EUS-Guided versus Percutaneous Image-Guided Liver Biopsy: A Battle for Supremacy!

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Abstract

Liver biopsy has been the gold standard investigation for diagnosing and staging liver diseases. Image-guided percutaneous liver biopsy is a time-tested technique for obtaining the liver tissue in diffuse liver diseases. However, it is contraindicated in patients with ascites, altered mental status, skin infections, coagulopathy, and thrombocytopenia. It is associated with adverse events including postprocedure pain, bleeding, and pneumothorax. Transvenous liver biopsy can be performed in most cases with these contraindications, but it is an expensive technique and has its own inherent risks. Endoscopic ultrasound (EUS)-guided liver biopsy (EUS-LB) is a relatively new technique that has shown promising results and seems to have a potential of replacing percutaneous liver biopsy. In this news and views, we discuss the results of a randomized controlled trial (RCT) comparing EUS-guided and percutaneous techniques of liver biopsy. This RCT reported that percutaneous technique is superior in terms of diagnostic adequacy and total expenditure without any significant adverse effects compared with EUS-LB. EUS-LB is a promising technique that needs to be further explored in terms of appropriate situations in which it can be preferred over percutaneous or transvenous routes.

Keywords
► endoscopic ultrasound
► liver biopsy
► ultrasound
► bleeding

Introduction

The liver is a unique organ, as it derives its blood supply from both the systemic arterial and portal venous systems. Liver parenchyma can be diffusely involved in storage disorders, infiltrative diseases and metabolic abnormalities, and in patients with chronic liver disease, with or without cirrhosis. Despite the ever-expanding list of noninvasive investigations, liver biopsy still serves as a "gold standard" test for evaluating liver parenchymal diseases.[1] Liver biopsy can be targeted when a specific lesion needs to be biopsied, or it can be untargeted when done for conditions with diffuse hepatic involvement. Along with its diagnostic role, liver biopsy can also be used to assess the severity or stage a liver disease.[2]

The first liver biopsy was performed in 1883 by Paul Ehrlich.[3] Thereafter, with time, the technique of liver biopsy has evolved from a blind to a real-time, imaging-guided procedure.[4] However, despite being image guided, percutaneous liver biopsies are not without complications. Post-biopsy complication rates can vary from 0.3 to 3.3%. Most common complications are postprocedure pain, and bleeding that can occur in up to 10.9% of patients. Percutaneous liver biopsy is contraindicated in patients with ascites, coagulopathy and local site infection and uncooperative patients.[5,6]Transvenous (transjugular) liver biopsy was added to the armamentarium in 1973 as an alternative to percutaneous biopsy in patients with ascites or coagulopathy.[7]

Endoscopic ultrasound (EUS) has been found to be useful in diagnosing and treating a variety of hepatic conditions, including focal hepatic lesions (such as focal nodular hyperplasia, regenerative nodular hyperplasia, and hemangioma), simple hepatic cysts, abscesses, and portal hypertension.[8] The major limitations of EUS include limited visualization of the right and caudate lobes and increased risk of complications in patients with altered anatomy, in additions to the risk of EUS-fine-needle aspiration (FNA) such as bleeding and perforations.[9] There is ample evidence to support the use of contrast-enhanced, EUS-guided coiling and glue injection in the treatment of gastric or ectopic varices associated with portal hypertension.[10] The use of contrast-enhanced, harmonic EUS has, therefore, further widened the horizon of indications and enhanced diagnostic performance of EUS in these conditions. The advent of EUS-guided liver biopsy (EUS-LB) in recent years has further widened the ever expanding diagnostic and therapeutic potential of EUS in liver diseases.

EUS-LB was introduced in 2005.[11] It was performed using a 19G tru-cut biopsy needle. While the specimens yielded were small (median complete portal tract = 2), a diagnosis was reached in 90% cases. Since then, there have been many improvements in the needle used to perform EUS-LB.[12] 19 G FNB needles were found to be more effective than FNA needles, in terms of adequacy of the sample. They have now come into standard practice for EUS-LB. EUS-LB offers certain advantages over percutaneous biopsy, including easy access to both lobes, easy access in obese or pregnant patients, and decreased postprocedure pain.[13] Since EUS-LB is performed under sedation, it can be done with ease in pediatric population.[14] Furthermore, the procedure can be done in the same sitting when performing a diagnostic EUS for evaluation of jaundice or liver pathology.

Clinical usefulness of a liver biopsy depends on the adequacy of the sample obtained. British Society of Gastroenterology published a guideline on liver biopsy in 2020 and stated that for a liver biopsy sample to be deemed adequate, it should be at least 20 mm in length and should contain 11 or more complete portal triads (CPT).[2] The yield of a procedure for an adequate liver biopsy specimen depends on multiple factors, including the type of needle being used, with fine needle biopsy needles being more efficacious than aspiration needles, the caliber of the needle used (19 G better), degree of tissue fragmentation, and architectural distortion.[12,15,16,17]

The adequacy and clinical safety of EUS-LB and percutaneous liver biopsy have been compared in many retrospective studies previously. Pineda et al compared the total specimen length and CPT in biopsies taken using percutaneous route (18 or 20 G needle), transjugular route (18 or 19 G needle), and EUS guided transgastric/transduodenal route (19 G FNA needle). They found that EUS-guided biopsy yielded a longer total specimen when both lobes were biopsied and concluded that EUS-LB yields specimens at least comparable to, and in some cases better than, percutaneous or transjugular liver biopsy.[18] Shuja et al retrospectively compared the adequacy of EUS-LB done using a 19 G FNA needle with percutaneous

and transvenous liver biopsy. While the total specimen length was longest for EUS route, maximum number of CPT were seen with percutaneous biopsy. This disparity was attributed to the wider gauge of needles used for percutaneous biopsy. Importantly, significant postprocedure complications were seen more commonly with image-guided biopsies (p = 0.03).[19] Ali et al conducted a retrospective study comparing the efficacy of EUS-LB when using a 19 or 22 G Fork-tip SharkCore biopsy needle with percutaneous liver biopsy. Median core length and number of portal tracts was higher per sample with percutaneous route. However, EUS-LB was associated with a shorter hospital stay and need for analgesics.[20] In another retrospective study, Bhogal et al found the safety profile, technical success rate, and diagnostic adequacy of all three routes to be similar (►**Table 1**).[21] Despite having so many published studies on the topic of EUS-LB, there has been no randomized controlled trial (RCT) conducted to date to compare the efficacy of liver biopsy using percutaneous and EUS-guided transgastric/transduodenal route. In this edition of "News and Views," we shall discuss the first RCT conducted by Bang et al, which was first published online in *Gut* on March 25, 2021.[22]

In this study, consecutive patients eligible for the trial were recruited between July 2019 and November 2020. Patients with mass lesions and those with irreversible coagulopathy were excluded from the trial. Estimated sample size was 34 (17 patients in each group) and randomization was implemented using block randomization method with a 1:1 allocation ratio. Patients were randomized to either percutaneous or EUS-LB. It was impossible to blind the patients or the performing physicians to the procedure. However, the reporting pathologists and the outcome investigators were blinded. EUS-LB was performed using linear array echoendoscopes under propofol sedation (n = 21). 19G FNB needle was used and biopsy was obtained without suction or fanning, with two passes per patient from either lobe of liver and specimen from each pass sent separately. Right lobe biopsy was performed only if no suitable site was available in the left lobe. A maximum of 10 to-and-fro needle movements were performed during each pass, but in most patients, it was confined to less than five to-and-fro movements. Percutaneous biopsy was performed using a 16 G Biopince needle (n = 19) and the need for sedation was left at the discretion of the treating physician. Single specimen was obtained per patient and all specimens were sent for processing in containers filled with 10% formalin. Optimal specimens were defined as length of > 25 mm after fixation and presence of 11 or more CPT. The primary outcome was to compare the rate of procurement of optimal specimens. Secondary outcomes included comparison of maximum specimen length, total number of CPT, duration of procedure, adverse effects, pain scores, and procedural costs.

While final diagnosis was made with all the specimens, more optimal specimens were obtained with percutaneous route (57.9% vs. 23.8%; p = 0.028). Although the number of CPT were similar, the median specimen length obtained was longer with percutaneous route (26 mm vs. 16.5 mm; p = 0.004). Moreover, a final diagnosis was obtained on all

Table 1 Synopsis of studies on EUS-LB

Author Year Study type	Procedure (n)	Needle used	Technique	Total specimen length (mm)	CPT	Adverse events (n)
Shuja et al[19] 2019 Retrospective	EUS-LB (69)	19 G FNA needle (Expect Flexible; Boston Scientific)	Saline primed Suction + 3 passes	45.8 (20.7)	10.84 (7.23)	0
	PCLB (47)	18 G needle	Right lobe 2–3 passes	43 (13.4)	15.9 (6.74)	Pneumothorax (1), HA pseudoaneu-rysm(1), pain (4)
Pineda et al[18] Retrospective	EUS-LB (110)	19 G FNA needle (Expect or Expect Flexible; Boston Scientific)	Suction + 2–3 passes; 7–10 actuation /pass 2nd lobe biopsy depending on endoscopist discretion	38 (24–81)	14 (9–27)	NA
	PCLB (27)	18-gauge, 19-gauge, or 20-gauge needle (Coaxial Temno Needle [CT-2015])	NA	25 (15–18)	10 (7–16)	NA
Ali et al[20] Retrospective	EUS-LB (30)	19- or 22-gauge Fork-tip SharkCore biopsy needle (Medtronic)	Heparin flush; suction + Either lobe biopsied 2 passes-2–3 actuations/pass	25 Fragmentation in 40%	5	Pain (1)
	PCLB (60)	18 G CorVocet nee-dle (Meritmedica)	NA	31 Fragmentation in 10%	13	0
Bhogal et al[21] Retrospective	EUS-LB (135)	19-G needle (Expect FNA 2013 to 2017, Acquire FNB 2017 to 2019 Boston Scientific)	NA	34.7 (100)	19.7 (10)	Pain (1), 30-day mor-tality (1)
	PCLB (287)	NA	NA	29.2 (90)	17.4 (9)	Pain (1); bleeding (1)
Bang et al[22] RCT	EUS-LB (21)	19-G FNB needle (Acquire, Boston Scientific)	Suction – Max 10 passes 2 passes. Right lobe biopsy if no suitable site in left	19.2 (6.9)	> 10 in 17 (81%)	0
	PCLB (19)	16-gauge biopsy needle (Biopince)	1 core obtained. Second pass if no specimen on 1st	25.9 (4.3)	> 10 in 18 (94.7%)	0

Abbreviations: CPT, complete portal tract; EUS-LB, endoscopic ultrasound-guided liver bioscopy; FNA, fine-needle aspiration; FNB, fine-needle biopsy; PCLB, percutaneous liver biopsy; RCT, randomized control trial.

single pass biopsy specimens procured percutaneously, whereas in two of 21 patients in EUS group, specimens from both passes had to be assessed cumulatively to obtain the final diagnosis. There were no adverse events in either group. Postprocedure visual analog scale (VAS) score for pain was higher for percutaneous method at 1 hour but similar there-after and the total mean cost accrued was significantly higher with the EUS method.

Commentary

The authors of the study need to be lauded for the innovative and paradigm-changing RCT that was eagerly awaited. While the diagnostic yield of liver biopsy by both methods was sim-ilar, percutaneous method appears to be more appropriate when the objective of the biopsy was to assess the severity and stage the disease. Authors speculate that likely reason

for superiority of percutaneous method is the design of EUS needles, which are not a fully core obtaining needles in contrast to percutaneous needles, and the fact that FNB needle tip is partially flexed, as it is moves back and forth in different trajectories during EUS guidance, whereas the percutaneous needle uses a single-cut motion in a straight plane. Moreover, the authors found that the EUS-based approach was more costly with longer procedural duration, and there was no added advantage in safety profile.

Image-guided percutaneous liver biopsy is the workhorse for decades and has performed very well in daily clinical practice. The added advantage of percutaneous method is that it is widely available, does not need special expertise, and is cheaper. Because of the inherent properties, EUS-guided methods is going to be expensive, less widely available, and will need special expertise. Therefore, to be widely advocated, it needs to perform better than percutaneous method in diagnostic yield and safety profile. Moreover, any added information it provides would tilt the balance toward EUS-LB. Previous retrospective comparative studies have reported similar diagnostic yield as well as safety profile of both the procedures, and the current RCT has confirmed these results. Moreover, tissue fragmentation has been a concern with EUS-LB, and this RCT has confirmed that the quality of liver biopsy obtained with percutaneous method is better than EUS-LB. The only advantage of EUS-LB in the current RCT seems to be lesser pain scores postprocedure.

Theoretically, additional advantages of EUS approach could be simultaneous evaluation of pancreas, gallbladder, common bile duct, and other structures along with concurrent endoscopy to evaluate for varices. However, the clinical and cost implications of this additional information need to be prospectively studied. EUS-guided portal pressure measurement is a promising tool for evaluation of patient with liver diseases and could make EUS-guided approach a one-stop diagnostic tool.[23] In the present clinical practice, percutaneous liver biopsy seems to be a better option. However, there seems to be a cohort of patient who would benefit from EUS-guided procedures specifically (based on pain sensitivity, body habitus, need for concomitant endoscopy, and both lobe biopsy).

Author Contributions
1. Shubhra Mishra: drafting of manuscript.
2. Nikhil Bush: drafting of manuscript.
3. Surinder Singh Rana: critical evaluation of manuscript.

Conflicts of Interest
There are no conflicts of interest and no financial disclosures to be made by any of the authors.

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