



# *Metastasi epatiche da Carcinoma del Colon-Retto*

*Paziente con metastasi epatiche non  
resecabili wild type*



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Negrar 18 Ottobre 2016



# Dati del paziente

- donna, età: 64 aa
- Anamnesi patologica:  
Ipertensione arteriosa in terapia farmacologica:
  - Bisoprololo 2,5 mg ½ cp/dieNon assume altri farmaci a domicilio

# presentazione clinica

- Febbraio 2014: episodi diarroici ricorrenti associati ad addominalgic. In precedenza alvo riferito normale
- Perdita di peso (circa 4 Kg negli ultimi 3 mesi)
- Esegue esami bioumorali su consiglio del curante con riscontro di anemia: Hb 8,9 g/dL
- Giunge in PS per febbre e leggera dispnea
- - Rx torace: addensamento parenchimale con versamento pleurico lobo inferiore sx
- - Ecografia addome sup-inf: evidenza di 4 formazioni espansive lobo epatico dx; sensibile ispessimento concentrico delle pareti del colon a livello della flessura splenica

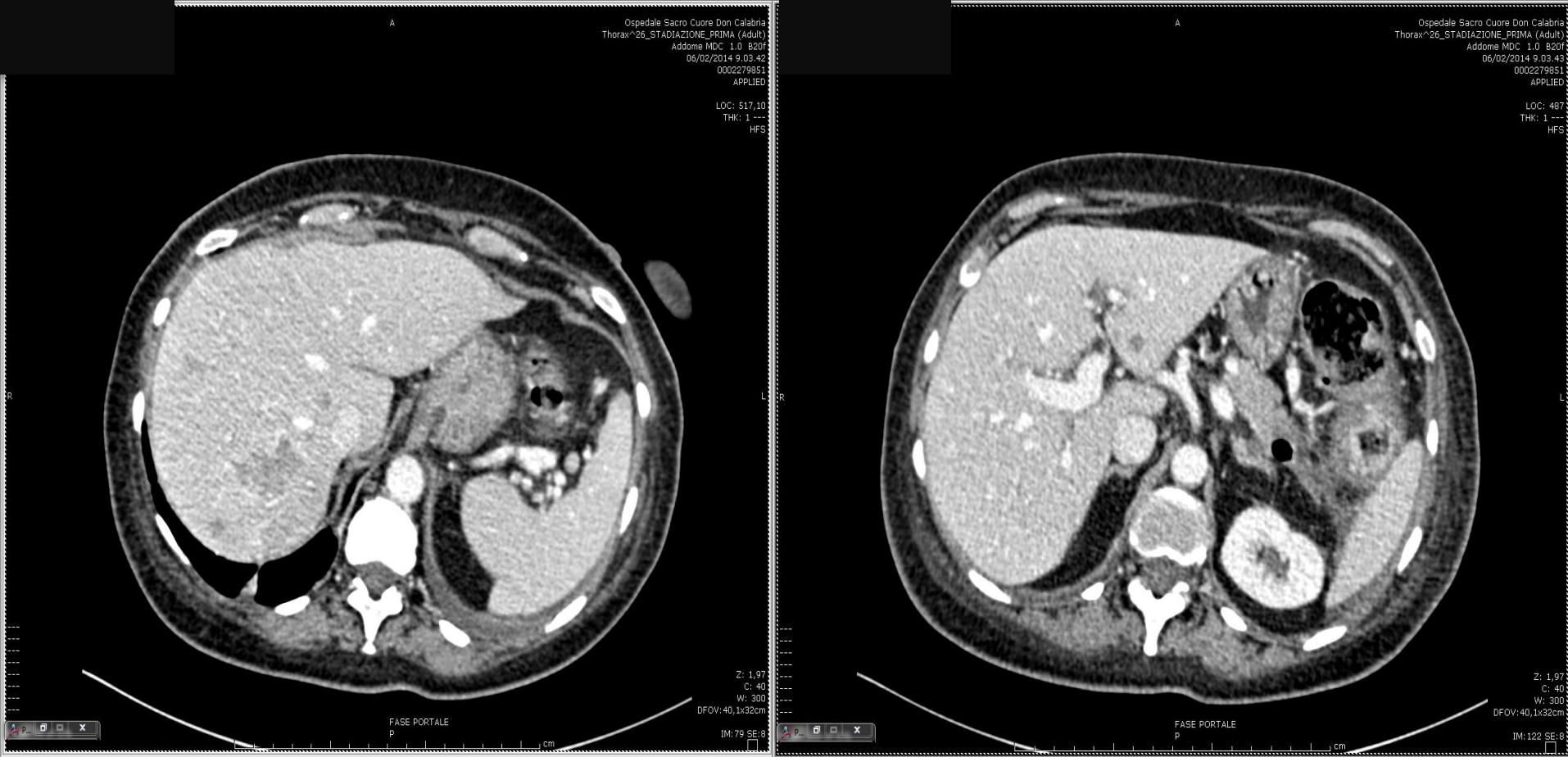
**Febbraio 2014**  
**Ricovero presso la locale Medicina**



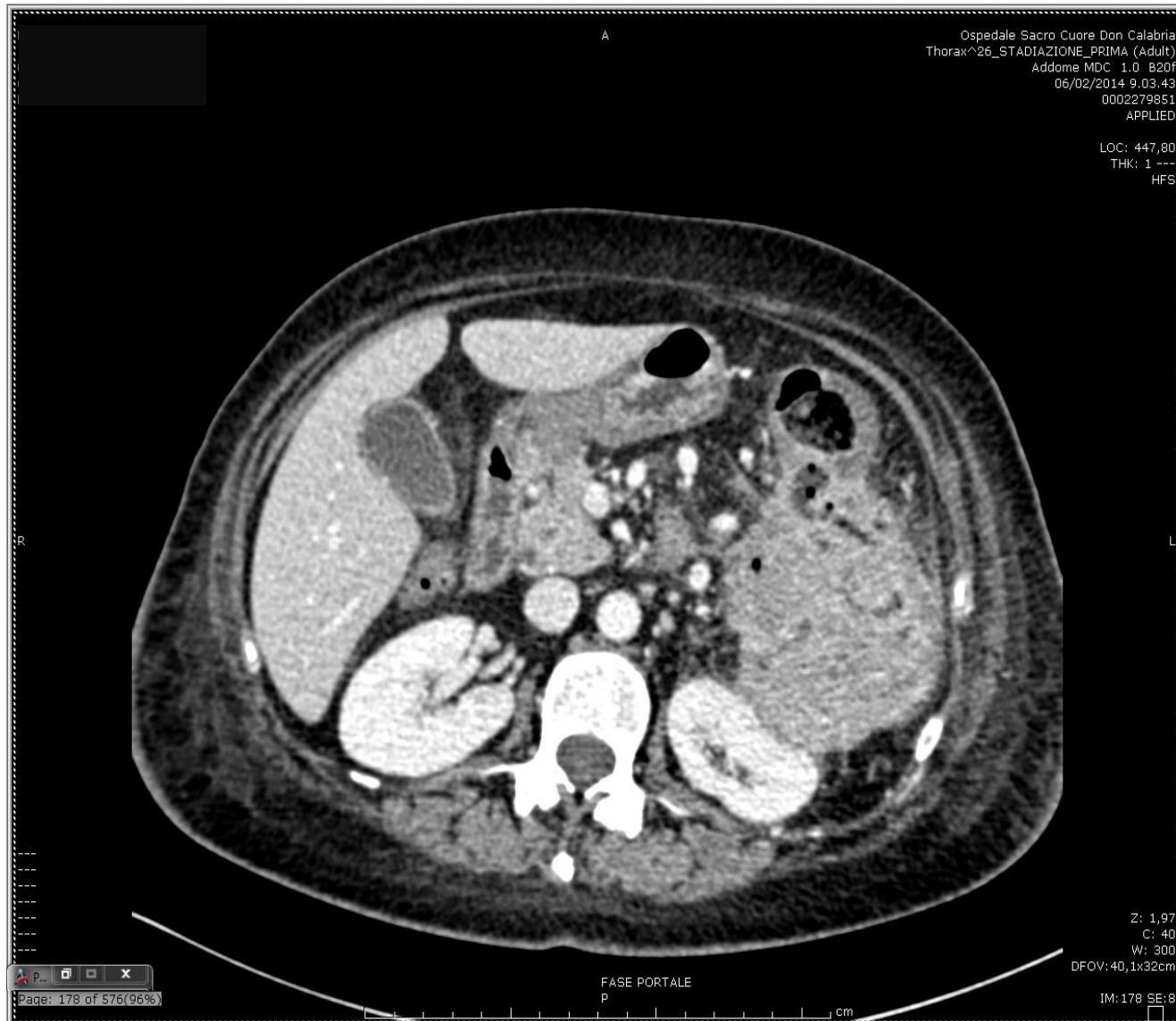
- EO: epatomegalia con margine inferiore a 2 cm circa dal margine costale
- Esami bioumorali: anemia, CEA 7.5 microgr/L funzionalità epatica e renale nella norma.

**Colonscopia**: a 40 cm dal margine anale manicotto stenosante superato a fatica dallo strumento pediatrico esteso per circa 10 cm: **Adenocarcinoma**





**TAC torace-addome:**  
plurime neoformazioni nodulari epatiche la maggiore del diametro di 35 mm a livello del lobo dx (S7). Cospicuo ispessimento delle pareti del colon discendente con evidenza di formazione espansiva del diametro di circa 10 cm che raggiunge lo spazio perirenale sx e apparentemente infiltrata il rene omolaterale.  
Conferma di versamento pleurico sx con atelettasia del lobo inferiore



- 20/02/14 **Laparotomia**

**voluminosa neoplasia a livello angolo colico sx coinvolgente Rene sx e Milza. Conferma di multiple neoformazioni epatiche coinvolgenti entrambi i lobi**

**Resezione chirurgica con nefrectomia/surrenalectomia sx,  
splenectomia ed ovariectomia sx**

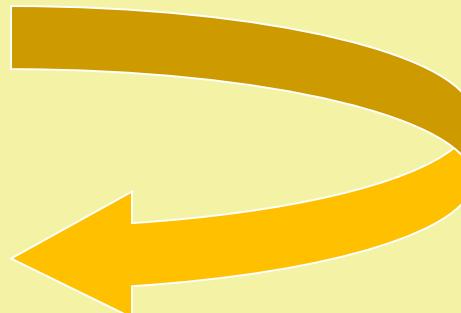


- Adenocarcinoma G2 del diametro di 9 cm con infiltrazione della parete a tutto spessore; non segni di sconfinamento nel tessuto adiposo peritumorale con presenza di ampie aree di flogosi a carattere ascessuale prive di colonizzazione neoplastica.
- Rene e surrene sx, milza ed ovaio sx esenti da malattia
- Infiltrato infiammatorio peritumorale presente
- Invasioni vascolari e perineurali non evidenti
- Budding tumorale non evidente
- N 0/35
- Liquido di lavaggio peritoneale con assenza di cellule neoplastiche

**Stadio pT2N0M1**

# Iter terapeutico

RAS/BRAF wild type



**2/4/2014 FOLFIRI + Cetuximab**

**7/2014 restaging dopo 6 cicli**

- TAC torace – addome seguita da RMN addome sup:**  
riduzione numerica e volumetrica delle neoformazioni epatiche alla TAC che appaiono ad aspetto calcifico. Alla RMN 5 lesioni, le maggiori in S7 (16 mm), al passaggio S6/S7 di 12 mm. Altre 3 lesioni con dimensioni tra 4 e 6 mm. Apparente coinvolgimento esclusivo sul lobo dx

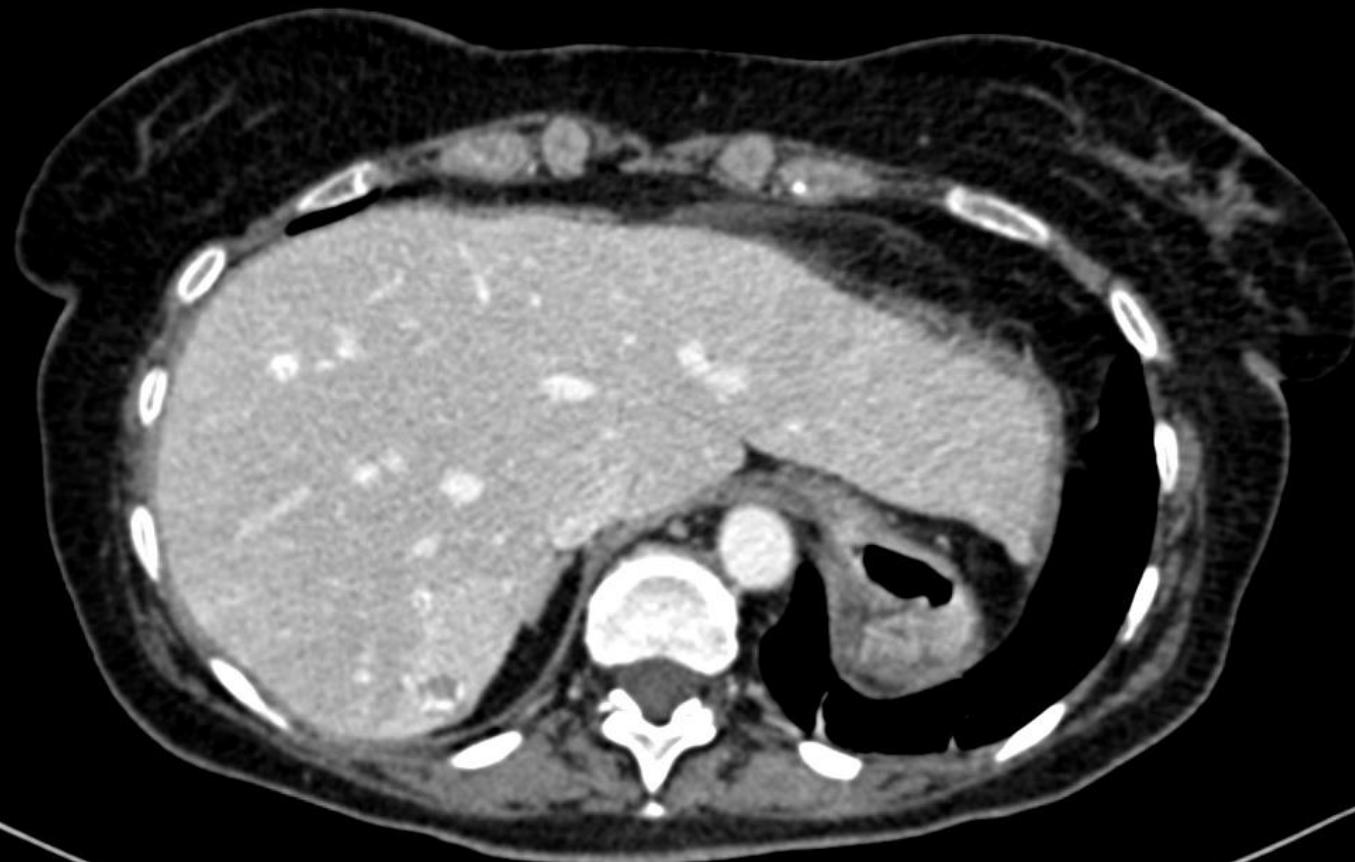
Tromboembolia polmonare su rami dx e sx asintomatica

CEA normalizzato già dopo 2 cicli

PS 0

A

Ospedale Sacro Cuore Don Calabria  
TAC ADDOME COMPLETO MDC  
Addome MDC 1.0 B20f  
02/07/2014 13.31.21  
0002331791  
APPLIED  
LOC: 583,40  
THK: 1 ---  
HFS



FASE PORTALE

P

cm

Z: 1,97  
C: 72  
W: 384  
DFOV: 43,9x35cm

IM: 108 SE: 9

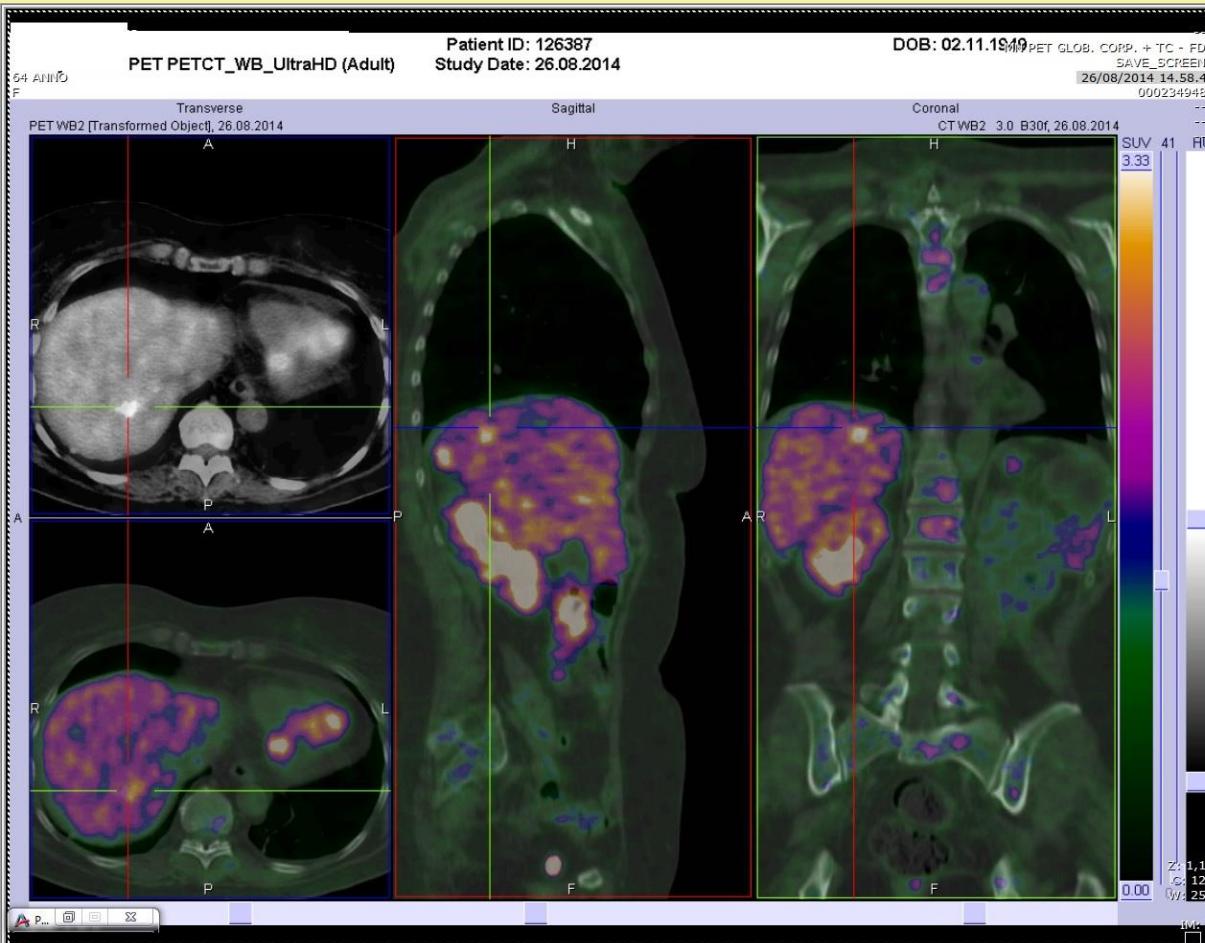


# Luglio 2014: prosegue trattamento FOLFIRI + Cetuximab

Agosto/Settembre 2014: restaging dopo ulteriori 4 cicli (10 in totto)

- **PET-TC con fdg:**

si segnalano 4 aree ipermetaboliche subcentimetriche al lobo epatico dx.  
Non apparenti localizzazioni a sx.



- **TAC Torace Addome:**

quadro invariato rispetto al precedente di Luglio.  
Regredita la TEP

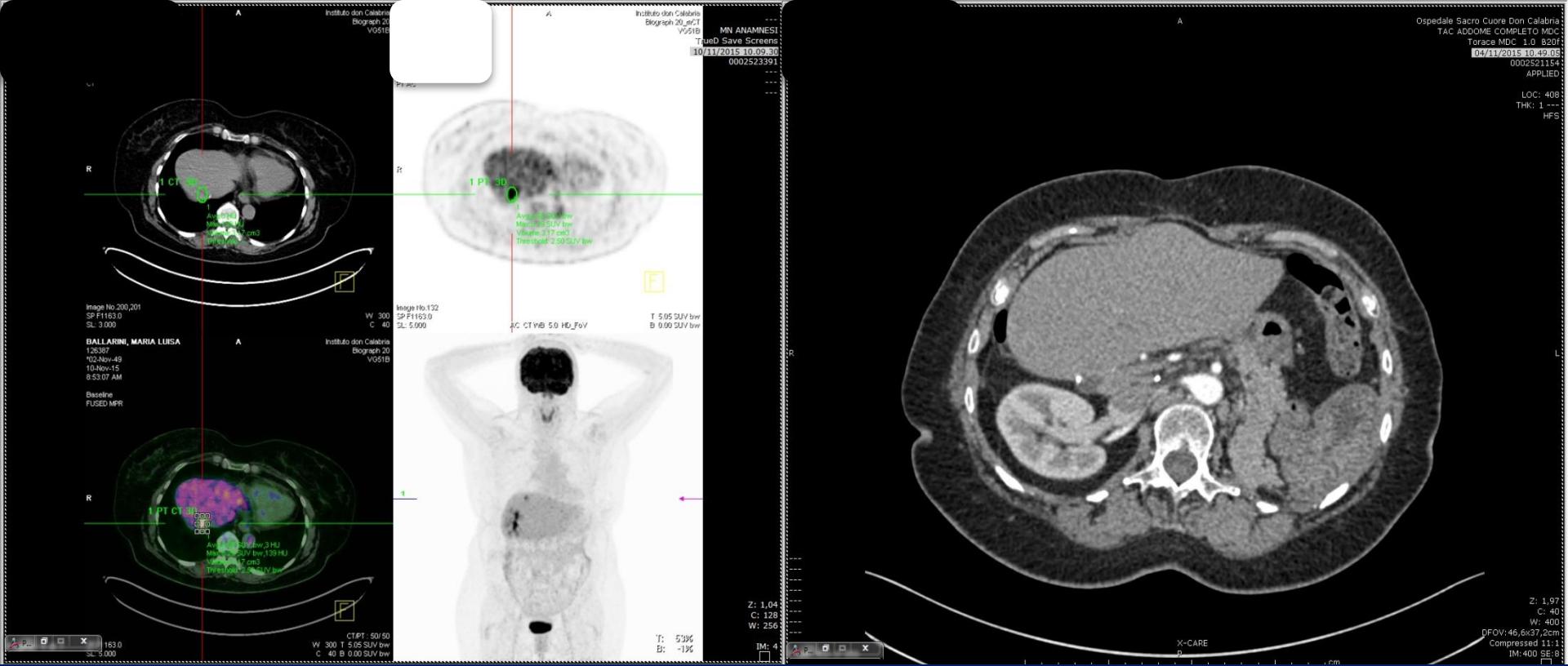
# Iter terapeutico

Settembre 2014:  
Eseguiti 10 cicli in toto FOLFIRI + Cetuximab

- 9/10/2014: esplorazione chirurgica con ecografia intraoperatoria  
conferma di malattia a dx ed assenza di coinvolgimento a livello del lobo sx.  
Legatura del ramo dx della v. porta e colecistectomia
- 17/11/2014: epatectomia dx allargata  
si riconoscono 4 focolai metastatici associati ad aree necrotico- calcifiche

Gennaio 2015:  
Ristadiazione dopo circa 8 settimane dalla chirurgia  
TAC torace addome: assenza di malattia

**FOLLOW UP**



Ottobre 2015:

TAC torace addome:

“nei settori dorsali del parenchima epatico in adiacenza alla vena cava inferiore e clips chirurgiche si riconosce lesione focale solida del diametro di 14 mm”

PET-TC fdg:

“conferma della lesione segnalata alla TAC (15 mm, SUV8) ed evidenza di altre 3 piccole focalità di incerto significato

# **dal 16/11/2015 riprende FOLFIRI + Cetuximab**

**Febbraio 2016** restaging dopo 4 cicli

**- TAC torace – addome:**

riduzione volumetrica della recidiva epatica (da 14 mm a 7 mm)

**- PET -TC fdg:**

non si segnalano accumuli focali in sede epatica ma solo modeste disomogeneità di distribuzione del tracciante in assenza di chiari accumuli

**11/4/2016:**

relaparotomia esplorativa con ecografia intraoperatoria che conferma unica lesione paracavale dx.

**Resezione epatica atipica comprendente la lesione**

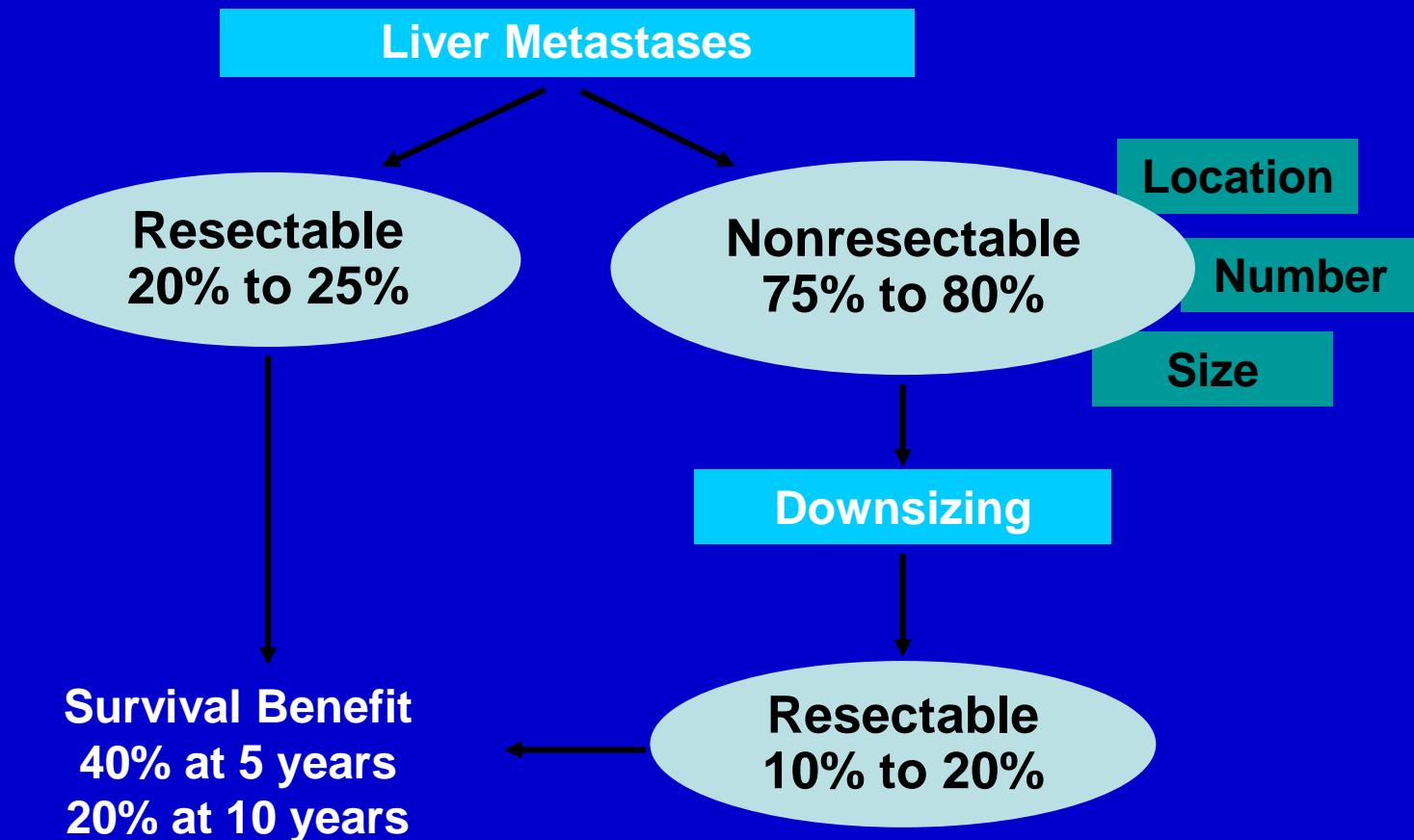
**FOLLOW UP**

32 mesi dalla chirurgia sul primitivo  
11 mesi: Intervallo libero da malattia

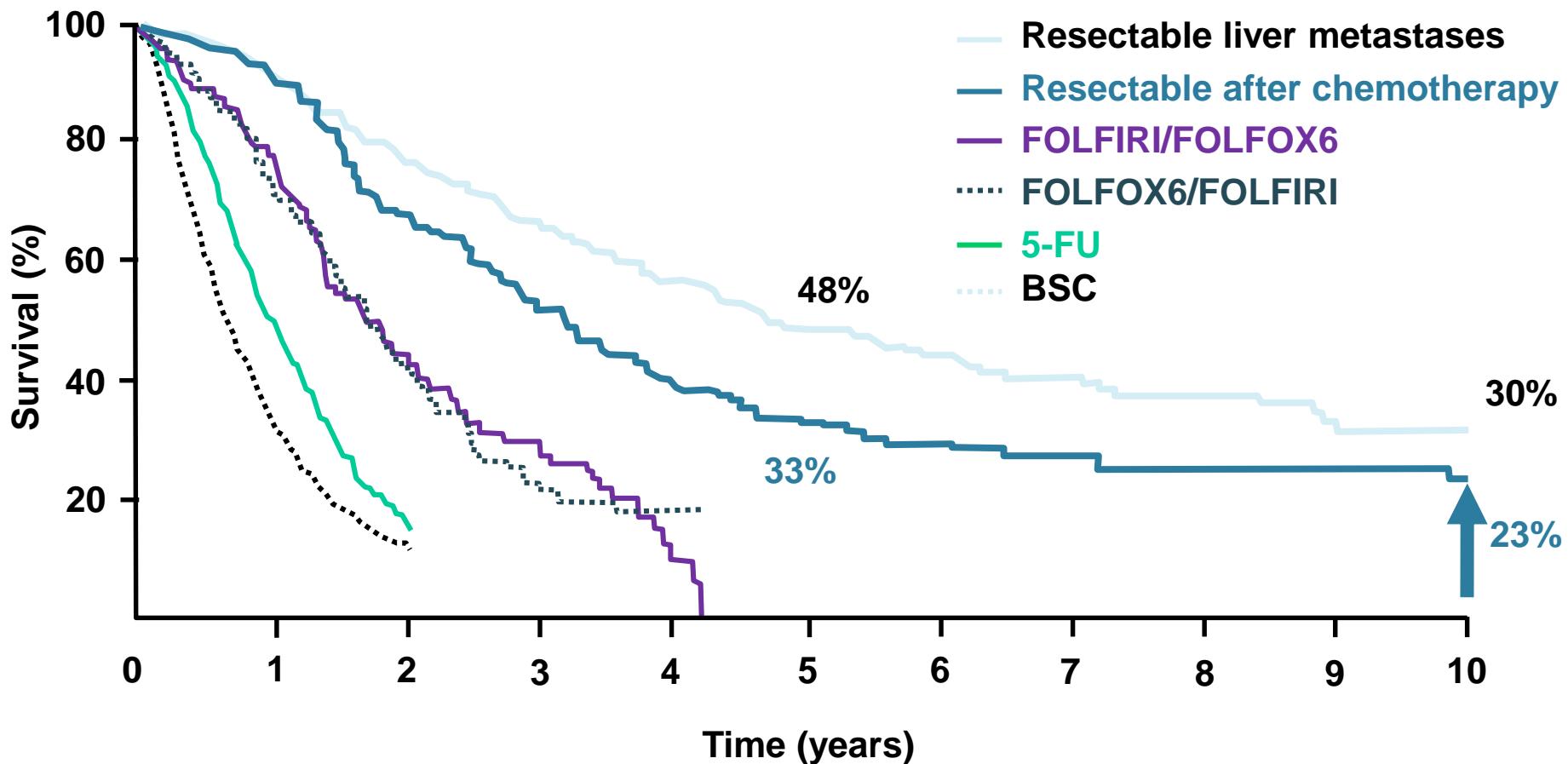
# Liver Metastases in Colorectal Cancer: Outcomes

Approximately 20 to 30% of pts have liver only metastases on diagnosis

Approximately 30 to 40% of pts have liver-only metastases at recurrence

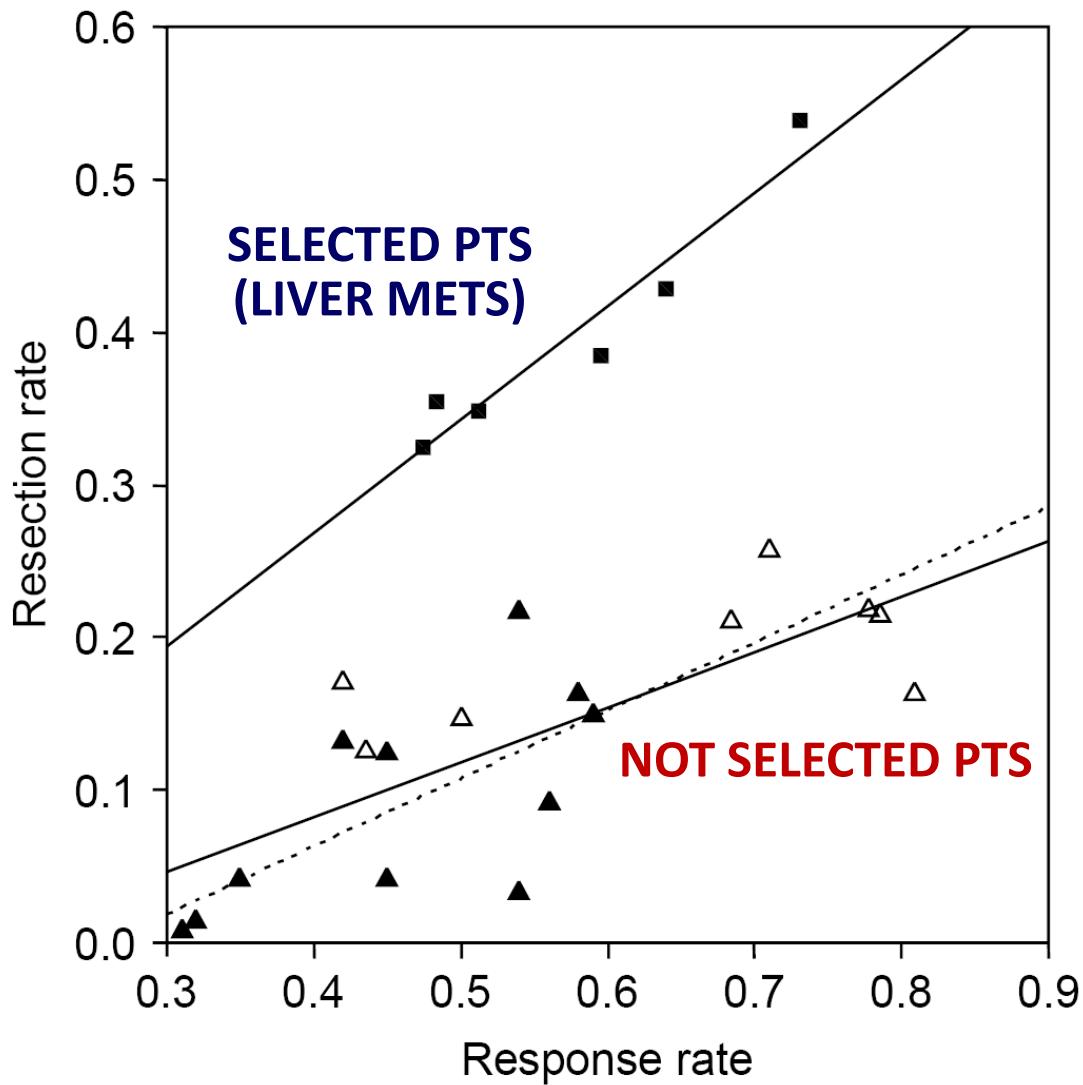


# OS dopo chemioterapia e resezione di metastasi epatiche



Colon Cancer Collaborative Group, Br Med J 2000; Tournigand et al, J Clin Oncol 2004;  
Adam et al, Ann Surg 2004

# Tumour response and resection rates



## Rate of liver resection following CT

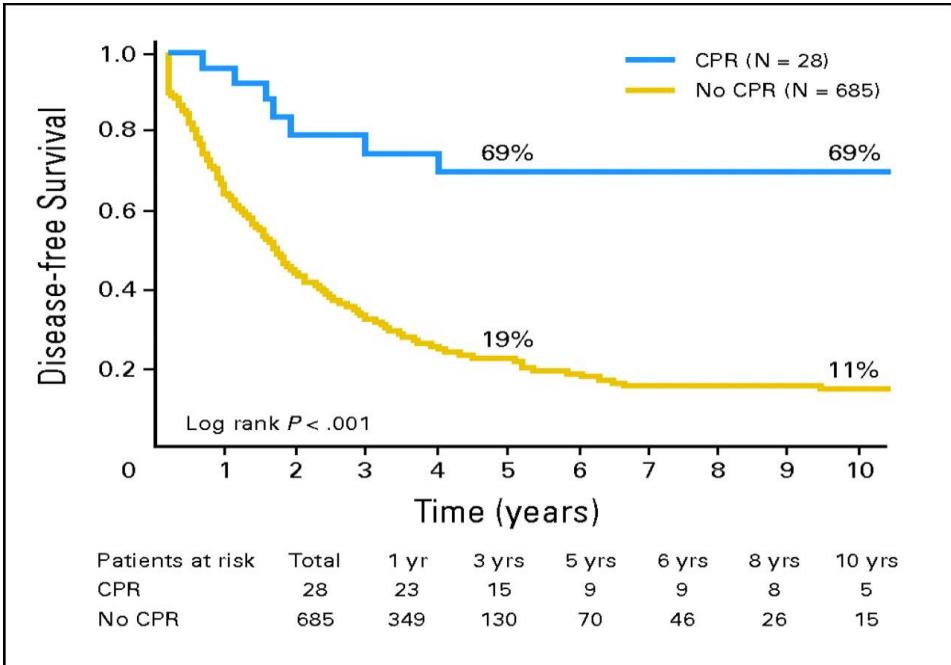
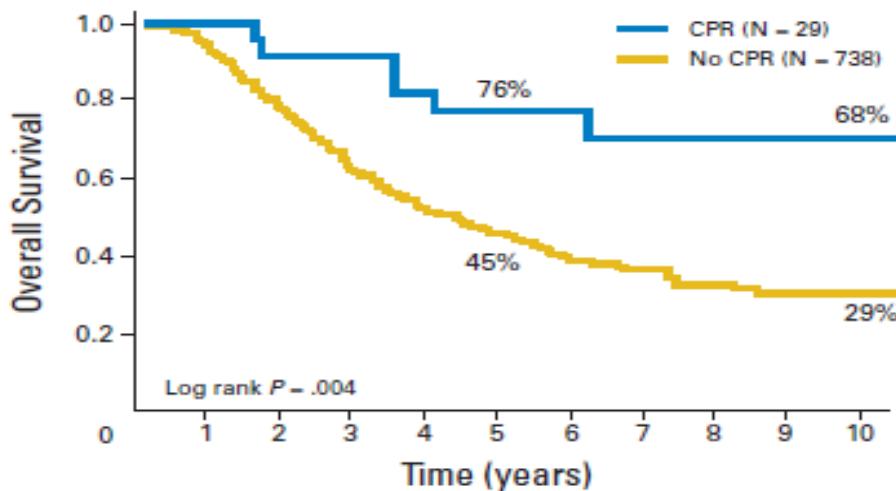
- Data from studies/retrospective analyses with “selected pts”, only liver MTS ( $r=0.96$ ) ( $p=0.002$ )
- △ Data from studies/retrospective analyses with “non selected pts” ( $r=0.74$ ) ( $p<0.001$ ), solid line
- ▲ Not selected pts: only phase III trials ( $r=0.67$ ) ( $p=0.024$ ), dashed line

## Complete Pathologic Response After Preoperative Chemotherapy for Colorectal Liver Metastases: Myth or Reality?

René Adam, Dennis A. Wicherds, Robbert J. de Haas, Thomas Aloia, Francis Lévi, Bernard Paule, Catherine Guettier, Francis Kunstlinger, Valérie Delvart, Daniel Azoulay, and Denis Castaing

## Fattori predittivi di risposta patologica completa

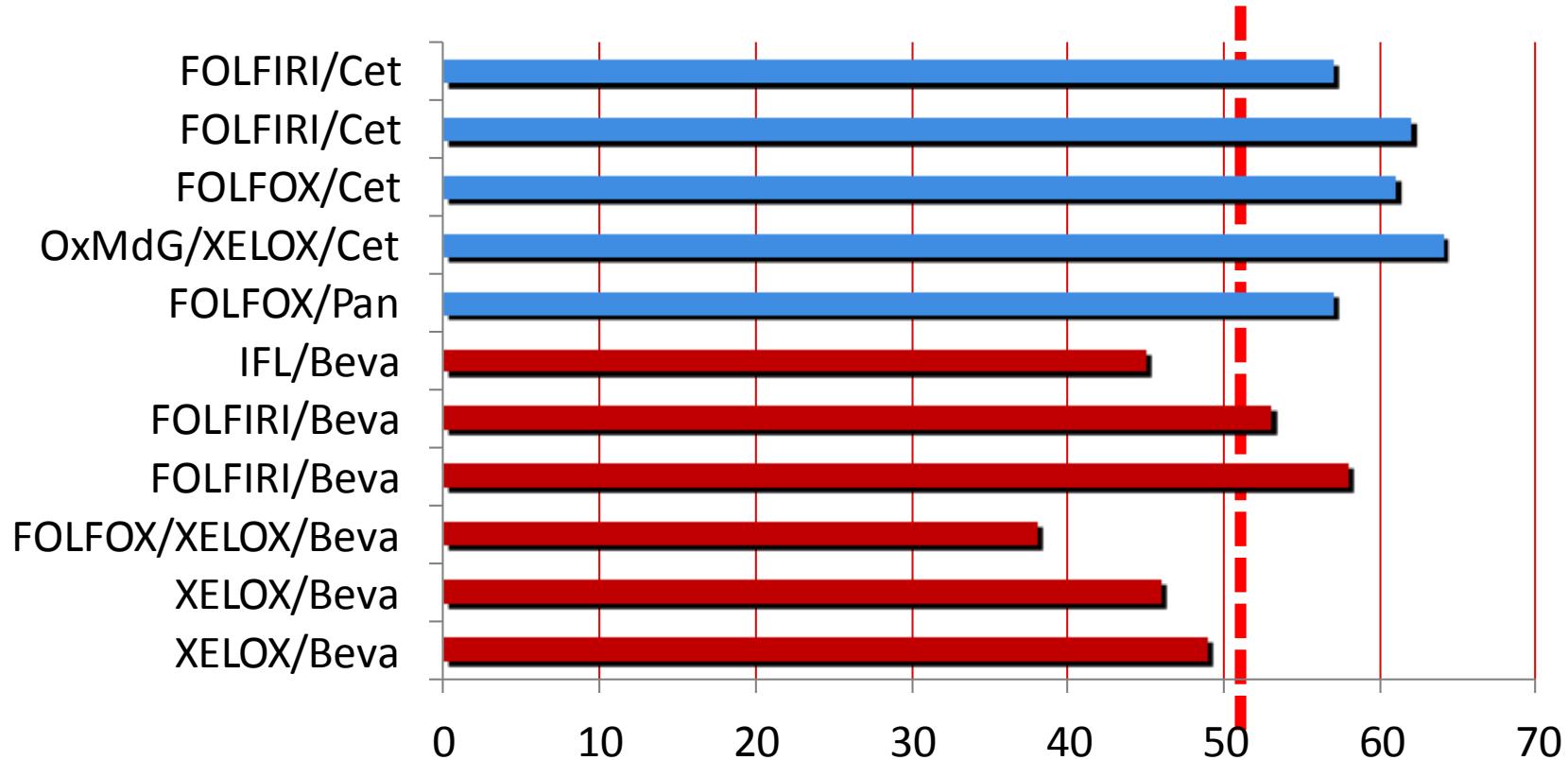
	<b>p</b>	<b>RR</b>
Età ≤60 anni	0,03	4,1
Diametro ≤3 cm	0,05	3,1
CEA ≤30 ng/ml	0,03	5,6
cCRC/RP dopo CHT	0,04	3,9



# Studi di fase III in pazienti non selezionati con regimi di chemioterapia a due/tre farmaci

Regime	N.	RR (%)	Resezione metastasi (%)	Autore
IFL FOLFOX IROX	264	31	1	Goldberg, 2004
	267	45	4	
	265	35	4	
5FU/AF (AIO) 5FU/AF (AIO) + IRI	216	34	1	Köhne, 2005
	214	64	3	
FOLFIRI FOLFOX	109	56	9	Tournigand, 2004
	111	54	15	
FOLFIRI FOLFOX	178	34	5,1	Colucci, 2005
	182	36	4,4	
XELOX FUOX	171	37	10	Diaz-Rubio, 2007
	171	46	12,9	
FOLFIRI FOLFOXIRI	147	34	4	Souglakos, 2006
	138	43	10	
FOLFIRI FOLFOXIRI	122	41	6 (12 solo epatiche)	Falcone, 2007
	122	66	15 (36 solo epatiche)	

# RR (%) di combinazioni di doppiette e farmaci biologici



Van Cutsem et al, NEJM 2009, JCO 2011; Bokemeyer et al, JCO 2009; Maughan et al, ASCO 2010; Douillard et al, ECCO-ESMO 2009, JCO 2010, ASCO 2011; Hurwitz et al, NEJM 2004; Saltz et al, JCO 2008; Tabernero et al, 2010; Falcone 2013; Heinemann et al, ASCO 2013

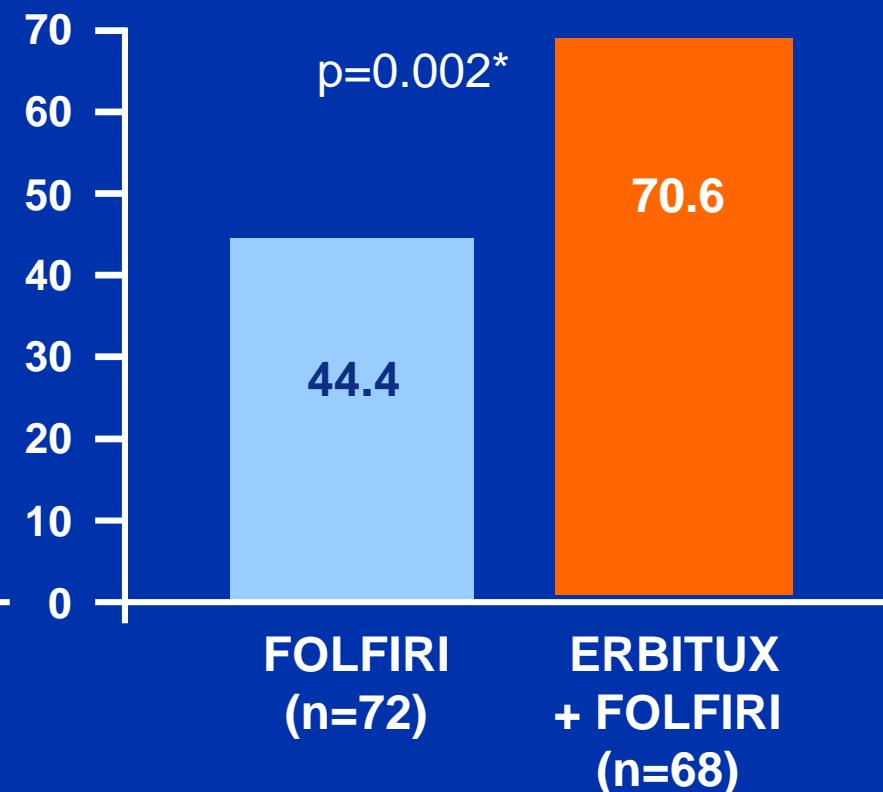
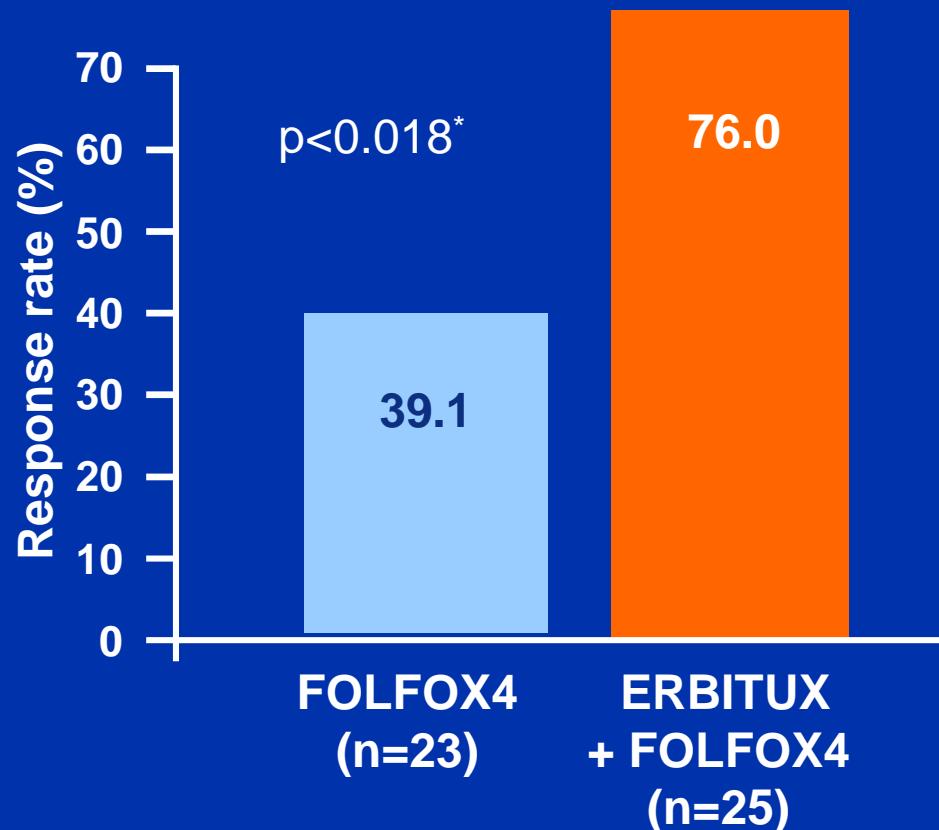
## ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

*recommendation 13: conversion therapy.*

- In potentially resectable patients (if conversion is the goal), a regimen leading to high RRs and/or a large tumour size reduction (shrinkage) is recommended [II, A].
- There is uncertainty surrounding the best combination to use as only few trials have addressed this specifically:
  - In patients with *RAS* wild-type disease, a cytotoxic doublet plus an anti-EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A].
  - In patients with *RAS*-mutant disease: a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab [II, A].
- Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

# Liver limited disease

**CETUXIMAB + CHEMOTHERAPY:**  
**Response in pts with KRAS wt tumors (OPUS & CRYSTAL trials)**



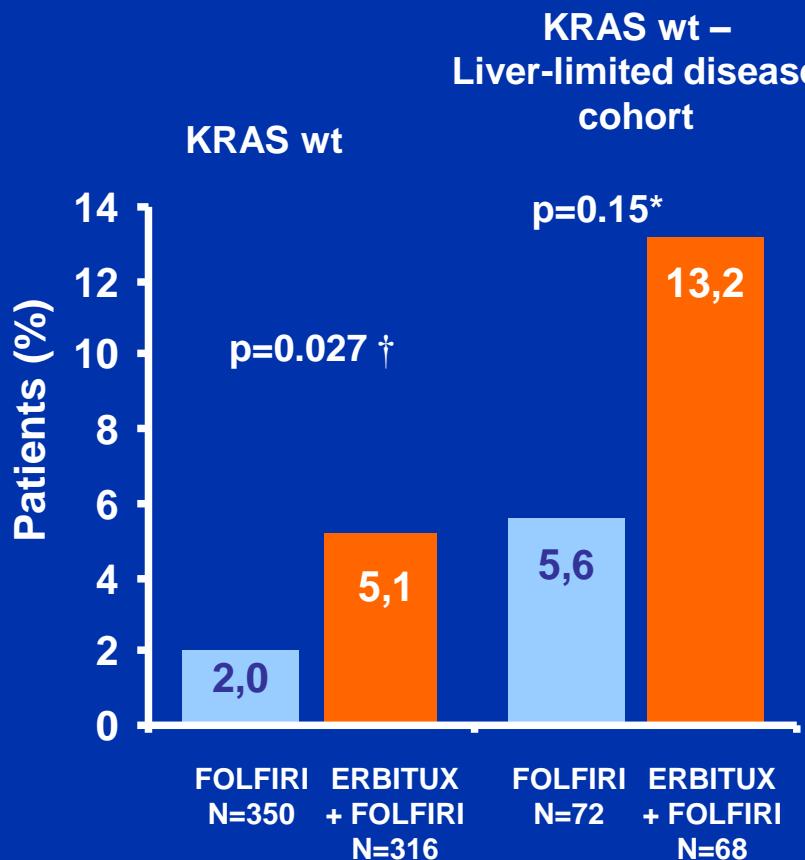
\*Fisher's exact test

Van Cutsem et al. ASCO GI 2011, Abs 472

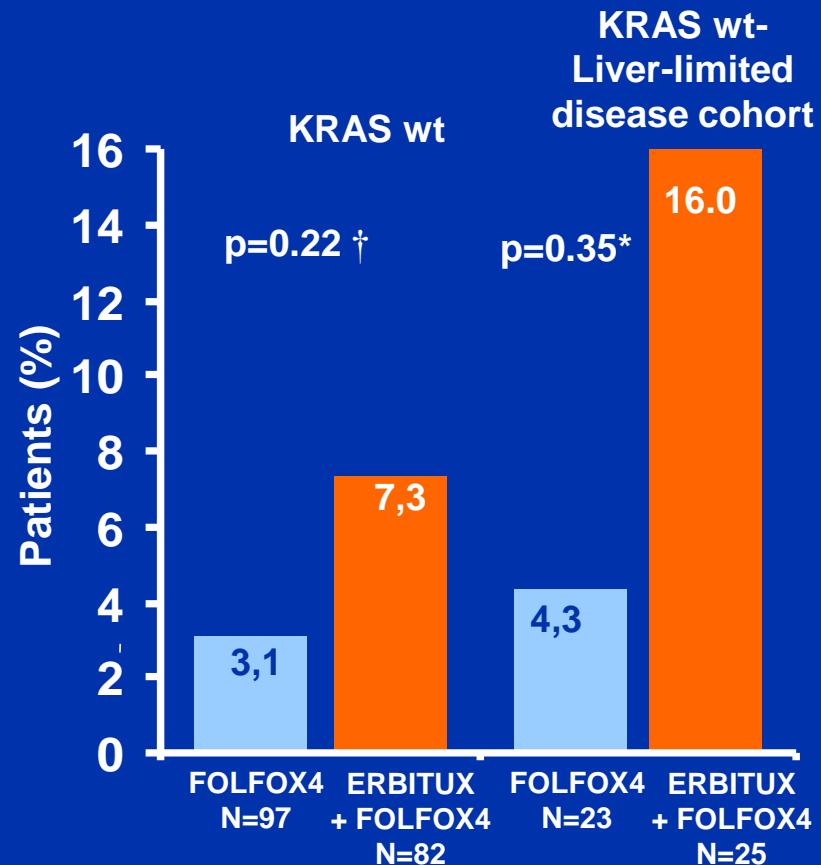
# ERBITUX significantly increases response rate resulting in high resection rate



## CRYSTAL R0 resection rate



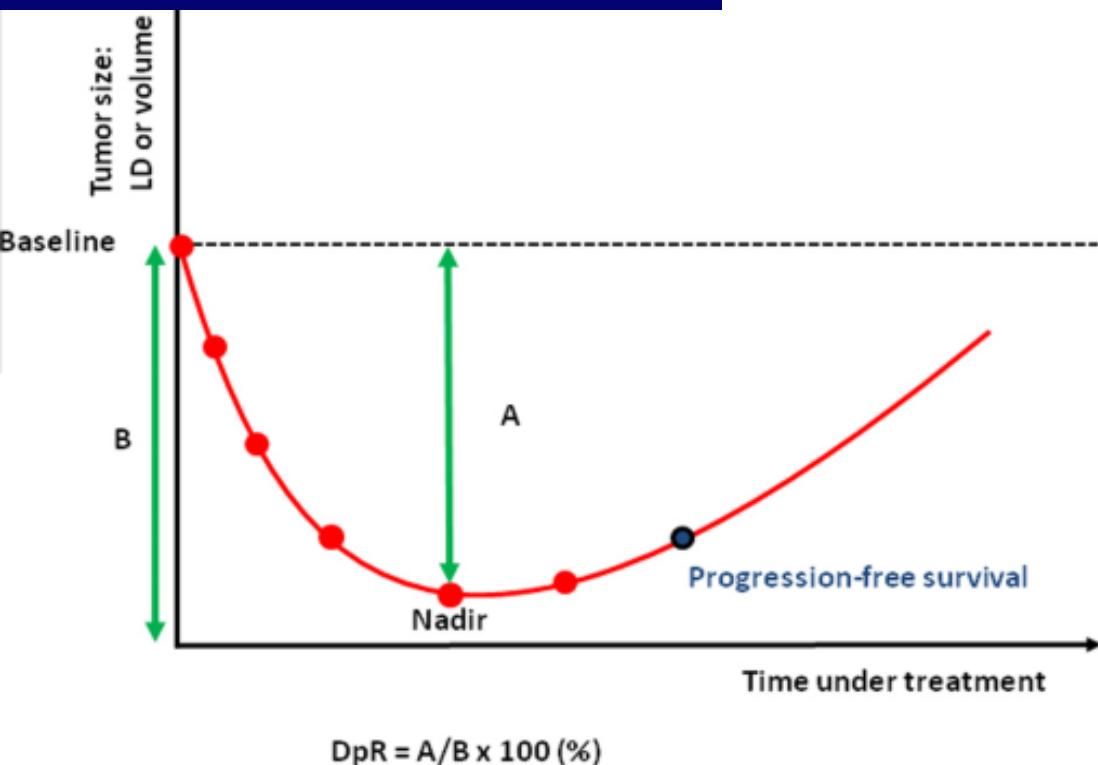
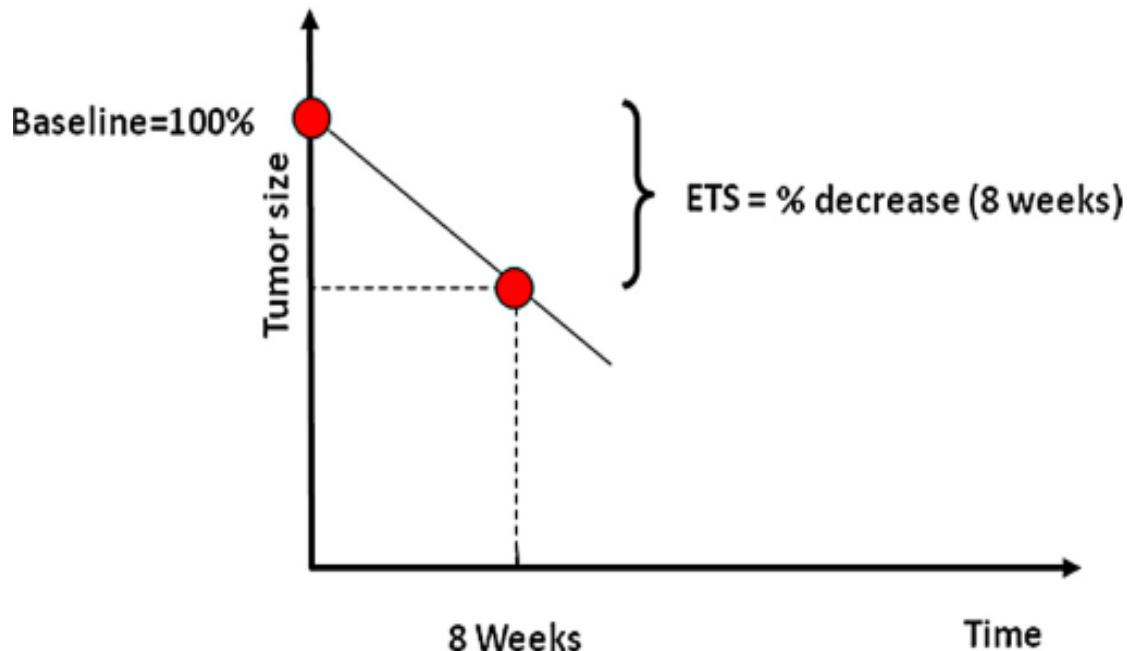
## OPUS



Van Cutsem et al. ASCO GI 2011, Abstract No. 472

## Early tumour shrinkage (ETS):

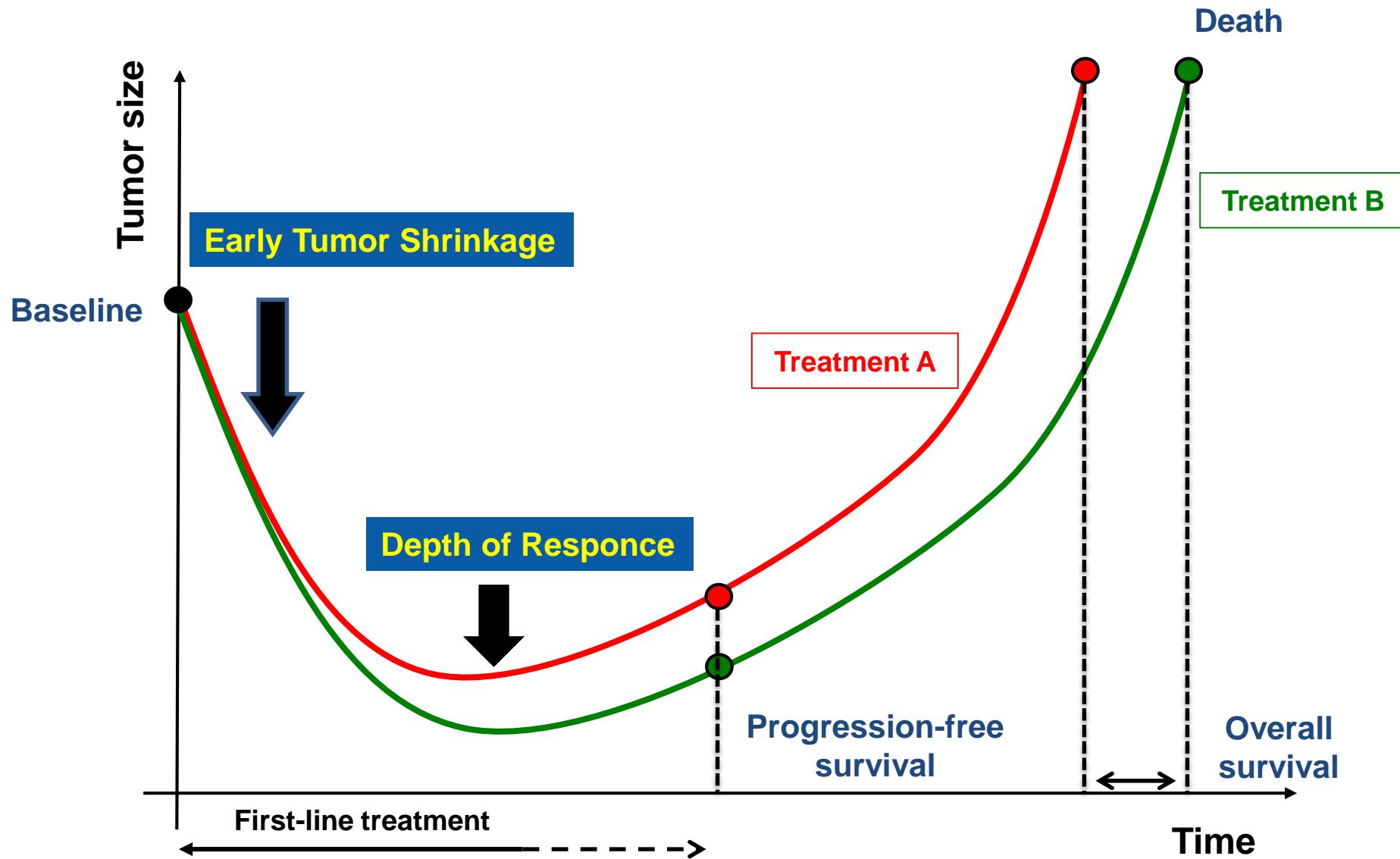
Riduzione rispetto al basale delle dimensioni delle lesioni target valutate radiologicamente considerando la somma dei diametri maggiori (cut off 20-30%)



## Depth of Response (DpR):

Riduzione del tumore espresso in valori percentuali calcolato al nadir rispetto al basale.  
Calcolo effettuato sulla somma dei diametri maggiori delle lesioni target

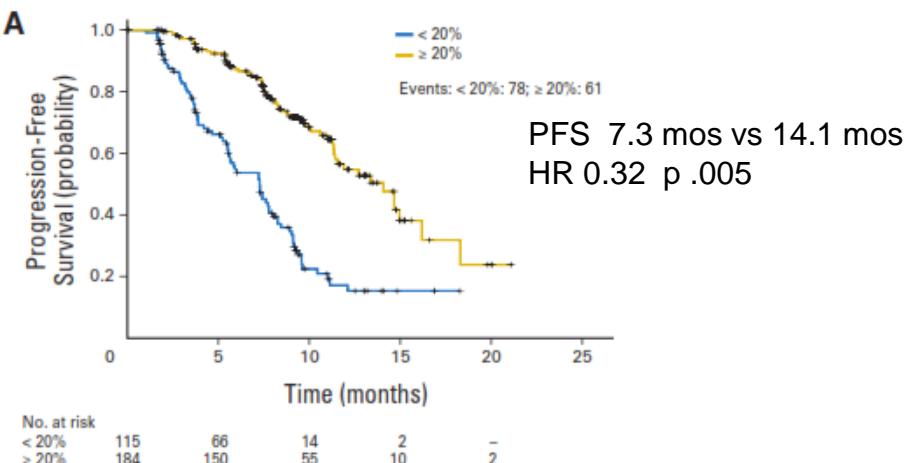
# Potential impact in survival



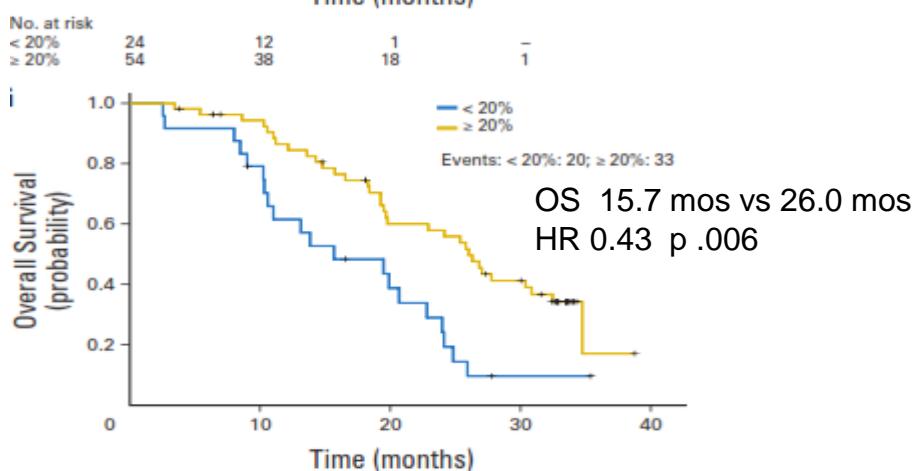
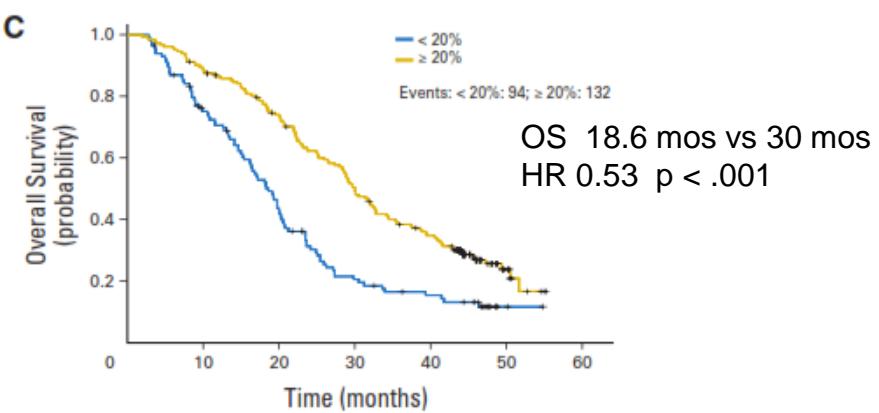
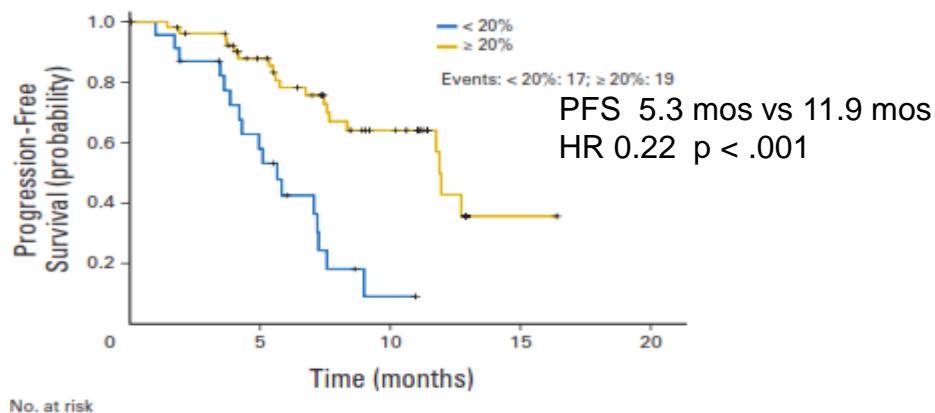
## Use of Early Tumor Shrinkage to Predict Long-Term Outcome in Metastatic Colorectal Cancer Treated With Cetuximab

*Hubert Piessevaux, Marc Buyse, Michael Schlichting, Eric Van Cutsem, Carsten Bokemeyer, Steffen Heeger, and Sabine Teijpar*

### CRYSTAL (wild type KRAS)



### OPUS (wild type KRAS)





## Review

## Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC)

Volker Heinemann <sup>a,b</sup>, Sebastian Stintzing <sup>a,\*</sup>, Dominik P. Modest <sup>a</sup>,  
Clemens Giessen-Jung <sup>a</sup>, Marlies Michl <sup>a</sup>, Ulrich R. Mansmann <sup>c</sup>



Gain in survival ( $\Delta$  PFS,  $\Delta$  OS) comparing ETS to non-ETS.

Study (reference)	Regimen	PFS (months)			OS (months)		
		ETS <20%	ETS $\geq 20\%$	$\Delta$ PFS (months)	ETS <20%	ETS $\geq 20\%$	$\Delta$ OS (months)
FIRE-I <sup>§</sup> [24]	FUFIRI/mIROX	6.1	9.9	3.8	17.8	27.5	9.7
CRYSTAL <sup>*</sup> [28]	FOLFIRI + cetuximab	7.3	14.1	6.8	18.6	30.0	11.4
	FOLFIRI	7.4	9.7	2.3	18.6	24.1	5.5
OPUS <sup>*</sup> [27]	FOLFOX-4 + cetuximab	5.7	11.9	6.2	15.7	26.0	10.3
	FOLFOX-4	7.2	7.2	0	17.8	21.6	3.8
CIOX <sup>SS,*</sup> [26]	CAPIRI/CAPOX + cetuximab	4.7	8.9	4.2	15.8	31.6	15.8
PRIME <sup>*</sup> [38]	FOLFOX + panitumumab	5.7	11.0	5.3	10.7	30.0	19.3
	FOLFOX	5.7	9.3	3.6	16.6	25.1	8.5
ACCORD 13 [31]	FOLFIRI + bevacizumab/ XELOX + bevacizumab	9	10	1.0	22	33	11
Ye [36]	FOLFIRI/FOLFOX6 + cetuximab	4.8	11.8	7.0	18.7	38.0	19.3
	FOLFIRI/FOLFOX6	4.6	8.0	3.4	17.7	30.6	12.9
TRIBE [32]	FOLFOXIRI + bevacizumab/ FOLFIRI + bevacizumab	10.0 <sup>#</sup>	12.7 <sup>#</sup>	2.7	22.4	35.8	13.4

**Table 2**  
**ETS in EGFR-targeted therapeutic regimens.**

Parameter	CRYSTAL*				OPUS*	
	N = 631				N = 168	
	Cetuximab	FOLFIRI	FOLFIRI	Cetuximab	FOLFOX-4	
ETS (%)	<20	≥20	<20	≥20	<20	≥20
Shrinkage rate (%)	38	62	51	49	31	69
OS (months)	18.6	30	18.6	24.1	15.7	26.0
HR		0.53		0.71		0.43
P-Value		<0.001		0.006		0.006
PFS (months)	7.3	14.1	7.4	9.7	5.7	11.9
HR		0.32		0.58		0.22
P-Value		<0.001		<0.001		<0.001

**Table 3**

Relation of ETS, DpR and survival in randomised 1st-line studies.

Parameter	FIRE-3*		PEAK*		TRIBE	
	FOLFIRI + Cet	FOLFIRI + Bev	FOLFOX + Pani	FOLFOX + Bev	FOLFOXIRI + Bev	FOLFIRI + Bev
No of patients evaluated	236	257	88	82	221	222
ETS cut-off	≥20	≥20	≥30	≥30	>20	>20
ETS rate (%)	68.2	49.1	64	45	64	51
Depth of response (%)	48.9	32.3	65	46	42.2	33.8
(DpR) P-Value	<0.0001		0.0007		0.0009	

Cet, cetuximab; Pani, panitumumab; Bev, bevacizumab; ETS, early tumour shrinkage; FOLFIRI, 5-fluorouracil/irinotecan/leucovorin; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin.

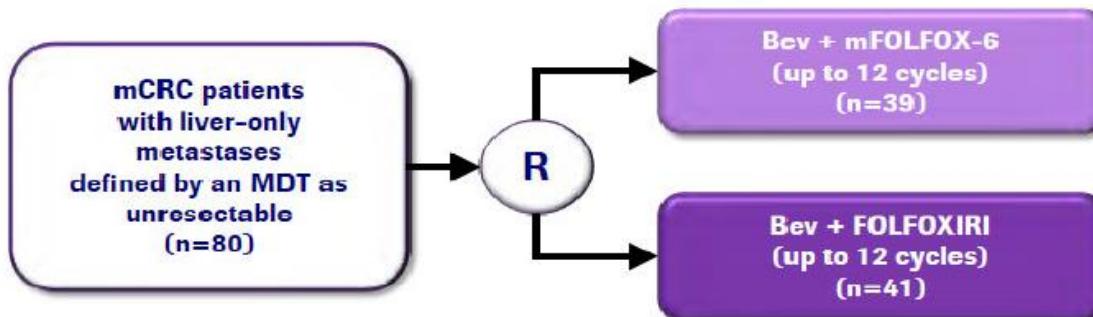
\* Evaluation of patients with RAS wild-type tumours.



**Grazie per l'attenzione**

OLIVIA: phase II study of bevacizumab + mFOLFOX6 vs bevacizumab + FOLFOXIRI in patients with initially unresectable liver-limited mCRC

Gruenberger et al Ann.Oncol 2015

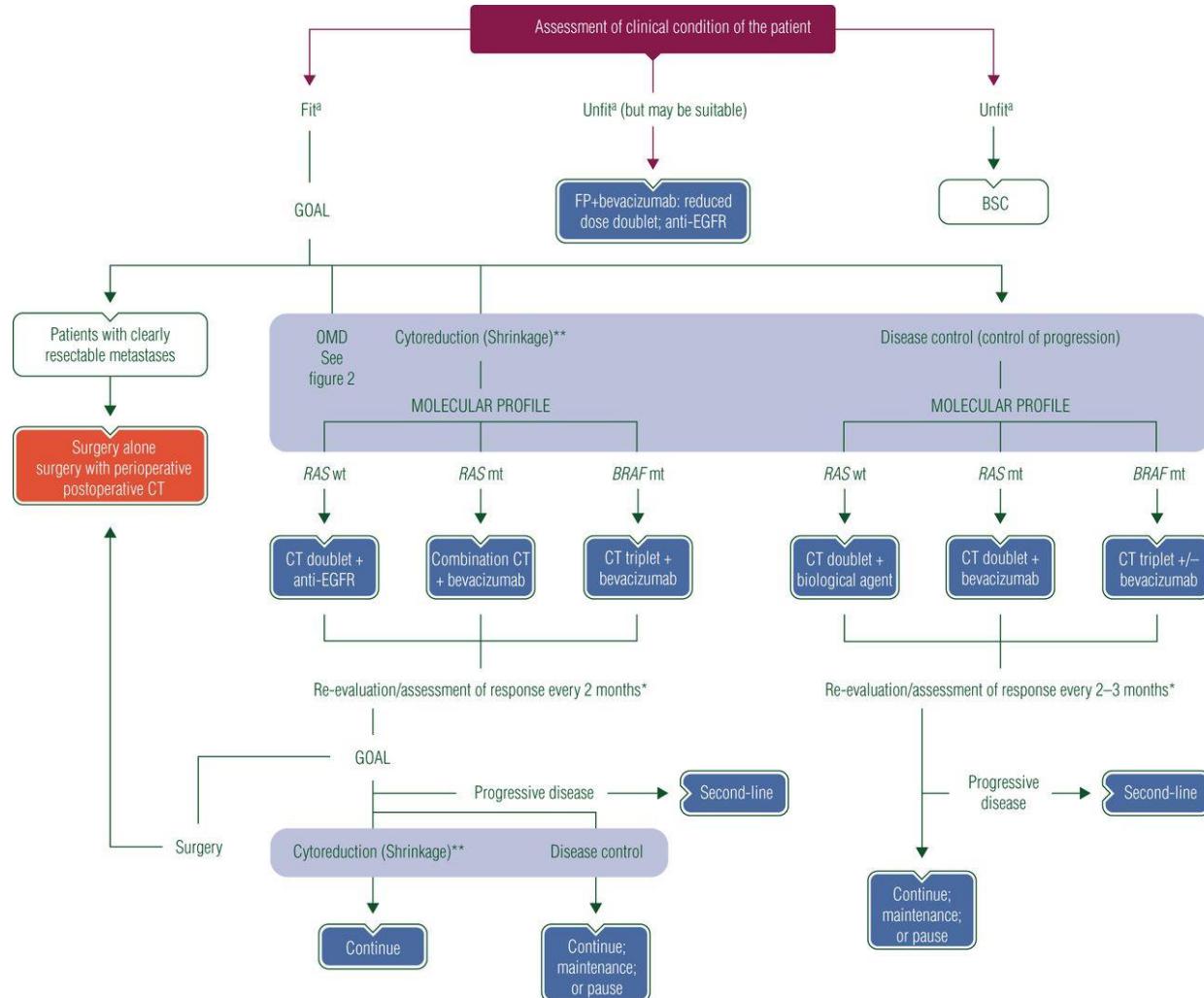


- Primary endpoint: overall resection rate (R0/R1/R2)
- Secondary endpoints: ORR (by RECIST), PFS, RFS, OS and safety

	FOLFOX-6+ bev N = 39	FOLFOXIRI + bev N = 41	p
<b>Response Rate</b>	61.5%	80.5%	0.061
<b>R0 Resections</b>	23.1%	48.8%	0.017
mPFS (mos)	12.0	18.8	0.0002

mOS not reached in FOLFOXIRI-Bev vs 32.2 mos in mFOLFOX-6 + Bev

# Zurich treatment algorithm.



E. Van Cutsem et al. Ann Oncol 2016;27:1386-1422

# Efficacy according to treatment group and metastatic site: CRYSTAL



Parameter*	LLD		Non-LLD	
	CT n=72	CT + ERBITUX n=68	CT n=278	CT + ERBITUX n=248
<b>PFS</b>				
Median, months	9.2	11.8	8.1	9.5
HR		0.56		0.74
[95% CI]		[0.32–0.97]		[0.58–0.94]
p-value†		0.035		0.012
<b>OS</b>				
Median, months	27.7	27.8	17.4	22.5
HR		0.85		0.79
[95% CI]		[0.57–1.28]		[0.65–0.95]
p-value†		0.44		0.013

\*Stratified hazard and odds ratios are for CT + ERBITUX vs CT alone groups; †stratified log-rank test  
 CI, confidence interval; CT, chemotherapy; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; PFS, progression-free survival

# Efficacy according to treatment group and metastatic site: OPUS



Parameter*	LLD		Non-LLD	
	CT n=23	CT + ERBITUX n=25	CT n=74	CT + ERBITUX n=57
<b>PFS</b>				
Median, months	7.9	11.9	6.0	7.6
HR		0.64		0.59
[95% CI]		[0.23–1.79]		[0.37–0.93]
p-value†		0.39		0.023
<b>OS</b>				
Median, months	23.9	26.3	16.4	19.8
HR		0.93		0.80
[95% CI]		[0.44–2.00]		[0.54–1.21]
p-value†		0.86		0.29

\*Stratified hazard and odds ratios are for CT + ERBITUX vs CT alone groups; †stratified log-rank test  
 CI, confidence interval; CT, chemotherapy; HR, hazard ratio; LLD, liver-limited disease; OS, overall survival; PFS, progression-free survival

# Early tumor shrinkage and survival in KRAS wt patients treated with FOLFOX4 + ERBITUX



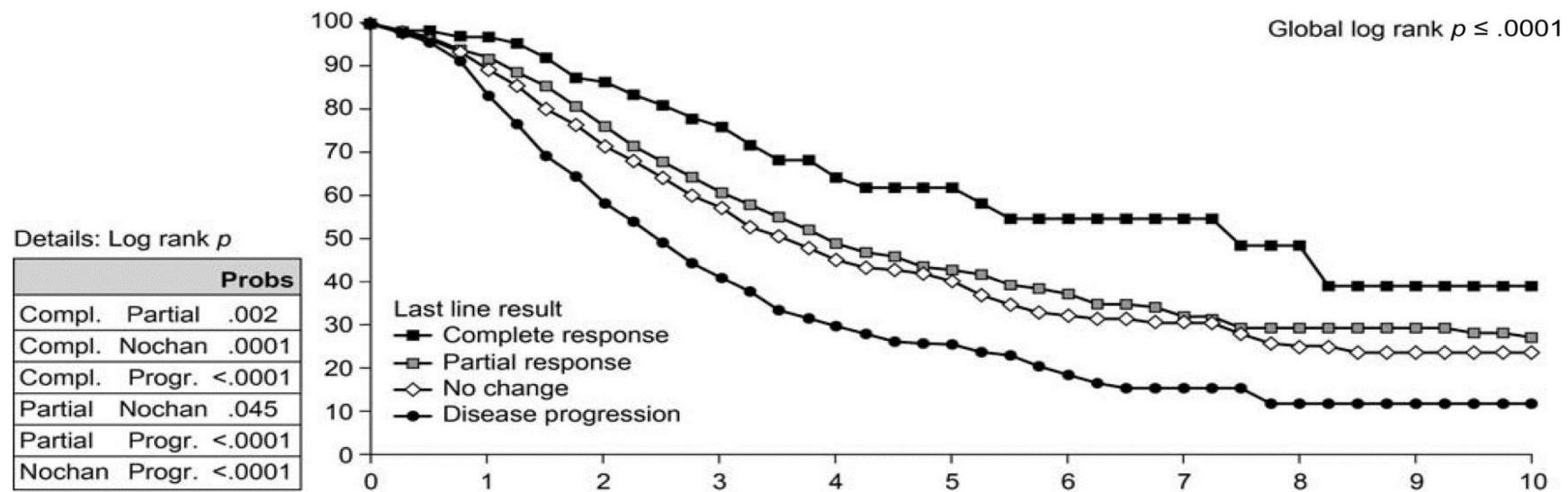
Parameter	Tumor shrinkage	
	<20% n=24	≥20% n=54
<b>PFS</b>		
Median, months	5.7	11.9
[95% CI]	[4.5–6.8]	[11.6–12.2]
HR	0.24	
[95% CI]	[0.12–0.49]	
p-value*	<0.0001	
<b>OS</b>		
Median, months	15.7	26.1
[95% CI]	[6.2–25.2]	[22.8–29.3]
HR	0.41	
[95% CI]	[0.23–0.73]	
p-value*	0.002	

\*Log-rank

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; wt, wild-type

Piessevaux et al. ASCO GI 2011, Abstract No. 398

# Overall survival probability in relation to response to preoperative chemotherapy in 4,851 patients undergoing a first resection of colorectal liver metastases from the LiverMetSurvey



Number of patients exposed

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Compete response	191	133	87	54	30	17	12	9	5	4	3
Partial response	2,727	1,738	1,015	586	310	190	103	73	44	34	22
No change	893	563	324	188	109	79	44	35	24	18	18
Disease progression	395	258	147	74	40	28	17	11	6	4	3

# RR e resecabilità di metastasi epatiche con triplette e bevacizumab in studi di fase III

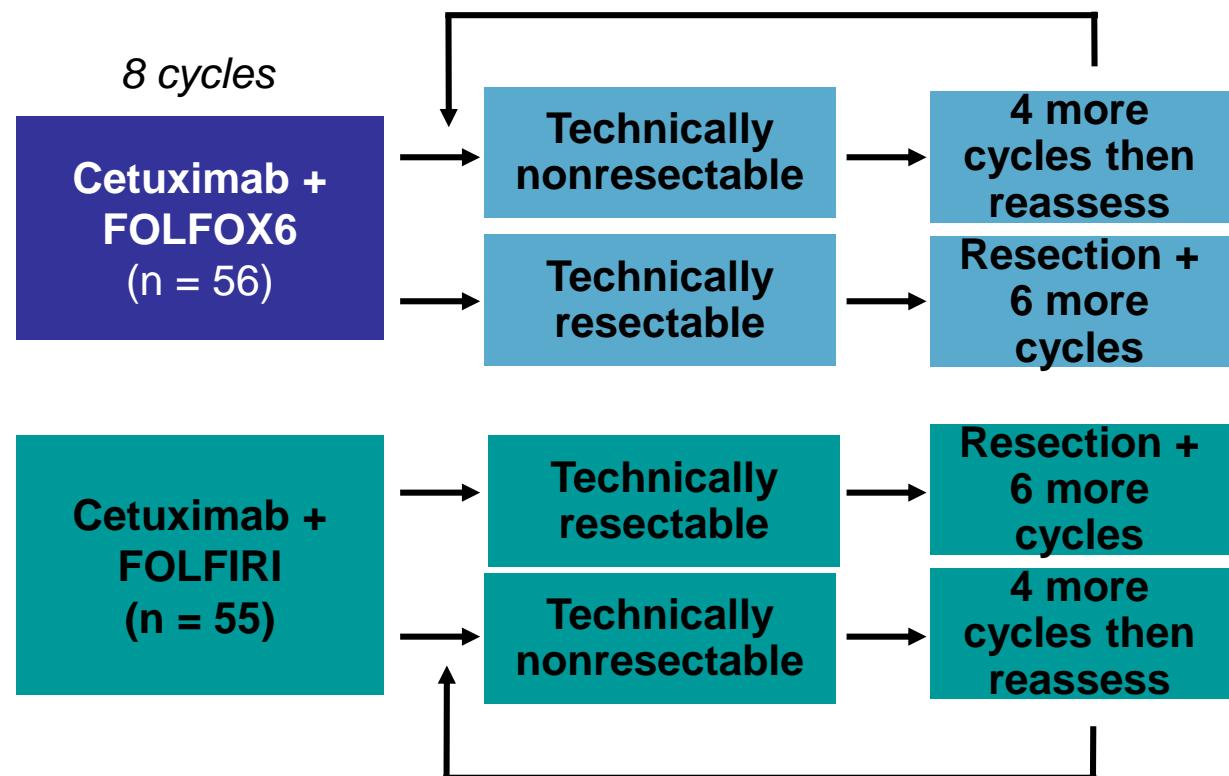
Regime	N.	RR (%)	Resezione (%) Meta epatiche	Resezione (%) Meta epatiche (M1 solo epatica)	Autore
FOLFIRI	122	41	6	12	Falcone et al
FOLFOXIRI	122	66	15	36	2007
			p=0,033	p=0,017	
<b>FOLFIRI + Bevacizumab</b>	<b>254</b>	<b>53</b>	<b>12</b>	<b>28</b>	<b>Loupakis et al NEJM</b>
<b>FOLFOXIRI + Bevacizumab</b>	<b>250</b>	<b>65</b>	<b>15</b>	<b>32</b>	<b>2014</b>
			p=0,327	p=0,823	

# CELIM: Neoadjuvant Cetuximab for Nonresectable CRC Liver Metastases

*Stratified by reason for nonresectability, PET scan use at staging, EGFR status*

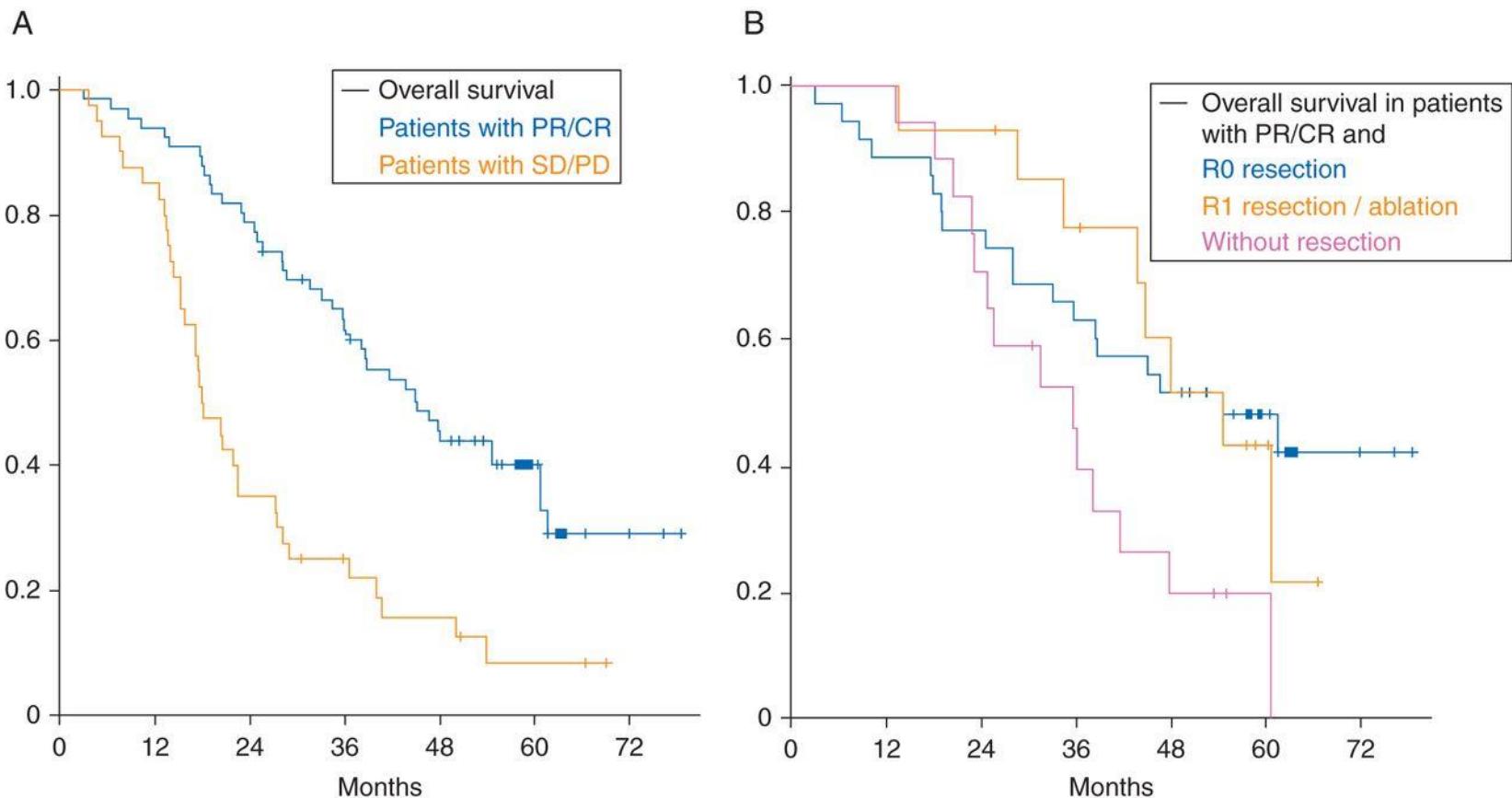
**nonresectable CRC liver mets:**  
- no extrahepatic mets,  
> 4 mets  
- inadequate future liver remnant,  
- infiltration of both portal vein or arteries branches

111 pts



Outcome	ERBITUX + FOLFOX6 (n=53)	ERBITUX + FOLFIRI (n=53)	All patients (n=106)
ORR, <sup>a</sup> %	68	57	62
SD, %	28	30	29
Resection type, %	ERBITUX + FOLFOX6 (n=53)	ERBITUX + FOLFIRI (n=53)	All patients (n=106)
R0 resections	38	30	34
R1 resections/resections + RFA	2	8	5
RFA	9	6	8
R0/R1 resections/RFA	49	43	46
R2 resections	2	6	4
Exploratory laparotomy	6	2	4
Technically nonresectable (n=57)			
R0 resections, %	28 <sup>a</sup>	40 <sup>a</sup>	33

## Overall survival according to tumour response and resection



	R0 resection	No resection	
PFS (median mos)	9.9		
OS (median mos)	53.9	21.9	HR 0.29 p < .001

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LOC: -1073,60

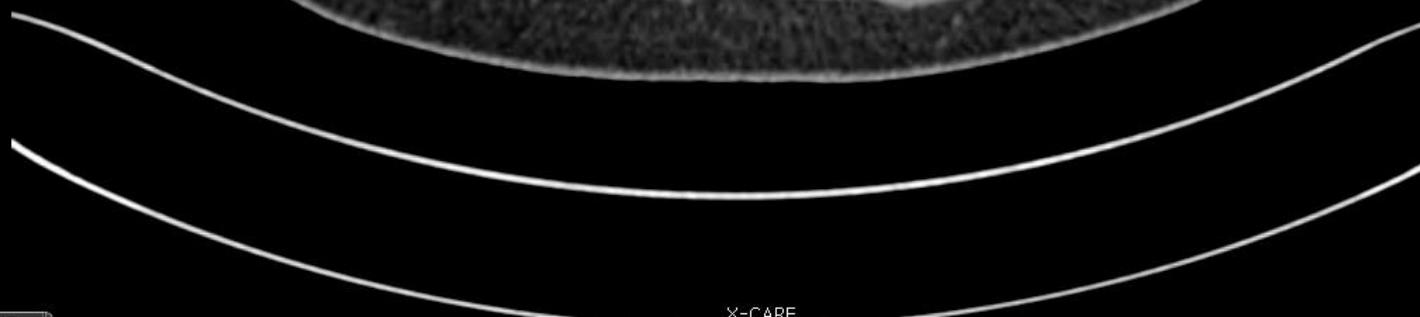
THK: 1 ---

HFS



R

L



X-CARE

P

cm



Z: 1,97

C: 40

W: 400

DFOV: 46,4x37cm

Compressed 11:1

IM: 232 SE: 4

# Metastasi epatiche potenzialmente resecabili

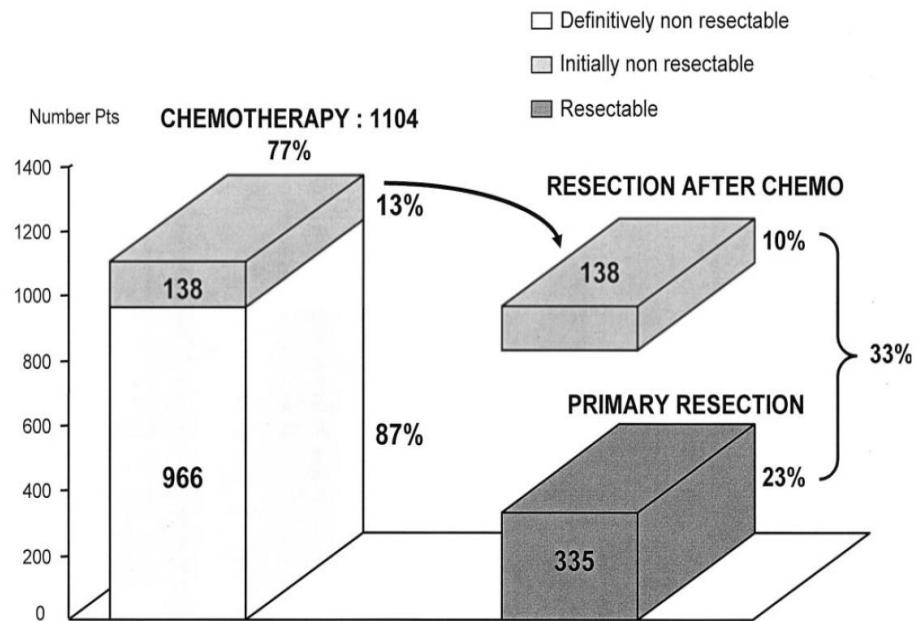
- **Background**
  - 15-20% dei pazienti con metastasi epatiche resecabili dopo CT
  - 15-20 % "lungo-sopravviventi" liberi da malattia (a 10 anni)
- **Quesiti**
  - Quale regime di chemioterapia ?
  - Ci sono vantaggi nell'aggiunta di biologici ?
- **obiettivi della CT**
  - Raggiungere shrinkage adeguato
  - Elevato numero di Risposte obiettive (RR)
  - Valore prognostico della chemiosensibilità

# Rescue Surgery for Unresectable Colorectal Liver Metastases Downstaged by Chemotherapy

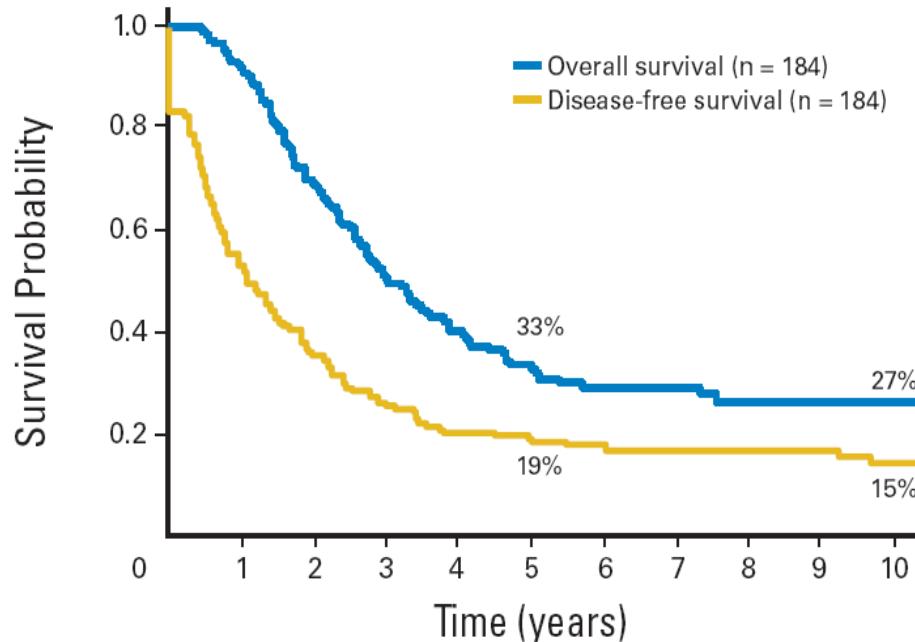
**Adam R, Ann Surg, 2004**

## Patients With Initially Unresectable Colorectal Liver Metastases: Is There a Possibility of Cure?

René Adam, Dennis A. Wicherts, Robbert J. de Haas, Oriana Ciacio, Francis Lévi, Bernard Paule, Michel Ducreux, Daniel Azoulay, Henri Bismuth, and Denis Castaing

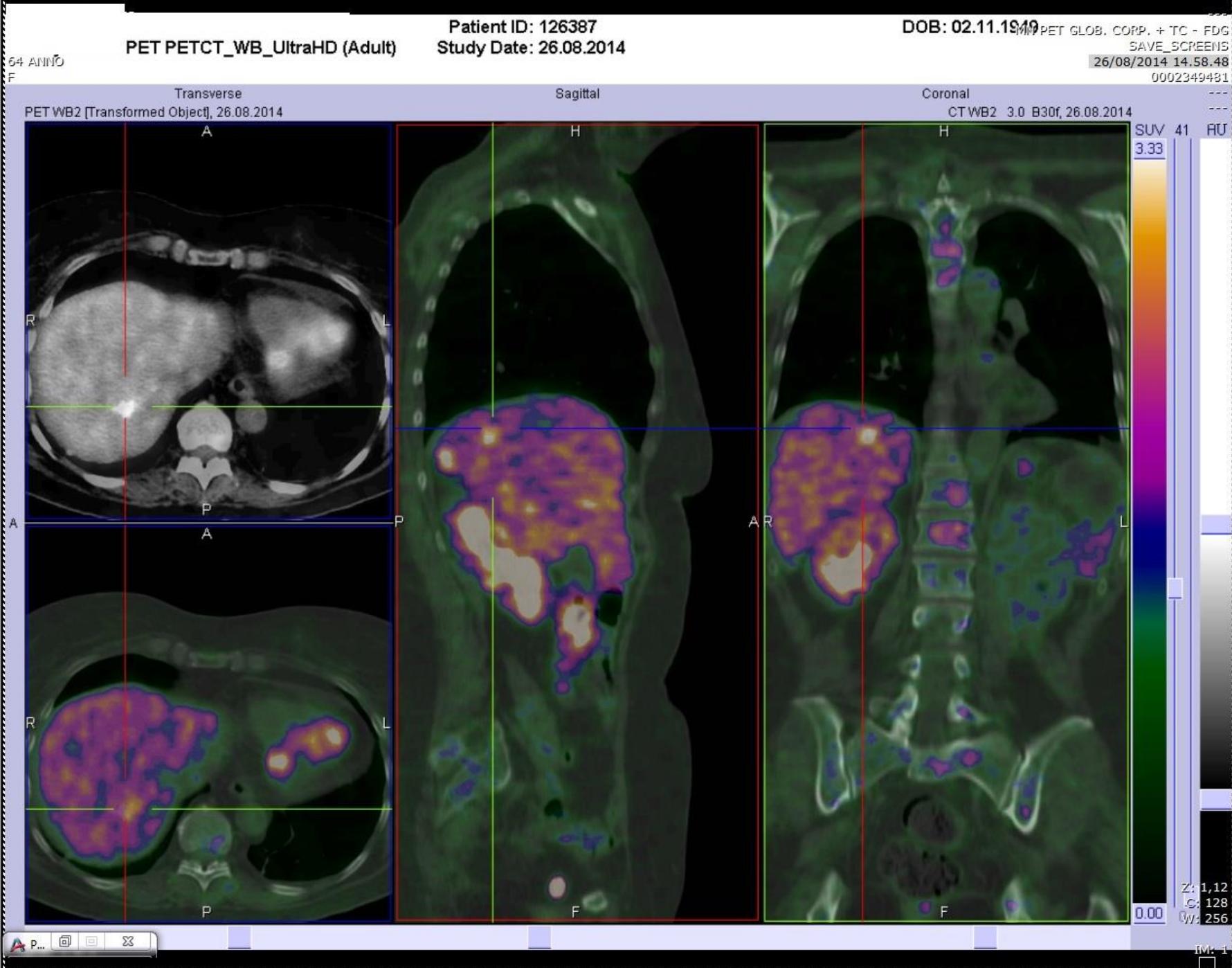


**FIGURE 1.** Paul Brousse Experience (1988–1999) in the management of colorectal liver metastases.



# **Chemoterapia + Biologico nella malattia inizialmente non resecabile**

- Dati retrospettivi
- La maggior parte dei dati provengono da analisi di sottogruppi in studi di fase III
- Dati a favore dell'utilizzo del biologico provenienti da studi di fase II
- Criteri di resecabilità variabili tra studi diversi



**Gennaio 2015:  
Ristadiazione dopo circa 8 settimane dalla chirurgia  
TAC torace addome: assenza di malattia**

**FOLLOW UP**



**Ottobre 2015:**

– TAC torace addome:

“nei settori dorsali del parenchima epatico in adiacenza alla vena cava inferiore e clips chirurgiche si riconosce lesione focale solida del diametro di 14 mm”

- PET-TC fdg:

“conferma della lesione segnalata alla TAC (15 mm, SUV8) ed evidenza di altre 3 piccole focalità di incerto significato

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