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Abstract

Endoscopic ultrasound (EUS) is a minimally invasive diagnostic and therapeutic modality with a number of established as well as evolving uses in patients with chronic liver disease. Compared to other diagnostic tools such as cross-sectional imaging or conventional endoscopy, EUS has been shown to increase diagnostic sensitivity and therapeutic success for many clinical scenarios and applications with a low rate of adverse events. In this review, we discuss and focus on the current and growing role of EUS in the evaluation and/or treatment of hepatobiliary masses, hepatic parenchymal disease, portal hypertension, esophageal and other varices, and indeterminate biliary strictures.

Key words: Endoscopy; Cirrhosis; Liver mass; Liver biopsy; Variceal bleeding

Core tip: Endoscopic ultrasound (EUS) is a minimally invasive diagnostic and therapeutic modality with numerous existing and emerging applications in patients with chronic liver disease. In this review, we discuss the role of EUS in the evaluation of hepatobiliary masses, hepatic parenchymal disease, portal hypertension, and indeterminate biliary strictures. We also review how EUS can serve as an ancillary tool to conventional endoscopic and other therapies, including the use of EUS for the treatment of variceal bleeding.

INTRODUCTION

Endoscopic ultrasound (EUS) has been established as a valuable diagnostic tool in gastroenterology since its inception in the 1980s. EUS has proven valuable in patients with liver disease when conventional endoscopy or cross-sectional imaging are insufficient or inconclusive or when surgical interventions pose excessively high risk. In more recent years, EUS has seen an expansion in its therapeutic applications, many of which are germane to the management of chronic liver disease. In this review, we discuss the indications for, performance, impact, and safety of EUS, both diagnostic as well as therapeutic, in patients with chronic liver disease, with a focus on hepatobiliary masses, hepatic parenchymal disease, portal hypertension, esophageal and other varices, and indeterminate biliary strictures.

EUS IN THE EVALUATION OF LIVER MASSES

The differential diagnosis of a liver lesion is broad, with many benign as well as malignant potential etiologies. While the majority of solitary lesions are benign (*e.g.*, hepatic cysts, focal nodular hyperplasia, hepatic adenoma, hemangioma, regenerative nodules), malignant etiologies [*e.g.*, hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and other metastatic masses] have serious consequences and rely on timely diagnosis[1]. Accurate characterization and diagnosis of liver masses comprises an important topic and area of research in modern practice, as clinical mimics may exist, and some masses may be particularly challenging to definitively diagnose.

Evaluation of small lesions

Cross-sectional imaging with computed tomography (CT), magnetic resonance imaging (MRI), and transabdominal ultrasound followed by transcutaneous image-guided biopsy is generally the accepted method of evaluation for liver masses[2]. However, cross-sectional imaging has proven to be less sensitive for smaller (< 10 mm) lesions[3,4]. For these smaller masses, EUS has been found to have improved sensitivity, with the ability to position the probe closer to the liver surface. A prospective study of 574 patients with gastrointestinal or pulmonary malignancy who underwent EUS found that EUS discovered liver lesions in 14 patients with a mean size of 1.8 cm (range 0.5 cm to 5.8 cm), while CT was only able to identify 3 of the lesions[5]. Further studies have supported the observation that EUS can identify liver lesions smaller than 5 mm in diameter, many of which may be missed by CT[6,7]. EUS has also been shown to detect more metastatic lesions compared to CT and is capable of characterizing lesions that are too small to characterize by CT[8] (Figure 1). Indeed, in a retrospective study of 336 patients who underwent EUS for a malignant diagnosis, EUS was able to detect smaller liver metastases compared to CT scan (mean 8.8 mm *vs* 15.3 mm, respectively)[9]. There are little data regarding the comparison of EUS and MRI for the detection of small lesions; however, MRI is generally considered more sensitive than CT, and in one study, appeared to have similar diagnostic accuracy as EUS[10].

Performance of EUS in the evaluation of liver masses

The sensitivity of EUS has been examined and validated by multiple studies. DeWitt *et al*[11] reviewed 77 malignant and benign liver lesions that underwent EUS-guided fine needle aspiration (FNA) using a 22-gauge needle (mean 3.4 passes) and found the sensitivity of EUS-FNA to be between 82% and 94%. In a prospective study of 41 patients with known or suspected malignancy and concomitant liver lesions, EUS-FNA was successfully performed in 40 of 41 patient using a 22-gauge needle and a mean of 1.4 passes (in one patient, the authors report it was not possible to aspirate sufficient material)[12]. For malignant lesions, a combination of cytology and histology yielded a sensitivity and specificity of 94% and 100%, respectively[12].

Recently, EUS criteria have been proposed to select liver lesions that may be
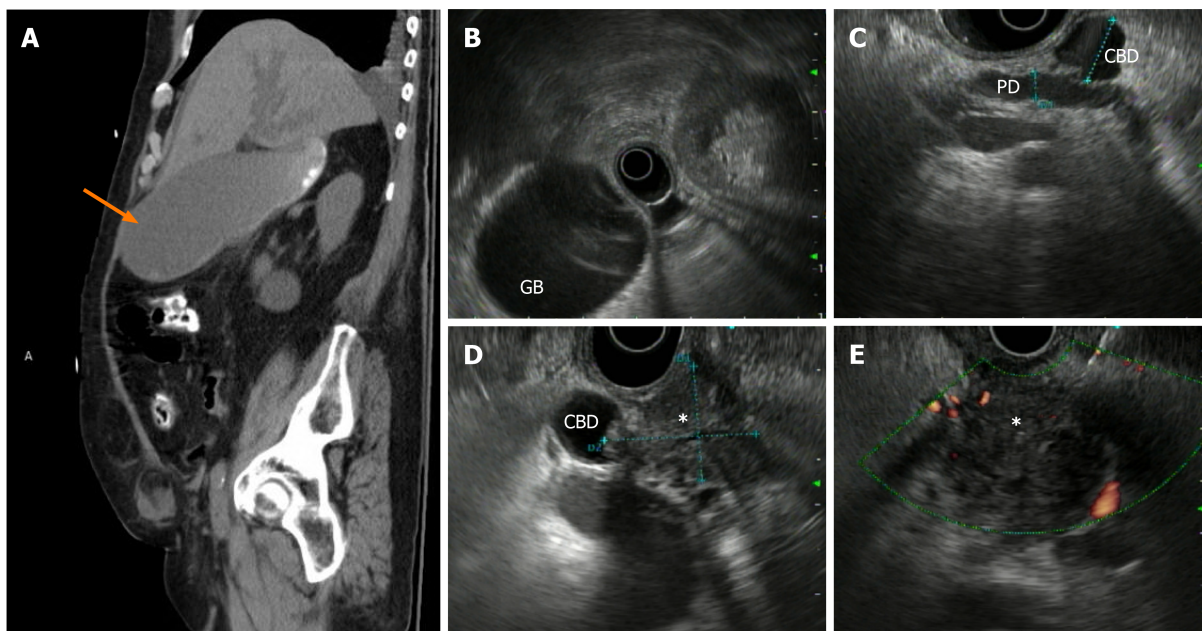
Figure 1 Endoscopic ultrasound in the diagnosis of obstructive jaundice. An 80-year-old male with a history of non-alcoholic fatty liver disease presented with new onset of painless jaundice, physical examination consistent with Courvoisier's sign (palpable gallbladder), and laboratory test results suggestive of severe biliary obstruction. A: Distended gallbladder (arrow) seen on computed tomography, sagittal view. B: Distended gallbladder seen on endoscopic ultrasound. C: Double duct sign consisting of a dilated common bile duct (CBD) and dilated pancreatic duct. D: A poorly-marginated, hypoechoic pancreatic mass (asterisk) invading the distal CBD. E: Fine-needle biopsy of the pancreatic mass (asterisk), which led to tissue diagnosis of adenocarcinoma and facilitated subsequent management. GB: Gallbladder; PD: Pancreatic duct; CBD: Common bile duct.

malignant and need to be sampled. Derived from a retrospective review of a cohort of 100 patients, features suggestive of benign masses were hyperechogenicity and distinct geographic shape (Figure 2) while those suspicious for malignancy included masses with two components, presence of post-acoustic enhancement, distortion of adjacent structures, hypoechogenicity, and size ≥ 10 mm[9]. These criteria were subsequently validated in a separate cohort of 100 patients with pathology or imaging as the gold standard and then used to generate a 16-point scoring system based on tested criteria. Using a cut-off of 3 points, the combined sensitivity, specificity, and positive predictive value (PPV) in predicting a malignant hepatic mass was found to be 85%, 82%, and 88%, respectively[9].

In addition to being an effective diagnostic tool, especially for smaller liver lesions, EUS-guided fine needle biopsy (FNB) also appears to be an effective "rescue" method when percutaneous tissue acquisition has failed or been deemed unsafe. A study of 23 patients who needed a pathological diagnosis of a liver mass who failed percutaneous biopsy or where percutaneous biopsy was contraindicated (due to coagulopathy, ascites, inadequate sampling, or lack of visualization by cross-sectional imaging) found that EUS-FNB with a 22-gauge core biopsy needle (except for one patient in whom a 25-gauge needle was used) was a reliable alternative[13]. EUS-FNB was technically successful in 21 of the 23 lesions (93%), adequate tissue for pathology was obtained in 19 patients, and the overall diagnostic accuracy for malignancy and specific tumor type were 90.5% and 85.7%, respectively, with a median of 2 passes (range 1 to 5) during biopsy. None of the patients had adverse events related to the procedure[13].

Though CCA may also present as a liver mass, the role of EUS in the management of CCA is less clear. A 2014 systemic review and meta-analysis identified six studies (196 patients) that investigated the role of EUS for the detection of CCA where biopsy was available as the gold standard[14]. The overall pooled sensitivity in 196 patients was 66%. In five of the six studies, EUS identified a mass in 25% to 100% of patients; one study did not report data regarding the presence of a mass. The pooled sensitivity of EUS for CCA in studies that detected a mass on EUS (146 patients) was 80%[14].

EUS-GUIDED LIVER BIOPSY FOR THE EVALUATION OF LIVER PARENCHYMA

Despite advances in the biochemical and imaging-based evaluation of parenchymal
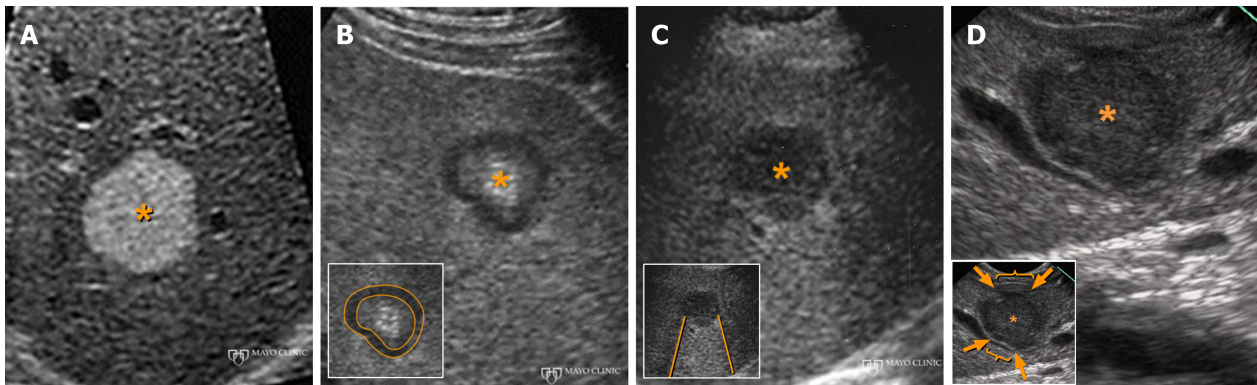
Figure 2 Characteristics of benign and malignant liver masses. A: A distinctly demarcated hyperechoic lesion consistent with a benign hemangioma. B: A liver lesion with both iso/hypoechoic parts peripherally (outlined in orange in inset) and central hyperechoic parts suggestive of malignancy. C: A hypoechoic mass exhibiting post-acoustic enhancement (outlined in orange in inset) as frequently seen in malignancy. D: A hypoechoic, poorly demarcated mass distorting adjacent strictures (orange arrows and brackets in inset) suggestive of malignancy.

liver disease, a liver biopsy is still frequently needed to determine the etiology and grade the severity of liver pathology. Microscopic examination of hepatic tissue is often a requisite step in the workup after other tests, including serology, imaging, and endoscopy, have failed to provide a diagnosis. Traditionally, a percutaneous or transjugular approach has been used to obtain a liver biopsy[15,16]. In addition to sonographic and other hepatic imaging data that can be obtained *via* EUS, in recent years, EUS-guided liver biopsy (Figure 3) has become an alternative to traditional methods of liver biopsy as it allows for examination of the upper gastrointestinal tract, pancreas, and the biliary tree with ultrasonic visualization of the liver, while also allowing for acquisition of tissue during the same session. This modality thus allows for a one step diagnosis in patients being referred for abnormal serum liver tests who also have an indication for upper endoscopy.

Performance of EUS-guided parenchymal liver biopsy

In the earliest example of EUS-guided liver sampling, 2 patients underwent EUS-guided biopsy of the liver using a Tru-Cut biopsy (TCB) needle (Cook Medical, Bloomington, IN, United States) as part of the evaluation for abnormal liver tests[17]. Subsequently, a retrospective study found that TCB was able to provide adequate tissue for histological diagnosis in 100% of patients[18]. However, the high success rate was not able to be reproduced in a prospective case series where adequate tissue was obtained in only 19% of patients[19]. This low success rate was thought partly to be due to the small size and stiffness of Tru-Cut needles used.

In 2012, a prospective case series of 22 patients undergoing same-session EUS and liver biopsy using a 19-gauge FNA needle [EchoTip® (Cook Medical, Bloomington, IN, United States)] was able to obtain adequate tissue in 91% (20/22) of patients (with mean portal tract count of 9 and aggregate specimen length of 36.9 mm), demonstrating that EUS-guided liver biopsy could be successfully performed with a regular 19-gauge FNA needle[20]. A large multicenter trial of 110 patients confirmed efficacy and feasibility of using a 19-gauge needle [Expect™ or Expect™ Flexible (Boston Scientific, Marlborough, MA, United States)][21]. Median length of specimens was 38 mm (0 mm - 203 mm), and 105 patients had specimens with over six complete portal triads (PTs) and length > 15 mm. Pathological diagnosis was possible in 108/110 (98%) of cases. One patient developed a subcapsular hematoma but did not require further intervention to control bleeding. This study was limited by the fact that only five patients were found to have cirrhosis which is important as specimen fragmentation has been reported to occur at higher rates in patients with cirrhosis, resulting in decreased specimen adequacy[22].

Over the years, additional studies have been performed to compare various biopsy needles and refine the EUS-guided liver biopsy technique. A summary of these studies is detailed in Table 1. Studies which have compared needle size have generally found that a 19-gauge needle is superior to smaller 20- or 22-gauge needles due to the significant drop in specimen adequacy rate with smaller needles[23-25]. In a randomized study comparing a 19-gauge Expect™ Flexible needle (Boston Scientific) versus a 22-gauge SharkCore™ [Medtronic, Minneapolis, MN] needle in 80 patients, the 19-gauge needle produced more adequate specimens than the 22-gauge needle (88% *vs* 27%, respectively), primarily attributed to greater tissue fragmentation with the 22-gauge needle[23]. Use of a heparin-primed needle has also been reported to
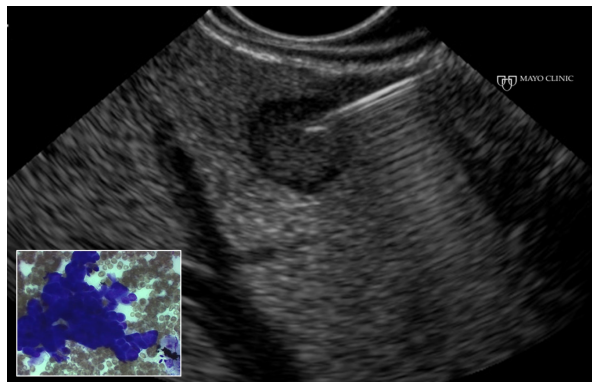
Figure 3 Endoscopic ultrasound-guided fine needle biopsy of a hypoechoic hepatic lesion first seen on non-invasive imaging; cytopathology was consistent with metastasis from pancreatic ductal adenocarcinoma (inset).

improve tissue adequacy compared with dry needle techniques[26]. In a prospective crossover study evaluating various suction techniques in 120 biopsy specimens from 40 participants, specimen adequacy rate was 98%, 93%, and 80% in the wet heparin (needle flushed with heparin), dry heparin (needle flushed with heparin then flushed with air), and dry needle (no heparin used) groups. The use of heparin has been shown to be safe and not interfere with specimen processing[27], and the improved yield is thought to be due to the reduction in blood clot formation within the biopsy needle with the use of heparin[26].

Safety of EUS-guided liver biopsy

To date, there are no head-to-head comparisons of liver lesion biopsy performed under the guidance of cross-sectional imaging versus EUS in a randomized control study. However, a recent retrospective study of 30 patients who underwent EUS-guided liver biopsy and 60 patients who underwent percutaneous liver biopsy found that EUS-guided liver biopsy was associated with a significantly shorter hospital stay (median time of hospital stay 3 h *vs* 4.2 h) and less pain (median pain score 0 *vs* 3.5)[28]. In this study, no patients had significant adverse events. The risk of adverse events with EUS-FNA appears to be comparable to the adverse event rate of FNAs of other types of lesions. In a systematic review of 51 studies (10941 patients), the overall rate of adverse events in patients undergoing EUS-FNA of liver lesions was 2.3% (8/344), compared to 3.6% and 2.8% for ascites and pancreatic cystic lesions, respectively[29]. A more recent retrospective study reported a similar adverse event rate of 2.9%[9]. In contrast, a retrospective study of 3357 percutaneous liver biopsies over 36 years reported an adverse event rate of 4%[30]. Adverse events after EUS-FNA of liver lesions include abdominal pain, nausea, fever, bleeding, duodenal perforation, and death as summarized in Table 2.

EUS ELASTOGRAPHY

Elastography generally refers to an imaging modality that assesses for changes in the elasticity of tissue, as can be seen with fibrotic, inflammatory, or malignant processes. Reduced elastic rebound suggests stiffer tissue, which in the context of liver disease, tends to be an indicator of fibrosis, cirrhosis, or other pathologic processes. Elastography has been shown to have a high correlation with the degree of histologic fibrosis and can also be helpful in the assessment of sequelae of advanced fibrosis and cirrhosis such as the presence of varices, risk of variceal rupture, and prediction of HCC development[31].

Traditionally, transabdominal ultrasound has been the platform for hepatic elastography technique. However, transabdominal elastography is often limited by ascites, body habitus, and narrow intercostal spaces[31]. EUS elastography (EUS-EG) can overcome many of these aforementioned limitations. Although originally developed to examine deeper abdominal tissues (*e.g.*, pancreas), recent studies have found that it can also be useful in the assessment of chronic liver disease, and in particular, solid liver masses[32]. In a recent prospective study of 50 patients, Schulman *et al*[33] found that EUS-EG was able to distinguish between normal, fatty, and cirrhotic tissue with a strong predictive value (area under the receiver operating characteristic curve, 0.865). In this study, the use of EUS-EG added a mean of 5 mins to the

Table 1 Comparison of needle performance in endoscopic ultrasound-guided liver biopsies

Ref.	Design	Exclusion criteria	Needle	Median (range) number of complete portal tracts	Median (range) aggregate specimen length, mm	Median (range) number of passes	Adequacy (%)	Complications (number of patients)
Human studies								
Stavropoulos *et al*[20], 2012	Prospective (*n* = 22 patients)	Suspected/known malignancy; Platelet < 50, INR > 1.5; Use of antiplatelets within 7 days; Inability to provide informed consent; Pregnancy	19-G EchoTip® FNA (Cook Medical)	9 (1-73)	36.9 (2-184.6)	2 (1-3)	91%	None
Diehl *et al*[21], 2015	Prospective, non-randomized (*n* = 110 patients)	Malignant liver disease; Platelet < 50, INR > 1.5; Use of antiplatelets within 5 days; Inability to provide consent; Pregnancy	19-G Expect™ FNA (Boston Scientific) or 19-G Expect™ Flexible FNA (Boston Scientific)	14 (0-68)	38 (0-203)	1 or 2	98%	Pericapsular hematoma (1)
Sey *et al*[82], 2015	Cross-sectional (*n* = 75 patients)	Liver lesion or presence of varices Prior upper GI or liver surgery; Use of antiplatelets not held prior to procedure; Platelet < 50, INR > 1.5	19-G EchoTip® ProCore FNB (Cook Medical) (*n* = 30)	5 (0-24)	20 (5-60)	2 (1-3)	97%	None
			19-G Quick-Core® FNB (Cook Medical) (*n* = 45)	2 (0-15)	9 (0-25)	3 (1-7)	73%	Abdominal pain (2)
Shah *et al*[83], 2017	Retrospective (*n* = 24 patients)	Not stated	19-G SharkCore™ FNB (Medtronic)	31.5 (5-85)	65.6 (17-167.4)	2	87.5%	Abdominal Pain (2); Subcapsular bleeding (1)
Mok *et al*[23], 2018	Randomized cross-over (*n* = 80 patients)	Platelets < 50, INR > 1.5; Diagnosis of cirrhosis ; Under 18 years age; Inability to provide informed consent; Pregnancy	19-G Expect™ Flexible FNA (Boston Scientific)	7.4[13]	76.5[13]	1	88%	None
			22-G SharkCore™ FNB (Medtronic)	6.19[13]	66.9[1,3]	1	68%	Abdominal Pain (1)
Cadaveric studies								
Lee *et al*[84], 2017	Nonrandomized (*n* = 2 livers)	N/A	19-G EchoTip® ProCore FNB (Cook Medical)	3.33[1]	473[2]			N/A
			19-G EZ Shot 2 FNA (Olympus Corporation)	4.00[1]	298[2]			
			19-G Expect™ Slimline FNA (Boston Scientific)	4.42[1]	426[2]			
			19-G SharkCore™ FNB (Medtronic)	8.83[1]	507[2]			

			18-G TruCore™ (Argon Medical Devices)	7.00[1]	155[2]			
Schulman *et al*[25], 2017	Randomized (n = 2 livers)	N/A	19-G SharkCore™ FNB (Medtronic)	6.2[1]			85.4%	N/A
			22-G SharkCore™ FNB (Medtronic)	3.8[1]			85.4%	
			19-G EchoTip® ProCore FNB (Cook Medical)	1.7[1]			About 19%	
			19-G Expect™ FNA (Boston Scientific)	1.9[1]			About 46%	
			18-G Quick-Core® FNB (Cook Medical)	2.5[1]			83.3%	
			18-G Coaxial Temno® (CareFusion)	3.5[1]			81.3%	
Bovine studies								
Eskandari *et al*[24], 2019	Nonrandomized (n = 1 bovine liver)	N/A	19-G Acquire™ FNB (Boston Scientific)	11.8[1]	71.30[1]	5		N/A
			22-G Acquire™ FNB (Boston Scientific)	6.4[1]	44.94[1]	5		
			19-G SharkCore™ FNB (Medtronic)	10.4[1]	51.50[1]	5		
			22-G SharkCore™ FNB (Medtronic)	1.4[1]	20.89[1]	5		
			19-G EZ Shot 3 Plus FNA (Olympus Corporation)	10.2[1]	71.77[1]	5		
			20-G EchoTip® ProCore FNB (Cook Medical)	7.2[1]	79.79[1]	5		

[1]Mean.

[2]Total specimen length.

[3]Results not statistically significant. INR: International normalized ratio; G: Gauge; FNA: Fine needle aspiration; FNB: Fine needle biopsy; N/A: Not applicable.

procedure, and none of the patients had any periprocedural adverse events; however, this study was limited by the fact that not all patients had corresponding biopsy data. With the ability to evaluate for hepatobiliary masses, parenchymal liver abnormalities, and complications of portal hypertension (*e.g.*, varices), EUS-EG may improve efficiency and reduce the number of procedures when more than one organ requires evaluation. As data on this relatively new modality are limited, additional studies are needed prior to its use in clinical practice.

EUS-GUIDED TREATMENT OF HEPATIC LESIONS

In addition to be a diagnostic modality, EUS has been found to be an effective tool in the treatment of hepatic lesions. The use of EUS may facilitate more targeted interventions (in part as a result of closer proximity between the EUS probe and the lesion of interest) as well as shorter recovery time compared with percutaneous approaches (by eliminating the need to puncture the skin)[34].

Treatment of cystic liver lesions

Table 2 Most frequent adverse events associated with endoscopic ultrasound-guided liver biopsy

Adverse event	Event frequency/number of patients in the study
Abdominal pain or nausea	7/499[9,85]
Fever	2/167[85]
Bleeding	1/167[85]
Duodenal perforation	2/332[9]
Death	1/167[85]

Simple hepatic cysts are benign lesions that are commonly found incidentally on routine imaging, with most patients asymptomatic and without need for further intervention[35]. However, larger cystic lesions can cause abdominal pain and distension, among other symptoms or complications, resulting in the need for further management. Surgical therapy has traditionally been regarded as the treatment of choice for symptomatic hepatic cystic lesions, though this intervention carries considerable morbidity[36,37]. Percutaneous aspiration can be considered in certain cases but is frequently associated with cyst recurrence[38]. Ethanol lavage therapy (either *via* percutaneous approach or EUS-guided) has recently been found to be an effective and safe alternative to conventional surgical and percutaneous aspiration therapies[39,40]. While percutaneous ethanol lavage is generally more feasible for right-lobe hepatic cysts, the EUS-guided approach appears to be particularly useful for left-lobe cysts. Furthermore, the EUS-guided approach appears to have better outcomes compared to the percutaneous approach. In a study of 17 patients with hepatic cysts undergoing percutaneous or EUS-guided aspiration and ethanol lavage, patients who underwent EUS-guided sclerotherapy had a higher median reduction in cyst volume (100% *vs* 97.5%, $P = 0.011$), a higher number of completely resolved cysts within 1 year (5 out of 8 patients *vs* 0 out of 10 patients, $P = 0.005$), and a shorter hospital stay (4.5 d *vs* 6.5 d, $P = 0.048$) compared with patients who underwent a percutaneous approach[39]. EUS-guided drainage (as with percutaneous drainage) also appears to be an effective treatment for infected (known or suspected) hepatic cysts[41].

EUS-guided drainage of non-hepatic collections (*e.g.*, pancreatic pseudocysts and walled-off necrosis[42]) are technically essentially the same for patients with and without chronic liver disease and thus is not discussed in the present review.

Treatment of solid liver lesions

Solid hepatic masses include abscesses and malignancies. Similar to the treatment of cystic lesions, solid masses have traditionally been treated with surgical or percutaneous drainage; however, morbidity and mortality is relatively high with these approaches[43]. In recent years, EUS-guided drainage of liver abscesses has been found to be both safe and feasible, with a lower rate of adverse events and a shorter hospital stay compared with percutaneous drainage[34]. For hepatic metastases, EUS-guided ablation using ethanol appears to be a viable alternative treatment option to traditional therapies and has been found to result in clinical success in a number of cases[44-46]. Other experimental treatments utilizing EUS, including EUS-guided neodymium:yttrium-alumnium-garnet laser ablation and EUS-guided fiducial placement for stereotactic body radiation therapy have also been reported as safe and accurate minimally invasive methods of treating hepatic malignancies[47,48]. However, well-designed prospective studies are needed prior to the use of these novel therapies in clinical practice.

EUS IN PRIMARY SCLEROSING CHOLANGITIS

With advances in MRI technology, magnetic resonance cholangiopancreatography (MRCP) has generally replaced endoscopic retrograde cholangiopancreatography (ERCP) as the initial diagnostic as well as surveillance modality for primary sclerosing cholangitis (PSC)[49,50]. However, the sensitivity of MRCP is not without limitation, with one systematic review suggesting a sensitivity of MRCP of only 86%[51]. This has led to efforts to develop a less invasive but more accurate endoscopic modality to diagnose PSC[52]. In a prospective controlled study, patients with PSC had a larger mean ductal wall thickness compared with patients with uncomplicated inflammatory bowel disease (IBD) or cholelithiasis[53]. In another study, four EUS criteria (wall thickening ≥ 1.5 mm, irregular wall structure, significant changes of the

caliber of the common bile duct, and perihilar lymphadenopathy) were found to assist with the diagnosis of PSC in 33 patients with cholestatic liver enzyme elevation and either concurrent IBD or positive perinuclear antineutrophil cytoplasmic antibodies[54]. The authors found a sensitivity and specificity of 76.4% and 100%, respectively for the diagnosis of PSC if two out of the four aforementioned EUS criteria were present.

With regard to complications of PSC, indeterminate strictures pose a hallmark lesion and a frequently challenging entity from a clinical perspective. A recent systemic review and meta-analysis of eight studies including 294 patients found EUS to have superior sensitivity compared with ERCP with brushing and forceps biopsy in the diagnosis of indeterminate biliary strictures (75% *vs* 49%, respectively)[55]. EUS sensitivity is dependent on the location of the stricture (higher sensitivity for more distal strictures) and the underlying etiology (higher sensitivity for pancreatic cancer compared to CCA, for example)[56,57]. Thus, it has been proposed that stricture-location should be considered when deciding which diagnostic modality to use; when EUS is used for distal biliary strictures, irrespective of underlying PSC, its accuracy for malignancy detection has been reported to be as high as 96%[58].

However, despite these studies, EUS is still infrequently used as a diagnostic tool in PSC. There is also uncertainty on whether EUS is practical from a cost perspective. A cost-effective analysis found that an EUS instead of ERCP for indeterminate biliary strictures results in 0.13 additional QALYs (quality adjusted life years), but with an added cost of $2773.69[59]. However, after taking into consideration the increased sensitivity of EUS *vs* ERCP (74% and 42%, respectively), the study authors found EUS to be more cost-effective. Nevertheless, there has not been wide uptake of routine EUS in PSC.

ASSESSING PORTAL HYPERTENSION, VARICES, AND BLEEDING RISK WITH EUS

Portal hypertension is the defining hemodynamic change in cirrhosis that is associated with the major complications of variceal bleeding, ascites, and encephalopathy[60]. EUS can be used to diagnose splanchnic varices, predict the risk of bleeding, risk of recurrent bleeding, and guide therapeutic interventions (Figure 4)[61]. In early reports, EUS was found to be inferior to conventional esophagogastroduodenoscopy (EGD) in detecting esophageal varices. Caletti *et al*[62] compared EUS and conventional EGD findings in 40 patients with portal hypertension and 48 controls. The authors found a size-dependent sensitivity for EUS in detecting esophageal varices (14% for grade 1 varices *vs* 50% for grade 3 varices). Similarly, Burtin *et al*[63] reported a sensitivity of 25% for grade 1 varices and 89% for grade 3 esophageal varices. However, more recent studies have shown EUS to be comparable to conventional EGD in detecting esophageal varices. In a study of 66 cirrhotic patients, EUS was able to detect esophageal varices in 48 (72%) patients compared to 49 (79%) detected by EGD[64]. About half the patients in this study (31/66) had a previous episode of variceal bleeding which was treated by either band ligation or sclerosant injection. In a different study of 52 patients without a history of variceal bleeding, EUS was found to have a sensitivity of 96.4% when EGD was used as the gold standard[65]. The improved diagnosis of esophageal varices with EUS over the years has been attributed to the use of a smaller echo-endoscope tip in newer echoendoscope models (which exerts less pressure on the varices) as well as a higher video resolution found in newer echo-endoscopes (and their respective processors).

Predicting risk of esophageal variceal recurrence
EUS has also been found to be helpful in predicting the risk of esophageal variceal recurrence after band ligation or sclerotherapy. In one study, 38 patients who underwent sclerotherapy for esophageal varices were followed with EUS every 3-4 mo for at least two years[66]. The authors found that the risk of endoscopic variceal recurrence could be predicted by severe peri-esophageal collateral veins and large perforating veins of the esophagus, which in their study was seen on EUS as early as 3-4 mo prior to endoscopic variceal recurrence[66]. In a study of 30 patients receiving endoscopic variceal ligation, a gastric cardiac perforating vein diameter greater than 3 mm was associated with a higher likelihood of recurrence of esophageal varices (90.9% *vs* 21.0%, *P* < 0.01)[67]. In another study looking at EUS features before and after band ligation for a first esophageal variceal bleeding episode, presence of para-esophageal veins larger than 4 mm after band ligation was shown to predict variceal recurrence in 1 year with a sensitivity and specificity of 70.6% and 84.6%, respectively[68]. In a prospective study of 45 patients who underwent band ligation for F2/F3 varices, the presence of severe peri-esophageal varices (defined as para-
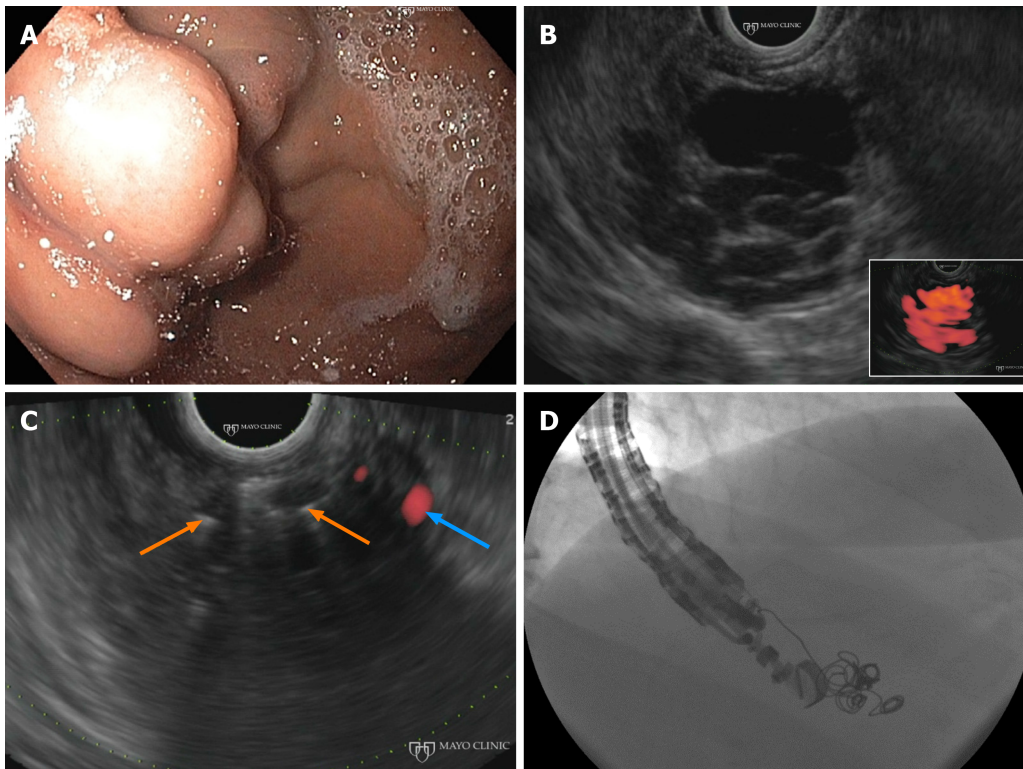
Figure 4 Endoscopic ultrasound-guided management of gastric varices. A: Gastric varices seen on endoscopy. B: Gastric varices appear anechoic on endoscopic ultrasound (EUS) grey-scale and are highlighted red by Doppler study (inset). C: Injection of embolization coils (orange arrows) into the varices results in near complete resolution of blood flow (blue arrow). D: Fluoroscopic visualization of EUS-guided coil embolization.

esophageal veins > 5 mm or peri-esophageal veins > 2 mm) and the presence of more than 5 esophageal collateral veins at baseline EUS were associated with a higher risk of variceal relapse in 1 year in a multivariate logistic regression analysis [odds ratio (OR) = 24.39; 95% confidence interval (CI): 2.34-253.78 and OR = 24.39; 95%CI: 2.34-253.78, respectively]. Of note, the reported confidence interval in this study was quite wide, likely due to the small sample size. High flow velocity in the left gastric vein and anterior branch dominant left gastric vein pattern also appear to be associated with a higher likelihood of esophageal recurrence in 1 year[69].

Predicting risk of esophageal variceal bleeding

In addition to predicting risk of variceal recurrence, EUS may also predict the risk of recurrent variceal bleeding. A retrospective study of 306 patients who underwent endoscopic sclerotherapy for moderate to large or high-risk esophageal varices found that patients that had recurrent bleeding within one year had higher rates of detectable perforating veins and inflowing type of perforating veins prior to therapy, as well as higher rates of detection of cardiac intramural veins, perforating veins, and the inflowing type of perforating veins 3-5 mo post-endoscopic sclerotherapy[70]. Another study found that the size of the diameter of para-esophageal veins (defined as veins external to the esophagus connecting to submucosal varices through perforating veins) was correlated with a higher rate of recurrent variceal bleeding[71].

EUS-GUIDED TREATMENT OF VARICES

Considering the ability of EUS to identify para-esophageal and perforating veins which can contribute to esophageal variceal recurrence, it has been hypothesized that EUS-guided treatment of esophageal varices may reduce esophageal varices recurrence. However, a randomized clinical trial comparing traditional sclerotherapy and EUS-guided sclerotherapy of the feeding veins to esophageal varices did not show a lower recurrence rate for the EUS group[72]. Additionally, no studies have compared EUS-guided therapy with band ligation for esophageal varices yet.

Unlike the case with esophageal varices, EUS appears to be significantly better than EGD in the detection and treatment of gastric varices, often thought to be more difficult to treat due to the inherent challenges with visualization of gastric varices.

Caletti *et al*[62] demonstrated EUS was able to identify gastric varices (described as anechoic, circular structures beneath the submucosa) in 22 of 40 patients with portal hypertension while conventional EGD was only able to identify gastric varices in 10 of 40 patients. Several other studies have confirmed the superiority of EUS in the detection of gastric varices compared to conventional EGD with detection rates varying from 35% to 100%[67,73,74].

Cyanoacrylate (CYA) glue injection has been used for the treatment of bleeding gastric varices due to its effectiveness and low risk of rebleeding[75,76]. For this intervention, EUS has been used both as a confirmatory adjunct and as a real-time guide for the treatment of gastric varices[77]. The presence of echogenic gastric varices and the absence of blood flow on doppler EUS can confirm the successful treatment of gastric varices after CYA injection, while the presence of blood flow in treated varices on follow up doppler EUS can suggest an increased risk of rebleeding[78].

EUS can also be used to facilitate obliteration of gastric and ectopic varices using metallic coils[79]. In a retrospective study, EUS-guided CYA injection and coil embolization were found to have similar rates of obliteration for primary and secondary prophylaxis of isolated gastric varices (IGV 1 and 2) with no patients having recurrent bleeding[80]. The number of treatment sessions needed was fewer in patients receiving coil embolization (82% of patients had complete obliteration of a perforating vein after one session of coil embolization *vs* 53% after one session of CYA). Furthermore, of the 12 adverse events that occurred in this study, 11 occurred in the CYA group, with nine patients developing an asymptomatic pulmonary embolism, one with chest pain, and another had a fever. In the coil group, one patient developed bleeding from esophageal varices.

To reduce the risk of glue embolization, a combination of coil and glue obliteration of gastric varices has been proposed. In a study of 30 patients with active or recent gastric fundic varices (GOV-2 and IGV-1) who underwent EUS-guided coil embolization followed by 2-octyl-CYA glue injection, immediate hemostasis was achieved in all patients with an average of 1.4 mL of glue needed per patient with no procedure-related complications[81].

CONCLUSION

EUS appears to be a relatively safe and effective diagnostic and therapeutic modality for many applications in patients with chronic liver disease. Compared with cross-sectional imaging, it has improved sensitivity for the identification of small liver lesions. It also allows for visualization and biopsy of the liver or lesions therein during the same session, potentially leading to earlier diagnoses. Despite previously reported difficulty with obtaining adequate tissue with earlier liver biopsy needles, newer generation needles appear to have largely overcome these earlier challenges. EUS also appears to be helpful in the evaluation of esophageal varices and the risk of future bleeding, as well as the treatment of gastric varices *via* glue injection or coil embolization. Lastly, EUS appears to be helpful in the diagnosis of indeterminate biliary strictures, though its application in this regard has remained relatively low. Given the strengths and advantages of EUS, it is expected that its clinical use and applications will grow.

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