Adjuvant Transcatheter Arterial Infusion Therapy for Hepatocellular Carcinoma: Not Yet for Everybody

Kevin P. Labadie, MD , and Jonathan G. Sham, MD

Department of Surgery, University of Washington, Seattle, WA

The recurrence of hepatocellular carcinoma (HCC) after curative-intent resection is unfortunately common, occurring in 50–70% of patients within 5 years.^{1–3} The most common distribution of recurrent disease is in the hepatic remnant, accounting for > 80% of recurrences.⁴ Given the propensity for and negative prognostic impact of intra-hepatic recurrence, surgeons and radiation and medical oncologists alike have long pursued strategies to decrease recurrence rates and improve survival in patients undergoing surgery for HCC. To date, multiple local and systemic cytotoxic therapies, catheter-delivered and external beam radiation, and local ablative techniques have been studied in an attempt to decrease the rates of recurrence, however none have been shown to conclusively improve disease-free survival (DFS) or overall survival (OS).⁵ The outcomes of adjuvant transarterial catheter-based therapies after curative-intent hepatectomy remain particularly controversial, with study comparisons confounded by heterogeneous procedural methods, inconsistent patient inclusion criteria, and non-randomized study design. In an attempt to address these shortcomings and provide clarity on this important clinical question, Hirokawa and colleagues performed a thoughtful randomized controlled trial evaluating the effectiveness of adjuvant transcatheter arterial infusion (TAI) and chemoembolization after curative-intent resection for HCC.⁶

In their recent work, Hirokawa and colleagues report long-term outcomes of a randomized control trial comparing adjuvant TAI therapy after initial curative-intent

hepatectomy for HCC with standard-of-care surveillance. Over 100 patients were randomized, with half receiving cisplatin-based adjuvant TAI followed by cisplatin/lipiodol transarterial chemoembolization (TACE), while the other half underwent hepatectomy alone. After a median follow-up of just over 5 years (61.2 months, range 1–84 months), patients in the intervention arm recurred at a statistically similar rate (62%) compared with those who received standard of care (66%). Furthermore, despite being safe and generally well-tolerated, no significant improvement in OS was observed between the two groups at 1, 3, or 5 years post resection. Upon examination of prognostic factors influencing relapse-free survival, low preoperative serum cholinesterase was associated with improved outcomes after adjuvant TAI/TACE, with a 5-year OS rate of 69%, compared with 28% in the control group.

This study elegantly complements a growing body of literature examining the effectiveness of adjuvant transarterial therapies for HCC. TACE is widely used after hepatectomy, particularly in east Asia, where several studies have supported its use.^{7–10} One particularly large phase III trial performed in China randomized 280 patients undergoing hepatectomy for hepatitis B virus-related HCC to either adjuvant TACE or observation.¹⁰ Patients who received adjuvant TACE experienced significantly longer recurrence-free survival and OS compared with those who received no additional therapy. However, survival benefit has not been observed in other studies, particularly in those that examine patients with lower-risk tumors, including smaller size or absence of microvascular invasion.^{11,12} A recent meta-analysis by Chen and colleagues analyzed the results of 40 studies, including over 4800 patients who received adjuvant TACE after curative-intent hepatectomy for HCC. In their analysis, Chen et al. found that adjuvant TACE was associated with improved DFS (hazard ratio [HR] 0.73) and OS (HR 0.71) in the adjuvant setting

compared with hepatectomy alone.¹³ Improvement in survival was most pronounced in patients at intermediate to high risk for postoperative recurrence, including those with tumor diameter > 5 cm, microvascular invasion, and multifocal disease.

The findings from Hirokawa and colleagues contrast with the apparent survival benefits described in these previous studies. Several factors likely play a role in this discordance, however chief among these is the high proportion of included patients with low-risk disease. Seventy-three percent of patients had tumors < 5 cm in size, 78% had no microvascular invasion, and 81% were unifocal. This is in direct contrast to the previously described work by Wang et al.¹⁰ where inclusion criteria mandated patients be either intermediate or high risk (> 5 cm, microvascular invasion, multifocal disease). Additionally, median relapse-free survival in the observation arm was a remarkable 35 months, compared with 6–24 months in previous reports.^{1–3} The ability of any adjuvant therapy to demonstrate clinical benefit with such robust control arm survival is a tall order. Also of note, 10 patients (6 from the control group, 4 from the adjuvant therapy group) were excluded from the per-protocol analysis due to early recurrence, with unclear influence on the outcomes of the study.

The association of low serum cholinesterase with improved relapse-free survival after adjuvant TAI/TACE supports the findings of several previous reports. As an enzyme that reflects hepatic synthetic function, high serum cholinesterase has been associated with favorable long-term survival in patients with recurrence after hepatectomy,^{14,15} as well as improved survival after sorafenib treatment in TACE-refractory intermediate-stage HCC.¹⁶ Since low serum cholinesterase is associated with chronic liver disease, it may reflect parenchyma at higher risk for intrahepatic recurrence or de novo disease, thus identifying a higher-risk population that have been shown to benefit from adjuvant TAI/TACE. Further investigation is warranted to establish the true value of preoperative serum cholinesterase as a predictive biomarker for patients both before and after treatment for HCC.

Finally, the anatomic distribution of adjuvant transarterial treatments remain a troublesome aspect when comparing these studies, and are an area of clinical debate. Adjuvant TAI/TACE to the resection bed is hindered by postoperative arterial anatomic changes and fails to treat the entire hepatic remnant, which is at high risk for tumor development,⁴ while adjuvant whole-liver transarterial infusion treats the entire remnant at lower, and presumably less effective, treatment dose. Several historical studies fail to describe in detail their adjuvant TAI/TACE technique. This difficulty may support the use of systemic therapy in the adjuvant setting for HCC. Although adjuvant sorafenib

failed to improve outcomes in the STORM trial,¹⁷ newer systemic agents (e.g. combination with atezolizumab and bevacizumab) have been shown to be superior to sorafenib in the first-line setting,¹⁸ and are ideal candidates for future adjuvant trials.

The current state of the evidence regarding adjuvant TACE in HCC reflects prevailing themes in oncology: tumor biology and patient selection are the most powerful determinants of therapeutic response. Indeed, in patients at high risk for recurrence after initial resection, mounting evidence indicates that adjuvant liver-directed therapy such as TAI/TACE may mitigate recurrence and prolong survival, however this is likely not the case in patients with lower-risk disease. Further characterization of pertinent patient factors, tumor characteristics, and novel biomarkers impacting treatment response are needed to guide appropriate patient selection for adjuvant therapy in HCC. While further refinement of an adjuvant treatment paradigm for HCC may become more common, Hirokawa et al. have shown that routine use of TAI/TACE after hepatectomy is not quite ready for prime time.

DISCLOSURES Kevin P. Labadie and Jonathan G. Sham declare no conflicts of interest.

REFERENCES

1. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. *Ann Surg*. 2015;261(5):947–55.
2. Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J Am Coll Surg*. 2003;197(5):753–8.
3. Poon RT-P, Fan S-T, Lo C-M, Liu C-L, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma. *Ann Surg*. 1999;229(2):216–22.
4. Baffy G. Decoding multifocal hepatocellular carcinoma: an opportune pursuit. *Hepatobiliary Surg Nutr*. 2015;4(3):206–10.
5. Akateh C, Black SM, Conteh L, Miller ED, Noonan A, Elliott E, et al. Neoadjuvant and adjuvant treatment strategies for hepatocellular carcinoma. *World J Gastroenterol*. 2019;25(28):3704–21.
6. Hirokawa F, Komeda K, Taniguchi K, Asakuma M, Shimizu T, Inoue Y, et al. Is postoperative adjuvant transcatheter arterial infusion therapy effective for patients with hepatocellular carcinoma who underwent hepatectomy? A Prospective Randomized Controlled Trial. *Ann Surg Oncol*. 2020. <https://doi.org/10.1245/s10434-020-08699-w>.
7. Tong Y, Li Z, Liang Y, Yu H, Liang X, Liu H, et al. Postoperative adjuvant TACE for patients of hepatocellular carcinoma in AJCC stage I: friend or foe? A propensity score analysis. *Onco-target*. 2017;8(16):26671–8.
8. Xie H, Tian S, Cui L, Yan J, Bai Y, Li X, et al. Adjuvant transarterial chemoembolization after hepatectomy significantly improves the prognosis of low-risk patients with R0-stage hepatocellular carcinoma. *Cancer Manag Res*. 2019;11:4065–73.
9. Sun JJ, Wang K, Zhang CZ, Guo WX, Shi J, Cong WM, et al. Postoperative adjuvant transcatheter arterial chemoembolization after R0 hepatectomy improves outcomes of patients who have

- hepatocellular carcinoma with microvascular invasion. *Ann Surg Oncol*. 2015;23(4):1344–51.
10. Wang Z, Ren Z, Chen Y, Hu J, Yang G, Yu L, et al. Adjuvant transarterial chemoembolization for HBV-related hepatocellular carcinoma after resection: a randomized controlled study. *Clin Cancer Res*. 2018;24(9):2074–81.
  11. Ye J-Z, Chen J-Z, Li Z-H, Bai T, Chen J, Zhu S-L, et al. Efficacy of postoperative adjuvant transcatheter arterial chemoembolization in hepatocellular carcinoma patients with microvascular invasion. *World J Gastroenterol*. 2017;23(41):7415–24.
  12. Jiang J-H, Guo Z, Lu H-F, Wang X-B, Yang H-J, Yang F-Q, et al. Adjuvant transarterial chemoembolization after curative resection of hepatocellular carcinoma: propensity score analysis. *World J Gastroenterol*. 2015;21(15):4627–34.
  13. Chen W, Ma T, Zhang J, Zhang X, Chen W, Shen Y, et al. A systematic review and meta-analysis of adjuvant transarterial chemoembolization after curative resection for patients with hepatocellular carcinoma. *HPB (Oxford)*. Epub 21 Jan 2020. <https://doi.org/10.1016/j.hpb.2019.12.013>.
  14. Ramachandran J, Sajith KG, Priya S, Dutta AK, Balasubramanian KA. Serum cholinesterase is an excellent biomarker of liver cirrhosis. *Trop Gastroenterol*. 2014;35(1):15–20.
  15. Shimada S, Kamiyama T, Orimo T, Nagatsu A, Asahi Y, Sakamoto Y, et al. Long-term prognostic factors of patients with hepatocellular carcinoma who survive over 10 years after hepatectomy. *J Surg Oncol*. 2020;121(8):1209–17.
  16. Takaki S, Fukuhara T, Mori N, Tsuji K. High cholinesterase predicts tolerance to sorafenib treatment and improved prognosis in patients with transarterial chemoembolization refractory intermediate stage hepatocellular carcinoma. *Mol Clin Oncol*. 2019;12(1):60–8.
  17. Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2015;16(13):1344–54.
  18. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–905.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.