Editorial Commentary

Recurrence beyond Milan criteria following liver resection for early-stage hepatocellular carcinoma: incidence, prediction and implications for treatment selection

Diamantis I. Tsilimigras[1], Ioannis Ntanasis-Stathopoulos[2], Dimitrios Moris[3]

[1]Division of Surgical Oncology, Department of Surgery, The Ohio State University, Wexner Medical Center and James Comprehensive Cancer Center, Columbus, OH, USA; [2]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [3]Department of Surgery, The Georgetown University School of Medicine, Washington, DC, USA

Correspondence to: Diamantis I. Tsilimigras, MD, PhD. Division of Surgical Oncology, Department of Surgery, The Ohio State University, Wexner Medical Center and James Comprehensive Cancer Center, 395 W. 12th Ave., Columbus, OH 43210, USA. Email: diamantis.tsilimigras@osumc.edu.

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We read with great interest the article by Fuster-Anglada *et al.* recently published in the *Journal of Hepatology* reporting a single-center experience on histological predictors of aggressive recurrence following liver resection of hepatocellular carcinoma (HCC) (1). The study analyzed a total of 218 patients with Barcelona Clinic Liver Cancer (BCLC) 0 or A HCC who underwent liver resection over the course of two decades [2000–2020] (1). The authors reported a prevalence of aggressive recurrence—defined as recurrence beyond Milan criteria—of as high as 35% with a 5-year survival rate of 81% (1). Among all pathologic features examined, the presence of microvascular invasion and/or satellitosis (mVI/S)—present in 39% of examined tumor samples—was the only independent predictor of recurrence, aggressive recurrence and overall survival (OS) (1). The authors concluded that these findings may have important implications for early-stage patient management, especially in the setting of adjuvant immunotherapy or *ab initio* liver transplantation (1). The authors should be commended for addressing the important issue of recurrence risk stratification following liver resection in early-stage HCC. However, we believe several aspects of the study warrant further discussion and clarification.

First, the authors quote an aggressive recurrence rate (i.e., recurrence beyond Milan criteria) following BCLC-0/A HCC resection of 35%, which appears disproportionately high for a cohort of very early (BCLC-0) or early (BCLC-A) stage HCC (1). Previous studies cited substantially lower rates of recurrence beyond Milan criteria following HCC resection (2-4), even across a broader spectrum of BCLC stages (0, A and B) (2). The authors attributed this finding largely to the presence of mVI/S (39%), yet it remains unclear whether variations in patient selection, surgical techniques or follow-up practices could at least in part account for the observed discrepancy. A comparison with larger cohort studies might provide valuable information and truly characterize the impact of mVI/S on aggressive recurrence rates following early-stage HCC resection.

The study spans a 20-year period during which significant advancements in surgical techniques, histopathologic evaluation and systemic therapies for HCC have occurred. It is unclear whether temporal changes were accounted for in the present analysis. For instance, did advancements in surgical or diagnostic methods influence outcomes over time? Furthermore, over the 20-year period, the BCLC classification system has undergone revisions with the definition of BCLC-A disease revised to include larger tumors (i.e., tumors >5 cm), which were initially considered BCLC-B stage. It is well known that larger tumor size strongly correlates with a higher incidence of mVI with

Table 1 Preoperative factors most strongly associated with non-transplantable recurrence (or recurrence beyond Milan criteria) at first recurrence following liver resection for HCC

Authors	Statistical approach	Preoperative factors
Pelizzaro *et al.* (3) (ITA.LI.CA group)	Traditional methods (i.e., Cox regression)	Tumor size, serum AFP
Lima *et al.* (8)	Traditional methods (i.e., Cox regression)	Serum AFP, ALBI score, radiologic TBS
Altaf *et al.* (9)	Artificial intelligence-based methods (i.e., ensemble model)	Radiologic TBS, serum AFP, NLR

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; HCC, hepatocellular carcinoma; NLR, neutrophil-to-lymphocyte ratio; TBS, tumor burden score.

tumors >5 cm showing almost double the rate of mVI on final pathology compared with tumors <5 cm (5). We are curious whether the authors believe that the changes in BCLC staging criteria over time might have affected the incidence of their main findings, i.e., aggressive recurrence and the presence of mVI/S on pathology.

Another point that needs further clarification is the surveillance protocol employed in the study. The authors reported that surveillance was based solely on ultrasound imaging, which raises concerns about the sensitivity and specificity for detecting extrahepatic or vascular recurrence. It is well known that ultrasound is operator-dependent and limited in its ability to detect subclinical or distant recurrences. Current National Comprehensive Cancer Network (NCCN) guidelines recommend multiphasic, high-quality, cross-sectional imaging [i.e., magnetic resonance imaging (MRI) or computed tomography (CT)] of the chest, abdomen and pelvis as the preferred method for surveillance following HCC resection (6) as these modalities offer superior detection of local and distant recurrences. The authors should clarify the surveillance protocol in their study, whether cross-sectional imaging was used, and whether or not any changes were made to the surveillance protocol over the span of 20 years.

The authors identified mVI/S as the only independent predictor of aggressive recurrence and worse OS in their study. The true clinical applicability of their finding is, however, unclear. Should patients with mVI/S on pathology undergo more intensive surveillance? Should they be considered for *ab initio* liver transplant? Should they be considered for adjuvant immunotherapy? The authors cited the recent, landmark IMbrave050 trial that demonstrated a recurrence-free survival (RFS) benefit with adjuvant atezolizumab and bevacizumab in high-risk HCC (7) suggesting that patients with mVI/S on pathology could perhaps benefit from adjuvant immunotherapy. Nevertheless, in their study, none of the enrolled patients received adjuvant therapy, thus whether or not immunotherapy could provide a survival benefit for these patients was not possible to assess. Additionally, 21 patients with mVI/S in this study eventually underwent transplantation based on the *ab initio* indication; nevertheless, data on long-term outcomes of these patients were not provided. We encourage the authors to provide these outcomes to further elucidate whether transplantation was beneficial in this patient cohort.

Perhaps more importantly, the presence of mVI/S can only be assessed postoperatively, limiting its utility for preoperative decision making. Accurate prediction of recurrence beyond Milan criteria using preoperative factors is critical to inform treatment strategies in the preoperative setting and potentially prioritize transplantation over resection in high-risk patients, avoiding a second morbid operation. Prior studies have utilized traditional statistical techniques and advanced machine learning methodologies to identify preoperative predictors of aggressive recurrence (*Table 1*) (3,8,9). Given the strong correlation between mVI/S and aggressive recurrence in this study, it would be worthwhile to explore preoperative factors associated with mVI/S to enhance clinical applicability in the preoperative setting.

In conclusion, the study provides important insights into histological predictors of aggressive recurrence following early-stage HCC resection with potential implications for adjuvant immunotherapy. We believe that addressing the above points would further strengthen the clinical applicability and robustness of the study findings. Accurate prediction of recurrence beyond Milan criteria following early-stage HCC resection is critical and further efforts should be made to enhance predictability both in the preoperative as well as the postoperative period. Development of such prediction tools can significantly help in the treatment decision making among HCC patients at risk for aggressive recurrence.

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