



Overview of International guidelines for CRS and HIPEC

Management of Peritoneal Surface Malignancy

Irkutsk, Sibiria

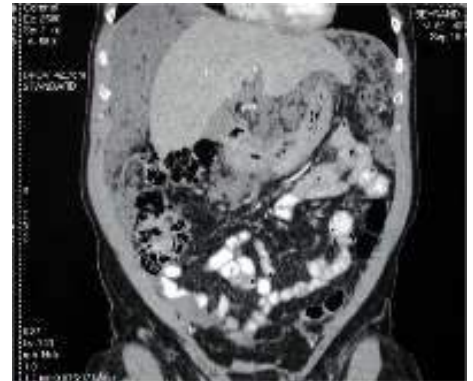
F.Quénet
ICM Montpellier
France

Peritoneal Carcinomatosis

A specific metastatic model?

Probably several different pathways in metastatic dissemination

- Diffuse dissemination in the abdominal cavity
- Isolated in 20% of the cases
- Often worse response to chemotherapy than in other metastatic locations (liver)

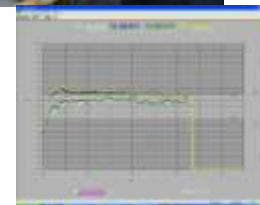
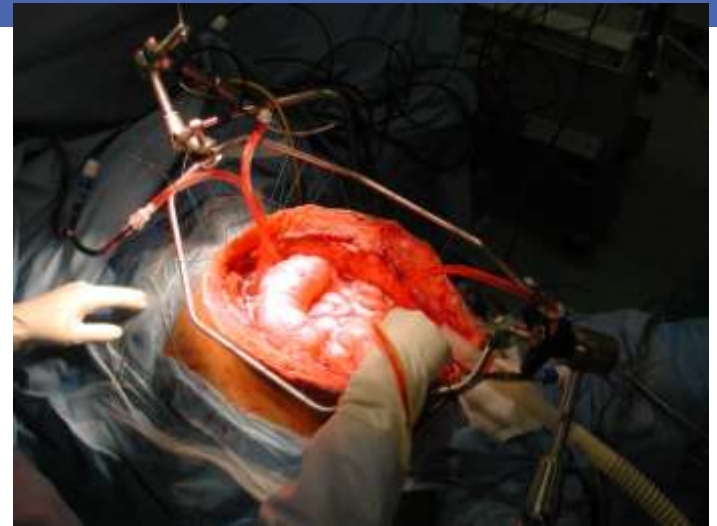


HIPEC & CRS

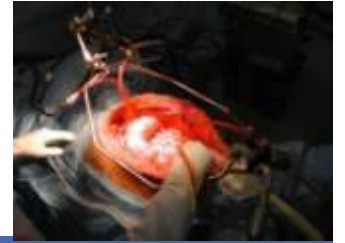
HIPEC:

1. Intra-peritoneal administration
2. Per-Op
3. Hyperthermia

Need of a maximal cytoreductive surgery to eliminate macroscopic disease (< 2mm)



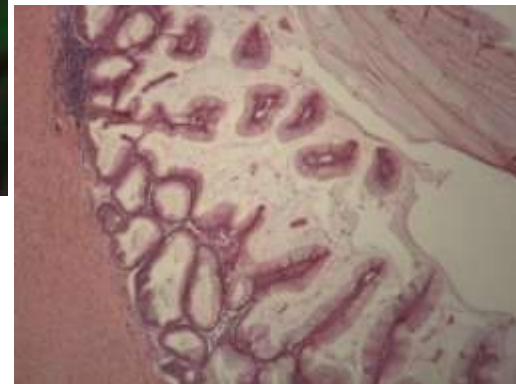
HIPEC : Treatment Synergism



- Targeted action on microscopic residual disease
- « Cytotoxic shock » per-op
- Direct access to peritoneal disease whilst systemic chemo is not always able to reach it.



1-Pseudomyxoma peritonei



Pseudomyxoma Peritonei



Without HIPEC

- ☐ 97 PMP treated by debulking (2,2 laparotomies) (1980-2002)
- ☐ 20% of patients underwent at least 3 **operations**
- ☐ 55% of complete resection
- ☐ **21% overall survival at 10 years**
- ☐ Median disease free interval was 24 months
- ☐ **Recurrence rate was 91%**

Early- and Long-Term Outcome Data of Patients With Pseudomyxoma Peritonei From Appendiceal Origin Treated by a Strategy of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Terence C. Chua, Brendan J. Moran, Paul H. Sugarbaker, Edward A. Levine, Olivier Glehen, François N. Gilly, Dario Baratti, Marcello Deraco, Dominique Elias, Armando Sardi, Winston Liauw, Tristan D. Yan, Pedro Barrios, Alberto Gómez Portilla, Ignace H.J.T. de Hingh, Wim P. Ceelen, Joerg O. Pelz, Pompiliu Piso, Santiago González-Moreno, Kurt Van Der Speeten, and David L. Morris

2298 patients from 16 specialized centres

- The median survival rate was 196 months (16.3 years)
- the median PFS rate was 98 months (8.2 years).
- The overall 5-, 10-, and 15-year survival rates were 74%, 63%, and 59%,

In Univariate & multivariate analysis, the use of HIPEC was associated with PFS (HR, 0.65; $P < .030$)

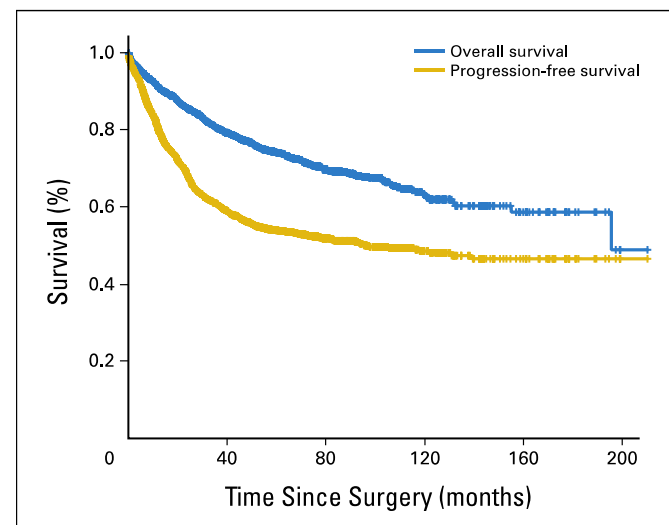


Fig 1. Overall survival and progression-free survival rates of 2,298 patients with appendiceal pseudomyxoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

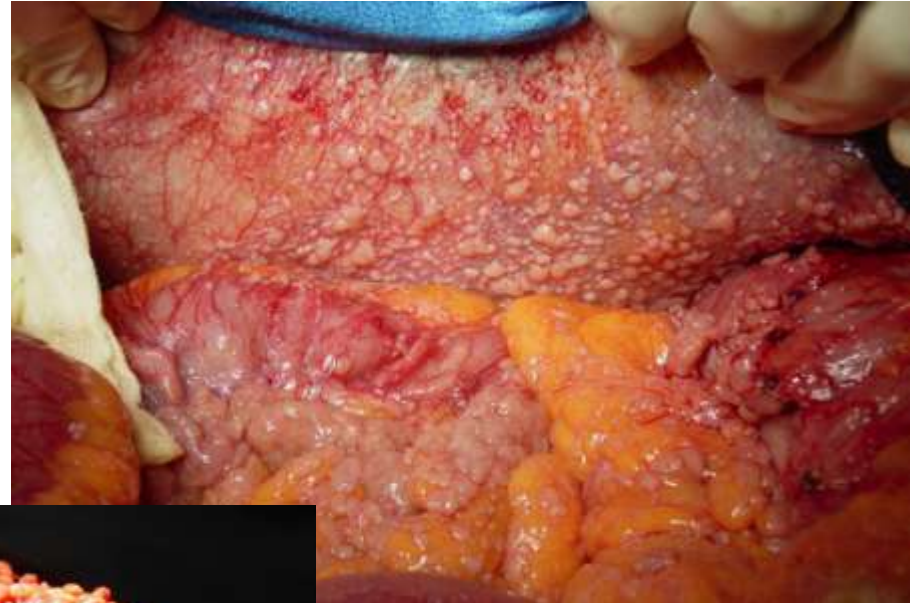
Conclusion Pseudomyxoma Peritonei



- CRS & HIPEC has become a worldwide standard of care
- Morbidity & mortality rates are no longer arguments against this approach
 - Mortality rate from 2 to 4%
 - Morbidity rate from 30 to 47%



2-Mesothelioma peritonei



Mésothéliomes/ Pronostic

Type histologique	Survie médiane (mois)
Multikystique	>54
Epithélioïde	63
Mixte/Sarcomatoïde	16

Traitement standard systémique:
Cisplatine-Alimpta (pemetrexed)

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: Multi-Institutional Experience

Tristan D. Yan, Marcello Deraco, Dario Baratti, Shigeki Kusamura, Dominique Elias, Olivier Glehen, François N. Gilly, Edward A. Levine, Perry Shen, Faheez Mohamed, Brendan J. Moran, David L. Morris, Terence C. Chua, Pompiliu Piso, and Paul H. Sugarbaker

- The overall median survival was 53 months (range, 1 to 235 months)
- The 1-, 3- and 5-year survival rates were 81%, 60%, and 47%,
- Multivariate analysis:
 - Epithelial subtype ($P < .001$)
 - Absence of lymph node metastasis ($P < .001$)
 - CC-0 to CC-1 ($P < .001$)
 - HIPEC ($P < .002$)

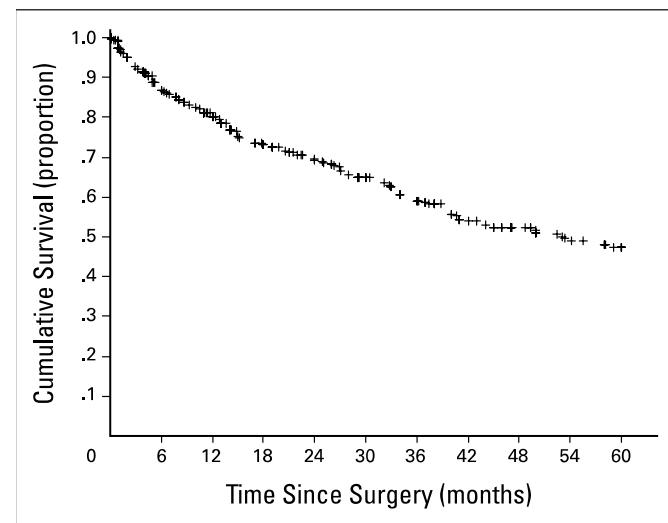


Fig 1. Overall survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma (n = 401). (+) Patients who were alive at the last follow-up.

Mesothelioma Peritonei

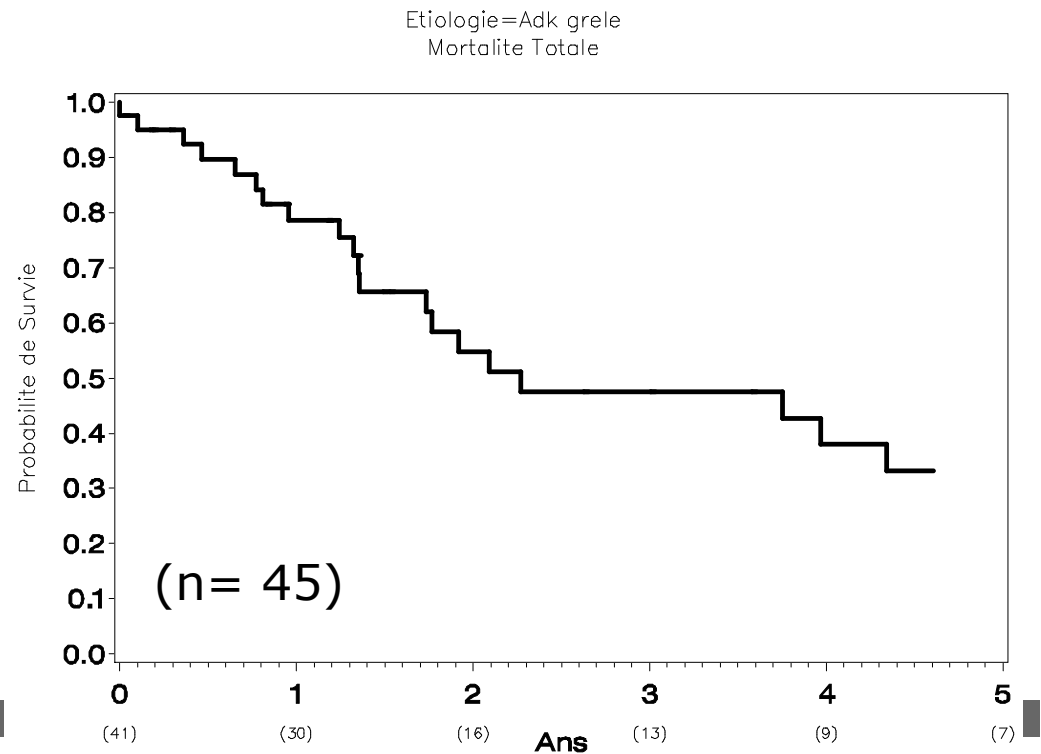
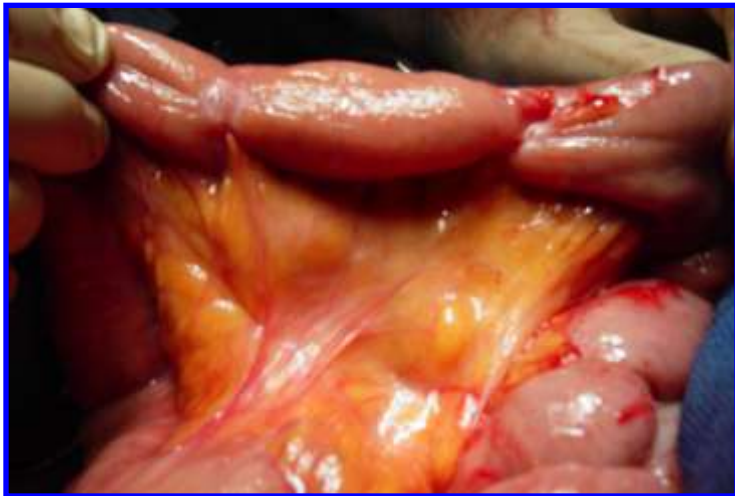


- This disease, previously considered a preterminal condition, now can be treated with CRS and HIPEC at experienced centers to provide a benefit in terms of long-term survival.



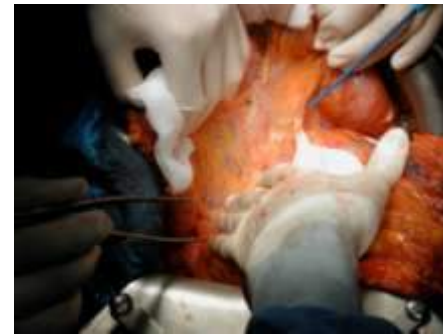
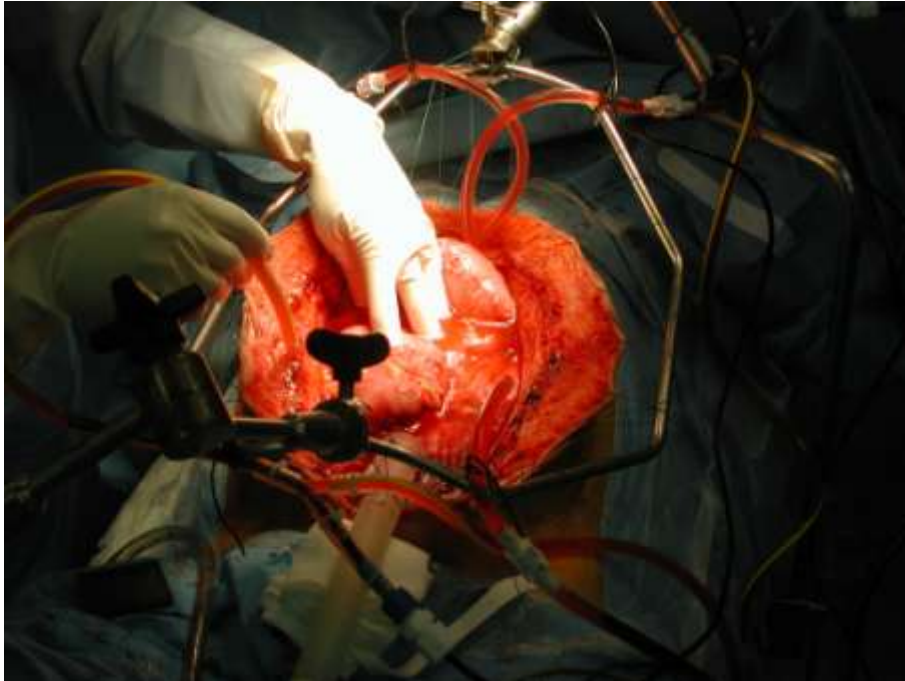
3- Small Bowell Adenocarcinoma

Résultats quasi-identiques à ceux du colon : 33% de survie à 5 ans





4- Gastric Adenocarcinoma



Major problem of the disease evolution



- More than 50% of potentially curable gastric cancer died of peritoneal recurrence
- 60% of all causes of gastric cancer deaths is from peritoneal carcinomatosis

Natural History

Sadeghi EVOCAPE 1 (*Cancer 2000*) : n=127. (prospective) Palliative systemic chemotherapy.

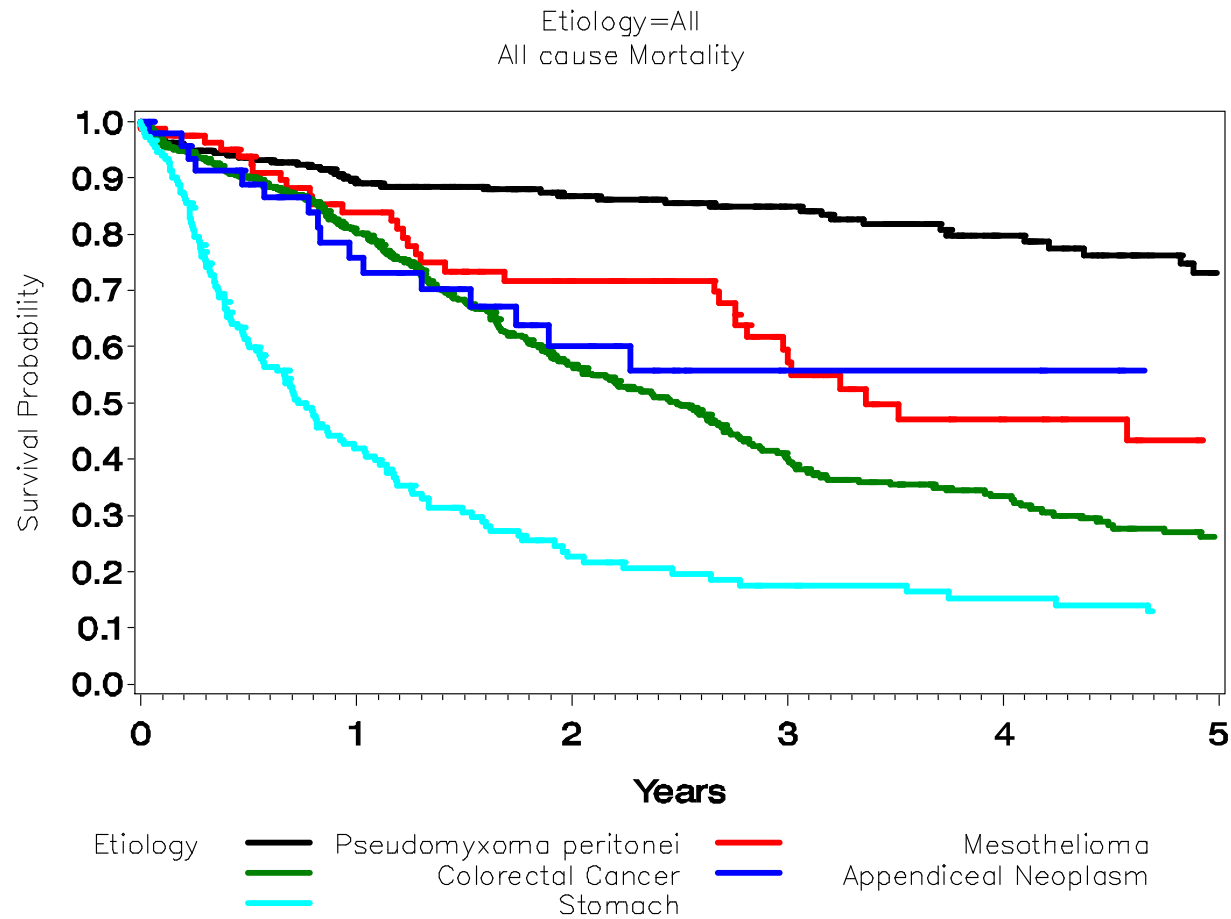
- Median survival : 3 months
- No real improvement of prognosis with new systemic agents
 - Trastuzumab < 20% of patients
- Metastatic gastric cancer in 2016
 - Median survival < 1 year

TABLE 6
Potential Prognostic Factors for the Survival of Gastric Carcinoma Patients with Peritoneal Carcinomatosis

	Median (mos)	Mean (mos)	P value
Peritoneal carcinomatosis			
Synchronous	2.8	4.8	P = 0.6
Not synchronous	3.1	5.1	NS
Initial pTNM staging			
T1,T2 (n = 8)	9.0	20.4	
T3 (n = 55)	4.0	9.7	P = 0.06
T4 (n = 62)	2.5	4.2	
Lymph node involvement			
N0	8.8	7.0	P = 0.52
N+	8.5	7.8	NS
PC staging			
Stage I	7.9	11.2	
Stage II	6.2	4.5	
Stage III	5.8	3.5	P = 0.001
Stage IV	1.9	2.6	
Differentiation			
WD and MD	4.2	5.2	P = 0.4
PD and UD	2.4	4.7	NS
Ascites			
Yes	1.4	3.6	P = 0.05
No	3.8	5.4	
Liver metastases			
Yes	1.0	2.6	P = 0.0009
No	3.3	5.3	

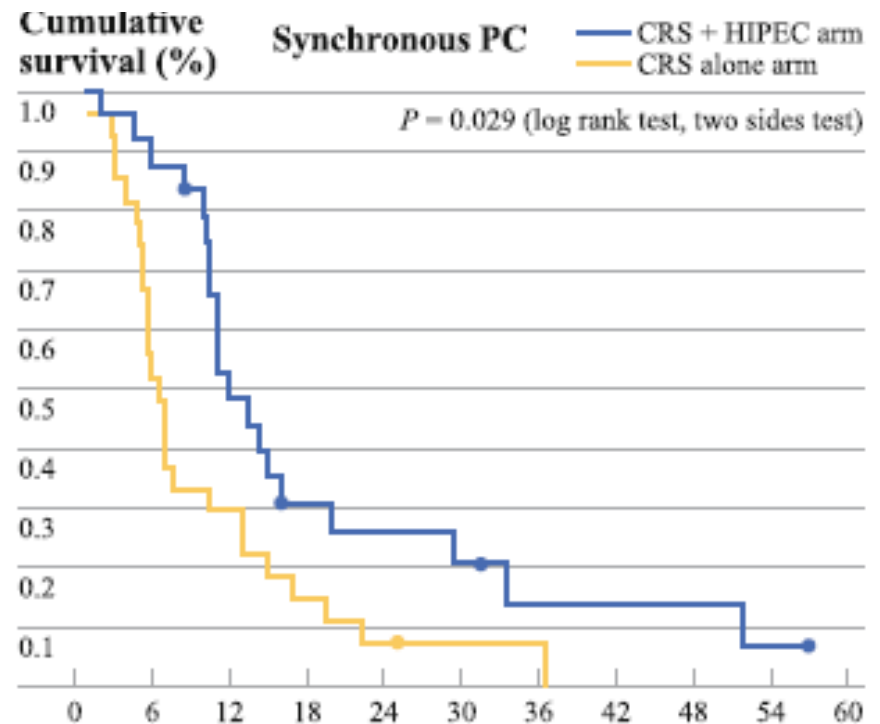
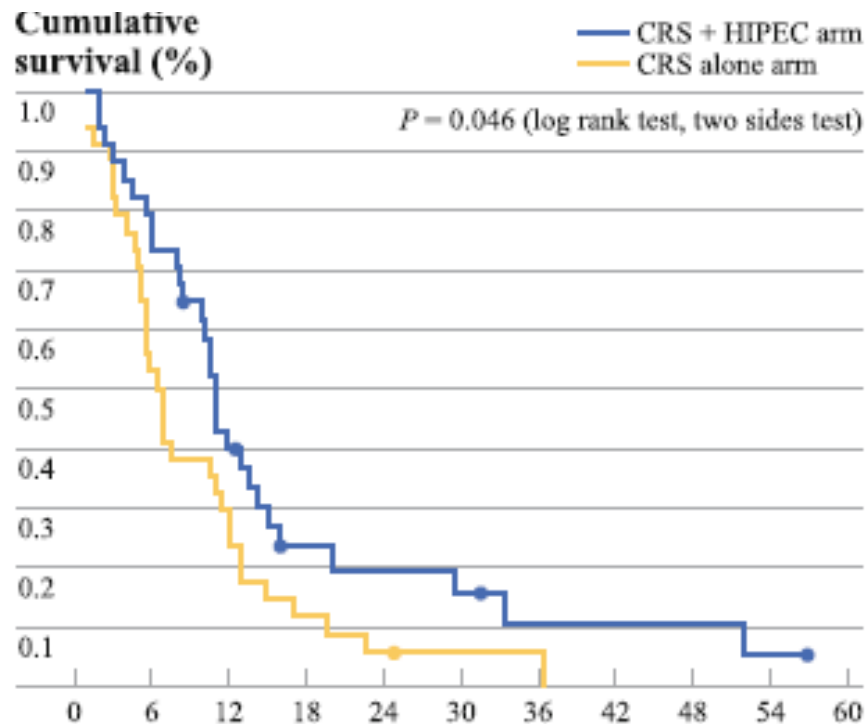
PC: peritoneal carcinomatosis; WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated; UD: undifferentiated; NS: not significant.

Overall survival according to etiology



Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Gastric Cancer: Final Results of a Phase III Randomized Clinical Trial

Xiao-Jun Yang, MD¹, Chao-Qun Huang, MD¹, Tao Suo, MD², Lie-Jun Mei, MD¹, Guo-Liang Yang, MD¹, Fu-Lin Cheng, MD¹, Yun-Feng Zhou, MD, PhD¹, Bin Xiong, MD, PhD¹, Yutaka Yonemura, MD, PhD³, and Yan Li, MD, PhD¹



HIPEC improved survival (p=0.046)

Meta-analysis of intraperitoneal chemotherapy in gastric cancer



➤ in established PC

- median survival varies from 6.1 months to 11.5 months after HIPEC
- with a median survival of up to 43.4 months in patients with complete cytoreduction
- A wide range of HIPEC techniques, perfusion times, and temperatures was used with mitomycin C, cisplatin, paclitaxel, etoposide, oxaliplatin, irinotecan, fluorouracil, or a combination of these.

Is There a Possibility of a Cure in Patients With GASTRIC Peritoneal Carcinomatosis?

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

- 10.4 % of patients cured
- All synchronous
- Median PCI of 3 (0-6)
- All were CC-0 resections
- 28% with signet ring cells
- 37% had neoadjuvant systemic chemotherapy • 14% had adjuvant systemic chemotherapy

First Message on Gastric Carcinomatosis



Cytoreductive and HIPEC are the only therapeutic combination that may allow actuarial 5-year survival of more than 10%

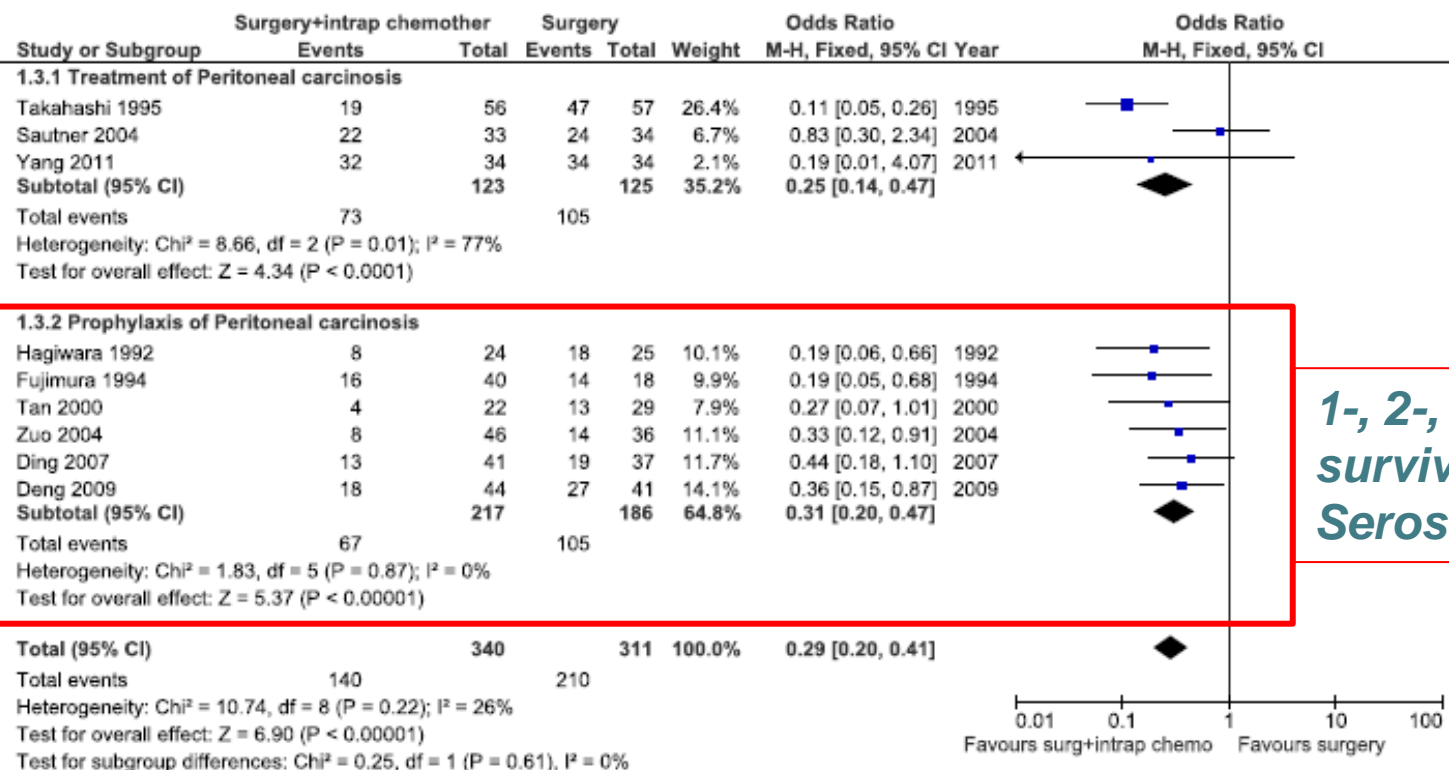
Interest of preventive treatment



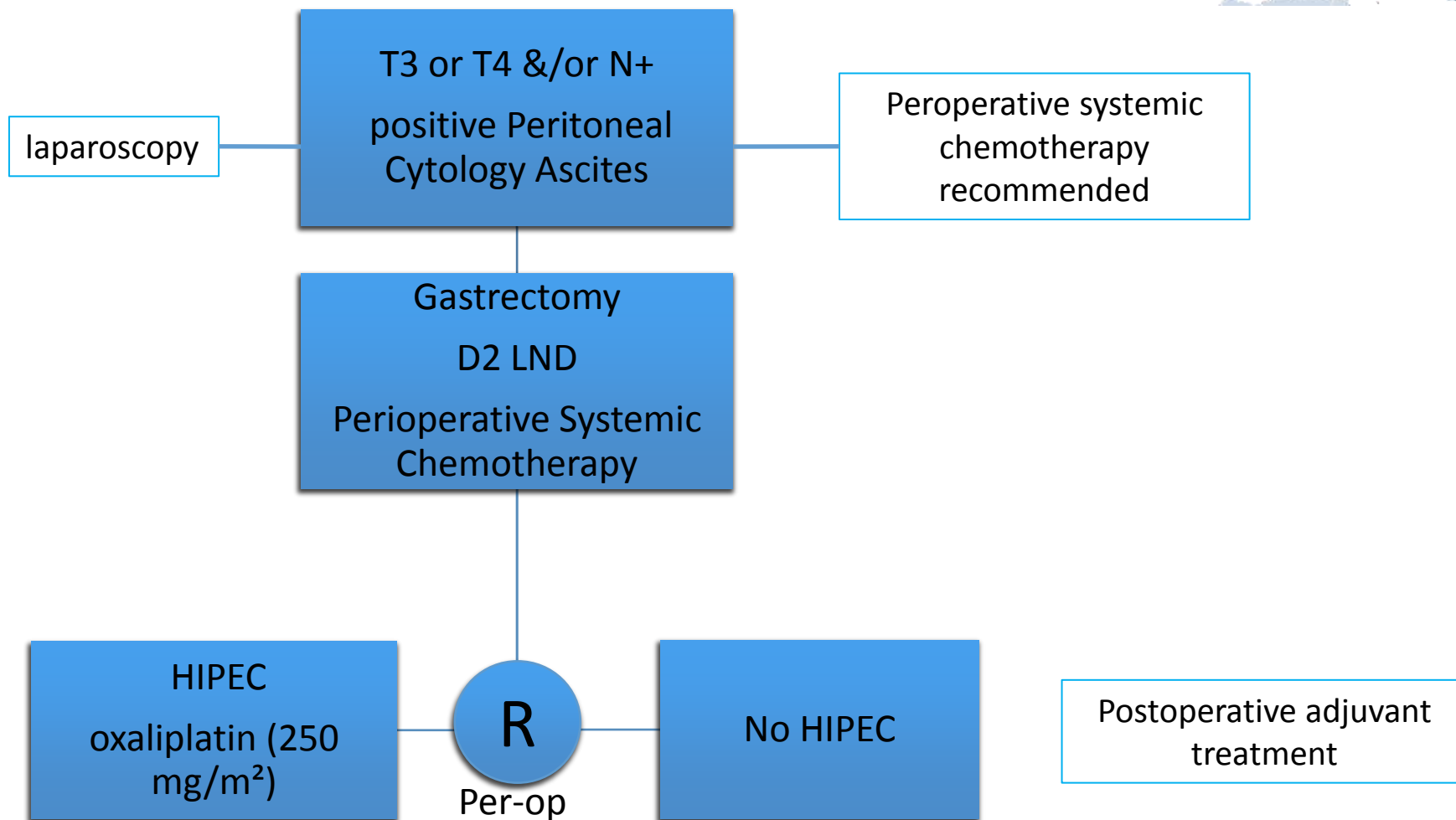
- 5-years survival rate of T3 and/or N+ still less than 30%
- 50% of gastric adenocarcinoma will develop peritoneal recurrence

To improve survival of locally advanced gastric adenocarcinoma we should prevent carcinomatosis development

Meta-analysis of intraperitoneal chemotherapy in gastric cancer

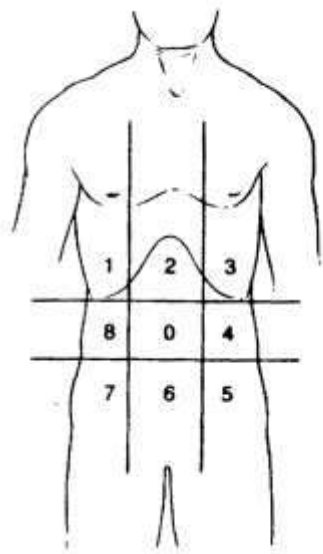


GASTRICHIP design

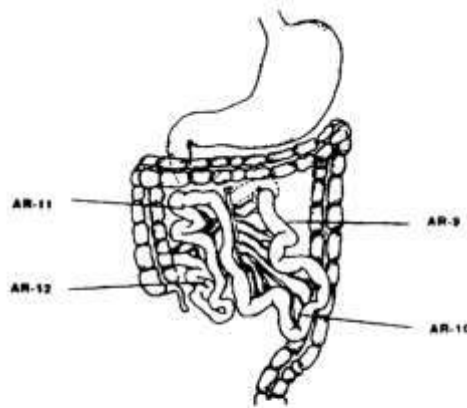




5- Colo-rectal Carcinomatosis



- 0 Central
- 1 Right upper
- 2 Epigastrium
- 3 Left upper
- 4 Left flank
- 5 Left lower
- 6 Pelvis
- 7 Right lower
- 8 Right flank



Treatment of Colorectal Peritoneal Carcinomatosis With Systemic Chemotherapy: A Pooled Analysis of North Central Cancer Treatment Group Phase III Trials N9741 and N9841

Jan Franko, Qian Shi, Charles D. Goldman, Barbara A. Pockaj, Garth D. Nelson, Richard M. Goldberg, Henry C. Pitot, Axel Grothey, Steven R. Alberts, and Daniel J. Sargent

➤ 2101 patients

➤ 17.4%. patients presented PC as the sole presentation of mCRC

➤ (n = 44, 2.1%)

➤ **Median OS PC was 12.7**

➤ HR = 1.32, 95% CI, 1.15 to 1.50; $P < .001$

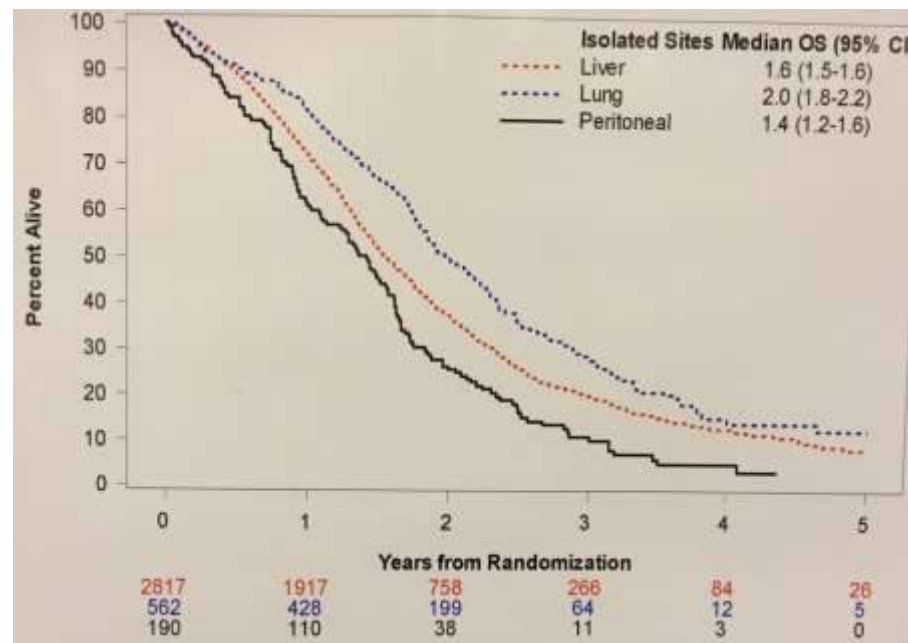
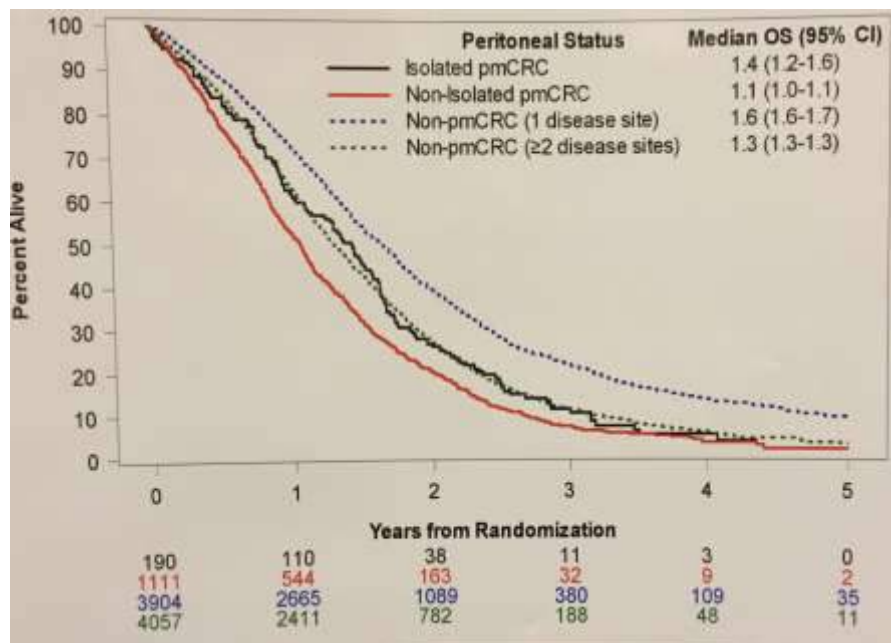
➤ After 7 years median follow-up

➤ 2,009 (98.5%) of 2,095 patients with known PC status have died.

Prognostic value of isolated peritoneal versus other metastatic sites in colorectal cancer patients treated by systemic chemotherapy:

Findings from 9,265 patients in the ARCAD database

Jan Franko, Qian Shi, Jeffrey P. Meyers, Volker Heinemann, Alfredo Falcone, Niall C. Tebbutt, Tim Maughan, Matthew Seymour, Leonard Saltz, Christophe Tournigand, Eduardo Díaz-Rubio, Ioannis Souglakos, Benoist Chibaudel, Joseph Moen, Almerly De Gramont, Richard A. Adams, Daniel J. Sargent, Axel Grothey



Courtesy of J.Franko, ASCO 2016

Survival Results

CRS & HIPEC is no Longer an Experimental Treatment

➤ Dutch Trial : 105 patients



➤ Complete cytoreduction : median OS 42.9 months

➤ After a 8-year follow up : 5-year survival rate 45% for R1

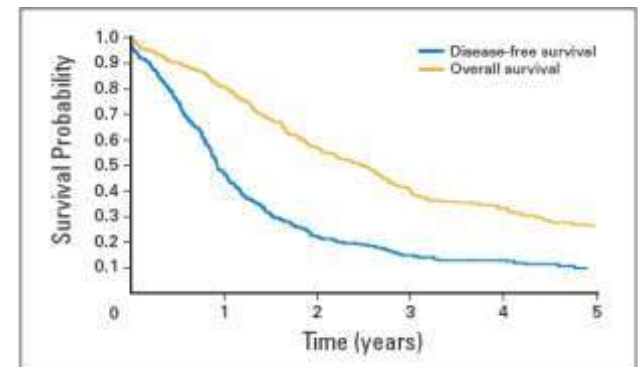
(V.Verwaal, Ann Surg Oncol. 2005 Jan;12(1):65-71 / Ann. Surg. Oncol. Vol. 15, No. 9, 2008)

➤ French multicentric study 523 patients

➤ Median OS 33 months

➤ 5-year OS 41%

(D.Elias & al JCO 2010)

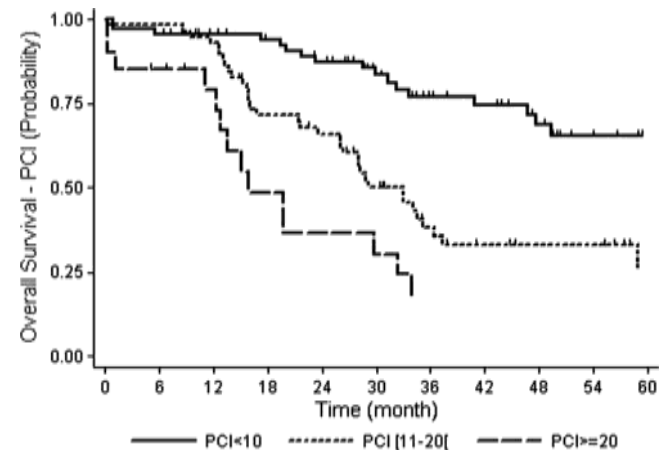
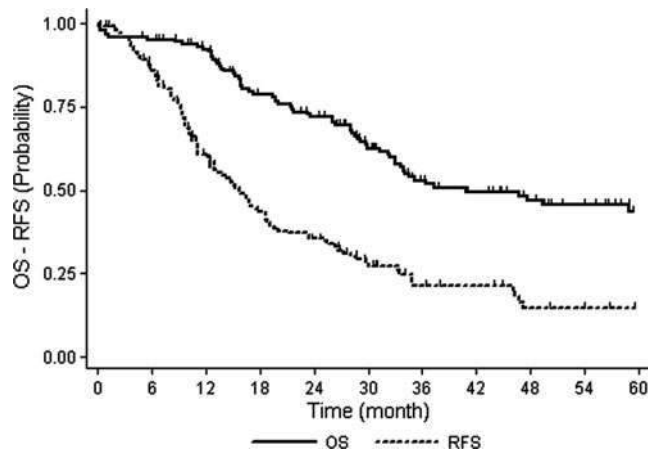


Survival Results

CRS & HIPEC is no Longer an Experimental Treatment

Results obtained prospectively by 2 experienced centers between 1998 and 2007 using oxaliplatin

- 5- year survival of the 146 patients was 48%
- Median overall survival 41 months



Is There a Possibility of a Cure in Patients With Colorectal Peritoneal Carcinomatosis Amenable to Complete Cytoreductive Surgery and Intraperitoneal Chemotherapy?

Diane Goéré, MD,* David Malka, MD, PhD,† Dimitri Tzanis, MD,* Vinicius Gava, MD,* Valérie Boige, MD, PhD,† Clarisse Eveno, MD,* Léon Maggiori, MD,* Frédéric Dumont, MD,* Michel Ducreux, MD, PhD,† and Dominique Elias, MD, PhD*

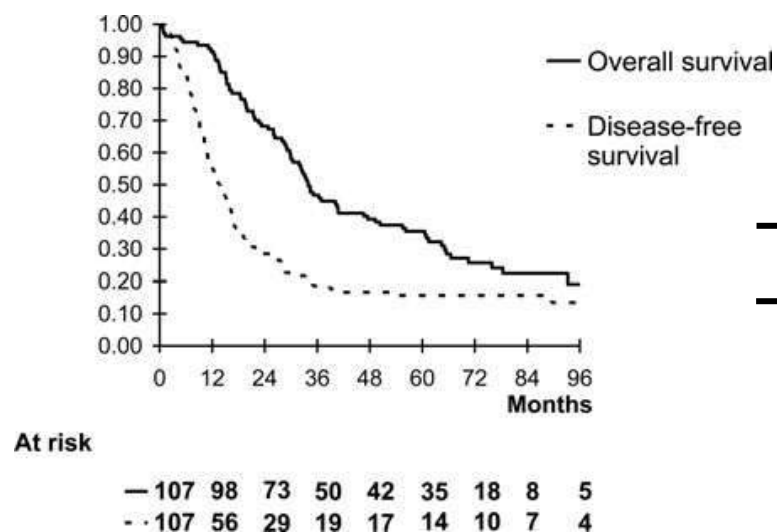


FIGURE 1. Overall survival and disease-free survival in 107 patients who underwent complete CRS with IPC.

16% were considered cured...

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

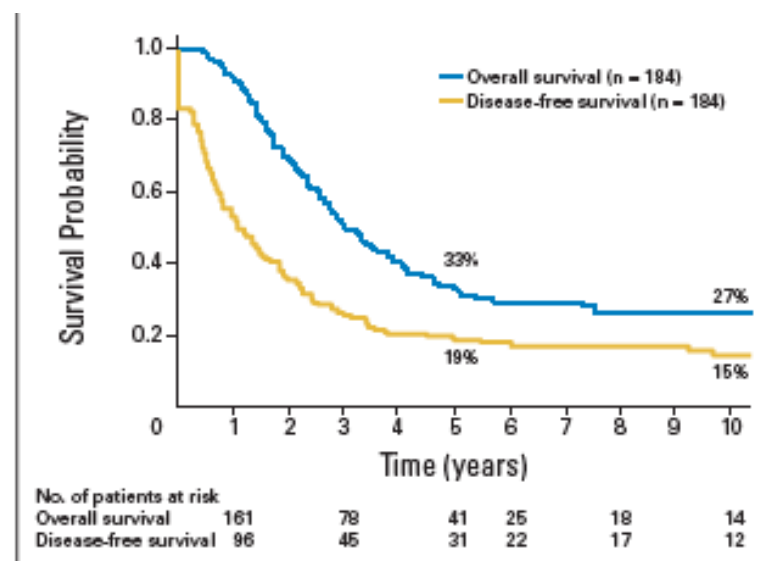
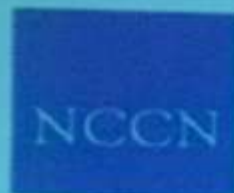


Fig 1. Overall and disease-free survival curves of patients with initially unresectable disease who underwent resection after downsizing chemotherapy.

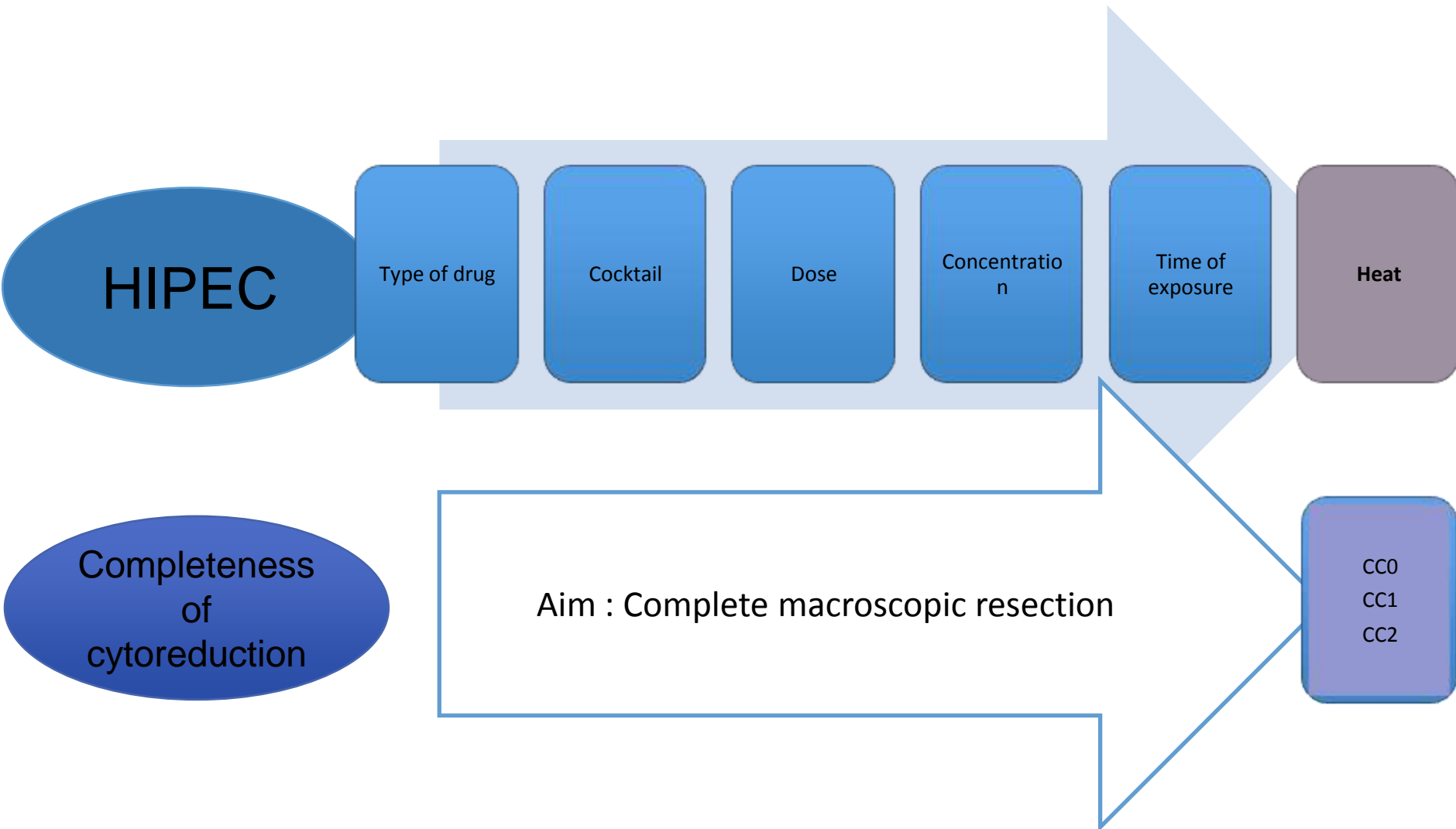
16% were considered cured...



Peritoneal Metastases

The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. The panel recognizes the need for (additional) randomized clinical trials that will address the risks and benefits associated with each of these modalities.

CRS & HIPEC



The of Oxaliplatin or Mitomycin C in HIPEC Treatment for Peritoneal Carcinomatosis from Colorectal Cancer: A Comparative Study

D. HOMPES, MD, PhD,^{1,2*} A. D'HOORE, MD, PhD,¹ A. WOLTHUIS, MD,¹ S. FIEUWS, PhD,³
B. MIRCK, MD,² S. BRUIN, MD,² AND V. VERWAAL, MD, PhD²

Oxaliplatin or Mitomycin C ?

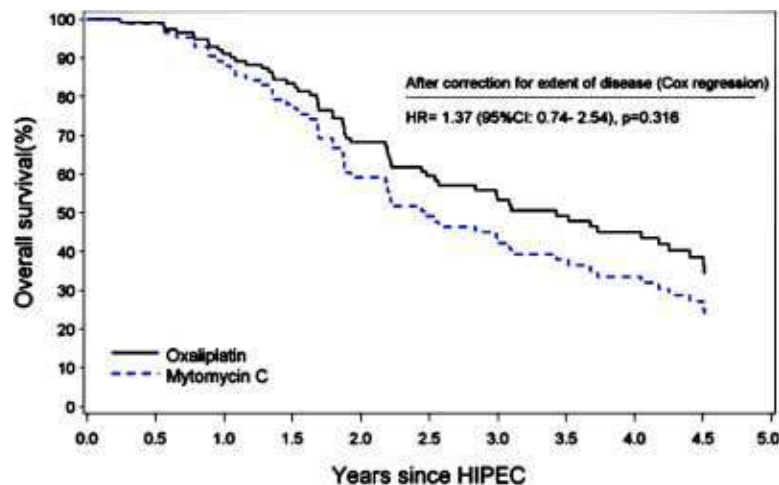


Fig. 1. OS after CCRS + HIPEC with Oxali versus MMC (after correction for extent of disease).

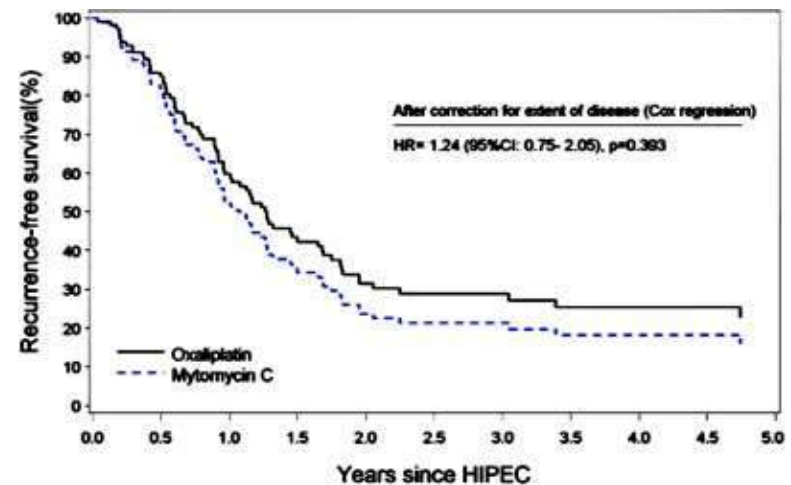


Fig. 2. RFS after CCRS + HIPEC with Oxali versus MMC (after correction for extent of disease).

No clear benefit in RFS and OS for HIPEC with Oxaliplatin or MMC



Results of Two Bi-Institutional Prospective Studies Using Intraperitoneal Oxaliplatin With or Without Irinotecan During HIPEC After Cytoreductive Surgery for Colorectal Carcinomatosis

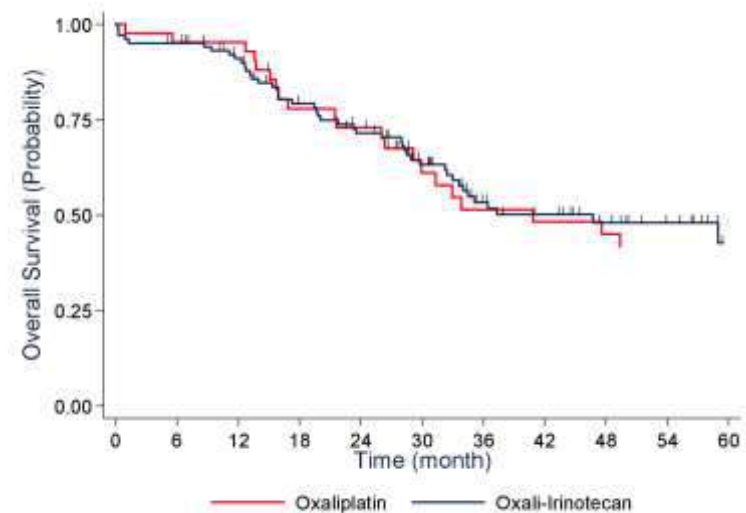
François Quenet, MD, Diane Goéré, MD,† Sanket Sharad Mehta, DNB,* Lise Roca, MS,‡ Frédéric Dumont, MD,† Mehdi Hessissen, MD,* Bernard Saint-Aubert, MD,* and Dominique Elias, MD†*

(Ann Surg 2011;254:294–301)

What is the specific role of HIPEC per se in this “package”?

There was not significant difference between:

- Median OS **ox alone 41 months**, (95%CI 29–61)
 - Median OS **ox-iri 47 months**, (95%CI 32-61)
- (p=0.94)





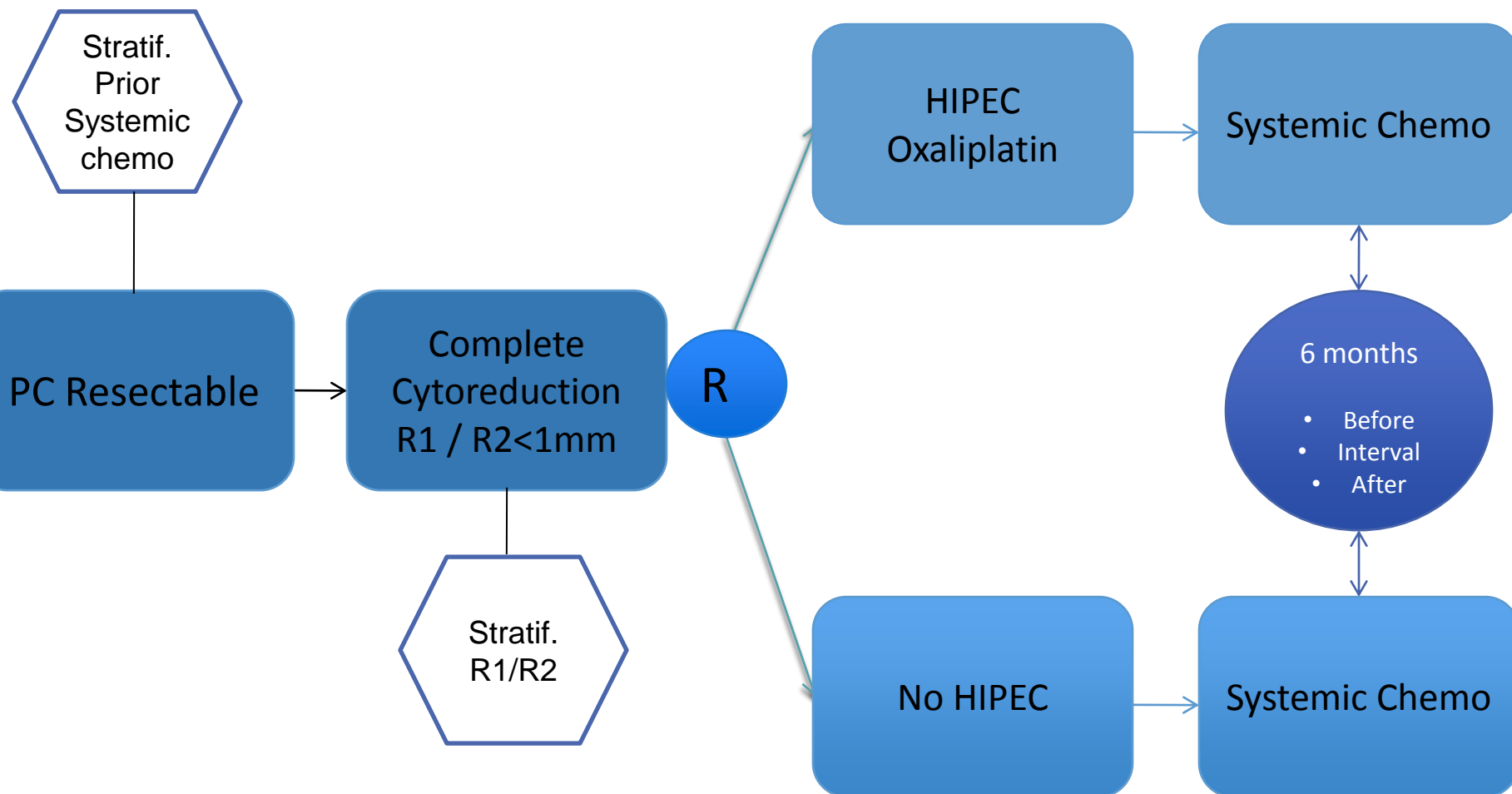
Prodige 7-Accord 15 Trial

Phase III trial Evaluating the Role of Intraperitoneal Chemohyperthermia (HIPEC) after maximal cytoreductive surgery of peritoneal carcinomatosis of colorectal origin

PI: F.Quénet



PRODIGE₇ TRIAL



Summary & Conclusion

➤ Standard of care for PMP & for mesothelioma

➤ Colorectal

- Encouraging survival results comparable to those obtained in colorectal liver metastasis treatment strategies
- Major ongoing Clinical Trials
 - PRODIGE 7
 - PROPHYLOCHIP/ COLOPEC

➤ Gastric

- Benefit of CRS & HIPEC in selected patients
- Encouraging survival results in prophylaxy: GASTRICHIP trial