



Surg Oncol Clin N Am  
12 (2003) 193–210

---

---

SURGICAL  
ONCOLOGY  
CLINICS OF  
NORTH AMERICA

---

---

# Arterial chemotherapy as adjuvant and palliative treatment of hepatic colorectal metastases: an update

Anton J. Bilchik, MD, PhD, FACS

*John Wayne Cancer Institute, 2200 Santa Monica Boulevard,  
Santa Monica, CA 90404, USA*

More than 130,000 new cases of colorectal cancer (CRC) are diagnosed annually, and more than 56,000 deaths are attributed to CRC each year [1]. This figure represents 10% of cancer-related deaths in the United States; CRC is second only to lung cancer. At the time of diagnosis, 20% to 25% of patients with CRC present with synchronous hepatic metastasis; an additional 20% to 25% of patients may develop metachronous liver metastasis [2–4]. Complete surgical resection of liver metastasis offers the only chance for cure [2–4] and produces a 5-year survival rate of 25% to 40% and a median survival of 25 to 40 months [2–5]. Unfortunately, only 20% of patients with CRC have completely resectable liver disease, which recurs in most of these patients [6]. At least half of the recurrences arise in the liver and most are identified within 2 years of resection [3].

Although certain chemotherapy regimens by themselves have produced modest benefits for patients with metastatic CRC, the overall results of systemic chemotherapy have been disappointing [4,7–10]. Systemic 5-fluorouracil (5-FU), the mainstay of treatment, has produced response rates of only 10% to 20% in clinical trials [4,7–11]. These rates could be improved by novel therapeutic agents and/or delivery systems that better target metastatic cells. The latter include infusion of chemotherapy through the hepatic artery. Hepatic arterial infusion (HAI) improves targeting of metastatic CRC because the hepatic artery is the primary supplier of blood to hepatic metastases. The fluoropyrimidine drug floxuridine (FUDR) is a promising agent for HAI because its first-pass rate of extraction by the liver is 94% to 99%, compared with 19% to 55% for 5-FU. FUDR therefore can

---

*E-mail address:* bilchika@jwci.org

1055-3207/03/\$ - see front matter © 2003, Elsevier Science (USA). All rights reserved.

PII: S 1055-3207(02)00079-0

be infused into the hepatic artery at a 100- to 400-fold higher concentration than systemic 5-FU, with minimal toxicity [12–15].

Initial studies with FUDR demonstrated an improvement in local control but not in overall survival [12,13,15,16]. These studies were criticized, however, because of patient crossover to systemic therapy and technical complications relating to placement of the hepatic pump. More recent studies have demonstrated a lower complication rate and better tolerance to treatment [11,17–20]. FUDR produces response rates of 40% to 60% and an apparently better outcome than that associated with standard systemic chemotherapy alone [12–15,21].

This article covers the technical aspects of HAI pump placement and reviews randomized studies of systemic therapy versus hepatic arterial FUDR, the palliative role of regional FUDR and novel systemic agents after hepatic cytoreduction, and the tailoring of regional therapy from novel techniques and molecular analysis.

### **Technical aspects of hepatic artery infusion pump placement**

A complete staging work-up should be performed prior to insertion of the HAI pump. This work-up includes colonoscopy and CT of the chest, abdomen, and pelvis. Positron emission tomography may be indicated to exclude extrahepatic disease. Arterial anatomy must be confirmed because 30% to 50% of patients have an anomalous arterial supply, usually from accessory vessels and/or replaced vessels. An accessory vessel supplies a lobe despite the presence of normal right and left lobar vessels. A replaced vessel is a right or left artery that does not arise from the common hepatic artery; the most common replaced vessel is a right hepatic artery originating from the superior mesenteric artery. Transfemoral arteriography will identify the arterial anatomy of the liver and confirm the patency of the portal vein. CT angiography has been used more recently because it rapidly provides three-dimensional views of the arterial anatomy (Fig. 1). An aberrant left hepatic artery is usually found in the superior aspect of the gastrohepatic ligament, and a replaced right hepatic artery is usually lateral to the common bile duct.

A right subcostal incision is performed and the abdomen explored for extrahepatic disease. Because cholecystitis is a potential complication of regional chemotherapy, a cholecystectomy is routine. The common hepatic artery is then mobilized medial to the common bile duct until the origin of the gastroduodenal artery is identified. The gastroduodenal artery is dissected distally as far as possible by ligating small arterial branches. The right gastric artery, and any variant lobar vessel, is then ligated. The superior borders of the stomach and the duodenum are skeletonized to avoid perfusion to these organs. A tie is used to ligate the gastroduodenal artery distally.

After the pump is primed with warm heparinized saline, an incision for a pump pocket is developed in the lower quadrant if the patient has a small

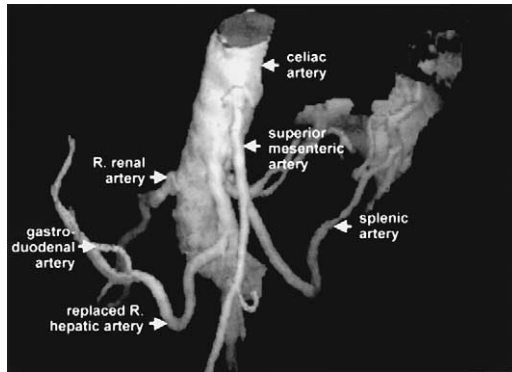


Fig. 1. CT angiogram showing three-dimensional image of hepatic arterial anatomy. R, right.

body habitus. Alternatively, the incision may be developed anterior to the rectus sheath in the upper quadrant, thereby avoiding a second incision. The catheter is passed through the fascia via a separate stab wound, and the pump is securely anchored to the fascia at four quadrants.

The gastroduodenal artery is the preferred insertion site, even in patients with variant anatomy, because collateral flow occurs almost immediately after its ligation. An angled vascular clamp is placed around this artery at the origin of the hepatic artery, and an arteriotomy is made. A beaded catheter is introduced into the artery and secured with a vascular clamp. Ties are placed proximal and distal to the catheter bead. Bilobar infusion is confirmed by injecting 5 ml of a 10% solution of fluorescein through the bolus port and then examining the liver, stomach, and duodenum with a UV Woods light. A radionuclide study using technetium-99 macroaggregated albumin (Amersham, Los Angeles, CA) should be performed before the pump is filled with FUDR.

## **Randomized studies of chemotherapy via hepatic arterial infusion**

### *Primary therapy*

Randomized studies of regional (HAI) versus systemic infusion of various chemotherapeutic agents were initiated 20 years ago. Most patients had unresectable disease and were stratified according to the percentage of liver involvement (Table 1) [11–13,15,16,22]. Although the response rates were better for regional (40%–62%) than systemic (10%–20%) chemotherapy, differences did not necessarily correspond to improved overall survival (see Table 1). This finding may reflect small populations, inadequate systemic chemotherapy, and/or high rates of crossover to systemic treatment because of the toxicity of HAI. Moreover, although a

Table 1  
Prospective randomized trials of HAI versus systemic chemotherapy for hepatic colorectal metastases

Group	No. patients	Response, %		P	Median overall survival, mo		P	Comments
		HAI	Systemic		HAI	Systemic		
Kemeny et al, 1987 [15]	162	52	20	.001	18	12	NS	Crossover
Chang et al, 1987 [12]	64	62	17	.003	20	11	.03	Extrahepatic disease
Hohn et al, 1989 [13]	143	42	10	.0001	17	16	NS	Crossover + extrahepatic disease
Martin et al, 1990 [16]	69	48	21	.02	12.6	10.5	NS	Extrahepatic disease
Rougier et al, 1992 [23]	163	43	9	.001	15	11	.02	Extrahepatic disease
Allen-Mersh et al, 1994 [27]	100	50			13.5	7.5	.03	No chemotherapy in systemic arm
Lorenz and Muller, 2000 [25]	168	45	20	.009	18.7	17.6	NS	Regional 5-FU not FUDR

Abbreviations: 5-FU, 5-fluorouracil; FUDR, floxuridine; HAI, hepatic arterial infusion; NS, not significant.

meta-analysis of these studies attributed a statistically significant survival advantage to HAI [17], it did not account for interstudy variability in the patient population: for example, several studies included patients with extrahepatic disease. The meta-analysis also did not account for differences in the type, dose, and duration of chemotherapy; some studies used FUDR for systemic and regional therapy, whereas others used 5-FU or other agents for systemic administration. In a French study of 163 patients, half of the patients in the control arm did not receive systemic therapy because control treatments were based on the standard care of each participating physician [23].

Biliary toxicity, in particular biliary sclerosis, was a major complication of HAI in at least three studies, resulting in insufficient doses of FUDR and crossover to systemic therapy [13,15,23]. Kemeny et al [24] subsequently demonstrated that concurrent HAI of dexamethasone significantly reduced the toxicity of FUDR. In their study, 50 patients with liver metastases received HAI of FUDR (0.3 mg/kg per day) with or without dexamethasone (20 mg) for 14 of 28 days. Although patients in the dexamethasone group received higher total doses of FUDR, only 9% demonstrated elevated bilirubin levels, versus 30% without dexamethasone. The addition of dexamethasone also increased response rates (71% versus 40%) and improved overall survival (21 versus 13 months).

In the multicenter German study reported by Lorenz and Muller [25], 168 patients at 25 treatment centers received 5-FU/leucovorin (LV) via HAI, 5-FU/LV via intravenous (IV) infusion, or FUDR via HAI (see Table 1). All patients had nonresectable liver metastases that did not exceed 75% of liver volume. The time to progression was 9.2 months with HAI 5-FU/LV, 6.6 months with IV 5-FU/LV, and 5.9 months with HAI FUDR. Respective median survival times were 18.7 months, 17.6 months, and 12.7 months. Patients whose intrahepatic tumor burden was less than 25% had a twofold increase in time to progression and a survival benefit following HAI of 5-FU/LV. Although this was a randomized study, both the hepatic toxicity and the crossover rate were extremely high: 34 (31%) of 101 patients did not complete the planned intrahepatic therapy regimen. This was in part because the study was initiated prior to publication of the dexamethasone study of Kemeny et al [24]. Of 57 patients assigned to the HAI 5-FU/LV arm, 12 were switched to systemic 5-FU/LV, 5 discontinued chemotherapy because of complications or death, and 2 were switched to nonstudy chemotherapy. Of 54 patients assigned to the HAI FUDR arm, 7 were switched to systemic 5-FU/LV, and 1 patient was switched to HAI 5-FU/LV. By contrast, the number of patients who received systemic 5-FU/LV treatment increased from 57 to 71. There was a significantly lower rate of extrahepatic disease progression with HAI 5-FU/LV (13%) than with HAI FUDR (41%), probably because FUDR is almost entirely metabolized in the liver and has little systemic effect. HAI 5-FU/LV, however, had a much higher rate of complications than HAI FUDR (40% versus 8%). Hepatic

toxicity of 5-FU may be explained by vasoconstriction secondary to the induction of protein kinase C in the vascular smooth muscle [26]. These factors may have masked any survival benefit.

Allen-Mersh et al [27] specifically addressed quality of life and survival in a study of 100 patients who received either HAI FUDR or systemic 5-FU for symptom palliation. The quality of life was better and the survival significantly improved in the HAI group. The survival benefit was associated with significant reductions in metastasis and serum carcinoembryonic antigen (CEA) levels. This study demonstrated that survival can be prolonged with a normal quality of life in patients with liver metastases from colorectal cancer.

### *Adjuvant therapy*

Although surgical resection remains the only potentially curative option for patients with hepatic metastases [2–4], the high rate of hepatic recurrence has led to several studies of adjuvant regional chemotherapy. These studies are based on the assumption that HAI targets micrometastasis in nonresected liver tissue, thereby reducing the chance of recurrence.

A study from the City of Hope National Medical Center (Duarte, CA) examined the results of systemic or regional chemotherapy administered alone or as adjuvant treatment following surgical resection of hepatic metastases [22]. The results of laparotomy were used to stratify 91 patients into three groups. Those with solitary resectable metastases underwent surgical resection alone or followed by HAI of FUDR; the respective times to recurrence were 9 months and 31 months ( $P < 0.03$ ). Patients with multiple resectable metastases underwent HAI of FUDR alone or after resection; respective survival rates were similar (Table 2). Patients with unresectable metastases underwent HAI of FUDR alone or after systemic infusion of 5-FU. As expected, median survival correlated with the extent of disease (37.3, 22.4, and 13.8 months for the three groups, respectively).

More recently, Kemeny et al [28], at Memorial Sloan-Kettering Cancer Center (New York, NY), compared two adjuvant chemotherapy regimens in 156 patients who had undergone resection of hepatic metastases. All patients received six cycles of systemic 5-FU with or without LV; one group also received six cycles of HAI with FUDR and dexamethasone. The 2-year overall survival rate was 86% with regional plus systemic therapy and 72% with systemic therapy alone ( $P = 0.03$ ). At a median follow-up of 62 months, respective median survival times were 72 months and 59 months (see Table 2). These differences were not statistically significant ( $P = 0.11$ ; Fig. 2A). The respective 2-year rates of hepatic disease-free survival were 90% and 60% ( $P < 0.001$ ; Fig. 2B).

Although the significant improvement in disease-free survival has led some oncologists to adopt the combination of regional and systemic therapy as their standard of care, the results of this study should be interpreted

Table 2  
Prospective randomized trials of HAI +/- systemic 5-FU after resection of hepatic colorectal metastases

Group	Regimen	No. patients	Overall survival						Disease-free survival, %	P
			Median, mo	P	2-y, %	P	5-y, %	P		
Wagman et al, 1990 [22]	HAI: FUDR Sys: None	5 6	37.3 28	NS	80	NS	40	NS	—	
Lorenz et al, 1998 [19]	HAI: 5-FU Sys: None	73 114	44.8 39.7	NS	60	NS	47	NS	—	
Kemeny N, et al, 1999 [11]	HAI: FUDR + Sys: 5-FU Sys: 5-FU	74 82	72.2 59.3	NS	85	.02	68	NS	.07 (2 y)	
Kemeny MM, et al, 2002 [29]	HAI: FUDR + Sys: 5-FU Sys: None	35 45	63.7 49	NS	80	NS	63	NS	.04 (4 y)	

Abbreviations: 5-FU, 5-fluorouracil; FUDR, floxuridine; HAI, hepatic arterial infusion; NS, not significant; Sys, systemic chemotherapy.

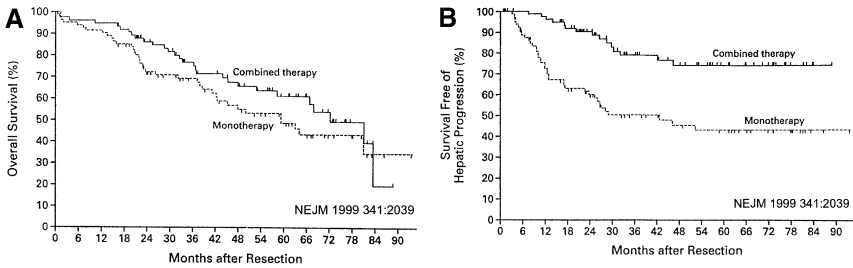


Fig. 2. (A) Overall survival after hepatic resection in patients receiving hepatic arterial infusion with floxuridine (HAI FUDR) and systemic 5-fluorouracil (5-FU) versus systemic 5-FU alone. (B) Hepatic progression-free survival after hepatic resection in patients receiving HAI FUDR and systemic 5-FU versus systemic 5-FU alone. (From Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999;341:2039–48.)

cautiously. First, the study group was relatively large but from a single institution. Second, there was no 5-year overall survival benefit, probably because only half of the patients were observed for 5 years and only six patients were included in the analysis at 80 months. Third, only 26% of patients assigned to regional plus systemic therapy received more than 50% of the planned dose of FUDR because of elevated levels of hepatic arterial enzymes. Fourth, the duration of regional plus systemic treatment was 35 weeks, whereas the duration of systemic therapy alone was 21 weeks. Finally, 13% of patients had positive margins; therefore, the apparent “disease-free” survival advantage may in fact represent palliation.

A multicenter study from the German Cooperative on Liver Metastases did not show a survival benefit for HAI of 5-FU after liver resection (see Table 2) [19]. An interim analysis after enrollment of 226 patients and 91 deaths showed a median survival of 34.5 months for adjuvant therapy versus 40.8 months for no adjuvant therapy. Corresponding median times to progression were 14 months and 13.7 months. Only 34 (30%) of the 113 patients assigned to adjuvant therapy completed the chemotherapy regimen, however. Median survival time was 45 months for the subgroup of adjuvant therapy patients who completed chemotherapy versus 39 months for patients who were not assigned to adjuvant therapy; a completed regimen of adjuvant therapy nearly doubled the median survival time to hepatic progression (44.8 versus 23.3 months).

This study’s high (70%) rate of failure to complete chemotherapy could be explained in part by the infusion of 5-FU through portocatheters (ports) rather than infusion pumps. These ports are associated with a high rate of technical complications and unreliable doses of infusion. This alone was responsible for early cessation of therapy in 19 patients. The high rate of adjuvant treatment cessation also reflected the use of 5-FU instead of FUDR; the latter has a higher hepatic extraction rate and therefore is more

effective and less toxic. This study also has been criticized because chemotherapy was given by surgeons and not medical oncologists.

In the United States, the only multicenter study of systemic versus HAI of chemotherapy after liver resection was conducted by the Eastern Cooperative Oncology Group (see Table 2) [29]. Patients with more than three liver metastases were excluded, and the study was closed to accrual after 9 years. Patients were randomly assigned to postoperative observation (control) or to hepatic resection followed by 4 cycles of HAI (FUDR) and 12 cycles of systemic infusional 5-FU. After a 9-year accrual period, there were 45 control patients and 30 chemotherapy patients. The 4-year disease-free survival rate was 25% for the control patients and 46% for the chemotherapy patients ( $P = 0.034$ ). The 4-year survival rate was 53% in the control group and 62% in the chemotherapy group ( $P = 0.6$ ).

### **Cytoreductive surgery and regional chemotherapy**

Because only 20% of patients are amenable to resection, ablative modalities such as cryosurgical ablation (CSA) or radiofrequency ablation (RFA) have become increasingly popular to treat unresectable hepatic metastases. Results of several studies have demonstrated that these techniques are safe, have no cumulative toxicity, and effectively destroy CRC metastases [20,30–37]. Nevertheless, the role of ablation (with or without concomitant resection) in the treatment of patients with CRC metastases is still debatable.

CSA safely destroys liver tumors by freezing them with liquid nitrogen [32,36]. Tumors can be precisely defined and completely eradicated under ultrasound guidance while sparing normal tissue. A median survival time of up to 26 to 30 months has been reported after CSA alone or in combination with hepatic resection [35,36]. In selected cases of metastatic CRC, the results of CSA may approach those of surgical resection [20,32,34,36].

RFA destroys tumor by generating heat within a lesion. A high-frequency alternating current causes thermal coagulation and protein denaturation. As the temperature is increased to more than 45°C, cellular proteins denature and ultimately cell death occurs. Unlike CSA, RFA uses relatively inexpensive instrumentation and can be performed in the operating room via celiotomy or laparoscopy, or in the radiology suite via a percutaneous approach. Its reported complications and recurrence rates are relatively low [30,31,37]. Nevertheless, as with hepatic resection, most patients experience tumor recurrence.

A novel group of drugs, the topoisomerase-1 inhibitors (CPT-11), appear to be effective against both untreated and refractory metastatic CRC [38,39]. Metastatic CRC lesions, in particular lung metastases, are often resistant to fluoropyrimidine drugs because of high thymidylate synthase (TS) gene expression [40,41]. CPT-11 bypasses this type of drug resistance [42–44]. In

randomized studies involving patients with advanced CRC, the median survival was significantly greater when irinotecan was added to 5-FU or 5-FU/LV [43,44]. Largely from these and other studies, irinotecan in combination with 5-FU and LV is now used as standard first-line therapy for metastatic CRC.

Because both irinotecan and regional FUDR are effective in patients refractory to systemic 5-FU [18,43,44], the combination of these agents is a rational approach to treat patients with recurrences [45,46]. The feasibility of administering systemic CPT-11 with HAI FUDR was recently reported by Kemeny et al [28]. Forty-six previously treated patients with unresectable liver metastases were treated concurrently with IV CPT-11 weekly for 3 weeks, HAI for 14 days, and in some cases, cryosurgery. Response rates were 74% without cryosurgery and 100% with cryosurgery. HAI FUDR had no effect on the metabolism of CPT-11.

Oncologists at the John Wayne Cancer Institute evaluated the role of cytoreductive surgery alone and in combination with both regional FUDR and systemic irinotecan for treatment of unresectable CRC hepatic metastases refractory to 5-FU. One hundred eighty-five patients whose hepatic metastases progressed (defined by changes noted on CT scan and/or by elevated or increasing CEA levels) during 5-FU therapy underwent cytoreductive surgery between July 1992 and August 1999 (Fig. 3). Two hundred twelve procedures were performed (25 patients underwent two procedures and 1 patient underwent three procedures). Curative resection was the goal, but when hepatic metastases were incompletely resectable because of liver dysfunction and/or the location or number of hepatic lesions, cytoreductive surgery, consisting of CSA with or without hepatic resection, was considered. Patients with less than 50% liver involvement, a good performance status, and absence of extrahepatic disease were considered candidates for cytoreduction. Patients undergoing cytoreduction had complete treatment of all identifiable sites of disease.

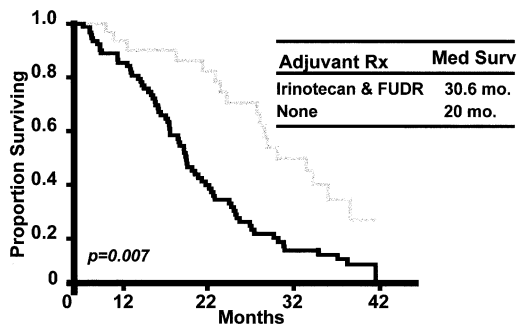


Fig. 3. Overall survival and median survival (Med Surv) times in patients undergoing cytoreduction alone versus combination of cytoreduction, CPT-11, and regional floxuridine (FUDR).

This trial evaluated irinotecan at a maximum dose of 125 mg/m<sup>2</sup> every week and HAI consisting of FUDR (0.18–0.2 mg/kg), dexamethasone (10 mg), and in some cases LV (10 mg/m<sup>2</sup>). Treatment with FUDR was planned for six cycles, starting 2 weeks after cytoreduction. Treatment with irinotecan also was planned for six cycles 4 weeks after surgery. The dose of either irinotecan or FUDR was then adjusted according to patient tolerance.

Although patients described in this study were from distinctly different periods (1992–1996 and 1996–1999), the patient characteristics were comparable in each treatment group (Table 3). One hundred fourteen patients were treated with cytoreductive surgery alone and 71 patients received irinotecan and FUDR in addition to cytoreduction (see Table 3). The median number (3–4) and size (4 cm) of lesions treated were comparable for each group. Thirty percent of patients had synchronous hepatic metastases and 70% of patients had metachronous metastases in each group. Forty-four patients (24%) had unilobar lesions and 141 patients (76%) had bilobar lesions. The median preoperative CEA level was 159 ng/dL (range, 0.2–4000 ng/dL). Sixty-seven patients (36%) underwent concurrent liver resections. Approximately 80% of patients completed at least three cycles of FUDR treatment. More than a 50% reduction in the total dose of FUDR was necessary in approximately 40% of patients. Thirty percent of patients treated with irinotecan required dose reductions because of toxicity. These rates of dose reduction for FUDR and irinotecan are similar to those reported previously [11,44].

At a median follow-up of 20 months, 123 patients (66%) had developed recurrence (Table 4). Forty-three patients (23%) had liver recurrences only, 60 patients (32%) had liver and extrahepatic recurrences, and 20 patients (11%) had extrahepatic recurrences only. Of the 103 (56%) patients with liver recurrence, 21 (11%) had hepatic lesions at the previous CSA site, and

Table 3

Characteristics of 185 patients undergoing cytoreduction alone and cytoreduction with regional FUDR and systemic CPT-11<sup>a</sup>

Characteristics	Cytoreduction ( <i>n</i> = 114)	Cytoreduction + irinotecan and FUDR ( <i>n</i> = 71)
Size of liver lesions	4 cm (1–15 cm)	4 cm (1–15 cm)
No. of liver lesions	3 (1–15)	4 (1–5)
Detection of lesions		
Synchronous	34 (30%)	20 (28%)
Metachronous	80 (70%)	51 (72%)
Distribution of lesions		
Unilobar	28 (25%)	15 (22%)
Bilobar	85 (75%)	56 (78%)
Preoperative CEA level	152	167

Abbreviations: CEA, carcinoembryonic antigen; FUDR, floxuridine.

<sup>a</sup> Equally matched for median follow-up (20 mo), age, comorbidity, and hepatic function.

82 (44%) had hepatic lesions away from the previous CSA site. The median time to progression was 10 months after cytoreduction alone and 19 months after cytoreduction plus adjuvant irinotecan and FUDR ( $P < 0.001$ ). There also were significantly more recurrences in the cytoreduction alone group (78%), compared with the irinotecan/FUDR group (48%;  $P < 0.05$ ). The incidence of liver recurrence in patients receiving FUDR and irinotecan was 37%, significantly less than in patients receiving no adjuvant therapy (68%;  $P < 0.01$ ). The proportion of patients developing extrahepatic recurrences also was significantly less in the group receiving adjuvant therapy (31%), compared with the group receiving no further treatment postoperatively (51%;  $P < 0.05$ ).

The median survival time of all patients was 38 months from diagnosis of liver metastases and 26 months from cytoreduction. Patients who underwent cytoreduction alone had a median survival time of 20 months compared with 30.6 months for those patients who also received irinotecan and FUDR ( $P < 0.007$ ; see Fig. 3). The 2-year survival rate for patients receiving adjuvant therapy was 75%, compared with 35% for patients receiving no additional treatment ( $P < 0.01$ ). This survival benefit was evident regardless of the presence of unilobar or bilobar lesions, synchronous or metachronous metastases, or the size and number of lesions (Table 5). The survival time of patients who underwent repeat CSA was 53 months from diagnosis of liver metastases and 42 months from the date of the first CSA. By univariate analysis, preoperative CEA levels and postoperative reduction in CEA correlated with improved survival. The median survival time was 31.7 months for patients who had more than a 60% reduction in CEA versus 9.8 months in those patients who had less than a 30% reduction in CEA.

The recurrence rates observed previously by oncologists at the John Wayne Cancer Institute [30,37,45] and others [20,31,32,34–36] after cytoreduction alone (using either CSA or RFA) and the survival advantage

Table 4  
Patterns of recurrences in patients undergoing cytoreduction<sup>a</sup>

Patterns of recurrence	Cytoreduction ( <i>n</i> = 114)	Cytoreduction + irinotecan and FUDR ( <i>n</i> = 71)
All recurrences	88 (77%)	35 (49%)*
Liver	76 (67%)	27 (38%)*
Recurrence at CSA site	14 (12%)	8 (11%)
Recurrence at different site	62 (54%)	19 (27%)*
Extrahepatic	58 (51%)	22 (31%)*
Progression-free survival	10 mo.	19 mo**

Abbreviations: CSA, cryosurgical ablation; FUDR, floxuridine.

<sup>a</sup> Median follow-up 20 mo/group.

\*  $P < 0.05$ .

\*\*  $P < 0.001$ .

Table 5  
Survival benefit in the FUDR CPT-11 group

Characteristics	Median survival, mo.	
	Cytoreduction ( <i>n</i> = 114)	Cytoreduction + irinotecan and FUDR ( <i>n</i> = 71)
Location		
Unilobar	21.7	33.0*
Bilobar	19.5	29.0*
Detection		
Synchronous	24.8	32.0*
Metachronous	22.1	28.3*
Number		
<3	23.5	32.5*
>3	20.0	27.0*
Size, cm		
<4	23.0	35.0*
>4	20.0	27.0*

Abbreviation: FUDR, floxuridine.

\* *P* < 0.05.

seen in patients receiving regional and/or systemic therapy after cytoreduction from this and an earlier study [45] underscore both the limitations of cytoreduction alone and the benefits of adjuvant chemotherapy in this setting. Currently, oncologists at the John Wayne Cancer Institute do not favor the use of cytoreduction alone in the treatment of patients with unresectable CRC metastases.

Despite failing systemic 5-FU, the patients in this study who received regional therapy with FUDR (in combination with systemic irinotecan) had lower rates of local recurrence and significantly longer survival times than patients who received no postoperative therapy. Previous studies have shown up to a 30% to 52% rate of response to FUDR in patients who are resistant to systemic 5-FU [18,21], demonstrating the efficacy of FUDR in previously treated patients. The results from this and the previous study [54] suggest that systemic irinotecan may be effective in decreasing the incidence of recurrent extrahepatic disease following cytoreductive surgery.

A therapeutic dilemma often arises for clinicians concerning the selection of patients for cytoreduction. One study [35] of 195 patients treated with CSA suggested that a tumor size of less than 3 cm correlated with a more favorable outcome. In Weaver et al's [36] study of 136 patients, size was not prognostic of better outcome following CSA. In addition, although the number of metastatic lesions has been shown to be of prognostic value in some series of patients [2,4,6,46,47], it has not been shown to be of significance in other series [36,48]. In an analysis of 1001 consecutive liver resections, Fong et al [4] proposed a disease-related composite score to better predict success after resection. The characteristics correlating with

decreased survival after resection include the following: presence of synchronous liver metastases, presence of more than one lesion, size of the largest lesion more than 5 cm, CEA level more than 200 ng/dL, and presence of a node-positive primary tumor [2,4,6]. Other factors that were highly predictive of therapeutic failure were the presence of extrahepatic disease and the involvement of the resection margin by tumor. Seifert et al [34] also suggested that incomplete cryotreatment correlated with decreased survival. In the John Wayne study, number and size of metastatic lesions were not prognostic factors. Both preoperative CEA levels of less than 100 and postoperative reduction in CEA levels by at least 30% were shown to be important indicators of improved survival; these levels also have been shown to correlate with survival in other studies [5,36,49]. A small postoperative reduction in CEA level likely represents inadequate treatment of liver lesions or occult disease. Future studies may better define prognostic factors that would refine the algorithm for treating patients with unresectable CRC hepatic metastasis.

### **Tailoring chemotherapy using molecular analysis**

Advances in molecular biology have resulted in the characterization of genetic alterations in colon cancer. This has led to the identification of specific targets to facilitate treatment. The molecular target of 5-FU that defines its cytotoxic activity is TS, the enzyme that catalyzes the rate-limiting step for DNA synthesis. Overexpression of TS has been correlated with resistance to 5-FU in several preclinical and clinical studies [50,51]. Molecular analysis of TS has therefore been proposed as one way of selecting patients for regional HAI with FUDR. Link et al [52] evaluated intratumoral TS mRNA in 24 patients receiving HAI. Fourteen patients had low TS levels and 10 patients had high TS levels. Of the patients with low TS levels, 9 of 14 (64%) responded, compared with 20% (2 of 10 patients) of patients with high TS levels. The median survival time was 26 months in patients with low TS levels and 16 months in patients with high TS levels.

Davies et al [53] evaluated colorectal liver metastases for TS using a specific antibody (TS106). Although TS staining was low in significantly more patients with a partial response than no response (75% versus 29%), TS staining intensity did not affect survival. HAI may have exerted a cytotoxic effect in some patients with high TS levels because regional FUDR may reach higher cytotoxic doses than systemic 5-FU. Previous systemic fluorouracil exposure also seems to increase the tumor cell resistance to regional FUDR by possible TS up-regulation. A prospective analysis of TS expression in colorectal liver metastases may be useful in determining which patients may benefit from the implantation of an infusion pump, thereby avoiding the cost and toxicity of ineffective treatment.

## Summary

Regional hepatic chemotherapy with FUDR significantly improves local recurrence rates and may impact overall survival in patients with hepatic colorectal metastases. The results of prospective randomized trials confirm that careful patient selection, a thorough knowledge of intricate hepatic arterial anatomy, and an understanding of the pharmacokinetics and delivery of FUDR optimize treatment efficacy. A multimodality approach that includes adjuvant therapy in addition to cytoreductive surgery offers promise for the treatment of unresectable hepatic metastases. Because many tumors recur in extrahepatic sites, the addition of novel systemic agents such as CPT-11 may further reduce recurrences. Molecular analysis of the tumor may ultimately help select patients who are good candidates for regional chemotherapy.

## Acknowledgments

This work was supported by funding from the Rogovin-Davidow Foundation, Los Angeles, California, and the Rod Fasone Memorial Cancer Fund, Indianapolis, Indiana.

## References

- [1] Greenlee RT, Hill-Harmon MB, Murray T, et al. Cancer statistics, 2001. *CA Cancer J Clin* 2001;51:15–36.
- [2] Fong Y, Blumgart LH. Hepatic colorectal metastases: current status of surgical therapy. *Oncology* 1998;12:1489–98.
- [3] Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997;15:938–46.
- [4] 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;230:309–18.
- [5] Preketes AP, King J, Caplehorn JR, et al. CEA reduction after cryotherapy for liver metastases from colon cancer predicts survival. *Aust N Z J Surg* 1994;64:612–4.
- [6] Fong Y, Salo J. Surgical therapy of hepatic colorectal metastases. *Semin Oncol* 1999; 26:514–23.
- [7] Buroker T, Kim PN, Groppa C, et al. 5 FU infusion with mitomycin-C versus 5 FU infusion with methyl-CCNU in the treatment of advanced colon cancer: Southwest Oncology Group study. *Cancer* 1978;42:1228–33.
- [8] Grafe TB, Vassilopoulos PP, Shingleton WW, et al. Results of a prospective randomized study of hepatic artery infusion with 5-fluorouracil versus intravenous 5-fluorouracil in patients with hepatic metastases from colorectal cancer: a Central Oncology Group study. *Surgery* 1979;86:550–5.
- [9] Macdonald JS, Kisner DF, Smythe T, et al. 5-fluorouracil (5-FU), methyl-CCNU, and vincristine in the treatment of advanced colorectal cancer: phase II study utilizing weekly 5-FU. *Cancer Treat Rep* 1976;60:1597–600.
- [10] Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990;322:352–8.

- [11] Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999;341:2039–48.
- [12] Chang AE, Schneider PD, Sugarbaker PH, et al. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg* 1987;206:685–93.
- [13] Hohn DC, Stagg RJ, Friedman MA, et al. A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. *J Clin Oncol* 1989;7:1646–54.
- [14] Kemeny M, Goldberg D, Beatty D, et al. Results of a prospective randomized trial of continuous regional chemotherapy and hepatic resection as treatment of hepatic metastases from colorectal primaries. *Cancer* 1986;57:492–8.
- [15] Kemeny N, Daly J, Reichman B, et al. Intrahepatic or systemic infusion fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. *Ann Intern Med* 1987;107:459–65.
- [16] Martin JK, O'Connell MJ, Wieand HS, et al. Intra-arterial floxuridine vs. systemic fluorouracil for hepatic metastases from colorectal cancer. *Arch Surg* 1990;125:1022–7.
- [17] Harmantas A, Rotstein LE, Langer B, et al. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma liver metastatic to the liver. *Cancer* 1996;78:1639–45.
- [18] Kemeny N, Conti JA, Cohen A, et al. Phase II study of hepatic fluorouridine, leucovorin and dexamethasone for unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 1994;12:2288–95.
- [19] Lorenz M, Muller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). *Ann Surg* 1998;228:756–62.
- [20] Tandan VR, Harmantas A, Gallinger S. Long-term survival after hepatic cryosurgery versus surgical resection for metastatic colorectal carcinoma: a critical review of the literature. *Can J Surg* 1997;40:175–81.
- [21] Venook AP. Update on hepatic intra-arterial chemotherapy. *Oncology* 1997;11:947–57.
- [22] Wagman LD, Kemeny MM, Leong L, et al. A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. *J Clin Oncol* 1990;8:1885–93.
- [23] Rougier P, Laplanche A, Huguier M, et al. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long term results of a prospective randomized trial. *J Clin Oncol* 1992;10:1112–8.
- [24] Kemeny N, Seiter K, Niedzwiecki D, et al. A randomized trial of intrahepatic infusion of fluorodeoxyuridine with dexamethasone versus fluorodeoxyuridine alone in the treatment of metastatic colorectal cancer. *Cancer* 1992;69:327–34.
- [25] Lorenz M, Muller HH. Randomized, multi-center trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000;18:243–54.
- [26] Mosseri M, Fingerth J, Varticovsky L, et al. In-vitro evidence that myocardial ischemia resulting from 5 fluorouracil of chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. *Cancer Res* 1993;53:3028–33.
- [27] Allen-Mersh TG, Earlam S, Fordy C, et al. Quality of life and survival with continuous hepatic artery floxuridine infusion for colorectal liver metastases. *Lancet* 1994;344:1255–60.
- [28] Kemeny N, Gonen M, Sullivan D, et al. Phase I study of hepatic arterial infusion of floxuridine and dexamethasone with systemic irinotecan for unresectable hepatic metastases from colorectal cancer. *J Clin Oncol* 2001;19:2687–95.
- [29] Kemeny MM, Adak S, Gray B, et al. Combined modality treatment for resectable metastatic colorectal carcinoma to the liver: Surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an intergroup study. *J Clin Oncol* 2002;20:1499–1505.

- [30] Bilchik AJ, Wood TF, Allegra D, et al. Cryosurgery and radiofrequency ablation for unresectable hepatic malignancies: a proposed algorithm. *Arch Surg* 2000;135:657–62.
- [31] Curley SA, Izzo F, Delrio P, et al. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. *Ann Surg* 2000;230:1–8.
- [32] Ravikumar TS, Kane R, Cady B, et al. A 5-year study of cryosurgery in the treatment of liver tumors. *Arch Surg* 1991;126:1520–3.
- [33] Sarantou T, Bilchik A, Ramming KP. Complications of hepatic cryosurgery. *Semin Surg Oncol* 1998;14:156–62.
- [34] Seifert JK, Junginger T, Morris DL. A collective review of the world literature on hepatic cryotherapy. *J R Coll Surg Edinb* 1998;43:141–54.
- [35] Seifert JK, Morris DL. Prognostic factors after cryotherapy for hepatic metastases from colorectal cancer. *Ann Surg* 1998;228:201–8.
- [36] Weaver ML, Ashton JG, Zemel R. Treatment of colorectal liver metastases by cryotherapy. *Semin Surg Oncol* 1998;14:163–70.
- [37] Wood TF, Rose DM, Chung M, et al. Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. *Ann Surg Oncol* 2000;7:593–600.
- [38] Rothenberg ML, Cox JV, DeVore RF, et al. A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. *Cancer* 1999;85:786–95.
- [39] Shimada Y, Yoshino M, Wakui A, et al. Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. CPT-11 Gastrointestinal Cancer Study Group. *J Clin Oncol* 1993;11:909–13.
- [40] Johnston PG, Fisher ER, Ruckette HE, et al. The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. *J Clin Oncol* 1994;12:2640–7.
- [41] Leichman L, Lenz HJ, Leichman CG, et al. Quantification of intratumoral thymidylate synthase expression predicts for resistance to protracted infusion of 5-fluorouracil and weekly leucovorin in disseminated colorectal cancers. *Eur J Cancer* 1995;31:1306–10.
- [42] Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413–8.
- [43] Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998;352:1407–13.
- [44] Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000;343:905–14.
- [45] Bathe OF, Franceschi D, Livingstone AS, et al. Increased thymidylate synthase gene expression in liver metastases from colorectal carcinoma: implications for chemotherapeutic options and survival. *Cancer J Sci Am* 1999;5:34–40.
- [46] Bengtsson G, Carlsson G, Hafstrom L. Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 1981;141:586–9.
- [47] Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. *Surgery* 1986;103:278–84.
- [48] Butler J, Attiyeh FF, Daly JM. Hepatic resection for metastases of the colon and rectum. *Surg Gynecol Obstet* 1986;162:109–13.
- [49] Preketes AP, Caplehorn JR, King J, et al. Effect of hepatic artery chemotherapy on survival of patients with hepatic metastases from colorectal carcinoma treated with cryotherapy. *World J Surg* 1995;19:768–71.
- [50] Johnston PF, Allegra CJ. Colorectal cancer biology: clinical implications. *Semin Oncol* 1995;22:418–32.
- [51] Lenz HJ, Leichman CG, Danenberg KD, et al. Thymidylate synthase mRNA level in adenocarcinoma of the stomach: a predictor for primary tumor response and overall survival. *J Clin Oncol* 1996;14:176–82.

- [52] Link KH, Kornmann M, Butzer U, et al. Thymidylate synthase quantitation and in vitro chemosensitivity testing predicts responses and survival of patients with isolated nonresectable liver tumors receiving hepatic arterial infusion chemotherapy. *Cancer* 2000;89:288–96.
- [53] Davies MM, Johnston PG, Kaur S, et al. Colorectal liver metastasis thymidylate synthase staining correlates with response to hepatic arterial floxuridine. *Clin Cancer Res* 1999;5:325–8.
- [54] Bilchik AJ, Wood TF, Chawla SP, et al. Systemic irinotecan or floxuridine chemotherapy prolongs survival after hepatic cryosurgery in patients with metastatic colon cancer refractory to 5-fluorouracil. *Clin Colorectal Cancer* 2001;1:36–42.