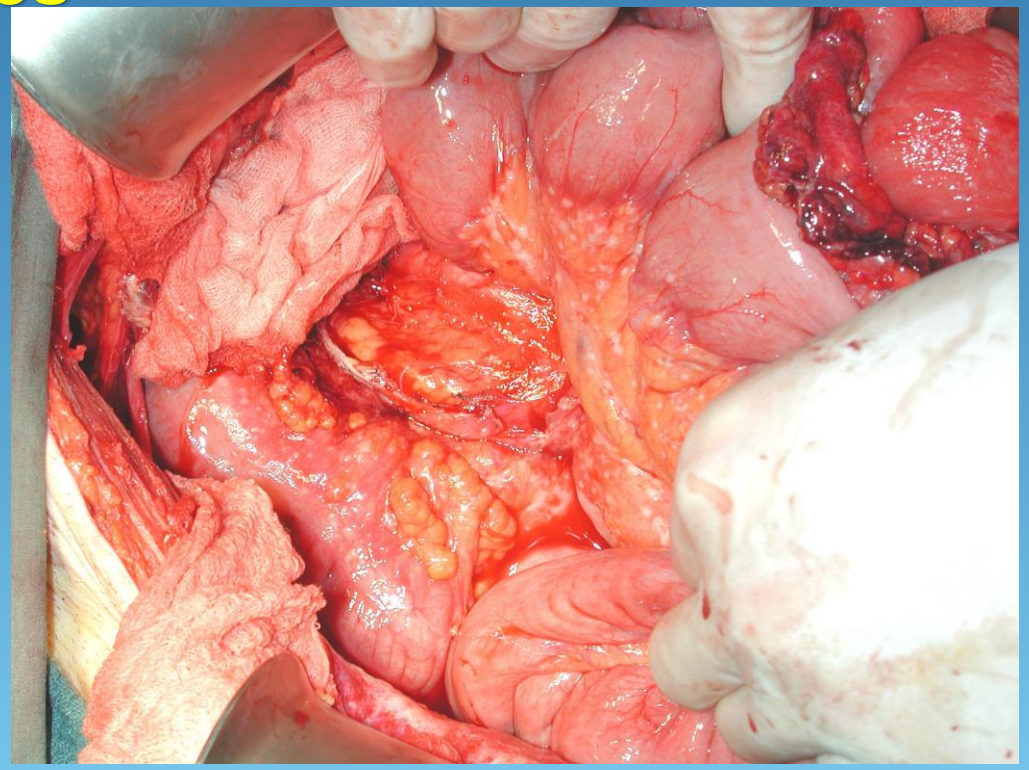
Colon Cancer with Peritoneal Disease – Who Benefits from HIPEC?

Joseph Skitzki MD, FACS

South Florida GI Cancer Symposium
April 12th, 2025

Colon Cancer with peritoneal metastases

- Peritoneum is the 2nd most common site of spread
- 4-7% CRC patients with synchronous peritoneal disease, 25% of all metastatic CRC patients
- Peritoneal metastatic CRC with shorter OS than lung, liver, other sites



World J Gastroenterol 2014 Sep 21;20(35):12493-12500
Lancet Oncology 2016 Dec:17(12):1709-1719

Systemic Chemotherapy Only

	Study name	Accrual period	Treatment comparisons*	Number of patients†	Patients with peritoneal metastasis
Saltz,[9] 2008	N016966	February, 2004–February, 2005	FOLFOX4 *vs* FOLFOX4+BEV *vs* XELOX *vs* XELOX+BEV	1965	252 (13%)
Tournigand,[10] 2006	OPTIMOX1	January, 2000–June, 2002	FOFOLX4 *vs* FOLFOX7->LV5FU2	612	37 (6%)
André,[11] 2007	OPTIMOX2	December, 2002–June, 2003	mFOLFOX7-> CFI->mFOLFOX7 *vs* mFOLFOX7->LV5FU2->mFOLFOX7	201	34 (17%)
Tournigand,[12] 2004	C97-3	December, 1997–December, 1999	FOLFIRI->FOLFOX6 *vs* FOLFOX6->FOLFIRI	220	29 (13%)
Koopman,[13] 2007	CAIRO	January, 2003–December, 2004	Cap+IRI->Cap+Ox *vs* Cap->IRI->Cap+Ox	703	42 (6%)
Tol,[14] 2009	CAIRO2	June, 2005–December, 2006	Cap+Ox+Bev in KRAS unselected population *vs* Cap+Ox+Bev + cetuximab ($KRAS^{wt}$) *vs* Cap+Ox+Bev+ cetuximab ($KRAS^{mut}$)	578	29 (5%)
Maughan,[15] 2011	COIN	March, 2005–May, 2008	5FU+Ox in unselected patients *vs* 5FU+Ox (Intermit) in unselected patients *vs* 5FU+Ox + cetuximab ($KRAS^{wt}$) *vs* 5FU+Ox + cetuximab ($KRAS^{mut}$) *vs* CAPOX *vs* 5FU+Ox (Intermit) *vs* CAPOX+ cetuximab ($KRAS^{wt}$) *vs* CAPOX+ cetuximab ($KRAS^{mut}$)	2271	331 (15%)
Seymour,[16] 2007	FOCUS	May, 2000–December, 2003	5FU->FOLFIRI *vs* 5FU->FOLFOX *vs* 5FU->IRI *vs* FOLFIRI *vs* FOLFOX	2070	313 (15%)
Seymour,[17] 2011	FOCUS2	January, 2004–July, 2006	FUFOL *vs* FOLFOX *vs* CAP *vs* CAPOX	454	86 (19%)
Diaz-Rubio,[18] 2007	03-TTD-01	April, 2002–August, 2004	FOLFOX *vs* XELOX	338	13 (4%)
Tebbutt,[19] 2010	AGITG MAX	July, 2005–June, 2007	CAP *vs* CAP+BEV *vs* CAP+BEV+ mitomycin	471	86 (18%)
Souglakos,[20] 2006	HORG 99.30	October, 2000–December, 2004	FOLFIRI *vs* FOLFOXIRI	282	73 (25%)
Falcone,[21] 2007	GONO	November, 2001–April, 2005	FOLFIRI *vs* FOLFOXIRI	242	35 (14%)
Moosmann,[22] 2011	FIRE II	September, 2004–December, 2006	CAPIRI+cetuximab ($KRAS^{mut}$) *vs* CAPIRI+cetuximab ($KRAS^{wt}$) *vs* CAPOX+cetuximab ($KRAS^{mut}$) *vs* CAPOX+cetuximab ($KRAS^{wt}$)	146	15 (10%)

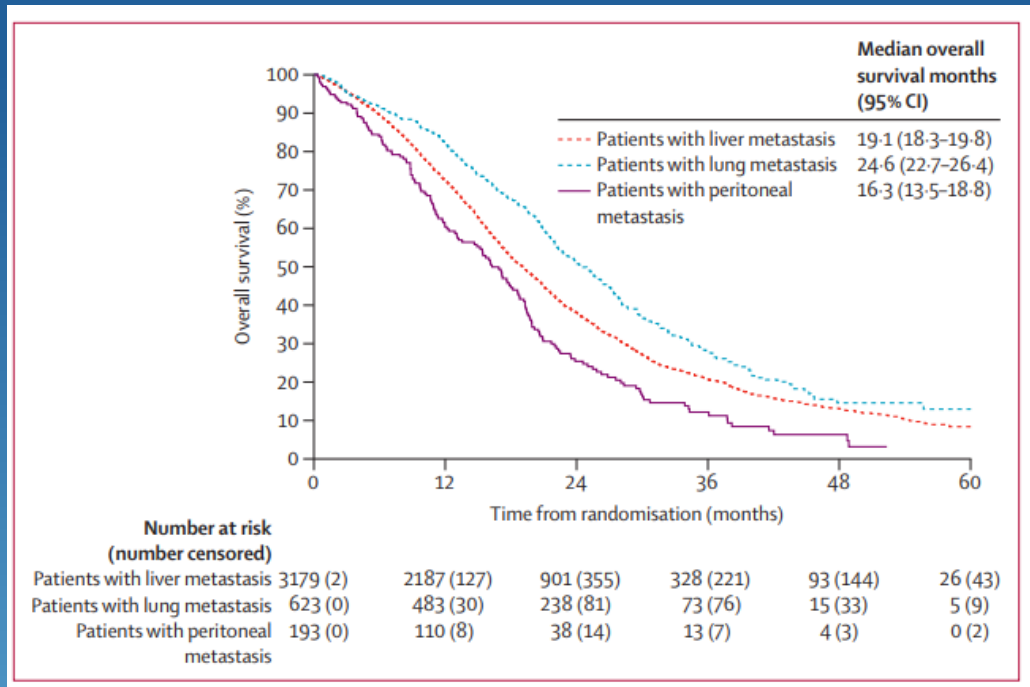


Figure 1: **Overall survival in patients with metastatic colorectal cancer with metastases in a single organ**

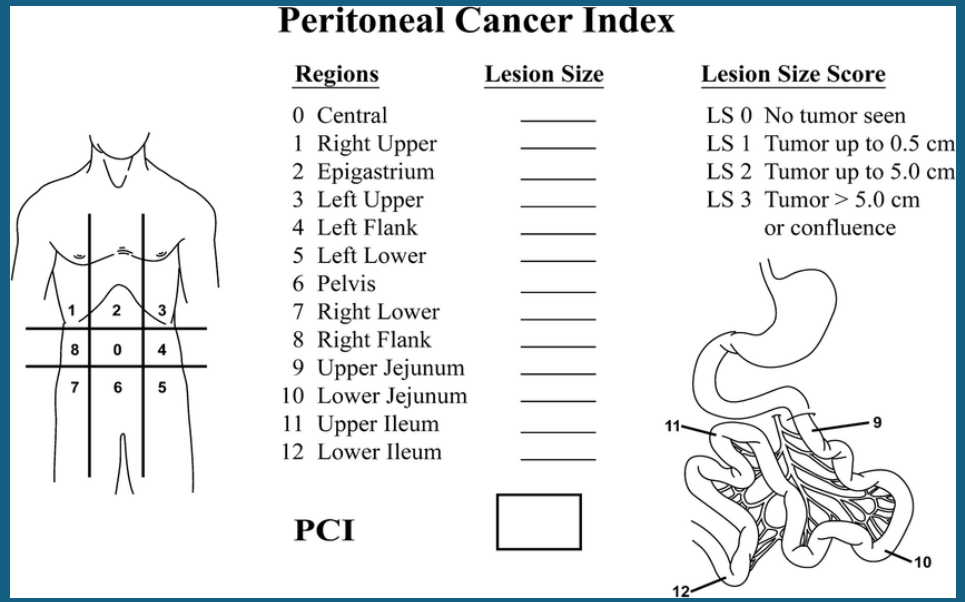
- **Median OS 16.3 months**
- **5-year survivors = 0**

Lancet Oncology 2016 Dec:17(12):1709-1719

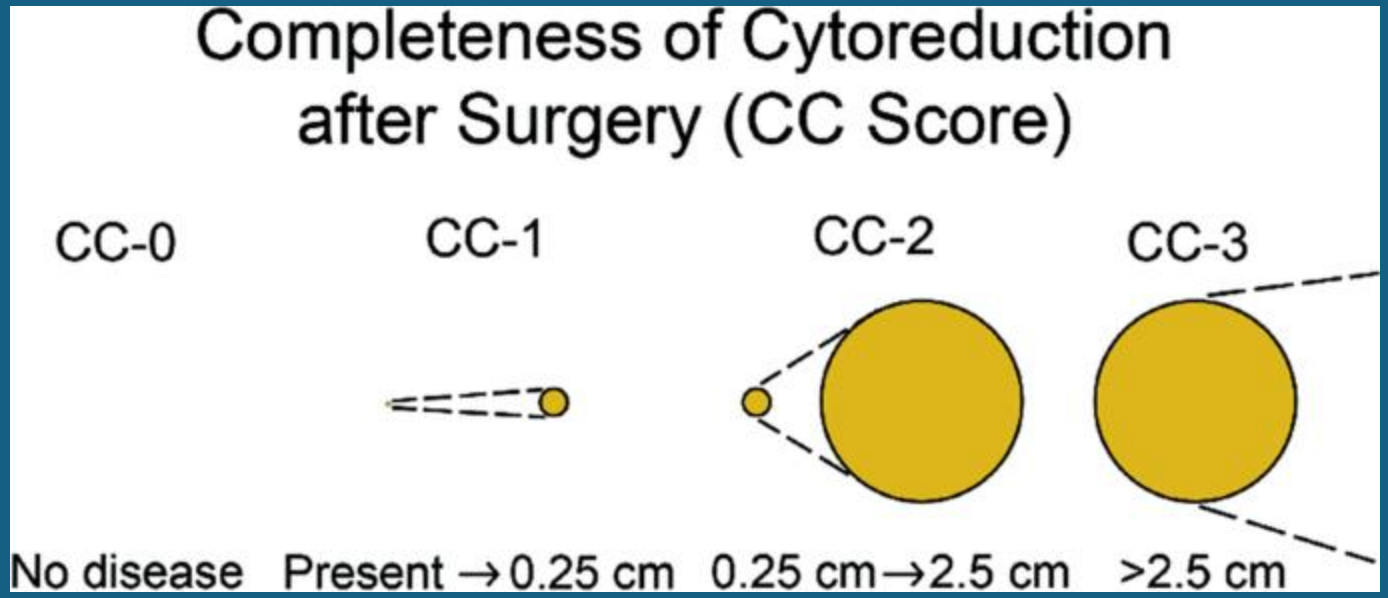
Defining HIPEC

- Cytoreduction/HIPEC (Heated IntraPEritoneal Chemotherapy)
- Cytoreduction – removing all visible tumor deposits

PCI – Peritoneal Cancer Index



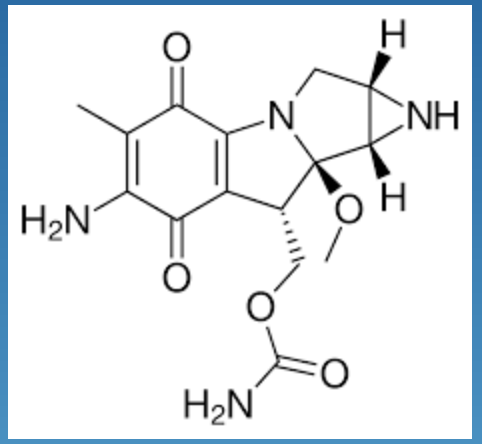
Completeness of Cytoreduction



BMC Geriatrics 2010 May: 10(Suppl 1):A11

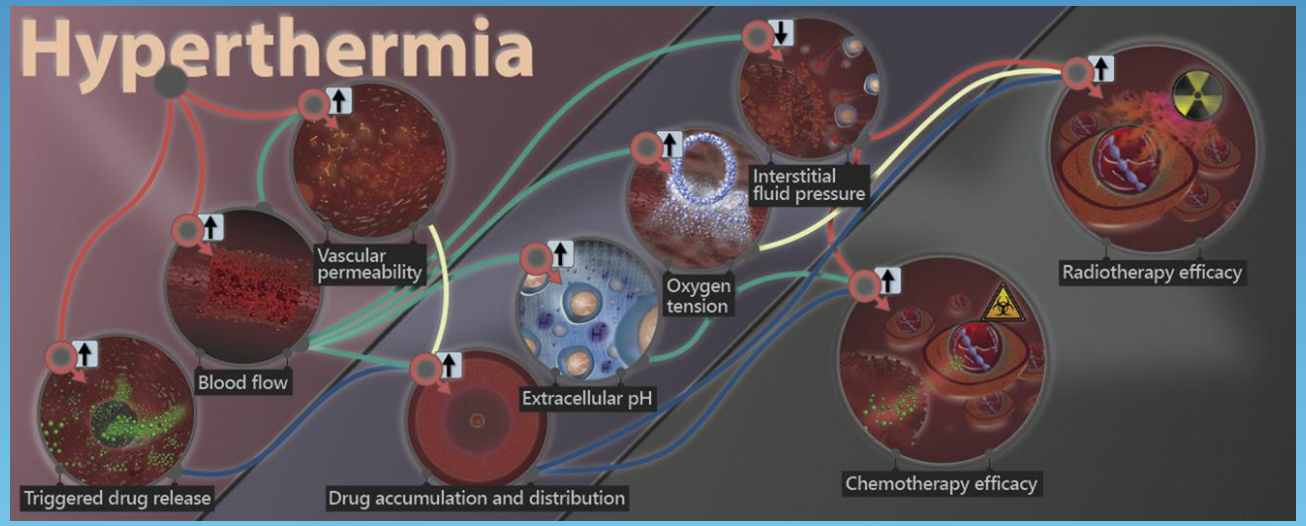
Defining HIPEC

- **HIPEC – usually Mitomycin C 30 mg at 42C for 90 minutes**



Proven topical agent – ophthalmology, bladder, peritoneum

- **Hyperthermia – In vitro - 42C for >60 minutes kills tumor cells**



Advanced Drug Delivery Reviews 2020 Vol 163-164, 98-124

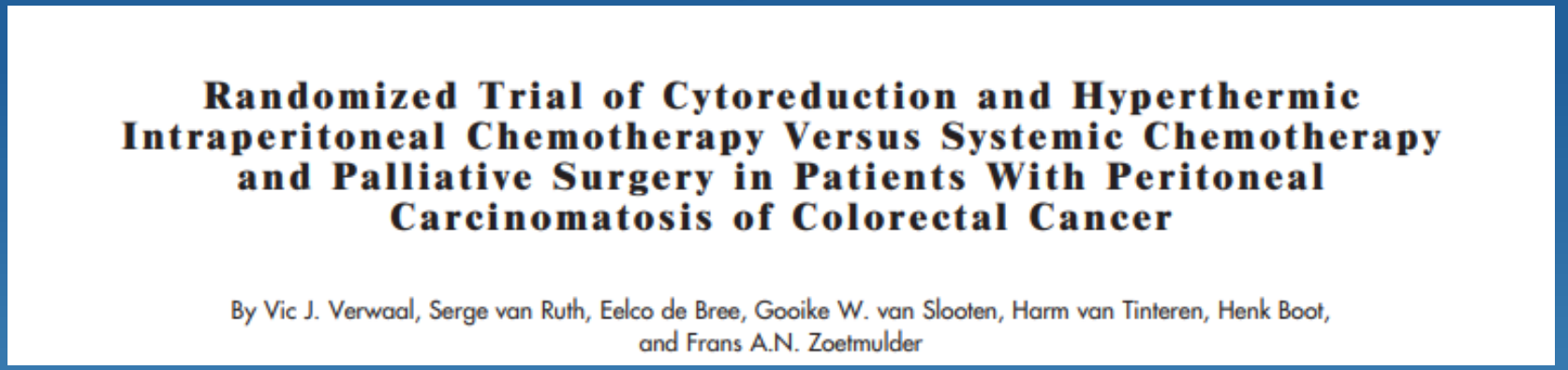
Cytoreduction/HIPEC

- "Kitchen Sink" approach
- Limited Phase III data – tons of Phase II and clinical series
- Debate has been contentious at times…. NCCN guidelines, lay press

The New York Times
Heated, Harrowing Chemotherapy Bat...

"This is cancer therapy at its most aggressive, a treatment patients liken to being filleted, disemboweled and then bathed in hot poison."

Phase III Trial for CRC (The "Dutch" Study)



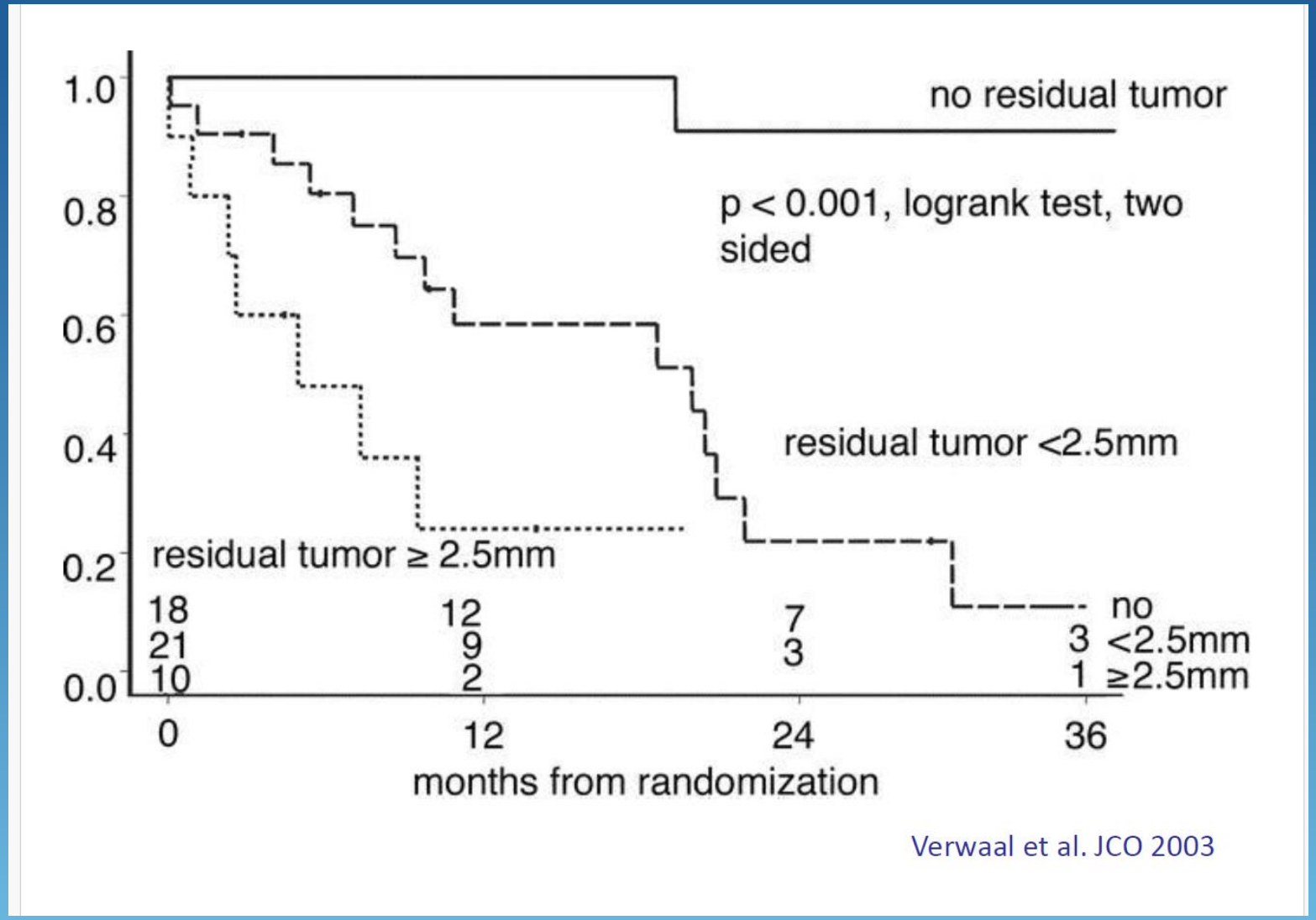
Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer

By Vic J. Verwaal, Serge van Ruth, Eelco de Bree, Gooike W. van Slooten, Harm van Tinteren, Henk Boot, and Frans A.N. Zoetmulder

- 105 patients with CRC carcinomatosis randomized:
  - Surgery/HIPEC with 6 mos IV 5-FU (54)
  - 6 mos IV 5-FU +/- palliative surgery (51)
- 55% synchronous peritoneal disease/45% were peritoneal recurrence
- 71% colon 12% rectum (17% appendix)
- 8% mortality 19% hematologic toxicity 15% fistulae
- Median survival - HIPEC 22.4 mos; IV – 12.6 mos
- 20% predicted 5 yr OS for HIPEC

J Clin Oncol 2003 21:3737-3743

Phase III Data



Verwaal et al. JCO 2003

Completeness of cytoreduction determined overall survival….

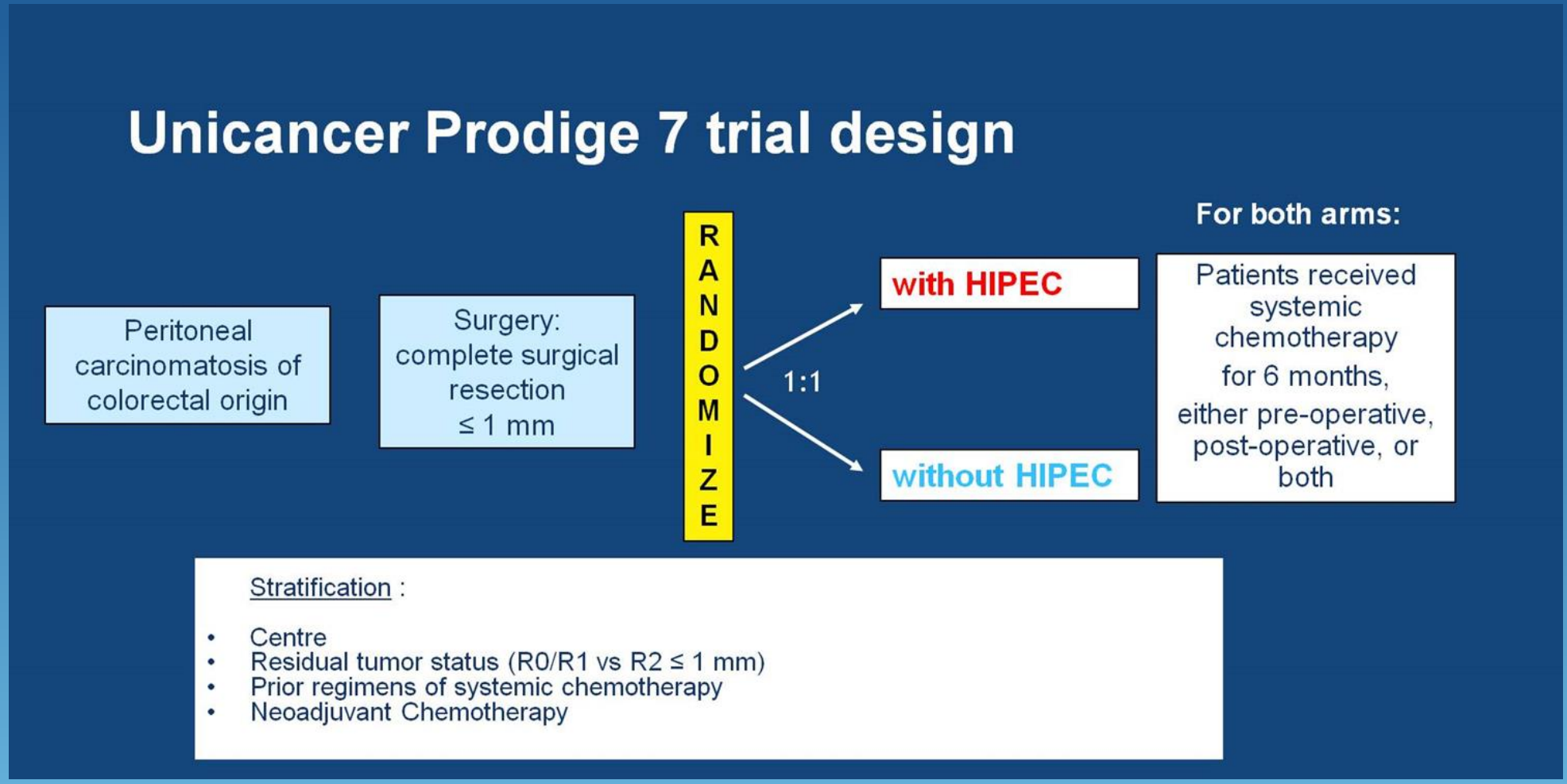
The "Dutch" Study Update

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,[1] Sjoerd Bruin, MD,[1] Henk Boot, MD, PhD,[2] Gooike van Slooten, MD,[1] and Harm van Tinteren, ScM[3]

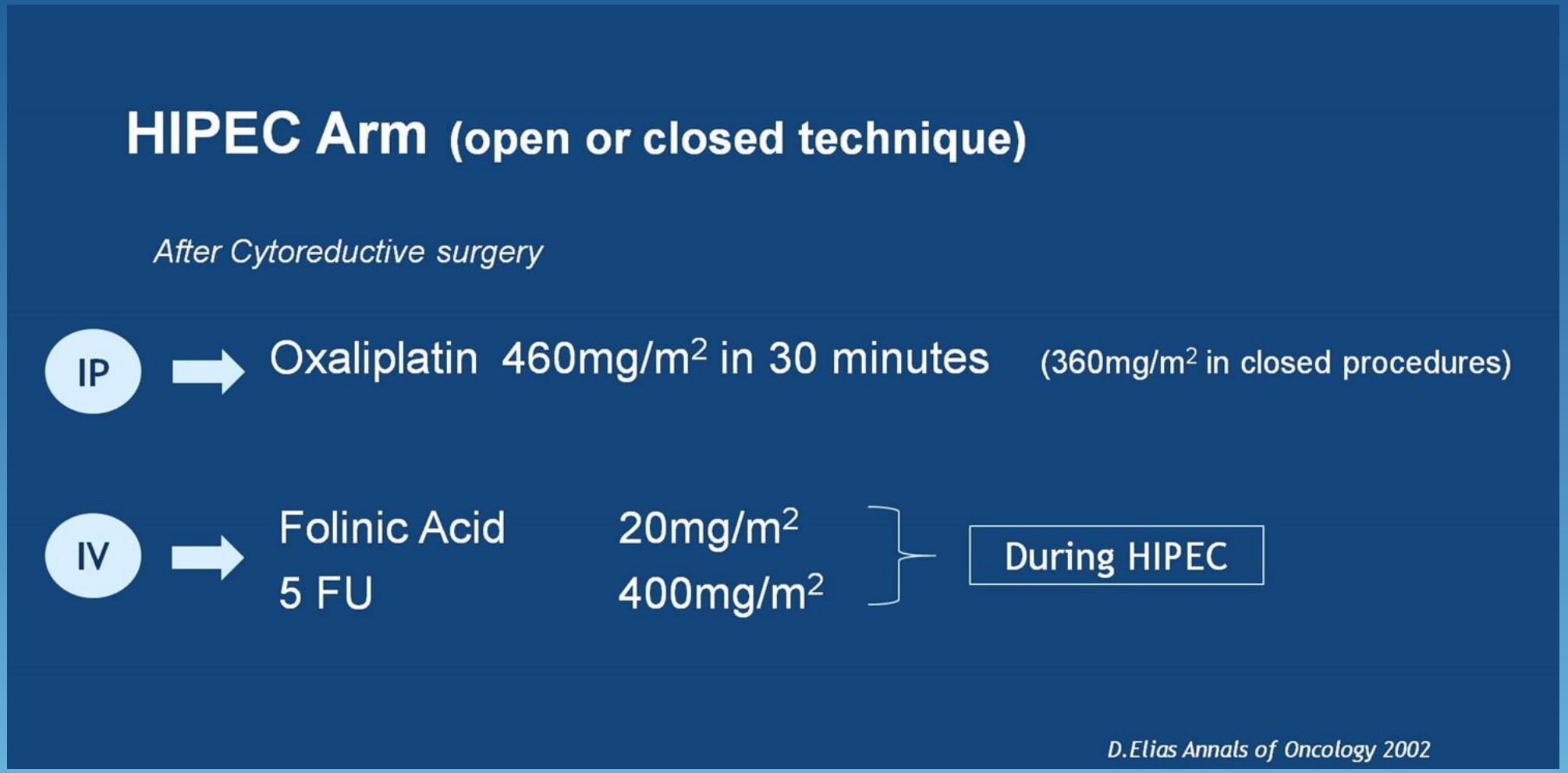
- Median follow-up 8 years (72-115 months)
- PFS 7.7 versus 12.6 months with HIPEC
- DSS 12.6 versus 22.2 months with HIPEC
- 45% 5 year OS for R1 resection

Phase III Trial PRODIGE 7 – The "French" Study



- Cytoreduction + HIPEC (133) Cytoreduction alone (132)

PRODIGE 7 – The "French" Study



Oxaliplatin rather than mitomycin C…

PRODIGE 7 – The "French" Study

Safety: Mortality

30 days	HIPEC	Non-HIPEC
Nb of patients	2	2
Cause of death	Pneumonia	Renal Failure
	IP Hæmorrhage	Multivisceral failure

Mortality rate at 30 days : 1.5%

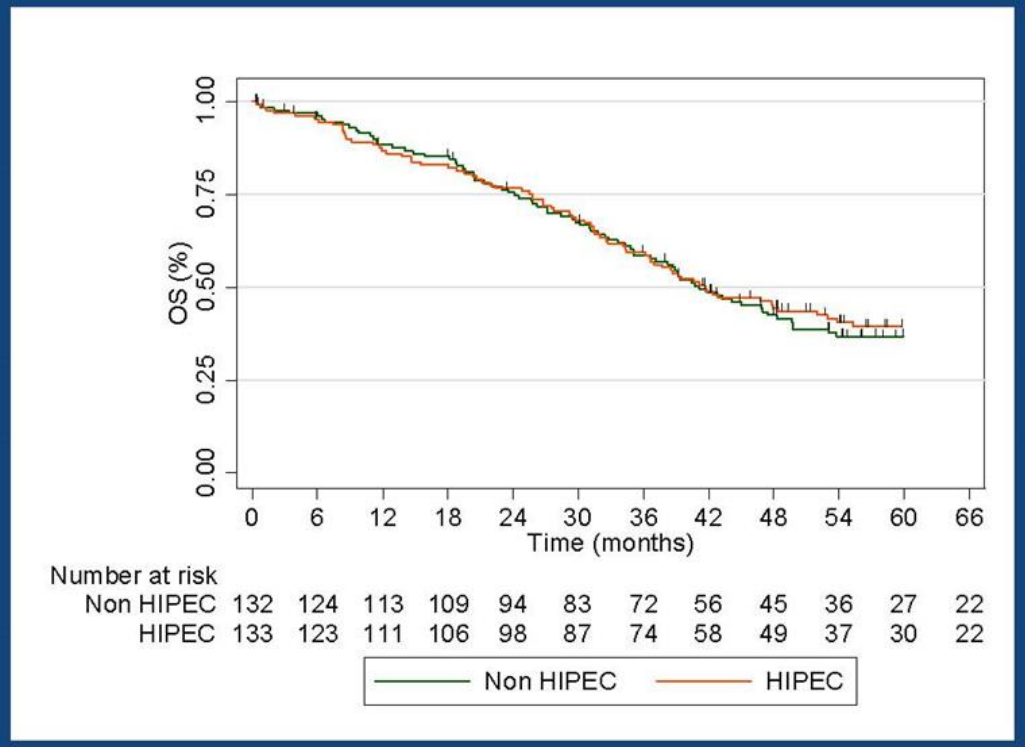
60 days	HIPEC	Non-HIPEC
Nb of patients	2	1
Cause of death	Pulmonary embolism	Acute respiratory distress
	Sepsis	

Total mortality rate : 2.6%

Low morbidity/mortality – contemporary rates

PRODIGE 7 – The "French" Study

Overall survival (ITT)



Median Follow Up: 64 months [95% CI:58.9-69.8]

	HIPEC	Non-HIPEC	P-value
Median Survival (months) [95% CI]	41.7 [36.2-52.8]	41.2 [35.1-49.7]	0.995
1-year Survival	86.9%	88.3%	
5-year Survival	39.4%	36.7%	

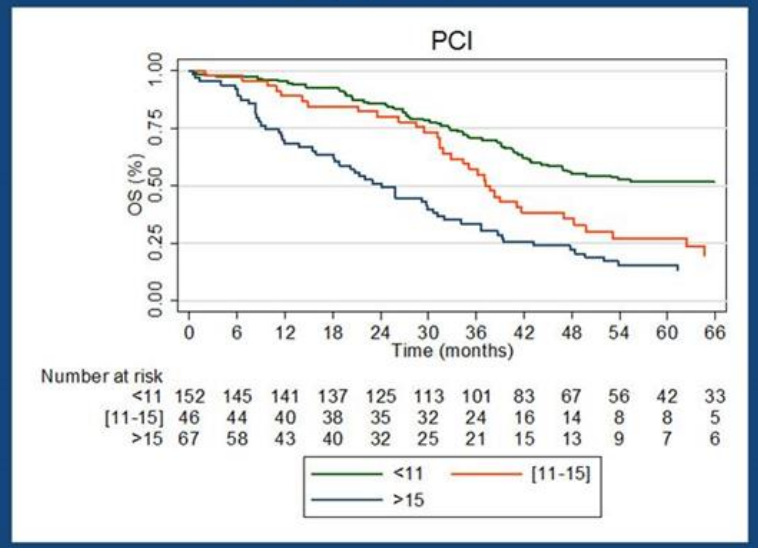
HR=1.00: 95%CI [0.73 - 1.37] p=0.995

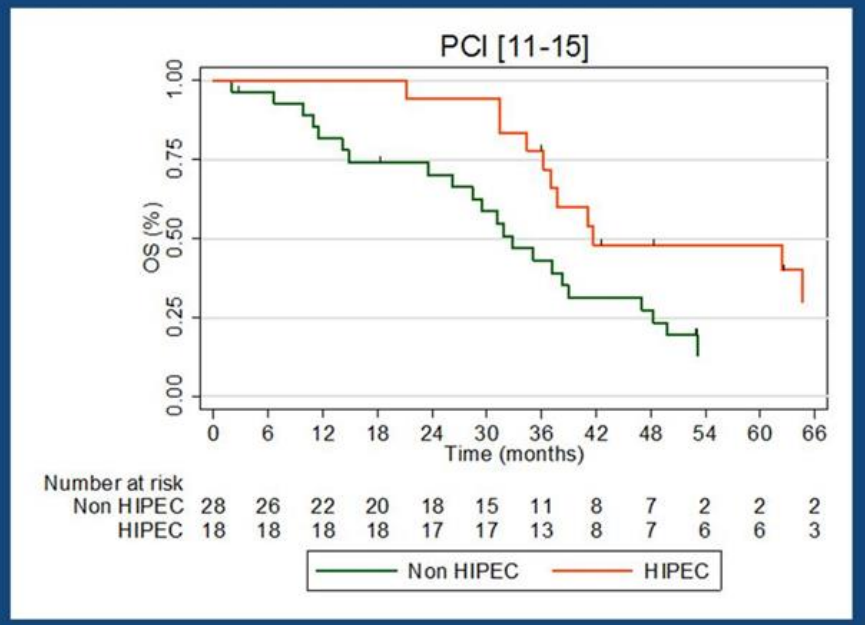
No benefit seen for adding HIPEC to cytoreduction….

PRODIGE 7 – The “French” Study

Overall survival and PCI

Entire population





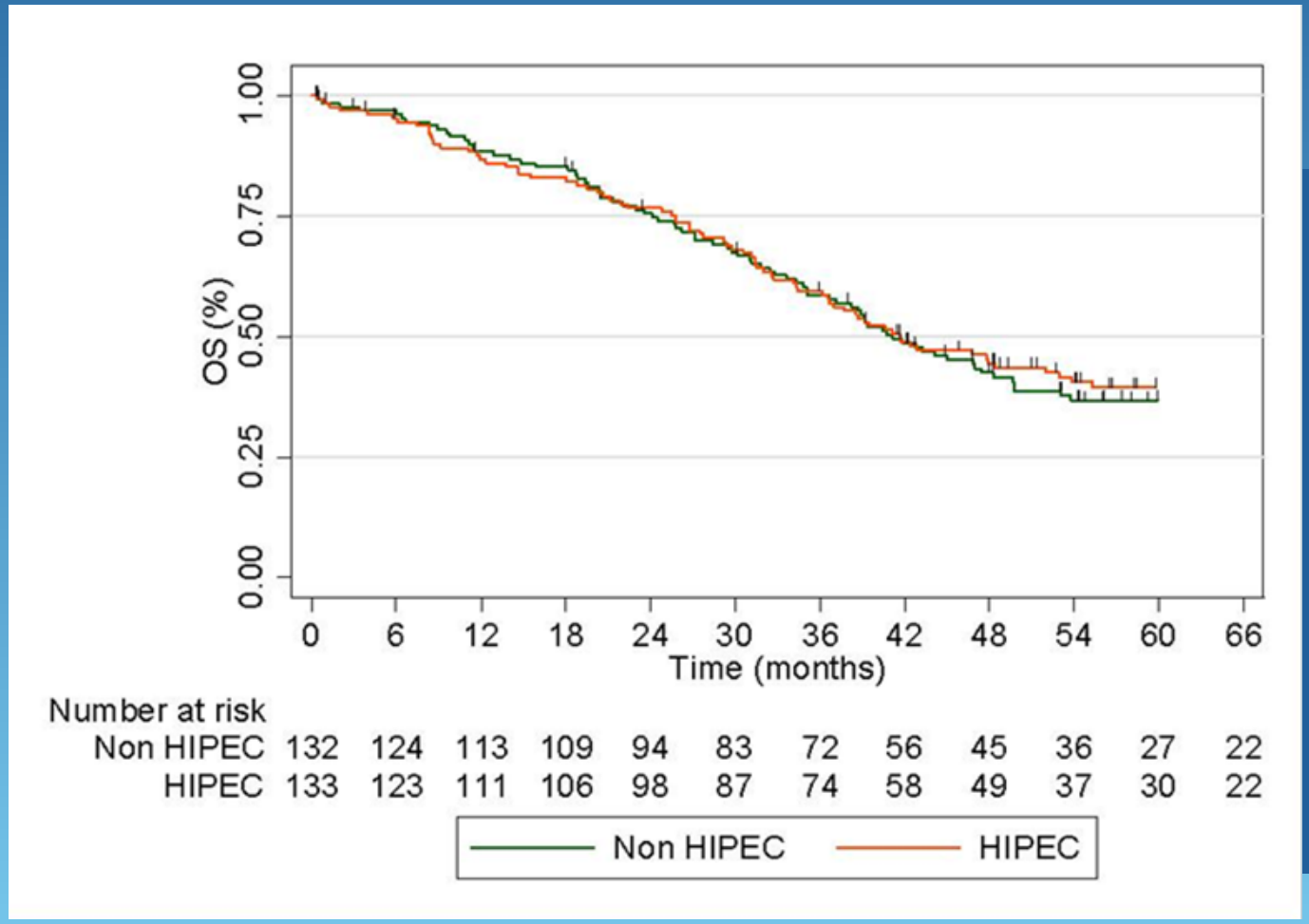
<11 HR= 1
[11-15] HR= 1.88 95%CI [1.25-2.88] p=0.003
16-24 HR= 3.57 95%CI [2.43-5.23] p<0.001

OS PCI [11-15]	HIPEC	Non-HIPEC	HR	P-value
Median Survival (months) [95% CI]	41.6 [36.1-nor reach]	32.7 [23.5-38.9]	0.437 [23.5-38.9]	0.0209

Questionable benefit for moderate PCI???

PRODIGE 7 – Conclusions

- Oxaliplatin-HIPEC had no impact on OS or PFS
- Cytoreduction alone showed good results (too good??)



- Low PCI patients
- Multiple Centers/Surgeons
- 30 min Oxaliplatin
- 5-FU infusion in OR
- No hyperthermia
- Cytoreduction alone results superior to any prior reports

Colon Cancer with Peritoneal Disease – Who Benefits from HIPEC?

3 criteria for eligibility

- performance status
- disease isolated to peritoneum
- disease that is amenable to a complete cytoreduction

Must be in the context of low morbidity/mortality

Cancer Medicine

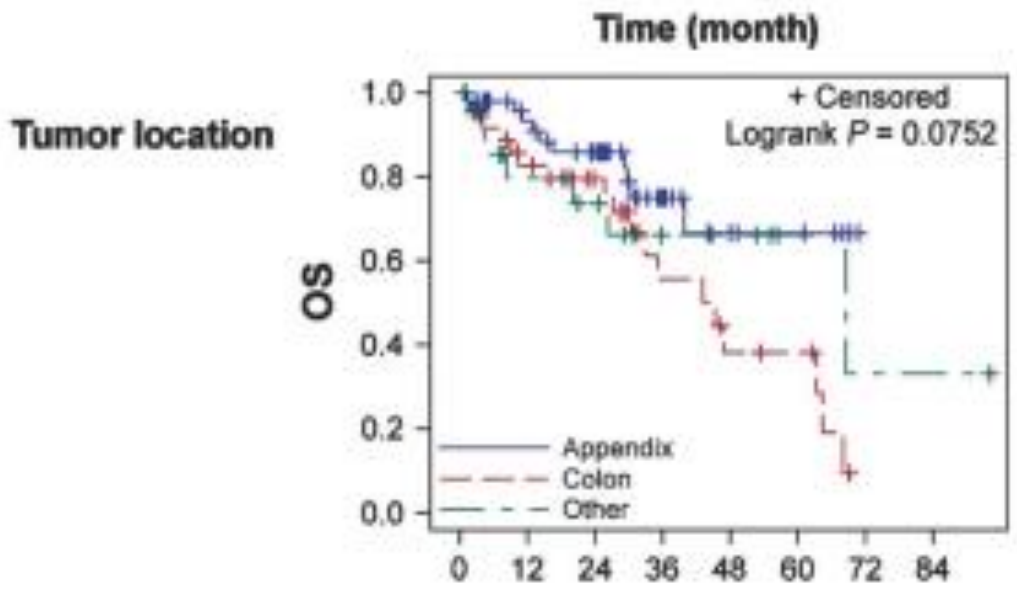
Open Access

ORIGINAL RESEARCH

A contemporary analysis of morbidity and outcomes in cytoreduction/hyperthermic intraperitoneal chemoperfusion

Michelle Haslinger[1,2], Valerie Francescutti[2], Kristopher Attwood[3], Judith Andrea McCart[4], Marwan Fakih[5], John M. Kane III[2] & Joseph J. Skitzki[2]

[1]Department of Surgery, University of Buffalo, Buffalo, New York
[2]Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, New York
[3]Department of Biostatistics and Bioinformatics, Roswell Park Cancer Institute, Buffalo, New York
[4]Department of Surgery, Mount Sinai Hospital and the University of Toronto, Toronto, Ontario, Canada
[5]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan



~ 38% CRC HIPEC patients alive at 5 years
~ half with no evidence of disease

??~15-19% patients benefit??

Thank You!!!!