

MALATTIA METASTATICA DEL  
CARCINOMA DEL GROSSO  
INTESTINO: TECNICHE E TERAPIE  
INNOVATIVE.

LA CHEMIO-IPERTERMIA  
INTRAPERITONEALE (HIPEC)

Ferrara, 29 Ottobre 2011

# Malattia metastatica del carcinoma del grosso intestino: carcinosi peritoneale

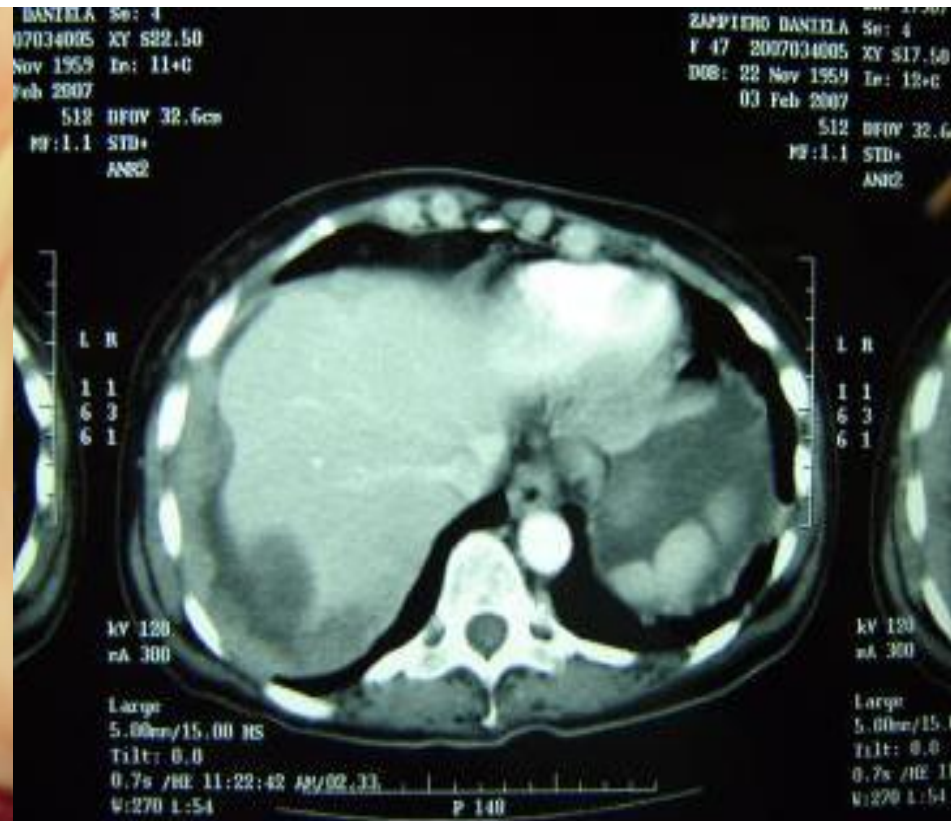
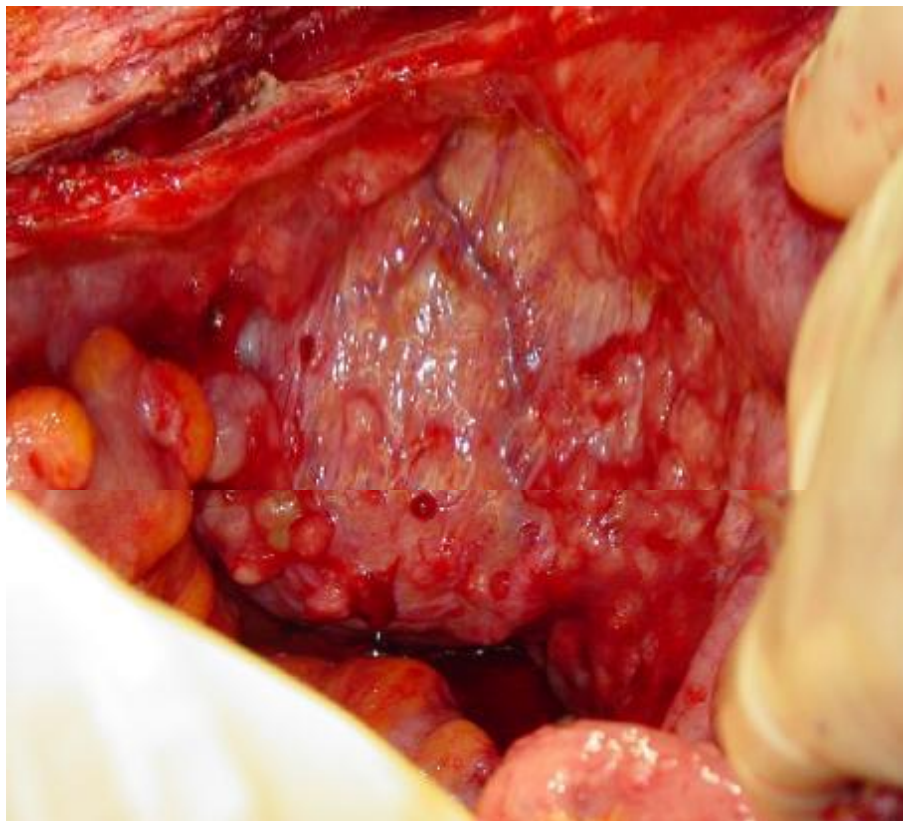
- .. Peritoneal Carcinomatosis (PC) from colorectal carcinoma is a form of disease progression that affects 30% to 40% of patients.

*(Shadeghi B et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 88: 358, 2000)*

- .. Natural history studies show that PC is *uniformly fatal*, with median survival (not exceeding) attaining 6 months.

*(Jayne DG et al. Peritoneal carcinomatosis from colorectal cancer. Br J Surg 89: 1545, 2002)*

# Peritoneal carcinomatosis



# Peritoneal Carcinomatosis (1)

- **Origin of peritoneal carcinomatosis:**
  - **primary** peritoneal tumours (mesothelioma)
  - **secondary** from cancers of peritoneal cavity organs (appendiceal, colorectal, gastric, and ovarian cancers)
- **Synchronous carcinomatosis** (detected during primary surgery).
- **Metacronous carcinomatosis** (detected at later stages with imaging techniques or at second-look surgery).

# Peritoneal Carcinomatosis (2)



## *Mechanisms of seeding and growth:*

- infiltration or perforation of serosa
- surgery: spreading of cancerous cells during operation
- lymph nodes and lymphatic vessels drainage
- venous invasion + surgical haemorrhage

à **free cancerous cells** in the peritoneal cavity

à **entrapment of cancerous cells** by fibrin

# Peritoneal Carcinomatosis (3)



## *Therapy:*

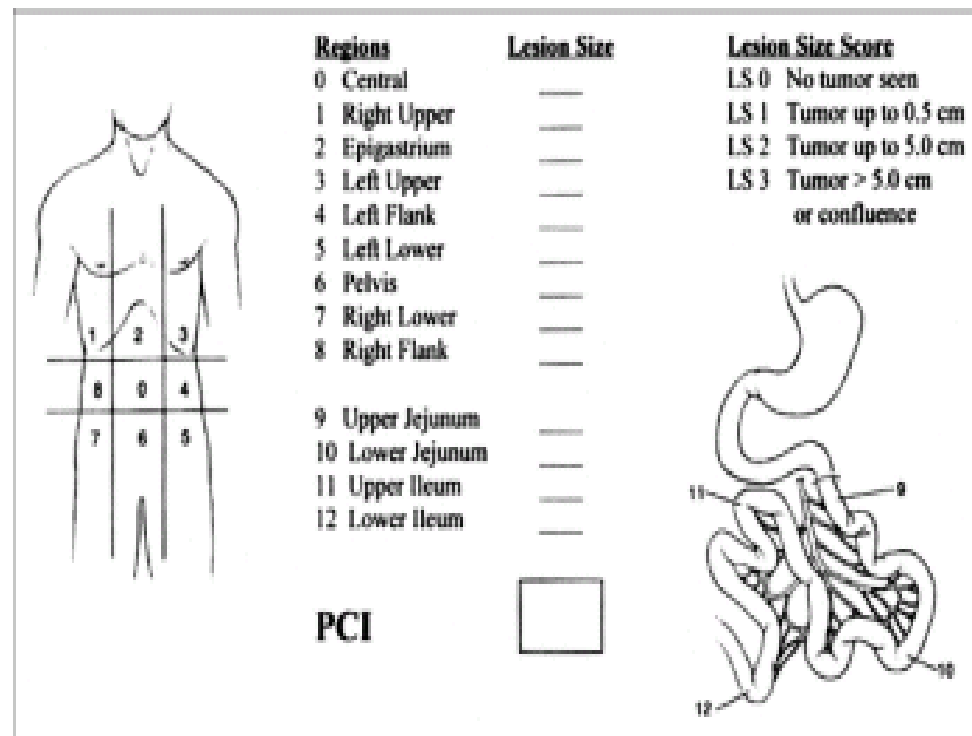
- .. the peritoneal cavity is poorly accessible by systemic/i.v. chemotherapy
- .. drugs injected i.v. achieve a low concentration in the peritoneal cavity because fo the “plasma-peritoneum barrier”
- .. this “barrier” is represented by sub-mesothelial tissue and capillary basal membranes, limiting the passage of hydrophylic or high-molecular weight drugs (Mitomycin C, Cisplatin and Doxorubicin)

# Peritoneal Carcinomatosis (4)

## *Therapy:*

- .. ***Cyto-Reductive Surgery (CRS):***  
surgical resection of the primary tumour + maximum number of secondary nodules, aiming to a  
***“macroscopic cyto-reduction”***
- .. ***Hyperthermic Intra Peritoneal Chemotherapy (HIPEC):*** pharmacologic destruction of micro-foci of residual neoplastic cells, aiming to a  
***“microscopic cyto-reduction”***

# Peritoneal Cancer Index (PCI)

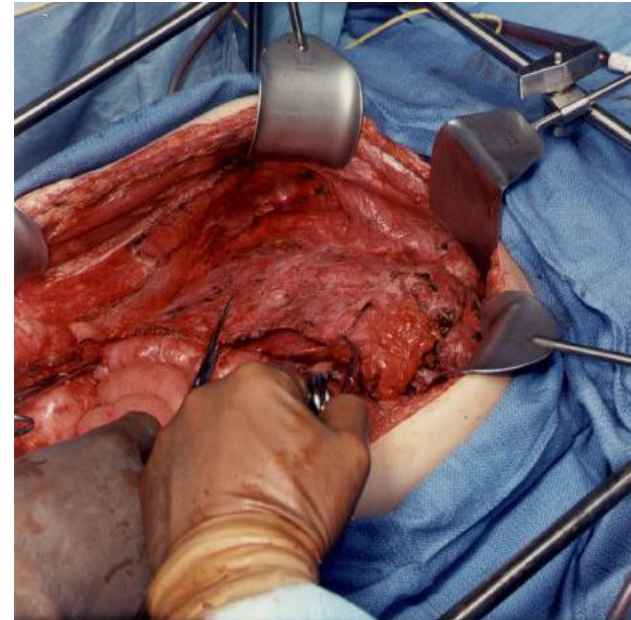


**Fig 1.** Peritoneal Cancer Index. The abdomen and the pelvis are divided into 13 regions. The lesion size of the largest sizes of the largest implants are scored 0 through 31 in each abdominopelvic region. They can be summated as a numerical score, which ranges from 1 to 39.

# Cyto-Reductive Surgery (CRS)


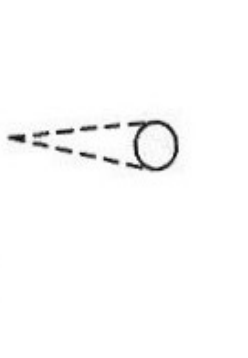
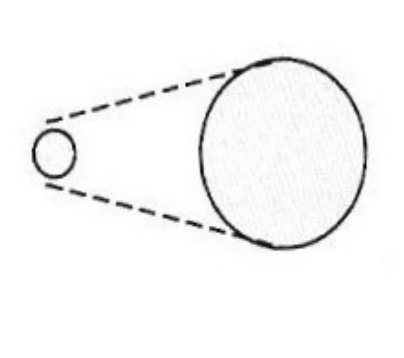
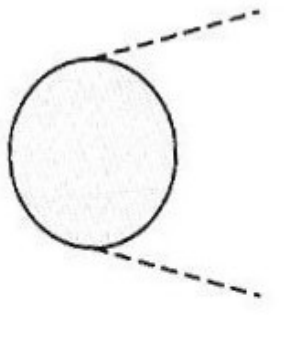
## ***Complete cytoreduction as described by Sugarbaker for PMP:***

- .. Greater omentectomy
- .. Splenectomy
- .. Left upper quadrant peritonectomy
- .. Right upper quadrant peritonectomy
- .. Lesser omentectomy
- .. Cholecystectomy
- .. Appendicectomy
- .. Right or total colectomy
- .. Partial or total gastrectomy
- .. Pelvic peritonectomy with anterior resection of recto-sigmoid colon
- .. Hystrectomy and bilateral salpingo-oophorectomy



*(Sugarbaker PH. Peritonectomy procedures. Ann Surg 221: 29-42, 1995)*

# Completeness of Cyto-reduction (CC)

<b>CC-0</b>	<b>CC-1</b>	<b>CC-2</b>	<b>CC-3</b>
			
No visible disease	< 0.25 cm	0.25 cm - 2.5 cm	> 2.5 cm
Gastric	PMP	Peritoneal Mesothelioma	or confluence
<b>COMPLETE</b> <i>(optimal, adequate)</i>	Colon		<b>INCOMPLETE</b> <i>(suboptimal, inadequate)</i>

# Principles of HIPEC



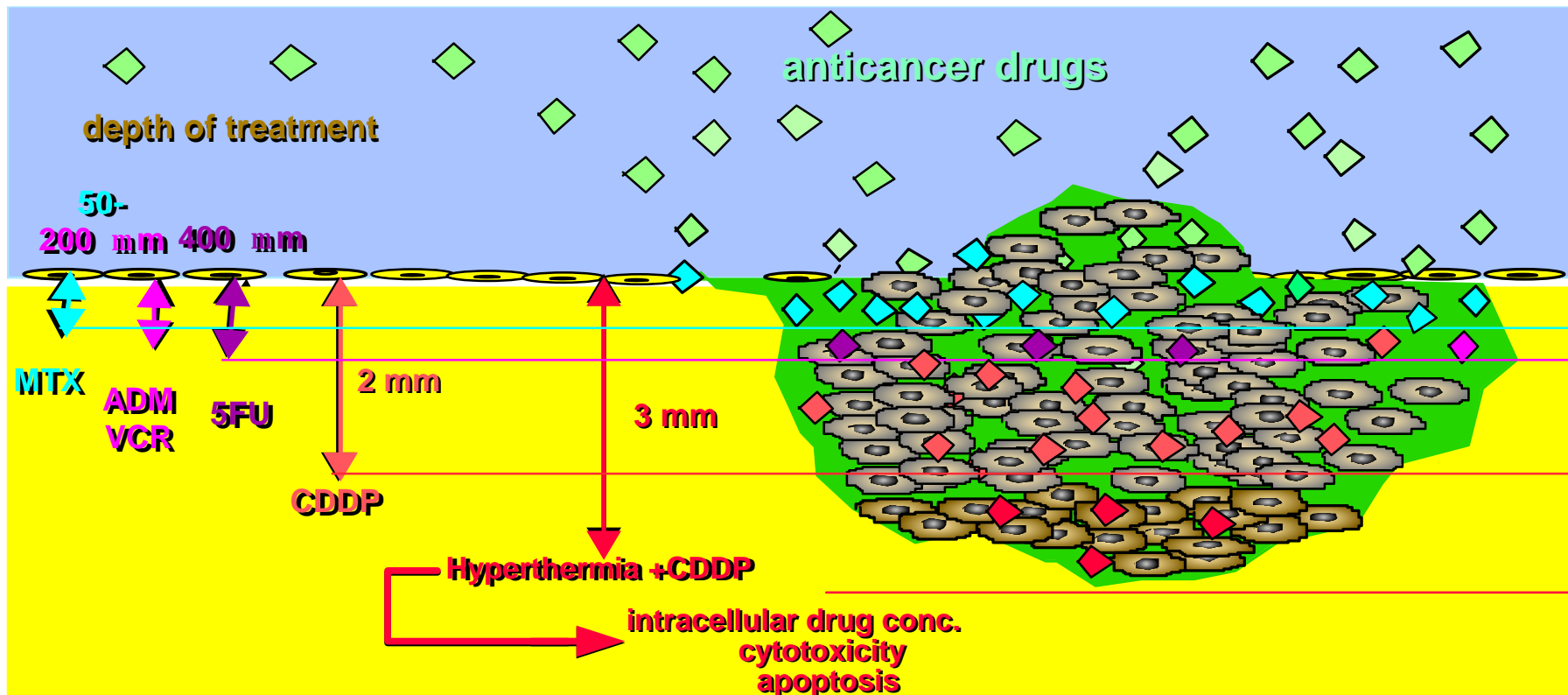
## *Pharmacological advantages:*

- .. higher (more effective) regional concentrations of the cytotoxic drugs
- .. temporary regional perfusion (30-90 min)
- .. reduced systemic absorption (lower systemic toxicity)
- .. hyperthermia (higher than physiologic temperature: 41° - 43°C)

# Effects of hyperthermia

Drug	Molecular weight	AUC <sub>pe</sub> /AUC <sub>pl</sub>	Response rate in normothermia	Tumour penetration
CDDP	300	14	65%	2-2.5 mm
DX	544	82.9	30%	4-6 cell layers
MMC	334	23,5	N.E.	3 mm

## Drug penetration distance from peritoneal surface after IP chemotherapy

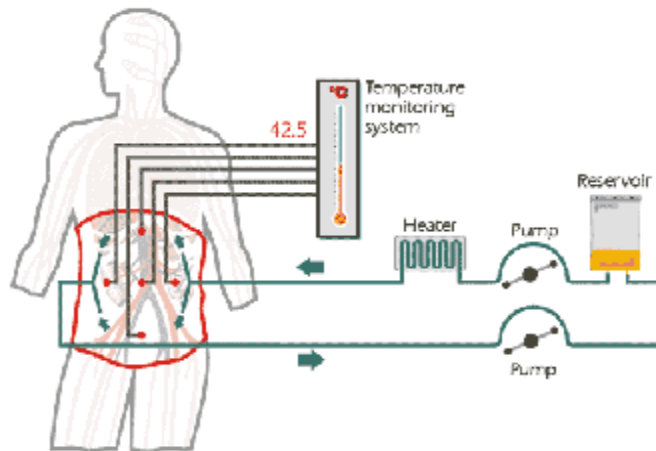
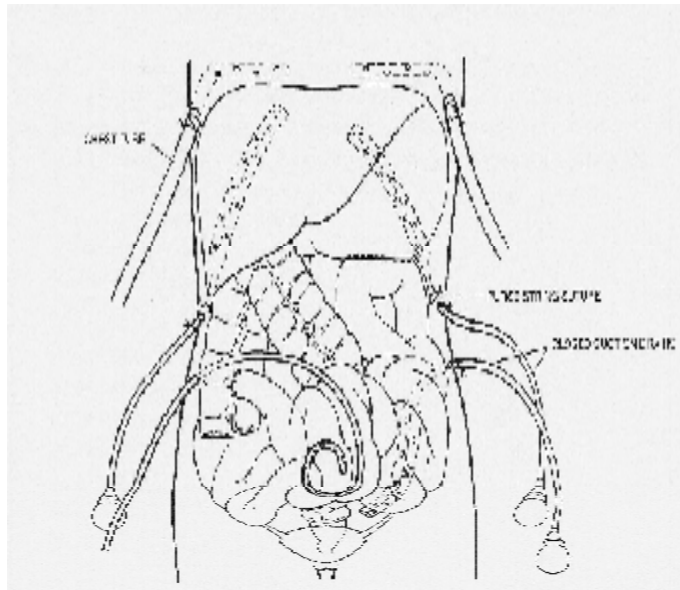


# HIPEC: cytotoxic drugs



- .. anthracyclines: Doxorubicin, Mitomycin C
- .. plant alkaloid and topoisomerase-1 inhibitor: Irinotecan
- .. platinum: Cisplatin (CDDP), Carboplatin, Oxaliplatin
- .. taxanes: Paclitaxel, Docetaxel

# HIPEC: materials & methods



# CRS plus HIPEC in colorectal cancer

- Dutch controlled, randomized, double-blind trial of 105 colorectal cancer Patients with PC.

Standard treatment (cytoreductive surgery plus adjuvant chemotherapy 5-FU-based; CRS+ACT) versus CRS plus hyperthermic intraperitoneal chemotherapy (HIPEC) and ACT.

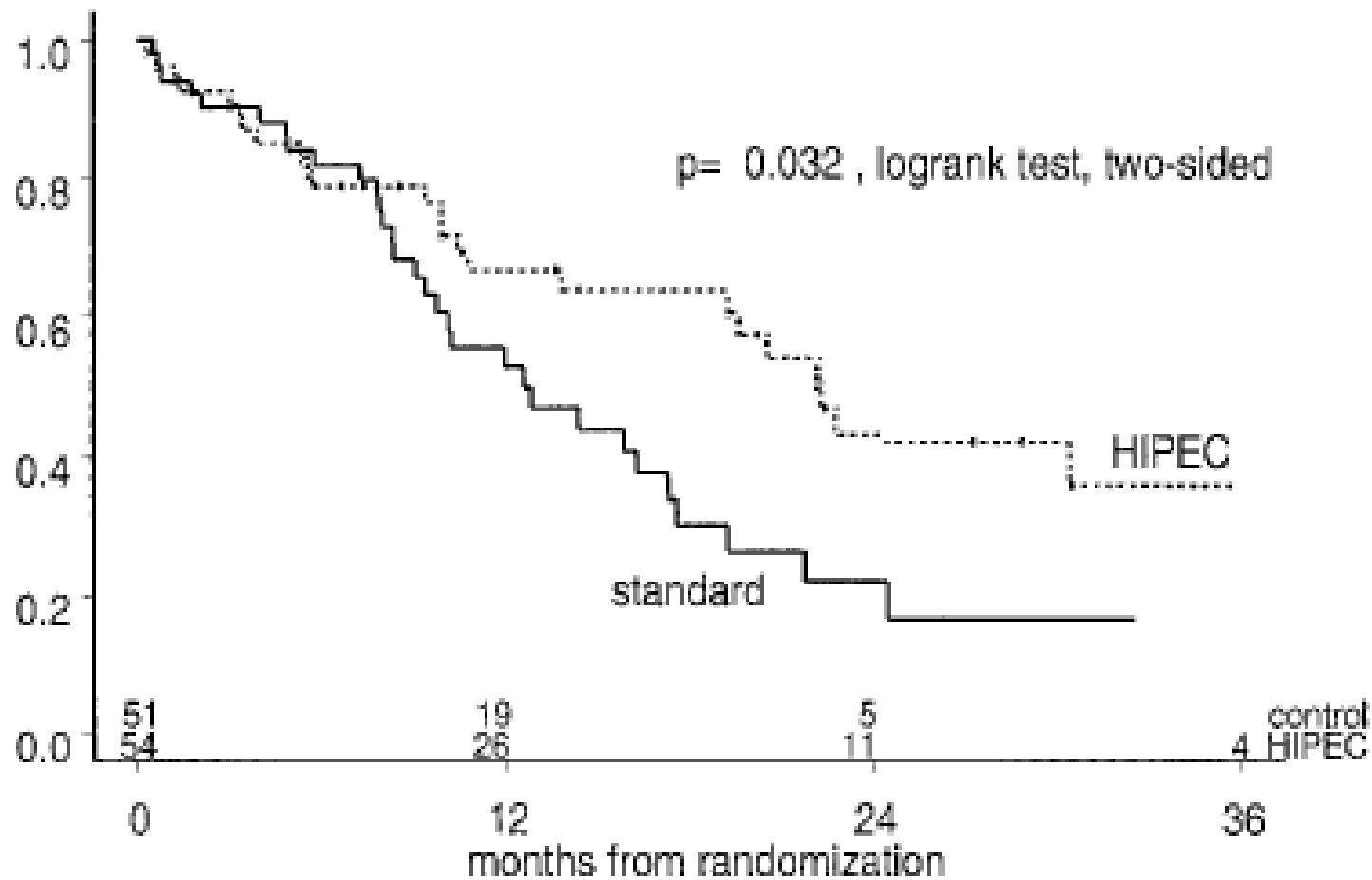
*38% 3-y survival (1) and 20% 5-y survival (2).*

*1) Verwaal VJ et al. J Clin Oncol 21: 3737-43, 2003*

*2) Verwaal VJ et al. Ann Surg Oncol 15: 2426-32, 2008*

# CRS plus HIPEC in colorectal cancer

(Verwaal VJ et al. *J Clin Oncol* 21: 3737-43, 2003)



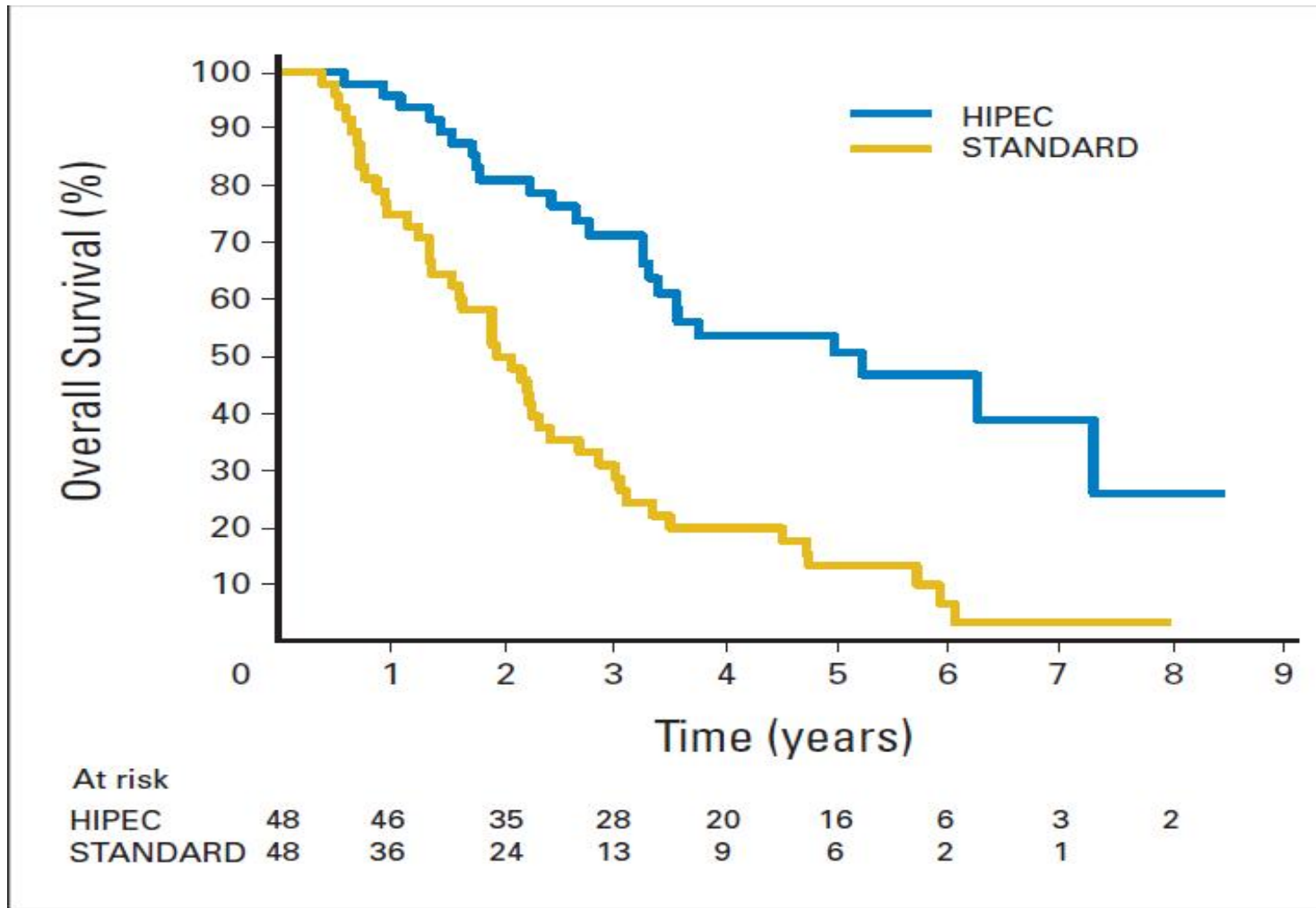
# CRS plus HIPEC in colorectal cancer

- .. In Patients with limited PC, treated by *modern Systemic Chemotherapy (SC)* with *FOLFOX/FOLFIRI/Capecitabine/Cetuximab/Paclitaxel/Carboplatin*: 5-y overall survival = 13%; median survival time = 23,9 mo.
- .. In Patients with limited PC, treated by *CRS + HIPEC + SC*: 5-y overall survival = 51%; median survival time = 62,7 mo.

*(Elias D. et al. J Clin Oncol 27: 681-5, 2009)*

# CRS plus HIPEC in colorectal cancer

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



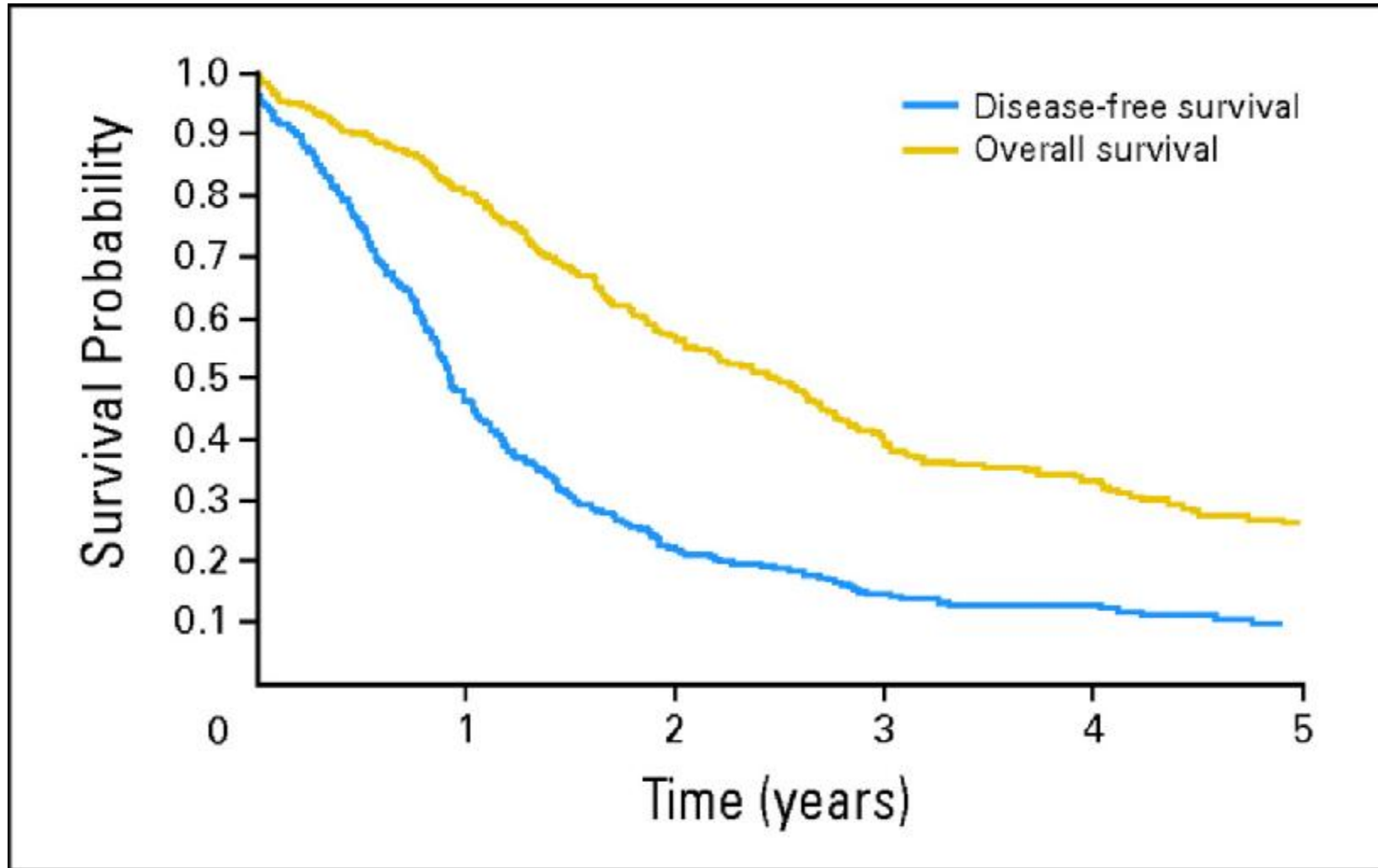
# CRS plus HIPEC in colorectal cancer

- .. French multi-institutional retrospective study of 523 *Patients with PC of colorectal origin.*
- .. After cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (*CRS + HIPEC*) median survival time: *30,1 mo.*
- .. 5-year overall survival rate: *27%.*
- .. 5-year disease-free survival rate: *10%*

*(Elias D et al. J Clin Oncol 28: 63-68, 2010)*

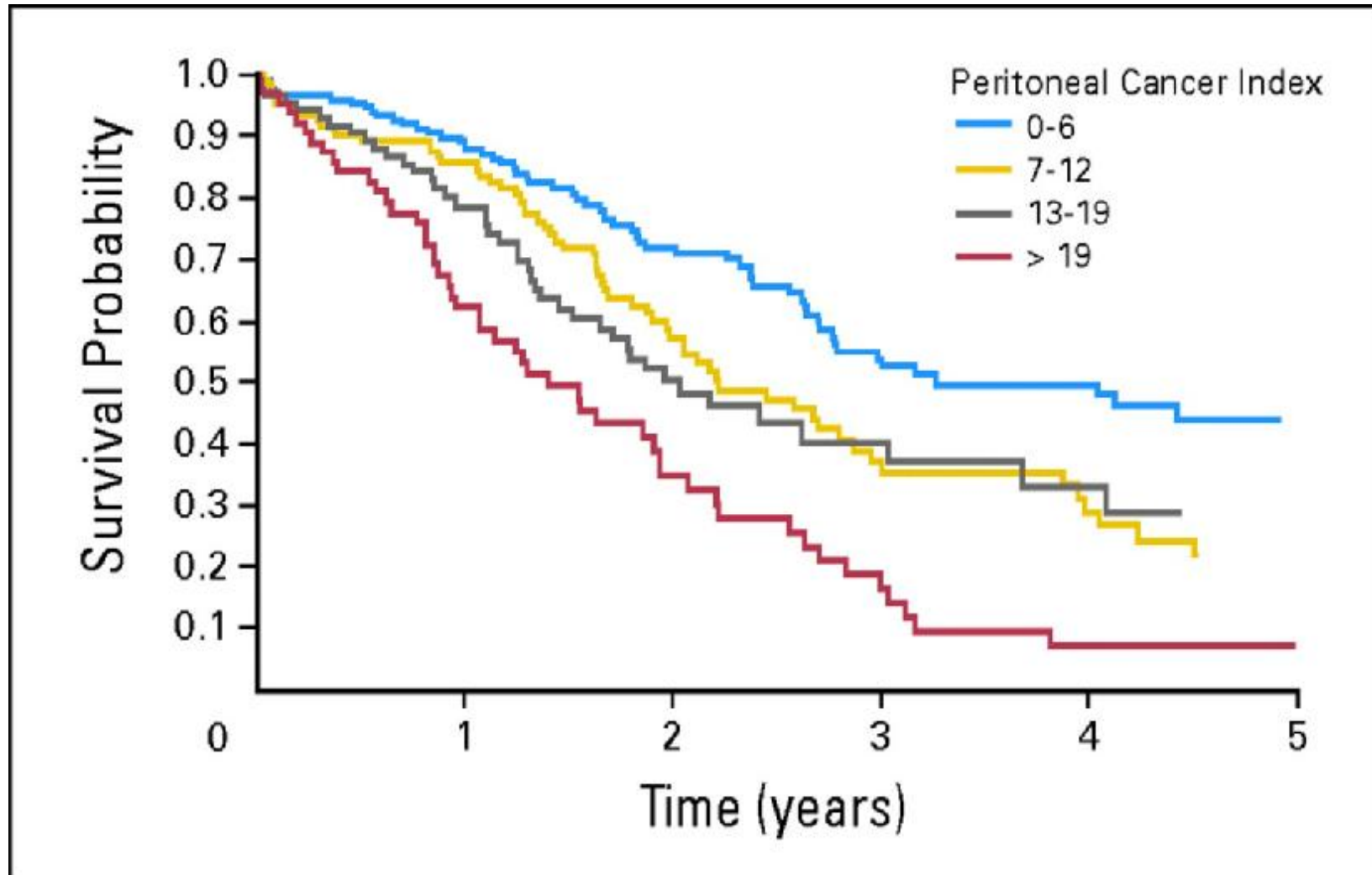
# CRS plus HIPEC in colorectal cancer

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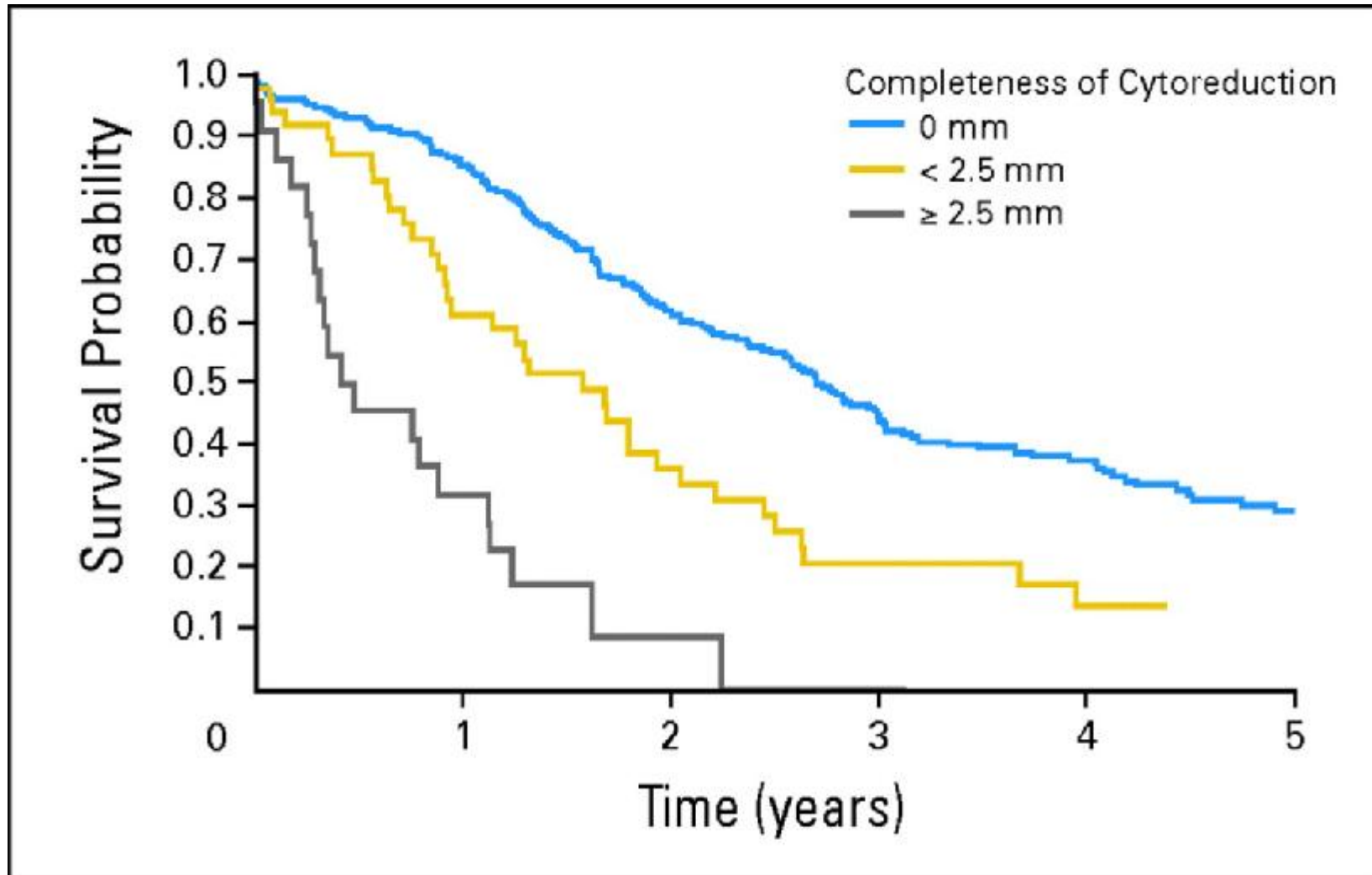
# CRS plus HIPEC in colorectal cancer

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# CRS plus HIPEC in colorectal cancer

(Elias D et al. *J Clin Oncol* 28: 63-68, 2010)



# HIPEC: ongoing clinical trials in USA

## COLORECTAL CANCER

- § *Standard Therapy With/Without Surgery and Mitomycin C in Treating Patients With Advanced Limited Peritoneal Dissemination of Colon Cancer.* Walter Reed Army Medical Ctr, Washington DC, A. Stojadinovic, MD – Prospective, Multicenter, Randomized, Phase III, August 2010
  
- § *Prospective Randomized Trial Evaluating Mandatory Second Look Surgery with HIPEC and CRS vs. Standard of Care in Subjects at High Risk of Developing Colorectal Peritoneal Metastases.* NIH Clinical Center, Bethesda, MD, I. Avital MD - Prospective, Randomized, Phase III, December 2009 (\*)
  
- *Surgery and Oxaliplatin or Mitomycin C in Treating Patients with Primary Colorectal Tumors or Tumors of the Appendix.* Wake Forest Univ. Health Ctr., Winston-Salem, NC, J.H. Stewart, MD - Prospective, Multicenter, Randomized, Phase II, April 2010 (\*)

# HIPEC: ongoing clinical trials in EUROPE & ASIA (1)

## COLORECTAL CANCER

- *Combined Anticancer Treatment of Advanced Colon Cancer (COMBATAC) by Pre- Post-Operative Chemotherapy with Cetuximab, Cytoreductive Surgery and HIPEC in Patients wild K-ras-positive.* Department of Surgery University of Regensburg, Germany, P. Pisu, MD - Prospective, Multicenter, Phase II, June 2009
- *Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis in Patients with Colorectal Cancer.* Departments of Surgery Radboud Univ. Med. Ctr., Nijmegen, and Catharine Ziekenhuis, Eindhoven, Netherlands, J.C.M. Verzijden, MD - Prospective, Multicenter, Randomized, Phase III, April 2010

# HIPEC: ongoing clinical trials in EUROPE & ASIA (2)

## COLORECTAL CANCER

- *Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus “in Principle” HIPEC in Colorectal Patients (ProphyloCHIP)*. Dept Surgical Oncology, Institut Gustave Roussy, Villejuif, France, D. Elias, MD - Prospective, Multicenter, Randomized, Phase III, October 2010 (\*)
- *Phase III Randomized Study for Peritoneal Carcinomatosis with and without HIPEC-Oxaliplatin, and Systemic Chemotherapy*. Dept Surgical Oncology, Institut Gustave Roussy, Villejuif, France, D. Elias, MD - Prospective, Multicenter, Randomized, Phase III, October 2010
- *Phase II Study to Evaluate Second-look Surgery plus HIPEC and CRS vs. Follow-up only, in Patients at High Risk to develop Peritoneal Carcinomatosis by Colorectal Cancer*. Depts Surgery INT, H. Sacco, H. S. Raffaele, Multimedica, Humanitas, IEO, Milan, Policl. S. Pietro (BG), H. Manerbio (BS), Italy, D. Foschi, MD, M. Deraco, MD - Prospective, Multicenter, Randomized, Phase II, July 2011 (\*)

# HIPEC: ongoing clinical trials in EUROPE & ASIA (3)

## COLORECTAL CANCER

- *Systemic Chemotherapy with or without HIPEC in Treating Patients Undergoing Surgery for Peritoneal Carcinomatosis from Colorectal Cancer.* Centre de Lutte Contre le Cancer (CLCC), Montpellier, Parc Euromedecine, Montpellier, France, F. Quenet , MD - Prospective, Multicenter, Randomized, Phase III, October 2010
- *Treatment of Primary Peritoneal Carcinosis of Digestive Origin Using Cytoreductive Surgery and HIPEC with Mitomycin C and Irinotecan.* Dept. Surgery, Centre Hospitalier Lyon Sud, France, O. Glehen, MD - Open, Non-Randomized, Phase II, June 2007
- *Surgery Plus Intraoperative Peritoneal Hyperthermic Chemotherapy (IPHC) to Treat Peritoneal Carcinomatosis.* Dept. Surgery and Cancer Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China, Kusatsu Gen Hospital, Japan, Yan Li, MD - Open, Prospective, Randomized, Phase II, February 2009

# Second-look surgery + HIPEC in colorectal cancer

Results of Systematic Second-look Surgery Plus HIPEC in Asymptomatic Patients Presenting a High Risk of Developing Colorectal Peritoneal Carcinomatosis.

*Elias D., Honoré C., Dumont F., Ducreux M., Boige V., Malka D., Burtin P., Dromain C., Goéré D.*

*Annals of Surgery, 254: 289-293, 2011*

*Departments of Surgical Oncology, Medical Oncology and Radiology, Institut Gustave Roussy, Villejuif, Cedex, France*

# Second-look surgery + HIPEC in colorectal cancer

(Elias D. et al. *Ann Surg* 254: 289-293, 2011)

- .. Patients at *high risk* for *recurrent PC*, curatively treated for colorectal cancer (R0-1), with minimal PC or ovarian metastases or perforated primary tumor at the time of first surgery.
- .. *No signs of recurrence* at 6 months (clinical, CT scan, tumor markers).
- .. Previously received *adjuvant chemotherapy* (5-FU + Oxaliplatin- or Irinotecan-based) over 6 months.

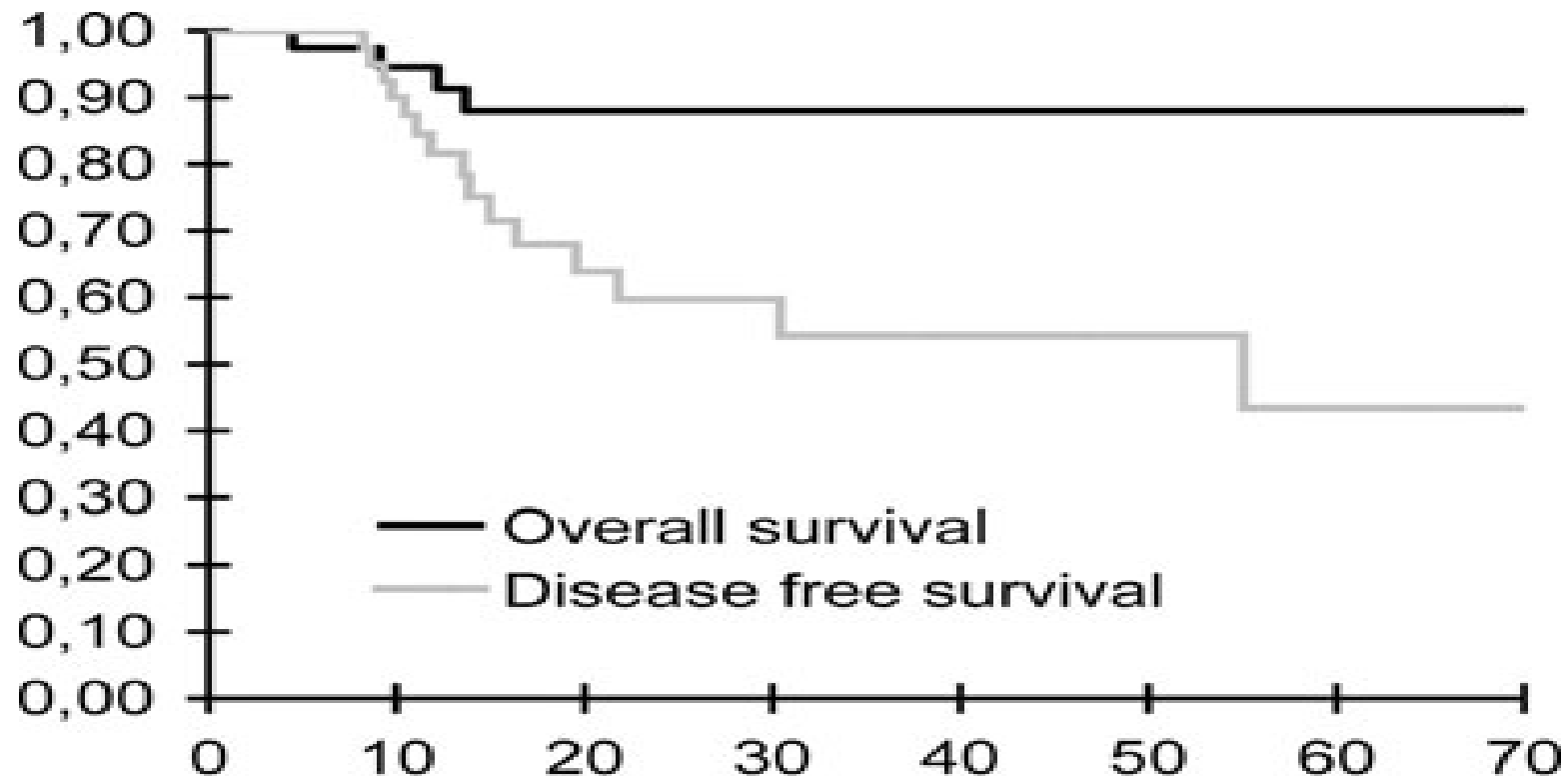
# Second-look Surgery + HIPEC in colorectal cancer

(Elias D. et al. Ann Surg 254: 289-293, 2011)

- .. *Second-look surgery* in 41 Patients 1 year after the first procedure, by resection of all macroscopic lesions.
- .. *HIPEC* systematically performed (Oxaliplatin 460 mg/m<sup>2</sup> in 2 L/m<sup>2</sup> of 5% Dextrose) at 43° C for 30 min.
- .. *Bidirectional i.o. chemotherapy* (400 mg/m<sup>2</sup> 5-FU + 20 mg/m<sup>2</sup> Leucovorin i.v.).
- .. Macroscopic PC present in 56% (23 Pts of 41).
- .. 5-y OS was 90% and the 5-y DFS was 44%.

# Second-look Surgery + HIPEC in colorectal cancer

(Elias D. et al. Ann Surg 254: 289-293, 2011)



Patients at risk

Months	0	10	20	30	40	50	60	70
Overall survival	41	31	24	19	18	12	11	9
Disease free survival	41	34	15	11	8	6	4	4

# EXPERIMENTAL STUDY



Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model.

Y.L.B. Klaver, T. Hendriks, R.M.L.M. Lomme, H.J.Y. Rutten, R.P. Bleichrodt and I.H.J.T. de Hingh

*Dept Surgery, Catharina Hospital, Eindhoven, Dept Surgery, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*

*British Journal of Surgery, 97: 1874-1880, 2010*

# HIPEC: need of long-term survival evidence

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- .. The combination of Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has been introduced as a treatment strategy for selected patients with peritoneal carcinomatosis (PC) from colorectal cancer (CRC).
- .. However whether the addition of HIPEC is essential to achieve the reported survival benefit remains unclear.
- .. Aim of the study was to determine if HIPEC can improve survival if used as an adjunct to CRS for the treatment of PC in a pre-clinical model.

# MATERIALS and METHODS

- .. 60 WAG/Rij *rats* inoculated intraperitoneally with the *rat colon carcinoma cell line CC-531*.
- .. 7 days after tumor transfer, laparotomy, *peritoneal cancer index (PCI)* calculation, scoring of the amount of residual tumor (CC) after CRS.
- .. Animals randomized into 3 *groups* (n = 20):
  - Group 1: CRS only* (greater omentectomy, electrocoagulation of unresectable nodules, splenectomy)
  - Group 2: CRS + HIPEC with Mitomycin C, 15 mg/m<sup>2</sup>*
  - Group 3: CRS + HIPEC with Mitomycin C, 35 mg/m<sup>2</sup>*
- .. *HIPEC* with closed abdomen at 42°C for 90 minutes.
- .. Primary outcome: *survival* (maximum follow up of 140 days).


# Exploration: greater omentum with tumor deposits



# HIPEC perfusion: closed technique

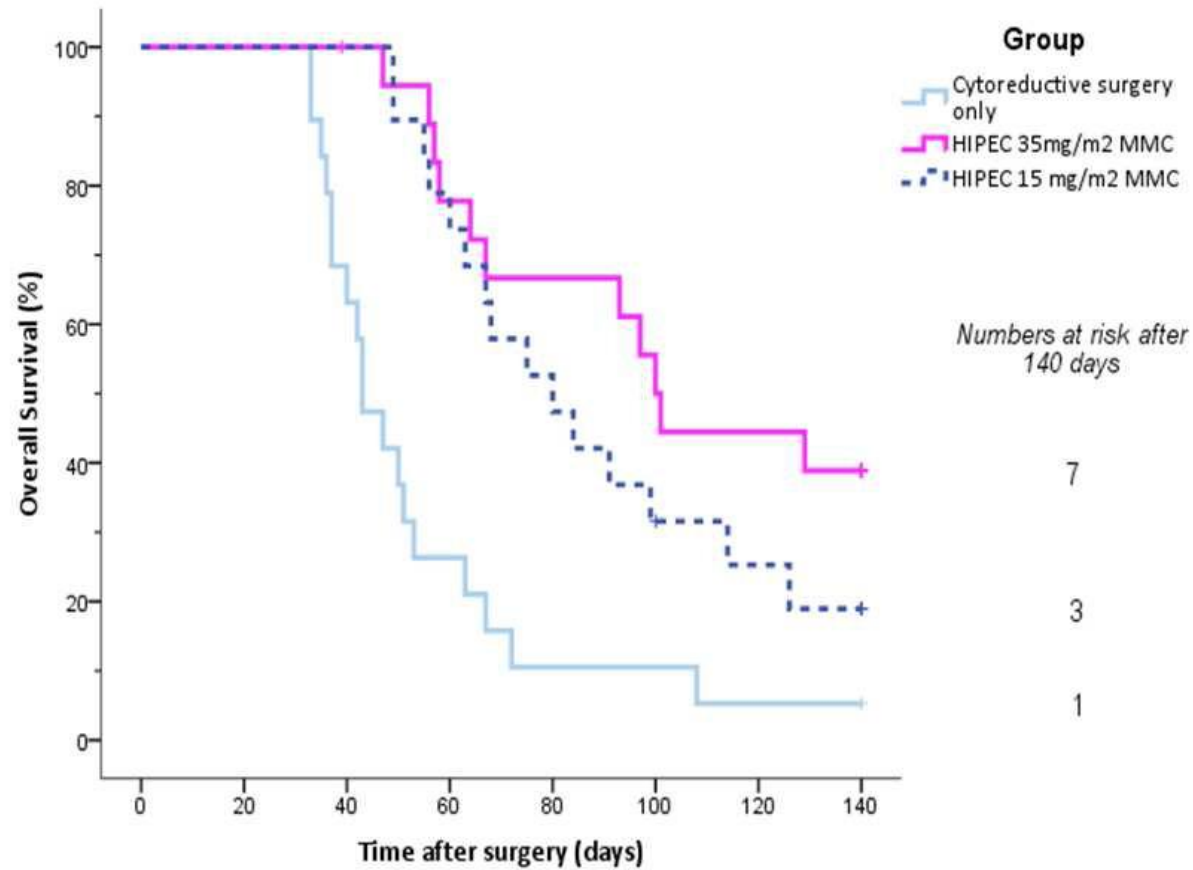


# RESULTS



	median survival (days)	<i>p</i> -value (compared to CRS only)
CRS only	43	
HIPEC 15 mg/m <sup>2</sup>	80	<i>p</i> <0.01
HIPEC 35 mg/m <sup>2</sup>	100	<i>p</i> <0.001

# KAPLAN-MEIER survival curves



# CONCLUSIONS



- .. This study shows that the reported beneficial effect of the combination therapy (CRS + HIPEC) *is not only a result of the surgical cytoreduction.*
- .. Addition of HIPEC to surgical procedures for peritoneal carcinomatosis is *essential to achieve the survival benefit* reported in clinical studies.