



The state of hepatic artery infusion chemotherapy in the management of metastatic colorectal cancer to the liver

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Abstract: Hepatic artery infusion (HAI) chemotherapy is a locoregional therapy for colorectal cancer liver metastasis that has been available since the 1980s. Multiple clinical trials have demonstrated the safety and efficacy of HAI with higher response rates compared to systemic chemotherapy alone. Clinical trials have shown the benefit of using HAI as a bridge to conversion to resection at a higher rate than systemic chemotherapy alone with rates as high as 60% in heavily pretreated patients. HAI in combination with systemic chemotherapy has also been associated with prolonged recurrence free survival and overall survival in the adjuvant setting. Specifically, the addition of HAI continues to show a benefit in prolonging overall survival, despite increased effectiveness of modern systemic chemotherapy (i.e., oxaliplatin and irinotecan). Lower recurrence and improved survival rates associated with HAI and systemic chemotherapy persist regardless of *RAS* mutational status.

Keywords: Biological tumor markers; locoregional liver therapy; cancer chemotherapy agents; colorectal cancer metastasis

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Rationale for hepatic artery infusion (HAI) chemotherapy

There are approximately 150,000 new cases of colorectal carcinoma diagnosed annually in the United States (1). Approximately 25% of patients present with metastatic disease at the time of diagnosis (2) and over 50% will develop metastasis to the liver at some point in their lifetime (3). Five-year overall survival (OS) in metastatic colorectal cancer (CRC) confined to the liver is approximately 20%, although complete resection can increase 5-year survival to over 50% in selected series (4-7).

Liver resection provides the only chance for cure in patients with colorectal liver metastases (CRLM), however, only 15–20% of patients with CRC metastases confined to the liver are deemed resection candidates at presentation.

Most patients with CRC die from metastatic disease, and two-thirds of CRC deaths are due to liver metastases (8).

For patients with initially unresectable CRLM, regional treatment of metastatic disease has been a topic of considerable interest given the underwhelming response rates to systemic chemotherapy alone with median survival of roughly 20 months (9). First line systemic chemotherapy for metastatic CRC includes a fluoropyrimidine combined with other agents in various schedules (10). Despite the advances of modern combination regimens [e.g., 5-FU/leucovorin/oxaliplatin (FOLFOX), 5-FU/leucovorin/irinotecan (FOLFIRI) and 5-FU/leucovorin/oxaliplatin/irinotecan (FOLFOXIRI) and targeted therapies including anti-epidermal growth factor receptor (EGFR) for *RAS* wild-type tumors, and anti-vascular endothelial growth

Table 1 Chemotherapeutic agents most commonly used for hepatic artery infusion chemotherapy

Agent	MOA	AE	HE ratio	Comments
5-FU	Thymidylate synthase inhibitor	Leukopenia, diarrhea	0.22–0.45	19–55% extracted by liver on first pass (18)
Floxuridine	Prodrug of 5-FU. Thymidylate synthase inhibitor	Biliary toxicity	0.69–0.92	94–99% extracted by liver on first pass (18)
Oxaliplatin	Diaminocyclohexane platinum agent	Neuropathy, abdominal pain	0.47 (19)	Used in Europe where floxuridine is not approved
Irinotecan	Camptothecin analogue; topoisomerase I inhibitor (20)	Diarrhea, neutropenia	Lower hepatic extraction	Converted to active metabolite SN-38 (20)

MOA, mechanism of action; AE, adverse effects; HE, hepatic extraction.

factor (VEGF) agents], response rates to first line therapy for metastatic CRC range from 34–66%; and up to 30–40% for 2nd line (11). Progression-free survival for first line agents is 5.1–13 months, and decreases to 1.7–7.3 months for second line agents (12). Therefore, HAI chemotherapy has become an attractive strategy for locoregional disease control and possible conversion to resection for patients with initially unresectable liver-dominant disease. HAI chemotherapy takes advantage of the liver anatomy and regional arterial supply to metastatic CRC lesions to deliver high concentration of chemotherapy with minimal systemic side effects. While most of the liver parenchyma derives its blood supply from the portal circulation, metastatic tumors derive their blood supply from the hepatic arteries via angiogenesis as the malignancy grows. Furthermore, the hepatic extraction of chemotherapy agents is much higher when infused through the hepatic artery. For example, one commonly used agent for HAI therapy, floxuridine (FUDR), has 400 times greater concentration in liver tumors when infused through the hepatic artery compared to systemic infusion (13).

HAI therapy has evolved in the last three decades with improved surgical techniques and discovery of new systemic agents. It is now an acceptable first line option in the United States for unresectable CRLM and a treatment option in the adjuvant setting; however, it remains infrequently used. Reasons for this include lack of widespread expertise with HAI therapy, requirement of a multidisciplinary team to manage therapy, and more widespread use of systemic chemotherapy in first-line settings (14).

Methods of implantation

The current gold standard for implantation is laparotomy, with insertion of a catheter into the gastroduodenal artery.

Prior to surgery, computed tomography angiogram is used to visualize the hepatic arterial anatomy to assess for aberrant anatomy and caliber of the gastroduodenal artery. Less invasive strategies of implantation, including laparoscopic and robotic placement, have been studied, but so far, none have demonstrated superiority in pump-related complications (15). Percutaneous trans-axillary insertion is associated with decreased length of hospitalization but with significantly higher rate of catheter-related complications (16,17).

Agents used for HAI chemotherapy

5-FU was the first agent to be used for HAI due to its early effectiveness as systemic therapy. Later FUDR, a prodrug of 5-FU, was found to have much higher concentration within tumor, with fewer systemic side effects compared to 5-FU (18). Modern chemotherapeutic agents such as irinotecan and oxaliplatin have been used mostly in Europe and Asia as shown in *Table 1* (19–22). These agents have a lower first-pass hepatic extraction compared to FUDR and a different systemic toxicity profile.

Role of HAI chemotherapy in current guidelines

Current National Comprehensive Cancer Network (NCCN) guidelines for metastatic CRC recommend that if metastatic disease is limited to the liver and is amenable to resection, surgery should be pursued as first line therapy. Adjuvant HAI with systemic therapy can follow, or adjuvant systemic chemotherapy alone. For patients with initially unresectable, liver-dominant disease, HAI with systemic chemotherapy can be pursued or systemic therapy alone. There is increasing popularity to consider earlier initiation of HAI in patients with initially unresectable disease who are chemotherapy-naïve to increase resection

Table 2 Trials comparing hepatic artery infusion chemotherapy to systemic chemotherapy

Study	Type	Year	n	Treatment	RR (%)	OS (months)	Crossover allowed
MSKCC (30)	Single center RCT	1987	48	HAI FUDR	53% [†]	17	Yes
			51	SYS FUDR	21%	12	
NCOG (31)	Multicenter RCT	1989	67	HAI FUDR	42% [†]	16.7	Yes
			76	SYS FUDR	10%	16.1	
Martin <i>et al.</i> (32)	Multicenter RCT	1990	33	HAI FUDR	48% [†]	12.6	No
			36	SYS 5-FU	21%	10.5	
Kerr <i>et al.</i> (33)	Multicenter RCT	2003	145	HAI 5-FU+ LV	22%	14.7	No
			145	SYS 5-FU + LV	19%	14.8	
CALGB (34)	Multicenter RCT	2006	68	HAI FUDR+ LV	47% [†]	24.4 [†]	No
			67	SYS 5-FU	24%	20	

[†], statistical significance. FUDR, floxuridine; HAI, hepatic artery infusion; 5-FU, fluorouracil; RCT, randomized controlled trial; NCOG, Northern California Oncology Group; CALGB, Cancer And Leukemia Group B; MSKCC, Memorial Sloan Kettering Cancer Center; n, number of patients; RR, response rate; OS, overall survival; LV, leucovorin.

rates (23). There is currently no role for HAI therapy in the neoadjuvant setting for patients with resectable disease. European Society for Medical Oncology (ESMO) guidelines do not currently recommend HAI (10).

Outcomes of HAI chemotherapy for unresectable disease

Conversion to resection is the goal of HAI and systemic chemotherapy, as resection is independently associated with prolonged OS (6,7). However, resectability of liver metastasis is surgeon and institution dependent, and therefore, reports of conversion to resection rates in available studies are difficult to interpret.

Available treatment options for unresectable CRLM limited to the liver were initially limited to systemic chemotherapy, with low conversion rates and poor OS. The first systemic chemotherapy used for metastatic CRC was systemic 5-FU, with a response rate of only about 20%, and average survival of approximately 11 months (24). Irinotecan and oxaliplatin were later developed and had a higher response rate (30–45%) and a slightly longer median survival of 15–19.5 months (25). In a single institution study from 1988 to 1999, the conversion rate with chemotherapy (which consisted mainly of 5-FU and leucovorin combined with oxaliplatin or irinotecan) was 12.5% (26). In more recent studies using modern combination therapy and targeted therapy, response rates

of up to 81% and conversion rates up to 60% are reported with combination FOLFOXIRI (5-FU/oxaliplatin/irinotecan) and bevacizumab (27,28). Modern systemic chemotherapy has increased survival in metastatic CRC patients to 18–30 months; however, disease progression and eventual death secondary to liver failure remain the biggest clinical challenges. Thus, there is a continued interest in HAI and other locoregional therapies including radiofrequency ablation, stereotactic body radiation, and chemoembolization as methods to stave off hepatic disease progression (29).

HAI therapy vs. systemic chemotherapy for unresectable disease

HAI alone was initially compared to available systemic chemotherapies for first-line use for unresectable CRLM. Multiple prospective clinical trials published in the late 1980s to early 1990s comparing HAI with systemic chemotherapy demonstrated superior response rates of HAI therapy but did not show consistent improvements in OS (30–33) (*Table 2*). To add to the skepticism towards HAI therapy, a 2006 meta-analysis of randomized controlled trials (RCTs) comparing HAI and systemic chemotherapy in unresectable disease showed that there was no survival advantage to HAI alone (35). This analysis, however, had several limitations including, small number of patients from single institutions, old HAI chemotherapy, and

Table 3 Recent studies of hepatic artery infusion chemotherapy with systemic therapy for unresectable colorectal cancer liver metastases

Study	Study type	No. pts.	HAI	SYS	RR	CTR
D'Angelica 2015 (42)	Single center, non-randomized phase II	49	FUDR	Oxaliplatin/irinotecan/bevacizumab or irinotecan/5-FU/LV/bevacizumab	76%	47%
Levi 2016 (43)	Multicenter, single arm phase II	64	Irinotecan/oxaliplatin/5-FU	Cetuximab	40.60%	29.70%
Lim 2017 (44)	Multicenter retrospective	61	Oxaliplatin	5-FU/leucovorin or 5-FU/bevacizumab or 5-FU/anti-EGFR therapy	21.3%	16.40%
Pak 2018 (45)	Single center, non-randomized phase II	64	FUDR	Oxaliplatin/irinotecan or 5-FU/leucovorin/irinotecan/bevacizumab	73%	52%

HAI, hepatic arterial infusion; SYS systemic therapy; RR, response rate; CTR, conversion to resection; 5-FU, fluorouracil; FUDR, fluorouridine; EGFR, epidermal growth factor; No., number; pts., patients.

allowance for cross over to HAI in patients who had initially failed systemic chemotherapy. To overcome these limitations, a multi-institutional prospective randomized clinical trial, Cancer And Leukemia Group B (CALGB) 9481, investigated response rate in patients receiving HAI FUDR compared to systemic 5-FU only, demonstrating significantly improved survival (24.4 *vs.* 20 months; $P=0.0034$) (34). In that study, 40–70% of patients with unresectable hepatic liver metastases who underwent HAI therapy later developed extrahepatic disease; thus, systemic chemotherapy combined with HAI was considered as a practical approach to control both intrahepatic and extrahepatic metastases (36).

HAI therapy with systemic chemotherapy was first studied by Safi *et al.* in 1989 in a phase I prospective study comparing HAI FUDR with HAI FUDR and systemic FUDR. The results of this study showed that addition of systemic FUDR to HAI FUDR therapy was well tolerated, with no significant difference in rates of toxicities between the two groups. However, no significant difference was found in response rate or extrahepatic recurrence (37). Further studies comparing systemic therapy alone with HAI therapy and systemic therapy were done. Many early studies using systemic 5-FU and FUDR showed improved response rates but no significant difference in survival. For example, in 2000, a prospective RCT by Allen-Mersh *et al.* compared HAI FUDR plus systemic 5-FU and leucovorin against systemic 5-FU and leucovorin alone and found greater response 45% *vs.* 23%, but no significant difference in survival rates (38).

In 2009, a study of 153 patients randomized to receive HAI FUDR alone or HAI FUDR and systemic 5-FU as first line therapy, demonstrated no difference in response (52.7% *vs.* 50.6%) and OS (18.0 *vs.* 19.1 months). Of the variables

considered as predictors of tumor response (including age, sex, stage, site of primary tumor, adjuvant therapy after primary tumor resection, extent of liver involvement) response to therapy and lower tumor burden (<50% of liver parenchymal involvement) were the only predictors of OS. OS in patients with <50% liver involvement compared to >50% was significantly greater (21.3 *vs.* 13.2 months) (39). These results suggest that HAI therapy can be more beneficial if likely responders can be identified through biomarkers such as gene mutational status.

With the introduction of oxaliplatin and irinotecan for systemic therapy in the late 1990s, a series of clinical trials tested the efficacy and safety of HAI with combinations of these modern agents (23) (*Table 1*). A single arm phase I study of 49 patients by Kemeny *et al.* at Memorial Sloan Kettering Cancer Center (MSKCC) compared HAI FUDR/dexamethasone added to systemic oxaliplatin and irinotecan in patients with adverse prognostic characteristics (at least 5 hepatic lesions to be enrolled, and 53% pre-treated patients with systemic chemotherapy). Their outcomes showed high response (92%) and conversion to resection rates (47%). Thirty-nine percent underwent R0 resection. Postoperative complications of hematoma and fluid collection occurred in only 2 (9%) patients, and significant toxicities included diarrhea (14%), neutropenia (23%), and neurotoxicity (23%) (40). Similarly, Goere *et al.* in 2010, analyzed 87 patients who received HAI oxaliplatin with systemic 5-FU and leucovorin, as second line therapy, and 21 of 87 patients (24%) underwent resection, with 5-year OS of 56% (41). More recently, studies continue to show high response rates up to 76% and conversion to resection up to 52% using various combinations of modern agents (42–45) (*Table 3*).

Table 4 Early trials of hepatic artery infusion chemotherapy in the adjuvant setting

Site	Type	Year	n	Treatment	OS	Median survival (months)	RFS	Comments
MSKCC (47)	RCT	1999	156	HAI + SYS 5-FU/LV	2 year: 86%	72.2	2 year: 90%	–
				SYS 5-FU/LV	72%	59.3	60%	
Germany (48)	RCT	1998	226	HAI 5-FU	NR	34.5	NR	Terminated early
				No treatment	NR	40.8	NR	
Intergroup (49)	RCT	2002	109	HAI FUDR+ SYS 5-FU	NR	63.7	4 year: 46%	–
				No treatment	NR	49	25%	
Greece (50)	RCT	2001	122	HAI mitomycin C, 5-FU, IL-2 + SYS	2 year: 92%	NR	NR	–
				SYS immunotherapy + chemotherapy	75%	NR	NR	

†, statistical significance. n, number of patients; OS, overall survival; RFS, recurrence-free survival; MSKCC, Memorial Sloan Kettering Cancer Center; RCT, randomized controlled trial; HAI, hepatic arterial infusion; SYS, systemic therapy; LV, leucovorin; FUDR, floxuridine; 5-FU, fluorouracil; NR, not reported; IL-2, interleukin 2.

Outcomes of adjuvant HAI therapy for resectable disease

Despite achieving R0 resection, relapse rates are over 50% within two years after resection, with 70% of recurrences involving the liver (36,46). The role of adjuvant therapy is thought to target micrometastases within the liver after curative resection of liver metastases. Early HAI studies demonstrated mixed results. While three studies at MSKCC, Greece, and an intergroup study showed increase in recurrence-free survival and OS, a study in Germany by Lorenz *et al.* did not show any survival benefit (Table 4). The study by Lorenz *et al.* compared adjuvant HAI of 5-FU to no treatment and showed lower median survival in the HAI group than in the control, and was terminated early (48). In 2004, a Cochrane review of seven available randomized adjuvant HAI studies showed no increase in OS; consequently, adjuvant HAI was not recommended by the authors (51).

More recently, a 2016 study by Kemeny *et al.* followed 287 patients that underwent adjuvant HAI with FUDR and systemic therapy after resection of liver metastases, from 1991 onward. The patients were divided into two groups: those treated before 2003 and after. Results of this study showed greater 5- and 10-year OS in those treated after 2003 compared to before 78% *vs.* 56%, and 61% *vs.* 40%, respectively. The rationale for choosing year 2003 as the division point, was that it was in 2003 that *RAS* mutation status was available at the institution, and 37% of *RAS* wild-type patients received cetuximab or panitumumab after

recurrence. Also, in 2004 institutional protocols shifted to modern combination systemic therapy including FOLFIRI or FOLFOX with bevacizumab. This greater OS in patients treated after 2003 was thought to be secondary to new targeted therapies including cetuximab, panitumumab, and bevacizumab, more aggressive surgical treatment of recurrences, and better imaging (52).

To further delineate the contribution of modern systemic chemotherapy from that of HAI therapy in improving OS, subsequent studies considered whether or not HAI therapy was given with perioperative modern systemic therapy as a subgroup analysis (53). One such study was a 21-year analysis of perioperative HAI therapy that included 2,368 consecutive patients who underwent curative-intent liver resection for CRLM at MSKCC from 1992 to 2012. The results showed prolonged 5-year OS for patients receiving HAI therapy, compared to those treated without HAI (52.9% *vs.* 37.9%, $P < 0.001$), and also greater 10-year OS (38.0% *vs.* 23.8%, $P < 0.001$). Subgroup analysis demonstrated that regardless of receiving modern systemic chemotherapy or not, or whether HAI was received in the preoperative or adjuvant setting, there remained a significantly greater OS in the HAI arm (54). For those that received preoperative modern systemic chemotherapy, median OS rates in the HAI arm and the no HAI arm were 77 and 45 months, respectively. For those that did not receive preoperative modern systemic chemotherapy, median OS rates in the HAI arm and the no HAI arm were 55 and 43 months, respectively. These results matched, on a larger scale those of prior studies (55). Results of this study

suggest that despite the increased effectiveness of modern systemic chemotherapy, there is still a benefit in OS with the addition of HAI therapy to systemic therapy in the perioperative setting.

Two RCTs are currently underway to further evaluate adjuvant HAI after resection of CRLM. The PUMP trial is a phase III trial underway in the Netherlands that seeks to assess efficacy of adjuvant HAI FUDR therapy in low risk patients. Low risk is defined as no more than 2 of 5 of the following factors: disease-free interval less than 12 months, node-positive CRC, more than 1 CRLM, largest liver metastasis more than 5 cm in diameter, serum carcinoembryonic antigen (CEA) above 200 µg/L (56). Patients are randomized to either resection without any adjuvant therapy (standard of care in the Netherlands) or implantation of pump at time of resection with 6 cycles of HAI FUDR. The primary endpoint of the study is progression-free survival. Secondary endpoints are OS, hepatic progression-free survival, safety, quality of life, and cost effectiveness. The study seeks to validate prior results at MSKCC for adjuvant use of HAI FUDR therapy (47).

PACHA-01 is an ongoing phase II/III trial comparing adjuvant systemic FOLFOX and HAI oxaliplatin + systemic 5-FU in patients with high risk of recurrence, defined as having 4 or more resected CRLM in patients who have undergone R0 or R1 resection and/or thermal ablation (57). The primary objectives are (I) to assess the 18-month hepatic recurrence-free survival in patients treated with HAI oxaliplatin + systemic 5-FU after curative intent surgery, and (II) demonstrate superiority in recurrence-free survival of HAI oxaliplatin compared to systemic oxaliplatin + 5-FU (FOLFOX). Secondary objectives include assessing feasibility, toxicity, and efficacy.

Molecular markers and outcomes of liver resection and HAI therapy

Testing for molecular markers is being increasingly used to guide selection of therapy, predict response to targeted therapies, and to offer more exact prognosis. Current NCCN guidelines recommend all patients with CRC have tissue genotyped for *RAS* and *BRAF* mutations, and mismatch repair (MMR) DNA testing or microsatellite instability (MSI) immunohistochemistry. About 20–40% of CRC patients carry a mutation in the *RAS* gene and about 10% carry a *BRAF* mutation (58–60). MSI due to defective MMR is present in about 15% of all CRCs (61).

RAS and *BRAF* mutations have been known to

independently predict poor prognosis in metastatic CRC and are both associated with resistance to EGFR targeted therapies. Since the discovery and usage of anti-EGFR antibodies, cetuximab and panitumumab approved in 2004 and 2007 respectively, *RAS* testing was the earliest molecular marker to become part of NCCN and American Society of Clinical Oncology (ASCO) guidelines in 2009 (62). There is stronger evidence supporting the negative prognostic significance of *RAS* than *BRAF*, due to the higher prevalence of *RAS* in CRC (63). A 2011 study showed increased rate of peritoneal and distant lymph node metastases with *BRAF*-mutant tumors, and lower OS (10.4 vs. 34.7 months) (59). Another large study at MSKCC showed that *BRAF*-mutant CRC less commonly presents with disease limited to the liver, and also showed shorter OS, 20 vs. 47 months ($P < 0.001$) when compared to *BRAF* wild-type (64).

There are few studies on the effect of molecular markers on the outcomes in HAI therapy. In a study of 169 patients with resected CRLM who underwent adjuvant HAI therapy, 3-year recurrence-free survival for *KRAS* wild-type and *KRAS*-mutant was 46% and 30%, respectively ($P = 0.005$) (65). *KRAS*-mutant tumors are also associated with higher cumulative incidence of bone (13.4% vs. 2%), brain (14.5% vs. 2%), and lung metastases (58% vs. 33.2%).

The only large study investigating the effects on *RAS* status on adjuvant HAI therapy included 674 patients with CRLM who had *KRAS* testing data at MSKCC. These patients underwent curative-intent hepatic resection, and received either adjuvant HAI with FUDR and systemic chemotherapy or systemic chemotherapy alone. When comparing baseline characteristics, patients in the HAI group had more advanced disease characterized by higher rates of synchronous disease, larger number of tumors, higher clinical risk scores, and rates of 2-stage hepatectomy. Results of the study showed that 5-year OS with HAI was prolonged, regardless of *KRAS* status. Adjuvant HAI was associated with improved 5-year OS in *KRAS* wild-type (76% vs. 57%, $P < 0.001$) and in *KRAS*-mutant (59% vs. 40%, $P < 0.001$) (66). HAI was an independent predictor of OS independent of *KRAS* status. The results of this study suggest that with the combination of HAI therapy and systemic therapy, *KRAS*-mutant tumors can achieve a 5-year OS that rivals that of *KRAS* wild-type tumors treated with systemic chemotherapy only (59% vs. 57%) (66).

Conclusions

HAI chemotherapy has come a long way through improved

surgical technique, increased institutional experience with pump implantation and monitoring, and discovery of new therapeutic agents. The future of HAI chemotherapy is hopeful as trials testing combination of chemotherapies are underway, and the optimal regimen and sequence of therapy are being determined. Furthermore, promising results of converting initially unresectable patients to resection may mean possible translation into use as neoadjuvant therapy. Identification of those patients likely to benefit from HAI through the identification of molecular markers continues to be of interest especially as new targeted systemic therapies become available. As the intricacies of the molecular pathways in CRC tumorigenesis are identified, an increasingly more targeted approach to CRC treatment will be sought. More clinical trials of HAI therapy distinguishing the response by CRC of different genotypic mutational status are warranted.

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Footnote

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