Review Article

Preoperative prediction of microvascular invasion: new insights into personalized therapy for early-stage hepatocellular carcinoma

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Abstract: Owing to advances in diagnosis and treatment methods over past decades, a growing number of early-stage hepatocellular carcinoma (HCC) diagnoses has enabled a greater of proportion of patients to receive curative treatment. However, a high risk of early recurrence and poor prognosis remain major challenges in HCC therapy. Microvascular invasion (MVI) has been demonstrated to be an essential independent predictor of early recurrence after curative therapy. Currently, biopsy is not generally recommended before treatment to evaluate MVI in HCC according clinical guidelines due to sampling error and the high risk of tumor cell seeding following biopsy. Therefore, the postoperative histopathological examination is recognized as the gold standard of MVI diagnosis, but this lagging indicator greatly impedes clinicians in selecting the optimal effective treatment for prognosis. As imaging can now noninvasively and completely assess the whole tumor and host situation, it is playing an increasingly important role in the preoperative assessment of MVI. Therefore, imaging criteria for MVI diagnosis would be highly desirable for optimizing individualized therapeutic decision-making and achieving a better prognosis. In this review, we summarize the emerging image characteristics of different imaging modalities for predicting MVI. We also discuss whether advances in imaging technique have generated evidence that could be practice-changing and whether advanced imaging techniques will revolutionize therapeutic decision-making of early-stage HCC.

Keywords: Microvascular invasion (MVI); early-stage hepatocellular carcinoma (early-stage HCC); imaging; preoperative diagnosis; clinical decision-making

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Introduction

Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer and due to its increasing incidence and mortality, is gradually becoming a global health problem (1-3). In recent decades, with the advance of imaging techniques, an increasing number HCC cases are being detected at the early stage. Although there are several curative treatments for early-stage HCC according to clinical practice guidelines (4,5), such as surgical resection (SR), liver transplant (LT) and radiofrequency ablation (RA), over half of the patients also experience early recurrence, which is defined as disease reoccurring within 2 years after curative treatments (6). Microvascular invasion (MVI) has been demonstrated to be an essential independent predictor for early recurrence and poor prognosis after surgery (6-8). Currently, the gold standard for MVI diagnosis remains postoperative histopathology, but this lagging indicator does not allow clinicians to select the most effective treatment for early-stage HCC at the time of therapy selection. For instance, if it is unknown whether a patient has MVI beforehand, SR or RA is commonly recommended as first-line treatment option for early-stage HCC when LT is not feasible or when both the enlistment and surgery criteria are met according to the 2022 edition of the Barcelona Clinic Liver Cancer (BCLC) guideline. This is because the local regulations for enlistment and priority policies may preclude effective LT for early-stage HCC until recurrence is apparent. However, if MVI can be preoperatively diagnosed, patients can consider LT for a better prognosis (9). Therefore, a noninvasive method for preoperative diagnosis of MVI would be highly desirable and may lead to LT being prioritized in those with early-stage HCC and MVI, thus optimizing the limited availability of donor organs and maximizing survival benefits.

In recent decades, imaging has gradually advanced and emerged as a valuable approach for noninvasively and preoperatively detecting MVI-derived pathological changes. Therefore, numerous studies on different techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and positron emission tomography (PET), have been conducted to explore their ability to predict MVI. These advancements in imaging for MVI diagnosis have allowed for the transition from relying on subjective qualitative radiologic features to the more accurate quantitative radiomics analysis. This has been achieved via the modeling of simple sequences or techniques and the combination of multiple indexes and different techniques with clinical biomarkers, which has greatly improved the diagnostic efficiency of MVI (10-12). However, although the studies in this field have achieved excellent results, there is still no consistent imaging criteria for MVI diagnosis, which greatly impedes its clinical application.

As MVI status is critical to informing the management of patients with HCC, preoperative prediction of MVI status is crucial. In this review, we summarize the underlying imaging mechanisms of MVI-related pathological changes and available imaging features and highlight the key advancements in imaging for predicting MVI. Through this, we hope to provide the reader with a useful reference regarding the role of imaging in the preoperative diagnosis and therapeutic management of patients with HCC and MVI. Importantly, preoperative diagnosis with MVI may revolutionize individualized treatment planning at the time of therapy selection for those with early-stage HCC.

Definition of MVI

Before 2013, when Rodríguez-Perálvarez *et al.* proposed a definition for MVI in a systematic review (8), there was no uniform definition of MVI in HCC among researchers. Rodríguez-Perálvarez *et al.*'s review defined MVI as the presence of malignant cell nest in vessels, including branches of the arteries, hepatic vein, and portal vein next to the tumor, lined with endothelial cells visible under microscopy. In addition, based on the existing research at the time, they suggested that MVI should include the invasion of small arteries or lymphatic vessels (8). In 2015, China released their first pathology guideline for diagnosing primary liver cancer (13). This guideline recommended that all types of tumor should be sampled based on the seven-point baseline sample collection protocol to ensure the accuracy of primary liver cancer diagnosis (*Figure 1*). It also indicated that all tissue sections should be assessed in evaluating MVI status and that that risk should be stratified according to the number and distribution of MVI as follows: no MVI; low-risk (M1), <5 MVI sites and ≤1 cm away from the tumor; and high-risk (M2), >5 MVI sites or >1 cm away from the tumor (*Figure 1*). The efficacy and accuracy of the sampling protocol and grading scheme was verified by a large-sample study, which recruited 16,144 patients from multiple centers in China (13). However, results from other researchers' indicated that the number of sampling sites and sampling location would affect the detection rate of MVI and lead to false-negative results. Therefore, they concluded that different sizes of tumor require that number

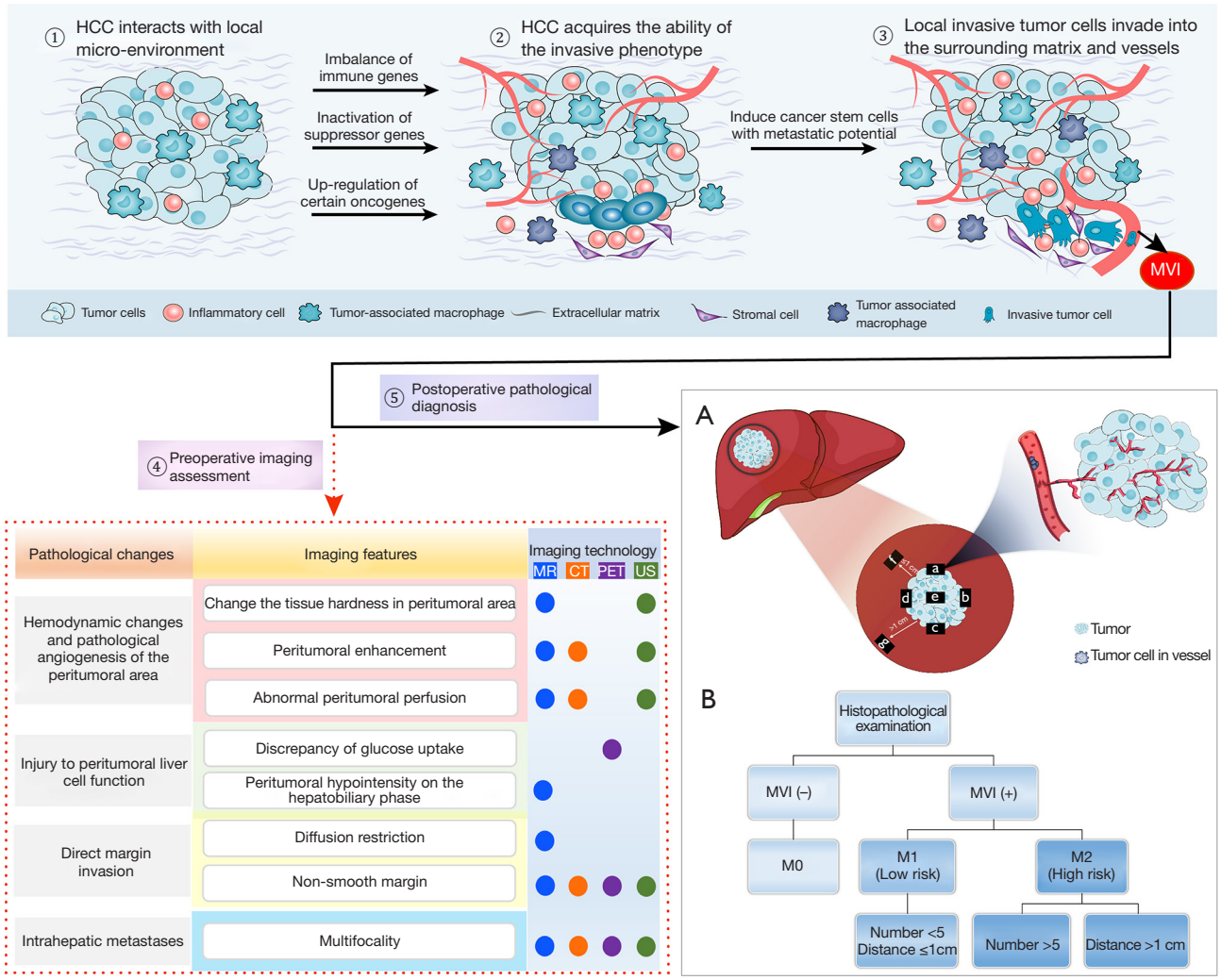


Figure 1 Multistep biological process of MVI and MVI-derived pathological changes via a variety of diagnostic methods. ① Carcinoma cells in HCC initially interact with the local microenvironment. ② A tiny fraction of cancer stem cells recruit a variety of stromal cells and inflammatory cells to create a reactive microenvironment and acquire the ability of the invasive phenotype via the upregulation of certain oncogenes, the inactivation of suppressor genes, and the imbalance of immune genes. ③ These cells respond to contextual signals that induce them to express invasiveness and metastatic dissemination. Subsequently, local invasive cells invade into the surrounding matrix and blood vessels. ④ MVI-related pathological changes and the manifestation of different preoperative imaging methods. ⑤ Postoperative histopathological examination remains the gold standard for clinical MVI diagnosis: (A) Chinese pathological diagnosis guidelines suggest that all kinds of liver cancer should be sampled based on the 7-point baseline sample collection protocol (a-g). MVI is a nest of malignant cells in microvessels only visible under a microscope. (B) Pathological grading of MVI according to Chinese pathological diagnosis guidelines. HCC, hepatocellular carcinomas; MVI, microvascular invasion; MR, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; US, ultrasound.

and location of the sampling sites be adjusted (14).

Pathogenesis and pathological changes of MVI

The progression of MVI in HCC involves sequential multistep biological process and a numerous factors, such as the interactions of tumor cells within the local microenvironment and the immune, endocrine, and metabolic status of the patient (15). Studies have identified the following steps in this process: First, a small fraction of

cancer stem cells (CSCs) of HCC act as the staple drivers of the aggressive biological progression of HCC through changing multiple regulatory mechanisms, including the upregulation of certain oncogenes, the inactivation of suppressor genes, and the imbalance of immune genes to transform into an invasive phenotype. Second, CSCs respond to contextual signals that induce them to express highly aggressive traits, such as invasiveness and metastatic dissemination, by activating the expression of epithelial-to-mesenchymal transition–inducing transcription factors (16,17). The subsequent epithelial-to-mesenchymal transition leads to a decrease in the amount of cell adhesion proteins and increases the expression of genes involved in cell migration and extracellular matrix degradation. Finally, these cancer cells lose their cell–cell adhesion, break through the tumor-surrounding extracellular matrix, use alternative energy sources and cellular motility to invade into the tumor-surrounding matrix and adjacent vessels, and enter into the hematogenous circulation. Moreover, the cancer cells from the primary tumor metastasize to the microenvironment of a distant tissue via physical translocation and then form metastatic foci through colonization (17). This multistep biological process is accompanied by a series of pathological changes, and these subtle changes can be discerned via biomarkers monitored by imaging and include hemodynamic changes and pathological angiogenesis in the tumor-surrounding area, tumor and peritumoral liver cell's function change, direct margin invasion, and intrahepatic or extrahepatic metastases (18-23) (*Figure 1*).

Hemodynamic changes and pathological angiogenesis of the peritumoral area

The pathological manifestation of MVI involves malignant cells nesting in peritumoral vessels (especially the minute portal vein branches) lined with endothelial cells, which cause these vessels to become obstructed. This may reduce portal venous blood flow and lead to the compensatory increase in arterial perfusion in this area (18). A series of studies have confirmed that portal venous arterial shunts is a staple mechanism for the preoperative prediction of MVI (18-20). Moreover, another study also found that MVI is related to the formation of neovasculature in peritumoral tissues (21). Neoplastic tumor cells secrete proangiogenic factors that can recruit various cells in nearby normal liver tissues to the position where angiogenesis is required (22). Meanwhile, increasing expression of placental growth factor and vascular endothelial growth factor receptor can stimulate tumor-surrounding pathologic angiogenesis and induce potential vascular invasion (21). Furthermore, cancer cells invading the microvessels of tumor-surrounding tissues can reduce the number of blood cells and change the local tissue's hardness; consequently, the hardness discrepancy of the tumor-adjacent tissue and tumor tissue decreases. These manifestation can be quantitatively measured by imaging (23).

Function change of tumor and peritumoral liver cells

Minute portal vein branches around the tumor being blocked by malignant embolus can lead to neoplastic arterial portal shunts, and this alteration in perfusion can result in functional impairment of hepatocytes or Kupffer cells around the tumor. Meanwhile, it can also cause a decrease in the expression of hepatocyte organic anion-transporting polypeptide transporters. Both of these phenomena are related to extracellular liver-specific contrast agent uptake (24), and the related hypointensity on imaging is due to the decrease of contrast agent absorbed by the peritumoral hepatocytes. In addition, HCC with MVI associated with poor tumor grade may have a significantly different level of glucose-6-phosphatase compared with normal hepatocytes and lead a discrepancy in glucose uptake (25).

Direct margin invasion

HCC with aggressive biological tendencies that directly invades the tumor capsule and protrudes into the nontumoral parenchyma can develop a nonsmooth margin, and studies have demonstrated that this can predict MVI-positive status with high accuracy (20,26). Furthermore, when the tumor margin is invaded by the tumor cells, the local microenvironment becomes more complex, with denser cellular structures and local tissue, and is more likely to develop irregular and heterogeneous lesions, thus further limiting the diffusion of water molecules (27).

Metastases

Research suggests that the peritumoral portal vein is an efferent vessel in HCC and is the least resistant channel for tumor cell escape (28). Once cancer cells invade in the efferent vascular cavity and extend beyond the capsule to portal vein branches, they adhere to the portal vein wall and interact with local endothelial cells. This is essential in facilitating tumoral embolism growth and spread, which

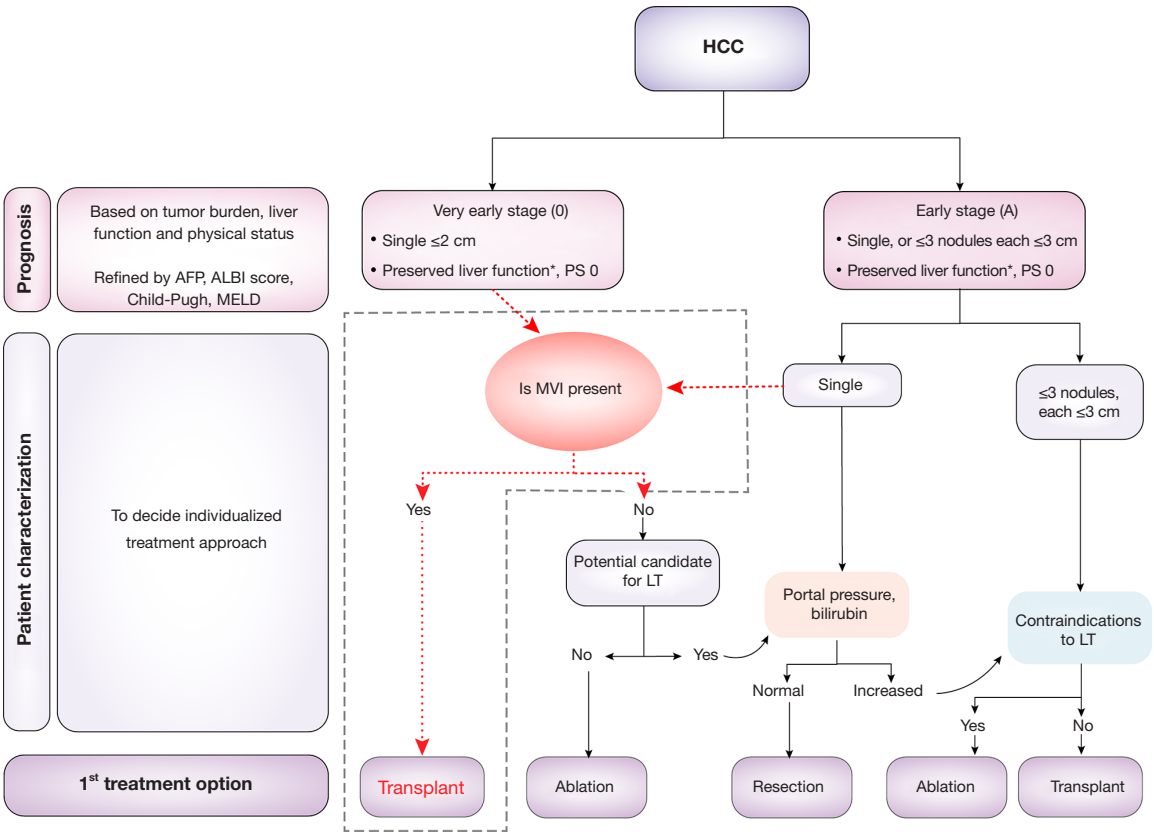


Figure 2 Flowchart of the proposed update to the BCLC treatment option. This figure is based on the BCLC 2022 update classification and has been modified by adding the MVI status, which advises patients with BCLC 0 and A tumors and MVI to consider LT as first-line treatment. *, liver function defined by Child-Pugh score and class. HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; MELD, model for end-stage liver disease; PS, performance status; MVI, microvascular invasion; LT, liver transplant; BCLC, Barcelona Clinic Liver Cancer.

ultimately disseminate through the portal vein branches to develop multifocal intrahepatic metastatic tumors (28,29). In addition, tumor thrombosis can also be found in hepatic veins or hepatic venous branches, although it has a lower incidence than in the portal system (28). When cancer cells invade into hepatic venous branches, this can lead to the development of metastatic foci in extrahepatic organs.

The clinical importance of MVI

Although significant developments in surgery have improved the outcomes of early-stage HCC, a high risk of early recurrence, even in stage 0 HCC, remains a major challenge in HCC therapy (4). A previous study found that early recurrence, as compared to later recurrence, is more likely to be associated with tumor-related biological aggressiveness, indicated by the presence of MVI and satellitosis, and to poor outcomes (30,31). Other studies have reported that almost one half of tumors ≤2 cm in size also have MVI, suggesting there may be a subtype of HCC with inherently more aggressive biology that can invade the intrahepatic vascular system at an early stage (28,32). Thus, MVI was recognized as a crucial index of prognosis within the T criteria in the eight edition of the American Joint Committee on Cancer staging system (33). The China liver cancer staging system likewise points out that MVI is an important predictor for assessing recurrence risk and therapeutic selections for HCC (34). The 2022 edition of BCLC guideline recommends that BCLC-0 and BCLC-A patients be treated with RA or SR as first-line curative treatment, but if MVI can be diagnosed before treatment, LT should be considered to decrease recurrence risk (9) (*Figure 2*).

Surgery usually is recommended as curative therapy for early-stage HCC according to current clinical practice

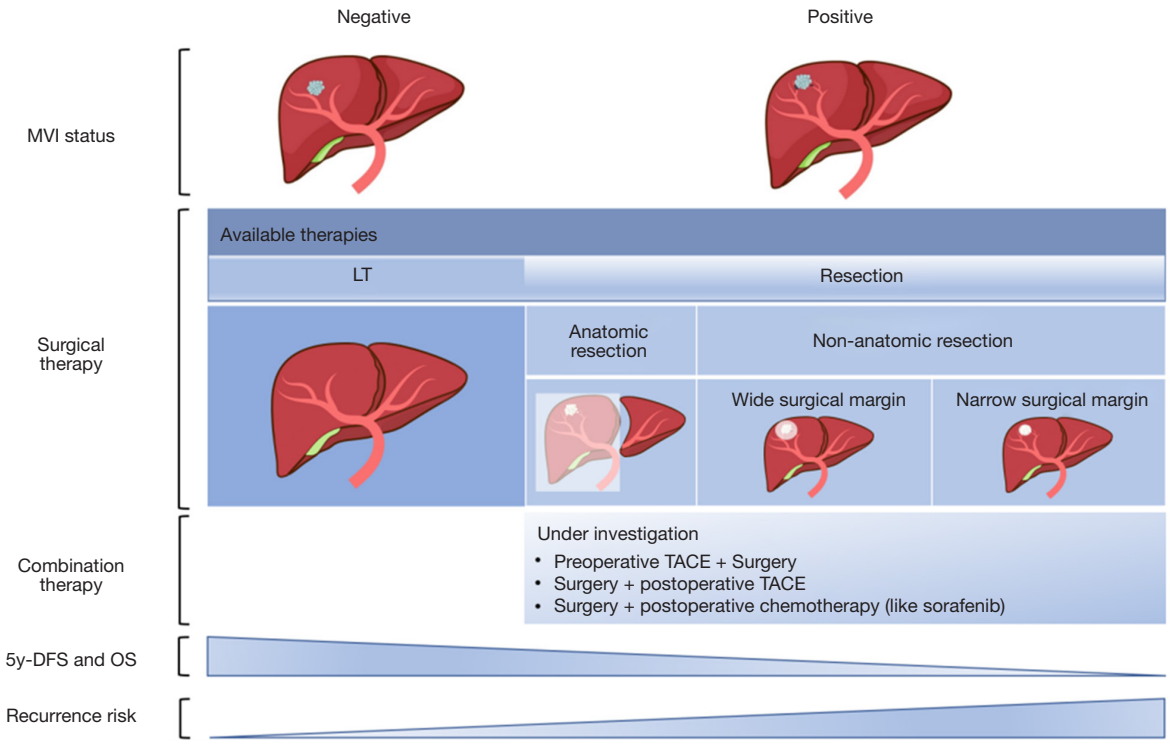


Figure 3 Current surgical therapies and prognosis of early-stage HCC with MVI status, which according to the available scientific evidence, the tumor is a size ≥2 cm. MVI, microvascular invasion; LT, liver transplant; TACE, transcatheter arterial chemoembolization; 5y-DFS, 5-year disease-free survival; OS, overall survival.

guidelines (3,4); however, about 70% of patients treated with SR and 25% of those treated with LT experience recurrence, and the 5-year overall survival (OS) rate is also unsatisfactory, at only 15–20% (35). Numerous studies have demonstrated that MVI is a strong risk factor correlated with these poor outcomes (1,5,9-12). Although it seems that LT could be more beneficial for prognosis than SR, LT requires the high availability of liver grafts, high expense, and highly stringent patient selection. Therefore, various alternative SR methods are used in clinical practice, such as anatomical resection and nonanatomical resection with wide surgical margin, but their effectiveness remains controversial among MVI-positive patients. In addition, in recent years, some studies have evaluated the efficacy of the more aggressive treatment of combining surgical and adjuvant therapies for improving the prognosis of MVI-positive patients (36-40) (*Figure 3*).

Although MVI is a well-known indicator of early recurrence and poor outcomes after curative therapy, it is a lagging indicator due to the current diagnostic criteria of postoperative histopathology. Meanwhile, preoperative biopsy is not recommended for patients with HCC who meet the clinical diagnostic criteria for undergoing surgery to reduce the risk of tumor rupture, bleeding, and spread. Therefore, a useful noninvasive prediction tool for MVI is urgently needed in the preoperative period for narrowing the gap between clinical therapy and pathology diagnosis. Patients' expectations need to be guided by the optimal use of the limited availability of donor organs, and so patients should be guided to select the most cost- and outcome-effective therapeutic plan.

Diagnostic imaging features of MVI

Medical imaging has played a crucial role in assessing HCC in recent decades. Clinical practice guidelines (41,42) have recommended imaging modalities, such as US, CT, or MRI, as first-line tools for the screening, diagnosis, staging, and surveillance of HCC. Advanced imaging technology has the advantage of being noninvasive and capable of completely assessing the tumor and host situation, potentially providing insights into the HCC's biology and heterogeneity before

treatment. Therefore, numerous studies have focused on medical imaging as a promising tool for predicting MVI prospectively and have explored the influence of MVI in the prognosis of HCC. A growing body of evidence suggests that several imaging features or combinations of features are correlated with the pathologic and molecular changes derived from MVI (Table S1). These imaging features include morphological features, such as tumor size, nonsmooth tumor margin, and peritumoral enhancement, which can manifest on the conventional enhanced imaging (CT, MRI, or US), and quantitative features based on functional or special scanning sequences, even computer-derived radiomics features (*Table 1*).

Conventional contrast-enhanced imaging features associated with MVI

Larger tumor and multifocality has also been reported to be able to predict MVI in HCC. A previous study found that larger tumor size had a greater weight for predicting the presence of MVI (20). Similarly, Wei *et al.* (43) reported that a tumor diameter larger than 5 cm was significantly related to MVI, yielding a sensitivity of 69.2% and a specificity of 61.2% when used as an independent predictor. Other MRI-based research found that when the number of tumors used for predicting MVI increased from ≥3 to ≥4, the specificity could be increased from 88.2% to 91.2% (44). Although there is no uniformity in the criteria of tumor size and number for predicting MVI, it is generally accepted that larger tumor and multifocality are positively related to the presence of MVI.

Nonsmooth tumor margin, a well-known, key feature for predicting MVI (45-49), is an external manifestation related to the aggressive biological behavior of HCC, specifically the invasion of the tumor capsule and tumor-surrounding tissue due to intrahepatic metastasis occurring through the portal venous system. Nonsmooth tumor margin has several forms, including focal extranodular extension, crescent extranodular extension beyond the tumor capsule, multinodular confluence appearance, and focal infiltrative margin. In evaluating the performance of nonsmooth tumor margin for predicting MVI in HCC, the results vary across studies due to the use of different scanning modalities. Renzulli *et al.* (140 patients) (20) conducted a study based on CT, and their results indicated that nonsmooth tumor margin is highly associated with the presence of MVI ($P<0.05$). However, Griffin *et al.* (50), found no correlation between MVI and nonsmooth tumor margin, which was evaluated on enhanced MRI. Currently, nonsmooth tumor margin is widely recognized as an important imaging feature for the clinical prediction of MVI, but the imaging mechanism of different imaging modalities varies, which can lead to differences in evaluation across observers due to the subjective nature of determining whether the tumor margin is smooth.

The tumor capsule, which can be categorized as complete, incomplete, or absent capsule, is defined as a thin, low-signal ring surrounding the tumor on the arterial phase and a high signal on the portal or delayed phase. A plethora of studies have shown that the capsule can act as a protective structure to prevent the tumor from invading adjacent normal liver tissue. Zhao *et al.* (51) and Chen *et al.* (52) found that an incomplete tumor capsule was related to MVI ($P<0.05$). However, other researchers reported that the absence of tumor capsule could not diagnose MVI [diagnostic odds ratio =0.90; 95% confidence interval (CI): 0.64–1.26] (53). In addition, their results also showed that an incomplete capsule had a relatively low sensitivity value of 0.56 (95% CI: 0.42–0.70) and specificity value of 0.68 (95% CI: 0.56–0.79), respectively, in predicting MVI. This may due to the fact that the tumor capsule can prevent tumor invasion to the tumor-surrounding hepatocyte to a degree, but the tumor also may invade the blood vessels in the capsule, thus still resulting in MVI. Consequently, the relationship between an incomplete tumor capsule and MVI is not inconsistent across the different study samples, and so caution is warranted in using tumor capsule to predict MVI in clinical practice.

Peritumoral enhancement is another widely proposed factor for predicting MVI in. MVI involves peritumoral vessels being invaded and obstructed by cancer thrombi from HCC, especially the minute portal vein branches adjacent to the tumor. This can lead to a change of the hemodynamic perfusion of peritumoral liver tissue, which manifests as a loss or reduction of portal blood flow and compensatory arterial hyperperfusion in this area (18). This change may be discerned on conventional enhanced images and is referred to as peritumoral enhancement, which is defined as the presence of a visible tumor-surrounding portion enhanced in the arterial phase and the later reversal of isoattenuation compared with the normal hepatocytes in the portal or delayed phase. Based on this mechanism, many studies based on a variety of imaging modalities have confirmed that peritumoral enhancement is essential for predicting MVI (18-20).

Radiogenomic venous invasion (RVI), first proposed by Banerjee *et al.* (54), is based on the observation that

Table 1 Description and schematic drawings of several MVI-related morphological imaging features in HCC

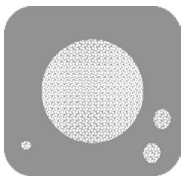
MVI-related imaging features	Schematic drawing	Explanation
1 Larger tumor		Tumor size >5 cm
2 Multifocality		Intrahepatic metastases are derived from the main tumor via the portal vein, ≥3 tumors
3 Nonsmooth tumor margin		
3.1 Focal extranodular extension		Focal extranodular extension in the delayed phase
3.2 Crescent extranodular extension beyond the tumor capsule		Crescent extranodular extension beyond the tumor capsule in the delayed phase
3.3 Multinodular confluence appearance		Multinodular confluent appearance in the arterial phase
3.4 Focal infiltrative margin		Tumor with focal infiltrative margin in the delayed phase
4 Peritumoral enhancement (peritumoral enhancement is considered present when both of the following criteria are satisfied)		
4.1 Arterial peritumoral enhancement		A variably shaped hyperintense area outside the tumor in wide contact with the tumor margin on the arterial phase enhancement

Table 1 (*continued*)

Table 1 (*continued*)

MVI-related imaging features	Schematic drawing	Explanation
4.2 Isointense with the normal liver tissue on delayed phase or HBP		A variably shaped area outside the tumor in wide contact with the tumor margin that tends to be isointense on the delayed phase or HBP
5 Peritumoral hypointensity on HBP		An irregular circumferential, wedge-shaped, or flame-like hypointense area of liver parenchyma located outside of the tumor margin
6 Radiogenomic venous invasion (positive status involves all three of the following conditions)		
6.1 Present internal arteries		Persistence of discrete arterial enhancement within the tumor in the venous phase
6.2 Absent hypodense halo		Lack of a rim of hypoattenuation partially or completely circumscribing the tumor in the portal venous or equilibrium phases of imaging
6.3 Absent tumor-liver difference		Lack a focal or circumferential sharp transition in attenuation between the tumor and the adjacent liver parenchyma

MVI, microvascular invasion; HCC, hepatocellular carcinoma; HBP, hepatobiliary phase.

conventional contrast-enhanced CT can reconstruct global HCC gene expression patterns, in which tumor imaging features are mapped to corresponding gene expression profiles (55,56). Banerjee *et al.* (54) identified three separate imaging features of RVI: internal arteries, refers to a tumor that exhibits discrete arterial enhancement in the venous phase; hypodense halo, refers to a tumor margin with a partial or complete rim of hypoattenuation; and tumor-liver difference refers to a focal or circumferential sharp transition in attenuation between the tumor and the adjacent nontumor tissue without a hypodense halo. A positive RVI status requires that all the above features be present at the same time. Banerjee *et al.* found that RVI could predict the presence of MVI in the SR-treated, LT-treated, and overall cohorts with a sensitivity of 84.0%, 66.7%, and 76.1%, respectively, and a specificity of 95.7%, 92.3%, and 93.8%, respectively. Although the research sample on RVI in predicting MVI is still relatively small, it may provide important reference value for the prediction of MVI in the future.

Imaging features associated with MVI based on functional and special scan sequences

Peritumoral hypointensity in the hepatobiliary phase (HBP)

Gadoxetic acid-enhanced MRI is a type of liver-specific intracellular contrast agent imaging and provides a special

hepatocellular parenchymal contrast during the late phase. In recent decades, it has been widely used for predicting MVI in HCC. Of note, irregular peritumoral hypointensity in the HBP has been found to be the MRI feature most suggestive of MVI (45,57,58). A hypointense signal is thought to be associated with impairment of organic anion-transporting peptides or the canalicular transporter multidrug resistance-associated protein 2 within hepatocytes or Kupffer cells, which are involved in the uptake of gadoxetic acid (24). A meta-analysis found that the peritumoral hypointensity on HBP was significantly associated with MVI (P<0.05) (59). In addition, Zhou *et al.* (60) found that peritumoral hypointensity on HBP was an independent risk factor for predicting MVI (P<0.05), yielding an area under the curve (AUC) of 0.883. Currently, although gadoxetic acid-enhanced MRI demonstrates excellent potential in predicting MVI, as a subjective indicator, its efficacy still varies. One study assessed the diagnostic efficacy of gadoxetic acid-enhanced MRI for MVI and found there to be significant interobserver variability, even among more experienced radiologists (61). Nevertheless, the unique peritumoral hypointensity in HBP is still one of the key features for predicting MVI; especially when combined with other features, such as nonsmooth margin and peritumoral enhancement, it can improve the diagnosis of MVI.

Diffusion restriction

Diffusion-weighted imaging (DWI) is a type functional imaging that can quantitatively measure water diffusion and generate different apparent diffusion coefficient (ADC) values. As mentioned above, when MVI in HCC is accompanied by peritumoral tissue and vascular invasion, the local tissue cellularity and integrity of cellular membranes, as well as the hemodynamics, may be altered. In turn, this can lead to the limitation of water diffusion and local microcirculation perfusion changes, and these changes can be reflected by the ADC value. Xu *et al.* (62) demonstrated that mean ADC (ADC_{mean}) value <1.227×10^{-3} mm^2/s is an independent predictor of MVI. A meta-analysis indicated that both minimum ADC (ADC_{min}) and true ADC values (D) in MVI-positive tumors were significantly lower than in MVI-negative tumors, and both parameters' value were under 1.00×10^{-3} mm^2/s in MVI-positive tumors. This may be due to the fact that both ADC_{min} and D are sensitive to cell count and total nucleic area (63). However, there is still no consistent cutoff value of ADC_{min} and D for diagnosing MVI (64).

The diffusion kurtosis imaging (DKI) is a special DWI model based on the non-Gaussian distribution model. The mean kurtosis (MK) and mean diffusivity (MD) values are the most widely used parameters in DKI, which can better and more accurately reflect the complexity of microstructure in tumor than can traditional DWI and tend to be associated with aggressive tumor biological behavior (65). One study found that MK had better diagnostic performance than did the conventional ADC value for predicting MVI and that MVI-positive patients had a higher MK value compared to MVI-negative patients (66); however, the effectiveness and reliability of MK and MD remain to be determined in large-sample research.

Intravoxel incoherent motion (IVIM) is another special DWI model, which involves adopting multi-b-value scans and double exponential model fitting. It can simultaneously reflect the diffusion of water molecules in tissues and microvascular blood perfusion, thereby better demonstrating tumor heterogeneity (67). Some studies have shown that intravoxel incoherent motion (IVIM) model-derived D value has a better diagnostic performance for MVI in HCC than does conventional ADC measured with the monoexponential model (66,68-71). Wei *et al.* (68) found that the D value of the whole tumor with MVI is significantly lower than that without MVI, while the D* and *f* value of whole tumor had no statistical significance between MVI and non-MVI. Similarly, Zhao *et al.* (71) reported that among IVIM parameters, only the D value of the tumor was an independent predictor of MVI, with a sensitivity of 66.7% and a specificity of 88.9% when the cutoff value was 1.16×10^{-3} mm^2/s. These results may be explained by the fact that in HCC with MVI, poor differentiation and more densely cell-packed structures are more likely, which can lead to the restriction of molecular diffusion (32); meanwhile, the D value potential may more accurately reflect this feature, as it is related to tissue cellularity (68,71). A recent study proposed using diffusion-derived vessel density (DDVD) to reflect the extent of tissue vessel density of HCC by calculating the signal difference between images when the diffusion gradient is off and images when the diffusion gradient is on (72); this requires only two b-values (with one being b=0 s/mm^2), resulting in a significantly shorter scanning time than that of the IVIM protocol. This study found that patients with MVI-positive HCC had a higher DDVD value than did those with MVI-negative HCC due to the fact that those

with MVI-positive HCC had a higher blood volume and more differentiated HCC. Although many studies have shown the potential for IVIM to predict MVI in HCC, there is still no consistent scanning protocol. Therefore, multicenter, large-sample studies are needed to confirm the optimal scan protocol of IVIM.

Hardness of tumor and peritumoral liver tissue

Magnetic resonance elastography (MRE) imaging allows for the noninvasive measurement of tissue stiffness and has been widely used to assess liver fibrosis. Recently, a study used a new MRE-based technique, termed slip interface imaging to quantify the degree of tumor-liver tissue adhesion in HCC via shear strain mapping (22). The alterations of the vasculature and extracellular matrix in the tumor-surrounding area caused by MVI leads to a reduction in the difference in shear stiffness of the stiffer tumor and softer normal tumor-surrounding tissue and a change in the sharp boundary of the tumor and normal tumor-surrounding tissue interface (22). Therefore, in MVI-positive patients, MRE-based shear strain at the tumor-liver interface decreases gradually, and the width of the transition in the mechanical properties at the boundary widen, which can be quantified by octahedral shear strain-percentage of low-shear-strain length (OSS-pLSL) derived from MRE. The results of this study indicated that peritumor OSS-pLSL was significantly higher in the MVI-positive group, with the recommended frequency for octahedral shear strain being 30 Hz (22). In addition, another study based on US elastography imaging found that the hardness and strain ratio of tissue near the tumor of an MVI-positive group were obviously lower than those of MVI-negative group in HCC, with peritumoral tissue hardness being identified as a protective feature for MVI (23). In addition, when two tumor features—peritumoral tissue hardness (cutoff 14.150) and maximum cancer diameter (cutoff 43.50 mm)—were used in the prediction model for MVI evaluation, this yielded an accuracy of 75.7% (23). The samples used in the research on elastography to evaluate MVI are still relatively small. In addition, due to the reliance on additional equipment and scanning techniques, its wide application for MVI prediction is also limited.

Iodine-specific maps and iodine concentration

Iodine-specific maps and iodine concentration can quantitatively evaluate abnormal hemodynamic changes of microvascular and provide functional information about the microcirculation of the tumor and tumor-surrounding liver parenchyma. Dual-energy CT (DECT)-based iodine-specific maps can indicate the existence or lack of local iodine in tissues and can be quantified. Quantifying tumor iodine uptake has been used to assess MVI status in patients with HCC, with the result supporting its potential use as a biomarker of MVI (73-75). Miyata *et al.* (76) reported that those with MVI-positive HCC had a lower arterial iodine concentration value and arterial density value than did those with MVI-negative HCC. Similarly, another study indicated that the spectral CT-specific parameters, including iodine concentration and normalized iodine concentration, in an MVI group were significantly higher than those in a non-MVI group (73). In addition, a lower kiloelectron volt value was found to improve the diagnostic performance from 0.71 (70 keV) to 0.81 (40 keV) (73). The combined analysis of perfusion CT and DECT parameters to evaluate tumor vascularity could provide quantitative data to complement the qualitative visual interpretation, thus increasing the precision of preoperative MVI prediction.

Maximum standardized uptake of tumor

^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET is an important functional molecular imaging that can reflect the metabolic activity and has become an essential technique in cancer imaging (77). Although MVI cannot be directly observed via PET/CT preoperatively, PET/CT can reflect the tumor's highly invasive and metastatic features and greater metabolic activity in comparison with normal liver tissues. One study reported that the maximum standard uptake value (SUV_{max}) of tumor of more than 3.2 was an independent predictor of MVI in HCC (78). Likewise, Kornberg *et al.* (25) found that preoperative PET-positive status, defined as ^{18}F-FDG uptake of the tumor significantly higher than that of in normal tumor-surrounding liver tissues, was related to MVI and had good diagnostic performance in predicting of MVI (sensitivity of 82.3%, specificity of 92%), in patients who underwent LT. They also found that the tumor maximum SUV_{max} to background liver mean standardized uptake value ratio ($T_{SUVmax}/B_{SUVmean}$) of ^{18}F-FDG uptake >1 was a reliable preoperative predictor of MVI and tumor recurrence after LT (79). Other researchers also found that $T_{SUVmax}/B_{SUVmean}$ value could preoperatively predict MVI, which at an optimal cutoff value 1.3, yielded a sensitivity of 85.5% and a specificity of 54.9% (80).

However, although numerous studies have demonstrated

that the tumor's SUV_{max} value is an important predictor of MVI, several studies and a meta-research found low sensitivity and low-to-moderate specificity of ^{18}F-FDG uptake in predicting MVI in HCC, the results suggest that PET/CT should not be used as a reliable maker to exclude MVI (81-83). Ahn *et al.* indicated that a $T_{SUVmax}/B_{SUVmean}$ >1.2 of ^{18}F-FDG PET may suggest the incidence of MVI in HCC, with a sensitivity of 56% and a specificity of 87% (81). Another study also used the same indicator to predict MVI, but the sensitivity and specificity for predicting MVI before LT or SR were only 55.2% and 69%, respectively (82). Despite the higher ^{18}F-FDG uptake of tumor is a helpful indicator for predicting outcomes of patients with aggressive HCC and an independent predictor of early recurrence in patients with living donor LT. Lee *et al.* also reported a relatively low diagnostic performance of higher ^{18}F-FDG uptake of tumor for MVI prediction (sensitivity of 45.5%, specificity of 83.9%) (83). Limited resolution and uptake in normal liver tissue is unstable due to susceptibility to hepatitis, cirrhosis, or other factors and can lead to differences in diagnostic performance across various studies. Therefore, the diagnostic efficacy of PET alone remains insufficient.

Radiomics and artificial intelligence

With high-throughput analysis in medical imaging being implemented via a range of data mining algorithms and statistical analysis tools, radiomics has become an emerging, powerful, and noninvasive tool for clinical research. It not only can detect nuanced features from conventional medical images that cannot be seen by the naked eye but also does not rely on radiologists' potentially biased expertise to determine imaging characteristics. Therefore, the research into quantitative radiomics has grown in recent years and has been increasingly used for MVI prediction in HCC. Radiomics, involves models or nomograms based on various imaging modalities including MRI (83-87), CT (49,88-90), PET (48,91,92), US (93-96). Several meta-analyses found that radiomics has good ability to preoperatively predict MVI status in HCC, with a median AUC ranging from 0.85 to 0.90 across different studies (89,97-99). Zhong *et al.* (99) also reported that CT and MR-based radiomics models have similar diagnostic efficacy in terms of AUC (0.85 *vs.* 0.87) and are significantly better than US-based radiomics models (AUC =0.74).

In the era of big data and precision medicine, radiomics modeling is being continually updated to improve the preoperative diagnosis of MVI in HCC. It is widely accepted that single-factor methods for diagnosing MVI often offer relatively poor diagnostic efficacy. An MRI-based radiomics study showed that the efficacy of a multisequence fusion radiomics signature in predicting MVI was better than a single sequence in both the training (AUC: 0.895 *vs.* 0.754; P=0.002) and validation cohorts (AUC: 0.837 *vs.* 0.705; P=0.040) (97). Furthermore, Shi *et al.* used a model based on the radiomics features of tumor derived from PET/CT, whose the diagnostic performance for MVI in HCC was 0.917 and 0.771 in the training and test cohorts, respectively. However, a combination of PET/CT radiomics with contrast-enhanced MRI features (ADC, hypovascular arterial phase enhancement pattern on contrast-enhanced MRI, and nonsmooth tumor margin) yielded a better predictive performance with an AUC of 0.996 and 0.953 in the training and test cohorts, respectively (48). Similarly, other researchers have also explored the role of combining multiple indices in the construction of a model for predicting the preoperative MVI status of patients with HCC. They incorporated several radiographic and clinical characteristics, including higher aspartate aminotransferase (AST) level (>40 U/L), higher alpha-fetoprotein (AFP) level (>400 ng/mL), nonsmooth tumor margin, extrahepatic growth pattern, ill-defined pseudocapsule, peritumoral arterial enhancement, presence of RVI, and higher radiomics score of entire-volumetric interest of the tumor (VOIentire), into the novel RR nomogram. The RR nomogram yielded AUCs of 0.909 in the training cohort and 0.889 in validation cohort for predicting MVI, and its accuracy was higher than that of simple clinical, radiologic, and radiomics features, respectively (49)

Limitations

Although noninvasive imaging methods are playing an increasing important role in predicting MVI of HCC, they still have some limitations. First, conventional contrast-enhanced imaging can only observe some of the morphological features related to MVI, such as nonsmooth tumor margin and peritumoral enhancement, which may be challenging to discern by human vision due to interobserver variability; moreover, they are difficult to compare due to differences in the prediction features and study population (diverse etiologies and sample size) (65). Second, functional and special scanning sequences, such as gadoxetic acid-enhanced MRI, MR, US elastography, and DWI, can improve the preoperative prediction efficiency of MVI to

some extent; however, the major disadvantages of these techniques, including the lack of consensus on cutoff points, the use of different scales and techniques by different institutions, and technically challenging acquisitions, have greatly hindered its clinical implementation (22,68). Finally, radiomics and artificial intelligence have achieved some exciting results in predicting MVI of HCC in recent decades; however, it is also difficult for radiomics to traverse the gap between a scientific research and clinically applicable methodologies. For instance there is no consensus regarding image acquisition schemes and segmentation methods, and radiomics models may result in variability in the quantification of radiomic features that are not biologically significant (98,99). Moreover, data-driven radiomics and machine learning are fundamentally incapable of interpreting the biological basis of the observed relationship. This disconnect between the radiomic models and their biological significance inherently limits their use in routine in clinical practice.

Future directions

MVI had been demonstrated to a critical risk indicator for early recurrence and poor prognosis in HCC. Given the shortage of cadaver donors and the challenges in diagnosis MVI preoperatively, many patients with early-stage HCC are MVI are recommended to undergo SR or RA as first-line curative treatment rather than LT, which has been associated with a relatively high recurrence rate and poor OS rate. Therefore, precise identification of MVI status preoperatively in patients with HCC is crucial for clinicians to select the most cost- and outcome-effective individualized therapeutic plan for early-stage HCC. Importantly, HCC with MVI has an aggressive biological behavior. Clinical trials should investigate whether MVI-positive HCC predicted via preoperative imaging modalities should be grade higher in staging guidelines in order to encourage more aggressive treatment regimens and reduce the recurrence rate.

Progress in preoperative diagnosis of MVI by imaging has advanced considerably over the past decades. This has included a shift from morphological and functional features to radiomics and artificial intelligence, from qualitative analysis of traits visible to the naked eyes to quantitative analysis of indiscernible traits (such as tumor size, peritumoral enhancement, and imaging texture), and from single features based on conventional or special scanning methods to fusion radiologic and radiomics signatures using multiple sequences or multiple modalities. These changes have dramatically improved the preoperative efficacy and accuracy in diagnosis MVI in the era of precision medicine. Although there is no consensus regarding this imaging features for diagnosing MVI, it has been widely accepted that combined features are superior to individual features in predicting MVI. On the basis of standardized contrast contrast-enhanced imaging (including Gadoxetic acid-enhanced MRI), combined functional or special scan sequences (such as DWI and perfusion imaging) hold promise for the preoperative prediction of MVI. In the future, large-sample, multicenter, and multinational clinical studies should be conducted to formulate the imaging-based diagnostic criteria of MVI.

Conclusions

MVI is significantly associated with aggressive biological behavior and has been demonstrated to be an independent predictor of early recurrence and poor OS in patients with HCC patients after SR and LT. Advanced imaging technologies hold promise for the reliable, noninvasive, and preoperative prediction of MVI status, which could reduce clinicopathological discrepancies and provide a useful tool for balancing patient desires and the limited pool of donor organs. This review may serve as a valuable reference for clinicians to implement personalized therapy and improve the prognosis of patients with HCC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-44/coif). The authors have no conflicts of interest to declare.

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