

World Journal of *Hepatology*

World J Hepatol 2019 April 27; 11(4): 335-411



MINIREVIEWS

- 335 Endoscopic ultrasound guided liver biopsy for parenchymal liver disease
Shah AR, Al-Hanayneh M, Chowdhry M, Bilal M, Singh S
- 344 MicroRNAs contribute to ATP-binding cassette transporter- and autophagy-mediated chemoresistance in hepatocellular carcinoma
Espelt MV, Bacigalupo ML, Carabias P, Troncoso MF

ORIGINAL ARTICLE**Basic Study**

- 359 Beneficial effects of losartan or telmisartan on the local hepatic renin-angiotensin system to counter obesity in an experimental model
Graus-Nunes F, Santos FDO, Marinho TDS, Miranda CS, Barbosa-da-Silva S, Souza-Mello V

Retrospective Study

- 370 Being accompanied to liver discharge clinic: An easy measure to identify potential liver transplant candidates among those previously considered ineligible
Sack J, Najafian N, DeLisle A, Jakab S
- 379 Effectiveness of venous thromboembolism prophylaxis in patients with liver disease
Yerke J, Bauer SR, Bass S, Torbic H, Militello M, Roach E, Hanouneh I, Welch S

Observational Study

- 391 Nonalcoholic fatty liver disease prevalence in an Italian cohort of patients with hidradenitis suppurativa: A multi-center retrospective analysis
Damiani G, Leone S, Fajgenbaum K, Bragazzi NL, Pacifico A, Conic RR, Pigatto PD, Maiorana C, Poli P, Berti E, Pace MC, Malagoli P, Bettoli V, Fiore M

CASE REPORT

- 402 Leukocytoclastic vasculitis caused by hepatitis C virus in a liver transplant recipient: A case report
Ferreira GDSA, Watanabe ALC, Trevizoli NDC, Jorge FMF, Diaz LGG, Araujo MCCL, Araujo GDC, Machado ADC

LETTER TO THE EDITOR

- 409 Yes-associated protein at the intersection of liver cell fate determination
Bai YF, Wang SW, Xu ZC, Zhu J, Zhang F

ABOUT COVER

Associate Editor of *World Journal of Hepatology*, Pietro Invernizzi, MD, PhD, Assistant Professor, Liver Unit and Center for Autoimmune Liver Diseases, Humanitas Clinical and Research Center, Rozzano 20089, Italy

AIMS AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, etc. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, etc.

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The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang* Proofing Editorial Office Director: *Ya-Juan Ma*

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ke-Qin Hu, Koo Jeong Kang, Nikolaos Pyrsopoulos

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

EDITORIAL OFFICE

Ya-Juan Ma, Director

PUBLICATION DATE

April 27, 2019

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

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Endoscopic ultrasound guided liver biopsy for parenchymal liver disease

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Author contributions: Bilal M and Singh S designed the outline for the manuscript; Shah AR, Al-Hanayneh M, Chowdhry M and Bilal M wrote critical portions of the initial manuscript; Bilal M and Singh S provided expert opinion, and edited the final version of the manuscript.

Conflict-of-interest statement: The authors report no conflict of interest and have no financial disclosures with respect to this manuscript.

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Manuscript source: Invited manuscript

Received: December 28, 2018

Peer-review started: December 29,

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Abstract

Liver biopsy plays an essential role in the diagnosis, evaluation and management of a vast proportion of liver diseases. Conventionally, percutaneous and transjugular approaches have been used to obtain liver biopsies. Endoscopic ultrasound guided liver biopsy (EUS-LB) has emerged as a safe and effective alternate in the past two decades. EUS-LB carries a role in evaluation of both benign and malignant diseases of the liver. It can offer higher resolution imaging of the liver and can detect smaller lesions than computed tomography scan of the abdomen or ultrasound scans with the option for doppler assistance to reduce complications. Current evidence demonstrates the superiority of EUS-LB for a targeted approach of focal lesion and there is also evidence of less sampling variability in heterogeneous parenchymal pathologies. These advantages combined with an improved safety profile had led to the rapid progress in the development of new techniques, equipment and procedures for EUS-LB. We provide a comprehensive review of EUS-LB for parenchymal liver disease.

Key words: Liver biopsy; Endoscopic ultrasound; Endoscopic ultrasound guided liver biopsy; Liver disease

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Core tip: In this review, we provide a comprehensive discussion on the role of Endoscopic ultrasound guided liver biopsy (EUS-LB) in parenchymal liver disease. This article summarized the technical aspects of EUS-LB; as well as debated its advantages and disadvantages. We also highlight new advancements and recently reported research

2018

First decision: March 5, 2019**Revised:** March 24, 2019**Accepted:** April 8, 2019**Article in press:** April 8, 2019**Published online:** April 27, 2019**P-Reviewer:** Altonbary A,
Garbuzenko DV, García-Flórez LJ,
Kitamura K, Neri V, Nishida T**S-Editor:** Cui LJ**L-Editor:** A**E-Editor:** Zhang YL

experiences.

Citation: Shah AR, Al-Hanayneh M, Chowdhry M, Bilal M, Singh S. Endoscopic ultrasound guided liver biopsy for parenchymal liver disease. *World J Hepatol* 2019; 11(4): 335-343**URL:** <https://www.wjgnet.com/1948-5182/full/v11/i4/335.htm>**DOI:** <https://dx.doi.org/10.4254/wjh.v11.i4.335>

INTRODUCTION

Liver biopsy plays an essential role in the diagnosis, evaluation and management of a vast proportion of liver diseases. History, physical exam, laboratory testing and radiological exams continue to be the mainstay in diagnosis of disease, however, the use of these modalities without liver biopsy can miss up to one-third cases of cirrhosis^[1]. Histological examination of biopsy samples can not only help identify the underlying pathophysiology of liver disorder but also quantify its severity. This has a significant impact on the management of as many as one-fifth of all patients with liver disease^[2]. In the past, liver biopsy was performed *via* the percutaneous route without image guidance^[3]. However this has now been largely replaced by ultrasound-guided or computed tomography (CT) guided biopsy to limit potential complications^[4,5]. When a percutaneous biopsy is not feasible a trans-jugular approach is used. Open or laparoscopic surgical biopsy is usually last resort. Endoscopic ultrasound guided liver biopsy (EUS-LB) is a technique that has recently gained popularity since it offers certain advantages over the traditional methods of obtaining tissue samples. Endoscopic ultrasound is an established imaging modality that is essential in the assessment of a broad array of luminal, hepatobiliary, and pancreatic disorders. It provides high resolution images of both lobes of the liver, hence allowing a potentially easier and safer biopsy technique whilst providing the opportunity to target focal hepatic lesions^[6]. The choice of technique is eventually based upon expertise of the operator, anatomical barriers and risk profile of the patient (coagulopathy, hepatic vascularity and presence of ascites). In this review, we provide a detailed comparison between EUS-LB and traditional modalities of liver biopsy.

APPROACHES TO LIVER BIOPSY

The advent of liver biopsies is dated back to the 19th century, with Paul Ehrlich reporting the first successful liver aspiration in 1883^[4,7]. However, it wasn't until four decades later that the first percutaneous liver biopsy was successfully performed in Germany in 1923^[4,5]. Even a century later this remains the preferred approach to obtaining hepatic parenchymal tissue^[3]. Over time, advances in imaging modalities have led to the addition of ultrasound and CT scan guided liver biopsy^[5,8].

Previously percutaneous liver biopsy (PC-LB) was performed "blindly" using percussion to identify the liver anatomy^[3]. This has now largely been replaced by image-guidance, either by ultrasonography or CT scan^[8]. Most commonly large gauge needles (16-18) are used, although depending on expertise smaller needles are also utilized at some centers^[9]. Percutaneous biopsy can be classified as transthoracic (transpleural) or subcostal depending on the site of entry. This requires an enlarged liver extending below the diaphragm for a safe approach. Pain, bleeding, infection, peritonitis, pleural injury resulting in pneumo- or hemo-thorax continue to be common complications of percutaneous biopsy^[9,10]. Image guidance partly mitigates these risks, but studies have reported adverse event rates up to 1%^[3,10].

Trans-jugular biopsy of the liver emerged as a viable technique in the 1960s based on the works of an interventional radiologist - Charles Dotter^[11]. Over time it has become an accepted and safe alternative to percutaneous biopsy in select settings^[12]. The internal jugular vein is cannulated to gain access to the hepatic vein, allowing tissue acquisition without the need to traverse the liver capsule^[13]. This approach is preferred in patients who have coagulopathy, hepatic peliosis, large volume ascites or morbid obesity^[12]. Rates of success have been reported as high as 97% and the complication rates as low as 1.3%^[14]. Complications include hepatic capsule perforation, major hemorrhage, pain from hematoma, hemobilia, arterial aneurysms and arrhythmias^[12]. Fortunately however, major complications are rare and minor bleeding from the access site and transient abdominal pain from hematomas are the

most commonly reported adverse events^[14,15].

EUS was developed in the 1980s and has been gaining popularity. This was further revolutionized in the early 1990s with the advent of Fine Needle Aspiration (FNA)^[16]. Significant advances have been made since then and now EUS is widely used as both a diagnostic and therapeutic modality. EUS-LB has recently emerged as another technique for obtaining liver tissue. Although as described earlier; several approaches and techniques are there for obtaining a liver biopsy, EUS-LB offers several advantages over conventional approaches. EUS offers a more precise localization and characterization of target tissue which helps to improve diagnostic yield^[17,18]. More so, it is arguably a less invasive and better tolerated approach than conventional methods^[15,19]. It offers the advantage of good access to both the lobes of liver and the presence of doppler assistance decreases the chances of complications^[20]. Other important considerations for choosing EUS-LB over conventional methods of liver biopsy include contraindications to percutaneous biopsy.

EUS GUIDED SAMPLING TECHNIQUES FOR PARENCHYMAL LIVER DISEASE

Since the onset of EUS-LB, multiple needle types and techniques have been reported for its use. In the next few segments, we review the historic timeline for various needle types and discuss the different techniques used to help in increasing the diagnostic yields of EUS-LB. Core sample obtained *via* EUS-LB is shown in [Figure 1](#).

How is a good quality liver biopsy defined?

The criteria for an adequate liver biopsy had been well defined. Per the American Association for the Study of Liver Disease (AASLD), adequacy of samples are defined as number of complete portal triads (CPTs) to be 11 and total sample length (TSL) of 30 mm, and with no or minimum fragmentation of the sample^[21]. However, the definition of adequacy for liver biopsy sample remains controversial in the literature^[22-26].

Needle types

Tru-cut biopsy: In 2002, the initial experience with EUS-LB was in swine models using Tru-Cut biopsy needles. In a study by Wiersema *et al*^[27], they performed EUS-LB of multiple peri-gastric organs using a 19 gauge Tru-Cut needle. The median TSL was 4 mm for liver samples and 78% had fragmentation, however the number of CPT was not reported. They reported difficulty in the procedure due to the use of the stiff needle since problems were encountered in making the needle bend to traverse through the flexible endoscope. They concluded that the method is safe and feasible, however did not meet criteria for adequate liver biopsy samples and were technically difficult. Due to the aforementioned reasons this method was not widely used.

However, in 2009, Gleeson *et al*^[28] also reported outcomes using the Tru-Cut needle. They reported that results of EUS Tru-Cut needle biopsy are comparable to those of trans-jugular liver biopsy. In their small study with the use of Tru-Cut needle on 9 patients, they reported the TSL of 16.9 mm and a median of 7 CPTs. Although the results do not suffice the criteria of having at least 11 CPT per AASLD^[21], they were able to reach a histopathologic diagnosis in all 9 patients. However, the study was retrospective and only included 9 patients.

Overall, the EUS Tru-Cut biopsy did not gain wide spread popularity for diagnosing parenchymal liver disease and more novel needles and techniques emerged which made Tru-Cut biopsies fall out of favor.

19 Gauge FNA “non tru-cut” needle: Several studies reported using 19 gauge FNA needle, with the first one published in 2012^[24]. In this study, Stavropoulos *et al*^[24] performed EUS-LB on patient undergoing EUS to rule out biliary obstruction when the exam was unrevealing. The median length of obtained specimens was 36.9 mm ranging from 2 to 184.6 mm, nine complete portal tracts (range: 1-73), diagnostic adequacy of 91%, and no post-procedure complications. The outcomes showed comparable biopsy quality results to percutaneous and trans-jugular liver biopsies. They concluded that for patients being investigated by endoscopic ultrasound for biliary obstruction; EUS-LB was a safe, reliable and cost-effective option to diagnose parenchymal disease.

In one large study published in 2015 by Diehl *et al*^[29], liver biopsy specimens obtained *via* EUS were sufficient for pathological diagnosis in 98% of the cases. The aggregate length of tissue acquired ranged from 0 to 203 mm with a median of 38 mm. A total of 0 to 68 CPTs were obtained and the median was 14. This led the authors to conclude that EUS-LB using a 19 gauge FNA needle, is a safe technique yielding

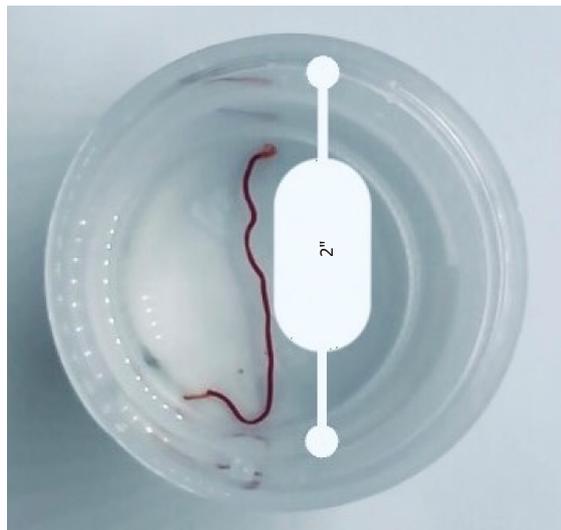


Figure 1 Core biopsy sample obtained via endoscopic ultrasound guided liver biopsy.

adequate tissue for pathological diagnosis in 98% of the patients.

This needle provides a higher diagnostic yield and is less technically challenging to use in comparison with the Tru-Cut biopsy needle. However, the ideal technique has not been yet defined and larger studies are needed. Different biopsy techniques are discussed in the next section.

19 Gauge Fine Needle Biopsy needle: A new 19 gauge fine needle biopsy (FNB) needle has shown promising results and a higher diagnostic yield. Schulman *et al*^[30] compared the different needle types and biopsy techniques. They studied 6 different needle types (four EUS-LB needles and two percutaneous needles) on human cadaveric tissue and had a total of 288 liver samples. They concluded that a novel 19 gauge needle (SharkCore 19 gauge FNB needle) had significantly better diagnostic yield compared to all other needle types in the study including the second FNB needle used in the study, the ProCore FNB (Echo Tip HD ProCore).

In this study four discrete suction techniques were used in addition to one fanning pass *vs* three fanning pass patterns of needle excursion. Analysis of the subgroups showed that three fanning pass needle excursion pattern was an independent prognosticator of CPT, however the suction techniques had no effect on the adequacy of the tissue sample when other variables were controlled. This type of needle also had overall less tissue fragmentation rates compared to the other needles with an 84% mean of core samples from tissue obtained using this needle. This study was double blinded and randomized, however was done on ex-vivo on cadaveric tissue. This needle type seems to have a promising future, however more studies need to be done on non-cadaveric diseased liver with comparison to other biopsy modalities to confirm its superiority and overall cost-effectiveness.

Biopsy techniques

Several techniques have been used to increase the diagnostic yield of EUS-LB. The technique for performing EUS-LB is demonstrated in Video 1. Diehl *et al*^[29] reported performing multiple movements with the needle “fanning technique” in which the needle is advanced to-and-fro at different areas to obtain tissue samples^[31].

Most endoscopists use full suction with needle aspiration as well. Suction techniques include ten-/twenty-/thirty-mL method. Alternatively, a slow-pull technique may be used where the stylet is drawn out from the needle once it is in the desired location^[7].

More recently, newer techniques have emerged in attempts to increase the diagnostic yields of EUS-FNB including the use of “wet suction”. In this technique a heparinized needle is used to reduce chances of coagulation and hence, improve tissue retrieval whilst minimizing comminution of tissues samples. A recent study by Mok *et al*^[32] compared this method to both “dry heparin” and “dry needle” technique. This was a prospective study on 40 patients, were they all had 3 EUS-FNA liver biopsies using the 3 different methods. In this method, needles are heparinized till drops are seen at the needle-point while ensuring no air is pushed through. Two milliliters of water are then drawn into the syringe and a twenty-milliliter vacuum-syringe is connected. They concluded that “wet suction” technique had better tissue

yield in comparison to “dry needle” method. However, the question remains if this technique is necessary or even useful when using the more novel FNB needles as these needles provided superior results regardless if wet suction was used or not.

Another recently described technique is the “modified 1-pass 1 actuation wet suction technique [EUS-modified liver biopsy sampling (EUS-MLB)]”. This was described in a study by Nieto *et al*^[33] They used the FNB-needle (SharkCore) which was prepped normal saline. Suction was applied to the FNB-needle at a depth of seven cm into the hepatic parenchyma. Large vessels were avoided using Doppler assistance. Both right and left lobes were sampled *via* a “rapid-puncture” and one actuation for each lobe. The authors concluded that “EUS-MLB” was effective and safe in evaluation of inexplicable liver disease. The median TSL in their study was 6 cm, and the median number of CPTs per TSL was 18.

ADVANTAGES OF EUS-GUIDED BIOPSY

Historically percutaneous liver biopsy was done “blind”, however in present times this has largely been replaced by image guided biopsy. Image guidance is postulated to help increase sampling adequacy and more importantly reduce complications^[4]. There is some controversy regarding this and conflicting data have been reported^[4,34]. In 1991, Vautier *et al*^[34] reported that ultrasound guidance does not reduce bleeding complications from PC-LB and concluded that image guided liver biopsy may not be safer than blind biopsy. A retrospective analysis looked at the complications and safety profile of liver biopsy in patients enrolled in the HALT-C trial^[35]. All the patients included in this trial had advanced chronic liver disease. A total of 2740 liver biopsies were performed and 90% were ultrasound guided. 16 of the total 29 cases of significant adverse events were from bleeding complications. EUS guidance aims to mitigate these complications further by better anatomical definition and doppler assistance.

Linear echoendoscopes were first introduced in the 1990s^[36]. Linear echoendoscopes allowed the use of doppler ultrasound and the ability to track needles in real-time. Combined with high resolution imaging, the intrahepatic vessels and major bile ducts can be easily identified and avoided during biopsy, hence reducing potential complications^[37].

Commonly a sixteen-gauge needle is used for percutaneous liver biopsy. On the contrary using nineteen-gauge needles for EUS-LB reduces possible complications. A large trial comprising over a hundred patients studied the diagnostic yield and safety of EUS-FNA using a 19-gauge needle^[29]. Reported diagnostic yield was 98% as measured by the tissue sample length and presence of complete portal tracts. Serious adverse event was reported in one patient who developed a sub-capsular hematoma that required only conservative management. The authors concluded that EUS-LB was a safe technique with comparable diagnostic accuracy to PC-LB. Adler *et al*^[38] performed a multicenter retrospective review of 200 patients, specifically looking at safety and performance when sampling solid lesions. They reported excellent diagnostic yield at 98.5%, however 6.5% of the patients needed a repeat procedure at some point. No adverse event was identified in the population. **Table 1** summarizes the diagnostic accuracy and adverse event rates of EUS-LB.

EUS guidance has the benefit to sample and evaluate both lobes of the liver, hence achieving more accurate representation of liver histology, potentially addressing concerns about sampling error^[24]. PC-LB and transjugular biopsies are both subject to sampling variability due to heterogeneity of parenchymal diseases^[39]. This variability can be reduced by sampling both the liver lobes. EUS-LB allows easier access to the right and left lobe of liver; thus minimizing this variability^[39].

For Pancreatic lesions EUS guided biopsy has proven superiority as an imaging modality for as it allows greater anatomical definition and higher resolution with the ability to sample ascites, local lymphatic structures and small liver nodules^[40]. There is some evidence suggesting that for smaller liver lesions EUS-LB is indeed also superior and safer than PC-LB with CT or ultrasound guidance^[41,42].

Other advantages of EUS-LB include a much shorter recovery time (about 4 h) than that of PC-LB (commonly at least 10 h)^[13,43,44]. Another potential benefit is that patients are sedated for the EUS procedure, thus EUS-LB is better tolerated in most instances as compared with PC-LB^[44,45]. However, it is important to remember that the benefits of sedation and anesthesia must be balanced against risk of respiratory depression. As described for trans-jugular biopsy, EUS-LB also has the potential advantage in patients with morbid obesity, large ascites, peliosis hepatis, and coagulopathy^[14,15].

Table 1 Current evidence of diagnostic accuracy and adverse event rates of endoscopic ultrasound guided liver biopsy

	Sample size	Diagnostic yield	Serious adverse events
Gleeson <i>et al</i> ^[28] , 2009	9	0%	0%
Schulman <i>et al</i> ^[30] , 2017	288	84%	NA (cadaveric tissue)
Stavropoulos <i>et al</i> ^[24] , 2012	22	91%	0%
Diehl <i>et al</i> ^[29] , 2015	110	98%	0.9%
Mok <i>et al</i> ^[32] , 2018	40	98% (wet suction)	0%
Nieto <i>et al</i> ^[33] , 2018	165	> 90%	1.8%
Adler <i>et al</i> ^[38] , 2018	200	98.5%	0%

DISADVANTAGES

Despite its advantages over the other liver biopsy techniques, the application of EUS-LB in everyday practice has yet to reach its full potential. One of the barriers to this is the relative novelty of the technique. PC-LB and trans-jugular approaches have been used in clinical practice much longer than EUS-LB and hence operators have more experience with these. The conventional techniques are also easier and require less technical expertise. This is especially true with the use of Tru-Cut needle for biopsy which is more technically demanding and may have variable sample yield^[46]. Tru-Cut needles have been largely replaced with more flexible needles that can be navigated with more ease^[27,47].

Left lobe of the liver can be approached through the gastric wall, whilst the right lobe is accessed *via* the duodenum. Right Hepatic Lobe sampling can be difficult in some cases due to difficulty in navigating the biopsy needle at sharp angles across the duodenum^[15,48]. This again is more of an issue with Tru-Cut needles which have limited flexibility^[47].

Another important consideration is the cost of procedure. EUS-LB has a much higher cost when compared to PC-LB and this can be prohibitive to the widespread use^[15,39]. However, this drawback is offset in patients who are undergoing an endoscopy for another indication (such as esophageal varices screening). EUS-LB may be done during the same session with little additional time and risk. Patients intolerant or non-compliant of pre-procedure preparation can also prove to be a challenge to successful EUS-LB. **Table 2** summarizes the comparison between PC-LB and EUS-LB.

CONCLUSION

Liver biopsy remains essential in diagnosis, evaluation and management of numerous liver diseases. Whilst percutaneous biopsy remains the test of choice, it has its drawbacks; and hence EUS guided liver biopsy has emerged over the recent past as a safe and effective alternative. Advantages of EUS-LB include easier access to both lobes of liver and improved diagnostic accuracy in heterogeneous parenchymal diseases as well as detecting multiple focal lesions. Procedure and recovery times are shorter with less reliance on patient cooperation. Additionally, the use of doppler assistance helps avoid blood vessels reducing risk of hemorrhage; which is the most common complication of liver biopsy.

Techniques of obtaining liver samples with EUS guidance and the equipment used, such as types of needles; is constantly changing. However, current evidence on EUS-LB techniques is conflicting and there is no consensus on the best technique and type of needle used. Nevertheless, most centers have published positive results from their individual experiences. Despite these advances cost barriers and sparsity of technical expertise continue to remain limiting factors for the wide spread use of EUS-LB.

Table 2 Comparison of percutaneous liver biopsy with endoscopic ultrasound guided liver biopsy

	PC-LB	EUS-LB
Anatomical definition	Likely improved with ultrasound guidance	Better than PC-LB and the addition of Doppler reduces complications
Imaging resolution	Lower	Higher
Diagnostic yield/accuracy		Comparable
Sampling error	Higher	Lower
Access to liver lobes	Predominantly right lobe sampling	Can easily sample both right and left lobes
Average recovery time	10 h	4 h
Technical difficulty	Lower	High
Cost	Low	High

PC-LB: Percutaneous liver biopsy; EUS-LB: Endoscopic ultrasound guided liver biopsy.

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