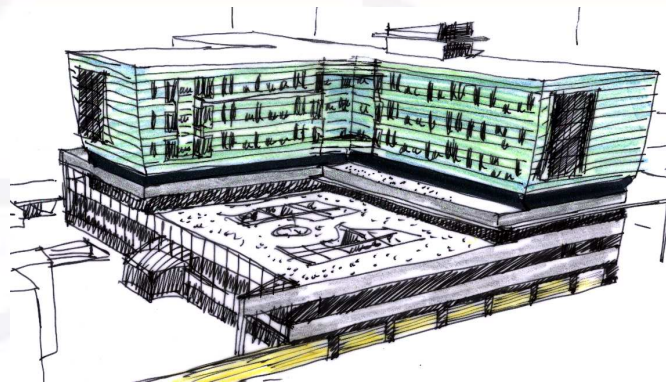


# Current standard in treatment of peritoneal carcinomatosis

## Data behind the HIPEC trials

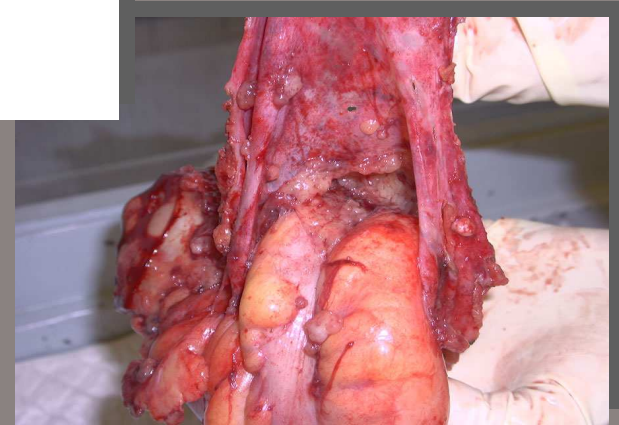
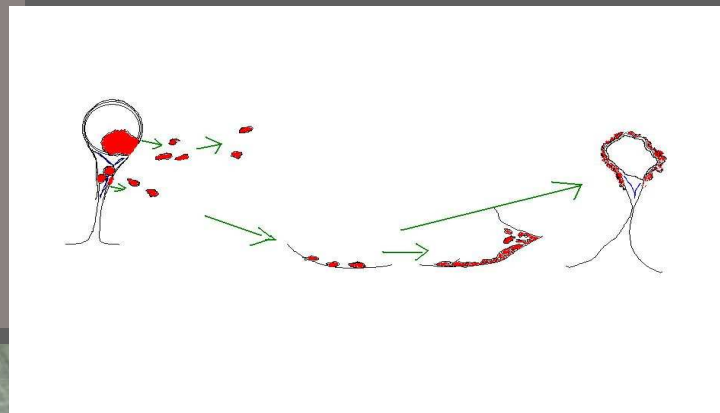


# Overview

- ▶ Peritoneal carcinomatosis
- ▶ “STANDARD” treatment
- ▶ HIPEC
- ▶ Results of treatment
- ▶ Counter side of treatment

# Peritoneal carcinomatosis

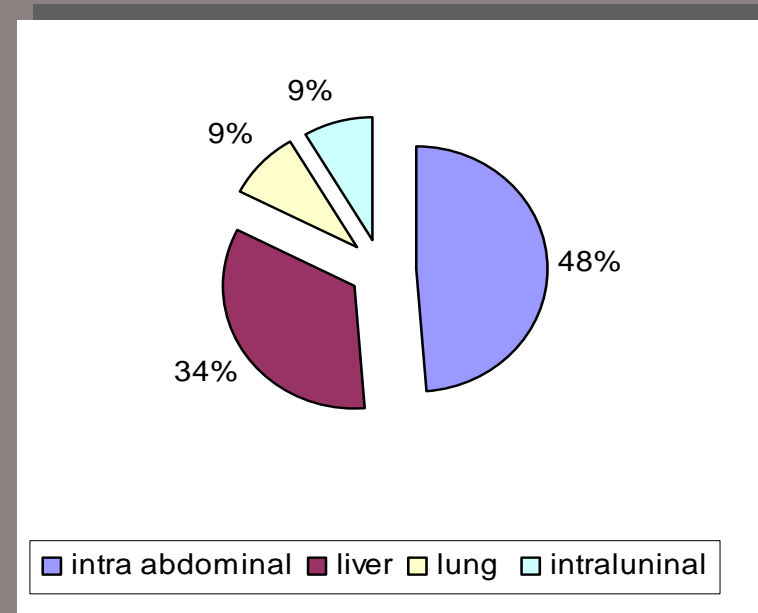
a local regional disease



# Stage IV colorectal cancer

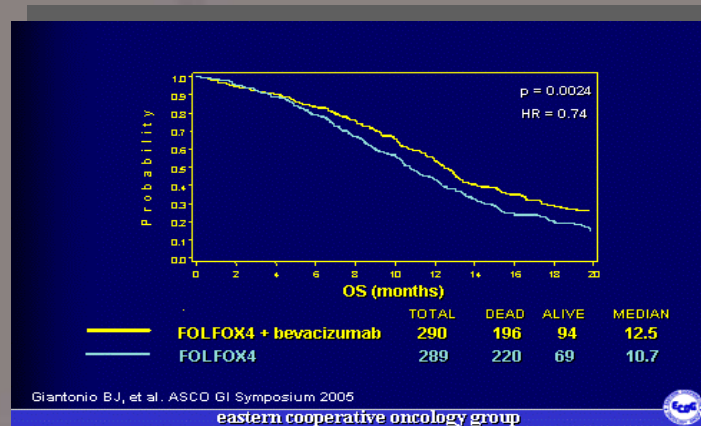
## Metastasized colorectal cancer

- ▶ Liver metastasis
- ▶ Lung metastasis
- ▶ Intra abdominal
- ▶ Intra luminal



# Treatment stage IV colorectal carcinoma

## Systemic chemotherapy median survival up to 20 months



	IFL + Placebo (n=412)	IFL + Bevacizumab (n=403)	P Value
Median survival (mo)	15.6	20.3	.00003
PFS (mo)	6.24	10.6	<.00001
ORR (%)	35	45	.0029
CR	2.2	3.7	
PR	32.5	41.2	
Duration of response (mo)	7.1	10.4	.0014

Hurwitz et al. N Engl J Med 350:2335-2342, 2004

# Bevacizumab plus irinotecan fluorouracil and leucovorin for metastatic colorectal cancer

		IFL + placebo	IFL + bevacizumab
Gender	Male	60	59
	Female	40	41
Mean age		59.2	59.5
ECOG perform.	0	55	58
	1	44	41
	2	<1	<1
Type of cancer	Colon	81	77
	Rectum	19	23
N of metastatic sites (%)	1	39	37
	>1	61	63
Prior cancer therapy (%)	Adjuvant chemoth	28	24
	Radiotherapy	14	15



Lyon 2008 *NEJM* 2004; 350: 2335 - 2342

NKI-AVL

# Bevacizumab plus irinotecan fluorouracil and leucovorin for metastatic colorectal cancer (n=923)

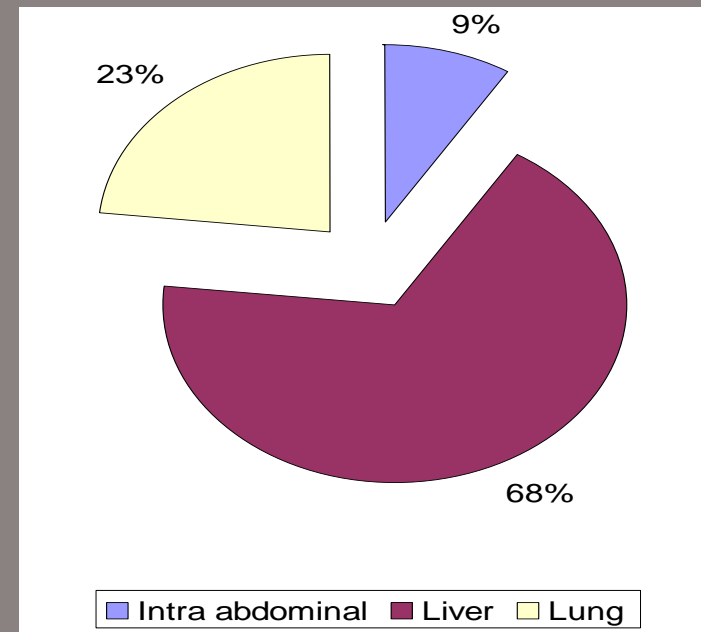
End point	IFL + placebo	IFL + bevacizumab	HR	p
Median survival	15.6	20.3	0.66	< 0.001
1 year survival	63.4	74.3		
PF survival	6.2	10.6	0.54	< 0.001
Response rate	34.8	44.8		0.004
Complete	2.2	3.7		
Partial	32.6	41.0		
Duration of response	7.1	10.4	0.62	0.001



# Inclusion in stage IV chemotherapy

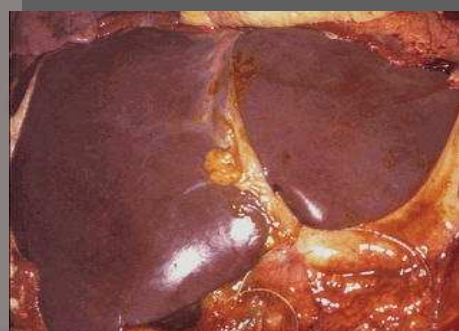
Measurable disease  
(RECIST criteria)

- ▶ Intra abdominal
- ▶ Liver
- ▶ Lung





# The difference in disease



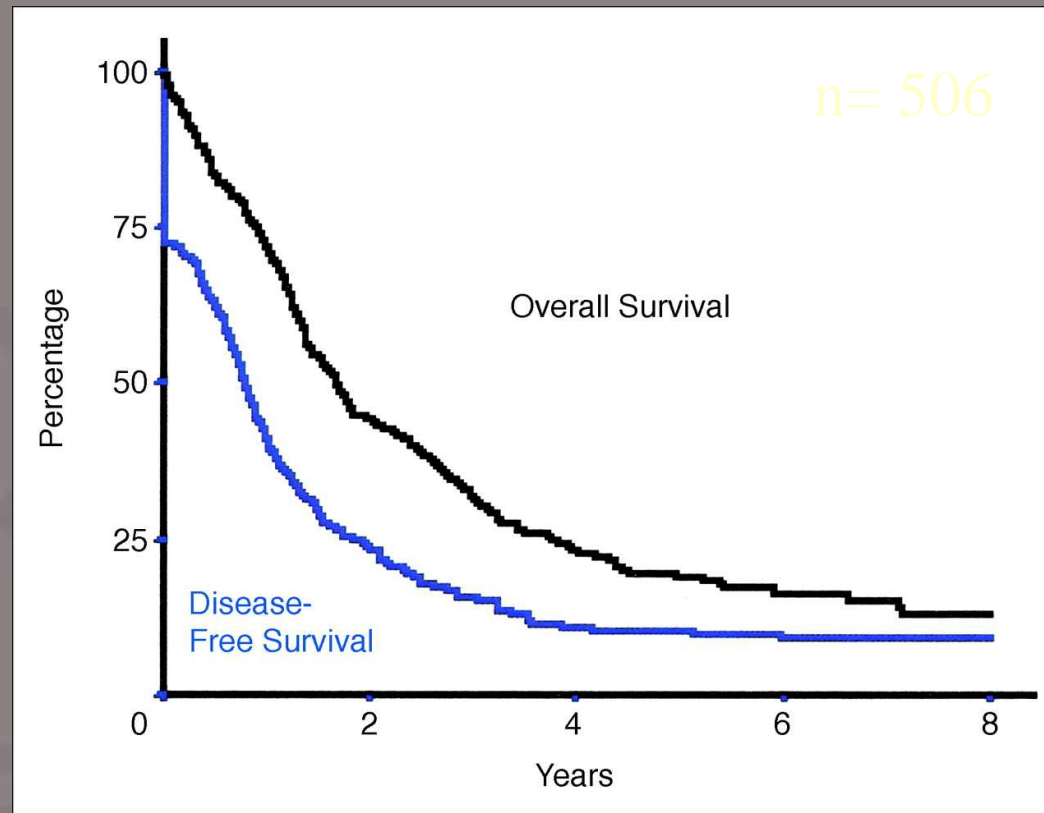
Measurable disease

Peritoneal carcinomatosis

# Data on systemic treatment of PC

- ▶ Median 6 months overall survival  
*Sadeghi e.a. Cancer 2000; 88: 358 – 363*  
*Jayne e.a. Br J Surg 2002; 89: 1545 – 1550*
- ▶ Median 12 months overall when treated  
*Bloemendaal EJSO 2005; 31: 1145 - 1141*

# Phase II data, collected



Shen, O. et al. *J Clin Oncol* 2004; 22: 3284-3292

Lyon 2008

NKI-AVL

# Questions on these data

- ▶ Different methods
  - ▶ MMC or oxaliplatin
  - ▶ Open or closed
  - ▶ EPIC or no EPIC
- ▶ Different selection criteria

# Original randomized trial

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## 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 Ruij, Eelco de Bree, Gooike W. van Slooten, Harm van Tinteren, Henk Boot, and Frans A.N. Zoetmulder

**Purpose:** To confirm the findings from uncontrolled studies that aggressive cytoreduction in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) is superior to standard treatment in patients with peritoneal carcinomatosis of colorectal cancer origin.

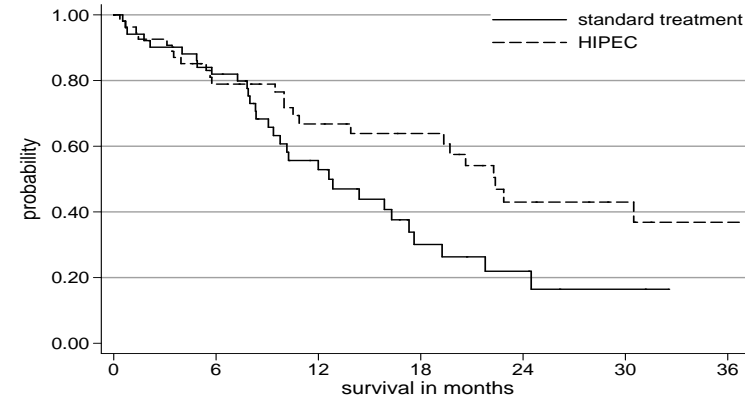
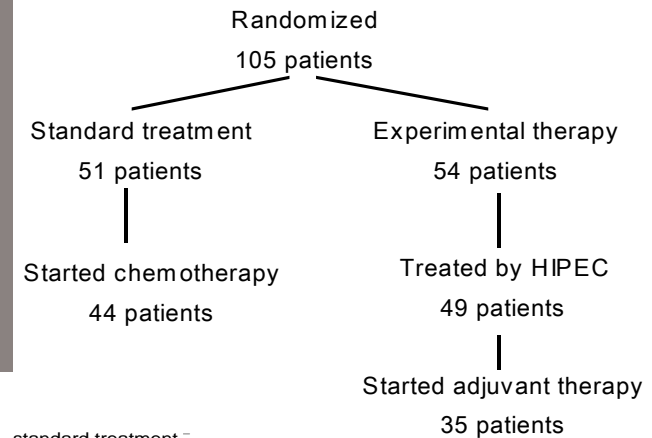
**Patients and Methods:** Between February 1998 and August 2001, 105 patients were randomly assigned to receive either standard treatment consisting of systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery, or experimental therapy consisting of aggressive cytoreduction with HIPEC, followed by the same systemic chemotherapy regime. The primary end point was survival.

**Results:** After a median follow-up period of 21.6 months, the median survival was 12.6 months in the standard therapy arm and 22.3 months in the experimental therapy arm (log-rank test,  $P = .032$ ). The treatment-related mortality in the aggressive therapy group was 8%. Most

complications from HIPEC were related to bowel leakage. Subgroup analysis of the HIPEC group showed that patients with 0 to 5 of the 7 regions of the abdominal cavity involved by tumor at the time of the cytoreduction had a significantly better survival than patients with 6 or 7 affected regions (log-rank test,  $P < .0001$ ). If the cytoreduction was macroscopically complete (R-1), the median survival was also significantly better than in patients with limited (R-2a), or extensive residual disease (R-2b) (log-rank test,  $P < .0001$ ).

**Conclusion:** Cytoreduction followed by HIPEC improves survival in patients with peritoneal carcinomatosis of colorectal origin. However, patients with involvement of six or more regions of the abdominal cavity, or grossly incomplete cytoreduction, had still a grave prognosis.

*J Clin Oncol* 21:3737-3743. © 2003 by American Society of Clin



Lyon 2008

NKI-AVL

# Protocol for the updated trial

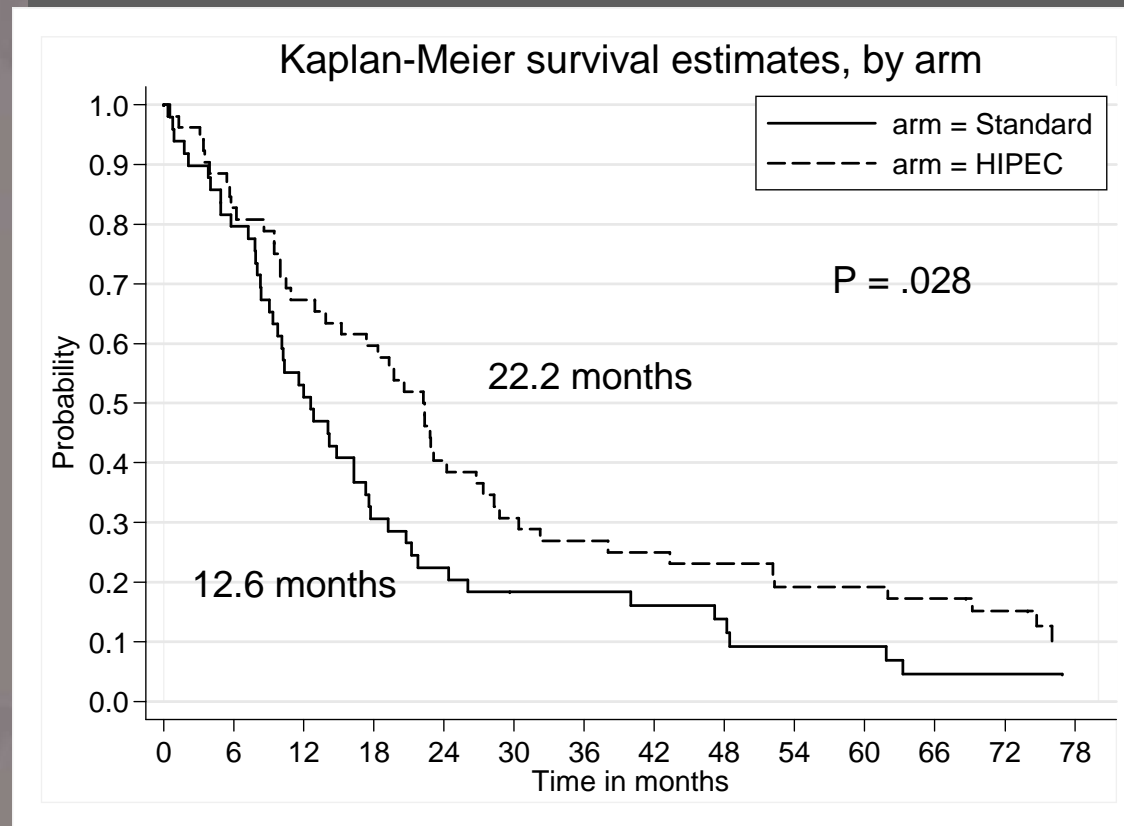
- ▶ On original patients and randomization
- ▶ Cross-over patients were censored at cross over
  - 2 Patients were crossed over
- ▶ Follow-up complete in all patients
  - Median follow-up 94 months

# Survival updated data

8-Year Follow-up of Randomized Trial: Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy in Patients with Peritoneal Carcinomatosis of Colorectal Cancer

Vic J. Verwaal, MD, PhD,<sup>1</sup> Sjoerd Bruin, MD,<sup>1</sup> Henk Boot, MD, PhD,<sup>2</sup> Gooike van Slooten, MD,<sup>1</sup> and Harm van Tinteren, ScM<sup>3</sup>

<sup>1</sup>Institute, Pleinlaan 121, 1066 CX Amsterdam, The Netherlands  
<sup>2</sup>Netherlands Cancer Institute, Amsterdam, The Netherlands  
<sup>3</sup>Netherlands Cancer Institute, Amsterdam, The Netherlands

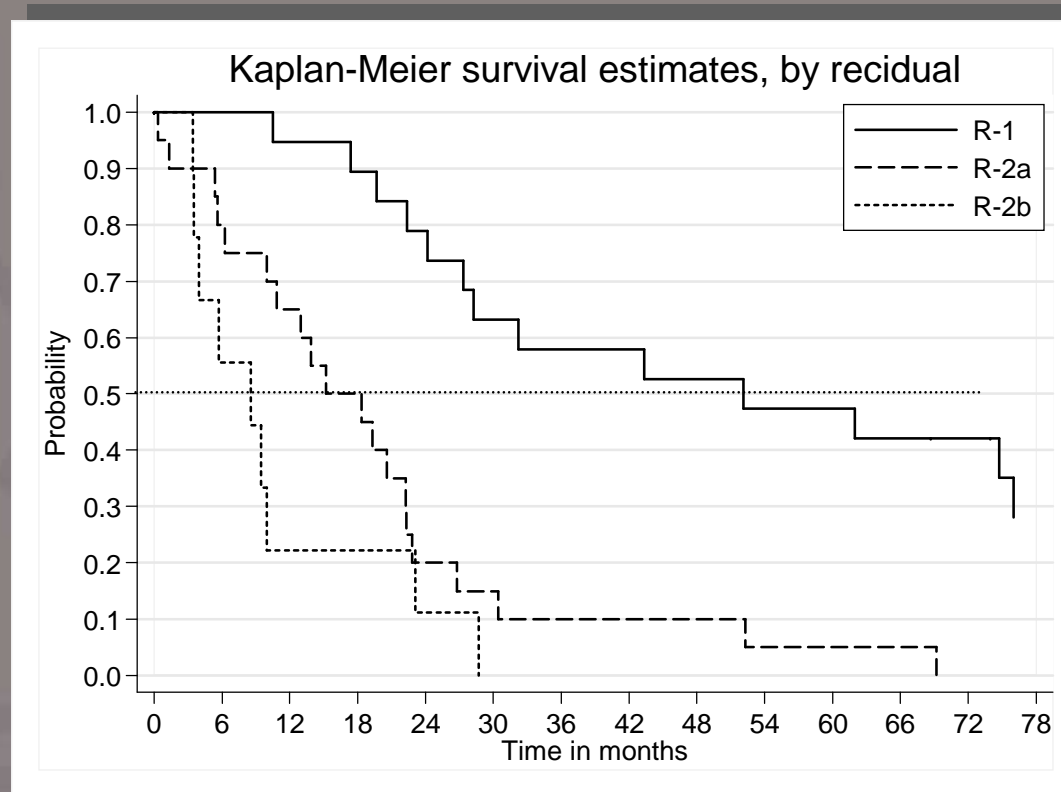


*Ann. Surg. Oncol.* Vol. 15, No. 9, 2008

Lyon 2008

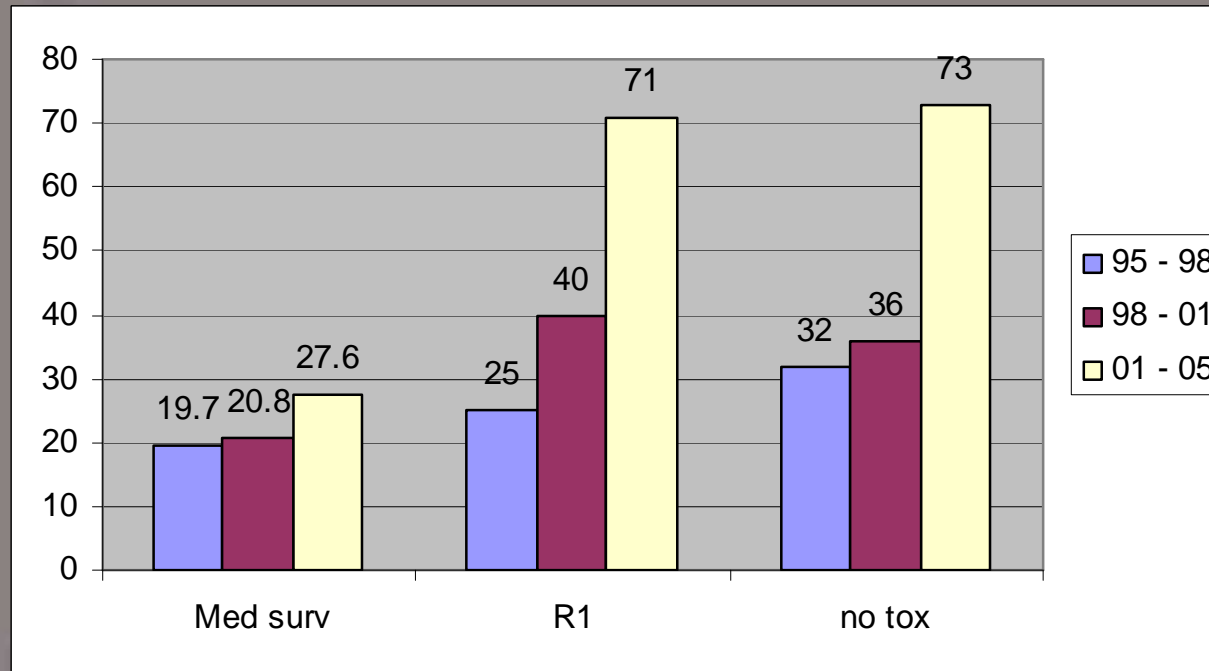
NKI-AVL

# Patients treated long term



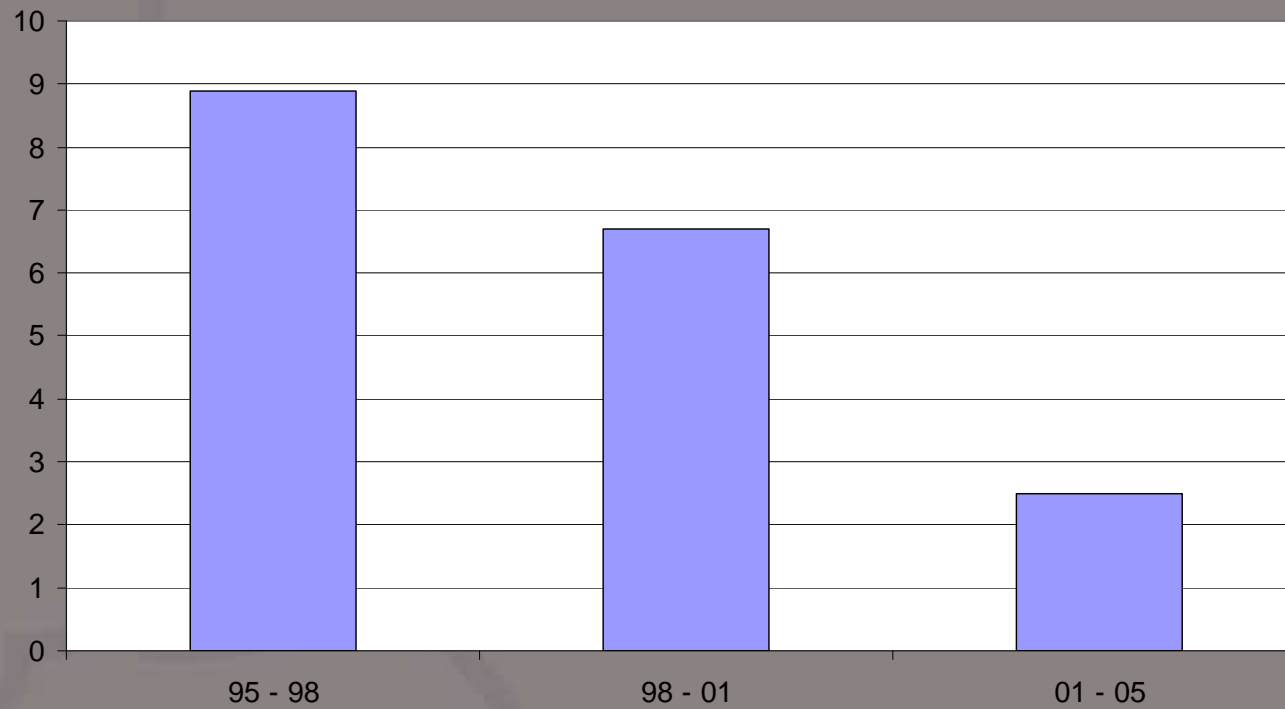


# Learning effect



# Mortality

Mortality



Lyon 2008

NKI-AVL

# Dutch HIPEC organization



# Dutch Organization

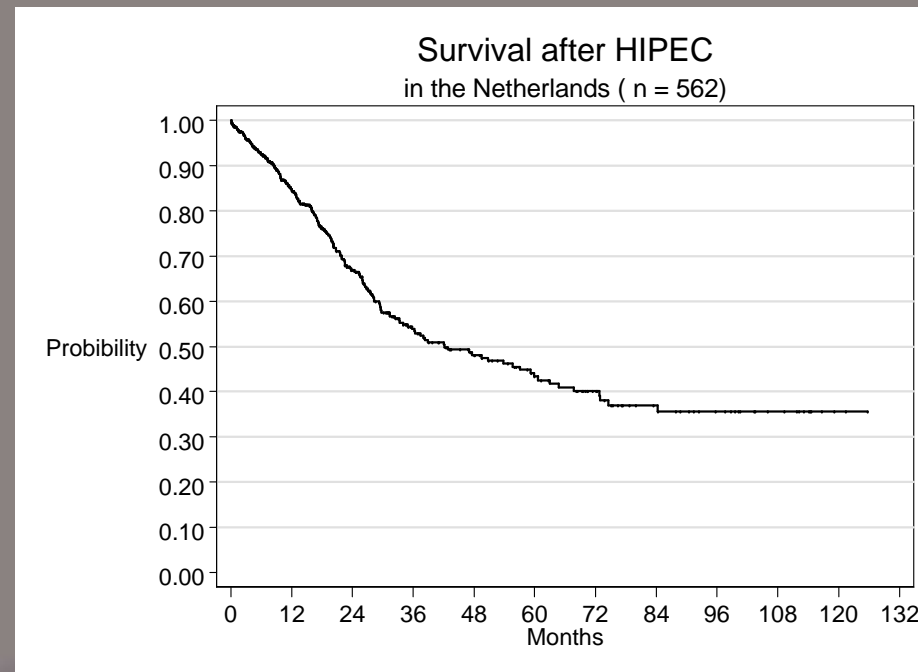
- The Netherlands Cancer institute
  - Active from 1995, 436 patients treated
- Antonius Hospital
  - Active from 2005, 80 patients treated
- UMCG
  - Active from 2006, 26 patients treated
- Catharina Hospital
  - Active from 2007, 20 patients treated



Lyon 2008

NKI-AVL

# Results in the Netherlands



# Summary

Peritoneal Carcinomatosis can be successfully treated with Cytoreduction followed by HIPEC and adjuvant chemotherapy

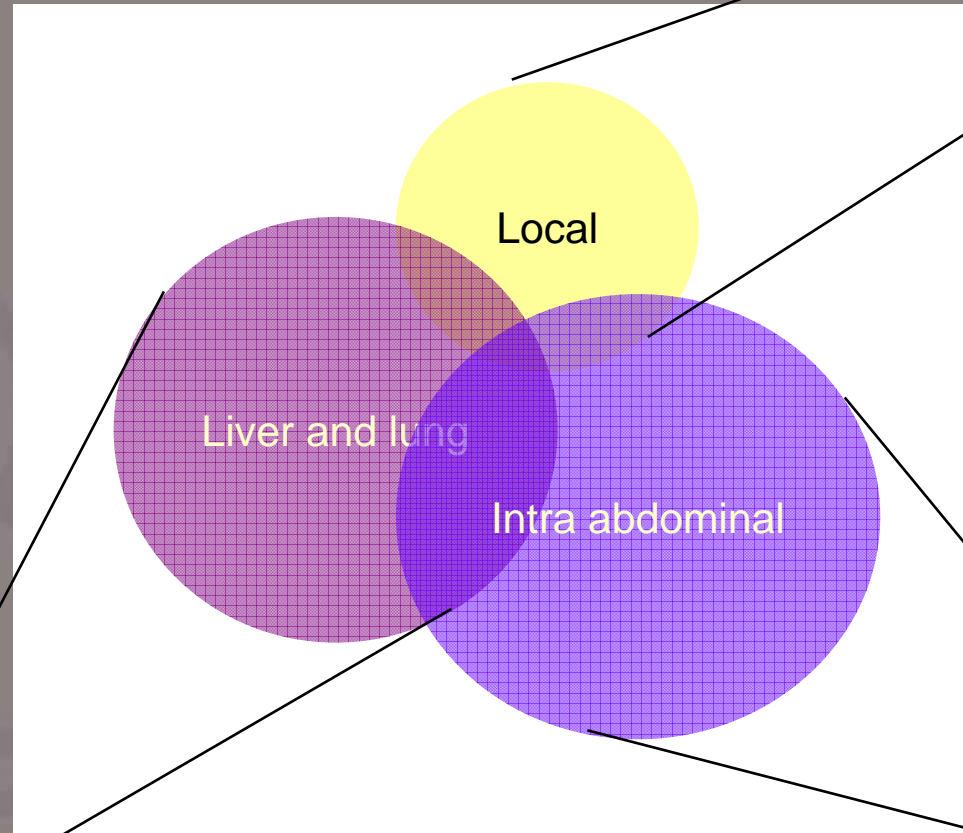
Peritoneal Carcinomatosis is a special sub-group of stage IV colorectal cancer



Lyon 2008

NKI-AVL

# Stage IV colorectal cancer



Resection data  
Medial survival  
32 months

Chemotherapy  
data  
Medial survival  
21 months

HIPEC data  
Medial survival  
22 months

# Thanks for the attention



Lyon 2008

NKI-AVL