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SALVAGE THERAPY TO MANAGE LIVER DISEASE IN MCRC

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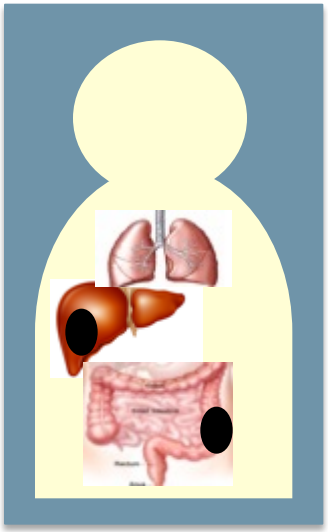
HOW DO WE TREAT LIVER ONLY MCRC?



- Histologic Confirmation
- Disease Extension
- Metastatic sites
- Disease Symptoms
- Inminent risk vs Indolent Disease
- Prognostic Biomarkers
- Comorbidities
- Functional Status
- Preferences and Expectations

GOAL

TREATMENT			NO TREATMENT
Group 0	Group 1	Group 2-3	
10%	20%	65%	5%
Resectable	Not Optimally Resectable	Irresectable	
CURATIVE	PALIATIVE - ONCOSPECIFIC	PALIATIVE – SYMPTOMATIC	

- Medicine Evidence Based (Efficacy + Toxicity/QoL)
- Drug Availability (Efficiency + Regulatory)
- Response Prediction Biomarkers

MEANS

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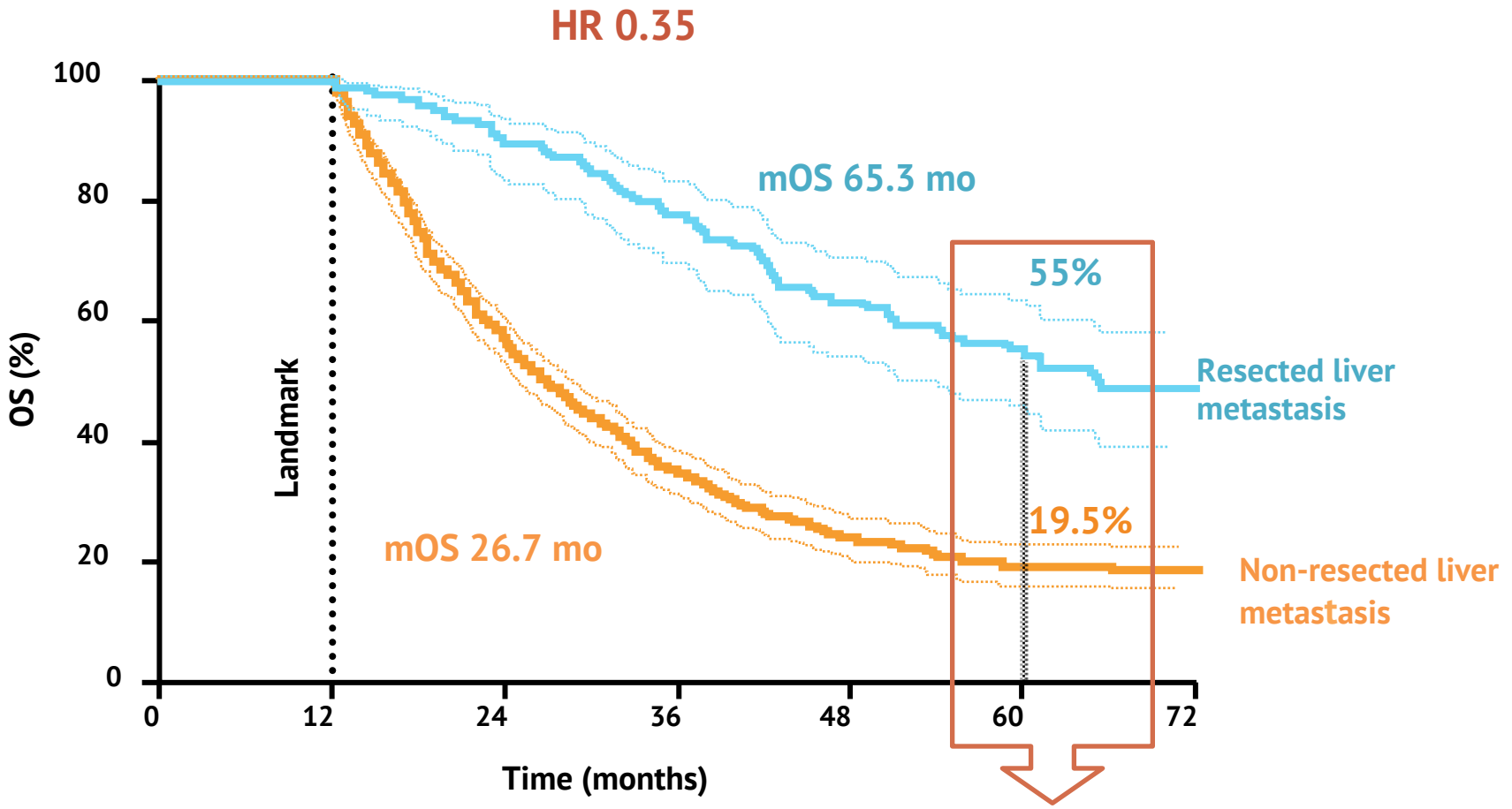
ESMO GUIDELINES: CLINICAL GROUPS AND TREATMENT AIMS

Group	Clinical presentation	Treatment aim	Treatment intensity
0	Clearly R0-resectable liver and/or lung metastases	• Cure, decrease risk of relapse	Nothing or moderate (FOLFOX)
1	Not R0-resectable liver and/or lung metastases only which • Might become resectable after response to induction chemotherapy • ±Limited/localized metastases to other sites, e.g. locoregional lymphnodes • Patient is physically able to undergo major surgery (biological age, heart/lung condition) and more intensive chemotherapy	• Maximum tumour shrinkage	Upfront most active combination regimen
2	Multiple metastases/sites, with • Rapid progression and/or • Tumour-related symptoms and/or risk of rapid deterioration • Co-morbidity allows intensive treatment	• Clinically relevant tumour shrinkage as soon as possible • At least achieve control of progressive disease	Upfront active combination: at least doublet

3	Multiple metastases/sites, with
	• Never option for resection
	• and/or no major symptoms or risk of rapid deterioration
	• and/or severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1 + 2)
		• Abrogation of further progression
		• Tumour shrinkage less relevant
		• Low toxicity most relevant
			Treatment selection according to disease characteristics and patients preference re toxicity and efficacy:
			• "Watchful waiting" (exceptional)
			• Sequential approach: start with
			  • Single agent, or
			  • Doublet with low toxicity
			• Exceptional triplets

MCRC: GROUP 0 & 1 MANAGEMENT



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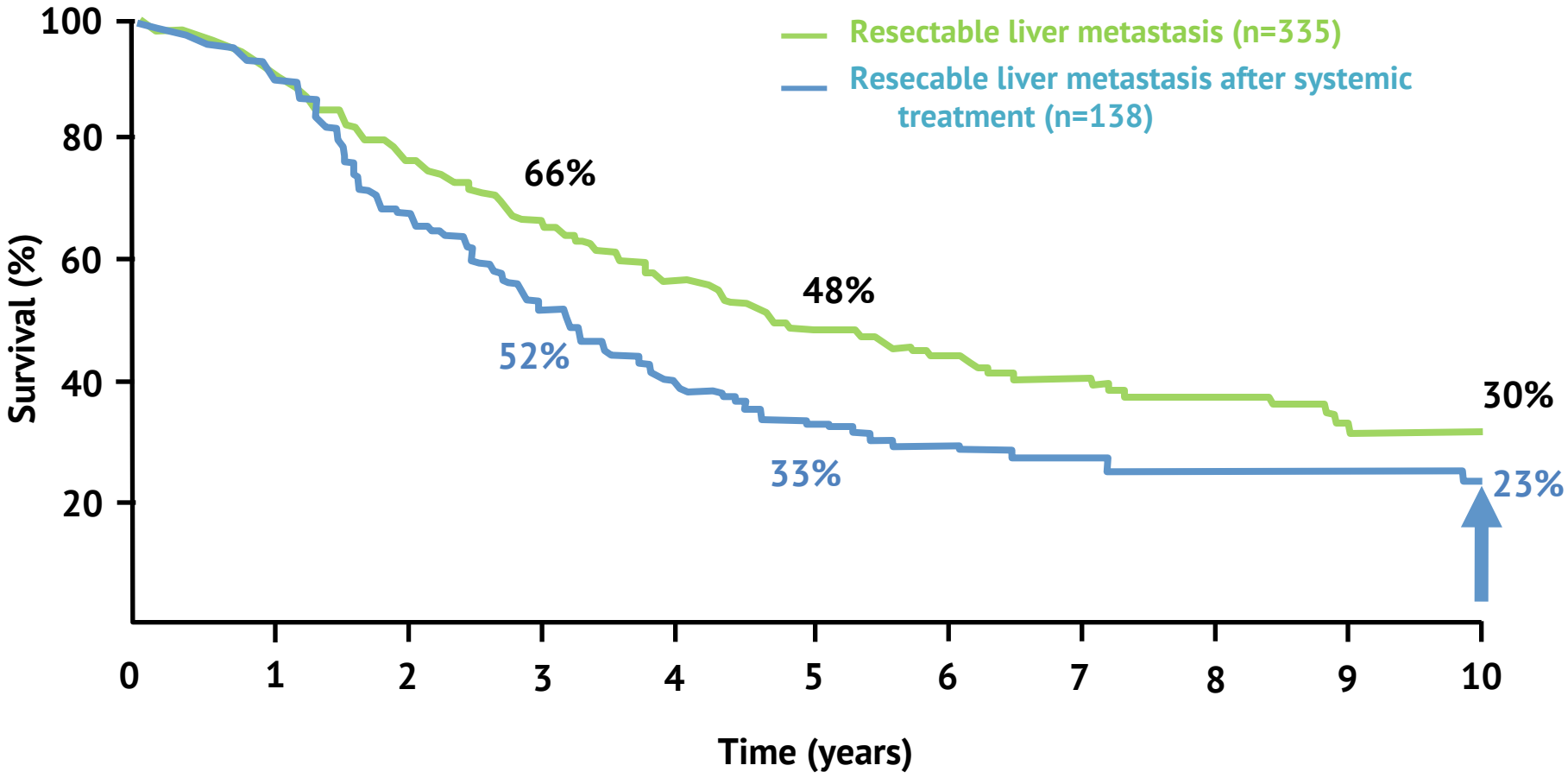
Kopetz, S. et al. J Clin Oncol 2009; 27:3677-3683

MCRC: GROUP 0 & 1 MANAGEMENT

Survival after liver mets resection



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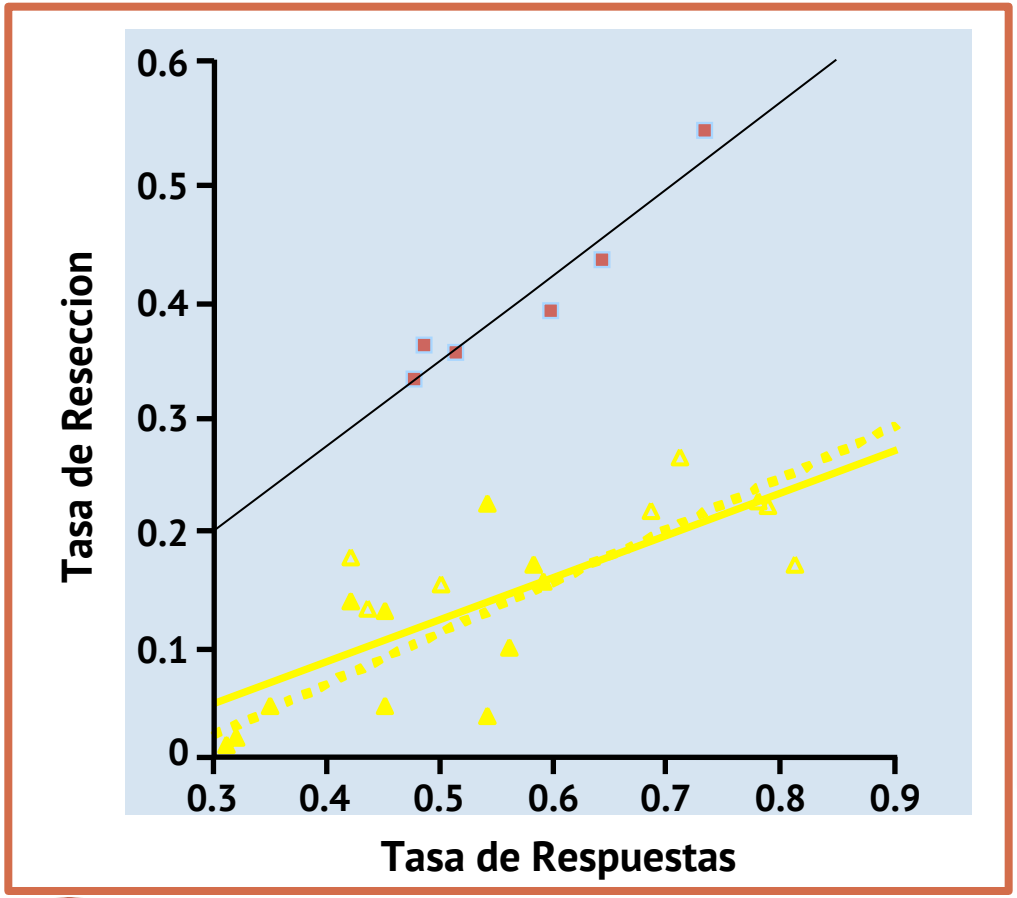
Adam R, et al. Ann Surg 2004;240:644–658

MCRC: GROUP 0 & 1 MANAGEMENT

Response Rate → Resection Rate



- Studies with selected patients (r=0.96; p=0.002)
- Studies with non-selected patiens (r=0.74; p<0.001)
- Phase III studies with non-selected patients (r=0.67; p=0.024)

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Folprecht G, et al. Ann Oncol 2005;16:1311–1319

MCRC: GROUP 0 & 1 MANAGEMENT RESECTABILITY

Old Criteria:

- Size <5 cm
- >1 cm margins
- Extrahepatic Disease
- < 3 lesions

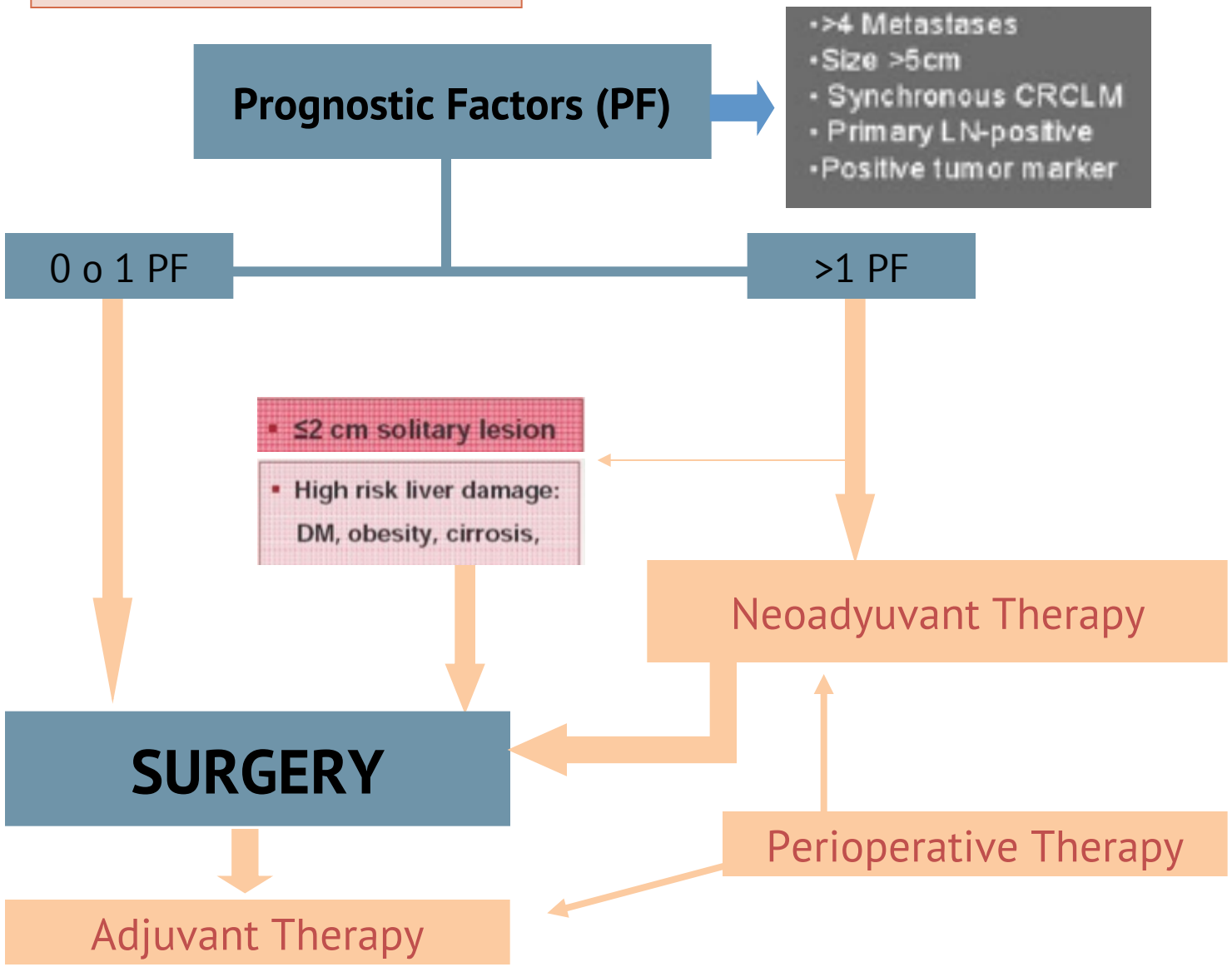
New Criteria:

- R0 resection
- >30% parenchyma
- Extrahepatic Disease (?)

Relative	Absolute
Extrahepatic metastases	Peritoneal carcinomatosis
Colonic recurrence	Multiple extrahepatic metastases
Solitary resectable peritoneal metastasis	Inability to perform hepatic R0 resection
Hilar lymph node metastases	

RESECTABLE (ESMO Group 0)

R0 & >30% liver remnant



Nordlinger, Ann Oncol, 2009

NON RESECTABLE

POTENTIALLY RESECTABLE
(ESMO Group 1)

No R0
<30% liver remnant
&/or
Technically Difficult

Conversion feasible?

Conversion Systemic Therapy

Most efective Treatment

The less cycles the better

Possibly NEVER RESECTABLE
(ESMO Group 2,3)

Palliative Systemic Therapy

Survival / Toxicity /QoL

Duration of Treatment?

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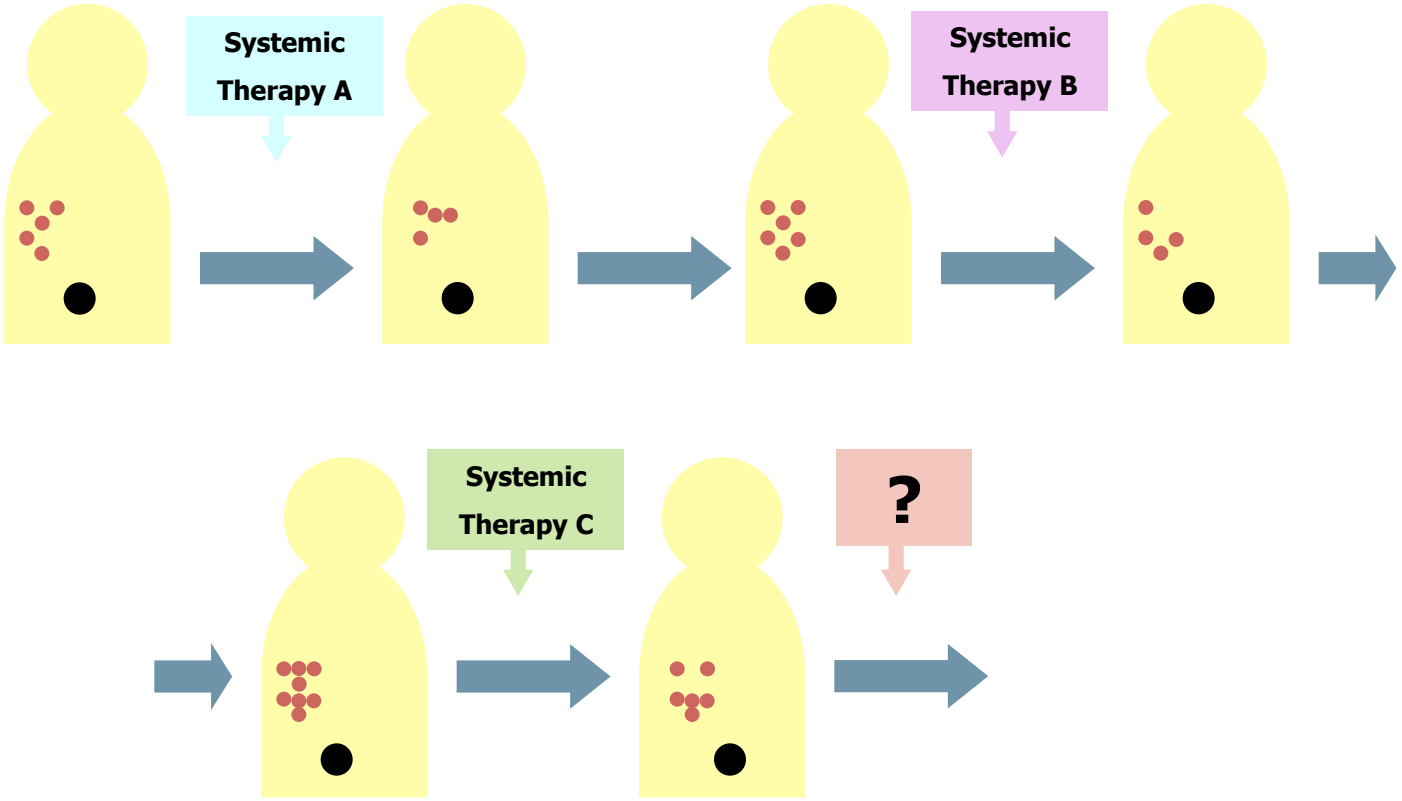
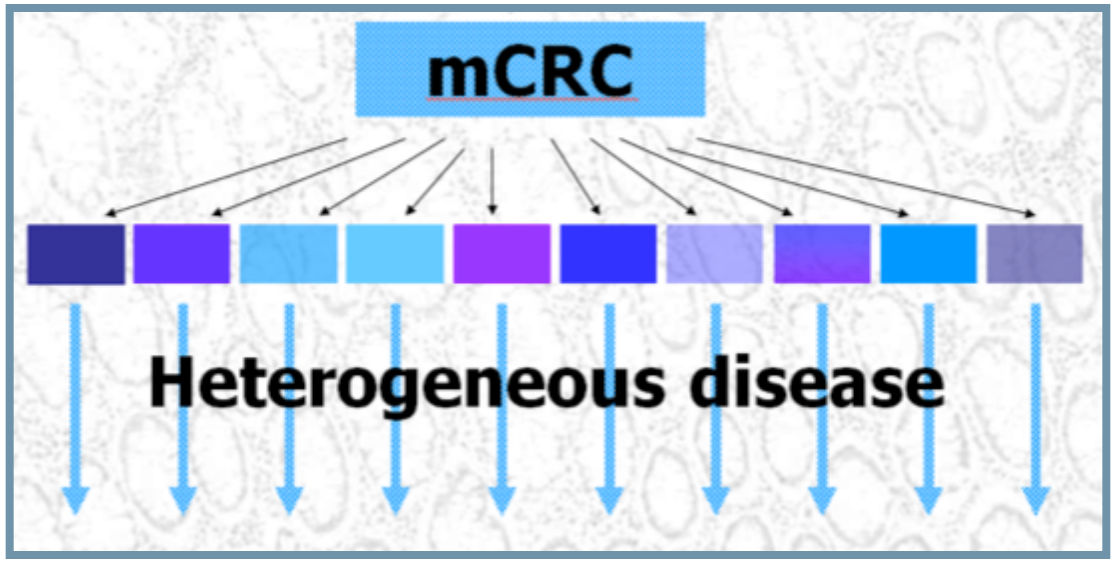
Nordlinger, Ann Oncol, 2009

LONG-TERM LIVER-ONLY MCRC





?

Long term liver-only mCRC

SALVAGE THERAPY FOR LIVER-ONLY MCRC

- Cryotherapy
- Radiofrequency ablation
- Microwave ablation
- Hepatic arterial infusion (HAI)
- Transarterial chemoembolization (TACE, DEBIRI)
- Ethanol injection
- Chemosaturation (percutaneous hepatic perfusion)
- Radioembolization 90Y

DEBIRI

Irinotecan is loaded and eluted from DC Bead by a reversible ionic-exchange mechanism

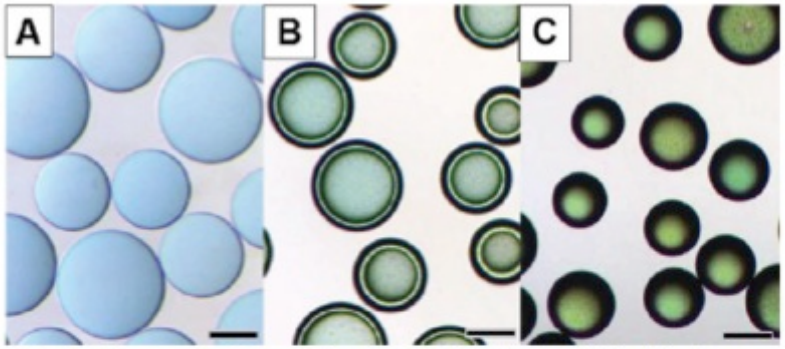
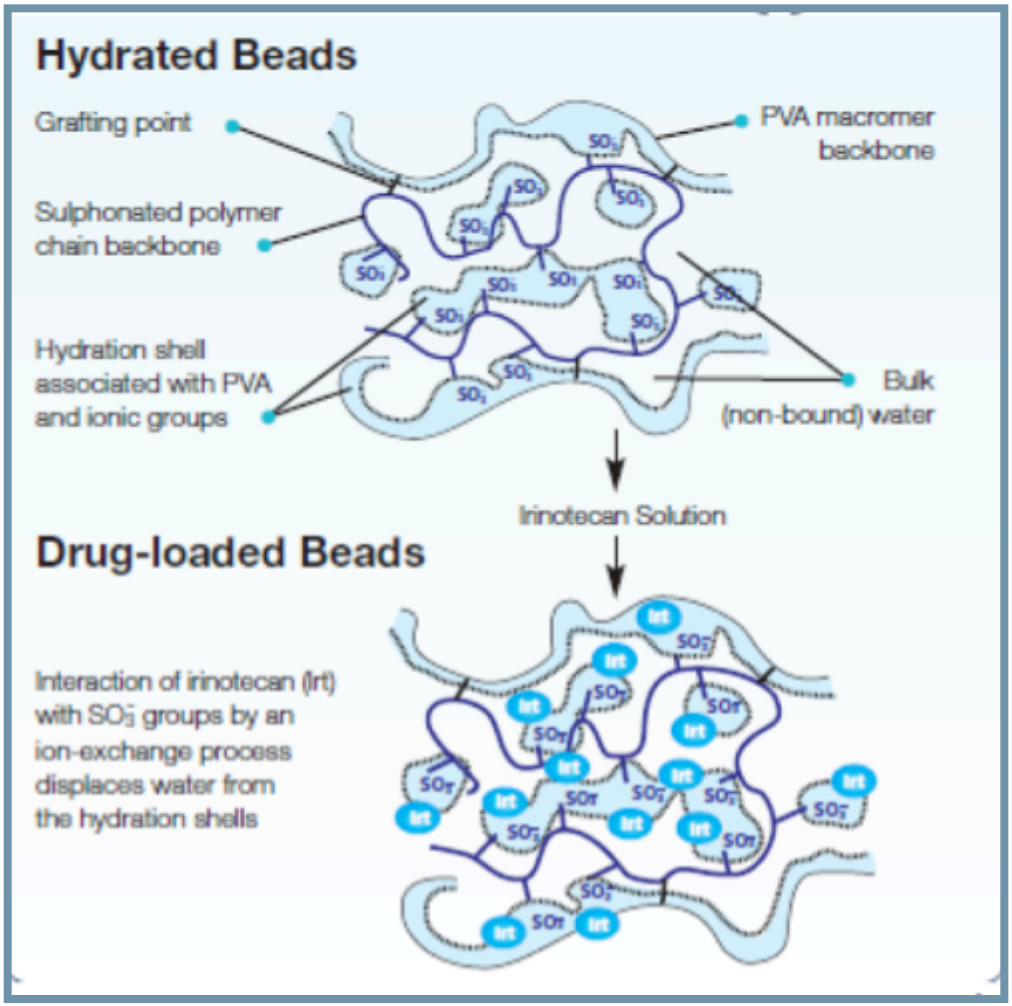


Fig. 1 – Micrographs of morphology of DEB (300-500µm) during irinotecan loading (50 mg/mL).

(A) Without drug loading, (B) after 7 min loading, and (C) after 20min. The scale bar shown is 200µm.

R. Taylor, Y Tang, M Gonzalez et al (2007) Pharmaceutical Sciences Vol.30, (1):7-14

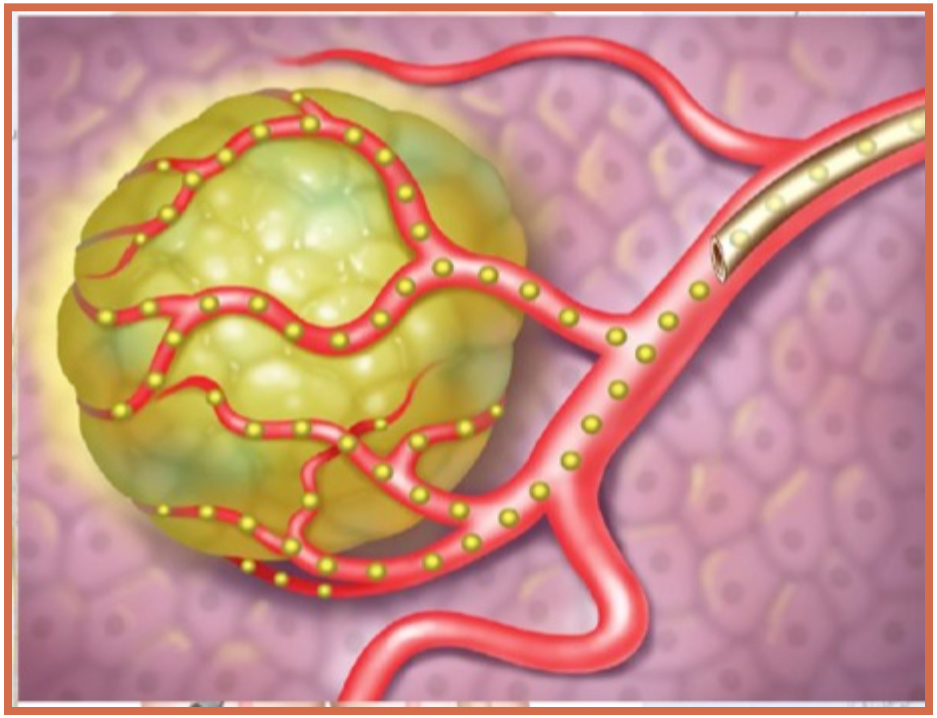


* Morise Z, Sugioka A, Kato R, Fujita J, Hoshimoto S, Kato T. Transarterial chemoembolization with degradable starch microspheres, irinotecan, and mitomycin-C in patients with liver metastases. J Gastrointest Surg 2006; 10: 249–258.

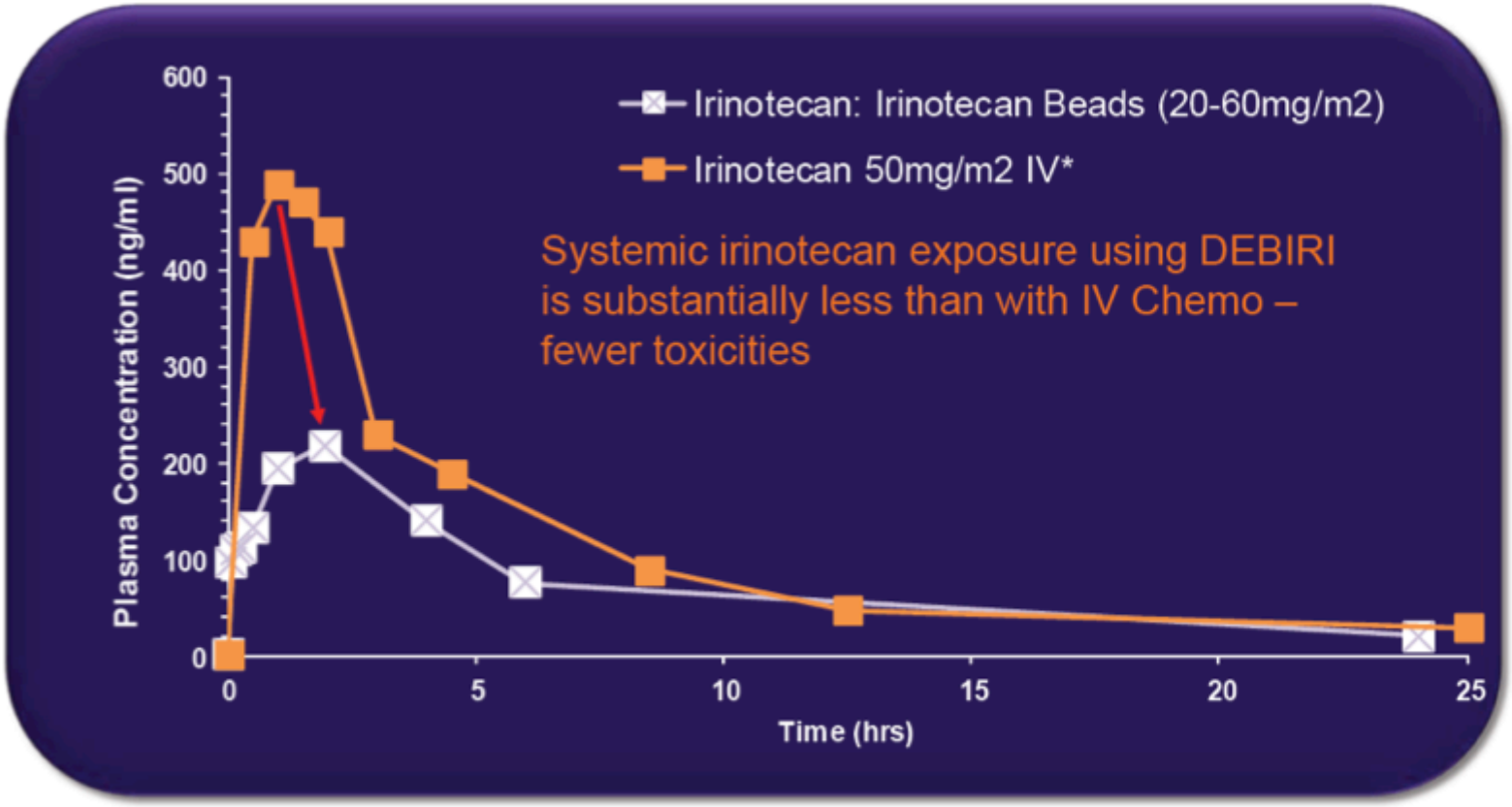
DEBIRI

Normal hepatic blood supply

- >80% portal circulation
- <20% arterial circulation



DEBIRI



Forni et al Can.Res. 54, 4347-4354

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Forni et al. Can.Res. 54, 4347-4354

RANDOMIZED CLINICAL TRIAL (RCT) - FIORENTINI

- 74 patients with refractory liver-only mCRC were randomized to:
  - 2 cycles of DEBIRI (n=36)
  - 8 cycles of systemic 5-FU/leucovorin/irinotecan (FOLFIRI) (n=38)
- Primary endpoint: OS
- Secondary endpoints: response, recurrence, toxicity, quality of life, cost and influence of molecular markers

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Fiorentini, Anticancer Res, 2012

RANDOMIZED CLINICAL TRIAL (RCT) - FIORENTINI

	DEBIRI	FOLFIRI
Number of patients	36 (35)	38 (35)
Gender (M/F)	20/16	24/14
Mean Age, years	64 (range 44-74)	63 (range 42-73)
Liver involvement (≤25% ≤50%)	26 10	26 12
Synchronous/metachronous disease	0/36	0/38
Number of metastases	4 (range 3-10)	4 (range 3-10)
Largest diameter of metastases (cm)	4.5 (range 2.5-8)	4 (range 2.5-8)
Performance status (0-1 and 2)	32 and 4	34 and 4
Extrahepatic metastases, n	0	0
Previous chemotherapy (2-3 lines)	23 13	25 14
Types of previous chemotherapy	13 FUFA, 18 FOLFOX, 13 IFL, 3 FOLFOX+BEVACIZUMAB 3 FU+CETUXIMAB	12 FUFA, 20 FOLFOX, 14 IFL, 5 FOLFOX+BEVACIZUMAB 3 FU+CETUXIMAB
Weight loss (1 to 3 Kg) in the last 8 weeks prior to study	20 (60%)	24 (63%)
ALBUMIN, g/dl (median)	4	3.9
CEA ng/ml	69 (range 3.5-473)	77 (range 2.5-611)
KRAS (WT M)	22/13	23/12
p53 (positive/negative)	22/13	20/15

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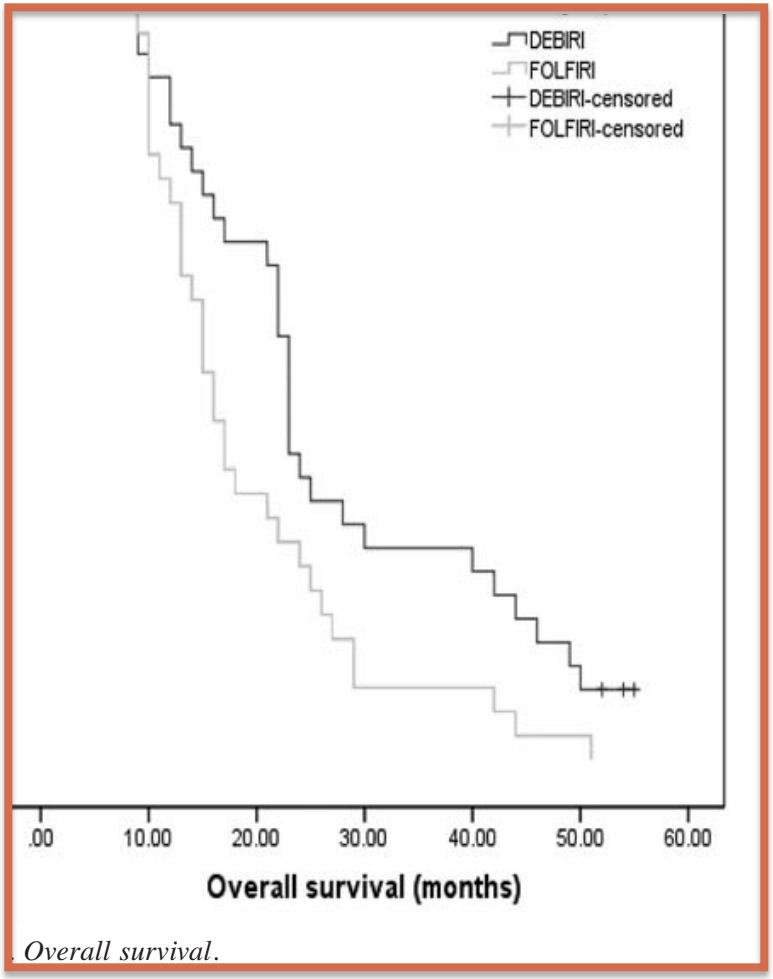
Fiorentini, Anticancer Res, 2012

RANDOMIZED CLINICAL TRIAL (RCT) - FIORENTINI



. *Overall survival*.

mOS DEBIRI: 22m (95% CI:21-23)
mOS FOLFIRI: 15m (95% CI:12-18)
P=0.031

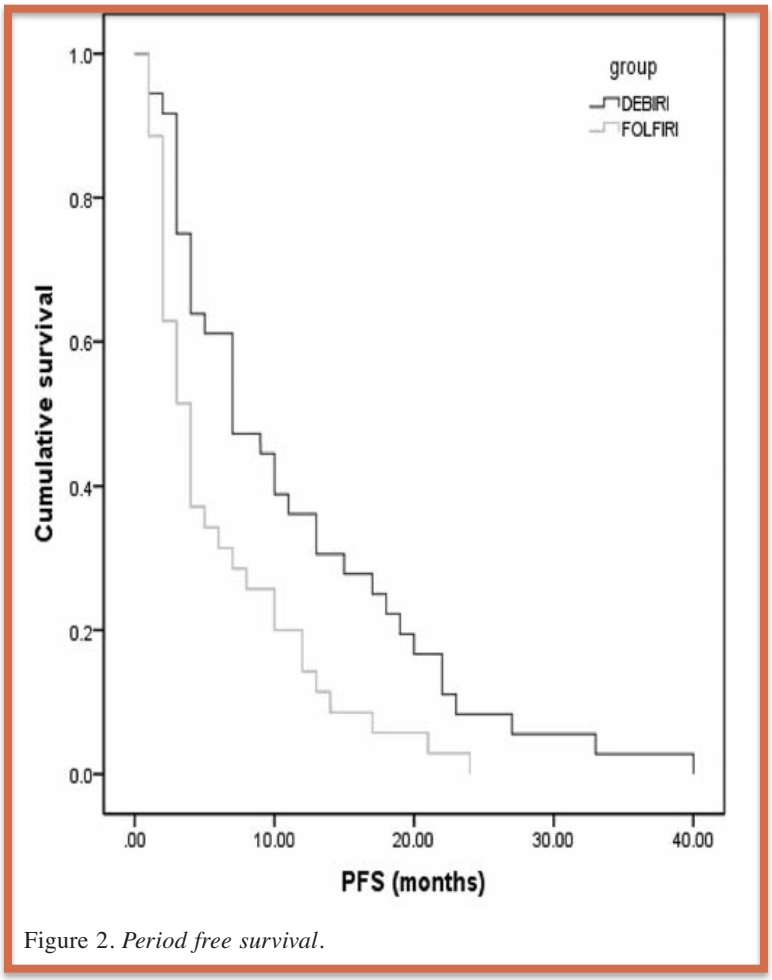


Figure 2. *Period free survival*.

mPFS DEBIRI: 7m (95% CI:3-11)
mPFS FOLFIRI: 4m (95% CI:4-5)
P=0.006

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Fiorentini, Anticancer Res, 2012

RANDOMIZED CLINICAL TRIAL (RCT) - FIORENTINI

Response	DEBIRI (n=35)	FOLFIRI (n=35)
Complete + partial	24 (68.6%)	7 (20%)
Stable disease	4 (11.4%)	12 (34.3%)
Progression	7 (20%)	16 (45.7%)

Fiorentini, Anticancer Res, 2012

RANDOMIZED CLINICAL TRIAL (RCT) - FIORENTINI

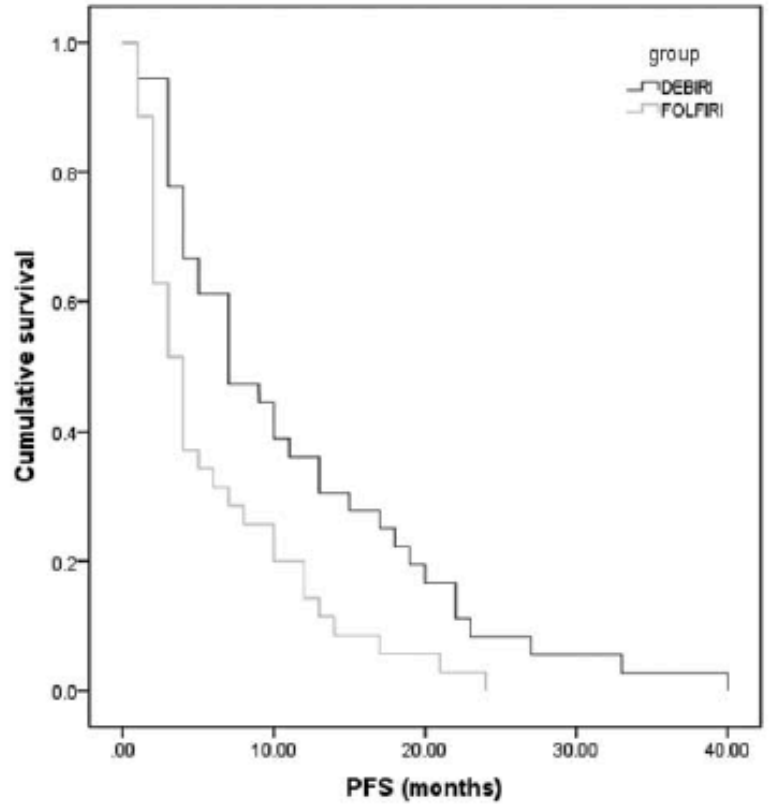

Figure 3. *Hepatic period free survival.*

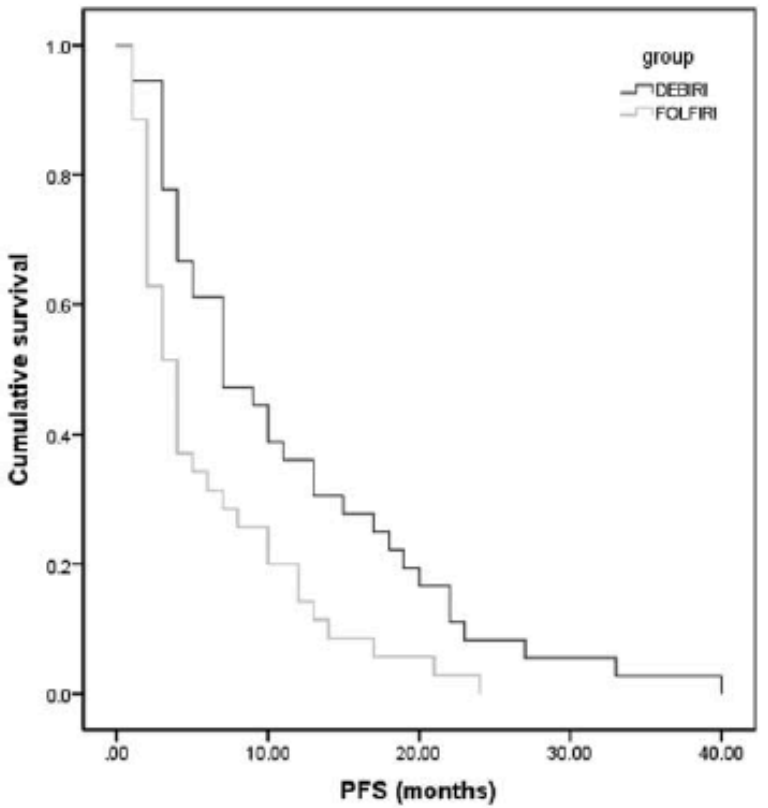

Figure 4. *Extra hepatic period free survival.*

mPFS DEBIRI: 7m (95% CI:21-23)
mPFS FOLFIRI: 6m
P=0.006

mPFS DEBIRI: 13m (95% CI:10-16)
mPFS FOLFIRI: 9m (95% CI:5-13)
P=0.64

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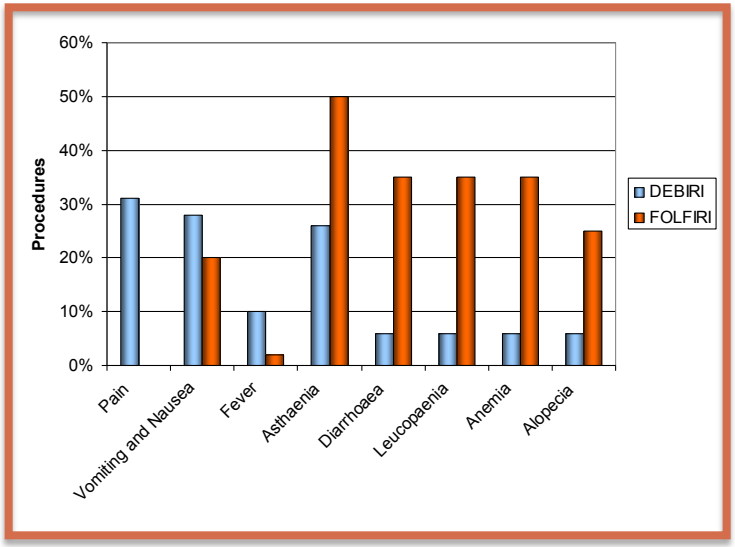
Fiorentini, Anticancer Res, 2012

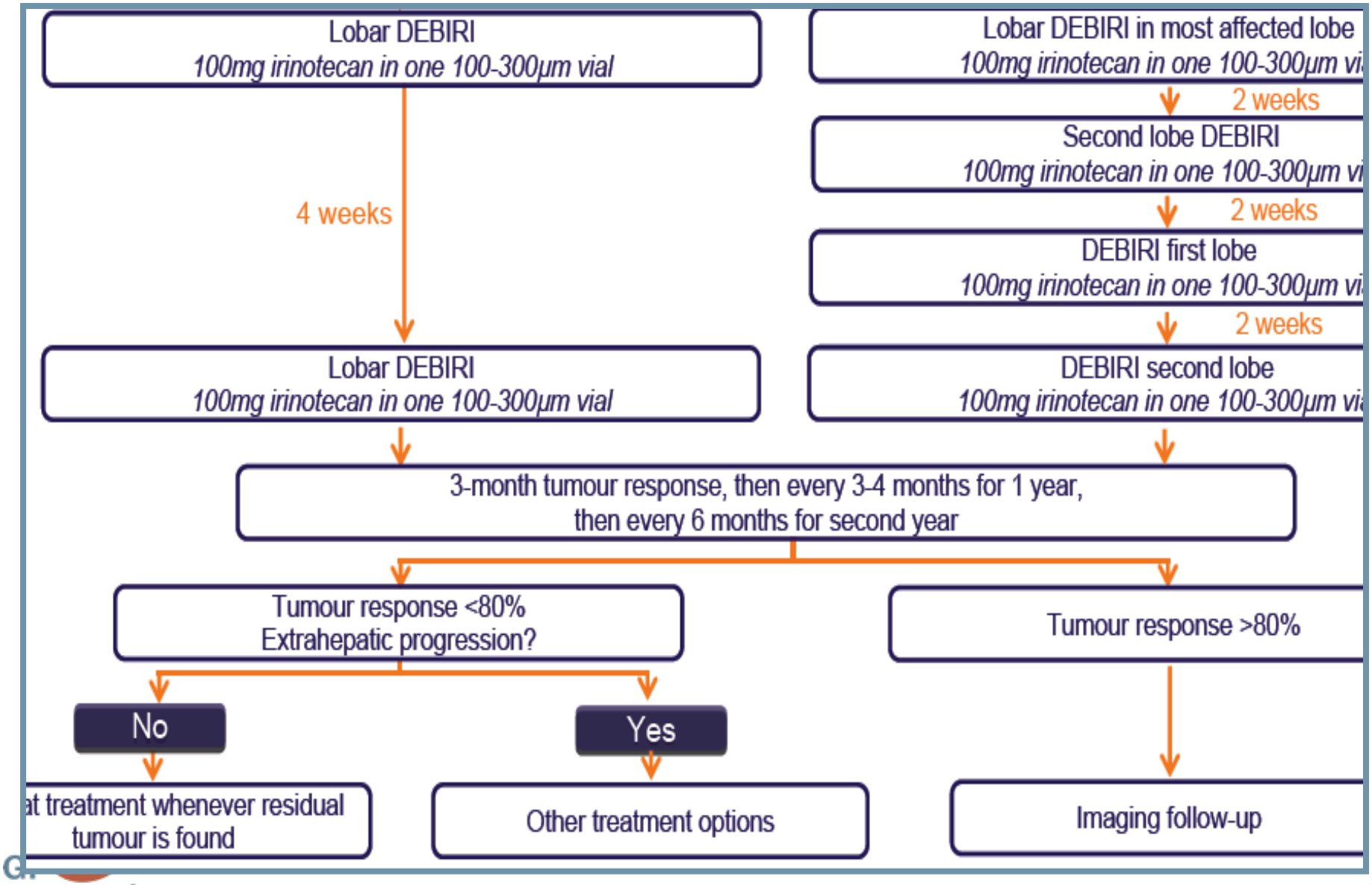
RANDOMIZED CLINICAL TRIAL (RCT) - FIORENTINI

Toxicity (Grade 2 and 3)	DEBIRI (% out of 70 cycles delivered)	FOLFIRI (% out of 277 cycles delivered)
Pain	30%	0%
Vomiting	25%	25%
Diarrhea	2%	35%
Asthenia	20%	50%
Leukopenia	5%	35%
Anaemia	5%	35%
Fever	15%	3%
Alopecia	5%	35%



Fiorentini, Anticancer Res, 2012

DEBIRI



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