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EDITORIAL – HEPATOBILIARY TUMORS

Hepatocellular Carcinoma Recurrence Risk in the Context of Emerging Therapies

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Despite generalized improvements in cancer outcomes over time, hepatocellular carcinoma (HCC) remains one of the deadliest cancers worldwide. The prevalence of primary liver cancer has actually increased the most rapidly of all cancers in the USA.[1] This is likely due, in large part, to nonalcoholic fatty liver disease (NAFLD), which is increasing to epidemic proportions worldwide.[2] This trajectory in NAFLD and HCC mirrors rates of obesity, cardiovascular disease, and diabetes. Conversely, with the development of groundbreaking treatment for hepatitis C viral infections and increased rates of hepatitis B virus vaccination, viral causes of HCC are decreasing.[3]

For early-stage HCC, surgery is the mainstay of treatment. Therefore, it is important to have an understanding of the biology of HCC. For an individual, it is important to clarify the benefits of a potentially major surgery. It is also important to quantify the risks to an individual based on tumor biology. To better understand risk, scoring systems have been developed for HCC, including the Barcelona Clinic Liver Cancer (BCLC) staging system and others.[4,5] A data-driven approach to shed more light on level of risk for recurrence after surgery is increasingly important.

In their article, Yao et al. seek to identify clinical features associated with HCC recurrence, as well as factors affecting survival outcomes for patients with recurrence.[6] This is a large retrospective cohort study with data from 11 hospitals over a period of 15 years. Nearly half of all patients studied developed HCC recurrence. They found preoperative factors associated with recurrence risk included alpha-fetoprotein level > 400 μg/L, tumor size > 5 cm, multiple tumors, satellite lesions, microvascular invasion, and intraoperative blood transfusion. These factors had prior supporting data to indicate their contribution to recurrence risk in HCC.[7–13] The significance of the current study is to validate these risk factors and further elucidate their contribution to post-recurrence survival.

The cohort represented in this multiinstitutional study consists of an exceptionally well-selected subgroup of patients with HCC. The authors report 50% recurrence-free survival at 5 years, which is better than most reported averages.[14] A higher than average proportion of these individuals had HCC in the absence of cirrhosis, and most were virally associated. This raises questions regarding the generalizability of these data to Western populations, considering the rising influence of NAFLD on development of liver disease and HCC. Factors associated with recurrence aligned with previously documented risk factors (e.g., AFP, tumor size, multifocal disease, and vascular invasion). Importantly, the authors also examined early versus late recurrence. Prior to the current study, many general assumptions could be made regarding improved prognosis with late recurrence, but this had not been highlighted with multiinstitutional data. In addition, the authors were able to report survival after recurrence. One major implication from this study is that late recurrence in HCC is often a highly salvageable situation if patients can be surveilled appropriately. While this is an important finding, the authors were unable to put a finer point on whether or not cases of delayed recurrence (greater than 2 years) represent de novo primary malignancy rather than true recurrences. There is a need to better understand multifocality and/or metachronous HCC to tease out true recurrences. Also, survival after surgical resection in HCC is confounded by liver failure as a cause of death. This is a

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major risk factor in those patients with underlying cirrhosis. Given the complexities of de novo cancers, challenges in determining cause of death and other similar issues, studies that help answer these questions are crucial.

In the era of precision oncology, recurrence risk and survival outcomes lie at the forefront of the modern management discussion for HCC patients. Until recently, the promise of effective adjuvant therapies for HCC was limited at best. The STORM randomized phase III trial examined adjuvant sorafenib tyrosine kinase inhibitor therapy versus placebo in resectable HCC patients and found no difference in survival outcomes, with increased morbidity in the sorafenib treatment group.[15] Aside from antiviral therapies, only transarterial chemoembolization (TACE) in patients with microvascular invasion demonstrated promise as an adjuvant therapy, and with limited data to support this practice.[16,17] In 2020, the initial results of the IMbrave150 randomized phase III trial were published. This assessed the effectiveness of a regimen of atezolizumab + bevacizumab versus sorafenib in advanced HCC patients with Child–Pugh class A cirrhosis.[18] This study found a 42% decrease in the hazard ratio for death in patients receiving the atezolizumab + bevacizumab regimen versus treatment with sorafenib. While this study was in unresectable patients, these impressive results have opened the door for several ongoing studies examining the role of immunotherapies in the adjuvant setting following curative-intent resection or ablation. Imbrave050 is currently evaluating postoperative atezolizumab + bevacizumab compared with active surveillance. Other studies include Checkmate9DX (nivolumab versus placebo), Keynote 937 (pembrolizumab versus placebo),[19] Emerald-2 (durvalumab versus durvalumab + bevacizumab versus placebo), and JUPITER 04 (toripalimab versus placebo, China only). Most of these studies will have primary results available in 2023.[20] As such, the role of recurrence risk in the use of emerging HCC therapies is yet to be determined. It will ultimately come down to a combination of the effectiveness of systemic therapies, the risk profile of these therapies, and the ability to identify patients at high risk of recurrence. The current study adds multiinstitutional data to help answer the latter question. As additional therapeutic options become part of adjuvant and neoadjuvant paradigms for HCC, the understanding of recurrence risk must advance in parallel. Emerging technologies, such as circulating tumor DNA (ctDNA), may provide ways to identify minimal residual disease and those at increased risk of recurrence.[21]

This study by Yao et al.[6] has provided useful multiinstitutional data to describe risk factors and patterns of recurrence and post-recurrence survival in HCC. Surgery remains the mainstay of treatment for resectable HCC. As the role of adjuvant or neoadjuvant therapeutic options will become clearer with time, understanding risk and patterns of recurrence will help in determining the optimal use of any potential therapies in the future and potentially point to a tailored risk-based and personalized approach to treatment.

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