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MINIREVIEWS

Endo-hepatology: An emerging field

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Abstract

Gastroenterologists have long been spearheading the care of patients with various forms of liver disease. The diagnosis and management of liver disease has traditionally been a combination of clinical, laboratory, and imaging findings coupled with percutaneous and intravascular procedures with endoscopy largely limited to screening for and therapy of esophageal and gastric varices. As the applications of diagnostic and therapeutic endoscopic ultrasound (EUS) have evolved, it has found a particular niche within hepatology now coined endo-hepatology. Here we discuss several EUS-guided procedures such as liver biopsy, shear wave elastography, direct portal pressure measurement, paracentesis, as well as EUS-guided therapies for variceal hemorrhage.

Key Words: Endoscopic ultrasound; Therapeutic endoscopic ultrasound; Hepatology; Liver disease; Liver biopsy

Core Tip: Endo-hepatology in an emerging field which utilizes diagnostic and therapeutic endoscopic ultrasound to help gastroenterologists diagnose and manage liver disease. Our paper will focus on liver biopsy, ultrasound and shear wave elastography, ascitic fluid sampling, portal pressure measurement, management of varices, and vascular interventions.

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INTRODUCTION

Gastroenterologists have long been spearheading the care of patients with various forms of liver disease. The diagnosis and management of liver diseases have traditionally been a combination of clinical, laboratory, and imaging findings coupled with percutaneous and intravascular procedures with endoscopy largely limited to screening for and therapy of esophageal and gastric varices. As the applications of diagnostic and therapeutic endoscopic ultrasound (EUS) have evolved, it has found a particular niche within hepatology now coined endo-hepatology which puts new endoscopic tools in the gastroenterologist's hands[1,2]. Liver disease in pre-cirrhotic and cirrhotic populations present different challenges. Pre-cirrhotic disease requires longitudinal management to evaluate fibrosis severity and strategies to prevent progression, whereas cirrhotic liver disease presents challenges in the management of portal hypertension. Additionally, biliary and hepatic malignancy can present challenges to diagnosis and therapy, that may be obviated by new techniques. Our paper will describe the role of endo-hepatology in these increasingly prevalent conditions.

LIVER BIOPSY

Liver biopsy has long been considered the gold standard to differentiate between several types of liver disease, using histological findings to distinguish between autoimmune etiologies, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, *etc.* Traditional liver biopsy involves a 16 or 18 gauge needle and a percutaneous approach. These biopsies were at one point targeted using a percussion method, however, this has been largely replaced by ultrasound (US) or computed tomography (CT) guided methods[3]. Despite imaging guidance, percutaneous liver biopsy can still lead to complications such as pain, hemorrhage, tumor-seeding, intestinal perforation, peritonitis, hemothorax or pneumothorax, bacteremia, and even death. Transjugular liver biopsy emerged as a safer alternative, particularly in patients with massive ascites, obesity, or coagulopathy[4], though this approach still carries a relatively high complication rate near 7%, including pseudoaneurysm, hemorrhage, bile leak, pneumothorax, and ventricular arrhythmia[5]. Through esophageal, gastric, and duodenal views, EUS offers exceptional detail in evaluating the biliary tract, liver, pancreas, stomach, esophagus, and mediastinal structures. Unlike conventional US or CT, EUS allows the liver to be visualized or conceptualized in a three-dimensional view, allowing the liver to be viewed through the Couinaud classification which divides the liver into eight separate functional units. Due to proximity, direct endosonographic visualization, and utilization of doppler ultrasound, there is increased potential for diagnostic success and a low rate of adverse events, approximately 2.5%[6] with EUS-guided liver biopsy[7]. The technique involves a linear echoendoscope that can locate either the right or left hepatic lobe. Using a fine needle biopsy (FNB) needle with a vacuum syringe, the endoscopist has the ability to biopsy either or both lobes of the liver and allows for several actuations with a single puncture of the liver capsule[8]. This approach can also offer a simultaneous endoscopic esophageal variceal screening, endoscopic shear wave elastography (SWE), or portal pressure gradient (PPG) measurement[9].

NON-INVASIVE MEASUREMENT OF FIBROSIS

Imaging such as SWE has proven useful as a non-invasive tool for measuring liver fibrosis with a correlation to histologically measured liver fibrosis[10]. This correlation, though, is affected by variability between the right and left lobes of the liver as transcutaneous SWE is typically performed over the right lobe of the liver[11]. Newer EUS processors have the capability to carry out SWE both in the right and left lobes of the liver, allowing for the assessment of fibrosis during endoscopy. While more invasive than traditional transcutaneous SWE, in those already undergoing endoscopic

evaluation or those with a body mass index > 35 which may require a special probe to assure accuracy, EUS-SWE appears to be both feasible and reliable[9,12]. Two-dimensional ultrasound views during EUS-SWE or EUS alone can also allow for routine hepatocellular carcinoma screening. Doing so during an EUS allows for simultaneous FNB of small or suspicious lesions which may be found during EUS evaluation[8,13].

PORTAL PRESSURE MEASUREMENT

Portal hypertension is the driving force for complications in liver fibrosis and cirrhosis. Portal venous pressure (PVP) measurement, therefore, is a key to anticipating complications. The current technique is similar to transjugular liver biopsy, during which a catheter is inserted into the jugular vein and advanced into the hepatic vein. The portal vein is not directly accessible *via* this approach, but the pressure can be estimated using wedge hepatic venous pressure (WHVP). The intravascular catheter is able to directly measure the WHVP and the free hepatic venous pressure, the difference of which is the PPG, which reflects the degree of portal hypertension (PH) and PVP[14]. In 2004, a porcine model was used to demonstrate the ability to use EUS to directly access the portal vein and measure portal venous pressure (PVP). This has been recreated in humans in a pilot study using a linear echoendoscope, a 25 gauge access needle, and a compact manometer. The portal vein and hepatic vein are able to be accessed directly, and their pressures are measured *via* the manometer. PVP was able to be measured and had a high degree of correlation with clinical and endoscopic parameters of PH including thrombocytopenia, ascites, portal hypertensive gastropathy, and gastroesophageal varices[14]. Despite the significant correlation of PVP to clinical outcomes, PPG remains as the current standard for measurement and is estimated *via* the WHVP rather than direct measurement of the portal vein. With additional expertise and safety outcomes data, one may yet find a role for this technology and technique in patients where traditional techniques will be ineffective, such as those with hepatic vein clots or those who have undergone prior vascular interventions.

COMPLICATIONS OF PORTAL HYPERTENSION: ASCITES

Accumulation of ascitic fluid is another common manifestation of advanced liver disease, often thought to be from an imbalance in the resorption of fluid due to elevated portal and oncotic pressure. The etiology of ascites and evidence of spontaneous bacterial peritonitis requires sampling the fluid directly. This is frequently done with a combination of imaging and abdominal paracentesis. EUS offers another modality to access ascitic fluid with higher sensitivity than CT and transabdominal ultrasound[15,16]. The ability of EUS to sample retroperitoneal, intra-abdominal collections and masses can also be applied to ascitic fluid. EUS has been previously described for use in direct sampling of fluid collections that may not be amenable to percutaneous drainage due to small volume or loculated collections[17]. EUS-guided paracentesis (EUS-P) has been shown to be technically feasible, however, the significance of risk associated with EUS-P including infection, contamination, and seeding of malignancy remains unknown. This is highlighted by the limitation that EUS-P cannot be performed in a sterile fashion as it requires puncture through the bowel lumen[18].

COMPLICATIONS OF PORTAL HYPERTENSION: VARICES AND VARICEAL HEMORRHAGE

The initial management of both bleeding and non-bleeding esophageal and gastric varices has largely been endoscopic[19]. All cirrhotic patients should undergo screening for esophageal varices after their diagnosis. The grading of varices can be quite subjective and is endoscopist dependent, taking into account diameter, location, character, and tortuosity of the vessel. In several studies, EUS has been more effective than esophagogastroduodenoscopy (EGD) in the detection of gastric and paraesophageal varices. Many of these lesions can appear as folds or submucosal lesions, but EUS allows the endoscopist to view below the mucosal surface and utilize doppler to

evaluate for blood flow. The use of doppler ultrasound increases the ability to detect varices, particularly in the duodenum, and collateral vasculature. Some EUS findings can also be used to determine the risk of variceal hemorrhage by evaluating the cumulative cross-sectional area of all distal esophageal varices, with a 76-fold increase per year with each 1 cm^2 increase in cumulative area. The utility of EUS in minimizing interobserver variability is limited by correlation with EGD and the lack of a standardized grading system for varices seen during EUS. Kane *et al*[20] applied transnasal high-resolution endoluminal ultrasound (HRES) and was able to demonstrate correlation to EGD. Furthermore, application of transnasal HRES allows examination without sedation.

Injection sclerotherapy, variceal ligation (EVL), or cyanoacrylate glue injection is usually performed relatively blindly during treatment of acute hemorrhage. EUS can allow for visualization of the lumen of the varix[21]. EVL has been the treatment of choice for esophageal variceal hemorrhage and for secondary prevention. Usually several endoscopies are required for complete variceal containment, and the most common post-procedure complication is post-EVL induced bleeding with an incidence of roughly 2.8%. This can be treated with a course of proton pump inhibitors, and further endoscopic interventions such as sclerotherapy or transjugular intrahepatic portosystemic shunt (TIPS) placement[22].

Injection of cyanoacrylate glue has been shown to have improved hemostasis and lower rebleeding rates in the treatment of gastric varices when compared to EVL[23]. This method, however, is technically more challenging and complications can be severe, including pulmonary and cerebral emboli. EUS-guided cyanoacrylate injection allows for direct visualization of the culprit vessel and confirmation of hemostasis utilizing doppler ultrasound[24]. EUS-guided microcoil embolization has been evaluated as a method of hemostasis with comparable efficacy and a decreased risk of migration or distant emboli[25]. Recently, EUS-guided deployment of coils in conjunction with cyanoacrylate injection has been demonstrated to reduce the risk of glue embolization, and can be more effective than coil embolization alone[26].

When endoscopic therapy of variceal hemorrhage is unsuccessful, interventional vascular procedures such as TIPS or balloon-occluded retrograde transvenous obliteration have been employed[22]. Recent studies using a porcine model have shown that even these predominantly surgical or endovascular procedures can also theoretically be carried out using EUS. Using an access needle, the hepatic vein is accessed, and a catheter is advanced further into an accessible branch of the portal vein. Using a lumen-apposing metal stent, the hepatic vein and portal vein are fistulized[27]. While this study was small and simply a proof-of-concept, it illustrates the future applications of EUS in the world of hepatology.

CONCLUSION

EUS-guided interventions may appear more invasive than the traditional percutaneous or intravascular procedures. However, with advantages in recovery time, diagnostic yield, and complication rates factored in, the EUS-guided procedures may be more efficient, thus more cost-effective. This is particularly apparent when considering multiple interventions can be combined into a single endoscopic procedure[8,9]. Furthermore, endoscopic screening and surveillance are commonly implemented in management of advanced liver disease, decreasing the overall risk applied by addition of EUS evaluation. More data regarding feasibility and safety is needed-particularly in regards to EUS-guided paracentesis, portal pressure measurement, and portosystemic shunting-and while endo-hepatology remains in its infancy, interventional EUS is well on its way to becoming an integral part of routine liver disease management and care.

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