10.6	**20.3**
Goldberg	2006	JCO	FOLFOX	9.7	19.0
Falcone	2007	JCO	FOLFOXIRI	9.8	**22.6**
Van Cutsem	2007	Ab. ASCO	FOLFIRI-Cetux.	8.9	-

Oxaliplatin : Retrospective Study

- 2 Groups of patients retrospectively selected
  - 48 underwent complete cytoreductive surgery & HIPEC with oxaliplatin
  - 48 retrospectively considered as resectable who have only be treated by systemic chemotherapy.



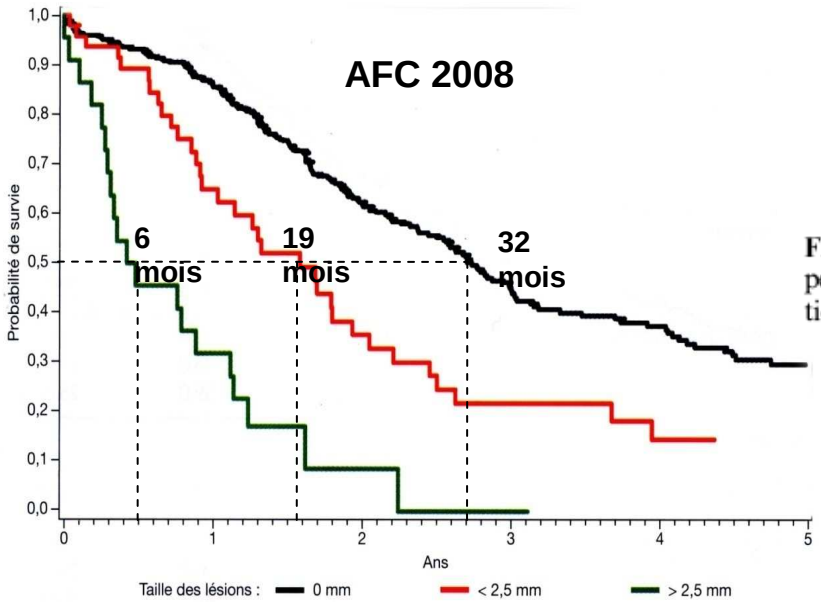
HIPEC: Median overall survival: 60.1 months

Standard: Median overall survival: 24.8 months

P= 0.0001

Elias & al in press JCO

Completeness of cytoreduction



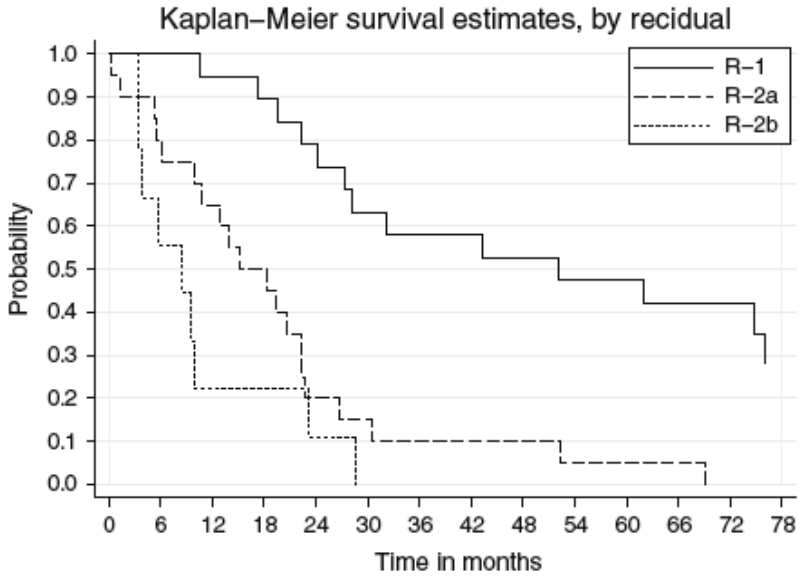
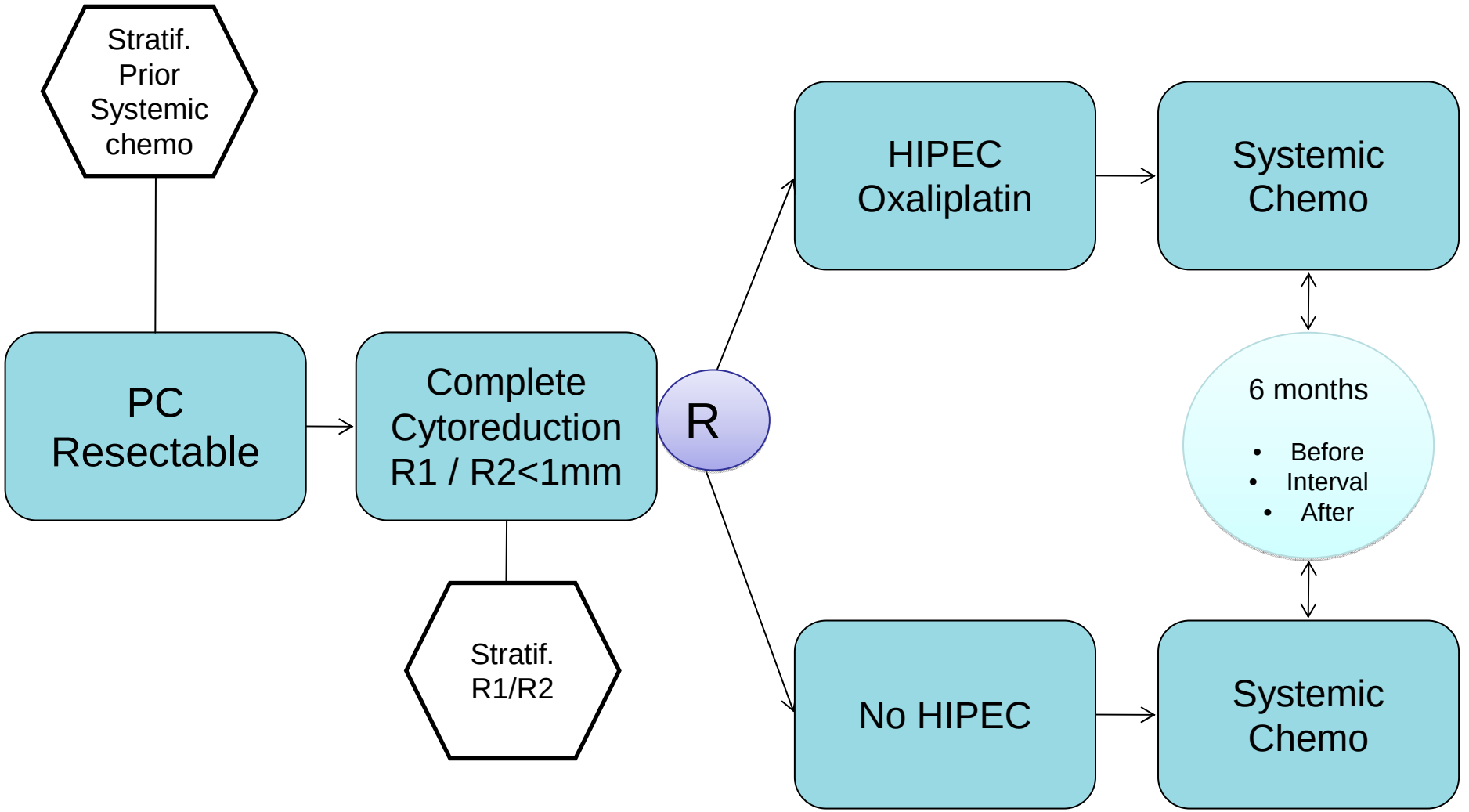


FIG. 3. Long-term results of cytoreduction followed by HIPEC in peritoneal carcinomatosis, divided to completeness of cytoreduction.

Verwall & al, Annals of Surgical Oncology 2008; 15(9):2426–2432
Elias, Gilly, Glehen. Carcinose péritonéales d'origine digestive et primitive. Arnette. Wolters Kluwer France, 2008.


Stratif.
Prior
Systemic
chemo
PC
Resectable
Complete
Cytoreduction
R1 / R2<1mm
Stratif.
R1/R2
R
HIPEC
Oxaliplatin
Systemic
Chemo
6 months
Before
Interval
After
No HIPEC
Systemic
Chemo

Phase III trial evaluating the role of intraperitoneal chemohyperthermia (HIPEC) after maximal cytoreductive surgery of peritoneal carcinomatosis of colorectal origin

F.Quénet, D.Elias, O.Glehen

Statistical design : to improve overall survival from 30 to 48 months

- Primary endpoint : overall survival
- Secondary endpoints :
  - PFS
  - Treatment safety

Duration	44 months
Number of patients	264
1st intermediate analysis	At 51 events, 34 months
2d intermediate analysis	At 102 events, 50 months
Final analysis	At 154 events, 71 months
Power of test	80
HR	0.625

VILLE	ORGANISME	INVESTIGATEUR	SIGNATURE CONVENTION	DATE D'ENREGISTREMENT DU 1er PT	NOMBRE DE PATIENTS ENREGISTRES	DATE DE RANDOMISATION DU 1er PT	PATIENTS RANDOMISES
LYON PIERRE BENITE	Hôpital Lyon Sud	Pr Oliver GLEHEN	18/12/07	0708/2008	11	20/08/08	4
MONTPELLIER	Centre Val d'Aurelle	Dr François QUENET	21/12/07	08/02/08	9	11/02/08	7
DIJON	CHU du Bocage	Pr Patrick RAT	02/01/08	01/04/08	4	08/04/08	1
TOULOUSE	Centre Hospitalier Purpan	Dr Guillaume PORTIER	30/04/08	15/05/08	1		
LYON CLB	Centre Léon Bérard	Dr Pierre MEEUS	25/06/08	16/09/08	1		
MARSEILLE	Institut Paoli Calmettes	Dr Olivier TURRINI					
VILLEJUIF	Institut Gustave Roussy	Dr Dominique ELIAS	08/01/08				
PARIS	Hôpital Lariboisière	Pr Marc POCARD	08/10/08				
NANCY	Centre Alexis Vautrin	Dr Frédéric MARCHAL	03/12/07				
STRASBOURG	Hôpital de Hautepierre	Dr Cécile BRIGANT	01/07/08				
NICE	Hôpital de l'Archet 2	Dr Jean-Marc BEREDER	11/01/08				
COLOMBES	Hôpital Louis Mourier	Pr Simon MSIKA	08/10/08				
GRENOBLE	CHU de Grenoble	Dr Catherine ARVIEUX					
ANGERS	Centre Paul Papin	Dr Gérard LORIMER	09/07/08				
REIMS	Institut Jean Godinot	Dr David KERE	04/07/08				
		TOTAL	13	5	26	3	12
			Conventions signées	Centres ayant enregistrés	patients enregistrés	Centres ayant randomisés	Patients randomisés

Results of a Systematic Second-Look Surgery in Patients at High risk of developing Colorectal Peritoneal Carcinomatosis

Elias D,

Goéré D, Boige V, Malka D, Ducreux M.

Institut Gustave Roussy,

Villejuif, France.

Prognostic Factors

- The **tolerance** of HIPEC is better when cytoreductive surgery is minimal.
- The **survival** after HIPEC is higher when the extent of PC is minimal.

Its better to treat early than late.

Rationale

- HIPEC is all the more « light » and all the more efficient when the PC is minimal. **But detecting minimal PC early is impossible either clinically or via imagery.**

- Hence it is logical to propose a **systematic second-look** to asymptomatic patients presenting a high risk of developing a PC.
- A delay of **1 year** was chosen…

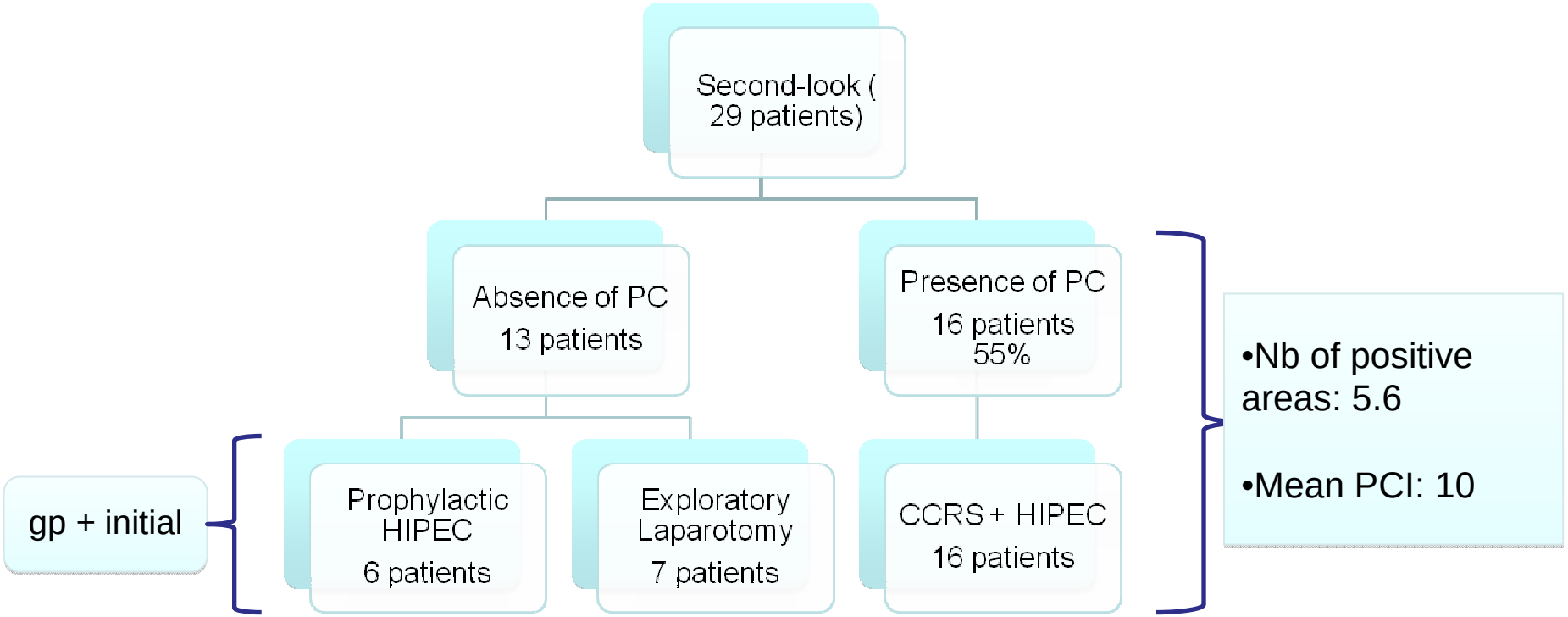
Patients and Methods

- From 1999 to 2006, 29 patients with a high risk of developing a PC **(without clinical or biological symptoms, nor detected by imagery)**, underwent a second look, 12 mois after their first surgery.

- **3 groups of patients were selected:**
  - G1: **Minimal macroscopic PC** (n=16) synchronous to the primary tumor (and which was completely resected during the same session)
  - G2 : **Synchronous ovarian metastases** (n=4),
  - G3 : **Perforation** of primary tumour (n=9).

- All these patients received the adjuvant standard treatment after the first surgery: 6 months of systemic chemotherapy (Folfox or Folfiri)

Patients & Methods



Results

A macroscopic PC was found and treated in 16/29 **(55%)** patients,

G1 Initial PC	G2 Ovarian Metastasis	G3 Perforation
10/16 (63%)	3/4 (75%)	3/9 (33%)

- **Morbidity (grade III/IV) was 14%.**
- **Mean hospital stay was 16 days**

(Elias D et al. Ann Surg 2008; 247: 445-450)

Survival (early results)

- **After a mean follow-up of 27 months (6-96):**

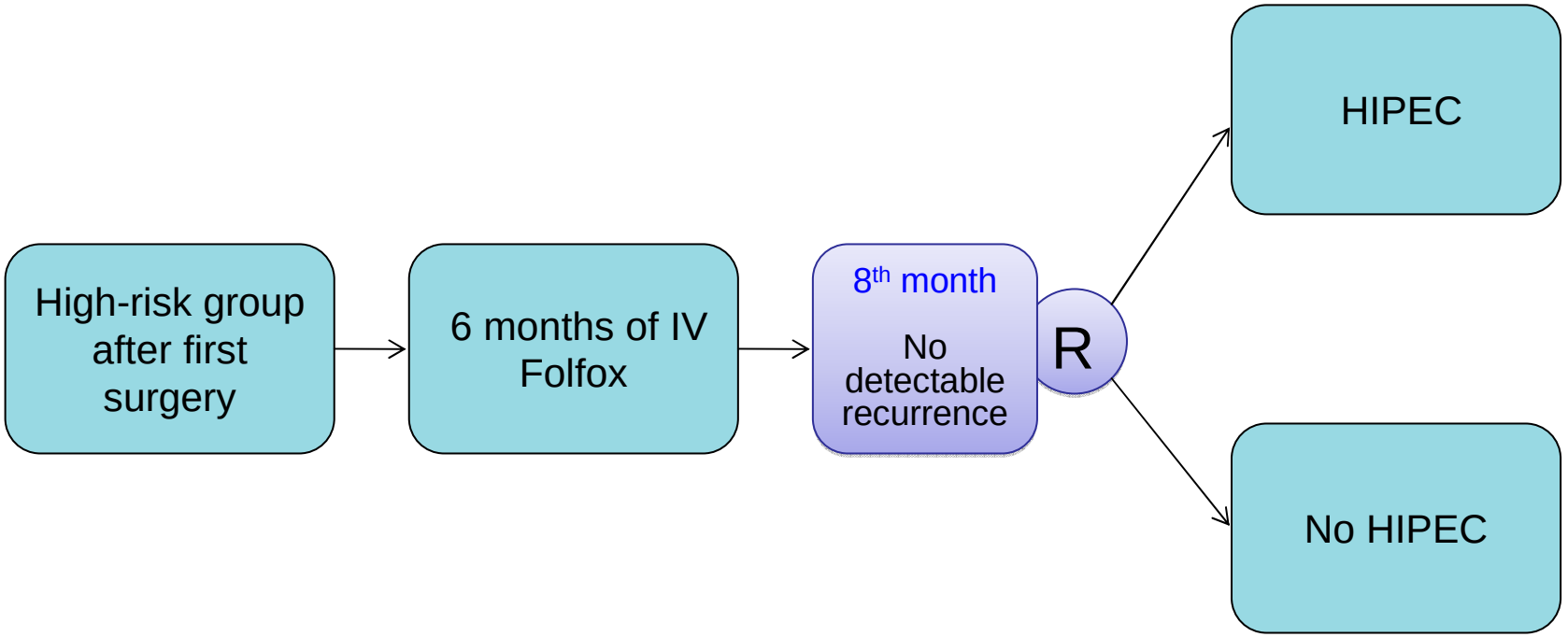
- **<u>For the 16 patients who underwent a resection of PC + HIPEC:</u>**
  - 8 (50%) are free of disease,
  - 4 (25%) recurred on peritoneum,
  - 4 (25%) recurred outside the peritoneum.

- **<u>For the 6 patients who underwent HIPEC, without detectable PC:</u>**
  - No recurrence (+++)

- **<u>For the 7 patients who did not undergo HIPEC:</u>**
  - 3 developped a PC (+++)

Second Look French Trial

D.Elias & al



Statistical design: **to improve 3 years PFS from 40 to 65%**
64 patients are needed in each group