Intra-arterial Infusion of Irinotecan-loaded Drug-eluting Beads (DEBIRI) *versus* Intravenous Therapy (FOLFIRI) for Hepatic Metastases from Colorectal Cancer: Final Results of a Phase III Study

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Abstract. *Background: Metastases to the liver receive most of their blood supply from the arterial route, therefore for patients with hepatic metastases from large bowel cancer, hepatic arterial infusion adopting drug-eluting beads preloaded with irinotecan (DEBIRI) may offer a chance of cure. Patients and Methods: In a multi-institutional study, 74 patients were randomly assigned to receive DEBIRI (36) versus systemic irinotecan, fluorouracil and leucovorin (FOLFIRI, 38). The primary end-point was survival; secondary end points were response, recurrence, toxicity, quality of life, cost and influence of molecular markers. Results: At 50 months, overall survival was significantly longer for patients treated with DEBIRI than for those treated with FOLFIRI (p=0.031, log-rank). Median survival was 22 (95% Confidence Interval CI=21-23) months, for DEBIRI and 15 (95% CI=12-18) months for FOLFIRI. Progression-free survival was 7 (95% CI=3-11) months in the DEBIRI group compared to 4 (95% CI=3-5) months in the FOLFIRI group and the difference between groups was statistically significant (p=0.006, log-rank). Extrahepatic progression had occurred in all patients by the end of the study, at a median time of 13 (95% CI=10-16) months in the DEBIRI group compared to 9 (95% CI 5-13) months in the FOLFIRI group. A statistically significant difference between groups was not observed (p=0.064, log-rank).The median time for duration of improvement to quality of life was 8 (95% CI=3-13) months in the DEBIRI group and 3 (95% CI=2-4) months in the FOLFIRI group. The difference in duration of improvement was statistically significant (p=0.00002, log-rank). Conclusion: This study showed a statistically significant difference between DEBIRI and FOLFIRI for overall survival (7 months), progression-free survival (3 months) and quality of life (5 months). In addition, a clinically significant improvement in time to extrahepatic progression (4 months) was observed for DEBIRI, a reversal of the expectation for a regional treatment. This suggests a benefit of DEBIRI treatment over standard chemotherapy and serves to establish the expected difference between these two treatment options for planning future large randomized studies.*

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Key Words: Liver metastases, chemoembolization, irinotecan, colorectal cancer, angiography, drug-eluting beads, DEBIRI, KRAS, p53, FOLFIRI.

In Europe, there were an estimated 412,900 new cases of colorectal cancer (CRC) diagnosed in 2006, with approximately 207,400 CRC-related deaths, representing the second highest cancer mortality rate (1). In the United States more than 150.000 CRC-related deaths were reported in 2009 (2).

Nearly 25% of CRC patients present with synchronous metastatic disease at first diagnosis, while an additional 40-50% develop metastases during the course of their disease (3, 4). The liver will remain the only site of metastatic disease until end-stage in most patients and a small number of patients will be candidates for surgical resection. Liver involvement is a major source of organ failure, morbidity, and generally leads to death in the majority of patients (4).

Surgical ablation is the standard treatment in patients with resectable liver metastases (LM) but results are frequently disappointing: 5-year survival after resection is 25-35%, and recurrence is common (5). In addition, 40%-60% of patients who undergo liver resection with curative intent will have new hepatic deposits. When surgery is not feasible, chemotherapy, radiofrequency ablation, intra-arterial chemotherapy and transarterial chemoembolization (TACE) are possible alternatives to achieving control of the disease in the liver.

Chemotherapy options for metastatic CRC have expanded over the past decades to include the newer agents irinotecan and oxaliplatin. Incorporation of these agents into regimens containing the traditional agents 5-fluorouracil (5-FU) and folinic acid for first or second-line treatment has extended median survival over 20 months but side-effects are common (6-8). When monoclonal antibodies and angiogenesis inhibitors were added to chemotherapy only a slightly increase of survival was reported (9-11). Despite new chemotherapy regimens and improvements in screening and diagnosis, the 5-year survival rate for patients with metastatic CRC remains dismally low at 5%, with limited options for patients with disease refractory to chemotherapy, or for ones that experience disease relapse.

Ablative techniques or locoregional delivery of drug allow localised, minimally invasive therapy without systemic toxicity or morbidity (12, 13). Hepatic arterial infusion in the treatment of non-resectable LM from CRC has demonstrated evidence of more responses but not a clear advantage in terms of survival (14-17). Recently a new randomized study has reported an advantage in survival stressing the importance of intra-arterial route of drug administration (18).

TACE is the administration of embolic particles mixed with chemotherapeutic drugs. It produces a shutdown of blood flow and the simultaneous release of high doses of the drug, increasing the drug concentration and exposure to the drug compared with standard intra-arterial infusion (19,20). TACE is currently approved as the standard of care for intermediate stage hepatocellular carcinoma without portal vein invasion, due to the survival benefits when compared to supportive care (21). In the last decade, TACE has been investigated for LM from CRCR (20, 22-25).

Clinical phase II studies consistently reported high response rates to TACE in the treatment of LM from CRC but randomized studies are lacking and the impact of this procedure on survival is unknown. We recently reported a preliminary evaluation at two years of a randomized trial (25). On the other hand, this technique was show to be associated to a variety of side effects, and the most common of them is post embolization syndrome (PES). TACE causes tissue ischemia, which induces expression of cytokines and inflammation. Not every patient will have PES; it is estimated to develop in 30% to 80% of patients. It consists of mild symptoms, but some patients do have pain in the right upper quadrant (RUQP), nausea, vomiting and fever. Elevation of liver enzymes occurs almost in every patient (20, 22-24). Probably the more extensive type of embolization performed, the greater the possibility of PES. Rare complications are liver abscess, liver failure, pancreatitis, renal failure (21, 24, 26). Adequate supportive therapy, thus, is required (27).

Recently, new polyvinyl alcohol beads capable of being loaded with doxorubicin or irinotecan (drug-eluting beads) have been developed. They release the drug after injection into the arterial network of the tumor (28-30). Embolization associated with the delivery of these particles permits flow in tumor-feeding arteries to be reduced thereby decreasing the washout of drugs and increasing the dwell time of anticancer drug around the tumor cells. Taylor *et al*. (28) observed that following porcine hepatic artery infusion of such beads with irinotecan (DEBIRI), maximum plasma levels were 70-75% lower for both irinotecan and SN-38, compared to intra-arterial bolus administration, with peak levels observed at 2 and 5 min after completion of the infusion procedure. Recently the use of DEBIRI has been reported for the treatment of patients with LM from CRC; it was reported as feasible and safe, with low toxicity and interesting responses (22, 24, 25).

Because of the uncertainty in drawing any definitive interpretation from these studies, a multicenter trial was designed in order to compare DEBIRI treatment with irinotecan, fluorouracil and folinic acid (FOLFIRI) given intravenously. In this design, no cross-over was allowed, so the trial addresses the fundamental question of whether DEBIRI therapy is more effective than systemic therapy for the treatment of LM from CRC. The primary end-point of the study was survival; secondary end-points were tumor response, toxicity, quality of life (QoL), and cost effectiveness. Tumor and LM biopsies from both groups were analyzed for KRAS and p53 in order to evaluate the utility of these molecular markers in predicting outcomes.

Patients and Methods

We reported a prospective multiple-institutional double-arm treatment study, approved by the Institutional Review Board was evaluated from December 2006 to December 2008 in which 74 patients presenting with LM from CRC were randomized to receive DEBIRI or systemic chemotherapy (FOLFIRI).

The study was conducted in compliance with the protocol and the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP). Informed consent was obtained from the each participant prior to evaluation, screening and treatment. The study was initiated in order to apply the criteria for appraisal of the quality of a study. We present a well-reported patient population, with high quality data and quality control, and with good clinically significant follow-up without loss of patients .

All patients were required to have histologically confirmed CRC with unresectable LM occupying less than 50% of the liver parenchyma and no radiological evidence of extrahepatic disease.

Patients who have previously received chemotherapy were not excluded if past therapy had been completed 3 months before protocol therapy. Patients who had received radiation to the liver, or had portal vein occlusion or ascites were excluded. Patients were excluded if they had a previous or concurrent malignancy and had to have total bilirubin level of ≤2 × upper limit of normal, with normal hematologic and renal function. A biopsy was required before registration to document LM with metastatic disease. Each patient was asked to complete health-related QoL instruments before treatment and every 3 months during participation in the study until 12 months. The following instrument was used: Edmonton Symptom Assessment System (31).

All patients had received at least two (45) or three (29) lines of chemotherapy. The percentage of liver involvement was ≤ 25% in 52 cases and ≤50% in 22 cases.

Drug doses and schedule. DEBIRI consisted of drug eluting beads loaded with irinotecan (Campto® injection solution) given twice at 200 mg (50 mg/ml) once a month.

Patients underwent DEBIRI administration using angiography. A catheter was placed as selectively as possible in order to isolate the blood supply to the metastases and achieve localized chemotherapy. Selective hepatic administration involved embolization of the right or left hepatic arteries separately as they branch from the proper hepatic artery. Highly selective administration involved embolization of branches leading off from the hepatic arteries, preferably the lesion itself or its feeding branches. The size of drug eluting beads was chosen to be 100–300 μm.

Patients undergoing DEBIRI were monitored closely after each procedure in case hepatic side effects developed, or any other factors became apparent that would exclude them from a adequate comparison with patients receiving systemic chemotherapy. Intravenous hydration, morphine, anti-emetic and antibiotic prophylaxis were provided to reduce PES.

Intravenous hydration started day -1 and continued on day 0, +1 and +3 consisting of 2000 ml/24 h infusion (1000 ml of saline solution, 1000 ml of 5% glucose) with the addition of ranitidine at 900 mg. Prophylactic treatment against nausea was 5 mg Tropisetron, before and at +6 h; 25 mg prednisone orally (or 8 mg dexamethasone *i.v.*) at 08.00 am and at 08.00 pm days 0 to +5.

Prophylactic treatment against pain was based on 10 mg morphine 30 min before TACE and 10 mg at +6 hours. Intra-arterial 80 mg lidocaine was given just before DEBIRI was adopted.

Prophylactic treatment against infection was based on 2000 mg Cefazolin *i.v.* at 08.00 am and at 08.00 pm day 0 to 2. The supportive treatment continued if required on days +3 to +5.

Systemic FOLFIRI chemotherapy consisted of intravenous irinotecan (Campto® injection solution) at 180 mg/m^2 on day 1 with folinic acid at 100 mg/m^2 as a 2 h infusion, followed by bolus of fluorouracil at 400 mg/m^2 and fluorouracil 600 mg/m^2 as 22 h infusion on days 1 and 2 every 2 weeks 8 times (4 months of treatment). Ondansetron (8 mg) and dexamethasone (12 mg) intravenously on day 1, and loperamide (2 mg) if required, were provided to control nausea, vomiting and diarrhoea.

Toxicity evaluation. All adverse events were recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, Version 3.0.

Calculation of tumour response. Tumour response was calculated using either contrast-enhanced spiral computed tomography (CT) or magnetic resonance imaging (MRI), with quantification of tumour response according to either Response Evaluation Criteria in Solid Tumors (RECIST) or European Association for the Study of the Liver (EASL) criteria (32-34). Treatment response using RECIST response criteria was categorized as complete response (CR) or partial response (PR). Complete response was defined by the disappearance of measurable disease, or the absence of arterial phase contrast enhancement as measured by CT, persisting for ≥4 weeks without the appearance of new measurable lesions. Partial response was defined as a ≥30% reduction in the sum of the products of the greatest diameter (length) and the greatest perpendicular diameter (width) of all measurable lesions compared with baseline, and no appearance of new measurable lesions. Stable disease (SD) represented cases in which neither PR nor progressive disease (PD) criteria were met, taking as reference the smallest sum of the greatest diameter recorded since the commencement of treatment. PD was defined by the occurrence of one of the following conditions: (i) the sum of the cross products of all measurable lesions, including new lesions, increases by >50% compared with the nadir, or (ii) new measurable lesions occur in any part of the body outside the liver.

Treatment response assessment using EASL criteria represented a measure of local tumour response based on tumour progression with respect to change in necrosis (35). The greatest diameter of viable tumour against greatest total tumour diameter is measured and initial measurements are compared with those after each DEBIRI treatment.

Molecular marker evaluation. The detections of *KRAS* activating mutations (most frequently at codon 12 and codon 13) was performed using the real-time polymerase chain reaction (36).

p53 protein expression was assessed by immunohistochemistry using paraffin sections. Patients with greater than 10% positive nuclei with moderate or strong staining were considered positive, whereas all others were negative.

Statistical methods. Patients were randomly assigned to DEBIRI or systemic therapy. Stratification factors included percentage liver involvement (≤25%, ≤50%); type of prior palliative chemotherapy with/without irinotecan; weight loss in three months; CEA; KRAS status; and p53 IHC.

The primary endpoint of the study was overall survival, defined as the time between the start of treatment and the death from any cause,

The study was designed to show an increase of 40% of median overall survival at 2 years' follow-up with an alpha error of 0.05 and a power of 0.8.

Secondary endpoint were time to progression (TTP), time to hepatic progression (THP), time to extrahepatic progression (TEP) and time to decline in quality of life (DQoL). TTP was defined as the time between start of treatment and documented progression or death of any cause; THP was calculated from start of treatment and documented progression of disease in the liver. TEP was defined as time from start to treatment and progression outside the liver; DQoL was defined as time since start to treatment and first decline in QoL.

Log rank test and Kaplan-Meyer curves were used to calculate the endpoints. Differences between categorical variables like toxicities were investigated using Fisher's exact test. All the *p*-values were two-sided. The analyses were performed as intent-to-treat.

IBM SPSS Statistics (International Business Machines Corporation, New York, NY, USA) was used for all calculations and plots. Differences between categorical variables like toxicities were investigated using Fisher's exact test. Both the log-rank test

Table I. *Patients' characteristics*.

	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

and the Cox proportional hazards model were used to assess the association of OS,TTP,THP, and TEP, with the clinical and histological variables.

In the evaluation of molecular markers, KRAS and p53 expression were measured as dichotomous variables (positive or negative). To estimate correlation between markers, the Spearman rank correlation was computed.

The study was designed with a primary QoL end points, which were measured by the scale of Edmonton (31).We hypothesized that patients in the DEBIRI arm would have better physical and social functioning and better health perceptions than patients in the FOLFIRI arm. We report an analysis at 50 months of median follow-up.

Results

Patients' characteristics. From December 2006 to October 2008, 144 patients were evaluated and 74 patients were randomly assigned: 36 to DEBIRI and 38 to FOLFIRI (Table I). No statistical differences among baseline characteristics were observed. One patient in the DEBIRI arm had disease progression prior to treatment; three patients in the FOLFIRI arm declined rapidly, leaving 35 treated patients in each arm for this report.

All patients, except four in each arm, had received adjuvant chemotherapy previously; all had metachronous metastatic disease. All patients had undergone primary tumor resection prior to random assignment. All surgical procedures took place at least 6 months prior to study treatment (range 7-20 months). Two sites enrolled patients. The number of cycles received were two and eight for the DEBIRI and systemic treatment arms respectively. A total of 70 cycles of DEBIRI were administered to 35 patients and 277 FOLFIRI cycles were administered to 35 patients.

Survival. At two years, survival was 56% for the DEBIRI group and 32% for the FOLFIRI group; at 30 months it was 34% and 9%, and at 50 months it was 15% and 0% respectively. Overall survival was significantly longer for patients treated with DEBIRI rather than FOLFIRI (p=0.031, log-rank) (Figure 1). Median survival was 22 (95% confidence interval CI=21-23) months for DEBIRI and 15 (95% CI=12-18) months for FOLFIRI, an increase of almost a half.

In all but one patient, progression first manifested within (but was not necessarily confined to) the liver.

A significant difference in progression-free survival (PFS) was observed: 7 (95% CI=3-11) months in the DEBIRI group compared to 4 (95% CI=3-5) months in the FOLFIRI group, and the difference between groups was statistically significant (p=0.006; Figure 2).

Considering only the liver, the median THP was 7 and 4 months (p=0.006; Figure 3) for the DEBIRI and FOLFIRI group respectively.

Extrahepatic progression had occurred in all patients by the end of the study. Median TEP was 13 (95% CI=10-16) months in the DEBIRI group compared to 9 (95% CI=5-13) months in the FOLFIRI group. A statistically significant difference between groups was not observed (p=0.64, log-rank, Figure 4).

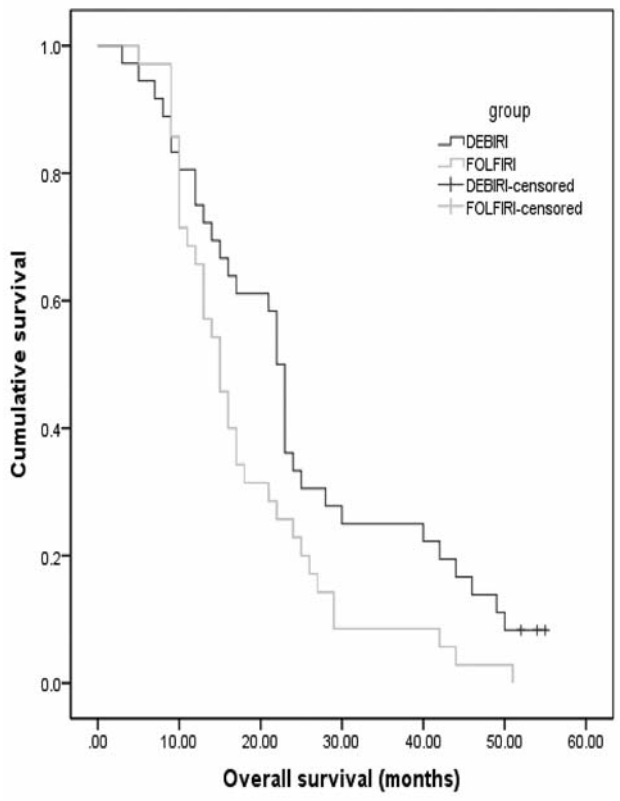

Figure 1. *Overall survival*.

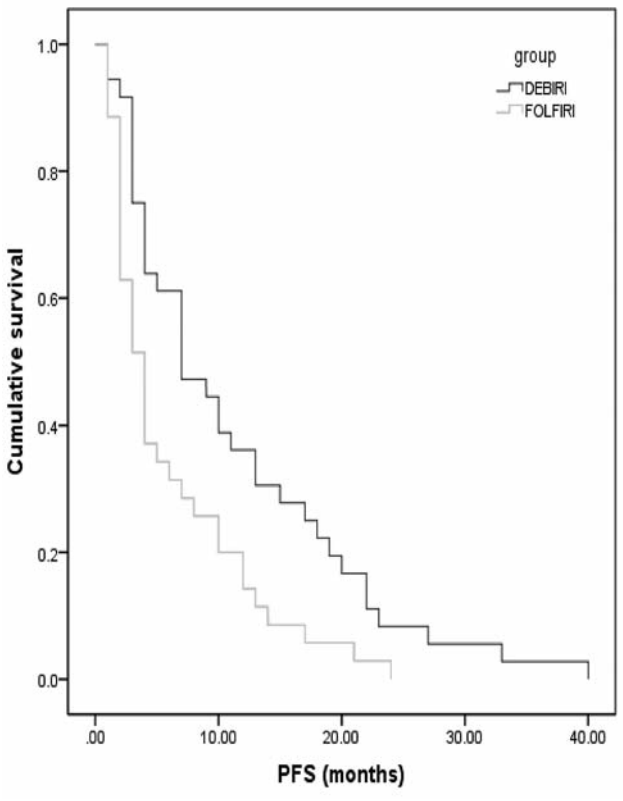

Figure 2. *Period free survival*.

A multivariate analysis based on the proportional hazards model was used to determinate the impact of variables associated with survival. Significant associations were apparent between the percent of liver involvement and albumin, alkaline phosphatase and lactate dehydrogenase (LDH) levels.

Overall treatment with DEBIRI remained significantly related to survival when each of these variables is considered separately with treatment arm. Specifically, treatment with DEBIRI remained significantly associated with survival when post-progression therapy is considered as a co-variate. There was an interaction between KRAS wild-type with the median survival of 26 months for patients receiving DEBIRI and 16 for those receiving FOLFIRI respect 19 months and 14 months for KRAS mutated-type, respectively.

Response. Among the 74 registered patients, 70 were included in response assessment, 35 in each arm. Overall response rate (CR+PR) in the liver in the DEBIRI group included 24 patients out of 35 eligible patients (68.6%) compared with 7 (20%) responses (CR+PR) in the systemic treatment group. SD was observed in 4 (11.4%) and 12 (34.3%) patients, respectively; PD was reported in 7 (20%) and 16 (45.7%) patients , respectively (Table II).

Table II. *Responses observed to therapy.*

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%)

Toxicity. Toxicity profiles differed between the two treatment arms (Table III). Neutropenia grade ≥3 occurred in 4% and 44% ($p<0.0001$), diarrhoea occurred in 6% and 18% ($p=.073$) and mucositis occurred in 1% and 20% ($p=0.00002$) of the DEBIRI and FOLFIRI groups, respectively. Liver enzyme elevations more than 3-fold the normal prices (58% and 8% $p<0.0001$), bilirubin elevation 18% and 1%; $p<0.00002$) occurred in the DEBIRI and FOLFIRI groups respectively. Of the patients in the DEBIRI group with increase of bilirubin more than 2.5 mg/dl due to treatment, all levels returned to normal, three weeks after treatment. There was no reduction or delay in DEBIRI group. The overall relative dose intensity for DEBIRI was 99%. In the group of patients receiving systemic chemotherapy, seven (20%) patients out of 35 required at least one dose reduction for hematological toxicity

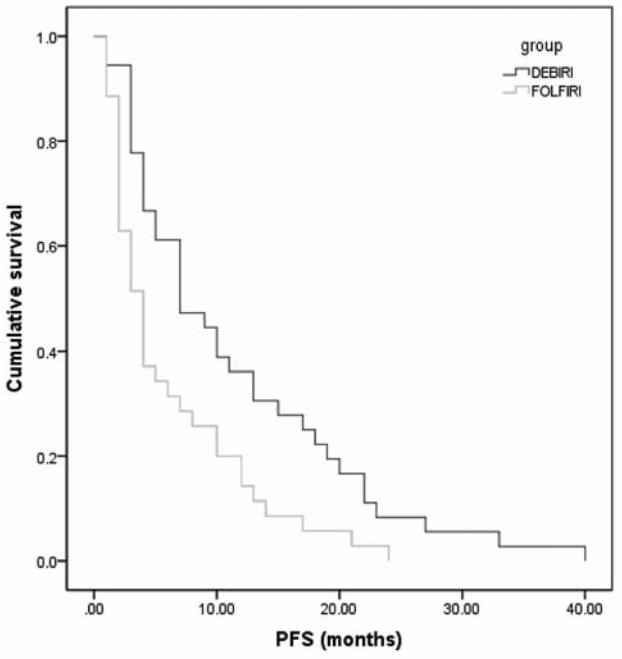

Figure 3. *Hepatic period free survival*.

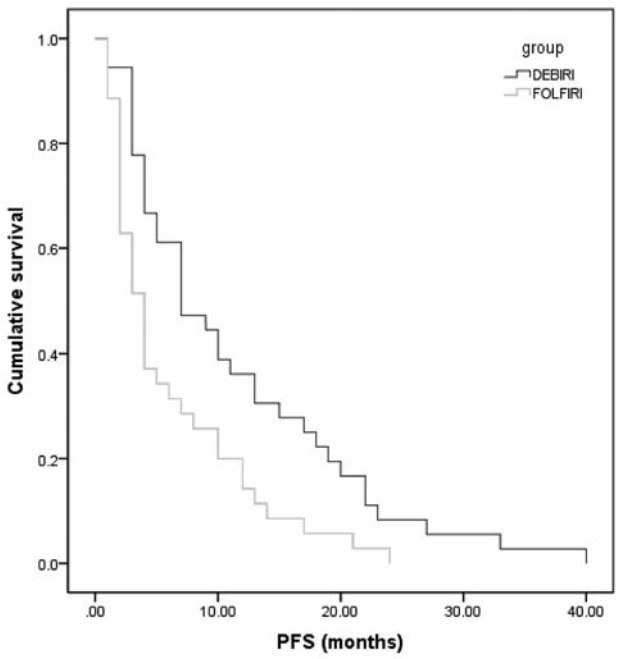

Figure 4. *Extra hepatic period free survival*.

Table III. *Toxicity observed during therapy*.

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%

and eleven (31%) patients had at least one delay in receiving treatment for hematological and gastrointestinal side effects. The overall relative dose intensity for FOLFIRI was 90% and the relative dose intensity for the individual drugs were 90%

QoL assessment. Fourty-nine (65.3%) patients completed all QoL assessments (baseline,1, 3, 6, 9 and 12 months). The most common reason for patient dropout was death. Analyses of data at 1 and 3 months, while most of the patients were receiving active protocol treatment, demonstrated that the physical functioning of the DEBIRI patients was better than that of those receiving systemic therapy at 1 (p=0.038) and 3 months (p=0.025); this was also performed at 8 months (p=0.025). The median DQoL (as defined by time from treatment to progression of symptoms or decline in QoL according to Edmonton) was 3 (95% CI=2-4) months in the FOLFIRI group and 8 (95% CI=3-13) months in the DEBIRI group. The difference in duration of improvement was statistically significant (p=0.0002, log-rank).

Molecular markers. In 70 out of 74 patients , biopsies from primary tumor and LM were evaluated for KRAS (n=35 patients) and p53 (n=35 patients).

In the DEBIRI arm, 14 out 14 patients with wild-type KRAS had evidence of major response and 9 out of 13 with *KRAS* mutation presented evidence of major response. In the DEBIRI group the survival was different with those with wild-type KRAS appearing to better OS than those with mutated KRAS, of 26 and 14 months, respectively (p=0.017).

Seven out of eleven patients in the DEBIRI group with enhanced immunohistochemical expression of p53 (positive) in tumor tissue had a median OS of 24 *vs*. 18 months for 4 out of 11 patients with low expression p53 (negative; p=0.6). Eleven in the FOLFIRI arm with enhanced immunohisto-chemical expression of p53 (positive) in tumor tissue had a median OS of 12 *vs*. 8 months for 4 patients with low expression of p53 (negative; p=0.6).

Sites of progression. The liver was the main site of progression in both arms: in 17 and 23 patients in the DEBIRI and FOLFIRI groups respectively. More than one site was reported in 18 and 12 patients, respectively (Table IV).

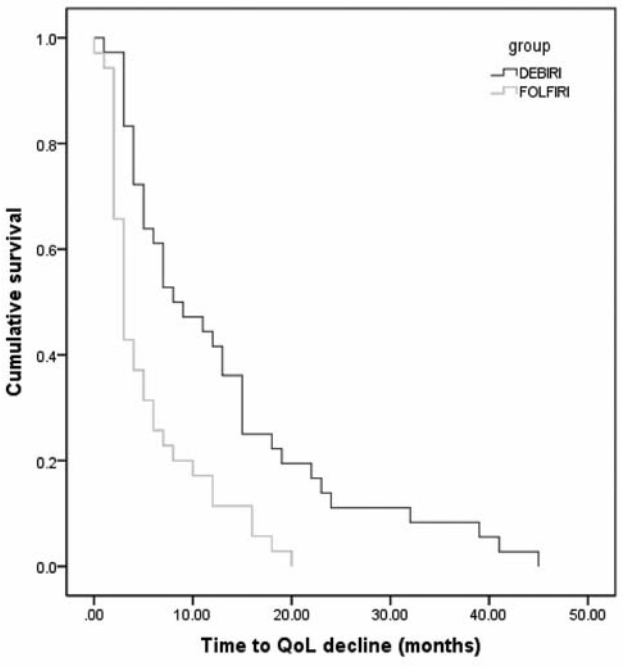

Figure 5. *Duration of clinical benefit to decline.*

Table IV. *Sites of disease relapse in the treated groups.*

	DEBIRI	FOLFIRI
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
Lympho nodes + peritoneal carcinosis	2	0

Table V. *Treatments at progression of disease in the treated groups.*

Type of therapy	DEBIRI	FOLFIRI
FU continuous infusion	8	4
FU continuous infusion + mitomycin	4	4
FOLFOXIRI	2	2
Herbal medicine + holistics	2	5
FOLFIRI + Cetuximab	3	2
FOLFOX + Bevacizumab	2	3
Palliative medicine	14	15

FU=5-fluorouracil; FOLFOXIRI=folinic acid, 5-fluororuracil, oxaliplatin, irinotecan; FOLFIRI=folinic acid, 5-fluororuracil, irinotecan.

Chemotherapy at relapse. Following evidence of progression, 19 patients received further chemotherapy in the DEBIRI group and 15 patients in the FOLFIRI group. Palliative medicine and miscellanea (Herbal medicine and holistics) were administered in 16 and 20 DEBIRI and FOLFIRI patients, respectively (Table V).

Treatment costs. In oncology, the issue of cost-effectiveness of new treatments is increasingly becoming a major issue. Over the last two decades, the US FDA has approved six new drugs for treatment of metastatic CRC: irinotecan, oxaliplatin, capecitabine, bevacizumab, cetuximab and panitumumab. In the metastatic setting, these treatments are only palliative. Six months of biweekly 5-FU plus folinic acid costs approximately €975 in Europe ($1300). Six months of treatment (2-week cycle) with FOLFOX/ bevacizumab, for an average of 1.8 m^2 patient, can cost €90,000 in Europe ($120,000 average selling price from 2008 plus 5% in the United States). Six months of FOLFIRI costs €37,000 ($50,000), and with the addition of cetuximab, this can increase to €87,000 ($115,000).

DEBIRI given twice, including interventional radiology expenses and supportive care, amounted to € 8,000 ($10,000) in 2010.

FOLFIRI given for 4 months (8 times), including insertion of venous device, antiemetic therapy and other medications, amounted to € 20,000 ($26,000) in 2011.

In our study costs are considerably in favour of DEBIRI with respect to FOLFIRI, even if the selling price for irinotecan, now off patent, has been reduced in many Europe.

Discussion

A comparison of DEBIRI *versus* systemic therapy in patients with non-resectable LM from CRC indicates that DEBIRI therapy prolonged the median survival (22 *vs*. 15 months), and was associated with a greater likelihood of objective tumor response in the liver (68,6% *vs*. 20%), enhanced THP of 7 compared to 4 months (p=0.006), whereas TEP was 13 and 9 for DEBIRI and FOLFIRI groups, respectively; and improved physical functioning during active treatment at 1, 3, 6, 9 and 12 months. The regional approach was not inferior to FOLFIRI in preventing extrahepatic metastatic progression (TEP; 13 *vs*. 9 months). These data appear to indicate that DEBIRI also has a systemic activity and that by controlling the liver disease it is possible to extend survival.

The like-li-hood of longer survival was greater in patients with lower tumor burden and better performance status. Although based on small numbers, primary tumor and liver biopsies in the DEBIRI arm demonstrated that the patients with wild-type KRAS and positive p53 on IHC had the best survival. The responses to DEBIRI were longer in those patients with wild-type KRAS; to our knowledge this has not been reported previously.

A criticism of this study is that the systemic chemotherapy used was FOLFIRI. New randomized studies have demonstrated that the addition of oxaliplatin, bevacizumab, cetuximab or panitumumab added to FOLFIRI will increase survival compared to FOLFIRI alone (9-11). This study was planned in 2005, at which time FOLFIRI was the standard of treatment in second- or third-line chemotherapy and the use of biological agents was not so widespread as now.

In this study, the survival advantage conferred by DEBIRI over systemic chemotherapy suggests that DEBIRI may represent a superior clinical treatment modality because both treatment groups had access to new drugs at progression. The significant difference in survival was shown to be attributable to the treatment arm, and remained significant, even when considering that the vast majority of patients received post progression therapy. This study emphasized the importance of the method of drug delivery and the superiority of intra-hepatic arterial infusion of drug eluting beads pre-loaded with irinotecan over systemic therapy, even if the treatment was irinotecan-based for both arms in patients with liver-only metastases.

TEP was similar in both groups. One could postulate that the use of concurrent systemic therapy with new agents in the DEBIRI group would have improved results. Studies of intra-arterial hepatic infusion with Floxuridine (FUDR) plus systemic irinotecan and oxaliplatin, even in previously treated patients, has produced response rates of ≥70% (37-38), obtaining substantially the same responses that we reported.

Both the regional and the systemic treatments were reasonably well tolerated. Patients allocated to receive the systemic FOLFIRI demonstrated a higher likelihood of grade 3 neutropenia, diarrhoea, and stomatitis. Patients allocated to receive DEBIRI reported higher likelihood of abdominal pain and increase of liver enzymes.

This study is the first to provide evidence that an infusion of embolic beads preloaded with irinotecan provides superior survival with better physical functioning when compared with the same chemotherapeutic compound administered systemically. Whether this regional strategy can be enhanced further, through the addition of concurrent systemic treatment, will be the focus of future studies.

This study suggests a benefit of DEBIRI treatment over standard chemotherapy and confirms preliminary data (25). We think that our study serves to establish the expected differences between these two treatment options for planning future large randomized studies.

References

1 Ferlay J, Autier P, Boniol M, Heanue M, Colombert M and Boyle P: estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol *18*: 581-592, 2007.

2 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ: Cancer statistics. CA Cancer J Clin *59(4)*: 225-249, 2009.

3 Van Cutsem E, Nordlinger B, Adam R, Kohnr CH, Pozzo G, Ychou M and Rougier P on behalf of the European Colorectal Metastases Treatment Group: Towards a pan-Europeran consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer *42*: 2212-2221, 2006.

4 Kemeny NE, Kemeny MM and Lawrence TS: Liver metastases. In:Abeloff MD, Armitage JO, Niederhuber JE and Lichter AS: Clinical Oncology, Third ed. Philadelphia: Elsevier Clinical Oncology pp. 1141-1178, 2004.

5 Fong Y, Fortner J, Sun RL, Brennan MF and Blumgart LH: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg *230*: 309-318; discussion 318-321,1999.

6 Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, maroun JA, Ackland SP, Locker PK, Pirrotta N, Elfring GL and Miller LL: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer: Irinotecan Study Group. N Engl J Med *343*: 905-914, 2000.

7 Alberts SR, Horvath WL, Sternfeld WC, Goldberg RM,Mahoney MO, Dakhil SR, Levitt R, Rowland K, Nair S, Sargent DJ and Donohue JH: Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group Phase II study. J Clin Oncol *23*: 9243-9249, 2005.

8 Goldberg RM, Sargent DJ, Morton RF,. Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts S: Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. J Clin Oncol *24*: 3347-3353, 2006.

9 Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med *351*: 337-345, 2004.

10 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350*: 2335-2342, 2004.

11 Chen HX, Mooney M, Boron M,Vena D, Mosby K,Grochow L,Jaffe C, Rubinstein L, Zwiebel J and Kaplan RS: Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: an NCI treatment referral center trial TRC-0301. J Clin Oncol *24*: 3354-3360, 2006.

12 Machi J, Oishi AJ, Sumida K, Sakamoto K, Furumoto NL, Oishi RH and Kylstra JW: Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first- and second-line management.Cancer J *12*: 318-326, 2006.

13 Berber E, Pelley R and Siperstein AE: Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol *23*: 1358-1364, 2005.

14 Mocellin S, Pasquali S and Nitti D: Fluoropyrimidine-HAI (hepatic arterial infusion) *versus* systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer.Cochrane Database sys rec *8;(3)*: CD007823, 2009.

15 Harmantas A, Rotstein LE and Langer B: Regional *versus* systemic chemotherapy in the treatment of colorectal carcinoma

metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. Cancer *78*: 1639-1645, 1996.
16 Kerr DJ, Mc Ardle CS, Ledermann J, Taylor I, Sherlock DJ, Schlag PM, Buckels J, Mayer D, Cain D and Stephens RJ: Intrahepatic arterial *versus* intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. Lancet *361*: 368-373, 2003.
17 Fiorentini G, Rossi S, Dentico P, Bernardeschi P, Calcinai A, Bonechi F, Cantore M, Guadagni S and De Simone M: Irinotecan hepatic arterial infusion chemotherapy for hepatic metastases from colorectal cancer: a phase II clinical study. Tumori *89(4)*: 382-384, 2003.
18 Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, Weeks JC, Sigurdson ER, hermdon JE 2nd, Zhang C and Mayer RJ: Hepatic arterial infusion *versus* systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol *24*: 1395-1403, 2006.
19 Fiorentini G: A new tool to enhance the efficacy of chemo-embolization to treat primary and metastatatic hepatic tumors. Expert Opin Drug Deliv *8(4)*: 409-413, 2011.
20 Vogl TJ, Zangos S, Eichler K, Yakoub D and Nabil M: Colorectal liver metastases:regional chemotherapy *via* transarterial chemo-embolization (TACE) and hepatic chemoperfusion: an update. Eur Radiol *17(4)*: 1025-1034, 2007.
21 Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J: Arterial embolization or chemoembolization *versus* systemic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet *359*: 1734-1739, 2002.
22 Aliberti C, Tilli M, Benea G, Fiorentini G. Trans-arterial chemoembolization (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: Preliminary results. Anticancer Res *26*: 3793-3796, 2006.
23 Morise Z, Sugioka A, Kato R, Fujita J, Hoshimoto S and Kato T: Transarterial chemoembolization with degradable starch microspheres, irinotecan, and mitomycin-C in patients with liver metastases. J Gastrointest Surg *10(2)*: 249-258, 2006.
24 Fiorentini G, Aliberti C, Turrisi G, Del Conte A, Rossi S, Benea G and Giovanis P: Intra-arterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase II clinical study. In Vivo *21*: 1085-1091, 2007.
25 Fiorentini G, Aliberti C, Montagnani F, Tilli M, Mambrini A and Benea G: trans-arterial chemoembolization of metastatic coloretal carcinoma (MCRC) to the liver adopting polyvinyl alcohol microspheres (PAM) loaded with irinotecan compared with FOLFIRI (CT): evaluation at two years of a Phase III clinical trial. Ann Oncol *21(suppl 89)*: viii 198-vii 224, 2010.
26 Salman HS, Cynamon J, Jagust M, Bakal C, Rozenblint A, Kaleva R, Negassa A and Wadler S: Randomized phase II trial of embolization therapy *versus* chemoembolization therapy in previously treated patients with colorectal carcinoma metastatic to the liver. Clin Colorectal Cancer *2*: 173-179, 2002.
27 Fiorentini G, Aliberti C, Benea G, Montagnani F, Mambrini A, Ballardini PL and Cantore M: TACE of liver metastases from colorectal cancer adopting irinotecan-eluting beads: beneficial effect of palliative intra-arterial lidocaine and post- procedure supportive therapy on the control of side-effects. Hepatogastroenterology *55(88)*: 2077-2082, 2008.
28 Taylor RR, Tang Y, Gonzalez MV, Stratford PW and Lewis AL: Irinotecan drug eluting beads for use in chemoembolization: *in vitro* and *in vivo* evaluation of drug release properties. Eur J Pharm Sci *30*: 7-14, 2007.
29 Lewis AL, Gonzalez MV, Lloyd AW, Hall B, Tang Y, Willis SL, Leppard SW, Wolfenden LC, Palmer RR, Stratford PW: DC Bead: *in vitro* characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol *17*: 335-342, 2006.
30 Lewis AL and Holden RR: DC Bead embolic drug-eluting bead: clinical application in the locoregional treatment of tumours. Expert Opin Drug Deliv *8(2)*: 153-169, 2011.
31 Nekolaichuk C, Watanabe S and Beaumont C: The Edmonton Symptom Assessment System: a 15-year retrospective review of validation studies (1991-2006). Palliat Med *22(2)*: 111-122, 2008.
32 Brown DB, Gould JE, gervais DA, Goldberg SN, Murthy R, Millward SF, Rilling WS, geschwind JF, Salem R, Vedantham S, Cardella JF, Soulen MC:Transcatheter therapy for hepatic malignancy: standardization of terminology and reporting criteria. J Vasc Interv Radiol *20(7 Suppl)*: S425-434, 2009.
33 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.
34 Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA and Benjamin RS: Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol *25*: 1753-1759, 2007.
35 Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM and Bruix J: Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma:are response evaluation criteria in solid tumors reliable? Cancer *115*: 616-623, 2009.
36 Carotenuto P, Roma C, Rachiglio AM, Tatangelo F, Pinto C, Ciardiello F, Nappi O, Iaffaioli RV, Botti G and Normanno N: Detection of KRAS mutations in colorectal carcinoma patients with an integrated PCR/sequencing and real-time PCR approach. Pharmacogenomics *11(8)*: 1169-1179, 2010.
37 Gallagher DJ, Capanu M, Raggio G and Kemeny N: hepatic arterial infusion plus systemic irinotecan in patients with unresectable hepatic metastases from colorectal cancer previously treated with systemic oxaliplatin a retrospective analysis. Ann Oncol *18(12)*: 1995-1999, 2007.
38 Kemeny N, Jarnagin W, Paty P, Gönen M, Schwartz L, Morse M, Leonard G, D'Angelica M, DeMatteo R, Blumgart L and Fong Y: Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. J Clin Oncol *23(22)*: 4888-4896, 2005.

Received January 26, 2012
Revised February 28, 2012
Accepted February 29, 2012