Review Articles

Current Concepts

Liver Biopsy

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PAUL Ehrlich is credited with performing the first percutaneous liver biopsy in 1883 in Germany.[1] After Menghini reported a technique for "one-second needle biopsy of the liver" in 1958, the procedure became more widely used. The average duration of the intrahepatic phase of previous liver-biopsy techniques had been 6 to 15 minutes.[2]

Liver biopsy is usually the most specific test to assess the nature and severity of liver diseases. In addition, it can be useful in monitoring the efficacy of various treatments. There are currently several methods available for obtaining liver tissue: percutaneous biopsy, transjugular biopsy, laparoscopic biopsy, or fine-needle aspiration guided by ultrasonography or computed tomography (CT). Each of these methods has advantages and disadvantages.

The size of the biopsy specimen, which varies between 1 and 3 cm in length and between 1.2 and 2 mm in diameter, represents 1/50,000 of the total mass of the liver.[3] Usually, for evaluation of diffuse liver disease, a specimen of 1.5 cm in length is adequate for a diagnosis to be made. The number of portal triads present in the specimen is important; most hepatopathologists are satisfied with a biopsy specimen containing at least six to eight portal triads, especially in cases of chronic liver disease in which the extent of injury may vary among portal triads. An adequate specimen is usually provided by all the needles currently used for liver biopsy. Specimens obtained with standard thin-bore or spring-loaded needles measure between 1.4 and 1.8 mm in diameter, and those obtained with Menghini or Tru-cut needles measure up to 2 mm in diameter.[4,5]

The indications for liver biopsy are outlined in Table 1. Even for patients in whom serologic tests point to a specific liver disease (Fig. 1 and 2), a liver biopsy can give valuable information regarding staging, prognosis, and management. For example, in patients with chronic hepatitis C infection, not only is there a poor correlation between symptoms or levels of serum alanine aminotransferase and histologic features of the liver, but also patients with completely normal levels of liver enzymes may be found to have clinically significant fibrosis or cirrhosis on biopsy (Fig. 3).[6] If the patient has mild disease and is infected with genotype 1a or 1b of the hepatitis C virus, a decision may be made to defer treatment. If a decision is made to treat such a patient with a combination of interferon and ribavirin and there are adverse effects, the treatment can be stopped. Conversely, if the patient has moderate-to-advanced disease, treatment will most likely be offered. If the patient has a virologic response and tolerable side effects with treatment, continued therapy would be strongly encouraged. The finding of cirrhosis on liver biopsy will determine the need for further examinations, such as upper endoscopy to rule out esophageal varices and screening for hepatocellular carcinoma with serial determinations of serum alpha-fetoprotein and liver ultrasonography.

Table 1. Indications for Liver Biopsy.

Diagnosis, grading, and staging of alcoholic liver disease, nonalcoholic steatohepatitis, or autoimmune hepatitis
Grading and staging of chronic hepatitis C or chronic hepatitis B
Diagnosis of hemochromatosis in index patient and relatives, with quantitative estimation of iron levels
Diagnosis of Wilson's disease, with quantitative estimation of copper levels
Evaluation of the cholestatic liver diseases primary biliary cirrhosis and primary sclerosing cholangitis
Evaluation of abnormal results of biochemical tests of the liver in association with a serologic workup that is negative or inconclusive
Evaluation of the efficacy or the adverse effects of treatment regimens (e.g., methotrexate therapy for psoriasis)
Diagnosis of a liver mass
Evaluation of the status of the liver after transplantation or of the donor liver before transplantation
Evaluation of fever of unknown origin, with a culture of tissue

In alcoholic liver disease, the severity of the clinical symptoms and the degree of liver-enzyme elevation correlate poorly with the extent of liver damage, particularly in patients who continue to drink alcohol. The long-term prognosis depends on the severity of hepatic injury.[7] In patients with alcoholic liver disease as well as nonalcoholic steatohepatitis (Fig. 4), liver biopsy may reveal fatty infiltration of the liver, balloon-cell degeneration, Mallory's bodies, and hepatocyte necrosis, with or without clinically significant fibrosis or cirrhosis. In primary biliary cirrhosis, serial liver biopsies help one to study the natural history, monitor the effects of therapy, or identify a recurrence of the disease after liver transplantation.[8-10]

Liver biopsy provides an accurate diagnosis in ap-

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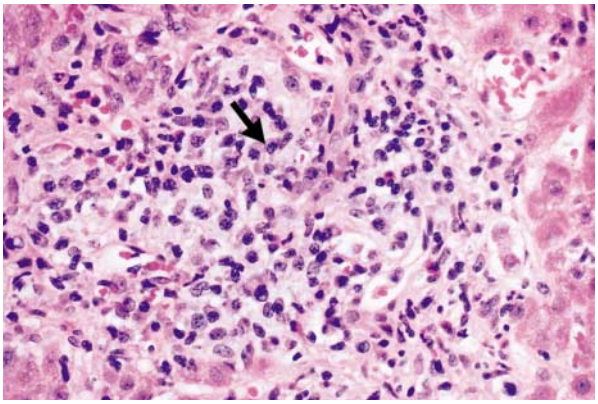

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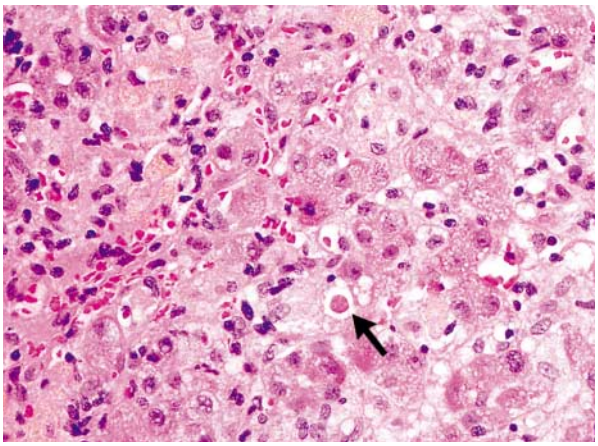

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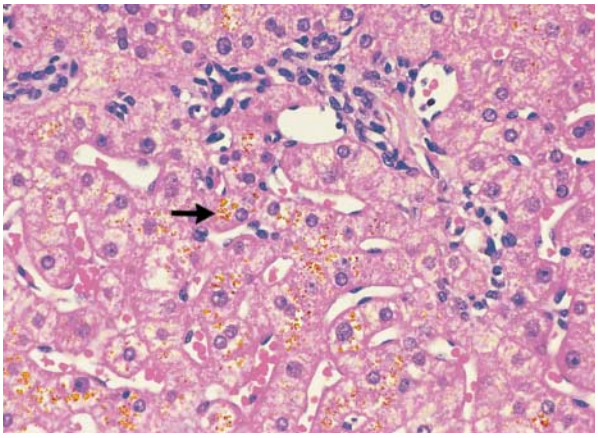
Figure 1. A Liver-Biopsy Specimen from a 32-Year-Old Man Presumed to Have Acute Hepatitis.

The specimen shows a portal mononuclear infiltrate with prominent plasma cells (arrow in Panel A) and lobular inflammation with apoptotic hepatocytes (arrow in Panel B), findings consistent with the presence of autoimmune hepatitis (hematoxylin and eosin, ×100).



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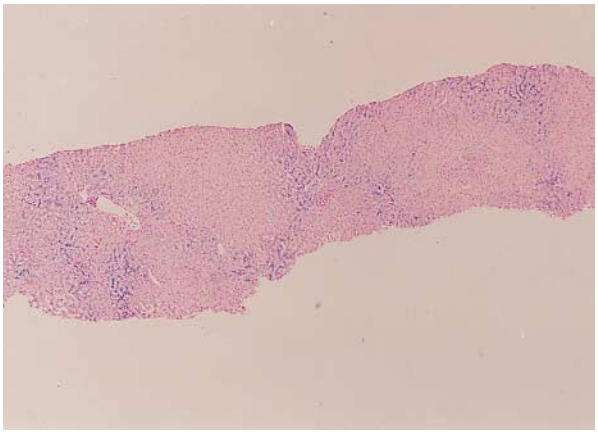

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Figure 2. Liver-Biopsy Specimens from a 38-Year-Old Woman with Increased Iron Saturation and Mild Hepatomegaly.

Panel A (hematoxylin and eosin, ×100) shows periportal deposition of brown pigment (arrow). Panel B (Perls' stain, ×10) shows periportal distribution of iron. The hepatic iron index was 2.0 (normal value, less than 1.0), which is consistent with the presence of idiopathic genetic hemochromatosis.

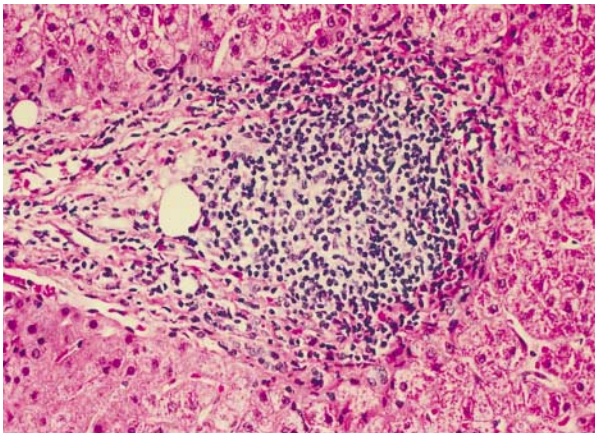
proximately 90 percent of patients with unexplained abnormalities revealed on liver-function tests.[11] The elucidation of various processes that occur in a transplanted liver — including immune rejection, systemic or infectious complications, drug toxicity, and the recurrence of primary disease — requires a liver biopsy.[12] Liver biopsy can also lead to the diagnosis of systemic disorders that can affect the liver, such as sarcoidosis, lymphoma, the acquired immunodeficiency syndrome, and amyloidosis.

PERCUTANEOUS LIVER BIOPSY

Procedures

Needles for percutaneous liver biopsy are broadly categorized as suction needles (Menghini needle, Klatskin needle, Jamshidi needle), cutting needles (Vim–Silverman needle, Tru-cut needle), and spring-loaded cutting needles that have a triggering mechanism. The cutting needles, except for the spring-loaded variety, require a longer time in the liver during the biopsy, which may increase the risk of bleeding.[13] A greater incidence of bleeding after biopsy has sometimes been observed with large-diameter needles.[14] If cirrhosis is suspected on clinical grounds, a cutting needle is preferred over a suction needle, since fibrotic tissue tends to fragment with the use of suction needles.[15] We routinely use spring-loaded needles.

Ultrasonography performed before a liver biopsy identifies mass lesions that are clinically silent and defines the anatomy of the liver and the relative positions



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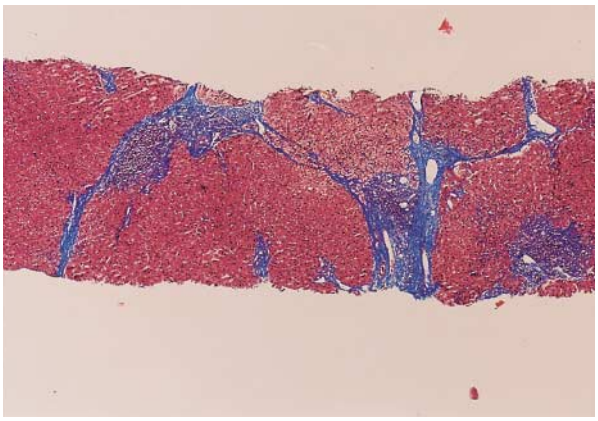

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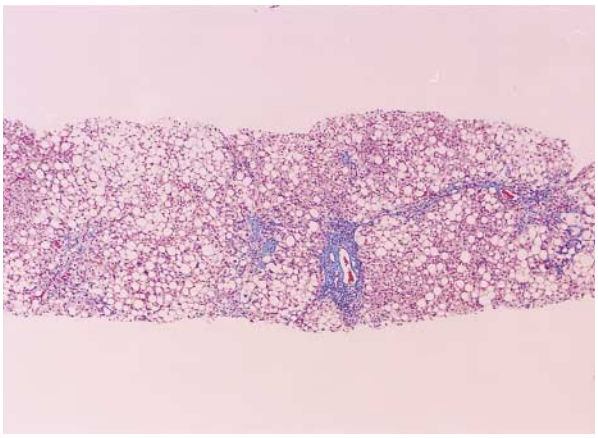
Figure 3. Liver-Biopsy Specimens from a 45-Year-Old Woman with Chronic Hepatitis C Virus Infection, in Whom There Was No Clinical Suspicion of Cirrhosis.

Panel A shows a dense portal infiltrate with the formation of lymphoid aggregates (hematoxylin and eosin, ×66). Panel B shows bridging fibrosis with architectural distortion and early cirrhosis (Masson trichrome, ×10).



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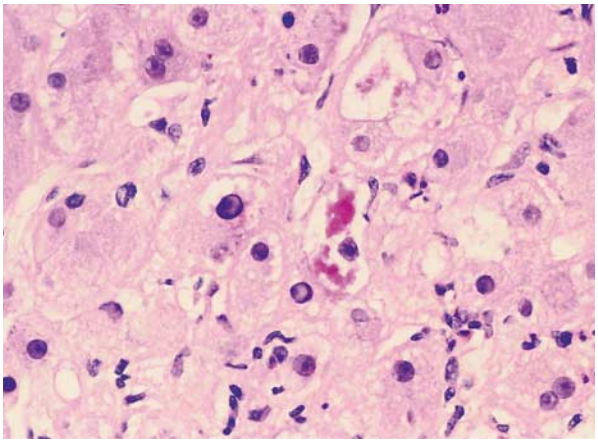

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Figure 4. Liver-Biopsy Specimens from a 40-Year-Old Man with Obesity, Diabetes, and Mildly Elevated Liver-Enzyme Levels.

The specimen in Panel A shows moderate-to-marked steatosis with increased fibrosis (trichrome, ×10). The specimen in Panel B shows a single cell (center) containing intracytoplasmic Mallory's bodies (hematoxylin and eosin, ×160). These findings are consistent with the presence of nonalcoholic steatohepatitis.

of the gallbladder, lungs, and kidneys. Most hepatologists agree that all patients should undergo ultrasonography of the liver before a percutaneous biopsy is performed. However, it is debatable whether the routine use of ultrasonography to guide the biopsy reduces the rate of complications, provides a higher diagnostic yield, or is cost effective.[16-23] We routinely use ultrasonography to mark the site for percutaneous biopsy.

It is now standard practice to perform liver biopsy on an outpatient basis, provided that various criteria are met. The Patient Care Committee of the American Gastroenterological Association has published practice guidelines for outpatient liver biopsy.[24] The patient must be able to return to the hospital in which the procedure was performed within 30 minutes after the onset of any adverse symptoms. Reliable persons must stay with the patient during the first night after the biopsy to provide care and transportation, if necessary. The patient should have no serious medical problems that increase the risk associated with the biopsy. The facility in which the biopsy is performed should have an approved laboratory, a blood-banking unit, an easily accessible inpatient bed, and personnel to monitor the patient for at least six hours after the biopsy. The patient should be hospitalized after the biopsy is performed if there is evidence of bleeding, a bile leak,

pneumothorax, or other organ puncture or if the patient's pain requires more than one dose of analgesics in the first four hours after the biopsy.

Contraindications

The contraindications to a percutaneous liver biopsy are listed in Table 2. Liver biopsy is a safe procedure when performed by experienced operators. Froehlich et al.[25] noted a lower complication rate for physicians who performed more than 50 biopsies a year. Prior ultrasonographic localization of the biopsy site may decrease the rate of complications for physicians who perform liver biopsies infrequently. "Blind" liver biopsies should be performed by experienced gastroenterologists, hepatologists, or transplantation surgeons and not by general internists.[5]

Complications of Percutaneous Liver Biopsy

Although the liver has a rich vascular supply, complications associated with percutaneous liver biopsy are rare. Sixty percent of complications occur within 2 hours and 96 percent within 24 hours after the procedure.[1,14] Approximately 1 to 3 percent of patients require hospitalization for complications after a liver biopsy, especially if the procedure was performed with a Tru-cut biopsy needle. Pain and hypotension are the predominant complications for which patients are hospitalized.[5,26]

Minor complications after percutaneous liver biopsy include transient, localized discomfort at the biopsy site; pain requiring analgesia; and mild, transient hypotension (due to a vasovagal reaction). Approximately one fourth of patients have pain in the right upper quadrant or right shoulder after liver biopsy. The pain is usually dull, mild, and brief.[27] Ongoing, severe pain in the abdomen should alert the physician to the possibility of a more serious complication, such as bleeding or peritonitis.

Although very rare, clinically significant intraperitoneal hemorrhage is the most serious bleeding complication of percutaneous liver biopsy; it usually becomes apparent within the first two to three hours after the procedure.[14,28] Free intraperitoneal blood may result from laceration caused by deep inspiration during the biopsy or may be related to a penetrating injury of a branch of the hepatic artery or portal vein. Risk factors for hemorrhage after liver biopsy are older age, more than three passes with the needle during biopsy, and the presence of cirrhosis or liver cancer.[14,26]

Findings of free intraperitoneal fluid on ultrasonography or CT should be correlated with the clinical assessment of the patient.[29] If hemorrhage is suspected, immediate arrangements for blood, platelets, and plasma should be made, and a surgeon and an angiographer should be alerted. Measures to improve the patient's hemodynamic status by the administration of intravenous fluids, blood products, or both may be sufficient. If hemodynamic instability persists for a few hours despite the use of aggressive resuscitative measures, angiography and embolization or surgical exploration is indicated.

Small intrahepatic or subcapsular hematomas can be noted after liver biopsy even in asymptomatic patients.[30] Large hematomas may cause pain associated with tachycardia, hypotension, and a delayed decrease in the hematocrit.[28] Conservative treatment of hematomas is generally sufficient.

The least common of the hemorrhagic complications is hemobilia, which usually presents with the classic triad of gastrointestinal bleeding, biliary pain, and jaundice[14] approximately five days after the biopsy.[31] Transient bacteremia has been reported in 5.8 to 13.5 percent of patients after liver biopsy,[32] and although such bacteremia is generally inconsequential, septicemia and shock can develop on rare occasions in patients with biliary obstruction and cholangitis. Currently, there are no recommendations for the routine use of prophylactic antibiotics in patients undergoing liver biopsy, including those with prosthetic valves or joints.[33]

Other rare complications of percutaneous liver biopsy include biliary ascites, bile pleuritis, bile peritonitis, pneumothorax, hemothorax, subcutaneous emphysema, pneumoperitoneum, pneumoscrotum, subphrenic abscess, carcinoid crisis, anaphylaxis after biopsy of an echinococcal cyst, pancreatitis due to hemobilia, and breakage of the biopsy needle.[14,28,34]

The mortality rate among patients after percutaneous liver biopsy is approximately 1 in 10,000 to 1 in 12,000.[13,28] Mortality is highest among patients who undergo biopsies of malignant lesions. Cirrhosis is another risk factor for fatal bleeding after liver biopsy.

TABLE 2. CONTRAINDICATIONS TO PERCUTANEOUS LIVER BIOPSY.

Absolute contraindications
Uncooperative patient
History of unexplained bleeding
Tendency to bleed*
Prothrombin time ≥3–5 sec more than control
Platelet count <50,000/mm³
Prolonged bleeding time (≥10 min)
Use of a nonsteroidal antiinflammatory drug within previous 7–10 days
Blood for transfusion unavailable
Suspected hemangioma or other vascular tumor
Inability to identify an appropriate site for biopsy by percussion or ultrasonography
Suspected echinococcal cysts in the liver
Relative contraindications
Morbid obesity
Ascites
Hemophilia
Infection in the right pleural cavity or below the right hemidiaphragm

*Although these criteria are considered absolute contraindications by most hepatologists, they can be corrected by transfusions of platelets or fresh-frozen plasma and are therefore not truly absolute.[12]

TRANSJUGULAR LIVER BIOPSY

Transjugular catheterization of the hepatic veins in human subjects was first described in 1967 as an approach to the biliary tract for cholangiography.[35] With transjugular liver biopsy, the liver tissue is obtained from within the vascular system, which minimizes the risk of bleeding. The indications for transjugular biopsy are outlined in Table 3.

The procedure involves percutaneous puncturing of the right internal jugular vein, the introduction, with the use of fluoroscopy, of a catheter into the right hepatic vein, and a needle biopsy of the liver performed through the catheter. The duration of the procedure is between 30 and 60 minutes. Electrocardiographic monitoring is required to detect arrhythmias induced by passage of the catheter through the heart.[36] Samples are retrieved from a needle passed through the catheter into the liver while suction is maintained. The samples obtained are small and fragmented, a disadvantage of the technique that may be improved with newer-generation technology.[37]

Adequate tissue for histologic diagnosis can be obtained from 80 to 97 percent of patients in centers where a large number of transjugular biopsies are performed.[38] The tissue specimen is usually 0.3 to 2 cm long, and the procedure generally requires multiple passes. A transjugular biopsy can also be performed at the same time as the placement of a transjugular intrahepatic portosystemic shunt. Failure to establish a diagnosis may be due to fragmentation of the tissue specimen.

In various studies, the rate of complications associated with transjugular liver biopsy ranges from 1.3 percent to 20.2 percent, and mortality ranges from 0.1 percent to 0.5 percent.[36,38] Complications of transjugular liver biopsy include abdominal pain, neck hematoma, transient Horner's syndrome, transient dysphonia, cardiac arrhythmias, pneumothorax, formation of a fistula from the hepatic artery to the portal vein or the biliary tree, perforation of the liver capsule (especially in small, cirrhotic livers), and death.

TABLE 3. INDICATIONS FOR TRANSJUGULAR LIVER BIOPSY.

Severe coagulopathy
Massive ascites
Massive obesity
Suspected vascular tumor or peliosis hepatis
Need for ancillary vascular procedures (e.g., transjugular intrahepatic portosystemic shunting, venography)
Failure of percutaneous liver biopsy

TABLE 4. INDICATIONS FOR AND CONTRAINDICATIONS TO LAPAROSCOPIC LIVER BIOPSY.

Indications
Staging of cancer
Ascites of unclear cause
Peritoneal infections
Evaluation of an abdominal mass
Unexplained hepatosplenomegaly
Contraindications
Absolute
Severe cardiopulmonary failure
Intestinal obstruction
Bacterial peritonitis
Relative
Uncooperative patient
Severe coagulopathy
Morbid obesity
Large ventral hernia

LAPAROSCOPIC LIVER BIOPSY

Diagnostic laparoscopy is especially useful in the diagnosis of peritoneal diseases, the evaluation of ascites of unknown origin, and the staging of abdominal cancer. It can be performed safely under local anesthesia with conscious sedation. However, the use of laparoscopic liver biopsy by gastroenterologists has declined in favor of less invasive radiologic procedures, and very few gastroenterology training programs now provide instruction in the procedure, which is usually performed by surgeons because of their growing experience with laparoscopic surgery. The indications for and contraindications to laparoscopic liver biopsy are outlined in Table 4. The complications include perforation of a viscus, bleeding, hemobilia, laceration of the spleen, leakage of ascitic fluid, hematoma in the abdominal wall, vasovagal reaction, prolonged abdominal pain, and seizures.[39]

FINE-NEEDLE ASPIRATION BIOPSY

Lundquist demonstrated that cytologic diagnosis based on material obtained by fine-needle liver aspiration compared favorably with the final histologic diagnosis based on surgical specimens.[40] Fine-needle aspiration biopsy of the liver is performed under ultrasonographic or CT guidance. Patients with a history of cancer and liver lesions are good candidates for fine-needle aspiration biopsy. The diagnostic accuracy ranges from 80 to 95 percent[3] and is substantially affected by the expertise of the cytopathologist. Cytologic findings that are negative for cancer do not rule it out.

Although ultrasound-guided or CT-guided biopsy is usually reserved for focal hepatic lesions, limited data suggest that diagnostically useful material can be obtained with automatic spring-loaded biopsy needles guided by ultrasound in over 95 percent of patients,[41] including those with diffuse liver disease. Fine-needle

aspiration biopsy is associated with a low risk of seeding of the needle tract with malignant cells and is generally a very safe procedure, even in patients with hemangiomas and echinococcal cysts.[42,43]

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