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Toward a future role for liver biopsy in HCC: literature evidence and survey-based perspectives from Korean experts

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The role of liver biopsy in hepatocellular carcinoma (HCC) is being re-evaluated in the era of precision oncology and biomarker-driven systemic therapy. Although histopathological examination remains the diagnostic gold standard, HCC is unique among solid tumors in that accurate non-invasive imaging criteria allow diagnosis without routine biopsy in selected clinical settings. However, increasing biological heterogeneity, expanding therapeutic options, and the growing need for molecular stratification have renewed interest in tissue-based evaluation. Recent international guidelines have gradually broadened the indications for liver biopsy, particularly in selected diagnostic scenarios, prior to systemic therapy, and for molecular profiling. Beyond diagnostic confirmation, liver biopsy provides important information for histological subtyping, prognostic stratification, and biomarker discovery. Advances in immunohistochemistry, next-generation sequencing, and artificial intelligence-assisted pathology have further enhanced the clinical value of tumor tissue. In parallel, contemporary cohort studies indicate that liver biopsy is associated with low complication rates when modern techniques and standardized peri-procedural management are applied. Despite these advances, the integration of liver biopsy into routine clinical practice remains limited. To contextualize this gap, the Korean Liver Cancer Association conducted a nationwide survey of HCC specialists. The survey showed that liver biopsy is infrequently performed in current practice due to perceived procedural risks and limited immediate impact on therapeutic decision-making. Taken together, accumulating evidence supports a reappraisal of the clinical role of liver biopsy in HCC. Optimizing procedural safety, standardizing indications, and integrating tissue-based molecular insights into therapeutic decision-making may help bridge the gap between emerging evidence and real-world practice. **(J Liver Cancer 2026;26:205-219)**

Keywords: Carcinoma, hepatocellular; Biopsy; Precision medicine; Biomarkers, tumor; Molecular targeted therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and the second in South Korea, underscoring its substantial global and national disease burden. This high mortality reflects not only the aggressive biology of HCC but also the fact that many patients are diagnosed at an advanced stage, when curative treatment options are limited. In recent years, however, significant progress has been made in HCC management, particularly with the advent of molecularly targeted agents and immunotherapies. These therapeutic advances have led to notable changes in treatment patterns. In South Korea, the proportion of patients receiving systemic therapy as initial treatment increased from 0.2% in 2008 to 9.6% in 2022, whereas those receiving best supportive care decreased from 31.7% to 21.3% over the same period.[1]

The landscape of systemic treatment for HCC has expanded considerably, with atezolizumab plus bevacizumab, durvalumab plus tremelimumab, and nivolumab plus ipilimumab now recommended as first-line options, alongside the earlier standards sorafenib and lenvatinib. In addition, numerous clinical trials are ongoing to further refine and expand systemic treatment strategies.[2] However, HCC remains a biologically heterogeneous and complex disease with diverse etiologies, most commonly arising in the context of chronic liver inflammation. This heterogeneity contributes to therapeutic resistance and presents major challenges to the development of reliable biomarkers. Although atezolizumab plus bevacizumab demonstrated superior survival outcomes compared with sorafenib, the objective response rate remains modest at approximately 27%,[3] highlighting the urgent need for predictive biomarkers and personalized therapeutic approaches.

While various clinical parameters, including imaging findings and blood-, urine-, and emerging stool-based markers, have been investigated as potential tools to guide therapy, tissue remains the most direct and informative source for characterizing HCC and the surrounding liver parenchyma. As treatment paradigms continue to evolve toward precision oncology, both the clinical and research communities are increasingly recognizing the importance of pathological tissue for biological stratification and biomarker development.

These developments prompt a re-examination of the traditional, imaging-centered approach to HCC diagnosis and management and raise critical questions regarding the contemporary role of liver biopsy. In this review, we summarize current evidence on the evolving clinical utility of liver biopsy in HCC and contextualize these findings using a nationwide survey conducted by the Korean Liver Cancer Association (KLCA), which assessed current practice patterns and expert perspectives. We further discuss emerging strategies for integrating tissue-based insights into modern HCC care.

WHY REAPPRAISE LIVER BIOPSY NOW?

The rationale for revisiting the role of liver biopsy in HCC reflects broader changes in contemporary HCC management, including the expansion of systemic therapies, the increasing emphasis on molecular stratification, and advances in tissue-based analytical technologies. The role of liver biopsy in HCC has historically been shaped by the high diagnostic accuracy of imag-

ing-based criteria and concerns regarding procedure-related risk in patients with underlying liver disease. While this approach has been effective for non-invasive diagnosis, it is increasingly challenged by the expanding use of systemic therapies, the marked biological heterogeneity of HCC, and the growing need for molecular stratification. Advances in histopathology, next-generation sequencing (NGS), spatial profiling, and artificial intelligence (AI)-assisted analysis have substantially increased the informational value obtainable from limited tissue. At the same time, shifts in HCC epidemiology, particularly the rising contribution of metabolic dysfunction-associated steatotic liver disease (MASLD), and contemporary data demonstrating improved procedural safety further support reconsideration of biopsy use. In parallel, biomarker-driven clinical trials and precision oncology initiatives increasingly depend on tissue availability, underscoring the need to move beyond a purely diagnostic view of liver biopsy toward its integration as a platform for biological insight and therapeutic personalization.

CURRENT APPROACHES TO LIVER BIOPSY IN HCC

Guideline-based approaches to liver biopsy in HCC

International guidelines for HCC recommend performing a tumor biopsy when hepatic lesions do not demonstrate the hallmark imaging features of HCC, specifically, arterial phase hyperenhancement with washout in the portal venous or delayed phases, in patients at high risk for HCC, or when imaging findings are suspicious for HCC in the absence of established risk factors.[4] When biopsy is performed, pathological reporting should include histological and immunohistochemical analyses in accordance with the international consensus recommendations and, if possible, subtype classification following the World Health Organization (WHO) guidelines.[5,6] The 2019 WHO classification describes eight morphological subtypes, with approximately 35% of HCC cases assignable to one of these categories.[4] Although these subtypes are not currently used to guide therapeutic decisions, they carry prognostic significance. For example, the macrotrabecular-massive (MTM) subtype is associated with poorer outcomes, whereas the clear cell subtype is linked to a more favorable prognosis. In addition, histological subtyping can inform postoperative management strategies, particularly in patients who have undergone curative treatments such as liver transplantation or surgical resection.

In recent years, major international guidelines have increasingly emphasized the role of pathological confirmation in advancing precision medicine, thereby assigning greater clinical relevance to liver biopsy (Table 1). Beyond conventional diagnostic indications, the 2023 American Association for the Study of Liver Diseases (AASLD) guideline advises considering biopsy for Liver Imaging Reporting and Data System (LI-RADS) categories LR-4 and LR-5 to support both diagnostic confirmation and molecular profiling.[5] The 2024 British Society of Gastroenterology (BSG) and the 2025 European Society for Medical Oncology (ESMO) guidelines go further, strongly recommending biopsy prior to initiating systemic therapy to confirm the diagnosis, citing the low complication rates associated with the procedure.[7,8] Both the AASLD and ESMO guidelines also underscore the importance of tissue acquisition to facilitate biomarker development and promote the integration of precision medicine into clinical practice.[5,8] The 2025 European Association for the Study of the Liver (EASL) guideline further recommends simultaneous biopsy of the non-tumoral liver parenchyma to assess background liver disease, including fibrosis staging and identification of coexisting liver conditions, particularly in patients with MASLD.[6]

With the advent of potent antiviral agents for hepatitis B and C, the incidence of virus-related liver disease is declining, even in regions with historically high prevalence such as the Asia-Pacific region.[9] In parallel, the prevalence of MASLD is steadily increasing and is projected to account for approximately 50-60% of chronic liver disease globally within the next five decades,[9] thereby contributing to a rising proportion of HCC. This epidemiological shift suggests that conventional reliance on established risk factors, previously used to justify non-invasive diagnosis, may become less applicable. Moreover, a substantial proportion of MASLD-related HCC arises in non-cirrhotic livers,[10,11] reinforcing the need for histological assessment. Consequently, the role of liver biopsy is expected to expand, not only to ensure diagnostic accuracy in accordance with current guidelines but also to support the advancement of precision medicine in HCC.

Clinical considerations in the use of liver biopsy for HCC

Liver biopsy in patients with HCC serves two primary objectives: establishing an accurate diagnosis and identifying biomarkers for prognostic assessment and prediction of treatment response. However, histological confirmation is generally not required for HCC diagnosis, and no tissue-based biomarkers have yet been incorporated into routine clinical practice to guide prognosis or therapeutic decision-making. The lack of immediate clinical utility has contributed to limited motivation among clinicians to per-

form liver biopsy, a finding that is consistent with the KLCA survey.

LI-RADS, developed to standardize imaging-based diagnosis of HCC, has been adopted by several international guidelines. LI-RADS categorizes hepatic lesions according to the likelihood of HCC, ranging from LR-1 (definitely benign) to LR-5 (definitely HCC). Additional categories include LR-M (probably malignant but not specific for HCC), LR-NC (non-categorizable) and LR-TIV (tumor in vein). Lesions classified as LR-5 can be diagnosed as HCC based solely on imaging, whereas lesions categorized as LR-4, LR-M, and LR-TIV are generally recommended for biopsy. Although the 2018 revision of LI-RADS improved diagnostic specificity, and the positive predictive value of LR-5 has been reported to reach up to 96%,[12] misclassification still occurs due to the inherent limitations of imaging-based assessment.

In a recent cohort of 220 patients with liver cirrhosis (LC) and imaging findings suspicious for HCC, 134 patients were confirmed to have HCC via biopsy. Among them, 89 were categorized as LR-5, 41 as LR-4, LR-M, or LR-TIV, and 4 as LR-3 or LR-NC according to the 2018 LI-RADS criteria. Of the 100 patients initially categorized as LR-5, only 89 were confirmed to have HCC on histology.[13] In another multicenter study from the United Kingdom involving patients with advanced HCC undergoing evaluation for sorafenib treatment, histopathological analysis revealed that 6.6% of 302 patients were ultimately diagnosed with cholangiocarcinoma (CC), combined HCC-CC, benign lesions, or other entities.[7] Although these studies may carry selection bias, they underscore the potential for diagnostic inaccuracies based on imaging alone. Consistently, in the KLCA survey, 80.5% of respondents reported having encountered unexpected pathological findings despite radiologic features highly suggestive of HCC. The most frequent alternative diagnosis was cholangiocarcinoma, followed by less common findings such as hepatic adenoma, focal nodular hyperplasia, regenerative or degenerative nodules, metastases, and other benign entities.

Since 2010, the Food and Drug Administration has approved an increasing number of oncology drugs, with approximately 38.9% classified as biomarker-driven therapies. In contrast, HCC remains among the major tumor types with few validated predictive biomarkers to guide treatment selection.[14] Currently, no robust predictive biomarker informs therapy choice, except for serum alpha-fetoprotein of at least 400 ng/mL as an eligibility criterion for ramucirumab. Consequently, patients who are candidates for systemic therapy generally follow uniform, sequential treatment pathways as outlined in the Barcelona Clinic Liver Cancer algorithm,[15] which may lead to suboptimal clinical outcomes. In this context, the absence of validated biomarkers reduces the incentive for clinicians to perform liver biopsy. Paradoxically, however, limited tissue acquisition also constrains biomarker discovery and validation, thereby perpetuating a cycle in which clinicians lack the means to identify patients most likely to benefit from specific therapies.

Table 1. Summary of international guidelines on liver biopsy in HCC

Guideline	Recommendations*
AASLD 2023	AASLD recommends considering liver biopsy for lesions categorized as LR-4 and LR-5 on non-invasive imaging, both to confirm the diagnosis and to enable molecular profiling
EASL 2025	Routine molecular analysis is not recommended (Level of Evidence 3, strong recommendation); however, liver biopsy may be performed for research purposes when deemed essential for advancing precision medicine When performing liver biopsy, it is suggested to obtain non-tumoral tissue for facilitating diagnosis, assessing fibrosis and inflammation, and evaluating comorbid factors, such as steatosis (Level of Evidence 3, weak recommendation)
BSG 2024	Tumor biopsy should be performed for HCC lesions when systemic therapy is being considered (evidence moderate; recommendation strong)
ESMO 2025	Tumor biopsy is recommended prior to the initiation of systemic therapy (Level III, Grade A) Next-generation sequencing should be considered for tumors with mixed histological features (Level IV, Grade A) To support biomarker development, tumor biopsy is recommended for all patients with HCC participating in clinical trials (Level IV, Grade A)

HCC, hepatocellular carcinoma; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; BSG, British Society of Gastroenterology; ESMO, European Society for Medical Oncology.
*Excludes general pathological diagnostic criteria for HCC, such as in patients without risk factors for HCC or in cases lacking typical imaging features on non-invasive studies. Level of evidence and strength of recommendations are presented as stated in each guideline.

SAFETY CONSIDERATIONS AND RISK MITIGATION IN LIVER BIOPSY FOR HCC

Procedure-related adverse events: contemporary perspectives

Contemporary studies have reported substantially lower rates of adverse events associated with liver biopsy. A large multicenter study from Germany reported an overall complication rate of 1.9% among 12,117 liver biopsy procedures. Documented complications included bleeding, visceral injury, pneumothorax, hypotension, and pain, with three deaths attributed to massive intraperitoneal hemorrhage following the procedure.[16] In another recent study conducted at tertiary centers in Italy, the reported complication rates were pain (7.4%), transient hypotension (0.8%), and bleeding (0.5%), with no fatal cases.[17]

Peri-procedural hemostasis and antithrombotic strategies

As many patients with HCC have underlying LC and associated alterations in the hemostatic system, bleeding complications remain a major concern when considering liver biopsy. In the KLCA survey, nearly all respondents (97%) reported routinely checking hemostatic laboratory parameters and correcting abnormalities, if necessary, before performing a biopsy. However, current evidence suggests that the bleeding risk may be overestimated.

According to the EASL guideline on bleeding management in LC patients,[18] liver biopsy, whether percutaneous or trans-jugular, is considered a low-risk procedure, with an estimated bleeding risk of ≤1.5%. Some studies have reported rates as low as <0.07%.[19-21] Routine prophylactic transfusion of fresh frozen plasma (FFP) is not recommended, and platelet transfusion is generally unnecessary when the platelet count exceeds 50×10^9/L.[22] In a study assessing the relationship between bleeding complications and international normalized ratio (INR) and platelet levels, transfusion with FFP and/or platelets in patients with INR ≤2.0 or platelet counts ≥25×10^9/L did not reduce bleeding risk.[23] Recommendations for managing bleeding risk, including laboratory thresholds and strategies for antiplatelet and anticoagulant therapy, are summarized in Table 2.

All respondents to the KLCA survey agreed that antiplatelet or anticoagulation therapy should be withheld prior to liver biopsy to minimize bleeding risk. A review of international guidelines supports this approach. The EASL guideline recommends that the management of these medications in LC patients should follow the same principles as in patients without LC.[18] According to the Society of Interventional Radiology, percutaneous liver biopsy is categorized as a high-risk procedure for bleeding, and antiplatelet and anticoagulant agents should therefore be discontinued in advance.[24] The BSG provides a clear protocol for managing these medications prior to biopsy, recommending that antiplatelet and anticoagulant therapy be withheld. For patients receiving dual antiplatelet therapy, particularly those with cardiac stents, it is advised that aspirin be continued while clopidogrel should be temporarily discontinued.[25]

Needle-track tumor seeding: risk assessment and prevention

Needle-track tumor seeding after liver biopsy remains an important concern among clinicians. In the KLCA survey, 27.8% of respondents reported having encountered seeding events. However, a meta-analysis reported a relatively low overall incidence of approximately 2.7%, with a median follow-up of 17 months after the procedure.[26] In candidates for liver transplantation, preoperative fine-needle aspiration biopsy did not adversely affect clinical outcomes, including tumor recurrence and overall survival, compared with patients who did not undergo preoperative biopsy. Interestingly, 11 patients (4%) were ultimately diagnosed with non-HCC, including 10 who had not received a preoperative biopsy.[27] Taken together, although needle-tract seeding remains a valid concern, the event appears to be relatively uncommon and of little clinical significance. Therefore, the decision to perform a biopsy should be individualized, carefully balancing potential diagnostic and therapeutic benefits against this risk for each patient.

Technical advances to optimize tissue yield and procedural safety

To maximize tissue yield while minimizing complications, the coaxial introducer needle technique has become an increasingly preferred method for liver biopsy in patients with HCC.[28] After advancing the coaxial needle to a position immediately anterior to the target lesion, multiple core biopsy specimens can be obtained through a single liver puncture using an automated biopsy gun. This approach not only provides sufficient tumor tissue for comprehensive histopathologic and molecular analysis but also minimizes the number of capsular penetrations, thereby reducing the risks of bleeding and tumor seeding (Fig. 1).

Real-time ultrasound guidance remains the standard imaging modality for liver biopsy. Recent technological advances now al-

low for the fusion of pre-acquired computed tomography or magnetic resonance imaging with real-time ultrasound.[29] This fusion imaging technique enables precise targeting, particularly in patients with multiple hepatic lesions demonstrating heterogeneous imaging characteristics or in those with tumor regions showing suboptimal responses to systemic therapy. By facilitating targeted sampling of specific lesions or intra-tumoral subregions, fusion imaging improves the accuracy of histological subtype identification and molecular characterization, including the assessment of therapeutic resistance. Ultimately, these advances enhance both diagnostic yield and procedural safety, thereby supporting the implementation of personalized treatment strategies in HCC management.

TISSUE-BASED BIOMARKERS IN HCC: FROM BIOLOGICAL INSIGHT TO CLINICAL APPLICATION

There is growing interest in the development of biomarkers to guide treatment decision-making in HCC. Tumor tissue remains the most direct and comprehensive source for molecular and histopathological analyses, supporting techniques such as immunohistochemistry, NGS, single-cell RNA sequencing, and, more recently, spatially resolved transcriptomics and AI-driven pathology. These advanced approaches provide critical insights into tumor heterogeneity, the immune microenvironment, and predictive markers of treatment response, thereby facilitating the incorporation of precision medicine into HCC management.

Prognostic stratification through tissue biomarkers

Prognostic biomarkers are essential for risk stratification of patients according to clinical outcomes, thereby informing individualized treatment strategies. Although no systemic adjuvant therapies are currently approved for patients with HCC following curative treatments, several clinical trials are underway to evaluate adjuvant and neoadjuvant therapies in this setting.[30] Identifying patients at high risk of recurrence through prognostic biomarkers may help guide enrollment in these trials and optimize therapeutic benefit. Furthermore, risk stratification based on prognostic prediction allows for the tailoring of post-treatment surveillance programs in patients who have undergone curative interventions.

Table 2. Summary of guideline recommendations for bleeding risk management during liver biopsy

Guideline	Hemostasis parameters and transfusion thresholds	Management of antiplatelet and anticoagulant agents
AASLD 2009	No established cut-off for PT INR and platelet count predicting bleeding risk	Discontinue antiplatelet agents several to ten days prior (Class I, Level C)* Discontinue anticoagulant agents, including warfarin at least 5 days prior (Class I, Level C)
EASL 2022	Hemostasis tests (PT INR, aPTT, platelet count, and fibrinogen) generally not predictive (Level of Evidence 3, strong recommendation) FFP correction of PT INR not recommended (Level of Evidence 2, strong recommendation) Platelet transfusion not recommended if >50×10^9/L or if bleeding can be locally controlled (Level of Evidence 3/4, strong recommendation)	Manage antiplatelet and/or anticoagulant agents as in non-cirrhotic patients (Level of Evidence 4, strong recommendation)
BSG 2020	PT INR 1.5-2.0 not a contraindication but associated with increased bleeding risk in patients with hepatic fibrosis and portal hypertension (strength of recommendation moderate; evidence moderate) FFP not recommended if PT INR ≤2.0 (strength of recommendation strong; evidence moderate) Platelet transfusion may be considered if <50×10^9/L (strength of recommendation moderate; evidence weak)	Stop clopidogrel, prasugrel, ticagrelor 7 days prior Aspirin, withhold 3-7 days prior Dual antiplatelet therapy, stop clopidogrel and continue aspirin
SIR 2019	Suggested cutoff PT INR ≤2.5 Platelet count ≥30×10^9/L Fibrinogen ≥100 mg/dL	Aspirin, discontinue 3-5 days prior Clopidogrel, discontinue 5 days prior Additionally, the guideline provides recommendations for the management of other anticoagulant and antiplatelet agents

AASLD, American Association for the Study of Liver Diseases; PT, prothrombin time; INR, international normalized ratio; EASL, European Association for the Study of the Liver; aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; BSG, British Society of Gastroenterology; SIR, Society of Interventional Radiology.
*Level of evidence and strength of recommendations are presented as stated in each guideline.

Although not yet incorporated into routine clinical practice, advances in molecular and genetic analyses, including NGS, have enabled the development of a morpho-molecular classification of HCC based on histological features. This classification broadly divides HCC into two major subtypes: proliferative and non-proliferative classes, each associated with distinct biological behaviors and clinical outcomes.[31] Tumors within the proliferative class are often linked to hepatitis B virus infection and exhibit aggressive characteristics, such as poor differentiation and vascular invasion, which are indicative of a poorer prognosis. Histological subtypes in this category include progenitor, MTM, and scirrhous HCC. In contrast, non-proliferative HCCs generally display less aggressive behavior and are more frequently associated with hepatitis C virus infection or alcohol-related liver disease. These tumors are typically well differentiated and show greater chromosomal stability. Representative subtypes include steatohepatitic HCC and *CTNNB1*-mutated HCC.

Among the histological subtypes, the MTM and progenitor types are particularly associated with poor prognosis.[31] The MTM subtype accounts for approximately 10-20% of HCC cases and is enriched for tumor protein p53 (*TP53*) mutations and fibroblast growth factor 19 amplification.[31,32] In patients who underwent surgical resection or radiofrequency ablation (RFA), the MTM subtype was identified as an independent predictor of both early and overall recurrence; notably, it was the only significant predictor of recurrence in patients treated with RFA.[32] The progenitor subtype, defined by cytokeratin 19 expression and often enriched for *TP53* mutations, has been reported to emerge following locoregional therapies such as transarterial chemoembolization or local ablation in some cases.[33,34] This phenotypic transformation may be associated with rapid disease progression or treatment resistance, underscoring the necessity of tumor tissue analysis. Recognizing their prognostic relevance, the 2025 EASL guidelines on HCC recommend that histopathological reporting of MTM and progenitor subtypes be included, particularly for patients undergoing curative treatments, to help guide post-treatment surveillance and therapeutic planning.[6]

Beyond the established morpho-molecular classification of HCC, advances in spatial transcriptomics have revealed fine-grained intratumoral heterogeneity. High-resolution spatial maps of HCC transcriptomes have identified gene signatures associated with intrahepatic satellite nodules and poor survival, while spatial immune scoring systems based on immune cell localization within tumor and peritumoral compartments have outperformed conventional staging systems in predicting recurrence.[35,36] These findings highlight the potential of spatially informed prog-

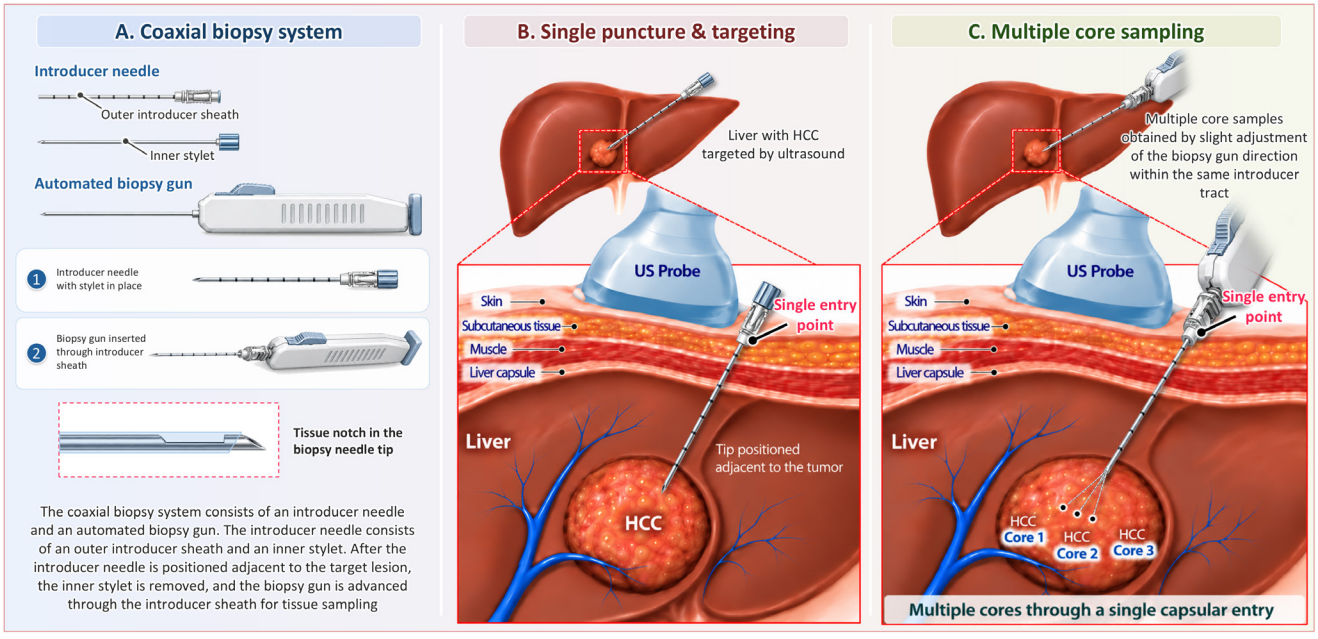


Figure 1. Coaxial introducer–based biopsy technique for efficient and safe tissue sampling in HCC. (A) The coaxial system consists of an outer introducer sheath and an inner automated biopsy gun, (B) after a single percutaneous puncture, the introducer is positioned at the target lesion under image guidance, allowing stable and precise targeting, (C) multiple core samples can be obtained by adjusting the biopsy gun angle within the introducer, while maintaining a single capsular entry and confining the biopsy tract within the tumor, thereby improving tissue yield and procedural safety. HCC, hepatocellular carcinoma.

nostic biomarkers to capture microenvironmental features that are not detectable by bulk profiling.

In parallel, digital pathology enables quantitative assessment of histological risk features. Automated image analysis has demonstrated that higher proportions of MTM-HCC architecture, as well as the presence or extent of microvascular invasion and vessels encapsulating tumor clusters, are independently associated with recurrence.[37] By transforming historically subjective morphologic assessments into calibrated, reproducible scores, computational pathology helps standardize prognostic stratification. Deep-learning models applied to whole-slide images have further improved risk prediction for overall survival and post-resection recurrence. For example, Saillard et al.[38] developed a model that achieved a concordance index of 0.78 for post-resection survival, surpassing traditional risk models. Importantly, these approaches also yield interpretable features, including poor differentiation, vascular invasion, and immune infiltration, thereby bridging AI-derived predictions with pathologic understanding.

Predictive tissue biomarkers informing therapeutic response

Although no biomarker has yet demonstrated sufficient clinical utility to predict treatment response in HCC for routine clinical use, numerous ongoing studies continue to explore potential markers that may guide treatment selection.[39] Initial efforts focused on programmed death-ligand 1 (PD-L1) expression, given its relevance as a target of the first approved immune checkpoint inhibitors, including nivolumab and atezolizumab. However, clinical trials have not shown a consistent or significant correlation between PD-L1 expression and treatment response in HCC.[40-42]

Emerging evidence suggests that more comprehensive immunological profiling may offer predictive value. In a study involving 358 patients with HCC, specific immune-related parameters such as the regulatory T cell to effector T cell (Teff) ratio, Teff activation status, CD274 (PD-L1) expression, $CD8^+$ T cell infiltration, and the expression of myeloid inflammation-related genes were associated with improved efficacy of atezolizumab-bevacizumab combination therapy.[41] Beyond immune-related markers, several tumor-intrinsic and microenvironment-derived biomarkers are currently under investigation for their potential predictive relevance.[39] In parallel, deep learning models applied to routine hematoxylin and eosin stained whole-slide images have shown promise in inferring immune gene signatures and predicting responses to atezolizumab and bevacizumab. AI-based pathomics scores derived from histological features have been shown to correlate with vascular endothelial growth factor signaling, immune infiltration, and clinical outcomes.[43,44]

Emerging molecular targets and therapeutic opportunities

Multi-omic profiling technologies have identified key molecular alterations associated with HCC, including mutations in the telomerase reverse transcriptase promoter (*TERTp*), aberrations in the Wnt signaling pathway, and alterations involving *TP53* and *MYC*. While many of these genetic abnormalities were once considered difficult to target, ongoing research is actively exploring their therapeutic potential. Among these, *TERTp* mutations represent the most prevalent molecular alteration in HCC, occurring in approximately 40% to 60% of cases.[45-48] As a result, therapeutic strategies targeting telomere maintenance mechanisms have gained considerable attention. Investigational approaches include oligonucleotides that disrupt telomerase binding, nucleoside analogues that inhibit telomere elongation, small-molecule TERT inhibitors, and TERT-directed immunotherapies.[49] In preclinical HCC models, antisense oligonucleotide (ASO) therapy targeting TERT has demonstrated efficacy in suppressing tumor growth.[50]

In addition, several targeted strategies are currently under clinical and preclinical investigation, including inhibitors of the Wnt/β-catenin pathway, therapies directed against *TP53* mutations, and ASO-based approaches targeting MYC.[51-53] These developments hold promise for expanding the therapeutic armamentarium and advancing personalized treatment strategies in HCC. Biopsy-derived tissue remains indispensable for validating these targets, enabling biomarker-driven patient enrollment in clinical trials, and supporting the development of companion diagnostics.

Glypican-3 (GPC3) is another HCC-enriched membrane antigen with diagnostic, prognostic, and therapeutic relevance, being overexpressed in approximately 70-80% of HCCs while absent in normal adult liver. A recent biopsy-based study reported that GPC3 positivity was associated with poorer overall survival and a lower objective response rate in patients with advanced HCC treated with atezolizumab plus bevacizumab.[54] In addition, GPC3-directed therapies, including monoclonal antibodies, antibody-drug conjugates, CAR-T cells, and peptide vaccines, are being actively investigated.[55] Thus, GPC3 illustrates how biopsy-derived tissue may support prognostic stratification, clinical trial enrichment, and future companion diagnostic development in HCC.

Integrating tissue and liquid biopsy in HCC

Tumor biopsy in HCC is ideally performed using a core needle approach. However, given the substantial intratumoral and intertumoral heterogeneity of HCC, a single biopsy specimen may not fully represent the molecular diversity of the entire tumor. Comprehensive multi-omic analyses assessing heterogeneity in HCC have revealed marked variations across genomic, transcriptomic, proteomic, and metabolomic levels. This biological complexity presents a major challenge to the efficacy of targeted therapies and contributes to treatment resistance.[56]

In this context, liquid biopsy, which analyzes circulating tumor cells, cell-free DNA, non-coding RNAs, and extracellular vesicles, has emerged as a valuable complementary approach to traditional tissue biopsy.[57] Liquid biopsy is minimally invasive, allows serial sampling, and enables real-time monitoring of disease progression and treatment response.[58] Moreover, it has the potential to capture heterogeneity from both primary tumors and metastatic or microenvironmental components.[59]

Beyond this conceptual complementarity, several studies have quantified the concordance and added value of combining tissue and liquid biopsy in HCC. Targeted sequencing of plasma cell-free DNA detected an average of 47% of the mutations identified from multiregional HCC tissues, underscoring that a single tissue core may underrepresent tumor-wide molecular diversity.[60] In a separate cohort, 81% and 97% of the mutations detected in tissue were also identified in plasma circulating tumor DNA (ctDNA) in non-hypermutator and hypermutator cases, respectively, supporting ctDNA as a window into the primary tumor.[61] Conversely, combining tissue and ctDNA analysis increased the detection rate of clinically relevant alterations, such as *CTNNB1* mutations, beyond that achieved with tissue alone.[62] Discordance between the two approaches may therefore reflect not only technical limitations but also spatial heterogeneity, temporal tumor evolution, treatment-induced clonal selection, low ctDNA shedding, or sampling bias from a single tissue core. Accordingly, baseline tissue biopsy may anchor the diagnosis, histological subtyping, and spatial or immune-contextual interpretation, whereas serial liquid biopsy may complement tissue analysis by monitoring molecular progression, emergent resistant clones, and treatment response over time.

KLCA SURVEY

The KLCA conducted a nationwide survey between December 2024 and January 2025 to assess contemporary practice patterns and expert perspectives regarding the role of liver biopsy in HCC. The survey was distributed through an online survey platform to a subset of KLCA members involved in HCC care. The survey was sent to 340 eligible members, and 137 physicians responded, yielding a response rate of 40.3%. The questionnaire included items on respondent characteristics, current biopsy practices, prior experience with biopsy-related complications, use of tissue for ancillary pathological or molecular testing, and attitudes toward the diagnostic and prognostic roles of liver biopsy in HCC. The questionnaire was reviewed by the study investigators for content and clarity before distribution. Survey data were analyzed descriptively. For items allowing multiple responses, each option was summarized according to the proportion of respondents selecting that option. Items permitting multiple responses were indicated in the questionnaire. The full questionnaire is provided in Supplementary Appendix 1.

Among the 137 respondents, specialists in internal medicine accounted for 60%, followed by radiology (19%), surgery (14%), and radiation oncology (5%), with most respondents practicing in secondary or tertiary care centers. The principal findings are summarized below, with additional context provided in other sections of this review.

Overall, liver biopsy was infrequently performed in routine practice. For diagnostic purposes, 54% of respondents reported performing biopsy in fewer than 10% of cases or not at all. Similar patterns were observed before initiation of systemic therapy (52%) and after disease progression on standard systemic treatments (62%) (Fig. 2). Respondents attributed this practice primarily to the perception that biopsy is unnecessary when imaging features are typical for HCC, its limited perceived role in immediate treatment decisions, and ongoing concerns regarding procedure-related complications. Perceptions of procedural risk were closely linked to prior clinical experience. Approximately one-third of respondents (33.6%) reported having encountered at least one major complication related to liver biopsy during their clinical careers. These experiences included bleeding, needle-track seeding, severe pain, infection, and rare fatal events. Such reports reflect cumulative exposure over extended periods of practice and may include historical or indirect cases, rather than contemporary per-procedure complication rates.

Among clinicians who performed liver biopsy, the subsequent use of tissue for pathological or molecular analyses varied. Forty-one percent of respondents indicated that immunohistochemical or molecular testing was not routinely requested, whereas 10.5% reported performing these analyses in most cases (Fig. 3A). In addition, 9.5% of respondents reported routinely obtaining

non-tumoral liver parenchyma in more than 10% of biopsy procedures, with a subset indicating that this approach was applied in nearly all cases (Fig. 3B).

Despite these practice patterns, attitudes toward the future role of liver biopsy were more favorable. With respect to its diagnostic role, 52% of respondents favored maintaining current guideline recommendations, while 63% supported selective biopsy acquisition to facilitate biomarker development, and 37% endorsed a more proactive approach. In cases of diagnostic uncertainty or differential diagnosis, 54% indicated that they would consider performing a biopsy. Regarding prognostic applications, including biomarker development before or after systemic therapy, 51% supported selective expansion of biopsy use within existing recommendations, and 50% expressed support for broader adoption.

Taken together, 65% of respondents agreed that the use of liver biopsy in HCC should expand in the future, particularly in response to evolving treatment paradigms and the growing emphasis on precision medicine aimed at improving clinical outcomes (Fig. 4).

A PRACTICAL FRAMEWORK FOR INTEGRATING LIVER BIOPSY INTO HCC CARE

Building on the literature and the survey findings above, a selective, purpose-driven framework may help translate these observations into practice (Fig. 5). The central question is whether a biopsy result would change diagnosis, treatment allocation, trial eligibility, or molecular interpretation. When the answer is no, typically for radiologically diagnostic HCC in a high-risk patient with no additional molecular or trial objective, routine biopsy is not required. When the answer is yes, biopsy should be considered. Relevant target populations include patients with indeterminate or atypical imaging and those in whom a competing diagnosis is suspected, consistent with current guideline indications.[5] Notably, even when imaging features are typical for HCC,

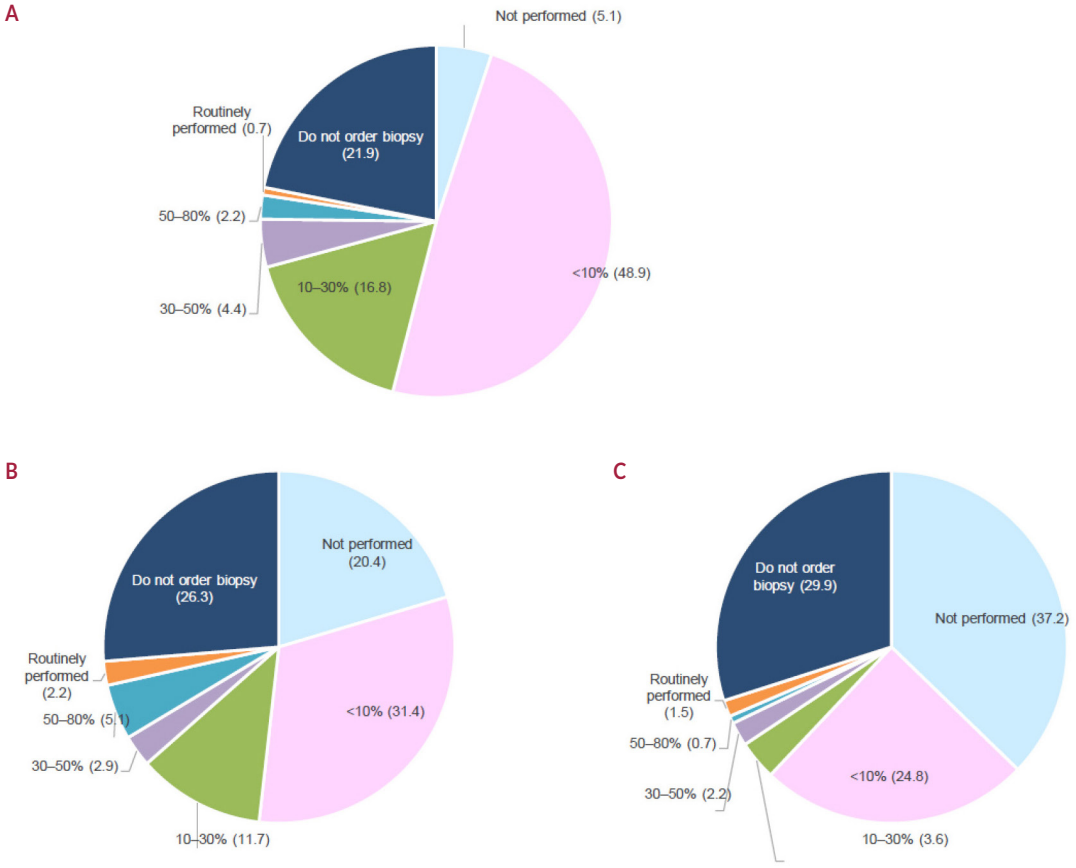


Figure 2. Proportion of survey respondents performing liver biopsy. (A) at the time of HCC diagnosis, (B) prior to initiating systemic therapy, and (C) after systemic therapy proves ineffective. Numbers in parentheses indicate percentages of respondents. HCC, hepatocellular carcinoma.

biopsy may still be informative when molecular profiling, histological subtyping, or assessment of the background liver is expected to aid care or research, in line with guideline recommendations that increasingly emphasize tissue acquisition for precision medicine.[8]

Once an indication is established, the biopsy workflow should be organized before tissue acquisition. Pre-procedural review of hemostatic parameters and antithrombotic agents, with correction only when indicated, supports procedural safety, while image-guided core needle biopsy, preferably using a coaxial technique, can maximize tissue yield through a single capsular puncture.[28] Sampling should target viable tumor and, when relevant, include non-tumoral parenchyma to characterize the background liver, in keeping with guideline recommendations for patients with metabolic dysfunction–associated steatotic liver disease.[6] Specimens should then be triaged for histology, immunohistochemistry, and molecular profiling, with pre-analytic factors such as tumor cellularity, necrosis, and fixation considered in advance when next-generation sequencing is planned. Ultimately, tissue obtained in this way can inform diagnosis, prognosis, and prediction, and (together with serial liquid biopsy) support individualized, biologically informed HCC care (Fig. 5).

CONCLUSIONS

The continued advancement of precision and personalized medicine in HCC increasingly depends on the integration of pathological insights into diagnostic, prognostic, and therapeutic decision-making. Although liver biopsy has traditionally played a limited role in routine practice, accumulating evidence demonstrates its expanding value as a platform for biological characterization and biomarker development in contemporary HCC management. In this context, the KLCA survey provides important real-world perspective, revealing both current barriers to biopsy use and broad expert support for its selective expansion, with 65% of respondents endorsing a greater role for tissue acquisition to enable precision oncology. These survey findings should be interpreted as real-world context rather than definitive estimates, given their reliance on self-reported, cumulative experience and on

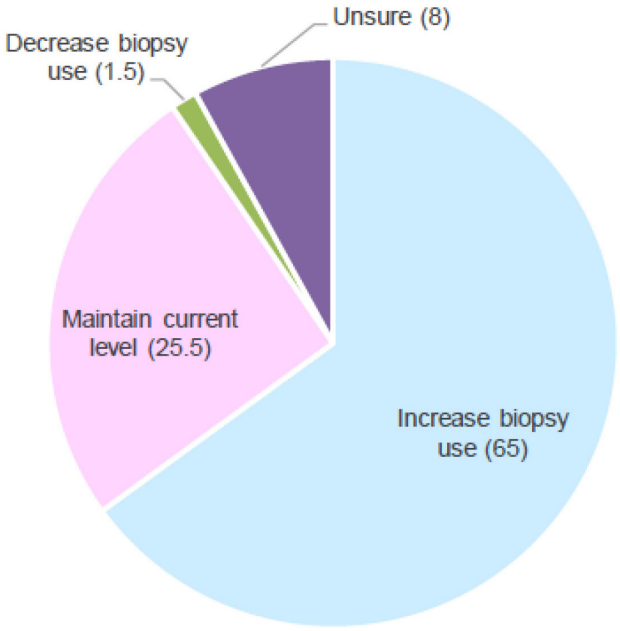


Figure 4. Proportion of survey respondents supporting increased utility of liver biopsy in future HCC management. Numbers in parentheses indicate percentages of respondents.

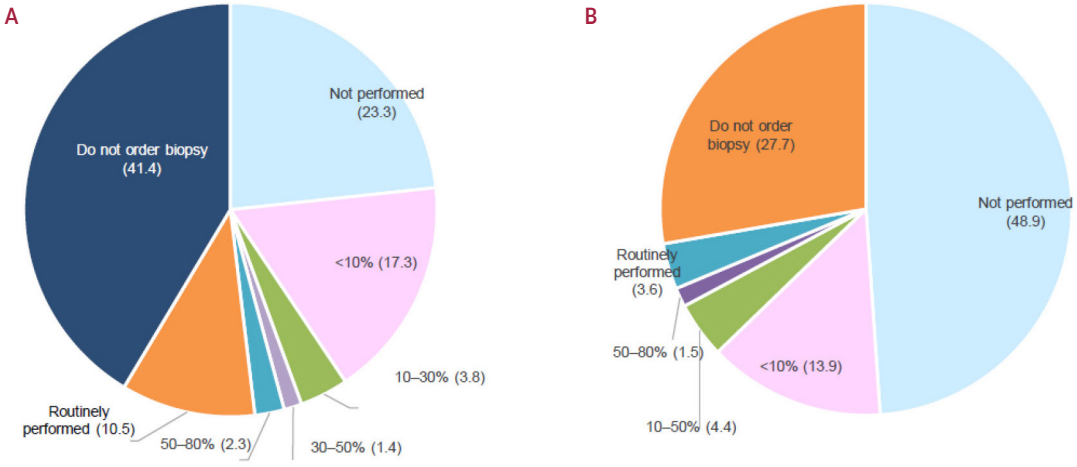


Figure 3. Proportion of survey respondents performing liver biopsy. (A) who perform immunohistochemical staining or genetic analysis, and (B) who obtain non-tumoral liver tissue during biopsy. Numbers in parentheses indicate percentages of respondents.

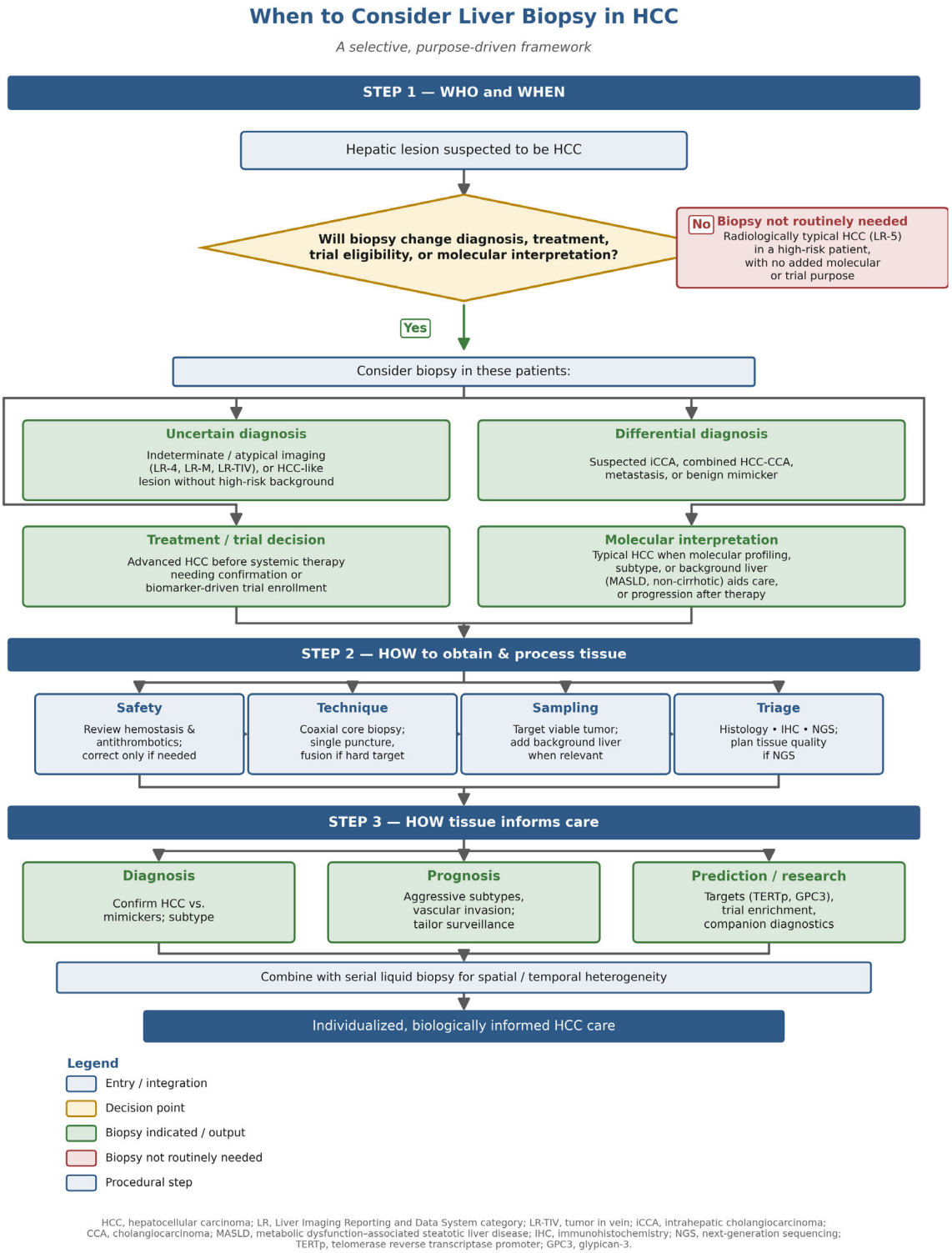


Figure 5. A practical framework for liver biopsy in HCC. A selective, purpose-driven workflow for liver biopsy in HCC. Step 1 defines the target population by asking whether biopsy would change diagnosis, treatment, trial eligibility, or molecular interpretation; routine biopsy is not required for radiologically typical HCC (LR-5) in a high-risk patient when no additional molecular or trial purpose exists, whereas imaging-typical HCC still qualifies when tissue adds molecular, subtype, or background-liver information. Step 2 outlines how tissue is obtained and processed (pre-procedural safety, image-guided coaxial core biopsy, targeted sampling, and specimen triage for histology, immunohistochemistry, and molecular profiling). Step 3 summarizes how tissue informs diagnosis, prognosis, and prediction/research, and which patients benefit, with serial liquid biopsy as a complementary approach. Abbreviations are defined within the figure.

voluntary participation by a predominantly Korean, internal medicine–weighted group of experts. Together, these findings underscore the need to move beyond a purely imaging-centered paradigm and to reframe liver biopsy as an enabling tool rather than a diagnostic exception.

Re-evaluating the role of liver biopsy in HCC should therefore focus on optimizing procedural safety, refining guideline-based indications, and integrating biopsy-derived molecular insights into clinical workflows and research frameworks. Such an approach has the potential to bridge the gap between emerging evidence and real-world practice, ultimately supporting more individualized and biologically informed care for patients with HCC.

Conflicts of Interests

Haeryoung Kim, Jeong-Ju Yoo, Hye Won Lee, Pil Soo Sung, and Sun Young Yim were Editorial Board members of *Journal of Liver Cancer* at the time of submission and revision, and were not involved in the review process of this article.

Su Jong Yu, Han Ah Lee, Yuri Cho, Jae-Geun Lee, Jihyun An, Jinhong Jung, Dong Ho Hyun, Hyun Phil Shin, Sang Min Yoon, and Minjong Lee became Editorial Board members of *Journal of Liver Cancer* following the board transition on July 1, 2026, and were not involved in the peer review or decision-making process for this manuscript. Otherwise, the authors have no conflicts of interest to disclose.

Ethics Statement

This study was based solely on previously published literature and did not involve the recruitment of additional patient participants; therefore, IRB approval was not required. An expert survey was conducted on a voluntary basis after participants were informed of the study purpose, and completion of the survey was considered to imply consent; thus, the requirement for written informed consent was waived.

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Data Availability

Not applicable.

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Supplementary Materials

Supplementary data can be found with this article online https://doi.org/10.17998/jlc.2026.08.27.

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