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Endoscopic Ultrasound-Guided Liver Biopsy (EUS-LB): An Endoscopic Solution to the Unmet Needs of Liver Tissue Acquisition and Beyond

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Abstract

Aim and Objective Endoscopic ultrasound-guided liver biopsy (EUS-LB) is now increasingly being used across the globe as a method of liver tissue acquisition. This method is widely accepted by many professionals as it can overcome many shortcomings of percutaneous liver biopsy and transjugular liver biopsy. The aim of the study is to obtain the adequate and optimal biopsy rate associated with EUS-LB.

Materials and Methods This is a retrospective observational study. Consecutive patients undergoing EUS-LB during the study period who were willing to consent were taken up for the study.

Results Total 91 patients were taken up for the study. Median age of study population was 44 years out of which 39 patients were males and 52 were females (42.9 and 57.1%). Adequate biopsy rate (according to European Association for the Study of Liver Disease criteria) and optimal biopsy rate (according to American Association for the Study of Liver Diseases criteria) were 89 (81/91) and 60.4% (55/91), respectively. Rate of conclusive diagnosis was 95.6% (86/91). The commonest diagnosis encountered was nonalcoholic steatohepatitis) (23, 25.3%), followed by autoimmune hepatitis (17, 18.7%). Additional diagnostic information was obtained by endosonography during EUS-LB in 21 patients (23.1%). Gallstone disease was found in four (4.8%) patients, chronic calcific pancreatitis in two (1.9%) patients, significant abdominal lymphadenopathy defined as lymph node more than 1.5 cm in five (5.8%) patients, and esophageal or gastric varices in ten (10.6%) patients. One case of self-limiting biopsy site ooze was seen in EUS-LB and the patient was having cirrhosis.

Keywords
- EUS-LB
- liver tissue
- unmet need

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Conclusion This study showed a high diagnostic outcome and safety profile with EUS-LB technique. EUS-LB can achieve excellent histological yield when performed with optimal technique. Moreover, it is possible to obtain additional information during the procedure from diagnostic endosonography that is done as a part of EUS-LB.

Introduction

Liver biopsy is an invasive procedure that aims at the diagnosis of liver lesions and diffuse liver disorders. It also assesses the severity of liver damage. Two main conventional methods of tissue biopsies are as follows:

Percutaneous Liver Biopsy

Percutaneous liver biopsy is considered to be the oldest and the most conventional method. This procedure is utilized in performing targeted liver biopsy and nontargeted liver biopsy for focal liver lesions and diffuse liver disorders respectively. It can be done under image guidance to minimize complication and to obtain better results. On the contrary, blind biopsy is contraindicated in the current clinical practice. There are two types of percutaneous liver biopsy:

- Cutting type
- Aspiration type

Cutting type is the preferred among the two. For nonlesional indication, 16 G needle is preferred. The risk of bleeding following percutaneous liver biopsy is increased in those with coagulopathy and ascites. To overcome this difficulty, other modalities of liver biopsies were developed.[1]

Transjugular Liver Biopsy

This method has an advantage over percutaneous liver biopsy due to the fact that it can be done in patients with coagulopathy.[1] Fragmentation of tissue samples and not being able to take targeted biopsy are the main drawbacks of transjugular liver biopsy (TJLB). As the right atrium is traversed, arrhythmias are common during the procedure.[2] Similar to the conventional percutaneous liver biopsy, cutting type and aspiration type needles are used for which 18G or 19G needles are used.

Shortcomings of percutaneous liver biopsy are as follows:

- Increased morbidity and mortality
- Difficult to perform in patient with coagulopathy

Shortcomings of TJLB are as follows:

- Fragmentation of tissue sample
- Targeted biopsy from liver lesion is not possible

Endoscopic Ultrasound-Guided Liver Biopsy

Endoscopic ultrasound-guided liver biopsy (EUS-LB) can overcome many shortcomings of percutaneous liver biopsy and TJLB. It is routinely done with 19G EUS fine-needle biopsy (FNB) needles. Following are the advantages of this EUS-LB:

- Targeted and nontargeted liver biopsies can be done through this biopsy.
- It can be done in patients with international normalized ratio (INR) up to 2.
- It has less tissue fragmentation compared with TJLB.
- Needle entering the liver can be viewed in real-time (intrahepatic vessels and bile duct can be spared from injury).[3]
- Both lobes of the liver can be accessed.
- It provides minimal patient discomfort.
- EUS-LB can access liver lesions that may not be safely accessible by routine US or computed tomography.[4]
- It provides better results in obese individuals compared with percutaneous liver biopsy.
- It is safe in pregnant females requiring liver biopsy.

Recent meta-analysis by Mohan et al reported a histologic diagnosis rate of 93.9%. The incidence of adverse events was 2.3%.[5] In terms of the total length of specimen and complete portal tracts (CPT) obtained, EUS-LB was comparable to percutaneous liver biopsy with no difference in the incidence of severe adverse events.[6] So far there are only few studies conducted on EUS-LB. We aimed at studying the safety, efficacy, histological adequacy, and other information obtained from EUS-guided liver biopsy.

Methods

This is a retrospective observational study. The study was conducted for a period of 3 years from February 2020 to April 2023. Consecutive patients undergoing EUS-LB during the study period who were willing to give consent were taken up for the study. The study was performed after approval from the institutional ethics committee. This study has been conducted honoring the Declaration of Helsinki Declaration. Each participant's identity has been kept anonymous.

Inclusion Criteria

The participants of the study were adults aged more than or equal to 18 years in need of liver biopsy for the evaluation of:

- Altered liver function test
- Portal hypertension and etiology of cirrhosis

Exclusion Criteria

Contraindications for EUS-LB like

- Using antiplatelets or anticoagulants within the last 5 days
- Inability to provide informed consent
- Moderate-to-gross ascites
- Child C cirrhosis
- INR more than 2.0[1]
- Platelet count less than 50,000/μL[3]

Techniques

EUS-guided liver biopsies were performed using linear echo endoscope (GF - UCT 180 Olympus, Tokyo, Japan) and 19G FNB needle (Acquire TM, Boston Scientific Marlborough, MA, United States). The biopsies were done by an endoscopist who had experience in taking EUS-guided fine-needle aspiration (FNA) and FNBs. We have taken all the liver biopsy samples using "wet technique".

In the wet technique, first, stylet of the FNB needle was removed following which the FNB needle was flushed with a small amount of heparin until the heparin droplet came out from the end of the needle making sure that the needle was not flushed with air. Suction syringe was prepared using 2 mL of water followed by a 20 mL vacuum created into the suction syringe. Suction syringe was attached to the FNB needle. The EUS examination was done after putting the candidate in the left lateral position. All patients undergoing the procedure were sedated with midazolam or propofol. After achieving adequate sedation, an echo endoscope is introduced. Liver was assessed from the proximal stomach and first part of duodenum. FNB needle was then introduced into the liver (via transgastric approach or transduodenal approach) after undergoing a color Doppler imaging that demonstrates blood vessels in the tract. This will help in avoiding accidental puncture of any blood vessel thereby drastically reducing the risk of bleeding or any other lethal events that might occur as a part of the procedure. After the puncture, 3 or 4 back and forth motions of needle were done using the fanning technique. Only one pass was taken. On acquisition of liver tissue, the specimen is pushed with the help of needle stylet onto the cell block cassette which is nothing but a plastic mesh, and very gently saline is flushed over the specimen that helps in removing blood stains and blood clots. Multiple pieces of liver tissue were seen over the mesh after saline flushing. These multiple cores were then "floated" off the mesh into a 10% formalin solution. Then the core sample was sent to our liver section of histopathology department. Histopathology reporting was done by a pathologist who has experience of reporting for more than 100 liver biopsies and it was cross examined by another pathologist with similar experience. Pain postprocedure was assessed by pain scale chart (level 1–10) and score more than 4 was considered significant.

Study Outcomes

The study's primary outcome was sample adequacy. Sample adequacy was assessed based on:

- Total specimen length (TSL).
- Number of CPTs.

CPT is defined as a portal tract with all three portal structures (branches of the portal vein, hepatic artery, and bile duct) within a complete circumference. For sample adequacy of liver biopsy specimens, there is variation with respect to the definition on the basis of various criteria that were put forth.

- European Association for the Study of Liver Disease (EASL) criteria for adequacy of liver biopsy specimen.

TSL of more than or equal to 15 mm with more than or equal to 6 CPTs (adequate liver biopsy).[7]

- American Association for the Study of Liver Diseases (AASLD) criteria for adequacy of liver biopsy specimen.

TSL of more than or equal to 20 mm with more than or equal to 11 CPTs (optimal liver biopsy).[7]

In this study, a sample with TSL of more than or equal to 15 mm and more than or equal to 6 CPTs was considered as adequate biopsy. A sample with TSL of more than or equal to 20 mm and more than or equal to 11 CPTs was considered as optimal biopsy.

Primary Objective of the Study

- To detect adequate biopsy rate with EUS-LB
- To detect optimal biopsy rate with EUS-LB

Secondary Objective of the Study

- To detect rate of successful pathological diagnosis
- To detect additional diagnostic information that can be obtained from endosonography
- To detect rate of adverse events with EUS-LB especially pain postprocedure by pain scale chart (level 1–10)
- To detect factors associated with acquisition of optimal and adequate sample.

Statistical Analysis

Continuous data were expressed as median and range or mean and standard deviation based on test of normality. Categorical data were expressed as frequency and percentage. Univariate analysis was done using chi-squared and *t*-test. A *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 20.0.

Results

Total 91 patients were taken up for the study. Median age of study population was 44 years. Thirty-nine patients were males and 52 were females (42.9 and 57.1%). Ascites were present in 5 out of 91 patients (5.5% cases). Esophageal varices were seen in 10 patients (10.9%). ►**Table 1** listed other baseline characteristics of the study population.

TSL, number of complete portal tract, rate of conclusive diagnosis, adequate biopsy rate, and optimal biopsy rate.

The median TSL was 4.06 cm or 40.6 mm (range: 10–98 mm). The median number of CPTs was 13 (range: 2–35; ►**Table 2**). Adequate and optimal samples were seen in 81 (89%) and 55 (60.4%) cases. A conclusive diagnosis was achieved in 95.6% (86/91) of the patients (►**Table 3**). The commonest diagnosis was nonalcoholic steatohepatitis (NASH; 23, 25.3%), followed by autoimmune hepatitis (AIH; 17, 18.7%).

Table 1 Baseline characteristics of study population

	Minimum	Maximum	Mean	SD
Alkaline phosphatase (IU/L)	47	784	173.44	161.115
SGPT(IU/L)	12	409	87.11	95.532
Serum protein (mg/L)	4.48	10.30	7.2125	1.28016
Serum albumin mg/L	1.75	4.95	3.8452	0.75632
Bilirubin (mg/L)	0.31	24.50	3.0692	5.21114
SGOT (IU/L)	15	409	68.00	79.936
PT-INR	0.89	1.69	1.2722	0.19205
Platelet count, X 10^3 µL	50	821	205.84	126.586

Abbreviations: PT-INR, prothrombin time test-international normalized ratio; SD, standard deviation; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

Table 2 TSL and CPT of EUS-LB

	N	Minimum	Maximum	Mean	SD
TSL (in mm)	91	1.0	9.8	4.06	2.0012
CPT	91	2.0	35.0	13	6.2745

Abbreviations: CPT, complete portal tract; EUS-LB, endoscopic ultrasound liver biopsy; SD, standard deviation; TSL, total specimen length.

Table 3 Adequate biopsy rate, optimal biopsy rate, and rate of conclusive diagnosis among study population

Adequate biopsy rate in study population		
	Frequency	Percentage
Inadequate	10	11.0
Adequate	81	89.0
Total	91	100.0
Optimal biopsy rate in study population		
	Frequency	Percentage
Suboptimal	36	39.6
Optimal	55	60.4
Total	91	100.0
Rate of conclusive diagnosis		
	Frequency	Percentage
Inconclusive	5	4.4
Conclusive	86	95.6
Total	91	100

Table 4 Additional diagnostic information obtained from Endosonography during EUS-LB

	Frequency	Percentage
No additional information	70	76.9
Gallstone disease	4	4.8
Chronic calcific pancreatitis	2	1.9
Significant abdominal lymphadenopathy	5	5.8
Esophageal or gastric varices	10	10.6
Total	91	100.0

Abbreviation: EUS-LB, endoscopic ultrasound liver biopsy.

Predictors of Optimal Biopsy and Adequate Biopsy

Among the variables analyzed, none of the variables were statistically significant in predicting the optimal biopsy rate and adequate biopsy rate (*p*-values were not significant). The variables analyzed includes age, sex, presence or absence of ascites, presence of compensated cirrhosis, lobe from which biopsy was taken, serum bilirubin, total protein, serum albumin, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, platelet count, and INR. The variables were analyzed with chi-squared test and *t*-test.

Additional Diagnostic Information Obtained during Endosonography

Additional diagnostic information or other information means information like presence of Gall stones, Lymphadenopathy etc which we get during diagnostic endo sonographic testing which was done along with EUS-LB. Additional diagnostic information was obtained by endosonography during EUS-LB in 21 patients (23.1%). Gallstone disease was found in four patients (4.8%), chronic calcific pancreatitis in two (1.9%) patients, significant abdominal lymphadenopathy defined as lymph node more than 1.5 cm was found in five patients (5.8%), esophageal or gastric varices in ten patients (10.6%; ►**Table 4**). Diagnostic information that was diagnosed beforehand EUS-FNA by the imaging (including conventional US and computed tomography/magnetic resonance imaging) done during evaluation of patient the patient were not included as additional diagnostic information.

Adverse Events during EUS-LB

None of the patients had pain scale chart score of more than 4 postprocedure and none of the patient required opioids for the management of postprocedural pain. One case of self-limiting biopsy site ooze was seen and the patient was having cirrhosis.

Discussion

EUS-LB is widely being used as a method of liver tissue acquisition for both targeted and nontargeted liver biopsies. The increased acceptance of EUS-LB is due to the fact that it can overcome many shortcomings of percutaneous liver biopsy and TJLB.

Our primary focus for the study was solely based on EUS-LB and how it can satisfy the unmet need of tissue acquisition. It has many additional benefits.

In our study, adequate biopsy rate (according to EASL criteria) and optimal biopsy rate (according to AASLD criteria) were 89 (81/91) and 60.4% (55/91), respectively. Rate of conclusive diagnosis was 95.6% (86/91). In study by Sarkar et al, adequate biopsy rate was 98.7% and in study by Rai et al it was 100%.[1,9] The commonest diagnosis was NASH (23, 25.3%), followed by AIH (17, 18.7%). One case of self-limiting biopsy site ooze was seen in EUS-LB and the patient was having cirrhosis. Additional diagnostic information was obtained by endosonography during EUS-LB in 21 patients (23.1%). Gallstone disease was found in four patients (4.8%), chronic calcific pancreatitis in two patients (1.9%), significant abdominal lymphadenopathy defined as lymph node more than 1.5 cm in five patients(5.8%), and esophageal or gastric varices in ten patients (10.6%).

Meta-analysis of 33 studies that was on EUS-LB showed an 84% specimen adequacy and 95% pooled rate of conclusive diagnosis. The adverse events were 3%.[8]

In Indian study by Rai et al, median TSL was 5.8 cm.[9] In study by Sarkar et al, TSL was 3.2 cm.[1] In our study, the median TSL was 4.06 cm or 40.6 mm (range: 10–98 mm). The median of CPTs was 13.

Percutaneous liver biopsy usually targets right lobe than left lobe. EUS-LB study by Sharma et al compared left lobe EUS-LB with right lobe EUS-LB and bilobar EUS-LB. On comparison, mean TSL and mean number of CPT were similar between right and left lobe EUS-LB.[3] Diagnosis between the two lobes showed substantial concordance. Similarly study by Diehl et al also showed that yield from right and left lobe was similar.[10] In our study, 73.1% samples were obtained from the left lobe with pathological diagnosis established in 63/66 (95.4%) cases. Thus, EUS-LB from the left lobe has similar diagnostic accuracy as the right lobe sampling and provides an adequate sample following the procedure.

Only 19G EUS FNB needle was used in the study and hence comparison between different gauge and different types of needles was not possible in this study.

Concerning the optimal number of passes required for a diagnostic sample, Ching-Companioni et al compared the diagnostic outcome of single versus multiple needle actuations for EUS-LB.[11] Specimens obtained using three actuations had significantly higher CPTs (17.25 ± 6.2 vs. 24.5 ± 9.88; $p < 0.008$) and longer aggregate specimen length (6.89 ± 1.86 cm vs. 12.85 ± 4.02 cm; $p < 0.001$). Priming of the needle with heparin reduces the bloodiness of the specimen without interfering with the results of histopathology. In a study by Rai et al, single pass slow pull technique with 19G needle yielded tissue diagnosis of 100% (total number of patients in the study were 50).[9] In this study also, wet suction was used in all the patients leading to sample adequacy in 89% using the criteria of more than 6 CPTs. As far as the pass and actuation (to and fro movement of needle) is concerned, in our study out of 91 cases, we got adequate sample by doing one pass and three actuations in 88 patients, while in remaining 3 patient we had to perform two passes and three actuations in each pass.

To the best of our knowledge, this is the largest study on diagnostic outcome of EUS-LB from India. It is one of the largest single-center studies on EUS-LB. Since the data are from a single center, there is homogeneity of data and so generalization can be done with ease. Despite the many benefits, there are several limitations encountered in this study, retrospective nature being the first. There is no comparator arm to assess efficacy as compared with percutaneous biopsy.

To conclude, this study shows a high diagnostic outcome and safety profile with EUS-LB technique. EUS-LB can achieve excellent histological yield when performed with optimal technique. Moreover, it is possible to get additional diagnostic information during EUS-LB from diagnostic endosonography that is done as a part of EUS-LB. Ultimately, standardizing EUS-LB technique and patient selection, in addition to ongoing multidisciplinary collaboration, will be critical to its widespread adoption.

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Conflict of Interest
None declared.

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