



REVIEW ARTICLE – HEPATOBILIARY TUMORS

The Landmark Series: Hepatic Arterial Infusion Pump Chemotherapy for Colorectal Liver Metastases and Intrahepatic Cholangiocarcinoma

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ABSTRACT

Background. Hepatic arterial infusion pump (HAIP) chemotherapy delivers continuous locoregional chemotherapy directly to the liver, maximizing intrahepatic tumor exposure while minimizing systemic toxicity. Originally developed at Memorial Sloan Kettering Cancer Center, HAIP chemotherapy with floxuridine is increasingly used for colorectal liver metastases (CRLM) and intrahepatic cholangiocarcinoma (iCCA). This paper presents a review of phase II and III trials, retrospective studies, and ongoing prospective trials was conducted to evaluate the efficacy of HAIP floxuridine combined with systemic regimens in patients with unresectable and resectable liver-confined CRLM and iCCA.

Results. In unresectable CRLM, HAIP yields conversion rates between 20 to 55% resulting in 5-year overall survival (OS) up to 50%. In the setting of adjuvant HAIP after resection of CRLM, a first large randomized controlled trial (RCT) showed a 2-year OS of 86% compared with 72% in patients with adjuvant systemic therapy alone. In a second RCT, the median OS was 47 months after HAIP with systemic chemotherapy versus 34 months without adjuvant chemotherapy. For unresectable iCCA, studies have found

a response rate of 21% and a 3-year OS of 3% following systemic therapy alone (ABC trials), while outcomes for patients receiving HAIP chemotherapy combined with systemic therapy have included response rates up to 58% and 3-year OS up to 43%.

Conclusion. Hepatic arterial infusion pump floxuridine is an effective locoregional treatment that improves survival in patients with liver-confined CRLM and iCCA. Confirmation from ongoing RCTs is awaited to define its role alongside evolving systemic therapies.

Hepatic arterial infusion pump (HAIP) chemotherapy delivers chemotherapy directly to the liver via a subcutaneous pump, enabling continuous administration and percutaneous refilling. Developed at Memorial Sloan Kettering Cancer Center in the 1980s, HAIP is now increasingly adopted in cancer centers across the United States and, more recently, Europe.

Hepatic arterial infusion pump chemotherapy is based on two key principles: (1) liver tumors primarily receive blood from the hepatic artery rather than the portal vein, and (2) the chosen chemotherapeutic agents undergo extensive first-pass metabolism, allowing high doses with minimal systemic toxicity.^{1–3} Floxuridine, the preferred agent, is metabolized to 5-fluorouracil and has a 95% first-pass effect, resulting in near-undetectable systemic levels (<10 ng/l).^{4,5} This allows for a 200-fold to 400-fold increase in tumor exposure with negligible systemic toxicity.⁵

COLORECTAL LIVER METASTASES

Hepatic arterial infusion pump chemotherapy is primarily used for colorectal liver metastases (CRLM) and intrahepatic cholangiocarcinoma (iCCA). It is a locoregional treatment that is administered in combination with standard systemic treatment. Hepatic arterial infusion pump chemotherapy is primarily used for liver-confined unresectable disease. For CRLM, it is also applied in the adjuvant setting. Phase II and III trials have demonstrated favorable progression-free survival (PFS) and overall survival (OS) with HAIP plus systemic chemotherapy compared with systemic chemotherapy alone.⁶⁻⁹ This “Landmark series” manuscript summarizes existing evidence and ongoing trials exploring HAIP chemotherapy with floxuridine.

Colorectal cancer (CRC) is the second-leading cause of cancer-related death worldwide, with ~50% of patients developing CRLM.¹⁰ Liver resection and ablative therapies offer the only potential cure, resulting in 10-year survival rates of 25%.¹¹ However, up to 75% of patients develop recurrence, predominantly in the liver.^{11,12} Colorectal liver metastases are often unresectable and may remain unresectable after systemic treatment. While adjuvant systemic therapy has demonstrated improvements in progression-free survival (PFS) among patients with resectable CRLM, evidence from three randomized controlled trials (RCTs) indicates that perioperative chemotherapy does not confer a significant overall survival benefit in this setting.^{12-14,15,16} In both settings, patients could benefit from locoregional chemotherapy to treat unresectable or micrometastatic disease.^{13,14}

Induction HAIP in Unresectable CRLM

Hepatic arterial infusion pump chemotherapy for unresectable CRLM primarily aims to convert unresectable CRLM to resectable disease. When a complete resection remains unfeasible, disease control is often achieved and can extend OS.

In a phase II trial, D’Angelica et al. treated 64 patients harboring unresectable CRLM with HAIP combined with systemic chemotherapy.^{13,14} Despite a median of 14 tumors and two-thirds having previously received systemic chemotherapy, long-term results show that 52% of patients underwent a complete resection after HAIP chemotherapy.¹⁴ Accordingly, overall response rates were 73% for all patients and a staggering 86% for chemotherapy-naïve patients. The 5-year OS was 36% in all patients and 51% in chemotherapy-naïve patients.¹⁴

Inspired by these promising results, the PUMP-IT trial aimed to replicate these results in the Netherlands. This phase II study investigated the feasibility of HAIP combined with systemic chemotherapy for patients with liver-only, borderline resectable or unresectable CRLMs.¹⁷ Thirty-one

patients were enrolled with a median of 13 tumors and received HAIP chemotherapy with floxuridine in addition to systemic FOLFOX or FOLFIRI. The primary endpoint of feasibility was met in 90% of patients (defined as two cycles of HAIP and systemic therapy). The disease control rate at 6 months was 79% and 9 patients (30%) underwent surgical resection.¹³ Figure 1 illustrates the radiologic response observed in patients treated with HAIP floxuridine.

A retrospective study of MSKCC investigated 58 consecutive patients who received HAIP for unresectable CRLM, without prior systemic treatment.¹⁸ A total of 55% of patients underwent a complete response or conversion to resection after a median of seven cycles of systemic therapy and four cycles of HAIP. For the entire cohort, the median OS was 53.0 months and the 5-year OS was 45%. A complete pathological response after resection was found in seven patients (22%). These results compare favorably to outcomes of patients with unresectable CRLM after systemic treatment alone.¹⁹⁻²¹

More recent publications outside Memorial Sloan Kettering showed conversion rates between 20 and 30%.^{22,23} Duke University published a large retrospective study of HAIP chemotherapy in 102 patients with unresectable CRLM.²³ Despite patients received a median of 12 cycles of systemic treatment before HAIP placement, 20% underwent complete resection following HAIP chemotherapy. The median OS from pump implantation was 38 months. Northwestern published their pilot in which 23 patients with unresectable CRLM with a median of 10 (interquartile range [IQR] 6–15) preoperative liver metastases were treated with HAIP floxuridine with concomitant systemic chemotherapy.²² Of 23 patients, seven (30%) were converted to a resectable disease and underwent complete resection.

Two ongoing randomized controlled trials (RCT) are investigating systemic treatment with or without HAIP chemotherapy with floxuridine in patients with unresectable CRLM. The United States multicenter trial enrolls patients after 3 to 6 months of first-line systemic treatment without disease progression (*NCT05863195*). The PUMP-IT Trial is the Dutch nationwide trial, including only chemotherapy-naïve patients (*NCT06857773*). The primary endpoint of both RCTs is overall survival (Fig. 1). Table 1 provides an overview of all prospective trials.

Adjuvant HAIP in Resectable CRLM

Two RCTs have investigated the use of adjuvant HAIP chemotherapy for CRLM. The first RCT, conducted at MSKCC, randomized 156 patients following surgical resection of CRLM to HAIP + 5-FU versus 5-FU alone.²⁴⁻²⁶ The primary outcome of 2-year OS was 86% versus 72% ($p = 0.03$) and the median PFS was 31 months versus 17 months ($p = 0.02$), both favoring HAIP. The second RCT,

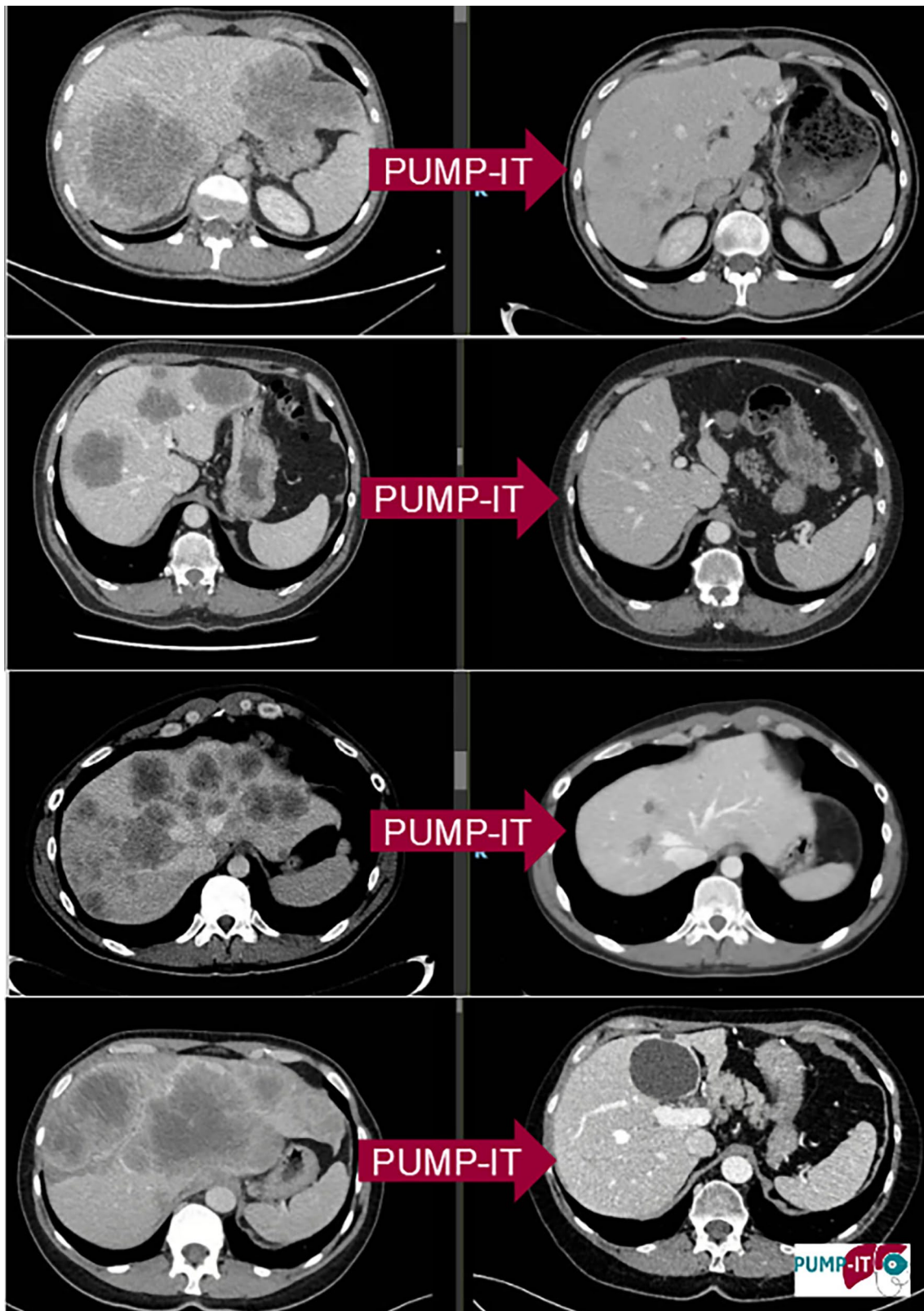


FIG. 1 Radiologic response in unresectable patients treated with HAIP (Krul et al.¹⁷). Left panel: Radiologic imaging of liver metastasis prior to treatment with HAIP floxuridine. Right panel: Radiologic response of liver metastases after 6 months of treatment of HAIP floxuridine

TABLE 1 Overview of all published and ongoing prospective trials investigating HAIP chemotherapy in colorectal liver metastases

	Inclusion period	Type of study	Country	N	Treatment	Status
<i>HAIP for unresectable CRLM</i>						
Kuhlmann (PUMP-IT RCT) <i>NCT06857773</i>	2024-current	RCT	The Netherlands	306	HAIP with systemic chemotherapy (FOLFOX/FOLFIRI)	<i>Ongoing</i>
Lidsky (The PUMP trial) <i>NCT05863195</i>	2023-current	RCT	USA	408	HAIP with systemic chemotherapy (FOLFOX/FOLFIRI)	<i>Ongoing</i>
Victory ²⁹	2022-current	Phase II	USA	24	HAIP with systemic chemotherapy (FOLFOX/FOLFIRI)	<i>Ongoing</i>
Lassen (Excalibur 2) <i>NCT06313203</i>	2021-current	RCT	Norway	45	HAIP with systemic chemotherapy vs. systemic chemotherapy	<i>Paused</i>
Lassen (Excalibur 1) <i>NCT06313203</i>	2021-current	RCT	Norway	45	Systemic chemotherapy with Liver-TX vs. systemic chemotherapy with HAIP vs. Systemic chemotherapy	<i>Paused</i>
Kuhlmann (PUMP-IT) ¹⁷	2021-2023	Phase II	The Netherlands	31	HAIP with systemic chemotherapy (FOLFOX/FOLFIRI)	Published
Hernandez <i>NCT03366155</i>	2019-current	Phase II	USA	23	HAIP with systemic chemotherapy	Completed
Yuhing <i>NCT03493061</i>	2018-2022	Phase II	China	60	HAIP with CPT-11	Completed
D'Angelica ¹³	2007-2010	Phase II	USA	49	HAIP with systemic chemotherapy	Published
<i>Adjuvant HAIP in resectable CRLM</i>						
Grunhagen (PUMP Recurrence) <i>EudraCT: 2019-003966-42</i>	2021-2023	Phase II	The Netherlands	45	Adjuvant HAIP	Completed
Groot Koerkamp (The PUMP trial) ²⁷	2019-current	RCT	The Netherlands	230	Adjuvant HAIP	<i>Ongoing</i>
Groot Koerkamp (PUMP pilot) ³⁰	2018-2019	Phase II	The Netherlands	40	Adjuvant HAIP	Published
Kemeny ²⁴	1990-1997	RCT	USA and Australia	109	HAIP and systemic 5-FU	Published
Kemeny ²⁵	Not reported (Published 1999)	RCT	USA	156	HAIP with systemic chemotherapy fluorouracil, with or without leucovorin	Published

N number; RCT Randomized controlled trial; CPT-11 irinotecan; HAIP Hepatic arterial infusion pump; RCT Randomized controlled trials; 5-FU Fluorouracil

a multicenter trial, randomized 109 patients to HAIP with floxuridine plus systemic 5-FU or versus no adjuvant treatment.²⁴ The recurrence-free rates at 4 years were 46% with HAIP chemotherapy versus 25% without ($p = 0.04$), consistent with prior findings. The median OS was 47 months after HAIP with systemic chemotherapy versus 34 months without adjuvant chemotherapy.

One major criticism of HAIP chemotherapy has been the assumption that modern systemic regimens, such as oxaliplatin- or irinotecan-based therapies, render HAIP obsolete. To address this, a large retrospective study at Memorial Sloan Kettering Cancer Center ($N = 2,368$; 1992–2012) evaluated outcomes in patients who underwent resection of colorectal liver metastases followed by either systemic chemotherapy alone or systemic chemotherapy combined with adjuvant HAIP using floxuridine.⁷ After propensity score matching,

adjuvant HAIP was associated with significantly longer overall survival (adjusted hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.59–0.76; $p < 0.001$). Importantly, the survival benefit persisted even among patients treated after 2003 with modern systemic regimens, such as FOLFOX and FOLFIRI (median OS 67 vs. 47 months, $p < 0.001$). Sub-group analyses revealed particularly striking improvements in patients with low clinical risk scores (median OS 89 vs. 53 months, $p < 0.001$) and in node-negative patients (129 vs. 51 months, $p < 0.001$). These findings, together with prior randomized trials, consistently support the integration of HAIP chemotherapy as an effective adjuvant strategy to improve long-term outcomes following curative-intent resection of colorectal liver metastases.

The ongoing Dutch PUMP trial enrolls patients with resectable CRLM and a low CRS of 0 to 2.²⁷ Up to 230

patients will be randomized to resection alone or resection plus adjuvant HAIP with floxuridine. Neither arm will receive systemic therapy, because this is not the standard of care in the Netherlands. Initial results are expected in 2026.

HAIP for Recurrent CRLM

Adjuvant HAIP may also improve OS after complete resection and/or ablation of recurrent CRLM. A retrospective study of recurrent CRLM (n = 374) found a median hepatic disease-free survival of 46 versus 18 months and OS of 89 versus 57 months ($p = 0.002$) in HAIP vs. non-HAIP groups.²⁸ Five-year OS was 66% versus 47% ($p = 0.001$).

The ongoing phase II Dutch PUMP- III trial is the first prospective, non-randomized trial that investigates HAIP in patients with recurrent, liver-confined CLRM. In this single-arm multicenter trial, patients received HAIP Floxuridine after repeat resection and/or ablation. All 45 patients have completed treatment and initial results are expected in 2025 (*EudraCT number: 2019-003966-42*).

INTRAHEPATIC CHOLANGIOCARCINOMA

Intrahepatic cholangiocarcinoma (iCCA) is a biliary tract cancer arising from the epithelial cells of the intrahepatic bile ducts. Intrahepatic cholangiocarcinoma is the most common primary liver cancer after hepatocellular carcinoma. Because of its rising incidence, it is currently the most common biliary tract cancer.^{31,32} Patients often present with non-specific symptoms, such as abdominal pain, weight loss, and fatigue. If the tumor is growing towards the liver hilum, patients may also present with jaundice. Only approximately 15% of patients are eligible for curative resection, because the disease is often diagnosed at an advanced stage.³³

Gemcitabine with cisplatin has long been the standard of care for patients with advanced biliary cancer.³² A subgroup analysis of the ABC trials examined the effects of systemic chemotherapy with gemcitabine plus cisplatin in patients with unresectable iCCA confined to the liver. They found a response rate of only 21% and a 3-year OS of 3%.³² This has

long represented the benchmark for additional locoregional treatments that aim to further improve OS. More recently, two RCTs investigated the addition of immunotherapy to the backbone of gem-cis in patients with advanced biliary tract cancer. The TOPAZ-1 trial found a further improvement in OS with the addition of durvalumab to gemcitabine with cisplatin (HR 0.76, 95% CI 0.64–0.91).^{34,35} The Keynote-966 trial found an improved median OS with the addition of pembrolizumab compared with gemcitabine and cisplatin alone (HR 0.83, 95% CI 0.72–0.95).³⁶ Both trials have not reported mature OS at 3 years or OS for the subgroup of patients with iCCA; however, the new benchmark for 3-year OS is likely increased to approximately 15% (Table 2).

Induction HAIP Therapy in Unresectable iCCA

Approximately half of all patients with advanced iCCA have disease confined to the liver.³⁷ A large study of MD Anderson showed that most patients (>70%) with iCCA, regardless of stage and treatment, die from disease progression in the liver.³⁸ Moreover, patients with advanced iCCA in the ABC trials had the same OS curves whether they had liver-confined or extrahepatic disease. This provides the key rationale for considering locoregional therapies, including HAIP chemotherapy in patients with advanced iCCA.³⁷

In a comprehensive meta-analysis, the efficacy and safety of HAIP chemotherapy in patients with unresectable iCCA has been investigated.³⁹ A total of 12 studies were analyzed with 154 patients after excluding overlapping cohorts. No RCT has been published, and only three studies were phase II trials. Patients treated with HAIP chemotherapy combined with systemic chemotherapy had a pooled 3-year overall survival of 40%. This compares favorably to the 3% for patients who received systemic chemotherapy alone.^{39,40}

Hepatic arterial infusion pump chemotherapy has been investigated in four nonrandomized phase II trials for unresectable iCCA, of which three were performed at MSKCC.^{6,8,9} The most recent PUMP-2 from the Netherlands was presented at ASCO-GI in 2024.⁴¹ These four phase II trials are summarized in Table 2 and compared with the

TABLE 2 Phase II trials HAIP chemotherapy for liver-confined iCCA vs. gemcitabine-cisplatin in the ABC trial

	Jarnagin ⁸	Kemeny ⁹	Cercek ⁶	Groot Koerkamp ⁴¹	Lamarca/ABC trial ³⁷
Year	2009	2011	2020	2024	2020
N	26	18	42	50	32
Response rate	54%	39%	58%	46%	21%
Median OS	30	31	25	23	17
1-year OS	88%	90%	90%	80%	63%
2-year OS	67%	65%	50%	50%	25%
3-year OS	29%	31%	43%	33%	3%

N Number; OS Overall survival

benchmark results of the ABC trials for patients with liver-confined advanced iCCA. These four trials differed in patient and tumor characteristics as well as in treatment regimens. Nevertheless, they all found a consistent response rate of approximately 50% and a consistent 3-year OS of approximately 35%. These results are far superior to the benchmark of the ABC trials. Moreover, they also appear superior to the new benchmark with additional immunotherapy; the TOPAZ-1 and Keynote-966 both have a response rate of less than 25% and a 3-year OS that is approximately 15%, although with immature data. Table 3 provides an overview of all prospective trials.

These promising outcomes led further to an ongoing multicenter and multinational RCT initiated by MSKCC for patients with unresectable iCCA confined to the liver (*NCT01862315*). A total of 164 patient will be randomized to receive either HAIP chemotherapy combined with gemcitabine and oxaliplatin or gemcitabine and oxaliplatin alone. Future studies should investigate HAIP chemotherapy with or without the new standard of care for systemic treatment that includes immunotherapy (Table 3).

Adjuvant HAIP Therapy in Resectable iCCA

Approximately 15% of patients with iCCA undergo a complete resection. Unfortunately, these patients have a risk of approximately 80% recurrence. Approximately half of all recurrence occur only in the liver. Hepatic arterial infusion pump chemotherapy could therefore also improve OS in the adjuvant setting for patients with resected iCCA. This is currently being investigated in the ongoing PUMP IV

trial (EU Clinical trial number: 2024-512105-82-00). This is a multicenter phase II trial conducted in the Netherlands with a sample size of 63 patients. Patients will receive HAIP in addition to resection. The purpose of this trial is to assess effectiveness of adjuvant HAIP chemotherapy with floxuridine in patients with resectable iCCA. The primary endpoint is hepatic recurrence-free survival.

CONCLUSION

Hepatic arterial infusion pump chemotherapy with floxuridine represents a promising locoregional strategy for patients with liver-confined CRLM and iCCA. For unresectable CRLM, multiple prospective studies have demonstrated high response rates, meaningful resection conversion rates, and prolonged overall survival. In the adjuvant setting, randomized trials and a large retrospective analysis have consistently shown a survival benefit when HAIP chemotherapy is added to resection. Similarly, in unresectable iCCA, HAIP combined with systemic chemotherapy has yielded response rates and 3-year overall survival outcomes that significantly exceed those achieved with systemic therapy alone. Ongoing phase II trials investigate the role of HAIP chemotherapy in the adjuvant treatment of resectable iCCA and recurrent CRLM. Despite differences in patient populations and treatment protocols, results have been remarkably consistent across centers and countries. Upcoming randomized controlled trials will be critical in confirming the efficacy of HAIP and defining its role in the modern therapeutic landscape, particularly in the context of evolving systemic regimens.

TABLE 3 Overview of all published and ongoing prospective trial investigating HAIP chemotherapy in cholangiocarcinoma

	Inclusion period	Type of study	Country	N	Treatment	Status
<i>Unresectable iCCA</i>						
Lassen <i>NCT06313203</i>	2025-current	Phase II	Norway	39	HAIP or SIRT, with gemcitabine and oxaliplatin	<i>Ongoing</i>
Jarnagin <i>NCT04891289</i>	2021-current	RCT	USA/ The Netherlands	45	HAIP with systemic chemotherapy	<i>Ongoing</i>
Mayo <i>NCT04251715</i>	2021-current	Phase II	USA	30	Induction systemic mFOL-FIRINOX followed by HAIP with systemic mFOLFIRI	<i>Ongoing</i>
Groot Koerkamp ⁴¹	2020- 2022	Phase II	The Netherlands	50	HAIP with systemic gemcitabine and oxaliplatin	Completed
Cercek ⁶	2013- 2019	Phase II	USA	42	HAIP with systemic gemcitabine and oxaliplatin	Published
Kemeny ⁹	2007–2009	Phase II	USA	18	HAIP with systemic bevacizumab	Published
Jarnagin ⁸	2003–2007	Phase II	USA	26	HAIP with systemic chemotherapy	Published
<i>Adjuvant iCCA</i>						
Groot Koerkamp <i>NCT06888063</i>	2025–current	Phase II	The Netherlands	40	HAIP with systemic gemcitabine and oxaliplatin	<i>Ongoing</i>

N Number; RCT Randomized controlled trial; HAIP Hepatic arterial infusion pump; SIRT Selective internal radiation therapy; iCCA intrahepatic cholangiocarcinoma; IL-2 interleukine-2; mFOLFIRINOX Modified folinic acid, fluorouracil, irinotecan, oxaliplatin; mFOLFIRI Modified folinic acid, fluorouracil, irinotecan

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