Intra-Arterial Chemotherapy

8

Rohit Chandwani and Michael I. D'Angelica

Introduction

Colorectal cancer is the third most common malignancy worldwide, with 1.3 million new cases in 2012 alone [1]. At the time of diagnosis, 25% of patients will have synchronous liver metastases; overall, up to 60% will develop hepatic metastases at some point in their disease course [2, 3]. That the liver is both the predominant site of metastatic colorectal cancer (mCRC) and frequently the only site of metastatic disease affords the opportunity to pursue liver-directed therapeutic options.

The liver-directed therapy with the most well-established effect on disease outcome is complete resection. Resection, in well-selected cases, offers the best opportunity for long-term survival and cure, with 5-year survival rates of 30–50% [4–6]. Many of these patients will recur, but frequently they can receive salvage therapy with resection [7]. However, only approximately 25% of patients with isolated colorectal liver metastases (CLM) are resectable at the time of first presentation [8]. Systemic chemotherapy—typically with 5-FU, leucovorin, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) in the first-line setting—offer response rates of 35–50%, with median survival in the range of 16–20 months [9]. With the recent addition of newer biologic agents that target VEGF, EGFR, or mutated BRAF, response rates are increased to 60% and median survival is increased to 26–28 months, but these results are typically in patients with KRAS wild-type tumors [10–12]. Moreover, neoadjuvant systemic chemotherapy converts only a minority of patients (25–30%) to surgical resectability [13, 14]. Furthermore, second-line systemic chemotherapy has very low response rates (in the range of 10–35%) [15, 16].

Together, these data illustrate that the majority of patients with hepatic metastases are neither resectable nor converted to resectability by standard chemotherapy. Because these patients have liver-only metastatic involvement, several forms of regional therapy have been explored. Among these are ablative treatments (cryoablation, radiofrequency ablation [RFA], microwave ablation [MWA], irreversible electroporation [IRE], transarterial embolization (bland, transarterial chemoembolization) [TACE], radioembolization (with ytrrium-90 [Y90]), and hepatic arterial infusion [HAI] chemotherapy). This chapter reviews the rationale, technical considerations, and outcomes of the last of these—intra-arterial chemotherapy.

R. Chandwani, MD, PhD
Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
e-mail: chandwar@mskcc.org

M.I. D'Angelica, MD (✉)
Department of Surgery, Division of Hepatopancreatobiliary Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
e-mail: dangelim@mskcc.org

E. de Santibañes et al. (eds.), *Extreme Hepatic Surgery and Other Strategies*,
DOI 10.1007/978-3-319-13896-1_8

Rationale for Intra-Arterial Chemotherapy

The utility of intra-arterial chemotherapy is underscored by several key anatomic considerations. First, the liver has a dual blood supply, with normal hepatocytes deriving 2/3 of their blood flow via the portal vein, and the remaining 1/3 from the hepatic artery. In contrast, CLMs derive the bulk of their blood supply from the hepatic artery [17]. Injection of floxuridine (FUDR) into the hepatic artery has been shown to concentrate the drug 15-fold in tumor relative to normal parenchyma; injection into the portal vein has no such effect [18], Importantly, the presence of the gastroduodenal artery (GDA) is also crucial to the use of intra-arterial chemotherapy. Redundancy between the celiac axis and superior mesenteric artery (SMA) distribution allows for catheterization and distal ligation of the GDA without any resultant ischemia.

From a pharmacologic standpoint, the liver's function in drug metabolism is key to enabling first-pass extraction of chemotherapy administered via the hepatic arterial route. This can substantially elevate local concentrations of the chemotherapeutic agent, while minimizing systemic exposure. Several agents have been evaluated, and the pharmacologic properties of HAI administration of each are reviewed in Table 8.1. Most notably, FUDR features a short half-life (10 min) and high first-pass extraction (94–99%) that produce a 400-fold concentration of drug in the liver, with minimal spill-over into the general circulation [19]. As several chemotherapeutic agents have steep dose–response curves, higher doses of chemotherapy should translate into an increase in the degree to response.

Several clinical scenarios afford an opportunity for HAI therapy. Patients with unresectable CLM and no evidence of extrahepatic disease represent a large cohort who stand to benefit from a liver-directed therapy. In addition, HAI can be administered as an adjuvant therapy for patients undergoing definite surgical resection of CLMs. Recurrence after complete resection of CLM occurs in at least two-thirds of patients, and half of these recurrences will be limited to the liver [7, 20–23].

Table 8.1 Pharmacologic properties for hepatic arterial infusion of various agents

Agent	Half-life (min)	Fold increase in hepatic concentration
Bis-chloroethyl-nitrosurea	5	6–7
Cisplatin	20–30	4–7
Dichloromethotrexate	–	6–8
Doxorubicin	60	2
5-Fluorouracil (5-FU)	10	5–10
Floxuridine (FUDR)	10	100–400
Mitomycin C	10	6–8

Hepatic Arterial Infusion (HAI) Pump Therapy

Intra-arterial chemotherapy can be administered by the placement of hepatic arterial ports, percutaneously placed catheters, or hepatic arterial infusion (HAI) pumps. The most extensively studied of these modalities in CLM has been the HAI pump—an implantable infusion pump that delivers a continuous infusion of chemotherapy. Several chemotherapeutic agents can be administered via the pump, but FUDR is the most commonly given in the United States, while 5-FU has historically been used in Europe and Japan [24–26]. Patients with unresectable CLM or patients undergoing hepatectomy may undergo HAI pump placement, with or without concomitant colon resection.

Technical Considerations

Hepatic arterial infusion (HAI) pump placement requires careful assessment of the arterial anatomy of the liver, suitability of the abdominal wall, and the assessment of extrahepatic disease. The initial evaluation of a patient with mCRC should include cross-sectional imaging of the chest, abdomen, and pelvis, usually via computed tomography (CT) to look for radiographically evident extrahepatic disease. HAI pump

placement is generally not indicated in patients with apparent lung or peritoneal involvement. However, in carefully selected patients with minimal extrahepatic disease and a substantial burden of CLM, HAI treatment can be considered [27]. For patients with unresectable disease, a staging laparoscopy should be considered, as up to 1/3 of patients will have evident extrahepatic disease [28]. When extrahepatic disease is encountered and the judgment is that it is sufficient to preclude HAI pump placement, intraoperative frozen section is of obvious importance.

The preoperative evaluation should also consist of a CT arteriography to evaluate the hepatic arterial anatomy. Given standard anatomy, the preferred conduit for placement of the catheter is the gastroduodenal artery (GDA), as this is the side-branch immediately proximal to the proper hepatic artery. However, up to 34% of patients will have variant anatomy that requires special consideration [29]. The hepatic arterial anatomic variants are summarized in Table 8.2, and include replaced or accessory left and right hepatic arteries and combinations of multiple variants. Determination of the exact nature of the aberrant anatomy via careful review with the radiologist is imperative, as these findings impact the operative plan.

Suitability of the abdominal wall is also a key consideration, as patients with large ventral hernias or prior operations may have attenuated musculofascial layers of the abdominal wall. The operative plan usually consists of pump placement in the lower abdomen, typically on the left side to avoid the potential use of a future right subcostal incision. In obese patients with large subcutaneous spaces and in patients with large hernias, placement of the pump itself on the lower chest wall can enable location and access to the pump, as well as minimize the risk of flipping. Any one of a number of incisions can be employed for HAI pump placement, including an upper midline incision, right subcostal incision, or a limited hockey-stick incision. Of note, the pump itself should be placed in a subcutaneous pocket via a separate incision with tunneling of the catheter into the peritoneal cavity. Regardless of the incision type chosen, preoperative antibiotics are important in this setting, as are other standard preoperative precautions.

Intraoperatively, the hepatic artery and its branches should be carefully dissected and skeletonized. The right gastric artery should be divided, and the distal CHA, proximal proper hepatic artery (PHA), and GDA identified, encircled and freed from surrounding attachments. Proper identification and mobilization of these structures, including the entire extrapancreatic GDA, are critical. During this dissection, consideration should be given to removing portal lymph nodes in the vicinity of the CHA and the porta hepatis, as these can occasionally be interpreted as sources of extrahepatic perfusion. A cholecystectomy is also performed, as HAI therapy delivered to an in-situ gallbladder (via

Table 8.2 Summary of hepatic arterial anatomic variants

Variant	Daly et al. (1984) (n = 200) (%)	Michels (1966) (n = 200) (%)	Kemeny et al. (1986) (n = 100) (%)	Curley et al. [30] (n = 180) (%)	Allen et al. [31] (n = 265) (%)
Normal	70	55	50	63	63
Variant GDA	6	–	9	9	11
Accessory R hepatic	4	7	4	1	1
Replaced R hepatic	6	12	16	12	6
Accessory L hepatic	3.5	8	1	2	10
Replaced R hepatic	4	10	16	11	4
Other	5	2.5	1	2	5

Adapted from Allen PJ et al. [31]

the cystic artery) will cause chemical cholecystitis. All branches of the CHA, PHA, and GDA are divided and ligated to minimize perfusion of the pancreas, duodenum, or stomach by the pump. The left and right hepatic artery are similarly dissected for approximately 2 cm from the PHA origin to ligate any branches that may serve as conduits for extrahepatic perfusion [32]. Finally, a hepatic arterial pulse is palpated, while the GDA is temporarily occluded to ensure there is not retrograde flow in the GDA owing to celiac stenosis. If there is retrograde flow, an attempt to release the arcuate ligament may re-establish normal flow. If this is not successful, one can consider placing the catheter in the CHA, allowing flow to the liver through the GDA into the PHA.

Vascular control is obtained, and the distal GDA is ligated at its most distal point. In the case of standard anatomy, a transverse arteriotomy is made in the GDA, and the catheter is inserted up to the confluence with the hepatic artery. Positioning of the catheter tip is crucial, as the proximal GDA should neither be exposed to full concentrations of chemotherapeutic agent, nor should the catheter protrude into the lumen so far as to induce thrombosis. The optimal approach when there is aberrant anatomy is ligation of the aberrant vessel(s) and placement of the catheter in the GDA, as cross-perfusion is extremely reliable. Cross-perfusion is often visible at the time of operation, and occurs in almost everyone by 4 weeks after the operation. In a series of 52 patients with variant anatomy, all but one had adequate bilobar perfusion at 4 weeks [31]. Cannulation of a vessel other than the GDA is associated with a significantly elevated incidence of catheter-related complications and limited catheter durability, and is not preferred. When the GDA is not available, we generally prefer placement in the right or left hepatic artery (with ligation); in rare situations, vascular graft placement to create a "GDA" for catheter insertion is required. In the case of variant GDA anatomy, ligation of either in situ (left or right) hepatic artery may be necessary if the GDA arises from the contralateral vessel.

When placed at the time of major hepatectomy, the technical considerations are no different, except that the stump of the ligated arterial branch may be employed to perfuse the remnant liver if the GDA is not available. Of note, ligation of aberrant left or right arteries to a remnant liver for catheter placement should be performed with caution, as it may exacerbate postoperative liver dysfunction. In the face of a remnant liver perfused by a replaced hepatic artery, pump placement (into the GDA) should probably be deferred rather than employing direct cannulation of the replaced vessel.

The catheter is secured in place with silk ties, and the pump reservoir is placed in the pump pocket. Bilobar perfusion of the liver and the absence of extrahepatic perfusion are confirmed by either fluorescein or half-strength methylene blue injection into the side port of the pump. If extrahepatic perfusion is detected (most commonly to the duodenum and head of pancreas), a search for any vessel ensues with ligation and retesting. The catheter is then flushed with heparinized saline and wounds are closed. Postoperatively, perfusion is assessed by a radionuclide pump flow study using technetium 99m (^{99m}Tc)—sulfur colloid and ^{99m}Tc-labeled macroaggregated albumin (MAA). This study is used to detect extrahepatic perfusion (occurs in 5–7% of cases) that can usually be salvaged by angiographic intervention [33, 34]. Incomplete hepatic perfusion can also occur, but usually resolves on a repeat scan obtained a few weeks after the index study. If resolution is not apparent, there may be a missed accessory vessel not ligated at the first operation, and consideration to angiography should be given.

Alternative Modes of Intra-Arterial Chemotherapy

While the implantable hepatic artery infusion pump is the most commonly employed device, there are other means of access to the hepatic arterial tree. One of the earliest approaches was the placement of a subcutaneous port with

a catheter terminating in the hepatic artery. A large randomized MRC/EORTC study evaluating HAI 5-FU/leucovorin with systemic 5-FU/LV, however, featured a 36% rate of catheter-related complications that limited dose administration [24]. Subsequent studies exploring the role of IV oxaliplatin via HAI catheters placed in the GDA but using a subcutaneous pump showed significant improvement in the rate of catheter-associated complications of 10–15% [35].

Percutaneously placed catheters have also been explored. Arru et al. evaluated percutaneous axillary artery catheters as compared to implantable pumps, finding a 43% rate in the percutaneous group of an issue, causing either an interruption or end to treatment (versus 7% in the implantable pump group) [36]. Several studies have also attempted to develop and refine the use of intercostal artery catheters, either with a subcutaneous port or with an attached pump [37].

Recent attention has turned to minimally invasive surgical placement of implantable pumps. A number of initial case series established feasibility of a laparoscopic approach; the largest of these describes an experience with 38 patients, among whom there was one mortality and no pump-related morbidity [38]. Another series featuring 29 patients demonstrated that aberrant anatomy could be addressed safely via a laparoscopic approach and without significant perioperative morbidity [39]. Despite its widespread application, a robotic approach to HAI catheter and pump placement has yet to be studied in any systematic fashion.

Outcomes in Unresectable Disease

HAI pump chemotherapy for unresectable CLM has been extensively studied. Over the last 20 years, ten phase III trials (Table 8.3) comparing HAI with systemic chemotherapy have been conducted; three subsequent meta-analyses have evaluated these findings further still. Overall, there is relative concordance among the studies that response rates are higher with HAI. Nine of the ten studies employed FUDR as the HAI chemotherapeutic—each showed response rates of 42–62%, compared to response rates of 9–24% for systemic chemotherapy in these trials [45]. However, all of these studies employed older systemic regimens consisting of intravenous FUDR, 5-FU alone, or 5-FU/leucovorin, rather than modern regimens incorporating either irinotecan or oxaliplatin.

Despite the substantial increases in response rate, these studies have often failed to detect a difference in overall survival. Several factors have contributed to this phenomenon. Most

Table 8.3 Randomized trials of HAI therapy versus systemic chemotherapy for unresectable CLM

Study	Patients	HAI regimen	Systemic regimen	Response rates (HAI vs. systemic)	Overall survival (HAI vs. systemic)
MSKCC [40]	162	FUDR	FUDR	50% vs 20%	25% vs 20%
NCI (Chang, 1987)	143	FUDR	FUDR	42% vs 10%	44% vs 13%
NCOG [41]	64	FUDR	FUDR	62% vs 17%	30% vs 20%
City of Hope (Wagman, 1990)	41	FUDR	5-FU	55% vs 20%	–
Mayo (Martin, 1990)	69	FUDR	5-FU	48% vs 12%	–
French [42]	163	FUDR	5-FU	44% (HAI only)	22% vs 10%
HAPT [43]	100	FUDR	5-FU or BSC	–	–
German (Lorenz and Muller, 2000)	168	FUDR	5-FU/LV	43% vs 22%	–
EORTC [24]	290	5-FU/LV	5-FU/LV	22% vs 19%	–
CALGB [44]	135	FUDR/Dex	5-FU/LV	47% vs 24%	51% vs 35%

Adapted from Kemeny and Epstein (2012)

notably, early studies at MSKCC (99 patients) [40] and in the Northern California Oncology Group (NCOG) trial [41] both allowed crossover between groups (which occurred frequently), making an intention-to-treat analysis of overall survival meaningless. Those studies that did not allow for crossover and have shown differences in overall survival—namely the Hepatic Artery Pump trial (HAPT) and a French trial—are confounded by the fact that patients in the control arms frequently received only best supportive care rather than 5-FU [42, 43].

Among these ten studies comparing HAI with systemic chemotherapy, the CALGB 9481 trial is the most recent. In this trial, no crossover was permitted, and 134 patients were randomized to either systemic 5-FU/LV (via the Mayo Clinic regimen) or HAI (consisting of FUDR, LV, and dexamethasone). Dexamethasone was added in this series because of earlier data showing decreased biliary toxicity with the addition of steroid to HAI [46]. Again, response rates were significantly higher with HAI (47% vs 24%) and there was a significant improvement in overall survival (24.4 vs 20 months; $p = 0.0034$) [44].

Three meta-analyses of these trials have been performed, with variable results in determining a survival advantage. This inconsistency has been driven by variable exclusion criteria among the trials for either methodological reasons or because of concerns about study design—especially for those trials where some control patients received best supportive care only, or crossover was allowed. The most recent meta-analysis, published in 2007, includes all ten trials and attempts to account for their design flaws. The authors conclude that HAI was associated with a significantly elevated response rate (42.9% vs 18.4%), but this did not translate into an improvement in overall survival (hazard ratio 0.9; $p = 0.24$) [47]. Given the extreme heterogeneity of these trials, it remains difficult to draw any firm conclusions from these meta-analyses.

As mentioned above, these trials predate the development of modern and more effective systemic chemotherapeutic regimens incorporating oxaliplatin or irinotecan. In addition, several of these studies detected a high frequency of extrahepatic progression (40–70%) in patients treated with HAI. More recent studies have attempted to exploit the lack of systemic exposure to chemotherapy with HAI FUDR treatment, and evaluate the efficacy of HAI chemotherapy combined with systemic chemotherapy. The first of these studies involved 95 patients randomized to HAI FUDR with or without intravenous FUDR, and showed similar response rates (~60%) but higher extrahepatic recurrence in the HAI-only group (79% vs 56%; $p < .01$) [48].

Several phase I and II studies have since combined HAI with systemic chemotherapy (Table 8.4). The first of these evaluated 46 patients given HAI consisting of FUDR + dexamethasone in conjunction with systemic irinotecan; response rates were 74% in these pre-treated patients, with an overall survival (OS) of 20 months following pump placement [49]. Similar results were seen with addition of systemic FOLFOX (oxaliplatin +5-FU/leucovorin); in 15 patients, a response rate of 87% with a median OS of 22% was obtained [50]. The combination of oxaliplatin and irinotecan yielded the best results, with a pooled analysis of 49 patients showing a 92% response rate and an OS of 51 months for previously untreated patients and 35 months for previously treated patients. Also of note was that 47% of these individuals converted from unresectable to resectable disease

Table 8.4 Studies of HAI therapy combined with modern systemic therapy

Study	Patients	HAI regimen	Systemic regimen	Response rate (%)	Median overall survival (from pump placement)
Kemeny et al. [49]	56	FUDR/Dex	Irinotecan	74	20 months
Kemeny et al. (2005a)	15	FUDR/Dex	Oxaliplatin + irinotecan	90	28 months
Kemeny et al. (2005a)	21	FUDR/Dex	FOLFOX	87	22 months
Kemeny et al. (2005b)	37	FUDR/Dex	Sideport mitomycin C	70	20 months

Adapted from Kemeny and Epstein (2012)

[51]. A more recent phase II study with 49 patients (two-thirds previously treated) treated with HAI and modern systemic chemotherapy (initially with bevacizumab) showed high response rates of 76% and a conversion to resectability in 47% of the 49 patients. Median survival was 38 months for the whole cohort [52].

In addition to the extensive literature on FUDR, there are also data to support the use of oxaliplatin administered via HAI. In a phase II study to evaluate the efficacy of HAI oxaliplatin + systemic 5-FU/LV, 28 patients underwent placement of HAI catheters. The rate of catheter dysfunction was low, and the overall response rate was 64% [53]. A subsequent study in patients who previously failed systemic chemotherapy again showed a high response rate of 62% [54].

Together, these non-randomized phase I and early phase II studies demonstrate high response rates and long overall survival in patients given modern systemic chemotherapy in conjunction with HAI chemotherapy. Though these patients were non-randomized and selected, the response rates and survival data observed in these data are unprecedented in any cohort of patients with mCRC treated with systemic therapies alone. Moreover, as FOLFOX and FOLFIRI have become well-established standard first-line systemic regimens, HAI in the more recent era has most commonly been studied in the second-line setting. When one considers the low response rates for second- line systemic therapy (10–15%), combined HAI and systemic therapy has demonstrated remarkably high response and survival rates. Moving forward, these impressive results mandate randomized trials to isolate the specific effect of the addition of HAI therapy in patients with CLM, and to determine if intra-arterial chemotherapy should be pursued in a first-line or salvage setting for patients with unresectable disease.

Outcomes as Adjuvant Therapy Following Hepatic Resection

Following hepatic resection of CLM, at least two-thirds of patients will recur, and approximately half of these will have intrahepatic recurrence. The benefits of systemic chemotherapy alone in the adjuvant setting have been tested in randomized studies. Initial studies did not show a benefit to adjuvant 5FU chemotherapy [55]. Further, adjuvant FOLFIRI did not improve outcomes compared to 5FU alone [56]. The most well-known trial (EORTC 40983) which employed perioperative (pre and post-operative) FOLFOX4, demonstrated a minimal increase in progression-free survival (PFS) but did not show an improvement in overall survival [57, 58].

Several randomized studies have sought to determine if HAI chemotherapy diminishes the rate of recurrence and improves overall survival. In a study from our institution, 156 patients were randomized to adjuvant systemic 5-FU/LV or systemic 5-FU/LV + HAI FUDR. The addition of HAI in this population increased 2-year survival (86% vs 72%; $p = 0.03$), with median survival also increased in the HAI + systemic chemotherapy group (72 vs 59.3 months) [59]. At the 6-year follow-up, median PFS was significantly increased with HAI (31.3 vs 17.2 months; $p = 0.02$), as was hepatic PFS (not reached for HAI group vs 32.5 months; $p < 0.01$) [60]. A subsequent intergroup trial randomized 109 patients to resection alone versus resection with both FUDR via HAI and systemic 5-FU [61]. Recurrence-free survival (the primary endpoint) at 4 years was improved with adjuvant therapy (46% vs 25%; $p = 0.04$), but there was no difference observed in overall survival.

Retrospective analyses of patients undergoing liver resection have suggested that the administration of adjuvant HAI is associated with increased overall survival. One multivariate analysis of over 1,000 patients identified HAI as an independent predictor of survival, with a median OS of 68 months for HAI vs 50 months for no HAI [62]. Similarly, a retrospective analysis of 612 patients undergoing liver resection from 1985 to 1994 showed improved 10-year overall survival in those patients receiving HAI in the adjuvant setting (38% vs 15%) [63].

As before, these early randomized studies and retrospective analyses predated modern systemic chemotherapeutic regimens. Since then, small phase I and phase II

non-randomized studies combining adjuvant HAI with irinotecan and oxaliplatin have been performed. The first of these, performed in 96 patients, showed a 2-year survival of 89% in patients treated with HAI FUDR/dexamethasone + systemic irinotecan [64]. In a separate study, 35 patients were given FOLFOX in conjunction with HAI FUDR/dexamethasone, with a 4-year survival which was improved to 88% at a median follow-up of 43 months [65]. Further support for the effect of adjuvant HAI was observed in a retrospective case-matched analysis of 125 patients who received adjuvant systemic FOLFOX/FOLFIRI alone, and 125 patients who received FOLFOX/FOLFIRI combined with HAI-FUDR. Overall survival at 5 years was significantly greater in the HAI group (72% vs 52%; $p = 0.004$) [5].

A recent study examined the efficacy of HAI oxaliplatin in the adjuvant setting. Following surgical resection, 3-year disease-free survival was 33% in patients treated with HAI oxaliplatin + systemic 5-FU, compared to only 5% in patients treated with systemic chemotherapy alone [35]. As this study was non-randomized, further investigations are necessary to support the use of intra-arterial oxaliplatin.

In sum, the data supporting the use of intra-arterial chemotherapy via HAI in the adjuvant setting is similar to that for unresectable disease. Randomized studies comparing the combination of HAI and systemic 5-FU/leucovorin to the latter alone indicate that HAI probably improves both disease-free and overall survival. The more recent small-phase I and II studies that follow the introduction of irinotecan and oxaliplatin also suggest that there is probably a benefit to the addition of adjuvant HAI-FUDR. Nonetheless, while there are no randomized data to support the use of HAI-FUDR (as compared to modern systemic chemotherapy) in the adjuvant setting, it is important to recall that systemic chemotherapy also remains unproven as an effective adjuvant therapy. Further studies remain needed to establish the optimal adjuvant therapy following CLM resection.

Complications

Despite the abundance of evidence to suggest that HAI chemotherapy has a role in unresectable disease, adjuvant therapy, and as a means of conversion to resectability, the use of HAI is limited to only a few centers. The lack of widespread application is likely due to the complexity of managing the administration of HAI chemotherapy, and complications that can arise from both HAI placement and HAI therapy.

Early series reported the complication rate of HAI placement as anywhere between 12 and 41% [30, 34, 66]. More recently, a review of 544 patients at our institution revealed an overall pump-related morbidity of 22%, with a low operative mortality (30-day: 0.9%) [33]. Vascular complications comprised about half of the overall complications, and included thrombosis of the hepatic artery, arterial hemorrhage, and extrahepatic or incomplete perfusion of the liver. Catheter occlusion, dislodgment, or erosion constituted 25% of the total; pump failure, however, was quite low 5% at 6 months, and 16% at 2 years.

In the above series, the pump could be salvaged from complications in 45% of cases. Extrahepatic perfusion, for one, is typically addressed by proceeding directly to transfemoral angiogram and embolization of the culprit vessel. Only rarely is surgical ligation necessary. Similarly, incomplete perfusion is frequently due to a missed accessory vessel that can be angiographically addressed; following embolization, repeat ^{99m}Tc scan after 3–4 weeks demonstrates adequate crossover perfusion.

Arterial or catheter thrombosis are the most concerning complications, as these are typically difficult to salvage and preclude continued HAI therapy. However, these complication are quite rare—in our series, 13 cases (2%) of arterial thrombosis and 11 cases of catheter thrombosis occurred—and typically occurred late. Anticoagulation or thrombolytic therapy can salvage the former complication (31% of the time), but is of little use in the case of catheter thrombosis. Infectious complications are not common, but special attention must be paid to the pump

pocket during insertion. A low threshold is maintained postoperatively for the use of parenteral antibiotics if there are any skin changes that are concerning.

Finally, biliary sclerosis is an important consideration as a long-term complication of HAI therapy. In a study by Ito and colleagues, the incidence of biliary sclerosis was 5.5% among patients receiving adjuvant HAI FUDR and 2.2% in unresectable patients [62]. No patient died of biliary complications. Only rarely does sclerosis of the biliary tree, typically most pronounced in the common hepatic duct, ultimately require dilatation and/or stenting. Dose modifications and concomitant use of dexamethasone are critical, and generally anticipate and prevent this issue [46]. Other methods to reduce hepatic toxicity further have been explored—these include circadian administration of FUDR and alternating FUDR with 5-FU bolus [26, 67].

Conclusions

Intra-arterial chemotherapy for CLM has been extensively studied, with numerous studies having been performed over the last 30 years. Much of the literature is centered on the administration of FUDR along with dexamethasone, which is delivered by continuous HAI via an implantable pump attached to catheter terminating in the native gastroduodenal artery. In patients with unresectable CLM, the use of HAI chemotherapy is associated with high response rates in the first- and second-line setting, and frequent conversion to resectability. In patients undergoing definitive surgical resection, the addition of HAI chemotherapy appears to delay hepatic recurrence and increase overall survival. While the body of literature is limited in part by the absence of level I evidence in the era of modern systemic chemotherapy, there remains an abundance of retrospective and early-phase studies that indicate that HAI should be a key component of the armamentarium used to address metastatic colorectal cancer.

References

1. Stewart BW, Wild C. International Agency for Research on Cancer, World Health Organization. World Cancer Report; 2014. 630 p.
2. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309–18. discussion 18–21. Epub 1999/09/24
3. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg. 2008;247(1):125–35. Epub 2007/12/25
4. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235(6):759–66. Epub 2002/05/30
5. House MG, Kemeny NE, Gonen M, Fong Y, Allen PJ, Paty PB, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. Ann Surg. 2011;254(6):851–6. Epub 2011/10/07
6. Smith JJ, D'Angelica MI. Surgical management of hepatic metastases of colorectal cancer. Hematol Oncol Clin North Am. 2015;29(1):61–84. Epub 2014/12/06
7. Butte JM, Gonen M, Allen PJ, Peter Kingham T, Sofocleous CT, DeMatteo RP, et al. Recurrence after partial hepatectomy for metastatic colorectal cancer: potentially curative role of salvage repeat resection. Ann Surg Oncol. 2015;22:2761–71. Epub 2015/01/13
8. Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J, et al. Guidelines for resection of colorectal cancer liver metastases. Gut. 2006;55(Suppl 3):iii1–8. Epub 2006/07/13
9. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343(13):905–14. Epub 2000/09/28
10. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. Oncology. 2010;78(3–4):237–48. Epub 2010/06/05
11. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1065–75. Epub 2014/08/05
12. Saltz L, Badarinath S, Dakhil S, Bienvenu B, Harker WG, Birchfield G, et al. Phase III trial of cetuximab, bevacizumab, and 5-fluorouracil/leucovorin vs. FOLFOX-bevacizumab in colorectal cancer. Clin

Colorectal Cancer. 2012;11(2):101–11. Epub 2011/11/08
13. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010;11(1):38–47. Epub 2009/11/28
14. Nordlinger B, Van Cutsem E, Rougier P, Kohne CH, Ychou M, Sobrero A, et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. Eur J Cancer. 2007;43(14):2037–45. Epub 2007/09/04
15. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Final results from a randomized phase 3 study of FOLFIRI {+/−} panitumumab for second-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25(1):107–16. Epub 2013/12/21
16. Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015;16(5):499–508. Epub 2015/04/17
17. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954;30(5):969–77. Epub 1954/09/01
18. Sigurdson ER, Ridge JA, Kemeny N, Daly JM. Tumor and liver drug uptake following hepatic artery and portal vein infusion. J Clin Oncol. 1987;5(11):1836–40. Epub 1987/11/01
19. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. Semin Oncol. 1983;10(2):176–82. Epub 1983/06/01
20. Cardona K, Donataccio D, Kingham TP, Allen PJ, DeMatteo RP, Fong Y, et al. Treatment of extensive metastatic colorectal cancer to the liver with systemic and hepatic arterial infusion chemotherapy and two-stage hepatic resection: the role of salvage therapy for recurrent disease. Ann Surg Oncol. 2014;21(3):815–21. Epub 2013/11/19
21. Muratore A, Polastri R, Bouzari H, Vergara V, Ferrero A, Capussotti L. Repeat hepatectomy for colorectal liver metastases: a worthwhile operation? J Surg Oncol. 2001;76(2):127–32. Epub 2001/02/27
22. Topal B, Kaufman L, Aerts R, Penninckx F. Patterns of failure following curative resection of colorectal liver metastases. Eur J Surg Oncol. 2003;29(3):248–53. Epub 2003/03/27
23. Vigano L, Capussotti L, Lapointe R, Barroso E, Hubert C, Giuliante F, et al. Early recurrence after liver resection for colorectal metastases: risk factors, prognosis, and treatment. A LiverMetSurvey-based study of 6,025 patients. Ann Surg Oncol. 2014;21(4):1276–86. Epub 2013/12/19
24. Kerr DJ, McArdle CS, Ledermann J, Taylor I, Sherlock DJ, Schlag PM, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. Lancet. 2003;361(9355):368–73. Epub 2003/02/08
25. Nishiofuku H, Tanaka T, Aramaki T, Boku N, Inaba Y, Sato Y, et al. Hepatic arterial infusion of 5-fluorouracil for patients with liver metastases from colorectal cancer refractory to standard systemic chemotherapy: a multicenter, retrospective analysis. Clin Colorectal Cancer. 2010;9(5):305–10. Epub 2011/01/07
26. Stagg RJ, Venook AP, Chase JL, Lewis BJ, Warren RS, Roh M, et al. Alternating hepatic intra-arterial floxuridine and fluorouracil: a less toxic regimen for treatment of liver metastases from colorectal cancer. J Natl Cancer Inst. 1991;83(6):423–8. Epub 1991/03/20
27. Ammori JB, D'Angelica MI, Fong Y, Cercek A, Dematteo RP, Allen PJ, et al. Hepatic artery infusional chemotherapy in patients with unresectable colorectal liver metastases and extrahepatic disease. J Surg Oncol. 2012;106(8):953–8. Epub 2012/07/04
28. Grobmyer SR, Fong Y, D'Angelica M, Dematteo RP, Blumgart LH, Jarnagin WR. Diagnostic laparoscopy prior to planned hepatic resection for colorectal metastases. Arch Surg. 2004;139(12):1326–30. Epub 2004/12/22
29. De Cecco CN, Ferrari R, Rengo M, Paolantonio P, Vecchietti F, Laghi A. Anatomic variations of the hepatic arteries in 250 patients studied with 64-row CT angiography. Eur Radiol. 2009;19(11):2765–70. Epub 2009/05/28
30. Curley SA, Roh MS, Chase JL, Hohn DC. Adjuvant hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases. Am J Surg. 1993;166(6):743–6. discussion 6–8. Epub 1993/12/01
31. Allen PJ, Stojadinovic A, Ben-Porat L, Gonen M, Kooby D, Blumgart L, et al. The management of variant arterial anatomy during hepatic arterial infusion pump placement. Ann Surg Oncol. 2002;9(9):875–80. Epub 2002/11/06
32. Perez DR, Kemeny NE, Brown KT, Gewirtz AN, Paty PB, Jarnagin WR, et al. Angiographic identification of extrahepatic perfusion after hepatic arterial pump placement: implications for surgical prevention. HPB (Oxford). 2014;16(8):744–8. Epub 2013/12/19
33. Allen PJ, Nissan A, Picon AI, Kemeny N, Dudrick P, Ben-Porat L, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. J Am Coll Surg. 2005;201(1):57–65. Epub 2005/06/28
34. Campbell KA, Burns RC, Sitzmann JV, Lipsett PA, Grochow LB, Niederhuber JE. Regional chemotherapy devices: effect of experience and anatomy on complications. J Clin Oncol. 1993;11(5):822–6. Epub 1993/05/01

35. Goere D, Benhaim L, Bonnet S, Malka D, Faron M, Elias D, et al. Adjuvant chemotherapy after resection of colorectal liver metastases in patients at high risk of hepatic recurrence: a comparative study between hepatic arterial infusion of oxaliplatin and modern systemic chemotherapy. Ann Surg. 2013;257(1):114–20. Epub 2012/12/14
36. Arru M, Aldrighetti L, Gremmo F, Ronzoni M, Angeli E, Caterini R, et al. Arterial devices for regional hepatic chemotherapy: transaxillary versus laparotomic access. J Vasc Access. 2000;1(3):93–9. Epub 2007/07/20
37. Castaing D, Azoulay D, Fecteau AH, Bismuth H. Implantable hepatic arterial infusion device: placement without laparotomy via an intercostal artery. J Am Coll Surg. 1998;187(5):565–8. Epub 1998/11/11
38. Cheng J, Hong D, Zhu G, Swanstrom LL, Hansen PD. Laparoscopic placement of hepatic artery infusion pumps: technical considerations and early results. Ann Surg Oncol. 2004;11(6):589–97. Epub 2004/05/20
39. Van Nieuwenhove Y, Aerts M, Neyns B, Delvaux G. Techniques for the placement of hepatic artery catheters for regional chemotherapy in unresectable liver metastases. Eur J Surg. 2007;33(3):336–40. Epub 2006/11/07
40. Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. Ann Intern Med. 1987;107(4):459–65. Epub 1987/10/01
41. Hohn DC, Stagg RJ, Friedman MA, Hannigan Jr JF, Rayner A, Ignoffo RJ, 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(11):1646–54. Epub 1989/11/01
42. Rougier P, Laplanche A, Huguier M, Hay JM, Ollivier JM, Escat J, 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(7):1112–8. Epub 1992/07/01
43. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. Lancet. 1994;344(8932):1255–60. Epub 1994/11/05
44. Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol. 2006;24(9):1395–403. Epub 2006/03/01
45. Kingham TP, D'Angelica M, Kemeny NE. Role of intra-arterial hepatic chemotherapy in the treatment of colorectal cancer metastases. J Surg Oncol. 2010;102(8):988–95. Epub 2010/12/18
46. Kemeny N, Seiter K, Niedzwiecki D, Chapman D, Sigurdson E, Cohen A, 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(2):327–34. Epub 1992/01/15
47. Mocellin S, Pilati P, Lise M, Nitti D. Meta-analysis of hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the end of an era? J Clin Oncol. 2007;25(35):5649–54. Epub 2007/12/11
48. Safi F, Bittner R, Roscher R, Schuhmacher K, Gaus W, Beger GH. Regional chemotherapy for hepatic metastases of colorectal carcinoma (continuous intraarterial versus continuous intraarterial/intravenous therapy). Results of a controlled clinical trial. Cancer. 1989;64(2):379–87. Epub 1989/07/15
49. Kemeny N, Gonen M, Sullivan D, Schwartz L, Benedetti F, Saltz L, 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(10):2687–95. Epub 2001/05/16
50. Kemeny N, Jarnagin W, Paty P, Gonen M, Schwartz L, Morse M, et al. Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. J Clin Oncol. 2005;23(22):4888–96. Epub 2005/07/13
51. Kemeny NE, Melendez FD, Capanu M, Paty PB, Fong Y, Schwartz LH, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. J Clin Oncol. 2009;27(21):3465–71. Epub 2009/05/28
52. D'Angelica MI, Correa-Gallego C, Paty PB, Cercek A, Gewirtz AN, Chou JF, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. Ann Surg. 2015;261(2):353–60. Epub 2014/03/22
53. Ducreux M, Ychou M, Laplanche A, Gamelin E, Lasser P, Husseini F, et al. Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. J Clin Oncol. 2005;23(22):4881–7. Epub 2005/07/13
54. Boige V, Malka D, Elias D, Castaing M, De Baere T, Goere D, et al. Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. Ann Surg Oncol. 2008;15(1):219–26. Epub 2007/09/27
55. Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008;26(30):4906–11. Epub 2008/09/17

56. Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol. 2009;20(12):1964–70. Epub 2009/07/02
57. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007–16. Epub 2008/03/25
58. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14(12):1208–15. Epub 2013/10/15
59. Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999;341(27):2039–48. Epub 1999/12/30
60. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med. 2005;352(7):734–5. Epub 2005/02/18
61. Kemeny MM, Adak S, Gray B, Macdonald JS, Smith T, Lipsitz S, 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(6):1499–505. Epub 2002/03/16
62. Ito H, Are C, Gonen M, D'Angelica M, Dematteo RP, Kemeny NE, et al. Effect of postoperative morbidity on long-term survival after hepatic resection for metastatic colorectal cancer. Ann Surg. 2008;247(6):994–1002. Epub 2008/06/04
63. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25(29):4575–80. Epub 2007/10/11
64. Kemeny N, Jarnagin W, Gonen M, Stockman J, Blumgart L, Sperber D, et al. Phase I/II study of hepatic arterial therapy with floxuridine and dexamethasone in combination with intravenous irinotecan as adjuvant treatment after resection of hepatic metastases from colorectal cancer. J Clin Oncol. 2003;21(17):3303–9. Epub 2003/08/30
65. Kemeny N, Capanu M, D'Angelica M, Jarnagin W, Haviland D, Dematteo R, et al. Phase I trial of adjuvant hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone plus systemic oxaliplatin, 5-fluorouracil and leucovorin in patients with resected liver metastases from colorectal cancer. Ann Oncol. 2009;20(7):1236–41. Epub 2009/02/24
66. Heinrich S, Petrowsky H, Schwinnen I, Staib-Sebler E, Gog C, El-Ganainy A, et al. Technical complications of continuous intra-arterial chemotherapy with 5-fluorodeoxyuridine and 5-fluorouracil for colorectal liver metastases. Surgery. 2003;133(1):40–8. Epub 2003/02/04
67. Hrushesky WJ. Cancer chronotherapy: a drug delivery challenge. Prog Clin Biol Res. 1990;341A:1–10. Epub 1990/01/01