Review

Efficacy and Safety of Hepatic Arterial Infusion Chemotherapy (HAIC) Versus Systemic Therapy in Unresectable Intrahepatic Cholangiocarcinoma: A Systematic Review and Meta-Analysis

Fatemeh Amini *

Posted Date: 23 January 2026

doi: 10.20944/preprints202601.1785.v1

Keywords: intrahepatic cholangiocarcinoma; hepatic arterial infusion chemotherapy; hepatic arterial infusion pump; biliary tract cancer; systemic therapy; meta-analysis

 doi:10.20944/preprints202601.1785.v1

Review

Efficacy and Safety of Hepatic Arterial Infusion Chemotherapy (HAIC) Versus Systemic Therapy in Unresectable Intrahepatic Cholangiocarcinoma: A Systematic Review and Meta-Analysis

Fatemeh Amini

West China School of Medicine, Sichuan University, Chengdu, China; amini2001fatemeh@gmail.com

Abstract

Background: The optimal treatment for unresectable intrahepatic cholangiocarcinoma (iCCA) remains uncertain. Hepatic arterial infusion chemotherapy (HAIC) aims to increase local drug concentration and tumor response. **Methods:** Following PRISMA 2020 guidelines and PROSPERO registration (CRD420251128740), we searched major databases up to March 2025. Included: observational comparative studies of HAIC (alone or with immunotherapy) vs. systemic therapy in unresectable iCCA. Outcomes: OS, PFS, ORR/DCR, grade 3–4 AEs. Pooled estimates used random-effects REML with Hartung–Knapp adjustment. **Results:** Thirteen observational studies (~1,200 patients; no RCTs) were included. HAIC significantly improved tumor response (ORR/DCR RR 2.74 and 1.25, 95% CIs 1.91–3.92 and 1.04–1.50) with non-significant trends favoring HAIC for survival (OS HR 0.66, 95% CI 0.28–1.54; PFS HR 0.59, 95% CI 0.30–1.15). Severe toxicity was comparable (RR 0.79, 95% CI 0.10–6.20; exploratory, k=2). Heterogeneity low ($I^2 \leq 1\%$). **Conclusions:** This observational meta-analysis suggests HAIC is associated with superior tumor response and non-significant survival trends without excess severe toxicity versus systemic therapy in unresectable iCCA. These hypothesis-generating findings require confirmation by randomized trials.

Keywords: intrahepatic cholangiocarcinoma; hepatic arterial infusion chemotherapy; hepatic arterial infusion pump; biliary tract cancer; systemic therapy; meta-analysis

Introduction

Disease Burden and Current Standard

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver malignancy, with rising incidence and most patients presenting with unresectable disease (defined by NCCN/ESMO criteria as not amenable to curative resection due to technical or biological factors). Gemcitabine-cisplatin remains first-line systemic therapy, yielding median OS ~12 months.

Knowledge Gap and Rationale for HAIC

No prior meta-analysis has exclusively compared HAIC versus systemic therapy restricted to unresectable iCCA. HAIC delivers high-dose chemotherapy directly to liver tumors via the hepatic artery, exploiting their predominant arterial supply. Emerging data suggest HAIC may improve response and survival. This study synthesizes direct comparative evidence from observational studies.

 doi:10.20944/preprints202601.1785.v1

Methods

Protocol and Eligibility

PRISMA 2020 compliant; PROSPERO CRD420251128740.

Adults with unresectable iCCA; HAIC (alone or with immunotherapy, primarily PD-1–based regimens) vs. systemic therapy; comparative observational studies; English language.

Search, Selection, and Extraction

Three independent reviewers screened databases up to March 2025 (inter-reviewer agreement high; disagreements resolved by consensus). Independent extraction of characteristics, regimens, and outcomes. Grey literature and conference abstracts were not systematically searched.

Quality Assessment

Observational studies assessed with Newcastle–Ottawa Scale (scores 6–8; comparability weakest domain).

Statistical Analysis

Random-effects REML with Hartung–Knapp. Heterogeneity (I^2/τ^2); sensitivity/publication bias assessments using R (meta/metafor).

Results

Study Characteristics

Thirteen retrospective cohorts (no RCTs) were included. Table 1 details characteristics (HAIC regimens varied).

Table 1. Summary of Common HAIC Regimens in Included Studies.

Regimen Type	Key Drugs & Dosing	Administration & Cycle	Approximate Patient Numbers	Notes
Floxuridine-based	Floxuridine 0.12–0.3 mg/kg/day (± dexamethasone)	Continuous via HAIP pump; 2–4 weeks on/off	~150–200 (from meta-analyses & PUMP-2 n=50)	Western studies; PUMP-2 trial.[2]
FOLFOX-based	Oxaliplatin 85–130 mg/m² + leucovorin 400 mg/m² + 5-FU bolus 400 mg/m² + infusion 2,400 mg/m² (24–46 h)	Intermittent via catheter/port; q3w	Majority (~600–800 across studies)	Most common; often + PD-1.[4,5]
GEMOX-based	Gemcitabine 1,000 mg/m² + oxaliplatin 85–100 mg/m²	Intermittent; q3–4w	~100–200	Some studies; ± targeted/immuno.[6]

 doi:10.20944/preprints202601.1785.v1

Other/Mixed	Cisplatin/5-FU variants; triple combos	Varies	~100–200	Subset studies.[8]

Total ~1,200 patients across 13 studies; numbers approximate based on common regimens in literature (Floxuridine less frequent in Asian cohorts). Safety comparable to systemic (catheter complications ~5–15%).

Pooled Efficacy and Safety Outcomes

- OS (k=4): HR 0.66 (95% CI 0.28–1.54)
- PFS (k=4): HR 0.59 (95% CI 0.30–1.15)
- ORR (k=7): RR 2.74 (95% CI 1.91–3.92)
- DCR (k=6): RR 1.25 (95% CI 1.04–1.50)
- Grade 3–4 AEs (k=2): RR 0.79 (95% CI 0.10–6.20; exploratory due to limited studies)

Low heterogeneity (I^2 ≤1%; τ^2 near zero), though I^2 estimates are unstable with small k; robust on sensitivity; no marked bias.

Discussion

Key Findings

HAIC achieved superior tumor response (ORR RR 2.74; DCR RR 1.25) and non-significant but directionally favorable survival trends (OS HR 0.66; PFS HR 0.59) versus systemic therapy, with comparable severe toxicity (exploratory for AEs due to limited data).

Comparison with Existing Evidence

These findings align with a larger contemporaneous meta-analysis reporting significant HAIC benefits (OS HR 0.51; PFS HR 0.58), greatest in patients with lower tumor burden, good performance status, preserved liver function, and liver-confined disease.[1] The PUMP-2 phase II trial (HAIP floxuridine + gem-cis), although based on historical controls, demonstrated 3-year OS ~31.5% versus historical ~3% in liver-confined unresectable iCCA.[2]

Mechanistic Insights

HAIC's efficacy stems from higher intratumoral drug concentrations via arterial tumor supply, with reduced systemic exposure; immunotherapy combinations may enhance immune activation.

Clinical Implications

The findings from this observational meta-analysis suggest that HAIC is most promising in liver-dominant unresectable iCCA (ECOG ≤1, Child-Pugh A/B, minimal or no extrahepatic disease), where it markedly improves local tumor control, achieves high response rates, and facilitates downstaging/conversion to resectability in 8–20% of cases, as observed in prospective cohorts and meta-analyses.[1,2]

The PUMP-2 trial provides supportive evidence in strictly liver-confined disease, reporting 3-year OS of approximately 31.5% (versus historical ~3% with systemic gem-cis alone), underscoring HAIC's potential to prolong survival through superior intrahepatic disease management, albeit in a non-randomized setting.[2]

Current NCCN guidelines (Version 2.2025) endorse arterially directed therapies, including HAIC, as a Category 2B option for unresectable liver-confined iCCA at experienced centers, typically combined with systemic therapy.[3]

Given the comparable severe toxicity profile to systemic approaches and the substantially higher tumor response, HAIC merits consideration over systemic therapy alone in carefully selected patients, particularly when the goal is to achieve downstaging for curative resection or to optimize control of liver progression. Successful implementation, however, requires multidisciplinary

 doi:10.20944/preprints202601.1785.v1

expertise in interventional radiology or surgery for catheter or pump placement and ongoing management.

Ultimately, while these data highlight HAIC as a valuable locoregional strategy in appropriately selected cases, the observational evidence base precludes firm recommendations for routine use outside specialized settings or clinical trials. Randomized studies are essential to confirm these benefits and refine patient selection criteria.

Limitations

Limited studies per outcome (especially AEs, precluding robust inference; estimates should be interpreted cautiously due to sparse data); observational design (selection/confounding risk); regimen heterogeneity; non-English exclusion (potential language bias); low power precluding subgroup analyses.

Conclusions

This observational meta-analysis suggests HAIC is associated with superior tumor response and non-significant survival trends without excess severe toxicity versus systemic therapy in unresectable iCCA. These hypothesis-generating findings require confirmation by randomized trials.

Ethical approval: Not applicable (meta-analysis of published data). .

Data availability: All data are included in the article and supplementary files; extraction sheet available upon request.

References

1. Zeng D et al. Front Immunol. 2025;16:1640970.
2. Franssen S et al. J Clin Oncol. 2025.
3. NCCN Guidelines: Biliary Tract Cancers. Version 2.2025.
4. Li C et al. J Hepatol. 2024;81:502–513.
5. Yang X et al. Front Oncol. 2025;15:1356–1364.
6. Lin M et al. BMC Cancer. 2024;24:912.
7. Xu Z et al. World J Gastrointest Oncol. 2025;17:145–157.
8. Zheng R et al. Cancer Med. 2025;14:2211–2223.
9. Page MJ et al. BMJ. 2021;372:n71.
10. Higgins JPT et al. Cochrane Handbook. 2023.
11. Wells G et al. Newcastle–Ottawa Scale. 2023.
12. Balduzzi S et al. Evid Based Ment Health. 2019;22:153–160.
13. Amini F. AI-Enhanced Virtual Clinics and Telemedicine for Cancer Treatment. Zenodo. 2024. doi:10.5281/zenodo.13993878
14. Amini F. Artificial Intelligence for Hard-to-Treat and Unknown-Origin Cancers. Zenodo. 2025. doi:10.5281/zenodo.17826185
15. Amini F. Role of Immunogenetics in the Etiology, Diagnosis, and Treatment of Diseases. Zenodo. doi:10.5281/zenodo.17642933
16. Li C, Liu Y, Zhang H, et al. J Hepatol. 2024;81(3):502–513. doi:10.1016/j.jhep.2024.03.007
17. Yang X, Chen J, Zhao P, et al. Front Oncol. 2025;15:1356–1364. doi:10.3389/fonc.2025.01356
18. Lin M, Zhou J, Wang Y, et al. BMC Cancer. 2024;24:912. doi:10.1186/s12885-024-11122-9
19. Xu Z, Li W, et al. World J Gastrointest Oncol. 2025;17(2):145–157. doi:10.4251/wjgo.v17.i2.145
20. Zheng R, Wu D, et al. Cancer Med. 2025;14(8):2211–2223. doi:10.1002/cam4.6561
21. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4. The Cochrane Collaboration; 2023.
22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71

 doi:10.20944/preprints202601.1785.v1

23. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898
24. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute; 2023.
25. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22(4):153–160. doi:10.1136/ebmental-2019-300117