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Archives of Gastroenterology Research Commentary

# Endoscopic Ultrasound-Guided Liver Biopsy, Is It Ready for Prime Time?

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We would like to further analyze several different issues that were addressed in the manuscript "The efficacy and safety of endoscopic ultrasound-guided liver biopsy versus percutaneous liver biopsy in patients with chronic liver disease: a retrospective single-center study." [1]. This study compared outcomes between liver biopsies performed through endoscopic ultrasound (EUS) and percutaneous routes at the University of Missouri School of Medicine from January 2018 through August 2019. The purpose of this commentary is to take an in-depth look at the following: value of liver biopsy, techniques of liver biopsy, utility of EUS guided liver biopsy, and future hold of EUS-guided liver biopsy.

The global burden of chronic liver disease is substantial. Approximately 1.5 billion had chronic liver disease in the year 2017; nonalcoholic fatty liver disease representing nearly 60%, followed by viral hepatitis alcoholic liver disease (40%) [2]. A recent study reported an estimated age-standardized incidence rate of chronic liver disease and cirrhosis of 20.7 per 100,000 in 2015, which is an alarming 13% increase from the year 2000 [3]. In addition, the estimated worldwide annual deaths from cirrhosis and liver cancer, the main complications of chronic liver disease, are 1.2 million deaths/year and 790,000 deaths/year, respectively [4].

Liver biopsy continues to be the gold-standard with regards to diagnosis and staging of the majority of liver diseases [5,6]. Serologic markers certainly have helped in diagnosing various autoimmune and viral-related liver diseases. Furthermore, laboratory testing and imaging studies such as liver elastography have allowed us to non-invasively assess fibrosis. Unfortunately, there are shortcomings with these forms of testing. False positives or laboratory errors will lead to misleading diagnoses. Situations can also arise during which there are diagnostic dilemmas, such as an obese patient with positive autoimmune serology and elevated liver chemistries [5]. Finally, Transient Liver Elastography (Fibroscan), a non-invasive assessment of liver disease can be limited in many patients such as those with severe obesity and ascites. Moreover, Fibroscan is not approved for assessment of liver disease in some conditions such as hemochromatosis and Wilson's disease. In this era of advanced technologies, though the number of methods for diagnosing liver disease has increased, liver biopsy remains the best means for clinicians to understand the underlying pathology, grade, and stage liver disease. Indeed, several recently published experts and leading societies' statements recommended using liver biopsy as one of the most powerful and validated tool for assessment and prognostication of liver disease [7-13].

Liver biopsy provides the clearest picture by its nature of taking actual tissue samples of the liver and allowing review under the microscope. Features such as cholestasis, portal, lobular inflammation, necrosis, and fibrosis, along with specific cell types including plasma cells, neutrophils, lymphocytes, and neoplastic cells greatly aid in diagnosis. Staining can also be helpful in both infectious and certain autoimmune-related liver diseases. Microscopic evaluation of the liver tissue is particularly useful when the serologic work-up for elevated liver tests is unrevealing. Situations for which random liver biopsy is diagnostically necessary for patients with abnormal liver chemistries include serologic marker-negative autoimmune liver diseases, alcohol-related liver disease in the dishonest or confused

patient, nonalcoholic steatohepatitis in the patient with BMI>35 kg/m$^2$, degree of inflammation in chronic viral hepatitis, drug-induced liver injury, iron quantification for hemochromatosis, copper quantification in Wilson's disease, and post-liver transplant rejection. Of course, random liver biopsy also provides information on stage of fibrosis, which provides prognostic information for patient and treating provider. Liver biopsies allow pathologists to assess the degree of cellular activity, such as in fulminant liver disease, which may prompt expedited interventions, including discontinuation of certain treatments, initiation of certain medications such as corticosteroids, and even liver transplantation evaluation.

Targeted liver biopsy plays a crucial role in diagnosing liver lesions, particularly if imaging studies are indeterminate. A targeted liver biopsy of a liver mass or a metastatic lesion of other primary source can lead to initiation of appropriate treatment. Although not commonly performed, biopsy-proven hepatocellular carcinoma remains the optimal method for diagnosing indeterminate liver lesion seen on cross-sectional abdominal imaging. For other benign liver lesions including vascular and non-vascular masses, liver biopsy can also provide guidance on future imaging and surveillance. Thus, both random and targeted liver biopsies are often essential in the diagnosis, prognosis, and treatment of many liver diseases.

The most utilized technique for histopathological assessment of the liver continues to be percutaneous transthoracic liver biopsy. The first liver biopsy ever reported was done via percutaneous route by Dr. Paul Ehrlich in 1883 [14]. Historically, percutaneous biopsy required percussion of the liver: caudal tapping over the right hemithorax between anterior and midaxillary lines until peak dullness was heard [15]. More recently, imaging modalities have helped guide percutaneous liver biopsy. Ultrasound-guided/marking liver biopsy is the preferred imaging for biopsy [16,17]. It is a relatively inexpensive mode of providing real-time imaging without exposing patients to radiation. The ultrasound transducer is generally directed with a cranial trajectory. The transducer may be utilized continuously throughout the procedure or to mark the site of needle insertion. Usually the performing clinician will attempt to position the needle within the lowest intercostal space and above the rib to prevent injury to the intercostal neurovascular bundle. Computed tomography (CT) also may be employed for percutaneous liver biopsy. While this imaging modality does not allow for real-time imaging and subjects patients to radiation, it can be more helpful in obese patients or for better visualization of lesions during targeted biopsy. The two major techniques utilized for percutaneous biopsy are coaxial and single needle [15]. Coaxial technique requires two needles—one often placed near a targeted liver lesion utilized to guide the second which is placed through the first needle to obtain samples. Single needle involves a core biopsy needle to be placed into the liver, where one or more biopsies are then taken. Quite often local anesthetic medication is utilized, but intravenous conscious sedation and even general anesthesia can be given if necessary and clinically safe during the procedure.

Transjugular liver biopsy is another technique to obtain tissue [18,19]. First performed in 1967, transjugular biopsy has been often chosen due to contraindications to percutaneous biopsy, such as obesity, ascites, and coagulopathy. Clinicians now are selecting the transjugular route as it allows for evaluation of portal hypertension through obtaining hepatic wedge pressure measurements during the procedure. Ultrasound is needed to access the right internal jugular vein. A vascular sheath is then advanced into the inferior vena cava, at which point pressure in right atrium can be measured. A catheter is then advanced into the hepatic vein and is then exchanged for an occlusion balloon, which will subsequently be placed in the mid-portion of the hepatic vein to allow for hepatic wedge pressure and free hepatic vein measurements. The hepatic wedge pressure is thought to estimate the portal pressure, which then allows for portal-systemic gradient to be calculated after subtracting the free hepatic pressure from the wedge hepatic pressure. Following pressure measurements, the occlusion balloon is removed, and a guiding cannula is advanced into the hepatic vein. Multiple biopsies are then generally taken using a needle system. Previously transjugular liver biopsies have often been insufficient due to small size and fragmentation of the sample. However, improvement in equipment and handling of the specimens has led to better samples. Local anesthetic agents are invariably used, however usually at least conscious sedation is also administered to patients.

Laparoscopic biopsy is no longer obtained as frequently unless the patient undergoes a procedure for another indication. Usually the biopsy takes place in the operating room under general anesthesia [5]. Laparoscopic biopsy has the benefit of allowing gross inspection of the liver by the surgeon prior to obtaining the biopsy. It also allows for patient to not have to undergo a separate procedure to obtain the biopsy. Depending on the performing surgeon and instrument used, samples can be adequate or inadequate for evaluation.

EUS-guided liver biopsy is one of the most recent approaches of obtaining liver tissue [20]. The first reported EUS-guided biopsy was performed in 1991 on the upper gastrointestinal tract by Dr. Peter Vilmann [21,22]. Vilmann et al. performed the first multicenter prospective study on EUS-guided fine needle aspiration (FNA) on 457 patients, including 192 lymph nodes, 145

extraluminal masses, 115 gastrointestinal wall lesions, and 22 cystic lesions [23]. EUS-FNA has become the gold standard in diagnosing several intra-abdominal lesions accessible by the echoendoscope, especially pancreatic lesions. More recently, fine needle biopsy (FNB) needles have been developed to collect core tissue from solid organs or lesions. Endoscopists have employed FNB needles in situations during which FNA did not provide adequate tissue sampling despite several passes and have found FNB to be more cost-effective than FNA [6]. Core needle biopsies have been utilized during random liver biopsies, most frequently 19-gauge needle. More recently, the 22-gauge FNB needles have been studied for EUS. Core needles generally preserve the tissue architecture compared to fine aspiration needles [20,24,25]. Similar to EUS studies performed on other organs, many studies evaluating different needles on random liver biopsies have found superior results with FNB compared to FNA [15,17,26-28]. Overall, EUS-guided liver biopsies have demonstrated FNB needles produce longer specimens with longer pieces of core tissue and more portal tracts, than those of FNA.

During EUS-guided liver biopsy, the left, right or both hepatic lobes are usually identified and sampled using the procedure. For left lobe liver biopsy, the echoendoscope is positioned in the proximal stomach. The right hepatic lobe is usually identified and sampled while the echoendoscope is positioned at the duodenal bulb or second portion of duodenum. Prior to advancing the needle, Doppler ultrasound is used to ensure no vascular structures are inadvertently punctured. Utilizing a transgastric or transduodenal approach should avoid this complication as well [29,30]. Acquisition of tissue is dependent on the type of needle used. EUS utilizes negative pressure with suction, usually through dry or wet suction technique [20]. Heparin solution can be used to prime the needle and prevent clotting in the needle. These techniques have led to variable results in fragmenting samples, though the wet suction technique appears to have had the most success at producing viable tissue. Mild/limited suction has generally been applied to FNB. FNB often requires what is known as a fanning technique, during which passes are made back-and-forth between different areas of the liver [31]. In our study, all EUS-LB were performed using a 19- or 22-gauge Fork-tip SharkCore biopsy needle (Medtronic, Massachusetts, United States) [1]. The 19-gauge needle was most commonly used because it has shown superiority over 22-gauge needle [6,10]. The needle is prepped using 'wet suction' technique where needle stylet is removed and flushed with heparin prior to attaching a vacuum syringe and maximal suction was applied via a syringe. There are several types of FNB needles that have been studied and compared, including the rigid Tru-cut (Merit Medical) and more flexible EchoTip (Cook Medical), ProCore (Cook Medical), SharkCore (Medtronic), Acquire needle (Boston Scientific), and EZ shot 3 plus needle (Olympus).

There are certainly advantages to EUS-guided liver biopsy versus the other methods of obtaining hepatic tissue. EUS allows for a detailed view of a patient's anatomy in real-time. This allows for proper sampling of multiple lobes and avoidance of other structures, including the adjacent vasculature [32]. Hence, this should lead to fewer adverse outcomes for patients. Furthermore, as noted in our study, EUS is more often performed under general anesthesia, compared to percutaneous and transjugular liver biopsies [1]. This thus leads to more patient comfort. Our study revealed statistically significant less pain scores with EUS-guided approach in comparison to percutaneous approach [1]. EUS has also been found to take about half the length of procedure time of transjugular liver biopsies, on average of 20 minutes versus 40 minutes [33].

Beyond liver biopsies, endoscopic ultrasound can evaluate the surface contour of liver, detect early esophageal or perigastric varices and signs of early portal hypertension. Moreover, EUS-FNA can obtain free abdominal fluid for assessment [34].

Endoscopic ultrasound-guided liver biopsy continues to evolve. A 2015 multicenter study found a 98% yield of diagnostic liver biopsies with EUS—all using the 19-gauge FNA needle [35]. With improved needles aimed at providing better core samples, the diagnostic yield is only expected to be more successful in time. A recent study in Korea found improvement in diagnostic accuracy and sensitivity with FNB compared to FNA in hepatic solid masses [30]. Perhaps the largest advance being made in this field is the use of endoscopic ultrasound in portal pressure measurement and other portal vein interventions, which can take place concurrently during EUS-guided liver biopsy. EUS can allow access to the portal vein to directly measure the pressure and thus calculate a more accurate portal-systemic gradient in cases of presinusoidal portal hypertension, including portal vein thrombosis and schistosomiasis [36]. By comparison, transjugular liver biopsies are not able to measure the portal vein directly. Multiple groups have performed pressure measurements endoscopically in both human and animal studies through use of a digital pressure transducer. These groups have found success with the transgastric approach at accurately measuring portal pressures, based on similar values obtained to those of transjugular liver biopsies. Furthermore, endoscopic access to the portal vein may also allow for EUS-guided Transhepatic Intrahepatic Portosystemic Shunt (TIPS). The procedure was performed in five pigs in a 2017 study, utilizing a lumen-apposing metal stent, however further refinement will be needed prior to performing human studies [26].

Finally, with access to the portal vein, EUS can lead to sampling of the venous blood to potentially detect tumor cells. A 2015 study found that portal vein blood samples via EUS contained a higher number of circulating tumor cells compared to peripheral blood in pancreatic cancer patients [37].

In our study, we found that the safety of EUS-guided liver biopsy is comparable to the safety of percutaneous liver biopsy. Furthermore, EUS-guided liver biopsy was associated with shorter hospital stay, less frequency of reported pain, and, as a result, less use of opiates [1]. Indeed, EUS-guided liver biopsy suffers from some limitations. The procedure needs to be better defined with the number of needle passes and actuations within a liver lobe. In our experience, we found 2-3 passes are sufficient to produce a pathologically interpreted sample. However, EUS may not be widely accessible in all hospitals and settings. The procedure needs expertise in the field of endoscopic ultrasound. Moreover, the machine is expensive as are the devices utilized for the procedure. Patients undergoing EUS-guided liver biopsy often require conscious sedation or anesthesia, furthering the cost of the procedure in comparison to percutaneous liver biopsy. Nevertheless, percutaneous liver biopsy usually requires patients to be admitted for several hours and may be associated with added procedural costs and need for nursing and frequent vital signs monitoring. There are currently no cost-effectiveness analysis comparing the two approaches.

This is certainly a time of advancement for endoscopic ultrasound procedures, particularly for liver conditions. Though the major organizations including American Association for the Society of Liver Diseases (AASLD) still recognize percutaneous liver biopsy as the gold standard for obtaining random tissue, EUS-guided liver biopsy is safe and demonstrating improved sampling and comparable results to percutaneous liver biopsy. We believe that endoscopic ultrasound will continue to play more of a role in random liver biopsies and may one day be the standard of care.

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