



Hepatic arterial infusion pump chemotherapy for unresectable intrahepatic cholangiocarcinoma: a systematic review and meta-analysis

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BACKGROUND

Most patients with intrahepatic cholangiocarcinoma (iCCA) present with advanced disease since the disease is often asymptomatic in earlier stages. The majority are not eligible for curative surgery and overall survival (OS) without treatment is less than 5 months. Approximately 70% of patients with unresectable iCCA die of liver failure. The Advanced Biliary Cancer (ABC) randomized controlled trials established gemcitabine and cisplatin as standard of care for patients with unresectable iCCA, with OS of 16.7 months in the subgroup of patients without extrahepatic disease who were treated with systemic chemotherapy, with no survivors beyond 3 years. The purpose of this systematic review and meta-analysis was to examine survival outcomes for patients with unresectable iCCA receiving hepatic artery infusion (HAI) therapy providing regional delivery of chemotherapy directly to the liver.

METHODS

The literature search resulted in nine published studies addressing OS in iCCA patients receiving HAI therapy. Three studies were phase II clinical trials, one was a prospective dose-escalation study, and the remaining five were retrospective cohort analyses. There were 154 unique patients in these studies and data were pooled for analysis. Patients were included from December 1990 to June 2019 and median follow-up ranged from 29.3 to 43.8 months.

The primary endpoint was OS, reported as a weighted median OS and a pooled OS at 1, 2, 3, and 5 years. One study did not report 3-year OS for a small cohort (n=10) of patients. Thus, the weighted median OS and 3-year OS results are based on 144 patients, while 1- and 2-year OS results are based on 154 patients. A secondary endpoint was progression-free survival (PFS).

RESULTS

The weighted median OS was 29.0 months, ranging from 25.0 to 39.0 months. In contrast, the ABC trials with unresectable iCCA patients receiving systemic chemotherapy alone reported a median OS of 16.7 months. The weighted median PFS was 11.4 months, ranging from 9.0 to 12.8 months.

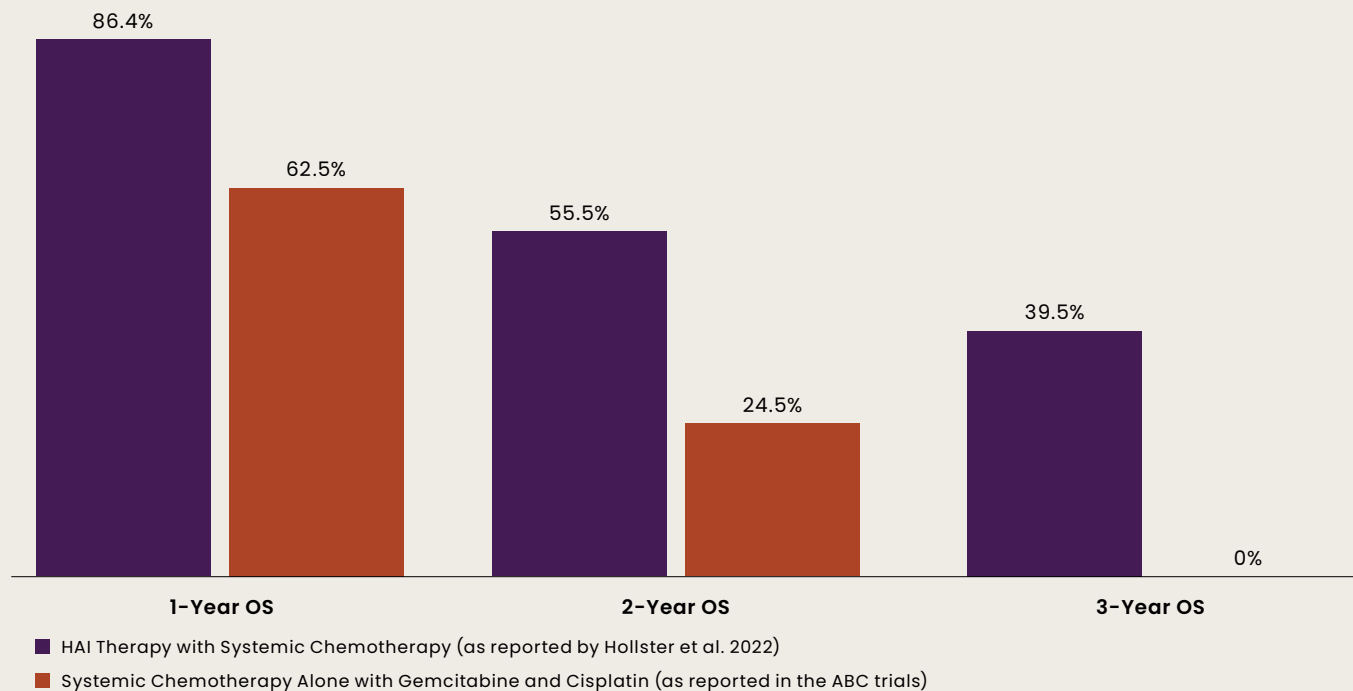
Pooled 1-year OS for patients receiving HAI therapy was 86.4% (95%CI: 81.0-91.8%). For 2- and 3-year OS, the rates were 55.5% (95%CI: 47.8-63.3%) and 39.5% (95%CI: 31.5-47.4%), respectively. Three studies reported 5-year OS rates for 106 unique patients, and the pooled analysis resulted in a 5-year OS of 9.7% (95%CI: 0.0-23.4%). Sensitivity analyses based on only the three phase II prospective trials (N=104) found similar results (weighted median OS = 27.8 months; 1-year OS = 87.5%, 2-year OS = 57.7%, 3-year OS = 36.4%).

Overall Survival and Progression-Free Survival Results for Patients with Unresectable iCCA Receiving HAI Therapy

Median OS	29.0 months	Range: 25.0 – 39.0 months
1-Year OS Rate	86.4%	95%CI: 81.0% – 91.8%
2-Year OS Rate	55.5%	95%CI: 47.8% – 63.3%
3-Year OS Rate	39.5%	95%CI: 31.5% – 47.4%
5-Year OS Rate	9.7%	95%CI: 0.0% – 23.4%
Median PFS	11.4 months	Range: 9.0 – 12.8 months

Patients with unresectable iCCA receiving HAI therapy had superior results when compared to outcomes reported in the ABC trials where patients received systemic chemotherapy alone. While median OS was 12.3 months longer for HAI patients (29.0 vs. 16.7 months), it is the ability of HAI to offer unresectable patients a chance at longer term survival that is perhaps most impressive. While 3-year OS was 39.5% for patients receiving HAI therapy, no patients in the ABC trials survived beyond 3 years.

1-, 2-, and 3-Year Overall Survival for Unresectable iCCA Patients with and without HAI Therapy



LIMITATIONS

- There is a lack of randomized controlled trials to include in the analysis.
- The number of relevant studies and patient counts are small which can result in less precise estimates.
- Most study data originated at a single institution (Memorial Sloan Kettering Cancer Center).

CONCLUSION

The addition of HAI for unresectable iCCA patients offers the possibility of survival beyond 3 years with nearly 39.5% alive 3 years after diagnosis compared to no survivors at 3 years as reported by ABC trials for patients who received systemic chemotherapy alone.

TAKEAWAYS

- This systematic review of 9 publications demonstrated HAI was associated with **substantial improvement in survival for iCCA patients**.
- Patients with unresectable iCCA receiving HAI in addition to systemic chemotherapy had a **39.5% 3-year OS**, while no survivors were reported in the ABC trials, in which only systemic chemotherapy was used.