Editorial

Challenges and prospects in prediction and treatment for hepatocellular carcinoma with microvascular invasion

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Microvascular invasion (MVI) is an independent risk factor for early recurrence of hepatocellular carcinoma (HCC) after local treatment as well as poor prognosis in patients with HCC (1-3). MVI is an important factor for management of patients with HCC; however, MVI is based on a histopathological diagnosis using resected surgical specimens and is thus difficult to determine preoperatively. Recently, Lee *et al.* developed a new MVI risk score using the following 4 non-histological parameters: (I) alpha-fetoprotein (AFP); (II) protein induced by vitamin K absence-II (PIVKA-II); (III) arterial peritumoral enhancement on hepatobiliary phase of magnetic resonance imaging (MRI); (IV) peritumoral hypointensity on hepatobiliary phase of MRI (4). They also reported that, in HCC patients with MVI, the HCC recurrence rate was lower in patients treated with hepatic resection than with radiofrequency ablation (RFA) and proposed that patients with HCC who were at high risk of MVI should be treated with hepatic resection rather than RFA (4). This editorial summarizes the recent progress of the prediction method for MVI and discusses the therapeutic strategy for small HCC with MVI.

Imaging modalities are crucial tools to characterize HCC. Especially, MRI with hepatobiliary contrast agents provides important findings regarding biological characteristics of HCC (5). Lee *et al.* previously reported that a combination of two or more of the following findings could be used as a preoperative imaging biomarker for predicting MVI: (I) arterial peritumoral enhancement, (II) a non-smooth tumor margin, and (III) peritumoral hypointensity on hepatobiliary phase of MRI (6) (*Table 1*). For that study, the sensitivity for MVI was reported to be 54.6% (6), which was relatively low. In the recent study by Lee *et al.*, the MVI risk score was based on not only MRI findings but also on serum tumor markers such as levels of AFP and PIVKA-II (4). Although the new prediction model showed higher sensitivity for MVI than the model from their previous study (4), the sensitivity was 65.2% and further improvement is needed. Sumie *et al.* reported that gross classification of HCC (single nodular with extranodular growth type or confluent multinodular type) was useful to predict the presence of MVI (7). Furthermore, Yuan *et al.* reported that long noncoding RNA associated with MVI promoted angiogenesis and predicted poor recurrence-free survival of patients with HCC who underwent hepatectomy (8). Thus, the sensitivity of the MVI prediction model may be improved by the additional use of the gross classification of HCC and detection of the presence of long noncoding RNA (*Table 1*).

Assessment of findings is an issue for the prediction model using imaging modalities. In the recent study by Lee *et al.* MRI findings were assessed by two board-certified radiologists with more than 6 years of experience in abdominal imaging (4). The interobserver agreement values for the arterial peritumoral enhancement and peritumoral hypointensity were 0.91 [95% confidence interval (CI): 0.85–0.96] and 0.81 (95% CI: 0.72–0.89), respectively (4). Thus, there were discrepancies in the assessment of MRI findings between both radiologists, although they had sufficient experience in abdominal imaging. Recently, artificial intelligence has accelerated progress in diagnosis of medical imaging. Radiomics is an innovation in medical

Table 1 Predictive factors for HCC with MVI

Factors	Reference
AFP	(4)
PIVKA-II	(4)
Arterial peritumoral enhancement on hepatobiliary phase of MRI	(4,6)
Peritumoral hypointensity on hepatobiliary phase of MRI	(4,6)
Non-smooth tumor margin	(6)
Gross classification of HCC (single nodular with extranodular growth type or confluent multinodular type)	(7)
Long noncoding RNA	(8)

HCC, hepatocellular carcinoma; MVI, microvascular invasion; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; MRI, magnetic resonance imaging.

imaging analysis in which images are analyzed using an automated high-throughput extraction technique to process large amounts of quantitative features from medical images (9). Radiomics has the advantage of high repeatability, indefatigability, and no interference of human subjectivity (10). Radiomics has been successfully applied to the diagnosis and prognosis prediction of HCC (11). In addition, Feng *et al.* established a radiomics model predicting MVI by extracting radiomics features from the intratumoral and peritumoral regions of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced MRI (12). They used a least absolute shrinkage and selection operator (LASSO) in a logistic regression model to enhance the prediction accuracy and reduce the dimensions of 1,044 features, such that, finally, 10 features were selected to establish the final model. The sensitivity of the radiomics model for MVI was reported to be 88.2% and 90.0% in training and validation sets, respectively (12). Although there are limitations in radiomics, including retrospective studies with a small number of patients, radiomics has been applied to MVI prediction using contrast enhanced computed tomography images as well as ultrasound images (13,14). Further study will be focused on the use of multimodality imaging data for the prediction of MVI.

The recent study by Lee *et al.* demonstrated that the recurrence rate of HCC with MVI was lower in patients treated with hepatic resection than with RFA (4). Their findings are in good agreement with previous reports and hepatic resection should be considered as the first-line therapeutic strategy for small HCC with MVI. However, in HCC patients with MVI, the recurrence rate of HCC is approximately 30% 2 years after hepatic resection (4), indicating that a new therapeutic strategy is required for HCC with MVI. At present, 4 therapeutic options have been reported for HCC with MVI (*Table 2*). First, a high preoperative hepatitis B virus (HBV) DNA level is known to be an independent risk factor of MVI (15); antiviral treatment administered more than 90 days before hepatic resection was reported to reduce the incidence of MVI and early tumor recurrence after hepatic resection for HBV-related HCC (15). Second, a wide margin of hepatic resection (≥1 cm) has been reported to show better 5-year recurrence-free and overall survival rates compared to a narrow margin of hepatic resection (<1 cm) in HCC patients with MVI (16). Third, postoperative adjuvant transcatheter arterial chemoembolization was reported to improve disease-free survival and overall survival for HCC patients with MVI compared to hepatic resection alone (2,17). Fourth, the use of postoperative adjuvant sorafenib therapy was reported to improve overall survival compared to hepatic resection alone for HCC patients with MVI (18) (*Table 2*). Recently, programmed cell death 1 ligand 1 (PD-L1) expression in HCC was reported to be associated with MVI (19), and, therefore, anti-PD-L1 antibody is a hopeful adjuvant therapy after hepatic resection in patients with HCC with MVI. A phase 3 clinical trial, CheckMate 9DX, is now ongoing, which investigates the impact of adjuvant therapy of nivolumab on recurrence-free survival in patients with HCC who are at high risk of recurrence after curative hepatic resection or ablation (NCT03383458) (*Table 2*).

This editorial summarizes the recent progress of prediction methods for HCC with MVI and discusses the therapeutic strategy for small HCC with MVI. The recent study by Lee *et al.* demonstrated a new MVI risk score using MRI findings and tumor markers such as AFP and PIVKA-II. Although the MVI risk score is better than the previous

Table 2 Therapeutic strategies for prevention of HCC recurrence after curative resection of HCC with MVI

Therapeutic strategy	Reference
Preoperative antiviral treatment for HBV	(15)
A wide margin of hepatic resection (≥1 cm)	(16)
Postoperative adjuvant transcatheter arterial chemoembolization	(2,17)
Postoperative adjuvant therapy with sorafenib	(18)
Postoperative adjuvant therapy with nivolumab (phase 3 clinical trial)	NCT03383458

HCC, hepatocellular carcinoma; MVI, microvascular invasion; HBV, hepatitis B virus.

prediction model using MRI findings alone, the diagnostic ability of the MVI risk score requires improvement. In addition, although hepatic resection is the first-line therapy for HCC with MVI, the recurrence rate of HCC with MVI is high even after curative hepatic resection. Thus, a new prediction method and therapeutic strategy need to be developed for HCC with MVI.

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Footnote

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