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Endoscopic ultrasound guided liver biopsy: Recent evidence

Kemmian D Johnson, Passisd Laoveeravat, Eric U Yee, Abhilash Perisetti, Ragesh Babu Thandassery, Benjamin Tharian

ORCID number: Kemmian D Johnson (0000-0001-6472-8402); Passisd Laoveeravat (0000-0001-6855-0437); Eric U Yee (0000-0001-9643-6439); Abhilash Perisetti (0000-0003-4074-6395); Ragesh Babu Thandassery (0000-0002-5357-4847); Benjamin Tharian (0000-0002-7797-3738).

Kemmian D Johnson, Department of Internal Medicine, Louisiana State University Health Sciences Center, New Orleans, LA 70112, United States

Passisd Laoveeravat, Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX 79430, United States

Eric U Yee, Department of Pathology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States

Abhilash Perisetti, Benjamin Tharian, Department of Internal Medicine, Division of Gastroenterology, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States

Ragesh Babu Thandassery, Department of Internal Medicine, Division of Gastroenterology, Central Arkansas Veterans Health Care System, Little Rock, AR 72205, United States

Corresponding author: Ragesh Babu Thandassery, MD, Assistant Professor, Department of Internal Medicine, Division of Gastroenterology, Central Arkansas Veterans Health Care System, Little Rock, AR 72205, United States. ragesh.thandassery@va.gov

Abstract

Liver biopsy (LB) is an essential tool in diagnosing, evaluating and managing various diseases of the liver. As such, histopathological results are critical as they establish or aid in diagnosis, provide information on prognosis, and guide the appropriate selection of medical therapy for patients. Indications for LB include evaluation of persistent elevation of liver chemistries of unclear etiology, diagnosis of chronic liver diseases such as Wilson's disease, autoimmune hepatitis, small duct primary sclerosing cholangitis, work up of fever of unknown origin, amyloidosis and more. Traditionally, methods of acquiring liver tissue have included percutaneous LB (PCLB), transjugular LB (TJLB) or biopsy taken surgically via laparotomy or laparoscopy. However, traditional methods of LB may be inferior to newer methods. Additionally, PCLB and TJLB carry higher risks of adverse events and complications. More recently, endoscopic ultrasound guided LB (EUS-LB) has evolved as an alternative method of tissue sampling that has proven to be safe and effective, with limited adverse events. Compared to PC and TJ routes, EUS-LB may also have a greater diagnostic yield of tissue, be superior for a targeted approach of focal lesions, provide higher quality images and allow for greater patient comfort. These advantages have contributed to the increased use of EUS-LB as a technique for obtaining liver tissue. Herein, we provide a review of the recent evidence of EUS-LB for liver disease.

Core tip: Endoscopic ultrasound guided liver biopsy is a safe and effective approach to obtaining liver biopsies that may serve as an alternative to traditional methods. Our goal is to collect and review the most recent data on the advances in endoscopic ultrasound guided liver biopsies, while also weighing the advantages and disadvantages of utilizing conventional methods of liver biopsy (percutaneous liver biopsy, transjugular liver biopsy, surgical liver biopsy).

INTRODUCTION

Needle biopsy of the liver was first performed by Dr. Paul Ehrlich in 1883[1]. Since then, the role and technique of tissue sampling has evolved tremendously. Liver biopsy (LB) provides essential clinical information regarding diagnosis, prognosis, evaluation and management of various diseases of the liver[2]. Though patient history, clinical exam, imaging and laboratory tests including serology aid in the initial diagnosis of liver disorders, histological analysis continues to play an essential role in discovering the etiology and magnitude of liver disease, especially when preliminary, less invasive methods of evaluation are inconclusive[3]. Without tissue acquisition, nearly one-third of cases of liver cirrhosis can be overlooked in patients presenting with abnormal liver tests and absent diagnostic serology, though the widespread availability and non-invasive nature of fibro -elastography has helped reduce the need for biopsies[4].

There are several approaches available to acquire a LB. Conventionally, LBs have primarily been performed through the computed tomography (CT) or ultrasound (US) guided percutaneous (PC) route[1]. In cases in which this approach is contraindicated or unavailable, a fluoroscopy guided transjugular (TJ) approach may be employed, which may be combined with measurement of hemodynamics in the portal system[5,6]. Less commonly, a surgeon may perform a LB during laparoscopy/laparotomy[2]. However, there are procedure-related risks including mortality related to traditional methods of acquiring liver tissue. Major complications following LB are rare, occurring at a rate of approximately 1%, while mortality rates occur at 0.2%[7]. The most common complications include hemorrhage and pain[8,9]. Further, the use of PCLB and TJLB may have substantial variation in histologic yield[10].

Endoscopic US guided LB (EUS-LB) is a sampling technique that has surfaced as an effective alternative to traditional methods of obtaining liver tissue both for focal and parenchymal disease[11]. In addition to an improved safety profile, EUS-LB presents numerous advantages over PC and TJ routes of biopsy. Briefly, EUS-LB allows for higher quality images of both hepatic lobes, which allows for a safer biopsy technique and improved ability to access focal liver lesions[12]. Additionally, EUS-LB is conducted under sedation, allowing for reduced procedural anxiety and increased patient comfort[13]. Ultimately, the decision on the route of tissue acquisition largely relies upon the indications for the LB, the patient risk profile and the experience of the endoscopist, including the procedural volumes.

Given the superiority of EUS-LB in various aspects, this article aims to provide an update on the emerging evidence, indications, technique, advantages, and complications. This will ultimately help physicians determine the most appropriate method of LB.

INDICATIONS FOR LB

The use of imaging, including newer modalities like transient elastography and serology, has helped decrease the need for LBs. For instance, in a patient with established cirrhosis, a solid liver lesion with certain characteristics on magnetic resonance imaging and compatible tumor markers, the diagnosis is presumably hepatocellular carcinoma and would not necessarily require a LB[14]. Similarly, in cases in which a liver lesion is most likely related to metastasis from a proven primary cancer, biopsy may not be indicated unless there is enough evidence to the contrary or tissue is needed for diagnostic confirmation or workup for specialized molecular tests[14].

However, there are several clinical scenarios that warrant LB. One of the most common utilities of LB is diagnosing the etiology of complex liver disease that cannot be reasonably identified by imaging, serology or laboratory values[14]. LB can also useful in distinguishing cases where there are disease processes that overlap such as in autoimmune hepatitis and drug induced liver injury[15]. Additionally, LBs are essential to establishing a diagnosis and staging of diseases such as nonalcoholic steatohepatitis (NASH), chronic liver disease due to hepatitis B and C, autoimmune hepatitis, and acute liver failure of indeterminate etiology, amongst other liver diseases[16]. LB can also help diagnose systemic diseases, such as amyloidosis and sarcoidosis, that can affect the liver and assist in the work up of pyrexia of unknown origin[1,16].

LBs can be crucial to assessing disease severity and establishing prognosis. While serology is useful to establish a diagnosis of viral hepatitis, the LB helps to quantify the extent of inflammation or fibrosis, as well as identification of concomitant disease processes, which may have significant prognostic implications[16]. Similarly, in hemochromatosis, the presence of fibrosis can predict the risk of transformation to hepatocellular carcinoma[16,17]. Transient elastography techniques have decreased the need for LB in deciding on treatment options in many conditions like chronic viral hepatitis. With the availability of directly acting antivirals for treatment of chronic hepatitis C infection, fibrosis staging is most of the time performed using transient elastography. But in chronic viral hepatitis and many other hepatitis diseases like auotoimmune hepatitits, alcoholic and non alcoholic steatohepatitis, assessment of grade of activity can be accomplished only by LB. Distinguising some of the rare conditions like nodular regenerative hyperplasis from cirrhosis can be accomplished only with LB[2,16].

METHODS OF LB

The methods of LB are mainly categorized into three groups including traditional methods, surgical based, and EUS-guided approaches. Each method has its own pros and cons as summarized in Table 1.

Traditional methods of acquiring LB

PCLB: The earliest known PC biopsy of the liver was conducted in the early 1900s and has since remained the primary method of sampling liver tissue[18]. In the PCLB method, a biopsy site is pinpointed over the liver, an incision is made in the skin aseptically under local anesthesia, and a needle is inserted into the liver to obtain a tissue sample[19]. In its infancy, the PCLB was performed without image guidance from the right lobe of the liver and was identified by percussion of the liver, with breath held in inspiration[20]. However, this is now performed under CT or ultrasonographic guidance, minimizing adverse events[21]. Early operators commonly used a 14 or 16-gauge (G) needle to obtain a core biopsy specimen. However, most operators now utilize 16-18G needles to obtain biopsy[22,23].

While use of CT or US guided biopsy has helped to decrease inadvertent punctures of adjacent organs, complications still occur[24]. The most common complication is hemorrhage[22]. Minor complications occur in nearly a quarter of cases, the most common being pain at the site of biopsy[25]. Other reported complications include peritonitis[26], hypotension[27], infection, gallbladder perforation[28], pneumothorax or hemothorax[29], transient bacteremia[30] and mortality[7,31].

Advantages/disadvantages of PCLB: One of the advantages to employing the PCLB method is that operators are more familiar with this method and have a better understanding of this technique and of the specimen. Thus, compared to newer methods, this is comparatively easier to use and demands less technical skill[11]. Additionally, the PCLB route is cost effective, allowing for widespread use in various clinical settings.

Table 1 Advantages and disadvantages of liver biopsy methods

	Percutaneous liver biopsy	Transjugular liver bipsy	Surgery	Endoscopic ultrasound guided liver biopsy
Indication	Mainstay method of liver biopsy for unexplained abnormal LFTs, assessing, staging, diagnosing liver disease	Coagulopathy; ascites; morbid obesity; failure of percutaneous liver biopsy ; thrombocytopenia	Undergoing surgery for another indication	Undergoing endoscopy for another indication
Complications	Pain; hemorrhage; peritonitis; hypotension; infection; gallbladder perforation; pneumothorax; hemothorax	Hemorrhage; pain capsule perforation; arterial aneurysms; arrhythmias	Hemorrhage, abdominal wall injury; intraperitoneal injury; anesthesia related complications	Hemorrhage; abdominal pain; infection
Advantage	Well-known procedure; cost effective; less technical skills required	Decreased risk of complications; more tolerable; useful in patients with comorbidities	Can take LB while performing another procedure	Increased tolerability; decreased recovery time; decreased complications; bi-lobar access; decreased sampling variability; View anatomical/vascular structures
Disadvantage	Increased sampling variability; less tolerable; require more passes; increased risk of complications	Limited view of liver parenchyma and vascular anatomy; increased sample fragmentation	Invasive; requires surgical specialty	Costly, if not performed along with another endoscopic procedure

While the PC route is cost effective and well-known, several disadvantages exist[2]. There is increased likelihood of sampling variability. Patients experience more discomfort at the puncture site, which could at times last for weeks, as the needle traverses multiple layers to access the liver and could potentially injure the intercostal nerves and vessels. Additionally, lower image resolution, higher post procedure recovery time and higher risk of complications are also disadvantages to this technique[32]. Lastly, compared to other methods, the PC method typically requires more passes to acquire an adequate tissue sample, thus increasing the risk of complications and the level of discomfort[32,33].

TJLB: Liver tissue can also be sampled *via* a TJ route, which was introduced in 1964 by Dotter[34]. In this method, an interventional radiologist introduces a guidewire into the jugular vein (commonly the right JV), followed by a needle sheath, and advanced down into the hepatic veins via the inferior vena cava, to measure portal hemodynamics and to sample the liver, circumventing the liver capsule and peritoneum. A smaller 18 or 19 G fine-needle aspiration (FNA) needle is currently being used[34,35].

This method is typically reserved for patients who have a coagulopathy, need measurement of portal pressures and gradients, are morbidly obese, or have significant ascites[1,19,36]. In patients with acute liver failure of indeterminate etiology where metastatic liver infiltration is suspected, alcoholic hepatitis, or abnormal liver tests in patients who are bone marrow transplant recipients, this method is preferable[37,38].

Complications following TJ LB are rare, 2.5%-7.1%[36,39]. A retrospective study (*n* = 601) by Mammen *et al*[39] of patients who had undergone TJLB reported a 2.5% complication rate. Kalambokis *et al*[5] also conducted a large systematic review (7649 TJLBs) on TJLB and found an overall complication rate of 7.1%. Major complications following TJLB include pain and hemorrhage[36]. An inherent risk of this method includes complications related to placement of the jugular catheter[16]. Other complications include inadequate sample size, hepatic hematoma, pyrexia, arrhythmias, abdominal pain, pneumo-thorax, haemobilia, carotid puncture, hypotension, capsular perforation, hepatic portal vein fistula and hepatic artery aneurysm[5].

Advantages/disadvantages of TJLB: One of the main advantages to this method is the decreased risk of overall complications compared to PCLB, even with multiple passes[32]. Given that the TJLB method avoids the liver capsule, there is little risk of causing injury to Glisson capsule and subsequent pain. As such, patients report increased tolerability and less pain. Secondly, this allows for decreased use of analgesia for pain control[2,32] .

Other advantages to the TJLB is its ability to be used in patients who have contraindications to PCLB. For example, this allows for assessment of liver disease in

patients with coagulopathy and acute liver failure[40]. This approach can also be utilized for dual purpose in patients with cirrhosis who require multiple interventions such as measurement of hepatic venous pressure and transjugular intrahepatic portosystemic shunt placement in addition to obtaining tissue sample[41].

The TJLB method, however, is limited in its ability to view the liver parenchyma and vascular anatomy on ultrasound. Another disadvantage of TJLB is that samples obtained have typically been more fragmented and smaller in size compared to PCLB, making pathologic evaluation at times inconclusive[1,42].

Laparoscopy/laparotomy

Laparoscopy or laparotomy represents another option for hepatic tissue acquisition that is typically used when a patient is already undergoing surgery for another indication and gross liver abnormalities are noted[43]. LBs undertaken with this approach are mostly done by wedge resection or cutting/aspiration needle. It is most useful in targeted biopsies of liver masses, staging tumors and in patients found to have inconclusive results using the PCLB or TJLB method[2].

Complications: Adverse events following the surgical approach to LB include hemorrhage, abdominal wall injury, intraperitoneal injury and those related to use of anesthesia[2].

Advantages/disadvantages: One advantage to the surgical approach to LB is that it allows for ample tissue collection, and has an extremely high diagnostic tissue yield[43]. In a retrospective study of laparoscopic LBs by Vargas *et al*[44], a conclusive diagnosis of cirrhosis was made in 93 percent of 1794 cases. Additionally, the surgical approach allows for evaluation of the gross features of the liver, as well as other important peritoneal structures. Studies have shown that the added ability to grossly evaluate the liver allows for detection of up to 30% more cases of liver cirrhosis than with LB alone[45]. Operators can also coagulate puncture sites immediately in the event of bile leakage or overt hemorrhage, which allows for LB in patients with higher risks of bleeding[46].

A disadvantage to the surgical approach is that surgery is more invasive, hence limiting its use to patients who require surgery for some other indication. A laparoscopic LB can also be more expensive, further limiting its widespread routine use[2].

EUS-LB

EUS, developed in the late 1980s and refined in the 1990s, represents a more recent approach to acquiring hepatic tissue for histological analysis[47-49]. Ever since the availability of core biopsy needles, they have been used exclusively for EUS-LB, rather than conventional fine needles. The latter is currently utilized when cytology is sufficient and tissue architecture is not critical to diagnosis. In this approach, the left lobe of the liver is identified by the echo-endoscope from the stomach and the right lobe (Figure 1) from the duodenal bulb. With use of color doppler imaging, proper care is taken to ensure there are no vascular structures along the needle path[19]. Commonly, a 19-G core biopsy needle is used to sample the left lobe followed by the right lobe[2].

Adverse events/complications: EUS-LB is generally safe, with few adverse events reported in the literature (Table 2). In a meta-analysis of studies (n = 437) reporting on EUS-LB, the rate of adverse events was 2.3%, with minor bleeding as the primary complication[50]. Additionally, Diehl *et al*[51] conducted a multicenter, prospective study (n = 110) on the diagnostic yield and safety of EUS-LB done for evaluation of abnormal liver enzymes. Out of 110 participants, one patient who had a medical history of coagulopathy and thrombocytopenia developed a non-active pericapsular hematoma that was managed conservatively[51]. Adler *et al*[52], Mok *et al*[53], Gleeson *et al*[54] and Stavropoulos *et al*[55] have conducted similar studies (n = 200, 40, 9 and 22, respectively) regarding EUS-LB with a 0% rate of complications.

Advantages of EUS-LB: There are several advantages to utilizing the EUS-LB technique over more conventional methods of acquiring tissue samples. Generally, the EUS-LB is less invasive compared to the surgical/transjugular routes, translating to lower patient and procedure related adverse events. The EUS-LB provides clinicians with a real-time, detailed view of the biopsy needle through the course of the liver and the trajectory can be changed if needed as part of the "fanning" technique to get a more representative sample[11,56] (Figure 1). Multiple cores can be obtained if needed, without increasing patient discomfort, though traditionally we take one core each from the right and left lobes. This ultimately helps to better identify and avoid important anatomic structures (intrahepatic vessels, major bile duct, *etc*.)
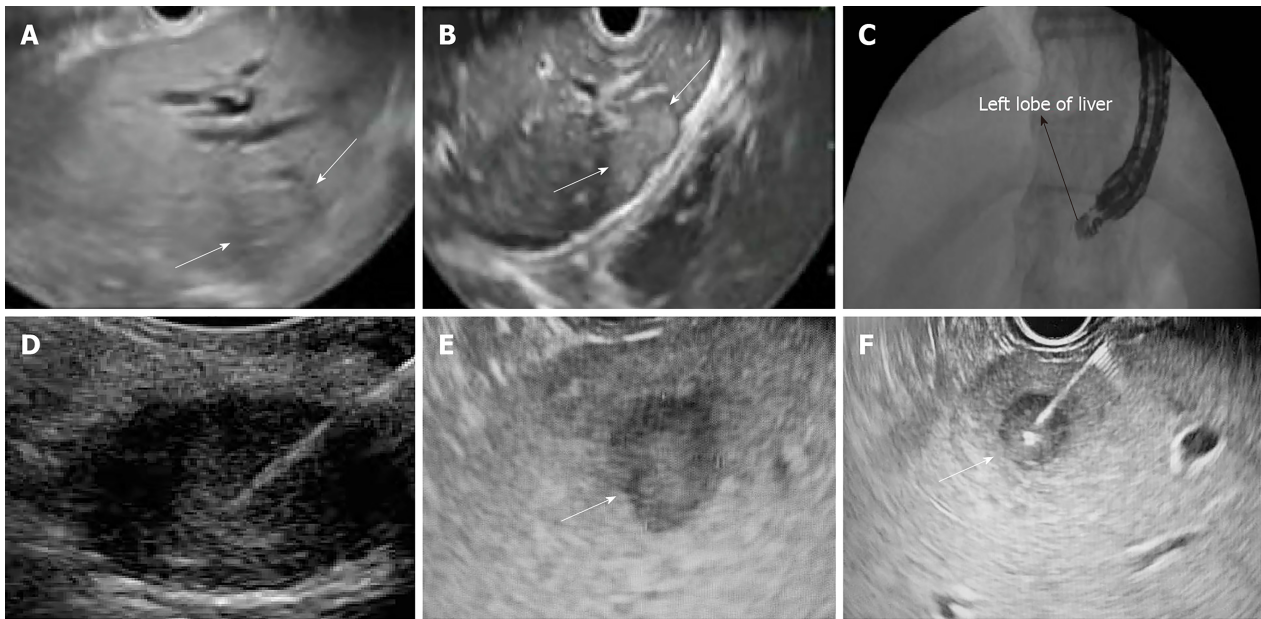
Figure 1 The endoscopic ultrasound guided liver biopsy provides clinicians with a real-time, detailed view of the biopsy needle through the course of the liver.

due to the proximity of the ultrasound device to the liver[56,57]. Whereas the PC and TJ methods have limited access to sample different areas of the liver, the EUS method allows greater access to both hepatic lobes, increasing the adequacy and yield of tissue[55,58]. Additionally, EUS allows for detection of smaller hepatic lesions and retroperitoneal structures (*i.e.*, lymph nodes) and sampling of neighboring organs that are occasionally missed by CT scan[59,60].

Patients also benefit from EUS-LB. Given that the anticipation and uncertainty of procedures may provoke anxiety in patients, EUS-LB is performed with either conscious sedation or under anesthesia, improving patient tolerance[61]. The procedure is quick, adding only a few minutes to the overall procedure time as shown by Diehl *et al*[13]. Post procedural discomfort is significantly lower in our experience in comparison to PC. Additionally, compared to conventional LB methods, EUS-LB has an average recovery time of four hours compared to ten hours in the PC method[62,63]. Patients are normally observed in the recovery room for 30 min as for any other EUS biopsy unlike 4 h for PCLB, which allows for rapid patient turnover and increased efficiency[13]. EUS-LB would also be suitable for individuals who are obese and may not be appropriate for the PCLB approach as well as for those who refuse the latter. Lastly, for patients who are planning to undergo an endoscopic procedure for another medical indication (*e.g.* screening for Barrett's, gastroesophageal reflux disease, varices or esophagogastroduodenoscopy done as part of evaluation of dyspepsia) a LB can be performed simultaneously if required under the same anesthesia, reducing time, cost and risk of multiple procedures just for tissue acquisition.

Disadvantages of EUS-LB: While EUS-LB has favorable components compared to earlier techniques, there are some disadvantages associated with its use. First, EUS-LB is a relatively new technique. As such, many clinicians who have grown accustomed to obtaining liver samples via the PC or TJ route have less experience utilizing this method[50]. Similarly, the process of learning to use traditional methods of LB is much simpler compared to the higher level of technical skills required to learn and utilize the EUS-LB[64]. The core biopsy, though it often meets the criteria proposed by international societies (as mentioned in Table 3), will be smaller, as the needle commonly used is a 19G fine needle biopsy (FNB) for EUS, compared to a 16G in the PCLB route. Additionally, undergoing endoscopy for the sole purpose of LB can be expensive, therefore limiting widespread utilization[19].

COMPARISON OF THE ADEQUACY OF DIAGNOSTIC SAMPLES AMONG LB METHODS

Obtaining an adequate histological sample is a vital step in the process of establishing a diagnosis. Various authorities have attempted to create objective parameters to

Table 2 Comprehensive review of studies on endoscopic ultrasound guided liver biopsy

Ref.	Study design	n	Indication	Needle used	No of passes	CPTs	TSL	Insufficient sample	Adverse events
Wiersema *et al*[70], 2002	Prospective cohort	9	No medical indication	19G Tru-cut	NR	1	4 mm	0	None
Gleeson *et al*[54], 2008	Retrospective case series	9	Hepatic parenchymal disease	19G Tru-cut	2	7	16.9 mm	0	None
DeWitt *et al*[71], 2009	Prospective case series	21	Hepatic parenchymal disease	19G Tru-cut	3	2	9 mm	10%	None
Stavropoulos *et al*[55], 2012	Prospective case series	22	Abnormal LFTs	19G FNA (non-Tru-cut)	2	9	36.9 mm	9%	None
Gor *et al*[73], 2014	Prospective case series	10	Abnormal LFTs; Suspected cirrhosis	19G FNA (non-Tru-cut)	3	9.2	14.4 mm	0	None
Diehl *et al*[51], 2015	Retrospective cohort	110	Persistent transaminitis	19G FNA Expect Flexible	1 to 2	14	38 mm	2%	Self-limited bleeding
Lee *et al*[67], 2015	Prospective cohort	21	Rescue for PCLB	22G FNB, 25G FNB	2	NR	NR	9.50%	None
Pineda *et al*[66], 2016	Retrospective cohort	110	Abnormal LFTs of Unknown Etiology	19G FNA Expect/Flexible	3	14	38 mm	2%	NR
Sey *et al*[72], 2016	Prospective Cross-sectional	75	Suspected parenchymal disease	19G FNB ProCore; 19G FNB Tru-Cut	2; 3	5; 2	20 mm; 9 mm	3%; 27%	None; Pain
Schulman *et al*[79], 2017	Prospective ex-vivo	48	No medical indication	18G1 (percutaneous); 18G2 (percutaneous); 19G FNA Expect; 19G FNB ProCore; 19G FNB SharkCore; 22G FNB SharkCore	1 to 2	2.5; 3.5; 1.9; 1.7; 6.2; 3.8	NR; NR; NR; NR; NR; NR	16.7%; 18.7%; 54%; 81%; 14.6%; 14.6%	None
Mok *et al*[53], 2017	Prospective cross-over	20	Elevated LFT Unknown Etiology	19G FNB; 22G FNB SharkCore	NR	7.4; 6.1	76.5 mm; 66.9 mm	2.5%; 2.5%	None; Pain
Shah *et al*[75], 2017	Retrospective chart review	24	Abnormal LFTs, pancreaticobiliary disease	19G FNB SharkCore	2	32.5	65.6 mm	4%	Pain; Subcapsular bleeding
Saab *et al*[87], 2017	Retrospective chart review	47	Biliary tract disease, abnormal LFTs	19G FNB SharkCore	NR	18	65 mm	0	Self-limited liver; hematomas
Ching-Companioni *et al*[83], 2018	Prospective randomized	40	Abnormal LFTs	19G FNA Expect Flexible; 19G FNB Acquire	1; 1	38; 16.5	11.8 mm; 16.3 mm	0	Pain
Nieto *et al*[76], 2018	Prospective observational	165	Unexplained abnormal LFTs, biliary obstruction	19G FNB SharkCore	1	18	60 mm	0	Abdominal pain; Self-limited hematoma
Mok *et al*[80], 2018	Prospective cross-over	40	Parenchymal liver disease	19G FNA Expect Flexible; 19G FNA Expect Flexible; 19G FNA Expect Flexible	3	4; 4; 7	23.9 mm; 29.7 mm; 49.2 mm	20%; 7%; 2%	Postprocedural bleeding

Rombaoa *et al*[69], 2018	Retrospective chart review	8	Unexplained abnormal LFTs, hepatitis B staging, cirrhosis	19G FNB Acquire	2	9.4	NR	NR	None
Shuja *et al*[68], 2019	Retrospective observational cohort	69	NASH fibrosis staging	19G FNA Expect Flexible	3	10.84	45.8 mm	NR	None
Hasan *et al*[77], 2019	Prospective nonrandomized trial	40	Elevated liver enzymes	22G FNB Acquire	2 L; 1 R	42	55 mm	0	Self-limiting abdominal pain
Bazerbachi *et al*[78], 2019	Prospective cohort	41	NAFLD diagnosis, staging	22G FNB Fork-tip	2	26	24 mm	0	Postprocedural pain

FNB: Fine needle biopsy; FNA; Fine needle aspiration; TSL; Total Specimen length; CPT: Complete portal tracts; *n*: Number of study participants; NAFLD: Non-alcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis.

assess the adequacy of samples, with very little consensus (Table 3). Adequacy has largely been described by the length of total specimen (TSL) and/or number of complete portal triads (CPTs), which includes the portal vein, hepatic artery and bile duct[65]. Occasionally, the length of the longest piece (LLP) of tissue is also included as a defining element. Nonetheless, few studies have directly compared the adequacy of histologic samples acquired through conventional and novel methods of LB.

Pineda *et al*[66] conducted a retrospective study comparing the adequacy of LB tissue samples obtained through the PCLB, TJLB and EUS-LB methods. PCLB was obtained with spring-loaded 18G, 19G, or 20G needles. TJLB samples were obtained with 18G or 19G needles and EUS-LB samples were obtained with regular 19G FNA needles. The number of CPTs and TSL using the EUS-LB method was found to be equivalent to PCLB and TJLB when only the left lobe was sampled. However, the study found that CPTs and TSL were significantly higher through the use of EUS-LB when both lobes were biopsied[66]. Similarly, a 2015 study (*n* = 21) by Lee *et al*[67] found that EUS-FNB could deliver adequate tissue samples and serve as an effective rescue method of LB in patients in which the PCLB method failed to obtain adequate tissue or render a diagnosis. Shuja *et al*[68] also retrospectively (*n* = 152) compared the adequacy of biopsies using the EUS-LB, PCLB, and TJLB methods for staging NASH fibrosis and found that EUS-LB produced increased TSL compared to traditional methods, with fewer complications. Likewise, Rombaoa *et al*[69] conducted a 2018 retrospective study (*n* = 8) of patients who had undergone EUS-LB with a 19G Acquire needle for abnormal LFTs, hepatitis B staging and cirrhosis. In the same study, they compared procedural and specimen results of patients who had a biopsy with the PCLB and EUS-LB method and found that numbers of CPTs were similar for both, but length of procedure and recovery times were much lower for patients in the EUS-LB group[69]. As it seems, EUS-LB is comparable to conventional methods, while improving safety profile and providing a more efficient method of obtaining liver tissue. Figure 2 demonstrate the histology of LB from the EUS approach.

EUS-LB: Early Tru-Cut needle
Early studies evaluating the efficacy of EUS-LB describe initial experiences using the 19G Tru-cut needle, albeit with variable outcomes. In a 2002 study, Wiersema *et al*[70] described EUS-LB using a 19G Tru-Cut needle in swine models that produced a median TSL of 4 mm with 100% procurement of core tissue samples. However, the authors in this study reported procedural difficulty due to the rigidity and inflexibility of the needle while going through the endoscope[70]. Later, Gleeson *et al*[54] conducted a case series review of nine patients who had undergone EUS-LB with the 19G Tru-cut needle for a variety of indications (*i.e.*, dilated CBD, abnormal liver tests with suspicious image findings and tumor staging). The mean TSL was 16.9 mm, median number of CPTs was seven, and adequate diagnostic material was acquired in 100% of cases[54]. However, in a 2009 study by DeWitt *et al*[71], 21 patients were evaluated for benign liver disease with the same Tru-Cut biopsy needle. A histologic diagnosis was obtained in 90% of cases, but the size of the samples did not meet standard criteria for histologic assessment[71]. The Tru-Cut needle, partially due to the inflexible design, was deemed difficult to use, limiting its widespread adoption.

EUS-LB with FNA
Given the limited adoption of the early TruCut needle, the search for alternative EUS-LB needles led to the use of a 19G EUS–FNA needle, which has long served as the

Table 3 Summary of society guidelines for adequate liver biopsy

Medical society	Total specimen length	Complete portal triads	Needle size
American Association for the Study of Liver Diseases	2-3 cm	≥ 11	16G
European Association for the Study of the Liver	15 mm	-	-
Asian Pacific Association for the Study of the Liver	15 mm	≥ 10	16G

mainstay for obtaining hepatic tissue. Multiple studies have demonstrated the accuracy and practicality of EUS-FNA using the 19G needle[71-73]. In 2012, Stavropoulos *et al*[55] conducted a prospective case series of EUS-LB with a regular non-Tru-cut 19-G FNA needle in 22 patients with abnormal LFTs of unclear etiology. With a median TSL of 36.9 mm, median of 9 CPTs and a diagnosis achieved in 91% of cases, the authors concluded that EUS-FNA with a 19G FNA needle was effective with good diagnostic yield[55]. Later, in a 2014 study (*n* = 10) by Gor *et al*[73], patients had an EUS-LB with a 19G FNA needle for abnormal LFTs. There was a yield of 100% diagnostic adequacy, a mean TSL of 14.4, and a mean CPT of 9.2 with no reported complications[73]. In 2015, Diehl *et al*[51] presented a large multicenter study (*n* = 110) in patients with elevated liver enzymes who had an EUS-LB with a 19G FNA needle. The median TSL was 38 mm, with a median of 14 CPTs, yielding adequate tissue for diagnosis in 98% of the cases. Adverse events were uncommon, but bleeding was reported in one patient with a history of coagulopathy[51]. Though widely implemented, EUS-FNA may be limited in its ability to provide core tissue samples with good architecture. Further, the diagnostic yield of FNA is variable, depending on needle the size and type, operator experience as well as the obtainability of rapid onsite evaluation (ROSE).

EUS-LB with FNB

The increasing utility of EUS-FNB, partly due to the advent of newly designed, more flexible, biopsy needles (EchoTip, ProCore, SharkCore, Acquire needle, EZ shot 3 plus needle, *etc*.) may improve diagnostic yield of LBs, and reduce or possibly negate the need for ROSE[74].

In a 2016 cross-sectional study (*n* = 75) Sey *et al*[72] compared the diagnostic yield of a novel reverse bevel 19G FNB ProCore needle with the early 19G Tru-cut biopsy needle. The authors found that EUS-LB with the newer ProCore needle produced specimens with a longer median length (20 mm *vs* 9 mm), more CPTs and more adequate specimens with fewer passes. Shah *et al*[75] reached a similar conclusion in a retrospective study (*n* = 24) of patients with abnormal LFTs and pancreatobiliary conditions, who had undergone EUS-LB with a novel 19G FNB SharkCore. A histologic diagnosis was achieved in 96% of cases, with a median TSL of 65.6, median CPT of 32.5 and a median of two passes. Nieto *et al*[76] conducted a recent 2018 retrospective study (*n* = 165) using a modified 1-pass wet suction technique in patients with elevated LFTs of unclear etiology who had undergone EUS-LB for exclusion of biliary obstruction. The median TSL in their study was 6 cm, the median number of CPTs was 18 and the authors concluded that EUS-LB with the modified 1-pass wet suction technique was safe and effective.

Recent studies have also demonstrated potential use with a smaller, 22G FNB needle. In a 2019 study (*n* = 40), Hasan *et al*[77] analyzed biopsy results of patients referred for evaluation of elevated LFTs. There were two passes made from each hepatic lobe, yielding a median TSL of 55 mm, a median CPT of 42, and 100% specimen adequacy. Self-limiting abdominal pain was the only complication reported. In another recent 2019 prospective study (*n* = 41), Bazerbachi *et al*[78] demonstrated that EUS-LB with a 22G fork-tip core biopsy needle can be accurately used to stage non-alcoholic fatty liver disease (NAFLD) and may be superior to magnetic resonance elastography (MRE) in detecting early fibrosis is NASH. The median TSL was 2.4 cm, median CPT was 26 and 100% of samples achieved adequacy in staging fibrosis.

Comparison of diagnostic samples by needle: EUS-FNA vs EUS-FNB

Different authors have conducted comparative evaluations of EUS-LB with FNA and FNB in attempt to establish a pattern of superiority. In a large 2017 study, Schulman *et al*[79] directly compared the histologic samples of six different LB needles (19G Expect FNA needle, 19G SharkCore FNB needle, 22G SharkCore FNB needle, 19G Procore FNB needle and two 18-G PC needles) that were used on human cadavers. The mean number of CPTs (6.2) was significantly higher in specimens taken with the novel 19G SharkCore FNB needle. Similarly, both the 22G and 19G SharkCore FNB needle achieved the highest specimen adequacy and percent of core samples, suggesting
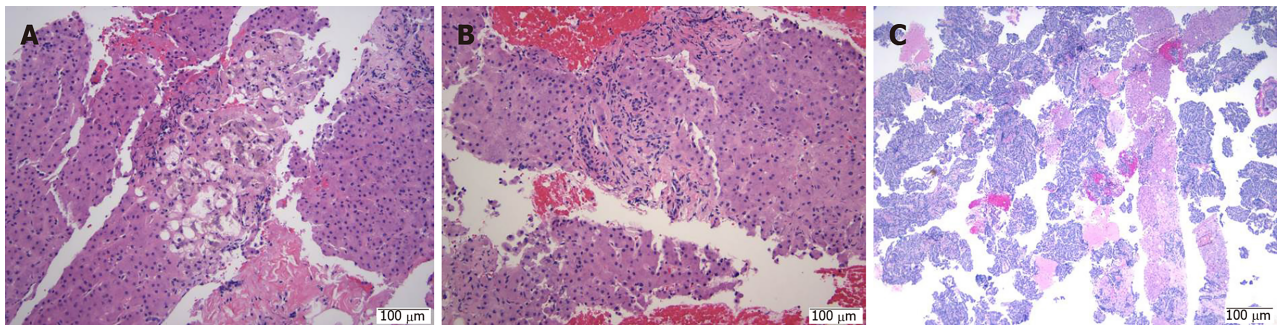
Figure 2 Histology of liver biopsy from the endoscopic ultrasound approach. A: Liver parenchyma with macrovesicular steatosis and focal ballooning degeneration (200× magnification, hematoxylin-eosin staining); B: Liver parenchyma with portal tract (center, 200× magnification, hematoxylin-eosin staining); C: Liver biopsy performed to target a mass lesion that was a clinically suspected metastasis (40× magnification, hematoxylin-eosin staining). The majority of the biopsy is composed of pleomorphic epithelioid cells in sheets and trabeculae that was suggestive of metastatic germ cell tumor.

superiority to the PC and 19G FNA needle in EUS-LB. Another recent study (*n* = 20) by Mok *et al*[80] evaluated tissue adequacy of a 22G FNB needle and a 19G FNA needle and found that the 19G FNA needle had greater tissue adequacy. However, a major limitation of this study is that the authors compared two different types of needles and two different gauges, making it difficult to conclude that the findings observed in this study were due differences in gauges and not the result of both variables compounded.

A meta-analysis by Khan *et al*[81] found similar diagnostic yield between EUS-FNA and EUS-FNB, but only when ROSE was used with FNA. Without ROSE, FNB produced better diagnostic adequacy in solid lesions and required fewer passes to reach a diagnosis. Similarly, another meta-analysis of studies comparing sample quality between the FNB ProCore needle and the standard FNA needle also showed comparable sampling and diagnostic results. However, the ProCore needle was able to obtain a diagnosis with fewer passes[82]. To further compare, a prospective trial (*n* = 40) of EUS-LBs demonstrated that 19G FNB needles produced specimens with longer specimen length, longer pieces of tissue core and more CPTs compared to 19G FNA needles[83].

Tissue acquisition techniques

Different techniques of tissue acquisition have been proposed to improve the diagnostic yield of EUS-LB. Many endoscopists use suction techniques or a slow-pull technique with FNA[7]. Some of the common EUS-LB suction techniques include dry heparin, dry suction technique (DRST) and wet suction technique (WEST). High negative pressure suction with an air-filled pre-vacuum syringe has been used in conventional EUS-FNA, but diminishes the sample quality by increasing the amount of blood in the specimen[84]. The WEST, on the other hand, was designed to address this specific issue and improve tissue yield. The WEST essentially uses pre-flushed saline instead of air. A prospective study found significantly greater cellularity and improved diagnostic yield in the WEST compared to DRST[85]. Similarly, use of a heparinized needle to prevent coagulation has been shown to improve tissue yield for EUS-LB. In a 2018 prospective study (*n* = 40) by Mok *et al*[53], three LB samples were taken from each patient, using the DRST, dry heparin and wet heparin techniques. Specimens taken with the wet heparin suction technique had less tissue fragmentation, produced more CPTs, and maintained increased aggregate specimen length and longer lengths of the longest piece compared to both dry methods[53]. Other techniques used include the fanning technique, which is used to obtain more tissue with fewer passes and the slow pull technique, which relies upon the negative pressure within the needle as the stylet is being slowly removed by the assistant during FNA "throws"[86].

While these techniques are useful for EUS-FNA, few studies have explored techniques that can be applied when using newer FNB needles. The modified 1-pass 1 actuation wet suction technique, however, may show promise. One recent retrospective study (*n* = 165) described the modified 1-pass 1 actuation wet suction technique with a 19G EUS-FNB (SharkCore) needle in patients evaluated for abnormal liver chemistries. The median TSL was 6 cm and the mean of CPTs was 7.5 cm, suggesting an effective technique[76]. Saab *et al*[87] also concluded that the 19G core biopsy needle with the use of the modified one-pass wet suction technique was more accurate in diagnosing and staging NAFLD compared to MRE.

EUS-LB in special populations

Gastric bypass: Patients with altered anatomy, such as a gastric bypass, may also undergo EUS-LB safely and effectively. Amongst the cohort of patients evaluated for abnormal liver enzymes or liver disease in a prospective study by Diehl *et al*[51], 2/110 participants presented with a surgical history of a Roux-en-Y gastric bypass. Due to their altered anatomy, the right lobe of the liver was inaccessible. Therefore, EUS-LB of only the left lobe was taken, albeit successfully, through the transgastric approach, with sufficient tissue to render a diagnosis, and no procedural complications[51].

Liver transplant patients: Patients with a history of liver transplantation comprise a unique group in which LB may be required. Indications for LB in this population include histologic evaluation (in pre-transplant liver donors), monitoring for evidence of graft injury, confirming a diagnosis in patients with acutely abnormal LFTs, assessing the degree of injury or fibrosis, and monitoring changes following therapeutic intervention[88]. A retrospective study, in which nearly a quarter of participants were liver transplant patients, found that EUS-LB was safe and effective in evaluating post liver transplant patients with abnormal liver chemistries. EUS-LB was performed successfully with a 19G core needle via modified wet suction technique, with no complications or adverse events noted in the transplant group[89]. Multiple larger studies are needed to clearly identify the role of EUS-LB in post-transplant patients as they pose unique challenges in terms of post-surgery status, anatomical variations and higher risk of post procedure infections.

Pediatric patients: Much of the existing literature regarding the efficacy of EUS-LB is limited to studies pertaining to the adult population, but very few studies have evaluated the use of EUS-LB in the pediatric population. Johal *et al*[90] reported the first known case series (*n* = 3) demonstrating the usefulness and safety of EUS-LB in three pediatric subjects who were evaluated for persistently elevated liver enzymes of unclear etiology. The biopsy was successfully performed with a 19G EUS-FNA needle and allowed for good histological return in all three cases yielding CPTs of 20, 31 and 16, and a tissue lengths of 30 mm, 53 mm and 62 mm. No procedure related adverse events or complications were noted in any of the children. Additional studies in this particular population are needed, but preliminary reports suggest that EUS-LB in pediatric patients is safe and effective[90].

CONCLUSION

LB is an essential tool in diagnosing, evaluating and treating various diseases of the liver. While the traditional PCLB and TJLB methods are established and have been used extensively, there are some disadvantages to their use. Thus, EUS-LB represents a more novel, effective and safe alternative to obtaining hepatic tissue with several advantages. EUS-LB allows for detection of smaller lesions and bi-lobar liver sampling, which in turn improves tissue yield and obtains more representative sampling, allowing for greater diagnostic potential. The use of real time imaging guidance with doppler also helps reduce inadvertent injury to pertinent anatomic structures and procedure related complications. While cost and availability of expertise are possible barriers to the widespread use of this technique, EUS-LB offers several benefits that should be given appropriate weight when choosing a method of LB. More evidence is needed in terms of multi-center trials with randomization before this technique can be adopted as a new standard.

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