Published in final edited form as:

Clin Colorectal Cancer. 2012 March ; 11(1): 31–37. doi:10.1016/j.clcc.2011.03.029.

Hepatic Arterial Infusion and Systemic Chemotherapy after Multiple Metastasectomy in Patients with Colorectal Carcinoma Metastatic to the Liver: A North Central Cancer Treatment Group (NCCTG) Phase II Study, 92-46-52¹

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Abstract

BACKGROUND—Patients with multiple liver metastases from colorectal cancer are at high risk of recurrence after resection. Hepatic artery infusion (HAI) alternating with systemic therapy after surgical resection may improve survival following surgery.

METHODS—Patients with liver-only metastases from colorectal cancer amenable to resection/ cryoablation were eligible. Prior adjuvant chemotherapy for a completely resected primary was allowed. Alternating courses of HAI and systemic therapy included floxuridine (FUDR) via HAI. Systemic chemotherapy consisted of bolus leucovorin plus 5-fluorouracil (5-FU).

RESULTS—49 patients were able to undergo complete resection of their liver metastases with 44% having more than 4 hepatic metastases and 78% having bilobar disease. 36 patients were able to initiate HAI FUDR alternating with systemic therapy. Patients received a median of 3.5 cycles

¹This study was conducted as a trial of the North Central Cancer Treatment Group and Mayo Clinic and was supported in part by Public Health Service grants CA-25224, CA-37404, CA-15083, CA-63826, CA-35101, CA-35195, CA-35448, CA-35415, CA-60276, CA-63848, CA-52352, CA-37417, CA-35103, and CA-63849 from the National Cancer Institute Department of Health and Human Services. The content is solely the responsibility of the authors and does not necessarily represent the views of the National Cancer Institute or the National Institute of Health.

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(range 1–4) and 3 cycles (range 0–6) of therapy with HAI FUDR and systemic therapy, respectively. At the time of the final analysis the estimated median disease-free survival and hepatic disease-free survival are 1.2 years (95% CI: 0.9–2.1) and 1.8 years (95% CI: 1.8–NA), respectively. Eleven patients (31%) are alive. All surviving patients have a minimum of 5.5 years of follow-up

CONCLUSIONS—This trial of adjuvant chemotherapy in completely resected patients with unfavorable characteristics demonstrates apparent improvement in outcome compared to historical series treated with surgery alone. However, the results of this trial and other randomized trials of HAI do not appear to support its use at this time due to the development of more effective systemic options.

INTRODUCTION

Close to 150,000 people in the U.S. will develop colorectal cancer,¹ of which approximately 15 to 17 % will present initially with stage IV disease.¹ In addition, approximately 40% of patients undergoing potentially curative resection for stage II and III disease will subsequently develop recurrent disease.² The liver represents one the most common sites of metastasis in colorectal cancer. Approximately 10 to 25% of patients presenting with metastatic disease will have liver involvement, while 40 to 70% of patients who develop metastatic disease after a potentially curative resection will have liver involvement.³ In one-third of patients presenting with advanced disease the metastases are confined to the liver, while among patients who develop metastatic disease after curative resection of their primary tumor nearly half will have liver-only disease.^{3,4}

Initial reports from patient series of benefit from the resection of liver metastases originally appeared over 30 years ago.^{5,6} Surgery remains the only option for potential cure in patients with liver only metastases from colorectal cancer. However, only about 10 to 20% of patients are initially considered eligible for resection, primarily based on either an excessive tumor burden or adverse tumor location at presentation.⁷ With modern surgical approaches the number of patients undergoing resection is increasing. Recent surgical series are now reporting a 5-year survival rate of 25 to 37% and a median survival of 24 to 42 months with up to a third or more of patients remaining disease free.^{8–10} Nearly half of recurrences after resection involve the liver with the vast majority restricted to the liver.¹¹

Based on the potential of liver recurrence following resection patients who have undergone resection may be candidates for regional infusion therapy. Trials of patients receiving hepatic artery infusion (HAI) therapy after resection have reported an increased time to treatment failure as well as a decrease in hepatic recurrence compared to resection alone.^{12,13} These trials were built upon the prior observation of benefit from regional therapy for patients with unresectable liver metastases from colorectal carcinoma.^{14–16} In one of these studies the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) evaluated intrahepatic floxuridine (FUDR) versus systemic 5-fluorouracil (5-FU) for patients with unresectable colorectal liver metastases.¹⁶ That trial confirmed significantly higher tumor response rates for intrahepatic FUDR (55%) compared to systemic 5-FU (17%, $p < 0.01$) and significantly longer time-to-hepatic progression with intrahepatic FUDR compared to systemic 5-FU. Despite the higher response rate with FUDR, no improvement in survival was seen due to the more frequent extrahepatic tumor progression in the FUDR-treated group. Two additional phase III trials comparing intrahepatic versus systemic FUDR for the treatment of colorectal liver metastases confirm these results.^{17,18}

A pilot Mayo/NCCTG study of systemic 5-FU and leucovorin (LV) combined with HAI FUDR demonstrated that this regimen is tolerable.¹⁹ Among 40 eligible patients who received therapy, 62% had regression of their liver metastases. Median time to tumor

progression was 9 months and the median survival was 18 months. The toxicity was tolerable. No cases of biliary sclerosis were seen. Based on this pilot study a prospective Mayo/NCCTG trial of systemic 5-FU and LV combined with HAI FUDR following hepatic resection was performed.

Methods

Eligibility Criteria

Patients were potentially eligible for participation in the trial if they had either a previously resected colon or rectal cancer or presented with potentially resectable synchronous colon or rectal cancer with liver metastases. At the time of preregistration patients were required to have liver metastases that were determined to be potentially resectable. To complete registration to the trial patients had to have a minimum of 2 metastases if bilobar or 3 if unilobar that were either completely resected or ablated. Patients with a solitary metastasis or 2 unilobar metastases were considered eligible if 1 or more satellite lesions were present.

Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0–1. Hematologic and chemistry parameters were to be in acceptable ranges including white blood cell count $\geq 3.6 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, and direct bilirubin within normal limit (UNL).

Patients were allowed to have prior adjuvant therapy with 5-FU with or without LV or levamisole. Prior hepatic artery infusion of 5-FU or FUDR was not allowed. Prior adjuvant or neoadjuvant radiation for rectal cancer was allowed.

Patients were not eligible if pregnant or lactating and were required to use adequate contraception methods to prevent pregnancy during treatment. Other contraindications included pre-existing chronic liver disease. Any history of prior malignancy diagnosed within 5 years was not allowed, with the exception of basal or squamous cell carcinoma or the skin and cervical carcinoma *in situ*.

This trial was approved by the Mayo Institutional Review Board (IRB) and the IRBs of the participation institutions. A signed written informed consent was obtained from all patients prior to initiating therapy.

Treatment

At the time of surgery multiple wedge resections or a combination of lobectomy or segmentectomy with wedge resections was permissible. Intraoperative ultrasound of the liver was recommended prior to resection, but not required. It was expected that all metastatic lesions identified by preoperative CT scan and those found by intraoperative palpation or intraoperative ultrasound would be resected unless otherwise contraindicated. Hepatic cryoablation was allowed as the sole modality for surgical ablation of all metastatic lesions or used in conjunction with resection. If possible, it was preferred to have the dominant metastasis surgically resected.

In patients that were found to have anatomy appropriate for placement of a HAI catheter it was recommended that all side branches distal to the site of catheter placement along the upper border of the pylorus and duodenum, including the right gastric artery, should be ligated and divided to prevent misperfusion of the distal stomach and proximal duodenum and therefore lessen the risk for chemical gastritis and duodenitis.²⁰ It was also recommended that ligation of side branches proximally along the common hepatic artery to the celiac axis should also be done to prevent back flow of chemotherapy and perfusion of the upper gastrointestinal tract with FUDR. To prevent chemical cholecystitis a

cholecystectomy was advised. Once the catheter was in place intraoperative assessment of perfusion was required by infusion of 5 mL of fluorescein via the catheter or port. Postoperatively, a technetium sulfur colloid radionuclide liver scan was required to assess liver perfusion.

Following recovery from surgery (i.e., 21–56 days) the planned chemotherapy treatment was started. FUDR was given at a dose of 0.2 mg/kg/day over 14 days for a total of 4 2-week treatments. Following each 2-week FUDR infusion and a 1 week break patients received an intravenous combination of 5-FU 425 mg/m²/day and LV 20 mg/m²/day daily for 5 days for a total of 4 5-day treatments. A 1 week break occurred after each 5-day treatment with 5-FU and leucovorin prior to the next cycle of FUDR. Patients therefore received 4 cycles of alternating therapy, each cycle being 5 weeks in length. Two additional cycles of intravenous 5-FU and leucovorin alone were then given. In these two cycles the 5-FU and LV were given as described above over 5 days followed by a 3 week break.

FUDR was held or modified based on observed toxicities. If gastroduodenitis, upper gastrointestinal ulceration, SGOT or alkaline phosphate $> 2 \times$ upper limit of normal, any increase in the direct bilirubin, or grade 2 or greater diarrhea was observed during the FUDR infusion the FUDR was held. If severe dyspepsia/gastritis or if gastrointestinal ulceration occurred the dose of FUDR was decreased by 75%. The dose was decreased for moderate chemical hepatitis and 75% for severe hepatitis. FUDR was discontinued for any evidence of biliary stricture or failure to recover after 4 weeks of rest. Appropriate dose reductions or delays were provided for 5-FU.

Evaluation, Disease Assessment, & Follow-Up

Once chemotherapy was started patients were seen at the start of each cycle of treatment. A CBC and chemistries (SGOT, alkaline phosphatase, direct and total bilirubin, and creatinine) were obtained periodically during treatment and at the start of each cycle of therapy. A CT scan was obtained following the completion of protocol directed therapy every 3 months times 4 and then every 6 months to 5.5 years. Patients were seen at the time of the CT scans and had a CBC and chemistries performed at that time.

Statistical Considerations

The primary endpoint was 5-year survival measured from the date of resection/cryoablation. Since 5-year survival was expected to be 5–10% in patients with multiple hepatic metastases who undergo surgical resection without adjuvant chemotherapy, the aggressive combined modality treatment outlined in this protocol was to be considered insufficiently successful if the true 5-year survival rate was 10% or less. On the other hand, a 5-year survival of 30% was considered clinically beneficial. Hence, we were interested in testing the null hypothesis that the true success proportion was at most 10% (i.e. $H_0: p \leq 0.10$) versus the alternative hypotheses that the true success proportion was at least 30% (i.e. $H_a: p \geq 0.30$). To test this hypothesis, we planned to accrue a total of 33 eligible patients who initiated chemotherapy, followed them for 5 years, and computed the success proportion. If the observed success proportion was at least 30%, i.e. if at least 7 of the 33 survived more than 5 years, we were to consider the regimen as being worth further study. This single stage phase II design has significance level of 0.042 when the true success proportion is 10%, and a power of 91% for detecting a true success proportion of 30%.

Adverse events were collected via NCI CTC version 1.0. The percent of targeted dose administered to each patient for a given cycle was calculated as the total dose administered divided by the protocol specified dose, targeted for the cycle. Patterns of treatment failure, toxicity, including complications associated with the intra-arterial catheter, were

summarized. Frequency tables with Chi-square and Fisher's Exact tests were used to explore the relationships between dichotomous variables. The distributions of time to recurrence, disease free survival, and survival were estimated using the method of Kaplan-Meier.²¹ Cox proportional hazards models were used to explore the associations of covariates with time to recurrence, disease-free survival, and survival. All p-values reported are two-sided, unless otherwise specified. The statistical package used to perform analyses was SAS – Version 9.1 (<http://www.sas.com>).

Definitions of Endpoints—Time to recurrence was defined as the time from metastasectomy, cryoablation, and/or radiofrequency ablation to documentation of disease recurrence. If a patient died without a documentation of disease recurrence, the patient was considered to have had a recurrence of their disease at the time of their death unless there was sufficient documented evidence to conclude recurrence did not occur prior to death. In the case of a patient never returning for any evaluations post-surgery (i.e., metastasectomy, cryoablation, and/or radiofrequency ablation), the patient was censored for recurrence on day-1, post-surgery.

Disease-free survival was calculated as the time from registration to death or recurrence, whichever was earlier. Hepatic disease-free survival was calculated as the time from registration to death or hepatic recurrence, whichever was earlier, however, if the first recurrence was extra-hepatic then censoring occurs at the recurrence date.

Survival was defined as the time from surgery to death due to any cause. Patients lost to follow-up were censored for these endpoints at the date of last contact (or disease assessment), as applicable. All patients were followed for disease recurrence and survival for a period of 5.5 years post-registration to address the primary endpoint. Data was censored at this time point for analyses.

Results

Patient Enrollment

114 patients were evaluated for the trial, and 104 underwent laparotomy (9 were declared ineligible, and one was unable to get surgery due to denial of insurance coverage). Of those 104 patients, complete resections were unable to be achieved in 55 due to reasons shown in Figure 1. The remaining 49 patients achieved complete surgical resection of their disease. However, 13 of the 49 patients were unable to initiate hepatic artery infusion/systemic therapy due to reasons shown in Table 1. Post-operative deaths (3) were due to multiple infarctions of the remaining hepatic segments, abdominal hemorrhage during metastasectomy, and sudden cardio-respiratory distress. Between November 23, 1993 and June 14, 1999, a total of 36 patients initiated hepatic artery infusion/systemic therapy within the planned 21–56 days of metastasectomy.

Patients Receiving Hepatic Artery Infusion/Systemic Therapy

Patient Characteristics (Table 1)—Patients were predominantly Caucasian, having ECOG PS of 0 (vs 1), and 33% of patients had more than 4 metastatic lesions. A majority of patients presented with bilobar (78%) or >2 unilobar (17%) metastases. Ninety-seven percent of patients had at least one hepatic metastases resected with a median of 4 metastases resected. Cryoablation was infrequent, occurring in only 6 (17%) of patients.

Hepatic Artery Infusion/Systemic Therapy Administration and Toxicity

Patients received a median of 3.5 administrations of treatment (range 1–4) for HAI and a median of 3 administrations of treatment (range 0–6) for systemic therapy. Table 2 displays

the percent of targeted dose administered, by agent and administration. Fourteen patients experienced 17 delays in treatment. The reasons for discontinuing treatment early included: recurrence (27 patients), toxicity (2 patients), death unrelated to study treatment (hemorrhage secondary to warfarin in the setting of a perforated necrotic small bowel as a consequence of adhesions), and patient refusal (2 patients).

Nineteen of 36 evaluable patients (52.8%) experienced at least one Grade 3 adverse event and 9 of 36 experienced a Grade 4 adverse event (25.0%). No grade 3 or 4 hematologic events occurred. Grade 3+ non-hematologic adverse events included elevated liver enzymes (5 patients), chemical hepatitis (10 patients), infection (1 patient), lethargy (5 patients), stomatitis (5 patients), and diarrhea (8 patients). No fatalities related to HAI or systemic therapy were reported.

Patient Outcome for Patients Receiving Treatment (Table 3)

Twenty-eight (78%) patients have experienced disease recurrence, with 18 patients including the liver at first recurrence. The estimated median disease-free survival (DFS) and hepatic disease-free survival (HDFS) are 1.2 years (95% CI: 0.9–2.1) and 1.8 years (95% CI: 1.8-NA), respectively. Eleven patients (31%) were alive at the time of last followup. All surviving patients have a minimum of 5.5 years of follow-up (Figure 2).

Discussion

Seven randomized trials have evaluated HAI therapy following surgical resection of hepatic metastases from colorectal carcinoma.^{12,13,22–27} However, only 3 of these trials had a meaningful number of patients randomized to either HAI or systemic therapy (Table 4). Two of the randomized trials evaluated surgery alone versus surgery followed by HAI of FUDR or 5-FU. In one of these trials patients with 2–4 resected hepatic metastases were randomized to resection alone versus HAI with FUDR combined with systemic infusional 5-FU.¹² This trial showed a significant decrease in hepatic recurrence with HAI as well as nonsignificant improvement in overall survival (63.7 versus 49.0 months). In another trial that had assessed the use of surgery alone versus surgery followed by HAI of 5-FU 226 patients were enrolled.²³ Overall survival was longer for those undergoing surgery alone (40.8 months) versus those receiving HAI of 5-FU (34.5 months). It is notable that in this trial only 34 of the 108 patients randomized to the HAI arm in this trial were able to complete the planned therapy.

In a trial from Memorial Sloan-Kettering Cancer Center, patients were randomized to systemic chemotherapy alone, with either bolus 5-FU and leucovorin or continuous infusion 5-FU, versus systemic chemotherapy combined with HAI FUDR.^{13,22} Seventy-four patients were randomized to combined therapy and 82 to systemic therapy. A significant benefit was seen in patients receiving combined therapy. The median survival in the group receiving combined therapy was 68.4 months compared to 58.8 months for those receiving systemic therapy alone. At two years the rate of survival free of hepatic recurrence was 90 percent in the combined therapy group compared to 60 percent in the systemic therapy only group ($p < 0.001$). However, recurrence outside the liver appeared similar in both groups.

Our trial had a lower rate of 5-year survival compared to the other two trials using FUDR. However, this likely reflects a higher risk group. Eligibility for our trial required patients to have either bilobar metastases or multiple unilateral metastases. In the trial led by Lorenz et al 50% of patients had one liver metastasis,²³ while in the trial lead by N. Kemeny et al approximately 30% of patients had only one metastasis.¹³ The trial led by M. Kemeny restricted enrollment to patients with 1–3 metastases.¹² As with these other trials, the protocol-directed therapy was shown to be tolerable in those who were able to initiate

therapy. In this trial approximately one-quarter of patients were unable to initiate therapy related to either pump-related issues or other issues. This rate was likely related to the early experience with pumps and the high risk group of patients enrolled in the trial.

Several recent trials have attempted to evaluate newer approaches with HAI therapy in the adjuvant treatment of patients undergoing resection of liver metastases from colorectal cancer. A NCCTG led trial, N9945 (NSABP CI-66), assessed the potential benefit of systemic capecitabine and oxaliplatin alternating with HAI FUDR. This phase II trial met the prespecified endpoint of >85% survival at 2 years and was clinically tolerable.²⁸ A phase III trial of capecitabine and oxaliplatin alone versus systemic capecitabine and oxaliplatin alternating with HAI FUDR was attempted, but closed early because of poor accrual. The future of adjuvant therapy using HAI remains uncertain. A recent Cochrane analysis concluded that HAI is not of meaningful benefit as part of adjuvant therapy for resected liver metastases.²⁹ Given the development of more active systemic therapy options clinical research is now primarily focused on this approach.

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Figure 1.

Figure 2.

Table 1

Patient Characteristics (N=49)

Characteristic	No Therapy (N=13)		Received Therapy (N=36)	
Age, Median (Range)	61.0	(47–75)	61.5	(25–75)
No. of Metastases Resected, Median (Range)	4.0	(1–9)	4.0	(0–10)*
Baseline ECOG Performance Status, No. (%)				
0	9	(69%)	25	(69%)
1	4	(31%)	11	(31%)
Gender, No. (%)				
Female	5	(38%)	13	(36%)
Male	8	(62%)	23	(64%)
Extent of Metastases, No. (%)				
Bilobar	10	(77%)	28	(78%)
>2 Unilobar	2	(15%)	6	(17%)
≤ 2 Unilobar with satellite lesions	1	(8%)	2	(6%)
No. Hepatic Metastases Cryoablated, (%)				
Missing	1	(8%)		
0	12	(92%)	30	(83%)
1	0	(0%)	5	(14%)
2	0	(0%)	1	(3%)
Type of Procedure, No. (%)				
Resection Only	13	(100%)	30	(83%)
Cryoablation Only	0	(0%)	1	(3%)
Both types	0	(0%)	5	(14%)
Anaomolous hepatic circulation, No. (%)	6	(46%)	11	(31%)
Post Operative Complications, No. (%)	7	(54%)	10	(28%)
Adequate perfusion by IA Catheter, No. (%)	5	(45%)	36	(100%)
Reason for not receiving Adjuvant therapy, No. (%)				
Extra-Hepatic Disease	0	(0%)	0	(0%)
Unresectable or ablatable	0	(0%)	0	(0%)
Inadequate perfusion	5	(38%)	0	(0%)
Positive Margin	0	(0%)	0	(0%)
Other	8	(62%)	0	(0%)

* One patient had two metastases cryoablated, but no metastases resected.

Table 2

Percent of Targeted Dose Administered (N=36)

Administration	FUDR				5-FU			
	N	Mean	Median	Q1-Q3	N	Mean	Median	Q1-Q3
1 st	34	95	99	97-100	32	97	99	98-100
2 nd	29	66	52	40-100	25	85	80	74-99
3 rd	20	44	36	24-50	24	82	79	71-97
4 th	17	47	50	24-50	14	83	78	72-99
5 th	N/A				1	79	79	79-79
6 th	N/A				1	79	79	79-79

Table 3

Summary of Outcomes

Event Type	Did Not Receive Therapy (N=13)	Received Therapy (N=36)
Disease-Free Survival Median (yrs) (95% CI)	1.0 (0.4–1.6)	1.2 (0.9–2.1)
1 year	51.3(28–94)	58.1(44–77)
2 years	20.5(6–70)	40.7(27–61)
Hepatic Disease-Free Survival Median (yrs) (95% CI)	1.0 (0.4-NA)	1.8 (1.0-NA)
1 year	51.3(28–94)	66.4(52–85)
2 years	30.8(12–79)	49.1(34–71)
Survival Median (yrs) (95% CI)	1.5 (1.1–3.0)	3.0 (2.2–3.6)
1 year	76.9(57–100)	91.7(83–100)
2 years	46.2(26–83)	66.7(53–84)
5 years	15.4(4–55)	30.6(19–50)

* Kaplan-Meier methodology, with 95% CI.

Table 4

Randomized Trials of HAI as Adjuvant Therapy for Resected Liver Metastases from Colorectal Cancer

Trial	Therapy	Number	Median Hepatic DFS (months)	Median DFS (months)	Median Survival (months)
Current	HAI FUDR + IV 5FU/LV	36	21.6	14.4	36.0
Kemeny N ¹⁴	1. HAI FUDR + IV 5FU +/- LV	74	NR	31.3	68.4
	2. IV 5FU +/- LV	82	32.5	17.2	58.8
Kemeny M ¹³	1. HAI FUDR + CI IV 5FU	53	NR	NS	63.7
	2. Observation	56	20.2	NS	49.0
Lorenz ²⁴	1. HAI 5FU + LV	108	21.6	13.7	34.5
	2. Observation	111	24.0	14.2	40.8