The Evolving Role of Advanced Endoscopic Techniques in Hepatology

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Abstract: The role of advanced endoscopy in the field of hepatology has evolved rapidly over the last decade. Several novel diagnostic and therapeutic interventions can now be accomplished endoscopically both easily and safely in patients with liver disease; these include endoscopic ultrasound (EUS)-guided liver biopsy, EUS-guided measurement of the portal pressure gradient, EUS-guided therapy for gastric varices, and EUS elastography. This article highlights advances in endoscopic tools and techniques that can be applied in the field of hepatology.

Keywords
Elastography, endoscopic ultrasound–guided liver biopsy, portal pressure gradient measurement, gastric varices therapy

The use of advanced endoscopic techniques in the field of hepatology has expanded rapidly over the last decade. Several novel diagnostic and therapeutic interventions can now be accomplished endoscopically both easily and safely in patients with liver disease. For instance, liver biopsy specimens obtained under endoscopic ultrasound (EUS) guidance are comparable in quality with those obtained via percutaneous and transjugular approaches. The portal system can be safely accessed under EUS guidance to allow direct measurement of the portal venous pressure; this can provide important diagnostic and prognostic information in some patients with chronic liver disease and obviate the need for indirect measurements obtained by interventional radiologists through the transjugular approach. EUS elastography also is available in clinical practice, and although its role in the management of patients with liver disease is still evolving, it may prove to be a useful tool in the near future for measuring liver stiffness. Patients with suspected cirrhosis or chronic liver disease can be evaluated for portal hypertension with endoscopic screening for esophageal varices, EUS elastography, direct measurement of the portal pressure gradient (PPG), and EUS-guided liver biopsy (EUS-LB) if needed, all during the same endoscopic session.

Endoscopic Ultrasound–Guided Liver Biopsy

Liver biopsy is an essential tool for evaluating and managing various diseases of the liver. Traditionally, percutaneous liver biopsy (PCLB) and transjugular liver biopsy (TJLB) have been used to acquire tissue samples. EUS-LB is emerging as an effective, safe, and well-tolerated alternative to PCLB and TJLB. EUS-LB allows easy access to both hepatic lobes for sampling (the left lobe from the proximal part of the stomach and the right lobe from the duodenal bulb), which increases tissue adequacy and yield.[1-3] In addition to parenchymal biopsies, EUS-LB can be used for targeted biopsies of focal liver lesions. Compared with computed tomography, magnetic resonance imaging, and transabdominal ultrasound, EUS is able to detect smaller hepatic and retroperitoneal lesions (<1 cm), which has significant importance, especially in patients for whom a liver transplant is being considered.[4,5] EUS-LB provides a high-quality, real-time view while the biopsy specimen is obtained, and the needle trajectory can be changed to target a specific lesion if needed. Furthermore, injury to adjacent vascular structures can be avoided by applying real-time Doppler.[6] The American Association for the Study of Liver Diseases has published quantitative parameters for an adequate liver biopsy specimen: the presence of at least 11 complete portal triads (CPTs) and a total specimen length (TSL) of at least 2 to 3 cm.[7]

The current preferred technique for EUS-LB is to use a 19-gauge core biopsy needle with a curvilinear echoendoscope, which allows real-time visualization of the needle track in the liver. In a multicenter study by Diehl and colleagues, 110 patients underwent EUS-LB with a 19-gauge fine-needle aspiration (FNA) needle for the evaluation of hepatic dysfunction.[8] The obtained specimens were sufficient for a diagnosis in 98% of the patients; the median TSL was 38 mm and the median number of CPTs was 14. Self-limited bleeding was reported in only 1 patient, who had a medical history of coagulopathy and thrombocytopenia.[8] Emerging data suggest that EUS-LB with a 19-gauge fine-needle biopsy (FNB) needle provides better histologic specimens than does the technique in which FNA needles are used.[9] A retrospective study reported that a diagnosis was achieved in 96% of the patients, with a median number of CPTs of 32.5, a median TSL of 65.6 mm, and a median of 2 passes.[10] A modified 1-pass wet suction technique for EUS-LB was superior to dry suction in terms of increasing the tissue yield.[11,12] A recent prospective study (n=40) that evaluated EUS-LB with a 22-gauge FNB needle to stage patients with nonalcoholic fatty liver disease reported 100% specimen adequacy, with a median TSL of 2.4 cm and a median number of CPTs of 26.[13]

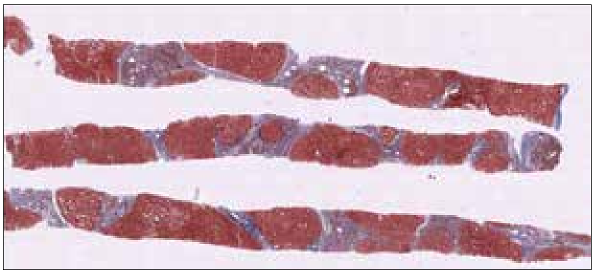

Figure 1. Three long cores of cirrhotic liver obtained via endoscopic ultrasound–guided liver biopsy performed with a 19-gauge core biopsy needle. Reproduced from Diehl DL[16] with permission from Elsevier.

When Pineda and colleagues evaluated the adequacy of liver biopsy tissue samples obtained by EUS-LB, PCLB, and TJLB, they found that EUS-LB produced a significantly longer TSL than either PCLB or TJLB.[14] Furthermore, EUS-LB produced more CPTs than PCLB did[14] and resulted in fewer complications[15] (Figure 1).

In patients with liver disease, EUS-LB and upper gastrointestinal endoscopy (typically used for screening/surveillance of gastroesophageal varices) can be simultaneously performed in 1 session, potentially increasing efficiency and lowering cost.[16] EUS-LB is less invasive than PCLB, and the recovery time after the procedure is significantly shorter. A recent study showed that 92% of patients were pain-free at 1 hour after EUS-LB.[17] EUS-LB can be successfully performed in patients who have undergone a Roux-en-Y gastric bypass by accessing the left hepatic lobe via the gastric pouch.[8] EUS-LB also can be performed safely and effectively in recipients of liver transplants.[18] EUS-LB is contraindicated in cases of severe coagulopathy or ascites; TJLB is favored in these situations to avoid bleeding in patients with coagulopathy and secondary bacterial peritonitis in patients with ascites.[7]

Endoscopic Ultrasound–Guided Portal Pressure Gradient Measurement

The PPG is an important prognostic indicator in patients with chronic liver disease. A hepatic venous pressure gradient greater than 5 mm Hg defines portal hypertension, and a hepatic venous pressure gradient 10 mm Hg or greater is defined as clinically significant portal hypertension. Conventionally, the PPG is obtained indirectly via a transjugular approach, which permits measurement of the free and wedge hepatic venous pressures. Direct percutaneous portal vein catheterization is usually avoided because of the high risk for complications.[19] EUS-guided access to the portal venous system has been studied as an alternative to standard percutaneous routes due to the proximity of the portal vein to the gastrointestinal tract. This procedure has been deemed safe and feasible in porcine models.[20-22] EUS-guided portal pressure gradient (EUS-PPG) measurement in humans was first reported in 2014.[23] Subsequently, a prospective pilot study evaluated the use of EUS-PPG measurement in 28 patients with

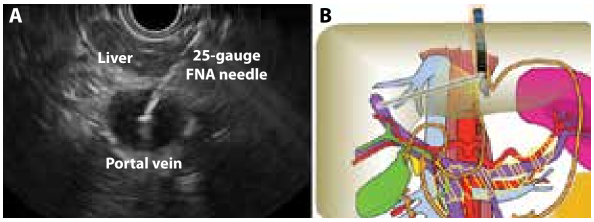

Figure 2. EUS-guided passage of a 25-gauge FNA needle into the portal vein (**A**). Representation of EUS-guided portal vein puncture (**B**). Reproduced from Samarasena JB, Chang KJ[24] with permission from Elsevier.

EUS, endoscopic ultrasound; FNA, fine-needle aspiration.

suspected or confirmed cirrhosis. The PPG was estimated by using a 25-gauge needle and a compact manometer. The needle was inserted initially into the portal vein and then into the hepatic vein or the inferior vena cava if the hepatic vein was difficult to access. The PPG was then calculated by subtracting the hepatic vein pressure from the portal vein pressure or inferior vena cava pressure (Figure 2).[24] Huang and colleagues performed EUS-PPG measurement in 28 patients and reported a 100% technical success rate, with no adverse events such as bleeding, infection, and hospitalization.[25] The PPG ranged from 1.5 to 19 mm Hg; correlation with clinical and endoscopic parameters was excellent, and the time required for the procedure was less than 30 minutes in each patient. Interestingly, most patients in this study also underwent EUS-LB during the procedure, with no major adverse events reported.[25]

Despite these promising data, more prospective multicenter trials will be required to validate the results before this new technique can be widely used in clinical practice. However, a comprehensive endoscopic evaluation of patients with chronic liver disease by a gastroenterologist is now possible, in which variceal screening, EUS-PPG measurement, and EUS-LB can all be conducted in a single session.

Endoscopic Ultrasound–Guided Therapy for Gastric Varices

Bleeding related to portal hypertension remains a major complication of cirrhosis. Endoscopic interventions play a critical prophylactic and therapeutic role.[26] Even though gastric variceal bleeding occurs less frequently than esophageal variceal bleeding, it can be fatal and is usually associated with higher rates of morbidity and mortality.[27]

The role of EUS in the management of gastric varices has evolved within the last few years. From a diagnostic point of view, the rate of gastric varix detection has been shown to be higher with EUS than with direct endoscopy.[28] Obliteration of vascular flow through the varix, which has prognostic implications, can be confirmed by Doppler assessment.

The endoscopically guided injection of tissue adhesive for the treatment of gastric varices has been reported. In this procedure, *n*-butyl-2-cyanoacrylate is usually diluted with lipiodol to avoid needle entrapment within the vessel or premature polymerization within the needle.[29] Systemic embolization of glue (ie, pulmonary embolism, cerebral embolism, or splenic artery embolism) and the formation of gastropleural or gastromediastinal fistulae are some of the most feared complications associated with this technique.[30] The risk for embolization increases with the use of a large volume of adhesive agent, rapid injection, and rapid variceal flow.[29] With EUS-guided cyanoacrylate injection, the bleeding vessel can be targeted precisely, lowering the required dose of adhesive agent and potentially reducing the risk for embolization.[31] Furthermore, Doppler can be used to rule out residual flow and confirm eradication after treatment.[32] EUS-guided coil embolization therapy is a second and newer technique for the endoscopic management of gastric varices. A multicenter retrospective study that compared EUS-guided coil embolization with EUS-guided cyanoacrylate injection reported a 90% obliteration rate, with significantly fewer cases of pulmonary embolism in the coil embolization arm.[33]

Binmoeller and colleagues evaluated the concomitant use of glue injection and coil embolization to lower the risk for systemic embolization.[34] In this technique, coils are first deployed into the gastric variceal lumen; this slows the blood flow, facilitating glue polymerization and preventing the systemic migration of glue. After coil deployment, 2-octyl cyanoacrylate is injected, and then hemostasis is confirmed with color Doppler.[34] A pilot study included 30 patients with active or recent gastric variceal bleeding who were poor candidates for a transjugular intrahepatic portosystemic shunt (TIPS). These patients were treated with EUS-guided coil embolization and glue injection. The success rate was 100%, and follow-up endoscopy showed complete variceal obliteration in 95.8% of patients. None of these patients required salvage TIPS placement. An extended follow-up study of EUS-guided glue-and-coil treatment, in which 152 patients (143 with type 1 isolated gastric varices and 9 with type 2 gastroesophageal varices) were followed for more than 1 year, reported success rates of 99%. Complete variceal obliteration was confirmed with follow-up EUS in 93% of the patients. Pulmonary embolism developed in 1 patient. Moreover, 26% of the patients in this study were undergoing treatment as primary prophylaxis, with complete obliteration in 96% of them (Figure 3).[35]

Figure 3. Endoscopic image (**A**) and EUS image (**B**) of a type 1 isolated gastric varix. EUS-guided deployment of a coil via a 19-gauge needle (**C**). Reproduced from Bhat YM et al[35] with permission from Elsevier.

EUS, endoscopic ultrasound.

Endoscopic Ultrasound Elastography

Liver biopsy remains the gold standard for assessing the degree of hepatic fibrosis; however, this method is invasive and not suitable for serial monitoring of the dynamic changes associated with hepatic fibrosis. Elastography has rapidly evolved as one of the most commonly used noninvasive technologies in clinical practice for the assessment of hepatic fibrosis. Several elastography modalities exist, including transient elastography, acoustic radiation force impulse imaging, 2-dimensional shear-wave elastography (SWE), and magnetic resonance imaging elastography; these have been validated for use in clinical practice.[36,37] The use of transabdominal ultrasound–based elastography is limited in patients with a high body mass index, severe hepatic atrophy, or ascites.[38,39]

EUS elastography is a novel noninvasive technology in which image enhancement is used to measure tissue stiffness; this is accomplished by evaluating EUS images before and after the application of slight pressure to the target tissue with the ultrasonography probe.[40,41] For EUS real-time elastography (EUS-RTE), a conventional EUS probe is attached to a processor with software installed. The compression required for recording is provided by physiologic vascular pulsation and breathing movements. The most recent iteration of this procedure allows the qualitative and quantitative evaluation of tissue stiffness.[42,43] A prospective blinded study that included 50 patients with a normal liver, a fatty liver, or a cirrhotic liver on transabdominal imaging showed that EUS-RTE could distinguish among these types. EUS-RTE may be more sensitive than transabdominal elastography because signal penetration of the thinner gastric wall is better than penetration of the thicker abdominal wall.[44] The effectiveness of the compression approach, which is also known as strain elastography, depends on the operator's experience and ability to locate the target tissue. SWE, which was introduced in the early 2000s, offers a faster, automated alternative to strain elastography. EUS-guided shear-wave elastography (EUS-SWE) is a method to measure and quantify tissue stiffness noninvasively.[45] Ongoing clinical trials are currently evaluating the effectiveness of EUS-SWE in estimating the degree of hepatic fibrosis in patients with chronic liver disease. This technique may prove useful in the future because it has the ability to survey and quantify the entire region of interest, thus optimizing the indications for biopsy and minimizing unnecessary sampling. EUS-SWE can also be used for the serial monitoring of dynamic changes in hepatic fibrosis in patients undergoing surveillance endoscopy for esophageal varices. A further advantage of EUS-SWE over transabdominal ultrasound is that its use is not limited by ascites or a thickened abdominal wall.[46]

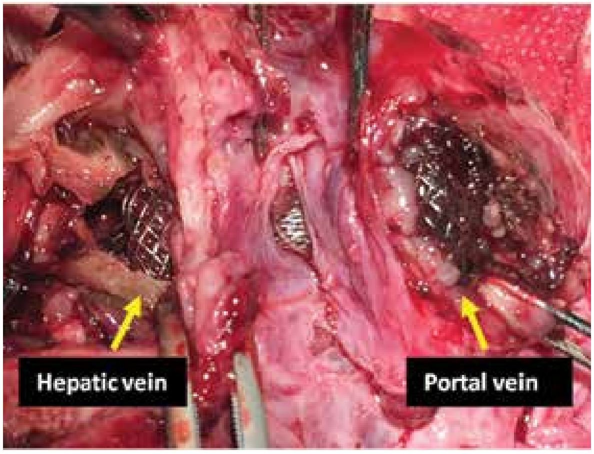

Figure 4. Necropsy image showing a stent located between the portal and hepatic veins. Reproduced from Schulman AR et al[49] with permission from Elsevier.

Future Directions

Multiple studies in animals have evaluated the technical feasibility of EUS-guided intrahepatic portosystemic shunt placement.[47,48] One study reported no adverse events after the deployment of a fully covered lumen-apposing metal stent between the portal and hepatic veins to create a shunt in pigs (Figure 4).[49] EUS-guided ablation therapy techniques, such as radiofrequency ablation and photodynamic therapy, have been described in the management of hepatic and biliary malignancies.[50] These techniques are useful for lesions that are difficult to access with conventional methods. Under EUS guidance, lesions have been accessed more precisely with minimum injury to surrounding tissue.[51] EUS-guided portal injection chemotherapy for liver metastases can increase the intrahepatic concentrations of chemotherapeutic agents and decrease systemic toxicity.[52]

Conclusion

The role of advanced endoscopy in hepatology is evolving rapidly, so it is now possible to perform a variety of diagnostic and therapeutic interventions such as EUS-LB, EUS-PPG measurement, and EUS elastography. Because of the minimally invasive nature of these interventions, their safety and efficacy in the hands of experienced operators, and the availability of new accessories and technologies, their use will continue to increase in the management of patients with liver disease.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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