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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Selective Intra-arterial Chemotherapy with Floxuridine as Second- or Third-Line Approach in Patients with Unresectable Colorectal Liver Metastases

Panagiotis Samaras, MD[1], S. Breitenstein, MD[1], S. R. Haile, MD[2], F. Stenner-Liewen, MD[1], S. Heinrich, MD[1], J. Feilchenfeldt, MD[1], C. Renner, MD[1], A. Knuth, MD[1], B. C. Pestalozzi, MD[1], and P. A. Clavien, MD, PhD[1]

[1]Swiss HPB (Hepato-Pancreatico-Biliary) Center, Departments of Oncology and Surgery, University Hospital Zurich, Zurich, Switzerland; [2]Biostatistics Unit, Institute of Social and Preventive Medicine University of Zurich, Zurich, Switzerland

ABSTRACT

Background. An outcome assessment was performed of patients with unresectable colorectal liver metastases (CRLM) treated in second or third line with floxuridine (FUDR)-based hepatic artery infusion (HAI).

Methods. Twenty-three patients who were pretreated with systemic (immuno)chemotherapy received FUDR-HAI alone or combined with systemic chemotherapy. We reviewed patient charts and our prospective patient database for survival and associated risk factors.

Results. Patients received FUDR-HAI for unresectable CRLM from January 2000 to September 2010. Twelve patients (52%) received concurrent systemic chemotherapy. Median overall survival (OS), progression-free survival (PFS), and hepatic PFS were 15.6 months (range, 2.5–55.7 months), 3.9 months (range, 0.7–55.7 months), and 5.5 months (range, 1.6–55.7 months), respectively. The liver resection rate after HAI was 35%. PFS was better in patients undergoing secondary resection than in patients without resection (hazard ratio [HR] 0.21; 95% confidence interval [95% CI] 0.07–0.66; $P = 0.0034$), while OS showed a trend toward improvement (HR 0.4; 95% CI 0.13–1.2; $P = 0.09$). No differences were observed in OS ($P = 0.69$) or PFS ($P = 0.086$) in patients who received FUDR-HAI alone compared with patients treated with combined regional and systemic chemotherapy. No statistically significant differences were seen in patients previously treated with one chemotherapy line compared with patients treated with two lines. Presence of extrahepatic disease was a negative risk factor for PFS (liver-only disease: HR 0.03; 95% CI 0.0032–0.28; $P < 0.0001$). Toxicities were manageable with dose modifications and supportive measures.

Conclusions. FUDR-HAI improves PFS and results in a trend toward improved OS in selected patients able to undergo liver resection after tumor is downsized.

Colorectal carcinoma is the fourth most frequent cause of cancer mortality worldwide.[1] At diagnosis, 25% of all colorectal cancer patients have distant (synchronous) metastases, and another 30% develop metastatic disease later in their disease course. In cases of a relapse after resection of the primary tumor (metachronous metastases), the liver is the only affected organ in 50% of the patients.[2]

Chemotherapy by hepatic artery infusion (HAI) has been applied for more than 50 years with the rationale to increase the exposure of liver tumors to cytotoxic drugs by direct application through the hepatic artery.[3,4] The drug most commonly used for intra-arterial application is floxuridine (FUDR), an active metabolite of 5-fluorouracil. The advantage of FUDR is a rapid first-pass effect in the liver with limited systemic toxicity.[5] HAI has been used to downsize unresectable colorectal liver metastases (CRLM) as well as in the adjuvant setting after resection of CRLM.[6–15] We have previously reported encouraging data by combining HAI with portal vein ligation in an attempt to downsize unresectable CRLM, demonstrating a response

P. Samaras and S. Breitenstein contributed equally to this article.
B. C. Pestalozzi and P.-A. Clavien share senior authorship.

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P. A. Clavien, MD, PhD
e-mail: clavien@access.uzh.ch

rate of 58% (6 of 11 patients) and a resection rate of 38% (4 of 11 patients).[16]

When HAI was introduced on a routine basis in a few centers, effective systemic chemotherapy was not available for the treatment of colorectal cancer. Recent advances in the systemic treatment of colorectal cancer using combinations of chemotherapeutic and biological agents as first-line therapy in nonresectable CRLM showed impressive response rates of up to 68% and resection rates of up to 38%.[17–20] However, studies comparing HAI with systemic immunochemotherapy are missing, and thus the current role of regional chemotherapy as first-, second-, or third-line treatment has not yet been clarified. A recently published meta-analysis comparing HAI with systemic chemotherapy failed to identify differences between the two treatment strategies, mostly because HAI was only assessed as a sole treatment and not considered in combination with systemic chemotherapy.[21,22]

Experience with HAI at our institution began 10 years ago, which was used either as a sole treatment or, more recently, in combination with systemic chemotherapy. HAI was mainly used as a second- or third-line downsizing strategy in nonresectable CRLM. The aim of the present study was to report on the survival of our CRLM patients treated with FUDR-HAI alone or combined with systemic chemotherapy, as well as to identify risk factors prognostic for survival.

METHODS

We retrospectively analyzed patients with unresectable CRLM who were treated with FUDR-HAI after implantation of a subcutaneous HAI pump at our hepato-pancreato-biliary center based on a prospective database including all surgical and medical procedures. All patients analyzed had been pretreated with systemic chemotherapy or systemic immunochemotherapy for advanced disease. Adjuvant chemotherapy was considered a previous treatment line only if applied within 12 months before onset of FUDR-HAI.

The primary endpoint of this analysis was survival (overall survival [OS], progression-free survival [PFS], and hepatic PFS). Secondary endpoints were treatment efficacy (response rates and resectability), prognostic factors, adverse events, and surgical complications.

Response was assessed on imaging data available by means of the Response Evaluation Criteria in Solid Tumors. In patients without available imaging data, response was assessed by analyzing the radiographic reports or the entries of the attending physicians in the patient charts.

Surgical complications were documented according to a treatment-oriented complication score.[23] Adverse events were coded as documented in the patient charts according to the NCI Common Terminology Criteria for Adverse Events v3.0 (http://ctep.info.nih.gov/reporting/ctc_v30.html).

Two different catheter systems were used for HAI therapy: an Arrow 3000-30 (Codman 3000; Johnson and Johnson, Raynham, MA), and a Medtronic IsoMed Constant Flow Pump (Medtronic, Minneapolis, MN). The treatment strategy for every patient with CRLM was discussed and determined at a multidisciplinary board meeting of our Swiss hepato-pancreato-biliary center attended by surgeons, medical and radiation oncologists, radiologists, and gastroenterologists. HAI was predominantly considered in fit patients with nonresectable CRLM.

Resectability was assessed according to a modern aggressive approach depending on macroscopic complete resectability of all lesions providing sufficient remnant liver tissue.[24,25] In case of imminent R2 resection, additional ablative treatment was performed intraoperatively (cryoablation or radiofrequency ablation) to treat all CRLM. Limited but resectable extrahepatic disease was not considered to be a contraindication for pump implantation.

All patients provided written informed consent for scientific evaluation of their data before implantation of the pump system. The analysis was approved by our local ethics committee.

Operative Technique

Laparotomy was performed by a right subcostal incision. All patients underwent cholecystectomy to avoid chemical cholecystitis. The implantation of the arterial catheter was subsequently performed by the Watkins technique.[26] After careful preparation of the common hepatic artery and ligature of the right gastric artery, the gastroduodenal artery was identified and ligated 1.5 cm distal its runoff from the hepatic artery. The catheter was inserted into the gastroduodenal artery and advanced to the junction of the common hepatic and gastroduodenal arteries without extending into the lumen of the hepatic artery. The catheter was fixed by bidirectional ligation on either side of its cuff. Fluorescein was injected into the catheter to indicate its exact position and to exclude misperfusion. The correct liver perfusion was proven by the Wood's lamp. The infusion pump was implanted into a subcutaneous pocket in the right lower abdominal wall. In the case of an additional left hepatic artery, the nondominant left artery was ligated because intrahepatic shunts rapidly reconstitute and provide sufficient blood supply to the liver within a few days.[27] An aberrant or replaced right hepatic artery was considered to be a contraindication for catheter implantation and HAI.

Treatment Regimens

FUDR-HAI was administered every 28 days as a 14-day infusion at 0.12 mg/kg × 30 divided by flow rate. Dexamethasone 20 mg and heparin 30,000 IU were added and the pump volume completed with normal saline. On day 15 of every cycle, the pump reservoir was emptied and refilled with dexamethasone 20 mg, heparin 30,000 IU, and normal saline.

Additional systemic chemotherapy consisted of a FOLFOX-like regimen with oxaliplatin 100 mg/m^2 on day 1, leucovorin 400 mg/m^2 on day 1, and 5-fluorouracil 1200 mg/m^2 over 46 h. One patient received a combination of oxaliplatin 100 mg/m^2 on day 1 and irinotecan 150 mg/m^2 on day 1. Concurrent systemic chemotherapy was administered every 2 weeks. FUDR dose and systemic chemotherapy dose were adapted in cases of hematologic or nonhematologic toxicity. In addition, a strict dose adjustment algorithm was used to modify FUDR dosing depending on liver function tests during every cycle.[28] All patients had follow-up including laboratory assessment at least every 2 weeks. Imaging by computed tomographic scan, positron emission tomography–computed tomography, and/or magnetic resonance imaging was usually performed every 2 to 3 months.

Statistical Analysis

Descriptive statistics are presented in the form of medians (range) for continuous variables and counts (percentage) for all categorical variables. Survival estimates were computed by the method of Kaplan and Meier.[29] Cox proportional hazard regression was used to estimate univariate hazard ratios and to test the statistical significance of risk factors for survival.[30] Only P values of <0.01 were considered statistically significant as a result of the small number of patients. All analyses were performed in the R programming language (http://www.R-project.org).

RESULTS

Patient Demographics

From January 2000 to September 2010, a total of 23 patients with unresectable CRLM received FUDR-HAI and were eligible for the final analysis. All patients had bilobar disease, and 19 patients (83%) had more than four CRLM. Patients had previously received either one ($n = 17$; 74%) or two ($n = 6$; 26%) lines of systemic chemotherapy. Eleven patients (48%) had received irinotecan-based combination chemotherapy, and 12 patients (52%) had received oxaliplatin-based combination chemotherapy. Other lines were 5-fluorouracil monotherapy ($n = 4$; 17%) and raltitrexed monotherapy ($n = 1$; 4%). Eight patients (35%) had also received additional immunotherapy combined with their chemotherapy. Patient characteristics are listed in Table 1, including surgical interventions performed simultaneous to the pump implantation, usually consisting of a portal vein ligation and/or wedge resections of adjacent metastases. In addition, these characteristics were well balanced between the subgroups analyzed.

TABLE 1 Characteristics of 23 patients

Characteristic	Value
Age (years)	
<60, *n* (%)	10 (43)
≥60, *n* (%)	13 (57)
Median	60.3
Range	39.7–76.9
Sex, *n* (%)	
Male	18 (78)
Female	5 (22)
Synchronous disease, *n* (%)	
Yes	19 (83)
No	4 (17)
Bilobar disease, *n* (%)	
Yes	23 (100)
No	0 (0)
Liver-only disease, *n* (%)	
Yes	19 (83)
No	4 (17)
Lung, *n* (%)	1 (4)
Regional lymph nodes, *n* (%)	3 (13)
No. of liver metastases, *n* (%)	
≤4	4 (17)
>4	19 (83)
Previous systemic chemotherapy, *n* (%)	
Yes	23 (100)
1 regimen	17 (74)
2 regimens	6 (26)
No	0 (0)
Including immunotherapy	8 (35)
Previous major hepatic resection, *n* (%)	
Yes	2 (8)
No	21 (92)
Device, *n* (%)	
Arrow	17 (74)
Medtronic	6 (26)
Additional hepatic intervention at pump placement, *n* (%)	
No intervention	5 (22)
Portal vein ligation with or without wedge	9 (39)
Wedge resection	7 (31)
Hemihepatectomy with or without wedge	2 (8)

The patients received FUDR-based HAI for a median of 4 cycles (range, 2–8). In one patient, a pump malfunction occurred after the first cycle of FUDR, and therefore, he received intra-arterial bolus 5-fluorouracil instead of FUDR in the further course. One patient received two courses of intrahepatic irinotecan (40 mg) in addition to FUDR.

HAI was combined with systemic chemotherapy in 12 patients (52%), while 11 patients (48%) received HAI as a sole treatment. Concomitant systemic treatment consisted of a FOLFOX-like regimen ($n = 11$; 48%), or irinotecan/oxaliplatin ($n = 1$; 4%).

Response and Survival

The median OS for all patients was 15.6 months (range, 2.5–55.7 months) (Fig. 1). The median PFS was 3.9 months (range, 0.7–55.7 months), and the median hepatic PFS was 5.5 months (range, 1.6–55.7 months). No difference in median OS (hazard ratio [HR] 1.21; 95% confidence interval [95% CI] 0.48–3.08; $P = 0.69$) or hepatic PFS (HR 0.79; 95% CI 0.33–1.91; $P = 0.6$) was observed in patients who were treated with FUDR-HAI alone compared with patients treated with combined regional and systemic chemotherapy. Nevertheless, patients receiving a combined treatment showed a trend toward improved PFS (median 3.4 vs. 5.5 months; HR 0.45; 95% CI 0.18–1.14; $P = 0.086$). No differences in OS (HR 1.3; 95% CI 0.51–3.32; $P = 0.58$), PFS (HR 0.68; 95% CI 0.27–1.72; $P = 0.41$), or hepatic PFS (HR 1.02; 95% CI 0.42–2.48; $P = 0.96$) were observed in patients treated during the early period (years 2000–2004) compared to patients treated during the later period (years 2005–2010). Also, no significant differences in OS (HR 1.5; 95% CI 0.56–4.04; $P = 0.41$), PFS (HR 2.68; 95% CI 0.94–7.6; $P = 0.055$) or hepatic PFS (HR 2; 95% CI 0.74–5.41; $P = 0.16$) were observed in patients who had previously been treated with one line of systemic chemotherapy compared with patients treated with two previous lines of chemotherapy.

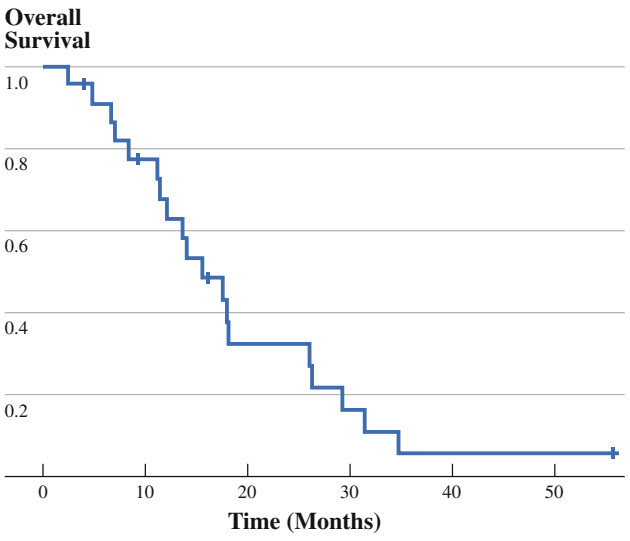

FIG. 1 Kaplan-Meier analysis of the overall survival (OS) of the patients after treatment with HAI. Median OS was 15.6 months (range 2.5–55.7 months)

Six (26%) of 23 patients with nonresectable CRLM showed tumor regression, while 7 patients (30%) had stable disease. Hence, FUDR-HAI produced an overall response rate of 26% and a disease control rate of 56%. Hepatic resection could be performed after HAI in 8 patients (35%) (Table 2). Surgery was performed after a median of 3 cycles of FUDR-HAI (range, 2–5 cycles). The median OS in the patients undergoing resection after HAI was 26.1 compared to 12.1 months in the patients who did not undergo resection (HR 0.4; 95% CI 0.13–1.2; $P = 0.09$). The median PFS in the resected patients was 6.7 months compared to 2.8 months in the unresected patients (HR 0.21; 95% CI 0.07–0.66; $P = 0.0034$) (Fig. 2). The corresponding median hepatic PFS were 6.7 and 3.3 months, respectively (HR 0.39; 95% CI 0.14–1.09; $P = 0.062$).

TABLE 2 Treatment efficacy in 23 patients with nonresectable disease

Characteristic	Value
Treatment	
HAI only, *n* (%)	11 (48)
HAI plus systemic chemotherapy, *n* (%)	12 (52)
HAI cycles, median	4
HAI cycles, range	2–8
Response to HAI, *n* (%)	
Complete response	0 (0)
Partial response	6 (26)
Stable disease	7 (30)
Progressive disease	10 (44)
Overall response rate	6 (26)
Disease control rate	13 (56)
Secondary hepatic resection performed, *n* (%)	8 (35)
Hemihepatectomy with or without wedge	4 (21)
Wedge resection only	4 (8)
Not possible	15 (65)
Resectability assessment ($n = 8$), *n* (%)	
R0 resection	4/8 (50)
R1 resection	0/8 (0)
R2 resection	4/8 (50)
Additional ablative treatment	4/8 (50)

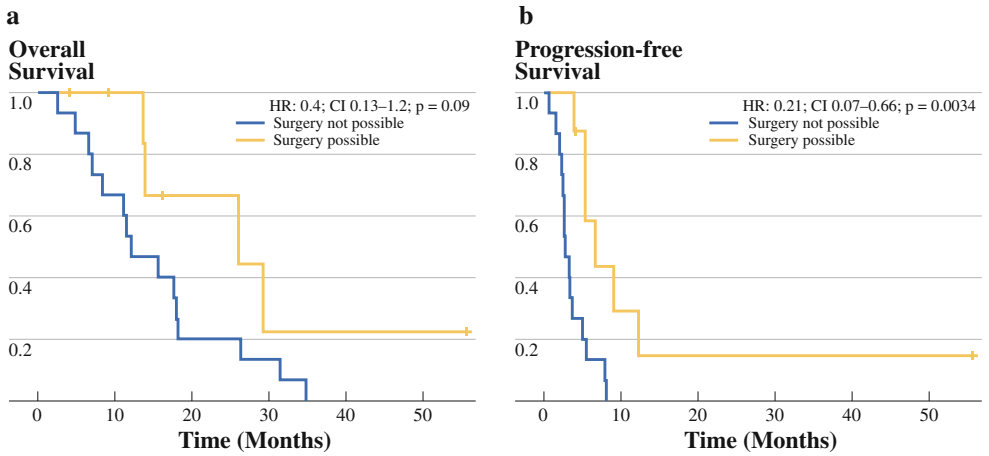

FIG. 2 **a** Kaplan-Meier analysis of the overall survival (OS) of the resected patients compared with the patients not resected after treatment with hepatic arterial infusion (HAI). Median OS were 26.1 months vs. 12.1 months, respectively (hazard ratio [HR] 0.4; 95% confidence interval [95% CI] 0.13–1.2; $P = 0.09$). **b** Kaplan-Meier analysis of the progression-free survival (PFS) of the resected patients compared with the patients not resected after treatment with HAI. Median PFS was 6.7 months vs. 2.8 months, respectively (HR 0.21; 95% CI 0.07–0.66; $P = 0.0034$)

Risk Factor Analysis

Extrahepatic disease was the only negative risk factor for PFS by univariate analysis (liver only vs. extrahepatic disease: HR 0.03; 95% CI 0.0032–0.28; $P < 0.0001$), but without affecting OS ($P = 0.09$). The other evaluated parameters had no statistically significant effect on PFS or OS (Table 3).

Surgical Complications

Three (13%) complications of less than grade III and only one (4%) complication of grade III or more (pump pocket seroma requiring percutaneous drainage, grade IIIa) occurred after pump implantation.

Liver resection after downsizing HAI was associated with four complications of grade I or II (50%), and two complications of grade III or more (25%, one patient with encephalopathy [grade IVa] and one patient with a biloma requiring percutaneous drainage [grade IIIa]) were observed (Table 4).

Adverse Events and Toxicities

Complications and toxicities of grade III or more were documented in 8 patients (35%) (Table 5). The most frequent adverse events observed during chemotherapy were diarrhea ($n = 4$; 17%), infections ($n = 3$; 13.5%), and enterocolitis ($n = 3$; 13.5%). The occurrence of biliary toxicity grade III or more was observed in 1 patient (4%). Toxicities of HAI and systemic chemotherapy were manageable by interruption of the treatment or reduction of the FUDR dose. The pump system could be rescued by antibiotic treatment in two documented cases (9%) of pump infection. The pathogens isolated were *Enterobacter cloacae* and *Escherichia coli.*

TABLE 3 Prognostic factors for survival by univariate analysis

Parameter	Overall survival				Progression-free survival			
	HR	Lower 95% CI	Upper 95% CI	*P* value	HR	Lower 95% CI	Upper 95% CI	*P* value
Liver only vs. extrahepatic disease	0.37	0.11	1.22	0.09	0.03	0.003	0.28	0.0000
Age ≥65 vs. <65 years	0.48	0.13	1.74	0.26	0.39	0.13	1.21	0.09
Colon vs. rectum primary disease	1.48	0.57	3.83	0.42	1.25	0.5	3.14	0.63
Synchronous vs. metachronous disease	0.68	0.22	2.15	0.51	0.42	0.13	1.32	0.13
No. of previous chemotherapy lines	1.5	0.56	4.03	0.41	2.68	0.94	7.59	0.06
≥4 lesions vs. <4 lesions	1.41	0.45	4.39	0.56	1.12	0.36	3.44	0.85
Combined treatment vs. HAI alone	1.21	0.48	3.08	0.69	0.45	0.18	1.14	0.09

HR hazard ratio, *95% CI* 95% confidence interval, *HAI* hepatic arterial infusion

TABLE 4 Surgical complications after pump implantation and hepatic resection

Complication	After device implantation ($n = 23$)	After hepatic resection ($n = 8$)	Grade
Hemorrhage	1	1	II
Urinary tract infection	1	–	II
Laryngitis	1	–	I
Encephalopathy	–	1	IV
Transient hepatic insufficiency	–	1	II
Reflux esophagitis	–	1	II
Leakage of hepaticojejunostomy	–	1	II
Pump pocket seroma	1	–	III
Biliary fistula/biloma	–	1	III

Grading according to the Clavien-Dindo classification[23]

TABLE 5 Adverse events during hepatic arterial infusion[a]

Toxicity ($n = 22$)	Grade III, n (%)	Grade IV, n (%)
Pump infection	2 (9)	–
Other infection	3 (13.5)	–
Diarrhea	3 (13.5)	1 (4.5)
Bile duct stricture/sclerosing cholangitis	1 (4.5)	–
Enterocolitis	3 (13.5)	–
Fatigue	1 (4.5)	1 (4.5)
Bilirubin elevation	1 (4.5)	1 (4.5)
ASAT elevation	1 (4.5)	1 (4.5)
Alkaline phosphatase elevation	3 (13.5)	–

ASAT aspartate aminotransferase

[a] More than one adverse event per patient is possible

DISCUSSION

This analysis demonstrates efficacy of FUDR-HAI as second- or third-line treatment in patients with unresectable CRLM. The median OS was 15.6 months, and the disease of every third patient became surgically resectable.

Survival benefit associated with HAI correlated with response rate and resectability of CRLM. The response rate to regional intra-arterial chemotherapy, applied as second- or third-line treatment, was 26%. The disease of 8 (35%) of 24 patients with initially unresectable CRLM became resectable after FUDR-HAI. Resected patients had a significantly prolonged PFS (6.7 vs. 2.8 months; $P = 0.0034$), while the OS difference did not reach statistical significance (26.1 vs. 12.1 months; $P = 0.09$). This finding is promising considering the fact that HAI was generally offered to patients with extensive disease (100% had bilobar disease, 83% had >4 CRLM) even in the presence of extrahepatic lymph node metastases or small indeterminate pulmonary nodules because other treatment options were lacking and systemic chemotherapy regimens had failed. The development of new therapeutic agents greatly improved the efficacy of chemotherapy in the treatment of colorectal cancer. Modern regimens achieved response rates of up to 68% and resection rates of up to 38%.[17–20] However, the response rates reported by modern regimens used as second-line treatment are up to 23%, which is lower than the response and resectability rates of the present analysis.[31–33]

Interestingly, in our series, no further downsizing or resectability of the tumors could be achieved by the application of >5 cycles of FUDR-HAI, although in the literature patients were described as often receiving substantially more cycles.[34,35] Although to our knowledge the correlation between the number of cycles and treatment efficacy has never been investigated, it is known that toxicity of FUDR, and particularly biliary toxicity, increases during HAI treatment, requiring dose modifications or treatment discontinuation.[7,36,37]

Because HAI prevents intrahepatic tumor progression but has less influence on extrahepatic disease, it is most likely that further improvements may be achieved by the combination of HAI with systemic chemotherapy. Our data support this assumption: patients receiving regional treatment combined with a FOLFOX-like systemic regimen showed a trend toward an improved PFS compared with patients treated with FUDR-HAI alone, but without impact on OS. The lack of a marked difference of the OS may be mainly due to the limited patient number analyzed. Hence, prospective studies with larger patient cohorts have to be performed to answer this important question. Phase 1 clinical trials have defined the appropriate dosage to be used when combining FUDR-HAI with systemic chemotherapy.[38,39] So far, no data are available regarding the impact of monoclonal antibodies such as bevacizumab or cetuximab/panitumumab added to systemic treatment and FUDR-HAI. Only a few trials have been published combining FUDR with systemic chemotherapy. Response rates of 74% have been reported for FUDR-HAI in combination with systemic irinotecan.[28] Of note, the same regimen yielded only a 43% response rate in patients previously treated with systemic oxaliplatin.[35] The highest efficacy, with a response rate of 92%, was reported for a combination of systemic oxaliplatin and irinotecan. The impressive OS was different for chemotherapy-naive patients (50 months) compared with previously treated patients (35 months).[40] We have analyzed the impact of the number of previous treatment lines on patient outcome. Our patients had received either one or two lines of systemic

chemotherapy before FUDR-HAI, with a substantial subset of patients also having received additional immunotherapy. No statistically significant differences were seen between these two patient groups, but as expected, patients with only one previous line had a tendency for longer PFS.

Our risk factor analysis identified the presence of extrahepatic disease as the only statistically significant risk factor for disease progression. This finding confirms the lack of systemic effect as the main limitation of HAI and highlights the importance of adequate patient selection. In our experience, HAI should only be used for a downsizing strategy in patients without evidence of extrahepatic disease.

Surgical complications related to the pump placement are an important aspect of HAI. The most commonly reported complications are pump pocket hematoma and seroma (0.3–15%).[41,42] Placement of HAI pumps requires experience. As for all surgical procedures, a learning curve has been described by Allen et al. in the largest single-institution experience regarding technical complications of HAI.[41] In our series, only one local complication related to pump implantation occurred (a fluid collection that could be resolved by repeated aspiration). All of the other complications were related to the additional surgical procedures at the liver and were not caused by the pump implantation.

Regarding HAI toxicity, the unique pharmacological profile of FUDR needs to be considered. FUDR remains the best drug for selective continuous intra-arterial chemotherapy because it has a high total body clearance and first-order kinetics.[5] Biliary toxicity is the most relevant side effect of FUDR, which may be minimized by appropriate FUDR dosing, the use of an aggressive dose-adjustment algorithm, and the addition of dexamethasone via the hepatic artery.[7,28,34] In the present series, only a few adverse events of grade III or more occurred during intra-arterial treatment, mainly diarrhea and enterocolitis. They were all manageable by symptomatic treatment or dose modifications. Taken together, FUDR-HAI, provided either alone or combined with systemic chemotherapy, should be used only in experienced centers as a result of the high technical and clinical demands of this treatment.

The main limitations of our analysis are its retrospective nature and the small number of patients. Additionally, our patients were treated outside of a controlled clinical study and differed considerably regarding number and duration of preceding treatments and hepatic interventions performed. However, by carefully analyzing the prospectively collected data, we were able to distil clinically meaningful results and shed light on the current value of FUDR-HAI in patients with colorectal cancer. Similarly, we have attempted to define the further course of investigation because randomized prospective trials are not available.

In conclusion, FUDR-HAI shows promising results as a second- or third-line treatment in patients with nonresectable CRLM. Resectability was achieved in one third of the patients. This was the major factor impacting on survival of our patients. On the basis of our results, FUDR-HAI in combination with a FOLFOX-like systemic regimen is an option for pretreated patients with liver-only disease. The strategy of combining FUDR-HAI with effective systemic chemotherapy and immunotherapy in selected patients should be investigated in further prospective trials.

Conflict of interest The authors declare no conflict of interest.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74–108.
2. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol.* 1997;15:938–46.
3. Clarkson B, Young C, Dierick W, et al. Effects of continuous hepatic artery infusion of antimetabolites on primary and metastatic cancer of the liver. *Cancer.* 1962;15:472–88.
4. Sullivan RD, Norcross JW, Watkins E Jr. Chemotherapy of metastatic liver cancer by prolonged hepatic-artery infusion. *N Engl J Med.* 1964;270:321–7.
5. Ensminger WD. Intrahepatic arterial infusion of chemotherapy: pharmacologic principles. *Semin Oncol.* 2002;29:119–25.
6. Kemeny N, Daly J, Reichman B, et al. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. *Ann Intern Med.* 1987;107:459–65.
7. Kemeny NE, Niedzwiecki D, Hollis DR, et al. 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.* 2006;24:1395–403.
8. Rougier P, Laplanche A, Huguier M, et al. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial. *J Clin Oncol.* 1992;10:1112–8.
9. Clavien PA, Selzner N, Morse M, Selzner M, Paulson E. Downstaging of hepatocellular carcinoma and liver metastases from colorectal cancer by selective intra-arterial chemotherapy. *Surgery.* 2002;131:433–42.
10. Tang ZY, Zhou XD, Ma ZC, et al. Downstaging followed by resection plays a role in improving prognosis of unresectable hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int.* 2004;3:495–8.
11. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med.* 1999;341:2039–48.
12. Lorenz M, Muller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). *Ann Surg.* 1998;228:756–62.
13. Tono T, Hasuike Y, Ohzato H, Takatsuka Y, Kikkawa N. Limited but definite efficacy of prophylactic hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases: a randomized study. *Cancer.* 2000;88:1549–56.

14. Lygidakis NJ, Sgourakis G, Vlachos L, et al. Metastatic liver disease of colorectal origin: the value of locoregional immunochemotherapy combined with systemic chemotherapy following liver resection. Results of a prospective randomized study. *Hepatogastroenterology.* 2001;48:1685–91.
15. Pilati P, Mammano E, Mocellin S, et al. Hepatic arterial infusion for unresectable colorectal liver metastases combined or not with systemic chemotherapy. *Anticancer Res.* 2009;29:4139–44.
16. Selzner N, Pestalozzi BC, Kadry Z, et al. Downstaging colorectal liver metastases by concomitant unilateral portal vein ligation and selective intra-arterial chemotherapy. *Br J Surg.* 2006;93:587–92.
17. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol.* 2010;11:38–47.
18. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOX-IRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25:1670–6.
19. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med.* 2009;360:1408–17.
20. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350:2335–42.
21. Mocellin S, Pilati P, Lise M, Nitti D. Meta-analysis of hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the end of an era? *J Clin Oncol.* 2007;25:5649–54.
22. Pestalozzi BC, Gruttadauria S, Clavien PA. Hepatic arterial infusion: the beginning of the combination era. *J Clin Oncol.* 2008;26:2231–2.
23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240: 205–13.
24. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? *J Clin Oncol.* 2005;23:8490–9.
25. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med.* 2007;356:1545–59.
26. Watkins E Jr, Khazei AM, Nahra KS. Surgical basis for arterial infusion chemotherapy of disseminated carcinoma of the liver. *Surg Gynecol Obstet.* 1970;130:581–605.
27. Rayner AA, Kerlan RK, Stagg RJ, Price DC, Hohn DC. Total hepatic arterial perfusion after occlusion of variant lobar vessels: implications for hepatic arterial chemotherapy. *Surgery.* 1986;99: 708–15.
28. Kemeny N, Jarnagin W, Gonen M, et al. Phase I/II study of hepatic arterial therapy with floxuridine and dexamethasone in combination with intravenous irinotecan as adjuvant treatment after resection of hepatic metastases from colorectal cancer. *J Clin Oncol.* 2003;21:3303–9.
29. Kaplan E, Meier, P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457–81.
30. Cox D. Regression models and life tables. *J R Stat Soc Ser B.* 1972:197–220.
31. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351:337–45.
32. Rothenberg ML, Cox JV, Butts C, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. *Ann Oncol.* 2008;19:1720–6.
33. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol.* 2007;25:1539–44.
34. Kemeny N, Seiter K, Niedzwiecki D, et al. A randomized trial of intrahepatic infusion of fluorodeoxyuridine with dexamethasone versus fluorodeoxyuridine alone in the treatment of metastatic colorectal cancer. *Cancer.* 1992;69:327–34.
35. Gallagher DJ, Capanu M, Raggio G, 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.* 2007; 18:1995–9.
36. Chang AE, Schneider PD, Sugarbaker PH, et al. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg.* 1987;206:685–93.
37. Hohn DC, Stagg RJ, Friedman MA, et al. A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. *J Clin Oncol.* 1989;7: 1646–54.
38. Kemeny N, Gonen M, Sullivan D, et al. Phase I study of hepatic arterial infusion of floxuridine and dexamethasone with systemic irinotecan for unresectable hepatic metastases from colorectal cancer. *J Clin Oncol.* 2001;19:2687–95.
39. Kemeny N, Jarnagin W, Paty P, et al. Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. *J Clin Oncol.* 2005;23:4888–96.
40. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol.* 2009;27:3465–71.
41. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg.* 2005;201:57–65.
42. Heinrich S, Petrowsky H, Schwinnen I, et al. Technical complications of continuous intra-arterial chemotherapy with 5-fluorodeoxyuridine and 5-fluorouracil for colorectal liver metastases. *Surgery.* 2003;133:40–8.