Editorial

Scoring microvascular invasion in hepatocellular carcinoma: are we meeting the grade?

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Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality and has rising global incidence (1). A perplexing aspect of this disease is the high rate of recurrence (50–70%) after curative-intent, margin negative surgical resection (2). While *de novo* HCC arising from baseline chronic liver injury is a driver of late recurrences, most recurrences occur over a short interval and are thought to be spread from the index malignancy. In this context, a key pathogenic driver of relapse is microvascular invasion (MVI), a process by which malignant cells are shed by the primary tumor into hepatic and portal venous circulation, promulgating distant and intrahepatic metastases, respectively (3). In a series of 454 surgically resected HCC cases, MVI was found to be a more accurate predictor of recurrence and overall survival (OS) than the Milan criteria (4).

Given the prognostic significance of MVI, considerable effort has been invested in defining and characterizing this histopathologic feature. A basic definition for MVI is the presence of malignant HCC cells located within an endothelial-lined vascular lumen in peritumoral hepatic tissue. MVI is identified by microscopic evaluation of surgically resected specimens using standard hematoxylin and eosin (H&E) stain. Importantly, MVI identification is not trivial, with high reported rates of interobserver differences among pathologists (5). Because tissue architecture is required for this diagnosis, needle-based biopsy is not a reliable testing method, and preoperative identification remains a major challenge in the field.

Initially, MVI was characterized as a binary variable (present or absent), but multiple groups have subsequently proposed grading systems to stratify MVI by severity, with the goal of teasing out more accurate prognostic stratification. Variables incorporated into grading schema include diameter of the tumor emboli, number of cancer cells per cluster, distance from the primary tumor edge, number of vessels involved, and embolic features such as adhesion or invasion of the vessel wall (6-10). Most proposed grading systems include permutations of two or three of these variables, and there remains ongoing debate regarding the significance of each variable and the optimal combination (3).

In this issue of *HSBN*, Yao *et al.* present their multi-institutional experience utilizing an MVI grading system proposed by the Liver Cancer Pathology Group of China to prognostically stratify HCC patients treated with margin-negative surgical resection (11). In this study, 227 patients were treated at one of three hepatobiliary centers in China from 2017–2021. All patients had Barcelona Clinic Liver Cancer (BCLC) Stage 0/A disease

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(solitary lesion, no macrovacular invasion, no distant metastases) and successfully underwent curative-intent, margin negative (R0) surgical resection. Patients less than 18 years of age, those treated with neoadjuvant therapy, or those with recurrent disease were excluded. MVI was identified by two senior pathologists according to the Chinese MVI three-tiered grading system (MVI-TTG) (12). In this system, MVI was graded as follows: M0 (no MVI), M1 (1–5 sites of MVI ≤1.0 cm away from the main tumor), M2 (>5 sites of MVI ≤1.0 cm or any MVI occurring >1.0 cm away from the main tumor). Primary endpoints included recurrence-free survival (RFS) and OS.

In this analysis, MVI was identified in 42% of patients (30.4% M1 and 12.1% M2). Five-year OS rates were 60.7% M0, 57.4% M1, 29.7% M2 (P<0.001), and 5-year RFS rates were 44.4% M0, 36.5% M1, and 17.5% M2 (P<0.001). MVI positivity was significantly associated with known adverse biologic traits including larger tumor size, higher preoperative alpha-fetoprotein (AFP) level, presence of satellite nodules, incomplete tumor encapsulation, and poor tumor differentiation. When comparing M0 *vs.* M1 disease on univariate analysis, the authors observed no statistically significant difference in RFS [M1 hazard ratio (HR) =1.29; 95% confidence interval (CI): 1.00–1.93; P=0.058] nor OS (M1 HR =1.22; 95% CI: 0.90–1.86; P=0.089). However, on multivariable analysis, M1 was associated with significantly worse RFS (M1 HR =1.20; 95% CI: 1.03–1.89; P=0.040) and OS (M1 HR =1.28; 95% CI: 1.05–2.07; P=0.035). In contrast, M2 disease was significantly associated with adverse prognosis compared to M0 status on all analyses (adjusted RFS HR =1.67, 95% CI: 1.06–2.64, P=0.027; adjusted OS HR =1.97, 95% CI: 1.15–3.38, P=0.013).

Several interesting observations come from this analysis, and new questions arise. It was unexpected to observe only subtle differences in prognosis between M0 *vs.* M1 groups. Instead, we would have anticipated prognostic clustering between the M1/M2 groups (both MVI positive), with M0 patients faring significantly better. There are two possible explanations for this discrepancy. First, in this analysis, M1 disease was defined as 1–5 sites ≤1.0 cm away from the primary tumor, and approximately 48% of these patients had a negative surgical margin ≥1.0 cm. Therefore, it might be that M1 disease was adequately extirpated with surgical resection alone in most cases. A second possibility is that the biology of M1 disease is more like M0 disease despite both M1/M2 grades being MVI positive. This latter explanation seems less plausible given the tight association between M1/M2 disease with respect to other clinicopathologic variables.

Based on these findings, is taking a larger surgical margin (≥1.0 cm) appropriate to hedge against the possibility of M1 disease in approximately one third of patients? This approach would theoretically treat both M0 and M1 patients, which represented 88% of the cohort in this analysis. In a recent prospective randomized trial comparing narrow (1 cm) *vs.* wide (2 cm) resection margins for HCC, it was demonstrated that a larger margin was associated with significantly lower rates of recurrence and longer survival, though this study was not performed in the context of MVI status (13). Finally, M2 patients did poorly regardless of margin width in this study. While it is possible that larger margins (e.g., ≥2.0 cm) might improve outcomes for M2 disease, we must consider the possibility that this degree of microscopic invasion is beyond the reasonable scope of surgical resection.

We must also question the quality of prognostic stratification provided by the MVI-TTG. While M2 disease (12% of cases) represents a subset of patients that clearly do far worse, over 80% of patients in this study had M0 or M1 disease for which there was minimal prognostic stratification. Would including other variables such as emboli diameter or number of cells improve the quality of prognostic separation in a three-tiered system? The optimal combination of such variables remains undetermined, and further international collaborative efforts are necessary to better address this question.

Like prior analyses, Yao *et al.* show that MVI status is associated with other known adverse clinicopathologic variables. However, the authors do a nice job of further stratifying this information, showing that severe MVI grade (M2) is proportionally associated with these markers, including AFP level, tumor size, and number of satellite nodules. MVI has consistently been shown to be independently associated with survival outcome measures on adjusted analyses regardless of other clinicopathologic markers, suggesting that it uniquely points to a certain aspect of HCC biology. For MVI to occur, cancerous cells must acquire capabilities to disrupt junctions/adhesions, break down extracellular matrix and migrate, and utilize alternative energy sources. These changes are commonly observed with epithelial-to-mesenchymal transition (EMT), a process in which malignant cells dedifferentiate from a polar, adherent phenotype into mobile-mesenchymal states with more aggressive and resilient biology. There is accumulating evidence that the presence of MVI is associated with detection of the EMT phenotype in the primary tumor (14,15). Therefore, it might be that MVI

is both a symptom and a biomarker of tumors undergoing EMT, though further basic and translational research endeavors are necessary to substantiate this relationship.

Finally, a useful insight from this analysis by Yao *et al.* is that MVI grading might be a useful tool for risk-stratifying patients postoperatively to inform surveillance and adjuvant therapy protocols. Specifically, given the abysmal outcomes associated with M2 status, perhaps these patients should be considered for enhanced surveillance protocols and clinical trial enrollment for prophylactic locoregional and systemic adjuvant therapies.

In conclusion, we would like to congratulate the authors on this well designed and executed analysis. The insights from this study support our gradual transition towards a more nuanced interpretation of HCC prognostication that will hopefully inform future translational research endeavors as well as surveillance and adjuvant therapy protocols.

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