Liver biopsy has been the major diagnostic test for liver disease for many years. The first liver aspirate is credited to Paul Ehrlich, in 1883, and the first percutaneous liver biopsy was performed in 1923. Yet, it was not until Menghini reported his 1-second needle biopsy of the liver that the procedure became widely accepted. There are a number of limitations of percutaneous liver biopsy, including sampling error, interobserver and intraobserver variability, and the risk of rare but serious complications.

Liver biopsy has been performed by a number of routes: percutaneous, transvenous, and surgical (both laparoscopy and laparotomy), and now, in this issue of Gastrointestinal Endoscopy, guided by EUS. The procedure, regardless of the way it is performed, is expensive and invasive, and there are some questions in relation to its accuracy for staging liver fibrosis.

The primary indication for liver biopsy has been for the diagnosis of parenchymal diseases of the liver and the diagnosis of liver mass lesions. However, with the availability of accurate blood tests for virology, immunology, and genetic markers, liver biopsy for a diagnosis is now less common. The major use of biopsy today is to stage the degree of fibrosis in patients in whom the etiology of liver disease is already known.

Because the amount of liver tissue removed at percutaneous biopsy only represents approximately 1/50,000 of the total liver volume, the potential for sampling error is obvious. Autopsy and laparoscopy series have estimated that cirrhosis may be missed on a single blind percutaneous liver biopsy in 10% to 30% of cases. A study that examined laparoscopic liver biopsy of both left and right lobes observed that cirrhosis was noted on one side but not the other in 14.5% of cases and a difference of at least 1 stage between lobes was found in 33.1%. Sampling error is influenced by the size and number of biopsy specimens taken. An adequate specimen should be at least 15-mm long and contain at least 5 portal tracts. Most percutaneous biopsy specimens are taken with 16-gauge to 18-gauge needles. An adequate biopsy specimen size is extremely important in the assessment of fibrosis because of chronic viral hepatitis, one of the most common indications for liver biopsy today. Even these recommendations on the size of liver biopsy may underestimate the required amount of liver tissue. One study, which used computer-generated modeling, suggested that a biopsy-specimen length of 25 mm had a 25% error rate. This sheds some doubt on the validity of liver biopsy when one considers that, even in the most experienced hands, only a sixth of liver biopsy specimens are longer than 20 mm.

Because of the cost, morbidity, and inherent sampling limitations of liver biopsy, there has been a major interest in discovering new, noninvasive ways to stage liver fibrosis. To this aim, there has been an explosion in the number of tests to assess the stage of liver fibrosis, including direct and indirect biomarkers, transient US elastography, and magnetic resonance (MR) elastography. These tests have been shown to be useful in differentiating advanced fibrosis and cirrhosis from earlier stages of fibrosis but less useful in distinguishing between the early stages. Many different biomarkers and panels of biomarkers have been evaluated for the assessment of hepatic fibrosis. No single serum biomarker has been shown to act as a true surrogate marker of fibrosis as yet. A review of 14 studies of fibrosis markers in patients with chronic hepatitis C demonstrated that selection of arbitrary cutoff levels can rule in or rule out fibrosis in 35% of patients. These panels of biomarkers were not shown to reliably differentiate between stages of fibrosis. Transient US elastography (Fibroscan; Echosens, Paris, France) is a novel technique that relies on an increase in liver stiffness, which is seen in advancing stages of hepatic fibrosis. It is a very useful test in distinguishing advanced fibrosis (METAVIR F3–F4) from earlier stages (F0–F2). The sensitivity for diagnosing cirrhosis is 87% and specificity is 91%. In addition, excellent accuracy has been demonstrated in the diagnosis of earlier stages of fibrosis but, again, not in distinguishing between the actual stages.

Although EUS-guided liver biopsy represents an interesting method of obtaining liver tissue, we do not believe that it will replace percutaneous liver biopsy, even with refinements in technique.
Fibroscan has the advantages of being noninvasive, inexpensive, easily performed, reproducible, and acceptable to the patient. In addition, sampling error may be reduced compared with liver biopsy, irrespective of route, because the volume of liver assessed is approximately 100 times that of liver biopsy. MR elastography is a modification of MR imaging sequences by using a dedicated probe that can simply be added to the standard protocols used for assessment of liver or biliary lesions and appears to be accurate in distinguishing early from advanced fibrosis.17

In this issue of Gastrointestinal Endoscopy, DeWitt et al3 describe EUS-guided Tru-cut biopsy (EUS-TCB) in 21 patients with benign liver disease. This procedure has been used for biopsy of various intra-abdominal organs and EUS-guided FNA has been used to sample hepatic malignancies. To our knowledge, this is the first reported use of EUS-guided TCB in benign hepatic disease. Although this represents an interesting method of obtaining a liver biopsy, we do not think that it will replace percutaneous liver biopsy, even with refinements in technique. The biopsy needle used was 19 gauge, compared with 16 gauge to 18 gauge for most percutaneous biopsies. In addition, the samples obtained were shorter than most at percutaneous biopsy. Multiple passes were needed to obtain an adequate total length of liver tissue (median 3 passes), and, yet, an overall sample length of 15 mm was only obtained in 4 of 21 patients, with a median total sample length of 9 mm in the 21 patients. It is known that performing multiple passes increases the risk of complications with percutaneous liver biopsy,18,19 and this probably be the case with EUS-TCB. Of the biopsy specimens, 29% were less than 3 mm in length, a size that would be unlikely to yield any useful information. The samples also only had a median of 2 complete portal tracts, because of both the short samples and the narrow diameter of the needle. Only 6 of 21 or 29% of samples had 6 or more portal tracts.

The investigators report that a histologic diagnosis was obtained in 90% of the biopsy specimens but was sufficient to provide clinical diagnostic information in 71%. Although a histologic diagnosis may have been made in 90%, doubt would have to be raised regarding confidence in the diagnosis in view of the small samples. It is particularly important to highlight that, in the 4 patients in whom the biopsy was performed for suspected cirrhosis, none of the samples were deemed sufficient to exclude cirrhosis. This finding must be critically examined in light of the 70% to 90% accuracy of percutaneous liver biopsy and sensitivity of more than 80% when using Fibroscan in the diagnosis of cirrhosis. The diagnosis of cirrhosis is extremely important in view of the risks of developing portal hypertension and hepatocellular carcinoma. The advantages of screening for these complications of cirrhosis are now well established to institute prophylactic treatment against variceal bleeding and early treatment of hepatocellular carcinoma.20-22

Furthermore, the technique could not be considered an alternative to transjugular liver biopsy, because patients undergoing transjugular biopsy generally have thrombocytopenia, coagulopathy, or ascites. The specimens yielded by the technique would be considered inadequate by most experienced pathologists and do not meet any of the generally accepted criteria for adequacy of biopsy. In addition, only the left and caudate lobes can be sampled with this technique. There were no significant complications with EUS-TCB, but this may be partly explained by patient selection. The patients were all outpatients, without evidence of portal hypertension on imaging. The platelet count was >150,000/mcL (normal 150,000-450,000/mcL) and international normalized ratio ≤1.2 (0.9-1.1), and none of the patients had previous liver surgery. This group of patients represents a group at an extremely low risk of complications. It is difficult to imagine that the complication rate from this procedure would be any different than percutaneous biopsy overall, with the possible exception of pneumothorax.

Although the current methods of performing liver biopsy are expensive, performing the procedure by EUS will only increase the costs associated with the procedure. Even if the procedure were restricted to patients who need a liver biopsy and who are undergoing EUS for another reason, we believe that the inadequacy of the specimens would lead to repeating the liver biopsy by another route at a later date, which puts the patient at a higher risk of complications. Although this procedure may be an alternative to natural orifice transluminal endoscopic surgery (NOTES) biopsy, as the investigators suggest, it is not our opinion that NOTES biopsy is an acceptable alternative to percutaneous liver biopsy. There have been enormous advances in hepatology in recent years. Percutaneous liver biopsy remains an excellent method of obtaining liver tissue, albeit with the limitations outlined above. Transjugular liver biopsy is an acceptable alternative in patients with a contraindication to percutaneous biopsy. Although EUS-TCB appears very interesting, we believe that the noninvasive assessment of liver fibrosis is a more important goal than new ways of obtaining liver tissue for histologic assessment.

DISCLOSURE

The following author disclosed financial relationships relevant to this publication: N. H. Afdhal: EchoSens, consultant, grant support from EchoSens and consultant, research support from Quest Diagnostics. The other author disclosed no financial relationships relevant to this publication

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