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Role of endoscopic ultrasound in liver disease: Where do we stand in 2017?

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Abstract

Endoscopic ultrasound (EUS) was first introduced into medical practice in 1980s as a diagnostic imaging modality for pancreatic pathology. EUS has the unique advantage of combining ultrasound and endoscopy to obtain detailed information of the gastrointestinal tract. Over the past decade, the use of EUS in liver diseases has been increasing. EUS, which was initially used as a diagnostic tool, is now having increasing therapeutic role as well. We provide a review of the application of EUS in the diagnostic and therapeutic aspects of liver disease. We also look at the evolving future research on the role of EUS in liver diseases.

Key words: Endoscopic ultrasound; Liver disease; Portal hypertension; Liver lesions

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Core tip: We have summarized the up-to-date literature on the emerging role of endoscopic ultrasound (EUS) in liver disease. This brief review summarizes both the diagnostic and therapeutic role of EUS in focal hepatic lesions, portal hypertension, liver abscess and hepatic cysts. We have also summarized the future research on this subject.

Sarairoh HA, Bilal M, Singh S. Role of endoscopic ultrasound in liver disease: Where do we stand in 2017? *World J Hepatol*

INTRODUCTION

The evaluation of liver disease has been progressively changing over the last few decades with advancement of new technologies. Computed tomography (CT), conventional ultrasound and magnetic resonance imaging has have been the principal means for evaluating hepatic disease for long time^[1].

Endoscopic ultrasound (EUS) was first introduced into medical practice in 1980s as a diagnostic imaging modality for pancreatic pathology^[2]. It is distinctive in its ability to differentiate the histological layers of the gastrointestinal (GI) tract wall as well as the periluminal structures^[3]. EUS has the unique advantage of combining ultrasound and endoscopy to obtain detailed information of the GI tract. With recent advances in technology, advanced physicians' training and the expanding use of EUS, its role has grown dramatically to include both diagnostic and therapeutic aspects in gastrointestinal, pancreatic and hepatobiliary tree disease^[1].

In this review, we aim to summarize the application of EUS in diagnostic and therapeutic aspects of liver diseases. EUS performances in diagnostic and therapeutic aspects of liver disease include diagnosis and management of focal hepatic lesions, simple hepatic cysts, hepatic abscesses and portal hypertension. Limitations of EUS include limited access to the right hepatic lobe and increased risk of complications in those with anatomical alteration of the GI tract. Complications, although rare, can happen during EUS-guided fine needle aspiration (FNA) and include esophageal and duodenal perforation. We also look at the evolving future research on the role of EUS in liver diseases.

DIAGNOSTIC USE OF EUS, CONTRAST ENHANCED HARMONIC EUS, EUS-GUIDED FNA IN FOCAL HEPATIC LESIONS

Focal hepatic lesions are divided into benign lesions (such as hepatic cysts, focal nodular hyperplasia, regenerative nodular hyperplasia, abscess, adenoma or hemangioma) and malignant lesions (such as hepatocellular carcinoma, intrahepatic cholangiocarcinoma, biliary cystadenoma and metastatic liver disease)^[4]. Those lesions were classically diagnosed with combination of conventional imaging such CT and transabdominal ultrasound and percutaneous liver. EUS was first used

in liver imaging in 1997^[5] and since then its use has become increasing popular.

EUS, especially when combined by cytology, has been used not for evaluating intra-abdominal masses only, but also for staging purposes^[6-9]. In recent review by Srinivasan *et al*^[4], EUS has shown superiority in detecting focal hepatic lesions compared with conventional CT and trans-abdominal ultrasound, especially for small lesions. A recent study comparing the diagnostic sensitivity of EUS and CT scan showed that of 574 patients, 14 had liver lesions that were visualized by EUS, however, only 3 of those 14 patients had their lesions visualized by CT scan prior to the use of EUS^[10]. Another study by Awad *et al*^[11] showed that EUS could detect additional hepatic lesions in 28% of patients with a history of known liver mass that were detected initially by CT scan. Similarly, other reports have shown that EUS can detect liver lesions that were missed by conventional imaging modalities^[12]. Fujii-Lau *et al*^[13] proposed diagnostic criteria to differentiate between benign hepatic lesions and malignant metastatic lesions according to the lesion's characteristics on EUS. These criteria include lesion's shape, borders, echogenicity, homogeneity and size. These EUS criteria were applied to 200 patients who were diagnosed with malignancy using EUS-FNA. The authors concluded that EUS criteria may help in distinguishing benign from malignant hepatic lesions with a positive predictive value of 88%. The authors also suggested that the use of EUS criteria can guide the decision to perform EUS-FNA on a liver mass or not. The limitations of their study was that it was a single center study and the EUS criteria was validated by one expert endosonographer only.

The use of contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) for liver disease has evolved recently. Since the liver cells have a dual blood supply, CH-EUS is divided into three phases according to timing from contrast injection; arterial phase, portal phase and late phase^[14]. According to contrast enhancement imaging, increased arterial enhancement and late-phase contrast washout indicate hepatocellular carcinoma, while peripheral-rim like hyper enhancement followed by subsequent washout is visualized in metastatic liver cancer^[15]. In cases of hemangioma, peripheral nodular hyper enhancement associated with sustained enhancement in the late phase is usually visualized^[15]. A comparable study by Liu *et al*^[16] showed that CH-EUS is the same if not superior to CT scan in characterization and visualization of focal hepatic lesions.

The use of EUS was not limited to visualization only, but also in obtaining tissue biopsy for diagnostic purpose. EUS guided fine needle aspiration (FNA) has played a major role in revolutionizing the diagnosis of focal hepatic lesions. EUS-FNA is a minimally invasive procedure that is utilized for procurement of tissue

Table 1 Complication of endoscopic ultrasound guided fine needle aspiration compared with percutaneous fine needle aspiration

EUS guided FNA	Percutaneous FNA
Bleeding ^[18]	Bleeding ^[21,22]
Pain ^[18]	Severe pain ^[21]
Fever ^[18]	Punctured gall bladder ^[21]
Hemoperitoneum ^[23]	pneumothorax ^[21]
Death ^[23]	Syncope ^[21]
	Hemoperitoneum ^[24]
	Hypovolemic shock ^[24]
	Death ^[22]

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

of hepatic lesions. Currently, its use is limited to the left lobe, the proximal right lobe, the hilum and part of the intrahepatic biliary tract^[17]. EUS-FNA has a theoretical advantage over classical percutaneous biopsy in patients with cirrhosis, since percutaneous approach may be difficult in these patients owing to the presence of ascites and coagulopathy^[4]. Previous reports on the safety and efficacy of EUS-FNA have yielded encouraging results. In a survey by tenBerge *et al.*^[18], which included data from twenty-one centers of 167 cases of EUS-FNA of the liver lesions, it was shown that EUS-FNA was able to diagnose malignancy in 23 out of 26 (89%) of cases after a non-diagnostic trans-abdominal ultrasound guided FNA. Safety of EUS-FNA was also tested, with only 1% rate of major complication was reported. EUS-FNA was also shown to be safe with only 1% rate of major complications. Several other studies have shown the sensitivity of EUS-FNA for diagnosis of malignancy in liver lesions ranging from 82%-94%^[19,20]. Table 1 summarizes the complications of EUS guided FNA and percutaneous FNA^[18,21-24].

EUS-GUIDED LIVER BIOPSY

Liver biopsy remains the cornerstone in the diagnosis of liver diseases^[25]. Percutaneous liver biopsy was first described in 1923^[26] before the transjugular approach was suggested in 1973^[27]. Limitations of percutaneous approach are significant sample variability^[25] and risk of adverse events that include pain at site of biopsy, bleeding, marked hypotension and pneumothorax^[21]. The transjugular approach for liver biopsy entails accesses to the liver parenchyma through superior vena cava and hepatic vein, hence the liver capsule is not punctured^[25]. This approach is preferred in those with coagulopathy, marked ascites and in morbidly obese patients^[25]. Recently, EUS was used to obtain liver biopsy. EUS-guided liver biopsy (EUS-LB) was first described in animal studies in 2002^[28], with favorable outcome and safety profile. EUS-LB in humans was described by Dewitt *et al.*^[29]. A case series of 21

patients who underwent a transgastric EUS guided Tru-cut biopsy with a 19-gauge needle. Histologic diagnosis was successfully obtained in 90% of specimens (19/21), however, only 71% (15/21) were helpful for clinical diagnosis. No adverse events were reported in any of the patients. In another retrospective study of 9 patients, Gleeson *et al.*^[30] were able to show that Tru-cut biopsy is safe and at the same time yields suitable tissue for diagnostic purposes of liver disease.

THERAPEUTIC EUS-FNA OF FOCAL HEPATIC LESIONS

Recently some case reports have highlighted the therapeutic role of EUS in liver lesions as well^[31-34]. This includes the use of EUS to guide alcohol injection and laser ablation of hepatic lesions. Barclay *et al.*^[31] described a case of 3.3 cm metastatic liver lesion treated with multiple EUS-guided ethanol injections. Follow-up imaging showed a decrease in tumor size to less than 2 cm. Hu *et al.*^[32] also reported a patient with pancreatic adenocarcinoma with metastasis to retroperitoneal lymph nodes and left hepatic lobe. Following pancreatoduodenectomy and chemotherapy, patient underwent successful ethanol injection of left hepatic lesion with no significant post-procedure complications. Other examples of therapeutic intervention include EUS-guided Nd:YAG (neodymium-doped yttrium aluminum garnet; Nd:Y₃Al₅O₁₂) laser ablation of hepatocellular carcinoma^[35].

THERAPEUTIC USE OF EUS IN SIMPLE HEPATIC CYSTS

Hepatic cysts are mostly asymptomatic, and estimated to occur in 5% of population^[36]. The female: Male is approximately 1.5:1 among those with asymptomatic simple hepatic cysts (SHC) while it is 9:1 in those with symptomatic or complicated SHC^[36]. SHC is generally diagnosed incidentally on abdominal imaging. Only 10%-16% of such cysts are symptomatic^[4]. Symptoms are due to mass effect, rupture, hemorrhage and infection^[36], and include abdominal pain, nausea, vomiting, early satiety, obstructive jaundice and hepatomegaly^[4,36]. Management of SHC has varied over the years. Treatment options include surgical approach (open deroofting, laparoscopic deroofting, complete cyst resection and hepatectomy), percutaneous aspiration and sclerotherapy^[4,36-40]. Prior reports have shown that percutaneous aspirations is associated with recurrence rate, as high as 100%, that can be seen as early as two weeks^[38,40]. A recent systematic review by Wijnands *et al.*^[39] evaluated the role of percutaneous sclerotherapy in the management of SHC. The authors included 16 studies and reported cysts volume reduction ranged between 76% to 100% after a median follow-up period

of one to fifty-four months. In 10 of these studies, 72% to 100% patients reported improvement of symptoms, while 56% to 100% patients reported symptoms resolution. In regards to safety, three studies reported ethanol intoxication incidence, manifested as headache, nausea and flushing, with frequency of intoxication as high as 93%. The risk of intoxication increased with increased sclerotherapy duration, and increased volume of ethanol used^[39].

In recent years, EUS guided ethanol lavage has emerged as a popular treatment modality of SHC. In 2014, Lee *et al.*^[41] did a single center retrospective cohort study comparing EUS guided and percutaneous ethanol lavage for treatment of large hepatic cysts. A total of 10 cysts were drained by percutaneous approach with placement of drainage catheter, while 8 cysts were drained using EUS guided ethanol lavage. In EUS-guided group, cysts were drained in a 1-step approach without the placement of a catheter. Both approaches were efficacious. Results revealed a 97.5% and 100% reduction in cysts size at 11.5-mo follow-up and 15-mo follow-up, respectively. The authors concluded that there is an excellent symptomatic and radiological response in both groups. EUS-guided approach is more effective for left liver lobe cysts while percutaneous approach is better in right sided liver cysts^[41]. Despite positive results, further multi-center trials are needed to confirm these findings, since this was a single center study.

THERAPEUTIC USE OF EUS IN LIVER ABSCESSSES

Liver abscesses are defined as encapsulated collection of suppurative material within the liver parenchyma^[42]. They are the most common intra-abdominal abscesses with a reported incidence of 8-20 cases per 100000 hospitalized patients per year in the United States^[43]. Historically, pyogenic liver abscess has been managed with either surgical or percutaneous interventions^[44]. Since 2001, the number of percutaneous procedures has doubled, while the number of surgical procedures has decreased by about 20%^[45]. Percutaneous abscess drainage has a success rate of up to 100%^[46], hence making it the first line drainage technique. On the other hand percutaneous drainage is associated with side effects including catheter dislodgment, subcapsular hematoma, drainage from catheter exit site^[47], hepato-venous fistulas^[48] and hepato-colic fistulas^[49]. In recent years, EUS guided drainage for liver abscesses has emerged an alternative approach since it was first proposed by Seewald *et al.*^[50] in 2005. The authors reported a case of an 11 cm hepatic abscess within the left lobe of the liver that was successfully drained through trans-gastric approach using EUS with no complications or recurrence on follow-up. Since then, several other case reports and series have described

successful EUS guided drainage of liver abscess *via* trans-gastric and trans-duodenal approaches^[51-56]. In a retrospective report by Ogura *et al.*^[57], 27 patients who underwent either EUS-guided abscess drainage or percutaneous abscess drainage, the clinical success rate of EUS-guided group was superior to that of the percutaneous group, at 100% and 82%, respectively. Safety and hospital stay was also superior in EUS guided group^[57]. Although this data is encouraging, more prospective studies are still needed to compare the safety and efficacy of both interventions.

EUS AND PORTAL HYPERTENSION

Diagnostic aspect

Portal hypertension is the hallmark of end stage liver disease or advanced fibrosis. Hepatic venous pressure gradient (HVPG) greater than 5 mmHg is defined as portal hypertension. Esophageal varices (EV) form when HVPG is greater than 10 mmHg and the chances of EV bleeding occurs when HVPG exceeds 12 mmHg^[58,59]. Esophagogastroduodenoscopy (EGD) has been the cornerstone for diagnosis, surveillance and treatment of EV^[60]. Over the last decade EUS has emerged as an important tool for evaluation of gastroesophageal varices^[61].

EUS can effectively measure the size of EV by using the sum of the cross-sectional surface area of all the EV in the distal third of the esophagus^[62]. While upper gastrointestinal endoscopy continues to be the gold standard in detecting EV, EUS has better sensitivity in detecting gastric varices^[63]. In one study EUS was able to detect gastric varices twice more than conventional EGD^[63]. Since EUS can detect vascular changes better, some experts believe that EUS can easily differentiate thickened gastric folds from small gastric varices that can be difficult to diagnose *via* EGD^[64]. EUS like EGD can not only diagnose esophageal and gastric varices but can also predict the risk of bleeding. One report showed that the detection of hemocystic spots *via* EUS predicted the chance of variceal hemorrhage^[65].

The other advantage of EUS is increased sensitivity in detection of collateral veins around the esophagus. These veins can be small in size, called peri-esophageal collateral veins, or large in size; para-esophageal collateral veins^[61]. In one study from China, EUS was able to detect extra-luminal venous abnormalities in greater than 90% of patients with cirrhosis^[66]. Some gastroenterologists argue that the early detection of gastroesophageal varices, and other venous abnormalities in cirrhosis *via* EUS might reduce the need of liver biopsy if the etiology of cirrhosis is clear, *e.g.*, alcohol use and long standing viral hepatitis^[67].

The detection of collateral vasculature does not only have diagnostic significance, but also has prognostic value. Prior studies have shown that the presence of severe collateral and perforating veins can help predict

Table 2 Animals studies regarding endoscopic ultrasound-guided intrahepatic portosystemic shunt placement

Ref.	Animals	Type of needle	Success rate
Schulman <i>et al</i> ^[79]	5 pigs	19-G-needle	100%
Buscaglia <i>et al</i> ^[80]	10 pigs	19-G-needle	100%

the chance of recurrence of esophageal varices before and after treatment^[68-70]. Konishi *et al*^[70] performed a study evaluating the risk of recurrence of esophageal varices after band ligation based on presence of vascular structures around the gastric cardia detected *via* EUS. They reported that over 90% of patients with severe perforating veins seen on EUS prior to variceal band ligation had recurrence of varices^[70]. In another study by Masalaite *et al*^[71], severe esophageal collateral veins seen during EUS were shown to be independent risk factors for recurrence of varices. This suggests that this subset of patients might need closer follow-up as compared to patients who do not have perforating veins.

Therapeutic aspect

Over recent years, EUS has found role in management and treatment of gastroesophageal varices as well. The role of sclerosing therapy under EUS guidance is becoming increasingly popular. One randomized trial from Brazil showed encouraging results demonstrating that EUS guided sclerotherapy was equally effective as compared to standard endoscopic sclerotherapy for esophageal collateral vessels^[72]. Where treatment of esophageal varices *via* EGD continues to be the standard of care, bleeding from gastric varices continues to be a challenge for endoscopists around the globe. Gastroesophageal varices type 2 (GOV-2) are usually large in size and lead to significant bleeding. These varices cannot be effectively treated by band ligation, and therapy targeting the accompanying perforating and collateral veins is needed. Due to these challenges, EUS guided therapy with precise localization of these veins is becoming exceedingly popular^[73]. The two common modalities include EUS guided cyanoacrylate injection and EUS guided coil embolization^[73,74]. Lee *et al*^[66] performed a study in which 54 patients with bleeding due to gastric varices underwent EUS every two weeks, with injection of cyanoacrylate until obliteration of gastric varices. The authors reported that this intervention lead to decrease in recurrence of bleeding and improved survival in this group of patients^[66]. A multi-center study also compared the use of cyanoacrylate injection (CI) with EUS guided coil embolization (CE) for treatment of bleeding gastric varices^[75]. The results of this study were promising and showed that both EUS guided CI and CE were effective in treatment of gastric varices, however, CE had less side effects and needed less

number of sessions for eradication of gastric varices. EUS guided sclerosis has also been successfully used to treat bleeding rectal varices in some cases^[76].

The role of EUS in portal hypertension seems to be growing even more. Recently an animal study reported comparable results of portal pressure gradient measurement by EUS guided manometer approach with interventional radiology guided portal pressure measurement^[77]. The same group of investigators also performed a pilot human study in which 28 patients underwent EUS guided portal pressure measurement with a hundred percent success rate and no adverse events^[78]. Whereas further studies with larger sample size are needed in this regard, EUS guided portal pressure measurement might be a breakthrough for gastroenterologists and hepatologists in taking care of patients with cirrhosis. Animal studies (Table 2) have also shown that EUS can potentially be used for creation of intra-hepatic portosystemic shunts^[79,80]. Historically the intra-hepatic portosystemic shunt has been placed using a trans-jugular approach under angiography (TIPS). Although this procedure as suggested has been technically feasible in animals, major concerns should be addressed before its application in patients with advanced liver disease. Those concerns include high risk of bleeding, severe infections and technical difficulties in stent placement^[81].

COMPLICATIONS OF EUS

Due to specific mechanical properties of echoendoscopes used for EUS and the evolving training of advanced endoscopy specialists, there is a low, and yet noteworthy risk of complications with EUS. Majority of the complications related to EUS occur during EUS-FNA^[82]. The mortality associated with EUS and EUS-FNA is 0.02%^[82]. The major adverse complication with EUS is perforation. Gastrointestinal perforation can happen, especially at areas of angulation and in the presence of unexpected anatomical changes^[82]. A survey conducted in Germany, including 67 centers, reported 32 complications associated with EUS. Esophageal perforation occurred only in 8 of almost 85000 diagnostic EUS procedures^[83]. Another survey among members of American endosonography club in 2002 reported 16 esophageal perforations that occurred after almost 44000 EUS procedures were performed, and more than half of those occurred with endoscopists who had less than one year of experience performing EUS^[84]. Duodenal perforations occur more frequently than esophageal perforation^[82]. In a prospective EUS online registry, 10 events of gastrointestinal perforations in 13988 diagnostic EUS procedures were noted, with duodenal perforation accounting for 60% of these cases^[82]. A survey by Lachter^[85] investigated the mortality in patients who had a complication during EUS. The authors reported that 13 out of 18

(73%) fatalities resulted from duodenal tears causing retroperitoneal perforations, with four of those thirteen patients having duodenal diverticula.

CONCLUSION

The role of EUS has evolved greatly in recent years. Initially thought to be a great tool for diagnostics, EUS has now several therapeutic implications as well. Since expansion of EUS in liver diseases, it is emerging as a great tool for gastroenterologists and hepatologists to manage several liver related conditions. Focal hepatic lesions have always been a challenge for hepatologists. With recent advancements in EUS, it has shown superiority in detecting focal liver lesions as compared to conventional CT scan and ultrasound imaging modalities. Moreover, recently several therapies including EUS guided ethanol and EUS-guided Nd:YAG (neodymium-doped yttrium aluminum garnet; Nd:Y₃Al₅O₁₂) laser ablation are also used to treat focal hepatic lesions. Similarly, recent data is showing that EUS guided liver biopsy may potentially be more safer than percutaneous liver biopsy when done by an experienced endosonographer. In regards to portal hypertension, EUS can detect early changes of portal hypertension and hence provides early and accurate assessment of overall clinical status. Despite encouraging results from available data, further research including randomized control trials is needed, before the use of EUS can be generalized in liver diseases.

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