Phase II Trial of Hepatic Artery Infusional and Systemic Chemotherapy for Patients With Unresectable Hepatic Metastases From Colorectal Cancer

Conversion to Resection and Long-term Outcomes

Michael I. D'Angelica, MD, Camilo Correa-Gallego, MD,* Philip B. Paty, MD,* Andrea Cercek, MD,† Alexandra N. Gewirtz, BA,† Joanne F. Chou, MPH,‡ Marinella Capanu, PhD,‡ T. Peter Kingham, MD,* Yuman Fong, MD,* Ronald P. DeMatteo, MD,* Peter J. Allen, MD,* William R. Jarnagin, MD,* and Nancy Kemeny, MD†*

Purpose: Evaluate conversion rate of patients with unresectable colorectal-liver metastasis to complete resection with hepatic-arterial infusion plus systemic chemotherapy including bevacizumab (Bev).

Patients and Methods: Forty-nine patients with unresectable colorectal liver metastases (CRLM) were included in a single-institution phase II trial. Conversion to resection was the primary outcome. Secondary outcomes included overall survival (OS), progression-free survival, and response rates. Multivariate and landmark analyses were performed to evaluate survival differences between resected and nonresected patients.

Results: Median number of tumors was 14 and 65% were previously treated patients. A high biliary toxicity rate was found in the first 24 patients whose treatment included Bev. The remaining 25 patients were treated without Bev. Overall response rates were 76% (4 complete responses). Twenty-three patients (47%) achieved conversion to resection at a median of 6 months from treatment initiation. Median OS and progression-free survival for all patients were 38 (95% confidence interval: 28 to not reached) and 13 months (95% confidence interval: 7–16). Bev administration did not impact outcome. Conversion was the only factor associated with prolonged OS and progression-free survival in multivariate analysis. On landmark analysis, patients who had undergone resection had longer OS than those who did not undergo resection (3-year OS: 80% vs 26%). Currently, 10 of 49 (20%) patients have no evidence of disease (NED) at a median follow-up of 39 months (32–65 months).

Conclusions: In patients with extensive unresectable CRLM, the majority of whom were previously treated, 47% were able to undergo complete resection after combined HAI and systemic therapy. Conversion to resection is associated with prolonged survival.

Keywords: bevacizumab, colorectal liver metastasis, fluxoridine, hepatectomy, intrahepatic infusional chemotherapy

(*Ann Surg* 2015;261:353–360)

There are more than 140,000 cases of colorectal cancer yearly in the United States. Approximately 60% will develop liver metastases.[1] Complete resection of single-site colorectal liver metastases (CRLM) is associated with 5-year disease-specific survival rates of approximately 50%.[2] Although most patients recur after partial hepatectomy, approximately 20% are cured.[3,4] However, the vast majority (80–90%) present with unresectable disease.[5] Modern combination chemotherapy for unresectable CRLM rarely results in 5-year survival and is associated with a median survival of roughly 20 months.[6] Some series have demonstrated that patients may be downstaged from an initially inoperable to a potentially resectable state,[7–12] with similar 5-year survival rates to patients who were initially resectable.[12–14] A significant problem with studies that have reported conversion to complete resection is their retrospective nature and a lack of clear definitions of irresectability and the response required for conversion to resection.[15] Furthermore, the ability to resect extensive bilobar metastases has improved dramatically during the last 2 decades, widening the scope of patients now considered for resection.[16–21]

Hepatic-arterial infusion (HAI) chemotherapy has significantly higher response rates (RRs) than systemic chemotherapy[22–24] and has become an attractive option for treatment of patients with unresectable CRLM. The high hepatic extraction rate[25] of HAI floxuridine (FUDR) limits its systemic toxicity and allows its use in combination with systemic agents. Prior phase I and II studies from our institution have shown such combinations to be safe and to exhibit RRs between 52% and 75% in previously treated patients and even higher in chemotherapy-naïve patients.[26,27] In a previously reported retrospective analysis of patients with extensive unresectable CRLM receiving HAI and systemic chemotherapy as part of a phase I trial, we observed conversion to resection in 47% of a heavily pretreated group of patients.[27,28] On the basis of prior data demonstrating significant improvement in survival with the addition of bevacizumab (Bev) to systemic chemotherapy, we felt that the addition of Bev to our HAI and systemic regimens was worthy of further study.[29] The aim of this phase II study was to prospectively evaluate the rate of conversion to complete resection in patients with unresectable CRLM treated with HAI and systemic chemotherapy plus Bev in the context of strictly prespecified definitions of irresectability.

PATIENTS AND METHODS

After protocol approval by our institutional review board, patients with histologically confirmed colorectal carcinoma with unresectable CRLM and no extra-hepatic disease on cross-sectional imaging performed within 6 weeks of enrollment were approached for enrollment; informed consent was obtained from every patient. Irresectability was determined by 2 hepatobiliary surgeons and 1 radiologist and defined as technical (a margin-negative resection requires resection of 3 hepatic veins, both portal veins, or the retrohepatic vena cava; or, a resection that leaves <2 adequately perfused and drained segments) or biological (>6 metastases in a single lobe, with 1 lesion

From the Departments of *Surgery; †Medicine; and ‡Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY.

Disclosure: The authors declare no conflicts of interest.

Reprints: Michael I. D'Angelica, MD, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. E-mail: dangelim@mskcc.org.

ISSN: 0003-4932/14/26102-0353
DOI: 10.1097/SLA.0000000000000614

≥5 cm; or ≥6 bilobar metastases). Although there is no standard definition of biological irresectability, the criteria given represent patients with aggressive biology and a very high risk of recurrence. Exclusion criteria included prior treatment of CRLM with resection, thermoablation or radiation, inadequate end organ function, or Karnofsky performance score of less than 60%.

Pretreatment evaluation included contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis; CT-angiogram to determine arterial anatomy[18]; F-fluorodeoxyglucose positron emission tomography; HAI pump placement[30,31]; tissue biopsy; and normal perfusion-flow scan (^{99m}Technetium-labeled macroaggregated albumin study—TcMAA) through the pump.

Chemotherapy Regimens

Patients were assigned to receive best systemic chemotherapy in combination with HAI FUDR on the basis of their chemotherapy history. Patients who had received 2 or less cycles of oxaliplatin and had no persistent neuropathy received intravenous systemic oxaliplatin (85 mg/m^2), irinotecan (125 mg/m^2), and Bev (5 mg/kg). Those patients with prior treatment including more than 2 cycles of oxaliplatin received systemic irinotecan (150 mg/m^2) and 5-fluorouracil (2000 mg/m^2 48 hours of infusion), leucovorin (400 mg/m^2) and Bev. HAI FUDR was given at 0.12 mg/kg/d × kg × pump volume/flow rate and Dex at 1 mg/d × pump volume/flow rate with heparin and saline. Both were delivered over a 14-day continuous infusion through the pump.[28] Patients started treatment at least 2 weeks after pump placement. Therapy was administered in a 4-week cycle. HAI therapy was started on day 1 of each cycle, and the pump was emptied and filled with heparin (30,000 units) and normal saline on day 15. Systemic chemotherapy was administered on day 1 and day 15 of each cycle.

Toxicity Evaluation

All toxicities were rated by the NCI Common Terminology Criteria for Adverse Events (v 3.0).[32] Patients were evaluated at least every 2 weeks during treatment. Evaluation included physical examination, complete blood count, complete metabolic panel, and carcinoembryonic antigen. Biliary toxicity was graded as previously reported.[28,33]

Study Design and Statistical Analysis

This is a prospective, nonrandomized, single-institution phase II trial registered in clinicaltrials.gov (Registration # NCT00492999). The primary end point was resectability rate. Resectability assessment was made after the fourth cycle and then every 2 cycles. Response was evaluated according to World Health Organization criteria.[34] Technically unresectable patients with sufficient response to allow complete resection with adequate future liver remnant proceeded to laparotomy for potential resection. Biologically unresectable patients with radiologic response or stable disease after 4 cycles of chemotherapy were taken to resection if technically feasible.

At the time of trial design, the reported conversion rates were approximately 15%.[9–11,13] A sample size of 49 patients was estimated to provide 90% power (type I error: 10%) to detect an increase in conversion rate from 15% to 30%. Although our prior retrospective review suggested a conversion rate of 47%, we wanted this trial to be powered to at least detect a doubling of the historical rate. Secondary end points included overall survival (OS), progression-free survival (PFS), RRs and tolerability and safety.

OS, PFS, and time to hepatic progression were measured from the start of HAI therapy and estimated by Kaplan-Meier methods. In patients who underwent resection, progression was defined as the development of any new site of disease. A Cox proportional hazards model was used to evaluate the association between conversion and survival outcomes, treating surgery as time-dependent covariate. The models were adjusted for clinical risk score (CRS) as a binary variable [high (CRS = 3, 4, 5) vs low (CRS = 0, 1, 2)] or other variables significantly associated with outcomes on univariate analysis ($P < 0.10$).[35]

To compare and graphically display the survival outcomes of patients who underwent resection versus those who did not undergo resection, we used a landmark analysis using conversion to resection at 12 months of treatment as a predefined landmark time. Patients who did not have 12-month follow-up were excluded from the landmark analysis. The landmark analysis is an effective approach of removing the bias that exists in this type of analysis in which survival outcomes are compared among patients defined by other outcome (conversion to resection).[36] Correlation between clinical-pathologic characteristics and resection was examined using Fisher exact test for categorical variables or Wilcoxon rank sum test for continuous variables. All analyses were performed using SAS statistical software (V9.2; Cary, NC).

RESULTS

Patient and Treatment Characteristics

A total of 102 patients with unresectable CRLM were assessed for eligibility between July 2007 and November 2010. Of these, 53 were not included in the protocol (1 had a myocardial infarction; 2 had other comorbid medical issues; 34 had extra-hepatic disease; 1 extrahepatic perfusion after pump placement; 2 developed jaundice after surgery; 1 had no tumor on path report; 1 FUDR started early; 1 patient refused; 1 peritoneal hematoma; 8 resected; and 1 signed to another protocol). Forty-nine patients were enrolled. General demographics and presentation characteristics are detailed in Table 1.

Toxicity

Details of chemotherapy-related major toxicity are summarized in Table 2. The overall grade 3/4 toxicity rate was 41% (20/49). The first 24 patients accrued to the protocol received Bev and experienced an unexpectedly high rate of biliary toxicity, with 3 patients requiring biliary stents. Based on these and additional data from other clinical trials that demonstrated increased biliary toxicity related to the addition of Bev to HAI FUDR.[33,37,38] Bev was removed from the treatment after authorization from the institutional review board and protocol amendment. The subsequent 25 patients enrolled had a 28% rate of grade 3/4 toxicity and a significantly better biliary toxicity profile. Seven patients (14%) experienced a grade 1 or 2 complication associated with pump placement.

Most patients (32/49, 65%) received protocol treatment as either second (21/32) or third-line (11/32) therapy. Twenty-nine patients (59%) received systemic irinotecan and 5FU/LV and 20 patients received systemic oxaliplatin and irinotecan. By 3 months of treatment, patients had received a median of 67% of the planned dose of HAI FUDR (range: 59–83%), 88% of oxaliplatin (range: 80–100%), and 86% of irinotecan (range: 80–100%). By 6 months, the median percentage of the planned doses were 42% (range: 33–50%), 59% (range: 49–85%), and 67% (range: 55–83%), respectively.

Response and Conversion to Resection

The overall RR was 76%, with 36 partial (PR) and 1 complete response (CR). Chemotherapy-naïve patients had an RR of 82% (14/17), 1 being a CR. In previously treated patients, the RR was 72% (23/32). Patients with and without Bev treatment had similar RR (75% vs 76%; $P = 1.0$). Large volume responses were common (Fig. 1).

Twenty-three (47%) patients converted to resection at a median of 6 months from treatment initiation (range: 3–22 months). Table 1

TABLE 1. Patient Characteristics and Comparison of Resected and Nonresected Cases

	All Patients		No Resection	Resection	
	N	%	n (%)	n (%)	*P*
Total	49	100	26	23	
Age, yr					
Median (IQR)	56 (48–64)		53 (45–64)	59 (52–63)	0.67
Sex					
Male	29	49	15 (58)	14 (61)	0.94
Synchronous disease					
Yes	46	94	25 (96%)	21 (91%)	0.89
Number of liver tumors					
Median (IQR)	14 (7–23)		17 (10–27)	9 (6–15)	0.13
Prior chemotherapy					
Yes	32	65	19 (73%)	13 (57%)	0.36
Bev					
Yes	24	49	15 (58%)	9 (39%)	0.29
Clinical risk score					
3, 4, 5	44	90	24 (92%)	20 (87%)	0.91
Size of largest tumor					
>5 cm	16	33	10 (38%)	6 (26%)	0.55
LN positivity					
Yes	39	80	22 (85%)	17 (74%)	0.55
CEA >200					
Yes	15	31	10 (38%)	5 (22%)	0.37
Disease-free interval					
<12 mo	46	94	25 (96%)	21 (91%)	0.89
Criteria for irresectability					
Biological	3	6	1 (4%)	2 (8%)	0.91
Technical*	46	94	25 (96%)	21 (92%)	0.98
Response rate					
WHO PR or CR, n (%)	37	76	16 (61%)	21 (91%)	0.04

*Includes irresectability because of bilateral vascular involvement (R0 resection would require resection of bilateral portal veins, inferior vena cava, and/or 3 hepatic veins), or a functional liver remnant <2 segments.

CEA indicates carcinoembryonic antigen; IQR, interquartile range; LN, lymph node; PR partial response; CR, complete response; WHO, World Health Organization response criteria.

TABLE 2. Toxicity Profile Stratified by Bevacizumab Administration

	Bev (n = 24)		No Bev (n = 25)		Total (n = 49)	
Toxicity Event	**No.**	**%**	**No.**	**%**	**No.**	**%**
Gr 3/4 Diarrhea	9	38	5	20	14	29
Gr 3 Alk	8	33	2	8	10	20
Gr 3 AST	5	21	3	12	8	16
Gr 3 Abdominal pain	5	21	1	4	6	12
Gr 3/4 Neuro	4	17	2	8	6	12
Biliary stents	3	13	1	4	4	8
Gr 3 Bilirubin	2	8	0	0	2	4
Gr 4 Bilirubin	1	4	1	4	2	4
Gr 3 WBC	1	4	0	0	1	2
Gr 2 HGB	1	4	1	4	2	4
Gr 3 Nausea	1	4	1	4	2	4
Gr 3 Vomiting	1	4	2	8	3	6
Gr 3 Mucositis	1	4	0	0	1	2
Gr 4 Platelets	0	0	1	4	1	2

Alk indicates alkaline phosphatase; AST, aspartate aminotransferase; HGB, hemoglobin; WBC, white blood cell count.

compares the characteristics of these patients with those who could not undergo resection. Two of the 3 biologically unresectable patients in the cohort underwent resection after a PR (1 as a 2-stage procedure). The third patient experienced progression of disease and was thus not considered a candidate for resection. Most patients (17/23) underwent formal anatomic resections (2 or more contiguous segments) accompanied by contralateral wedge resections and/or ablations. The remaining 6 patients underwent multiple, bilateral wedge resections or segmentectomies, in combination with ablation. Altogether, 16 patients underwent concurrent ablation. Six patients underwent preoperative portal vein embolization. One patient had concurrent extrahepatic disease (celiac lymph node) resected at the time of liver resection. Five patients underwent a 2-stage resection. Four additional patients underwent the first of a planned 2-stage resection that was

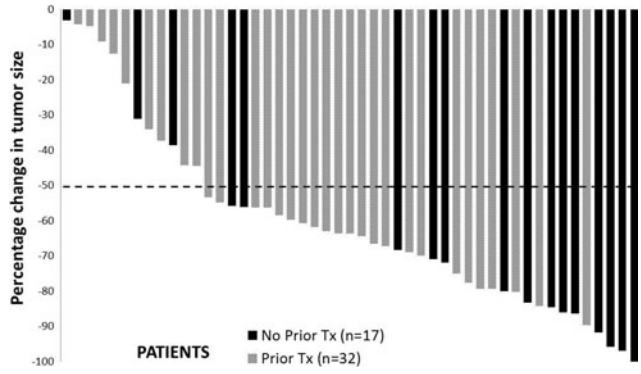

FIGURE 1. Waterfall plot illustrating the percentage of decrease in tumor size after treatment with hepatic arterial infusion of floxuridine/dexamethasone + best systemic therapy. Solid bars represent patients who had not received prior systemic chemotherapy (n = 17). Dashed line separates responders and nonresponders by World Health Organization criteria.

not completed because of progression of disease; these patients were not considered as resected. Fifteen of 23 specimens showed a significant pathologic response to chemotherapy (≥75%), 3 of whom were pathologic CRs. Five resected patients (22%) had positive margins on pathologic examination.

Eight patients (35%) experienced a complication after resection, only 1 (4%) being grade 3 or greater (a postoperative biloma requiring percutaneous drainage). There were no 90-day postoperative deaths.

Survival

The median follow-up time was 38 months. Median OS was 38 months [95% confidence interval (CI): 28 to not reached) (Fig. 2A). Median survival for chemo-naïve patients has not been reached [95% CI: 28 months to not reached (NR)] whereas previously treated patients had a median OS of 32 months (95% CI: 16 to NR); $P = 0.08$. One- and 3-year OS for chemo-naïve patients was 94% (95% CI: 65–99) and 75% (95% CI: 46–90) versus 91% (95% CI: 74–97) and 44% (95% CI: 26–61) for previously treated patients (Fig. 2A). Conversion to resection was the only factor associated with prolonged OS on univariate and multivariate analysis adjusting for CRS (Table 3).

The median PFS was 13 months (95% CI: 7–16). PFS for chemo-naïve and previously treated patients was 20 (95% CI: 6–26) and 10 (95% CI: 6–15) months; $P = 0.08$ (Fig. 2B). Two patients coded as progression ultimately came for resection: 1 with nodal disease resected after prolonged observation and 1 with a new liver lesion on imaging felt to be progression but ultimately proven to be benign fatty infiltration. Conversion to resection remained an independent predictor of prolonged PFS in multivariate model after adjusting for prior chemotherapy, CRS, and percent liver involvement (hazard ratio: 0.31 [95% CI: 0.15–0.62], $P < 0.001$) (Table 3).

Landmark Analysis

Twenty patients underwent resection by the prespecified landmark time. These patients had longer OS than those who did not undergo resection (3-year OS: 80% vs 26%; Fig. 3A). There was no difference in PFS as seen in Figure 3B (median PFS: 8 months for both groups) or time to hepatic progression (median time to hepatic progression: 33 vs 27 months; Fig. 3C) between resected and unresected patients. Follow-up time was 27 months (interquartile range: 24–40 months) and 17 months (interquartile range: 14–42 months) for resected and unresected patients, respectively.

Postresection Recurrence, Salvage Procedures, and Long-term Disease-free Survival

Of the 23 resected patients, 6 remained free of recurrence (1 died of unrelated reasons) at a median follow-up since resection of 28 months (range: 12–61 months). Of the remaining 17 patients who recurred after resection, 8 underwent complete resection and/or ablation of their liver-only (n = 7) or lung-only (n = 1) recurrences. Of these 8 patients, 4 remained with no evidence of disease (NED) at a median follow-up of 5 months (range: 3–21 months) from the salvage procedure. One additional patient remained free of disease at 57 months after a radiologic CR without resection. In total, 10 of 49 (20%) patients are currently NED at a median follow-up of 39 months (32–65 months).

DISCUSSION

In well-selected patients, complete resection of CRLM is associated with long-term survival. Untreated patients typically survive less than 1 year,[3,5] whereas treatment with modern systemic chemotherapy is associated with a median survival of approximately 2 years but is rarely, if ever, curative. In a recent trial comparing systemic chemotherapy with thermal ablation for CRLM, the systemic chemotherapy arm had a reported median survival of 40 months. Although this seems to be an improvement in outcomes, this reported survival is likely related to selection (patients had to have <10 tumors, no tumor larger than 4 cm, and no prior failure of chemotherapy) and the fact that 10% of these patients ultimately underwent resection.[39] For those patients on second-line therapy, survival is usually less than 15 months. In patients with unresectable CRLM, a multidisciplinary approach combining chemotherapy to reduce tumor burden and a proactive approach to resection have been associated with long-term survival similar to that of patients with initially resectable disease.[9,40,41] Conversion to complete resection is, therefore, a reasonable goal of treatment.

Resection of unresectable CRLM after downstaging with systemic chemotherapy has been reported in retrospective series.[9,13,40,42] These studies report resection rates between 12 and 38%. Although these data provide evidence that this strategy can be effective, limitations inherent to retrospective studies temper the conclusions that can be drawn from those reports. Definitions of what constitutes unresectable disease are highly variable and were generally not prespecified. Furthermore, the true denominator of patients with unresectable disease is often unclear or not reported. Therefore, the conversion rate may be inaccurate and overestimated.

In a recent study, 111 patients with unresectable CRLM were randomized to receive FOLFOX or FOLFIRI in addition to cetuximab. This study had prespecified criteria for irresectability; however, upon review of preoperative images by a panel of 7 surgeons, 32% of the patients enrolled were judged to be resectable at presentation. This raises obvious questions about the reported conversion rate of 46%.[41] Another prospective phase II trial evaluating irinotecan and 5FU/LV reported conversion to complete resection in 33% of patients; however, pretreated patients were excluded.[11,43] Modern prospective trials evaluating first-line systemic chemotherapy in unresectable CRLM have demonstrated RR between 47% and 68% and conversion to complete resection between 24% and 34%, which may be higher with the addition of biologic agents.[11,15,44] However, RRs in the second- or third-line setting range between 6% and 32%, with median OS between 10 and 20 months.[45,46]

The use of HAI chemotherapy to convert patients with unresectable CRLM to complete resection has also been reported. In

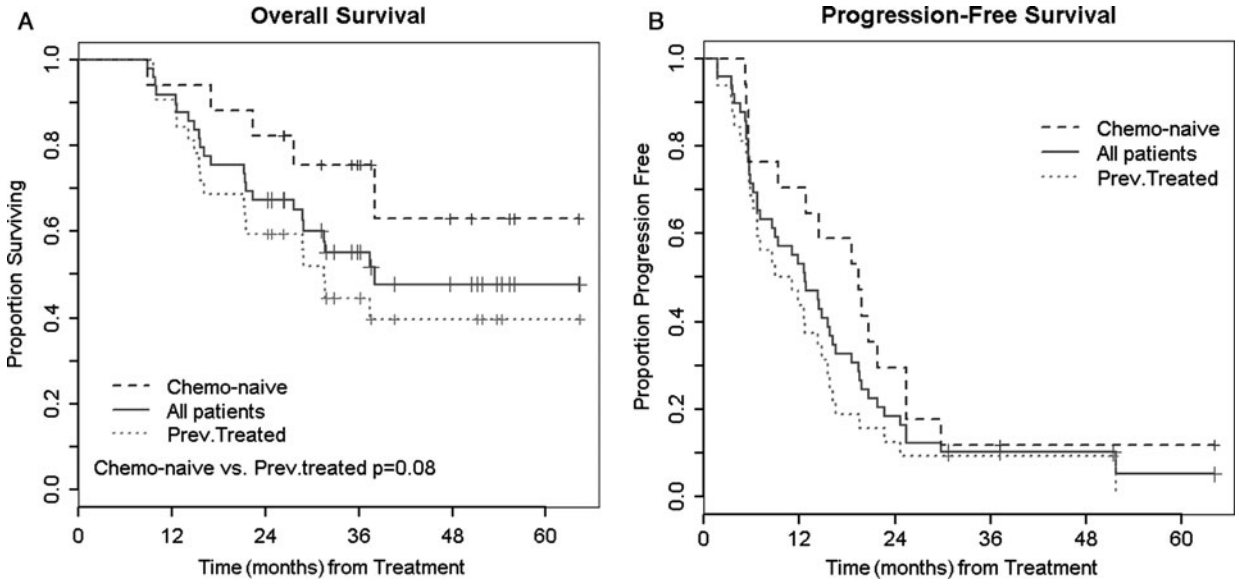

FIGURE 2. Overall (A) and progression-free (B) survival in 49 patients treated with HAI and systemic chemotherapy. Survival was calculated since treatment started. Graphs depict all patients (solid line) and stratified by prior therapy (dashed line: chemo naïve; dotted line: previously treated).

TABLE 3. Cox Regression Model for Overall and Progression-free Survival

	Overall Survival						Progression-free Survival					
	Univariate			Multivariate			Univariate			Multivariate		
Clinical Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age at diagnosis			0.32						0.51			
≥60	0.64	0.26–1.55					0.81	0.44–1.50				
<60	1						1					
Tumor involvement	1.02	0.95–1.08	0.62				1.01	0.97–1.05	0.55			
Synchronous tumor									0.83			
Yes	1.4	0.18–10.3	0.84				0.88	0.27–2.87				
Prior chemotherapy			0.08			0.11			0.08			0.03
Yes	2.40	0.88–6.40		2.2	0.83–6.23		1.74	0.93–3.27		2.1	1.06–4.32	
Liver involvement (%)	1.02	0.98–1.06	0.27				1.03	0.99–1.05	0.06	1.03	0.98–1.06	0.20
Clinical risk score*												
3, 4, 5	1.12	0.26–4.80	0.93	0.8	0.18–3.53	0.77	1.43	0.50–4.08	0.5	0.92	0.31–2.69	0.92
Largest tumor ≥5 cm												
Yes	1.14	0.48–2.68	0.8				1.42	0.75–2.64	0.3			
CEA >200												
Yes	1.2	0.50–2.84	0.7				1.02	0.53–1.97	0.9			
LN positivity												
Positive	3.21	0.75–13.7	0.1				1.7	0.81–3.54	0.2			
Disease-free interval												
<12 mo	1.39	0.18–10.3	0.7				0.88	0.27–2.87	0.8			
BEV												
Yes	1.08	0.46–2.49	0.9				0.8	0.44–1.44	0.5			
Conversion to surgery†												
Yes	0.17	0.05–0.52	**0.02**	0.16	0.05–0.49	**0.001**	0.26	0.15–0.48	**<0.0001**	0.31	0.15–0.62	**0.001**

*The individual variables in the clinical risk score (largest tumor >5 cm, CEA >200, LN positivity, and disease-free interval) were not included in the multivariate regression. Only the total score as a binary variable [ie, high (CRS: 3, 4, 5) versus low (CRS: 1, 2)] was included.

†Resection was coded as time-dependent covariate in the regression model.

CEA indicates carcinoembryonic antigen; HR, hazard ratio; LN, lymph node. Bold values represent statistically significant difference.

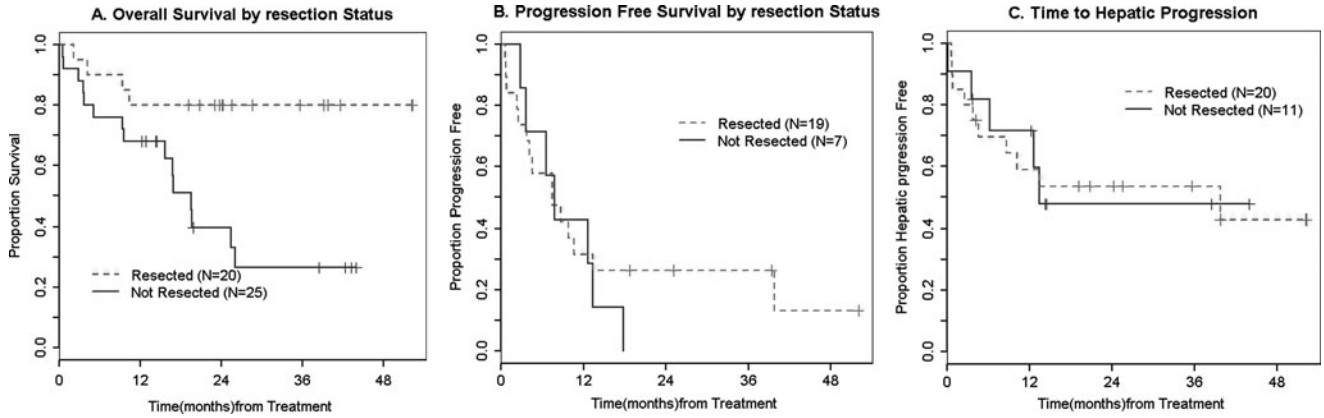

FIGURE 3. Landmark analysis. Time zero means 12 months from start of treatment. A, Overall survival: 4 patients without 12 months of follow-up were excluded. $P = 0.005$. B, Progression-free survival: 23 patients without 12 months of follow-up were excluded. $P = 0.60$. C, Time to hepatic progression: 18 patients without 12 months of follow-up were excluded. $P = 0.96$.

2002, Clavien et al reported a pilot study using HAI for unresectable liver tumors.[47] Twenty-three patients with unresectable CRLM were treated with HAI FUDR and no additional systemic treatment. Response to therapy allowed resection in 6 patients (26%). Two prior phase I trials reported that combination HAI and systemic oxaliplatin and irinotecan were well tolerated with an acceptable toxicity profile. The RR in these patients was 92% despite half of them being previously treated. Median survival from the start of chemotherapy was 51 and 35 months for chemotherapy-naïve and pretreated patients, respectively. Furthermore, in a separate retrospective analysis of these trials, it was reported that 47% of patients experienced sufficient response to allow complete resection.[27,28]

We designed the present prospective phase II trial specifically to evaluate the rate of conversion to resection in patients with unresectable CRLM treated with combination HAI and systemic chemotherapy. The trial was powered to detect an increase in conversion to resection from 15% to 30% based on current data at the time of design. This was felt to represent approximately a doubling of the conversion rate reported with systemic chemotherapy. Although the power analysis is now necessarily based on dated references, this is a limitation of any prospectively designed, executed, and reported trial. Furthermore, conversion to resection rates with current chemotherapy regimens is not significantly different. Although the initial chemotherapy was planned to be combined with Bev, the biliary toxicity of this combination (see later) did not allow half of the patient cohort to receive the Bev. Irresectability was prospectively defined and previously treated patients were allowed in the trial. Combination HAI and systemic therapy resulted in very high RRs in both previously treated (72%) and chemotherapy-naïve patients (82%)—overall 8% CR (4 patients). The primary end point of the study (conversion to resection) was achieved, with 47% of patients undergoing complete resection. Among the whole cohort, OS was 38 months, and 1- and 3-year survival rates were 92% and 55%, respectively. Of note, chemo-naïve patients had OS rates of 94% and 75% at 1 and 3 years, respectively. These results are encouraging, especially considering the high rate of previously treated patients, the large bulk of disease, and oncologic adverse features that most patients exhibited, and that 94% of patients had technically unresectable disease.

The combination regimens used in this trial were generally well tolerated. The rate of grade 3/4 toxicity was 41%, the most common event being grade 3 to 4 diarrhea and elevation of liver function tests. Major biliary toxicity was experienced by 13% of patients who received Bev, prompting its removal from the protocol. In our experience, the rate of biliary toxicity after HAI chemotherapy with FUDR is low (5.5%) and has been felt to occur in relation to the high concentration of chemotherapy in the arterial vessels feeding the bile duct.[48] We have also observed an increase in biliary toxicity when combining Bev and HAI FUDR in other protocols[37] and do not recommend the use of this combination. Although unproven, it is plausible that the antiangiogenic effect of Bev has an impact on biliary arterial capillaries, leading to ischemia and to an increased susceptibility to HAI-related biliary sclerosis. This underscores the importance of close monitoring of liver function tests and dose adjustments in patients receiving HAI therapy. Moreover, the surgical morbidity observed (35%—with only 1 major complication) compares favorably with our previously published experience.[2,49]

Although this trial was not designed to evaluate survival differences between resected and unresected patients, we performed a landmark analysis to evaluate this issue. At the landmark time of 12 months after initiation of HAI therapy, 20 patients had undergone resection. Median survival was significantly better in these patients undergoing resection (3-year OS: 80% vs 26%). Despite similar PFS and a 24% 1-year recurrence-free survival, it is important to note that 20% of patients (10/49) were rendered disease-free, with resection after initial progression (2 patients) or with salvage resection and/or ablation after recurrence (8 patients); and 39% of the patients who underwent resection are NED at the last follow-up. This underscores the idea that these (highly selected) patients may be rendered disease-free with resection, and despite a very high risk of recurrence, their survival is still positively impacted by the possibility of salvage. Although there is insufficient follow-up time, natural history data[50] suggest that these patients with long-term disease-free survival may be cured. Importantly, despite apparently longer follow-up time in the resected group, fewer events (deaths) are observed in this group; this again underscores the positive impact of resection on survival seen in the multivariable Cox regression.

The results of this trial may be difficult to extrapolate to the general population of patients with unresectable CRLM. The enrolled patients represent a unique population of relatively young patients with good functional status who present with extensive and heavily pretreated disease. Furthermore, conversion to resection is a somewhat subjective end point. Although this trial clearly defines resectability and what must occur to become resectable, these definitions and related decisions reflect the bias of institutional practices and may not be reflective of practices at other institutions. Nonetheless, this prospective trial demonstrates the possible outcomes with

a combination of HAI and systemic chemotherapy and resection whenever possible. Although the encouraging survival may be as much related to selection as it is to the treatment regimen, the rate of long-term disease-free survival, with or without salvage therapies after resection, is an indisputable outcome that rarely occurs with systemic chemotherapy alone.

CONCLUSIONS

The results from this phase II clinical trial show that selected patients with strictly defined unresectable CRLM, despite pretreatment with systemic chemotherapy and unfavorable oncologic characteristics, can experience enough response after combination treatment with HAI and systemic therapy to become resectable. Despite high recurrence rates, our findings show that salvage therapy is feasible, and a significant proportion of patients remain free of disease after prolonged follow-up. A role for HAI chemotherapy in unresectable CRLM is supported by our findings; however, randomized studies are needed to further define this role in comparison with systemic chemotherapy. Furthermore, these findings cannot be attributable to the use of Bev due to its early removal from the trial design related to an unanticipated high toxicity profile.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62:10–29.
2. House MG, Ito H, Gonen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg*. 2010;210:744–752, 752–755.
3. D'Angelica M, Brennan MF, Fortner JG, et al. Ninety-six five-year survivors after liver resection for metastatic colorectal cancer. *J Am Coll Surg*. 1997;185:554–559.
4. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol*. 2007;25:4575–4580.
5. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg*. 1990;77:1241–1246.
6. Sanoff HK, Sargent DJ, Campbell ME, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. *J Clin Oncol*. 2008;26:5721–5727.
7. Garufi C, Torsello A, Tumolo S, et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer*. 2010;103:1542–1547.
8. Beppu T, Hayashi N, Masuda T, et al. FOLFOX enables high resectability and excellent prognosis for initially unresectable colorectal liver metastases. *Anticancer Res*. 2010;30:1015–1020.
9. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg*. 2004;240:644–657; discussion 657–658.
10. Delaunoit T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from intergroup N9741. *Ann Oncol*. 2005;16:425–429.
11. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol*. 2004;15:933–939.
12. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) 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;25:1670–1676.
13. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996;224:509–520; discussion 520–522.
14. Lam VW, Spiro C, Laurence JM, et al. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. *Ann Surg Oncol.* 2012;19:1292–1301.
15. 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.
16. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. *J Clin Oncol*. 2011;29:1083–1090.
17. Kingham TP, Tanoue M, Eaton A, et al. Patterns of recurrence after ablation of colorectal cancer liver metastases. *Ann Surg Oncol*. 2012;19:834–841.
18. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. *J Am Coll Surg*. 2013;216:201–209.
19. Gold JS, Are C, Kornprat P, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. *Ann Surg.* 2008;247:109–117.
20. Wicherts DA, Miller R, de Haas RJ, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann Surg*. 2008;248:994–1005.
21. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann Surg*. 2000;232:777–785.
22. 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;206:685–693.
23. 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;107:459–465.
24. 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;24:1395–1403.
25. Ensminger WD, Rosowsky A, Raso V, et al. A clinical-pharmacological evaluation of hepatic arterial infusions of 5-fluoro-2'-deoxyuridine and 5-fluorouracil. *Cancer Res*. 1978;38:3784–3792.
26. Kemeny N, Conti JA, Cohen A, et al. Phase II study of hepatic arterial floxuridine, leucovorin, and dexamethasone for unresectable liver metastases from colorectal carcinoma. *J Clin Oncol*. 1994;12:2288–2295.
27. 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;27:3465–3471.
28. 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;23:4888–4896.
29. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350:2335–2342.
30. 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.
31. Daly JM, Kemeny N, Oderman P, et al. Long-term hepatic arterial infusion chemotherapy. Anatomic considerations, operative technique, and treatment morbidity. *Arch Surg.* 1984;119:936–941.
32. National Cancer Institute (NCI). Common terminology criteria for adverse events v3.0 (CTCAE). http://www.eortc.be/services/doc/ctc/ctcaev3.pdf. Published August 9, 2006.
33. Kemeny NE, Jarnagin WR, Capanu M, et al. Randomized phase II trial of adjuvant hepatic arterial infusion and systemic chemotherapy with or without bevacizumab in patients with resected hepatic metastases from colorectal cancer. *J Clin Oncol*. 2011;29:884–889.
34. World Health Organization. WHO handbook for reporting results of cancer treatment. http://whqlibdoc.who.int/publications/9241700483.pdf. Accessed March 1, 2014.
35. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230:309–318; discussion 318–321.
36. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. *J Clin Oncol*. 2008;26:3913–3915.
37. Cercek A, D'Angelica M, Power D, et al. Floxuridine hepatic arterial infusion associated biliary toxicity is increased by concurrent administration of systemic bevacizumab. *Ann Surg Oncol.* 2014;21:479–486.

38. Kemeny NE, Schwartz L, Gonen M, et al. Treating primary liver cancer with hepatic arterial infusion of floxuridine and dexamethasone: does the addition of systemic bevacizumab improve results? *Oncology.* 2011;80:153–159.
39. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol*. 2012;23:2619–2626.
40. Ardito F, Vellone M, Cassano A, et al. Chance of cure following liver resection for initially unresectable colorectal metastases: analysis of actual 5-year survival. *J Gastrointest Surg*. 2013;17:352–359.
41. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol*. 2005;16:1311–1319.
42. Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol*. 1999;10:663–669.
43. Barone C, Nuzzo G, Cassano A, et al. Final analysis of colorectal cancer patients treated with irinotecan and 5-fluorouracil plus folinic acid neoadjuvant chemotherapy for unresectable liver metastases. *Br J Cancer*. 2007;97:1035–1039.
44. Skof E, Rebersek M, Hlebanja Z, et al. Capecitabine plus Irinotecan (XELIRI regimen) compared to 5-FU/LV plus Irinotecan (FOLFIRI regimen) as neoadjuvant treatment for patients with unresectable liver-only metastases of metastatic colorectal cancer: a randomised prospective phase II trial. *BMC Cancer*. 2009;9:120.
45. Carneiro BA, Ramanathan RK, Fakih MG, et al. Phase II study of irinotecan and cetuximab given every 2 weeks as second-line therapy for advanced colorectal cancer. *Clin Colorectal Cancer*. 2012;11:53–59.
46. Bennouna J, Borg C, Delord JP, et al. Bevacizumab combined with chemotherapy in the second-line treatment of metastatic colorectal cancer: results from the phase II BEVACOLOR study. *Clin Colorectal Cancer*. 2012;11:38–44.
47. Clavien PA, Selzner N, Morse M, et al. Downstaging of hepatocellular carcinoma and liver metastases from colorectal cancer by selective intra-arterial chemotherapy. *Surgery.* 2002;131:433–442.
48. Ito K, Ito H, Kemeny NE, et al. Biliary sclerosis after hepatic arterial infusion pump chemotherapy for patients with colorectal cancer liver metastasis: incidence, clinical features, and risk factors. *Ann Surg Oncol*. 2012;19:1609–1617.
49. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg*. 2002;236:397–406; discussion 406–407.
50. Adam R, Wicherts DA, de Haas RJ, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol.* 2009;27:1829–1835.