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Chapter 1

Liver Biopsy - Indications, Procedures, Results

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1. Introduction

Liver biopsy (LB) is the most common procedure performed in clinical hepatology. Histological assessment of the liver, and thus, LB is traditionally the "reference standard" in the diagnosis and management of parenchymal liver diseases. Definitive diagnosis often depends on LB, and much of understanding of the characteristic features and natural history of liver diseases is based on information obtained by serial liver biopsies. During the last 60 years as the result of a better understanding of liver disorders, appearance of newer entities and advent of novel hepatic imaging techniques, the indications for LB have evolved. Whereas in the past LB was often performed as the initial investigation in the workup of liver disease of unknown aetiology, today the most common indication for LB includes staging of chronic hepatitis. A variety of methods exist for getting a liver tissue specimen. These take account of a percutaneous method, a transvenous (transjugular or transfemoral) approach, and intra-abdominal biopsy (laparoscopic or laparotomic). All LB techniques require specific training so as to ensure appropriate-sized specimen retrieval and the lowest rate of complications. However, because LB is an invasive procedure that carries a definite, albeit small, risk of complications, controversy persists with regard to its precise indications in various clinical situations, its clear contraindications, the optimal technique for its performance (and whether certain modifications improve its safety), and training requirements for clinicians. The aim of this chapter will be summarize the existing clinical practice of LB with an emphasis on the technique, indications, contraindications, quality of LB specimens and risk of complications.

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2. Indications

Historically, LB was applied almost exclusively as a diagnostic tool [1]. Nevertheless, as the result of natural history data and the introduction of many new therapies for patients with liver disease, histological assessment of the liver has now got on an important role in clinical management. Therefore, LB currently has three major indications: for diagnosis, for assessment of prognosis and/or to assist in the management of patient with known liver disease.

Diagnosis
•Identification and staging of parenchymalandcholestatic liver diseases
-alcoholic liver disease
-non-alcoholic steatohepatitis
-autoimmune hepatitis
-primary biliary cirrhosis
-primary sclerosing cholangitis
-metabolic and mitochondrial storage liver diseases such as Wilson's disease, hemochromatosis, Gaucher's disease
•Evaluation of persistent abnormal liver biochemical tests after negative or inconclusive serologic workup
•Evaluation of the type and extent of drug-induced liver injury
•Evaluation of fever of unknown origin or immunocompromised patients with hepatomegaly or elevated liver enzymes levels
•Diagnosis of multisystem infiltrative disorders
- Identification and determination of the nature of focal/ diffuse intrahepatic abnormalities on imaging studies
Prognosis - Staging of known liver disease
•Evaluation of pre-transplant living-related donor
•Evaluation of post-transplant patient with abnormal liver tests (rejection vs. infectious aetiology)
Management – Developing treatment plans based on histologic analysis
•Pre-treatment evaluation and staging of chronic hepatitis
•Evaluation of effectiveness of therapies for liver diseases (*eg*, autoimmune hepatitis)

Table 1. Indications for liver biopsy

LB is performed to evaluate diffuse parenchymal or focal liver disease (see table 1). LB is mainly helpful in patients with diagnostic uncertainty(eg, in patients with atypical features). Available data show that liver histology will, in a proportion of patients, point to a specific diagnosis [2] and lead to a change in patient management [3,4]. LB has long been considered as an important diagnostic adjunct in the evaluation of otherwise unexplained abnormalities of liver biochemical tests. For example, LB may exclude serious liver disease or detect unsuspected non-alcoholic fatty liver disease (NAFLD) or intrahepatic sclerosing cholangitis after an otherwise negative biochemical, serologic and radiologic evaluation [3]. Needle LB for diagnosis remains important in cases of coexisting disorders such as steatosis and HCV [5] or an "overlap" syndrome of primary biliary cirrhosis (PBC) with autoimmune hepatitis (AIH) [6].

Other indications for LB include documentation of alcoholic liver disease and assessment of its severity; evaluation of otherwise unexplained fever, particularly in patients with Acquired Immune Deficiency Syndrome (AIDS); detection of underlying granulomatous liver disease. LB also provides important diagnostic information regarding drug-induced liver injury. Liver histology is appropriately considered in conjunction with clinical and laboratory data in case of hereditary disorders, eg hemochromatosis (quantitation of the level of iron), Wilson's disease (quantitation of the level of copper), and alpha-1 antitrypsin deficiency.

Liver histology may also be useful in detection of infiltrative processes such as amyloidosis [7]. Moreover, liver histology is often helpful in the setting of acute liver failure (ALF) [8].

An additional main use of LB is in assessing disease severity, particularly fibrosis, which, as a precursor to cirrhosis, may predict the emergence of complications of portal hypertension and also liver-related morbidity and mortality.

Owing to the wide use and superior resolution of cross-sectional imaging such as ultrasonography (US), computed tomography, and magnetic resonance imaging, focal lesions are being detected more often. Fortunately, the same technologic advances allow us to confidently establish a diagnosis without biopsy in most cases. Nevertheless, sometimes a biopsy of a suspected neoplasm will help change management. In this case, careful consideration of biopsy technique is important, as neoplasms have a higher bleeding risk and the potential to seed other sites along the biopsy tract or in the abdominal cavity [9]. At present, most biopsies currently performed for parenchymal disease are not to make a specific diagnosis but to assess liver damage, particularly in situations where (prognostic) information about fibrosis may guide consequent treatment. For example, histological analysis of the liver in patients with chronic HCV-induced liver disease gives information about the grading (inflammatory activity) and the staging (degree of fibrosis) that predict the course of disease; the treatment is often advocated for those with at least moderate to severe staging, but may be withheld when fibrosis is minimal or absent [10]. Liver histology is also generally used in disease monitoring of patients with AIH [11]. Monitoring the plasma cell score on LB may help predict relapse when a physician is considering reducing or discontinuing immunosuppressive therapy [12]. For further information on the role of histological analysis in the management of individual liver diseases, is possible to see guidelines for HCV [10], HBV [13], hemochromatosis [14], cholestatic liver diseases [15], AIH [11], and Wilson's disease [16].

Assessment of liver histology after orthotopic liver transplantation (OLT) is highly valuable to assess for allograft rejection and the presence and intensity of disease recurrence. Controversy persists regarding the precise indications for LB. Among these controversies are the following:

- The precise cut-off of serum aminotransferase levels that should prompt a LB: any persistent elevation, 1.5 times the upper normal limit, or 2 standard deviations above the mean [17,18]. Even the definition of the upper limit of normal is controversial [19-21].
- The need for LB in patients presumed to have NAFLD. Whereas imaging studies are sensitive for detecting steatosis, they are relatively not sensitive and nonspecific for detecting inflammation and fibrosis. Only on liver histology can distinguish fatty liver from steato-

hepatitis, which can lead to fibrosis and cirrhosis. LB is often considered if serum alanine aminotransferase (ALT) levels remain elevated after a modification of lifestyle and risk factors [22].

- The need for LB in all patients with PBC and primary sclerosing cholangitis (PSC). In most cases the diagnosis can be established on the basis of a cholestatic pattern of liver chemistries and either anti-mitochondrial antibodies in PBC [6] or endoscopic retrograde cholangiopancreatography (ERCP) in PSC [23]; scoring systems based on quickly established clinical variables could be used to assess prognosis and response to therapy.
- The need for protocol liver biopsies in all liver transplant recipients. A high rate of histologic abnormalities in the absence of liver biochemical test abnormalities has been described as late as 10 years after transplantation [24].

Overall, in patients without a definitive pre-biopsy diagnosis, LB has been shown to change the clinical diagnosis in 8% to 10% and to change the management in 12% of patients [25]. However, changes in management are often of minor importance [3].

3. Biopsy technique

Performance of LB requires an adequate sized and dedicated space suitable for focused physician effort as well as safe patient recovery. There are different approaches for obtaining liver tissue: percutaneous, transjugular, laparoscopic, and intraoperative, each having advantages and disadvantages. The biopsy technique is chosen on the basis of the indication, risks, and benefits in the individual patient. The most common approach for collecting a liver sample is percutaneous LB, either blinded or under US guidance. It is quick and safe procedures commonly performed by gastroenterologists or hepatologists in out-patient settings.

A variety of needles are available for percutaneous LB; they are broadly classified into suction needles (Menghini, Klatskin, Jamshidi), cutting needles (Vim-Silverman, Tru-cut), and spring-loaded cutting needles that have a triggering mechanism. The choice of a specific type of needle depends in part on local preference. Cutting needles usually produce a larger sample and are less likely to yield inadequate specimens than are suction needles, but they probably result in more complications [26], probably because the needle remains in the liver longer. Cutting needles can be useful in patients with cirrhosis. Suction needles are quicker (in the liver for a briefer time), easier to use, and less expensive, but tend to produce more fragmented samples. Disposable biopsy needles and biopsy guns are often used. A typical biopsy gun uses a modified 18-, 16-, or 14-gauge Tru-cut needle that is fired by a fast and powerful spring mechanism.

If the patient is not relaxed, a mild sedative should be administered just before the biopsy [27]. The current data on the use of prophylactic antibiotics is inconclusive. Prophylactic antibiotics have been recommended for patients at increased risk of endocarditis or with biliary sepsis [28]. However, recent results suggest that prophylactic administration of

antibiotics following apercutaneous liver biopsy does not have a significant impact on the post-procedure results or incidence of infection [29]. During the procedure, patients placed in the supine position with the right hand resting behind the head [30]. For the blind approach (also referred to as the percussion-palpation approach), caudal percussion is helpful in selecting the site for the biopsy over the hemithorax between the anterior and mid-axillary lines, until an intercostal space is reached where dullness is maximal at the end of expiration. The intercostal space below this point (usually in the 7^{th}-8^{th} intercostal space) is used. A local anesthetic, typically lidocaine (without adrenaline), is administered with a 25-gauge needle first subcutaneously and into the intercostal muscle and finally down to the diaphragm and the capsule of the liver to reduce pain. The biopsy is performed while the patient holds a breath in full expiration [31]. With a suction needle, aspiration is applied, and the needle is rapidly introduced perpendicularly to the skin into the liver and withdrawn quickly (within 1 second). This is the critical step in performing the biopsy to minimize the risk of lacerating the liver and inducing bleeding. If insufficient tissue is obtained on the first pass [32], a second pass is performed at a different angle. After the biopsy, the patients is usually kept on the right lateral decubitus position for up to 2 hours to reduce the risk of bleeding and the pulse and blood pressure are monitored. Post-procedure monitoring has evolved over time. Most complications manifest within the first few hours [26], and under certain circumstances more and more patients are being discharged just 1 or 2 hours after imaging-guided biopsy. Rightly, the recommended observation time after biopsy is between 2 to 4 hours. To direct the needle away from other organs and large vascular structures, physicians often use US guidance. The US has been used either throughout the entire procedure (real-time) or immediately before (site marking) through a technique in which the patient subsequently has LB performed at the marked site. US guidance is the most controversial issue associated with LB [33-35]. Potential LB sites marked by percussion were changed in between 3 and 15% of patients after US was performed [36,37]. In an uncontrolled Italian study, routine identification of the puncture site by US led to a diagnostic tissue sample in 99% of patients [35]. In diffuse liver disease, US marking or guidance has been associated with lower rates of pain, hypotension, and bleeding [31]. In a survey of 2084 liver biopsies in France, US guidance is used in 56% of cases (in 34% to determine the puncture site and in 22% to guide the biopsy) and is thought to reduce the frequency of severe complications [38]. Cost-effectiveness analyses have suggested that routine US guidance in clinical practice increases the cost of LB but may be cost-effective, with an incremental cost of $2731 to avoid one major complication [39,40]. In addition, a large, randomized, prospective trial found that US use lowered the rate of post-biopsy hospitalization (most common reason for hospital admission was pain). Indeed there is a long track record of safety for performing percutaneous LB without imaging guidance. Thus, the role of US to guide percutaneous LB remains controversial. Use of ultrasound is not mandatory. A transjugular biopsy route offers a reasonable alternative to standard biopsy in high-risk patients (eg presence of massive ascites, severe coagulopathy, morbid obesity with a difficult to identify flank site or fulminant hepatic failure) [41]. With transjugular LB, the liver tissue is obtained from within the vascular system, which minimizes the risk of bleeding [42,43]. The procedure is performed by interventional radiologists or hepatologists under X-ray videofluoro-

scopy. Electrocardiographic monitoring is required to detect arrhythmias induced by passage of the catheter through the heart [41,44]. The patient is positioned supinely, with the head rotated opposite to that of the right internal jugular vein to be punctured, under local anesthesia using the Seldinger technique; then, a catheter is introduced into the hepatic vein under fluoroscopic control, and a needle biopsy of the liver performed through the catheter. Samples are retrieved from a Menghini or Tru-cut needle passed through the catheter into the liver. The transjugular approach permits concomitantly measurement of hepatic venous pressure gradient or opacification and imaging of the hepatic veins and inferior vena cava [45] helping in the diagnosis and management of select group of patients, particularly those with cirrhosis. In the past, a drawback of transjugular biopsy was the small and fragmented samples obtained. Better needles and more experience have led to improved quality of specimens. However, a transjugular LB is available only at a limited number of tertiary care facilities. Mortality is low (0.09%) [41], but perforation of the liver capsule can be fatal [46]. With laparoscopic approach, specific lesions can be identified and targeted precisely; thus it is especially useful in the diagnosis of peritoneal disease, the evaluation of ascites of unknown origin and abdominal mass, the staging of abdominal cancer. Laparoscopic LB is a safe procedure that can be performed under local anesthesia with conscious sedation, although it requires expertise that is not readily available. Absolute contraindications include severe cardiopulmonary failure, intestinal obstruction, bacterial peritonitis; relative contraindications are severe coagulopathy, morbid obesity, and a large ventral hernia [33]. For most parenchymal liver diseases, the extra time and cost required for laparoscopy are not justified by the increased yield. Liver biopsies (needle or wedge) can also be obtained during abdominal surgery whenever liver disease is suspected. In many instances, an abnormal appearance of the liver during surgery for an unrelated procedure (most often cholecystectomy) is the first indication of an underlying liver disease. It is generally performed either with typical needle devices or by wedge resection by those with special expertise. While intraoperatively obtained liver biopsies have the added advantage of obtaining adequate tissue sampling under direct vision from grossly visible/suspicious lesions, they are suboptimal for assessment of liver fibrosis and inflammation, due to preponderance of Glissen's capsule, wider portal tracts in the subcapsular area, and frequent but inconsequential surgically induced hepatitis. Other advantages are the ability to evaluate for potential extrahepatic spread of malignancy and to look for a cause of unexplained ascites (peritoneal biopsy). The major disadvantages are cost and the added risk of anesthesia. Therefore, needle biopsy should be the technique of choice at laparotomy.

4. Contraindications

Although LB is often essential in the management of patients with liver disease, physicians and patients may find it to be a difficult undertaking because of the associated risks.

The consensus guidelines of contraindications for percutaneous LB are listed in Table 2.

Absolute
•Uncooperative patient
•History of unexplained bleeding
•Tendency to bleed
-Prothrombin time "/> 3-4 sec over control
-Platelet counts < 50.000/mm3
-Prolonged bleeding time (≥10 min)
•Unavailability of blood transfusion support
•Recent use of aspirin or other nonsteroidal anti-inflammatory drugs (within last 7-10 days)
Relative
•Ascites
•Morbid obesity
•Infection in the right pleural cavity or below the right hemidiphragm
•Suspected hemangioma or other vascular tumor
•Hydatid disease (Echinococcal cysts)

Table 2. Contraindications to percutaneous LB

Percutaneous LB with or without image guidance is appropriate only in cooperative patients. As for any procedure, the patient that undergoes a LB should be able to understand and cooperate with the physician's instructions. An academic concern is that if the patient accidentally moves when the biopsy needle is in the liver, then a tear or laceration may occur (which would in turn greatly increase the risk of bleeding). Thus uncooperative patients who require LB should undergo the procedure under general anesthesia or via the transvenous route.

Coagulopathy is generally considered a contraindication to percutaneous LB, but the precise parameters that preclude LB are unsettled [47]. Generally, LB should be withdrawn when the prothrombin time (PT) is more than 3-4 seconds above the control value (International Normalized Ratio, INR>1.5) or when the platelet count is less than 60.000/mm3 [48]. Nevertheless, it is important to emphasize that the relationship of abnormal indices of peripheral coagulation to the occurrence of bleeding after LB in patients with acute as well as chronic liver disease is uncertain, as limited data are available [47,49]. In patients with mild to moderate prolongation of PT, administration of fresh frozen plasma or appropriate clotting factor concentrates may allow safe performance of a LB, as in hemophiliacs [50]. A low platelet count is probably less likely to result in bleeding in a cirrhotic patient with hypersplenism than in a leukemic patient with a comparable platelet count but platelet dysfunction. Probably, platelet dysfunction due to aspirin use is a major risk factor as well. Whether patients with renal insufficiency are at increased risk of bleeding complications after LB is also uncertain [28]. In summary, the decision to perform LB in the setting of abnormal hemostasis parameters should continue to be reached as the result of local practice because there is no specific INR and/or platelet count cut-off at or above which potentially adverse bleeding can be reliably predicted.

A LB is precluded by tense ascites, because the liver will bounce away from the needle, thereby preventing adequate sampling of tissue, and the ascites will provide insufficient tamponade in case of bleeding. In patients with tense ascites requiring a LB, a transvenous approach is commonly recommended. Acceptable options include total paracentesis performed immediately prior to percutaneous biopsy or transvenous or laparoscopic biopsy.

Relative contraindication is morbid obesity; in this case, transjugular biopsy is a logical alternative.

A standard LB is probably contraindicated by extrahepatic biliary obstruction, bacterial cholangitis, and the risk of bleeding after LB appears to be increased in patients with a known hematologic malignancy involving the liver [28].

Although LB in patients with mass lesions is usually safe, biopsy of known vascular lesions (ie hepatic hemangioma) should generally be avoided [51]. Patients who require LB and who have a large vascular lesion identified on imaging should undergo the procedure using real-time image guidance. Biopsy of potentially malignant lesions should be undertaken with care because it is believed that tumour vessels are more likely to bleed [51] and it can be also associated with a risk of tumour spread [52,53].

Biopsy of infectious lesions is generally safe. In the past, the presence of an echinococcal cyst was considered a contraindication to LB, because of the possibility of disseminating cysts throughout the abdomen and the risk of anaphylaxis. However, with recent advances in treatment, echinococcal cysts can be aspirated safely under ultrasound guidance [54].

5. Complications

When performing a LB, should be aware of multiple potential complications that may occur after biopsy.At the time that informed consent is obtained, it is reasonable to outline these complications clearly, warn the patient of the potential pain, and mention in a general statement that other complications, albeit rare, can occur.

Although the percutaneous biopsy is invasive, associated complications are rare, occurring in up to 6%, and 0.04% to 0.11% can be life threatening [33].

The different complication rates were attributed to variation in technique and to differences in the needles used, as well as differences in the severity of the liver disease and selection criteria in different centers.

The most common complication after percutaneous LB is pain [55]. Approximately 25% of patients have pain in the right upper quadrant or right shoulder; the pain is usually dull, mild and brief. Right upper-quadrant pain does not seems to be related to approach (i.e. subcostal vs. intercostal) [56]. The mechanism of pain following percutaneous biopsy is most likely a result of bleeding or possibly bile extravasation from the liver puncture wound, with subsequent capsular swelling, although the exact mechanism remains uncertain [57]. When present, pain can generally be managed with small amounts of narcotics. A decision

about when to investigate with imaging and/or to hospitalize the patient for observation due to pain should be made on a case-by-case basis.

MAJOR
•Dearth
•Haemorrhage (intraperitoneal, intrahepatic, haemothorax)
•Perforation of the gallbladder or of the bowel
•Pneumothorax, haemothorax
•Biopsy of the right kidney or the pancreas
•Intrahepatic arteriovenous fistula
•Bile peritonitis
MINOR
•Pain (biopsy site, right upper quadrant and right shoulder pain)
•Transient hypotension (vasovagal response)
•Pneumoperitoneum
•Hemobilia
•Infection (bacterial sepsis, local abscess)
•Intrahepatic and subcapsular hematoma

Table 3. Complications of percutaneous liver biopsy

Transient hypotension, due to vasovagal reaction, can occur, particularly in patients who are frightened or emotional.

Major complications were defined as life threatening or those that required hospitalization, prolonged hospitalization or those that resulted in persistent or significant disability. Most serious complications occur within 24 hours of the procedure, and 60% happen within 2 hours; between 1% and 3% of patients require hospitalization [33].

The most common serious complication is bleeding because of transection of a vascular structure [26]; bleeding may occur in the absence of pain. Mild bleeding, defined as that sufficient to cause pain or reduced blood pressure or tachycardia, but not requiring intervention, occurs in about 1/500 biopsies [58]. Severe bleeding is defined clinically by a change in vital signs with imaging evidence of intraperitoneal bleeding. Such bleeding has been estimated to occur in between 1 in 2.500 to 1 in 10.000 biopsies after a percutaneous approach for diffuse liver disease [59]. Although very rare, clinically significant intraperitonealhemorrhage is the most serious bleeding complication of percutaneous LB; it usually becomes apparent within the first 2-3 hours after the procedure [26]. Free intraperitoneal blood may result from laceration of the liver capsule 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. The likelihood of hemorrhage increased with older age, presence of cirrhosis or liver cancer, and number of passes (≥ 3) with the needle during biopsy. The relationship between LB complications and the number of needle passes is well documented [51]. The frequency of complications increased with the number of passes performed at a rate of 26.4%, with one pass vs.

68% with two or more passes ($P< 0.001$) [38]. An additional factor in determining the risk of hemorrhage may be the type of needle used; cutting needles are more likely to result in hemorrhage than suction needles [26]. Severe bleeding requires hospitalization and is most often managed expectantly with placement of intravenous catheters, volume resuscitation by the administration of intravenous fluids and blood transfusion as necessary. If hemodynamic instability persists for a few hours despite the use of aggressive resuscitative measures, angiography with selective embolization of the bleeding artery or surgery (to ligate the right hepatic artery or resect a section) is required.

Subclinical bleeding leading to intrahepatic or subcapsular hematomas may be noted after LB even in asymptomatic patients. It is occurs in up to 23% of patients [60] and can be detectable by US. Large hematomas may cause pain associated with tachycardia, hypotension, and a delayed decrease in the hematocrit [33]. Conservative treatment of hematomas is generally sufficient.

After tranvenous biopsy bleeding is extremely rare because of the Glisson capsule is not breached except as a procedural complication from within the liver [61].

The least common of the hemorrhagic complications is hemobilia, which usually presents with the classic triad of gastrointestinal bleeding, biliary pain, and jaundice [26] approximately 5 days after the biopsy [62].

Transient bacteremia has been reported in 5.8 to 13.5 percent of patients after LB [63], and although such bacteremia is generally inconsequential, septicaemia and shock can rarely occur in patients with biliary obstruction and cholangitis.

Biliary peritonitis caused by puncture of the gallbladder is rare (0.00001% frequency) but can be fatal [64].

Pneumothorax, hemothorax, subcutaneous emphysema, perforation of any of several organs (lung, colon, and kidney), subphrenic abscess are other complications reported with LB. Pneumothorax may be self-limited but may require more aggressive intervention depending on the severity of symptoms. Visceral perforation is usually managed expectantly. In most situations, observation is all that is required, although surgical intervention may be needed in the case of gallbladder puncture and persistent bile leak, or in the case of secondary peritonitis.

Differences in complication rates, either minor or major, have been reported between the blind and US-guided LB. The use of US guidance can prevent inadvertent puncture of other organs or large intrahepatic vessels. US may also reduce the incidence of major complications such as haemorrhage, bile peritonitis, pneumothorax, etc.

With respect to the impact of the experience of the operator to the rate of complications, the evidences are controversial. A survey performed in Switzerland showed that the complication rate of percutaneous LB was mainly related to the experience and training of the operator, in particular a lower complication rate was reported for physicians who performed more than 50 biopsies a year [65]. Another study showed that the rate of complications in percutaneous LB was 3.2% if the operator had performed <20 biopsies, and only 1.1% if the

operator had performed more than 100 biopsies [64] In contrast, Chevallier et al. showed that the operator's experience did not influence either the final histological diagnosis or the degree of pain suffered by patients [66].

In adult series, the rate of major complications associated with transjugular LB is low (0.5%; liver puncture-related, 0.2%; non-liver punctureрelated,0.3%), considering that it is currently performed in patients with coagulopathy [41]. Minor complications were significantly more frequent with Menghini needle, possibly related with the difficulty in controlling the depth of puncture increasing the risk of capsular penetration [46].

MINOR	
Pyrexia	Hypotension
Neck hematoma, bleeding	Abdominal pain
Neck pain	Subclinical capsular perforation
Carotide puncture	Small hepatic hematoma
Transient Horner's syndrome	Hepatic-portal vein fistula
Transient dysphonia	Hepatic artery aneurysm
Arm numbness/palsy	Biliary fistula
Supraventricular arrhythmia	Haemobilia
MAJOR	
Large hepatic hematoma	Ventricular arrythmia
Intraperitoneal haemorrhage	Pneumothorax
Inferior vena cava or renal vein perforation	Respiratory arrest

Table 4. Complications of transjugular liver biopsy

Factors associated with liver and non-liver puncture related complication rates included number of passes (liver puncture-related), young age, and number of transjugular biopsies.

The complications after laparoscopic LB 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 [67].

The most quoted mortality rate after percutaneous LB is less than or equal to 1/10.000 biopsies. Mortality is typically related to bleeding. Mortality is highest among patients who undergo biopsies of malignant lesions. Cirrhosis is another risk factor for fatal bleeding after LB. Mortality after transvenous biopsy was 0.09% [41] in adult series, but may reflect the selection of higher risk patients for this intervention. Indeed, mortality is significantly higher in children; smaller livers and horizontal hepatic veins may increase the technical difficulty and risk of capsular perforation, which might be minimized by combined fluoroscopic and US guidance [68].

6. Pathological considerations

Even though LB gives significant diagnostic and prognostic information and helps define treatment plans, it must be recognized that sampling variability and intra observer variability may restrain the diagnostic value of LB. The quality of LB is usually determined by length, width, fragmentation and complete portal tracts (CPTs) [33].

Sample size can affect the diagnostic accuracy of LB specimens [33]. s almost always means that size of the needle biopsy specimen should be of large enough size to accurately assess the degree of liver injury. Considering that a biopsy sample taken from an adult corresponds to a fraction of just 1/50,000th of the whole liver, a biopsy specimen would seem to be inadequate in the case of diffuse diseases, such as a chronic viral hepatitis, in which the liver changes may be unevenly distributed.

Several studies demonstrated that cirrhosis can be missed on a single blind percutaneous LB in 10%-30% of cases [69-71]. In a detailed study, Colloredo et al. [72] carefully evaluated the impact of sample size on correct stadiation of liver fibrosis in patients with chronic hepatitis C. By reducing progressively the dimensions of the same LB, they reported that the smaller the sample analyzed, the milder the diagnosis made by the pathologist with respect to the stage of fibrosis. The reduction in length (<2 cm) led to a significant decrease in number of complete portal tracts and underestimation of grading and staging. The study by Colloredo et al also introduced the concept of a ''minimum number of CPTs.'' Since the number of portal tracts is proportional to biopsy size [73], there was evidence that with fewer than 11 to 15 CPTs grade and stage are significantly underestimated [72]. The lower number of complete portal tracts may explain the lower diagnostic accuracy obtained with smaller samples [73,74]. Guido and Rugge have suggested that a biopsy sample ≥20 mm containing at least 11 CPTs should be considered reliable for adequate staging [75]. Other authors have recommended even bigger samples, up to 25 mm in length [76]. Scheuer suggested that ''bigger is better'' [77]. Very recently, the American Association for the Study of Liver Diseases (AASLD) has recommended a biopsy sample of at least 20–30 mm in length, and containing at least 11 CPTs [48].

In summary, an adequate (although probably still imperfect) sample needs to be at least 2 cm long (1.4 mm width, 16G) and to contain no fewer than 11 CPTs. These criteria have been adopted rapidly as optimal standards.

Of equal importance to adequate specimen size is the necessity that a pathologist experienced in liver disease interprets the biopsy, ideally in partnership with the clinician who performed the biopsy and/or whom is caring for the patient. Rousselet et al. reported that the degree of experience of the pathologist (specialization, duration, and location of practice) may have a significant impact on the diagnostic interpretation of LB, even higher than that related to characteristics of the specimen (length, fibrosis class number, miscellaneous factors) [78].

Assessment of disease severity with liver histology is supported by a wide body of literature [79]. Complex scoring systems, such as the Knodell scoring system [80] and its re-

vised form, the Ishak scoring system [81] have been developed for grading and staging of chronic viral hepatitis, and there is now a similar score for steatohepatitis [82]. Nevertheless, these are not highly reproducible and are only appropriate for statistical analysis of (large) cohorts of patients in clinical trials. In clinical practice, it was recommended to use the simple systems with three to four categories such as METAVIR [83] rather than complex (Ishak) scoring system [48].

7. Further research

Until a few years ago, LB was the only tool for the diagnosis of liver disease. However, the indications for performing a LB have undergone changes in the last decade. Given the invasive nature of LB, several simple and non-invasive methods (radiologic, immunologic, biochemical, genetic markers) have been studied and proposed as surrogates of liver histology. The main advantages of serum biomarkers vs. LB include being less invasive and the possibility to be easily repeated to monitor the status of liver disease. However, at this time, they are primarily useful for detecting advanced fibrosis or for excluding minimal or no fibrosis. They are not sufficiently accurate for assessing disease progression or the effect of therapy. Due to inadequate diagnostic accuracy or to lack of sufficient validation, current guidelines do not recommend serum biomarkers a substitute for LB that is still considered the reference standard. Notably, non-invasive serum biomarkers, when combined, may reduce by 50%-80% the number of liver biopsies needed for correctly classifying hepatic fibrosis. Serum biomarkers for liver fibrosis are particularly useful for the initial assessment as well as for long-term monitoring of particular subsets of patients (ie, chronic hepatitis C). In this view, combination algorithms of the most validated non-invasive methods for liver fibrosis and LB represent a rational approach to the diagnosis of liver fibrosis in chronic liver diseases. Novel imaging techniques, such as measuring the elasticity of the liver using transient elastography (Fibroscan) [84], may assess fibrosis more directly. However, the use of such techniques in routine clinical practice has not been well defined and require further investigation. LB cannot be avoided completely, but should be used in those cases in which non-invasive methods show poor accuracy. Nevertheless, large scale, prospective, independent studies are needed in other aetiologies of CLDs. Many questions about LB remain and they require much more research. For instance, it is not clear which biopsy devices or techniques are best. In addition, few if any studies have assessed the biopsy's long-term effects. Because the liver is cut and bleeds during procedure, there will be some subsequent scarring.

8. Conclusions

LB continues to play a central role in the evaluation of patients with suspected liver disease, but many aspects of the procedure remain controversial. For example, the precise degree of serum ALT elevations that should prompt a LB is debated, as is the need for LB in all patients with suspected NAFLD and chronic hepatitis C. The importance of LB in arriving at a

diagnosis of diffuse parenchymal liver disease is being diminished by accurate blood testing strategies for chronic viral hepatitis, autoimmune hepatitis, and primary biliary cirrhosis. Further, imaging tests are superior to LB in the diagnosis of primary sclerosing cholangitis. However, many cases remain in which diagnostic confusion exists even after suitable laboratory testing and imaging studies. Diagnosing infiltrative disease (eg, amyloidosis, sarcoidosis), separating benign fatty liver disease from steatohepatitis, and evaluating liver parenchyma after liver transplantation are best accomplished by LB.

Percutaneous LB is contraindicated in patients with severe coagulopathy and ascites, but the degree of coagulopathy that contraindicates a LB is controversial. Also controversial are the technical aspects of LB, particularly the choice of needle (cutting vs. suction) and the use of US to mark or guide the biopsy site. Bleeding is the major complication of LB, with a risk of 0.3%; cutting needles are more likely to cause hemorrhage than are suction needles. While needle biopsy is still the mainstay in diagnosing hepatic fibrosis, its days of dominance seem limited as technology improves. When physical examination or standard laboratory tests reveal clear-cut signs of portal hypertension, LB will seldom add useful information. Similarly, when imaging studies provide compelling evidence of cirrhosis and portal hypertension, needle biopsy is not warranted. The combination algorithms warrant further evaluation in all chronic liver diseases, as they may help decrease the number of liver biopsies required. Moreover, transient elastography is playing an ever-increasing role in the assessment of hepatic fibrosis and will significantly reduce the need for biopsy in patients with liver disease.

Clearly, as our knowledge of various liver disorders advances and new especially non-invasive diagnostic tests are developed, the role of LB in medical practice will continue to evolve. Emergence of better imaging techniques, surrogate serological markers of liver fibrosis are among the many new and exciting developments that hold promise for the future.

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