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REVIEW

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The evolving role of liver biopsy: Current applications and future prospects

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Abstract

Histopathologic evaluation of liver biopsy has played a longstanding role in the diagnosis and management of liver disease. However, the utility of liver biopsy has been questioned by some, given the improved imaging modalities, increased availability of noninvasive serologic tests, and development of artificial intelligence over the past several years. In this review, we discuss the current and future role of liver biopsy in both non-neoplastic and neoplastic liver diseases in the era of improved noninvasive laboratory, radiologic, and digital technologies.

Keywords: hepatic pathology, liver biopsy, liver pathology, pathology

INTRODUCTION

Histopathologic evaluation of liver biopsy has long been a mainstay in the evaluation and management of both neoplastic and non-neoplastic liver disease. However, the increased availability of noninvasive serologic tests and improved imaging modalities over the past several years has, for some, brought into question the utility of liver biopsy. The most recent American Association for the Study of Liver Diseases (AASLD) guideline states that liver biopsy is indicated to diagnose liver diseases that do not have a laboratory/blood-based test to establish the diagnosis, in atypical clinical presentations of suspected or known liver diseases, and to determine if a patient has multiple co-existing liver diseases.[1] Liver biopsy also has a role in prognostication and treatment guidance in non-neoplastic liver diseases and is necessary for biomarker assessment in some hepatic and metastatic neoplasms.[1] Per the European Association for the Study of Liver (EASL), though noninvasive markers are often used in a first-line assessment for liver disease workup in some patients, liver biopsy is an important tool available to hepatologists when deciphering the etiology of liver disease in complicated patients or in cases where there is disagreement between patient presentation and noninvasive testing results.[2] In this review we will discuss the role of liver biopsy in an era of less-invasive emerging technologies.

LIVER BIOPSIES IN NON-NEOPLASTIC CONDITIONS

Liver Biopsies in the evaluation of abnormal serum liver function tests

Serum liver function tests are essential to the initial assessment of hepatobiliary disease. In patients with suspected liver injury, clinical history and laboratory studies are the first-line evaluation to rule out viral

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AI, artificial intelligence; AMA, antimitochondrial antibody; B-HCA, B-catenin mutated HCA; CCA, cholangiocarcinoma; EASL, European Association for the Study of Liver; EMA, European Medicines Agency; FDA, Food and Drug Administration; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; I-HCA, inflammatory hepatocellular adenoma; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemical; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; PBC, primary biliary cholangitis; WD, Wilson disease.

hepatitis, autoimmune conditions (autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis), drug or toxin-associated liver injury, and hereditary and metabolic diseases.[3] Liver biopsy is reserved for patients in whom laboratory and clinical data do not provide a definitive diagnosis or to stage and grade the degree of injury present, even when the cause is known. In a study of 383 patients who underwent liver biopsy for evaluation of unexplained abnormal liver tests between 2014 and 2018, histological evaluation was able to provide a clinical diagnosis in 87% of cases. The most common diagnoses were autoimmune hepatitis (38%), metabolic dysfunction–associated steatotic liver disease (MASLD; 33%), and DILI (32%). Histological evidence of clinically silent cirrhosis was found in 5% of patients.[4] Another study similarly reported that liver biopsy yielded a diagnosis for most patients with unexplained abnormal liver tests, the most common being MASLD. Twenty-six percent of patients had fibrosis, and 6% with silent cirrhosis. In 18%, liver biopsy data resulted in a change in clinical management, including in 3 families who were entered into screening programs for heritable liver diseases.[5] These data underscore the importance of pursuing liver biopsy for cases in which a definitive diagnosis cannot be made using laboratory and imaging evaluation.

Liver biopsies in steatotic liver disease

MASLD, previously referred to as NAFLD is a leading cause of chronic liver disease.[6] It is estimated that 30% of the world population is affected by MASLD and the forecasted global MASLD prevalence in 2040 is 55.2%.[7,8] MASLD encompasses both steatosis without steatohepatitis and metabolic dysfunction–associated steatohepatitis (MASH, formerly known as NASH). MASH is characterized by steatosis, ballooning degeneration of hepatocytes, and lobular inflammation (Figure 1A) and it is estimated that up to one in four patients with MASLD have MASH.[9,10] When MASH develops, it can advance to fibrosis, cirrhosis, and HCC.[11,12]

Liver biopsy is the current gold standard for diagnosing MASLD/MASH and is the most reliable method to . determine the severity of liver inflammation and establish fibrosis stage.[13] Fibrosis is often present, typically starting in zone 3 in a pericellular pattern (Figure 1B), but it is not required for the diagnosis of MASH.[14] Other disease processes, such as DILI, Wilson disease, viral hepatitis, etc. should be excluded clinically when making a diagnosis of MASLD/MASH.[6] Liver biopsy plays a critical role in ruling out other disease processes in patients with MASLD/MASH, especially autoimmune liver diseases. One or more serum autoantibodies, such as antinuclear antibody and antismooth muscle antibody, may occur in 20%–35% of patients with MASLD/MASH, including pediatric patients.[15–17]

In recent years, noninvasive markers and methods have been developed to assess MASLD/MASH. These noninvasive strategies generally rely on serum biomarkers (such as enhanced liver fibrosis and FibroTest), imaging biomarkers (such as ultrasound-based FibroScan and MRI-based MRE) or a combination of these 2 approaches.[18–21] However, these tests have limitations and are unreliable in patients with early or mid-stage MASH. The reported performance varies significantly depending on the clinical context.[18,22,23] One study assessed 82 patients who received vibration-controlled transient elastography (VCTE) and biopsy within 1 month and found that 35.4% of patients had a major fibrosis discrepancy (defined as fibrosis stage 3–4 on VCTE, when biopsy showed stage 0–1); and 21% of patients had steatosis discrepancy (no or mild steatosis on VCTE, when biopsy showed severe steatosis).[22]

In considering the foregoing liver biopsy, it is useful to acknowledge that histopathology provides information that cannot be provided by noninvasive tests. A pathologist can not only report the presence of fibrosis and steatosis but also subtle findings such as the microscopic location of the abnormal collagen deposition and hepatic microarchitecture alterations.[24] In addition, biopsy has the advantage of differentiating MASLD from other chronic liver diseases[25–27] or additional pathology.[4,24] Although not a clinical indication, histologic evaluation of liver biopsies also plays a critical role in drug development for MASH. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend histological liver biopsy evaluation as the main inclusion criterion and primary efficacy/endpoint in new MASH drug development.[27–29]

Liver biopsy in autoimmune hepatitis

Autoimmune hepatitis (AIH), a historically rare entity that is increasing in incidence, has a variable clinical presentation both in age of onset[30] and in severity of symptoms, ranging from incidental detection of elevated liver enzymes to severe acute liver failure.[31] Liver biopsy in AIH provides information regarding the severity of inflammation, fibrosis stage, and evidence of other conditions. Recent consensus recommendations for updated histologic criteria of AIH from the International AIH Pathology Group include a portal pattern of likely AIH in which the characteristic histologic features include a dense plasma cell-rich portal inflammatory infiltrate, possibly with plasma cell clusters ≥ 5 plasma cells[32] and interface hepatitis (Figure 1C). Approximately 30% of patients with AIH have cirrhosis at presentation due to a lengthy subclinical disease course. Since serum serologies, such as antinuclear antibody, antismooth muscle

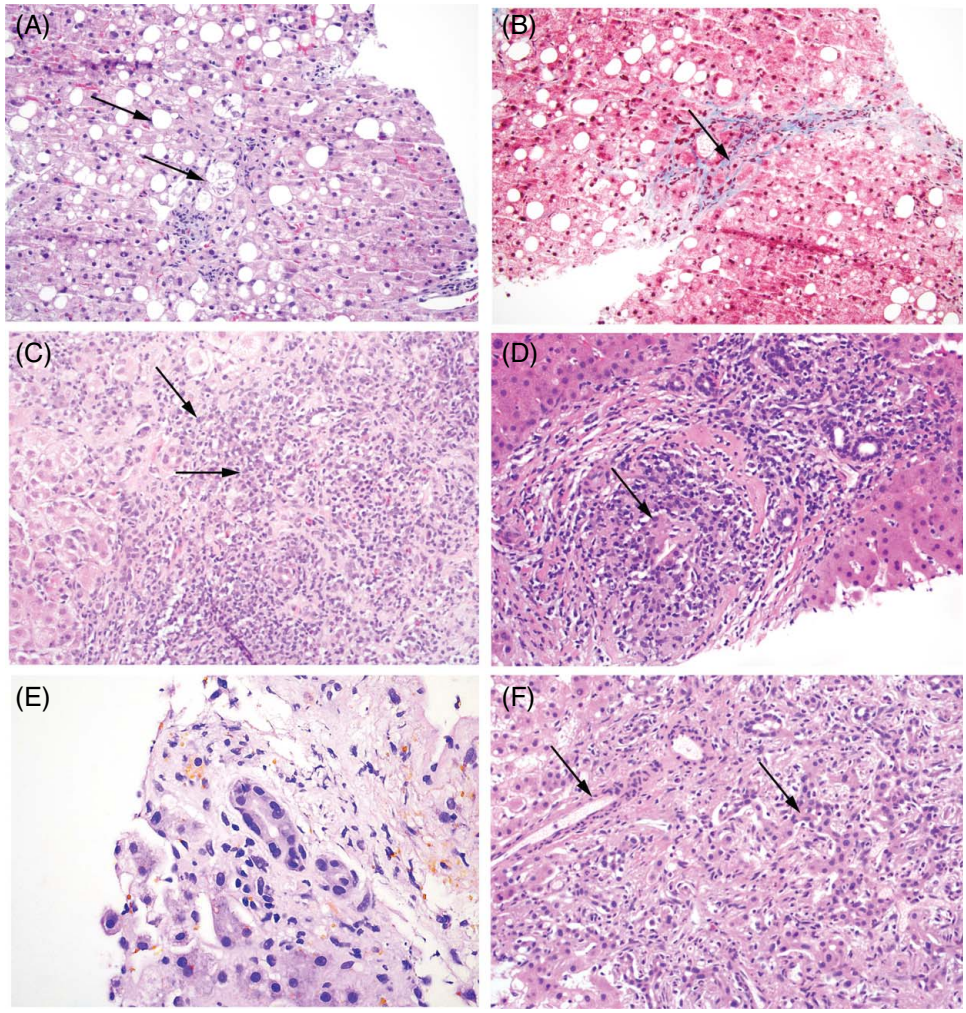

FIGURE 1 (A) Macrovesicular steatosis (long arrow) and ballooning degeneration of hepatocytes (short arrow) in metabolic dysfunction–associated steatohepatitis (H&E; ×20). (B) Pericellular fibrosis (arrow) in metabolic dysfunction–associated steatohepatitis (Masson Trichome; ×20). (C) Plasma cell-rich portal chronic inflammatory infiltrate (short arrow) with interface hepatitis in autoimmune hepatitis (long arrow) (H&E; ×20). (D) Florid duct lesion (arrow) in primary biliary cholangitis (H&E; ×20). (E) Bile duct injury in hepatic graft-versus-host disease (H&E; ×40). (F) Prominent bile ductular reaction (long arrow) and unpaired artery (short arrow) in focal nodular hyperplasia (H&E; ×20). (G) Focal nodular hyperplasia with "map-like" glutamine synthetase immunohistochemical staining (×20). (H) Inflammatory-type hepatic adenoma with thick-walled artery (long arrow) and sinusoidal dilatation (short arrow) (H&E; ×20). (I) Positive C-reactive protein immunohistochemical stain in inflammatory-type hepatic adenoma (×20). (J) HCC (long arrow); background liver (short arrow) (H&E; ×20). (K) Loss of reticulin staining in HCC (long arrow); intact reticulin staining in background liver (short arrow) (reticulin; ×20). (L) Cholangiocarcinoma, small duct type (H&E; ×20). Abbreviation: H&E, Hematoxylin and Eosin.

antibody, and liver kidney microsomal antibody are insufficiently sensitive or specific to render a confident diagnosis of AIH, clinicopathologic scoring systems have been developed to aid in the diagnosis.[32–34] Liver histology plays a central role in these scoring systems, such that most international guidelines continue to require liver biopsy as an integral part of the diagnostic evaluation and treatment decisions.

Liver biopsy in primary biliary cholangitis

Primary biliary cholangitis (PBC) leads to chronic cholestasis and usually progresses slowly over many years. Characteristic histologic features of primary biliary cholangitis include the florid duct lesion that is typically seen in the early stage of PBC (Figure 1D).[35] Bile duct injury in PBC is caused by the autoimmune destruction of small interlobular bile ducts due to abnormal expression of the pyruvate dehydrogenase E2 subunit which is the target of the antimitochondrial antibody (AMA), which is seen in 95% of patients with PBC.[36]

Liver biopsy is no longer required in all patients for a diagnosis of PBC, as the diagnosis can be made if 2 of the following 3 criteria are met: evidence of cholestasis based on elevation of ALP, presence of AMA or other PBC-specific autoantibodies (sp100 or gp210) if in the absence of positive AMA, or demonstration of non-suppurative destructive cholangitis on biopsy.[37]

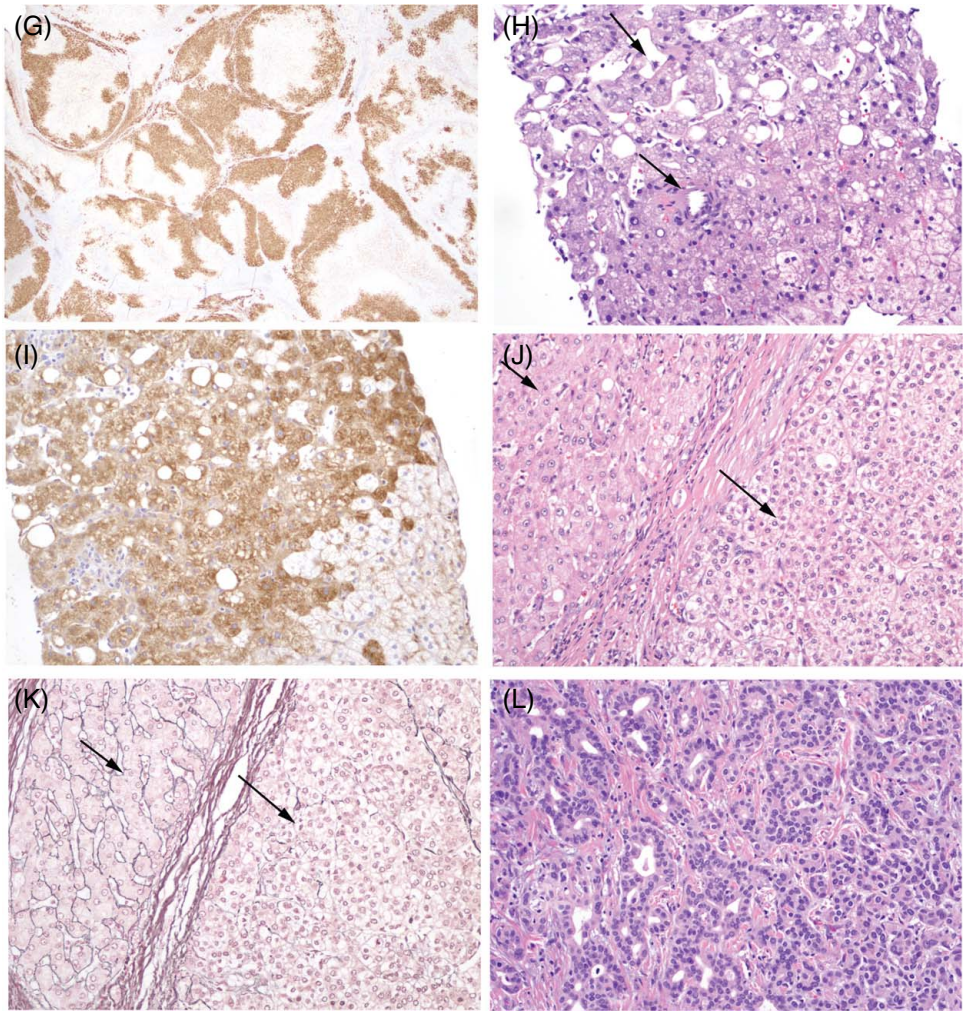

FIGURE 1 *(Continued).*

However, biopsy should be considered in patients with chronic cholestasis, particularly in the setting of negative serologic testing for AMA and negative radiologic workup for large bile duct obstruction or other potential causes of cholestasis.[38] Liver biopsy establishes the diagnosis of PBC or points toward other causes of cholestasis. Biopsy is also indicated if there is clinical suspicion of an overlap syndrome with AIH, which could alter treatment by addition of immunosuppressive therapy.[39–41]

Liver biopsy in DILI

The histologic interpretation of liver biopsies obtained due to suspected DILI can be challenging since the histologic changes of DILI can overlap with other liver diseases, including AIH, biliary tract diseases, viral hepatitis, MASLD, vascular liver diseases, and benign tumors.[40,41] A diagnosis of DILI is always made in conjunction with clinical history (medication list) and laboratory results, paying attention to the timing of liver injury relative to medication usage, and liver enzyme improvement after stopping the potentially offending drug. Polypharmacy and the presence of a background of other liver diseases can complicate biopsy interpretation.

The true utility of liver biopsies in DILI is relatively unexplored, though some studies on this topic have been published. In 2022, Ahmad and colleagues randomly selected 50 patients already enrolled in the DILI Network who had liver biopsies performed to evaluate the utility of liver biopsy in patients with suspected DILI. Overall, they showed the liver biopsy review significantly altered the causality scores in the categories of definite, possible or unlikely, frequently shifting cases in the “possible” or “probable” categories to either definite or unlikely. Further, the study showed that the biopsy results guided clinical treatment with corticosteroids in some cases and suggested infectious causes in others. Overall, the study highlighted that liver biopsy in clinically suspected DILI was helpful,

particularly in distinguishing DILI from some infections, AIH, MASLD, and alcohol-associated liver disease.[41]

Distinguishing DILI specifically from AIH can be especially challenging due to overlapping histologic and clinical features. A study by Suzuki and colleagues sought to characterize the histologic findings of liver biopsy that could aid in determining a diagnosis of AIH versus DILI. They concluded that while no single histologic feature differentiates DILI from AIH, the constellation of histologic findings, including inflammatory cell type and location, severity of inflammation, and presence of canalicular cholestasis can be helpful in conjunction with clinical information to help distinguish DILI from AIH.[42] In 2023, the joint conference of the Drug-Induced Liver Injury Consortium and the International Autoimmune Hepatitis Group reported their consensus opinion that liver biopsy has utility in confirming DILI with histology resembling AIH and in ruling out the presence of other entities. However, they also highlighted the need to improve liver biopsy evaluation to better understand histologic patterns of injury in DILI to help distinguish DILI from AIH prior to immunosuppressive treatment. Further, the groups agreed on the need for molecular marker discovery in tissue to help distinguish between the DILI and AIH.[43] Overall, liver biopsy continues to be a helpful tool in the diagnosis of DILI versus AIH in many cases. However, the histologic distinction of drug-induced AIH pattern of AIH from de novo AIH remains a challenge that will require future studies with a larger cohort[42,43]

Post-transplant liver biopsy

Liver biopsy is the gold standard procedure to diagnose the cause of post-transplant abnormal liver chemistries, the differential diagnosis of which includes acute T-cell mediated, chronic and antibody-mediated allograft rejection,[44] infection, recurrent disease, biliary injury, vascular injury, DILI, or post-transplant lymphoproliferative disorder. Although the clinical context and timing can raise suspicion for one cause over another, most clinical situations require a biopsy for a definitive diagnosis.

Liver biopsy in graft-versus-host disease

Hepatic involvement by graft-versus-host disease is a cause of serious liver dysfunction in patients who are post-hematopoetic stem cell transplantation for hematologic malignancies, some solid organ malignancies, or certain hematologic diseases. There is a large differential diagnosis for hepatic injury in patients who underwent post-hematopoetic stem cell transplantation with overlapping clinical and laboratory features, which liver biopsy can help resolve.[45] In addition to diagnosis, a liver biopsy of hepatic involvement by graft-versus-host disease specifically can help assess for disease activity, the severity of duct injury/loss (Figure 1E), and fibrosis stage.[46,47]

Liver biopsy in portosinusoidal vascular disease/noncirrhotic portal hypertension

The term “portosinusoidal vascular disease” (PSVD) was introduced by De Gottaradi and colleagues in 2019 to provide an all-encompassing name for a heterogenous group of conditions in patients without cirrhosis with portal hypertension.[48,49] Various terms have been used in the literature to describe this entity, including noncirrhotic portal fibrosis, idiopathic portal hypertension, hepatoportal sclerosis, noncirrhotic intrahepatic portal hypertension, nodular regenerative hyperplasia, and obliterative portal venopathy. Specific histologic features of PSVD include obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal fibrosis.[49,50] According to the most recent AASLD and EASL guidelines on vascular liver disorders, as well as in the diagnosis of the newly coined PSVD, liver biopsy is essential to exclude cirrhosis[51,52] and to assess for the histologic features of PSVD[48] in patients with portal hypertension but without clinical evidence of cirrhosis.

Liver biopsy in Wilson disease and hereditary hemochromatosis

Wilson disease (WD) has a wide spectrum of clinical presentation and can present in both the pediatric and adult age groups. Timely diagnosis is imperative as treatment can prevent further injury of the liver and other organs by copper deposition.[53,54] Per the AASLD 2022 practice guidance for WD, while liver biopsy is not routinely required for a diagnosis of WD, it has utility in providing grading and fibrosis staging and allows for the assessment of histologic features that are consistent with WD, though the histologic appearance of WD can be very variable.[53] An adequate liver biopsy also provides tissue for quantitative copper analysis if needed for diagnostic confirmation of WD.[53] Further, recent studies have demonstrated that metallothionein immunohistochemistry has a high sensitivity for a diagnosis of WD, similar to that of quantitative copper, and could serve as a more accessible, cost-effective, and efficient screening tool for WD on liver biopsies from patients in which WD is suspected.[54,55]

In hereditary hemochromatosis, liver biopsy is helpful mainly to exclude other underlying liver diseases and to stage fibrosis in patients with a ferritin >1000 ng/mL, who are at increased risk for advanced fibrosis.[56,57]

LIVER BIOPSIES IN NEOPLASTIC CONDITIONS

Biopsy of hepatic neoplasms

Liver biopsy interpretation of primary liver neoplasms can be challenging for pathologists because of the limited material and overlapping histologic features. However, neoplastic liver biopsies can help provide not only the accurate diagnosis, but also prognostic information and behavior prediction of the neoplasm, thus resulting in more appropriate clinical management. While metastatic tumors are most common in the liver, we will specifically focus on the utility of liver biopsy in hepatocellular adenoma (HCA), HCC and intrahepatic cholangiocarcinoma (iCCA).

Liver biopsy in hepatocellular adenoma

HCA is a clonal hepatocellular proliferation that typically occurs in the liver and is not affected by chronic liver disease. HCAs can be subclassified into different molecular subgroups, some of which are associated with additional histologic findings and distinct immunohistochemical (IHC) staining patterns that serve as a surrogate marker for the underlying molecular abnormality in an HCA. The molecular subgroups of HCA include inflammatory hepatocellular adenoma (I-HCA), hepatocyte nuclear factor 1A-HCA, B-catenin mutated HCA (B-HCA exon 3 or B-HCA exon 7-8), and Sonic Hedgehog HCA, although occasionally, some HCA (~10%) remain unclassified. Biopsy of HCA is important to allow for the diagnosis and subtyping, given that certain HCA subtypes are associated with an increased risk of malignant transformation. These include the B-HCA exon 3, beta-catenin mutated I-HCA, and rarely hepatocyte nuclear factor 1A-HCA.[58–60]

The histologic differential diagnosis of HCA includes focal nodular hyperplasia (FNH) and well-differentiated HCC. FNH typically has a distinct appearance with multiphase MRI with hepatobiliary-specific contrast. If the diagnosis of FNH is confirmed on imaging, biopsy is not typically indicated. However, in cases where imaging is inconclusive, biopsy of the lesion may be helpful to determine whether the lesion is an FNH versus HCA, which is important as management of these 2 lesions differs.[60] FNH can be difficult to distinguish from HCA, particularly I-HCA. FNH typically has broad bands of fibrosis within the lesion on biopsy, which correspond to the central scar seen radiologically and grossly, which contains abnormal vascular structures and an accompanying bile ductular reaction (Figure 1F). Prior to the relatively recent molecular characterization of HCAs, I-HCA was often considered to be an FNH.[58] Glutamine synthetase immunohistochemistry can be helpful in this differential diagnosis as FNH has a characteristic "map-like" staining (Figure 1G) within the lesion, while glutamine synthetase IHC staining in HCA can have a variety of patterns (which are not "map-like") depending on the HCA subtype or molecular alteration.[59] When considering FNH specifically from I-HCA, C-reactive protein and/or serum amyloid A IHC stains should be positive in I-HCA (Figure 1H, I) but not FNH.

Similarly, biopsy is helpful in differentiating HCA from well-differentiated HCC when imaging is inconclusive for a diagnosis of HCC.[60] Reticulin stain on the biopsy can be helpful in distinguishing between HCA and HCC in that there can be reticulin loss in HCC (Figure 1J, K). Glypican-3 is an IHC stain that can also be useful in that it sometimes can be positive in HCC and negative in HCA.

Overall, biopsy continues to play an important role in patients with suspected HCA, not only for accurate diagnosis but also for molecular characterization, subtyping, and prognostic information,[61,62] which guides clinical management.

Liver biopsy in HCC

On CT scan and MRI, HCC > 1 cm and arising in a background of known cirrhosis typically have a characteristic appearance composed of an arterial phase hyperenhancement followed by portal venous or delayed phase washout.[63] Given that advanced imaging techniques are overall successful in characterizing liver lesions > 1 cm in size in patients with cirrhosis, the role of liver biopsy in the diagnosis of HCC has diminished over the years.

Noninvasive diagnosis of HCC allows patients to avoid undergoing a liver biopsy and potential biopsy-related complications including pain (most common), bile peritonitis, gallbladder perforation, pneumothorax, hemorrhage, hemothrorax, hemobilia, or potentially tumor seeding along the needle path during biopsy; however, the risk of the latter is thought to be very low and is usually treated successfully by ablation or resection with no significant added morbidity or mortality.[64,65]

While the advances in imaging techniques have given patients the opportunity to avoid potential adverse outcomes due to liver biopsy, there is utility and benefit in having HCC biopsy tissue available. Microscopic analysis of even small biopsy fragments of HCC can provide histologic prognostic information that can be useful in patient care by identifying the presence or absence of features that cannot be visualized on imaging. These include the identification of morphologic subtypes such as macrotrabecular massive, which is associated with a poorer outcome,[66] while lymphocyte-rich HCC portends a better prognosis.[67] HCC biopsy analysis also allows for the identification of small vessel vascular invasion, the presence of which is associated with poorer outcomes, advanced stage, and distant metastases.

Additionally, a relatively recently described unique HCC vascular pattern, vessel encapsulating tumor clusters has also been associated with poorer prognosis.[68] While the data on these histologic subtypes do not affect the therapeutic approach yet, their potential for clinical importance depends on additional studies made possible by the existence of clinical samples.

For many patients, a confirmatory liver biopsy in suspected HCC is required to allow chemotherapy to proceed. Childs and colleagues conducted a prospective multicenter study of a cohort of 361 patients with advanced HCC who were found to be eligible for systemic therapy for HCC at multidisciplinary tumor board. Of the patients who ultimately received a confirmatory biopsy, 7% received diagnoses other than HCC, including cholangiocarcinoma (CCA), combined HCC-CCA, neuroendocrine carcinoma, breast carcinoma, or benign lesions demonstrating that these patients could have received inappropriate therapy had they not been biopsied, underscoring the importance of liver biopsy in radiologically suspected HCC.[69] Similarly, a study by Brusset et al[70] showed that of 100 LI-RADS 5 (definitely HCC on imaging) lesions included in their study, 11 lesions were misclassified and on biopsy were found to have diagnoses of metastatic colorectal adenocarcinoma or CCA, further supporting the need of biopsy confirmation of radiologically suspected HCC prior to initiation of systemic treatment.

The most recent practice guidelines form the American Association for the Study of Liver Diseases (AASLD) supports the use of confirmatory liver biopsy in HCC, particularly in patients with liver nodules without cirrhosis or without hepatitis B infection, as LI-RADS criteria are not applicable in these patients.[71] The AASLD guidelines also support the use of liver biopsies in clinical trials for all LR 4–5 nodules and for patients not enrolled in clinical trials, not only for the prevention of misdiagnosis but also for the availability of tissue for molecular analysis.[71] The decrease in HCC tissue availability for molecular and genomic analysis has caused a delay in identifying potential diagnostic biomarkers and therapeutic targets in HCC, compared to other cancers. While to date there has been no successful biomarker identified in HCC leading to targeted therapies, besides AFP $>/=400$ ng/mL and ramucirumab in advanced HCC, increased availability of HCC tissue for future molecular analyses would be imperative to gain further understanding of the heterogeneous and complex molecular profile of HCC, and potentially lead to growth and development of targeted therapies for patients in the future.

Liver biopsy in iCCA

Liver biopsy also plays a significant role in the diagnosis and molecular characterization of iCCA.[72] The current World Health Organization classification of digestive tumors divides iCCA into 2 main categories, which include small duct type (Figure 1L) and large duct type.[73] Recent genomic profiling studies of iCCA have identified genomic alterations that allow for prognostic information in small duct iCCA where fibroblast growth factor receptor 2 fusions are associated with better prognosis, while iCCA with isocitrate dehydrogenase 1 and isocitrate dehydrogenase 2 mutations have a worse prognosis.[74] In addition to prognostic information, molecular testing of iCCA biopsy tissue can allow for the identification of targetable mutations in iCCA. In 2023, Goyal and colleagues enrolled 103 patients with iCCA who had disease progression on previous systemic therapy with unresectable or metastatic fibroblast growth factor receptor 2 fusion or rearrangement-positive tumors. In this study, the patients received futibatinib, a selective irreversible FGFR inhibitor, and 42% of patients had a measurable clinical response with a median duration response of 9.2 months.[75] In 2021, Yoon et al[76] showed that chemotherapy response was more favorable in small duct type iCCA with isocitrate dehydrogenase 1 and BAP1 mutations than large duct type iCCA with SMAD4 and KRAS mutations. Finally, 1%–3% of CCA that have mismatch repair deficiency/are microsatellite instability-high have a favorable response to programmed death-1 inhibitor therapy.[77,78] Therefore, in addition to accurate diagnosis, molecular characterization of iCCA biopsy tissue also provides prognostic information and an enhanced understanding of treatment responses to particular types of chemotherapy and immunotherapy.

THE ROLE OF LIVER BIOPSY IN EMERGING TECHNIQUES

Liver biopsy versus Liquid biopsy?

Molecular characterization of tumors via liquid biopsy is typically performed using circulating tumor DNA, RNA, exosomes from peripheral blood, or circulating tumor cells. Liquid biopsy has been suggested as a minimally invasive alternative to the traditional liver biopsy that can also be easily repeated to monitor tumor biomarker changes in patients over time. An additional benefit of liquid biopsy, specifically in HCC, includes the ability to capture the molecular heterogeneity of HCC and its microenvironment that could potentially provide support in the radiologic diagnosis of early HCC, which can be a challenge.[79] However, there has been a lack of reproducibility in liquid biopsy studies due to a lack of standardized collection and analysis methods.[80] Also, since biopsy of HCC is less widely performed given the ability to diagnose HCC radiologically, lack of HCC tissue availability has led to delayed identification of HCC biomarkers. Therefore, paradoxically, increasing the frequency of liver biopsy is imperative to expedite the

TABLE 1 Utility of liver biopsy across liver diseases

Disease	Characteristic histologic features	Liver biopsy utility
Metabolic dysfunction–associated steatohepatitis	Steatosis, ballooning degeneration of hepatocytes, lobular inflammation, zone 3 pericellular fibrosis	Grade severity of inflammation, establish fibrosis stage and exclude other disease processes
Autoimmune hepatitis	Dense plasma cell-rich portal inflammatory infiltrate, interface hepatitis, lobular chronic inflammation	Grade severity of inflammation, establish fibrosis stage, and exclude other disease processes
Primary biliary cholangitis	Florid duct lesions, portal chronic inflammatory infiltrate with plasma cells	Rule out other causes of chronic cholestasis in the setting of negative AMA, negative imaging for large bile duct obstruction, or other causes of cholestasis; rule out overlap with AIH; fibrosis stage
Drug induced liver injury	Nonspecific inflammatory pattern; can histologically mimic AIH or other causes of liver disease	Distinguish DILI from AIH, infections, MASH, alcohol-associated liver disease
Acute T-cell–mediated rejection	Mixed (mostly lymphocytic) portal inflammatory infiltrate, bile duct inflammation/injury, venous endothelial inflammation	Diagnosis; exclusion of chronic or antibody-mediated reaction, infection, recurrent disease, biliary injury, vascular injury, DILI, post-transplant lymphoproliferative disorder, or other disease processes
Hepatic graft-vs.-host disease	Bile duct injury +/− epithelial apoptosis, bile duct loss, mild portal and lobular inflammation composed mainly of lymphocytes, +/− cholestasis	Determine the severity of bile duct injury or loss, establish fibrosis stage, and exclude other disease processes
Portosystemic vascular disease	Obliterative portal venopathy, herniated portal veins, nodular regenerative hyperplasia	Assess for PSVD histologic features; exclude cirrhosis
Wilson disease	Variety of nonspecific histologic features; steatosis, glycogenation of nuclei, portal and lobular inflammation, Mallory-Denk bodies, acidophil bodies, fibrosis	Timely diagnosis, grading, establish fibrosis stage, tissue availability for quantitative copper analysis or metallothionein immunohistochemistry
Hereditary hemochromatosis	Iron deposition predominantly within hepatocytes	Exclude other diseases; establish fibrosis stage in patients with ferritin >1000 ng/mL
Hepatic adenoma	Hepatocytes arranged in trabeculae 1–2 cells thick with unpaired arteries and no portal tracts	Exclude focal nodular hyperplasia and HCC, molecular characterization, subtyping, and prognostic information
Well-differentiated HCC	Tumor cells are arranged in a variety of growth patterns including trabecular, macrotrabecular, pseudoglandular, or solid	Diagnostic confirmation, prognostic information, tissue availability for molecular analysis, and biomarker identification
Intrahepatic cholangiocarcinoma	Small duct type: cuboidal tumor cells arranged in small anastomosing tubules Large duct type: columnar tumor cells arranged in large glands often containing mucin	Diagnostic confirmation, prognostic information, molecular testing for targeted therapies

Abbreviation: HCC, hepatocellular carcinoma.

identification of important HCC biomarkers that could be eventually followed in blood, thus allowing for further insight into the molecular characterization of these tumors and eventually leading to successful targeted therapies for HCC in the era of precision medicine.

The role of digital pathology and artificial intelligence in liver biopsy

Artificial intelligence (AI) technology has the potential to play a transformative role in all subspecialties of pathology including liver pathology. With the use of high throughput scanning devices that capture digital images of liver biopsies on a glass slide, digital pathology slides have the capability to be assessed with computational processing that can glean biological, clinical, and prognostic information that is not discernable by the human eye.[81] Several studies have shown the potential utility of AI in the evaluation of both neoplastic and non-neoplastic liver biopsies. In 2022, Cheng et al[82] developed a deep learning AI model for diagnosis of hepatocellular nodular lesions, which was able to risk-stratify nodules and aid pathologists in differentiating well-differentiated HCC from other hepatocellular nodules in biopsies with suboptimal tissue. In 2023,

Zeng et al[83] demonstrated the use of AI as a biomarker on HCC liver biopsies to predict the sensitivity of atezolizumab-bevacizumab in patients with HCC. Several AI pathology tools are also in development in the study of MASLD liver biopsies, including those to assist pathologists by improving reproducibility in grading and staging, improved assessment of MASLD progression, and regression of fibrosis by assessing features that are not appreciated by the human eye. These AI techniques could improve diagnostic and prognostic information clinically and aid in improving the identification of endpoints in drug development.[84] However, there are currently limitations and barriers to the implementation and clinical use of AI. AI validation in pathology is a challenging process that requires multi-institutional participation prior to clinical use.[85] High cost of AI hardware can pose a barrier, and at this time, high volume of slide scanning can be difficult and time-intensive. Regulatory body approval (FDA in the United States) of an AI algorithm is a rigorous process and approval is required prior to use in pathology.[85] Nonetheless, the involvement of AI in pathology has the potential to revolutionize the practice of liver pathology and liver biopsy interpretation in the coming years. It is predicted that AI will likely play a future role as a tool to assist the pathologist in reporting on liver biopsies more comprehensively and solidify the role of liver biopsy in patient care going forward, by allowing the pathologist to provide not only diagnosis but possibly also more detailed prognostic information, prediction of disease progression, and treatment response to specific therapeutic agents.

CONCLUSIONS

Liver biopsy continues to play an essential role in the accurate diagnosis of non-neoplastic and neoplastic liver disease. Beyond diagnosis, minute fragments of liver tissue contain an abundance of information allowing for improved treatment guidance, prognostication, targeted therapies, molecular characterization, and biomarker identification. Liver biopsy remains a mainstay in the workup and management of liver disease, and its utility and relevance are evolving alongside improved and emerging radiologic, serologic, and AI technologies (Table 1).

CONFLICTS OF INTEREST

Marie Robert consults for Takeda, Alimentiv, Path AI, and Teva. She received grants from Astra-Zeneca. The remaining authors have no conflicts to report.

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