Adjuvant antiviral therapy for the prevention of hepatocellular carcinoma recurrence after liver resection: indicated for all patients with chronic hepatitis B?

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide with an increasing incidence that affects all major demographic groups (1,2). Hepatitis B virus (HBV) infection is a major risk factor and leading cause of HCC development, accounting for approximately 33% of HCC cases worldwide (and up to 2/3 of cases in under-developed countries) (3,4). Although HCC often develops in a background of cirrhosis, HCC can develop in patients with chronic HBV even in the absence of cirrhosis due to active viral replication leading to hepatocarcinogenesis. While several treatment strategies exist for the management of HCC, surgical resection remains the preferred choice for patients with early disease, preserved liver function and appropriate functional status. Unfortunately, surgical resection in patients with underlying chronic HBV infection is associated with a high incidence of recurrence (5,6).

Over the last several years, there has been increasing evidence that antiviral treatment can decrease the incidence and progression of HCC among patients with chronic HBV infection (7-9). Even more promising, antiviral therapy may be critical in preventing HCC recurrence following resection or transplantation of HCC. In 2013, Yin *et al.* reported a randomized controlled trial (RCT) that evaluated the impact of nucleotide/nucleoside analog (NA) treatment on postoperative outcomes of patients with HBV-related HCC. Consistent with their concurrently published observational data, the authors observed a marked decrease in HCC recurrence and HCC-related deaths among patients who received postoperative antiviral therapy. Interestingly, the effect was noted among patients both with high HBV DNA levels ($\geq 10^4$ copies/mL) and low viral DNA levels (10). This study was, however, somewhat limited by the randomization methodology and imbalances between the two groups, making the conclusions less generalizable. Huang *et al.* later re-affirmed these findings through a relatively large single institution RCT. The investigators randomized 200 patients with chronic HBV who had undergone an R0 resection of HCC to either antiviral therapy or no treatment. All patients had good liver function with Child-Pugh class A and no previous HCC treatment or antiviral therapy. The authors reported an improvement in overall and recurrence-free survival (11). Contrary to Yin *et al.*, the study only enrolled patients with high preoperative HBV-DNA levels (>2,000 IU/mL). As such, the impact of antiviral therapy on HCC recurrence in patients with low HBV-DNA remained unclear.

This study by Huang *et al.* (12) sought to answer this question. Specifically, in a recent issue of *Annals of Surgery*, Huang *et al.* reported the results of a single institution RCT evaluating the impact of postoperative antiviral therapy on HCC recurrence and survival following resection of HBV-related HCC. Following margin-negative resection, 200 patients (100 in each arm) with low (<2,000 IU/mL) preoperative HBV-DNA levels were randomized to receive the antiviral agent telbivudine daily versus no treatment.

The patients in the antiviral group had a better 5-year overall (64% *vs.* 44%) and recurrence-free (52% *vs.* 32%) survival, as well as a lower rate of HBV reactivation and a higher rate of undetectable HBV levels on follow-up. Importantly, the antiviral agent was orally administered, inexpensive, and associated with minimal toxicity. Of note, patients who developed HBV reactivation or demonstrated nonresponse to telbivudine were successfully switched to entecavir.

While the role of antiviral therapies in decreasing HCC incidence and recurrence is not a new concept (10,11,13,14), the results reported in this RCT address a very specific population (patients with low serum HBV DNA levels) in which data had been deficient. Furthermore, this study reaffirms several important aspects of the relationship between HBV and HCC carcinogenesis. First, the data confirm the potential for HBV reactivation even in patients with low preoperative serum HBV-DNA levels (15,16). For example, while greater than 70% of the patients in each group had undetectable HBV-DNA levels (<200 IU/mL), reactivation occurred in over 25% of patients who did not receive antiviral therapy. Therefore, low preoperative viral load was neither protective of reactivation nor tumor recurrence. Huang *et al.* (17) previously identified Hepatitis B surface antigen (HBsAg) as a distinguishing factor in HCC recurrence risk among patients with low preoperative HBV-DNA. Similar findings were reported by Sohn *et al.* (18), who noted that HBsAg levels ≥4,000 IU/mL were an independent risk factor of late recurrence. High HBsAg is thought to represent the integrated form of the virus, which might represent more infected hepatocytes, despite low viremia (17). While the exact mechanism of oncogenesis in chronic HBV infection is unclear, viral integration into the host, chronic inflammation and high expression of HBV protein X have been implicated (19). Theoretically, integration and host DNA disruption should be less frequent in patients with low viral counts. However, the presence of high HBsAg, despite low viral counts represents ongoing inflammation and thus increased risk of HCC carcinogenesis. Although HBsAg was not measured in the current study, HBs-Ag could be a potential mitigating factor in predicting late recurrence among patients with low HBV-DNA levels.

The study also highlights the relationship between early and late recurrence of HCC among patients with chronic hepatitis. Similar to the results of antiviral therapy among patients with high preoperative HBV-DNA levels (11), the study by Huang *et al.* demonstrated that antiviral therapy led to reductions in late (>2 years), but not early (<2 years) recurrences. This finding is not necessarily surprising since many investigators have postulated that early recurrence can be associated with tumor-related factors while late recurrence has been related to underlying HBV replication and the development of *de novo* tumors. Indeed, in the current study, early recurrence was associated with more traditional risk factors such as tumor size greater than 5 cm, lack of encapsulation, the presence of satellite nodules, and presence of portal vein thrombus, whereas late recurrence, on the other hand, was also associated with the Ishak fibrosis score and the presence of detectable HBV DNA. These subset analyses suggest that active treatment of HBV can reduce the incidence of new HCC (i.e., late recurrence) while additional oncologic-focused adjuvant strategies may be needed to reduce the incidence of early tumor recurrence.

Huang *et al.* should be congratulated on a well-designed RCT. While previous studies had suggested that patients with HCC and high preoperative HBV DNA levels benefited from postoperative antiviral therapy, the current study affirmed the significant benefits of antiviral therapy even among patients with low (and undetectable) preoperative HBV DNA levels. Future studies should aim to further explore the role of antiviral therapy in the prevention of HBV-related HCC, as well as investigate other adjuvant therapy strategies to reduce the incidence of early recurrence in high-risk patients undergoing liver resection. Given its ease of administration, low cost, favorable side effect profile, and significant improvements in recurrence-free and overall survival, these data add to an existing body of literature supporting the use of postoperative antiviral therapy in all patients with HBV-related HCC undergoing curative intent resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods

and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Where Do We Go? Hepatology 2014;60:1767-75.
3. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: Results from the global burden of disease study 2015. JAMA Oncol 2017;3:1683-91.
4. Maucort-Boulch D, de Martel C, Franceschi S, et al. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. Int J Cancer 2018;142:2471-7.
5. Hung IF, Poon RT, Lai CL, et al. Recurrence of Hepatitis B-Related Hepatocellular Carcinoma Is Associated With High Viral Load at the Time of Resection. Am J Gastroenterol 2008;103:1663.
6. Saab S, Yeganeh M, Nguyen K, et al. Recurrence of hepatocellular carcinoma and hepatitis B reinfection in hepatitis B surface antigen–positive patients after liver transplantation. Liver Transpl 2009;15:1525-34.
7. Papatheodoridis GV, Chan HL, Hansen BE, et al. Risk of hepatocellular carcinoma in chronic hepatitis B: Assessment and modification with current antiviral therapy. J Hepatol 2015;62:956-67.
8. Matsumoto A, Tanaka E, Rokuhara A, et al. Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: A multicenter retrospective study of 2795 patients. Hepatol Res 2005;32:173-84.
9. Singal AK, Salameh H, Kuo YF, et al. Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. Aliment Pharmacol Ther 2013;38:98-106.
10. Yin J, Li N, Han Y, et al. Effect of Antiviral Treatment With Nucleotide/Nucleoside Analogs on Postoperative Prognosis of Hepatitis B Virus–Related Hepatocellular Carcinoma: A Two-Stage Longitudinal Clinical Study. J Clin Oncol 2013;31:3647-55.
11. Huang G, Lau WY, Wang ZG, et al. Antiviral Therapy Improves Postoperative Survival in Patients With Hepatocellular Carcinoma: A Randomized Controlled Trial. Ann Surg 2015;261:56-66.
12. Huang G, Li PP, Lau WY, et al. Antiviral Therapy Reduces Hepatocellular Carcinoma Recurrence in Patients With Low HBV-DNA Levels: A Randomized Controlled Trial. Ann Surg 2018. [Epub ahead of print].
13. Chuma M, Hige S, Kamiyama T, et al. The influence of hepatitis B DNA level and antiviral therapy on recurrence after initial curative treatment in patients with hepatocellular carcinoma. J Gastroenterol 2009;44:991-9.
14. Wu CY, Chen Y, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis b virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 2012;308:1906-14.
15. Lee JI, Kim JK, Chang HY, et al. Impact of postoperative hepatitis B virus reactivation in hepatocellular carcinoma patients who formerly had naturally suppressed virus. J Gastroenterol Hepatol 2014;29:1019-27.
16. Xie ZB, Wang XB, Fu DL, et al. Postoperative hepatitis B virus reactivation in hepatitis B virus-related hepatocellular carcinoma patients with hepatitis B virus DNA levels <500 copies/mL. Onco Targets Ther 2016;9:4593-603.
17. Huang G, Lau W, Zhou W, et al. Prediction of hepatocellular carcinoma recurrence in patients with low hepatitis b virus dna levels and high preoperative hepatitis b surface antigen levels. JAMA Surg 2014;149:519-27.
18. Sohn W, Paik YH, Kim JM, et al. HBV DNA and HBsAg Levels as Risk Predictors of Early and Late Recurrence after Curative Resection of HBV-related Hepatocellular Carcinoma. Ann Surg Oncol 2014;21:2429-35.
19. Ng SA, Lee C. Hepatitis B virus X gene and hepatocarcinogenesis. J Gastroenterol 2011;46:974.

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