



Results of a Prospective Randomised Trial Assessing Survival at 30 Months of Polyvinyl Alcohol Microspheres Preloaded with Irinotecan (DEBIRI™) vs FOLFIRI in Patients with Hepatic Metastases from Colorectal Cancer

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Introduction (1)



- Liver metastases (LM) from colorectal cancer (CRC) occur in more than 50% of patients
- 5-year survival after resection is 25-35%, but recurrence is common
- For unresectable LM the survival is 5% at 5 years
- Palliative chemotherapy is the mainstay of treatment

Introduction (2)



- Toxicity is common and median survival is about 22 months with the addition of monoclonal antibodies
- Ablative or trans-arterial techniques allow localised, minimally invasive therapy without systemic toxicity or morbidity
- Catheter-delivered arterial treatments include TACE with polyvinyl alcohol microspheres (Drug-Eluting Beads – DEB)

Drug-Eluting Beads and Irinotecan (DEBIRI™): Basic data



- DEB (DC Bead®) are loaded with irinotecan (IRI) 50mg/ml. The loading of IRI does not affect its ability to be suspended in contrast agent or delivered through a catheter
- Following porcine hepatic artery infusion of DEBIRI™, maximum plasma levels were 70-75% lower for both Irinotecan and SN-38, compared to intra-arterial bolus administration (*Taylor RR Eur J Pharm Sci. 2007 Jan; 30(1):7-14*)

Randomised Study: DEBIRI™ vs FOLFIRI



- DEBIRI™ is a combination of local drug infusion with selective embolisation of the liver metastases-feeding arteries. It is feasible and safe (*ASCO-GI 2007, abs # 356; IN VIVO 2007, 21, 6; ASCO-GI 2008 abs # 480*)
- The study was designed to show an increase of 40% of median overall survival (MS, primary endpoint) at 2 years follow-up (HR = 0.72 using Kaplan-Meier method)
- Response rate, progression-free survival and quality of life (Edmonton Symptom Score) were secondary endpoints

Study Design: DEBIRI™ vs FOLFIRI



Eligible patients

Liver-limited mCRC refractory to chemotherapy

Randomisation

74 patients

Arm A

DEBIRI™ (2 administrations)
36 patients

Chemotherapy
Palliative Care

Arm B

FOLFIRI (8 administrations)
38 patients

Chemotherapy
Palliative Care

Patients and Methods



- From December 2006 to December 2008, 74 patients were randomised:
 - 36 patients received DEBIRI™ once a month for two treatments. Intravenous hydration, morphine, anti-emetic and antibiotic prophylaxis were provided to DEBIRI™ Arm
 - 38 patients received FOLFIRI (IRI 180mg/m² on day 1 with LV 100mg/m² as 2-hour infusion, followed by FU 400mg/m² bolus and FU 600mg/m² as 22-hour infusion on days 1 and 2 every 2 weeks for 8 cycles. Anti-emetics and Dexamethazone were provided to CT Arm

Patient Characteristics



	DEBIRI™ (D)	FOLFIRI (CT)
Number of patients	36	38
Sex (M/F)	20/16	24/14
Age	64 (range 44-74)	63 (range 42-73)
Liver involvement ($\leq 25\%/ \leq 50\%$)	26/10	26/12
Synchronous/metachronous disease	0/36	0/38
Number of metastases	4 (range 3-10)	4 (range 3-10)
Largest diameter (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	0	0
Previous chemotherapy (2lines/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 in 2 months	20 (60%)	24 (63%)
ALBUMIN, g/dl (median)	4	3.9
CEA ng/ml	69 (range 3.5-473)	77 (range 2.5-611)
K-RAS (WT/M)	22/14	26/12
P53 (positive/negative)	22/12	20/18

DEBIRI™: Supportive Therapy

(Fiorentini G et al: Hepatogastroenterology 2008; 55(88):2077-82)



Intravenous (iv) hydration started day -1 and continued on day 0, +1, +2

- 2000ml bag/24h infusion (1000ml of saline solution 1000ml of glucose 5%) with the addition of Ranitidine 900mg

Prophylactic treatment against pain

- Morphine 10mg one vial iv 30 minutes before DEBIRI™ and one vial at +6 hours
- Intra-arterial Lidocaine 5ml just before DEBIRI™

Prophylactic treatment against nausea

- Tropisetron 5mg, 1 vial iv before and 1 vial at +6 hours
- Prednisone 25mg orally (or Desamethasone 8mg iv) at 08.00am and at 08.00pm on day 0, +1, +2, +3, +4, +5

Prophylactic treatment against infection

- Cefazolin 2000mg iv at 08.00am and at 08.00pm day 0, +1, +2
- The supportive treatment is continued if required on day +3, +4, +5

DEBIRI™: Administration



- Diagnostic angiography (DSA) was performed
- Under fluoroscopic guidance, a solution of 4ml of DEB 100-300 μ m loaded with IRI 200mg and mixed with non-ionic contrast medium was injected into the artery feeding the metastases

Results



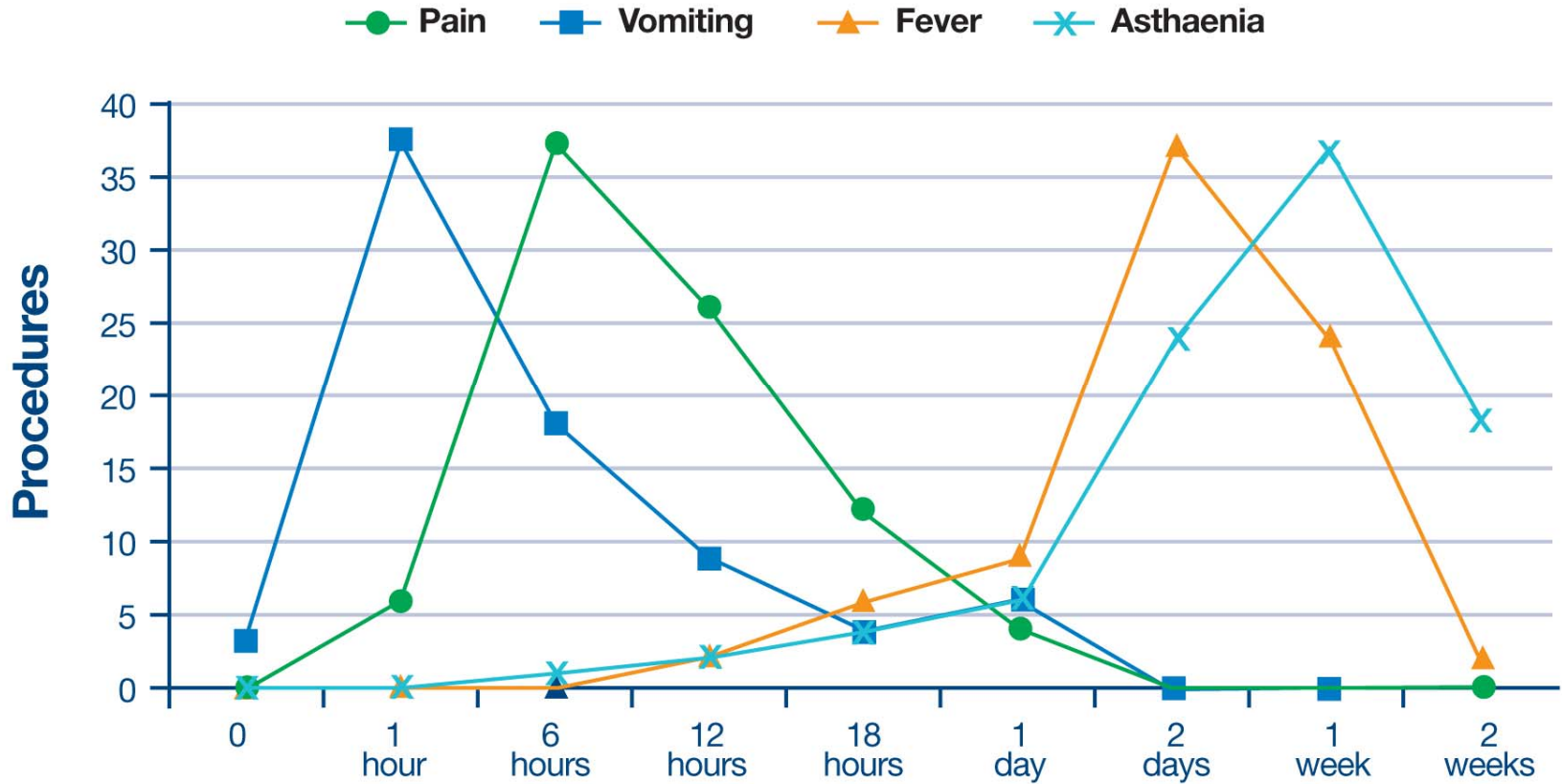
- 3 out of 38 FOLFIRI (CT) patients were not available for all evaluations (1 declined and 2 refused)
- 1 out of 36 DEBIRI™ (D) patients had early disease progression
- 35 (CT) and 35 (D) patients were analysed for this report
- 70 cycles of DEBIRI™ with a relative dose intensity of 99% and 272 FOLFIRI cycles with a relative dose intensity of 90% were administered

Observed Toxicity (G2-G3)



Toxicity (all procedures)	70 DEBIRI™	272 FOLFIRI
Pain	30%	0%
Vomiting	25%	25%
Diarrhoea	2%	35%
Asthenia	20%	50%
Leukopenia	5%	35%
Anaemia	5%	35%
Fever	15%	3%
Alopecia	5%	35%

Appearance of Toxicity in DEBIRI™ Arm



Responses Observed



	DEBIRI™ 35 patients	FOLFIRI 35 patients
Complete and partial responses	24 (68.6%)	7 (20.0%)
Stable disease	4 (11.4%)	12 (34.3%)
Progression	7 (20.0%)	16 (45.7%)

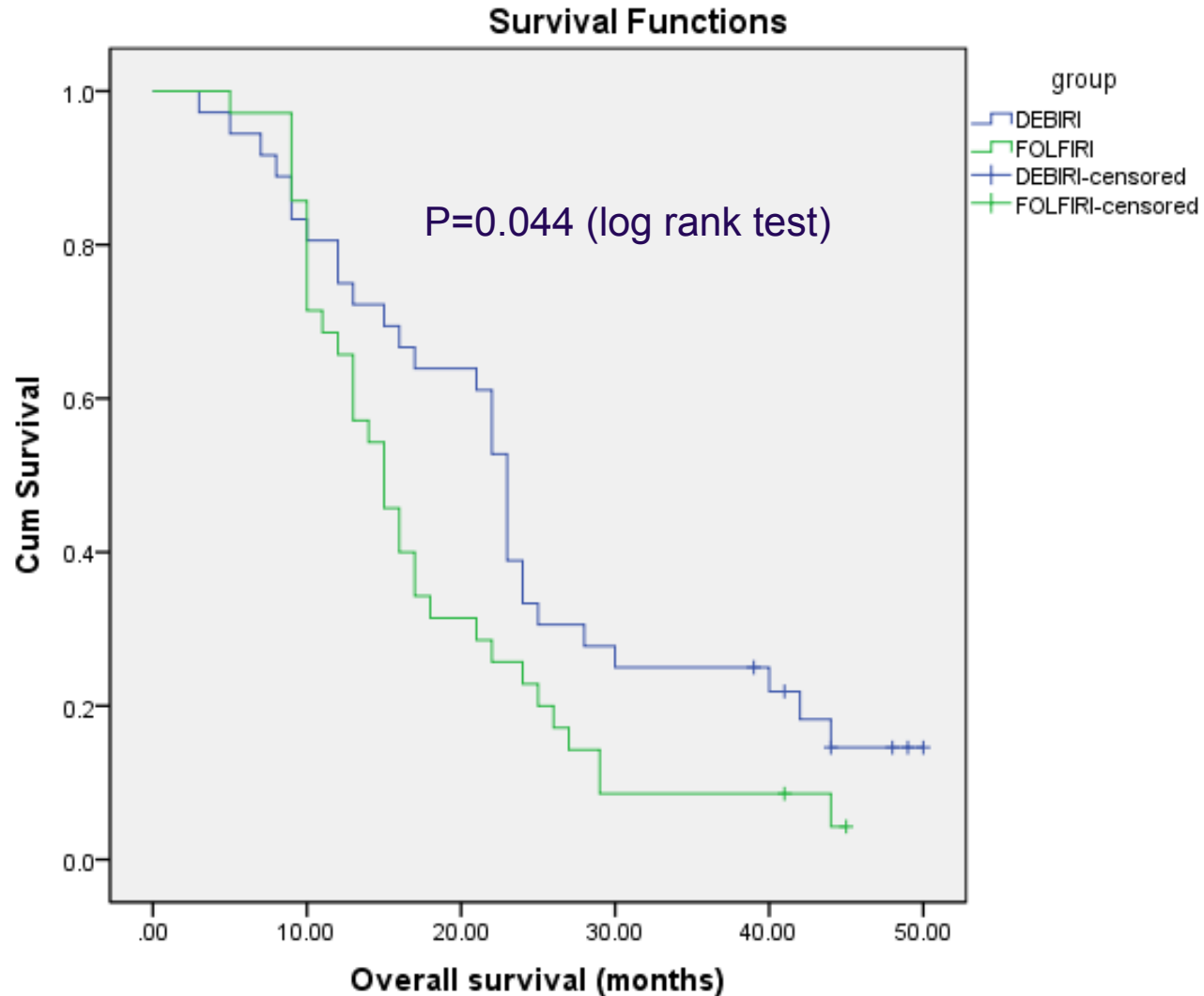
Results

(at median follow-up 30 months range 26-48)

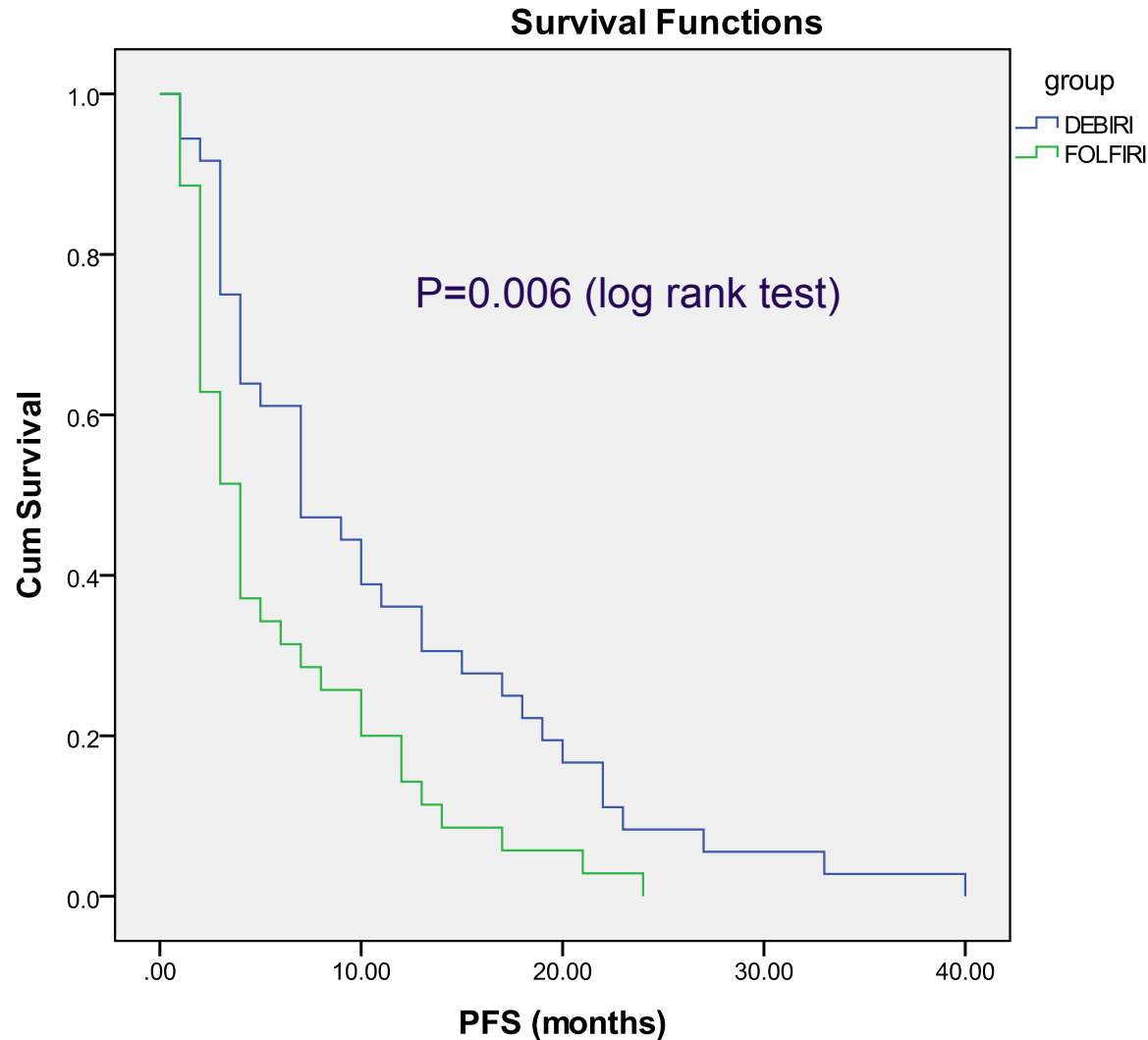


Arm	Median Overall Survival (Months)	PFS (Months)	Acute Toxicity (G2-G3)	Late Toxicity (G2)	Edmonton Score Improvement (from baseline)	Cost per Patient (Euros)
DEBIRI™ (D) (n=34)	23	7	70%	20%	60%	7,000 (2 D)
FOLFIRI (CT) (n=35)	15	4	25%	80%	22%	24,000 (8 CT)

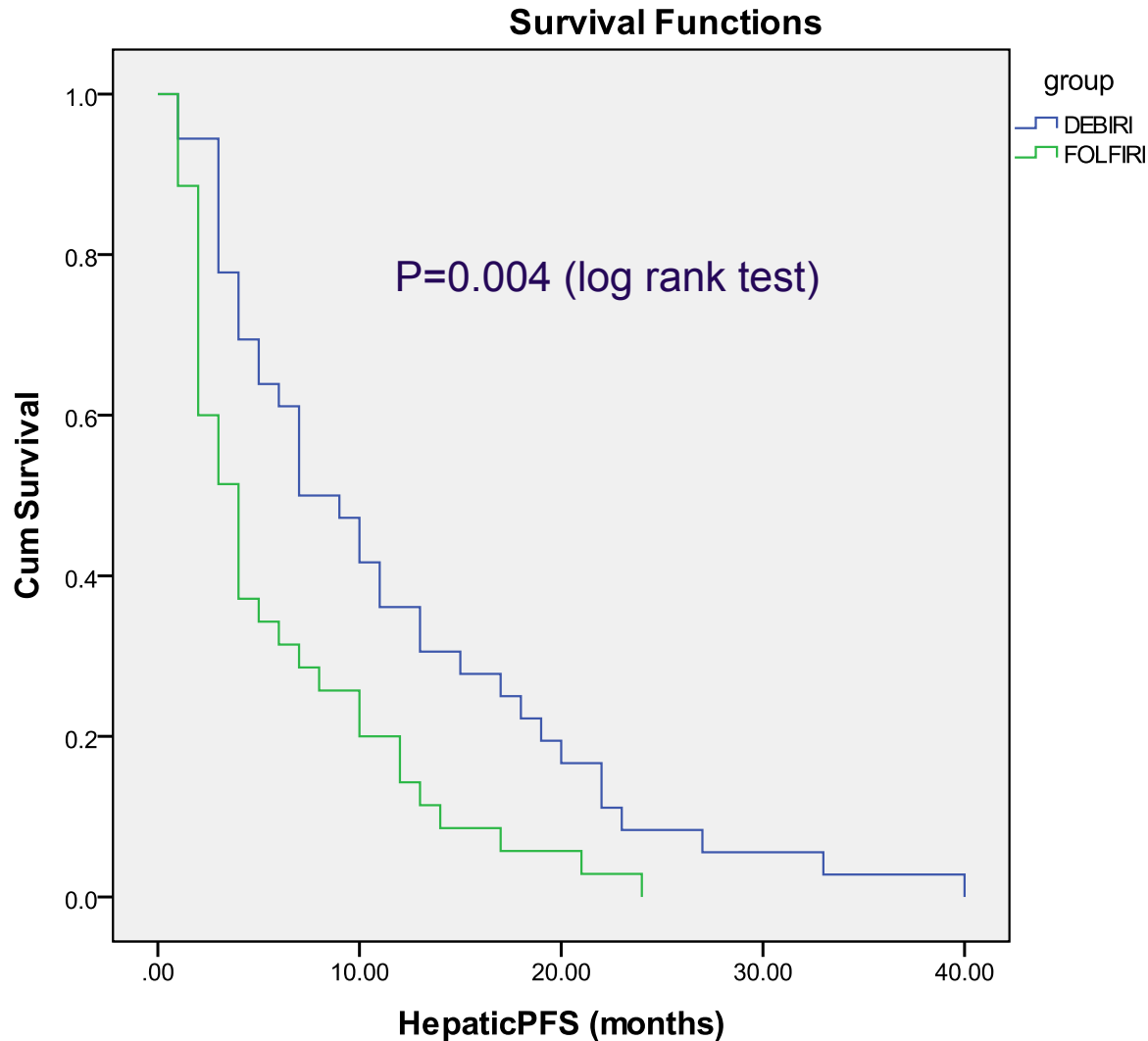
Kaplan-Meier Curve: Overall survival (OS)



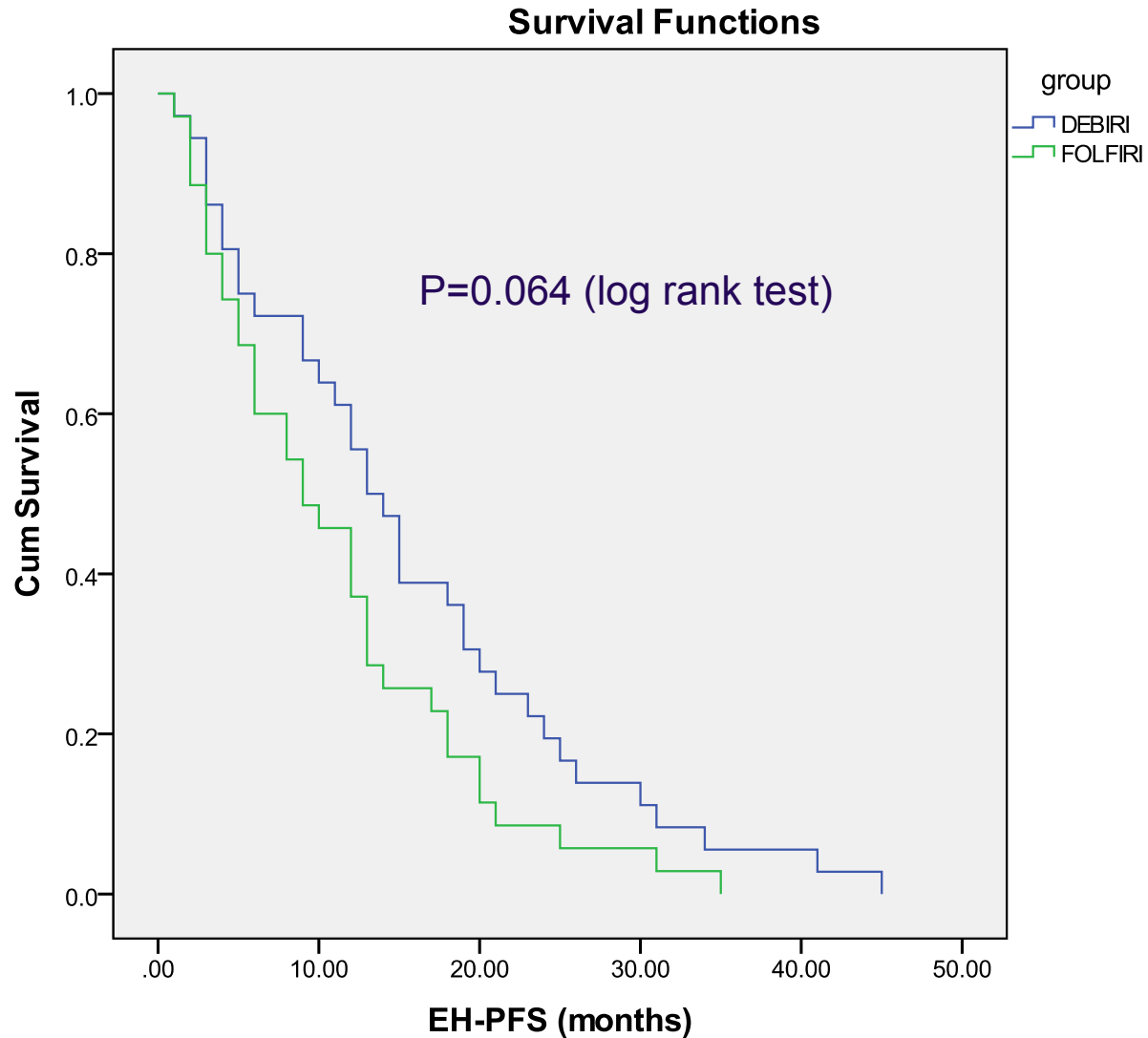
Kaplan-Meier Curve: Progression-free survival (PFS)



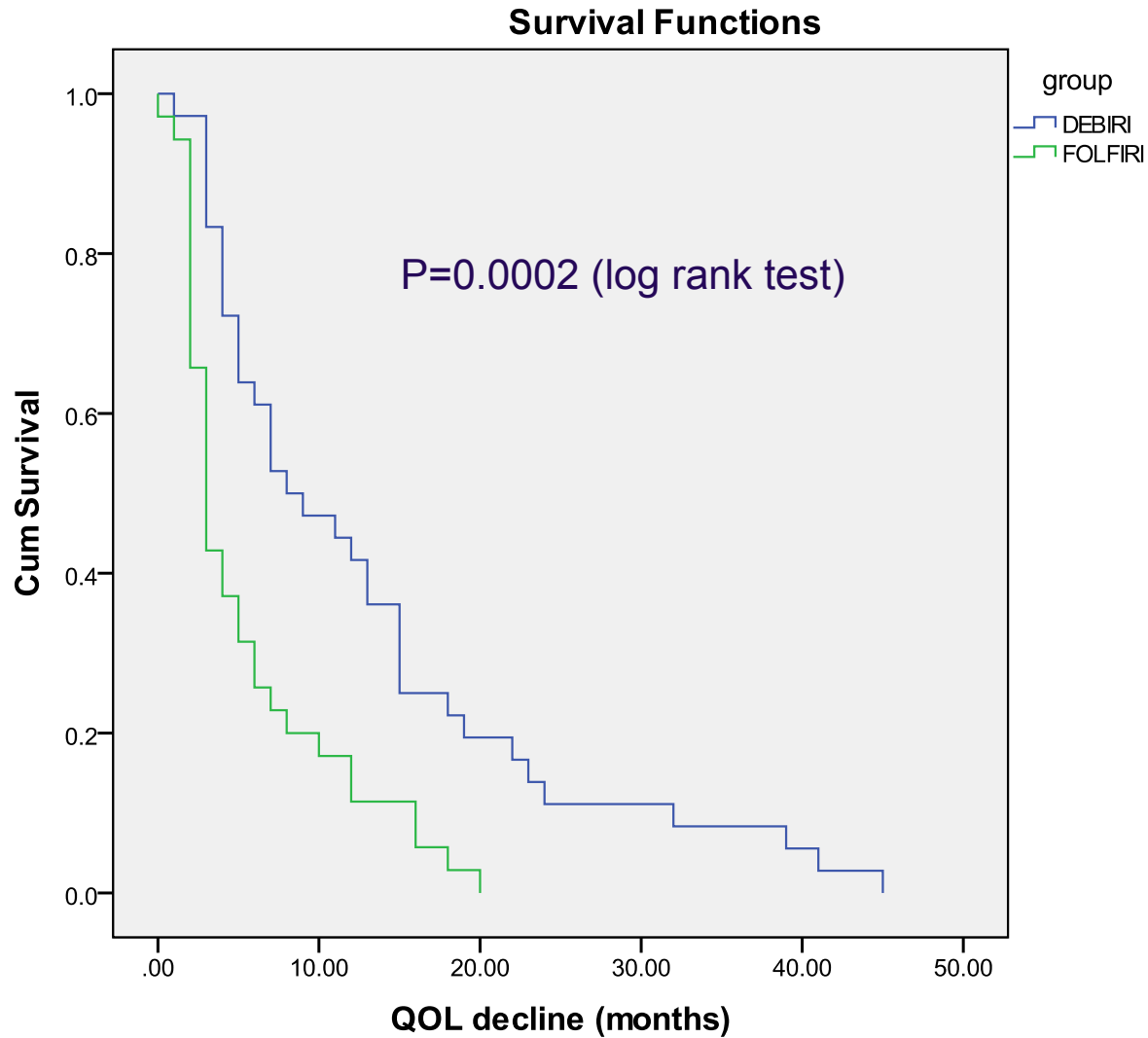
Kaplan-Meier Curve: Time to hepatic progression



Kaplan-Meier Curve: Time to extrahepatic progression



Kaplan-Meier Curve: Time to decline in QOL



Sites of Progression



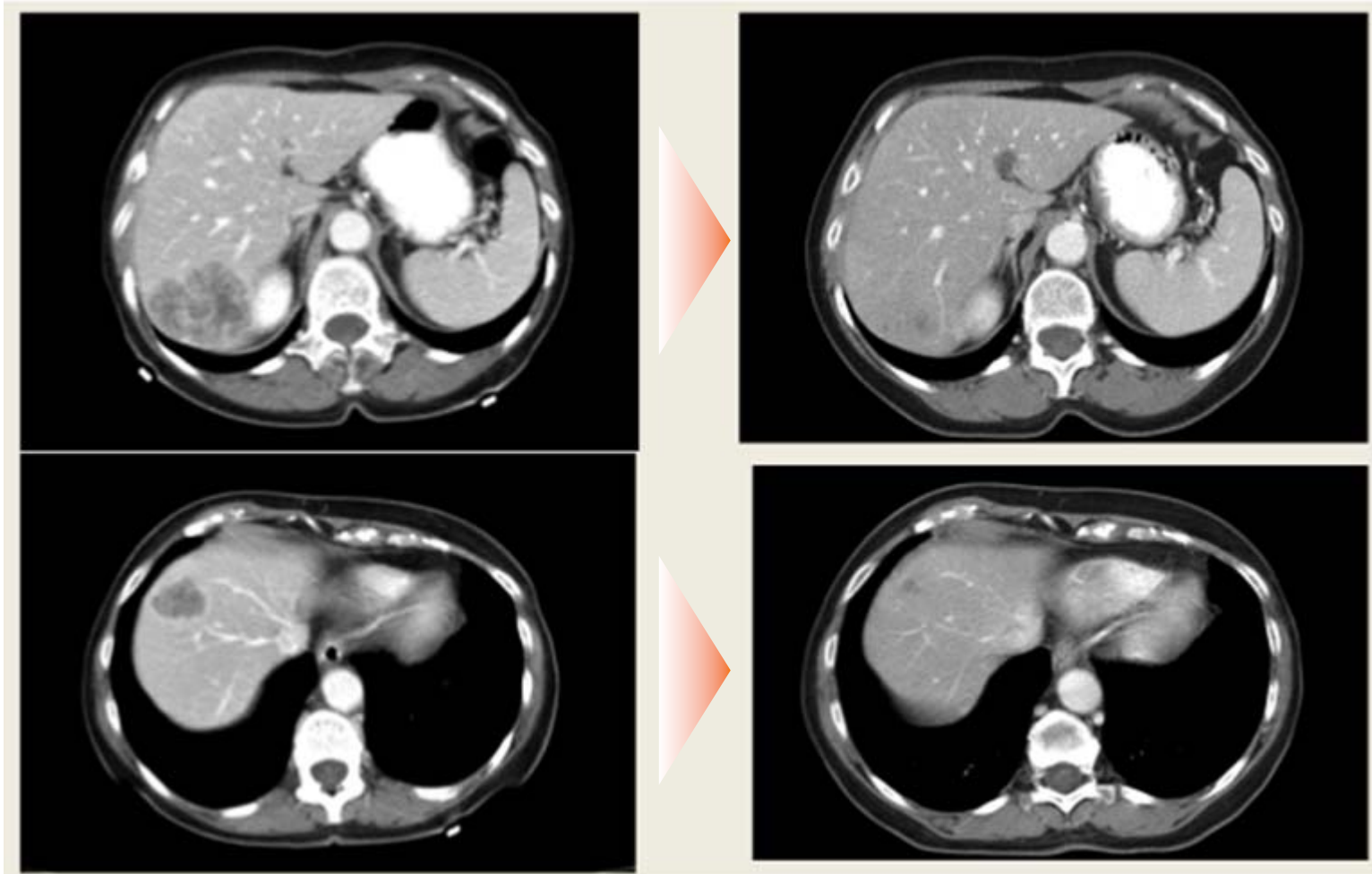
Arm	DEBIRI™ (D)	FOLFIRI (CT)
Number of patients treated	35	35
Liver	17	23
Liver + Lung	8	7
Liver + Lung + Bones	3	3
Liver + Peritoneal Carcinosis	2	1
Liver + Lung + Brain	1	1
Lymphonodes + Peritoneal Carcinosis	2	0

Therapy at Progression

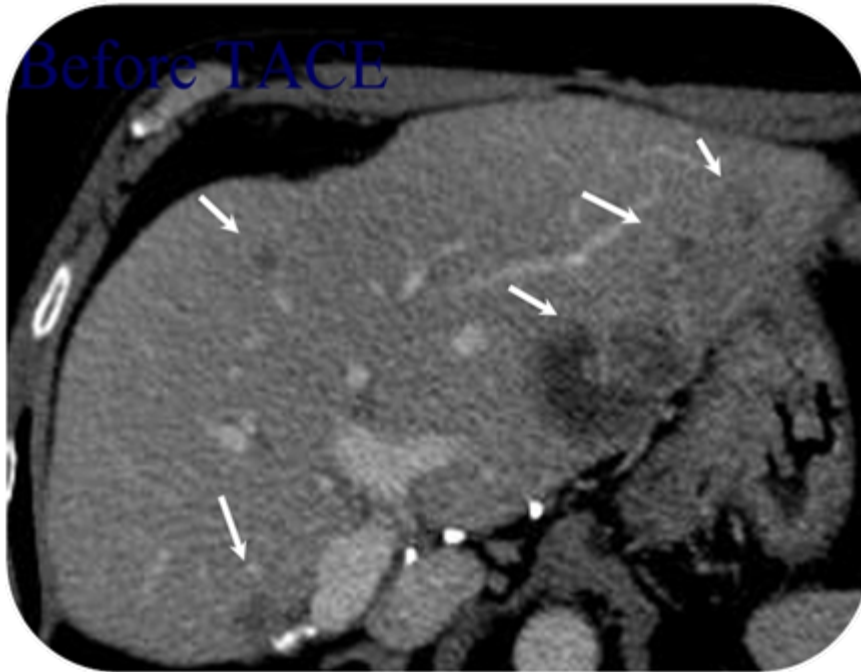


Type of Therapy	DEBIRI™ (D)	FOLFIRI (CT)
FU c.i.	8	4
FU c.i. + Mitomycin	4	4
FOLFOXIRI	2	2
Herbal Medicine + Holistics	2	5
FOLFIRI + CETUXIMAB	3	2
FOLFOX + BEVACIZUMAB	2	3
Palliative Medicine	14	14

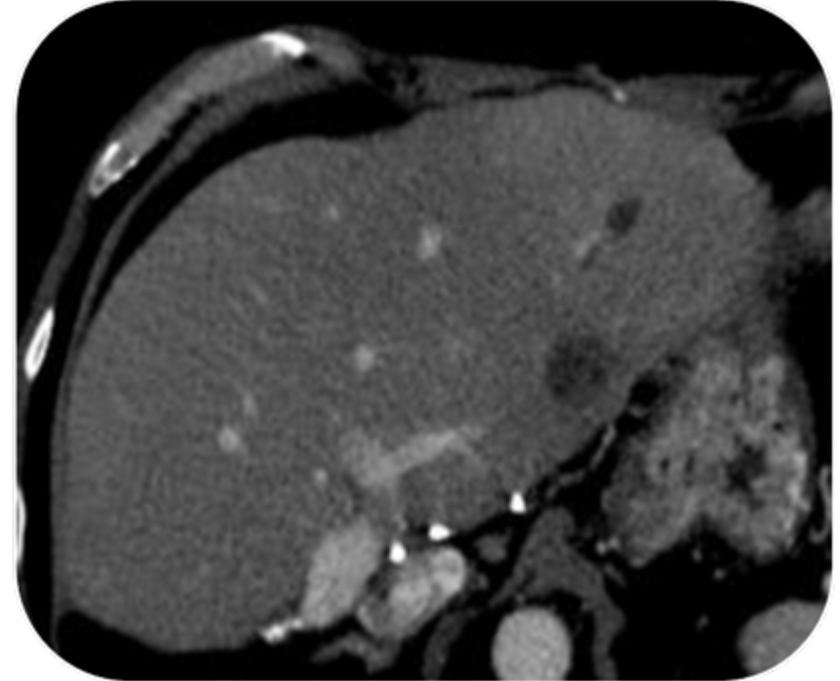
DEBIRI™ Case 1: Partial remission lasting 190 days



DEBIRI™ Case 2: Partial remission lasting 180 days



Before DEBIRI



6 months after DEBIRI

Conclusions (1)



- DEBIRI™ achieved the primary study endpoint by improving median overall survival when compared to FOLFIRI
- DEBIRI™ statistically produced a significant increase in overall survival, progression-free survival and quality of life
- DEBIRI™ significantly reduced costs when compared to systemic FOLFIRI

Conclusions (2)



- DEBIRI™ reported more immediate toxicity (related to post-embolisation syndrome – PES) than FOLFIRI. These symptoms can be reduced with periprocedural medications
- Late toxicity (mainly leukopenia, anaemia, diarrhoea, asthenia and alopecia) were more common with FOLFIRI
- Our study is the first in literature which reports a clear survival benefit of an intra-arterial hepatic therapy over systemic chemotherapy in patients pretreated with at least two lines of chemotherapy