

# Hepatic artery chemotherapy in the management of colorectal metastases

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Each year in the USA, approximately 200,000 people are diagnosed with primary colorectal cancer; 75,000 patients with colorectal cancer do not survive, and half of those who survive develop tumor recurrence. Sixty percent of recurrences are found in the liver, <10% of which will be resectable. Patients at high risk of developing metastases from colorectal cancer are those with T3 lesions, node-positive disease, a rectal vs colonic primary tumor, and vascular invasion determined by pathologic examination. The National Comprehensive Cancer Network has different patient surveillance guidelines for node-positive patients and node-negative patients. For node-positive patients, the guidelines recommend a carcinoembryonic antigen (CEA) level every 3 months and a computed tomography (CT) scan initially and annually thereafter. For node-negative patients, the guidelines recommend a CEA level every 6 months and a CT scan at 1 and 2 years (1).

In 1976, Wood et al reviewed the natural history of unresected colorectal liver metastases (2). Patients with a solitary liver lesion could expect to have a 1-year survival rate of 60%. If disease was disseminated, survival drastically declined to 6% at 1 year. Overall, for patients with metastatic colorectal cancer, the median survival was 6 to 12 months.

Surgical resection has been accepted as the gold standard treatment for colorectal liver metastases. *Table 1* outlines some of the larger series of patients who have undergone surgical resection for colorectal liver metastases (3–7). The overall operative mortality rate has remained low at 2% to 4%, and the 5-year survival rate has ranged from 25% to 37%. However, even with resection, patients still have a 35% to 40% risk of tumor recurrence in the liver within 2 years. In 1999, Fong examined characteristics that may act as prognostic indicators in 1001 patients who underwent resection for colorectal liver metastases (7). The following were found to have a significant impact on outcome: >1 metastasis, lesion >5 cm, CEA level >200 ng/mL, node-positive disease, and a positive resection margin. Patients with 1 or 2 of these factors were considered to have a favorable outcome. Patients with  $\geq 3$  factors were found to have a significantly worse prognosis and should be considered for adjuvant trials. The presence of extrahepatic disease or >1 year of disease-free interval did not have a significant impact on outcome.

Systemic chemotherapy has been the established adjunctive treatment for these patients, though the survival rate of 35% in patients who receive chemotherapy has been disappointing. A postulated hypothesis for this low survival rate is persistence of

**Table 1. Studies of operative mortality and survival rates for surgical resection of liver metastases**

Author (reference)	n	Operative mortality (%)	5-year survival (%)	10-year survival (%)
Adson et al (3)	141	2	25	—
Hughes et al (4)	607	—	33	—
Rosen et al (5)	280	4	25	—
Fong et al (6)	577	4	35	—
Fong et al (7)	1001	4	37	22

residual microscopic disease that cannot adequately be addressed with systemic chemotherapy. Cryoablation, thermal ablation, and hepatic artery infusion (HAI) chemotherapy represent additional surgical modalities for patients with metastatic colorectal cancer. The aim of HAI chemotherapy is to treat the microscopic disease directly and therefore increase survival rates for patients with colorectal liver metastases.

HAI chemotherapy was first investigated in the 1950s. Initially, it required repeated percutaneous placement of the hepatic artery catheter and use of an external pump. Subsequent introduction of subcutaneous port access allowed ambulatory treatment but was associated with high rates of catheter thrombosis and infection. In the 1980s, implantable pumps were introduced. These devices are produced by several companies; multiple sizes and flow rates are available. The implantable systems require catheter placement via laparotomy and construction of a subcutaneous pocket for the pump. These systems allow ambulatory treatment and avoid repetitive arterial access.

The rationale for delivering chemotherapy through the hepatic artery is multifaceted. In 1987, Ridge et al studied hepatic blood supply through the hepatic artery and portal vein (8). Animal studies using pathologic specimens and clinical studies using labeled floxuridine (FUDR) showed that metastases receive twice the amount of nutrient blood supply from the hepatic artery as from the portal vein. Daly et al showed a 50% response rate for regional therapy via the hepatic artery and a 0% response

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rate for infusion via the portal vein (9). When metastases are 2 to 3 mm, they may receive blood from the portal vein, but after they enlarge, blood is supplied mainly from the hepatic artery. HAI allows high doses of chemotherapy to be given directly to the tumor while sparing normal liver parenchyma (supplied by the portal vein) and minimizing systemic toxicity.

Table 2 outlines the drugs most commonly used in HAI chemotherapy. FUDR has a high hepatic-to-systemic ratio and is almost completely extracted by the liver. Therefore, it has become the favored chemotherapeutic agent for HAI. Originally, when FUDR was used in HAI therapy, patients had a significant risk of developing biliary sclerosis. Dexamethasone was added to the FUDR regimen in an attempt to reduce this risk. It was shown to slightly reduce the risk of biliary sclerosis but also significantly increase tumor response rates from 45% to 71% and patient survival from 16 months to 23 months (11). Dexamethasone is now standard in the FUDR infusion regimen for HAI.

The success of HAI therapy depends on appropriate patient selection. Before patients receive HAI therapy, they should exhibit no evidence of extrahepatic disease since patients with extrahepatic disease will not benefit from the therapy. Positron emission tomography has been useful in identifying such patients. In addition, the patient must have a patent portal vein, be suitable for abdominal surgery, have no evidence of infection, and be able to comply with regular refill appointments. Once a patient is deemed eligible for HAI chemotherapy, preoperative assessment should include baseline laboratory tests, a chest radiograph, a CT scan of the abdomen and pelvis, and a recent colonoscopy. An arteriogram may be obtained to delineate hepatic anatomy, although this varies among centers. During HAI chemotherapy, liver function tests must be monitored for the development of hepatitis or biliary sclerosis. If elevated levels do not quickly resolve, then chemotherapy should be withheld. Biliary sclerosis is treated with endoscopic retrograde cholangiopancreatography and a biliary stent.

HAI pump placement begins with an exploratory laparotomy to rule out extrahepatic disease. A cholecystectomy is performed to prevent postoperative chemical cholecystitis, which can develop in 40% of patients. Identification of aberrant anatomy is of utmost importance in placing HAI pumps. Common variants are a right hepatic artery arising from the superior mesenteric artery, a left hepatic artery arising from the left gastric artery, or trifurcation of the gastroduodenal, right hepatic, and left hepatic arteries. The aberrant hepatic artery and any branches of the gastroduodenal artery are ligated to prevent misperfusion of the gastrointestinal tract. The catheter is bidirectionally fixated within the gastroduodenal artery to prevent dislodgment. A pocket is constructed superficial to the rectus fascia, and the catheter is tunneled subcutaneously. Proper catheter placement and perfusion pattern are confirmed intraoperatively using fluorescein. A postoperative technetium 99m scan is recommended to again confirm placement of the pump and its perfusion pattern prior to chemotherapy infusion. Chemotherapy infusion may be started as early as 1 week after surgery depending on the patient's medical condition. The pump must be refilled every 2 to 4 weeks depending on pump size and flow rate.

A laparoscopic approach to HAI pump placement has been described by Urbach et al (12). Technical steps remain identi-

**Table 2. Drugs commonly used in hepatic artery infusion therapy for treatment of liver metastases\***

Drug	Hepatic/systemic ratio	% Hepatic extraction
Floxuridine	400	95–99
5-Fluorouracil	10–100	19–81
Mitomycin-C	3	15–20
Cisplatin	5	10–20
Doxorubicin	2	20–30

\*Adapted from reference 10.

cal to those of an open procedure with proposed benefits of less pain, a shorter recovery time, and the avoidance of laparotomy in higher-risk patients. As the field of minimally invasive surgery evolves, laparoscopic placement of HAI pumps may become more common.

Complications related to the pump include pump pocket hematoma/seroma, which can often be drained percutaneously; pump pocket infection; and pump inversion or migration. Other potential complications include bleeding from the gastroduodenal artery and catheter dislodgment with organ misperfusion. Misperfusion may result in peptic ulceration, pancreatitis, or biliary sclerosis. If misperfusion is detected, 2 treatment options are available: transcatheter embolization and repeat laparotomy with catheter revision. The former has a reported success rate between 75% and 100% depending on extrahepatic vs intrahepatic misperfusion (13).

Flow rate accuracy depends on several variables, including viscosity of the infusion solution, arterial pressure at the catheter tip, and body temperature. If body temperature rises or air pressure decreases, a higher dose of chemotherapy will be delivered. In addition, pump reservoir volume can influence flow rate accuracy, reflecting the importance of compliance with refill appointments.

As with many new surgical techniques, surgeon experience appears to influence initial HAI complication rates. In 1993, Campbell et al found a complication rate of 33% for surgeons who had performed <10 HAI pump placements vs 7% for surgeons who had performed >10 procedures (14). In addition, Civelek et al found that >90% of patients with variant anatomy had chemotherapy misperfusion vs <10% of patients with normal hepatic anatomy (15). Thus, HAI pumps should be placed and managed by surgeons familiar with hepatobiliary anatomy and physiology.

Early nonrandomized studies of HAI therapy showed high response rates but numerous complications. The high complication rate was probably related to use of outdated chemotherapy drugs and incorrect dosing of FUDR. Randomized studies of HAI vs systemic chemotherapy showed significant tumor response rates but no clear survival benefit. The data from these studies may have been biased by allowing patient crossover between treatment arms. New combinations of chemotherapy and appropriate patient selection are expected to produce a >70% response rate—twice the rate of systemic chemotherapy. Despite the design problems of these early studies, they identified patients who

**Table 3. Randomized studies of hepatic artery infusion vs systemic therapy in patients with unresectable liver metastases**

Site (reference)	Regimen	Response rate (%)	Median survival (months)
MSKCC (16)	HAI-FUDR	52	18
	Sys-FUDR	20	11
NCI (17)	HAI-FUDR	62	17
	Sys-FUDR	17	12
NCOG (18)	HAI-FUDR	42	17
	Sys-FUDR	10	16
Mayo (19)	HAI-FUDR	48	13
	Sys-5FU	21	11
France (20)	HAI-FUDR	21	11
	Sys-5FU	9	11

MSKCC indicates Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; NCOG, Northern California Oncology Group; Mayo, Mayo Clinic; HAI, hepatic artery infusion; FUDR, floxuridine; sys-5FU, systemic 5-fluorouracil.

would benefit most from HAI: patients whose metastatic disease was limited to the liver, whose liver was <70% involved with tumor, and who had a good performance status.

To date, 8 randomized trials for patients with unresectable disease have been published, the largest of which are summarized in Table 3 (16–20). Tumor response rates were significantly better than those with systemic treatment, although median survival was not significantly different. These trials had several deficiencies: systemic FUDR was used instead of the current therapy, systemic 5-fluorouracil; >50% of the French control group received no therapy; study designs allowed crossover between treatment arms; patients with extrahepatic disease were included; and some patients failed to receive the intended dose or duration of HAI therapy. The Cancer and Leukemia Group B will be further studying survival rates in this patient population. Patients will be prospectively randomized to receive either HAI-FUDR and systemic leucovorin or systemic 5-fluorouracil and leucovorin. Overall survival, p53 and thymidylate synthase levels (which may indicate how responsive a patient will be to traditional systemic therapy), cost, and quality of life will be evaluated.

Four randomized trials have evaluated HAI as adjuvant therapy after curative resection (21–24). The City of Hope stratified 100 patients according to the degree of hepatic involvement. Time to treatment failure was prolonged from 9 months to 31 months for patients with a single metastasis. In addition, 5-year survival increased from 7% to 30% in patients with multiple metastases. Memorial Sloan-Kettering Cancer Center randomized 156 patients after resection and stratified patients by number of metastases and any previous treatment. Endpoints of the study were overall survival, survival without hepatic recurrence at 2 years, and survival without any metastases at 2 years. Patients were stratified to 6 cycles of HAI-FUDR, dexamethasone, and systemic 5-fluorouracil/leucovorin or to 6 cycles of systemic 5-fluorouracil/leucovorin alone. A significant survival advantage was detected for patients in the HAI therapy arm, with an 86% vs 72% 2-year survival rate ( $P < 0.03$ ). The median survival for

patients in the HAI group was increased by approximately 13 months, although this did not reach statistical significance. Also, 90% of patients demonstrated no hepatic recurrence (vs 60% on monotherapy;  $P < 0.001$ ), and 57% of patients had no evidence of metastatic disease (vs 42% on monotherapy;  $P < 0.07$ ) at 2 years.

Two metaanalyses also support the use of HAI vs systemic chemotherapy (25, 26), showing a local response rate of 41% vs 14% and an increased median survival time of 16 months vs 13 months, respectively. These studies also showed a 10% and 6% increased survival rate at 1 and 2 years, respectively.

Costs and quality of life become important factors when new therapeutic techniques are introduced. The implantable pump system costs approximately \$9000 at Baylor University Medical Center. Hospital costs depend on the extent of treatment needed, that is, resection and HAI, or HAI therapy alone. The HAI pump system obviates the need for repeated inpatient chemotherapy treatments, and the patient may be fully active during the course of treatment. Allen-Mersh et al studied the quality of life in patients with an HAI pump vs patients treated with systemic chemotherapy (27). In patients who were either untreated or whose disease was unresectable, they found a significant decrease in patients' physical symptoms, anxiety, and depression with use of HAI chemotherapy.

Exciting new directions in HAI therapy for metastatic colorectal cancer to the liver include use of high-dose bolus mitomycin-C, hemofiltration, the ONYX-015 virus, and monoclonal antibodies.

In summary, HAI therapy should be considered for all patients with metastatic colorectal cancer confined to the liver. HAI-FUDR therapy has improved tumor response rates for patients with resectable and unresectable disease. Also, HAI therapy appears to improve 2-year survival rates for patients who have undergone hepatic resection. A trend toward survival advantage for patients with unresectable disease has been identified, although it remains to be statistically proven. Furthermore, HAI may improve quality of life for patients, while cost is congruent with treatment for other severe medical illnesses.

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