

The evolving role of liver biopsy: what are the gold standards today?

S.P. Dourakis

Liver biopsy can be of great help in the diagnosis of diffuse or localized liver diseases and the assessment of their severity. Liver biopsy can be performed by the blind percutaneous technique (in diffuse diseases), by ultrasonographic or computerized tomographic visualization, by the transjugular route and laparoscopically. Radiographic guidance is certainly needed in localized diseases, such as tumours, and when there is a doubt about the location of the liver.¹

The level of transaminase elevation does not adequately reflect the severity of the liver disease and correlates poorly with histology. Moreover, early stages of cirrhosis are generally detectable only by liver biopsy since they cannot be identified by radiological techniques alone. Biopsy does not establish a firm etiologic diagnosis in most cases. Nevertheless, biopsy directs clinicians to rational, economic and time-saving further steps in investigation. Biopsy is still considered the most accurate means to determine the necro-inflammatory activity (grading) and fibrosis (staging), to predict prognosis, to exclude unsuspected secondary diagnosis and to monitor response to treatment of chronic viral hepatitis. Nevertheless, liver biopsy is not a necessary prerequisite for treatment. Liver biopsy plays an important role in the diagnosis of autoimmune hepatitis, primary biliary cirrhosis, nonalcoholic steatohepatitis (NASH), Wilson's disease and haemochromatosis (with a quantitative hepatic copper and iron level).¹ Neither clinical or laboratory data can ensure or exclude NASH and liver biopsy continues to be considered the gold standard for diag-

nosis. NASH maybe is the cause of cryptogenic cirrhosis. Liver biopsy cannot diagnose drug-induced liver disease with certainty, but it can suspect it, sometimes very strongly. A hidden or forgotten drug intake may be unmasked by liver biopsy findings and motivate clinicians to more vigorous inquiries, including a search for herb therapy. Granulomas are mostly non-specific and ask for intensive clinical investigation. Generally speaking, every patient with a transaminases level increase for more than 6 months should have a liver biopsy. Liver biopsy is usually not needed in the diagnosis and management of acute hepatitis or acute cholestatic jaundice, exceptions being situations where the diagnosis remains unclear despite thorough clinical and laboratory investigation.¹

Limitations of liver biopsy include contraindications, complications, sampling error and underestimation of cirrhosis, inter- and intra-observer variations, and expense. Absolute contraindications for liver biopsy are the uncooperative patient, history of bleeding, coagulopathy, high-grade biliary obstruction and biliary sepsis. Relative contraindications of percutaneous blind liver biopsy are ascites and morbid obesity. Complications are mild, such as moderate pain (20%), severe pain requiring intravenous analgesia or narcotics (3%), and vasovagal response (2%), or severe (haemoperitoneum, bile peritonitis, pneumothorax, punctured viscera) in 0.57%.² Mortality is 1-3/10,000, and morbidity 3/1,000.¹ Atropine and/or conscious sedation may prevent vasovagal reactions and/or anxiety and their use should be considered before or shortly after biopsy in case of such reactions. Nine percent of the patients would never want a biopsy performed again.² The incidence of complication is proportional to clinician expertise, number of biopsies taken (more than three) and presence of relative contraindications. Liver biopsy is expensive directly (equipment, observation period in the hospital, clinician and pathologist fees) and indirectly (time off work and home).

2nd Department of Medicine, Medical School, Athens University, Hippokraton General Hospital, Athens

Author for correspondence:

S.P. Dourakis, 28 Achaia st, 115 23 Athens, Greece.
Tel 210 6918464, 6932272477, FAX 210 6993693,
e-mail: spiros@ath.forthnet.gr

Liver biopsy can be done safely as an outpatient procedure. Needle liver biopsy removes only about 1/50,000 of the liver and so carries substantial sampling error, especially in small biopsy specimens. Cirrhosis (mainly macronodular) can be missed in 10-30% of cases of single blind liver biopsy. Most studies suggest that an adequate biopsy should be at least 15mm (better bigger than 25mm³) in length and contain greater than five (better more than eleven) portal tracts.^{4,5} The type of needle used to perform the biopsy is also important. Cutting needles (Tru-cut) obtain a better representation of liver fibrosis than the widely used Menghini suction needle.⁶ Many studies have shown good inter- and intra-observer reproducibility for the staging of fibrosis (60-90%) but not for the grading of inflammatory scores in standardized grading systems, including Knodell, Ishak, METAVIR or Scheuer scores.⁷ The easy - to - use computer-aided image analysis to calculate the area of liver biopsy composed of fibrous tissue has been tried.⁷ Use of immunohistochemical techniques for detection of proteins of matrix deposition (such as α -smooth muscle actin etc) may add to our ability to assess both the activity of ongoing fibrogenesis as well as potential reversibility.⁷

There is a need for assessment of liver fibrosis by using non-invasive surrogate markers to classify patients as having mild or significant fibrosis. Measurement of serological tests at the index biopsy and then observation over time may help clinicians follow disease and suggest if and when a second biopsy may be necessary. Combinations of markers may have good predictive values for detecting the presence of significant fibrosis.⁸ Non-invasive fibrosis marker panels have greatly improved in recent years, such as AST to platelet ratio index (APRI)⁹ or γ -globulin, γ -GT, total bilirubin, α_2 microglobulin, haptoglobin and apolipoprotein A₁ (FIBROTEST)¹⁰ but their role in practice needs refinement. Their ability to separate stages of fibrosis need to be improved. Moreover, promising results have been obtained from measuring fibrosis-related molecules (such as laminin, metalloproteinases etc) circulating in blood involved in the deposition or removal of extracellular matrix but have not yet become a tool for routine diagnostics.¹¹ Further studies are under way in United States and Europe and the results may help to define the role of fibrosis markers in clinical practice. The use of Proteomics with SELDI-TOF MS (surface-

enhanced laser desorption/ionization time-of-flight mass spectrometry) seems promising for non-invasive assessment of fibrosis.¹²

In conclusion, needle liver biopsy remains the primary tool for the diagnosis of liver diseases and for the staging of liver fibrosis. Clinicians should interpret the histological findings in the broader clinical context. Because liver biopsy is an invasive procedure and not without complications, it should be used selectively only when it will contribute materially to management and therapeutic decisions. Patient preference for therapy without liver biopsy should not prohibit treatment.

REFERENCES

1. Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med* 2001; 344:495-500.
2. Cadranel J-F, Rufat P, Degos F. Practices of liver biopsy in France: Results of a prospective nationwide survey. *Hepatology* 2000; 32:477-481
3. Bedossa P, Dargere B, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003; 38: 1449-1457
4. Colloredo G, Guido M, Sonzogni A, et al. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. *J Hepatol* 2003; 39:239-244
5. Demetris AJ, Ruppert K. Pathologist's perspective on liver needle biopsy size? *J Hepatol* 2003; 39:275-277
6. Regev A, Berho M, Jeffers LJ, et al. Sampling error associated with needle liver biopsy in patients with chronic hepatitis C virus infection. *Hepatology* 1999; 30:67A
7. Scheuer PJ, Standish RA, Dhillon AP. Scoring of chronic hepatitis. *Clin Liver Dis* 2002; 6:335-347.
8. Fontana RJ, Lok ASF. Noninvasive monitoring of patient with chronic hepatitis C. *Hepatology* 2002; 36:S57-64.
9. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; 38:518-526.
10. Imbert-Bismut F, Ratziu V, Pieroni L et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001 357:1069-1075.
11. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. *Am J Gastroenterol* 2004; 99: 1160-1174
12. Hui AY, Poon TCW, Chan HLY, et al. Serum proteomic profiling predicts liver fibrosis in chronic hepatitis B. *Gastroenterology* 2004; 126(suppl 2):A-669.