REVIEW ARTICLE

The Indications for Liver Biopsy

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SUMMARY

Background: Despite improvements in serological and radiological techniques, liver biopsy remains the most reliable way to diagnose diffuse hepatic disease and hepatic nodules. The indications for this invasive technique must be weighed against the small, but not negligible, risk of a complication.

Methods: The indications for liver biopsy are summarized on the basis of a selective review of the literature, including the published recommendations and position statements of specialty societies in Germany and abroad. The conclusions are supplemented with an evaluation of the authors' own experience.

Results: The success of liver biopsy depends not only on the selection of the puncture method and on due attention to the relative and absolute contraindications, but also on the experience of the person carrying out the procedure. For patients with hepatitis of various etiologies, liver biopsy is used not only to establish the cause of the disorder, but also to assess the degree of inflammatory activity (grading) and the extent of fibrosis (staging).

Conclusion: Liver biopsy enables the reliable diagnosis of hepatic lesions and is an important aid to treatment planning and prognostication.

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Percutaneous, ultrasound-guided liver biopsy (the Menghini method) has become a worldwide standard. The method is simple, rapid, inexpensive, and quite safe, although controlled prospective data about it are scarce. Significant complications arise in about 1% of biopsies, with less than 0.1% mortality (1). The main complications are post-interventional hemorrhage and bile leakage; injuries to other organs (gall bladder, lung, kidney) and bacteremia are rare. The risk of hemorrhage depends on the type of hepatic disease present and on the presence or absence of portal hypertension (e1, e2). Hemorrhage is more likely in biopsies of diffusely infiltrative hepatic diseases, e.g., amyloidosis and malignant processes such as lymphomatous infiltrates.

Laparoscopic liver biopsy yields more information than percutaneous liver biopsy, as it enables macroscopic inspection of the hepatic surface. Performing a biopsy under laparoscopic vision also ensures that the tissue cylinders will be large enough for further processing in the pathology department (2). The mini-laparoscopic technique with 3-mm trocars (maximum size) makes the procedure safer without limiting the surgeon's view of the liver, and it also enables simultaneous inspection of the peritoneum, spleen, and other intraperitoneal structures (2). In a laparoscopic biopsy, the surgeon can coagulate the puncture site at once in case of visible bleeding or bile leakage. This, in turn, makes it feasible to perform liver biopsies on patients who are at elevated risk of hemorrhage.

Transjugular liver biopsy is a reasonable option for patients with severe coagulopathies, but it carries the risk of complications of jugular catheter placement. Mini-laparoscopic biopsy is preferred for patients with hepatopathies of uncertain type, because focally altered areas can be targeted for biopsy, and the risk of a non-representative biopsy is lower. Moreover, laparoscopic biopsy is superior to percutaneous biopsy for the recognition of cirrhosis; laparoscopy is thus preferred when the purpose of the biopsy is to assess the level of activity of a chronic liver disease, unless cirrhosis has already been diagnosed from the clinical findings or laboratory tests. The same is true when definitive findings have been obtained by non-invasive measurements of fibrosis, such as fibroscan or elastography. The specificity and sensitivity of such tests are still a matter of debate, however, with adequate documentation in clinical studies only for hepatitis C (e3).

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TABLE

Liver biopsy: degrees of indication for establishing the diagnosis, for staging and/or prognostication, and for treatment planning

	Diagnosis	Staging/Prognosis	Treatment
Hepatitis B	---	+++	++
Hepatitis C	---	+++	+++
Autoimmune hepatitis	+++	+++	+++
Primary sclerosing cholangitis	+++	+++	---
Primary biliary cirrhosis	++	+++	+
Overlap syndrome	+++	+++	++
Nutritional-toxic/alcoholic steatohepatitis	+	+++	+
NAFLD/NASH	+++	+++	+
Iatrogenic-toxic	+++	+	+
Hemochromatosis	+++	+++	+++
Wilson's disease	+++	+++	---
A1AT deficiency	+	++	---
Acute liver failure	+++	+++	---
S/p liver transplantation (rejection, re-infection)	+++	++	+++
Tumor:			
HCC	++	---	---
LCA	+++	---	+++
Metastases	+++	---	---

The relevance of biopsy to diagnosis, staging/prognostication, and treatment decisions is rated as follows:
 ---, irrelevant; +, occasionally relevant; ++, usually relevant; +++, highly relevant;
 NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis;
 A1AT, alpha-1-antitrypsin; HCC, hepatocellular carcinoma; LCA, liver-cell adenoma

For ultrasound-guided percutaneous biopsies of diffuse hepatic disease, the Menghini needle has been found to afford the best combination of safety and positive findings. Vacuum aspiration through the Menghini needle yields biopsy cylinders of up to 5 cm in length. For focal lesions, on the other hand, it is better to obtain targeted cutting biopsies with a Tru-Cut needle. The Tru-Cut needle is helpful, too, when the tissue to be biopsied is of a harder consistency, as the biopsy cylinders are relatively stable. Semi-automatic biopsy guns make the procedure much easier. Laparoscopic biopsies are also best performed with a semi-automatic biopsy gun; the greater safety of laparoscopic biopsies enables the surgeon to take multiple tissue samples, even from both lobes of the liver, if desired. Fine-needle biopsies have the lowest hemorrhagic risk of all, but they often yield an inadequate amount of tissue and should thus only be used for tumor biopsies in patients at high risk of bleeding. An overview is given in the *Table*.

As liver biopsy is an invasive procedure with potential complications, patients should give their informed consent in writing after receiving full

information of its indications, risks, and alternatives, no later than the day before the procedure. For safety, the platelet count should be above 50/nL, and the Quick value over 50% (e4). If these values are not met, platelets and/or plasma should be given before the procedure, and the biopsy should be performed with the mini-laparoscopic technique or by jugular puncture, if possible (e5).

Biopsy of diffuse diseases of the liver

Viral hepatitis

Viral hepatitis can be reliably diagnosed by serology. The purpose of liver biopsy is not to secure the initial diagnosis, but to determine the degree of inflammatory activity (grading) and the extent of fibrosis (staging), and to diagnose potentially comorbid conditions of the liver. In hepatitis B infection, the demonstration of a significant degree of fibrosis and/or inflammation is a decisive factor both for the indication for treatment and for the choice of an antiviral treatment strategy (3, 4). In hepatitis C, liver biopsy is performed mainly to weigh the potential benefits of treatment against its side effects and risks. This holds for newer virustatic agents as well, and particularly for patients infected with viral genotype 1.

Summary: For patients with viral hepatitis, liver biopsy is used for grading, staging, and the exclusion of comorbidities.

Autoimmune hepatitis

The diagnosis of autoimmune hepatitis (AIH) requires the histological demonstration of hepatitis (5). Histology is a component of all diagnostic scores (6) and is important for grading and staging. Especially in advanced stages when liver function tests are only mildly elevated, histological examination may reveal very severe inflammatory changes necessitating high-dose immunosuppressive treatment (7).

In general, AIH is characterized by an irregular pattern of fibrosis. There is often a macronodular cirrhosis that can only be recognized by macroscopic-laparoscopic inspection (8) (*Figure 1 a–c*). This is relevant to treatment decisions, as the effective steroid medication budesonide, for example, cannot be used to treat AIH if cirrhosis is present. Biopsy also aids treatment monitoring in AIH. Patients who achieve both normal transaminase concentrations and normal IgG levels under treatment can be safely considered to be in remission, even without confirmation by biopsy. Those, however, who have either normal transaminase concentrations or normal IgG levels, but not both, should undergo liver biopsy: in about half of all such cases, biopsy reveals persistent, marked inflammatory changes that necessitate more intensive immunosuppression (7).

Summary: In AIH, liver biopsy is important for securing the initial diagnosis (as an integral component of the diagnosis score) and for treatment monitoring over the course of the disease.

Figure 1: Macroscopic and microscopic views of cirrhosis

- a) Laparoscopic view of macronodular cirrhosis due to autoimmune hepatitis
- b) Autoimmune hepatitis type 1, cirrhosis in liver biopsy (hematoxylin-eosin stain [H & E])
- c) Autoimmune hepatitis type 1, cirrhosis in liver biopsy (elastica-van-Gieson stain [EvG])

Cholestatic liver diseases

The differential diagnosis of cholestatic liver diseases is performed on the basis of laboratory tests, serology, and ultrasonographic examination. If ultrasound reveals no obstruction or other abnormality of the biliary pathways, histology is needed to complete the diagnostic assessment. If the biliary pathways are obstructed, biopsy carries a higher risk of bile leakage and bacteremia, so non-invasive imaging studies are preferable to a biopsy.

Although drug-induced liver damage often shows a cholestatic pattern, liver biopsy can distinguish it fairly reliably from an autoimmune disease (9).

Primary biliary cirrhosis (PBC) can be diagnosed on serological grounds alone by the demonstration of a high titer of anti-mitochondrial antibodies (AMA) specific for the E2 subunit of pyruvate dehydrogenase (usually designated AMA-M2). A biopsy is nonetheless recommended, at the time of initial diagnosis, if the additional presence of (secondary) autoimmune hepatitis is suggested either by laboratory tests (high transaminase or IgG concentrations) or by serology (SLA/LP-autoantibodies). About 20% of PBC patients have AIH as well (1, 10). PBC with secondary AIH takes a more aggressive course, usually does not respond completely to standard treatment with ursodeoxycholic acid (UDCA), and generally necessitates immunosuppressive treatment, as does AIH without PBC (11).

Primary sclerosing cholangitis (PSC) can also be an indication for liver biopsy, despite the traditional opinion to the contrary. Before a biopsy is performed, however, the characteristic sclerosing changes in the biliary pathways should be sought by endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) (12). Like PBC, PSC is accompanied by secondary AIH in up to 20% of cases; this should probably be treated with immune suppression (11). Early PSC can easily be missed by ERCP or MRCP because of the limited extent of destruction in the biliary pathways. As a result, biopsy is increasingly playing a role as an additional means of diagnostic evaluation in such cases (source: Quass A et al., personal communication).

PSC with changes in the smaller intrahepatic biliary pathways (small-duct PSC) can only be diagnosed by histology. Although small-duct PSC has a markedly better prognosis, it can still undergo progression to classic PSC (13). IgG4-associated cholangitis also requires a biopsy for definitive diagnosis (13).

As a rule, all other types of cholestatic change in the liver can only be diagnosed by biopsy.

Summary: In patients with cholestatic liver diseases, liver biopsy is a valuable means of detecting or ruling out the autoimmune disorders in this diseases class, when the laboratory findings are inconclusive.

FIGURE 2

Frequency distribution of diagnoses made by liver biopsy

a) Liver-tissue cylinder with diagnosis: malignant disease

listed by disease entity; 1429 liver-tissue cylinders total;

CUP, cancer of unknown primary

b) Liver-tissue cylinder with diagnosis: metastases

listed by type of primary tumor; 886 liver-tissue cylinders total;

statistics for 2010, Pathology Dept., Ruhr-Universität Bochum;

GIST, gastrointestinal stroma tumor

Fatty liver and fatty-liver hepatitis

Histological examination enables the differentiation of alcoholic from non-alcoholic fatty-liver disease. More importantly, it is an aid to the assessment of inflammation and fibrosis. While fatty liver *per se* is fairly innocuous, fatty-liver hepatitis (ASH or NASH) often leads to cirrhosis and to hepatocellular carcinoma (14). The distinction between fatty liver and fatty-liver hepatitis is hard to draw from laboratory tests alone, as the elevation of transaminase concentrations provides no more than a rough guide. Nonetheless, biopsy should only be performed after careful consideration of the implications a positive biopsy would have for further treatment (14). A biopsy finding may help motivate the patient to change his or her lifestyle permanently for the better, particularly if the biopsy reveals advanced fibrosis. Unlike noninvasive tests, such as elastography, biopsy enables the precise diagnosis and staging of non-alcoholic steatohepatitis (NASH) as well (15).

Summary: Liver biopsy is an aid to the differential diagnosis of fatty-liver disease. Histological examination reveals the degree of fibrosis (staging) and any potential comorbidities.

Storage diseases and metabolic diseases

Hemochromatosis is the most common hereditary storage disease of the liver. Not all homozygotes for the hemochromatosis (HFE) gene develop the disease. Patients who have already developed cirrhosis before hemochromatosis is diagnosed or treated are at elevated risk of hepatocellular carcinoma (HCC); in such cases, biopsy is the diagnostic gold standard for the exclusion of cirrhosis as a precancerous lesion. Wilson's disease (a copper-storage disease) is hard to diagnose by laboratory testing and cannot always be unambiguously diagnosed, even by histology. When a liver biopsy is performed for a suspected diagnosis of Wilson's disease, a quantitative copper measurement should also be considered. Such measurements can be made retrospectively on paraffin-fixed biopsy specimens. In hemochromatosis, too, the amount of stored iron in an archived biopsy specimen can be quantified. This is particularly useful in cases where an iron-storage disease is suspected but no genetic mutations have been found (16).

Alpha-1-antitrypsin (A1AT) deficiency sometimes escapes detection by laboratory testing but can be reliably diagnosed by liver biopsy. A1AT deficiency

is often an important contributing cause in alcohol-induced liver disease.

Summary: Liver biopsy can provide the initial diagnosis of storage diseases and metabolic diseases of the liver when the laboratory findings are inconclusive. It also enables histological determination of the extent and stage of the disease.

Hepatopathy of unknown cause; acute liver failure

A liver biopsy is indicated, as a rule, if the history, physical examination, laboratory tests, and serology have failed to yield a definitive diagnosis in a patient with elevated liver function tests. This is also true in the case of acute liver failure of unknown cause, or of so-called cryptogenic cirrhosis.

If marked hepatic inflammatory changes are found in a patient with drug-induced, toxic, or autoimmune liver damage, glucocorticosteroid treatment may be indicated.

A common scenario is that of a patient with marked pre-existing liver damage—e.g., of a combined nutritional and toxic type—who develops acute liver failure after exposure to further hepatotoxic substances. Biopsy provides a reliable assessment of the extent of hepatic necrosis and, in particular, of the regenerative potential of hepatic tissue (17), although the prognostic value of the extent of necrosis is currently a matter of debate. The findings of some studies imply that the liver can no longer recover if the biopsy reveals more than 70% necrosis (18).

Summary: In these cases, liver biopsy serves as an aid to etiological diagnosis and prognostication.

Biopsy of hepatic nodules

No all-encompassing rule can be stated as to the role of biopsy for focal hepatic lesions, as these can be found in diverse clinical situations, in some of which their proper clinical management is debated. Nonetheless, as long as the biopsy sample is representative (i.e., has not missed the histologically most important part of the lesion or lesions), a biopsy can provide information not just about the degree of malignancy of a focal lesion, but also about any abnormalities that may be present in the surrounding liver tissue. With regard to the potential problem of biopsy-track metastases, there are conflicting data in the literature. In a recent meta-analysis, the frequency of this problem is estimated at 2.7% overall (0.9 % per year), but the authors point out that there has not been a single published case of a biopsy-track metastasis affecting a patient's survival (19). In hepatocellular carcinoma, the frequency of biopsy-track metastases ranges from 0.0095% to 5% in published series. Most studies are retrospective and without histological confirmation, and compare patients with a wide variety of tumor types and stages, multiple tumor nodules, and/or ascites.

The indications for a liver biopsy should be determined in the individual clinical setting and should be

considered judiciously if cirrhosis is present. Some studies have shown that biopsies of liver nodules can provide, not just a definitive diagnosis of the tumor, but also valuable information about the biology of hepatocellular carcinoma (e.g., grading and proliferation) (20) (*Figure 2a*).

Biopsy of a solitary lesion in a non-cirrhotic liver

Hemangioma and focal nodular hyperplasia (FNH) are lesions that need no treatment if asymptomatic. A biopsy is indicated only if imaging studies have not yielded a clear diagnosis. This is now only rarely the case, as (contrast-enhanced) ultrasonography, computerized tomography (CT), and/or magnetic resonance imaging (MRI) are generally conclusive.

Liver-cell adenoma is sometimes hard to distinguish from well-differentiated hepatocellular carcinoma. In such cases, a biopsy is advisable if the imaging studies are inconclusive.

If the histological findings turn out to be inconclusive as well, it must be decided whether to repeat the biopsy or proceed to partial hepatectomy. The risk that liver-cell adenoma will transform into hepatocellular carcinoma is very low and depends on the histological subtype. Men and persons with metabolic diseases are more likely to develop a liver-cell adenoma/hepatocellular carcinoma (21). The literature suggests that the risk of hemorrhage during surgery for a large liver-cell adenoma may well be higher than that of malignant transformation (22).

Biopsy of a solitary lesion in a cirrhotic liver

A solitary hepatic lesion in a patient with known hepatic cirrhosis is likely to be a hepatocellular carcinoma.

If the radiological findings are compatible with HCC, biopsy is unnecessary. If surgical/curative treatment is not feasible, then a biopsy should be considered in order to establish the diagnosis, in case other treatments, such as chemotherapy or alcohol injection, are planned. Our own experience has shown that a solitary nodule in a cirrhotic liver may well be a tumor of another type than HCC, even if the AFP value is (moderately) elevated: The possibilities include a neuroendocrine tumor, a lymphomatous infiltrate, and intra-hepatic cholangiocarcinoma (23). The indications for biopsy differ in the European and American specialty societies' guidelines. The European Association for the Study of the Liver (EASL) considers a biopsy to be obligatory for lesions of size 1 to 2 cm. In contrast, the American Association for the Study of Liver Diseases (AASLD) recommends no biopsy for lesions larger than 1 cm, as long as two different imaging studies have yielded clear, concordant findings (24).

Individual cases cannot always be dealt with according to the guidelines. In particular, the differential diagnosis of lesions less than 1.5 cm in size can be difficult. A so-called dysplastic nodule, which is a precancerous stage of HCC in the setting of

cirrhosis, is very difficult to diagnose on the basis of a punch biopsy unless further clinical details (size) are given; yet such a finding is very important, for example, when the question of transplantation is being considered.

Biopsy usually suffices to differentiate HCC from intrahepatic cholangiocarcinoma (ICC).

Biopsy of multiple focal hepatic lesions

Focal liver changes (single or multiple) should be diagnosed by the targeted biopsy of one lesion, as the histological finding serves as the basis for further treatment and prognostication. No biopsy is needed, however, when the lesion is clearly a metastasis of a known primary tumor. The most common indications for liver biopsy in our own case series in the Pathology Department of the Ruhr-Universität Bochum are summarized in *Figure 2b*.

A pathologist needs not only a biopsy sample, but also clinical information, in order to perform an efficient differential diagnosis of liver metastases. Especially in the case of adenocarcinomatous infiltrates, close collaboration of the clinicians with the pathologist can obviate the need for costly immunohistochemical studies. The possibility of an intrahepatic cholangiocarcinoma (ICC) should always be thought of when a biopsy reveals adenocarcinomatous metastases and an extrahepatic primary tumor cannot be found (20).

Predictive markers in tumor tissue are increasingly being analyzed for the purpose of personalized tumor therapy. When no primary tumor can be found, biopsy samples from liver metastases can be used for such analyses.

Conflict of interest statement

Prof. Tannapfel has served as a paid consultant for the Merck, Sanofi, Falk, Pfizer, Amgen, AstraZeneca, Lilly, and Novartis companies. She has received lecture honoraria and reimbursement of travel expenses from the Sanofi, Falk, Pfizer, Amgen, and Apda companies.

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KEY MESSAGES

- Despite improvements in serological and radiological techniques, liver biopsy is still the most reliable way to diagnose diffuse hepatic disease and hepatic nodules.
- The indications for this invasive technique must be weighed against the small, but not negligible, risk of a complication.
- Liver biopsy can be used to assess the degree of activity of an inflammatory process and the extent of fibrosis.
- Liver biopsy is very important as a means of securing the initial diagnosis of autoimmune diseases affecting the liver, including autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), mixed forms with features of both AIH and PSC (“overlap syndrome”), and primary biliary cirrhosis (PBC).
- Among all diagnostic methods for hepatic nodules, liver biopsy has the greatest sensitivity and specificity with respect to the determination of malignancy.

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