REVIEW

COREY A. SIEGEL, MD
Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center/Dartmouth Medical School, Lebanon, NH

ANNE M. SILAS, MD
Department of Radiology, Dartmouth-Hitchcock Medical Center/Dartmouth Medical School, Lebanon, NH

ARIEF A. SURIAWINATA, MD
Department of Pathology, Dartmouth-Hitchcock Medical Center/Dartmouth Medical School, Lebanon, NH

DIRK J. VAN LEEUWEN, MD, PhD
Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center/Dartmouth Medical School, Lebanon, NH

Liver biopsy 2005: When and how?

ABSTRACT

Clinical imaging and serologic testing are increasingly replacing biopsy for diagnosing hepatic diseases. However, more biopsies are being done to stage and grade hepatitis C and fatty liver disease, to diagnose space-occupying lesions (typically with fine-needle aspiration biopsy), and to assess response to therapy. If biopsy is planned, it is important to evaluate its indications and risks and, if other physicians are involved, who is responsible for what.

KEY POINTS

Hepatitis C accounts for most liver biopsies performed worldwide today. The biopsy stage and grade can help guide management. However, some physicians rely on noninvasive tests only, including markers of fibrosis.

The role of biopsy in hemochromatosis is undergoing rapid evolution, and alternatives may obviate the need for biopsy.

Whether biopsy is necessary in patients with fatty liver disease is controversial. An argument for biopsy is that if patients know they have advanced fibrosis or cirrhosis, they will be more motivated to adhere to their medical regimens and to change their lifestyles.

Many physicians prefer imaging-guided biopsy for both diffuse parenchymal and focal lesions.

Contraindications can now often be circumvented by alternative biopsy techniques, including the transjugular approach. Interventional radiologists have become indispensable partners in selecting the optimal technique.

THE ROLE of liver biopsy, the traditional gold standard for assessing liver disease, continues to evolve. Fewer biopsies are being done for diagnosis, as noninvasive tests can now be done instead in many cases.[1] At the same time, more biopsies are being done to help guide the management of hepatitis C and nonalcoholic steatohepatitis and to assess responses to therapy, prompted by increased awareness of these diseases and newer therapies for them. Also on the increase is fine-needle aspiration biopsy of space-occupying lesions.

Currently, there is only one specific practice guideline proposed by a professional society on the appropriate indications and methods for liver biopsy.[2] Surveys of current practices are regularly reported, however.

This review gives the general practitioner an update about when and how liver biopsy should be performed.

INDICATIONS FOR LIVER BIOPSY

Liver biopsy is performed to evaluate diffuse parenchymal or focal liver disease. Most biopsies currently performed for parenchymal disease are not to make a specific diagnosis but to assess liver damage (the degree of inflammation and fibrosis) or the response to therapy.

In our institution, which does not have a liver transplantation program, nearly 50% of all liver biopsies performed in 2001 to 2003 were for staging vs only 15% for diagnosing the cause of parenchymal liver disease. The rest were mostly fine-needle aspiration biopsies of space-occupying lesions. In contrast, in the past, nearly all biopsies were done for diagnostic purposes, including differentiation of

TABLE 1

Indications for liver biopsy at Dartmouth-Hitchcock Medical Center, 2001–2003

INDICATION	NUMBER	%
Staging		
Hepatitis C	245	40
Fatty liver disease	40	7
Primary biliary cirrhosis	7	1
Hemochromatosis	3	< 1
Autoimmune hepatitis	1	< 1
Hepatitis B	1	< 1
Diagnostic, parenchymal		
Abnormal liver function tests, multiple etiology	86	14
Drug-induced hepatotoxicity	4	< 1
Abnormal iron study	4	< 1
Diagnostic, focal liver lesions		
Space-occupying lesions	219	36
Total	610	100

TABLE 2

Typical indications for liver biopsy for parenchymal liver disease

Staging or grading

Hepatitis B or C
Has predictive value for disease outcome and response to therapy

Hemochromatosis
Cirrhosis increases the risk for hepatocellular carcinoma
Imaging or blood tests or age may make biopsy unnecessary

Fatty liver disease
To distinguish nonalcoholic steatohepatitis from nonalcoholic fatty liver disease and to exclude coexisting pathology

Diagnostic

Abnormal liver function tests suspicious for multiple etiologies
eg, nonalcoholic steatohepatitis with strongly elevated antinuclear antibodies and abnormal iron studies, or co-infection with HIV and hepatitis C in a patient with abnormal liver function tests taking hepatotoxic drugs

Suspected drug-induced injury
If new drug, multiple drugs, or drug without known hepatotoxicity

Abnormal iron studies
If negative genetic tests for hemochromatosis

bile duct obstruction from parenchymal liver disease.

A few indications accounted for most of the biopsies (TABLE 1). For instance, 245 (82%) of the 297 staging biopsies were for hepatitis C, and 86 (91%) of the 104 diagnostic biopsies for parenchymal disease were in cases in which liver function test results were abnormal and multiple causes were suspected (TABLE 2).

Liver biopsy is indicated if it can supply information that imaging or blood tests cannot and that will help with patient management. Another use is in clinical research. Risks and benefits should be weighed in the individual patient.

PARENCHYMAL LIVER DISEASE

Hepatitis C

Hepatitis C accounts for most liver biopsies performed worldwide today.[3]

Biopsy findings may help guide management. The biopsy stage (degree of fibrosis) and grade (inflammatory activity) predict the course of disease[4,5] and response to therapy. Pathologic scoring systems such as the METAVIR score (developed in Europe)[6] and the Hepatitis Activity Index (HAI) (developed in the United States)[7] are now commonly used (FIGURE 1). Treatment is recommended if there is significant fibrosis (METAVIR score ≥ F2, typically ≥ F3, HAI ≥ F3) or inflammation.[8]

We believe that such a tailored approach is often appropriate, and we use biopsies in guiding treatment. Treatment may have severe side effects, is costly, and may fail in up to 50% of patients. Some patients tolerate therapy very poorly and become severely anemic, potentially needing costly interventions. Patients with stage F1 or F2 fibrosis might not have to undergo treatment and can avoid such potential complications. A patient who wishes to be treated in any event and a patient who has obvious cirrhosis on imaging with no suspicion of other disease will not benefit from biopsy, because treatment will be done anyway unless otherwise contraindicated.

Some physicians do not rely so much on biopsy, however. Some do not order it if the patient is infected with hepatitis C genotype 2 or 3 and therefore needs only 6 months of

Liver biopsies for staging hepatitis C

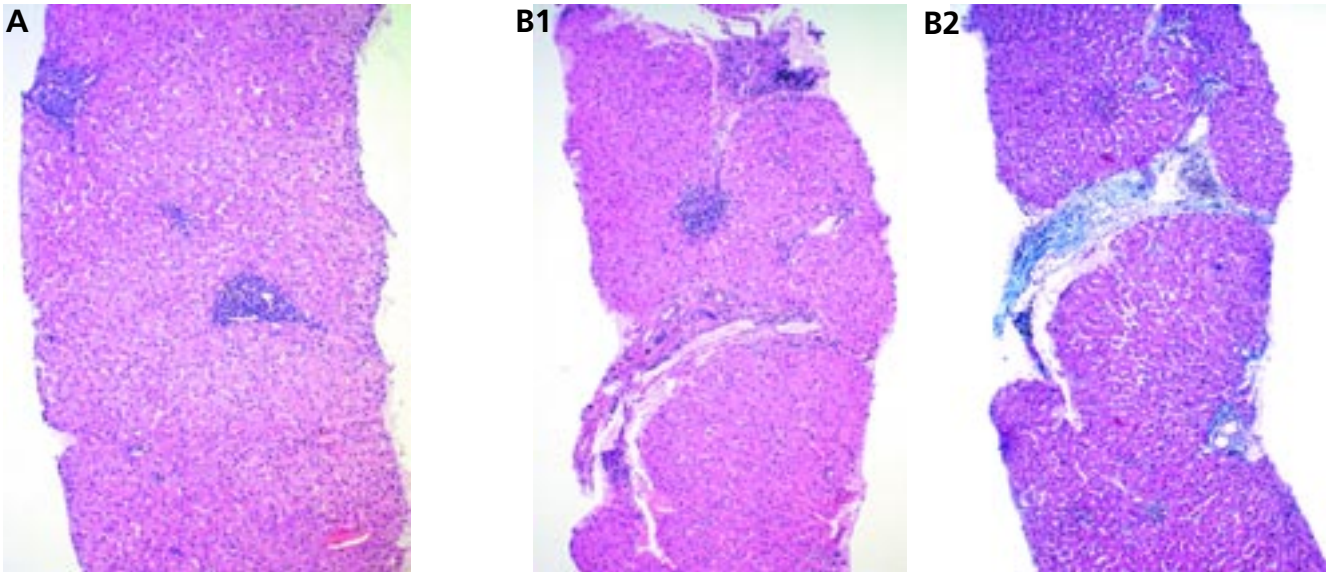


FIGURE 1. Liver biopsies in two patients (A and B) with comparable clinical characteristics with respect to duration of disease and genotype. **A,** very limited pathology; somewhat dense periportal inflammation with mild fibrosis consistent with F0-F1 disease on the METAVIR staging scale, which runs from F0 (mild disease) to F4 (cirrhosis) (Hematoxylin and eosin stain, × 25). **B1**, suggestion of septa formation (hematoxylin and eosin, × 25), further illustrated by the connective tissue stain (**B2,** trichrome, × 25). Nodules are developing, and this patient has at least F3 disease.

therapy, which they deem a relatively limited burden to the patient. (In contrast, patients with genotype 1, the most common genotype in the United States, need 12 months of therapy.) Some simply treat all patients who wish to be treated, believing that biopsy is not cost-effective.

Guidelines from the American Association for the Study of Liver Diseases (AASLD) discuss this topic in detail.[9]

Alternatives to biopsy. New blood tests may make it possible for patients to avoid the risks and discomfort of biopsy, and they cost less.[10–13]

FibroTest (Oneida TheraDiagnostics, Ltd, London, UK) measures alpha-2-macroglobulin, haptoglobin, apoprotein A1, gamma-glutamyl transpeptidase, and total bilirubin to test for fibrosis.

ActiTest (also from Oneida TheraDiagnostics) measures the same substances plus alanine aminotransferase.

FIBROSpect (Prometheus Laboratories, Inc, San Diego, CA) measures hyaluronic acid, tissue inhibitor of metalloproteinases, and alpha-2-macroglobulin; the serum concentrations are combined in an index that helps to discriminate between F0-F1 and F2-F4 disease.

Although these tests are promising, they currently are most valuable in broadly differentiating patients with significant fibrosis (F2, F3, or F4 on the METAVIR scale) from those with minor if any fibrosis (F0 or F1) and are used mostly in drug trials. They should be interpreted with caution in individual patients. Views on this topic are evolving, and readers should keep a close eye on developments.[14]

Most liver biopsies are performed to assess hepatitis C

Hepatitis B

Liver biopsy is rarely done in "healthy carriers" of hepatitis B virus (now called "inactive HBsAg carriers"), ie, patients with anti-HBe antibodies, persistently normal aminotransferase levels, very low or undetectable levels of hepatitis B virus DNA in their blood, and normal ultrasonographic findings. In such cases, the benefit of biopsy is rather limited unless confounding disease is suspected.

At the other extreme are patients with obvious cirrhosis on imaging. Those with cir-

rhosis and active disease as reflected by elevated aminotransferase levels are likely to be treated in any case; there is hardly any additional benefit from biopsy.

Nevertheless, active disease on liver biopsy predicts a response to any of the currently available drugs (interferon, nucleoside analogues)—useful information in planning management.[15,16] Furthermore, cirrhosis on liver biopsy indicates a high risk of hepatic decompensation if interferon is given; nucleoside analogues are the drugs of choice in this situation.

Fatty liver disease

Whether biopsy is necessary in patients with fatty liver disease is controversial.

Biopsy may distinguish nonalcoholic fatty liver (NAFL) from nonalcoholic steatohepatitis (NASH).[17] The former, which affects approximately one fourth of the US population and up to two thirds of obese people, is believed to have a benign course and is in fact less a disease than a metabolic state.[18]

NASH is much less common and has a worse prognosis.[19] Most patients with NASH have metabolic syndrome, ie, hypertension, insulin resistance, obesity, and dyslipidemia.[20] In a patient with elevated aminotransferase levels in whom the common causes are excluded, this circumstantial evidence (metabolic syndrome) makes the diagnosis of NASH unnecessary. The finding of a fatty liver on ultrasonography or computed tomography (CT) can support the diagnosis, although one should be careful with the interpretation: fat may indeed be present, but this finding does not say anything about the degree of inflammation nor the presence of fibrosis, iron, or granulomas.

The workup of abnormal iron studies has changed rapidly with genetic testing

Metabolic syndrome requires proper therapy, including optimal diabetic management and weight reduction, whether or not nonalcoholic steatohepatitis is histologically confirmed. Therefore, many physicians question what biopsy truly adds.

An argument for biopsy is that if patients know they have advanced fibrosis or cirrhosis, they may be more motivated to adhere to their medical regimens and to change their lifestyle, should all the other health benefits of these measures not suffice to convince them.

Hemochromatosis

The workup of patients with abnormal iron studies has changed rapidly in the last decade with increased awareness, more frequent requests for iron studies, and the advent of genetic testing,[21] and it continues to be refined. The AASLD practice guidelines and a consensus report are helpful.[22,23]

The transferrin saturation, the first test to order if iron overload is suspected, is the serum iron concentration divided by the total iron-binding capacity, obtained after overnight fasting. A value exceeding 45% raises the suspicion of the diagnosis of hemochromatosis, and values greater than 50% in women or 60% in men have a sensitivity of 92%, a specificity of 93%, and a positive predictive value of 86%.

Serum ferritin. As a practical matter, if both the serum ferritin concentration and the transferrin saturation are elevated, the patient likely has iron overload. However, because ferritin is an acute-phase reactant, elevations can also reflect concomitant fatty liver disease, nonalcoholic steatohepatitis, active viral hepatitis, alcoholic hepatitis, or other systemic diseases. In confirmed hemochromatosis, levels greater than 1,000 ng/mL indicate a higher likelihood of hepatic fibrosis and cirrhosis.

Aminotransferase concentrations may be mildly elevated in hemochromatosis, but elevations may also indicate concomitant diseases.

Genetic testing is appropriate once the suspicion of hemochromatosis has been raised. More than 90% of patients with hemochromatosis are homozygous for the C282Y mutation in the *HFE* gene. A smaller percentage are "compound heterozygotes," ie, they are heterozygous for the C282Y mutation and also heterozygous for a different mutation, H63D, or occasionally are homozygous for the H63D or rarer mutations. Heterozygosity for one of the mutations is usually associated with lesser degrees of iron overload; in the past, heterozygous patients were typically identified by a low hepatic iron index. The phenotypic disease expression is not solely determined by the *HFE* genes, however.[24]

Reduced role of biopsy for diagnosis. Liver biopsy, the traditional gold standard for

the diagnosis of hemochromatosis, continues to have a higher diagnostic yield, both to exclude hemochromatosis (if hepatic iron levels are normal) or to confirm it when iron is present in a diagnostic pattern.[25]

The hepatic iron index, defined as the liver iron concentration in micromoles per gram of dry liver weight divided by the patient's age, reflects iron accumulation over the patient's life. This information helps in equivocal cases to differentiate patients with true hereditary hemochromatosis from others with much slower, usually clinically irrelevant iron accumulation. The latter patients, ie, those with a hepatic iron index of 1.5 to 1.9 µm/g, are now recognized as being typically heterozygous for *HFE* mutations. However the hepatic iron index is not needed as often now that genetic testing is widely available.

Biopsy for staging. In some patients the clinical features strongly suggest or confirm hemochromatosis. Magnetic resonance imaging should usually suffice in cases of advanced disease such as cirrhosis or hepatocellular carcinoma. However, if the disease stage is unclear, biopsy offers important prognostic information.

A cholestatic pattern on testing is common, but classic cholestatic diseases are rare

Significant fibrosis or cirrhosis substantially increases the risk of hepatocellular carcinoma.[26] More and more patients with these findings are being screened periodically with alpha-fetoprotein measurements and cross-sectional imaging to detect curable malignancy. However, recent data suggest that fibrosis or cirrhosis is so unlikely in a young patient (< 40 years) who has typical features, including a serum ferritin concentration lower than 1,000 ng/mL, homozygosity for C282Y, and normal aminotransferase levels, that he or she can be treated with phlebotomy without undergoing biopsy.[27]

Biopsy may confirm the diagnosis in atypical presentations, including cases not associated with any of the currently known *HFE* mutations.[28] On biopsy, inflammatory cells are typically not prominent in hemochromatosis.

Biopsy to detect comorbid diseases. Biopsy may be appropriate if comorbid diseases are suspected, such as metabolic syndrome, alcohol abuse, or hepatitis C. Even if genetic testing shows homozygosity for *HFE* genes, the biopsy may help to understand further pathologic aspects.

If in doubt about the diagnosis and treatment, clinicians should not hesitate to consult an expert. The pathologic role of iron overload in patients with concomitant diseases (hepatitis C, alcoholism, nonalcoholic steatohepatitis) remains unresolved.[23] Many clinicians treat these patients with phlebotomy, but evidence of benefit or cost-effectiveness is lacking.

Autoimmune hepatitis

Autoimmune hepatitis is defined by variable clinical, chemical, and histopathologic features. A validated scoring system proposed by an international panel[29,30] can be of considerable help in making the diagnosis.

Although biopsy is not absolutely necessary for diagnosis, it helps in diagnosis and in staging. Classic histologic features include interface hepatitis (formerly called "piecemeal necrosis"), rosettes, absence of biliary features, and presence of plasma cells. A strong diagnosis is important because of the implications of initiating long-term immunosuppression.

Flare-ups during adequate immunosuppressive therapy in a compliant patient should raise the suspicion of another problem. For example, we once successfully treated a patient with autoimmune hepatitis with steroids. Even with adequate immunosuppression, however, her liver disease flared repeatedly, with aminotransferase levels in the range of 100 to 220 U/L. During this same period, she gained weight and developed diabetes. A follow-up biopsy showed typical nonalcoholic steatohepatitis, preventing an unnecessary and potentially deleterious increase in immunosuppressant medications.

Cholestatic liver disease

A cholestatic pattern of test results (increased alkaline phosphatase and gamma-glutamyl transpeptidase levels) is often detected during routine health or insurance testing. The classic cholestatic diseases—primary biliary cirrhosis and primary sclerosing cholangitis—are in fact rare.

Primary biliary cirrhosis is diagnosed by

Biopsy changed the diagnosis

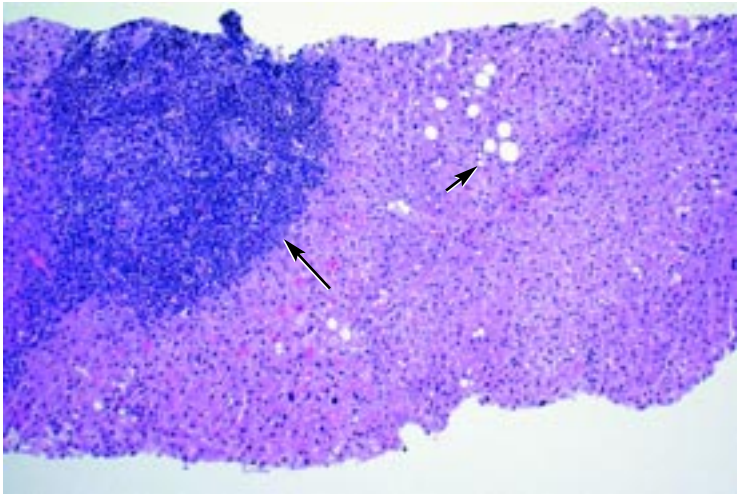


FIGURE 2. A morbidly obese patient (who would be expected to have nonalcoholic steatohepatitis) also had features of primary biliary cirrhosis (antimitochondrial-antibody positive, elevated immunoglobulin M). Liver biopsy shows a typically florid bile duct lesion (long arrow) consistent with primary biliary cirrhosis stage 1. Minimal fat is present (short arrow), but there is no evidence of nonalcoholic steatohepatitis.

Imaging can replace biopsy

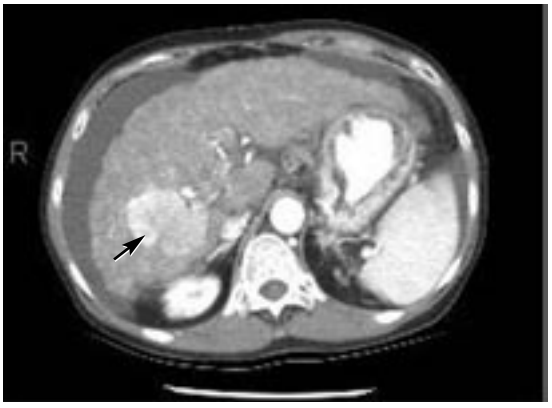


FIGURE 3. Clinical deterioration in the setting of longstanding cirrhosis. Nodular liver with ascites and a newly hypervascular lesion with elevated alpha-fetoprotein are pathognomic for hepatoma (arrow). Biopsy is not necessary and can be risky.

In retrospect, we did an injustice to many patients with 'alcoholic hepatitis'

specific testing for antimitochondrial antibodies and elevated immunoglobulin M (IgM); primary sclerosing cholangitis is diagnosed by biliary imaging. A small-duct variant of primary sclerosing cholangitis can be found on biopsy but cannot be detected by current imaging techniques. Primary sclerosing cholangitis in children often has less pronounced imaging features. Biopsy is rarely indicated for the specific diagnosis of these diseases if classic features are present.

Biopsy does have a role in assessing the stage of primary biliary cirrhosis, especially if cross-sectional imaging leaves doubt. An adequate sample must be obtained because the disease can be very unevenly distributed. The finding of stage 1 or 2 disease may help to reassure the patient for the time being. However, the clinical evolution is what matters most for the prognosis. Biopsies may also be helpful in assessing the response to therapy.

Recognized variants of autoimmune hepatitis include so-called overlap syndromes, eg, autoimmune hepatitis plus either primary sclerosing cholangitis or primary biliary cirrhosis.[31] Liver biopsy may help identify the predominant process in these cases.

Other diagnoses to consider include granulomatous diseases (patients with sarcoidosis may need radiography first and, less often, liver biopsy), drug side effects, nonalcoholic steatohepatitis, infections, and cancer. The findings on biopsy (granulomas, inflammation, centrilobular changes) may narrow the diagnosis significantly.

A special category of cholestasis typically occurs in patients in the intensive care unit who have underlying chronic disease. Usually, multiple causes play a role, including septicemia, total parenteral nutrition,[32] and others. Biopsy gives very limited benefit, although the pathologic findings are often quite impressive.

Alcoholic liver disease

For many decades, typical "alcoholic hepatitis" was often diagnosed on liver biopsy, and some patients' medical records were filled with somewhat judgmental comments about their persistent denial of alcohol intake. In retrospect, we did many patients an injustice. The typical patient with nonalcoholic steatohepatitis may also use or abuse alcohol, and it has been argued that alcohol is one of the "second hits" that cause this type of inflammation in predisposed patients.[18,19,33]

Liver biopsy remains important in some patients, both to assess severity and potential reversibility and to confirm suspected confounding disease.

Drug-induced liver disease

Drug hepatotoxicity may be clear-cut on the basis of known toxicity and chronology. For example, isoniazid causes progressively elevated aminotransferase levels, whereas rifampin causes isolated unconjugated hyperbilirubinemia. However, if the patient is taking multiple medications, new medications, or medications without known hepatotoxicity, liver tests may be more confusing.

Start by evaluating the typically described patterns of abnormalities on liver function tests—predominant aminotransferase elevations in hepatocellular disease, and alkaline phosphatase bilirubin and gamma glutamyl transpeptidase elevations in cholestatic disease or granulomatous disease.[34] This may lead to a likely diagnosis, but biopsy can truly be enlightening and occasionally point to unsuspected diagnoses.

For example, in one of our patients in whom drug hepatotoxicity or cryptogenic liver failure was assumed, biopsy showed viral inclusions and pointed toward unrecognized herpes simplex infection. We also had a patient referred to us with "decompensated cirrhosis with major fluid retention due to hepatitis B." After clinical review and liver biopsy, we determined that the patient had veno-occlusive disease due to azathioprine given as part of an immunosuppressive regimen after renal transplantation—a potentially reversible condition.

If biopsy is considered in a case of drug or herbal hepatotoxicity, the earlier it is done the better. Once the disease progresses, the risk of coagulopathy or ascites increases, and histologic features may become less specific.

Methotrexate hepatotoxicity

Whether to perform serial biopsies routinely to assess hepatotoxicity in patients receiving methotrexate remains controversial. Some guidelines call for biopsy to be done before starting treatment and after each 1.5 g of the drug is given, but these guidelines are heeded less often.

A considerable part of the pathologic changes that were described in early studies may in retrospect have been due to hepatitis C or nonalcoholic steatohepatitis. Also, in patients with psoriasis, we and others found that the information gained from biopsy rarely led to a change in therapy: patients could rarely be convinced to stop the sole therapy that made their disabling psoriasis melt away.

A recent study further calls into question the need for so many serial liver biopsies in patients receiving methotrexate. After finding that severe disease was much less frequent than previously thought, the authors suggested that biopsy be done after every 5 g of methotrexate rather than 1.5 g.[35]

We suggest a patient-tailored approach. Risk factors for hepatotoxicity that argue in favor of biopsy include alcohol use, diabetes, and abnormal ultrasonographic findings.[36] One should also consider first giving the patient methotrexate for a few weeks to see if he or she can tolerate it (some may not) and then consider the risks and benefits of biopsy.

A consensus conference would be helpful to resolve controversial and conflicting guidelines on this topic.

Before liver transplantation

In patients with acute liver failure who are candidates for liver transplantation, liver biopsy can occasionally be useful in cases in which the cause matters. For example, herpes simplex infection may respond to therapy; diffuse metastatic disease presenting as subacute liver failure would exclude the patient from transplantation.

If considering a biopsy for suspected significant drug toxicity, the earlier the better

Liver function and its clinical evolution typically determine the need for transplantation. Furthermore, liver biopsy results can be misleading in some cases. For example, if the sample is taken from a regenerating nodule, the findings may suggest less parenchymal damage than there truly is.[37]

In patients with end-stage decompensated cirrhosis, the cause rarely matters before transplantation, and therefore most of them do not need liver biopsy as part of their transplant evaluation.

After liver transplantation

With today's improved immunosuppressant medications, acute rejection occurs less often than in the past. Therefore, liver biopsy is generally less often performed.

However, abnormal liver tests in trans-

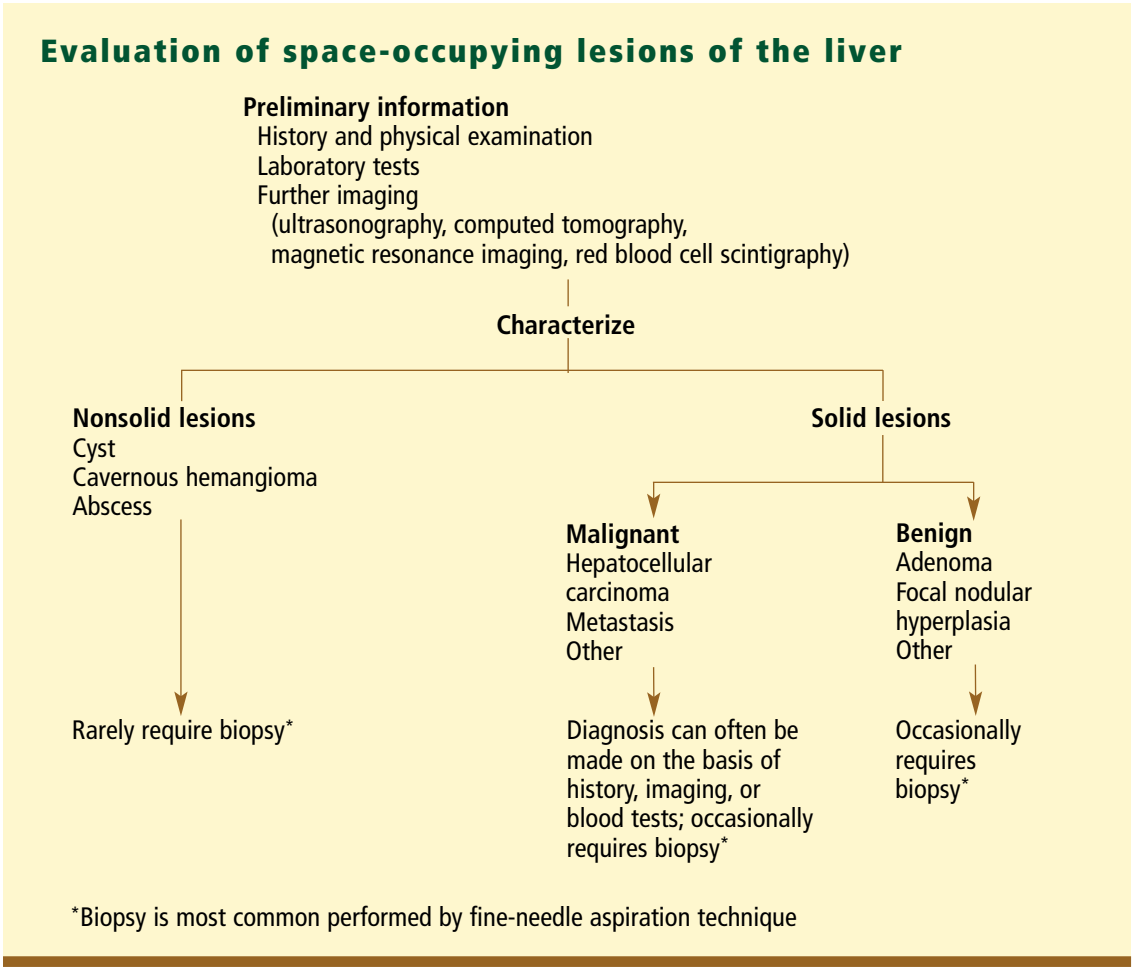


FIGURE 4

We now do most liver biopsies with the patient under conscious sedation

plant recipients can be due to many causes, including opportunistic infections, surgical complications, and drug hepatotoxicity.[38] In addition, one should consider recurrence of the original disease, such as autoimmune hepatitis or primary biliary cirrhosis. Hepatitis B recurrence is now less common, but recurrence of hepatitis C is increasingly a major clinical problem. Histologic changes may precede clinical and biochemical disease.[39] Biopsy may be the only way to sort out these complicated issues.

Other diagnostic indications

It is not uncommon for multiple causes of liver disease to be considered, which hinders certain therapeutic decisions (FIGURE 2). The aforementioned patient with autoimmune hepatitis plus nonalcoholic steatohepatitis and the other with azathioprine-induced veno-occlusive disease are such examples, as are liver transplant recipients. Other scenarios include suspicion of opportunistic infection, diffuse malignant liver infiltration, co-infection with human immunodeficiency virus and hepatitis C, and uncertainty about what degree side effects of drugs (ie, highly active antiretroviral therapy) play a role.

In these cases biopsy may help to identify the predominant process and guide treatment.

SPACE-OCCUPYING LESIONS

Owing to the wide use and superior resolution of cross-sectional imaging such as ultrasonography, computed tomography, and magnetic resonance imaging, space-occupying lesions are being detected more often. Fortunately, the same technologic advances allow us to confidently establish a diagnosis without biop-

sy in most cases, and typically one or two studies suffice.[40,41]

The technique of choice partly depends on local availability and expertise. Internists and oncologists have increasingly come to accept that, for example, patients with cirrhosis, elevated alpha-fetoprotein, and a hypervascular tumor on imaging do not need a liver biopsy to confirm hepatocellular carcinoma (**FIGURE 3**).[42]

However, sometimes a biopsy of a suspected neoplasm will help change management. In this case, careful consideration of biopsy technique and careful patient selection are important, as neoplasms have a higher bleeding risk and the potential to seed other sites along the biopsy tract or in the abdominal cavity.[43]

FIGURE 4 is an algorithm for assessing space-occupying lesions. In difficult cases, when contemplating biopsy, a multidisciplinary team should review the indications, the risks, and the safest approach.

TABLE 3

Major complications of liver biopsy

COMPLICATIONS	RISK
Death	1:10,000–1:12,000
Bleeding	1:100
Bile leak	1:1,000
Any pain	1:4
Significant pain	1:10–1:20

Rare complications of liver biopsy

- Hemobilia
- Pneumoperitoneum
- Pneumoscrotum
- Pneumothorax
- Septic shock
- Subphrenic abscess
- Intrahepatic arteriovenous fistula
- Carcinoid crisis

DATA FROM REFERENCES 32, 34–36.

RISKS OF BIOPSY

The major complications of percutaneous liver biopsy include bleeding and bile leakage. In addition, patients should be informed that afterward as many as 30% of patients experience right upper-quadrant pain, shoulder pain, or both, which is severe in 1% to 3%.[44–46] The mortality rate is approximately 1 in 10,000 to 12,000.[44,45]

At the time that informed consent is obtained, it is reasonable to outline these major complications clearly, warn the patient of the potential pain, and mention in a general statement that other complications, albeit rare, can occur (**TABLE 3**).[32,34–36]

The pain immediately after liver biopsy can be very distressing, and some patients remember the procedure with horror. We and many others now do most biopsies with the patient under conscious sedation (typically using midazolam with fentanyl or meperidine). This adds the small risk and the cost of conscious sedation to the procedure. However, our patients already have an intravenous line inserted before the procedure, so the added cost is somewhat mitigated. Patients remain remarkably cooperative, usually breathe somewhat superficially, and will hold their breath if instructed. We have not as yet experienced any disadvantages, and a pleasant advantage is that patients are very appreciative.

CONTRAINDICATIONS TO BIOPSY

There are hardly any contraindications to biopsy once an appropriate indication is identified. The issue is rather how the biopsy should be done.

The major contraindication to percutaneous liver biopsy is significant coagulopathy. However, direct evidence is lacking that abnormal clotting parameters (prothrombin time, international normalized ratio [INR]) are the determinant.[2,47] Most bleeding (> 90%) occurs with an INR less than 1.3. Probably, platelet dysfunction due to aspirin use or renal failure and severe illness with liver failure are major risk factors as well.

Relative contraindications are morbid obesity and major ascites. In these cases, transjugular biopsy is a logical alternative. The technique can potentially be combined with wedged hepatic pressure and venography to further assess liver disease, although this is not routinely done and requires specific expertise.[48]

The major contraindication to percutaneous liver biopsy is significant coagulopathy

TABLE 4

Suitable candidates for outpatient liver biopsy

Cooperative patient with clear understanding of the plan

Has a chaperone who can observe him or her closely over the next 12 to 24 hours

Lives within 60 to 90 minutes of a medical facility (preferably the one at which the biopsy was performed)

Platelet count > 60,000–80,000, prothrombin time < 4 seconds prolonged, no recent use of non-steroidal anti-inflammatory drugs, no clinical history suggestive of coagulopathy

AFTER THE BIOPSY

Postprocedure monitoring has evolved over the past decades. The safety of outpatient percutaneous liver biopsy is no longer disputed. As long as patients are carefully selected and suffer no complications, they can safely be discharged home after approximately 4 to 6 hours.[49,50] Most complications manifest within the first few hours,[51] and under certain circumstances more and more patients are being discharged just 1 or 2 hours after imaging-guided biopsy.

If the criteria in TABLE 4 are not met, plans should be made for overnight observation.

BIOPSY TECHNIQUE

The biopsy technique is chosen on the basis of the indication, risks, and benefits in the individual patient (FIGURE 5).

Percutaneous 'blind' biopsy. Most liver biopsies in the United States are performed percutaneously, often under ultrasound guidance. This also is the least expensive and least invasive method and gives an adequate specimen for the pathologist to review. It is performed by gastroenterologists, hepatologists, internists, and more recently by physician's assistants.[52] At our institution, 50% of all liver biopsies from 2001 through 2003 were performed by gastroenterologists using this technique (TABLE 5).

Transjugular biopsies in the United States are performed mostly by interventional radiologists in patients at high risk (eg, with impaired clotting, gross ascites, morbid obesity, or fulminant hepatic failure).[53,54] At our hospital, only 5% of biopsies performed in the past 3 years have been transjugular, but they account for up to one third in certain centers.[55]

In the past, a drawback of transjugular biopsy were the small and fragmented specimens obtained. Better needles and more experience have led to improved quality of specimens, and in fact multiple specimens can easily be obtained.[53–56] These improvements, along with excellent patient tolerance of this technique,[55] may eventually make it the preferred method, even though it is more costly.

Ultrasound-guided or CT-guided biopsies are in the United States typically performed by radiologists and less frequently by gastroenterologists. They are done either when a space-occupying lesion needs to be sampled or if the patient's anatomy makes finding landmarks difficult. Some gastroenterologists routinely do all biopsies under ultrasound guidance.

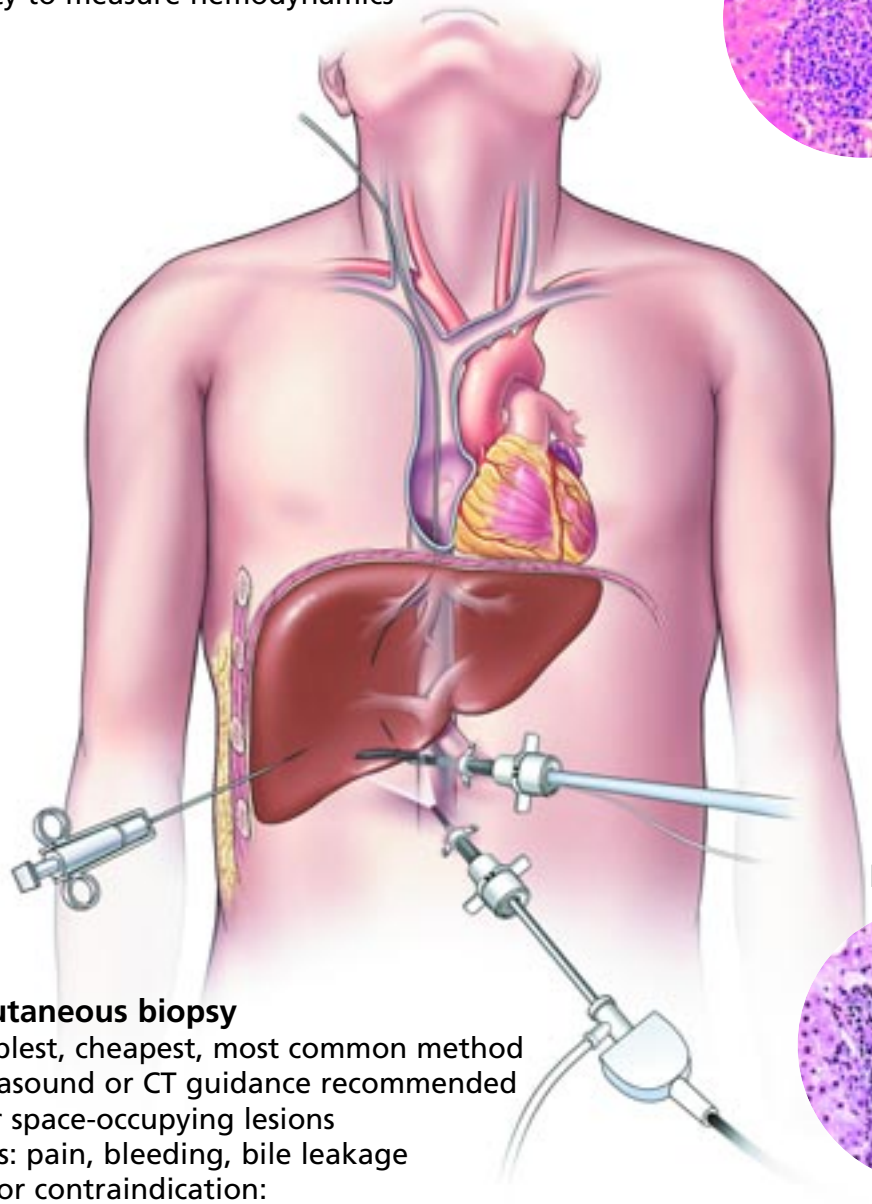
Laparoscopic biopsy. Many hepatologists used to perform laparoscopic biopsies, and in fact the combination of visualizing the entire liver and the information provided by the biopsy material dramatically upgrade the quality of staging disease severity.[57,58] Other advantages of laparoscopic or open biopsies are the ability to evaluate for potential extrahepatic spread of malignancy, to look for a cause of unexplained ascites (peritoneal biopsy), and to obtain large wedge resections of the liver. Intraoperative imaging with ultrasound probes may further define an abnormality.

The major disadvantages are cost and the added risk of anesthesia. A shortage of operating rooms prevents easy scheduling in many centers. If by chance a patient with suspected liver disease is to undergo abdominal surgery (ie, open or laparoscopic cholecystectomy or appendectomy), an opportunity presents itself if the surgeon can be notified and his or her

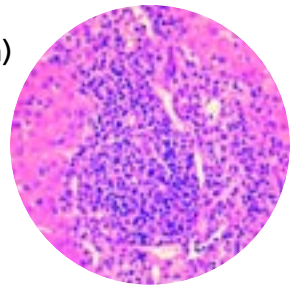
More and more patients are being sent home just 1 or 2 hours after their liver biopsy

How should liver biopsy be performed?

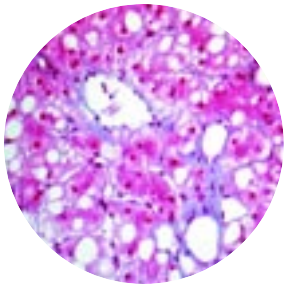
Transjugular biopsy
Safer than percutaneous biopsy if coagulopathy is present
Less risk of intraperitoneal hemorrhage
(but bleeding can occur due to liver capsule perforation)
Major pain rarely an issue
Ability to measure hemodynamics



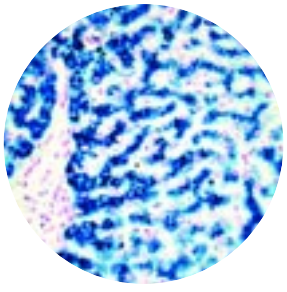
Hepatitis C



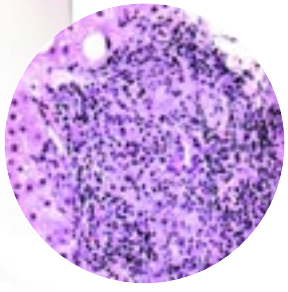
Nonalcoholic steatohepatitis



Hemochromatosis



Primary biliary cirrhosis



Percutaneous biopsy
Simplest, cheapest, most common method
Ultrasound or CT guidance recommended for space-occupying lesions
Risks: pain, bleeding, bile leakage
Major contraindication: significant coagulopathy
Relative contraindications: morbid obesity, ascites

Laparoscopic or open biopsy
Can obtain largest specimen
Can visualize peritoneal cavity
Most invasive and expensive method

FIGURE 1

assistance requested in advance. One should specifically ask the surgeon to obtain an adequate needle or wedge specimen as opposed to a superficial forceps biopsy.

Endoscopic ultrasonography sometimes provides an opportunity to easily sample liver tissue.

THE FUTURE

Advanced serologic markers, high-tech imaging, endoscopic innovation, and the dawn of genetic testing will continue to affect the way liver biopsy is used in clinical practice. The practice of liver biopsy continues to evolve and will remain an important component in the evaluation of liver disease.

Two important issues need to be addressed. First, with direct referral and easy access to interventional procedures, practitioners increasingly delegate biopsies to others who may not be acquainted with the patient. In these cases, envisioned benefits of the procedure need to be very clear to avoid misunderstandings with potential dramatic consequences.[59]

Second, the value of liver biopsy depends above all on the quality of tissue samples. A liver biopsy for staging of disease benefits the patient only if an adequate specimen is submitted for evaluation. There is national and international concern that too many samples do not satisfy even minimum standards.

TABLE 5

Liver biopsy technique and operator at the Dartmouth-Hitchcock Medical Center

	2003	2002	2001
Technique			
Percutaneous	75	90	138
Transjugular	7	8	13
Imaging-guided	9	6	7
Fine needle aspiration	56	62	62
Laparoscopic or open	29	35	13
Operator			
Gastroenterologist	79	90	143
Radiologist	68	76	77
Surgeon	29	35	13
Total	176	201	233

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ADDRESS: *Dirk J. van Leeuwen, MD, PhD, Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756.*