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Intra-arterial chemotherapy for liver metastases

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Introduction

Colorectal cancer (CRC**) is one of** the leading cancers globally in terms of both incidence and cancer-related mortality [1]. There are approximately 150,000 new cases diagnosed annually, with an average 50,000 deaths per year, in the United States [2].

Liver metastatic disease is the main prognostic driver for patients with colorectal cancer. Approximately 25% of patients will have synchronous liver metastases at initial diagnosis, and over 50% will develop liver metastases during their lifetime [3].

The liver is the most frequent and often the only site of metastatic disease in patients with colorectal cancer due to the fact that venous drainage from the colon and rectum allows metastases to travel to the liver via the portal vein. Since the liver is the most common site of metastatic disease for patients with CRC, liver-directed therapies have been developed and increasingly incorporated in the treatment paradigm.

The rationale for the use of hepatic arterial infusion (HAI) chemotherapy is based on the unique anatomy of the liver. Healthy liver tissue has a dual blood supply receiving most of its perfusion from the portal vein. Liver tumors, on the other hand, mainly derive their blood supply from the hepatic artery [4]. This characteristic is exploited to allow delivery of high concentrations of chemotherapy selectively into the liver metastases.

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Management of colorectal liver metastases (CRLM) is an ever evolving and expanding field. Liver resection, where feasible, remains the only chance for cure in these patients, and is the preferred definitive therapeutic approach. The majority of patients, approximately 85%, with CRLM, however have unresectable disease at presentation with a 5 year survival of less than 10% when treated with systemic chemotherapy alone [5,6]. In such patients, the use of liver-directed chemotherapy via hepatic arterial infusion may be used in conjunction with systemic chemotherapy in an effort to reduce the burden of liver disease and convert to resection.

In those patients who are able to undergo complete resection, nearly 70% develop recurrent disease, typically within the 2 years, and 30–50% will recur within the liver alone [7,8]. HAI chemotherapy is used in this setting as an adjuvant treatment in conjunction with systemic chemotherapy to reduce the risk of recurrence.

This article will summarize the role of HAI chemotherapy in the treatment of metastatic CRC to the liver.

Background of HAI

HAI chemotherapy takes advantage of the anatomical structure of the liver with its dual blood supply. Regional arterial supply to metastatic tumors allows for the delivery of high chemotherapy concentrations with minimal systemic toxicities.

One way to deliver HAI chemotherapy is via a catheter surgically inserted into the gastroduodenal artery and connected to a subcutaneously implanted pump, which is placed at laparotomy. Laparoscopic and robotic approaches have been used for implantation as less invasive strategies. [9]. Other options for HAI administration is to use a hepatic arterial port, or through a percutaneously placed catheter connected to an external pump.

The liver predominantly metabolizes certain drugs during the first pass through the hepatic arterial circulation, which results in high local concentrations of the drug with minimal systemic toxicity. The most suitable drugs for HAI are those with high total body clearance and short plasma half-life[10,11].

5-FU was the first agent to be used for HAI. Later Floxuridine (FUDR), a prodrug of 5-FU, was found to have much higher concentration within tumor, with even fewer systemic side effects compared to 5-FU. FUDR is now the most widely used agent in internal pumps because of its short half-life and high first-pass metabolism rate allowing for increased concentration of the drug in hepatic tumors and very low concentrations systemically [12].

More modern chemotherapy agents have also been used for HAI therapy including irinotecan [13] and oxaliplatin [14,15]. These drugs have a lower first-pass hepatic extraction compared to FUDR and a different systemic toxicity profile. A study from China of 31 patients evaluated the use of HAI with irinotecan and oxaliplatin with bolus FUDR given only every 4–8 weeks, with a 61% response rate and a median survival of 24.8 months[16]. Irinotecan is not as effective due to a lack of an hepatic extraction advantage [17].

The systemic toxicity rate with HAI FUDR is very low given the high extraction rate of 95%[18,19]. Toxicity from HAI FUDR therapy includes mainly biliary toxicity and gastric ulceration secondary to extrahepatic perfusion. Extra-hepatic perfusion of FUDR into the gastrointestinal tract can cause diarrhea, pancreatitisu and/or gastroduodenal ulceration [20]. Biliary toxicity is the most common side effect of HAI FUDR, seen as an elevation of the liver enzymes[21]. As a result, it is imperative to closely monitor liver function tests every 2 weeks during therapy and adjust the FUDR dose based on the liver enzymes.[Table 1]

Dexamethasone can be combined with HAI FUDR to decrease the risk of biliary toxicity. A randomized study of HAI therapy with FUDR with or without dexamethasone in patients with liver metastatic CRC highlighted that hyperbilirubinemia occurs in about one-third of patients treated with FUDR therapy alone. The addition of dexamethasone reduced the incidence of hyperbilirubinemia from 30% to 9%. FUDR in combination with dexamethasone also improved the response rate [22].

HAI therapy has very much evolved in the last 30 years in conjunction with improved surgical techniques and the emergence of modern systemic chemotherapy agents. In the United States, HAI therapy is now an acceptable first line option for unresectable CRLM and is also a treatment option in the adjuvant setting after liver resection. However, it remains infrequently used, much of which can be explained by the level of resources needed to deliver this therapy, with specific technical expertise and knowledge as well as the requirement of a multidisciplinary team to manage treatment. Fortunately, the potential of HAI chemotherapy in the management of select patients with CRLM is increasingly being acknowledged, and new centers are appearing with specialist interest in this treatment modality across the world [23,24].**n**

HAI as adjuvant therapy after liver resection

Hepatic resection for colorectal liver metastases has improved 5-year survival rates [25,26]. The recurrence rate following liver resection for CRC metastases however remains high, at 60–70%, usually occurring within 2 years, and 70% of recurrences occur in the liver [27,28,29]

Adjuvant liver -directed therapy with HAI can target residual micrometastatic disease in the liver, to reduce the risk of hepatic recurrence and improve survival. Early on, four randomized trials compared adjuvant HAI therapy after resection of CRLM with either adjuvant systemic therapy or a no-treatment control arm. The results were mixed. Of these four studies, three showed a significant decrease in hepatic disease-free survival (DFS) as well as overall survival [30–34].However, the study by Lorenz et al, which compared adjuvant HAI with 5FU to no treatment, failed to show a survival benefit, and was terminated early.

In 2004, a Cochrane review of seven randomized adjuvant HAI studies showed no OS improvement, and HAI was not recommended by the authors based on this. The Cochrane review is now somewhat outdated. It incorporated a total of 592 patients from 7 randomized studies, published between 1990 and 2002, comparing adjuvant HAI to systemic therapy alone/observation. The studies used a variety of HAI therapies including: FUDR, 5-FU,

5-FU/mitomycin. Only one of these studies incorporated a combination of adjuvant systemic (5-FU alone) chemotherapy and HAI in the investigational arm. The review demonstrated that a significant reduction in liver recurrence was observed in the HAI group; however, there was no overall survival advantage favoring the investigational approach and HAI therapy was associated with greater toxicity [35].

A more recent report in 2016 from Memorial Sloan Kettering Cancer Center compared the long-term survival of 287 patients with resected CRLM that received adjuvant HAI and systemic therapy on four consecutive adjuvant protocols from 1991 to 2009. The patients were divided into two groups based on whether they received therapy before or after the year 2003, in an effort to reflect changes in the systemic chemotherapy combinations being utilized in the management of CRC patients. 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. 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 difference in the 3-year and 5-year overall survival bet{ween the two patient groups (after 2003 or before 2003) was 92% and 73% versus 78% and 56% ($p < 0.01$), respectively, demonstrating the excellent survival obtained with resection, HAI, and modern chemotherapy [36]. Another recent publication from MSKCC looked at 2368 consecutive patients who underwent liver resection of colorectal metastases; 785 had HAI and 1583 did not. The HAI group of patients had a significantly higher disease burden (i.e. significantly increased clinical risk score)[25]but still had a longer median survival of 67 versus 44 months for those treated with adjuvant systemic chemotherapy alone ($p < 0.01$) [37].The analysis which spanned over 21 years from 1992 through 2012 also assessed whether or not HAI therapy was administered with peri-operative modern systemic chemotherapy as a subgroup analysis. 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 independent of receiving modern systemic chemotherapy or not, and regardless of whether HAI was received in the preoperative or adjuvant setting, there remained a significantly associated greater OS in the HAI arm. 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.

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 [38].

Currently, there are two ongoing randomized clinical trials being conducted to further assess the role of adjuvant HAI after resection of CRLM. The first is a phase II trial, the so-called PUMP trial ,which is being performed in the Netherlands that is planned to evaluate the efficacy of adjuvant HAI FUDR therapy in "low risk" patients. Low risk for recurrence 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 (39). Patients are randomized to either resection without any adjuvant therapy or HAI pump placement 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 aim of the study is to corroborate prior results at MSKCC for adjuvant HAI FUDR (31). A second study currently underway is a phase II/III trial, PACHA-01, which is comparing adjuvant systemic FOLFOX and HAI oxaliplatin + systemic 5-FU in patients deemed “high risk” for recurrence, defined as having 4 or more resected CRLM in patients who have undergone R0 or R1 resection and/or thermal ablation (40). The primary objectives are to assess the 18-month hepatic recurrence-free survival in patients treated with HAI oxaliplatin + systemic 5-FU after curative intent surgery, and demonstrate superiority in recurrence-free survival of HAI oxaliplatin compared to systemic oxaliplatin + 5-FU (FOLFOX).

HAI in the Metastatic setting

Early studies using HAI FUDR alone demonstrated increased objective response rates compared to systemic chemotherapy with intravenous FUDR or 5-FU alone (41 vs. 14%, respectively; $p < 0.01$), but failed to show an overall survival advantage[41]. Using HAI 5-FU alone, lower response rates were seen(24%) with a median survival of 19.2 months [42]. In a randomized study comparing HAI plus systemic bolus 5-FU/leucovorin (LV) ($n = 40$) or HAI alone ($n = 36$), increased survival was observed in the combined group (20 vs. 14 months, $p = 0.0033$), but without a significant increase in response rate [43]. More recently, evaluation of HAI with modern systemic agents such as irinotecan and oxaliplatin has been conducted. A study assessing HAI FUDR plus systemic irinotecan in previously treated patients led to a response rate of 74% and a median survival of 21 months [44]. Another study evaluated HAI therapy with systemic oxaliplatin combined with irinotecan or 5-FU/LV (FOLFOX) demonstrated further improvement. Of those who received HAI FUDR plus oxaliplatin and irinotecan,90% had a partial response and median survival was 35.8 months [45]. In a Chinese study, which included patients with extra-hepatic disease,HAI FUDR plus systemic FOLFOX produced a response rate of 68.6% and a median survival of 25 months [46].

In KRAS wild-type patients, systemic chemotherapy agents which target the epidermal growth factor(EGFR), such as cetuximab and panitumumab, can be used. In more recent 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 ($p < 0.003$) [47].

For patients who fail first-line chemotherapy, modern systemic chemotherapy agents such as irinotecan alone [48], irinotecan and cetuximab [49], and FOLFOX [50] 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 [51, 52].

In a 2016 study 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.19 of 57 (33%) patients had a partial response and 31 (54%) had stable disease[53].

Converting unresectable to resectable liver disease with HAI

The majority of patients with colorectal liver metastases present with initially unresectable disease. In the absence of extra-hepatic metastases, liver resection is a potentially curative, therapeutic option that has been proven to positively impact overall survival in this patient group [26, 54–57]. Considering the improved outcomes observed in patients who undergo liver resection for CRLM, the goal of therapy for those with unresectable liver metastases should focus on optimizing the response rate to facilitate surgery. The correlation between response rate and resection rate is high in the setting of liver-confined colorectal metastases ($r = 0.96$, $p = 0.002$) [58].

In patients who are diagnosed with inoperable liver-limited disease, systemic chemotherapy can decrease tumor size and convert approximately 15–30% of unresectable patients to resectability, especially when targeted chemotherapy agents are used [59,60].

However even in the era of modern systemic chemotherapy, no significant improvement in prognosis has been observed with combinations such as FOLFOX, FOLFIRI and FOLFOXIRI, as well as the use of targeted therapies including anti-epidermal growth factor receptor (EGFR) for *RAS* wild-type tumors, and anti-vascular endothelial growth factor (VEGF) agents].Response rates to first line therapy in metastatic CRC range from 34–66%; while in the second line response rates remain low, typically ranging from 4–15%[61]. In patients with KRAS wild type tumors, with the use of anti-EGFR therapy, higher responses up to 30–40% for 2nd line have been demonstrated, 62). Progression-free survival for first line agents is 5.1–13 months, and decreases to 1.7–7.3 months for second line agents (63). Therefore, liver-directed strategies such as HAI chemotherapy represents an attractive option for locoregional disease control and possible conversion to surgical resection for patients with higher-volume liver-dominant metastatic colorectal cancer to improve prognosis. Decisions regarding the management of CRLM should ideally be made by a hepatobiliary multidisciplinary team [64].

The definition of resectability has become more complex, and can be institution and surgeon dependent, making it difficult to compare data. Over time, the boundaries of hepatic resection have been pushed further, with improvements in surgical techniques. One core feature when determining operability is to ensure that the future liver remnant after surgery is sufficient to maintain adequate liver function. The majority of studies indicate that resected patients have outcomes similar to those patients with initially resectable colorectal liver metastases and that long-term survival and cure is possible[65].

HAI alone was initially compared to available systemic chemotherapies for first-line use for unresectable CRLM. Superior response rates of HAI therapy were repeatedly demonstrated in multiple early prospective trials but this did not translate into consistent improvements in OS [66–69]. Initial randomized studies in the first line setting which compared HAI FUDR monotherapy to systemic 5-FU in patients with unresectable CRLM led to overall response rates between 42% and 47% for the HAI groups versus 9–24% for the systemic chemotherapy arms [67,70,71]. 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 (72). Later phase I/II studies of HAI with modern systemic chemotherapy found this combination strategy to be safe and effective, with responses of 64–100% amongst patients with previously untreated, liver-limited, unresectable disease. In previously treated patients with CRLM, response rates of 74–85% have been observed with combination HAI and modern systemic chemotherapies.

Furthermore, 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 (73). There were several limitations to this analysis however including single institution studies with small numbers of patients, outdated HAI chemotherapy regimens, and allowance for cross over to HAI in patients who had initially failed systemic chemotherapy. To address 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, with a significant improvement in survival demonstrated(24.4 *vs.* 20 months; P=0.0034) (70).

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, the only predictors of OS were response to therapy and lower tumor burden (<50% of liver parenchymal involvement).OS in patients with <50% liver involvement compared to >50% was significantly greater (21.3 *vs.* 13.2 months) (74). These results suggest that HAI therapy can be more beneficial if likely responders can be identified through biomarkers such as gene mutational status.

As mentioned previously, 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 in combination with modern agents (75.) A single arm phase I study of 49 patients conducted 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). 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. Thirty-nine percent underwent R0 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. (76). In 2010, Goere *et al.* analyzed 87 patients who received HAI oxaliplatin with systemic 5-FU and leucovorin, as second line therapy, and 24% (21/87) of patients were converted to resection, with 5-year OS of 56% (77). Further studies continue to consistently show high response rates up to 76% and conversion to resection up to 52% using various combinations of HAI with modern agents (78–81).[Table 2]

HAI has also demonstrated anti tumor activity and improved survival in patients with refractory CRC. In 39 patients progressing on oxaliplatin therapy and then treated with HAI FUDR/Dex plus systemic irinotecan, the response rate was 44%, with18% of these patients ultimately undergoing resection or ablation [84]. 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 [15]. 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 [85].

The addition of biologic agents such as bevacizumab to liver-directed and combination systemic chemotherapy has also been studied. Increased biliary toxicity was observed when concurrent administration of systemic bevacizumab was employed. The addition of bevacizumab did not improve response rates or conversion rates to liver resection [82]. A prospective study by D'Angelica et al of 49 patients with advanced, unresectable liver-limited colorectal cancer treated with HAI and best systemic chemotherapy yielded a response rate of 76%. [78]The conversion rate to liver resection was 47% at 6 months after treatment start, and of note, 65% of the study population had been previously treated with systemic chemotherapy. Median overall survival for all patients was 38 months.

There was a low rate of surgical complications post liver resection with only one individual experiencing a grade 3 adverse event (a biloma requiring percutaneous drainage). A high degree of biliary complications was evident in the first 24 patients who also received concurrent systemic bevacizumab. Bevacizumab was discontinued for the following 25 patients who were enrolled. The conversion to resection was the only factor associated with longer overall survival and PFS.

A landmark analysis confirmed a higher 3-year overall survival among patients who underwent liver resection compared to those that remained unresectable (80% versus 26%). At a median follow-up of 39 months (32–65 months), 10 of the 49 patients (20%) had no evidence of disease [78]. 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% [83].

Other indications for HAI -Intrahepatic cholangiocarcinoma

HAI chemotherapy in combination with systemic chemotherapy has also been proven as an effective and safe treatment in patients with unresectable intrahepatic cholangiocarcinoma with locally advanced or metastatic disease confined to the liver.

Intrahepatic cholangiocarcinoma (IHC) is rare but increasing in incidence and mortality[86,87]. Most patients with IHC present with either unresectable or distant metastatic disease, for which the prognosis is poor. [88,89]. Most patients with advanced IHC present with disease confined to the liver that is unresectable owing to tumor location and/or multifocal involvement. Even in patients with resectable disease, 60% of patients develop recurrent disease [88,90]. Currently, the standard systemic therapy for IHC remains platinum-based chemotherapy in combination with gemcitabine, with marginal improvement in median overall survival to 11.7 months[91,92].

Results with HAI chemotherapy have been encouraging in this patient group, with evidence supporting its use dating back over 30 years ago[93]. In a phase 2 trial, 34 unresectable patients (26 ICC; 8 HCC) received HAI FUDR with an objective response rate of 47%, and 1 patient with initially unresectable ICC proceeded to resection. Median progression-free survival (PFS) was 7.4 months, and disease-specific survival was 29 months[94]. Similar outcomes were observed in a subsequent study, in which 22 patients (18 ICC; 4 HCC) were treated with HAI FUDR plus bevacizumab. In this trial, median PFS and OS were 8.5 and 31.1 months, respectively. However, this study was prematurely terminated owing to increased biliary toxicity associated with bevacizumab[95] In a retrospective review of 78 ICC]patients, who underwent treatment with combined HAI FUDR and systemic chemotherapy, the OS was superior compared with patients who received systemic treatment alone (30.8 vs 18.4 months, respectively; $P<.001$)[96] More recently, a multicenter phase 2 trial assessing HAI FUDR combined with systemic gemcitabine and oxaliplatin (GemOx) in unresectable IHC was published by Cercek et al. [97]A response rate of 58% and an excellent disease control rate of 84% in the primary tumor was demonstrated at 6 months. More recently, the combination of intraarterial 5-FU and oxaliplatin also showed some activity in a phase 2 trial in which 37 patients with locally advanced biliary tract malignancies (32 ICC; 1 EHC; 4 gallbladder cancer) were included. In this trial, the response rate, PFS, and OS were 16%, 6.5 months, and 13.5 months, respectively.[98]

Summary /Discussion

CRC is a major public health problem throughout the world, and the liver is the most common site of metastatic spread and the main driver in terms of prognosis in the majority of patients. Great advances have been made with the use of liver directed therapies such as HAI chemotherapy when incorporated into the treatment paradigm. The role of HAI chemotherapy in CRLM is now well established by numerous prospective and retrospective studies.

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 offering the patients the chance for cure with the use of HAI and systemic therapy versus systemic therapy alone. In patients who receive HAI in the adjuvant setting after liver surgrey, HAI therapy given with systemic chemotherapy can increase disease free survival and hepatic disease free survival. In summary, HAI with systemic chemotherapy is

a reasonable treat- ment option in select patients with oligometastatic disease to the liver in order to achieve improved outcomes.

Administration and delivery of HAI therapy can certainly be complex which explains in large part its relatively infrequent use in the global oncology community to date. It is important to stress the value and inherent need of a dedicated multidisciplinary infrastructure incorporating all aspects of HAI management such as surgical, medical, radiologic, and nursing to run a successful HAI program. In recent years, the potential of HAI therapy is being increasingly acknowledged and more centers in the United States and Europe are emerging as advocates in the field, with several phase II and phase III trials underway currently.

Future directions in the field will entail refinements in the patient selection process, including the identification of those patients likely to benefit from HAI through the identification of molecular markers as well as the inclusion of increasing data of molecularly-driven systemic therapies into clinical trial design. Furthermore, a key component to progressing the field is the establishment of multi-institutional registries comparing combination hepatic arterial infusion regimens with not only systemic chemotherapy alone, but also with alternative liver-directed treatment approaches (eg, yttrium-90 radioembolization and transarterial chemoembolization) increasingly used in CRLM, in an effort to improve survival, in a patient group with an inherently poor prognosis.

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Key Points-

1. The liver is the most common site for metastases from colorectal cancer, occurring in more than 60% of patients and represents the main prognostic driver.
2. Systemic chemotherapy alone is non-curative, with 2-year survival rates of approximately 40%.
3. The management of colorectal cancer liver metastases (CRLM) continues to evolve, with surgery, where feasible, the preferred therapeutic strategy. Less than 15–20% of patients however are deemed resection candidates at presentation.
4. HAI chemotherapy is delivered with the goal of converting patients to resection, reducing the risk of recurrence, treating recurrent disease and most importantly improving overall survival.
5. Hepatic arterial infusion therapy with FUDR and dexamethasone is safe and effective when administered in combination with systemic chemotherapy for the management of CRLM.
6. In patients with unresectable CRLM, combination HAI with systemic chemotherapy can convert approximately 50% of patients to resection even in the setting of prior therapy.
7. In patients with refractory disease, response rates are in the 30% range with a median survival of 20 months.
8. In patients given adjuvant HAI and systemic therapy after liver resection, a recent update of protocol patients demonstrated a five-year overall survival rate of 78% for this combination approach when adjuvant HAI FUDR was used with modern systemic chemotherapy combinations.

Table 1:

Algorithm for HAI FUDR dose reduction

Liver enzymes	**Reference Value**	**% FUDR Dose**
AST (at pump emptying or day of planned re-treatment, whichever is higher)	0 to <2 x reference value	100%
	2 to <3 x reference value	80%
	3 to < 4 x reference value	50%
	> 4 x reference value	Hold
Alk Phos (at pump emptying or day of planned re-treatment, whichever is higher)	0 to < 1.2 x reference value	100%
	1.2 to <1.5 x reference value	50%
	>1.5 x reference value	Hold
Tbili (at pump emptying or day of planned re-treatment, whichever is higher)	0 to < 1.2 x reference value	100%
	1.2 to <1.5 x reference value	50%
	>1.5 x reference value	Hold
Recommencing FUDR treatment after Hold		
Reason for Treatment Delay	**FUDR resumed when value has returned to:**	**% FUDR dose**
AST elevation	2 x reference value	25% of last dose
Alk phos elevation	1.2 x reference value	25% of last dose
Tbili elevation	1.2 x reference value	25% of last dose

HAI, hepatic arterial infusion; FUDR, floxuridine; AST, aspartate aminotransferase; Alk phos, alkaline phosphatase; Tbili, total bilirubin.

Table 2:

Recent studies of hepatic artery infusion chemotherapy with systemic therapy for Unresectable colorectal cancer liver metastases

Author	Study Design	Sample Size	HAI Drug	Systemic	Response Rate	Conversion to Resection
D'Angelica (78) *	Phase II	49	FUDR	Oxaliplatin/irinotecan/bevacizumab or irinotecan/5FU/Lv/bevacizumab	76%	47%
Levi (79)	Phase II	64	Irinotecan/oxaliplatin/5FU	Cetuximab	40.6%	29.7%
Lim (80)	Retrosp ective	61	Oxaliplatin	5FU/Lv or 5FU/bevacizumab or 5FU/anti-EGFR	21.3%	16.4%
Pak (81) *	Phase II	64	FUDR	Oxaliplatin/irinotecan or 5FU/Lv/irinotecan/bevacizumab	73%	52%

HAI, hepatic arterial infusion; FUDR, Floxuridine; 5FU, Fluorouracil; Lv, leucovorin; EGFR, epidermal growth factor;

*same trial including an update and expansion

Data from Refs [78–81]