



# Liver Biopsy in Chronic Liver Diseases: Is There a Favorable Benefit: Risk Balance?

Dominique Larrey, Lucy Meunier, José Ursic-Bedoya

Liver and Transplantation Unit, Montpellier School of Medicine and IRB-INSERM-1183, Montpellier, France.

## ABSTRACT

Liver biopsy is still useful in selected clinical situations in which it is the only tool to obtain information necessary for the diagnosis, the prognosis, and the decision for treatment. Main examples are viral hepatitis with confounding co-morbidities, non alcoholic fatty liver disease, and autoimmune liver diseases.

**Key words.** Liver biopsy. Chronic liver disease. Cirrhosis. Fibrosis. Co-morbidities.

## INTRODUCTION

Historically, liver biopsy has three major roles: for diagnosis, for assessment of prognosis (disease staging), and/or to facilitate therapeutic management decisions.<sup>1,2</sup> Indications for liver biopsy have changed over recent years because of the development of sensitive, specific tests for the diagnosis of several chronic liver diseases (i.e. serological tests for viral hepatitis, and genetic testing for hereditary hemochromatosis).<sup>1-3</sup> The development of noninvasive tools for the evaluation of liver fibrosis, initially in chronic hepatitis C, including numerous serum markers (e.g. Fibrotest Fibrometer, APRI score, FIB-4), as well as measurement of liver stiffness by transient elastography, have led to a marked decrease in the indication liver biopsy.<sup>3-5</sup> These new non invasive technics have been recently tested in the main other chronic diseases.<sup>6-12</sup>

The purpose of this brief review is to recall the present technics used to perform liver biopsy, their safety, and limitations, and the indications balanced with the new non-invasive methods of evaluation of main chronic liver injuries.

## PROCEDURES OF LIVER BIOPSY<sup>1-3</sup>

Typically, liver biopsy is performed on a “same day” basis, using several methods with specific advantages and disadvantages:

- The simplest procedure is percutaneous biopsy performed with a different type of needles, a procedure increasingly guided by ultrasonography. The contraindications are: uncooperative patient, coagulopathy, ascites, suspicion of vascular tumor or echinococcal cyst. The most severe complications are rare, occurring within the first hours. They include intraperitoneal bleeding, liver hematoma, hemobilia, transient bacteremia, pneumothorax, hemothorax and lead to hospitalization in 1-3% of patients. The mortality rate is estimated to be around 1/10,000, mostly related to fatal bleeding in patients with cirrhosis. Minor complications include transient discomfort at the biopsy site, requiring analgesia and mild, transient arterial hypotension due to a vasovagal reaction.
- Transjugular biopsy, involves percutaneous puncturing of the right internal jugular vein, introduction of a catheter in the right hepatic vein, and a needle biopsy of the liver performed through the catheter.<sup>1,2,13</sup> This technics allows estimating portal vein pressure as well as to place a transjugular intrahepatic portosystemic shunt.<sup>13</sup> The main indications for transjugular liver biopsy are contraindications of percutaneous liver biopsy.
- Laparoscopic biopsy: is rarely used for the assessment of chronic liver diseases.<sup>1,2</sup>
- The main limitations of liver biopsy<sup>5</sup> are that it is an invasive procedure that is prone to sampling errors and to intra- and interobserver variations.<sup>5,14</sup> The required

criteria for the size of the liver sample allowing an adequate histologic assessment are met inconstantly: sample measuring at least 20-30 mm in length containing more than 11 complete portal tracts, keeping in mind that it represents only about 1/50 000 of the total mass of the liver.<sup>1,2</sup>

## INDICATIONS OF LIVER BIOPSY IN THE MAIN CHRONIC LIVER DISEASES

### Chronic hepatitis C

There is a large amount of data validating non-invasive methods to replace liver biopsy.<sup>4,15</sup> Furthermore, the tremendous improvement in treatment efficacy and safety make the grading of inflammation and fibrosis much less important than before for the indication of treatment. Now, new anti-viral combinations are recommended to almost all stages of HCV liver diseases.<sup>15</sup> Liver biopsy remained indicated in very selected situations: invalid non-invasive tests of fibrosis, association of HCV infection with other causes of chronic liver injuries including alcohol abuse, obesity, diabetes, making it difficult to determine the role of each causes.<sup>4,15</sup>

### Chronic hepatitis B<sup>4,6</sup>

In patients without sign of cirrhosis, liver biopsy is traditional proposed to determine the levels of inflammation and fibrosis, which are among the criteria for indication of treatment in addition to HBV DNA levels above 2,000 IU/mL, and serum increased ALT levels.<sup>6</sup> In contrast, patients with HBV DNA > 20,000 IU/mL and ALT > 2x ULN can start treatment even without a liver biopsy. A non-invasive method for the estimation of the extent of fibrosis and, most critically from a monitoring perspective, to confirm or rule out cirrhosis is useful in patients who start treatment without liver biopsy. Elastography may also be used for decisions on treatment indications. For instance, patients with chronic HBV infection either with normal ALT and liver stiffness > 9 kPa, or with elevated ALT but below 5x ULN and liver stiffness > 12 kPa are considered to have severe fibrosis or cirrhosis.

### Alcoholic liver disease (ALD)<sup>7</sup>

The precise indications of liver biopsy are not well established in routine practice. However, it is indicated in patients with aggressive forms of ALD requiring specific therapies (e.g. corticosteroids) and in patients with other cofactors suspected of contributing to liver disease.

Several serum markers to estimate liver fibrosis derived from HCV, seem to be efficient in patients with

ALD but with different cut-offs. Liver stiffness measurement has been proposed for assessing hepatic fibrosis in patients with ALD. However, the existence of inflammation, cholestasis may interfere with the assessment.

### Non alcoholic fatty liver disease (NAFLD)<sup>8</sup>

Liver biopsy is essential for the diagnosis of non alcoholic steatohepatitis (NASH) and is the only procedure that reliably differentiates non alcoholic fatty liver (NAFL) from NASH, despite limitations due to sampling variability. The NAFLD Activity Score (NAS) scoring system is used for the evaluation of disease severity. Non-invasive markers are currently developing and should aim to:

- 1) In primary care settings, identify the risk of NAFLD among individuals with increased metabolic risk.
- 2) In secondary and tertiary care settings, identify those with worse prognosis, e.g. severe NASH.
- 3) Monitor disease progression.
- 4) Predict response to therapeutic interventions. Achieving these objectives could reduce the need for liver biopsy.

### Autoimmune liver diseases

Liver biopsy is considered a prerequisite for the diagnosis of autoimmune hepatitis (AIH).<sup>9</sup> It is also used to guide treatment decisions.<sup>9</sup> A non-invasive diagnostic score to predict inflammatory activity and severity of fibrosis based on routine laboratory parameters in AIH has been recently proposed and may be a useful tool for monitoring disease activity during treatment. Presently, however, it cannot substitute the need for a biopsy, particularly at diagnosis.<sup>9</sup>

The diagnosis of primary biliary cholangitis (PBC) requires the presence of two of three criteria: biochemical cholestasis marked by increased alkaline phosphatase, detection of anti-mitochondria antibodies type 2 and histological lesions consistent with PBC.<sup>10</sup> Liver biopsy is indicated in absence of anti-mitochondria antibodies or when there is the suspicion of an overlap syndrome associating PBC with AIH. Liver stiffness measurement has been recently proposed to avoid liver biopsy in typical and noncomplicated cases.<sup>10</sup>

### HFE-Hemochromatosis<sup>11</sup>

Liver biopsy is not anymore required for the diagnosis in patients with homozygosity for C282Y and increased body iron stores. Liver biopsy has still a role in case of hypoferritinemia confounding cofactors and to assess liver fibrosis. Serum ferritin < 1,000 mg/L and normal AST in

absence of hepatomegaly exhibit a strong negative predictive value for the presence of severe fibrosis. Transient elastography can also be helpful for determination of advanced fibrosis.

## DRUG-INDUCED LIVER INJURIES (DILI)<sup>12</sup>

Liver biopsies may be indicated in DILI-induced chronic hepatitis and cirrhosis to allow both a diagnosis and the assessment of fibrosis. Some examples are: 1) DILI with drugs leading to NASH and phospholipidosis with fibrosis, for instance, amiodarone. 2) Chronic intoxication by vitamin A. Histological examination may show accumulation of vitamin A in hepatocytes. 3) DILI with autoimmune features. Liver biopsy may help to distinguish it from idiopathic autoimmune hepatitis. Elastography has replaced liver biopsy for the follow-up of methotrexate long term treatment.

## MISCELLANEOUS

Liver biopsy remains indicated in rare chronic liver diseases (e.g. Wilson's disease, storage diseases, glycogenosis, amyloidosis) and in cases of chronic abnormalities of liver tests of unknown origin.

In conclusion, liver biopsy is increasingly replaced by non-invasive methods of evaluation of fibrosis but keep a key-role in the diagnosis of several chronic liver diseases.

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### Correspondence and reprint request:

Prof. Dominique LARREY, M.D., Ph.D.  
Service d'Hépatologie-Gastroentérologie et Transplantation and  
IRB-INSERM 1183, Hôpital Saint Eloi  
80 rue Augustin Fliche  
34295 Montpellier Cedex 5  
France  
Tel: 00 33 4 67 33 70 61, Fax: 00 33 4 67 33 02 57  
E-mail: dom-larrey@chu-montpellier.fr