

# A UNICANCER phase III trial of Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) for Colorectal Peritoneal Carcinomatosis.

**Prodige 7 - ACCORD 15 trial.** NCT00769405, N° EudraCT : 2006-006175-20

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# Background

	Events/total	Median overall survival (months)*	Hazard ratio†	p value
<b>All patients with one site of metastasis</b>				
Site of metastasis				<0.0001§
Liver only	2269/3179	19.1 (18.3–19.8)	0.75 (0.63–0.88)	0.0004
Lung only	391/623	24.6 (22.7–26.4)	0.53 (0.44–0.64)	<0.0001
Peritoneal only	159/193¶	16.3 (13.5–18.8)	Reference	..

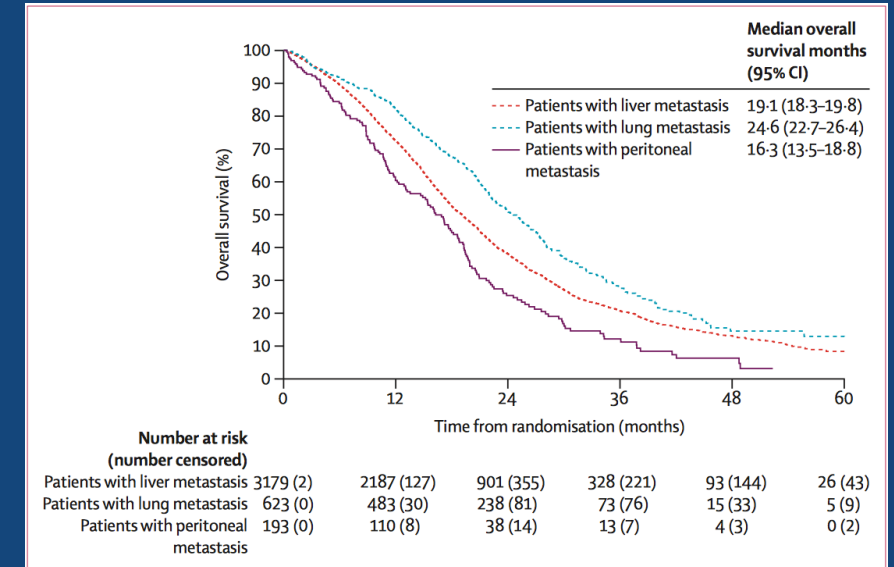


Figure 1: Overall survival in patients with metastatic colorectal cancer with metastases in a single organ

Peritoneal metastases from colorectal cancer are associated with significantly worse prognosis, whether they were the only site of metastasis

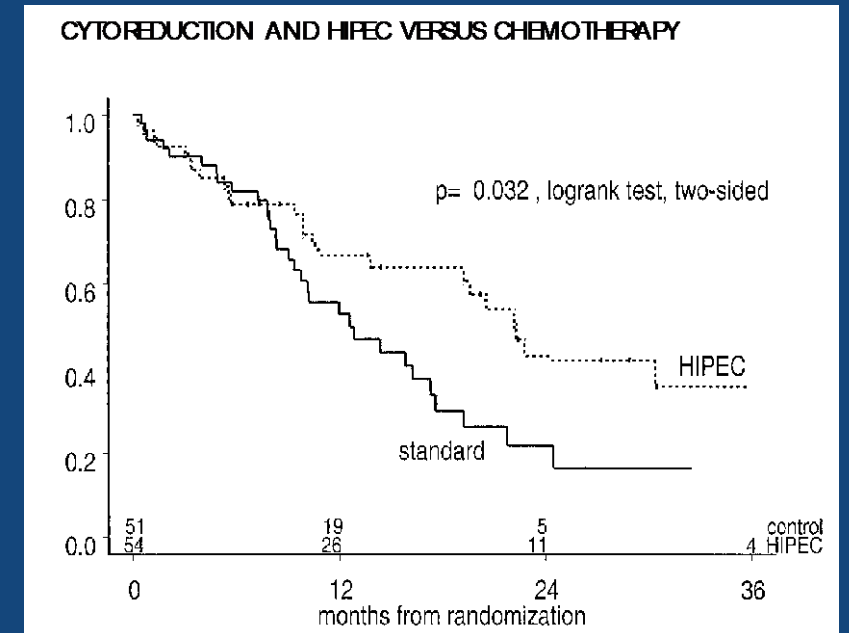
ARCAD colorectal cancer database Franko et al Lancet Oncol 2016

# Background

Retrospective studies CRS + HIPEC

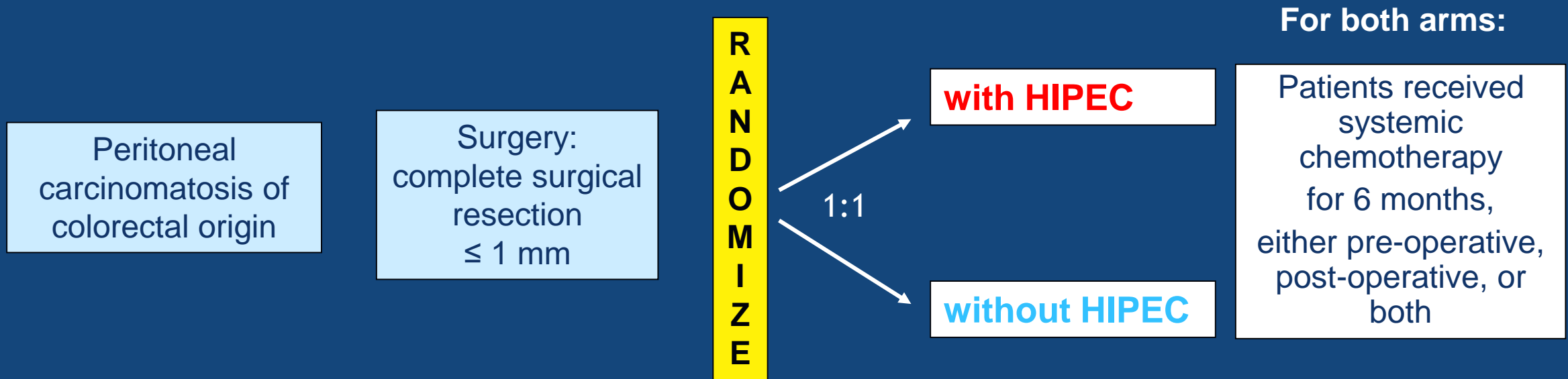
Authors	Nb of Patients	Median OS	Source
Glehen	506	32	JCO 2004
Elias	523	33	JCO 2009
Chua	110	38	Ann Surg Oncol 2011
Quenet	146	41	Ann Surg 2011
Prada-Villaverde	539	33	J Surg Oncol 2014

Phase III study



V.Verwaal, *Ann Surg Oncol.* 2003  
*Ann Surg Oncol.* 2008

# Unicancer Prodigie 7 trial design



## Stratification :

- Centre
- Residual tumor status (R0/R1 vs R2  $\leq 1$  mm)
- Prior regimens of systemic chemotherapy
- Neoadjuvant Chemotherapy

# Main Inclusion Criteria

- Histologically confirmed colorectal cancer
- Absence of extra peritoneal metastases including hepatic and pulmonary metastases
- Peritoneal Cancer Index (PCI) < 25
- Macroscopically complete (R0/R1) or with residual tumor tissue  $\leq$  1mm (R2)
- All patients had to be treated with systemic chemotherapy for 6 months
- Patients non previously treated with HIPEC
- Patients aged  $\geq$  18 and  $\leq$  70 years old

# HIPEC Arm (open or closed technique)

*After Cytoreductive surgery*

**IP** → Oxaliplatin 460mg/m<sup>2</sup> in 30 minutes (360mg/m<sup>2</sup> in closed procedures)

**IV** → Folinic Acid 20mg/m<sup>2</sup>  
5 FU 400mg/m<sup>2</sup> } **During HIPEC**

*D.Elias Annals of Oncology 2002*

# Endpoints

- **Primary:** Overall survival
- **Secondary:**
  - Recurrence-free survival
  - Toxicity (NCI-CTC version 3.0 grading)
  - Morbidity including surgical complications
  - Prognostic factors of survival

# Statistical Framework

## Hypothesis

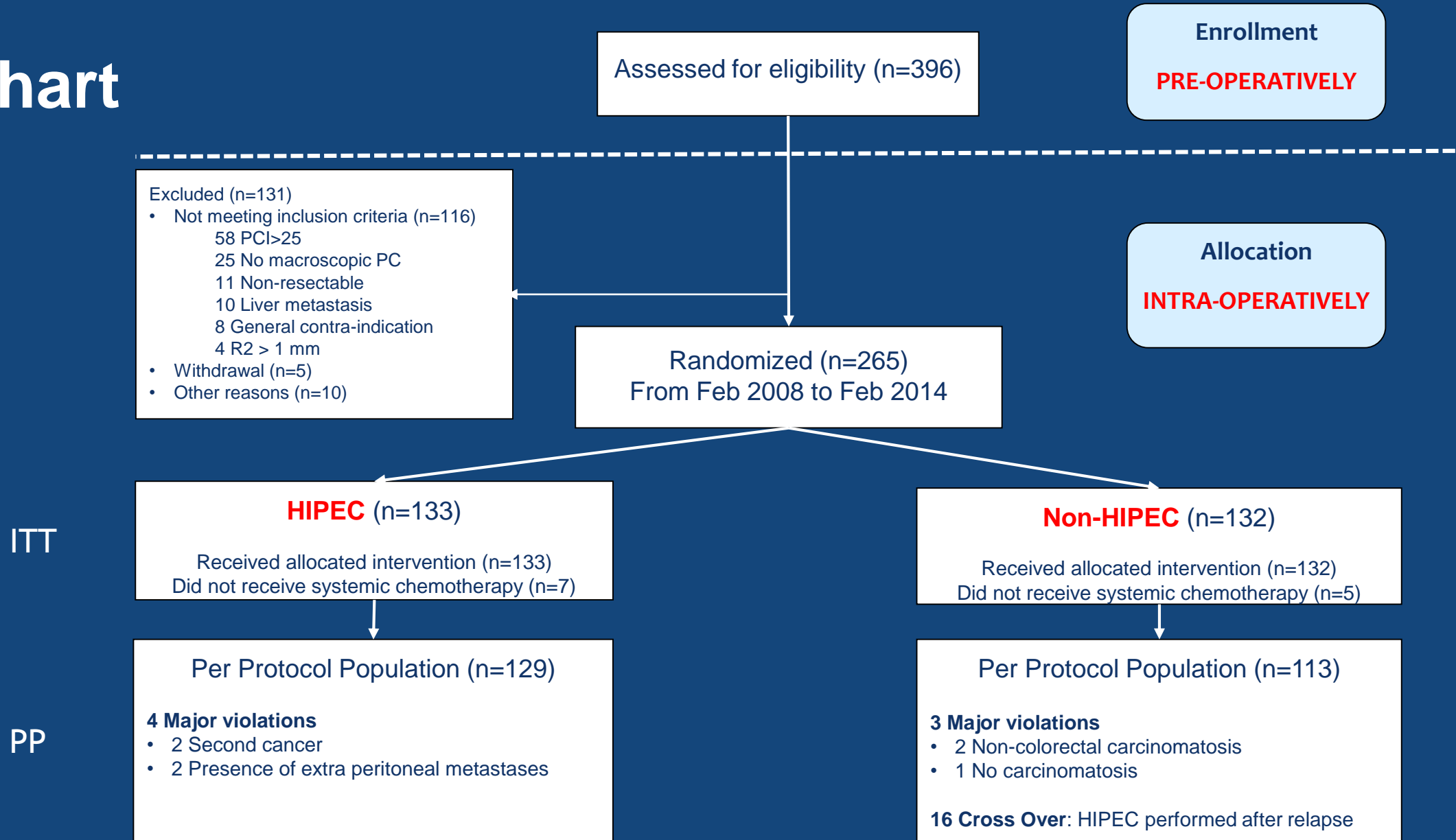
Study designed to have 80% power to detect an increase in **median overall survival from 30 to 48 months (HR 0.625)**

## Sample size

- **264 patients** required to reach 154 events for final analysis, based on the use of the log-rank test with a two-sided significance level of 5%,  $\beta = 20\%$
- 2 Planned interim analyses after observation of 51 and 102 events
- Intent to treat analysis (ITT)



# Flow Chart



# Baseline Characteristics

Demography	HIPEC		Non -HIPEC	
	n	(%)	n	(%)
Men	65	48.9	67	50.8
Women	68	51.1	65	49.2
WHO performance status				
0	105	79.5	100	76.9
1	26	19.7	30	23.1
2	1	0.8	0	
Missing	1		2	
Primary Tumour Localisation				
Right colon	51	38.3	50	37.9
Transverse colon	10	7.5	8	6.1
Left colon	57	42.9	58	43.9
Rectum	12	9.0	14	10.6
Missing	1	0.8	4	3.0
Primary Tumour Treatment				
Surgery	107	80.4	100	75.8
Chemotherapy	65	48.9	63	47.7
Previous Treatment of PC				
Surgery	29	21.8	37	28.0
Chemotherapy	19	14.3	20	15.2



# 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%

# Safety: Morbidity at 30 days

		HIPEC		Non-HIPEC		p-value
		n	(%)	n	(%)	
<b>All complications</b>	All grades	87	65.4	73	55.3	0.092
	Grades 3-4-5	54	40.6	41	31.1	0.105
<b>Intra-abdominal complications</b>	All grades	46	35.0	39	29.6	0.379
	Grades 3-4-5	35	26.3	23	17.4	0.080
<b>Extra-abdominal complications</b>	All grades	69	51.9	54	40.9	0.073
	Grades 3-4-5	35	26.3	28	21.2	0.329

No difference between the two arms

# Morbidity at 30 days: Intra-abdominal complications

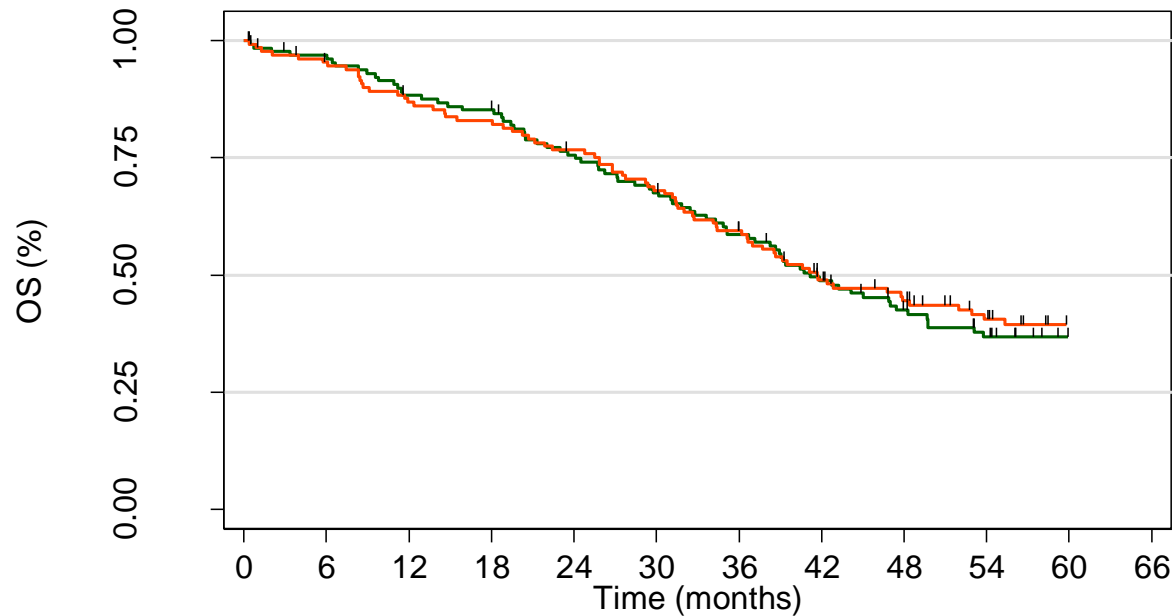
		HIPEC		Non-HIPEC		Total		p
		n	%	n	%	n	%	
Digestive fistula	Grades 3-4	14	10.5	8	6.1	22	8.3	NS
Abscesses	Grades 3-4	7	5.3	4	3.0	11	4.2	NS
Peritonitis		4	3.0	4	3.0	8	3.0	NS
Peritoneal hemorrhages	Grades 3-4-5	11	8.3	3	2.3	14	5.3	NS
Abdominal wall complications	Grades 3-4	4	3.0	2	1.5	6	2.3	NS
Others	Grades 3-4	11	8.3	8	6.1	19	7.2	NS

# Morbidity at 60 days

	Grades	HIPEC		Non-HIPEC		p-value
		n	%	n	%	
All Complications	3-4-5	32	24.1	18	13.6	0.030
Intra-abdominal complications	3-4	8	6	4	3	0.377
Extra-abdominal complications	3-4-5	27	20.3	16	12.1	0.071

Hospital Stay	days	range	days	range	P-value
	18.0	[8;140]	13.0	[1;62]	<0.0001

# Overall survival (ITT)



Number at risk

	0	6	12	18	24	30	36	42	48	54	60	66
Non HIPEC	132	124	113	109	94	83	72	56	45	36	27	22
HIPEC	133	123	111	106	98	87	74	58	49	37	30	22



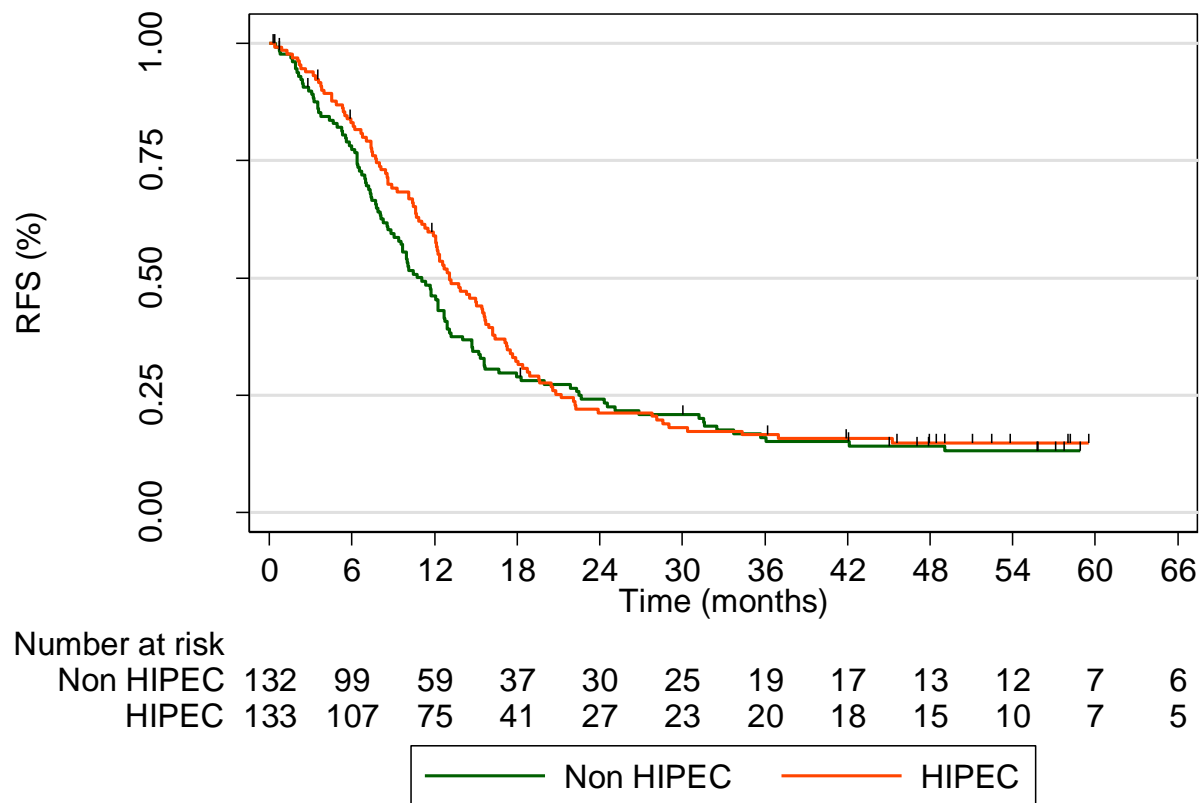
Median Follow Up: 64 months [95% CI:58.9-69.8]

	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



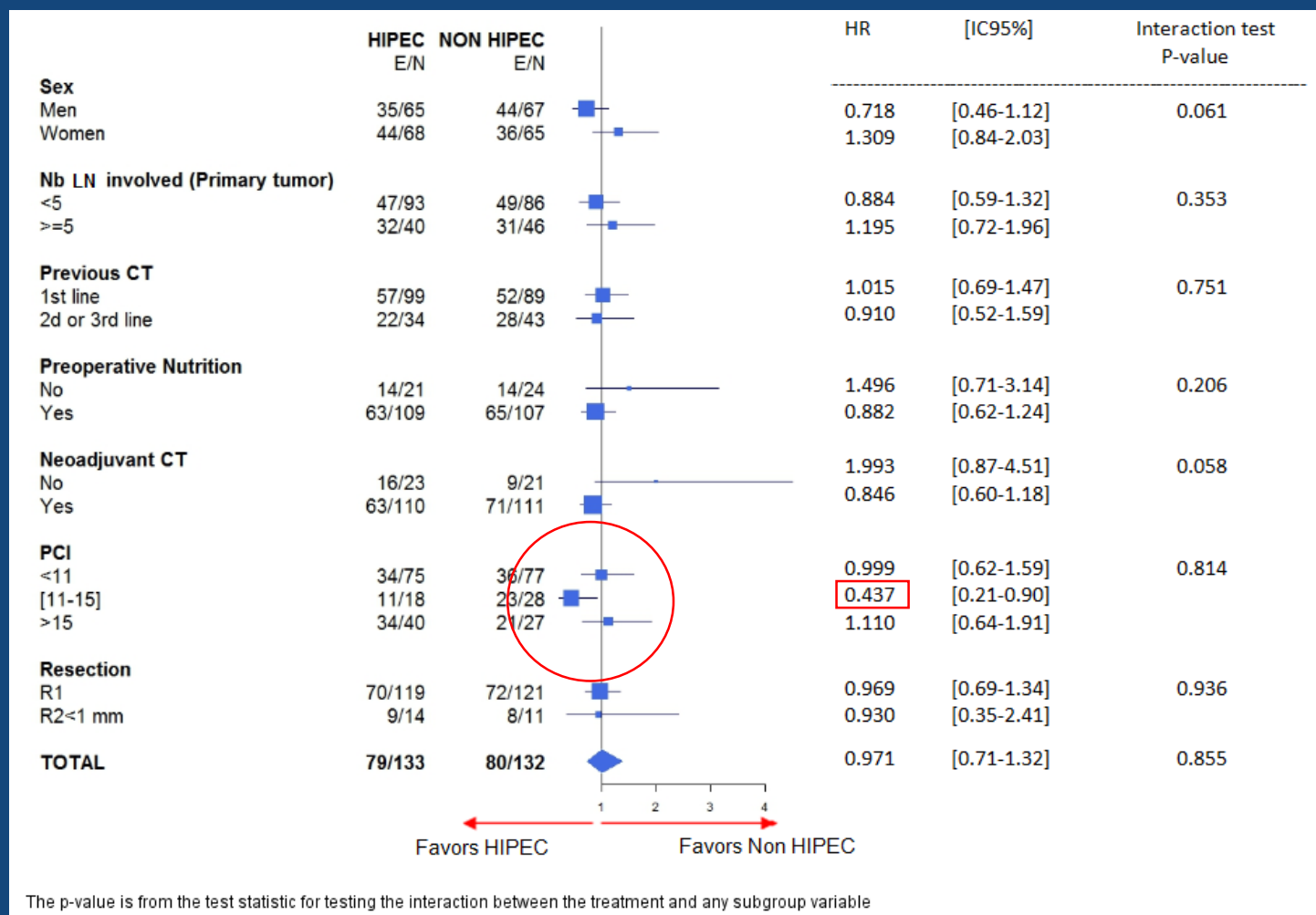
# Relapse-free survival (ITT)



	HIPEC	Non-HIPEC	P-value
Median Survival (months) [95% CI]	13.1 [12.1-15.7]	11.1 [9.0-12.7]	0.486
1-year Survival	59.0%	46.1%	
5-year Survival	14.8%	13.1%	

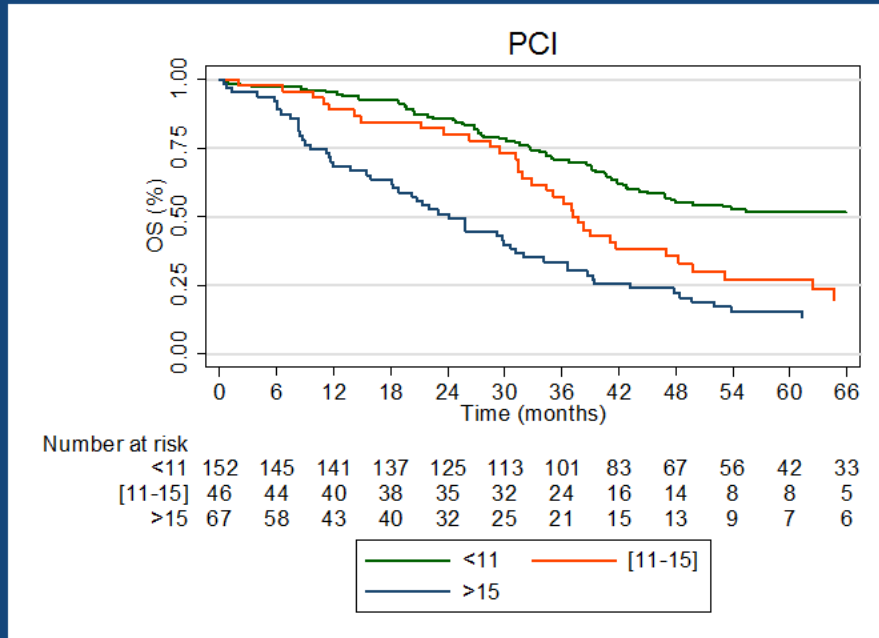
**HR=0.908: 95%CI :[0.69-1.19] p=0.486**

# Forest Plot for Overall Survival

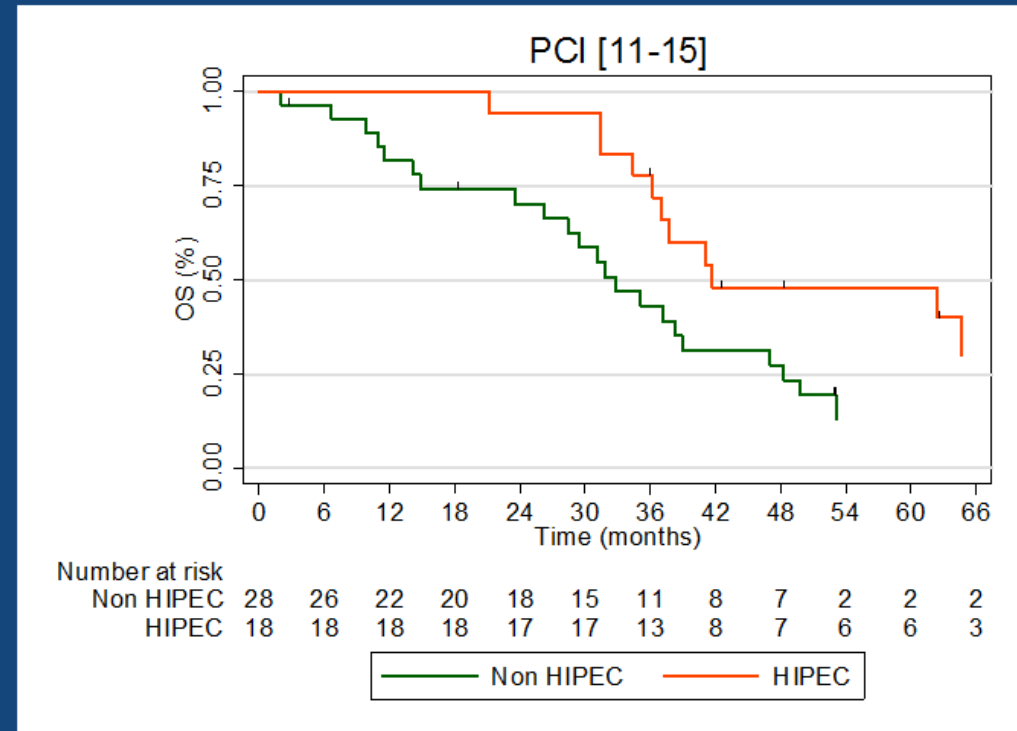


# Overall survival and PCI

## 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

# Conclusions

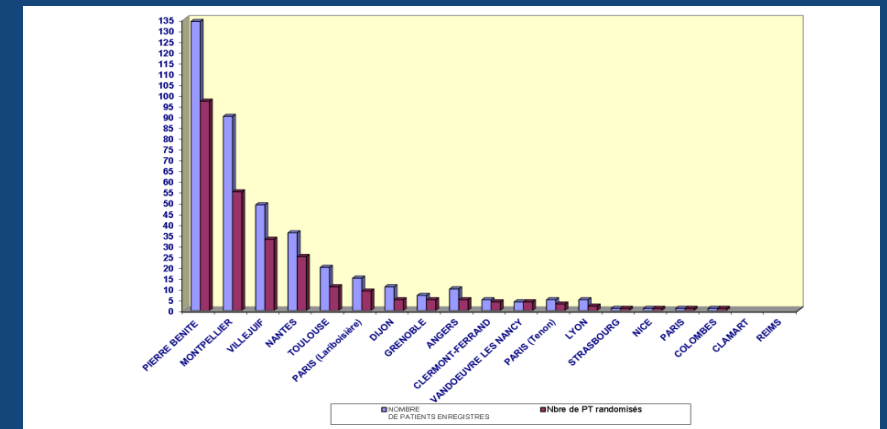
- The addition of oxaliplatin-HIPEC on the top of cytoreductive surgery does not influence both OS and RFS
- There were more late post-operative complications with HIPEC
- The curative management of PC from colorectal cancer by cytoreductive surgery alone shows unexpected satisfactory survival results

# Acknowledgements



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