Ann Surg Oncol (2023) 30:660–662
https://doi.org/10.1245/s10434-022-12746-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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EDITORIAL – HEPATOBILIARY TUMORS

Optimizing Treatment Strategies with Preoperative Assessment for Microvascular Invasion in Hepatocellular Carcinoma

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As the most common primary malignancy of the liver, hepatocellular carcinoma (HCC) has long been considered a worldwide health crisis. In the USA, after nearly two decades of steady increases in incidence and despite recent trends indicating a stabilization of new occurrences, liver cancer remains the fifth-leading cause of cancer-related death for men and the seventh most common cause of cancer-related death among women.[1] By 2040, it is projected that liver cancer will surpass colorectal cancer to become the third-leading cause of cancer-related death in the USA.[2]

Among patients presenting with potentially curable disease, surgery, either in the form of resection or transplant, remains the mainstay of treatment for patients with HCC, with management decisions largely dictated by degree of underlying liver dysfunction. In efforts to improve individualized risk stratification and guide treatment selection, scoring systems such as the Barcelona Clinic Liver Cancer (BCLC) staging system have been developed and incorporate information about the patient's general health, liver function, and tumor burden to provide an algorithmic approach to treatment.[3] For the 5–10% of patients presenting with early-stage disease and without cirrhosis, surgical resection is associated with long-term survival comparable to that of patients undergoing transplant, achieving 5-year survival rates approaching 70%.[4] Unfortunately, in the absence of effective adjuvant therapy to date, high recurrence risk remains the major Achilles' heel of resection as curative treatment for this disease.

To characterize recurrence risk among candidates for curative-intent resection and improve patient selection, investigations have identified a variety of clinicopathological factors associated with recurrence.[5] Microvascular invasion (MVI), in particular, has been closely linked to more aggressive tumor biology and an important determinant of disease recurrence.[6,7] Unfortunately, identification of this negative prognostic pathologic feature has been limited to the postoperative setting.

In their article, Endo et al. sought to develop and validate a clinical risk prediction tool for identifying risk of MVI in the preoperative setting among patients with HCC.[8] This is a large, retrospective cohort study that included data from 689 patients who underwent curative-intent resection for HCC over a two-decade period from 12 international institutions. Most patients were classified as Child–Pugh A (95.6%) and MVI was detected on final pathology in nearly half (46.9%) of the patients included in the study. Three readily available preoperative characteristics were identified as independently associated with presence of MVI: serum alpha-fetoprotein (AFP), an imaging-based tumor burden score (TBS) incorporating tumor size and number of lesions, and the neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation. After randomly assigning patients in a 1:1 ratio between test and validation

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First Received: 22 August 2022
Accepted: 17 October 2022
Published Online: 30 October 2022

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cohorts, the investigators developed and validated a preoperative clinically based model to predict presence of MVI. On the basis of the *c*-index of the test and validation cohorts (0.71 and 0.72, respectively), the model was determined to be a good discriminator for predicting presence of MVI.

In addition to creating this model, the authors reaffirm the negative prognostic impact associated with MVI, demonstrating that presence of MVI resulted in significantly worse 3-year disease-free survival (DFS) (31.5% versus 52.8%, $p < 0.001$) and 5-year overall survival (OS) (42.4% versus 64.8%, $p < 0.001$). Furthermore, MVI was independently associated with a 35% increased risk of disease recurrence and 66% increased risk of death. Using their model, the authors were able to stratify patients relative to prognosis and demonstrated that patients at high risk of MVI were associated with worse DFS and OS. Interestingly, high MVI risk was associated with a nearly threefold increased risk of early recurrence (within 8 months) and recurrences were more often extrahepatic and at multiple sites. Finally, when stratified by margin status, resection margin did not impact DFS among patients at low risk of MVI; however, R1 resection status was associated with worse DFS among patients at high risk of MVI.

This study raises several important concepts related to optimal risk stratification and treatment selection for patients with potentially curative early-stage HCC. First, although this study provides further evidence demonstrating the negative role of MVI on prognosis among patients with HCC, it is unlikely to alter selection of initial definitive operative treatment. Although the recent update of the BCLC staging system recommends consideration of upfront liver transplant for patients with solitary HCC if high-risk recurrence predictors such as MVI are present,[3] evidence has suggested that MVI is also associated with poor prognosis among patients undergoing transplant and independently associated with disease recurrence.[9] In fact, the negative impact of MVI may actually be worse for patients undergoing transplant compared with resection.[7] Unfortunately, with the majority of recurrences occurring at extrahepatic sites or at multiple sites, they are also frequently outside Milan criteria and not candidates for salvage transplant.[10]

The finding that a positive resection margin was associated with increased risk of disease recurrence among patients at high risk for MVI, but not associated with DFS among low-risk patients, may provide evidence in support of incorporating wider margins into operative planning for high-risk patients. It also supports the role of minimal or R1 margin resection (enucleation) in selected patients with well-defined hepatocellular carcinoma harboring a capsule or a pseudo-capsule.[11,12] Optimal resection margins in HCC remain undefined. The one prospective randomized controlled trial examining this topic compared narrow (1 cm) versus wide (2 cm) resection margins in patients with solitary HCC and found that narrow margins were associated with increased risk of disease recurrence and lower 5-year OS with nearly 30% of recurrences occurring at the resection margin.[13] Conversely, systematic reviews and meta-analyses on this issue have been conflicting.[14,15] Although this study cannot provide recommendations for optimal resection margins in patients at high risk for MVI, it would seem prudent to plan for wider surgical margins and ensure R0 resection in this population of patients.

Finally, this study highlights that among this high-risk population of patients, identifying effective adjuvant therapies will be key to improving outcomes among patients undergoing curative-intent resection for HCC. Adjuvant local regional therapies such as transarterial chemoembolization (TACE)[16] and stereotactic body radiotherapy (SBRT)[17] have shown promise in patients with MVI. On the basis of the initial results of IMbrave150,[18] the role of adjuvant immunotherapy (atezolizumab plus bevacizumab) following curative-intent resection or ablation for HCC is currently under investigation in IMbrave050[19] as well as a host of other emerging therapies.[20] Furthermore, as the use of these therapies begin to be explored in the neoadjuvant setting, this model may find utility as a valuable pretreatment risk stratifying tool to be included in future clinical trial designs.

This international multi-institutional study by Endo et al.[8] provides an easily accessible and user-friendly online clinical tool to determine risk of MVI in patients undergoing curative-intent resection for early-stage HCC. This study highlights the negative impact that MVI portends regarding recurrence and overall prognosis and provides evidence supporting careful operative planning to ensure negative resection margins to reduce disease recurrence. In the future, effective adjuvant therapies will be critical to optimizing outcomes in patients with this marker of aggressive disease biology.

FUNDING No funding was received for this article.

DISCLOSURES The authors have no conflicts of interest to declare.

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