Endo-Hepatology: The Buzz Goes Much beyond Liver Biopsy—A Narrative Review

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Abstract

The word endo-hepatology evokes many perceptions. Some believe it to be the emerging new interventional branch and some believe it to be an extension of endoscopy. Nonetheless, it has continued to evolve into an exciting area of active work. With the advent of endoscopic ultrasound (EUS) based procedures, new vistas have opened up. EUS-guided liver biopsies, portal hypertension management, and multiple new procedures are being described. EUS also plays a large role in the management of patients in the peritransplant period. With this review, we present an overview of the role of EUS in the field of hepatology as well as during the peritransplant period and its applications.

Keywords
- endotransplant hepatology
- endo-hepatology
- EUS-guided liver biopsy
- EUS in hepatology

Introduction

Endo-hepatology has been the buzz word in recent years in the field of hepatology. It has been labeled as a new upcoming field that has the potential to revolutionize the field of clinical and transplant hepatology.

Traditionally, we have relied on multiple variables like clinical, laboratory, and imaging techniques to help in diagnosing and managing patients with liver diseases. Clinically, the management of patients with advanced cirrhosis includes diagnosis, surveillance, and therapeutics, which depend on a multidisciplinary approach with the need for specialists in hepatology, interventional radiology, surgery, pathology, and interventional endoscopy. Gastroenterologists and hepatologists have been at the forefront of care with endoscopy as an indispensable part of everyday practice of hepatology. The word endo-hepatology came into existence to highlight the expanding role of endoscopic ultrasound (EUS) in the field of hepatology. Endoscopic therapies like glue injection and variceal ligation have always been the mainstay of endoscopic interventions but with EUS, a whole new domain of possible interventions have opened up.

One the earliest mentions of this word endo-hepatology was in the review article by Chang et al[1] in 2012, which reviewed the use of EUS in various ailments of the liver, mainly in the management of gastric varices. They mentioned that it would be most ideal if the assessment and management of liver disease and portal hypertension could be performed and done by the primary caregiver. This draws parallel from the domains of esophagology and pancreatobiliary disorders, where functional testing and treatment are usually given by the same caregiver. They wanted to define this integration or overlap of endoscopic procedures within the practice of hepatology as Endo-Hepatology. The same authors in 2018[2] wrote an editorial regarding the same for EUS.

The applications of EUS in hepatology are now widespread across many domains. It now entails applications of EUS-based methods for both diagnostic and therapeutic purposes. EUS can be used for various applications at all points in the

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spectrum, starting from precirrhotic phase to advanced decompensated cirrhosis.

Methods

A database search was done using PubMed, Google Scholar, and Embase using the following keywords: "Endohepatology," "Role of EUS in Liver Disorders," "EUS guided liver biopsy," "Role of EUS in evaluation for liver transplant." Relevant articles, particularly original, prospective and retrospective studies, and case series in English language were reviewed. Non-English language literature was not included in the review. Articles pertaining to extrahepatic biliary obstruction have been excluded.

►**Table 1** details the current and possible future applications of EUS in hepatology.

Diagnostic Applications of EUS in Hepatology

Assessment of Hepatic Parenchyma

EUS provides a unique window for assessment of hepatic parenchyma. This transgastric and transduodenal window helps in better delineation and provides for artifact-free areas from where elastography, particularly shear wave elastography (SWE), can be performed. Various methods of elastography have been developed and validated, principally strain elastography and SWE have been associated with use with EUS.[3] EUS SWE allows noninvasive assessment of liver fibrosis when transabdominal elastography may be inadequate (obesity, etc.). As compared to strain elastography, SWE is done in a target lesion and it is measured at meters per second (m/s) or in kilopascals (kPa). The area of interest is kept in an evaluation box away from cystic structures, blood vessels, or in areas of calcifications. In recent years, there has been a trial that tried to compare the diagnostic utility of EUS SWE and transabdominal vibration-controlled transient elastography with liver histology. One of these randomized trials noted that EUS SWE has comparable area under the receiver operating characteristic (AUROC) curve to vibration-controlled transient elastography for patients with fibrosis and cirrhosis.[4] In the field of endo-hepatology, it is clear that EUS-based elastographies, both strain-based and SWE, are useful adjuncts to EUS examination and particularly in evaluation of liver parenchyma. In particular, EUS elastography gives the benefit of evaluation for fibrosis in both the lobes. Apart from its role in endo-hepatology, EUS elastography has applications in other organs as well. Recent clinical experience of comparing SWE with strain elastography in chronic pancreatitis showed SWE or SWE appears to correlate better with EUS criteria than with strain elastography.[5] It has also been reported to be useful in cases of solid pancreatic masses.[6]

EUS Evaluation of Varices (Both Gastric/Esophageal Varices)

EUS evaluation of portal hypertension was one the earliest applications of EUS in the field of endo-hepatology. It gives clear insight to delineate the complex vascular anatomy involved in portal hypertension. EUS with application of flow Doppler is extremely useful for differentiation of thickened gastric folds and varices and detection of the so-called "deep varices." There have been various studies delineating the role of EUS in the evaluation of paraesophageal varices. In the study by Lee et al,[7] EUS was able to detect gastric varices in 30.8% of patients as compared to 17.3% detected by endoscopy. Thus, EUS is capable of identifying vascular anatomy in patients with suspected portal hypertension

Table 1 Current and future applications of EUS in hepatology

	Diagnostic	Therapeutic
Current clinical applications	1. Assessment of esophageal varices	1. EUS-guided glue injection of varices
	2. Assessment of gastric varices	2. EUS-guided glue and coil injection for gastric varices
	3. Assessment of hepatic parenchyma with shear wave elastography	3. EUS-guided RFA or cryoablation of liver lesions
	4. EUS-guided contrast-enhanced assessment of liver lesions	4. EUS-guided drainage of postresection/transplant collections
	5. EUS-guided liver biopsy	5. EUS-guided shunt closure
	6. EUS-guided portal pressure measurement	
	7. EUS-guided lymph nodal biopsy in HCC	
	8. EUS-guided paracentesis	
Potential future applications		1. EUS-guided TIPS
		2. EUS-guided injection therapies like chemotherapeutics agents
		3. EUS-guided ascites paracentesis

Abbreviations: EUS, endoscopic ultrasound; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TIPS, transjugular intrahepatic portosystemic shunting.

and this early identification of varices may preclude liver biopsy in patients where etiology is clearly known. This leads to an argument of combining a diagnostic endoscopy with EUS in patients when there is clinical suspicion of portal hypertension, but noninvasive tests are not confirmatory.

EUS is also useful for evaluation of collaterals in and around the stomach and also for complete evaluation of the spleno-portal axis. Identification of these collaterals and perforating veins is important as they are associated with recurrence of varices after eradication or recurrence after variceal ligation.[8] EUS is also unique in that it allows for accurate visualization of left gastric vein, whose size is associated with the presence of varices.[9] Its role has been extended to identification of shunts, particularly large spleno-renal and gastro-renal shunts, which can thus be targeted for therapeutic interventions in patients who have recurrent hepatic encephalopathy. The measurement of hepatofugal flow in the left gastric vein particularly above 12 cm/s is a high-risk factor for early recurrence of esophageal varices that have been treated with banding or sclerotherapy.[10]

Transabdominal USG-guided estimation of mesenteric fat has been advocated as a marker for Metabolic-dysfunction Associated Steatotic Liver Disease (MASLD). Similar studies have been using EUS. EUS-guided estimation of celiac artery mesenteric fat thickness (CAMEUS) was studied by Baroud et al.[11] They performed a retrospective analysis of 155 patients and a prospective validation of 21 patients with obesity and nonalcoholic steatohepatitis (NASH) who received paired EUS examinations with CAMEUS measurement, magnetic resonance elastography (MRE) with liver stiffness measurement (LSM), and liver biopsies with nonalcoholic fatty liver disease (NAFLD) activity score (NAS) measurement at the time of intragastric balloon (IGB) insertion and removal after 6 months. They found that CAMEUS is a novel marker and it correlates with various metabolic indices and can be easily incorporated in routine EUS practice for patients with metabolic syndrome or MAFLD.

EUS Assessment and FNA/FNB of Hepatic Lesions and Contrast Enhancement

Various segments of the liver are accessible from various stations like gastroesophageal (GE) junction and duodenum. From the stomach, the left lobe segments are easily seen including the liver hilum. Segments V–VI and hepatoduodenal ligament structures are visible from the duodenum station. EUS is an excellent modality for detection of small liver metastasis that may not be detectable on computed tomography (CT) or magnetic resonance imaging (MRI). In a prospective study of almost 730 patients by Okasha et al, patients who underwent EUS for staging or sampling of gastrointestinal (GI), pancreatic, or thoracic malignancy, EUS detected focal liver lesions in 20.5% of patients, whereas CT/MRI detected lesions in 13.6% of patients.[12]

In the study by Singh et al,[13] the diagnostic yield of EUS versus CT for detection of hepatic metastasis was 98 versus 92%. EUS in combination with elastography also adds more information. Using a cutoff of 170 to discriminate between benign and malignant tumors, the sensitivity and accuracy were 92.5 and 88.6%, respectively.[14]

Using contrast-enhanced EUS (CE-EUS) adds another dimension to the evaluation of hepatic lesions. It helps further in understanding the vascularity and contrast uptake of the hepatic lesions. Two types of contrast agents are available, Sonozoid and Sonovue. The same are also utilized for evaluation of pancreatic lesions. CE-EUS is also useful for assessing the response to treatment in cases of hepatocellular carcinoma (HCC) although standard of care is use of cross-sectional imaging like MRI and CT for evaluation of radiological response.[15] The above additional tools like CE-EUS and elastography can also be utilized for selecting the targets for fine needle aspiration biopsy (FNAB) when combined with EUS.

There are many studies describing the use of EUS fine needle aspiration (FNA)/fine needle biopsy (FNB) of hepatic lesions in the literature; the possible complication rate is around 0 to 6%. Ichim et al[16] in their study of 48 patients of FNA of focal liver lesions found positive results for malignancy in 47 patients. In 83% of the patients, the biopsy was taken from the left lobe and in the rest from the right lobe. Concurrent sampling was also done from additional sites. There were no significant short-term or long-term complications. In another large series of EUS FNB from focal hepatic lesions by Chon et al,[17] 58 patients underwent EUS FNB from solid masses in the liver. The FNB was done by 20-, 22-, and, in some cases, 25-gauge needles. The diagnostic accuracy was 89.7%, with specimen adequacy for histology and immunohistochemistry of 91.4%. There was one patient with bleeding post biopsy. The study concluded that EUS FNB with core biopsy needle was safe and accurate for diagnostic sampling of solid hepatic masses. There have been many other smaller studies that looked into EUS-guided FNA/FNB of focal hepatic lesions with diagnostic yields varying from 75 to 100% and with acceptable complication rates.[18–22]

EUS-Guided Liver Biopsy

EUS-guided liver biopsy (EUS-LB) has been a topic of hot debate across the world in the last few years. Numerous articles and studies have been published regarding its role and place in clinical practice. Much hype has been generated by various hepatologists and interventional endoscopists who want to incorporate EUS-LB as a part of routine GI practice and avoid percutaneous biopsies. Many studies have compared EUS-LB to percutaneous LB (PC-LB). Most of the studies do not clarify whether they are comparing with USG-guided plug PC-LB or conventional fluoroscopic-guided PC-LB. The standard of care of comparison with EUS-LB should be USG-guided plug percutaneous biopsy. There are usually two points of comparison, complication rate and adequacy of tissue specimen for diagnosis. In a recent comprehensive review, Choudhary et al[23] critically analyzed the available data. In their analysis, they showed that EUS-LB is at best similar in tissue adequacy and in some studies inferior too. There are no studies that have shown that PC-LB is inferior. For adequacy of tissue, PC-LB provides opportunity of multiple passes with a single puncture via the sheath, whereas one

has to take multiple punctures for multiple passes via EUS-LB. The advocated benefit of EUS-LB is also of bilobar biopsy in a single sitting, particularly in the cases of liver donors where it is prudent to rule out significant steatosis, which can be nonuniform in its involvement.

In another recent meta-analysis by McCarty et al,[24] 656 patients from four prospective studies and one prospective analysis compared EUS-LB, PC-LB, and transjugular liver biopsy (TJLB) for adequacy of outcomes, which were the number of complete portal triads (CPT), total specimen length, as well as the length of the largest piece. The adequacy of EUS-LB specimen was 93.5% compared to 97.6% with TJLB and 98.3% with PC-LB.

In a similar meta-analysis by Mohan et al,[25] looking at efficacy and safety of EUS-LB, nine studies were included with 437 patients. The histological diagnosis was established in 93.9% of patients. The pooled rate of adverse events was 2.3%. When they did a subgroup analysis of various types of needles, the adverse event with a 19-guage FNA needle versus other core biopsy needles was 0.9% and the rate of diagnostic yield was 95.8%. This meta-analysis also showed that the FNA needles had a significantly lower rate of insufficient samples than core biopsy needles. This was attributed to the use of QuickCore biopsy needles, which were available in the United States at the time of the studies.

In a very interesting study by Schulman et al,[26] various EUS needle types were compared on human cadaveric tissue. It was reported that a 19-gauge FNB needle was associated with the maximal number of CPT. Also, a 22-guage FNB needle was not statistically different from an 18-gauge percutaneous needle. The yield of both 22- and 19-gauge FNB needles was similar, but the cores from 22-gauge needles were prone to more fragmentation during specimen processing. This fragmentation with 22-gauge needles led to the use of 19-gauge needles mostly worldwide for EUS-LB.

Looking beyond the needles, there have also been debates on various techniques applied during EUS-LB. The various techniques used include dry suction, slow-pull technique, wet suction technique, or no suction. In a study by Nieto et al,[27] the wet suction technique, which uses a saline-filled prevacuum syringe, showed high effectiveness for EUS-LB, using a 19-gauge SharkCore or a standard 19-gauge FNA needle with a single pass, one actuation technique. It has been emphasized that using dilute heparin instead of saline leads to a decrease in the formation of blood clots and better tissue handling. In a study by Mok et al,[28] wet suction was shown to be better than dry suction in terms of specimen length and mean CPT count.

To summarize, a combination of wet suction technique and 19-gauge needles (FNA/FNB) may offer the best results in least the number of passes in terms of adequacy of specimen, CPTs, and adverse events.

EUS-Guided Portal Pressure Measurements

Portal pressure dynamics have always been one of the important parameters to assess which gives prognostic information and can predict decompensation risk. The conventional way of measuring portal pressure was using transjugular portal pressure gradient (TJ-PPG) measurement. EUS-guided portal pressure gradient (EUS-PPG) measurement has recently been advocated and in use at various centers around the world.

The first human case on EUS-PPG measurement was reported in 2014 by Fujii-Lau et al.[29]

Huang et al[30] described the first human pilot study of 28 patients in which EUS-PPG was successfully done. They reported technical success of 100% with no adverse events. The study served as a method to demonstrate the expanding role of EUS to measure portal pressure dynamics.

Zhang et al[31] demonstrated the consistency of the EUS-PPG with transjugular Hepatic venous pressure gradient (HVPG) measurement in their study. In a study of 11 patients, both EUS-PPG and TJ-PPG were measured. In two patients, TJ-PPG could not be measured due to hepatic vein occlusion. The mean EUS-PPG and TJ PPG were 18.07 and 18.82, respectively. Pearson's correlation coefficient between the two methods was 0.923, which was significant.

EUS-PPG is a much more direct measure of PPGs as it involves direct puncture of the hepatic veins and the portal vein for measuring pressures in comparison to the transjugular route where the measurements are indirect. The best use of EUS-PPG is as a part of a multiprocedural system where it can be combined with endoscopy, variceal screening, EUS-LB, and EUS elastography. This done in a single sedation sitting is what is the most argued rationale of EUS-PPG and EUS-LB in current times.

EUS-PPG has been measured using the proprietary manometer from Cook Medical (Echotip Insight) although authors have described methods using modifications of standard manometer set to measure portal pressures. Lesmana,[32] in his preliminary study of 13 patients, described the use of commonly available pressure monitor, pressure sensor, and a pressure infusion set for measurement of portal pressures using the standard 22-gauge needle.

EUS assessment of the azygous vein, in terms of both diameter and flow characteristics, has been used in the assessment of portal hypertension. It has been shown in small studies[33,34] that the diameter of the azygous vein correlates with more severe portal hypertension, worsening Child–Pugh scores, and Model for End-stage Liver Disease (MELD) scores. The flow in the azygous vein also correlates with severity of portal hypertension.

EUS-Guided Paracentesis

Traditional methods of ascitic drainage or paracentesis are bedside procedures using transabdominal ultrasound guidance. In patients who have undergone multiple paracentesis or have abdominal scars, it may be difficult to perform a transabdominal paracentesis. EUS is one of the most sensitive tools to assess ascites and can pick up minimal ascites, which can be sampled for diagnostic evaluation. In the cases with loculated ascites or compartmentalization, EUS becomes a valuable method to sample ascitic fluid. It is also useful in cases of peritoneal carcinomatosis.[35]

Currently, various studies are limited to case series or case reports, and it is currently not in routine use for assessment of ascites in patients with liver disease.

►**Figs. 1** and **2** show the role of EUS in hepatology in various clinical settings.

Therapeutic Applications of EUS in Hepatology

EUS-Guided Management of Gastric Varices: Glue, Coil, Both, and More

EUS guided management of gastric varices is an established method of management of large gastric varices and also a rescue tool after a failed endoscopic glue therapy. One of the earliest descriptions of EUS-guided cyanoacrylate glue (CYA) injection was given by Romero-Castro et al.[36] They described five patients in whom gastric varices were injected using CYA. In view of the significant risk of embolization associated with glue injection, it was hypothesized that combination of embolization coils along with glue would reduce the required amount of glue injection for gastric varices. There are many advantages. The coil functions as a scaffold for the glue; it also alters the flow dynamics inside the varix, causing early thrombus formation, and the amount of glue and hence embolization rates decrease.

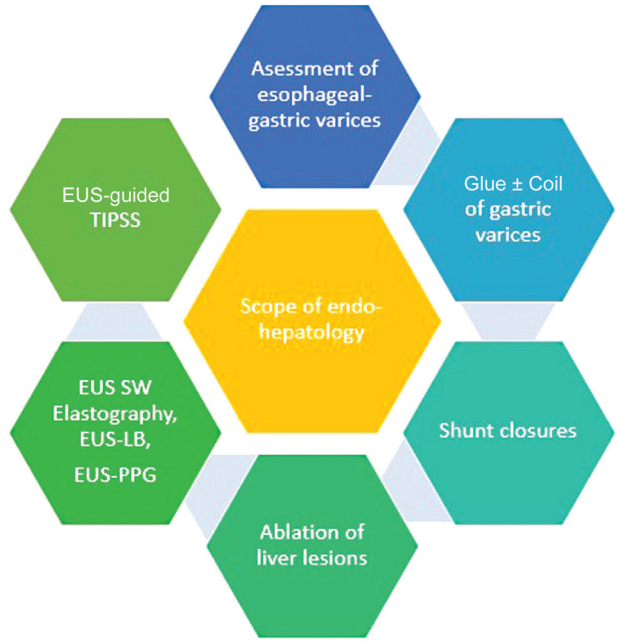

Fig. 1 Scope of endo-hepatology. EUS, endoscopic ultrasound; LB, liver biopsy; PPG, portal pressure gradient; SW, shear wave; TIPSS, transjugular intrahepatic portosystemic shunting.

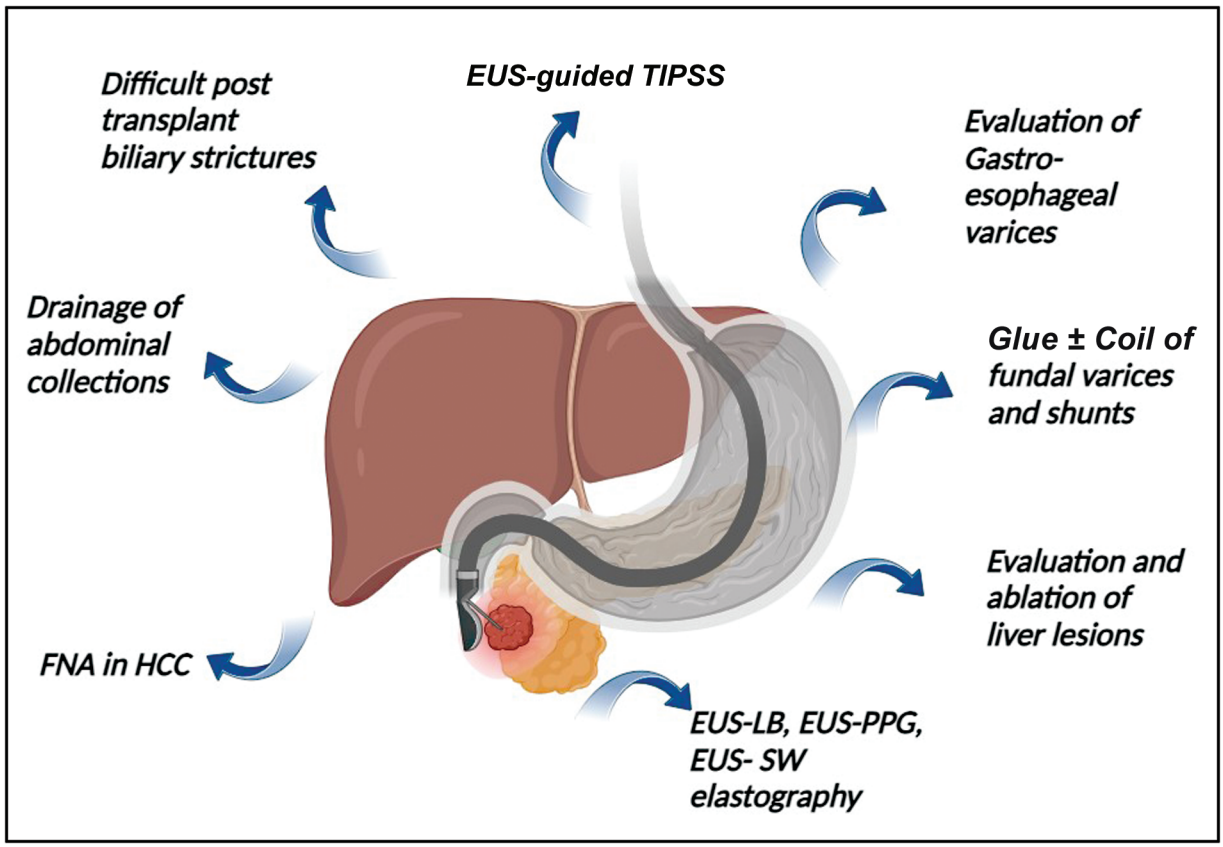

Fig. 2 Scope of endo-hepatology. EUS, endoscopic ultrasound; FNA, fine needle aspiration; HCC, hepatocellular carcinoma; LB, liver biopsy; PPG, portal pressure gradient; SW, shear wave; TIPS, transjugular intrahepatic portosystemic shunting. (Image created using Bio-render.)

This was first shown to be effective in large numbers by Bhat et al[37] who showed a 93% success rate of varix closure with a minimal 3% rebleeding rate. Further randomized trials and meta-analysis also confirmed these findings.[38,39] In a recent multicentric propensity-matched analysis, Samanta et al[40] also showed that EUS-guided therapy with coil and glue is a safe technique with better efficacy and lower rebleeding rate. Interestingly, they also showed that the size of the varix and the technique of therapy were independent predictors of rebleeding. A varix size of $\geq$17.5 mm had 69% predictive accuracy for the need for reintervention. Similar meta-analysis by Mohan et al,[41] in 2020, also showed EUS coil and glue in gastric varices to be superior to endoscopic glue alone.

Sharma et al,[42] in their retrospective study, showed for the first time that EUS-guided coil and glue therapy can also be utilized as the primary intervention in high-risk gastric varices. They defined high-risk varices as a varix size more than 2 cm with high-risk signs and patients with Child C cirrhosis.

Thus, EUS-guided management of gastric varices is now one of the mainstays for management of bleed from gastric varices. It can be used clinically in various situations as rescue therapy or even as primary therapy in high-risk cases.

EUS-Guided Ablation of Liver Lesions

EUS-guided therapeutic application in liver oncology is one of the most interesting applications in the field of endohepatology. EUS-guided management of liver tumors opens a new paradigm in the management of liver lesions as difficult-to-access areas like the left lobe and caudate lobe lesions can easily be targeted therapeutically. The EUS-guided ablation of liver lesions can be utilized by various techniques: injection therapies like alcohol injection using FNA needles, thermal ablative therapies like radiofrequency ablation (RFA), laser ablation by neodymium-aluminum-garnet, cryotherapy as well as brachytherapy.

- *Injection therapies*: Transabdominal-guided percutaneous injection therapies have been utilized for many years for HCC. Pure alcohol or ethanol can be injected directly into the tumor without damaging surrounding structures. Nakaji et al[43] showed the feasibility and outcomes of 12 cases of caudate lobe HCC using EUS-guided ethanol injection. The same can also be utilized for the management of oligometastatic liver lesions from pancreatic malignancy or colorectal malignancies.
- *EUS-guided RFA:* EUS-guided RFA has been utilized in the cases in which the percutaneous route is difficult due to obesity and deep-seated nodules in the liver. A dedicated needle with an electrode tip called EUSRA RFA electrode, developed by STARmed, Korea, has been utilized for this application. The same has also been utilized for ablation in cases of pancreatic neuroendocrine tumors. As of now, there are case reports of application of EUS-guided RFA for HCC, but it has potential for expanding applications in the future. De Nucci et al[44] showed its application in ablation of a large segment II-III-IVb HCC in a cirrhotic patient where surgery or percutaneous means were not possible. The HCC was treated using a 19-gauge water-cooled monopolar RFA needle and a dedicated generator system. It required two sessions and could be ablated successfully.
- *EUS-guided cryotherapy for liver lesions*: Cryotherapy has been tried both percutaneously and laparoscopically for ablation of HCC as well as cholangiocarcinoma, but they are yet to be incorporated in treatment guidelines. The results are diverse, and outcomes varied among studies. EUS-guided cryoablation has only been studied in animal models[45] as of now and requires further studies for evaluation of its role.
- *EUS-guided brachytherapy:* Jiang et al[46] showed in 26 patients the efficacy and safety of EUS-guided ^{125}I seed brachytherapy for malignant left-sided liver tumors that were difficult for transabdominal intervention. Technical success was achieved in 88.5% of patients. Complete response at 6 months was seen in 65.2% of patients. Repeat brachytherapy was done in patients with partial or incomplete response. These results need to be reproduced in larger studies for incorporation in clinical guidelines.

EUS-Guided Shunt Occlusion for Refractory HE

Rathi et al[47] recently described the role of EUS in the management of spontaneous porto-systemic shunts in patients of cirrhosis for refractory HE. Currently, the standard of care for management of shunt related HE is Balloon-occluded Retrograde Trans-venous Obliteration (BRTO) by interventional radiology. EUS-guided shunt occlusion (ETSO) described by Rathi et al was done in seven patients in nine sessions. Technical and clinical success was seen in six of seven patients. This human pilot study was for technical demonstration, and larger studies are needed for validation and standardization of the technique.

Endotransplant Hepatology: Expanding the Horizons of EUS in Hepatology

EUS comes as a handy tool with numerous implications in the pre- and posttransplant setting as shown in ►**Tables 2** and **3**. The scope of endotransplant hepatology includes not only evaluation of donors and recipients to decide transplant candidacy but also evaluation and management of posttransplant complications as shown in ►**Fig. 3**.

Applications of Endotransplant Hepatology in Pretransplant Setting

- *Donor evaluation:* Liver steatosis is the most common cause of donor rejection in the living donor liver evaluation. Donors with metabolic risk factors with or without borderline volumes often require liver biopsy for quantification of steatosis and for ruling out steatohepatitis.[61] Since steatosis can be patchy and a single-lobe biopsy may underestimate fibrosis, a bilobar liver biopsy is usually preferred. EUS-LB is a one-stop solution in such settings;

Table 2 Application of EUS in peritransplant setting

	Study	No. of patients	Clinical details	Procedure	Details	Remarks
Pretransplant clinical scenarios						
Donor liver biopsy	No literature available					
EUS FNA in HCC	Choudhary et al[48]	50	HCC with lymphadenopathy	42 abdominal and 8 mediastinal node EUS FNA	• Sample adequacy 92% – Metastasis in 15 (30%) – Granulomatous lymphadenopathy in 4 (8%) – Reactive change in 27 patients (54%)	• EUS FNA precluded transplantation in 30% of patients who had metastasis • 4 (8%) patients received antitubercular therapy before transplantation
EUS FNA in PUO	Choudhary et al[49]	46	Cirrhosis with PUO	50 (47 lymph nodes, 3 adrenal) EUS FNAs	• Sample adequacy 92% – Metastatic disease in 1 (adrenal) – Granulomatous change in 10 (6 positive with acid fast bacilli stain) – Histoplasmosis in 3 (2 adrenals, 1 lymph node) – 32 lymph nodes reactive	• EUS FNA modified management in 14/46 (30.4%) patients • Pathologic nodes had: – Significantly lower long-to-short axis ratio – Higher proportion of hypoechoic echotexture – Sharply defined borders
EUS-PPG	Rubin et al[50]	11	ESRD with suspected liver disease to determine kidney transplant candidacy	EUS-PPG paired with EUS-LB	• EUS-PPG successful in 10/11 (91%) patients • PPG < 5 in 8 and <10 mm Hg in all • Liver biopsy contained 22.5 (14.3–29.8) portal tracts • Cirrhosis confirmed in 1 (10%) and suspected in 2 (20%) fragmented biopsies	• Comprehensive staging of fibrosis and portal hypertension • Based on EUS-PPG results: – 9 (82%) patients went for kidney transplant alone (KTA) – 1 (9%) for combined liver kidney transplantation (CLKT)

Abbreviations: ESRD, end-stage renal disease; EUS, endoscopic ultrasound; FNA, fine needle aspiration; HCC, hepatocellular carcinoma; PPG, portal pressure gradient; PUO, pyrexia of unknown origin.

however, there are no published data in the literature on this select group of population.

- *Recipient evaluation*:
  - Patients with cirrhosis and HCC often have abdominal lymphadenopathy with or without fluorodeoxyglucose (FDG) avidity on positron emission tomography CT (PET-CT) at the time of evaluation for liver transplantation. It is important to exclude metastatic nodal disease to avoid a futile transplant. EUS-guided FNA of lymph nodes offers several benefits, such as sampling under real-time guidance, avoidance of porto-systemic collaterals, and proximity to the target. Choudhary et al have studied the role of EUS FNA in 50 prospective liver transplant recipients with HCC. The FNA material was adequate in 92% patients, 15 patients (30%) had metastasis precluding transplantation, 4 (8%) received antitubercular therapy in view of granulomatous lymphadenitis, and 27 (54%) had reactive lymphadenitis who underwent liver transplantation.[48]
  - Patients with cirrhosis who have pyrexia of unknown origin at the time of evaluation for liver transplantation may have lymphadenopathy. It is important to rule out an underlying infectious disease that may flare up in the posttransplant period. Choudhary et al have shown the impact of EUS FNA in modifying treatment in 14 of 46 (30.4%) such patients; 10 had granulomatous lymphadenitis, 3 histoplasmosis, and 1 had metastasis.[49]
  - Patients with chronic kidney disease with cirrhosis with or without portal hypertension often require HVPG measurement to rule out clinically significant Portal

Table 3 Evolving scope of endotransplant hepatology in posttransplant setting with review of available literature

	Study	No. of patients	Clinical details	Procedure	Details	Remarks
Posttransplant clinical scenarios						
HCC recurrence	Samuel et al[51]	1	Recurrence of HCC at porta hepatis after liver transplantation (LT)	EUS FNA of porta hepatis mass	• EUS showed 6.9 × 4.1 cm heterogeneously hypoechoic lesion at porta hepatis • FNA showed well-differentiated HCC	• EUS FNA is a safe and reliable modality for diagnosis of liver lesions even after LT
Abdominal collections	Uchida et al[52]	6	Symptomatic intra-abdominal fluid collection after LT	EUS-guided drainage and plastic stent placement	• Success rate 100% • 5 patients had abscess and 1 had biloma • Median endoscopic sessions 2.5 (1–4) until resolution • Procedure-related adverse events occurred in 2 patients and included peritonitis, bleeding, and stent migration • Follow-up: 63 (17–110) mo, recurrence occurred in 1 patient	• EUS-guided drainage is an effective and safe treatment for intra-abdominal fluid collection even in post-LT recipients
	Decker and Varadarajulu[53]	1	Perigastric abscess	EUS-guided drainage and plastic stent placement	• EUS-guided drainage of perigastric abscess with deployment of double pigtail stent • Stent removal after 2 wk	• EUS-guided drainage is minimally invasive, offers quick symptom relief, and is effective
	Takeishi et al[54]	2	Postsplenectomy pancreatic leakage–related fluid collection after LT	EUS-guided LAMS placement	• EUS-guided transgastric drainage of pseudopancreatic cyst with deployment of double pigtail and metal stent • Stent removal after 2 mo	• EUS-LAMS is effective in drainage of intra-abdominal pancreas leakage–associated fluid collections
Hepatic abscess	Toshima et al[55]	1	Refractory left lateral segment abscess after LT	EUS-guided FCSEMS placement	• EUS-guided transgastric drainage of refractory cholangiolar abscess with FCSEMS placement	• EUS-FC SEMS is safe and effective for abscess drainage
Liver allograft dysfunction	Han et al[56]	12	LT recipients with graft dysfunction	Single session EUS-LB and ERCP	• Technical success: 100% • Mean procedure time 66.8 ± 30.1 min (mean of 10.1 min for EUS-LB itself) • Liver sample tissue adequacy: 100% • Mean liver specimen length: 18.1 ± 13.4 cm • TCMR seen in 66.7% ($n = 8$) patients • Anastomotic strictures in 75.0% ($n = 9$) patients • Seven (58.3%) patients had concomitant diagnoses of TCMR and anastomotic strictures	• Single-session approach combining EUS-LB and ERCP is feasible and safe
Biliary strictures	Hüsing et al[57]	37	LT recipients with suspected biliary complications	EUS followed by ERCP	• 37 biliary complications detected in 32 patients • EUS overall sensitivity and accuracy of 94.6% in diagnosing biliary complications • EUS superior to ERCP in cases of biliary cast and ischemic cholangiopathy • EUS less reliable in diagnosing anastomotic strictures	• EUS can complement ERCP to improve diagnosis of biliary complications after LT

Table 3 (*Continued*)

	Study	No. of patients	Clinical details	Procedure	Details	Remarks
	Law et al[58]	1	Difficult biliary stricture in an LT recipient with HJ stricture	EUS-guided transhepatic antegrade stenting	• LT recipient with PSC who had HJ stricture • EUS-guided hepaticogastrostomy and FCSEMS were deployed across • Stent removal after 6 mo	• Potential and safe alternative to percutaneous transhepatic cholangiography
	Bukhari et al[59]	1	Difficult biliary stricture in an LT recipient with HJ stricture and bile cast syndrome	EUS-guided gastrojejunostomy (GJ)	• Failed multiple enteroscopy-assisted ERCPs for hepatoliths • EUS-guided creation of GJ • Endoscopic access through GJ LAMS • Cholangioscopy-guided electrohydraulic lithotripsy (EHL) and hepatic clearance	• EUS-guided alteration of complex surgical anatomy by creating EUS-GJ • It allows easy access to the bilioenteric anastomosis • Permits use of standard ERCP equipment
	Perez-Miranda et al[60]	1	LT recipient with disconnected bile duct	EUS-guided choledochoduodenostomy (CD) and magnetic compression anastomosis (MCA)	• EUS-CD with FCSEMS placement • Two magnets placed at each biliary stump, the proximal through EUS-CD, and distal through transpapillary SEMS • Patent biliary MCA after 10 d • Retrieval of magnets through EUS-CD • Newly formed biliary MCA stented with FCSEMS at ERCP	• EUS-guided anastomoses for biliary MCA allow subsequent biliary interventions

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FCSEMS, fully covered self-expandable metal stent; FNA, fine needle aspiration; HCC, hepatocellular carcinoma; HJ, hepaticojejunostomy; LAMS, lumen apposing metal stent; LB, liver biopsy; PSC, primary sclerosing cholangitis; TCMR, T-cell-mediated rejection.

hypertension (PHT) (HVPG < 10 mm Hg) to decide for kidney transplantation alone. EUS-PPG along with endoscopy and EUS-LB provides a comprehensive assessment regarding staging of fibrosis and portal hypertension. Rubin et al have shown the utility of EUS-PPG in 11 such patients to determine the candidacy for kidney transplant alone or combined liver and kidney transplantation.[50]

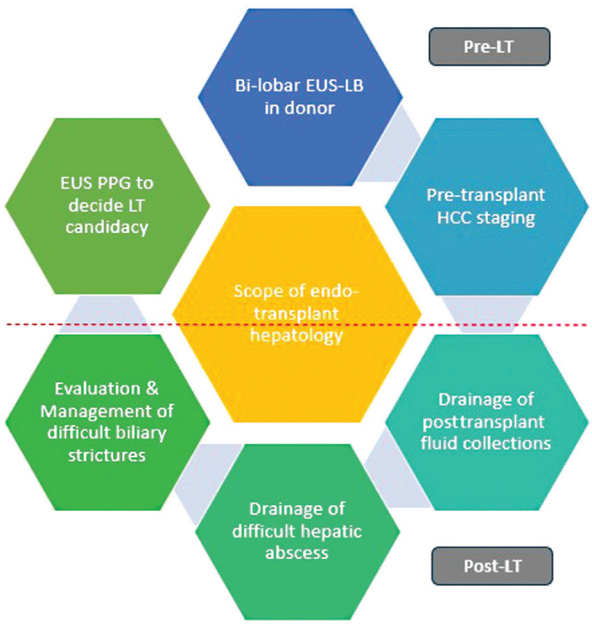

Fig. 3 Scope of endotransplant hepatology. EUS, endoscopic ultrasound; HCC, hepatocellular carcinoma; LB, liver biopsy; LT, liver transplant; PPG, portal pressure gradient.

Applications of Endotransplant Hepatology in Posttransplant Setting

Liver transplant recipients may develop cut-surface collections in the early posttransplant period in the living donor liver transplantation (LDLT) setting. In the late posttransplant period, the most common complications are T-cell-mediated rejection and biliary strictures. EUS is useful in the evaluation and management of such posttransplant complications. Also, EUS FNA has an important role in sampling lymph nodes in posttransplant lymphoproliferative disorder and HCC recurrence, as shown by Samuel et al.[51]

- *Drainage of abdominal collections:* Incidences of abdominal collections and biliary complications are higher in living versus cadaveric transplantation due to use of partial liver graft. Cut-surface collections, which occur near the porta, are usually not amenable for percutaneous sampling. Drainage of such collections is necessary to identify multidrug resistant (MDR) infectious agents and bile leaks. Patients with diagnosis of biloma at the time of single-time aspiration can be subjected to endoscopic retrograde

cholangiopancreatography (ERCP) in the same setting. ERCP with papillotomy ± stenting decreases the transpapillary pressure gradient to help in early resolution of biloma. Uchida et al have successfully shown use of EUS-guided drainage of abdominal fluid collections in six liver transplant patients.[52] Takeishi et al have used EUS-guided transgastric lumen apposing metal stent (LAMS) for drainage of pancreatic-associated fluid collections after LDLT in two patients.[54] However, LAMS placement should not be routinely used in drainage of posttransplant collections as most of these collections are nonpancreatic in origin (i.e., seroma, biloma) without an inflammatory wall.[62]

- *Drainage of intra-abdominal and hepatic abscess:* Liver abscess can form after liver transplantation in the presence of biliary stricture. Such cholangiolar abscesses, which are close to the porta and are not amenable to percutaneous drainage, can be drained easily by EUS. Toshima et al have shown EUS-guided internal drainage of refractory liver abscess using a fully covered self-expandable metal stent (FCSEMS).[55] Decker et al have reported the use of EUS in drainage of intra-abdominal abscess after a liver transplantation.[53]
- *Evaluation of graft dysfunction:* When a liver transplant recipient presents with deranged liver function tests, rejection and biliary stricture are the two common differentials. Biliary imaging, especially MR cholangiopancreatography (MRCP), is useful in ruling out biliary stricture. Patients who do not have biliary stricture undergo liver biopsy to rule out rejection, while those with stricture are subjected to ERCP and biliary stenting. Han et al have shown the utility of single-session EUS-LB and ERCP in liver transplant recipients with graft dysfunction.[56] In this pilot study of 12 patients, rejection was seen in eight (66.7%) patients on biopsy and anastomotic stricture in nine (75%) patients on ERCP. Concomitant diagnosis of rejection and stricture was made in seven (58.3%) patients. However, it would have been prudent to use EUS-LB only in the absence of anastomotic strictures.
  - Evaluation and management of biliary strictures:
  - EUS is superior to MRI and CT-based imaging in detecting biliary complications after LT. Hüsing et al have shown 94.6% sensitivity and accuracy in detecting biliary complications by EUS after LT.[57] EUS was superior to ERCP in diagnosing ischemic cholangiopathy and bile casts and inferior to ERCP in diagnosing anastomotic strictures.
  - Patients with difficult biliary strictures (like failed ERCP, Roux-en-Y construction) can be treated with EUS-guided antegrade stenting by hepatogastrostomy or hepatoduodenostomy. Law et al[58] have shown antegrade FCSEMS deployment after the creation of hepaticogastrostomy with EUS in a transplant recipient with primary sclerosing cholangitis (PSC) with Roux-en-Y hepaticojejunostomy.
  - Bukhari et al[59] have created EUS-guided gastrojejunostomy to facilitate endoscopic management of biliary cast syndrome in a liver transplant recipient with PSC. Endoscope was subsequently passed through LAMS and cholangioscopy-guided electrohydraulic lithotripsy was done intrahepatic biliary clearance.
  - Perez-Miranda et al[60] have shown use of EUS-guided choledochoduodenostomy and magnetic compression anastomosis for managing a disconnected bile duct after liver transplantation (►**Tables 2** and **3**).

Limitations and Gray Zones in Endo-Hepatology

Although endo-hepatology has come along a long way over the years, there are still areas that remain unanswered or partly answered. EUS-LB as described earlier has been advocated by emerging endoscopists, but its supremacy over the percutaneous route is still questionable. There have been studies, including meta-analysis, that try to answer this question.[23,63] EUS PPG is the next procedure on the horizon. However, questions regarding the ideal candidate for portal pressure measurement by EUS in clinical setting and its comparison with transvenous measurements, need to be answered. Newer procedures like ETSO still require validation in a larger subset of patients at multiple centers to become standard of care. EUS-guided primary management of gastric varices remains an unanswered question despite years of studies on portal hypertension.

Conclusion

Endo-hepatology as a field is here to stay and it has applications much beyond liver biopsy. We have introduced a new term, "endo-transplant hepatology," as there are many applications of EUS during the peritransplant time period. With the advent of newer therapies and the development of EUS-specific accessories, it is safe to assume that we are going toward a new era of complete endo-hepatology as envisioned almost a decade ago.

Author Contributions
P.R. contributed to the concept and reviewed the final draft and approved the manuscript. S.Z. contributed to the preparation of the manuscript, editing of the draft, and final approval of the manuscript. D.S., K.A., and S.B. contributed to the preparation of the manuscript and editing the draft, and final approval of the manuscript.

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Conflict of Interest
None declared.

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