Expert Consensus

Chinese expert consensus on the diagnosis and treatment of hepatocellular carcinoma with microvascular invasion (2024 edition)

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Background: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China. Surgical resection is the preferred treatment for HCC, but the postoperative recurrence and metastasis rates are high. Current evidence shows that microvascular invasion (MVI) is an independent risk factor for postoperative recurrence and metastasis, but there are still many controversies about the diagnosis, classification, prediction, and treatment of MVI worldwide.

Methods: Systematic literature reviews to identify knowledge gaps and support consensus statements and a modified Delphi method to develop evidence- and expert-based guidelines and finalization of the clinical consensus statements based on recommendations from a panel of experts.

Results: After many discussions and revisions, the Chinese Association of Liver Cancer of the Chinese Medical Doctor Association organized domestic experts in related fields to form the "Chinese expert consensus on the diagnosis and treatment of hepatocellular carcinoma with microvascular invasion (2024 edition)" which included eight recommendations to better guide the prediction, diagnosis and treatment of HCC patients with MVI. The MVI pathological grading criteria as outlined in the "Guidelines for Pathological Diagnosis of Primary Liver Cancer" and the Eastern Hepatobiliary Surgery Hospital (EHBH) nomogram for predicting MVI are highly recommended.

Conclusions: We present an expert consensus on the diagnosis and treatment of MVI and potentially improve recurrence-free survival (RFS) and overall survival (OS) for HCC patients with MVI.

Keywords: Hepatocellular carcinoma (HCC); microvascular invasion (MVI); consensus

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Introduction

Hepatocellular carcinoma (HCC), the fifth most prevalent malignancy in China, accounts for approximately 400,000 new cases annually (1). It ranks as the second leading cause of cancer-related mortality, surpassed only by lung cancer. Despite advancements in therapeutic strategies, surgical resection remains the cornerstone of HCC management in China. However, postoperative recurrence rates within 5 years alarmingly reach up to 50–70% (2,3), while recurrence after liver transplantation ranges from 4.3% to 57.8% (4-7). The propensity of HCC to invade blood vessels and thereby facilitate hematogenous spread is a pivotal factor contributing to its recurrence and metastasis. A critical area of concern is microvascular invasion (MVI), characterized by the presence of cancer cell nests within the lumens of small, endothelium-lined vessels that are detectable solely under microscopy. These nests are predominantly located within the tumor capsule and portal vein branches adjacent to the carcinoma. Emerging evidence underscores MVI's role as an independent prognostic factor for HCC recurrence and metastasis, highlighting its biological significance and impact on patient outcomes. Given the ongoing debates surrounding MVI's diagnostic criteria, classification, prognostication, and therapeutic approaches, the Chinese Association of Liver Cancer has taken a pivotal step. Leveraging the substantial body of evidence-based medicine, particularly contributions from Chinese scholars in the realm of treating HCC patients with MVI, the committee convened a multidisciplinary panel of experts. Through extensive deliberations, they formulated the "Chinese expert consensus on the diagnosis and treatment of hepatocellular carcinoma with microvascular invasion (2024 edition)". This document aims to guide clinical practice by synthesizing current knowledge and expert opinions on managing this complex condition. As the landscape of evidence-based medicine evolves, this consensus will undergo periodic revisions to incorporate the latest research findings, ensuring its relevance and utility in improving patient care outcomes in HCC management.

Highlight box

Key recommendations

- We provide recommendations for the diagnosis, classification, prediction, and treatment of microvascular invasion (MVI).

What was recommended and what is new?

- The classification of MVI was based on the number of MVI and the location of MVI from the hepatic tumor.
- We recommend comprehensive prediction methods (Eastern Hepatobiliary Surgery Hospital nomogram) to predict MVI.

What is the implication, and what should change now?

- Sintilimab, transarterial chemoembolization, radiotherapy and hepatic arterial infusion chemotherapy are recommended as adjuvant therapy for MVI.

Methods

This study comprised three stages, including: (I) systematic literature reviews to identify knowledge gaps and support consensus statements; (II) a modified Delphi method to develop evidence- and expert-based guidelines; (III) finalization of the clinical consensus statements based on recommendations from a panel of experts.

PubMed, Cochrane Library and Embase databases through May 31, 2023, to identify knowledge gaps in clinical guidelines, clinical consensus statements, and systematic reviews on diagnosis, prediction and treatment of MVI. In a modified Delphi process from July 2023 through December 2023, experts participated in three consecutive surveys (including two web-based surveys).

The first survey aimed to identify knowledge gaps and clinical presence needs in the definition, classification, prediction and treatment strategies of MVI in our country. Expert feedback was solicited through open-ended questions and "yes/no" questions asking about agreement with consensus statements. In the second survey, experts received literature specific to the revised consensus statements and indicated whether they agreed ("yes"/"no") with each statement. Per Delphi protocol, consensus for each statement was defined as having agreement from at least 80% of experts. Lastly, experts assigned proposed recommendation strengths to each consensus statement. Statement-specific consensus was considered favorable when at least 80% of panelists rated the recommendation strength of the statement as strong, week or good practice statement (GPS).

The evidence grading in this consensus follows the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (*Table 1*), adhering to the guidelines for evidence evaluation and recommendation grading as outlined by the GRADE Working Group (http://www.gradeworkinggroup.org/) and the "Oxford Centre for Evidence-based Medicine 2011 Levels of Evidence" (8,9). The strength of the expert recommendations is based on the GRADE system's guidance for grading recommendations.

Table 1 Grading of evidence in evidence-based medicine and expert recommendations

Category	Specific description
Grading of evidence quality	
A	High confidence that the observed value is close to the true value
B	Moderate confidence in the observed value: it is possible that the observed value is close to the true value, but there could also be a significant difference
C	Limited confidence in the observed value: the observed value may significantly differ from the true value
D	Very little confidence in the observed value: the observed value could greatly differ from the true value
Grading of recommendation strength	
Strong [1]	Clearly demonstrates that the benefits of the intervention outweigh the harms, or vice versa
Weak [2]	Uncertainty regarding benefits and harms, or evidence of any quality shows benefits are closely balanced with harms
GPS	Recommendation based on indirect evidence or expert opinion/experience

GPS, good practice statement.

This consensus has been registered on the International Practice Guidelines Registry and Transparency Platform (http://www.guidelines-registry.cn/), with the registration number PREPARE-2024CN185.

Results

Systematic literature review and survey results

The literature reviews identified 251 publications included in the qualitative synthesis. The first survey consisted of 12 questions and statements, which were modified in the second survey and finally summed up to eight statements in the third survey. All eight statements had favorable consensus. Experts expressed agreement on seven statements that received strong or moderate recommendations; one statement received at least 1 weak recommendation (Table S1).

Recommendations

Diagnosis and classification of MVI

Incidence, pathological diagnosis, and classification

The incidence of MVI in HCC ranges from 17.0% to 93.4% (10-21). The incidence of MVI is positively correlated with tumor diameter in HCCs. It ranges from 17.0–40.6% in tumors less than 3 cm (16,18,21-26), 31.0–42.5% in those between 3–5 cm (22,23,27,28), and 46.2–93.4% in HCCs larger than 5 cm (23,27,29-33). For multifocal HCCs, the incidence of MVI varies between 9.9% and 81.3% (4,13,17,23,34-37). Additionally, the incidence of MVI in HCCs meeting the Milan criteria is reported to be between 9.9% and 54.0% (4,13,38,39).

Certain pathological features of MVI, such as the number of invading microvessels (40-43), their distribution (43-45), intranodular cancer cell count (40,43,46), invasive typing (42), and invasion of microvessels with a muscle layer (44), significantly affect the prognosis of patients with HCC. Roayaie *et al.* (44) defined MVI as tumor cells visible in microvessels under a microscope. They then classified MVI into three classes based on two risk factors: a muscle layer in the invaded microvessels and a distance from the tumor body ≥1 cm. The three categories of MVI are B1 class: MVI present without other risk factors; B2 class: MVI with one risk factor; and B3 class: MVI with two risk factors. Other researchers (38,46,47) have defined MVI as the microscopic discovery of HCC invading one or more of the portal veins, hepatic vein, microartery, or lymphatic vessels. Iguchi *et al.* (46) proposed a classification of MVI based on intranodular cancer cell count and the number of MVIs, with two main types (low risk: MVI present without other risk factors; high risk: MVI number ≥2 or intranodular cancer cell count ≥50). Feng *et al.* (42) differentiated MVI into noninvasive (free and adherent types) and invasive (invasive and breakthrough types) MVI, and with further refinement based on the number of MVIs, they classified MVI into Type I (noninvasive MVI and number <5), Type II (invasive MVI or number >5), and Type III (invasive MVI and number >5). However, current MVI classifications are based on nonobjective indicators and still need to be validated by multicenter large-sample studies.

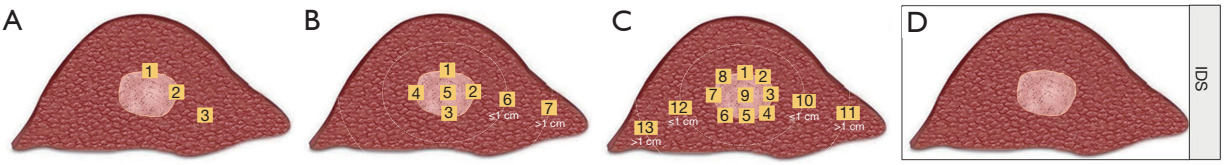

Figure 1 Pathological examination on specimen collection. (A) 3-point method; (B) 7-point method; (C) 13-point method; (D) IDS. IDS, image-matching digital macro-slide.

This consensus recommends the adoption of the pathological grading standard for MVI from the "Guidelines for the Pathological Diagnosis of Primary Liver Cancer" (10): M0: no MVI found; M1: ≤5 MVIs occurring in the peri-tumoral liver tissue area (≤1 cm); M2: >5 MVIs or MVI occurring in the distal peri-tumoral liver tissue area (>1 cm). Recent studies (20,48) have indicated that differentiating MVI according to this standard can be used to assess the prognosis of early-stage patients with HCC more accurately. The median overall survival (OS) for patients with M0, M1, and M2 disease was 61.1, 52.7, and 27.4 months (P<0.001), respectively, and the median disease-free survival (DFS) was 43.0, 29.1, and 13.1 months (P<0.001), respectively.

Recommendation 1: it is recommended to use the MVI pathological grading criteria as outlined in the "Guidelines for Pathological Diagnosis of Primary Liver Cancer": M0: No MVI found; M1: ≤5 MVI and occurring in the peri-tumoral liver tissue area (≤1 cm); M2: >5 MVI or MVI occurring in the distant peri-tumoral liver tissue area (>1 cm) (evidence level: C; recommendation level: strong).

Specimen sampling methods

Currently, the common methods for sampling liver cancer resection specimens include the 3-point method, 7-point method, 13-point method, and image-matching digital macro-slides (IDSs) (*Figure 1*). The Eastern Hepatobiliary Surgery Hospital (EHBH) (20) reported that the "7-point" method for diagnosing MVI could yield a 47.1% detection rate, which is comparable to the "13-point" method with a 51.3% detection rate (P=0.517). Both methods are significantly superior to the "3-point" method, which has a detection rate of 34.5% (P=0.048). Moreover, the "7-point" method is simpler and more practical than the "13-point" method.

However, another study (45) suggested that to improve the detection rate of MVI, the number of sampling points in the tissue adjacent to the cancer should not be fixed but positively correlated with the tumor diameter and number. The authors noted that for tumors with diameters of 1–3 cm, 3–5 cm, or greater than 5 cm, as well as for multiple tumors, the number of sampling points should reach at least 4, 6, 8, or 8, respectively; however, this recommendation still requires further research for validation. IDS refers to the process of slicing the entire liver cancer resection specimen, then further utilizing whole slide imaging (WSI) technology to obtain high-quality visual digital images, and finally analyzing and diagnosing the images, including pathological features of liver cancer such as MVI, using software that matches the scanner. It has been reported (49) that IDS can significantly improve the detection rate of MVI compared to the traditional "7-point" method, but IDS requires high equipment standards and involves a substantial workload in slide reading. With the current immature state of artificial intelligence (AI) diagnosis, its widespread application is limited (49).

Recommendation 2: it is recommended to use the "7-point method" for sampling liver cancer specimens (evidence level: B; recommendation level: strong), and IDS may be used where feasible (evidence level: C; recommendation level: strong).

Clinical typing

Clinical typing, which combines pathological typing and clinical characteristics, can not only more accurately predict the prognosis of patients with liver cancer with MVI but also refine the clinical treatment. Zhang *et al.* (50) constructed nomograms using variables such as alpha-fetoprotein (AFP), tumor capsule, tumor diameter, hepatitis B e-antigen (HBeAg), hepatitis B virus deoxyribonucleic acid (HBV-DNA), tumor number, and esophageal/gastric varices to predict the clinical prognosis of MVI-positive HCC patients. The EHBH reported (51) that the prognosis of HCC patients is significantly related to AFP, the presence of cirrhosis, tumor number, tumor diameter, MVI number, and distribution. Nomograms constructed using these factors, by calculating scores, can classify patients into three types. This clinical typing can accurately predict patient prognosis and only class C patients can benefit from

postoperative adjuvant transarterial chemoembolization (TACE). However, the generalizability of this clinical typing still needs further validation.

MVI prediction

MVI is currently the most important pathological feature that can guide the prevention and treatment of HCC recurrence. The diagnosis of MVI relies on histopathological examination of postoperative resection specimens rather than preoperative biopsy tissues. Due to the delayed results of postoperative pathological examinations, MVI information cannot guide preoperative and intraoperative treatment decisions. This highlights the necessity and importance of predicting MVI before surgery.

Clinical feature prediction

The advantage of using clinical features for predicting MVI lies in its easy application and rapid dissemination once successful. Common clinical features related to MVI prediction include age (52-57), gender (58-60), tumor diameter (61-68), number of tumors (61,67,69-74), tumor volume (12,75,76), tumor location (77), tumor morphology (26,78-81), degree of liver cirrhosis (56,82-86), portal hypertension (63,87,88), HBeAg (55,89), HBV-DNA (63,71,87,90,91), AFP (61,66,76,92-97), AFP-L3 (98-101), Des-gamma-carboxyprothrombin (DCP) (66,76,81,95,102-105), bilirubin level (96,106-109), alkaline phosphatase (ALP) (62,81), alanine aminotransferase (ALT) (59,110,111), aspartate aminotransferase (AST) (62,66,79,112), gamma-glutamyl transferase (GGT) (70,113-116), lactate dehydrogenase (LDH) (70), alpha-L-fucosidase (AFU) (86), neutrophil count (74,117), platelet count (90), lymphocyte count (106), hemoglobin (118), prothrombin time (PT) (59,119), international normalized ratio (INR) (19,53), C-reactive protein (59) and serum amyloid A (120), among others. Other clinical features included pathological characteristics (tumor differentiation (67,121-124), completeness of the tumor capsule (37,83,87,125), capsule invasion (26,126), satellite nodules (40,94,127), etc., the AST/ALT ratio (66), the neutrophil count/monocyte count (NLR) (62,128,129), the ALP/lymphocyte count (ALR) (130), the platelet count/lymphocyte count (PLR) (131,132), the GGT/lymphocyte count (GLR) (117,133), the GGT/platelet count (GPR) (117), the lymphocyte count/monocyte count (LMR) (54), the body mass index (BMI) (134,135), and the circulating tumor cell count (136). Pathological characteristics are primarily used for predicting MVI in liver tumor biopsies and serve as supplements for the missed detection of MVI by classic sampling methods.

It has been reported that the accuracy of single clinical feature prediction of MVI is not ideal. For example, the sensitivity of AFP for predicting MVI ranges from 44% to 64%, and the specificity ranges from 66% to 82% (112,137,138). The sensitivity of DCP for predicting MVI was 70%, with a specificity of 63%. The sensitivity and specificity of tumor diameter for predicting MVI were 50.0% and 70.9%, respectively (138). Therefore, clinical features are often used as one of the components of MVI prediction models and are not recommended for the independent prediction of MVI. For example, the combination of AFP, DCP, and tumor diameter for predicting MVI achieved an area under the curve (AUC) of 0.74 (95,102,104).

Imaging prediction

Imaging prediction has been the fastest-progressing area in predicting MVI in recent years. In particular, the introduction of radiomics has led to more accurate MVI prediction than image features, making it one of the most promising directions for MVI prediction development. Commonly used imaging features for predicting MVI include whether the tumor capsule is intact or invasive (65,78,81,90,109,110,139), whether the tumor margin is smooth (86,128,139-144), whether there is enhancement around the tumor (58,92,93,106,128,144-146), enhancement patterns (24,90,124,147,148), intratumoral artery visibility (69,106,139,144,149-151), lack of blood supply (152), and magnetic resonance imaging (MRI)-specific apparent diffusion coefficient (ADC) (22,65,110,153-156), peri-tumoral low density in the hepatobiliary phase (65,69,78,92,140,145,148,157), D-value (143,144,155,156,158,159), T1 relaxation time (154), T2 peri-tumoral low signal (24), MRI elastography characteristics (146,160,161), MRI-restricted spectrum imaging features (162), computed tomography (CT)-specific arterial phase CT value (163), ultrasound-specific high aspect ratio (164), minimum grayscale value (164), grayscale ratio (124), ultrasound elastography characteristics (165), positron emission tomography (PET)-CT-specific standardized uptake value (SUV) (100,166-171), etc. Previous studies indicated that single imaging features, such as tumor margin fuzziness or irregularity (sensitivity: 66–73%; specificity: 61–86%) (172,173), peri-tumoral low density (sensitivity: 43–55%; specificity: 87–90%) (145,173), arterial phase peri-tumoral enhancement (sensitivity: 59%; specificity: 80%) (145), ADC (sensitivity: 73%; specificity: 70%) (174), and PET-CT SUV values (sensitivity: 67%; specificity: 80%) (170), still cannot efficiently predict MVI.

Therefore, combining indicators for MVI prediction is recommended.

Since applying radiomics for MVI prediction, its development has been rapid. Several meta-analyses have estimated the ability of different imaging methods to predict MVI. CT radiomics predicts MVI with a sensitivity and specificity of 82% and 79%, respectively, and an AUC of 0.85–0.87 (175,176); MRI radiomics predicts MVI with a sensitivity and specificity of 79% and 81%, respectively, and an AUC of 0.87 (175,177); and ultrasound radiomics predicts MVI with a sensitivity and specificity of 79% and 70%, respectively, and an AUC of 0.74–0.81 (175,178), of which the predictive efficiency of ultrasound radiomics based on the original radio frequency (RF) signal is superior to that based on grayscale images (179). However, these studies were limited by small sample sizes, lack of external validation, and nonuniform inclusion criteria. Further large-scale validation of their predictive efficiency is necessary. Additionally, deep learning technology has also been preliminarily applied in the field of MVI prediction. Several studies have reported (180-188) AUCs ranging from 0.74 to 0.98, with the predictive accuracy peaking at 99.1%. Nonetheless, this technology still requires large-scale validation to confirm its predictive efficiency.

Comprehensive prediction methods

The combination of multiple factors could enhance the accuracy of MVI prediction over the use of a single factor. Lei *et al.* collected data from 1,004 early-stage HCC patients to train and evaluate an MVI predictive model, the EHBH nomogram, which included seven factors: tumor diameter, number of tumors, tumor capsule, AFP levels, platelet count, HBV DNA levels, and typical imaging enhancement features. At an optimal threshold of 200, the sensitivity, specificity and AUC were 73.5%, 76.6% and 0.81, respectively (90). Lee *et al.* (189) reported that using a combination of AFP levels, DCP levels, peritumoral enhancement, and peritumoral low density to predict the occurrence of MVI in patients with HCC <3 cm yielded an AUC, sensitivity, and specificity of 0.87, 65.2%, and 85.9%, respectively. Researchers used 377 patients from two centers to train and evaluate this model. Furthermore, West China Hospital (66) reported a study including 2,160 patients in which the combination of AFP levels, DCP levels, tumor diameter, satellite nodules, AST, and the AST/ALT ratio was used to predict MVI, with an AUC of 0.80. Another study (190) compared the above prediction methods and reported that the EHBH nomogram is the most stable and reliable among all current prediction methods.

Recommendation 3: it is recommended that HCC patients undergo preoperative MVI prediction, and using the EHBH nomogram for predicting MVI is highly recommended (evidence level: C; recommendation strength: weak).

MVI-guided treatment

HCC treatment with MVI follows two main principles: ensuring safety and improving oncological outcomes. Under the premise of ensuring treatment safety, based on the tumor situation and MVI information, the first treatment should include methods that are more effective for treating the primary lesion and MVI. Multidisciplinary comprehensive treatment is needed to reduce recurrence rates, prolong survival time, and improve quality of life.

First curative treatment

For the first treatment of HCC patients with MVI, few studies have compared the efficacy of different treatment methods, and there is a lack of prospective studies. Retrospective studies have shown that for patients with small HCC (diameter ≤3 cm) predicted preoperatively to be at high risk for MVI, liver resection, especially anatomical liver resection, has significantly better 5-year DFS and OS than percutaneous radiofrequency ablation (PRFA)/percutaneous microwave coagulation therapy (PMCT); for low-risk patients, the efficacy of liver resection is similar to that of PRFA/PMCT (16,26,189,191). For patients with HCC meeting the Milan criteria, the long-term prognosis of patients who underwent liver transplantation was better for MVI-positive patients than for those who underwent liver resection, while there was no significant difference in prognosis between patients who underwent anatomical liver resection and those who underwent liver transplantation for MVI-negative patients (192,193). However, another study (194) reported that compared to liver resection, liver transplantation does not provide a survival benefit for patients with resectable HCC with MVI, benefiting only MVI-negative patients. The exploration of MVI prediction is immature, and more clinical trials are needed to improve the ability of MVI to accurately guide early HCC treatment decisions.

Recommendation 4: for patients with resectable HCC, surgical resection is recommended as the first choice (evidence level: C; recommendation strength: strong); for patients with a diameter ≤3 cm who are predicted to be at low risk for MVI, either surgery or PRFA/PMCT can be chosen (evidence level: C; recommendation strength: weak).

Postoperative recurrence prevention

(I) Preoperative neoadjuvant therapy

It has been shown (195,196) that the degree of tumor necrosis induced by preoperative neoadjuvant TACE is negatively correlated with the detection rate of MVI in postoperative pathological examinations. A study from the EHBH (196) showed that in tumor resection specimens with more than 90% necrosis after TACE, the detection rate of MVI was lower than that in the control group that did not undergo TACE before surgery (8.1% *vs.* 34.2%, P<0.05); for those with 60–90% necrosis, the detection rates between the two groups were similar (47.1% *vs.* 43.3%, P>0.05); and for those with less than 60% necrosis, the detection rate in the TACE group was significantly greater than that in the control group (88.0% *vs.* 48.0%, P<0.05). Overall, neoadjuvant TACE before liver resection does not reduce the overall incidence of MVI or improve prognosis (196,197). Kim *et al.* (198) provided neoadjuvant TACE to patients who underwent liver transplantation and met the Milan criteria and showed that this treatment did not reduce the incidence of MVI or improve long-term survival. Currently, studies on the efficacy of neoadjuvant TACE for patients who are preoperatively predicted to be at high risk for MVI are scarce. A randomized controlled study from the EHBH showed that preoperative radiotherapy does not reduce the postoperative recurrence rate or prolong OS time in high-risk MVI patients (199), but this study had a small sample size, and the results still need to be verified by larger prospective studies.

Recommendation 5: it is not currently recommended to use TACE or radiotherapy alone as neoadjuvant therapy for HCC patients who are predicted to be at high risk for MVI (evidence level: C; recommendation strength: weak); to reduce postoperative recurrence rates, it is encouraged to conduct clinical trials of neoadjuvant therapy (GPS) in these patients.

(II) Intraoperative treatment

Compared with nonanatomic liver resection, anatomic liver resection offers superior long-term therapeutic effects for patients with pathologically MVI-positive HCC (26,92,115,119,200-209), and the efficacy of laparoscopic hepatectomy is like that of open hepatectomy (210). On the other hand, MVI-negative patients do not benefit from anatomic liver resection (206-208). In patients who undergo hepatectomy, in addition to the type of surgery, the width of the margin is also closely related to prognosis. Several studies have demonstrated significantly prolonged DFS and OS in patients with wide margin (margin distance ≥1 cm) resection (204,209,211-214). This prognostic value is even more important than that of anatomical liver resection (28,215-218), but whether MVI-negative patients could benefit from wide-margin resection remains controversial (81,213,214,218). Additionally, a prospective phase II clinical trial reported (219) that intraoperative radiotherapy significantly improved postoperative DFS and OS for patients with centrally located HCC with MVI and narrow margins, while this phenomenon was not observed in MVI-negative patients. Tumor intrahepatic dissemination and metastasis caused by MVI are major causes of death in patients. To ensure surgical safety, it is advisable to minimize and alleviate compression and flipping of the liver and tumor during surgery and to perform *in situ* resection to reduce and avoid the risk of intrahepatic dissemination. Preemptive ligation or blocking of corresponding watershed vessels also helps to reduce this risk.

Recommendation 6: it is recommended to perform anatomic liver resection or ensure a margin distance ≥1 cm for HCC patients predicted to be at high risk for MVI (evidence level: C; recommendation strength: strong); if anatomic liver resection is not possible or a margin distance ≥1 cm cannot be ensured, intraoperative radiotherapy may be used in equipped centers (evidence level: C; recommendation strength: weak).

(III) Postoperative adjuvant therapy

It has been reported that adjuvant therapy for HCC patients with MVI mainly includes the following measures:

(i) Antiviral therapy

For MVI-positive and hepatitis B-related HCC patients, standardized antiviral therapy can both protect liver function and reduce the recurrence rate, thereby improving long-term survival. Preoperative antiviral therapy can significantly reduce the incidence of MVI (91,220,221), and continuous postoperative antiviral therapy significantly prolongs DFS and OS (209,220,222-225). The commonly used anti-HBV nucleos(t)ide analogs include entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide.

(ii) Adjuvant TACE (A-TACE)

TACE, which has a short treatment cycle and high safety, is the most used postoperative adjuvant treatment for liver cancer in China. Several studies (209,226-230) have reported that TACE can reduce the recurrence rate and prolong the survival time of HCC patients with MVI, but it does not have this effect on MVI-negative patients (231,232). Additionally, two cycles of A-TACE appeared to have better efficacy than one cycle (233), but the reliability of this result still needs further confirmation. Additionally,

only class C patients in the Eastern Hepatobiliary MVI clinical classification group benefitted from A-TACE, and whether class A and B patients benefit still requires further research (51).

(iii) Adjuvant radiotherapy

Two prospective studies have shown that postoperative adjuvant radiotherapy significantly prolongs the DFS and OS of HCC patients with MVI (234,235), especially for those with narrow margins. Retrospective studies (236,237) indicated that postoperative adjuvant radiotherapy is superior to A-TACE, but there is limited research evidence in this area. The recommended technique for postoperative radiotherapy for HCC patients with MVI is conventional fractionated intensity-modulated radiation therapy, with a total dose of 50–60 Gy, and the target area should include 1.0–2.0 cm of liver parenchyma beside the surgical margin.

(iv) Adjuvant hepatic arterial infusion chemotherapy (HAIC)

A multicenter randomized controlled study in China that included 315 patients with HCC and MVI showed (238) that postoperative adjuvant HAIC based on the FOLFOX chemotherapy regimen significantly reduced the recurrence rate compared to the control group. Another meta-analysis (239) of 11 studies including 1,290 patients showed that postoperative adjuvant HAIC can benefit HCC patients in MVI subgroups.

(v) Postoperative targeted therapy or targeted combined immunotherapy

Although the STORM trial (240) failed to prove that sorafenib could reduce postoperative recurrence of liver cancer, it has been reported that postoperative sorafenib (241-243) or lenvatinib (244,245) can benefit HCC patients with MVI. The IMbrave050 study (246) of adjuvant treatment with atezolizumab combined with bevacizumab (T+A) reached its primary endpoint for DFS in the interim analysis, showing a 28% reduction in the risk of recurrence/distant metastasis or death [hazard ratio (HR) for DFS =0.72], suggesting that the T+A regimen could be an effective adjuvant treatment for HCC patients with MVI. A prospective randomized controlled study by the EHBH, which included 198 patients with HCC and MVI (247), reached its prespecified endpoint; compared with active monitoring, sintilimab significantly prolonged DFS (27.7 *vs.* 15.5 months, P<0.001), but further follow-up is required to confirm the difference in OS. Additionally, the results from several phase II or III clinical studies on preventing postoperative recurrence of liver cancer with targeted and immunotherapy combinations are pending. Before choosing targeted therapy and immunotherapy, it is necessary to assess the patient's general physical condition, liver function status, treatment risk, etc. Recommendations for baseline assessment and adverse reaction management refer to the "Chinese Expert Consensus on Immunotherapy for Hepatocellular Carcinoma (2021)" (248).

(vi) Postoperative local treatment combined with systemic treatment

Postoperative combined adjuvant therapy may be superior to single-agent adjuvant treatment. For instance, TACE combined with antiviral therapy (222) is superior to using antiviral therapy or TACE alone; TACE combined with sorafenib is superior to using sorafenib or TACE alone (249). However, all the above are retrospective studies. More solid evidence is needed in the future.

(vii) Post-liver transplantation adjuvant therapy

For MVI-positive liver cancer patients undergoing liver transplantation, in addition to routine early adjustment of the immunosuppressant regimen, it has been reported that therapeutic measures to prevent the recurrence of liver cancer with MVI after transplantation include systemic chemotherapy (250) and plasma exchange (251), but prospective studies are still needed to further clarify their efficacy.

Recommendation 7: postoperative antiviral therapy is recommended for hepatitis B-related HCC patients (evidence level: A; recommendation level: strong), and for patients diagnosed with MVI postoperatively, at least one of the following adjuvant treatments are recommended: T+A (evidence level: A; recommendation level: strong), sintilimab (evidence level: A; recommendation level: strong), TACE (evidence level: B; recommendation level: strong), radiotherapy (evidence level: B; recommendation level: weak), HAIC (evidence level: B; recommendation level: weak), lenvatinib or sorafenib (evidence level: C; recommendation level: weak).

Treatment after recurrence

It has been reported (252) that for MVI-positive HCC recurrence in Barcelona Clinic Liver Cancer (BCLC) stages 0/A, the efficacy of resection and radiofrequency ablation (RFA) is superior to that of TACE, but for stages B/C, the efficacy of the three treatments is similar. According to the "Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus" (253), and considering the consensus committee's discussion, this consensus recommends that even if the prognosis for MVI-positive

HCC recurrence is poor, PRFA/PMCT should be the first choice if indications are met; if the recurrence focus is solitary, there is no portal vein main trunk cancer thrombus, and if the time to recurrence (TTR) is ≥1 year, surgical resection may be considered. Moreover, the efficacy of comprehensive therapy for recurrent foci is superior to monotherapy. For example, TACE combined with RFA (254,255) or sorafenib combined with RFA (256) is superior to RFA alone in treating recurrent small HCC patients with MVI-positive primary tumors. Additionally, TACE combined with sorafenib is superior to TACE alone (257) in treating recurrent unresectable liver cancer with MVI-positive primary tumors. Therefore, treatment for MVI-positive HCC recurrence needs to be performed with caution, taking into consideration the location of the tumor recurrence, TTR, number, and distribution of recurrent lesions. It is recommended that the appropriate treatment plan be selected after discussion by a multidisciplinary team (MDT).

Recommendation 8: it is recommended to decide on the prevention and treatment plan for MVI-positive HCC recurrence after MDT discussion: if there are ≤3 recurrences and the maximum diameter is ≤3 cm, PRFA/PMCT is preferred; if the recurrence focus is solitary, there is no portal vein main trunk cancer thrombus, and TTR ≥1-year, surgical resection may be considered; for unresectable recurrence foci or early recurrence (TTR ≤1 year) and PMCT/PRFA cannot be performed, TACE is recommended (evidence level: C; recommendation level: strong).

Multidisciplinary diagnosis and treatment process

Through multidisciplinary collaboration, MDTs leverage the professional strengths of each discipline to maximize patient benefits, especially for the diagnosis and treatment of HCC patients with MVI, which necessitates the formulation of diagnostic and treatment plans through MDTs. Initially, it is essential to predict MVI for resectable liver cancer patients, preferring surgical resection for high-risk patients and ensuring anatomic liver resection or a resection margin of ≥1 cm whenever possible. Institutions equipped to do so may consider intraoperative radiation therapy for patients with narrow margins. For those at low risk of MVI, liver cancers ≤3 cm in diameter may be treated with resection or PRFA/PMCT, while surgical resection is preferred for liver cancers >3 cm. Subsequently, for postoperative pathological MVI-positive and hepatitis B-related patients, routine antiviral therapy postsurgery is recommended, along with at least one postoperative adjuvant treatment based on the patient's condition, including T+A, sintilimab, TACE, radiation therapy, HAIC, lenvatinib, or sorafenib. Finally, treatment plans for recurrent HCC patients with MVI need to be determined after MDT discussion.

Foresight

In recent years, significant progress has been made in the diagnosis, prediction, and treatment of HCC patients with MVI, but several issues urgently need to be addressed, such as the following: (I) the accuracy of predicting MVI still needs improvement. The prediction method recommended in this consensus also has many limitations and many important factors are not included in the nanogram, such as preoperative anticancer treatment, etc. A previous study confirmed that a single clinical indicator is insufficient to accurately predict MVI. Introducing new variables, such as omics data, may enhance the predictive accuracy. (II) The pathological examination of MVI needs further refinement. The most used pathological sampling method, the "7-point method", has a significantly lower detection rate for MVI than IDS. However, the widespread adoption of IDS is challenging; thus, balancing sampling, detection rates, and application needs further exploration (258). (III) Despite the large number of HCC patients with MVI in China, the current consensus recommendations are relatively limited. Future efforts should utilize China's vast case resources, integrated with the latest treatment advances such as targeted immunotherapy and dual immunotherapy, to conduct more randomized controlled trials to establish more effective treatment methods and plans for HCC patients with MVI. (IV) Further research into the molecular mechanisms of MVI in liver cancer is needed to identify new targets and therapies for treatment.

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