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EUS-guided left lobe liver biopsy: Safer modality with similar diagnostic yield as right lobe: a pilot study

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ABSTRACT

Background and study aims Percutaneous liver biopsy is traditionally done on the right lobe of the liver. Endoscopic ultrasound-guided liver biopsy (EUS-LB) can be performed on either the left or right lobe or as a combined bi-lobar biopsy. Earlier studies did not compare the benefit of bi-lobar biopsies to single-lobe biopsy for reaching a tissue diagnosis. The current study compared the degree of agreement of pathological diagnosis between the left lobe of the liver compared to right-lobe and with bi-lobar biopsy.

Patients and methods Fifty patients fulfilling the inclusion criteria were enrolled in the study. EUS-LB with a 22G core needle was performed separately on both the liver lobes. Three pathologists, who were blinded to the site of biopsy independently reviewed the liver biopsies. Sample adequacy, safety, and concordance of pathological diagnosis between left- and right-lobe biopsy of the liver were analyzed.

Results The pathological diagnosis was made in 96 % of patients. Specimen lengths from the left lobe and the right lobe were 2.31 ± 0.57 cm and 2.28 ± 0.69 cm, respectively (P = 0.476). The respective number of portal tracts were 11.84 ± 6.71 versus 9.58 ± 7.14; P = 0.106. Diagnosis between the two lobes showed substantial (κ = 0.830) concordance. Left-lobe (κ value 0.878) and right-lobe (κ = 0.903) biopsies showed no difference when compared with bi-lobar biopsies. Adverse events were observed in two patients, both of whom had biopsies of the right lobe.

Conclusions EUS-guided left-lobe liver biopsy is safer than right-lobe biopsy with similar diagnostic yield.

Introduction

Liver biopsy is the gold standard investigation for etiological diagnosis and prognostication of several liver diseases [1, 2]. Percutaneous liver biopsy (PLB) is the most common method, with or without image guidance and is mostly performed on the right lobe. Prolonged local pain, though usually mild, is reported in about 25 % of patients [3]. PLB-related bleeding is a serious adverse event (AE) which requires hospitalization in about 1 % to 3 % of patients [4]. Such unpredictable and serious complications make clinicians hesitant to consider PLB in clinical practice.

Alternate methods of obtaining liver biopsy are surgical and trans-jugular liver biopsy (TJLB). Surgery, either conventional or mini laparoscopy, for liver biopsy is scantly described in literature, and appears to be an aggressive approach to obtain tissue just for diagnosis. A randomized controlled trial of laparoscopic liver biopsy versus PLB found that laparoscopic liver biopsy was

more sensitive for diagnosis of cirrhosis with a similar safety profile [5]. It is more useful when performed alongside curative surgery [6].

TJLB is safe, even in the presence of ascites and/or coagulopathy. However, it is not routinely available at all centers and requires expertise. The technical success rate for TJLB is reported between 95 % to 96.8 % [7]. Failure of TJLB is mainly due to inability to cannulate the hepatic vein in 43 % of all unsuccessful cases [7]. However, tissue adequacy with TJLB is suboptimal. McAfee et al. reported overall tissue adequacy for diagnosis in 69 %, marginally adequate in 23 % and inadequate in 8 % of cases [8]. The overall TJLB-related AE rate varies between 1.3 % to 20.2 %, with major complications being observed in < 0.6 % [9, 10].

EUS-guided liver biopsy (EUS-LB) is a relatively new method with high tissue acquisition and histological accuracy of 93.8 %. The reported overall complication rate is 2.3 %, including bleeding in 1.2 % of cases [11]. The first report of EUS-LB documented adequate tissue length along with high diagnostic accuracy in 91 % of cases using a regular 19G fine-needle aspiration (FNA) needle [12]. Subsequent larger studies on EUS-LB also have reported high tissue acquisition with impressive diagnostic rates in up to 98 % patients along with minimal complications [13]. The major advantage with EUS-LB is that both the left and right lobes of the liver can be accessed, through the stomach and duodenum, respectively, thus providing the option of bi-lobar biopsy in the same session [14]. Acquiring tissue with EUS-LB from the right lobe of the liver may be slightly technically challenging compared to the left lobe due to the length of the echo-endoscope and interposing vital structures. EUS in hepatology provides simultaneous assessment of peri-gastrointestinal wall collaterals, portal vein or splenic vein thrombosis, novel direct measurement of portal-pressure gradient in select individuals, and intervening by variceal obliteration of gastric or ectopic varices using coil and or glue injection [15].

PLB acquires specimen from the right lobe of liver. There are some reports of discordance due to uneven distribution of steatosis and fibrosis in non-alcoholic-fatty liver disease (NAFLD) [16]. However, surgical liver biopsies during bariatric surgery showed reasonable concordance for steatosis and fibrosis between the two lobes of 79 % and 82 %, respectively [17]. Similar variations in interpretation of fibrosis have been noted in patients with chronic hepatitis [18]. A recent report also suggests that bi-lobar biopsies is likely to improve overall assessment of disease severity and fibrosis in NAFLD [19]. Therefore, we aimed to analyze the accuracy of EUS-LB in diagnosis of liver disease and its safety.

Objectives

The primary objective of the study was to evaluate the degree of agreement of histological diagnosis between right- and left-lobe liver biopsies with each other and individually in comparsion with combined bi-lobar biopsy (BLB).

Secondary objectives of the study were:

1. Safety of performing EUS-LB between left- and right lobe of liver.
2. Assessment of technical difficulty in doing EUD-LB from left and right lobes.

Patients and methods

This was a prospective observational pilot study conducted between January 22, 2020, and January 4, 2022, at a tertiary care center. The study was approved by the local Institutional Ethics Committee and registered in Clinicaltrials.gov (NCT04235855). All consecutive patients requiring liver biopsy at the Hepatology Clinic were screened for the study. The study was conducted in concordance with the declaration of Helsinki and informed written consent was obtained from every patient.

Patients were counseled about the available procedures for doing a liver biopsy and they all underwent esophagogastroduodenoscopy prior EUS-LB. This was done during the same session at which the liver biopsy was done.

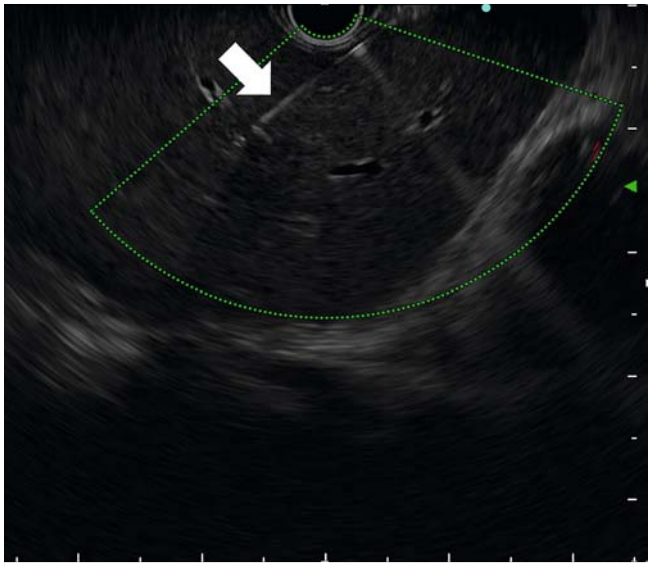
The inclusion criteria for EUS-LB were as follows: age ≥ 18 years; patients with abnormal liver function test of unknown etiology > 3 months; patients with NAFLD for diagnosis of non-alcoholic steatohepatitis (NASH) and fibrosis; patients with suspected autoimmune hepatitis (AIH), drug-induced liver injury (DILI), small duct primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC); and, in cases in which staging of fibrosis for hepatitis B was required.

The exclusion criteria were: platelet count < 50,000/µL; international normalized ratio (INR) > 1.5, concurrent use of anticoagulants or antiplatelet drugs within 5 days before the scheduled procedure, pregnancy, patients with decompensated chronic liver disease, biliary obstruction, or patients deemed unfit for the procedure due to either severe cardiac or pulmonary disease [20].

Procedure details

All patients underwent pre-anesthetic evaluation prior to EUS-LB. Patients were sedated using 1 % propofol at a dose of 0.5 to 1 mg/kg intravenously as a loading dose and repeated as required in 0.5 mg/kg increments every 3 to 5 minutes under anesthetist supervision [21]. EUS-LB was performed by one of the operators (SL, JB, RK) using a linear echo-endoscope (GF-UT-180, Olympus, Tokyo, Japan) and 22 G EUS FNB needle (Acquire, Boston Scientific Corp.). Interposing vessels, either in gastrointestinal wall or within the liver parenchyma, were avoided using color Doppler. The left lobe of the liver was accessed from the proximal stomach (trans-gastric approach) with the echoendoscope generally in a straight position. The right lobe of the liver was accessed from the first part of the duodenum (transduodenal approach) with the echoendoscope in the long position.

The 22G core needle with the stylet was passed into peripheral liver parenchyma through the capsule. In each pass, three to four actuations of up to 4 to 6 cm depth were made in a slightly different direction (fanning) of the liver parenchyma, avoiding major vessels while withdrawing the needle (stylet slow-pull technique). Before the final removal of the needle from liver, if any persistent flow signal was observed in the needle track on Doppler ('post Fine needle biopsy needle pathway



▶ **Fig. 1** EUS image showing 22G core needle (white arrow) acquiring biopsy from left lobe of liver.

color flow signal') suggesting active bleeding, the needle tip was kept in situ within the liver capsule for approximately 20 to 30 seconds until spontaneous hemostasis was achieved.

The sequence of EUS-LB was left lobe first, followed by right lobe under direct visualization (▶ **Fig. 1**). The total duration of the procedure was noted by the study coordinator. The start time was oral insertion of the echoendoscope and the end time was its final withdrawal from the mouth, after completion of EUS-LB.

The specimen obtained within the hollow needle was delicately expelled by the stylet into a Petri dish partially filled with saline. A scale kept adjacent to the Petri dish was used to measure the length of the obtained sample (▶ **Fig. 2**). Multiple passes were made by the endoscopist to achieve a cumulative sample length of at least 2 cm at bedside. The tissue samples were processed as per standard protocol of the institute. Separate formalin bottles were labeled and coded 'A' or 'B' for either lobe, which was recorded by the dedicated research coordinator. The liver biopsies were evaluated by two experienced pathologists (JK, SS) who were blinded about the lobe of origin. A senior pathologist (AS) gave the final bi-lobar biopsy report and was not aware of the individual lobe reports.

The technical ease of performing EUS-LB from the right and left lobes of the liver was graded on a 5-point Likert scale (1 easiest to 5 hardest) based on the position of the echoendoscope and the operator.

After the EUS-LB procedure, patients were monitored in the outpatient ward for the next 4 hours. The pain score was recorded using a visual-analog scale of 0 to 10 after recovery from the effects of sedation. Any patient with a pain score >4 was treated with intravenous paracetamol infusion. The surgical and interventional radiology team were informed about any procedure-related bleeding for timely intervention.

Definitions

The criteria described by Neuberger et al were used to assess adequacy of tissue acquired. A sample of at least 20 mm in length or with at least 11 portal tracts was considered as adequate while a sample less than 10 mm or with less than six portal tracts was considered inadequate. Any specimen sample falling between the above two measurements (at least 10 mm length and six portal tracts but less than 20 mm length and 11 portal tracts) was considered as compromised [20]. In this study, from each lobe, the combined length of tissue and their total portal tracts obtained after multiple passes or a single pass was taken for analysis. Technical success was defined as completion of liver biopsy from both lobes with the endoscopist confirming adequacy of the specimen.

Statistical analysis

Data were collected using case record forms designed to capture all the required information. Sample size calculation was not considered, as this was the first study to address the degree of agreement of histological diagnosis with EUS-LB. Continuous variables were expressed as mean and standard deviation (SD) if uniformly distributed or median and interquartile range (IQR) if it was not uniformly distributed. Categorical variables were expressed as n (%). The means of specimen length, number of portal tracts and percentage of steatosis between the two lobes were compared using an independent t-test. The degree of concordance between right and left lobe liver biopsies by two pathologists was assessed using Cohen's kappa. Also, concordance between individual lobe biopsy and combined biopsy was analyzed using Cohen's kappa (κ). Concordance was defined using the following scale:

κ < 0.0 = Poor
κ 0.0 to 0.2 = Slight
κ 0.21 to 0.4 = Fair
κ 0.41 to 0.60 = Moderate
κ 0.61 to 0.80 = Substantial
κ > 0.81 = Excellent

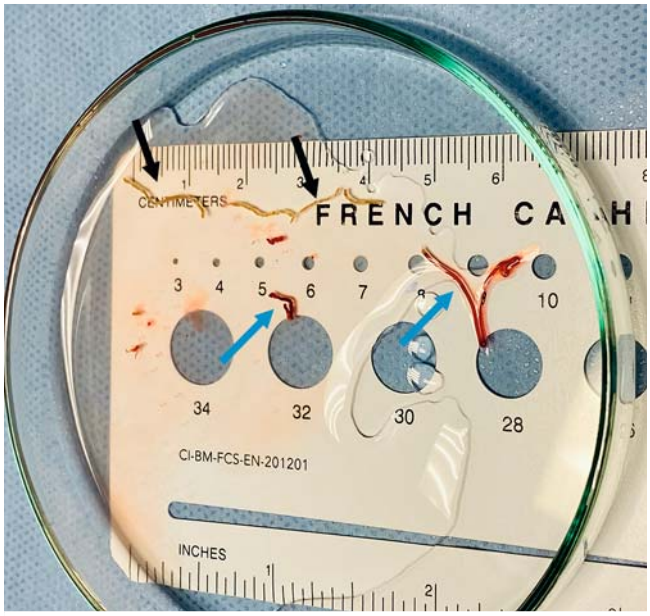
The proportion of adequate biopsy specimens was compared using Chi-square test. The grade of ease of doing EUS-LB from right and left lobes of the liver was compared using Mann-Whitney test. $P < 0.05$ was considered statistically significant. The SPSS version 25 (IBM Corp., Armonk, New York, United States) was used for statistical analysis.

Results

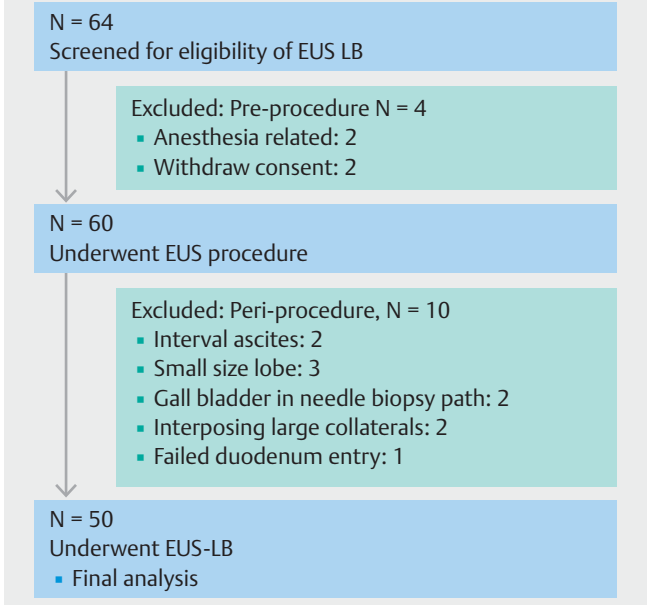
A total of 64 patients fulfilled the inclusion criteria and were eligible for liver biopsy. Fourteen patients were excluded for reasons explained in ▶ **Fig. 3**. Fifty patients (31 females, 19 males) underwent EUS-LB from both lobes of the liver.

Baseline characteristics

Baseline characteristics of patients are shown in ▶ **Table 1**. The common indication for EUS-LB was unexplained transaminitis 28 (56 %), cholestatic jaundice 20 (40 %), and jaundice with hemolysis in two (4 %).



▶ **Fig. 2** Liver tissue obtained by EUS-LB measured in Petri dish with a scale below. The black arrow indicates liver core tissue, and the blue arrow indicates blood clots acquired during the procedure.



▶ **Fig. 3** Consort diagram showing the recruitment and final analysis of patients. EUS, endoscopic ultrasound; EUS-LB, endoscopic ultrasound-guided liver biopsy; N, number of patients.

Procedure details

The median number of passes EUS-LB for the left lobe was two (range 1–4) and for the right lobe was 2.06 (range 1–4). Three patients had four passes per lobe (2 patients for right lobe, and 1 patient for left lobe). The mean duration of the procedure was 18.54 ± 4.54 minutes (range 14–23.08 minutes).

▶ **Table 1** Baseline characteristics of patients undergoing EUS-LB.

Parameter	Mean ± SD/no. (%)
Age (yr)	45.76 ± 12.20
Body mass index (BMI)	24.6 ± 4.8
Hemoglobin (g/dL)	11.51 ± 2.41
Platelet count (/uL)	2.10 ± 1.05
Total bilirubin (mg/dL)	9.29 ± 10.0
Direct bilirubin (mg/dL)	4.54 ± 5.96
Alanine amino-transferase (IU/L)	151.46 ± 159.83
Aspartate amino-transferase (IU/L)	181.46 ± 196.3
Albumin (g/L)	3.42 ± 0.58
PT	13.78 ± 4.39
INR	1.24 ± 0.34
Type 2 diabetes	25 (50 %)
Hypothyroidism	13 (26 %)
Essential hypertension	16 (32 %)

EUS-LB, endoscopic ultrasound-guided liver biopsy; PT, prothrombin time; INR, international normalized ratio; SD, standard deviation.

Adequacy of sample and pathological diagnosis

There was no significant difference between overall specimen length from the left and right lobes (2.31 ± 0.57 versus 2.28 ± 0.69; $P = 0.476$) as calculated after processing in the pathology laboratory. The length of the longest tissue obtained in a single pass was 3.1 cm in the right lobe and 3.6 in the left lobe. The number of portal tracts from the left and right lobes was similar (11.84 ± 6.71 versus 9.58 ± 7.14; $P = 0.106$). Tissue adequacy as determined by the tissue length and portal tracts assessed by the pathologist was 42 (84 %) from the left lobe compared to 38 (76 %) from the right lobe of the liver ($P = 0.3197$). The degree of steatosis expressed in percentage was 12.76 ± 16.53 in the left lobe versus 11.96 ± 16.0 in the right lobe ($P = 0.816$). Biopsy was deemed as inadequate in 4 (8 %) from the right lobe and one (2 %) from left lobe biopsy. The remaining eight (16 %) in right lobe and seven (14 %) in left lobe biopsies were deemed as compromised.

Pathological diagnosis concurred between the right and left lobe in 45 of 50 patients (90 %). There was excellent agreement on histological diagnosis between two blinded pathologists reporting right or left lobe biopsy ($\kappa = 0.830$). Similarly, excellent agreement was observed between left lobe biopsy compared with BLB ($\kappa = 0.878$) as well as between right lobe and BLB ($\kappa = 0.903$). The overall pathological diagnosis was possible in 48 patients (96 %) when both lobe biopsies were analyzed together. The final pathological diagnoses based on both lobes are shown in ▶ **Table 2**.

Disagreement between left and the right lobe biopsy was observed in five cases. In two cases, despite adequate tissue, a

▶ **Table 2** Pathological diagnosis obtained from liver biopsy.

Diagnosis	Left lobe liver	Right lobe liver	Combined (bilobar biopsy)
DILI	13	10	11
AIH	11	12	13
NASH	11	11	11
Dubin-Johnson Syndrome	1	1	1
BRIC	1	1	1
Bland cholestasis	3	3	3
PBC	1	0	0
PBC-AIH overlap	1	3	2
Wilson Disease	1	1	1
Small duct PSC	1	1	0
Tuberculosis	1	1	1
Inconclusive	3	4	3
Viral hepatitis	1	1	1
Siderosis	1	1	1
PSC- AIH Overlap	0	0	1

NASH, non-alcoholic steatohepatitis; BRIC, benign recurrent intrahepatic cholestasis; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; DILI, drug-induced liver injury.

definitive diagnosis on histology was not possible. In another two cases, right lobe and BLB confirmed autoimmune hepatitis. In the remaining case, neither right- nor left-lobe biopsy individually could identify overlap syndrome of AIH-PSC, which was established on BLB.

There was significantly higher technical difficulty for performing EUS-LB from the right [22] versus left lobe [22]; P= 0.001.

Adverse events

There were no anesthesia-related AEs. There was one (2 %) serious AE of intraperitoneal bleeding from a right lobe biopsy sit-requiring blood transfusion and controlled at laparoscopy. This patient underwent three passes during the acquisition of biopsy from the right lobe. There was one minor intraprocedure bleed, which spontaneously stopped.

Discussion

EUS-LB is a recent and evolving method of hepatic tissue acquisition. Most EUS-LBs are reported from the left lobe of the liver, with the literature focusing either on the biopsy length or tissue adequacy as the primary end point [23–25]. A recent meta-analysis reported a histological diagnosis rate of 93.9 % [26].

The standard of care is PLB, which targets the right lobe. From a clinical standpoint, it becomes important to establish whether EUS-LB, which is technically simpler, would match liver biopsy from the right lobe in terms of pathological diagnosis. Our study, which was designed to explore the concordance of left lobe biopsy for histological diagnosis, establishes that the left-lobe liver biopsy is equal to right-lobe biopsy.

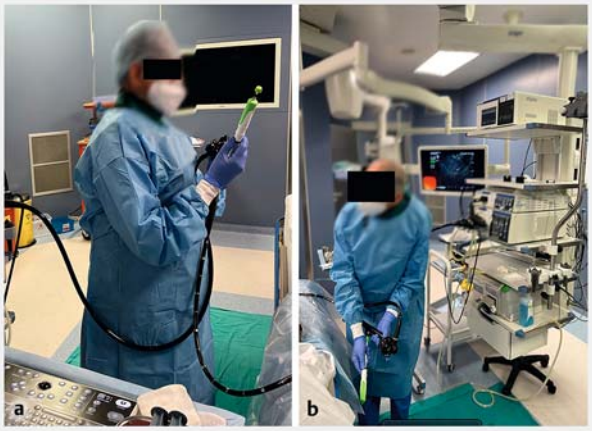
When a comparison is made between EUS-LB with the standard of care percutaneous liver biopsy, a previous study by Bhogal et al found no difference between specimens from liver biopsy obtained by either method as regards the length of the longest piece and the number of portal tracts, although the tissue length was longer in percutaneous liver biopsy [27]. Similar studies have found similar diagnostic accuracy between EUS-LB (88.8 %) and percutaneous liver biopsy sample (100 %) (P= 0.82) [28]. Therefore, it has been found that EUS-LB specimens are at least comparable to percutaneous liver biopsy specimens with a benefit to sample widely separated liver segments [14].

For EUS-LB, Mok et al reported higher tissue adequacy with 19G FNA (88 %) when compared with 22G FNB (68 %) [29]. Further studies reported that a core biopsy needle obtained longer tissue and samples from more portal tracts [29, 30]. Likewise, in the current study, we used a 22G FNB needle with good histological outcome. Gor et al obtained good mean tissue length of 3.6 cm and a median of nine portal tracts using a 19G FNA needle with a median of two passes [31]. The sample adequacy of 91 % matches our sample adequacy of 86 %, which was sufficient for diagnosis. Histological diagnosis is possible with compromised samples; however, the assessment of fibrosis and biliary pathology may be underestimated [20].

In patients with systemic diseases such as AIH and NASH, biopsy should be taken equally from both lobes of the liver, yet in this study, the biopsy from the right lobe of the liver picked up additional PBC cases. This could be a chance observation because there is no evidence that PBC more often involves the right lobe of the liver [32].

Unlike PLB, at present, there is no standardized criteria to assess sample adequacy for a specimen obtained by EUS-LB. The criteria for liver biopsy adequacy was originally described for PLB in which the operator usually makes a single pass [33]. In contrast, with EUS-LB, tissue is acquired in two to three passes; hence we propose that the cumulative length of the tissue measured at bedside should be considered for tissue adequacy in EUS-LB. This may be reconfirmed by the total number of portal tracts seen at pathology. If the standard criteria for percutaneous liver biopsy were considered to estimate sample adequacy, a significant proportion of samples in this study would have been suboptimal and would fall within the gray zone.

The overall AE rate with EUS-LB was low (2/50) with two bleeding events (one severe), both occurring with the right-lobe liver biopsy. This may be attributed to the occasional technical challenges due to the awkward position of either the echoendoscope or the endoscopist or both during the procedure (▶ **Fig. 4**). In addition, presence of several interposing vital structures (portal vein or its tributaries, hepatic artery, gastroduodenal artery, hepatic veins, gallbladder, and bile ducts) on the right lobe approach may increase the chance of complications. However, the sample size in this study was modest to provide a conclusive opinion on adverse outcomes from right-lobe biopsy and future head-to-head trials are required.



▶ **Fig. 4** Image showing the position of the endosonologist and the echoendoscope during EUS-LB a from the left lobe (**a**) and right lobe (**b**) of the liver.

To avoid any bias in our study, the independent pathologists were blinded regarding the liver lobe from which the biopsies was obtained. Biopsy specimens from each lobe were analyzed separately by the two pathologists. The final diagnosis was made by the third pathologist, who assessed tissues from both lobes and was unaware of the diagnosis made by the earlier pathologist. With such stringent criteria for pathological assessment, this study shows that left-lobe biopsy alone may be sufficient to establish the pathological diagnosis. Right-lobe liver biopsy did not statistically add to the overall histological diagnosis. Technical ease and feasibility of acquiring tissue from the left lobe of liver with equal efficacy would pave the way for only left-lobe EUS-LB.

EUS-LB from the right lobe is technically more difficult than the left lobe as perceived by the endosonologists. We used a 5-point Likert scale to quantify level of difficulty during the procedure by endosonologists. However, it is largely subjective and operator dependent.

The study demonstrates that EUS-LB is safe due to direct visualization while acquiring the liver tissue, thus avoiding interposing blood vessels and other vital structures.

This study had some limitations. It was a single-center study with a modest sample size. The decision to perform a liver biopsy was at the discretion of the treating physician and thus there was no uniform indication. Patients with cirrhosis of the liver with small lobes were excluded and this may require pre-biopsy proper imaging before advising EUS-LB.

Another limitation of this study was the use of a 22G needle, which was selected based on the data that were available at the time the study was designed, which showed that a 22G needle was a safer alternative for liver biopsy with diagnostic yield equal to that for larger needles [22]. Using a larger 19G needle could have provided longer core tissue and more portal tracts. Recent studies with a 19G needle for EUS-LB has shown longer core length (2.5 cm vs 1.2 cm, $P<0.00001$) with more portal tracts (8.8 vs. 3, $P<0.0001$), and longer, intact fragment length (0.75 cm vs. 0.32 cm, $P<0.0006$) [28].

The major strength of the study was that the pathologists were blinded about the tissue sample and three separate pathologists were independently involved in the diagnosis. In addition, EUS-LB was done by three operators to avoid bias.

Conclusions

EUS-LB may be safer from the left lobe of liver when compared to the right lobe. Obtaining a sample from the left lobe of the liver is technically easier, and is sufficient for reaching a final diagnosis, when compared to biopsy of right lobe of the liver or combined right and left lobes.

Competing interests

The authors declare that they have no conflict of interest.

Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
NCT04235855
TRIAL REGISTRATION: Prospective study NCT04235855 at ClinicalTrials.gov (http://www.clinicaltrials.gov/)

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