Diagnostic and interventional EUS in hepatology: An updated review

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ABSTRACT

EUS has become an increasingly used diagnostic and therapeutic modality in the armamentarium of endoscopists. With ever-expanding indications, EUS is being used in patients with liver disease, for both diagnosis and therapy. EUS is playing an important role in providing additional important information to that provided by cross-sectional imaging modalities such as computerized tomography and magnetic resonance imaging. Domains of therapy that were largely restricted to interventional radiologists have become accessible to endosonologists. From liver biopsy and sampling of liver lesions to ablative therapy for liver lesions and vascular interventions for varices, there is increased use of EUS in patients with liver disease. In this review, we discuss the various diagnostic and therapeutic applications of EUS in patients with various liver diseases.

Key words: ascites, EUS, fine-needle biopsy, liver biopsy, portal hypertension

INTRODUCTION

Traditional tools for the evaluation of liver disease include ultrasonography (USG), computerized tomography, and magnetic resonance imaging with percutaneous liver biopsy (LB). Therapy in liver disease is largely dependent on radiologic modalities. With advancement in EUS, there is an increasing interest in its use for evaluation and treatment of liver disease. Advantages of EUS remain its ability to visualize the liver from close proximity without significant intervening tissues. Furthermore, EUS gives excellent spatial resolution and helps in monitoring therapeutic interventions in real-time using modalities like color Doppler. The use of EUS-guided LB, EUS-guided sampling of focal liver lesions, EUS portal pressure gradient (EUS-PPG) measurement, and EUS for assessment of ascites is increasing with more expertise in EUS. EUS-guided coiling and glue injection (EUSC + G) as a therapy for gastric varices is in vogue. EUS-guided radiofrequency ablation for focal liver lesions is also being evaluated with encouraging

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results. With the emergence of endohepatology as a subspeciality of advanced endoscopy, we review the various diagnostic and therapeutic applications of EUS in patients with liver disease.

EUS-GUIDED LIVER BIOPSY

Recent advances in non-invasive assessment of liver fibrosis have greatly reduced need for LB. However, LB is still considered gold standard for assessment and quantification of hepatic fibrosis as well as in etiological workup of parenchymal liver disease when the clinical picture is unclear. Percutaneous (PC) route is most commonly employed for image-guided target identification and tissue acquisition. Transjugular (TJ) LB remains an alternative method in patients with coagulopathy/severe thrombocytopenia, significant ascites, morbid obesity, or in patients who also require portal pressure measurements.[1] LB can also be obtained during laparoscopy/laparotomy performed for other indications when there is concern regarding the presence of chronic liver disease.

EUS-guided LB has emerged as most recent approach for acquiring liver tissue for histological analysis [Figure 1]. The technique involves a linear echoendoscope for visualization of the left lobe of liver through proximal stomach and part of the right lobe through duodenum with real-time visualization of any intervening blood vessels and bile ducts.[2] The procedure usually requires moderate-to-deep sedation. In patients with altered anatomy due to past surgery such as Roux-en-Y gastric bypass, only transgastric approach is feasible. Indications for EUS-LB are same as for other routes of LB. Advantages of EUS-LB over other routes include shorter recovery time, decreased patient discomfort resulting in better patient tolerance, option for bi-lobar biopsy reducing sampling error in liver conditions with patchy involvement, ability to obtain

several needle passes in single liver capsule puncture and addition of Doppler to reduce complications.[3,4] It is less painful than the PC-LB as it does not traverse through the skin. The sedated procedure decreases fear and anxiety as well as eliminates the need of breath holds in pediatric population. The most optimal and cost-effective setting for its use is in patients with concomitant need for endoscopy for other indications such as variceal screening, dyspepsia evaluation, or as workup to rule out biliary obstruction. It can be preferred over PC route in morbid obesity, lack of cooperation, hemangiomas/cysts or patients who refuse latter.[1-5]

Meta-analysis of 8 studies and 437 patients by Mohan *et al.* have shown EUS-LB as safe and effective option for LB with a histologic yield of 93.9% and adverse event rate of 2.3% with minor bleeding as the predominant complication.[6] A recent meta-analysis of 23 studies with a total of 1326 patients by Baran *et al.* showed similar results with diagnostic yield increasing to ≥95% using EUS-fine needle biopsy (FNB) technique with either standard or core-type needles after excluding studies using true cut biopsy needle (Quick Core™) due to high failure rates (93% overall). On comparison of sample adequacy, this meta-analysis showed that EUS-FNB provided mean total specimen length (TSL) of 51 mm and number of complete portal tracts (CPT) as 15 which is greater than requirements of specimen length of ≥20 mm with ≥11 CPTs for reliable evaluation of underlying liver disease as per the American Association for the Study of Liver Diseases (AASLD).[7] Furthermore, specimen quality was better with bilobar than unilobar approach. Hence, EUS-LB seems to be a viable alternative to traditional methods of liver sampling in view of its evident safety and efficacy.

Despite initial concerns about the diagnostic yield of EUS-LB, refinement in technique and evolving

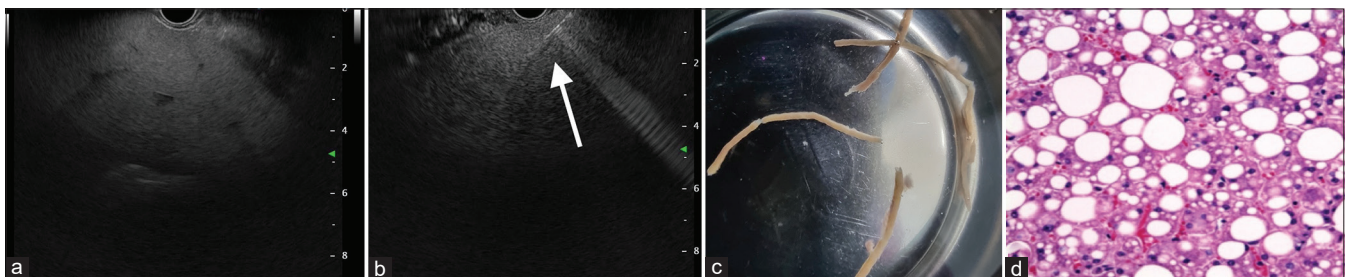**Figure 1.** EUS-guided liver biopsy. (a) Visualization of left lobe of liver through the transgastric window. Bright left lobe of liver with poor vascular markings seen. (b) Puncture taken for biopsy using 19G FNB needle. (c) Large core tissue acquired using single pass-3 actuation technique. (d) Diagnosis of non-alcoholic steatohepatitis confirmed on biopsy without presence of significant fibrosis. FNB: Fine-needle biopsy

evidence on optimal accessories have tried to settle this debate. FNB needles are considered superior to fine-needle aspiration (FNA) needles in terms of tissue acquisition and diagnostic yield.[7-9] Regarding the size of needle, emerging evidence suggests that 19 G needles are better than 22 G needles as several studies have reported higher tissue fragmentation and lesser adequate specimen with latter.[10-14] Recent randomized clinical trial (RCT) (*n* = 40) comparing the tissue yields and adequacy of a 19 G FNA versus 19 G Franseen-tip core biopsy FNB needle for EUS-LB demonstrated longer LB specimen and more CPT with EUS FNB needle without any serious adverse events.[15]

There are different type of FNB needles available and therefore the diagnostic accuracy of various FNB needles in EUS-LB need to be evaluated. Schulman *et al.*[16] in human cadaveric tissue and Eskandari *et al.*[17] in bovine liver compared different types of FNB needles including 19 G needles and reported non-significant higher mean number of CPTs for the Franseen needle and superiority of fork-tip needle in their respective analysis. Direct head-to-head comparison of these second-generation EUS-FNB needles by Aggarwal *et al.,*[18] Nieto *et al.,*[19] and Hashimoto *et al.,*[20] reported superiority of 19G Franseen tip needle (Acquire, Boston Scientific, Marlborough, MA) over the fork-tip needle (SharkCore, Medtronic Inc., Minneapolis MN). This was further supported by recent meta-analysis by Baran *et al.,*[7] which reported a statistically significant difference in the aggregate TSL of 75.9 mm versus 39.3 mm (*P* = 0.002) between the Franseen and Fork-tip respectively, although with comparable CPTs of 22.3 *versus* 17.7 (P = 0.38). Aggarwal *et al.*[18] attributed technical success of Franseen needle to geometrical shape of end needle tip and suggested that higher shearing force on tissue samples can result in increased risk of tissue fragmentation with fork-tip design. On the other hand, the Franseen needle design provides 3 equal cutting surfaces, resulting in a more intact core specimen.

Another issue that is to be considered before EUS-LB is preparation of the needle before performing the procedure. Dry suction requires 10–20 ml syringe to maintain suction after passing needle through liver whereas wet suction requires lubrication of needle lumen with either saline or heparin before suction is applied either using a syringe or by backward tension on stylet.[4] Recent evidence suggests wet suction technique results in better diagnostic yield (more CPTs

and increased aggregate specimen length) with less tissue fragmentation as compared to dry methods.[21,22] The use of heparin also decreases chances of clot formation. Technical issues such as depth of needle pass, number of passes, and total number of actuations required for better diagnostic yield are still a matter of debate. In contrast to previous studies using 1 to 10 actuations, Nieto *et al.* reported 100% specimen adequacy using modified 1-pass, 1-actuation (to-and-fro movement) wet suction technique when the needle was advanced 7 cm in liver parenchyma after priming with saline.[22] Some experts recommend that a 3-cm course of needle travel is usually sufficient with an option for deeper penetration if there are no intervening blood vessels.[23] Recent prospective RCT of 40 non-cirrhotic patients compared 1 pass, 1 actuation (1:1) with 1 pass 3 actuations with fanning (1:3) technique using 19-G FNB heparinized needle in terms of histologic yield and adequacy. Authors reported more CPTs (mean of 17.25 *vs.* 24.5; *P* <.008) and longer aggregate specimen length (6.89 cm *vs.* 12.85 cm; *P* < 0.001) with 1:3 technique[24] [Figure 1]. This study also reported that at least 2 passes ideally bi-lobar are more likely to provide tissue adequacy according to the AASLD guidelines. Despite no RCT evaluating the need for antimicrobial prophylaxis for EUS-LB, evidence from both recent meta-analyses reported no post procedural sepsis as an adverse effect suggesting that it is not required.[6,7] Once liver tissue is obtained, it is recommended to transfer sample directly to formalin from the needle so as to decrease risk of tissue fragmentation.[4,23]

Apart from already discussed issue about when should EUS-LB be offered to patient, its comparison in terms of efficacy and safety with PC method is important to guide clinicians in daily practice. Several studies have reported comparable or superior outcomes with EUS-LB as compared to other methods.[25-28] However, recent RCT and meta-analysis comparing PC and EUS-guided LB needs special mention. Bang *et al.*[29] in their RCT, reported that PC method yielded significantly more optimal specimens compared with the EUS approach (57.9% *vs.* 23.8%, *P* = 0.028). In addition, it was less costly than EUS-LB and only advantage of EUS-LB was less post procedure pain. A recent meta-analysis by Facciorusso *et al.* on a similar topic and including the aforementioned RCT and 6 other retrospective studies reported comparable diagnostic performance and safety profile between both methods. However, sensitivity analysis of 3 high-quality studies (including the above RCT) concerning primary

outcome (total length of biopsy specimen) depicted superior outcomes with PC method.[30]

EUS-LB is associated with certain limitations. One of the barriers to its widespread use is the relative novelty of the technique as well as increased cost compared to PC-LB. In addition, the use of 19 G needles in EUS-LB as compared to standard of care 16 G needles used in PC route can lead to shorter core biopsy samples.[2,3] Contraindications include platelets less than $50,000/\mu L$ or an international normalized ratio greater than 1.5 and massive ascites where TJ route is preferred.[16] Table 1 summarizes the major studies on EUS-LB.

In summary, the available evidence suggests that EUS LB is safe with complication rates lower or comparable to PC-LB. It is also clinically effective with reduced sampling error through fanning and ability to sample both lobes of the liver along with the ability to simultaneous evaluate pancreas, gallbladder, common bile duct, and other upper abdominal structures.

EUS AND MEASUREMENT OF PORTAL PRESSURE GRADIENT

Portal hypertension (PHTN) results from increased pressure in portal venous system. Cirrhosis is the most important cause of PHTN and measuring pressure in portal venous system is key to determine prognosis, response to therapy, postoperative outcomes, and anticipate complications in patients of cirrhosis.[40] Hepatic venous pressure gradient (HVPG) assessment is the current standard of measuring portal pressure indirectly. This technique involves advancing catheter to hepatic vein using the right jugular or femoral as possible routes. Portal vein (PV) is not directly accessible through this approach and direct PC method to measure portal pressure is highly invasive and no longer performed. Apart from being invasive and requiring intravenous contrast, HVPG measurement is not accurate in pre- or post-sinusoidal PHTN.[5,40-43]

EUS allows accurate visualization of PV both from the stomach and duodenum in view of high spatial resolution and proximity of vessel to the tip of echoendoscope; making it an attractive modality for PV interventions. EUS-guided PPG is calculated by first inserting 22 or 25 G needle into hepatic vein (middle hepatic vein is the most preferred target in view of large size and proper alignment with trajectory of

needle) followed by PV (umbilical portion of left PV is the usual target) to measure pressure in both the veins. The calculated difference in the pressure in both the veins gives estimated PPG. In situations, where hepatic vein is difficult to access, inferior vena cava can be targeted.[5,41,42] While recording pressures, the patient is kept supine with manometer at mid-axillary line. Each reading is noted after 40–60 s following pressure stabilization and usually mean of three readings is taken as final value. About 1 ml of heparinized saline is flushed through the primed FNA needle (no stylet) prior to each EUS reading. Huang *et al.* used this technique in 28 patients using 25 G FNA needle and compact manometer. They reported 100% technical success and no complications (PPG ranged from 1.5–19 mm Hg) with excellent correlation with clinical and endoscopic parameters of PHTN.[43] Recently, Zhang *et al.* determined the consistency between EUS-PPG and HVPG measurements in eleven patients with acute or subacute PHTN using a 22-G FNA needle and a central venous pressure measurement monitor. They reported high degree of correlation between both techniques.[44] There was no difference in time to perform either procedure and there were no adverse events. However, the sample size was small and the level of sedation was different in both procedures and hence, large multicenter studies are needed to validate these findings. EUS-PPG can be preferred in patients of liver disease requiring LB, variceal screening, and treatment along with measurement of PHTN, all in same setting.[45]

EUS IN MANAGEMENT OF FOCAL LIVER LESIONS

Imaging with USG, computerized tomography (CT), or magnetic resonance imaging (MRI) is fist-line non-invasive tools for the evaluation of primary or secondary lesions in the liver. However, EUS can detect small focal hepatic lesions usually less than 1 cm with better diagnostic accuracy than these traditional imaging methods [Figure 2].[46] Evaluating nature of these lesions is of utmost importance in preoperative planning, staging, and prognosis of malignant lesions. A recent prospective study in 730 patients evaluated role of EUS in detection of liver metastasis missed by routine cross-sectional imaging (CT or MRI) during staging of thoracic and gastrointestinal malignancies. They reported that EUS missed focal lesions in 7 patients, 6 of which were liver metastases (1.0% and 0.8%, respectively), while CT and MRI missed focal lesions

Table 1. Summary of major studies on EUS-guided liver biopsy

Reference/design of study/number of patients	Needle type	Technical success (%)/ diagnostic yield (%)	TSL (mm), median (range)	CPT, median (range)	Complications, n (%)	Number of passes (range)
Gleeson *et al.*[31]/ retrospective case series/*n*=9	19G/Quickcore	100/100	16.9 (8-28)	7 (5-8)	0	2 (1-3)
DeWitt *et al.*[32]/ prospective case series/*n*=21	19G/Quickcore	100/90	9 (1-23)	2 (0-10)	0	3 (1-4)
Stavropoulos *et al.*[33]/prospective case series/*n*=22	19G FNA (EchoTip)	91/91	36.9 (2-184.6)	9 (1-73)	0	2 (1-3)
Gor *et al.*[34]/ prospective case series/*n*=10	19G FNA (Expect)	100/100	14.4 (6-22)	9.2 (6-15)	0	3
Diehl *et al.*[35]/ prospective/*n*=110	19G FNA (Expect)	100/98	38 (0-203)	14 (0-68)	1 (0.9) mild bleeding	1-2
DeWitt *et al.*[36]/ prospective/ *n*=44 *n*=41	19G FNB (Procore) 19G FNB (Quick-Core)	95/88 78/62	15 (3-60) 3 (0-14)	Mean 10.4±4.7 Mean 1.3±1.9	6 (14.6) 8 (21.6)	1-3 1-3
Pineda *et al.*[25]/ retrospective/*n*=110	19G FNA (Expect)	100/100	38 (24-81)	14 (9-27)	None reported	1-4
Saab *et al.*[37]/ retrospective/*n*=47	19G FNB (Sharkcore)	100/100	65 (46-80)	18 (14-24)	2 (4.2) hematoma	Modified 1 pass
Shah *et al.*[38]/ retrospective/*n*=24	19G FNB (Sharkcore)	100/96	65.6 (17-167.4)	32.5 (5-85)	2 (8.3) pain, subcapsular bleeding	2 (1-3)
Mok *et al.*[21]/ prospective cross over study/*n*=40 dry control *n*=40 dry heparin *n*=40 wet heparin	19G FNA (Expect)	Technical success: 100 Diagnostic yield 80 92.5 97.5	23.9 (12.3-54.2) 29.7 (18.5-56.3) 49.2 (32.8-68.4)	4 (2-10) 4 (2-6) 7 (5-12)	1 (2.5) bleeding	1 1 1
Nieto *et al.*[22]/ retrospective/*n*=165	19G FNB (Sharkcore)	100/100	60 (43-80)	18 (13-24)	3 (1.8) pain, hematoma	1
Ching-Compagnioni *et al.*[15]/ prospective RCT/ *n*=20 *n*=20	19G FNA (Expect) 19G FNB (Acquire)	100/100	Mean=114 Mean=153	16.5 (6-38) 38 (0-81)	Pain (*n*=8; 40%) Pain (*n*=7; 35%)	2
Hasan *et al.*[39]/ prospective/*n*=40	22G FNB (Acquire)	100/100	55 (44.5-68)	42 (28.5-53)	6 (15) pain	3
Mok *et al.*[13]/ randomised crossover study *n*=40 *n*=40	19GFNA (Expect) 22G FNB (Sharkcore)	100 (technical success) Diagnostic yield 88 68	Mean=61 Mean=48.1	Mean=7.4 Mean=6.1	1 (1.2) pain	2 2
Aggarwal *et al.* [18]/prospective study/*n*=108	19G FNB (SharkCore) 19G FNB (Acquire)	100 (technical success) Diagnostic yield 79.4 97.2	Mean=13.86 Mean=15.81	Mean=7.07 Mean=9.59	1 (0.9)	2
Nieto *et al.*[19]/ retrospective study *n*=210 *n*=210	19G FNB (Acquire) 19G FNB (Shark Core)	100/100	Mean=65 Mean=60	Mean=24.0 Mean=19.5	Pain (*n*=4; 2%) hematoma, bile leak (*n*=2; 1%) Pain (*n*=5; 17%) hematoma (*n*=1; 0.5%)	2
Ali *et al.*[27]/ retrospective study/*n*=30	19G or 22G FNB (SharkCore)	100/100	25 (21-33)	5 (5-8)	1 (3.3) pain	2

Contd...

Table 1. Contd...

Reference/design of study/number of patients	Needle type	Technical success (%)/diagnostic yield (%)	TSL (mm), median (range)	CPT, median (range)	Complications, n (%)	Number of passes (range)
Patel *et al.*[12]/retrospective n=30 n=50 n=28 n=27	22G FNB (Acquire) 19G FNB QuickCore) 19G FNB (ProCore) 19G FNA (Expect)	100 (technical success) Diagnostic yield 66.7 46 82.1 81.5	Mean=38 Mean=47 Mean=39 Mean=84	Mean=6.9 Mean=3.0 Mean=7.3 Mean=16.9	Not reported	Not standardized
Bang *et al.*[29]/randomised trial/n=21	19G FNB (Acquire)	100/100 (91.5% from single pass)	16.5 (9.5-32.5)	≥10 CPT	0	2 (both lobes)

CPT: Complete portal tracts; TSL: Total specimen length
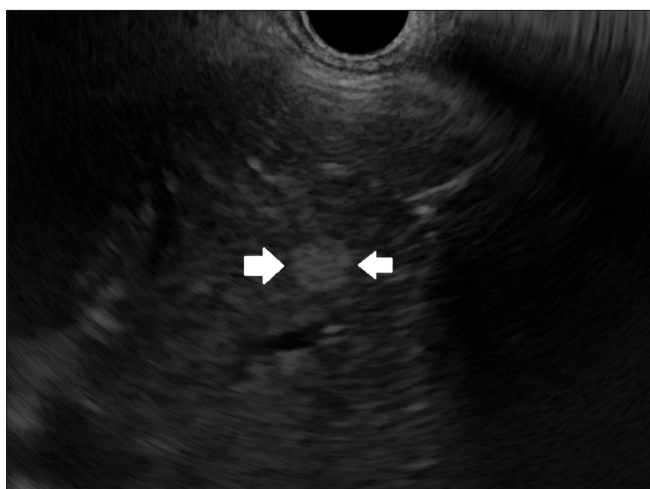

Figure 2. A small echogenic space occupying lesion detected in left lobe of liver on EUS (arrows)

in 58 patients, 42 of which were metastases (7.9% and 5.8%, respectively), and these were detected by EUS. The 6 metastatic lesions missed by EUS were in the right lobe of liver (segments V [3 patients], VI [2 patients], and VII [1 patient]).[47] Therefore, evidence supports the use of EUS as screening tool for detecting occult liver metastasis, especially in the left lobe of liver in setting of primary malignancies.[47-49] Meticulous screening of the liver should be routine in patients undergoing EUS examination for the staging suspected or known primary malignancy.[42,48,50] This approach can save patients from unnecessary attempted curative resection.

EUS enhancement techniques such as elastography and contrast-enhanced ultrasound further improve the capability of EUS to discriminate between benign and malignant focal hepatic lesions. This can aid in either reduced need to biopsy or better diagnostic yield with accurate characterization of lesions. EUS elastography evaluates the elasticity of tissue quantitatively on

standard B mode with color image in range from red to blue. This property can distinguish malignant and benign focal liver lesion with malignant lesions much stiffer than benign lesions.[51] Saldolescu *et al.* reported outcomes of EUS-Real time elastography (RTE) to differentiate benign and malignant (HCC, cholangiocarcinoma, and liver metastases) liver lesions in a pilot study. Malignant lesions were significantly stiffer with cut off of 170 for the mean hue histogram values recorded on the region of interest (ROI), the sensitivity, positive predictive value, and accuracy of differentiation of benign and malignant masses being 92.5%, 86.7%, and 88.6% respectively.[52]

The use of ultrasound contrast agents has an additive effect on capability of EUS for better characterization of focal liver lesion into benign and malignant with their ability to enhance microvascular architecture of the liver.[53] Contrast-enhanced EUS (CE-EUS) or contrast harmonic EUS (CH-EUS) takes advantage from dual blood supply of liver, and unique characteristics of vascular enhancement and washout of focal liver lesions results in their accurate depiction [Figures 3 and 4].[50] Oh *et al.* investigated the usefulness of CH-EUS for evaluating hepatic metastasis and found a better liver metastasis detection rate with CE-EUS as compared to traditional EUS (9.3% *vs.* 73.3%) with 100% technical success rate.[54] Similarly, a retrospective analysis in pancreatic cancer patients assessed the role of CH-EUS using Kupffer-specific contrast for the identification of liver metastases. The diagnostic accuracy of multidetector CT scan, traditional EUS, and CH-EUS was 90.6%, 93.4%, and 98.4%, respectively. The sensitivity of CH-EUS for detecting small liver metastasis less than 1 cm was considerably higher than other two modalities. Also in 2.1% of cases, metastasis was only detected on CH-EUS rather than other two modalities.[55]

The initial report for EUS-guided sampling of focal liver lesions was published in 1999 by Nguyen *et al.* in a series of 14 patients.[56] They documented that sampling was better as EUS could detect lesions smaller than 1 cm that were difficult to diagnose using CT scan [Figure 5]. While USG has been used extensively to sample liver lesions, EUS is advantageous in certain situations. In patients with ascites, PC sampling is difficult. EUS is technically feasible in this situation. Lesions that are poorly accessible by USG or CT scan, EUS may be an alternative modality.[57] DeWitt *et al.* published a large series of 77 patients with yield of 91.4% needing mean of 3.4 passes for acquiring tissue.[58] Better tissue acquisition, especially for histopathologic and molecular analysis is possible with the availability of newer generation EUS biopsy needles. A retrospective series published by Chon *et al.* showed a diagnostic yield of ~90% with a complication rate of 1.4% (bleeding) in a series of 58 patients undergoing EUS-guided sampling using core biopsy needle.[59]

EUS IN MANAGEMENT OF ASCITES

Ascites is a common manifestation of PHTN in advanced liver cirrhosis. Differential diagnosis of ascites includes various benign (tuberculosis, nephrotic syndrome, and cardiac ascites) and malignant etiologies.[60] Abdominal paracentesis with or without USG guidance is routine practice for diagnostic or therapeutic paracentesis. EUS offers an effective modality with sensitivity higher than abdominal USG and CT for the assessment of ascites.[61] The role of EUS for the evaluation of ascites in patients of cirrhosis is limited as it is not safe to wait for endoscopy to rule out spontaneous bacterial peritonitis. In analysis of 239 patients, delayed paracentesis was associated with 2.7-fold increase in in-hospital mortality.[62] Moreover, EUS-guided paracentesis requires puncture across bowel wall which can itself lead to contamination and risk of infection.

Malignancy-related ascites is the second-most common cause for ascites after end-stage liver disease.[63] EUS-guided paracentesis is useful in such cases and has shown to provide diagnostic information for the presence of ascites with sensitivity, specificity, positive predictive value, and negative predictive value of 94%, 100%, 100%, and 89%, respectively.[64] In addition, FNA from suspicious omental or peritoneal nodules can be obtained in the same setting.[65-67] EUS-guided paracentesis or sampling from peritoneal nodules is usually carried under cover of peri-procedure
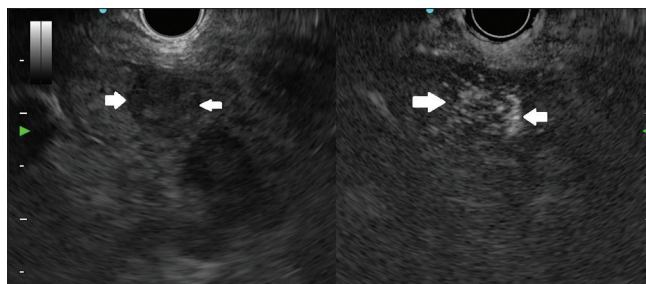

Figure 3. Contrast-enhanced EUS in patient with pancreatic neuroendocrine tumor: hyper-enhancing space occupying lesion in left lobe suggestive of metastasis
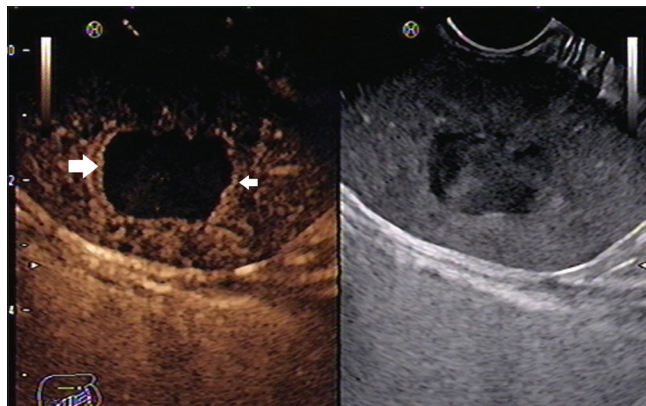
Figure 4. Contrast-enhanced EUS in patient with liver abscess: lesion with anechoic contents and enhancing wall

Figure 5. EUS-guided FNA of a small lesion in left lobe of liver. FNA: Fine-needle aspiration

antibiotics with 22 G FNA needle (although the use of 25 G needle has also been reported). Ascites can be visualized from trans gastric or trans duodenal window as anechoic space which may be triangular or irregular and peritoneal nodules may occur as hetero echoic nodules hanging into anechoic ascites.[65]

EUS can detect minimal ascites as small as 2.6 ml as shown by Suzuki *et al.*[68] Therefore, its role in

preoperative staging is advocated in cases where there is low volume of ascites or suspicion of peritoneal carcinomatosis to avoid unnecessary laparotomy. Contrast-enhanced EUS (CEUS) as discussed earlier enhance the diagnostic capability of EUS by providing information on enhancement pattern of suspected lesion. SonoVue and Sonazoid are most widely used ultrasound contrast agents.[69] Que *et al.* used CEUS in the evaluation of peritoneal metastases in 25 patients and reported a good role of this technique in the evaluation of angiogenesis of peritoneal nodules in thickened peritoneum.[70] Rana *et al.* reported the role of CEUS in differentiating malignant from tubercular ascites by demonstrating enhancement patterns of peritoneal nodules and thickened omentum in 13 patients. Metastatic peritoneal nodules showed fast radial enhancement whereas peritoneal nodules associated with tubercular ascites were hypo enhancing in their analysis.[71] However, this approach needs validation in large prospective studies.

ROLE OF EUS IN MANAGEMENT OF VARICES

Bleeding from varices represents a major decompensating event in cirrhotic patients, associated with a high mortality (up to 20%).[72] Bleeding from esophageal varices occurs more commonly than bleeding from gastric varices, considering a higher prevalence of esophageal varices in patients with PHTN.[73] Esophageal varices appear as rounded anechoic structures in the mucosal and submucosal layer on EUS, showing venous waveform on Doppler imaging.[74] EUS is inferior to endoscopy for the diagnosis of esophageal varices.[75] This may be because of compression of esophageal wall by the transducer. Furthermore, the varices are in close proximity to esophageal wall which may not be within the focal zone of the transducer. However, EUS is useful in visualization of periesophageal veins and gastric fundal veins [Figure 6]. In patients with larger esophageal varices, the sensitivity of detection of periesophageal veins increases.[75] EUS is also useful for the evaluation of azygous veins and thoracic duct. The presence of multiple periesophageal veins with large perforating veins may correlate with increased bleeding risk.[76] Also dilated azygous vein and thoracic duct signify clinically significant PHTN.[77,78] However, EUS is not better than endoscopy for confirming obliteration of esophageal varices.

EUS-guided sclerotherapy was similar to endoscopic sclerotherapy with respect to obliteration of esophageal varices in a previous randomized trial of 50 patients by De Paulo *et al.*[79] The presence of extensive collaterals and perforating veins was associated with increased recurrence. Direct injection of sclerosant using EUS into the perforating veins may be associated with lower risk of recurrence. In a previous study, Lahoti *et al.* demonstrated the efficacy of sclerosant injection using EUS into the perforating veins.[80] Mean of 2.2 sessions was needed to achieve obliteration of esophageal varices. However, one patient developed an esophageal stricture after injection. Injection sclerotherapy is cumbersome and has been superseded by endoscopic band ligation as the primary therapy for esophageal varices.[81] No comparative studies are available between EUS-guided sclerotherapy and endoscopic band ligation for esophageal varices. EUS-guided sclerotherapy for perforating veins is an option in patients with bleeding refractory to conventional band ligation and sclerotherapy. EUS-guided coiling, cyanoacrylate injection, or combination for obliterating periesophageal collaterals and perforating veins needs evaluation as a potential therapy in patients with refractory or recurrent esophageal variceal bleed.

Bleeding from gastric varices is known to occur in 16%, 36%, and 44% at follow-up over 1, 3, and 5 years, respectively.[82] While GOV1 is the most common type of gastric varix encountered in clinical practice, IGV1 has the highest propensity to bleed. Bleeding from gastric varices is known to be more profuse with a higher need for transfusions and a higher probability of rebleeding and death.[83] While clear guidelines are available for the management of esophageal variceal bleeds, there is a lack of consensus on the management of gastric variceal bleeds. Various therapies, endoscopic and radiological, are available for the management of gastric variceal bleed. Endoscopic glue injection remains the mainstay of therapy for gastric variceal bleed. The most important clinical indication of EUS in patients with PHTN remains the diagnosis and management of gastric varices. Gastric varices can be difficult to differentiate from enlarged gastric folds considering that they may lie in the deep submucosal layer.[84,85] Also, what may be seen endoscopically may represent only the tip of the iceberg with a large component being extramural. Hence, EUS is particularly useful in diagnosis of gastric varices and its anatomy [Figure 6].

EUS-guided glue injection was attempted initially to supersede endoscopic glue injection in view of advantages of direct visualization of injection into the

Figure 6. Role of EUS in diagnosis of gastric varices. (a) CT: Enhancing lesion arising from the gastric wall. (b) EUS: Anechoic lesion in the gastric wall. (c) The lesion shows vascularity on Doppler suggestive of gastric varix. CT: Computerized tomography

varix, potential to document obliteration using Doppler, no hindrance to endotherapy despite the presence of blood or food residue, and to reduce the total dose of cyanoacrylate used due to direct injection into feeding vessels.[86] Despite, high therapeutic efficacy, the procedure was associated with complications such as glue embolism and splenic infarction. EUS-guided coiling was introduced as a safer alternative, with the placement of vascular coils made of stainless steel or other alloys. They are available in various sizes, leading to vascular thrombosis and variceal obliteration.[87] Levy *et al.* were the first to report use of coils for variceal obliteration.[88] Coils are either 0.018" or 0.035" in size and introduced through the 22G and 19G needles, respectively. Either the stylet or a stiff guidewire is used to push the coil through the needle. Commercially available coils have a layer of wool coating on the outside to stimulate clot formation. Binmoeller *et al.* reported the use of a combination of coil with glue.[89] The placement of coils reduced the amount for glue injection in the varices and also reduced the risk of embolism while acting synergistically. Usually, 1–2 ml of cyanoacrylate glue is needed per session in addition to the coils based on the size of the varix for obliteration [Figure 7].[69] While the procedure can be done through a transgastric approach, a transesophageal approach is often preferred. The reasons include the scope position being orthograde in the esophagus making it more stable, avoiding puncture of already thinned out gastric variceal wall, and therapy having no hindrance from blood or food residue in the stomach. However, the transesophageal approach is technically challenging in the presence of esophageal varices and periesophageal collaterals.[90]

Table 2 summarizes the major studies using EUS intervention in patients with gastric varices. A recent meta-analysis comparing EUS intervention with endoscopic glue injection, showed better rates of variceal obliteration (84% *vs.* 63%, $P = 0.02$) with EUS while pooled treatment efficacy (93.2% *vs.* 91%,

$P = 0.4$) and rebleeding rates were similar (early rebleeding 7% *vs.* 5%, $P = 0.7$; late rebleeding 11.7% *vs.* 18%, $P = 0.1$).[101] The rate of recurrence of gastric varices was significantly lower with EUS intervention. In another meta-analysis, EUS Coil plus glue (EUS C + G) showed higher rates of technical and clinical success compared to either EUS-guided glue or coil alone. Furthermore, the rates adverse events were lower than EUS-guided glue injection and similar to coils alone.[102] EUS-guided interventions have been mainly used as secondary prophylaxis of bleeding as a rescue intervention after failed glue injection. Kouanda *et al.* looked at technical and clinical success of EUS coiling with glue for primary prophylaxis of gastric variceal bleed.[103] High-risk varices (>10 mm size with cherry-red spot) were obliterated using EUS C + G. The median number of coils needed was 1.5 (1–3) with mean volume of glue needed being 2 ml. Technical success was seen in 100% with obliteration confirmed in 67.7% in the first session only. Post therapy gastric variceal bleed was seen in 2.5% only, with no mortality reported on follow-up due to bleed. Hence, in centers with appropriate expertise, EUS C + G can be considered for primary prophylaxis of gastric variceal bleed.

In addition to these standard modalities, EUS-guided thrombin injection as an alternative to cyanoacrylate glue injection for gastric varices was first described by Frost and Hebbar.[104] Thrombin is said to have certain advantages over cyanoacrylate glue in the form of better safety profile with no embolization risk, technical ease of administration and also better safety for endoscopes. The combination of thrombin with coils is yet to be studied. In a recent study by Bazarbashi *et al.*, combination of coils with absorbable gelatin sponge was shown to have excellent technical success (100%) and safety without risk of embolization in a series of 10 patients with bleeding from gastric varices (100%). Contrast injection has also been used to guide EUS-guided therapy in gastric and rectal
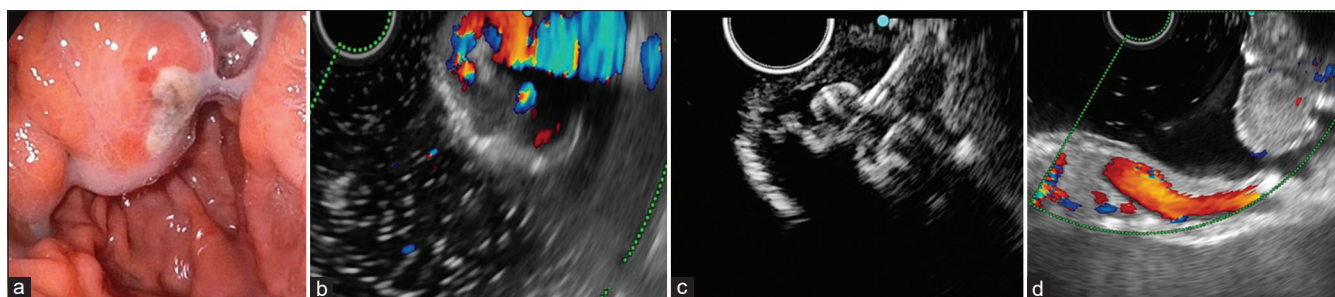
Figure 7. EUS-guided combined coil and glue injection after failed endoscopic glue injections. (a) Gastric varix with ulcer at the summit of varix. (b) EUS Doppler: Flow in gastric varix. (c) Coil being deployed through a 19G FNA needle into the varix EUS-guided. (d) Complete obliteration of flow in the varix after coiling and glue injection. FNA: Fine needle aspiration

Table 2. Summary of major studies on EUS-guided intervention for gastric varices

Study	Number of patients	Variceal obturation (%)	Rebleeding (%)	Adverse events (%)
		EUS-guided glue injection		
Romero-Castro *et al.* (2007)[91]	5	100	-	0
Gubler and Bauerfeind (2014)[92]	40	100	15	5
Bick *et al.* (2019)[93]	64	-	8.8	20.3
		EUS-guided coiling alone		
Romero-Castro *et al.* (2013)[94]	11	94.7	-	9.1
Fujii-Lau *et al.* (2016)[95]	14	100	-	7
Khoury *et al.* (2019)[96]	10	100	0	10
Mukkada *et al.* (2018)[97]	30 (15 required additional cyanoacrylate)	Repeat session of coiling needed in 10 patients	20	0
Bazarbashi *et al.* (2020)[98]	10	100	0	10
		EUS-guided coiling with glue injection		
Binmoeller *et al.* (2011)[89]	30	96	16.6	0
Bhat *et al.* (2016)[99]	152	93	3	3
Lôbo *et al.* (2019)[100]	16	73.3	-	25

varices for direct obliteration of the feeding vessels.[105] SonoVue contrast was injected prior to coiling to delineate the perforator feeding vessel. Complete obliteration could be achieved in all 6 patients in this study. Larger studies are needed for validation of these newer techniques in clinical practice.

EUS has also be used for therapy in ectopic varices. Ectopic varices are seen in the duodenum in 17% cases, jejunum and ileum in 17% cases, 14% in the colon, 9% in the peritoneum, and 8% in the rectum.[106] The duodenum and rectum are easily accessible using the echoendoscope. EUS helps in delineation of the feeding vessels for direct injection. EUS-guided coiling with glue for duodenal varices was first described by Kinzel *et al.*[107] EUS-guided glue injection has been described in case reports previously.[108] Sharma and Somasundaram described EUS-guided glue injection for rectal varices.[109] Coiling and glue injection have subsequently been described in rectal varices in multiple case reports.[110-112] Hence, EUS can be a potentially safe and effective therapy in gastric and ectopic varices and may be considered a therapeutic option in expert hands.

EUS-GUIDED ELASTOGRAPHY

The field of non-invasive assessment of liver disease is rapidly evolving and its use in routine clinical practice has increased over the past several years. This can be explained with fact that LB despite being gold standard for the assessment of fibrosis is not suited for serial monitoring of hepatic fibrosis as it is an invasive modality with potential complications. Transient elastography (TE) (FibroScan™) is mostly widely used method of elastography which requires transabdominal probe to assess liver stiffness or fibrosis using shear waves. Real-time elastography (RTE) is novel technique that uses image enhancement to display differences in tissue compressibility.[113] This technique unlike TE requires very little additional compression of ultrasound probe for image acquisition as regular pressure variation from pulsation of adjacent blood vessels is usually sufficient. Hence, inter- and intra-observer variability is

reduced.[114] Bilobar assessment is an added advantage over TE which mainly focus on the right lobe. EUS-RTE may be a feasible option in patients of liver disease already planned for endoscopic evaluation for varices or deranged LFTs, obese, narrow intercoastal space, and with significant ascites.[41] EUS-RTE is supposed to be a better option than transabdominal RTE in view of more proximity of sensor through transgastric approach.

EUS-RTE can be performed with both linear and radial echo endoscopes however linear scopes are preferred in view of additional option for sampling of any suspicious area. The area under evaluation is labeled as ROI. Software analyzes each pixel in the elastography ROI which is displayed with a hue that represents the relative strain value (hardness) of the tissue. Most systems are set up to use a chromatic map (red–blue–green) which displays hard areas in dark blue or blue while soft tissue areas are displayed in red or green.[115]

Liver fibrosis index (LFI) greater than 2.56 correlated with METAVIR scores of F4 in validation study in chronic Hepatitis C patients using RTE.[116] LFI calculated by EUS-RTE has shown to significantly correlate with abdominal imaging in patients with chronic liver disease and could distinguish normal, fatty, and cirrhotic-appearing livers (0.8, 1.4, and 3.2, respectively).[117] However, lack of liver biopsies and small sample size of cirrhotic group was a significant limitation of this analysis. Tu *et al.* demonstrated the higher diagnostic yield (sensitivity 87%) with combination of EUS, Fibroscan, acoustic radiation force impulse, and aspartate aminotransferase-to-platelet ratio for early-stage liver cirrhosis.[118] Rustemovic *et al.* compared EUS-elastography findings in patients of primary sclerosing cholangitis (PSC) with healthy subjects as controls who underwent EUS for suspected choledocholithiasis. They reported a sensitivity of 80%, specificity of 81%, and accuracy of 81% for the detection of PSC and suggested it to be useful noninvasive marker of PSC.[119]

EUS shear wave elastography (EUS-SWE) utilizes acoustically generated tissue shear wave propagation speeds to derive estimates of liver stiffness similar to TE. EUS-SWE is not affected by external abdominal fat which is potential limitation of transabdominal SWE and TE. EUS-SWE has been used to predict liver cirrhosis and fibrosis stage, respectively, in 2 small studies published as abstracts.[118,119] However, larger studies are needed to validate these findings before incorporating this technique in routine clinical practice.

EUS-GUIDED ABLATION OF LIVER TUMORS

Various ablative techniques are available for focal liver lesions such as fine-needle injection using alcohol (FNI), radiofrequency ablation (RFA), photodynamic therapy (PDT), and cryoablation (CYA).[120] EUS-guided FNI using ethanol has been used in cystic lesions in the liver. Nakaji *et al.* described EUS-guided ethanol ablation for a 1.8 cm HCC in view of close proximity to the inferior vena cava and hepatic veins.[121] EUS-guided portal injection chemotherapy using drug-eluting microbeads has been considered a potential therapy in patients with bilateral hepatic metastases.[122] Direct injection into the PV reduces systemic exposure and reduces toxicity. Irinotecan, doxorubicin, and albumin-bound paclitaxel nanoparticles have been shown to be beneficial in porcine models; however, no studies in humans are available. In another case report, de Nucci *et al.* described EUS-guided RFA for 2 patients with HCC and cirrhosis.[123] They report that EUS is particularly useful over PC approach in obese patients, presence of large interposing vessels or difficult locations (subcapsular, caudate, or left lobe). Laser interstitial thermal therapy using Nd: YAG laser has been previously used as a thermal ablative therapy in a case series of 4 HCC or metastatic colorectal cancer patients with 10 lesions, showing efficacy and safety via EUS access.[124] Choi *et al.* reported use of EUS-guided PDT in 4 lesions including 2 focal liver lesions with success. Both patients did not show progression after therapy for 5 months and mean size of lesion was 4 cm^3.[125] While EUS can be used to access lesions in the left and right lobe for these ablative techniques, there are no large-scale studies evaluating its use for this indication, with most studies being in animal models. There is a need for large prospective studies to analyze the safety and efficacy of these techniques.

EUS-GUIDED DRAINAGE OF LIVER ABSCESS AND BILOMA

PC drainage is the first-line method for drainage of liver abscesses. EUS is advantageous in difficult-to-access locations like the caudate lobe. Puncture through the transgastric route also avoids a PC catheter and avoids potential complications like

displacement of catheter.[126] EUS drainage can be mostly performed for left or caudate lobe abscesses. The first case of EUS-guided drainage of liver abscess by published by Seewald *et al.* in 2005.[127] A recent systematic review analyzed the role of EUS in the management of difficult-to-drain liver abscesses.[128] Fifteen studies with 40 patients were identified with technical success rate for EUS of 97.5%. In 65% of cases, fully covered self-expanding metal stent or lumen-apposing metal stents were used. Table 3 summarizes the major studies on EUS-guided drainage of liver abscesses. Shami *et al.* described in their case series EUS-guided drainage of symptomatic bilomas in 5 patients with complete resolution and no relapse on follow-up.[146] In another series by Tonozuka *et al.*, EUS-guided drainage of infected bilomas was done in 6 patients with technical success in all patients.[140]

Lorenzo *et al.* in their recent series described endoscopic management of complex bilomas in a series of 30 patients. EUS-guided transmural drainage was done in 14/30 patients, with clinical success in 75% of patients.[147] Hence, in patients with difficult to access liver abscess or biloma, EUS-guided drainage can be considered.

NEWER TECHNIQUES ON THE HORIZON

With increasing use of EUS, there are attempts to perform hepatic and portal vascular interventions, considering the proximity and ease of access. Zhang *et al.* recently demonstrated the use of transgastric EUS-guided access for partial splenic artery embolization for therapy in bleeding varices and hypersplenism.[148] They demonstrated direct puncture of

Table 3. Summary of major studies on EUS-guided drainage of liver abscess

Study	Year of publication	Number of cases	Location of Abscess	Approach - TG/TD/TE	Endoprosthesis for drainage	Complication
Seewald *et al.*[127]	2005	1	Left lobe	TG	Plastic catheter	None
Ang *et al.*[129]	2009	1	Left lobe	TG	Plastic stent	None
Noh *et al.*[130]	2010	3	Left lobe	TG	Plastic stent	None
Itoi *et al.*[131]	2011	2	1 left lobe 1 caudate lobe	TD	Plastic stent	None
Keohane *et al.*[132]	2011	2	Caudate lobe (2)	TG	Plastic stent	None
Ivanina *et al.*[133]	2012	1	Caudate lobe	TG	Plastic catheter	Catheter traversing the esophagus leading to paraesophageal collection-managed conservatively
Medrado *et al.*[134]	2013	1	Left lobe	TG	SEMS	Stent migration in the abscess 2 weeks, 10Fr DPS inserted within SEMS, entire assembly removed at 8 weeks
Alcaide *et al.*[135]	2013	1	Left lobe	TG	LAMS	None
Kawakami *et al.*[136]	2014	1	Left lobe	TG	BFMS	None
Koizumi *et al.*[137]	2015	1	Left lobe	TG	Plastic catheter	None
Kodama *et al.*[138]	2015	1	Left lobe	TG	Plastic catheter later replaced by SEMS	None
Ogura *et al.*[139]	2016	8	Left lobe 6 Right lobe 2	TG 6 TD 2	SEMS with plastic stent within	None
Tonozuka *et al.*[140]	2015	7	Left lobe 6 Right lobe 1	TG 6 TD 1	SEMS	None
Yamamoto *et al.*[141]	2017	1	Right lobe	TD	Plastic catheter	None
Carbajo *et al.*[142]	2019	9	Left lobe 3 Right lobe 6	TG 3 TD 6	SEMS	1 bleed and 1 perforation - managed conservatively
Rana *et al.*[143]	2020	14	Left lobe 11 Caudate lobe 3	TG 10 TE 4	Plastic stent	1 repeat procedure and exchange of stent
Chandra and Chandra[144]	2021	3	Caudate lobe 1 Left lobe 2	TG	Plastic stent	None
Molinario *et al.*[145]	2021	1	Left lobe	TG	LAMS with plastic stent within	None

TG: Transgastric; TD: Transduodenal; TE: Transesophageal; SEMS: Self expanding metal stent; LAMS: Lumen apposing metal stents; BFMS: Bi-flanged metal stent; 10Fr DPS: 7-French double-pigtail stent

splenic artery at the hilum with the placement of coil and glue for achieving partial embolization in 5 patients. 4 patients developed splenic vein thrombosis after procedure while 2 patients had worsening of ascites. The rate of embolization of splenic vasculature was approximately 65% without any bleeding events. Park *et al.* demonstrated the placement of PV stents through an intrahepatic access in live porcine model using EUS without any bleeding events.[149] EUS-guided intrahepatic portosystemic shunt placement was demonstrated in a live porcine model by Schulman *et al.*, using lumen-apposing metal stents for bridging the left hepatic and PVs.[150] All pigs survived for 2 weeks after procedure without any bleeding events and having a moderate technical demand. There is a need for more data in humans before these procedures can be practiced routinely.

CONCLUSIONS

EUS has evolved from being a diagnostic and therapeutic modality for the pancreaticobiliary tract to becoming increasingly useful in the field of hepatology. This may also encourage hepatologists to train in interventional EUS. EUS-LB and EUS-guided sampling for focal liver lesions can be considered the primary diagnostic modality in patients who are undergoing a concomitant upper endoscopy, yielding excellent results overall. EUS-PPG may be useful in patients to diagnose degree of PHTN and particularly useful in pre and post-sinusoidal PHTN where HVPG measurement has important limitations. There is increasing data to suggest the safety and efficacy of EUS C + G in the management of gastric varices, with need for comparative trials with interventional radiologic procedures such as BRTO and TIPS. EUS is a safe and effective modality for the treatment of bilomas and liver abscesses. EUS interventions in the field of hepatology have added to the ever-expanding role of interventional endoscopists in the management of liver disease.

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Surinder Singh Rana is an Editorial Board Member of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

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