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Consensus

Chinese Multidisciplinary Expert Consensus on the Management of Precancerous Lesions of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality worldwide. China accounts for nearly half of the global HCC burden, largely because of the high prevalence of hepatitis B virus infection and hepatitis B-related cirrhosis. Accumulating evidence indicates that low-grade dysplastic nodules, high-grade dysplastic nodules, and selected molecular subtypes of hepatocellular adenoma are closely linked to hepatocarcinogenesis and should be considered high-risk precursor lesions with malignant potential. Intervention during the precancerous stage may reduce HCC incidence and mortality, but standardized diagnostic criteria and evidence-based management strategies remain incompletely defined. To address this need, a multidisciplinary panel of Chinese experts developed this consensus on the diagnosis and management of precancerous lesions of HCC. The recommendations integrate recent advances in hepatology with expertise in imaging, pathology, and therapeutic decision-making. Their implementation is intended to support individualized risk assessment and multidisciplinary management, with the broader goal of improving early detection, reducing HCC incidence, and increasing long-term survival.

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Introduction

Hepatocellular carcinoma (HCC) imposes a substantial clinical, economic, and societal burden worldwide. Recent data indicate that China accounts for approximately half of the global HCC burden. In China, HCC ranks fourth in cancer incidence and second in cancer-related mortality.[1] HCC commonly evolves through a well-recognized sequence from chronic viral hepatitis to cirrhosis and, ultimately, malignant transformation.[2] Because the disease is often clinically silent, many patients are diagnosed at an advanced stage and are no longer candidates for potentially curative surgery. Consequently, the overall 5-year survival rate remains poor; the most recent national survey in China reported an age-standardized 5-year relative survival rate for liver cancer of only 14.4%.[3] Experience from other malignancies demonstrates that identification and management of precancerous conditions can prevent cancer development, underscoring the value of earlier intervention.[4,5]

Cirrhosis, irrespective of etiology, is the strongest risk factor for HCC. Viral hepatitis, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD) can all drive progressive liver injury and increase the likelihood of malignant transformation. MASLD, diabetes mellitus, and metabolic syndrome, characterized by obesity, insulin resistance, and dyslipidemia, are increasingly recognized as important contributors to HCC risk. The interaction between these risk factors and precancerous conditions highlights the need for systematic surveillance in at-risk populations.[6] Regular screening and timely intervention may improve outcomes, making earlier diagnosis and risk-adapted management a clinical priority.

Against this background, Chinese experts reviewed the international literature and integrated it with clinical experience. Specialists in hepatology, infectious diseases, hepatobiliary surgery, oncology, radiology, and pathology participated in structured discussions. These efforts clarified key concepts, diagnostic standards, screening strategies, treatment options, and follow-up practices for precancerous lesions of HCC. The first Chinese multidisciplinary expert consensus on the diagnosis and management of these lesions was published in China in January 2020, and an updated edition was released in December 2023. Because the evidence

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base remains limited and is evolving rapidly, this consensus should be regarded as an iterative document that will require periodic updates as new data become available.

Methods

A total of 110 experts from leading Chinese institutions, representing hepatology, infectious diseases, hepatobiliary surgery, oncology, diagnostic imaging, and pathology, convened to discuss advances in the diagnosis and treatment of precancerous lesions of HCC. All participants disclosed potential conflicts of interest and confirmed that their participation was uncompensated. A comprehensive literature search was performed in PubMed, China National Knowledge Infrastructure, Web of Science, MEDLINE, and EMBASE, with searches updated through August 2026.

The consensus was developed using the Delphi method, an approach well suited to topics for which high-quality clinical evidence is limited. Successive draft statements and related questions were circulated, discussed, and revised through hybrid expert meetings that combined online and in-person participation. Responses were rated on a five-point scale ranging from "strongly recommended" to "strongly not recommended". The level of agreement (LoA) for each statement was calculated as the percentage of panelists who selected the recommended option. Consistent with Delphi methodology, consensus was predefined as an LoA of at least 80%. On the basis of the LoA and the quality and consistency of the supporting evidence, each recommendation was classified as strong or weak. The final recommendations reflect the panel's collective interpretation of the available evidence and expert experience.

Definition of precancerous lesions of HCC

The characterization of precancerous lesions is based primarily on five criteria proposed by the US National Institutes of Health[7]: (1) the lesion is associated with increased cancer incidence; (2) cancers arising from the precancerous state originate from the constituent cells of the lesion; (3) the lesion is histologically distinct from normal tissue; (4) the lesion shares molecular and phenotypic features with its malignant counterpart while retaining distinguishable differences; and (5) diagnostic methods are available to identify the lesion. More recently, the National Cancer Institute Pre-Cancer Atlas program updated clinical and research considerations for defining precancer.[8] These considerations emphasize somatic clonal evolution in normal tissue, intrinsic and extrinsic drivers that disrupt tissue homeostasis, the distinction between benign growths and true precancer, potential non-cancer harms of lesions, and the characterization of additional precancerous foci identified in cancer resection specimens.

In patients with cirrhosis, hepatocarcinogenesis is a progressive, multistep process that begins with large regenerative nodules, progresses through low-grade dysplastic nodules (LGDN) and high-grade dysplastic nodules (HGDN), and culminates in HCC.[9] Hepatocytes in LGDN and HGDN may show subtle early morphological alterations, including reduced cell size. Compared with background cirrhotic nodules, they may also show steatosis, Mallory hyaline deposition, bile stasis, clear-cell change, and iron or copper deposition.[10,11] These features mark the transition toward HCC and support early detection and surveillance in patients with cirrhosis.

Beyond dysplastic nodules (DN), the increasing detection of hepatocellular adenoma (HCA) and the malignant potential of selected HCA subtypes have attracted growing attention. Although the etiology of HCA is not fully understood, associations with oral contraceptive use and other risk factors are well established, and HCA usually arises in noncirrhotic livers. Advances in genotyping and histological phenotyping have enabled more refined molecular classification. Importantly, β-catenin activation, hemorrhage, and tumor size greater than 5 cm are recognized risk factors for malignant transformation.[12,13]

Previous studies indicate that LGDN, HGDN, and selected molecular subtypes of HCA should be regarded as precancerous lesions with potential to progress to HCC. Pathological studies also demonstrate a stepwise increase in malignant transformation risk from LGDN to HGDN.

Chronic noninfectious liver diseases, particularly MASLD and alcohol-related liver disease (ALD), also contribute to chronic hepatic inflammation and may promote the formation of precancerous lesions.[14] Driven by chromosomal instability, microenvironmental remodeling, and oncogenic activation, these lesions substantially increase the likelihood of HCC development. They therefore warrant close attention and proactive management to reduce progression risk.[15] Early detection and effective intervention are essential for improving prognosis.

> ***Recommendation 1:*** Precancerous lesions of HCC occur mainly in patients with chronic hepatitis and cirrhosis. On the basis of recent clinicopathological studies, LGDN, HGDN, and β-catenin-activated HCA should be classified as precancerous lesions of HCC and should undergo careful surveillance and active management (LoA 87.38%, weak recommendation).

Screening for precancerous lesions of HCC

In individuals with precancerous lesions of HCC, risk factor-based stratification should guide surveillance intensity. Timely identification and diagnosis of these lesions are central to HCC prevention and may enable curative treatment.

Screening population

Recent epidemiological surveys in China show a shift in HCC etiology from viral hepatitis toward metabolic liver disease, thereby expanding the population that may benefit from surveillance.[16] The current "one-size-fits-all" approach to HCC screening should therefore move toward individualized, risk-adapted early detection. The International Liver Cancer Association and the 2025 European Association for the Study of the Liver (EASL) guidelines support risk stratification models that integrate clinical, molecular, and other biological indicators.[17] The EASL 2025 guidelines recommend targeted surveillance for individuals with an annual HCC risk exceeding 1.5% and suggest that risk scoring tools such as the age-male-albumin-bilirubin-platelets (aMAP) score may aid in identifying high-risk individuals.[18] For populations with precancerous lesions of HCC, risk stratification and cost-effectiveness should both be considered to maximize surveillance value. Regular surveillance is recommended for individuals with cirrhosis, hepatitis virus infection, ALD, MASLD, or glycogen storage disease-associated HCA. In particular, Asian men older than 40 years and Asian women older than 50 years with cirrhosis should undergo surveillance. Individuals with a family history of HCC also warrant surveillance because of hereditary predisposition.[19]

Screening methods

Screening primarily includes imaging and serum biomarker

testing. Common approaches include contrast-enhanced ultrasound (CEUS) combined with alpha-fetoprotein (AFP), des-gamma-carboxyprothrombin, also known as protein induced by vitamin K absence or antagonist II (PIVKA-II), and the *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3). Magnetic resonance imaging (MRI) with gadoxetic acid (Gd-EOB-DTPA) is also recommended because it can help differentiate LGDN, HGDN, and early HCC (eHCC).

Screening process

A stratified screening strategy is recommended. High-risk populations should first be identified using medical history and cost-effective, accessible screening methods. In individuals without intrahepatic nodules or lesions, abdominal ultrasound every 6 months is recommended. In those with intrahepatic nodules, further characterization with CEUS and/or Gd-EOB-DTPA-enhanced MRI is necessary. If lesion characterization remains uncertain but clinical suspicion for HCC is high, liver biopsy may be considered. Histopathological assessment of intrahepatic nodules remains the definitive method for diagnosing precancerous conditions. Before biopsy, platelet count, prothrombin time, and the presence of ascites should be assessed to ensure appropriate patient selection and procedural safety.

Biopsy can refine diagnosis and guide subsequent treatment decisions. In individuals classified as high or very high risk, serial imaging and serum biomarker assessment are essential. Follow-up at 3- to 6-month intervals is advisable to monitor changes in nodule size and imaging features. Gd-EOB-DTPA-enhanced MRI performed approximately every 6 months provides a more comprehensive assessment and may facilitate timely intervention when needed.[20]

Recommendation 2: Regular surveillance using imaging and tumor markers (AFP, PIVKA-II, and AFP-L3) is recommended for individuals at high or very high risk of HCC. This group includes patients with cirrhosis of any etiology, including ALD or MASLD, and those with β-catenin-activated HCA, particularly Asian men older than 40 years and Asian women older than 50 years. Surveillance should be performed every 6 months (LoA 97.09%, strong recommendation).

Recommendation 3: Patients with cirrhosis related to hepatitis B virus or hepatitis C virus should be considered at high risk of HCC and should undergo regular surveillance for early detection of precancerous lesions of HCC, regardless of sustained virological response after antiviral therapy (LoA 99.82%, strong recommendation).

Recommendation 4: Although curative treatment options are limited for patients with decompensated cirrhosis (Child-Pugh class B or C) because of liver failure or other complications, serial surveillance remains important. Early detection and intervention may still provide clinical benefit despite higher healthcare costs (LoA 96.11%, weak recommendation).

Diagnostic strategy for precancerous lesions of HCC

The diagnosis of precancerous lesions of HCC is challenging, particularly at early stages, when lesions are often less than 2 cm in diameter. Reliable preoperative detection methods and clinically applicable diagnostic criteria remain insufficient, resulting in low detection rates. Consequently, many cases are confirmed only by examination of postoperative resection specimens. Current diagnosis relies mainly on imaging, pathological assessment, and molecular diagnostic techniques.

Pathological diagnosis

Sample collection: Pathological examination remains the gold standard for diagnosing precancerous lesions of HCC. Samples are obtained mainly from postoperative resection specimens or preoperative liver biopsy. Important considerations for biopsy include: (1) sampling both the lesion and surrounding liver tissue; (2) recognizing that core needle biopsy has a higher diagnostic yield than fine-needle aspiration; and (3) ensuring close follow-up or timely repeat biopsy after an initial negative result, because the pathology of one nodule may not represent the characteristics or progression of other nodules.

Histological characteristics: In both preoperative and postoperative specimens, the main histological features of precancerous lesions of HCC include the following. (1) Dysplastic foci are dysplastic hepatocellular lesions measuring less than 1 mm and consist mainly of small-cell change and iron-negative hepatocyte clusters. (2) LGDN are composed predominantly of large-cell dysplastic hepatocytes with mildly increased cellular density (less than 1.3 times that of the surrounding liver), mild dysplasia, preserved portal tract structures, and no isolated small arteries or pseudoglandular structures. LGDN can be difficult to distinguish histologically. Dynamic network biomarker model scores have been reported to be significantly higher in LGDN than in cirrhosis, HGDN, or eHCC, suggesting that LGDN may represent a key transition point from cirrhosis to HGDN.[21] (3) HGDN are composed mainly of small-cell dysplastic hepatocytes with moderate to severe cytological and architectural atypia and increased cellular density (more than 1.3- to 2-fold higher than the surrounding liver). Isolated arteries may be observed and are often associated with an expansive growth pattern. When focal malignant transformation occurs within a nodule, the lesion is termed a nodule-in-nodule lesion. In a prospective histology-based cohort study, the hazard ratios for malignant transformation into HCC were 2.96 (95% CI, 1.20–7.31) for LGDN and 16.8 (95% CI, 6.19–45.6) for HGDN, relative to regenerative nodules.[22,23] (4) HCA usually presents as a solitary lesion sharply demarcated from adjacent liver tissue and may be surrounded by an incomplete fibrous capsule. Size varies from 1 to 30 cm. Blood supply vessels are often visible near the capsule. On cut surface, HCA is typically gray-red, soft, and relatively homogeneous, with possible fibrosis, bile stasis, hemorrhage, or necrosis.[24,25] Microscopically, HCA cells closely resemble normal hepatocytes but are slightly larger, show minimal atypia, and rarely have nuclear abnormalities. Tumor cells may undergo fatty or hyaline degeneration and may contain bilirubin or lipofuscin pigments. The cell plates are usually one to two hepatocytes thick.[26]

Immunohistochemical diagnosis: When routine sections of resection specimens do not allow a definitive diagnosis, immunohistochemistry is essential for diagnosis and differential diagnosis. (1) Glypican-3 (GPC-3), a cell-surface heparan sulfate proteoglycan, is significantly upregulated during malignant transformation of HGDN and may serve as an early warning marker of carcinogenesis. (2) CD34, a highly glycosylated type I transmembrane glycoprotein and calcium-binding protein family member, shows progressively increased sinusoidal capillarization and staining intensity during multistep progression from LGDN to HGDN and eHCC.[27] (3) Luo *et al.* reported significant downregulation of leukemia inhibitory factor receptor (LIFR) expression with concomitant CD34 upregulation during the transition from LGDN to

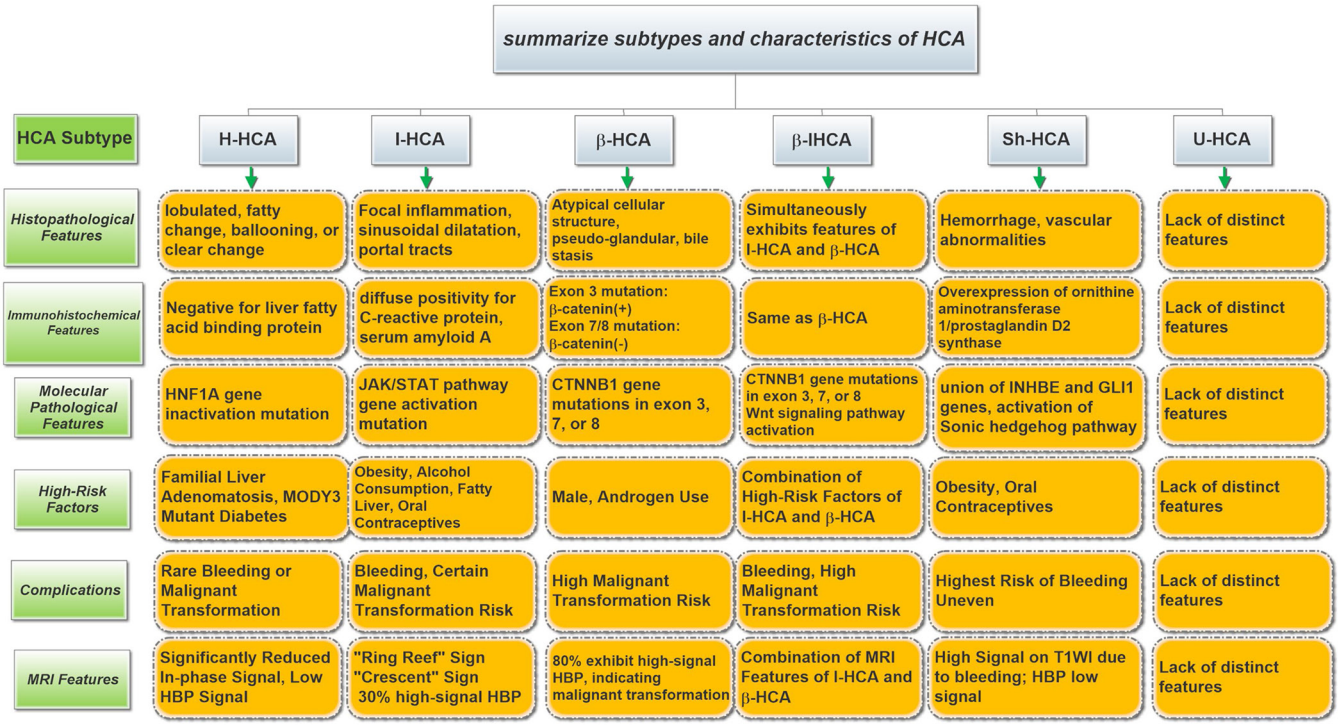


Fig. 1. Summary of the pathological, molecular, imaging, and clinical characteristics of HCA subtypes. HCA, hepatocellular adenoma; H-HCA, HNF-1α-inactivated hepatocellular adenoma; HNF1A, hepatocyte nuclear factor 1 alpha; I-HCA, inflammatory hepatocellular adenoma; β-HCA, β-catenin-activated hepatocellular adenoma; β-IHCA, β-catenin-activated inflammatory hepatocellular adenoma; sh-HCA, sonic hedgehog-type hepatocellular adenoma; U-HCA, unclassified hepatocellular adenoma; CTNNB1, catenin beta 1; INHBE, inhibin subunit beta E; JAK/STAT, Janus kinase/signal transducer and activator of transcription; GLI1, GLI family zinc finger protein 1; HBP, hepatobiliary phase; MODY3, maturity-onset diabetes of the young type 3; MRI, magnetic resonance imaging; T1WI, T1-weighted imaging.

eHCC. Simultaneous assessment of LIFR and CD34 yielded an area under the receiver operating characteristic curve of 0.960 and improved discrimination between HGDN and well-differentiated HCC.[28] These findings indicate that combined biomarker panels can improve discrimination between benign and malignant liver tumors. For example, the combination of GPC-3, heat shock protein 70 (HSP70), and glutamine synthetase (GS), with any two markers positive, provides 72% sensitivity and 100% specificity for HCC diagnosis.[29] A panel of CD34, GPC-3, GS, and HSP70 provides useful ancillary value in differentiating benign from malignant hepatocellular tumors.[30] In addition, a biomarker panel of sulfite oxidase (SUOX), aldo-keto reductase family 1 member B10 (AKR1B10), and CD34 showed 93.8% sensitivity and 95.2% specificity for well-differentiated small HCC, particularly for differentiating it from HGDN.[31] (4) HSP70 is usually not expressed in normal hepatocytes or HCA but is frequently overexpressed in HCC. GS may show strong diffuse positivity in both HCC and HCA; careful interpretation is therefore needed to avoid misclassification.[32] HCA can be further classified into subtypes using immunohistochemical and molecular pathological findings, as summarized in Figure 1.

Molecular pathology diagnosis: Several studies have provided insights that may support future molecular diagnostics for precancerous lesions of HCC. Llovet *et al.* analyzed candidate gene transcription profiles in DN and eHCC arising in cirrhosis using reverse transcription polymerase chain reaction. They identified differential expression of 12 genes in eHCC compared with DN, including TERT, GPC3, gankyrin, survivin, TOP2A, LYVE1, E-cadherin, IGFBP3, PDGFRA, TGFA, cyclin D1, and HGF. Five genes were upregulated and seven were downregulated. These expression changes showed high diagnostic accuracy, with receiver operating characteristic curve values of at least 0.8 and more than twofold changes.[33] Nault *et al.* found that TERT promoter mutations increased stepwise from LGDN (6%) to HGDN (19%) and eHCC (61%), suggesting that TERT promoter mutations may serve as predictive biomarkers of carcinogenesis risk in precancerous lesions.[34]

Jee *et al.* examined DNA methylation changes in samples from patients with cirrhosis, HGDN, eHCC, and advanced HCC (aHCC). Methylation levels increased progressively during HCC onset and progression, particularly CpG island hypermethylation. Methylation levels in eHCC and aHCC were significantly higher than those in cirrhosis and HGDN. Compared with cirrhosis and HGDN, eHCC also showed pronounced genome-wide DNA copy-number losses, including loss of tumor-suppressor gene copy numbers in chromosomal regions 4q and 13q. Transcriptomic analysis showed increased expression of endoplasmic reticulum stress-related genes in HGDN, whereas eHCC showed marked oncogene upregulation, highlighting the complex molecular transition from precancerous lesions to malignant disease.[35]

Several studies have specifically focused on artificial intelligence (AI)-assisted differentiation between eHCC and its precancerous precursor HGDN. To address this clinical dilemma, researchers developed a two-stage multiscale deep learning model (TMC-net) based on hematoxylin and eosin-stained whole-slide images. Through comparative transcriptomic analysis, four marker genes were identified. The resulting multimodal model, integrating histopathological and transcriptomic features, achieved values for the area under

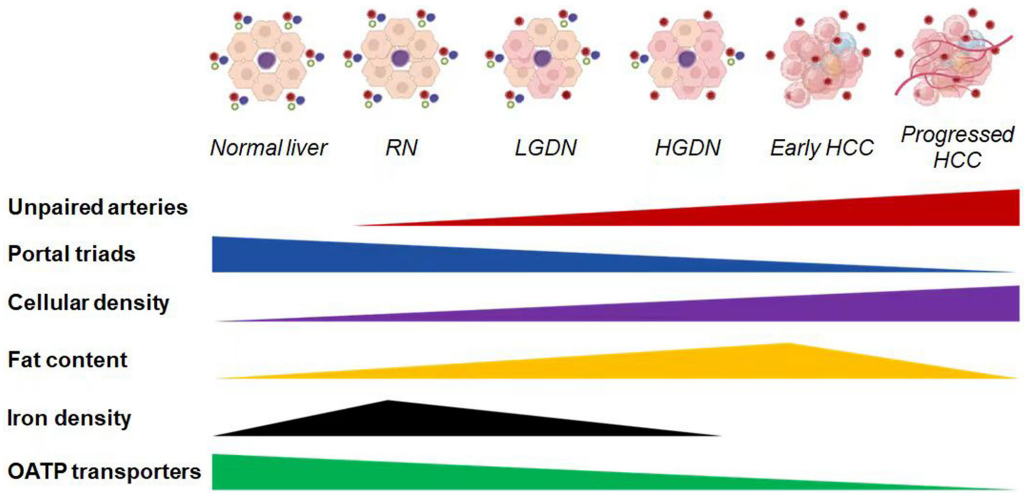


Fig. 2. Schematic diagram of the core pathological process in the multistep progression of HCC in the setting of cirrhosis. Imaging techniques can comprehensively reflect the evolution of these key pathological processes. Increased non-paired aberrant arterial blood supply within nodules appears as arterial phase hyperenhancement. Reduction of the portal venous triad is observed in the portal venous and/or delayed phases and is characterized by washout. Increased cellular density and disruption of nodular architecture appear as restricted diffusion on diffusion-weighted imaging. Fat deposition within nodules is indicated by decreased signal intensity on MRI opposed-phase images compared with in-phase images. Iron deposition is identifiable as low signal intensity across all imaging sequences. Reduced expression of organic anion transporting polypeptide (OATP) on the cell membrane manifests as low signal intensity on hepatobiliary-phase images of gadoxetic acid-enhanced MRI. HCC, hepatocellular carcinoma; HGDN, high-grade dysplastic nodule; LGDN, low-grade dysplastic nodule; MRI, magnetic resonance imaging; RN, regenerative nodule.

the receiver operating characteristic curve of 0.8875 and 0.9500 on internal and external test sets, respectively.[36]

Recommendation 5: Pathological examination is essential for diagnosing precancerous lesions of HCC. Core needle biopsy is recommended and should include the target lesion and adjacent transitional or nontumoral liver tissue to improve diagnostic accuracy. Expert pathological review is advised, particularly when distinguishing HGDN from early HCC. For HCA with available tissue, immunohistochemical and molecular pathological analyses should be performed for accurate subtyping (LoA 90.29%, strong recommendation).

Recommendation 6: For diagnostically challenging precancerous lesions, immunohistochemistry should be used to improve diagnostic accuracy. A panel including CD34, GPC-3, GS, and HSP70 is recommended. Additional markers, such as SUOX and AKR1B10, and TERT promoter mutation analysis may provide further diagnostic information (LoA 99.03%, strong recommendation).

Recommendation 7: In patients with suspected precancerous lesions or HCC and an initial negative biopsy result, repeat biopsy should be considered, especially when sampling is inadequate. If repeat biopsy is not performed or remains negative, close follow-up with multimodal imaging every 2–3 months and measurement of serum AFP, AFP-L3, and PIVKA-II is recommended to clarify the diagnosis (LoA 94.17%, weak recommendation).

Imaging diagnosis

Imaging is central to the diagnosis of precancerous lesions of HCC. The main modalities are ultrasound (US), CEUS, computed tomography (CT), and MRI. Used in a complementary manner, these modalities enable more comprehensive lesion assessment and support more informed diagnostic and treatment decisions.

Imaging diagnosis of LGDN and HGDN: Progression from regenerative nodule to LGDN, HGDN, eHCC, and aHCC is accompanied by incremental changes in blood supply, cellular density, fat content, iron deposition, and organic anion transporting polypeptide (OATP) expression on the cell membrane, as shown in Figure 2.

(1) US and CEUS: On conventional US, DN may appear as slightly hypoechoic or hyperechoic liver lesions, which makes differentiation from eHCC difficult. On CEUS, LGDN usually show isoenhancement across phases. HGDN show more variable patterns, including persistent hypoenhancement, early arterial hypoenhancement followed by later enhancement, or arterial hyperenhancement with mild hypoenhancement in the portal venous and/or delayed phases. The latter pattern may resemble eHCC. Time-intensity curve characteristics correlate with nodule blood supply and tissue structure. HCC typically shows a wash-in and wash-out pattern consistent with hypervascularity, whereas DN usually show a slow-in and slow-out pattern consistent with a more benign vascular profile.[37] (2) Dynamic contrast-enhanced CT: The diagnostic utility of CT for DN is limited, with reported sensitivities of approximately 20%–30% for LGDN and 65%–71% for HGDN.[38] Most DN appear as indistinct nodules with density similar to or slightly lower than that of the surrounding liver on unenhanced scans. During the arterial phase, enhancement is usually comparable to or slightly lower than that of the liver parenchyma. In the portal venous and delayed phases, variable washout may be observed. Some HGDN may show arterial phase hyperenhancement because of increased hepatic arterial supply. (3) Multiparametric contrast-enhanced MRI: MRI is the most accurate imaging modality for DN diagnosis. On unenhanced sequences, DN show variable signal intensity depending on iron, glycogen, and fat content. They are typically hypointense on T1- and T2-weighted images, although signal intensity may be slightly lower or higher than that of surrounding liver tissue. Fat-containing nodules, which may indicate HGDN or eHCC, show signal loss on opposed-phase

Table 1. Summary of MRI features of different hepatic nodules

Nodule	T2-weighted images	DWI	T1-weighted images	Arterial phase	Portal venous phase	Hepatobiliary phase
LGDN	Iso/slightly low/ slightly high	Iso/slightly high	Iso/slightly low/ slightly high	Iso	Iso/slightly low	Iso/slightly low
HGDN	Iso/slightly high	Iso/slightly high	Iso/slightly low	Iso/slightly high	Iso/slightly low	Slightly low
eHCC	Slightly high	Hyper	Slightly low	Iso or slightly high	Iso/slightly low	Slightly low/ hypo
aHCC	Slightly high	Hyper	Slightly low	Hyper	Slightly low	Hypo

LGDN, low-grade dysplastic nodule; HGDN, high-grade dysplastic nodule; eHCC, early hepatocellular carcinoma; aHCC, advanced hepatocellular carcinoma; DWI, diffusion-weighted imaging; hypo, hypointensity; hyper, hyperintensity; iso, isointensity; MRI, magnetic resonance imaging.

images compared with in-phase images. On diffusion-weighted imaging, DN may be isointense or slightly hyperintense because of increased cellular density and varying degrees of architectural disruption. On dynamic contrast-enhanced sequences, most DN have signal intensity comparable to that of background liver parenchyma in all postcontrast phases.[39] Some nodules show washout in the portal venous and delayed phases because of reduced portal venous supply. Certain HGDN may show arterial hyperenhancement as non-paired arterial blood supply increases. (4) Gd-EOB-DTPA-enhanced MRI: In the hepatobiliary phase (HBP), LGDN typically show isointensity, reflecting OATP expression comparable to that of the surrounding liver. In contrast, HGDN generally show mildly reduced signal intensity because of variable reduction in OATP expression. Imaging characteristics of these nodules are summarized in Table 1. Combining low HBP signal intensity, arterial hyperenhancement, and absence of restricted diffusion increases the diagnostic sensitivity and specificity for HGDN to 94.7% and 99.3%, respectively. Mild T2-weighted hyperintensity, restricted diffusion, and low portal venous phase signal intensity are key indicators for differentiating HGDN from eHCC.[40,41] In a multicenter retrospective study of hypovascular nodules with low HBP signal intensity and diameter ≤ 3.0 cm, 44% were aHCC, 20% were eHCC, 28% were HGDN, and 8% were LGDN. Serum AFP ≥ 100 ng/mL, well-defined nodule margins, low T1-weighted signal intensity, mild T2-weighted hyperintensity, and restricted diffusion were predictors of aHCC.[42] Multiple studies have shown that hypovascular HGDN with low HBP signal intensity are prone to malignant transformation.

Without treatment, approximately 15%–77.3% of these lesions may undergo malignant transformation within one year.[43,44] Risk factors for malignant transformation include cirrhosis, nodule diameter ≥ 10–15 mm, low T1-weighted signal intensity, mild T2-weighted hyperintensity, and restricted diffusion.[45,46] Increased arterial blood supply is the most important sign of nodule progression to HCC during follow-up; routine thin-section arterial phase imaging is therefore recommended.

Recommendation 8: Multiparametric contrast-enhanced MRI, which provides high soft-tissue resolution without ionizing radiation, is recommended as the preferred noninvasive imaging technique for diagnosing DN (LoA 96.11%, strong recommendation).
Recommendation 9: Gd-EOB-DTPA-enhanced MRI is a key diagnostic tool for DN. Mild-to-moderate T1 hypointensity, mild-to-moderate T2 hyperintensity, and diffusion restriction are important radiological indicators of malignant transformation to early HCC (LoA 96.12%, strong recommendation).
Recommendation 10: In high-risk individuals (e.g., patients with cirrhosis of any etiology) with newly detected liver nodules on ultrasound, further characterization is recommended. For diagnosing HGDN and early HCC, the diagnostic modalities can be ranked as follows: Gd-EOB-DTPA-enhanced MRI > multiparametric MRI without hepatobiliary contrast > dynamic CT > CEUS. Notably, for individuals with cirrhosis or other major risk factors, any rising tumor markers (AFP, PIVKA-II, AFP-L3) should prompt immediate contrast-enhanced CT or MRI evaluation. (LoA 88.35%, strong recommendation).

Imaging diagnosis of HCA: According to genetic, molecular, pathological, and clinical features, the 2019 World Health Organization classification divides HCA into six subtypes.[47] Although conventional imaging can contribute to HCA diagnosis, MRI is considered the leading modality for diagnosis, classification, and assessment of malignant potential.[48] HCA subtypes show variable appearances on multiparametric dynamic contrast-enhanced MRI.

Figure 1 summarizes the molecular, imaging, and clinical features of the main HCA subtypes. (1) HNF-1α-inactivated hepatocellular adenoma (H-HCA) typically shows slightly low signal intensity on in-phase T1-weighted images and mildly high signal intensity on T2-weighted images. Intralesional lipid deposition often results in signal loss on opposed-phase images. During the arterial phase, lesions show moderate enhancement, with more pronounced and sustained enhancement in the portal venous and delayed phases. On Gd-EOB-DTPA-enhanced HBP images, lesions usually show low signal intensity.[49,50] (2) Inflammatory hepatocellular adenoma (I-HCA) commonly shows slightly low signal intensity on in-phase T1-weighted images and mildly high signal intensity on T2-weighted images. Lesions show marked arterial phase enhancement with persistent enhancement in the portal venous and delayed phases. The "atoll sign" and "crescent sign" may also be present. On Gd-EOB-DTPA-enhanced MRI, I-HCA usually shows low HBP signal intensity, although approximately 30% of cases show high signal intensity or isointensity. (3) β-catenin-activated hepatocellular adenoma (β-HCA) has variable findings on unenhanced MRI because of differences in hemorrhage and necrosis. On dynamic contrast-enhanced sequences, some lesions show marked arterial phase enhancement resembling HCC, followed by washout in the portal venous and/or delayed phases. A capsule-like enhancement pattern may also be seen in the delayed

phase. Approximately 80% of cases show increased HBP signal intensity on Gd-EOB-DTPA-enhanced MRI. (4) β-catenin-activated inflammatory hepatocellular adenoma (β-IHCA) combines imaging features of I-HCA and β-HCA, including mildly to markedly high T2-weighted signal intensity, marked arterial phase enhancement, and high HBP signal intensity. (5) Sonic hedgehog-type hepatocellular adenoma (sh-HCA) is a newly recognized subtype associated with an increased risk of bleeding. On MRI, sh-HCA is characterized by high T1-weighted signal intensity related to hemorrhage and low HBP signal intensity. Malignant potential is positively associated with β-catenin activation and HBP signal intensity.[51]

Recommendation 11: Multiparametric contrast-enhanced MRI is recommended as the most accurate non-invasive imaging technique for the diagnosis, subtyping, and surveillance of HCA. Although imaging features vary by subtype, common findings include T1 hypointensity, mild-to-moderate T2 hyperintensity, arterial phase hyperenhancement, and persistent enhancement in the portal venous and delayed phases. Specific signs, such as the "atoll sign" or "crescent sign", may be present, and heterogeneous signal may reflect intratumoral hemorrhage (LoA 96.11%, strong recommendation).
Recommendation 12: Regular surveillance for HCA is recommended in selected populations, including women using oral contraceptives, individuals with inherited metabolic diseases, obesity or metabolic syndrome, a family history of HCA, men receiving androgen therapy, and pregnant women. Gd-EOB-DTPA-enhanced MRI is the preferred surveillance modality. Isointensity or hyperintensity in the hepatobiliary phase may suggest β-catenin activation and is an important predictor of malignant transformation (LoA 82.52%, strong recommendation).

Serological diagnosis

Conventional serological biomarkers: No definitive serum markers specific for precancerous lesions of HCC are currently available. Therefore, in high- and extremely high-risk populations, biomarker panels including AFP and its isoforms, PIVKA-II, GP73, osteopontin (OPN), and Dickkopf-1 (DKK-1) are often used as supplementary diagnostic tools. Patients with negative serum biomarkers but concurrent liver nodules require regular serological testing and close follow-up.

AFP and its isoform AFP-L3 can help identify HCC, including tumors < 2 cm in diameter; however, elevated AFP may also reflect hepatic injury and regeneration, which are common in acute and chronic liver disease and cirrhosis.[52] PIVKA-II has important diagnostic value for HCC, particularly in patients without AFP elevation. Combining AFP with newer biomarkers can improve diagnostic accuracy. Several clinical guidelines support the combined use of PIVKA-II, AFP, and AFP-L3 for early HCC screening and diagnosis.[53,54]

Emerging serological diagnostic methods: GP73 has emerged as a promising serum marker for early HCC diagnosis and postoperative recurrence surveillance, and elevated GP73 levels are often detected as HCC progresses.[55,56] OPN is a multifunctional phosphoglycoprotein that is highly expressed in several solid tumors. When combined with AFP for HCC detection, OPN shows 82% sensitivity and 77% specificity, suggesting potential as a molecular biomarker for early HCC diagnosis.[57,58] DKK-1, a member of the Dickkopf secreted protein family, improves HCC diagnostic accuracy when combined with AFP and may help distinguish HCC from precancerous conditions and chronic liver disease stages.[59] Circulating cell-free DNA (cfDNA) consists of fragmented DNA molecules released into plasma. Detection of genetic mutations in cfDNA may enable intervention at very early stages of disease progression.[60,61] cfDNA methylation patterns can also identify tumor-specific and tissue-specific markers, which may be useful for early HCC detection and surveillance.[62,63]

A nationwide multicenter initiative for early HCC detection used cfDNA whole-genome sequencing and 5-hydroxymethylcytosine profiling to develop a multi-omic, multidimensional high-fidelity (HIFI) scoring system. This approach achieved 95.42% sensitivity and 97.91% specificity for distinguishing HCC from non-HCC conditions. In patients with negative AFP or PIVKA-II results, HIFI maintained high sensitivity (90.9%–96.9%), thereby reducing missed diagnoses. For very early-stage (stage 0) and early-stage (stage A) HCC according to the Barcelona Clinic Liver Cancer staging system, HIFI testing achieved accuracies of 88.9% and 94.4%, respectively, outperforming AFP (22.2% and 16.7%) and PIVKA-II (55.6% and 61.1%).[64,65] Existing data suggest that the HIFI scoring system has consistent performance and high reproducibility, regardless of medical history, clinicopathological characteristics, or geographic region.

Beyond cfDNA mutation detection, circulating tumor DNA methylation profiling has emerged as a promising approach for early HCC detection, with studies demonstrating high diagnostic efficacy for early-stage HCC. Fragmentomic analysis of cfDNA—including fragment size selection, copy number variation profiling, and end-motif analysis—has also shown high performance for early diagnosis in high-risk populations.[66] Furthermore, exosomes carry diverse molecular cargoes (e.g., microRNAs [miRNAs], proteins, and lipids) that reflect the malignant potential of precursor lesions. Specific exosomal miRNAs, such as miR-122 (AUCAUC0.891), have been reported to outperform AFP for eHCC detection.[67,68]

Recommendation 13: Serum AFP, PIVKA-II, and AFP-L3 are recommended for HCC diagnosis and treatment monitoring in high-risk populations. The GALAD (gender, age, AFP-L3, AFP, and des-gamma-carboxy-prothrombin) score and miRNA-based assays may also support early detection. However, more accurate serum biomarkers for diagnosing precancerous lesions of HCC are still needed (LoA 90.29%, strong recommendation).
Recommendation 14: Individuals at intermediate to high risk for HCC should undergo further evaluation with imaging (US or MRI) and serum biomarkers (AFP, AFP-L3, and PIVKA-II), or liquid biopsy using cell-free DNA whole-genome sequencing. Extremely high HCC risk is suggested by any of the following: US-detected nodules ≤ 2 cm or atypical lesions, AFP ≥ 20 ng/mL, PIVKA-II ≥ 40 mAU/mL, AFP-L3 ≥ 15%, or high-risk cfDNA findings. Such individuals require close follow-up for early detection and intervention (LoA 90.29%, strong recommendation).

Treatment and surveillance of precancerous lesions of HCC

The management of precancerous lesions of HCC remains controversial because malignant transformation is complex and is influenced by underlying liver disease, environmen-

tal exposures, molecular subtype, and other variables. The optimal timing of intervention remains difficult to define. As diagnostic techniques improve, integrated assessment using imaging, molecular biology, and histopathology may facilitate timely intervention and improve long-term outcomes. Prospective studies based on molecular stratification are needed. Standardized treatment algorithms may enable more personalized care and improve survival.

Follow-up surveillance

Follow-up surveillance for DN: Although increasing attention has been paid to the atypical features and malignant potential of LGDN and HGDN, more definitive evidence and molecular markers are needed to support precise diagnosis and differentiation. This uncertainty has favored conservative management and has slowed the development of effective targeted treatments. For patients with decompensated cirrhosis or abnormal AFP-related serum markers, dynamic imaging surveillance every 3–4 months is recommended. For nodules < 1 cm in diameter, treatment is generally not recommended. For nodules > 1 cm, needle biopsy for histological examination may be considered when clinically appropriate. If nodule size remains stable, follow-up should be performed every 6 months. Patients with cirrhosis, whether related to hepatitis virus infection or other causes, should undergo regular semiannual follow-up.

Follow-up surveillance for HCA: Clinical decision-making and prognosis in HCA depend mainly on adenoma subtype and patient sex. In asymptomatic female patients without molecular evidence of β-catenin activation, several studies have shown minimal tumor progression during 18–24 months of surveillance after discontinuation of oral contraceptives or weight reduction, and some tumors regress substantially.

During surveillance, H-HCA, inflammatory HCA, and β-catenin-inactivated subtypes, particularly tumors < 5 cm, show no significant progression in many cases and may regress. Continued surveillance during pregnancy appears safe and feasible for women with HCA < 5 cm, provided that tumor enlargement or bleeding symptoms do not occur. Male patients with HCA and individuals receiving androgens may have a higher risk of β-catenin activation, symptomatic bleeding, and malignant transformation. Therefore, clinical intervention should be considered for all male patients with HCA, regardless of adenoma subtype, to reduce risk and improve outcomes.[13,14]

Recommendation 15: Invasive treatment is not recommended for DN < 1 cm in diameter. Instead, regular surveillance with Gd-EOB-DTPA-enhanced MRI and serum biomarkers such as AFP is recommended. However, immediate treatment should be considered if concerning imaging features are present, including growth to > 1 cm, mild-to-moderate T1 hypointensity, T2 hyperintensity, or diffusion restriction (LoA 91.26%, weak recommendation).

Recommendation 16: For asymptomatic female patients with HCA < 5 cm and no evidence of β-catenin activation, surveillance with multiparametric MRI, with or without Gd-EOB-DTPA, is recommended. Active tumor surveillance should continue for 6–12 months after discontinuation of oral contraceptives and weight reduction (LoA 86.41%, weak recommendation).

Local ablation therapy

Ablation for DN: Prognostic modeling studies of radiofrequency ablation (RFA) for hepatic nodules with HGDN suggest that progression from HGDN to HCC carries a substantial risk. Patients who received timely RFA had more favorable 5-year overall survival than control patients who were observed until HCC diagnosis and then underwent liver resection. In comparisons between patients with HGDN and those with well-differentiated eHCC treated with RFA, the HGDN group showed greater treatment efficacy within the first year, lower local tumor progression, and higher 1-, 3-, and 5-year overall survival. Therefore, for biopsy-proven or strongly suspected HGDN > 1 cm, local ablation with radiofrequency or microwave ablation may be considered.[69,70]

Ablation for HCA: HCA management is centered primarily on surgical resection. In recent years, however, local ablation has received increasing attention. Retrospective studies suggest that, in histologically confirmed HCA, pure RFA or RFA combined with surgical resection has safety and efficacy comparable to surgical resection alone for solitary or multiple nodules. Stereotactic radiofrequency ablation may further improve ablation precision and effectiveness. Retrospective studies of stereotactic radiofrequency ablation for HCA have reported few cases of distant recurrence. Because it is minimally invasive and associated with fewer complications, local ablation may be a promising alternative treatment option for selected patients with HCA.[71–73]

Recommendation 17: Local ablation is recommended for patients with single or multiple 1–3 cm liver nodules detected intraoperatively, provided that there are no absolute surgical contraindications and that comprehensive diagnostic workup, including imaging, serological tests, and pathology when necessary, has been completed. This approach is particularly suitable for lesions not adjacent to first-order vessels, major bile ducts, the gastrointestinal tract, or the gallbladder (LoA 94.17%, weak recommendation).

Recommendation 18: In male patients with HCA measuring 3–5 cm who are ineligible for surgical resection, local ablation is recommended as a viable treatment option, including for those with β-HCA, β-IHCA, or I-HCA subtypes, or those with underlying liver disease (LoA 92.23%, weak recommendation).

Surgical resection

Surgical resection for DN: Considerable progress has been made in identifying diagnostic markers and methods for detecting precancerous lesions of HCC. However, no broadly applicable and clinically reliable technique can yet distinguish HGDN from eHCC with sufficient certainty. To date, liver resection for HGDN has rarely been reported, largely because accurate preoperative diagnosis and precise intraoperative localization remain challenging. Further research in these areas is therefore needed. Studies of the natural history of precancerous lesions of HCC suggest that surgical resection may achieve curative treatment and reduce HCC incidence and recurrence in patients diagnosed with HGDN. Prospective studies of liver resection for HGDN should incorporate accurate preoperative diagnosis, intraoperative localization, and careful safety assessment. Given its minimally invasive nature, laparoscopic surgery may become the preferred approach for future surgical resection in appropriately selected patients.

Surgical resection for HCA: Surgical resection is considered the gold standard for HCA treatment. It is recommended for all male patients with HCA and for patients with high-risk

subtypes characterized by CTNNB1 exon 3 mutations and β-catenin activation. Resection is also recommended for HCA > 5 cm in diameter or for lesions showing continued growth. In female patients, surgery should be considered when tumors continue to enlarge beyond 5 cm despite discontinuation of oral contraceptives and weight management. Laparoscopic surgery has become the main resection approach, supported by preoperative imaging, three-dimensional reconstruction, intraoperative ultrasound, and other tools for thorough evaluation and surgical planning.[74,75] The extent of resection may include local excision, anatomical segmentectomy, or lobectomy. The procedure should be selected according to liver function, future liver remnant volume, and intraoperative assessment of liver texture. Surgery should be performed by experienced hepatobiliary surgeons to optimize safety and outcomes.

Recommendation 19: Liver resection is recommended for patients with a confirmed diagnosis of HGDN who develop imaging features typical of HCC during surveillance, provided that liver function is preserved (Child-Pugh class A), no surgical contraindications are present, lesion diameter is ≥ 2 cm, and future liver remnant is adequate. Laparoscopic resection is preferred and should be performed by experienced surgeons with expertise in intraoperative ultrasound and precise preoperative imaging localization (LoA 86.4%, weak recommendation).

Recommendation 20: Surgical resection is recommended for HCA > 5 cm in diameter or for lesions that progress to > 5 cm despite conservative measures, such as discontinuation of oral contraceptives. Resection is also advised for high-risk subtypes (β-HCA, β-IHCA, and I-HCA), regardless of size. Laparoscopic approaches, including local excision, anatomical segmentectomy, or hepatectomy, are preferred. The choice of technique should be individualized according to preoperative liver function, future liver volume, and intraoperative assessment (LoA 91.26%, strong recommendation).

Recommendation 21: Patients treated for precancerous lesions of HCC should undergo follow-up every 6 months. Gd-EOB-DTPA-enhanced MRI is the preferred imaging modality. Patients with focal carcinoma identified on postoperative pathology should be followed according to HCC surveillance protocols (LoA 91.26%, strong recommendation).

Other treatments

In addition to the treatment approaches described above, transarterial chemoembolization (TACE) and liver transplantation have been reported in selected patients with HCA.[76,77] Current recommendations for TACE include: (1) liver adenomatosis with multiple or diffuse lesions that are not amenable to radical treatment and without severe hepatic or renal dysfunction; and (2) patients who cannot tolerate surgery because of bleeding complications, in whom TACE may be used for preoperative hemostasis and tumor volume reduction. For patients with multiple HCAs, high-risk subtypes prone to malignant transformation, or glycogen storage disease unresponsive to medical therapy, liver transplantation may be considered when resection is not feasible. However, these strategies require validation in large prospective clinical trials before routine use can be recommended.

Conclusions

Research on precancerous lesions of HCC faces several challenges but also offers substantial opportunities. Future work should focus on establishing unified classification systems and definitive diagnostic criteria. Improving diagnostic precision, clarifying the molecular mechanisms that drive lesion emergence and progression, and developing treatments tailored to specific lesion profiles should be key priorities. To facilitate the implementation of these recommendations in clinical practice, a flowchart summarizing the consensus-based diagnostic and management strategy for precancerous lesions of HCC is provided in Figure 3.

AI has been extensively applied across the entire HCC care continuum, including risk prediction, imaging-based early diagnosis, treatment response forecasting, and prognosis.[78] In particular, deep learning and multimodal integration have enhanced the characterization of liver nodules and outperformed conventional biomarkers in some settings. For precancerous lesions, emerging studies have focused on distinguishing early HCC from high-grade DN—a challenging histological task—using deep learning on whole-slide images or radiomics from non-contrast MRI, achieving high discriminative accuracy. However, model generalizability and interpretability remain major hurdles. Future efforts should prioritize explainablemeworks, large-scale prospective validation, and the development of foundation models that incorporate longitudinal and multi-omics data. These advances will enable dynamic, personalized surveillance and timely intervention for lesions at high risk of malignant transformation, ultimately improving clinical decision-making in early hepatocarcinogenesis.

Ultrasound, CT, and MRI are widely used to detect liver abnormalities, but their sensitivity and specificity remain imperfect. More accurate and reliable diagnostic tools are urgently needed to improve early detection and intervention. These tools may include advanced imaging techniques and novel biomarkers detectable in blood or tissue biopsy specimens.

A deeper understanding of the molecular mechanisms underlying the development and progression of precancerous lesions is essential. Recent studies have identified genetic and epigenetic changes involved in the evolution of precancerous lesions into HCC. Further investigation is needed to define these mechanisms and identify actionable therapeutic targets. Such knowledge may support targeted therapies for specific precancerous lesion subtypes.

Advances in high-throughput and single-cell sequencing also provide promising opportunities for the assessment of precancerous lesions of HCC. Multi-omics approaches including transcriptomics, whole-genome sequencing, proteomics, metabolomics, and lipidomics enable comprehensive analysis of genetic and epigenetic alterations at single-cell resolution and can reveal intralesional heterogeneity. Recent studies integrating explainable deep learning with multi-omics data have identified progressive diagnostic biomarkers covering the "inflammation–cancer" transformation, including 12 plasma metabolic biomarkers associated with HCC progression. Metabolomic liquid biopsy dynamics have also been shown to predict eHCC and identify actionable candidates of human hepatocarcinogenesis.[79] The resulting insights may refine early screening and support personalized treatment strategies.

Research on precancerous lesions of HCC remains at an early stage and will continue to face important challenges. Addressing these challenges will help researchers and clinicians develop a more comprehensive understanding of lesion characteristics and progression patterns. This understanding

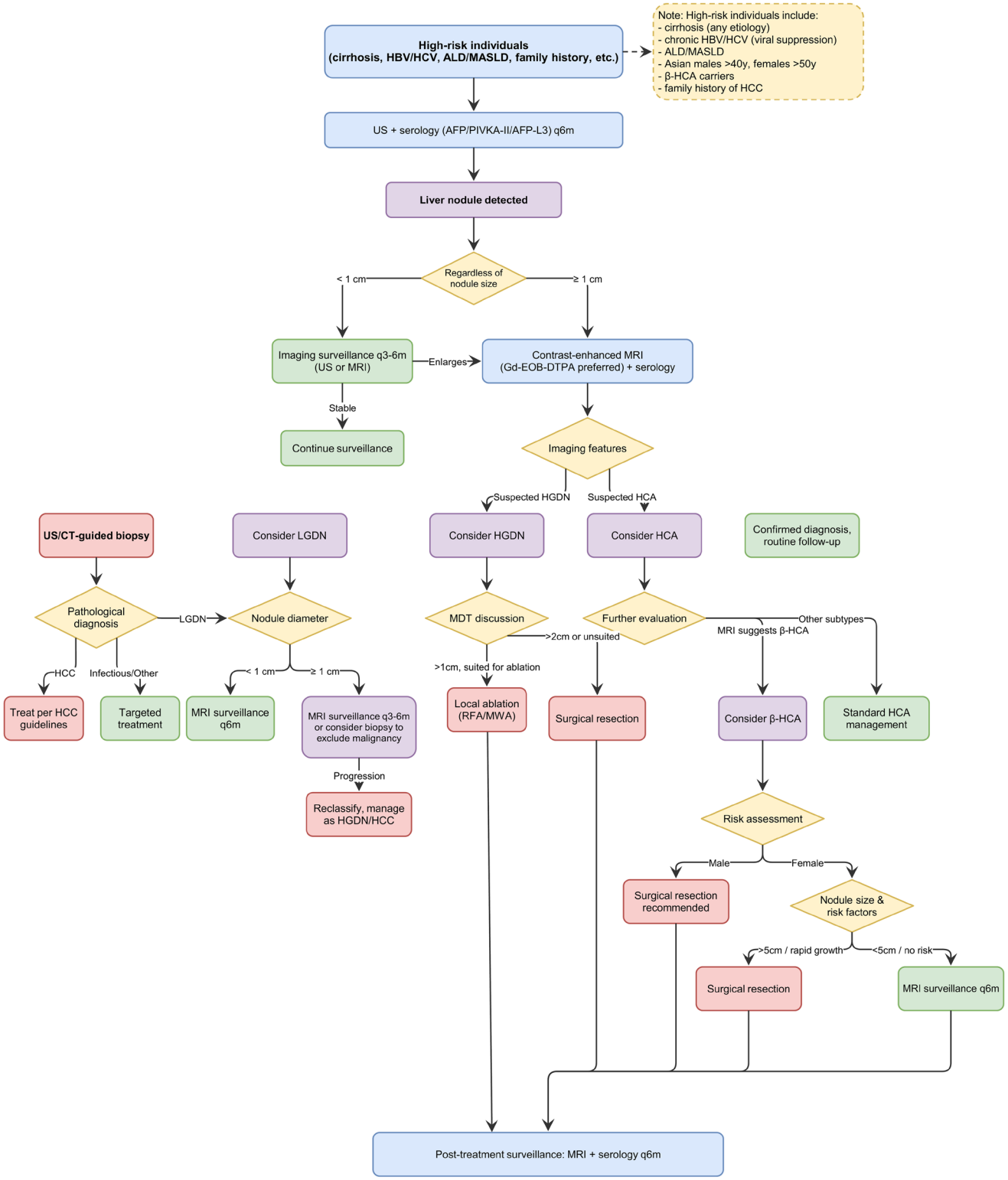


Fig. 3. Flowchart of the diagnostic and treatment decision-making strategy for precancerous lesions of HCC. AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; MRI, magnetic resonance imaging; CT, computed tomography; US, ultrasound; HGDN, high-grade dysplastic nodule; LGDN, low-grade dysplastic nodule; MDT, multidisciplinary team; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; RFA, radiofrequency ablation; MWA, microwave ablation; β-HCA, β-catenin-activated hepatocellular adenoma; q3-6m, every 3–6 months; q6m, every 6 months; y, years.

should improve diagnostic and therapeutic strategies and contribute to HCC prevention and management.

Overall, research on precancerous lesions of HCC is challenging but highly promising. Continued investigation is needed to establish unified classification systems, elucidate molecular mechanisms, develop targeted treatment strategies, and integrate advanced technologies to improve diagnostic accuracy and therapeutic efficacy. These advances are expected to improve HCC prevention and treatment and ultimately benefit affected patients.

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Conflict of interest

DZ has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Conception and design: XF and DZ. Provision of study materials and data assembly: XL, HJ, JK, YG, YW, and TH. Figure preparation: XL and HJ. Manuscript drafting: XL. Manuscript revision and final approval: all authors. All authors have approved the final version and publication of the manuscript.

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