

Treatment Options in Colorectal Liver Metastases: Hepatic Arterial Infusion

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Keywords

Hepatic arterial infusion, HAI · Colorectal liver metastases · Survival · Progression-free survival

Summary

Background: The liver is the most common site for metastases from colorectal cancer (CRC) with the majority of these patients having unresectable disease. **Methods:** This is a retrospective review of studies using hepatic arterial infusion (HAI) therapy to treat liver metastasis from CRC. A PubMed search of randomized controlled trials and retrospective studies from 2006 to present was conducted using the search terms ‘hepatic arterial infusion (HAI) therapy’, ‘colorectal cancer’, and ‘treatment of liver metastases’. **Results:** The first randomized studies comparing HAI to systemic therapy with 5-fluorouracil/leucovorin produced significantly higher response rates of 41 versus 14%. Systemic therapy has improved with the addition of irinotecan and oxaliplatin; however, the responses with HAI and these modern agents have also increased, with responses as high as 80%. For patients with wild-type KRAS, HAI and systemic therapy produced a median survival of 68 months. In patients with refractory disease, response rates are in the 30% range with a median survival of 20 months. Adjuvant HAI after liver resection has shown an increase of hepatic disease-free survival and overall disease-free survival when compared to systemic therapy alone in three of four randomized trials. A recent update of the adjuvant trials after liver resection at Memorial Sloan Kettering Cancer Center has shown a 5-year survival of 78%. **Conclusion:** HAI therapy has a role in treating hepatic metastases from CRC in both the resectable and unresectable setting.

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with approximately 1.4 million people diagnosed and almost 700,000 deaths in 2012 [1]. In the USA, CRC is the third leading cause of cancer death in both men and women, with an estimated 49,190 deaths to occur in 2016 [2].

The liver is the most common site for metastases, with approximately 60% of patients developing liver metastases throughout the course of their disease, which is a major cause of mortality [3]. Unfortunately, approximately 85% of patients will harbor unresectable disease in which the 5-year survival is typically 6–10% [4, 5]. Therefore, in these patients, treatment with systemic or liver-directed chemotherapy through hepatic arterial infusion (HAI) can be used to downsize the disease in the liver with the goal of conversion to resection [6–8].

For patients who are able to undergo surgical resection of liver metastases with or without adjuvant chemotherapy, an increased survival can be obtained. In recent decades, the 5-year survival for patients in the adjuvant setting has increased from 25–39% [9] to 40–50% [10]. The improvement in survival is attributed to several factors including newer systemic chemotherapy agents such as oxaliplatin [11] and irinotecan [12], effective combination chemotherapy regimens such as FOLFIRI and FOLFOX [13], and molecular targeted agents against the vascular endothelial growth factor [14] and epidermal growth factor receptor [15, 16]. Other factors that may improve survival include more effective surgical techniques [17, 18] and interventional radiology procedures [19].

Since the liver is the most common site of metastatic disease for patients with CRC, liver-directed therapies have been developed. This article will summarize the role of HAI chemotherapy in the treatment of metastatic CRC to the liver.

Methods

A PubMed search of randomized controlled trials and retrospective studies from 2006 to present was conducted using the search terms 'hepatic arterial infusion (HAI) therapy', 'colorectal cancer', and 'treatment of liver metastases'. Studies were excluded with less than 30 patients or which included other malignancies besides colon cancer.

Rationale of Hepatic Arterial Infusion Chemotherapy

There may be a stepwise pattern of metastatic spread in CRC with the cancer originating in the colon or rectum and spreading to the liver via the portal veins. The rationale for HAI chemotherapy is based on the dual blood supply in the liver, with liver metastases greater than 1 cm in diameter deriving blood supply from the hepatic artery, whereas normal hepatocytes are perfused by the portal vein [20]. HAI chemotherapy is administered in the gastroduodenal artery by a surgically implanted pump, a hepatic arterial port, or through a percutaneously placed catheter connected to an external pump.

Certain drugs with a high first-pass extraction can be delivered into the arterial circulation resulting in high drug concentrations in the liver with minimal systemic toxicity [21]. In choosing a drug agent for HAI, the aim should be i) to increase local concentration which increases therapeutic response and ii) to decrease systemic exposure and toxicity [22]. Floxuridine (FUDR) is the most widely used agent in internal pumps because of the short half-life and high first-pass metabolism rate allowing for increased concentration of the drug in hepatic tumors and lower concentrations systemically [21]. Newer chemotherapy drugs have also been used for intrahepatic therapy including irinotecan [23] and oxaliplatin [24, 25]. Chinese investigators using HAI CPT and oxaliplatin with bolus FUDR given only every 4–8 weeks produced a 61% response rate and a median survival of 24.8 months in 31 patients [26]. Irinotecan is not as useful due to a lack of an extraction benefit [27].

Toxicity of Hepatic Arterial Infusion Chemotherapy

Systemic toxicities such as nausea, vomiting, mucositis, and myelosuppression are very low with HAI FUDR since the extraction rate with HAI of FUDR is 95% [28, 29]. Extrahepatic profusion of FUDR into the gastrointestinal tract can cause diarrhea or gastric and duodenal ulcers [30]; however, the most common side effect of HAI FUDR therapy is biliary toxicity, being reflected in an elevation of liver enzymes or bilirubin [31]. Consequently, liver function tests should be monitored every 2 weeks during therapy and FUDR dose should be adjusted based on liver test results.

Dexamethasone can be combined with FUDR in the pump to decrease the risk of biliary toxicity [32]. In a randomized study, a decreased incidence of bilirubin elevation was seen in patients who received dexamethasone versus those who received FUDR alone (9

vs. 30%, respectively; $p = 0.07$) [32]. Other methods used to prevent biliary toxicity include alternating HAI FUDR with HAI 5-fluorouracil (5-FU) [33, 34].

Technical Aspects of Hepatic Arterial Infusion

Regional HAI chemotherapy can be administered by a hepatic arterial port or pump. The catheter can be placed percutaneously and connected to an external pump, or connected through a surgically implanted pump. At the time of surgical pump placement, the distal gastroduodenal artery, the right gastric artery, and small collateral branches supplying the stomach, small bowel, and pancreas are ligated. The pump is placed in a subcutaneous pocket in the abdomen. A cholecystectomy is performed to prevent chemotherapy-induced cholecystitis. Blue dye is injected to ensure bilobar perfusion and to assess for extrahepatic perfusion [35]. Surgically implanted pumps enable long-term infusion with good patency of the catheter and hepatic artery as well as a low incidence of infection [36, 37].

Hepatic Arterial Infusion in the Metastatic Setting

Early studies using HAI FUDR without systemic chemotherapy demonstrated increased objective response rates compared to systemic chemotherapy with intravenous FUDR or 5-FU alone (41 vs. 14%, respectively; $p < 0.01$), but did not show an increase in overall survival [38]. Using HAI 5-FU alone (not FUDR), response rates are somewhat lower (24%) and survival is 19.2 months [39]. In a randomized study comparing HAI plus systemic bolus 5-FU/leucovorin (LV) ($n = 40$) or HAI alone ($n = 36$), there was an increase in survival in the combined group (20 vs. 14 months, $p = 0.0033$), but no significant increase in response rate [40]. More recently, newer systemic agents such as irinotecan and oxaliplatin have been evaluated with HAI. A study using HAI FUDR plus systemic irinotecan in previously treated patients produced a response rate of 74% and a median survival of 21 months [41]. Another study using HAI with systemic oxaliplatin combined with irinotecan or 5-FU/LV (FOLFOX) demonstrated further improvement. Of those who received HAI FUDR plus oxaliplatin and CPT, 19 out of 21 (90%) had a partial response and median survival was 35.8 months [42]. In a Chinese study in which half of the patients had extrahepatic disease, HAI FUDR plus systemic mFOLFOX6 produced a response rate of 68.6% and a median survival of 25 months [43].

In patients who are KRAS wild-type, systemic chemotherapy agents which target the epidermal growth factor, such as cetuximab and panitumumab, can be used. In new studies in patients with KRAS wild-type tumors, the median survival has been reported to be as high as 30 months with modern systemic chemotherapy and cetuximab. In a review of 75 patients with unresectable liver metastases with known KRAS status treated with HAI and systemic chemotherapy, the median survival was 68 months for patients with KRAS wild-type tumors versus 29 months for patients with KRAS MUT ($p < 0.003$) (fig. 1) [44].

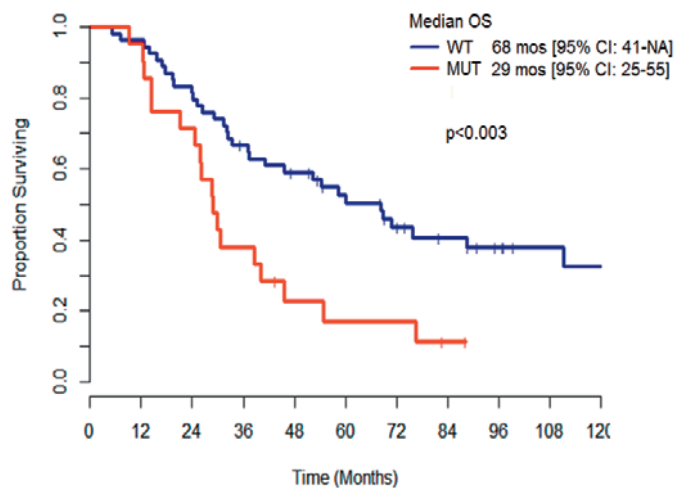


Fig. 1. Metastatic colorectal cancer: survival with hepatic arterial infusion and systemic chemotherapy.

Hepatic Arterial Infusion Chemotherapy in the Refractory Metastatic Setting

For patients who fail first-line chemotherapy, modern systemic chemotherapy agents such as irinotecan alone [45], irinotecan and cetuximab [46], and FOLFOX [47] produce response rates ranging from 9–22% and a median survival of 14 months or less. In patients who fail first- and second-line chemotherapy, therapeutic options are very limited. Regorafenib and TAS102 in the refractory setting demonstrate response rates of 1 and 1.6%, respectively, and a median survival of 6.4 and 7.1 months, respectively [48, 49]. In a recent publication of a heavily pretreated population of patients who had progressed after 5-FU/LV, oxaliplatin, and irinotecan therapies, the response rate was 33%, the median survival was 20 months, and the progression-free survival was 6 months after using HAI plus systemic therapy [50]. 19 of 57 (33%) patients had a partial response and 31 (54%) had stable disease.

Role of Hepatic Arterial Infusion in the Metastatic Setting: Converting Unresectable to Resectable Liver Disease

In patients who are diagnosed with liver-only metastases not amenable to surgery, treatment with systemic chemotherapy can decrease tumor size and convert approximately 15–30% of inoperable patients to operable [51], especially when targeted chemotherapy agents are used [52]. In a study conducted at Memorial Sloan Kettering Cancer Center, 49 patients with unresectable (i.e. lesions involving at least six segments in combination with involvement of major vessels which would require resection of vessels to achieve an R0 resection) CRC liver metastases were treated with HAI FUDR/Dex plus systemic oxaliplatin and irinotecan [8]. 92% of the 49 patients had a complete (8%) or partial (84%) response. 47% of patients were able to proceed with liver resection with curative intent. Figure 2 shows the volume of reduction in disease allowing patients to get to resection. In patients who were chemotherapy-naïve, the median survival was 50.8 months, and for patients who were previously treated the median survival was 35 months.

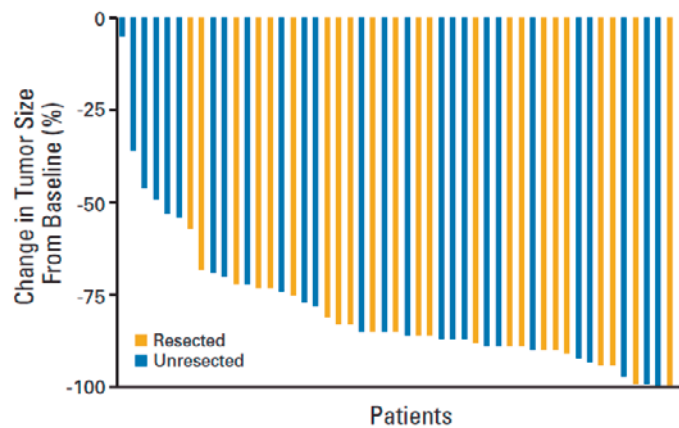


Fig. 2. Waterfall graph depicting the decrease in tumor measurements from baseline in patients treated with hepatic arterial infusion floxuridine/dexamethasone plus systemic oxaliplatin/irinotecan. –100 means 100% decrease in tumor. Blue bars represent patients who were not able to undergo resection. Gold bars represent patients who, though initially unresectable, after response with hepatic arterial infusion and systemic chemotherapy were able to undergo resection. Adapted from [8]. Reprinted with permission. © 2017 American Society of Clinical Oncology. All rights reserved.

D’Angelica et al. [53] evaluated 49 patients with unresectable liver metastases from CRC treated with HAI plus systemic chemotherapy in a prospective study. The overall response rate was 76%, 47% of patients were converted to resection at 6 months after treatment start, and median overall survival for all patients was 38 months. An updated analysis of this study with a median follow-up among survivors of 63 months reported a 52% conversion to resection at a median of 5 months, an overall survival of 37.4 months, and 5-year survival of 36% [54].

In 39 patients progressing on oxaliplatin therapy and then treated with HAI FUDR/Dex plus systemic irinotecan, the response rate was 44%, with 18% of these patients undergoing surgical resection or ablation [55]. In patients treated with HAI oxaliplatin via a port and systemic 5-FU/LV, of which 75% were previously treated, 19% of patients were converted from unresectable to resectable [25]. Another study with 54 patients who were all previously treated with prior systemic FOLFIRI or FOLFOX, HAI oxaliplatin via an intrahepatic arterial catheter connected to a subcutaneous port and systemic 5-FU/LV resulted in 18% conversion to resection [56].

Hepatic Arterial Infusion as Adjuvant Therapy after Hepatic Resection

HAI chemotherapy can be used in conjunction with surgery and systemic chemotherapy to target metastatic disease from CRC to the liver. Hepatic resection of colorectal liver metastases has improved 5-year survival rates [9, 57]. Nearly 70% of patients develop recurrent disease after hepatic resection, usually within 2 years, and 30–50% develop isolated hepatic metastases [58, 59]. Adjuvant regional therapy with HAI can target residual micrometastatic disease in the liver, in conjunction with systemic therapy to reduce systemic recurrence. Several randomized studies have compared HAI plus systemic therapy versus systemic therapy alone.

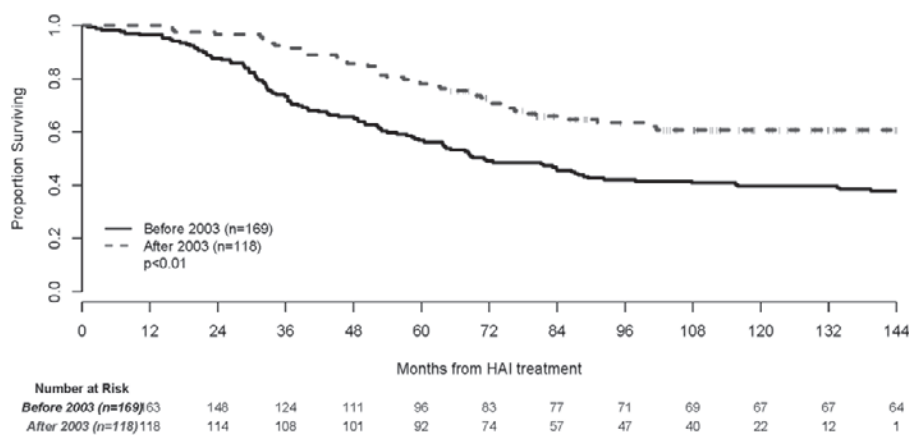


Fig. 3. Updated overall survival after adjuvant treatment with hepatic arterial infusion and systemic chemotherapy after liver resection. Adapted from [68]. Reprinted with permission. © 2017 John Wiley and Sons. All rights reserved.

Table 1. Randomized studies after liver resection: hepatic disease-free survival

Studies	n	2-year, %		5-year, %		p value
		HAI	SYS	HAI	SYS	
MSKCC	156	90	60	75	40	0.0001
ECOG	75	75	50	70	40 ^a	0.0001
Lorenz	186	median		43/27 ^a		NS
Lygidakis	122	90	60	85	50	0.0001

^aNo treatment in control arm.
HAI = Hepatic arterial infusion; SYS = systemic therapy.

A randomized trial at Memorial Sloan Kettering Cancer Center compared 156 patients who were resected and then randomized to receive HAI FUDR/Dex combined with systemic intravenous 5-FU/LV (n = 74) and 5-FU/LV alone (n = 82) [60]. The endpoint was 2-year survival which was significantly improved with HAI FUDR/Dex plus intravenous 5-FU/LV (86%) versus 72% for 5-FU/LV alone (p = 0.03). In addition, there was an excellent 2-year hepatic disease-free survival (HDFS) (90 vs. 60%, p < 0.001) for those who received HAI FUDR/Dex + intravenous 5-FU/LV versus systemic therapy alone. In 2005, updated results were published and showed a 10-year survival rate of 41% in the group who received HAI FUDR/Dex plus intravenous 5-FU/LV compared to 27.2% in the group who received intravenous 5-FU/LV alone, as well as a longer overall progression-free survival (31.3 vs. 17.2 months, respectively; p = 0.02) [61].

A trial done by the Eastern Cooperative Oncology Group and the Southwestern Oncology Group randomized patients after hepatic resection to HAI FUDR and intravenous 5-FU versus surgery alone [62]. The endpoint was disease-free survival (DFS). For those receiving HAI FUDR and intravenous 5-FU/LV versus no further therapy, the 4-year DFS was 46 versus 25%, respectively (p = 0.04), and liver recurrence-free survival was 67 versus 43%, respectively (p = 0.03).

DFS and HDFS of four randomized studies show a significant increase in HDFS and overall DFS in three of four studies (table 1).

HAI has been combined with more modern systemic therapy. A phase I/II study evaluated patients who underwent liver resection

followed by HAI FUDR/Dex plus systemic irinotecan [63]. There was a 2-year survival of 89% and at 18 months HDFS was 88% and overall DFS was 47%. Another phase I study evaluated HAI FUDR/Dex plus systemic oxaliplatin and 5-FU/LV after liver resection [64]. The 3-year survival was 88%; with a median follow-up of 43 months the median survival was not reached. At 3 years, hepatic progression-free survival was 86% and overall progression-free survival was 50%. A North Central Cancer Treatment Group (NCCTG) phase II study looked at adjuvant HAI FUDR plus systemic 5-FU/LV in 49 patients who had resection of bilobar disease [65]. Their endpoint was a 2-year survival of 85% which was reached.

Other retrospective studies have also shown that adjuvant HAI following liver resection prolongs hepatic progression-free survival and progression-free survival. A review by Ito et al. [66] on 1,021 patients showed that HAI therapy after liver resection was associated with improved overall survival in a multivariate analysis. Can similar results be obtained with modern systemic therapy alone? House et al. [67] looked at patients who were resected between 2001 and 2005 and matched 125 patients treated with modern therapy (FOLFOX or FOLFIRI) with 125 patients who received HAI plus systemic chemotherapy. With a median follow-up of 43 months, patients treated with HAI FUDR plus systemic chemotherapy had a higher 5-year survival compared to patients treated with systemic chemotherapy alone, i.e. 72 versus 52%, respectively (p = 0.004). The 5-year hepatic recurrence-free survival was also improved for patients treated with HAI plus systemic therapy versus those treated with systemic therapy alone, i.e. 79 versus 55%, respectively (p < 0.001).

A pooled analysis of patients enrolled into four consecutive prospective adjuvant protocols using HAI and systemic chemotherapy after liver resection was done at Memorial Sloan Kettering Cancer Center [68]. The analysis included 287 patients who were enrolled in trials from October 1991 to September 2009. Patients were divided into two groups: those treated before and those after 2003. The median follow-up for patients enrolled before 2003 was 15 years. In that group the systemic chemotherapy consisted of 5-FU/LV or irinotecan added to HAI. The 5-year survival was 56% (95% confidence interval (CI): 49–64%) and the 10-year survival was 40% (95% CI: 32–47%) with a median survival of 71 months

(fig. 3). For patients enrolled after 2003, the median follow-up was 9 years and the median survival has not been reached. Systemic chemotherapy consisted of FOLFOX, FOLFIRI ± bevacizumab. The 5-year survival was 78% (95% CI: 70–84%) and the 10-year survival was 61% (95% CI: 51–70%) (fig. 3).

The use of HAI plus systemic chemotherapy in relation to a patient's KRAS mutational status has been reported. In 169 patients who underwent liver resection followed by adjuvant HAI FUDR and systemic chemotherapy, the 3-year overall survival was 95 versus 81% for KRAS wild-type (n = 118) and KRAS mutated (n = 51) patients, respectively [69].

Conclusion

CRC is a major public health problem, and even with increased efforts of screening patients are still diagnosed with stage IV disease. Approximately 25% of patients will have metastatic liver disease at diagnosis. Some of these patients are potentially curable with a combination of liver therapies including liver surgery, ablation, and HAI therapy. Evaluation of patients with oligometastatic disease to the liver for liver therapies including HAI therapy should be routinely considered. In patients with unresectable metastases to the liver, HAI can be used with systemic chemotherapy to achieve increased response rates even in patients after progression

on first- and second-line chemotherapy. Results show an increased response and conversion to resection with the use of HAI and systemic therapy versus systemic therapy alone. For patients who have unresectable liver disease, the use of HAI plus systemic chemotherapy can convert patients to resection and allow patients to have a chance for cure. In patients who have resectable liver disease, HAI therapy given with systemic chemotherapy after resection can increase DFS and HDFS. Three of four randomized trials comparing HAI and systemic chemotherapy versus systemic chemotherapy alone or control showed a significant increase in DFS and HDFS. HAI can be administered via a surgically implanted pump, hepatic arterial port, or percutaneously placed catheter connected to an external pump. Systemic toxicities are very low with HAI due to a high first-pass extraction rate, allowing combination with systemic therapies. Hepatic toxicities have to be carefully monitored. In summary, HAI with systemic chemotherapy is a reasonable treatment option in select patients with oligometastatic disease to the liver in order to achieve improved outcomes.

Disclosure Statement

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