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Direttore OMC Gaetano Franceschi



Panello in pasta vitrea Donata del Chirurgo Rimini

Rimini Centro Congressi SGR  
venerdì 21 ottobre 2011  
ore 14:00 / 19:00

**Carcinoma del colon-retto**  
La medicina che cambia:  
l'approccio multidisciplinare  
al trattamento delle metastasi  
epatiche nell'era della target therapy

con il patrocinio dell'Associazione Italiana di Oncologia Medica

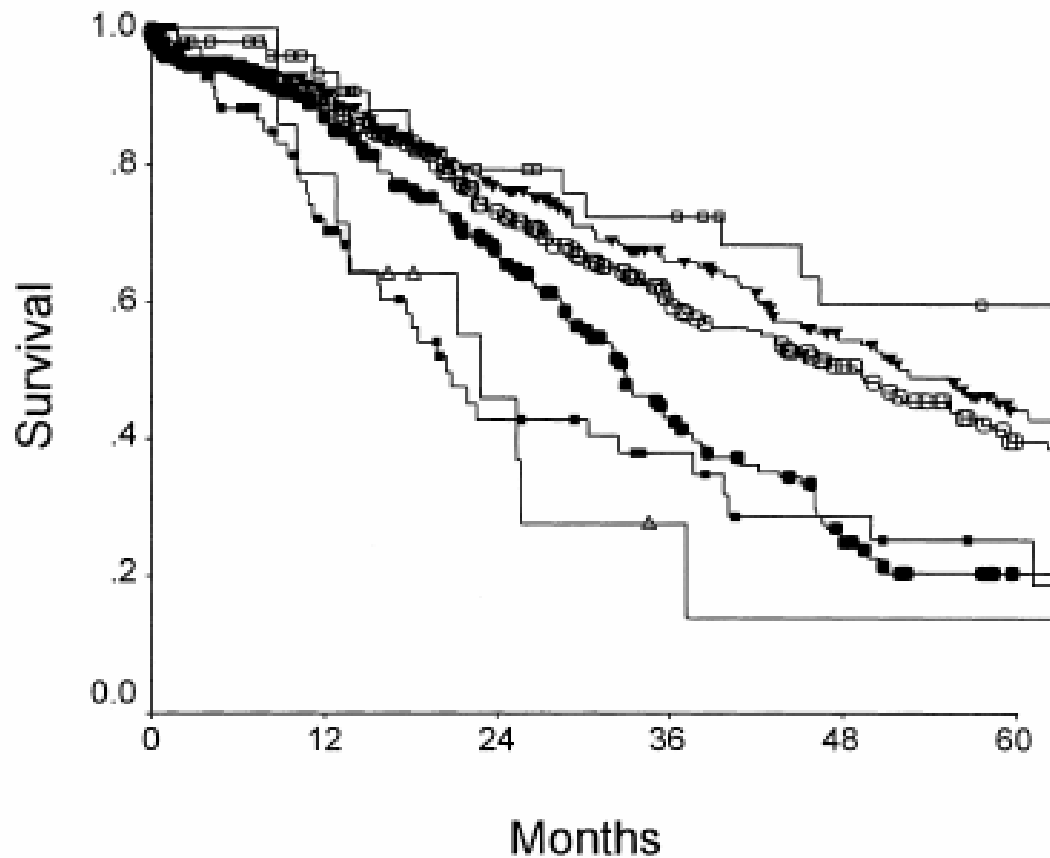


# Il trattamento delle metastasi epatiche operabili: Timing della chemioterapia 21 Ottobre 2011

Emiliano Tamburini  
U.O. Oncologia  
Rimini

## **Quale ruolo per la chemioterapia sistemica nella malattia resecabile?**

- preoperatoria**
- post operatoria**
- perioperatoria**



**Figure 3.** Survival after hepatic resection as related to clinical risk score. Open box: score = 0 (n = 52); filled triangle: score = 1 (n = 262); open circle: score = 2 (n = 350); filled circle: score = 3 (n = 243); filled box: score = 4 (n = 80); open triangle: score = 5 (n = 14).  $p < 0.0001$ .

**Table 5. CLINICAL RISK SCORE FOR TUMOR RECURRENCE**

Score	Survival (%)					Median (mo)
	1-yr	2-yr	3-yr	4-yr	5-yr	
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

Each risk factor is one point: node-positive primary, disease-free interval <12 months, >1 tumor, Size >5 cm, CEA >200 ng/ml.

Mumble,  
Mumble....



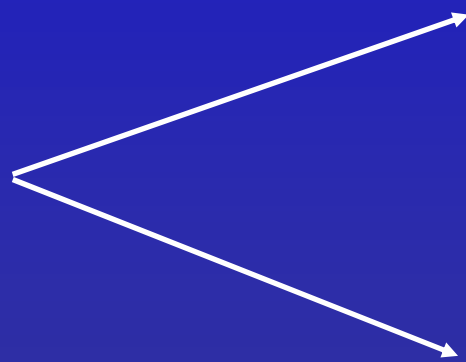
# Trattamento adiuvante dopo R0

**S  
U  
R  
G  
E  
R  
Y**

**R**

**LV5FU X 6m**

**Osservazione**

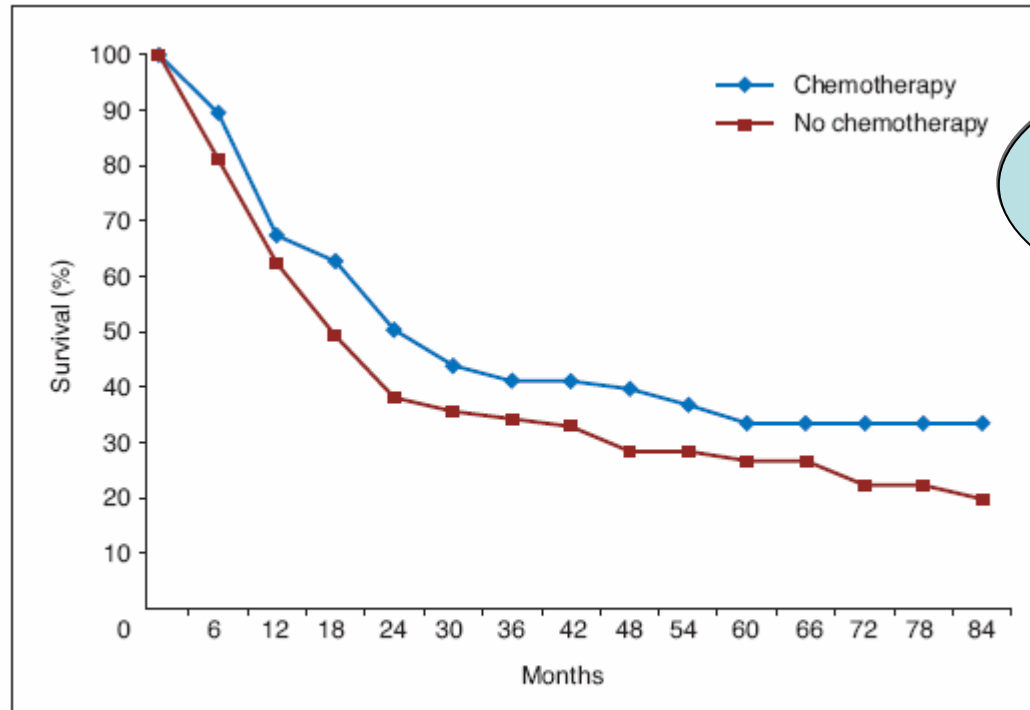


418 pazienti per evidenziare un aumento della sopravvivenza dal 30 al 45% a 5 y ponendo  $\alpha = 5\%$  e  $\text{Beta} = 90\%$

The aim of the study was to detect a 20% absolute difference in the 2-year disease-free survival between the control group and the treated group (20% to 40%). With a two-sided  $\alpha$  risk of 5% and a power of 90%, 200 patients were required, 134 events were expected.

R0 epatica o polmonare  
129 pazienti arruolati

<b>Trials</b>	<b>No pz</b>	<b>DFS</b>	<b>Δ DFS</b>	<b>OS</b>	<b>Δ OS</b>
<b>ENG</b>	107	45%vs35% (p=0,35)	+10% (4y)	57%vs47% (p=0,39)	+10% (4y)



R0 chirurgico, malattia epatica  
171 pazienti arruolati

**Fig 1.** Disease-free survival after liver resection according to whether patients received chemotherapy.

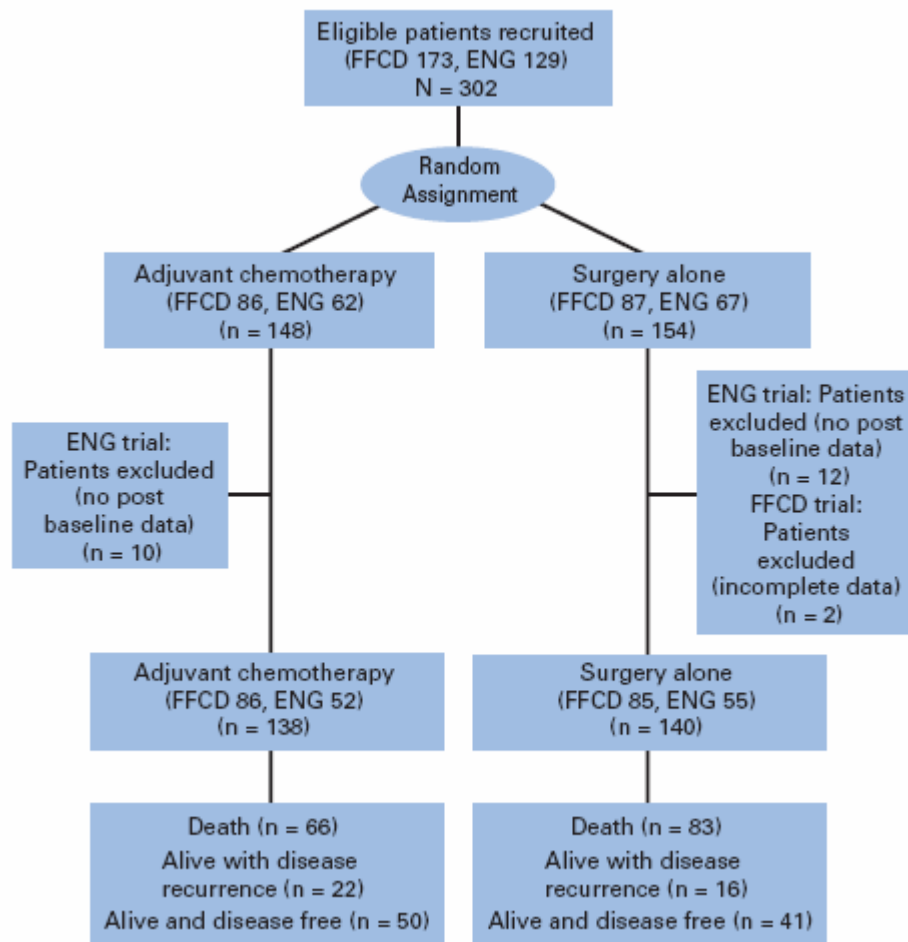
<b>Trials</b>	<b>No pz</b>	<b>DFS</b>	<b>Δ DFS</b>	<b>OS</b>	<b>Δ OS</b>
<b>FFCD</b>	171	33,5 vs 26,7 (p=0,028)	+6,8% (5y) +12,3(2y)	51,1%vs41,9% (p=0,13)	+9,2% (5y)

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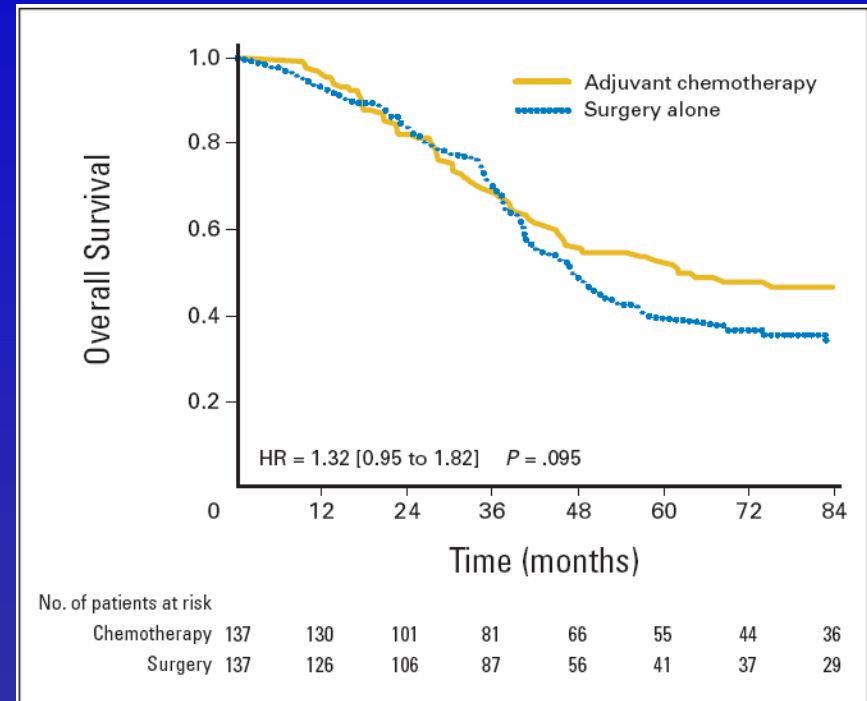
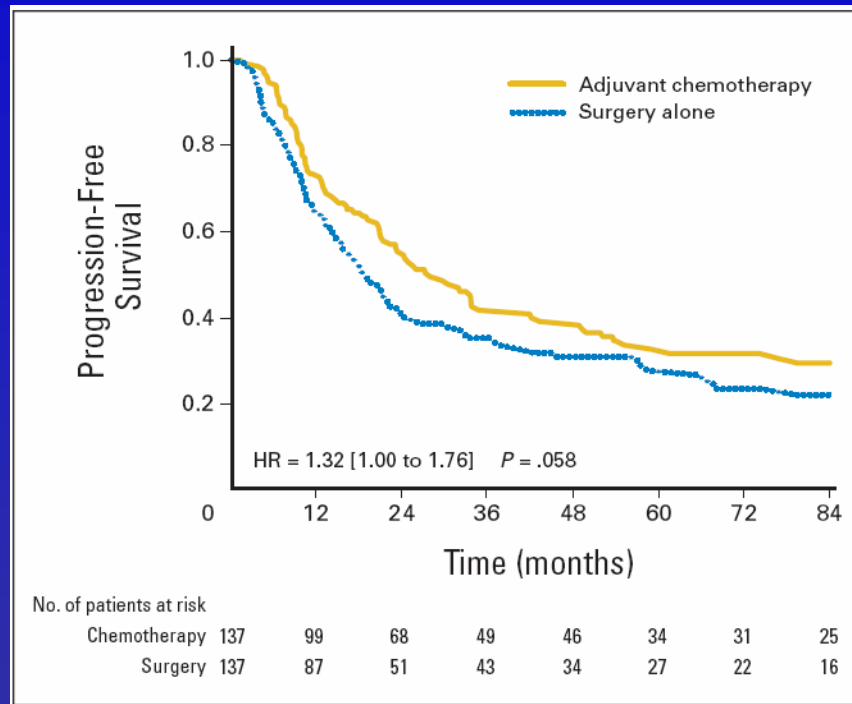
Portier, G. et al. J Clin Oncol 2006; 24:4976-4982.  
Langer B et al, ASCO 2002 Abstr 592.

## Adjuvant Chemotherapy After Potentially Curative Resection of Metastases From Colorectal Cancer: A Pooled Analysis of Two Randomized Trials

Emmanuel Mitry, Anthony L.A. Fields, Harry Bleiberg, Roberto Labianca, Guillaume Portier, Dongsheng Tu, Donato Nitti, Valter Torri, Dominique Elias, Chris O'Callaghan, Bernard Langer, Giancarlo Martignoni, Olivier Bouché, Franck Lazorthes, Eric Van Cutsem, Laurent Bedenne, Malcolm J. Moore, and Philippe Rougier



. With a total of 149 deaths and 38 recurrences without death in the pooled database, this pooled analysis should have 80% power at a two-sided .05 level to detect a hazard ratio (HR) of 0.66 in DFS between the two arms (corresponding to a reduction from 40% to 28.6% in 2-year relapse rate with adjuvant chemotherapy) and an HR ratio of 0.63 in OS between the two arms (corresponding to an increase from 30% to 46.8% in 5-year OS with adjuvant chemotherapy).



PFS 5y 36,7% vs 27,7%  
OS 5y 52,8% vs 39,6%

Trials	Pz	$\Delta$ PFS	$\Delta$ OS
ENG	107	+10% (4y)	+10% (4y) P=0,39
FFCD	171	+12,3% (2y) +6,8% (5y)	-0,9% (2y) +9,2% (5y)
Pooled Analysis	278	+15,1% (2y) +9% (5y) P=0,058	-1,6% (3y) +13,2% (5y) P=0,095

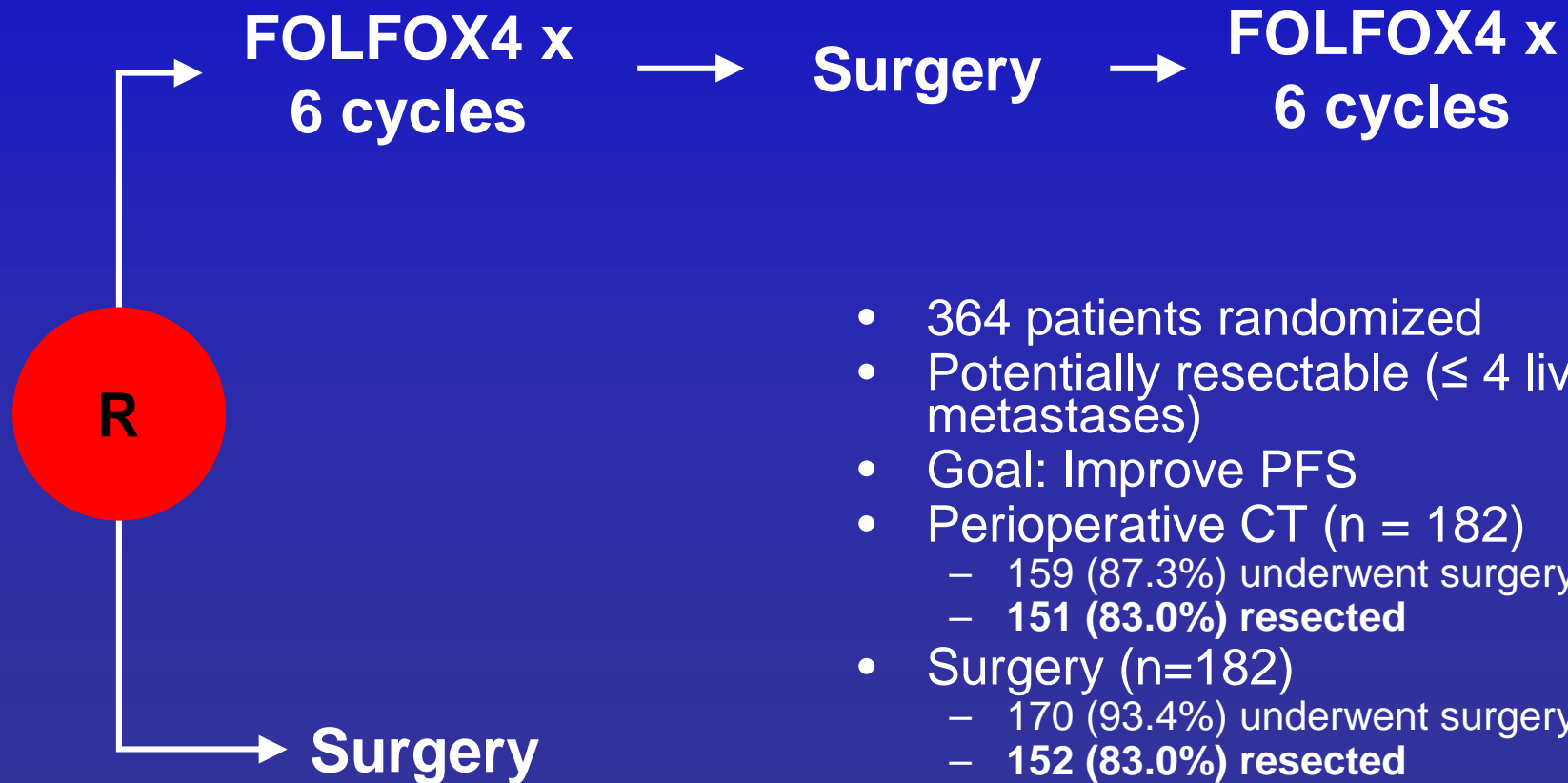
Dal 30 al 40% ( $\Delta$ +10%)  
(Alfa=5% Beta=90%)



960 pz!

# Trattamento Perioperatorio dopo R0

## EORTC 40983 (EPOC Trial)



- 364 patients randomized
- Potentially resectable ( $\leq 4$  liver metastases)
- Goal: Improve PFS
- Perioperative CT (n = 182)
  - 159 (87.3%) underwent surgery
  - **151 (83.0%) resected**
- Surgery (n=182)
  - 170 (93.4%) underwent surgery
  - **152 (83.0%) resected**

Nordlinger B, et al. ASCO 2007 Abstract LBA5

Nordlinger B et al, Lancet 2008 ; 371 : 1007-1016

The study was planned to detect a 40% increase in median progression-free survival, or equivalently an increase of the 3-year progression-free survival from 21·0% to 32·8%, in all patients randomly assigned to perioperative chemotherapy (hazard ratio [HR]=0·714) with 80% power at a two-sided 5% significance level, requiring 278 events. The trial was expected to provide this number of events after 6·5 years. However, at 6·5 years after trial start (Sept 20,

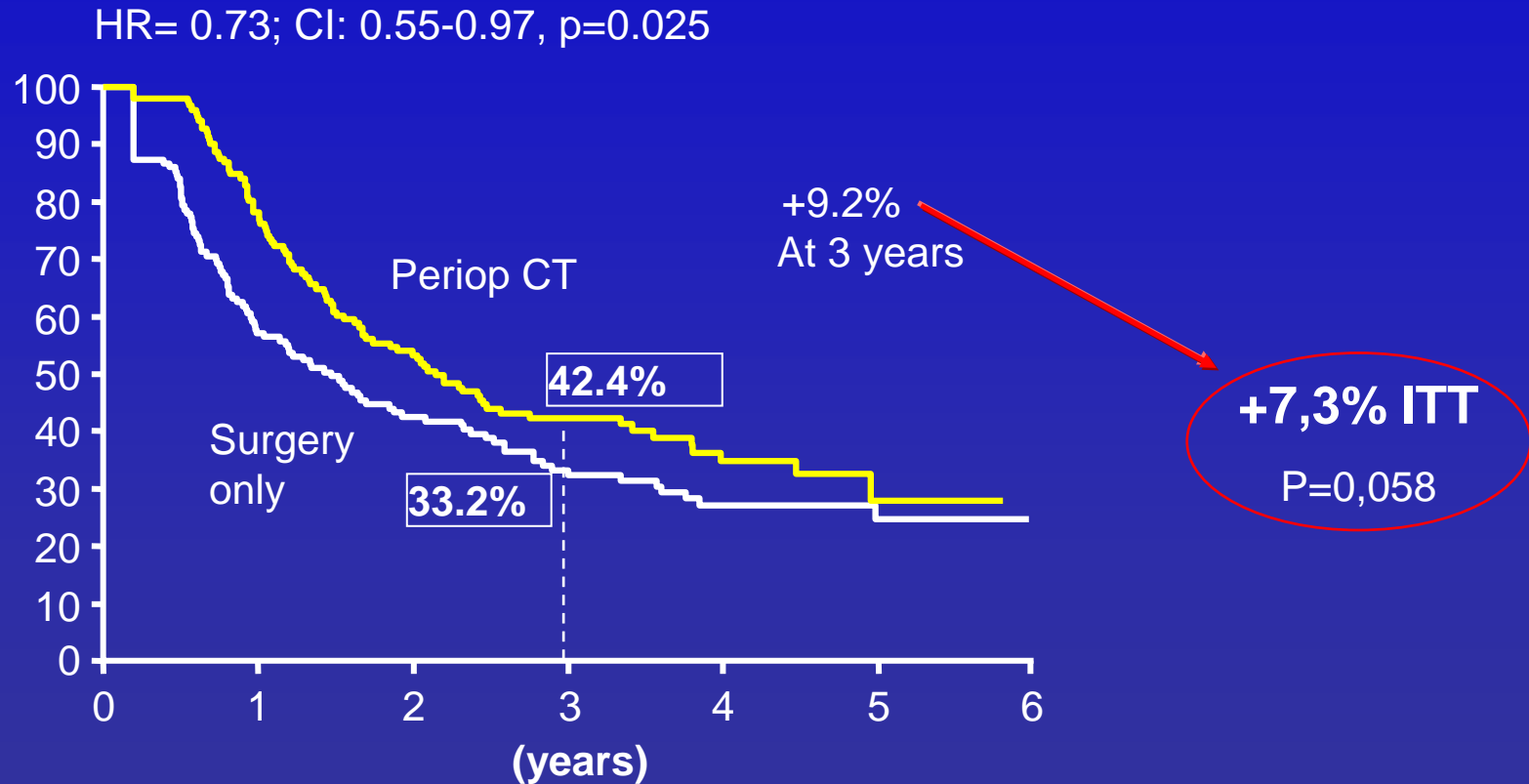


78 ospedali in 6,5 anni

364

0,7 pazienti anno per centro!!!!

# EORTC 40983: Progression-Free Survival in Resected Patients

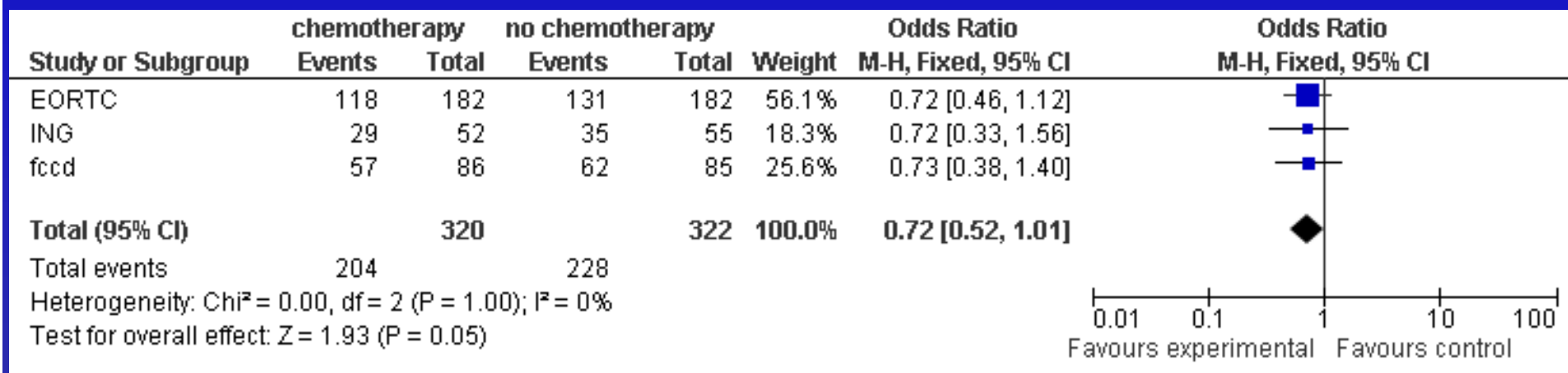


Number of patients at risk :

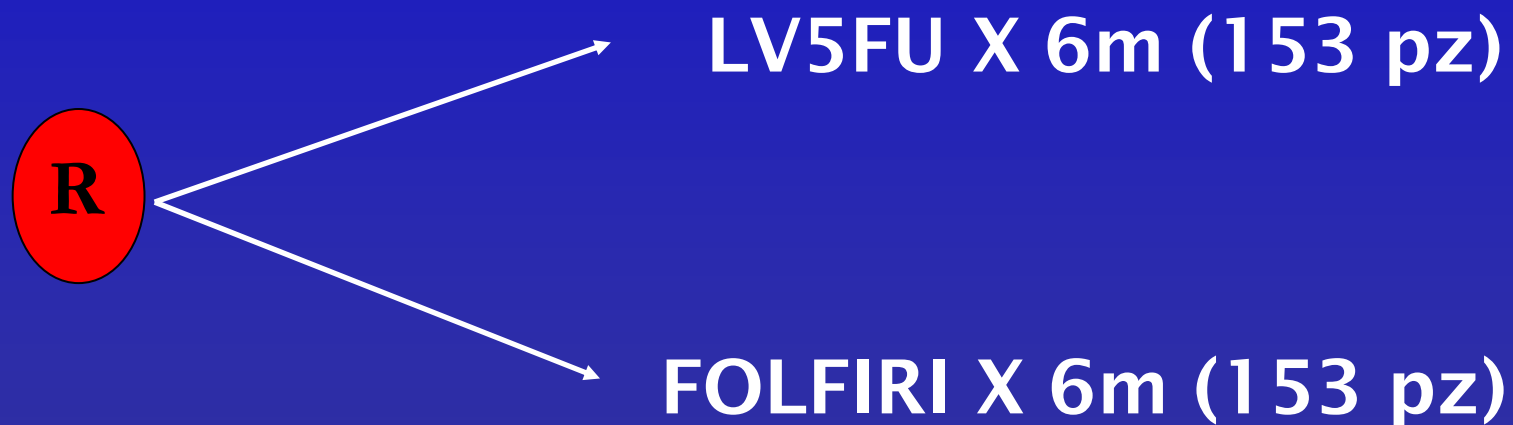
Surgery only	152	85	59	39	24	10
Periop CT	151	118	76	45	23	6

- **Conferma del vantaggio clinico nell'ordine del 1'8-10%**
- **Chemioterapia preoperatoria può essere presa in considerazione anche nel paziente con malattia resecabile**
- **Riduzione delle laparotomie inutili dal 10 al 4%**
- **Solo 14 pazienti (7,7%) ha avuto una progressione durante il trattamento preoperatorio (7 dei quali sono stati comunque portati ad R0 chirurgica)**

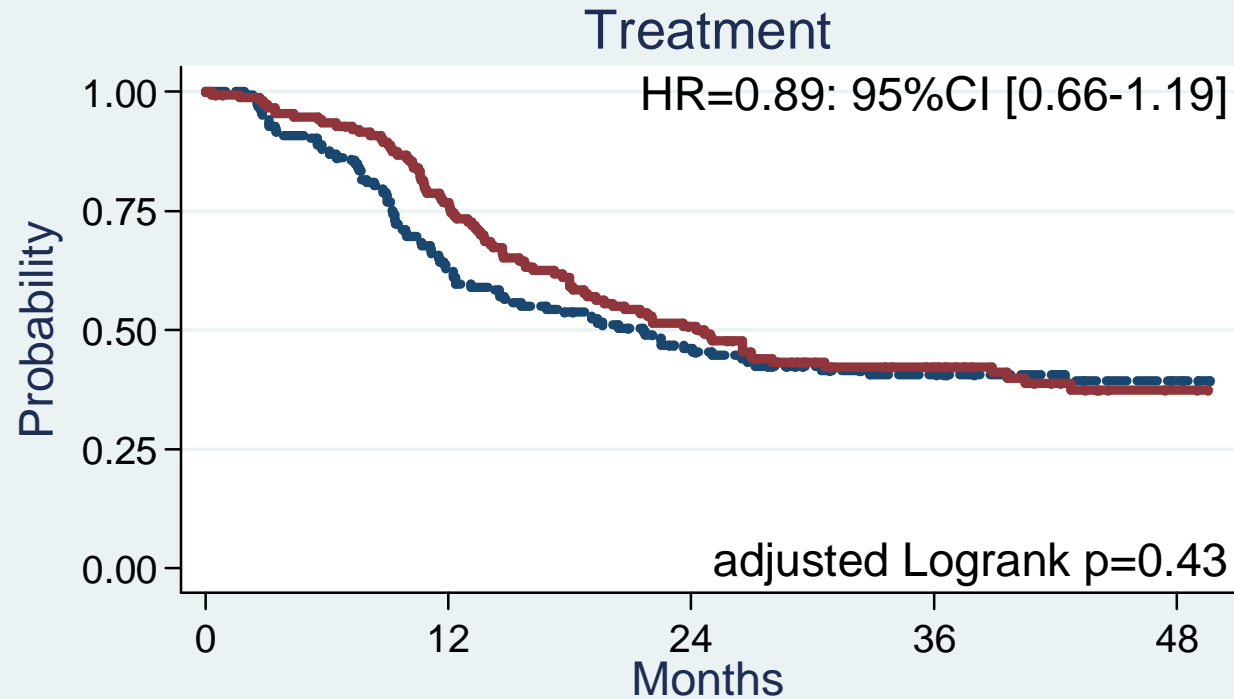
Trials	Pz	Braccio Standard	Braccio sperimentale	Δ PFS
ENG	107	S	S→5FU 6m	+10% (4y)
FFCD	171	S	S→5FU 6m	+12,3% (2y) +6,8% (5y)
Pooled Analysis	278	S	S→ 5FU 6m	+15,1% (2y) +9% (5y) P=0,058
EORTC	364	S	CT→S→CT	+7,3 /9,2 (3y)



# Adiuvante dopo R-0 per metastasi epatiche



# Disease-Free Survival



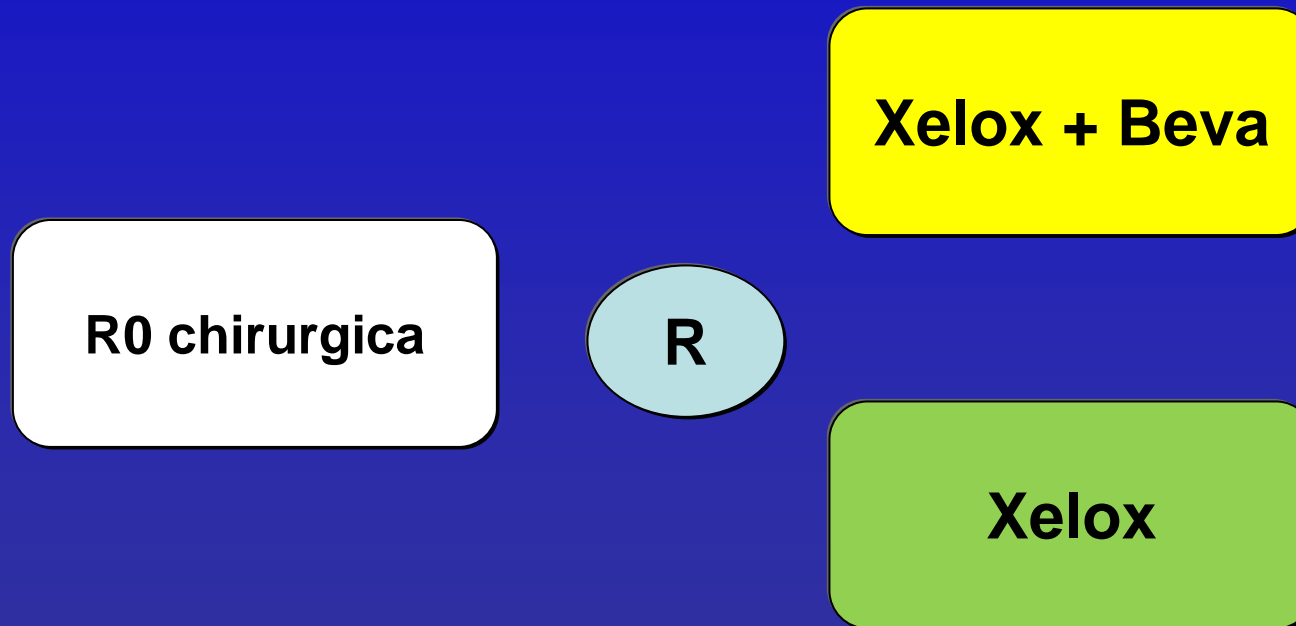
Number at risk

LV5FUs	153	95	65	44	25
LV5FUs+IRI	153	114	70	41	22

--- LV5FUs    — LV5FUs+IRI

**1-year DFS: 63% vs. 77%**  
**2-year DFS: 46% vs. 51%**

# Adiuvante dopo R-0 per metastasi epatiche Hepatica Trial



hypothesized that the addition of bevacizumab to CAPOX would result in a decrease of at least 1/3 of the hazard of progression (HR = 0.67) [34-36]. The total number of events that is necessary to provide 80% power to detect such a decrease, if truly present, with a 2 tailed logrank test at 5% significance is 191. Assuming

Hepatica Trials	Braccio Standard	Braccio sperimentale	P value
Paz	39	40	
2 year DFS	70%	52%	0,072

## Paziente 1

- Cea >200
- piu di 1 metastasi
- DFS < 12 mesi
- pN +

- Selezionare
- Aggredire precocemente le micrometastasi

Neoadiuvante

## Paziente 2

- Cea nei limiti
- 1 lesione di 2 cm
- DFS di 30 mesi
- pN0 primitivo

- Aggredire la malattia

Chirurgia

# Conclusioni

- Problema dell'arruolamento
- Ampia eterogeneità fra i pazienti
- Mancanza di standardizzazione chirurgica
- Un trattamento chemioterapico della durata di 6 mesi in questo setting andrebbe sempre considerato.
- Non ci sono dati circa la migliore sequenza
- Nessun ruolo dimostrato per gli agenti target
- Nessun ruolo per il cpt-11

*Ricordati che per il singolo paziente la statistica ha solo 2 possibili valori: zero e cento*