



Perioperative hepatic arterial infusion pump chemotherapy is associated with longer survival after resection of colorectal liver metastases: a propensity score analysis

Groot Koerkamp, B, Sadot E, Kemeny NE, Gönen M, Leal JN, Allen PJ, Cercek A, DeMatteo RP, Kingham TP, Jarnagin WR, D'Angelica MI / *Journal of Clinical Oncology*. 2017; 35(17): 1938-1944

BACKGROUND

Resection of colorectal liver metastases (CRLM) is associated with prolonged overall survival (OS). Following resection, most patients will develop recurrent disease, with half experiencing initial recurrence in the liver. Hepatic Artery Infusion (HAI) directs chemotherapy through the hepatic artery which provides the majority of the blood supply to CRLM. The chemotherapy used is floxuridine, which has very high first pass extraction in the liver. As a result, infusion of floxuridine into the hepatic artery allows for the high concentrations of the drug in the liver where microscopic disease may persist, with minimal systemic toxicity.

Perioperative systemic chemotherapy following resection of CRLM is generally recommended to delay recurrence, although randomized controlled trials (RCTs) have failed to demonstrate a difference in OS. Hepatic Artery Infusion, however, was previously shown in a RCT to significantly improve 2-year survival compared to systemic chemotherapy alone in patients following CRLM resection. The main criticism of this trial, however, was that it was conducted before the era of modern chemotherapy with irinotecan and oxaliplatin; thus, the intent of this analysis was to evaluate the impact of HAI in the context of contemporary chemotherapy.

METHODS

This real-world evidence study utilized data from the Memorial Sloan Kettering Cancer Center prospectively-maintained liver resection database of 2,368 consecutive patients who underwent a complete resection of CRLM between 1992 and 2012. Overall survival (OS) was compared between patients receiving systemic chemotherapy with and without HAI and was defined as the number of months from first resection of CRLM to death. A subgroup analysis was performed for patients receiving modern systemic chemotherapy (i.e., irinotecan, oxaliplatin), addressing the need to evaluate HAI in the era of modern chemotherapy.

RESULTS

Overall study results, including both older and modern chemotherapy regimens, showed that HAI plus systemic chemotherapy was independently associated with increased OS after CRLM resection compared to systemic chemotherapy alone (67 vs. 44 months, $p < 0.001$).

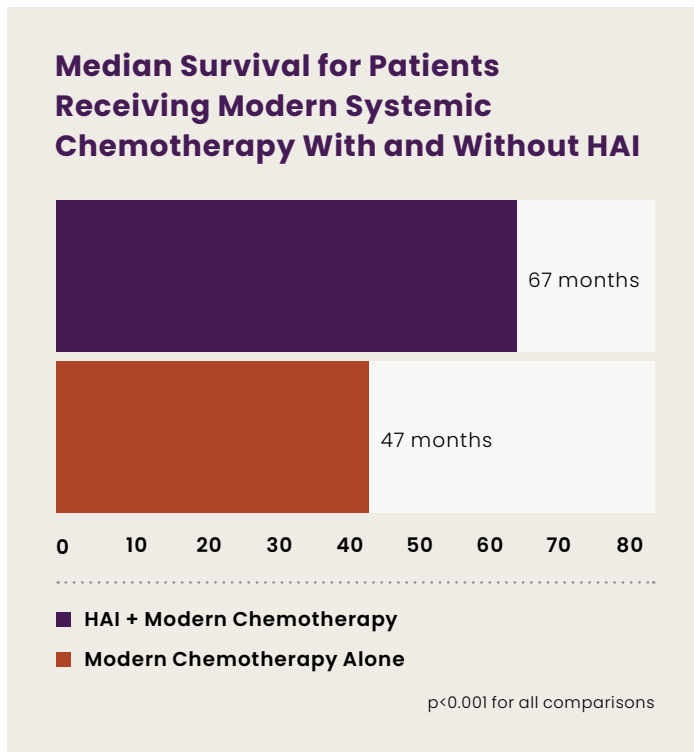
Furthermore, 5-year and 10-year survival rates were 40% and 60% higher, respectively, for HAI patients compared to those who did not receive HAI. Both 5-year (52.9% vs. 37.9%, $p < 0.001$) and 10-year (38.0% vs. 23.8%, $p < 0.001$) survival rates were significantly improved for the HAI therapy cohort. It is important to note that patients in the HAI therapy group had more advanced disease in terms of higher number of tumors, N2 disease, or synchronous CRLM compared to those without HAI. Additionally, those receiving systemic chemotherapy alone were older and more likely to have extrahepatic disease.

Overall Survival for Patients With and Without HAI (includes both, modern and older chemotherapy regimens)

	HAI + Systemic Chemotherapy N=785	Systemic Chemotherapy Alone N=1,583	p-value
Median OS	67 months	44 months	<0.001
5-year survival rate	52.9%	37.9%	<0.001
10-year survival rate	38.0%	23.8%	<0.001

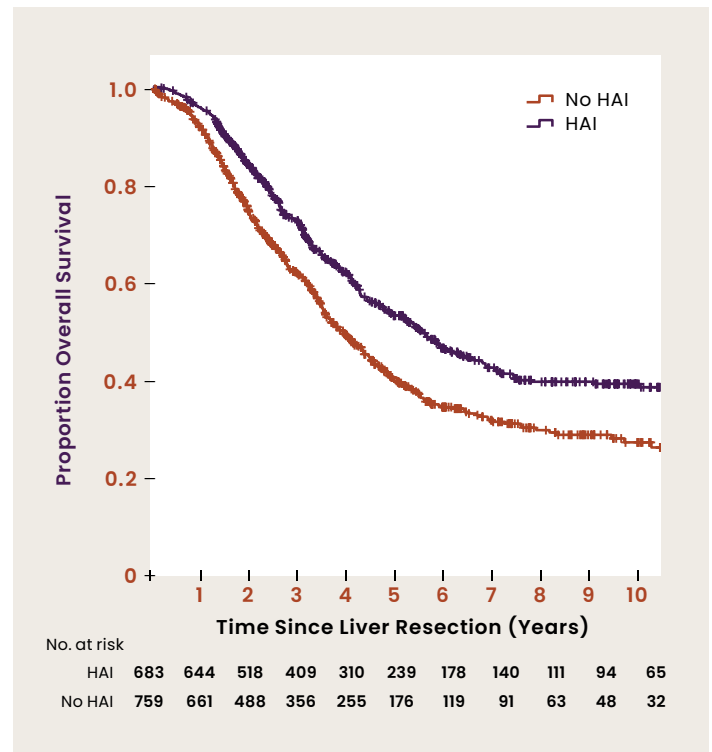
Modern Chemotherapy Subgroup Results

Among the subset of patients (N=1,442) receiving perioperative modern chemotherapy regimens containing irinotecan or oxaliplatin **median OS was 20 months longer for HAI patients** (N=683) compared to those with systemic chemotherapy alone (N=759) (67 vs. 47 months, p<0.001).



Survival Curve for Patients Receiving Modern Systemic Chemotherapy With and Without HAI After CRLM Resection

As seen in the Kaplan–Meier curve, patients treated with HAI plus modern systemic chemotherapy had consistently longer OS over the years of follow-up compared to those without HAI therapy.



LIMITATIONS

This study was not a randomized, controlled trial, therefore, unmeasured prognostic factors could be unbalanced across treatment groups and partly explain the difference in overall survival. The study covers a period of 21 years including the introduction of irinotecan, oxaliplatin, and targeted treatments.

CONCLUSION

Median OS was almost 2 years longer for patients receiving HAI plus systemic chemotherapy after CRLM resection compared to those receiving systemic chemo alone, even though patients in the HAI cohort had advanced disease. After CRLM resection, median OS was significantly improved for patient treated with HAI + modern systemic chemo vs modern systemic chemo alone (67 vs. 47 months, respectively(p<0.001)).

Adjuvant HAI therapy after CRLM resection improved 10-Year overall survival by 60%.

TAKEAWAYS

This study confirms prior RCT III data (Kemeny et. al, NEJM 1999) by demonstrating that the addition of HAI therapy to systemic chemotherapy after CRLM resection improves survival outcomes for patients even in the era of modern chemotherapy.