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ORIGINAL RESEARCH—CLINICAL

Endoscopic Ultrasound-Guided Liver Biopsy in Clinical Practice

Avik Sarkar,[1] Peter Dellatore,[1] Abhishek Bhurwal,[1] Amy Tyberg,[1] Haroon Shahid,[1] Carlos D. Minacapelli,[1,2] Michel Kahaleh,[1] Vinod K. Rustgi,[1,2] and Jose Nieto[3]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey; [2]Center for Liver Diseases and Masses, Rutgers Robert Wood Johnson School of Medicine, New Brunswick, New Jersey; and [3]Baptist Medical Center, Jacksonville Florida

BACKGROUND AND AIMS: Liver biopsies are traditionally performed using percutaneous, transjugular, or surgical approaches. Endoscopic ultrasound (EUS)-guided liver biopsy is a new modality to sample liver parenchyma. This technique allows sampling of both liver lobes and obviates the need for sampling error. However, there is paucity of literature demonstrating that EUS-guided liver biopsy provides adequate tissue sample for histologic analysis. This study aimed to review the experience of 2 large tertiary care centers to demonstrate the efficacy and safety of EUS-guided liver biopsy. **METHODS:** All patients undergoing EUS-guided liver biopsy between March 2018 and October 2019 between 2 tertiary care centers were included in this retrospective study. The main outcomes of the study included technical success of EUS-guided liver biopsy, details of the specimen (length of the specimen, number of complete portal tracts), and adverse events of EUS-guided liver biopsy. **RESULTS:** A total of 229 patients underwent EUS-guided liver biopsy at the 2 tertiary care centers. There was 100% technical success. Of the 229 patients, 226 patients (98.7%) had adequate tissue for histopathological evaluation with a mean total length of 3.20 cm and complete portal tracts of 20.2. Overall, 2.6% of patients had adverse events. **CONCLUSION:** Our study illustrates that EUS-guided liver biopsy provides adequate specimen for histologic analysis and is a safe, viable alternative to other methods of liver biopsy.

Keywords: Endoscopic ultrasound-guided liver biopsy; EUS; Liver biopsy

Introduction

The clinical indications for liver biopsy are evolving in the setting of newer noninvasive diagnostic tests for various liver pathologies. Liver biopsy continues to be essential, as there are several clinical scenarios in which these noninvasive tests are inconclusive, or may even be contradictory, and histopathology is required.[1,2] Liver biopsies are traditionally performed using percutaneous (PC), transjugular (TJ), or surgical approaches. These modalities can be invasive and may result infrequently in adverse events, such as severe pain, hemorrhage, pneumothorax, and unintended sampling of nonhepatic tissue.[3,4]

More recently, endoscopic ultrasound (EUS)-guided liver biopsy has emerged as an alternative.[2,3,5] EUS-guided liver biopsy (ELB) is a new approach to sample liver parenchyma that has shown promise given its safety profile, increased patient comfort, and ability to obtain large amounts of tissue. Tissue is often obtained from both the right and left lobes, obviating sampling error issues. It also has the added benefit of providing endoscopic evaluation, as these patients may simultaneously require screening for esophageal varices or evaluation of upper gastrointestinal pathology.

For histologic evaluation, an adequate sample must be obtained. This has been proposed by the AASLD to be greater than 11 portal tracts with specimen length of 2–3 cm after formalin fixation and obtained with a 16-gauge needle.[4] This has been controversial, with varying definitions of adequacy throughout the literature.[4,6–10] Concerns have been raised of adequacy of ELB obtained with a 19-gauge needle; however, studies thus far have been favorable.[3,7,11] It has even been shown to provide comparable or superior samples to PC and TJ approaches.[3]

We reviewed our large, 2-center experience with ELB with the purpose of demonstrating safety, specimen adequacy, diagnostic yield, and utility for clinical practice.

Methods

Patients

A total of 229 patients underwent ELB at 2 centers, and the procedures were conducted between March 2018 and October 2019. Subjects in this study were not in any prior studies and were studied retrospectively. Inclusion criteria included age 16 years or older, patients who required a liver biopsy in addition

Abbreviations used in this paper: **CPT, complete portal tract; ELB, endoscopic ultrasound-guided liver biopsy; EUS, endoscopic ultrasound; INR, International Normalized Ratio; PC, percutaneous; TJ, transjugular; TSL, total specimen length.**

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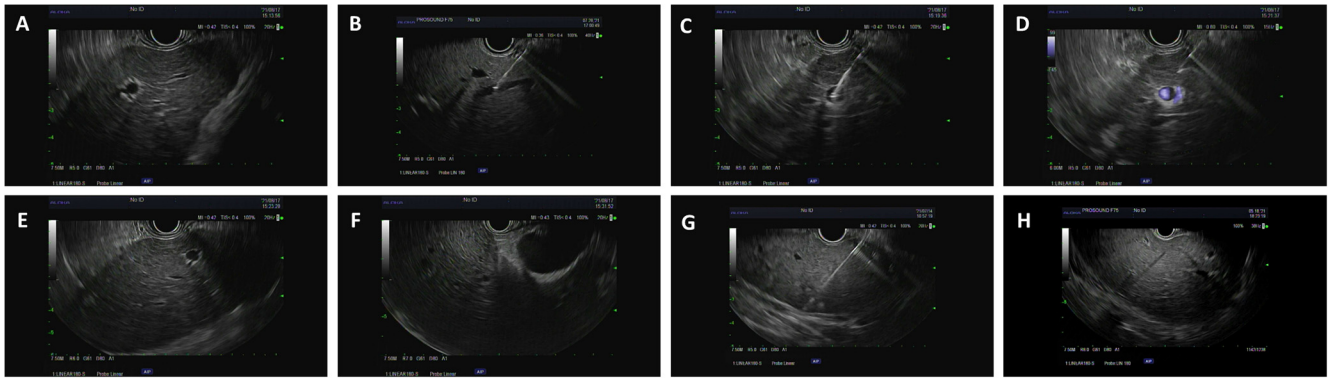

Figure 1. Real-time endoscopic ultrasound-guided liver biopsy. (A) Left lobe of the liver as viewed from GEJ, (B) EUS-guided needle advanced into the left hepatic vein, (C) EUS-guided needle advanced into the umbilical portion of the left portal vein, (D) Doppler evaluation of the umbilical portion of the left portal vein, (E) Left lobe of the liver as viewed from the cardia, (F) Right love of the liver as viewed from the duodenal bulb, (G) EUS-guided liver biopsy of the left lobe, (H) EUS image of track in the left lobe of the liver after liver biopsy with 19-gauge needle.

to esophagogastroduodenoscopy and/or EUS, and the possible need for bilobar liver biopsy.

ELB was selected as the method of liver tissue acquisition for patients who required variceal screening or surveillance and liver biopsy, patients who required an upper gastrointestinal evaluation and a liver biopsy, and patients with abnormal liver enzymes who had negative serologic and radiologic workup and required an EUS examination. In addition, indications included those who required an EUS to exclude biliary tract disease and, if negative, underwent liver biopsy or referral by a hepatologist for liver biopsy (ie, to evaluate the degree of liver fibrosis).

Exclusion criteria were the presence of malignant liver disease, decompensated liver disease, thrombocytopenia (platelets $<$50,000), coagulopathy (International Normalized Ratio [INR] $>$ 2.0), use of antiplatelet agents within 5 days of the procedure, inability to provide informed consent for the procedure, pancreaticobiliary EUS findings explaining abnormal liver function tests, presence of liver lesions, or pregnant status.

Data collection included patient demographics, presence of alcohol use, presumed etiologies of liver disease, total specimen length (TSL), complete portal tracts (CPTs), pathology report, adverse events, and pertinent laboratories. Complications were documented both by physician and nursing staff immediately after the procedure. In addition, hospital and outpatient charts were reviewed to identify complications in the weeks following the procedure. This retrospective study was approved by the institutional review boards of both participating centers.

Procedure

ELB is performed using a linear array echoendoscope with color Doppler imaging to confirm the absence of vascular structures in the path of the biopsy needle (Figure 1). The biopsy needle is then passed to an adequate depth, and tissue is obtained.[5] It offers the advantages of real-time imaging, EUS examination of the liver, and the ability to biopsy both the left and right lobes (Figure 1).[6]

EUS examinations were performed with a linear Olympus echoendoscope (GF-UE160-AL5; Olympus America, Center Valley, PA). Patients were placed in the left lateral decubitus position and were sedated with propofol administered by an anesthesiologist. A complete EUS examination was performed, including evaluation for ascites, varices, and masses. Biopsies were obtained using a 19-gauge EUS-fine-needle biopsy needle (19G Acquire; Boston Scientific, Marlborough, MA). Color Doppler imaging was used to identify vascular structures or bile ducts in the expected trajectory of the needle. The technique at Robert Wood Johnson hospital used a needle primed with heparin solution. Half suction was applied via a syringe filled with 2 mL of normal saline after 4–7 cm of the needle had entered the liver under direct EUS guidance. One to 3 passes were taken from the desired lobe with 2 to 4 rapid actuations with each pass after which the suction was turned off and the needle withdrawn from the liver. The left lobe was accessed by a transgastric route, and the right lobe was accessed by a transduodenal route. After completion of the procedure, the patient was observed in the recovery unit for 1 hour and either returned to the hospital for ongoing care or discharged to home. The technique used at Baptist Medical Center was similar, except that one 7-cm actuation approach was used to sample each lobe for a total of 1 actuation per lobe, as previously described.[12]

Specimen Handling

Once the needle was removed from the echoendoscope, the specimen was expelled using 500 USP units per 5 mL of Heparin Lock Flush Solution. As the specimen was being expelled, the needle was held over a pathology filter and 5 layers of 4 $\times$ 4 gauze to separate blood clots from the tissue specimen. A large amount of white core tissue was left in the filter and transferred into a formalin bottle. In patients undergoing bilobar biopsy, right and left lobe samples were placed in 2 separate bottles (Figure 2).

The tissue blocks were examined by a gastrointestinal pathologist after being stained with hematoxylin and eosin. The specimens were assessed for the largest intact core length, the TSL, and the number of CPTs.

Study Definitions

Complications within the study were defined as any deviation from the postprocedure clinical course. This was assessed

Figure 2. Gross specimen of an endoscopic ultrasound-guided liver biopsy with 19-gauge needle. (A) A tissue filter is used to collect liver tissue, separate blood clots, and assess biopsy quantity. (B) After collection and assessment, tissue specimen is transferred into a formalin bottle.

by the physician and nursing staff after the procedure. Long-term complications were assessed through chart review. Bleeding complications were defined as symptomatic blood loss requiring investigation, transfusion, or admission. Diagnostic yield was defined as adequate tissue for histologic diagnosis by the pathologist. Technical success was defined as successful tissue acquisition using the steps described for ELB. Technical failure was defined as inability to acquire tissue based on the previously mentioned ELB technique.

Statistical Analysis

All statistics were calculated using STATA version 16.0 (StataCorp, College Station, TX). All demographic and procedure-related variables were either continuous or categorical variables. The mean and standard deviation were calculated for continuous variables. Categorical variables were reported in percentage. All continuous variables were compared between the cohorts using Student *t* test, whereas categorical variables were evaluated using chi-square test. All *P* values were 2-sided, with .05 as the threshold for statistical significance.

Results

Between March 2018 and October 2019, 229 patients underwent ELB at our 2 centers. There were 99 patients from Robert Wood Johnson and 130 from Baptist Medical Center. The mean age was 54.41 years, with a female predominance. The mean body mass index was 31.16 kg/m^2, with 69.9% (n = 160) of patients endorsing the use of alcohol (Table 1). The most common indication for biopsy was abnormal liver enzymes of unknown etiology with negative serological and imaging evaluation. A large number of these patients required histologic evaluation to assess the degree of fibrosis. The most common etiology of liver pathology was nonalcoholic steatohepatitis found in 59.8% (n = 137) of patients.

There was 100% technical success. Of the 229 patients, 226 patients (98.7%) had adequate tissue for histopathological evaluation with a mean total length of 3.20 cm and CPT of 20.2. Biopsies of both the left and right lobes were performed in 188 patients or 82%. In these cases, the mean total length was 3.43 cm compared with 2.61 cm with single-lobe biopsy ($P < .02$). In addition, the mean CPT was higher with 21.0 compared with 13.7 with single-lobe biopsy ($P < .0001$; Table 2). Of the 229 patients, only one sample was affected by fragmentation that limited histologic evaluation. As for serological results, the mean total bilirubin was 2.6 mg/dL, aspartate transaminase 96.6 IU/L, alanine transaminase 118.9 IU/L, and INR 1.07 for patients undergoing liver biopsy in our study.

Six patients (2.6%) suffered adverse events (Table 3). Patients were called the day after the procedure and

Table 1. Demographics

Characteristics	Total number (n = 229)
Females	59.4% (n = 136)
Mean age	54.41 y (SD 15.37)
BMI	31.16 (SD 7.68)
Alcohol	69.86% (n = 160)

BMI, body mass index.

Table 2. Pathological and Laboratory Characteristics

Mean portal areas	20.16 (SD 9.34)
Mean length of the portal tract	3.20 (SD 2.85)
Mean total bilirubin	2.60 (SD 6.2)
Mean aspartate transaminase	96.61 (SD 162.09)
Mean alanine transaminase	118.92 (SD 224.11)
Mean International Normalized Ratio	1.07 (SD 0.21)

Table 3. Rate of Complications

Complication	Patients affected (n = 229)
Abdominal pain	1.75% (n = 4)
Death	0.44% (n = 1)
Subscapular hematoma	0.44% (n = 1)
Overall	2.6% (n = 6)

evaluated as an outpatient 1 month later for evaluation of adverse outcomes. Four of the patients had postprocedural abdominal pain that resolved without intervention. One patient had a subcapsular hematoma that responded to blood transfusion. One critically ill patient had abdominal bleeding during biopsy that resulted in death. There were no complications related to the liver biopsy technique otherwise.

Discussion

There have been significant developments in imaging modalities and serological tests that aid in the diagnosis of underlying liver pathology. However, the clinical utility of liver biopsy has not been replaced, as it still proves to be an essential diagnostic tool. This is particularly true in staging disease and to clarify pathologies with mixed presentations or overlap syndromes.[4] Histologic evaluation is sometimes necessary for prognostication and staging of liver disease to assist physicians in making therapeutic management decisions.[4]

The first description of ELB to obtain adequate tissue for histologic evaluation was by Dewitt et al[6] in 2009. Before this study, one use of EUS was for fine-needle aspiration of malignant lesions in the liver to obtain cytology.[13] Dewitt et al expanded on this to obtain core biopsies in 21 patients with suspected benign liver disease.[6] Histologic diagnosis was made in 90% of patients with no adverse events.[6] The samples were collected using a 19-gauge Tru-Cut needle, which failed to reach widespread use because of its inflexible design.[6,14] Disappointing tissue yields led to abandonment of this approach.[15] In 2012, a 19-gauge EUS–fine-needle aspiration was developed for ELB with good tissue yields and eventually led to the adaptation of the 19-gauge fine-needle biopsy needle with success.[7,9,11,16]

ELB has demonstrated several advantages. This includes not being limited by body habitus, providing real-time imaging to biopsy the desired target while avoiding vasculature and other nonhepatic tissue, and greater accessibility to liver parenchyma, as the entire left lobe and most of the right lobe can be reached from the stomach and duodenal bulb. Sampling error is minimized by obtaining separate biopsy specimens from the right and left lobes of the liver.[12] The ability to sample spatially distinct areas for biopsy may be useful for more accurate assessment of liver disease.[15,17] ELB also offers significant patient advantages. For patients, it is less painful than the PC approach while simultaneously providing endoscopic evaluation of the upper gastrointestinal tract. This enables concurrent esophageal variceal surveillance, often a required assessment in patients with underlying liver pathology.[10] This allows procedural efficiency.

PC and TJ are still the most common methods of liver biopsy, and although there have been no prospective trials, a retrospective comparison was previously performed against ELB. The study revealed in patients with bilobar ELB, the median TSL was 40 mm, and the median CPT was 17. In comparison, the median TSL was 25 mm and the median CPT was 10 for PC, and the median TSL was 34 mm and the median CPT was 15.5 for the TJ approach. In patients who received a biopsy of 1 lobe endoscopically, there was no significant difference when compared with PC and TJ.[3] This demonstrates that EUS is more than comparable to other liver biopsy modalities while offering the aforementioned advantages.

In our study, 226 patients had adequate tissue provided for a diagnosis making the diagnostic yield 98.7%. The mean CPT was 20.2, with a mean TSL of 3.20 cm. This demonstrates the ability of ELB and confirms its capability of providing adequate tissue for histologic analysis. Even by the standards of the controversial AASLD guideline that recommends a sample with greater than 11 portal tracts with an ideal size of 2–3 cm long after formalin fixation, ELB provided more than adequate samples. The final criterion of the AASLD requiring a 16-gauge needle was also deemed potentially unnecessary.[3,5–7,9–11] Biopsies of both lobes increase tissue yield while simultaneously decreasing sample variability, an advantage available by EUS. Therefore, ELB has proven to be more than sufficient in providing adequate tissue samples.

The major adverse event rate with PC and TJ liver biopsy specimens ranges between 0.5% and 2.1% and 0.56% and 6.5%, respectively.[7] Our study revealed a 2.6% adverse event rate with ELB, with most being minor. The safety profile of ELB was confirmed in our study, as the most common adverse event was abdominal pain. This occurred in 4 patients (1.75%) and resolved with no acute intervention in all cases. Our experience revealed a much lower rate of pain post-ELB than the published literature for ELB, which has shown postprocedure pain as high as 20%–30%.[2,12] Similar to other published reports, the discomfort resolves within an hour for most patients, sometimes requiring mild analgesics. This is in contrast to PC liver biopsy, with pain occurring in up to 84% of patients, including those with relatively mild discomfort.[4,18]

The most important complication of liver biopsy is bleeding, which, when severe, occurs intraperitoneally. In PC liver biopsy, severe bleeding (defined clinically and requiring hospitalization, transfusion, or radiological intervention or surgery) is estimated to occur in 1 in 2500 to 1 in 10,000 biopsies. Less severe bleeding (that is sufficient to cause pain or reduced blood pressure or tachycardia, but not requiring transfusion or intervention) occurs in approximately 1 in 500 biopsies.[4]

A recent meta-analysis on ELB revealed the pooled rate of bleeding was 1.2%.[5] In our study, the rate of bleeding was lower, with 2 patients (0.88%) having a presumed major bleeding complication. One patient became hypotensive and tachycardic with a hemoglobin 5.8 g/dL several hours after the procedure. An emergent computed tomography of the abdomen demonstrated a subcapsular hematoma. The patient responded to 2 units of packed red blood cells with no further signs of bleeding and was discharged home 2 days later.

Unfortunately, one patient had a presumed major bleeding complication after ELB, resulting in death. The patient had a history of NK/T-cell lymphoma and presented for management of melena. He was noted to have liver dysfunction (total bilirubin 15.6 mg/dL, direct bilirubin 13.5 mg/dL, alanine transaminase 594 IU/L, and aspartate transaminase 858 IU/L) with an INR of 1.0 and a platelet count of 22 K/μL. The biopsy was completed to assess for etiologies of liver injury such as drug-induced, hepatic sinusoidal obstruction syndrome, or malignant invasion. One unit of single donor platelets was given with a count of $>$50 K/μl on the day of ELB. Two passes were made using a transgastric approach. At the end of the procedure, the patient was found to be hypotensive and tachycardic with bleeding at the biopsy site. It was presumed that the patient had bleeding from the liver biopsy due to the marked thrombocytopenia and extensive hepatic involvement by his lymphoma.

Another advantage of ELB is postprocedural recovery time. After PC liver biopsy, patients are placed in the right decubitus position for 2–4 hours to tamponade the puncture site. After ELB, patients have no positional restrictions and are typically monitored in the recovery unit for 1 hour before discharge. The reduced recovery time associated with ELB is preferable for patients and also has the potential for health care cost savings.[15]

Limitations

The studies were not entirely representative of the general population and community practice, as procedures were being performed in tertiary care referral centers by experienced endosonographers. Another important limitation is not capturing all adverse events because of the retrospective nature of the study. The endoscopy unit policy at both centers is to contact all patients with a follow-up phone call in 24–48 hours, and therefore, major adverse events should not have been missed. This may account for our lower report for postprocedural abdominal pain.

Conclusions

Our experience demonstrated that ELB is capable of providing adequate tissue. This, in combination with a diagnostic yield of 98.6% and a complication rate of 2.6%, highlights its clinical utility and safety profile. ELB offers the advantages of patient comfort, concurrent endoscopic evaluation, and the ability to biopsy both left and right lobes to decrease sample variability and error. The technique is undergoing continuous evolution with improvement in diagnostic yield, and tissue samples obtained.

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Correspondence:
Address correspondence to: Vinod K. Rustgi, MD, MBA, Center for Liver Diseases and Liver Masses, Rutgers Robert Wood Johnson School of Medicine, 1 Robert Wood Johnson Place, Medical Education Building, Rm # 466, New Brunswick, New Jersey 08901. e-mail: vinod.rustgi@rutgers.edu.

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All authors were involved in data collection, writing the manuscript, and editing the manuscript.

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Data Transparency Statement:
Data, analytic methods, and study material will be made available to other researchers upon request to the corresponding author.