Endoscopic ultrasound-guided diagnosis and treatment of gastric varices

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Abstract

Gastric varices represent a common and severe complication in patients with portal hypertension, commonly seen in patients with cirrhosis and severe pancreatic disease. Endoscopic ultrasonography is a safe and efficacious approach that can perform real-time ultrasonic scanning and intervention for gastrointestinal submucosa, portal vein, its tributaries, and collateral circulations during direct endoscopic observation. Recently, various studies have been published about endoscopic ultrasound (EUS)-guided management of gastric varices, mainly including diagnosis, treatment, and prognostic analysis. This article reviews published articles and guidelines to present the development process and current management of EUS-guided gastric varices procedures.

Key words: Endoscopic ultrasound; EUS; diagnosis; treatment; gastric varices

Core tip: Gastric varices (GV) is a common and severe complication in patients with portal hypertension (PH), and GV bled more severely with a higher mortality rate than esophageal varices. With increased applications in GV management, endoscopic ultrasound (EUS) has demonstrated diagnosis and treatment benefits, particularly in cases of refractory bleeding or unsuitable for conventional therapies by preoperative assessments, and, thus, enriches originally-limited options. EUS advantages exist throughout the process, from

diagnosis, preoperative assessment, treatment, and efficacy evaluation to follow-up in GV patients. This article reviews published articles and guidelines to present the recent EUS-guided management of GV.

INTRODUCTION

Gastric varices (GV) represent complex and heterogeneous collections of vascular shunts between the portal splenic venous system and systemic veins in the abdomen and chest[1]. GV is a common and severe complication in patients with portal hypertension (PH). Patients with chronic liver and pancreatic diseases are at risk of developing PH. Compared with esophageal varices, Gastric varices bled in significantly fewer patients but bled more severely with a higher mortality rate[2]. Despite decades of advances in diagnosing and treating procedures, managing GV bleeding in patients with PH remains a unique clinical challenge. Accurately detecting PH and GV are critical in managing PH[3]. However, conventional gastroscopy cannot effectively observe small GV, portal veins, and their tributaries, not to mention its disability of real-time venous blood flow during and after endoscopic procedures. Meanwhile, effective treatment options for GV bleeding were limited. Even in patients undergoing emergency endoscopic treatment such as emergency ligation, rebleeding and mortality rates are still non-negligible[4]. With increased applications in GV management[5-7], endoscopic ultrasound (EUS) has demonstrated diagnostic and therapeutical benefits and enriches originally-limited options. This article reviews published articles and guidelines to present the development process and current management of EUS-guided gastric varices procedures.

CLASSIFICATION

Varied endoscopic classifications exist for GV[8], among which Sarin classification is the most commonly used. According to Sarin classification, GV exists in all 4 types, including isolated gastric varices type 1 (IGV1), isolated gastric varices type 2 (IGV2), gastroesophageal varices type 1 (GOV1), and gastroesophageal varices type 2 (GOV2). The Sarin classification was based on GV's location and its relationship with esophageal varices (EV)[2], while another one, the Hashizome classification, focuses on GV's form, location, and color[9]. Even though few EUS-based GV classifications were reported, esophagogastric varices were once investigated and classified into 3 types according to the vascular structures and locations, including the esophageal type, esophagogastric type, and solitary gastric type[10]. Another research in patients with cirrhosis proposed a new classification criterion for GV, which included 3 types of GV sizes and gastric wall abnormalities, respectfully[11].

EPIDEMIOLOGY

According to anatomic location, GV was classified as gastroesophageal or isolated gastric varices, and the reported incidence of GV varies in patients with PH (2-70%)[12]. The most common GV type is the lesser curve varix, which is also classified as type 1 gastroesophageal varices (GOV1, Sarin classification)[2]. GV makes up about 10–20% of all types of varices[2,13]. Previous studies have demonstrated that GV bleeding could happen at lower portal pressures when compared to oesophageal varices[14,15], and the cumulative risk for GV bleeding in patients with PH at 1, 3, and 5 years were reported to be as high as 16%, 36%, and 44% respectively[16]. Acute GV bleeding is one of the leading causes of death in cirrhotic patients, even in patients who underwent N-butyl-cyanoacrylate (NBC) injections. A retrospective study of 132 patients documented a 16.7% mortality rate within 6

weeks after NBC injection treatment[17]. Left-sided portal hypertension (LSPH) accounts for approximately 5% of extrahepatic PH and is characterized by isolated GV[18]. In patients with LSPH due to pancreatic disease, GV bleeding has been reported in approximately 8% to 15% of patients[19,20].

DIAGNOSIS

Endoscopic ultrasound (EUS) combines ultrasound imaging and traditional endoscopy to obtain real-time ultrasound images and provide detailed information about the gastrointestinal tract and the surrounding organs and vessels. EUS technology has enabled endoscopists to break through the observing limitation inside the digestive tract and greatly enriched GV's diagnosis and differential diagnosis. The combination of EUS with color or flow Doppler techniques facilitates better identification and monitoring of GV.

Accurate identification

EUS and mini-probes play a revolutionary part in GV identification. High frequencies mini-probes can increase the sensibility in identifying the minimal or initial varices and thus were beneficial to early diagnosis of esophageal and gastric varices[21]. EUS could assess both the intraluminal and extraluminal varices in cirrhotic patients and therefore improve the management of PH[22]. Linear or radial EUS should be recommended to distinguish GV from other causes for prominent gastric folds, especially in cases with no evidence of portal hypertension or cirrhosis, as reported in patients with gastrointestinal stromal tumor (GIST) or mucosa-associated lymphoid tissue (MALT) lymphoma[23,24]. PH and splenic vein thrombosis remain the leading causes of GV bleeding. Accurate identification of PH is essential in managing patients with cirrhosis and pancreatic disease and preventing complications, including

gastrointestinal bleeding. The endoscopic diagnosis of PH by conventional gastroscopy is mainly based on the visualization of bluish dilated tortuous varices, while gastroesophageal varices were not present in approximately 60% of patients with PH[25]. GV is located in a deeper submucosa than esophageal varices and is, therefore, difficult to differentiate from other causes for prominent gastric folds with conventional endoscopy. However, even blood flow in small varices not diagnosed by gastroscopy can be visualized by color Doppler endoscopic ultrasonography (CD-EUS), and the minimum diameter of varices detected was 2 mm in the 1990s [26]. Real-time portal pressures and liver biopsies can be acquired during one EUS procedure, so EUS has recently become increasingly popular in patients suspected of portal hypertension (PH) or liver cirrhosis[27]. Therefore, EUS is a practical approach for differentiating PH from other related diseases.

Preoperative evaluation

Predictors of GV bleeding include fundal varices, large varices (>5 mm), red color signs, and Child's C liver stage[28]. EUS can determine the bleeding risk of GV patients and facilitate timely therapeutic intervention for high-risk patients without active bleeding. EUS and high frequencies mini-probes can accurately measure the variceal radius and wall thickness, which supports subsequent identifications of patients at risk for variceal bleeding[29,30]. In addition, estimating the presence of GV in patients with massive active gastrointestinal bleeding is distressing, while CD-EUS can help better confirm GV, determine accessibility, and select a suitable treatment plan in these cases. CD-EUS and EUS-guided angiography can also assess GV's primary feeding vein system, fluid dynamics, and gastrorenal shunts[31,32], which is of great significance for the subsequent treatment selection of GV and the

reduction of postoperative complications. More importantly, EUS-guided evaluation is a reproducible and non-invasive approach.

Therapeutic evaluation

EUS procedures have been proven effective in assessing GV obliteration and identifying perforated veins, thus improving real-time monitoring and repeated injection management[5,8,33]. A prospective cohort study of 102 patients concluded that red signs, varices size, and presence of para-gastric veins indicated a high risk of GV rebleeding after endoscopic therapy, all of which were identifiable by EUS[34]. EUS can visualize the altered ultrasonic echo immediately during endoscopic treatments, and the disappearance of the original blood flow verified by CD-EUS was thought to be one indicator of real-time therapeutic efficacy[26]. Meanwhile, alterations of variceal radius and wall thickness assessed by EUS also predicted endoscopic and pharmacological efficacy[30]. CD-EUS allows assessments of vascular blood flow and possible morphologic or hemodynamic changes after endoscopic treatment. A prospective observational study of 30 patients demonstrated that feeder vessels of GV could be identified during endoscopic procedures, and GV would disappear immediately after targeted injections of these feeding vessels[35]. Furthermore, follow-up EUS after obliteration helps to identify the remaining flow in the perforating vein and decide whether to repeat endoscopic procedures to reduce the possibility of postoperative bleeding[36]. Previous studies have demonstrated severe peri-EV and large perforating EV detected by a 20 MHz mini-probe as valuable indicators for EV recurrence after endoscopic injection sclerotherapy[37]; in addition, biweekly EUS monitoring could identify requirements for repeated NBC injection and decrease recurrent bleeding rates (18.5% vs. 44.7%) in cirrhotic patients with bleeding GV[5]. Precise obliteration

assessment of targeted GV contributes to reducing injection doses and related fatal embolization, which is way safer and more objective than traditional estimation only by GV "hardening" after injection.

Treatment

Interventional EUS procedures have undergone tremendous development over the past three decades. EUS technology has evolved rapidly from a diagnostic tool to a promising therapeutic modality in patients with GV. Acute GV bleeding in patients with PH is a severe medical emergency, and the immediate therapeutic goals are to control bleeding, prevent early recurrence (within 5 days), and prevent 6-week mortality[38,39]. Direct endoscopic cyanoacrylate injection is recommended as first-line therapy for GV bleeding. Meanwhile, other injection procedures with the aid of EUS are increasingly performed due to their safety, efficiency, and accuracy[31]. EUS-guided injection procedures in GV patients included EUS-glue, EUS-coil, EUS-coil&glue, EUS-thrombin, EUS-coil&thrombin, and EUS-coil&gelatin[5,7,31,40]. Previous studies have reported that EUS-guided injection has a significantly lower rebleeding rate (8.8% vs. 23.7%) and requires a smaller amount of cyanoacrylate (2.0 ± 0.8 ml vs. 3.3 ± 1.3 ml) compared to direct injection in a randomized controlled trial[41]. A meta-analysis of 851 GV patients in 23 studies revealed that EUS-guided GV procedures demonstrated superior clinical efficacy than conventional endoscopic glue injection in obliteration, recurrence, and long-term rebleeding, which increasingly emphasizes the advantages of EUS-guided procedures in GV[42].

EUS-guided sclerotherapy

Endoscopic sclerotherapy has been reported effective in treating bleeding varices and preventing the first variceal bleeding[43]. However, endoscopic sclerotherapy demonstrated less effectiveness in GV than in esophageal varices. Commonly used sclerosants include ethanolamine oleate, glucose solutions, sodium tetradecyl, and acetic acid[44]. Larger injection doses are contemplated to avoid reduced efficacy caused by the early flush of injected sclerosants, but massive sclerosant injections may cause serious complications such as gastric necrosis and perforation[45]. In a prospective study of 92 consecutive, nonrandomized patients with variceal bleeding, it was concluded that endoscopic sclerotherapy only demonstrated temporary control of GV bleeding, and the high incidence of severe early rebleeding required alternative treatments or modified sclerotherapy techniques[46]. Balloon-occluded endoscopic sclerotherapy demonstrated an effective and safe prophylactic treatment for high-risk gastric varices with significantly reduced sclerotherapy volume in a prospective, randomized, comparative clinical trial, and this procedure can even be used in patients without gastrorenal shunts[47]. In contrast, EUS-guided sclerotherapy can offer a real-time observation during GV injection and reduce sclerosant dosage as well as complications by accurately injecting an appropriate amount of sclerosant into the target location. Meanwhile, EUS-guided sclerotherapy showed a lower recurrence rate and a more extended recurrence than conventional sclerotherapy in a randomized controlled trial of 50 patients with cirrhosis and varices[48]. However, considering that the survival disadvantage (33% vs. 62%) from ethanolamine oleate injection therapy was partially related to its lower hemostasis rate (55% vs. 88%) and higher early bleeding rates[49], experts believed that cyanoacrylate was superior to ethanolamine oleate in treating GV bleeding.

EUS-guided tissue adhesive injection

EUS-guided tissue adhesive injection is to inject tissue adhesive into the targeted GV via a fine-needle aspiration (FNA) device. Three leading tissue adhesives used in endoscopic injections are NBC, 2-octyl-cyanoacrylate, and NBC plus methacryloxysulfolane[50], among which NBC is the most commonly employed agent, and it has been proved to have a faster and firmer obliteration efficacy in GV than other alternatives, such as thrombin, absorbable gelatin sponge, and alcohol[51]. Endoscopic therapy with NBC is recommended for acute bleeding from IGV and those GOV2 that extend beyond the cardia[38]. Direct injection of tissue adhesives in GV patients was first reported by Soehendra et al. in 1986, which resulted in definitive hemostasis[52]. Many years later, EUS-guided cyanoacrylate injection was reported with technical success in 5 GV patients[31]. Since then, numerous studies have been conducted using EUS-guided cyanoacrylate injection procedures[36,53]. EUS visualization of GV may improve hemostasis efficacy due to precise targeting and real-time obliteration confirmation while remaining less affected by blood; therefore, EUS-guided procedures seem more suitable in active bleeding with no need for gastric rinsing[54]. Even though endoscopic injection therapy has been proven minimally invasive and effective[55], these procedures with sclerosants or glue may cause severe complications neither in EUS injections nor traditional injections, including systemic embolization, fever, pain, and recurrent bleeding[13,56]. Due to the potential presence of right-to-left shunts, traditional tissue adhesive injections may lead to fatal multiple systemic embolisms, so extreme caution was recommended for cyanoacrylate injection in adolescents with portal hypertension of unknown origin[57]. Therefore, reducing cyanoacrylate-related complications has always been one of the

research hotspots, while the critical point of reducing complications is to minimize the injection dose effectively. Consequently, the Clip-assisted cyanoacrylate injection procedure was reported to be safe, convenient, and efficacious in treating GV with concomitant gastrorenal shunt[58], and our center has recently recorded a modified EUS-guided selective NBC injection procedure in an LSPH patient with good hemostasis efficacy and no post-operational GI bleeding and ectopic embolism due to reduced injection dosage[59]. In addition, many details of EUS-guided injection procedures remain to be further explored, for example, 19- or 22-gauge needles have been used and reported without comparison in previous studies[36,53], and there is still no consensus on the exact EUS-guided tissue adhesive injection procedure.

EUS -guided coil embolization

EUS-guided coil embolization is to inject coils into the targeted blood vessels through EUS to interrupt the blood supply and thus achieve hemostasis. These coils are made up of light metal alloy and synthetic fibers, and they can obliterate GV with fewer embolization complications caused by tissue adhesive. EUS-guided coil embolization was firstly reported in a case report of successful hemostasis in refractory ectopic variceal bleeding[60], which provided a new idea for GV therapy. EUS-guided coil embolization in GV patients was reported shortly thereafter[61]. In the above study, the target site for puncture and coil placement was modified from GV to its perforating feeding vein, successfully blocking blood flow and reducing the number of coils[61]. Surprisingly, a follow-up study found that EUS-guided coil embolization could achieve GV disappearance in most patients with only one endoscopic intervention[36]. Although EUS-guided coil therapy appeared superior in

treating GV due to a higher technical success rate, fewer endoscopies, and a lower complication rate and reintervention rate[36,40], it remains to be determined whether the EUS-guided coil or tissue adhesive injection procedure is preferred. Coil migrating from the targeted varices and significant bleeding from the puncture site were both observed in previous studies[62,63]. Moreover, since the advantages of reduced endoscopic interventions and recurrent bleeding rates in EUS-guided coil embolization procedure comes at the expense of multiple coil placement and additional risks of radiation exposure, EUS-guided coil injection was believed to be significantly more expensive, technically more demanding, and not viable in many patients by some experts[64].

EUS-guided coil embolization combined with tissue adhesive injection

Despite EUS-guided tissue adhesive injection being reported to improve accuracy compared with conventional procedures, postoperative ectopic embolization and other complications were still disturbing. Meanwhile, although EUS-guided coil embolization demonstrated a relatively low probability of ectopic embolism, unsatisfactory hemostasis still existed in some patients. Both these approaches have their advantages and disadvantages. Since embolizations caused by cyanoacrylate were thought to be mainly related to the injection volume, reducing the injection dose has become a key to breakthrough. Coils with attached synthetic fibers may decrease the injected glue dosage (1ml less per patient than that in the conventional procedure), thereby reducing the incidence of ectopic embolism while achieving equal obliteration efficacy[65]. This new method combines EUS-guided tissue adhesive injection and coil embolization to achieve complementary advantages and satisfactory effectiveness. In the same study,

transesophageal injection access from the distal esophagus to the fundus was firstly introduced and demonstrated many benefits, including avoiding the difficulty of retroflex the endoscope, no hindrance caused by blood in the stomach, and no disruption of the gastric mucosa overlying GV[65]. Moreover, an observational study of GV patients revealed a 100% technical success rate and a 96.6% complete variceal obliteration rate in the EUS-guided coil and cyanoacrylate embolization procedure[35]. In a retrospective study of 152 patients with GV, 125 patients underwent EUS-guided combined injection of coils and cyanoacrylate glue, with a mean number of 1.4 coils (range 1-4) and 2 mL (range, 0.5-6) cyanoacrylate per patient; after a mean follow-up of 436 days, only 4 patients (3%) presented with mild delayed upper GI bleeding due to coil/glue extrusion[66]. Furthermore, compared with EUS-guided coil injection alone, EUS-guided coil embolization combined with tissue adhesive injection demonstrated a higher variceal occlusion rate (86.7% vs. 13.3%), a lower postoperative rebleeding rate (3.3% vs. 20%), and a lower reintervention rate (16.7% vs. 40%)[7]. A meta-analysis of 536 patients concluded that EUS combination therapy with coil embolization and cyanoacrylate injection appeared to be preferred for GV over EUS-based monotherapy among a variety of EUS-guided therapies available due to its lower adverse event rates compared to cyanoacrylate alone (10% vs. 21%) and similar rates compared to coil embolization alone (10% vs. 3%)[67]. Although the above studies supported the superiority of EUS-guided combined injection of coils and cyanoacrylate glue over the application of coils or cyanoacrylate glue alone[7,65,66], there is still a lack of evidence of optimal coil numbers and mid-long term complications. Moreover, some experts believed that standard endoscopic cyanoacrylate injections were easier to perform and more accessible for endoscopists worldwide. In contrast, EUS-guided joint injections

were more challenging and time-consuming and thus may be more beneficial for only a few selected and severe GV[68].

Other EUS-guided injections

Due to numerous complications after routine tissue adhesive injections[13,56,57], several studies have reported alternatives to cyanoacrylate, which included absorbable gelatin sponge (AGS), thrombin, ethanolamine oleate, and et al. AGS is a type of purified collagen with liquefaction ability and thus appears not associated with post-injection ulcerations. EUS-guided coil embolization and AGS was reported to be a novel alternative to cyanoacrylate with high clinical success rates and low risk for complications in treating bleeding GV in a retrospective review[40,69]. Some experts have also suggested human thrombin as a simple and practical alternative to tissue adhesives due to fewer complications[70,71], but thrombin demonstrated inferior GV obliteration efficacy than cyanoacrylate. Another case series reported successful hemostatic efficacy in a follow-up of 57 months after EUS-guided coil deployment with sclerosant (ethanolamine oleate, EO), whose authors believed that both isolated GV and their feeding veins would be reliably obliterated after this procedure[72]. However, most of these studies above compared their EUS-guided injection procedures only with conventional cyanoacrylate injections but not with EUS-guided cyanoacrylate injections, and thus further research with more patients is still needed.

EUS-guided endovascular treatments

Transjugular intrahepatic portosystemic shunt (TIPS) has been proven effective in reducing portal venous pressure and is especially recommended in patients with persistent variceal bleeding uncontrolled by endoscopic and medical

therapy and postoperative rebleeding within 5 days[38]. Nevertheless, TIPS could increase risks for patients with congestive heart failure, pulmonary hypertension, advanced cirrhosis, or hepatic encephalopathy[73]. EUS techniques offer real-time visualizations of various vascularity without radiation exposure and promising alternatives for endovascular therapy, such as EUS-guided intrahepatic portosystemic shunt (EIPS), EUS-guided portal pressure gradient (EUS-PPG), and EUS-guided partial splenic embolization (PSE). Compared with traditional puncture of the portal vein (PV) branch from the hepatic vein, a technically challenging procedure with serious complications, EUS guidance can directly confirm the vascular flow after stent deployment and expansion[74]. EIPS was recommended due to the advantages of non-transjugular access and reduced vascular injuries. EUS-guided portal venography with carbon dioxide using a 25 gauge FNA needle was reported feasible, technically simple, and safe in a porcine model a decade and a half ago[75]. Two years later, EUS-guided intrahepatic portosystemic shunt (IPSS) creation was reported to be a valuable alternative to conventional TIPS in a live porcine model with normal PV pressure[76]. After that, EIPS with direct portal pressure measurements proved a novel alternative to TIPS in a study of 5 Yorkshire pigs[74]. In a pilot study that enrolled 28 patients with liver diseases, EUS-PPG procedures demonstrated promising safety, availability, and simplicity in managing patients with liver disease[77]. Recently, EUS-PPG with a 22-gauge FNA needle demonstrated accuracy and security as an alternative to hepatic venous pressure gradient (HVPG) measurements in a prospective study of 12 patients with hepatic sinusoidal obstruction syndrome (PA-HSOS) or Budd-Chiari syndrome[6]. However, the major limitation of these 2 studies was the exclusion of patients with increased bleeding risks (patients with INR > 1.5 or platelet count < 50 were excluded)[6,77]. These above EUS technologies

are gradually transitioning from animal models to patients. Meanwhile, EUS-guided PSE was first reported in a patient with alcoholic cirrhosis and variceal bleeding as an alternative procedure for preventing recurrent GV bleeding and hypersplenism[78]. EUS-guided coil implantation and following glue injection were performed in isolated collateral outside the gastric wall in a perigastric location to achieve vascular embolization; reduced GV was confirmed by follow-up endoscopy, and authors believed that the access to the splenic artery through the gastric wall has the advantage of a shorter puncture path[78]. Despite all these developments in EUS-guided endovascular treatments, more data are yet demanded to compare EUS-guided and radiation-guided endovascular therapies.

LIMITATIONS

Although increased utilizations have demonstrated promising benefits of EUS-guided procedures, and some experts claim them as first-line strategies[11], EUS-guided interventions are not yet one of the routine endoscopic procedures for GV patients and are just recommended after failures of conventional therapies. Meanwhile, limited EUS-based GV classifications were reported, and most GV was classified by endoscopic criterion. Moreover, there is still a lack of acknowledged standards for EUS-guided procedures and their roles in primary prophylaxis, acute hemorrhage, and secondary prophylaxis in GV patients, and most studies were retrospective and nonrandomized studies with small numbers of GV patients. As such, limited data are available to evaluate the mid-long term efficacy and safety of various EUS-guided treatments. Further prospective randomized trials and guidelines are still needed to optimize EUS-guided procedures in GV. Furthermore, numerous treatment options exist for GV, among which EUS-guided procedures are mainly performed in tertiary care

centers due to the limited availability of EUS and well-trained specialists[27]. Under such circumstances, TIPS and balloon-occlusion retrograde transvenous obliteration (BRTO) were still the central and practical options for salvage therapies in patients with refractory variceal bleeding. Additionally, most previous studies focused on investigating the advantages of EUS-guided procedures over traditional endoscopic ones, while direct comparisons between diverse EUS-guided approaches are still limited.

CONCLUSION

EUS-guided diagnoses and treatments have recently emerged as convenient diagnostic procedures and promising hemostatic interventions for GV, particularly in cases of refractory bleeding or unsuitable for conventional therapies by preoperative assessment. EUS procedures have already proved capable of effective real-time visualization, accurate identification, and perioperative assessment in GV. Meanwhile, various EUS-guided GV injection approaches and highly effective endovascular procedures, such as EUS-guided coil embolization combined with tissue adhesive injection, EIPS, and EUS-guided PSE, demonstrated encouraging clinical outcomes and developmental potentials. These EUS-guided diagnoses and treatments are currently recommended for patients with appropriate affordability, disease severity, and collateral pathway anatomy in advanced EUS centers. Additionally, multidisciplinary discussion team (MDT) recommendations could provide preferable personalized management and a remarkably reduced rebleeding risk[22].

In conclusion, EUS technique advantages exist throughout the process, from diagnosis, preoperative assessment, treatment, and efficacy evaluation to follow-up in GV patients. EUS application by skilled EUS experts in proper GV

patients at the right time will improve their diagnosis, efficacy, and whole GV management.