—Review Article—

# Endoscopic ultrasound-guided liver biopsy

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## ABSTRACT

Liver biopsy remains the cornerstone in the diagnosis and management of liver disorders. Results of liver biopsy can often drive therapeutic decision-making. Unfortunately, studies have shown conventional biopsy techniques to carry significant sampling variability that can potentially impact patient care. Endoscopic ultrasound (EUS) is gaining traction as an alternative method of biopsy. For parenchymal disease, it can decrease sampling variability. It offers a more targeted approach for focal lesions. Its diagnostic yield and limited adverse event profile make it a promising approach for liver biopsy.

**Key words:** Endoscopic ultrasound (EUS), EUS-guided liver biopsy (EUS-LB), fine needle biopsy, liver biopsy, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), Tru-Cut biopsy

## INTRODUCTION

Liver biopsy plays a pivotal role in evaluating and directing the therapeutic management in patients with liver disease. While a thorough history and physical examination, serologic markers, and radiographic imaging are important, there remains a role for diagnostic liver biopsy. History and physical examination, and laboratory evaluation alone can miss significant fibrosis or cirrhosis in up to one-third of patients who do not undergo liver biopsy that presents with abnormal liver chemistries in the absence of diagnostic serology.[1] Liver biopsy can uncover the underlying etiology and the extent of liver damage, altering the therapeutic management in as many as 18% of patients.[1-6]

Access this article online

Quick Response Code:

Website: www.eusjournal.com

DOI: 10.4103/2303-9027.156711

Endoscopic ultrasound (EUS) has emerged as an essential diagnostic examination for the diagnosis and management of a wide range of gastrointestinal, hepatobiliary, and pancreatic diseases. The promise of a targeted biopsy with limited adverse events makes EUS an excellent modality to allow liver tissue acquisition for focal hepatic lesions. EUS also allows staging in malignant conditions by offering the potential to obtain image-guided direct biopsies of possible metastatic liver lesions, which can drastically alter the therapy. This review will serve to describe the various biopsy methods and evidence supporting the use of EUS in liver biopsy, both for focal and parenchymal disease, with particular focus on the emerging evidence including multicenter trials evaluating the safety of EUS-guided liver biopsy (EUS-LB).

## BACKGROUND AND CURRENT BIOPSY METHODS

Percutaneous liver biopsy was first reported in the 1920s,[7] with the transjugular approach pioneered in the

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**Received:** 2015-02-05; **Accepted:** 2015-03-30

1970s.[8] Percutaneous liver biopsy has evolved from a "blind" approach using percussion to an image-guided approach using ultrasonography (USG) or computed tomography (CT). Theoretically, the image guidance should reduce the complication rate. The percutaneous approach historically utilized a 16- or 18-gauge needle for tissue acquisition, although smaller needles (even as small as 20-gauge) may be used. The most common adverse event of percutaneous liver biopsy is pain, which can be located at the biopsy site or referred to the right shoulder.[9] Other complications include hypotension,[10,11] hemorrhage,[12] biliary peritonitis,[13] pneumothorax or hemothorax,[14] transient bacteremia,[15] tumor seeding,[16] and death.[17-19] A recent population-based study evaluated the complication rates and the direct cost of complication from percutaneous liver biopsy in 3,627 patients who underwent a total of 4,275 liver biopsies.[20] Of them, 32 patients (0.75%) had significant biopsy-related complications, with pain requiring admission and bleeding being the most common. Six patients (0.14%), all of whom had malignancies, died due to a complication from the procedure. The median direct cost of hospitalization for all the complications was $4,579 (range: $1,164-29,641).

Percutaneous liver biopsy for parenchymal liver disease may have significant sampling variability.[4-6] A recent study sought to assess the sampling error of liver biopsy and its impact on the diagnosis and assessment of severity in nonalcoholic steatohepatitis (NASH).[21] A total of 102 samples, obtained from the right hepatic lobe through an intercostal route using USG guidance, were collected from 51 patients with nonalcoholic fatty liver disease (NAFLD). The overall discordance rate for the presence of hepatocyte ballooning was 18%. This histologic feature would have been missed in 24% of the patients had only one biopsy been performed. The negative predictive value of a single biopsy in diagnosing NASH was found to be 0.74. The discordance rate of one stage or more was found to be 41%. Of the 17 patients with bridging fibrosis, six (35%) had one biopsy that demonstrated only mild or no fibrosis, which would have been understaged had only one biopsy been performed. The investigators concluded that histologic lesions of NASH are unevenly distributed throughout the hepatic parenchyma and thus, sampling error may result in misdiagnosis and in staging inaccuracies. Subsequent studies demonstrating similar findings further emphasized the need to optimize the approach for liver biopsy to maximize the diagnostic accuracy.[22,23] Bedossa *et al.* sought to assess the heterogeneity of liver fibrosis and the impact on the accuracy of assessment of liver biopsy and suggested that the length of the biopsy sample may contribute to sampling variability.[24] The American Association for the Study of Liver Diseases (AASLD) reviewed several subsequent studies and acknowledged sampling variability to be a potential pitfall of the current liver biopsy techniques.[25]

Transjugular liver biopsy is an accepted alternative in instances when a percutaneous technique is contraindicated, such as in patients with bleeding diathesis, coagulopathy,[7] presence of ascites,[26] peliosis hepatis,[27] and morbid obesity, or in an uncooperative patient,[28,29] or in the presence of infection in the right pleural cavity or below the hemidiaphragm. The transjugular approach accesses the parenchyma through the superior vena cava and the hepatic vein, which allows hepatic tissue acquisition without traversing the liver capsule.[26] In addition, this technique allows direct measurement of the hepatic venous pressure gradient, which can be used to predict a patient's risk of developing varices or variceal bleeding and help guide the management of those patients with portal hypertension due to cirrhosis. The minor complications include pyrexia, hematoma, bleeding, carotid puncture, Horner syndrome, dysphonia, arm numbness/palsy, supraventricular arrhythmia, hypotension, abdominal pain, capsular perforation, small hepatic hematoma, hepatic portal vein fistula, hepatic artery aneurysm, biliary fistula, or hemobilia. The major complications include large hepatic hematoma, intraperitoneal hemorrhage, inferior vena cava perforation, renal vein perforation, ventricular arrhythmia, pneumothorax, or respiratory arrest. A recent retrospective analysis of 601 transjugular liver biopsies found an overall complication rate of 2.5% (15/601).[30]

## EUS-LB FOR PARENCHYMAL DISEASE

Recently EUS has emerged as an alternative means to obtain liver biopsy with a low adverse event profile. This section will discuss the various techniques studied and the available clinical data, as it pertains to EUS-LBs for parenchymal disease.

### *EUS-guided Tru-Cut biopsy*

EUS-guided Tru-Cut biopsy utilizes a 19-gauge spring-loaded device to obtain an adequate histologic tissue sample (Quick-Core, Cook Medical, Bloomington, IN, USA). Under real-time EUS visualization, the needle

is advanced into the liver with the spring handle in the retracted firing position. Then, the spring handle is slowly pressed forward until resistance is felt, thereby advancing the specimen tray into the lesion. The operator must be aware that the specimen tray will extend approximately 2 cm beyond the needle tip. Further pressure is then added to the spring handle, which fires the device and obtains the tissue. Its demonstrated safety and reported utility for hepatic tissue acquisition in the swine model[31] prompted the investigators to evaluate its use in humans. The left lobe of the liver is readily accessible from the stomach, while the right lobe can be assessed from the duodenum.

Dewitt *et al.* described an initial experience with EUS-guided Tru-Cut biopsy in a benign liver disease.[32] Twenty one patients were evaluated and a histologic diagnosis was obtained in 19 (90%) patients. No adverse events occurred. The median total specimen length was 9 mm (range: 1-23 mm); however, the size of the samples obtained was typically smaller than those traditionally considered adequate for histologic assessment. Gleeson *et al.* sought to determine the utility of Tru-Cut EUS-LB for histopathologic evaluation to include the number of portal tracts.[32] Nine patients underwent a transgastric left liver lobe Tru-Cut biopsy. Adequate diagnostic material was acquired in all the nine cases, with a total of 63 complete portal tracts.

The Tru-Cut needle can be technically difficult to use, and failure to obtain tissue is common. The technique is less intuitive than the conventional EUS-guided fine needle aspiration (EUS-FNA). These reasons may account for the wide variability seen in studies evaluating the Tru-Cut technique.[32-34] The technically demanding nature of this needle, particularly when performed with the echoendoscope in a long position (such as the duodenum), and difficulty in obtaining adequate samples in general clinical use are the reasons as to why Tru-Cut biopsy has failed to reach widespread use and led investigators to seek alternative methods.

### *EUS-guided fine needle biopsy with a 19-gauge needle*

Investigation of EUS-LB with the use of a regular 19-gauge FNA needle (non-Tru-Cut needle) was first described by Stavropoulos *et al.*[35] This group evaluated the use of EUS-LB with a regular 19-gauge FNA needle in patients with abnormal liver function tests of unclear etiology. The patients were referred for EUS to exclude biliary obstruction; EUS-LB of the left lobe of the liver was done if no source of biliary obstruction was found. Using a 19-gauge FNA needle, 22 patients were found to have EUS with the same-session EUS-LB. There was a median specimen length of 36.9 mm (range: 2-184.6 mm), nine complete portal tracts (range: 1-73), diagnostic adequacy of 91%, and no postprocedure complications. The authors concluded that EUS-LB with the use of a 19-gauge FNA needle was feasible, safe, and provided significant diagnostic yield and specimen adequacy. In another study, 10 patients underwent EUS-LB for abnormal liver chemistries, with the most common indication being to exclude biliary obstruction.[3] All the biopsy specimens were obtained from the left lobe of the liver, via either a transgastric or transesophageal approach, with a 19-gauge needle and a total of three to-and-fro motions per pass. There was a yield of 100% diagnostic adequacy and an average core length of 14.4 mm (range: 6-23 mm), an average of 9.2 complete portal tracts per specimen, and no adverse events.

The largest clinical trial to date comes from Diehl *et al.*, in which 110 patients with elevated liver enzymes or hepatic disease underwent EUS-LB at eight different referral centers.[36] The use of full suction for the needle aspiration was at the endoscopist's discretion, with the majority of endoscopists preferring to use it. Doppler was used to identify an area of hepatic parenchyma, free of blood vessels or bile ducts, in the expected trajectory of the needle. There were 7-10 to-and-fro motions made per pass, utilizing the "fanning" technique to maximize tissue acquisition. A total of one or two passes were made in the left lobe, depending on the endoscopist's preference or the assessment of tissue yield that was obtained after the first pass. Right lobe FNA, when performed, was performed as per the endoscopist's preference, and done so with the technique of the left lobe. The liver biopsy specimens obtained were sufficient for pathological diagnosis in 89% of the cases. The median aggregate length of tissue acquired was 38 mm (range: 0-203 mm), with a median of 14 complete portal tracts (range: 0-68), which led the authors to conclude that EUS-LB is a safe technique yielding adequate tissue for pathological diagnosis in 98% of the patients. There was one bleeding complication in a patient with an international normalized ratio (INR) of 1.42 and a platelet count of 64,000, later found to have disseminated intravascular

coagulation. Computerized tomography (CT) imaging revealed a subcapsular hematoma. A subsequent angiogram did not reveal any active bleeding; thus, angioembolization was not required. The patient was managed conservatively.

EUS using Tru-Cut can be technically difficult to execute. Conversely, EUS-LB with the use of a 19-gauge needle allows multiple to-and-fro movements, yielding longer specimen samples. A single large multicenter prospective trial has confirmed its feasibility, safety, and diagnostic adequacy. Further studies of EUS-LB should be done to confirm the optimal technique potential advantages over other techniques. Additionally, further refinement in EUS needle technology may be beneficial. Table 1 summarizes the data from the preceding studies.

## EUS-FNA FOR METASTATIC LESIONS

Abdominal imaging [CT, magnetic resonance imaging (MRI), and transabdominal ultrasonography (USG)] are the diagnostic tests of choice to detect hepatic lesions suspicious of metastasis.[37-39] Unfortunately, these modalities are limited in their ability to detect hepatic lesions less than 1 cm.[40] In addition, although rare, percutaneous FNA for suspected metastatic lesions carries the risk of implantation metastasis.[16,41,42] Although unable to completely visualize the entirety of the liver, EUS can detect small hepatic lesions that may be otherwise missed by conventional imaging. EUS can delineate detailed anatomy of the liver from the transgastric and transduodenal routes with the exception of the right posterior segments.[43] The endoscopist must be keen toward the fact that EUS is a dynamic image, in contrast to static cross-sectional radiologic images (e.g., MRI or CT), and thus, must appreciate the numerous scan planes possible in real time, and the direction of scanning from the stomach or the duodenal bulb. In addition, EUS offers the potential to direct a biopsy needle into the liver for image-guided sampling, allowing direct confirmation of suspected metastatic lesions.

Initial data on EUS-guided FNA of the liver came from a prospective study by Nguyen *et al.*, which included a total of 574 consecutive patients with a history or suspicion of pulmonary or gastrointestinal malignant tumor.[44] EUS evaluation of the liver was done during the EUS examination. Of the 574 patients, 14 (2.4%) were found to have a focal liver lesion and underwent subsequent EUS-FNA for a total of 15 samples (one patient underwent EUS-FNA of two liver lesions). FNAs were done with a 22-gauge needle. Of the 15 liver samples obtained, 14 were malignant and one was benign with a new cancer diagnosis made in seven patients. By comparison, the preendoscopic CT was only able to identify liver lesions in three of the 14 patients (21%). There were no procedure-related complications. The authors concluded that EUS can detect small focal liver lesions not detected by CT, and EUS-FNA can confirm the diagnosis of suspected liver metastasis and establish cancer staging that may change the clinical management.

A large, retrospective, international survey by tenBerge *et al.* sought to assess indications, complications, and findings of EUS-FNA of the liver.[45] For a total of 167 cases, 21 centers responded to a globally distributed questionnaire. EUS-FNA was able to diagnose malignancy in 23 of 26 cases (89%) following a nondiagnostic FNA under transabdominal USG guidance. In addition, EUS localized a primary tumor in 17 of 33 cases (52%) in which the preceding CT imaging had only demonstrated liver metastasis without a primary tumor. The complication rate was 4%, with a major complication rate of 1%. The authors concluded that EUS-FNA should be considered when a hepatic lesion is poorly accessible to USG or CT-guided FNA or when these modalities are unable to make a diagnosis.

**Table 1. Summary of available data for EUS-LB for parenchymal disease**

| Study | Gleeson *et al.* | Dewitt *et al.* | Stavropoulos *et al.* | Gor *et al.* | Diehl *et al.* |
|---|---|---|---|---|---|
| Type of needle used | Tru-Cut | Tru-Cut | 19-gauge FNA | 19-gauge FNA | 19-gauge FNA |
| Number of patients | 9 | 21 | 22 | 10 | 110 |
| Number of passes | 2 (range: 1-3) | 3 (range: 1-4) | 2 (range: 1-3) | 3 | 1-2 (per lobe) |
| Specimen length (median, range) | 12 mm, 8-28 mm | 9 mm, 1-23 mm | 36.9 mm, 2-184.6 mm | 14.4 mm, 6-23 mm | 38 mm, 0-203 mm |
| Complete portal tracts (median) | 7 (range: 5-8) | 2 (range: 1-10) | 9 (range: 1-73) | 9.2 (range: 6-15) | 14 (range: 0-68) |
| Diagnostic yield | 100% | 90%* | 91% | 100% | 98% |
| Complications | 0 | 0 | 0 | 0 | 1 |

*Specimen adequacy = 19%

A large single-center study by Dewitt *et al.* sought to evaluate the clinical impact of EUS-FNA of benign and malignant solid liver lesions.[46] A database of cytologic specimens collected from 77 liver lesions in 77 patients was reviewed. Of these specimens, 45 were diagnostic for malignancy, 25 were benign, and seven were nondiagnostic. The sensitivity of EUS-FNA for malignancy ranged 82-94% depending on whether the seven nondiagnostic specimens were actually malignant or benign. Malignancy was identified by EUS-FNA in 41% of patients who previously had negative exams by CT alone ($n$ = 13), transabdominal USG alone ($n$ = 1), or a combination of both ($n$ = 3). Of the patients with malignancy identified via cytology, EUS-FNA changed the management in 86% of the subjects. Overall, there were no complications. The authors concluded that EUS-FNA is a safe and sensitive procedure with a potential to drastically impact patient management.

Singh *et al.* performed one of the first prospective studies directly comparing EUS to CT for the detection of liver metastasis.[47] In this single-center study, 132 patients with newly diagnosed tumors of the lung, pancreas, biliary tree, esophagus, stomach, and colon were included, with liver metastasis found in 26 patients. EUS proved to be superior to CT scan in diagnostic accuracy, 98% compared to 92%, respectively, ($P$ = 0.0578) and in its ability to detect the number of metastatic lesions in the liver, 40 compared to 19, respectively, ($P$ = 0.008). In eight cases, CT detected lesions that were too small to characterize, of which EUS-FNA correctly diagnosed three cases to be malignant and four cases to be benign. Lastly, there were no complications incurred as a result of EUS-FNA.

## EUS-FNA FOR HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide, responsible for up to 1,000,000 deaths per annum.[48] Early detection of HCC and accurate determination of the number and size of lesions is critical in selecting those who may be eligible for liver transplantation or resection. As previously described, the current radiologic modalities are limited in their ability to detect hepatic lesions less than 1 cm.[40] To date, there has been a handful of case reports/case series[49-52] and two single-center prospective studies[40,53] describing the success of EUS-FNA in the detection of HCC.

Awad *et al.* evaluated the utility of EUS in detecting and diagnosing hepatic masses in patients with HCC and metastatic lesions, hypothesizing that EUS could detect small (<1.0 cm) lesions undetectable by CT scan.[40] Fourteen patients with suspected liver lesions underwent EUS with subsequent FNA if liver lesions were confirmed, and FNA was deemed necessary by the endoscopist with a 22-gauge needle, using two passes per lesion. Each of the 14 patients also underwent dynamic CT scans in addition to EUS. In all the 14 patients, EUS successfully identified hepatic lesions ranging 0.3-14 cm. In addition, EUS was able to identify new or additional lesions in 28% (4 of 14) of the patients, all less than 0.5 cm in size, two of which were HCC and the other two were metastatic lesions. This led to the conclusion that EUS is a feasible preoperative staging tool for liver lesions suspected to be HCC or metastatic lesions. Furthermore, EUS can detect small hepatic lesions that conventional radiology may be unable to detect. Lastly, EUS-FNA can confirm additional metastatic lesions or HCC, which could potentially change clinical management.

Singh *et al.* compared the accuracy of EUS with CT for the detection of primary liver tumors in 17 patients with a high risk of developing HCC (hepatitis B, hepatitis C, or alcoholic cirrhosis).[53] Of the 17 patients, nine had a liver tumor (eight had HCC; one had cholangiocarcinoma). EUS-FNA was able to establish a tissue diagnosis in eight of the nine cases. EUS/EUS-FNA with a diagnostic accuracy of 94% exceeded the diagnostic accuracy of USG, CT, or MRI (38%, 69%, and 92%, respectively). EUS also detected a significantly higher number of nodular lesions compared to USG ($P$ = 0.03), CT ($P$ = 0.002) and MRI ($P$ = 0.04). Lastly, for HCC lesions there was a trend in favor of EUS for the detection of more lesions when compared to USG (8 *vs.* 2, $P$ = 0.06) and CT (20 *vs.* 8, $P$ = 0.06). There were no complications as a result of EUS-FNA. This led to the conclusion that EUS-FNA increases the accuracy of HCC staging by delineating those lesions that may otherwise be missed by CT and MRI and therefore, is a safe and accurate test for the diagnosis of HCC. The investigators recommended the use of EUS for suspected HCC, particularly when the patients are being considered for liver transplantation.

## CONCLUSION

Liver histopathology is an essential tool for the diagnosis of liver disease. The result of liver biopsy

often drives therapeutic management. Percutaneous liver biopsy has been the standard approach for liver tissue acquisition; however, studies have demonstrated it to be associated with sampling variability that may alter the therapeutic management. EUS-LBs offer a more targeted approach, particularly for focal lesions, thus, theoretically providing a higher yield.

Based on a review of the presently available published studies, there are several potential advantages of the use of EUS for liver tissue sampling. The ability to perform bilobar sampling may increase diagnostic accuracy in parenchymal disease. This is of particular importance, given the rise in the metabolic syndrome paralleling the increase in the diagnosis of NAFLD. In the realm of focal hepatic lesions, EUS appears to identify small metastatic lesions that could improve tumor stating as well as tissue acquisition. Thus, EUS-guided FNA also has an increasing indication for the sampling of metastatic malignancy. While the cost of EUS-LB may supercede that of conventional USG-guided biopsy, the advantages of EUS-LB as described above and the emerging role for EUS-LB in parenchymal disease ought to be considered when determining the optimal modality.

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**How to cite this article:** Parekh PJ, Majithia R, Diehl DL, Baron TH. Endoscopic ultrasound-guided liver biopsy. Endosc Ultrasound 2015;4:85-91.

**Source of Support:** Nil. **Conflict of Interest:** None declared.