Percutaneous Blind Biopsy Versus Laparoscopy with Guided Biopsy in Diagnosis of Cirrhosis: A Prospective, Randomized Trial

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A prospective controlled study of the diagnostic accuracy of blind percutaneous liver biopsy in comparison to laparoscopy plus guided biopsy for the recognition or exclusion of cirrhosis has been performed. One hundred twenty-six patients with a clinical diagnosis of chronic, diffuse, well-compensated liver disease were randomized into two groups and submitted either to percutaneous blind liver biopsy (PB: 64 patients) or to laparoscopy with guided biopsy (LB: 62 patients), in order to assess the accuracy of either procedure in diagnosing cirrhosis. PB correctly recognized or ruled out cirrhosis in 52 patients (82%). Inconclusive results were mostly false negative, as demonstrated by the presence on endoscopy of esophageal varices or by subsequent LB. LB demonstrated presence or absence of cirrhosis in all patients. The difference between the rate of accurate results of the two procedures is statistically significant. It is concluded that in patients without esophageal varices, LB should be the investigation of choice for the assessment of liver structure since the presence of cirrhosis can be missed in up to 20% of cases by PB.

The diagnosis of cirrhosis on blind biopsy has a rate of false negative results ranging from 9.3% (1) to 51% (2) or even to 80% (3) if the sample is less than 5 mm in length and there is macronodular cirrhosis. Sampling variability was found to range between about 70% (4) and 20% (5). The assessment of macroscopic features of liver and intraabdominal veins at laparoscopy is said to be more accurate than biopsy in recognizing cirrhosis (2, 6-8) and also to increase the accuracy of histology since the biopsy site is selected under direct vision in the more severely affected areas (9). Furthermore, laparoscopic recognition of cirrhosis was found to require less training and to be more reproducible than histologic diagnosis. However, a comparison of the diagnostic usefulness of laparoscopy and of biopsy is difficult, based on the available data, for several reasons.

Some studies (2, 6, 10) were carried out before the description of "minor" histologic features of cirrhosis, less evident than complete regenerative nodules and perinodular fibrosis (11, 12). It is therefore conceivable that a number of false-negative errors of histology reported in these early studies could have been avoided by adopting the present criteria for the recognition of cirrhosis.

In many studies (1, 8, 10) the respective value of laparoscopy and biopsy was assessed by comparison of macroscopic to histologic findings, while the biopsies had been taken under laparoscopic observation. This comparison does not mirror the clinical alternative between laparoscopy and biopsy. In fact, the standard laparoscopic exploration includes the histologic examination of laparoscopic biopsies which are taken from visually selected areas of the left lobe and therefore cannot be equated to those taken blindly from the right lobe.

All published studies, except one (8), are retrospective (1, 2, 6, 10). Therefore, they are subject to the general biases of retrospective research, such as missing data, unrecognized variation in routine procedures and diagnostic criteria, and so on.

The study reported here was a prospective, controlled, randomized trial that aimed to assess the accuracy of blind percutaneous liver biopsy (PB) as compared to laparoscopy plus guided biopsy (LB) in the recognition or exclusion of cirrhosis.

**MATERIALS AND METHODS**

One hundred thirty-six consecutive inpatients with clinical evidence of chronic, diffuse, well-compensated liver disease (CDLD) were selected for randomization. Selection criteria were: (1) clinical features of compensated chronic liver disease (ie, hepatosplenomegaly, palmar erythema and/or spider nevi; no evidence of ascites, encephalopathy, or previous variceal bleeding), associated with any abnormality of standard "liver tests," or; (2) aspartate aminotransferase values more than four times the upper limit along with twofold increase of γ-globulins for at least six months. Patients were not selected if they had previously undergone liver biopsy or laparoscopy.

All patients underwent upper gastrointestinal endoscopy and were classified as having portal hypertension if esophageal and/or gastric varices were found.

After selection, 10 patients were excluded from randomization because of contraindications to laparoscopy (abdominal surgical scars in seven) or biopsy (severe coagulation abnormalities in one, interposition of colon between liver and chest wall in two). The remaining 126 patients were randomized to PB (64) or LB (62) according to a randomization table. All patients were informed that they had been randomized in a clinical trial to allow the evaluation of a diagnostic procedure. None refused to participate in the study.

**Blind Percutaneous Biopsy**

All percutaneous biopsies were carried out by the same physician (LP) using a Vim-Silverman needle, under mild sedation with 5–10 mg diazepam. The intercostal approach on the mid-axillary line was always used. Tissue specimens were immediately fixed in 4% buffered formal saline, processed as usual for light microscopy, and stained with hematoxylin–eosin and with silver impregnation for reticulin. Slides were examined independently under code and without knowledge of clinical, laparoscopic, or laboratory data by two experienced observers. When there was discordance, biopsies were reviewed jointly in order to agree on a final diagnosis. Three histologic diagnoses were made:

- **Cirrhosis.** Diagnosis was based on presence of at least one regenerative nodule with perinodular fibrosis, or two or more "minor" features of cirrhosis, according to Scheuer (11) and Anthony et al (12). In the absence of overt nodularity minor features of cirrhosis are considered to be fragmentation of the specimen; fibrosis surrounding the greater part of a fragment of tissue, best seen on a reticulin preparation, or septa within the tissue; evidence of regeneration; differential growth; distortion of the reticulin framework, and variations in the appearance of liver cells from area to area; liver cell dysplasia; abnormal small portal tracts, with excessive numbers of efferent veins and abnormal relationships between the two; and unusually scanty lipofuscin in hepatocytes around efferent veins.

- **Indeterminate Architecture.** This was diagnosed when lobular architecture was distorted and/or some intralobular fibrosis was present, but did not reach the definition of minor features of cirrhosis.

- **Normal Lobular Architecture.** This was determined by at least three well-defined normal lobular fields in a specimen at least 10 mm long.

The histologic diagnosis of cirrhosis based upon regenerative nodules and perinodular fibrosis (type 1a) and the recognition of normal architecture (type 3) were accepted as final diagnoses, without further proofs.

According to the original protocol, patients with normal lobular architecture on PB should have undergone LB if there was clinical evidence of portal hypertension. However, this never occurred throughout the study. Patients with indeterminate architecture (type 2) and those with a diagnosis of cirrhosis relying upon minor features (type 1b) were considered cirrhotic if they had esophageal varices. Varices were accepted as conclusive evidence for cirrhosis because in a previous retrospective investigation (10) of 304 inpatients with coinciding laparoscopic and histologic diagnosis of cirrhotic (220 cases) or noncirrhotic (84 cases) CDLD, the predictive value for the diagnosis of cirrhosis of demonstration of esophageal varices at endoscopy was 97.8% (Table 1). In the absence of varices, subjects with type 1b and type 2 biopsies were reinvestigated by LB, or PB was repeated if the sample obtained on the first occasion was less than 10 mm long.

**Laparoscopy**

All examinations were performed by two operators (FR and SO; FR had experience of over 700 laparoscopies at the beginning of the study). A Wolf laparoscope with forward-viewing 180° optics was used. All procedures were carried out under mild anesthesia with propandide (Epontol®, Bayer) in an endoscopy suite.

Macroscopic diagnosis of cirrhosis was made on the following criteria: (1) diffuse nodules on the liver surface, or (2) shallow nodules (ie, nodules usually of large diameter, slightly protruding from the liver surface), if the