Published in final edited form as:

J Surg Oncol. 2018 March ; 117(4): 634–643. doi:10.1002/jso.24898.

Prospective Phase II Trial of Combination Hepatic Artery Infusion and Systemic Chemotherapy For Unresectable Colorectal Liver Metastases: Long Term Results and Curative Potential

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Abstract

BACKGROUND/OBJECTIVES—Combination hepatic artery infusion (HAI) and systemic (SYS) chemotherapy for unresectable CRLM results in high tumor-response rates. This study represents an update of long-term survival and conversion to resectability in patients with unresectable CRLM treated with HAI and SYS chemotherapy in a phase II study.

METHOD—The primary endpoint was complete resection. Multivariate and landmark analysis assessed the effect of complete resection on progression-free (PFS) and overall survival (OS).

RESULTS—From 2007 to 2012, 64 patients with median of 13 tumors were enrolled; 67% had prior chemotherapy. 33 patients (52%) were converted to resection. Median follow-up among survivors was 81 months. Median PFS and OS were 13 and 38 months, respectively, with 5-year-OS of 36%. Chemotherapy-naïve patients had 5-year-OS of 51%. Conversion to resection was the only independent factor prognostic of improved PFS and OS. Nine of 64 patients (14%) are NED (5 since initial resection, 3 after resection of recurrent disease, 1 from chemotherapy alone) at median follow-up of 86 months from treatment initiation, and 72 months from last operative intervention.

CONCLUSION—Combination HAI and SYS is an effective therapy for high-volume unresectable CRLM, resulting in a high rate of resection, long-term survival and the potential for cure.

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Disclaimers: None.

This study was presented as an oral presentation at the American College of Surgeons (ACS) Clinical Congress 2016 in Washington, D.C.

TRIAL REGISTRATION—#NCT00492999, <https://clinicaltrials.gov/ct2/show/NCT00492999>

Keywords

colorectal liver metastases; hepatic artery infusion chemotherapy; hepatectomy

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer worldwide, with over one million new cases annually, of which nearly 150,000 occur in the United States[1, 2]. Thirty-five to 55% of colorectal cancer patients will develop liver metastases, which is often the only site of distant disease [3–5]. Complete resection of colorectal liver metastases (CRLM) is the only potentially curative treatment option and is associated with prolonged survival [6, 7]. Unfortunately, up to 85% of patients with CRLM are unresectable at presentation [8–10]. With current systemic chemotherapy options, a small minority of these patients will have sufficient response to allow complete resection and clearance of disease [7, 11, 12].

Hepatic artery infusion (HAI) chemotherapy allows precise delivery of high-dose regional hepatic chemotherapy. Taking advantage of the anatomic dependence of metastatic liver tumors on hepatic arterial blood supply, HAI chemotherapy effectively delivers a high-concentration of drug to the liver disease, and minimizes any adverse effect on normal parenchyma[9, 13, 14]. 5-fluoro-2-deoxyuridine (FUDR) is a particularly suitable chemotherapeutic drug for intrahepatic delivery, with a high first-pass hepatic extraction of 94–99% [15]. The limited systemic exposure of HAI FUDR provides the opportunity for combinatory regimens with systemic agents, which has been demonstrated to be safe and effective, even in patients with multiple prior lines of therapy[16]. With conventional systemic (SYS) chemotherapy alone, the median survival for patients with unresectable CRLM is approximately 30 months [17–24]. In patients whose tumors are RAS-wild-type, a higher median survival of over three years has been reported [25–28]. Conversion to complete resection with SYS chemotherapy has been reported, but conversion rates are low, ranging from 13% to 27% [6, 7, 12, 29]. Furthermore, reports of conversion are methodologically flawed due to lacking or vague definitions of resectability.

Prior randomized trials of combination HAI and SYS chemotherapy have demonstrated promising results with response rates of 55–88% with nearly half of patients converting to complete resection[16, 30–32]. In our initial report of a phase II trial evaluating patients with unresectable CRLM, 47% were converted to resection after treatment with HAI and SYS chemotherapy. The present study represents the long-term results of this trial and includes an expansion cohort not originally reported [33]. We have also included an analysis of outcomes stratified by tumor KRAS mutational status. The primary objective of this study was to assess conversion to resection and to evaluate the long-term survival and curative potential of patients with unresectable CRLM in this expanded phase II of HAI FUDR in combination with best SYS chemotherapy.

METHODS

This is a prospective, non-randomized, single-institution phase II trial (Registration #NCT00492999) approved by the MSKCC institutional review board. Patients presenting with unresectable CRLM were evaluated for trial eligibility from July 2007 to July 2012. All patients had histologically-confirmed colorectal carcinoma and no evidence of extrahepatic metastatic disease on cross-sectional imaging performed within six weeks of trial enrollment. This protocol involved a two-step registration process. Patients were registered to Step 1 prior to pump placement, and then eligible patients were registered to Step 2 after pump placement. Only patients registered to both Step 1 and Step 2 were included. As previously reported, irresectability was determined by 2 hepatobiliary surgeons and 1 radiologist and primarily defined as technical irresectability (a margin-negative resection would require resection of all 3 hepatic veins, both portal veins, or the retrohepatic vena cava, or a resection would result in <2 adequately perfused and drained liver segments); a small group of patients were also defined as biologically irresectable due to burden of disease (>6 metastases in a single lobe, with 1 lesion ≥5cm; or ≥6 bilobar metastases) and also included [33]. The definition of irresectability used in this study was the result of the consensus among our institution's medical and surgical oncologists [34, 35]. Patients were excluded from this study if they had prior liver resection or radiation, any evidence of end organ insufficiency, or Karnofsky performance score <60%. Prior to treatment initiation, all patients underwent detailed cross-sectional imaging, HAI pump insertion, and tissue biopsy, as detailed in the original trial publication [33].

All patients were assigned to received HAI FUDR in combination with best SYS chemotherapy (either oxaliplatin/irinotecan or 5-FU/leucovorin/irinotecan) as determined by their prior chemotherapy history, in addition to Bevacizumab (Bev) [33]. Bev was given to the first 24 patients but subsequently discontinued due to unexpected biliary toxicity (reported below); after IRB authorization and protocol amendment, the subsequent 40 patients did not receive Bev treatment. Toxicities and complications were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 3.0 [36]. Biliary toxicity was graded as previously reported [30, 37]. Patients were evaluated at least every two weeks during treatment with physical examination, complete blood count, complete metabolic panel, and carcinoembryonic antigen. Molecular genotyping for the KRAS mutational status was performed, as previously described [38]. Mutations in KRAS (codons 12 and 13) were identified using the iPLEX assay (Sequenom Inc, San Diego, Calif.).

The primary endpoint evaluated in this study was conversion to complete gross resection. Patients with a sufficient response to treatment were explored for potential resection. Treatment response was evaluated using World Health Organization criteria [39]. Resectability was re-assessed after the 4th cycle of therapy and then every 2 cycles after that. Surgical strategies for resection included ablation and 2-stage resections. All attempts were made to resect all sites of prior disease; however, sites of radiographic complete response that were not visualized at surgery were not required to be resected. Secondary endpoints included overall survival (OS), progression-free survival (PFS), hepatic progression-free survival (HPFS), tumor response rate, and treatment-related toxicities and complications.

The initial study was powered using the historical conversion rate with systemic chemotherapy at the time of trial design of 15%. In order to detect at least a doubling of the historical rate with 90% power, a sample size of 49 patients was determined. Fifteen patients not reported in the original publication were added as an expansion cohort to further clarify and confirm our initial findings.

OS, HPFS, and PFS were measured from initiation of HAI and SYS chemotherapy. Patients who did not experience the event of interest by the end of the study were censored at time of last available follow-up. OS, HPFS, and PFS were estimated using Kaplan-Meier methods. A Cox proportional-hazards model was used to evaluate the association between clinical characteristics and survival outcomes. All identified KRAS mutations were classified as KRAS mutant (MUT), and, in the absence of any identified mutations, KRAS wild-type (WT). Conversion to resection was treated as a time-dependent covariate. The models were adjusted for age (for OS) and other significant variables on univariate analysis.

We conducted a landmark analysis using resection at 12 months as a pre-defined landmark time, in order to examine the effect of resection on OS using Kaplan-Meier methods[40]. The landmark analysis attempts to account for the inherent bias in comparing patients with favorable responses to those with less favorable responses. Patients who had less than 12-month follow-up were excluded from landmark analysis and patients resected after 12 months were counted in the non-resection group.

All *p* values were based on 2-tailed statistical analysis and $p < 0.05$ was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina) and R (13.0).

RESULTS

Patient Characteristics

A total of 117 patients with unresectable CRLM were reviewed for study eligibility between July 2007 and July 2012. Fifty-three patients were excluded from the study (34 had extrahepatic disease; 1 had extrahepatic perfusion after hepatic pump placement; 8 were resected at the time of pump placement; 2 had significant comorbidities; 4 developed post-operative complications; 1 had FUDR started early; 1 had no evidence of malignancy on pathology; 1 patient declined study enrollment; and 1 was enrolled in a different study). 64 eligible patients were enrolled. All but three patients were defined as technically unresectable. Patient characteristics are summarized in Table 1. The majority of patients had received prior chemotherapy (43/64, 67%); 30 patients had one prior therapy, 12 had two prior therapies, and 1 had three. Five patients did not have adequate specimen to determine KRAS status. Of the 59 patients who underwent KRAS genotyping, 39 had KRAS WT and 20 had KRAS MUT tumors. Upon study enrollment, the systemic protocol for 37 patients (58%) included systemic 5-FU/leucovorin/irinotecan while 27 (42%) received systemic oxaliplatin/irinotecan.

Toxicity

Grade 3/4 diarrhea occurred in 13% of patients and neutropenia occurred in 2% (Table 2). Elevated liver function tests was the most common toxicity with 20% of patients showing an increase in liver enzymes.

Patients who received Bev with HAI and SYS regimens had unexpectedly significant biliary toxicity, with three of 24 patients (13%) requiring biliary stenting. Among the remaining 40 patients treated without Bev, 1 (2.5%) required biliary stenting.

Response and Conversion to Resection

The overall response rate (RR) was 73%, with 47 patients having a complete or partial response (1 CR, 46 PR). Seventeen patients had stable disease (SD), and no patients had progression of disease. Chemotherapy-naïve patients had RR of 86%, with median percent volumetric response of 83%, including 1 CR in a patient with a KRAS WT tumor. Patients treated with prior chemotherapy had a 67% RR, with median volumetric percent response of 61%. Patients who did not receive Bev had similar RR to those who did (73% versus 75%, $p = .83$). Patients with KRAS WT tumors had improved RR compared to KRAS MUT (68% versus 56%, $p=.009$). Volumetric responses are illustrated for all patients in Figure 1.

Thirty-three patients (52%) were converted to resection at a median of 5 months from treatment initiation (2–22 months), meeting the primary endpoint of doubling the historical conversion rate. Twenty-eight of these 33 resected patients (85%) experienced PR to protocol treatment while 5 had a minimal response that allowed resection. Twelve underwent portal venous embolization (PVE) to increase the volume of their future liver remnant prior to resection. Seventeen patients underwent hemi-hepatectomy accompanied by contralateral wedge resections and/or ablations. Sixteen patients underwent a combination of wedge and segmental resections, of which 12 also had concurrent ablation. Eight of these 33 patients underwent a 2-stage resection. An additional 8 patients underwent the initial stage of a planned 2-stage resection but did not reach the second stage of resection (7 due to progression of disease and 1 due to death secondary to unrelated cardiac arrhythmia). These 8 patients were not considered resected. Of the 33 resected patients, 25 demonstrated significant pathologic response to chemotherapy (75% necrosis), with 3 demonstrating pathologic CR. Eight resected patients (24%) had a positive margin on pathology. Thirty-one patients (48%) did not reach resection; 1 had a sustained CR, 18 had PR, and 12 had SD.

There were no post-operative mortalities following HAI pump insertion or subsequent resection and/or ablation. There were no grade 3 or 4 adverse events following HAI pump insertion. Three of the 41 patients who underwent resection developed grade 3 intra-abdominal fluid collections, abscesses, or bilomas that resolved with operative or percutaneous drainage. There were no other grade 3 or 4 perioperative adverse events.

Long-term Follow up and Survival

The median follow-up for surviving patients was 81 months (58–114 months). There were 17 patients alive at last follow-up. Nine of these patients were NED, of whom 8 underwent resection and 1 had a durable CR and never had surgery for liver metastases.

Median OS from initial diagnosis for all patients was 46 months (95%CI 32.3–59.7 months). Median OS from treatment initiation for all patients was 38 months (95%CI 28.8–53.7 months) and 5-year OS was 35.8% [95%CI: 24.3%–47.5%] (Figure 2A). There was a significant difference in OS between chemotherapy-naïve and previously-treated patients (median 76.6 months [95%CI: 38.6–NR] versus 29.7 months [95%CI: 21.5–40.2 months], $p = 0.022$). The 5-year OS was 51.9% for chemotherapy-naïve patients [95%CI: 29.1%–70.6%] and 27.9% for previously-treated patients [95%CI: 15.6%–41.6%]. Patients who received Bev had similar 5-year OS compared to those who did not (41.6% [95%CI: 22.2%–60.0%] versus 35.0% [95%CI: 20.8%–49.5%]). Patients with KRAS WT tumors had similar 5-year-OS (41.0% [95%CI: 25.6%–55.7%]) to those with KRAS MUT tumors (35.0% [95%CI: 15.6%–55.2%]). Median PFS for the entire cohort was 13 months (95%CI: 9–16 months) (Figure 2B). However, 38 patients with initial progression of disease were able to undergo subsequent salvage resections, of whom four are currently NED and eight are AWD. Chemotherapy-naïve patients experienced longer PFS than previously-treated patients (median 19.7 months [95%CI: 13.1–23.4 months] versus 10 months [95%CI: 6.2–14.3 months], $p = 0.021$); Bev treatment did not have a significant effect on PFS ($p = 0.46$). Median HPFS for all patients was 16 months (95%CI: 11.9–19.7 months). At last follow-up, there were 5 patients with no evidence of hepatic progression. The KRAS mutational status did not affect either PFS or HPFS. On univariate analysis, the absence of previous chemotherapy treatment and conversion to resection were associated with improved OS. Only conversion to resection remained significantly associated with OS on multivariate analysis (Table 3). Age, prior chemotherapy, and conversion to resection were associated with PFS on univariate analysis. On multivariate analysis, only age and conversion to resection remained a significant predictor of PFS (Table 3).

Landmark Analysis

Thirty patients had undergone resection by the prespecified landmark time of 1 year. Three patients who underwent resection after 1 year were grouped for analysis with patients who never underwent resection. Four patients died without undergoing resection prior to the 1-year mark and were excluded from analysis. Patients who converted to resection had significantly prolonged OS compared to those who did not ($p = 0.001$, Figure 3). The 5-year OS of resected patients was 63.3% [95%CI: 43.6%–77.7%] and 12.5% for unresected patients [95%CI: 3.5%–27.3%] ($p = .001$). The median number of tumors was the only factor that was significantly different between the resected and non-resected groups (10 versus 14 tumors, $p = 0.043$). KRAS status was not associated with conversion to resection ($p=0.400$). No other patient, disease, or clinical characteristics were significantly associated with conversion to resection.

Curative Potential

Overall, nine of 64 patients (14%) are free of cancer at a median follow-up of 94 months from initial diagnosis (range 65–120 months), 86 months from protocol treatment initiation (range 61–109 months), and 72 months from time of last operative/ablative procedure (range 21–105 months) (Table 4). Of the 33 resected patients, five never had any evidence of disease recurrence at a median follow-up from liver resection of 77 months (64–105 months). Of the 9 patients currently free of disease, another three underwent successful

resection/ablation procedures for recurrences after hepatic resection. The follow-up time from the last salvage procedure for these 3 patients is 21, 39, and 53 months. One additional patient with radiologic CR to the study regimen never required liver resection but did undergo removal of an abdominal wall metastasis and pelvic lymphadenectomy for a single nodal recurrence and has since remained NED at follow-up time of 74 months from this procedure and 105 months from treatment initiation. Of the 9 NED patients, six were KRAS WT and three were KRAS MUT. An additional 8 of 64 patients (13%) are AWD at median follow-up time of 69 months (59–129 months) from initial diagnosis and 63 months from treatment initiation (58–114 months).

DISCUSSION

This study reached its primary endpoint with a conversion rate to complete resection of well over the anticipated doubling of the historical rate. Thirty-three of the 64 patients (52%) presenting with unresectable CRLM had sufficient radiologic response after treatment with combination HAI and SYS chemotherapy to undergo resection, demonstrating a significantly promising rate of conversion. Despite a high rate of prior treatment, the overall RR was 73% and median OS of all patients was 38 months with a significant difference in OS between those who were able to undergo resection and those who were not.

Studies on the use of SYS chemotherapy alone in patients with unresectable CRLM have reported a much lower conversion rate to resection, ranging from 13–38%[6, 12, 29, 41–43]. While these rates have improved since the initiation of our study, very few studies have reported results comparable to our 52% conversion to resection rate. As resection is the only potentially curative treatment option, this remains a critical outcome to consider. In these prior studies, resectability was often not clearly defined and thus, it is difficult to determine how truly unresectable these patients were at presentation. In comparison, the criteria for irresectability in our study were prospectively designed and defined at the initiation of this study. The relevance of our definition is demonstrated by the median number of tumors per patient in this study (13 tumors, IQR 8–24 tumors). In addition, in order to meet study eligibility, patients had to be determined to have unresectable disease by two hepatobiliary surgeons and one radiologist to ensure the maximum level of standardization throughout the study.

This trial also demonstrated significantly longer survival for patients who were converted to resection than the previously reported range of 35.2 to 48.4 months for converted patients from SYS chemotherapy alone[44–46]. Although our study patients all presented with an extensive burden of disease, the predicted 5-year OS for patients who were able to convert to complete resection was 63%, which is similar to the rate seen in patients with initially resectable disease, and higher than that demonstrated among patients converted to resection with SYS chemotherapy alone[12, 29]. This may represent an additional survival benefit from improved targeted local disease control with the addition of HAI chemotherapy [47]. These findings strongly support the use of combination HAI and SYS chemotherapy as a therapeutic strategy to improve the rate of conversion to resection and optimize long-term disease control. As SYS chemotherapy regimens continue to evolve, additional studies are

needed to evaluate the benefit of the potential benefit of the addition of HAI chemotherapy in combination with these novel treatment protocols.

Interestingly, when we evaluated the KRAS mutational status of study patients, we identified an improved RR to the study regimen for patients with KRAS WT tumors compared with KRAS MUT (68% versus 56%, $p=.009$). While KRAS has been demonstrated as a predictive marker of response of anti-epidermal growth factor receptor treatment for metastatic colorectal cancer, it is unclear whether if this also applies to other chemotherapy regimens [48, 49]. We did not find a significant association in our study between KRAS mutational status and conversion to resection or survival outcomes, which is potentially due to the relatively small size of the study population compared to prior studies and as this study was not powered to perform this subgroup analysis [50, 51]. However, the improved response among patients with KRAS WT tumors indicates a potential predictive biomarker role for KRAS when evaluating patients for combination HAI and SYS chemotherapy.

Additional methods to increase conversion to resectability can be used in conjunction with HAI and SYS chemotherapy. We employed surgical techniques such as intraoperative ablation and two-stage liver resections to achieve complete resection in patients with complex, bilobar metastases [52–56]. PVE can also be performed for patients who are deemed unresectable due to lack of sufficient volume in the future liver remnant; however, PVE does not address the issue of irresectability due to excessive tumor burden or unfavorable tumor location relative to major vessels or biliary structures [57]. Other loco-regional therapies such as Yttrium-90 radioembolization can also be considered for patients with liver-only, or liver-predominant, colorectal metastases. A few case reports have shown conversion to resection with Y-90 therapy; however, at our institution, Y-90 radioembolization has not been used as a downstaging strategy due to concerns over hepatic toxicity [58–60].

The possibility of cure for patients presenting with unresectable CRLM has only become a reality within the past decade due to development of effective chemotherapeutic regimens and combination surgical treatment strategies. Adam et al proposed the use of 5-year disease-free survival (DFS) as the most appropriate definition for cure among patients presenting with advanced disease requiring a combinatorial treatment approach, and identified a 16% cure rate among 184 patients with initially unresectable CRLM who were converted to resection with SYS chemotherapy alone [61]. Within our study population, six of 64 patients have achieved 5-year DFS, representing a potential cure rate of 9% overall, and of 15% among resected patients. This demonstrates the significant potential for combination HAI FUDR and SYS chemotherapy and resection in patients presenting with a substantial burden of biologically aggressive disease and failure of disease control on prior chemotherapy treatments.

The main limitation of this study is the rigorous patient selection process that resulted in patients with good functional status, which may not be an accurate representation of the overall population of patients with CRLM. In addition, while criteria for irresectability were prospectively defined, these are not standardized and may reflect an institutional bias. However, as a prospective trial, this study demonstrates the promise that combination HAI and SYS chemotherapy holds in dramatically improving outcomes for patients presenting

with unresectable CRLM with otherwise limited therapeutic options. The current availability of HAI chemotherapy is also limited to certain centers worldwide; however, we hope the high rates of conversion to resection and the survival benefits of HAI and SYS chemotherapy demonstrated in the present study will encourage more centers to incorporate this combinatorial regimen into their practice.

CONCLUSIONS

Combination HAI and SYS chemotherapy is an effective treatment regimen in patients with unresectable CRLM with a high rate of conversion to resection and long-term survival. Despite presenting with an advanced high burden of disease and failure on prior conventional therapies, prolonged disease-free survival and potential cure can still be achieved. Large-scale, prospective, randomized trials investigating this combinatory therapy are indicated to further define its long-term benefits and delineate the appropriate criteria for patient selection.

Acknowledgments

Sources of support: Dr. Linda Pak received support from the Clinical and Translation Science Center at Weill Cornell Medical Center and MSKCC (grant number UL1TR00457). This work was supported in part by NIH/NCI P30 CA008748 Cancer Center Support Grant.

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SYNOPSIS

This study represents an update of long-term survival and conversion to resectability in patients with unresectable CRLM in a phase II study treated with hepatic artery infusion (HAI) and systemic (SYS) chemotherapy. 33 patients (52%) were converted to resection and 9 patients (14%) are free of disease at median follow-up of 86 months from treatment initiation. Combination HAI and SYS is an effective therapy for high-volume unresectable CRLM, resulting in a high rate of resection, long-term survival and the potential for cure.

Figure 1. Waterfall plot demonstrating percentage decrease in tumor size in response to therapy. Dark bars represent patients previously treated with chemotherapy (n = 43); light bars represent patients without prior treatment (n = 21).

Figure 2.

A. Overall survival of 64 patients treated with systemic chemotherapy and HAI FUDR, stratified by prior chemotherapy exposure. Median survival was 38 months for all patients (n=64) (95% CI: 28.8–53.7). The median survival for chemo-naïve patients (n=21) was 76.6 months (95% CI: 38.6–NR) and 29.7 months (95% CI: 21.5–40.2) for previously treated patients (n=43) (p=0.022).

B. Progression-free survival of all patients stratified by prior chemotherapy exposure. Progression-free survival for all patients (n=64) was 13 months (95% CI: 9–16 months). Progression-free survival for chemotherapy-naïve patients was 19.7 months (95% CI: 13.1–23.4) and 10 months (95% CI: 6.2–14.3) for previously treated patients (p=0.020).

Figure 3.

Landmark analysis of overall survival: 4 patients without 12 months followup were excluded. Time zero means 12 months from start of treatment.

*HAI FUDR indicates hepatic artery infusional 5-fluoro-2-deoxyuridine.

Table 1

Patient Demographics and Presenting Characteristics

	All Patients N (%)
Total	64
Age, years	
Median (IQR)	55.5 (47–63)
Sex	
Male	36 (56%)
Synchronous disease	
Yes	61 (95%)
Bilobar disease	
Yes	61 (95%)
Number of liver tumors	
Median (IQR)	13 (8–24)
Prior chemotherapy	
Yes	43 (67%)
Clinical risk score	
3, 4, 5	58 (91%)
Size of largest liver tumor	
>5 cm	36 (56%)
LN positivity of primary tumor	
Yes	52 (81%)
CEA >200 ng/ml	
Yes	19 (30%)
Disease-free interval	
<12 months	61 (95%)
<i>KRAS</i> Status	
<i>KRAS</i> WT	39 (61%)
<i>KRAS</i> MUT	20 (31%)
Unknown	5 (8%)
Criteria for irresectability	
Technical *	61 (95%)
Biological	3 (5%)

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

* Defined as a margin-negative resection which would require resection of 3 hepatic veins, both portal veins, or the retrohepatic vena cava, or a resection would result in <2 adequately perfused and drained liver segments

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Table 2

Toxicity Profile Stratified by Bevacizumab Administration

Toxicity	All Patients n = 64 N (%)	Bevacizumab Treated n = 24 N (%)	No Bevacizumab n = 40 N (%)
Gr 3/4 Diarrhea	13 (20%)	8 (20%)	5 (13%)
Gr 3 Alk	13 (20%)	8 (33%)	5 (13%)
Gr 3 AST	13 (20%)	5 (21%)	8 (20%)
Gr 3 Abdominal Pain	7 (11%)	5 (21%)	2 (5%)
Gr 3/4 Neuro	6 (9%)	4 (17%)	2 (5%)
Gr 3 HGB	5 (8%)	1 (4%)	4 (10%)
Biliary Stent	4 (6%)	3 (13%)	1 (3%)
Gr 3 Bilirubin	4 (6%)	2 (8%)	2 (5%)
Gr 3 Vomiting	4 (6%)	1 (4%)	3 (8%)
Gr 3 Nausea	3 (5%)	1 (4%)	2 (5%)
Gr 3 WBC	2 (3%)	1 (4%)	1 (3%)
Gr 4 Bilirubin	2 (3%)	1 (4%)	1 (3%)
Gr 3 ANC	1 (2%)	0 (0%)	1 (3%)
Gr 4 Platelets	1 (2%)	0 (0%)	1 (3%)
Gr 3 Mucositis	1 (2%)	1 (4%)	0 (0%)

* Alk indicates alkaline phosphatase; AST, aspartate aminotransferase; HGB, hemoglobin; WBC, white blood cell count; ANC, absolute neutrophil count

Table 3

Univariate and Multivariate Cox Regression Analysis for Overall and Progression-Free Survival

	Overall Survival				Progression-Free Survival							
	Univariate			Multivariate		Univariate			Multivariate			
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age of diagnosis >55	0.659	0.370–1.175	0.157	0.698	0.367–1.328	0.272	0.533	0.317–0.895	0.017	0.56	0.316–0.995	0.048
Gender	0.845	0.473–1.509	0.568				1.024	0.612–1.714	0.928			
Prior chemotherapy Yes	2.122	1.098–4.103	0.025	1.812	0.893–3.684	0.100	1.912	1.093–3.344	0.023	1.563	0.858–2.847	0.144
Clinical risk score 3	1.139	0.408–3.181	0.803				1.039	0.415–2.603	0.935			
CEA >200 ng/ml	0.963	0.507–1.831	0.909				1.044	0.591–1.842	0.882			
LN positivity	1.810	0.804–4.075	0.151				1.387	0.717–2.681	0.331			
Largest tumor >5 cm	1.123	0.626–2.012	0.697				1.320	0.782–2.229	0.298			
Synchronous disease	0.582	0.180–1.888	0.367				0.815	0.253–2.630	0.732			
Bilobar disease	1.696	0.409–7.028	0.466				0.874	0.271–2.824	0.822			
Number of liver tumors	1.000	0.998–1.001	0.729				1.000	0.999–1.001	0.750			
KRAS MUT	1.120	0.586–2.139	0.732				1.209	0.690–2.120	0.507			
Bevacizumab	0.924	0.505–1.693	0.798				0.887	0.522–1.506	0.656			
Conversion to resection	0.269	0.145–0.500	<.001	0.255	0.134–0.485	<.001	0.534	0.297–0.930	0.036	0.469	0.253–0.870	0.016

* CEA indicates carcinoembryonic antigen; LN, lymph node. Bold values represent a statistically significant difference.

Table 4

Long-Term Surgical Treatment and Outcomes of 9 NED patients.

	# of Salvage Attempts	Time from Last Salvage	OS (months)	Previously Treated	# of Liver Tumors	Resected	Time from Liver Resection (months)
1	0		109	No	7	Yes	105
2	0		100	Yes	27	Yes	92
3	0		81	No	8	Yes	77
4	0		81	Yes	6	Yes	72
5	0		69	No	3	Yes	64
6	2	53	105	No	14	Yes	92
7	2	39	84	No	7	Yes	78
8	6	21	61	Yes	10	Yes	57
9*	1	74	105	No	27	No	-

* NED indicates no evidence of disease

* Patient exhibited complete response to combination HAI and systemic chemotherapy and achieved NED without need for resection.