ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Role of Endohepatology in the Management of Liver Disease

Ajaypal Singh, MD
Associate Professor of Medicine
Director, Center for Interventional & Therapeutic Endoscopy
Division of Digestive Diseases
Rush University Medical Center
Chicago, Illinois

G&H What is encompassed by the term *endohepatology*?

AS Broadly, the term *endohepatology* refers to endoscopic and endoscopic ultrasound (EUS)-guided interventions in patients with liver disease. This term is new, but patients with liver disease have been managed endoscopically for decades now. Most of this was limited to the management of bleeding from esophageal varices, portal hypertensive gastropathy, or gastric antral vascular ectasia. However, with the development of EUS-guided liver interventions over the past decade, we have a much bigger toolset now, which has led to the adoption of this term. Interventions that can be performed now with EUS include liver biopsy, portal pressure gradient measurement, coil embolization of gastric varices, and elastography.

G&H What are the overall advantages and disadvantages of using EUS in the setting of liver disease?

AS EUS provides easy access to the liver from the stomach and duodenum. It is not affected by body habitus, which is very important for the increasing number of patients with obesity and nonalcoholic fatty liver disease. Many patients with suspected or confirmed chronic liver disease are undergoing esophagogastroduodenoscopy (EGD) for other reasons. Combining EGD and EUS in the same session can be very cost-effective. These are the 2 main advantages, which make EUS a very attractive option.

On the other hand, if a patient does not need to undergo EGD for any other reason, performing EUS alone for some of these interventions can be somewhat cost-prohibitive. There is also a risk with using anesthesia, as well as risks inherent to the procedure. Most importantly, there is still a lack of long-term data and standardization for some of the newer EUS techniques.

G&H How does EUS-guided liver biopsy compare with percutaneous or transjugular approaches?

AS Percutaneous and transjugular approaches are the established methods of obtaining liver biopsies and have been used for decades now. With the percutaneous approach, ultrasound imaging is used to find an appropriate location for liver biopsy, and a 16- or 18-gauge needle is used to obtain the biopsy. This technique is fairly quick, safe, and easy. It does have some limitations, though. One is that real-time ultrasound is not always used. Once the ideal location is identified and the skin site is marked, the needle puncture is performed without real-time sonographic guidance. Also, patients can experience pain at the site of injection. The most important limitation is body habitus. In patients with obesity, ascites, or coagulopathy, it can be difficult to obtain a percutaneous biopsy. Despite all of these limitations, the overall safety profile is excellent, and the adverse event rate has been less than 1% to 3% in most large studies, with a diagnostic yield of approximately 95%.

The transjugular approach has its own advantages. It allows for the measurement of the hepatic venous pressure gradient, which is an indirect measurement of the portosystemic pressure gradient (PPG). This approach can be used in patients with coagulopathy. It is performed by interventional radiologist (IR) experts and involves 6 hours of recovery time. A minor disadvantage is that

IR-guided transjugular biopsies tend to be fragmented. However, this approach is still fairly safe, with reported adverse event rates of 5% to 7%.

EUS-guided liver biopsy was first described around 2 decades ago. As discussed, this approach makes sense when in the stomach or duodenum, which are next to the left and right lobes of the liver, respectively. Also, EUS can be used to evaluate both lobes of the liver, compared with only 1 side of the liver with the percutaneous or transjugular approach. EUS can also be used to look for abnormalities in the bile duct and pancreas, and to look for stigmata of chronic liver disease such as varices and portal hypertensive gastropathy. If large varices are present, interventions can be performed at the same time.

EUS-guided liver biopsy techniques and accompanying needles have recently undergone significant changes.

Initial studies on outcomes of EUS-guided liver biopsy for evaluation of parenchymal disease came out only 7 or 8 years ago and have shown that EUS-guided biopsy was feasible with a reasonable diagnostic yield. However, they did not show clearly that this approach was highly diagnostic with adequate total specimen lengths (TSLs) and complete portal tracts (CPTs), which are features of interest in liver biopsies. The American Association for the Study of Liver Diseases (AASLD) recommends that an adequate liver biopsy should have a TSL of at least 2 to 3 cm and at least 11 CPTs per biopsy specimen.

EUS-guided liver biopsy techniques and accompanying needles have recently undergone significant changes. It has been realized now that fine-needle biopsy needles are better than fine-needle aspiration needles. Studies have shown that Franseen-tip needles are better than fork-tip biopsy needles. It is also known now that 19-gauge biopsy needles are better than 22-gauge biopsy needles. Multiple studies have shown the techniques required to optimize the diagnostic yield for these biopsies, including the number of actuations and passes and the use of wet suction technique. A recent meta-analysis by Baran and colleagues included 23 studies with more than 1300 patients. The investigators found that the pooled mean TSL was 45 mm, and the pooled mean CPTs were around 16 per specimen, more than the AASLD recommendations. The diagnostic yield has come a long way from where it started.

However, there are some disadvantages to this approach. There is a risk of complications with every procedure that is performed. The meta-analysis showed that adverse events occurred in around 10% of patients, although the majority of events were minor; the most common was abdominal pain (1%).

G&H How can ultrasonographic elastography be used to measure fibrosis without biopsy?

AS Approximately one-third of the world population has nonalcoholic fatty liver disease and 5% of the population has the progressive form of the disease known as nonalcoholic steatohepatitis. More than 10% of these patients progress to advanced liver disease or cirrhosis and require liver transplant. The most important predictor of mortality is the degree of fibrosis in patients with chronic liver disease. Stage 2 or higher fibrosis indicates a worse prognosis. In the past, histology and liver biopsy were used as the standard to measure fibrosis, but elastography can now be used as a surrogate by measuring liver stiffness. Two different methods use ultrasound: strain elastography and shear-wave elastography. Shear-wave elastography is the more commonly used technique for measuring liver stiffness, whereas strain elastography is more of a semi-quantitative method. Shear-wave elastography can be performed via multiple modalities, including transient elastography, commonly known as FibroScan (Echosens), which uses a mechanical probe to produce sound waves in a single-element ultrasound transducer. Other techniques include 2-dimensional shear-wave elastography, which uses acoustic radiation force impulses. Most of the initial data for shear-wave elastography using transient elastography show a sensitivity and specificity of around 70% and 85%, respectively, for diagnosing significant fibrosis that is stage 2 or higher. The sensitivity and specificity for diagnosing cirrhosis approaches 90% because it is relatively easier to diagnose. However, most of the original studies about the efficacy of shear-wave elastography were conducted on patients with hepatitis C. In patients we are commonly seeing now, especially those with nonalcoholic fatty liver disease, a significant proportion can have inflammation, which can lead to exaggeration of fibrosis on elastography. Other factors that can affect elastography readings include obesity, presence of fluid around the liver, diabetes, sex, and even fasting.

G&H What is the current role of EUS-guided interventions in esophageal and gastroesophageal varices?

AS The approach to esophageal varices and type 1 gastroesophageal varices (GOVs) has mainly relied on endoscopy and endoscopic band ligation. The EUS platform has a limited role in these patients and has mainly been reported in only a few case studies when other modalities have failed.

Although type 2 GOVs and isolated gastric varices are less common and less likely to bleed than type 1 GOVs, they are a challenge because once they bleed, they are associated with higher transfusion requirements, mortality, and rebleeding rates. The option in these patients traditionally has been transjugular intrahepatic portosystemic shunt (TIPS) or balloon-occluded retrograde transvenous obliteration (BRTO), which are percutaneous interventions performed by IRs. TIPS is very effective but comes with risks such as worsening liver failure, cardiopulmonary overload (especially in patients with cardiac disease), and hepatic encephalopathy. BRTO requires expert IRs and high-quality imaging to identify shunts before interventions are performed. Thus, endoscopic injection of glue was the only traditional endoscopic option but is associated with challenges. The technique involves injecting glue into the varix only under endoscopic visualization, and it is not feasible to evaluate obliteration of the blood flow in the varix in real time, which makes it difficult to quantify the amount of glue injected. Most importantly, injecting endoscopic glue into a varix carries the risk of systemic and pulmonary embolization. Therefore, EUS-guided coil and glue embolization provides a safe and easy alternative, especially in patients who are not candidates or are high risk for TIPS.

> Patient selection is important before embarking on EUS-guided gastric variceal treatment.

There is no standardized technique, but the basics are fairly similar. Most cases are performed under general anesthesia. An endoscopy is performed first to evaluate the source of bleeding and rule out alternative etiologies. Then a linear echoendoscope is advanced, and the fundus of the stomach is typically filled with water to assist with better delineation of the varices. Once the bleeding varix (or varices) and the feeding vessels within the gastric wall are identified, the varix is punctured typically with a 19-gauge needle (although a 22-gauge needle can also be used). After confirmation of the needle within the varix with aspiration of blood, 1 or multiple coils can be injected into the varix under direct EUS guidance, depending upon the size of the varix and real-time confirmation of obliteration of blood flow on Doppler.

Studies have shown that injection of coils alone can be sufficient, but most endosonographers prefer to inject cyanoacrylate after coil deployment. No randomized controlled trials have compared IR approaches vs EUS-guided approaches, but multiple retrospective studies have demonstrated the high efficacy and safety profile of EUS-guided variceal treatment. In a 2016 study, Bhat and colleagues examined 152 patients with gastric variceal bleeding who were treated with an EUS-guided approach. Technical success was achieved in more than 99% of patients, and clinical success (defined as variceal obliteration on follow-up EUS examination) was achieved in 93%. Rebleeding was noted in only 3% of patients after complete eradication was achieved, and complications were reported in less than 10%, with the major complication of pulmonary embolism in only 1%. A more recent study by Kouanda and colleagues looking at 80 patients showed technical and clinical success of 100% and 97%, respectively, and an adverse event rate of only 5%.

Patient selection is important before embarking on EUS-guided gastric variceal treatment. There should be close multidisciplinary collaboration with hepatology, IR, transplant surgery, and intensive care unit (ICU) teams. The endoscopy staff, nurses, and technicians should be familiar with the tools and technique being used for EUS-guided variceal coil embolization. At my institution, all patients with bleeding gastric varices are admitted to the ICU and evaluated by hepatology, IR, and interventional gastroenterology teams. We review the imaging together, especially cross-sectional imaging, and look for the presence of shunts, which play an important role in deciding treatment. We prefer to use TIPS if the patient is not high risk for the procedure (especially if the patient has ascites, which would be helped by TIPS). However, if the patient is high risk for decompensation of liver disease from TIPS, is at risk for cardiac failure if TIPS was performed, or is already having problems with hepatic encephalopathy (which would worsen with TIPS), we tend to prefer an EUS-guided approach for gastric variceal treatment.

G&H Is there any support for using EUS in portal pressure gradient measurement?

AS EUS-guided portal pressure gradient measurement is an exciting technology but is still an emerging one. Conceptually, it is very appealing. Current measurement for hepatic and portal gradient involves IR-guided access to the hepatic vein, a direct measurement of the hepatic vein pressure, followed by wedged hepatic vein pressure, which

serves as a surrogate for portal vein pressure. The difference is then measured to calculate the hepatic venous portal gradient, which serves as a marker for PPG. However, with EUS from the stomach, the hepatic vein and portal vein can be directly punctured using a 25-gauge needle, and direct pressures can be obtained from both veins to get the difference for the actual portal pressure gradient.

However, studies are limited. There are only a few years' worth of data, and only retrospective studies have been performed. Multiple questions need to be answered before this approach is widely adopted. In addition, it is necessary to determine whether the portal pressure gradient measured with the EUS-guided approach and the hepatic venous portal gradient measured by the IR approach correlate. Several small studies show a favorably high degree of correlation. It is also important to know the effects of other variables (eg, endoscope pressure, scope position, and tension on the scope) on reliability and reproducibility of pressure measurements. More studies are needed to show that EUS-guided PPG measurement is reproducible with a high degree of user agreement. There is also a need for comparative studies with other modalities, especially IR-guided approaches.

G&H What is the future of endohepatology?

AS A number of experimental interventions are being studied in endohepatology. For example, there are several animal studies on the creation of TIPS, and hepatic artery interventions are also being studied. A lot of effort in the liver clinic is spent evaluating solitary liver lesions, and many patients undergo numerous imaging scans to figure out whether their lesions are benign or neoplastic. Artificial intelligence may have a large role to play in the evaluation of these lesions and, more importantly, to guide physicians.

In addition, studies have shown a greater than 10% increase in chronic liver disease over the past several decades mainly related to the obesity epidemic. Taking care of these patients is costly. Many of the interventions they need to undergo are only available in a hospital setting. Endohepatology offers the possibility of transitioning the care of these patients to outpatient endoscopy. Endoscopists can perform EUS-guided liver biopsy, portal pressure gradient measurement, and elastography all in an outpatient setting while the patient is undergoing an endoscopy for other reasons. Transitioning this care to an outpatient setting and being more cost-effective is what makes the future of endohepatology very exciting.

Disclosures

Dr Singh has no relevant conflicts of interest to disclose.

Suggested Reading

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