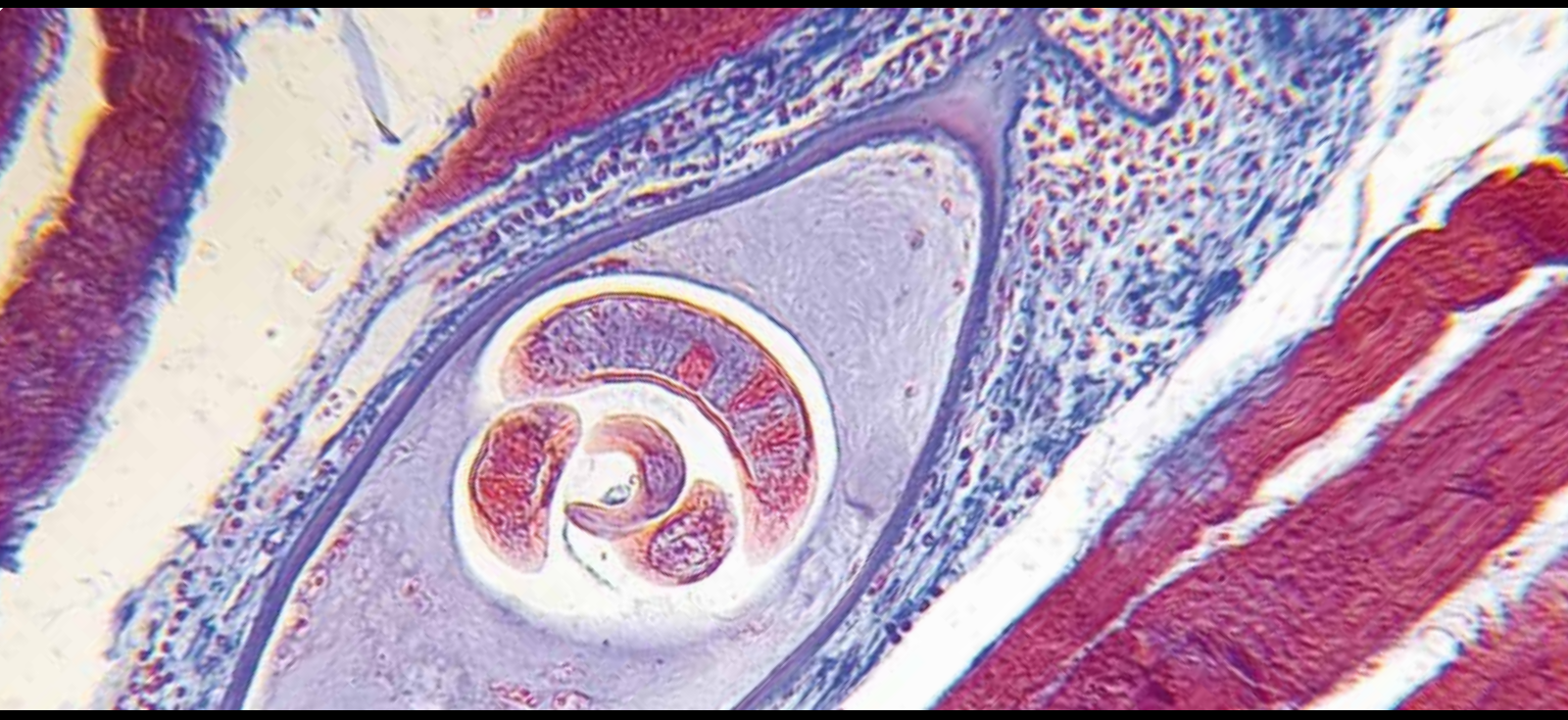
Gastroenterology Research and Practice

Therapeutic Endoscopic Ultrasonography

Guest Editors: Everson L. A. Artifon, Marc Giovannini, Siyu Sun, and Juan J. Vila



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Editorial Board

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Editorial

Therapeutic Endoscopic Ultrasonography

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The development of linear sectorial array EUS scopes in the early 1990s brought a new approach to diagnostic and therapeutic dimensions on EUS capabilities, opening the possibility to perform punction over direct EUS guidance. Endoscopic ultrasound (EUS) has evolved from a purely diagnostic imaging modality to an interventional procedure that provides a minimally invasive alternative to interventional radiologic and surgical techniques. This evolution was catalyzed by the introduction of linear echoendoscopes that provide continuous imaging and observation of needles and by therapeutic devices that pass through large-caliber working channels. The spectrum of EUS-guided interventions is today quite large including drainage of the pancreas, gallbladder, and other fluid collections; access to the pancreatic and biliary systems; celiac plexus interventions; vascular and ablative therapies.

Some new indications for interventional and therapeutic endoscopic procedures performed under EUS control have been developed in areas that have been purely surgical for many years. Indications, procedures, and related tools for EUS-guided endosurgery are described, all of which are experimental but may open a new corridor for endoscopists to enter a variety of transluminal procedures in real time without soiling the peritoneal or mediastinal cavity.

In this current issue, the readers can have emerging technologies applied to the endoluminal interventions made by using EUS view and another endoscopic resources. On the other hand, the procedures in the therapeutic EUS give us the possibility of having new access through the gastrointestinal wall to closed organs.

Beside new EUS-guided therapies, other authors in this collection have made a thorough review of the therapeutic capabilities of EUS. The application of EUS-guided therapy is especially appealing in oncological diseases, offering accurate and effective palliative treatment. This is possible mainly due to two EUS characteristics which are: firstly, its ability to deliver direct treatment to lesions unreachable by other means and secondly, the minimal invasiveness of EUS which allows outstanding results with low complication rate.

EUS-guided vascular therapy is a new promising field, because the variety of vascular pathology and the proximity of the vascular structures to the GI tract walls call for EUS-guided vascular procedures. Some reports have suggested that EUS-guided vascular procedure might offer benefits for refractory bleeding, and further development of this technique could potentially replace the interventional radiology in the abdominal vessels. A paper in this issue describes the literature review about EUS-guided vascular procedures, such as EUS-guided management of nonvariceal upper GI bleeding, and EUS-guided management of pseudoaneurysms, giving the reader a quick overview of the current state of research of EUS-guided vascular interventions.

Pancreatic cancer is a significant cause of morbidity and mortality. Current therapies, however, are of limited benefit in most patients. Recently, several studies have shown initial success with injection of various medications and therapies

into pancreatic tumors under the EUS guidance. This issue carries articles on EUS-guided injection of AdV-tk into the pancreatic tumor, which provide the ability to treat pancreatic cancer in a relatively minimally invasive manner, with a very low incidence of procedural-related complications. The latest cutting-edge technique might provide hope in treating the lethal disease in the foreseeable future.

In the articles included in this issue, the reader can find new endoscopic approaches by means of EUS to clinical problems or even complications derived from endoscopic maneuvers. These new technical solutions represent one step ahead in therapeutic endosonography. The clinical benefit and safety profile of some of these approaches must be confirmed in new studies, but they open new fields for clinical and experimental research.

The minimal invasive concept is an appropriate nomination to the therapeutic procedures that have been made by endoscopy. The endoscopic ultrasound offers to the endoscopy area a new technological eye to reach nonanatomic trajects creating fistulas or determining cytoreduction of masses. Otherwise, therapeutic endoscopic ultrasound or T-EUS is a new tool to those patients who are not operative candidates and in which we can offer a high quality of life (QOL) during a short survival.

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Clinical Study

EUS-Assisted Evaluation of Rectal Varices before Banding

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Rectal varices are an important cause of bleed. The bleeding can be sometimes fatal. Endoscopic management is possible and is generally done in emergency situation. Rectal variceal banding is useful. Hemodynamic evaluation has shown that the blood flow in rectal varices is from above downwards; however, the site of banding of rectal varices is unclear. This case series shows that the rectal varices should be banded at the highest point of inflow.

1. Introduction

Rectal varices (RVs) are an important cause of lower gastrointestinal bleed (LGIB) in portal hypertension (PHT) and have been reported to occur in 44% to 89% of cases of cirrhosis [1–3]. RVs are dilated submucosal portosystemic communications which extend from midrectum to the anorectal junction and are considered distinct from internal hemorrhoids, which are submucosal arteriovenous communications of the anorectal vascular plexus [4]. Pelvic angiography studies have revealed that most of the submucosal portosystemic communications (PSCs) of RVs have hepatofugal inflow to intrinsic rectal venous plexus (IRVP) through the wall of rectum by branches of superior rectal vein (SRV): a tributary of inferior mesenteric vein [5]. The SRV inflow to IRVP occurs at about 10 cm distance in lateral wall of rectum and the middle and inferior rectal veins (IRV) act as the outflowing channels [5] (Figures 1(a) and 1(b)). Four distinct zones of PSC have been shown in portal hypertension (PHT) near the esophagus, and anatomical studies have shown that similar portosystemic communications exist in rectum in PHT in relation to IRVP (Figure 1(b)) [6, 7].

The suspicion of RVs as the cause of bleeding can be made with a high index of suspicion when lower GI bleed is seen in absence of hemorrhoids, and colonoscopy shows blood in rectum. Bleeding usually happens from endoscopically evident rectal varices (EERV) but sometimes bleed can occur from varices, which are endoscopically inevident (EIERV). Endoscopic ultrasound (EUS) has been shown to be more sensitive in diagnosis of EIERV [8–10]. Endoscopic and EUS correlation of RVs has shown that RVs, classified as tortuous, nodular, and tumorous on endoscopic examination, have corresponding appearances on rectal EUS as single, multiple, and innumerable submucosal veins, respectively [11]. The hemodynamic evaluation (HDE) of RVs by EUS is routinely done at some centers to assess parameters like the site, size, velocity, or direction of flow [9, 12]. The HDE of these parameters can offer therapeutic advantage before the selection of endoscopic or interventional radiological therapy [13]. This case series was done to evaluate the role of EUS in detection of RVs and the role of HDE before selecting the optimal site of endotherapy.

2. Material and Method

Between Jan 2009 and October 2011 sixteen consecutive patients with portal hypertension and LGIB underwent evaluation for rectal varices. Patient consent was obtained prior to the procedure. Ethics committee of the Institution approved the study. The diagnosis of RVs was made by endoscopic examination or EUS in five cases. Endoscopic examination included initial proctoscopic/sigmoidoscopic examinations followed by a complete colonoscopy to rule out any other cause of bleeding. Patient confirmed or suspected to have

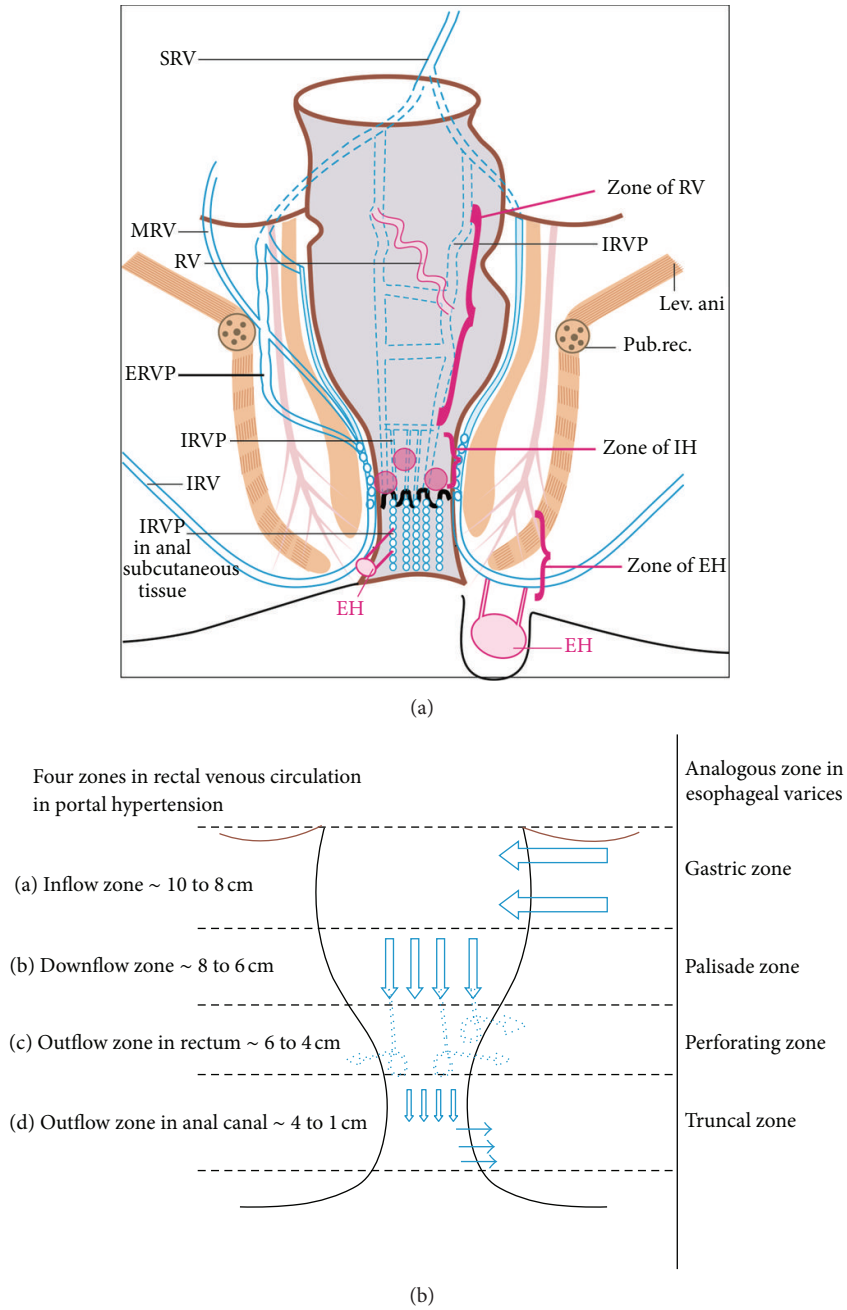

Figure 1: (a) The superior rectal vein (SRV) divides into two branches, which enter the lateral wall of rectum, about 10 cm above the dentate line. The middle and inferior rectal veins (MRV & IRV), empty into the caval system. The rectal veins form two plexuses, an internal one lying in the submucosa and the corresponding anal "Subcutaneous" tissue and an external one lying outside the muscular wall of the bowel below the level of the peritoneal reflection. The intrinsic rectal venous plexus consists of two groups of veins draining in opposite direction. The inferior group passes down to form the inferior rectal veins, and dilation of this group leads to formation of external hemorrhoids. The vessels of the superior group in the anal columns lead to the formation of internal hemorrhoids and in the rectum lead to the formation of rectal varices. (b) Four distinct zones of mucosal circulation are seen in rectum with similarity to esophageal circulation. The inflow area is analogous to the gastric zone, the downflow area is analogous to the palisade zone, the outflow area in rectum is analogous to the perforating zone, and the outflow area in anal canal is analogous to the truncal zone of esophageal varices.

Table 1: Baseline characteristics and endoscopic and EUS findings.

Headings	Case 1	Case 2	Case 3	Case 4	Case 5
Age/sex	35/M	40/F	50/M	38/F	23/M
Cause of portal hypertension	Cirrhosis (HCV)	Cirrhosis (HBV)	EHPVO, Cirrhosis (HBV)	EHPVO	Cirrhosis (alcohol)
Presenting symptom	LGIB 1st episode	LGIB 1st episode	LGIB 1st episode	Persistent LGIB after hemorrhoidectomy	Recurrent LGIB
Endoscopy finding	Tortuous varices	Tortuous varices	Tortuous varices	Normal rectal mucosa with presence of fresh blood	Appearance of Dieulafoy's ulcer
EUS findings					
(a) Inflow zone—size and number	3-4 (mm)/one	3-4 (mm)/one	2-3 (mm)/one	3-4 (mm)/one	3-4 (mm)/one
(b) Downflow zone—size and number	2-3/multiple	2-3/multiple	2-3/multiple	2-3/multiple	2-3/multiple
(c) Outflow zone (LR)—size and number	1-2/multiple	1-2/multiple	1-2/multiple	1-2/multiple	1-2/multiple
(d) Outflow zone—anal canal and number	Absent	Absent	~1 mm/multiple	Absent	~1 mm/multiple

HBV: hepatitis B virus, HCV: hepatitis C virus, inflow zone = 8–10 cm distance from anal verge, downflow zone = 6–8 cm distance from anal verge, outflow zone—upper rectum = 4–6 cm from anal verge, Outflow zone—anal canal = 1–4 cm from anal verge, LR: lower rectum.

RVs on endoscopy underwent diagnostic and hemodynamic evaluation by a radial endoscopic ultrasound scope (EUS) in the same session. The radial probe was advanced to 20 cm distance in rectum, which was filled with 100 to 250 mL of water. A color Doppler box with a focal distance of 3 to 4 cm was applied for entire circumference (360 degree) around the probe and continuous color Doppler application was done during slow withdrawal to the anus. The HDE of the venous circulation was done from higher up in rectum up to the anal verge and included the evaluation of site size and number of RVs, pararectal varices, and perforators (inflowing or outflowing) at three distances in rectum: 8 to 10 cm, 6 to 8 cm, and 4 to 6 cm. HDE was continued in the anal canal and the upper anal canal was identified by the puborectalis sling on EUS.

RVs were identified in the submucosal layer of rectal wall. The pararectal varices were identified in a location outside the wall of rectum. The perforators were identified as the communication traversing through the muscularis propria of rectal wall. The inflowing perforators were identified as flow signals towards the probe (red color) and outflowing perforators were identified as flow signals away from the probe (blue color). After HDE variceal ligation of RVs was done. If RVs were not suitably evident on endoscopy for banding, the information available on EUS was used for selection of site of banding.

3. Result and Discussion

In three cases detection was possible by endoscopy. EUS helped in identifying RVs in two. The clinical, endoscopic and EUS features of the patients are given in Table 1. Hemodynamic evaluation showed four areas of rectal venous circulation: inflow area (from 10 to 8 cm), downflow area (from 8 to 6 cm), outflow area in the lower rectum (6 to 4 cm), and outflow area in the anal canal. The EUS appearance in inflow area corresponded with highest point of RVs on endoscopy and in downflow area corresponded with endoscopic presence of multiple submucosal RVs (Figures 2(a), 2(b), and 2(c)). The EUS appearance in the outflow area in lower rectum corresponded with numerous smaller submucosal RVs and perforators, and the EUS findings in anal canal corresponded with small submucosal vessels and outflowing perforators through the middle part of anal canal (Figures 3(a) and 3(b)). The first three cases presented with LGIB for the first time and multiple EVL was done. The fourth case presented with recurrent LGIB endoscopic appearance suggested Dieulafoy ulcer and EUS confirmed presence of RVs. His bleeding stopped after banding but he had rebled after 48 hrs from a similar spot higher up in rectum, which was also banded (Figures 4(a)–4(h)). The last case presented with persistent LGIB with presence of fresh blood in rectum after surgery of hemorrhoids. Two bands were applied in anterior wall of rectum after the detection of varices by EUS (Figures 5(a) and 5(b)). None of the five cases had recurrence in a 6-month followup.

In this series 5 cases of RVs were detected (endoscopic detection $N = 3$, EUS detection $N = 2$). The detection of endoscopically inevident RVs was possible only by EUS in two cases, and potentially hazardous application of endoclips or coagulation methods on a bleeding point was avoided [1, 6, 7, 12]. The application of band on a normal looking mucosa on endoscopically inevident rectal varices stopped bleeding in a case of LGIB operated for internal hemorrhoids [8]. In this series the EUS was able to demonstrate the similarity of rectal venous circulation to esophageal venous circulation (Figures 1(a) and 1(b)) [13, 14]. The inflow area showed inflowing perforators communicating the pararectal varices

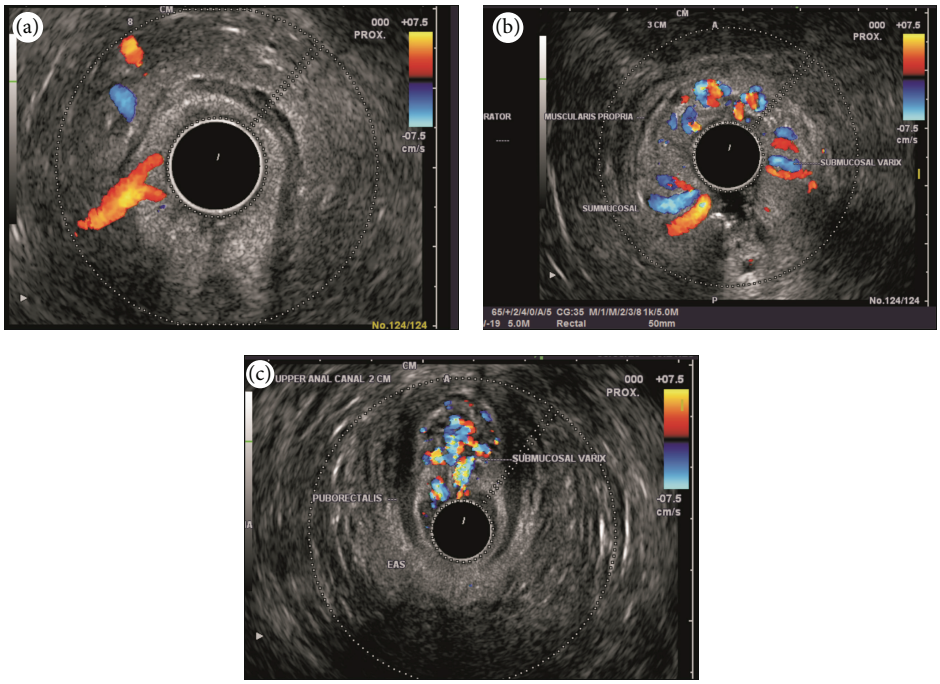

Figure 2: (a) An inflowing perforator of 3 mm diameter noted in the right lateral wall of rectum. (b) As the scope is pulled down towards the anorectal junction, the varices are seen circumferentially in the submucosa. (c) The varices are seen going anteriorly towards the genital plexus.

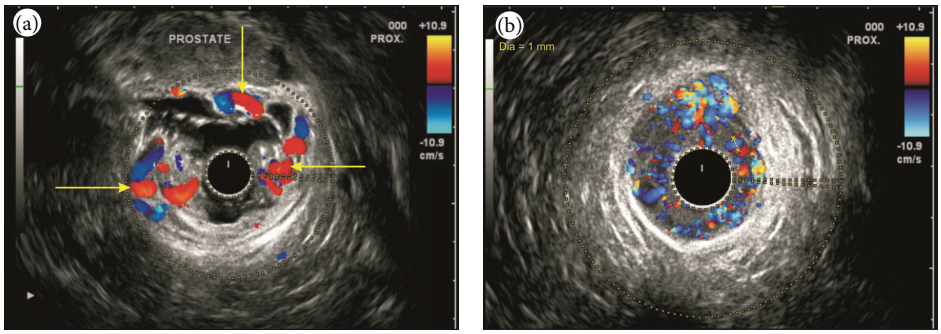

Figure 3: (a) As the scope is withdrawn towards the lower rectum, the submucosal varices were seen in anterior and lateral wall of rectum. (b) As the scope is pulled through the anus multiple small perforators <1 mm diameter were seen going through the muscular layer of anal canal.

with submucosal RVs and the downflow area showed the presence of RVs till the anorectal junction. The outflow area in lower rectum showed outflowing perforators in anterior and lateral wall of rectum, and the outflow area in anal canal demonstrated outflowing perforators. No standard algorithm is suggested for management of RVs. Balloon-occluded retrograde transvenous obliteration is aimed at obliterating the feeder vessel of superior rectal vein draining into inferior mesenteric vein while endoscopic obliteration takes care of submucosal blood vessels [10]. The hemodynamic evaluation can offer therapeutic advantage before the selection of endoscopic or interventional radiological therapy [13]. In this series hemodynamic evaluation helped in selection of banding closer to the feeder vessel near the inflow area at the highest point. The site, size, and direction of flow of RVs were evaluated, but the confirmation of inflow around 10 cm distance from anus was sufficient for selection of therapy, and banding of the highest point of RVs was done. This approach is contrary to the approach in a retrospective study where no hemodynamic evaluation was done and banding of the RVs was done close to the lowest point at anorectal junction [15]. This approach adopted in our series is analogous to obliteration of esophageal varices from the lowest point where the blood flow is from below upwards (Figures 6(a) and 6(b)).

4. Conclusion

To conclude EUS is helpful in identifying EIERV and in HDE of RVs. The identification of inflowing perforator to RVs at

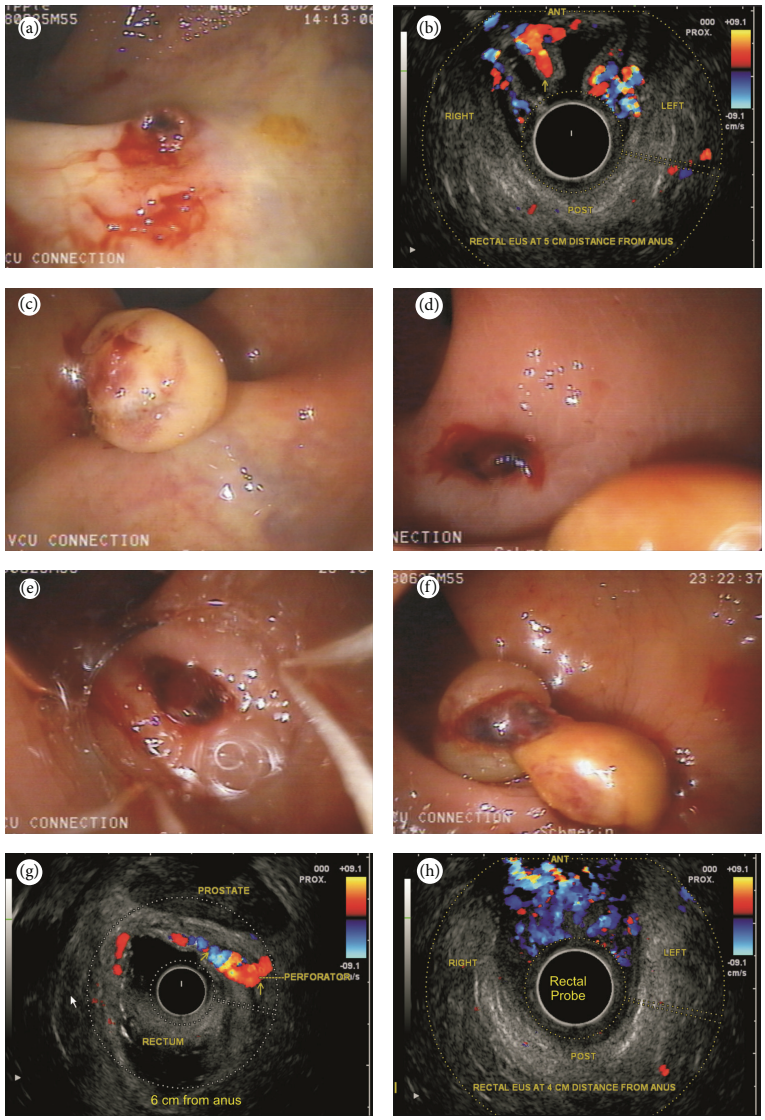

Figure 4: (a) An ulcer covered by a clot gives appearance of Dieaulafoy's ulcer. Clot could not be removed by flushing. (b) At about 6 cm distance in rectum inflowing perforators were noted in the submucosa of rectum. No pararectal varices were seen. (c) A band is applied on the clot as rectal varices were demonstrated by EUS under the ulcer. (d) The bleed stopped but after 24 hours patient rebleeds from a fresh point above the previously banded ulcer. (e) The new point of bleeding is caught inside the band. (f) Two bands are seen applied separately. (g) An inflowing perforator of the diameter of 3 mm is seen coming from the lateral wall of rectum before banding. (h) The diameter of rectal varices became smaller and more numerous as they were followed downwards the anorectal junction. At 4 cm distance the rectal varices are seen going towards the prostate.

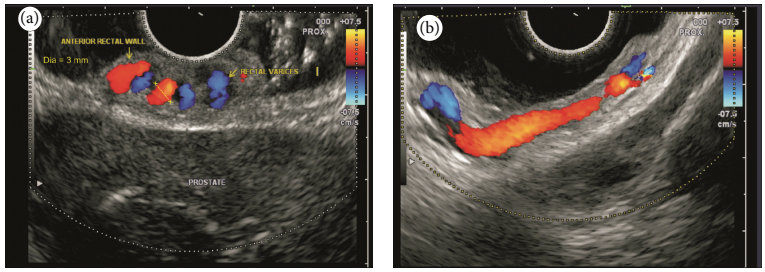

Figure 5: (a) Submucosal varices noted in a person who has undergone surgery for hemorrhoids. Presence of fresh blood was noted but endoscopy showed no rectal varices. (b) A long submucosal course of rectal varices is seen coming from the lateral wall of the rectum towards the anterior wall.

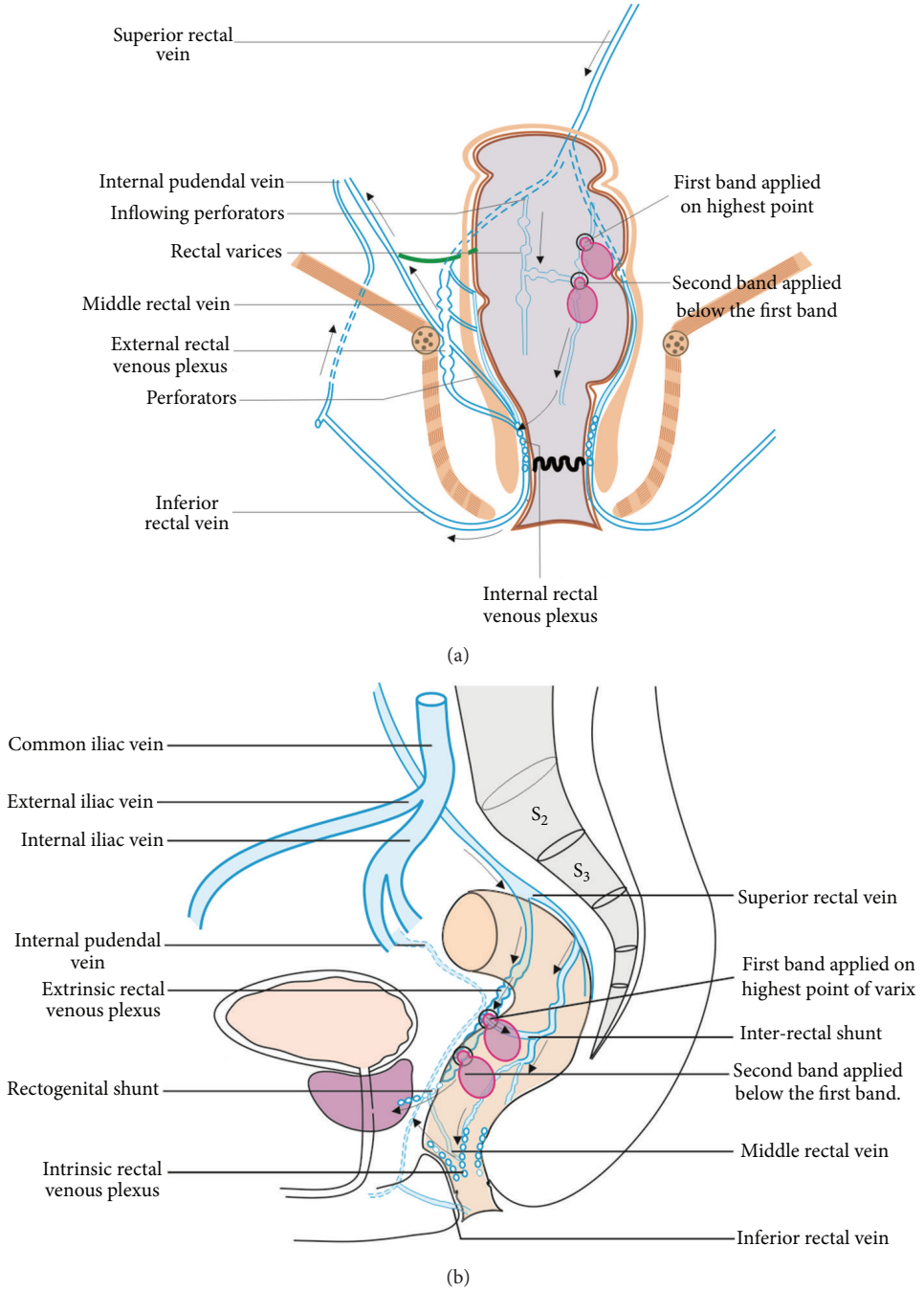

FIGURE 6: The direction of flow in rectal varices as shown in the figure is generally hepatofugal. The rectal varices are formed from these upper submucosal veins of intrinsic rectal venous plexus. From both the plexuses the portal hemorrhoidal blood works into systemic circulation through two portosystemic shunts (recto genital and inter rectal). The recto genital communication connect the rectal venous plexus with vesicoprostatic or vaginal venous plexus. The inter rectal communications occur between the three rectal veins. In rectal varices the banding should be done from above downwards.

about 10 cm distance in the rectum is helpful in selecting the optimum site of RVs banding. The banding of RVs should be done from above downwards.

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Review Article

EUS-Guided Vascular Procedures: A Literature Review

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Endoscopic ultrasound (EUS) is continuously stepping into the therapeutic arena, simultaneously evolving in different directions, such as the management of pancreatic and biliary diseases, celiac neurolysis, delivering local intratumoral therapy, and EUS-guided endosurgery. EUS-guided vascular procedures are also challenging, considering the variety of vascular pathology, proximity of the vascular structures to the GI tract wall, high resolution, and real-time guidance offering an attractive access route and precise delivery of the intervention. The literature on vascular therapeutic EUS demonstrates techniques for the management of upper GI variceal and nonvariceal bleeding, pseudoaneurysms, and coiling and embolization procedures, as well as the creation of intrahepatic portosystemic shunts. The paucity of studies, diversity of study designs, and the number of animal model studies hamper a systematic approach to the conclusion and decision making important to clinicians and healthcare policy makers. Nevertheless, theoretical benefits and findings up to date concerning technical feasibility, efficacy, and safety of the procedures drive further research and development in this rather young therapeutic arena.

1. Introduction

Since its beginning in the 1980s, EUS has evolved into a powerful diagnostic tool used widely for a number of GI conditions, successfully replacing other "gold standard" diagnostic modalities. In recent years, EUS is expanding to the interventional arena, usurping the management of pathology that was traditionally in the domain of therapeutic endoscopy, interventional radiology, and surgery. Therapeutic endoscopic ultrasonography (T-EUS) is developing simultaneously in different areas, such as the management of pancreatic and biliary diseases (e.g., pseudocyst drainage, cholangiopancreatography, etc.), celiac neurolysis, delivering local intratumoral therapy, EUS-guided endosurgery, and vascular procedures [1–4]. The variety of vascular pathology and the proximity of the vascular structures to the GI tract walls call for EUS-guided vascular procedures. Additionally, high resolution and real-time guidance offer precise delivery of the intervention, which is especially important when targeting tiny vascular structures. The literature on vascular therapeutic EUS offers a wide range of procedures that will be summarized in this review. The intention of this review is to give the reader a quick overview of the current state of research of EUS-guided vascular interventions. For more detailed descriptions of various techniques in this arena, we refer the readers to the original papers cited here.

2. Methods

PubMed/MEDLINE was searched to identify relevant publications in English. The following search string was used: {(EUS-guided or endosonography guided or endosonographic guidance or endoscopic ultrasound guidance or endoscopic ultrasound guided or echo-endosonography guided or echo-endosonographic guidance or endoscopic Doppler US guided or endoscopic Doppler ultrasound guided or endoscopic Doppler US guidance) AND (vascular or EUS-guided or varices or nonvariceal or pseudoaneurysm or Dieulafoy or Dieulafoy's or porto-systemic shunt)}. The final search was launched on January 29, 2013, with no time restrictions. Additionally, the Cochrane Library was searched.

Our PubMed/MEDLINE search yielded 1291 publications that were assessed for relevance according to title and

abstract by two reviewers, and potentially relevant papers were retrieved in full text. The bibliographies of publications identified as relevant were manually searched for potentially relevant titles, and additional publications were found. Finally, twenty published papers were included for analysis in this review. Abstracts presented at congresses were not included. We are aware that our search possibly missed relevant papers due to a relatively inconsistent and evolving terminology in this new therapeutic arena.

In this paper, the current literature on EUS-guided vascular procedures is summarized in a narrative form considering the paucity of the studies, great diversity of study designs (mostly pilot studies, case records, and small case series), and a number of animal model studies, hampering any systematic approach to the literature synthesis.

We were restricted to the literature on vascular procedures under real-time EUS guidance. There are various miniature ultrasound/Doppler probes available that can be introduced through a working channel of the standard endoscope [5, 6]. Studies describing the treatment with the aid of endoscopic Doppler ultrasound with Doppler probes or ultrasound miniature probes, which did not occur under real-time EUS guidance, are worth mentioning but were not included in this review [6–12]. Studies describing non-GI tract-related EUS-guided procedures were also not included.

3. Results and Discussion

Several areas of vascular procedures under the EUS-guidance could be identified throughout the available literature. For the purpose of this review, we have selected five areas of EUS-guided vascular procedures:

(1) EUS-guided management of nonvariceal upper GI bleeding;

(2) EUS-guided management of variceal bleeding;

(3) EUS-guided management of pseudoaneurysms;

(4) EUS-guided embolization of portal venous system;

(5) EUS-guided creation of portosystemic shunts.

In the next sections, each of these areas will be discussed overviewing the available literature.

3.1. EUS-Guided Management of Nonvariceal Upper GI Bleeding. Since a certain percentage of nonvariceal upper GI bleeding episodes are diagnostically challenging and refractory to a standard therapy (various endoscopic techniques, angiographic therapy), EUS-guided detection and management can offer an alternative in this group of patients. To date, EUS-guided therapy for nonvariceal upper GI bleeding has been described for the management of peptic ulcer disease, Dieulafoy's lesions, and bleeding tumors. EUS-guided management of the pseudoaneurysms, which also can bleed, will be discussed in the following section of this review.

Peptic ulcer disease is responsible for more than 50% of upper GI bleeding admissions to hospitals and has high recurrent bleeding rates and high mortality rates. Standard treatment, including nonendoscopic modalities, and upper GI endoscopy with injection therapy, thermal therapy, and/or clipping are safe and effective. However, relatively high rates of unsuccessful bleeding stoppage and recurrent bleeding are reported, occurring in up to 20% of patients [13–15]. EUS guided therapy offers therapeutic techniques that can potentially improve successful treatment, especially in the group of patients with unsuccessful bleeding stoppage and recurrent hemorrhage, therefore reducing recurrent bleeding rates and high mortality rates.

Levy et al. described a patient with recurrent upper GI bleeding from a duodenal ulcer previously treated with heater probe plus injection at two separate occasions. On EUS-examination, the authors visualized tortuous vessel branching from gastroduodenal artery to mucosa and, under the guidance of curved linear echoendoscope, they injected 3 mL of cyanoacrylate through a 22-gauge FNA needle pointing at the 1.5 mm wide branching vessel located within the ulcer. Success of the treatment was confirmed immediately by Doppler. There were no complications, and no rebleeding occurred during 14-month followup [16]. Elmunzer et al. in their animal pilot study created an artificial arterial bleeding model in the stomach (gastroepiploic vascular bundle was surgically placed in the submucosa). After endosonographic visualization of submucosal artery, dilute epinephrine injection or contact thermal coagulation were delivered directly to the vessel through the working channel of the forward-viewing echoendoscope under direct EUS guidance. The procedure was successful in both cases treated with epinephrine injection and in two out of four treated with contact thermal coagulation [17]. Gonzalez et al. successfully treated a patient who bled from the side branch of gastroduodenal artery with EUS-guided injection of cyanoacrylate, with no recurrence bleeding detected during 14-month followup [18].

Dieulafoy's lesion is a relatively rare vascular malformation that presents with an acute refractory often massive upper GI bleeding, with a rather unsatisfactory detection rate at repeated endoscopy in the case of nonactive bleeding at the time of endoscopy. Endoscopic ultrasound and/or Doppler ultrasound are highly sensitive for the detection of vascular structures in the GI tract wall, which is especially useful in the absence of an endoscopically visible lesion (e.g., ulcer or protruding vessel), giving theoretical advantages to EUS-guided detection and treatment over standard modalities.

Fockens et al. in their small study treated three patients with Dieulafoy lesions by EUS-guided sclerotherapy [19]. Under the direct guidance of rotating sector scanner EUS aided by an endoscopic picture, a 23-gauge needle was used to inject epinephrine/polidocanol in the lesions. All the procedures were successful without complications, with rebleeding episodes in one of the patients that were followed up. In the case record by Ribeiro et al., residual artery was detected by EUS with Doppler five months after local therapy of a Dieulafoy's lesion with rubber bands. Hereafter, thermal contact therapy following injection of absolute alcohol under direct EUS guidance successfully stopped blood flow in the artery, which was confirmed by Doppler [20]. Gonzalez et al. also reported successful EUS-guided 19-gauge injection therapy of two Dieulafoy lesions with no recurrence of bleeding during median followup of nine months [18]. Levy et al.

reported a patient with recurrent active upper GI bleeding from duodenum. No bleeding site was detected throughout multiple upper GI endoscopies, and random treatment with heater probe plus injection was undertaken at three occasions without success. On EUS, a 0.8 mm vessel branching from larger underlying vessel to the duodenal mucosa was visualized. Through a 22-gauge needle, 99% alcohol was delivered, and a band was placed over the site of injection. There were no complications and no rebleeding occurred during 23-month followup [16].

The current evaluation of EUS-guided interventions for the management of peptic ulcer bleeding and Dieulafoy's lesions is limited to anecdotal case records, one case series and one animal study, thus hampering any comparison with standard treatment options, and therefore recommendations cannot be given. However, the theoretical benefits of direct EUS and Doppler visualization of the "culprit" vessel responsible for the recurrent bleeding are evident, allowing precise treatment delivery and therefore possibly higher successful treatment rate in the groups of patients unsuccessfully treated or with recurrent bleeding. The feasibility and safety demonstrated in these publications are encouraging, hoping that future larger scale studies with appropriate study designs will possibly find some benefit, especially in some groups of t he patients (unsuccessful treatment, recurrent bleeding episodes).

3.2. EUS-Guided Management of Upper GI Varices and Variceal Bleeding. Endoscopic injection therapy and band ligation have been widely used for the management of bleeding and nonbleeding upper GI tract varices with a high success rate and with known complication rates [21, 22]. Yet a considerable percentage of patients are not managed successfully, having recurrent variceal bleeding [22, 23]. EUS has emerged as a valuable tool for the diagnosis, treatment planning, evaluation of treatment success, and estimation of recurrent bleeding potential, being able to visualize varices, perforating, and collateral veins, thus allowing to predict varices with a high risk for (recurrent) bleeding [24–26]. In the last years, EUS is continuously emerging as a therapeutic method for the management of upper GI varices, as guidance for injection therapy and coiling, or their combination. There are reports demonstrating feasibility, efficacy, and low complication rates of injection therapy for upper GI varices with the aid of EUS/Doppler, where EUS/Doppler was mostly used to detect and visualize the location for therapy, which was thereafter delivered through a standard forward-viewing endoscope [12, 27].

Treatment techniques under direct EUS guidance seem to be promising. Lahoti et al. were the first to demonstrate sclerotherapy for upper GI varices under real-time EUS guidance. In a small pilot study on five patients with esophageal varices, they injected sclerosant (sodium morrhuate) through a 2.5 mm catheter injector needle under EUS guidance directly to perforating vessels until "no flow" was detected by color Doppler [28]. To achieve varices obliteration, 2.2 sessions per patient were needed. The mean followup was 15 months, and no recurrent bleeding occurred. Romero-Castro et al. in their small case series injected cyanoacrylate-lipiodol into gastric varices at the level of perforating veins, under EUS guidance [29]. All the procedures were successful, without recurrent bleeding or other complications during followup. They postulated that targeting perforating veins would produce the maximal blood-flow blockage, with the lower amounts of cyanoacrylate needed, therefore reducing the rate of potential local and systemic complications. Gonzalez et al. in three patients from their pilot study performed EUS-guided injection therapy of varices and reported 100% success rate, without recurrent bleeding or major complications [18]. The most valuable study to date was undertaken by Andrade de Paulo et al. [30]. In their randomized controlled trial, they compared endoscopic sclerotherapy and EUS-guided sclerotherapy of esophageal collateral veins. The findings that recurrent variceal bleeding after endoscopic therapy is related to collateral veins lead them to the hypothesis that obliteration of these veins would reduce the risk of recurrent bleeding. In the first arm, 24 patients were treated with endoscopic sclerotherapy (ES group) using 3–5 mL of diluted ethanolamine oleate injected through a 23-gauge injector, depending on the size of the varix. In the second arm (EUS-ES group, 24 patients), the collateral veins were punctured under EUS guidance with 19- or 21-gauge needle, and the same sclerosant was injected. The procedures in both arms were repeated at 2-week intervals until the varices were eradicated. At the end of the interventional part of the study, EUS was performed in all patients in the first arm to detect the presence of collateral veins. The study groups did not differ in the number of procedures needed for varices eradication, total volume of sclerosant used, and pain or bleeding during/after treatment. In the ES group, eight patients (33.3%) had collaterals detected after treatment, whereas in the EUS-ES group collateral veins were undetected in any of the patients ($P = 0.004$). During followup (mean 22.6 months), four patients in the ES group (all had collateral veins detected at the end of the interventional part of the study), and two patients in the EUS-ES group (none had collateral veins detected at the end of the interventional part of the study) ($P = 0.32$), had varices recurrence without recurrent bleeding in both groups.

Injection sclerotherapy for upper GI varices has been associated with local complication and embolic incidents [2, 31]. The incidence of the latter can potentially be minimized by using coils that can be introduced under EUS guidance [32]. In their case record, Levy et al. described successful EUS-guided delivery of microcoils over 22-gauge needle to three varices for the treatment of acute bleeding from ectopic coledochojejunal anastomotic varices that occurred during ERCP [33]. Romero-Castro et al. reported a small case series of patients with severe gastric varices treated with EUS-guided coil embolization. They inserted coils into the perforating veins in order to block the blood flow. The varices were eradicated in three out of four patients, and no complications occurred in the successfully treated patients during five months of followup [34]. Binmoeller et al. in their study on thirty patients combined EUS-guided coiling and cyanoacrylate glue injection by transesophageal approach to the gastric fundal varices. They hypothesized that coils with attached synthetic fibers ("wool coils") inserted into

the varices prior to cyanoacrylate injection would function as a "barrier" for cyanoacrylate to outflow into the larger veins causing embolic events. In their procedure, after positioning and endosonographic visualization of gastric varices from the esophagus (through the diaphragmatic crus muscle), a 19-gauge FNA needle was inserted through the esophageal wall and diaphragm muscle directly to the gastric varix, following coil delivery and 1 mL of cyanoacrylate with immediate repetition of the procedure as needed until varix obliteration (Figure 1). The treatment was successful in 100% of the patients without complications during the mean 193 days followup, demonstrating the feasibility, efficacy, and safety of this novel method [32]. Weilert et al. in their case record demonstrated successful EUS-guided treatment of rectal varix. A large rectal varix was visualized by endosonography, and two coils following 1 mL of cyanoacrylate were delivered through a 19-gauge needle under direct guidance of EUS, achieving varix obliteration confirmed by Doppler. No bleeding occurred during or after the procedure, leaving the varix obliterated on EUS and Doppler four weeks later, and without recurrent bleeding during one-year followup [35].

EUS-guided management of the upper GI varices and variceal bleeding shares the same theoretical benefits with the EUS-guided management of nonvariceal upper GI bleeding; that is, the visualization of the "culprit" lesions—varices, perforating and collateral veins—allows thorough planning and precise delivery of treatment, as has been demonstrated through the procedures described in the cited papers. Again, in comparison to effective standard treatment modalities, EUS-guided management can offer additional benefit for the patients unsuccessfully treated and those with recurrent bleeding. The quantity of the publications in this area of EUS-guided vascular procedures indicates rapid evolvement, and probably more high quality studies might be expected for these techniques. The studies undertaken up to now underpin the postulated theoretical benefits of EUS-guided therapy over standard techniques, which is most robustly demonstrated in the elective treatment of patients with esophageal collateral veins.

3.3. EUS-Guided Management of Pseudoaneurysms. Visceral pseudoaneurysms are quite rare and serious complications of pancreatitis or abdominal surgery, with high mortality rates when ruptured. Management of visceral pseudoaneurysms includes interventional radiology procedures and surgery, with considerable morbidity and mortality [36, 37]. Percutaneous endovascular procedure is the first-line treatment of these conditions. However, it is often quite difficult to perform, and some aneurysms are practically "unreachable." Considering the great visualization, and relative proximity of the pseudoaneurysms to the GI tract allowing an attractive access route, EUS-guided procedures offer an alternative to the traditional management options.

Gonzalez et al. in their case record described the patient with chronic pancreatitis having a pseudocyst scheduled for EUS drainage. During the drainage attempt, an intracystic pseudoaneurysm of the splenic artery was injured and massive intracystic hemorrhage occurred. Since this was a potentially life-threatening condition, immediate puncture and cyanoacrylate injection under EUS guidance was performed, embolizing the distal arm of the splenic artery, therefore stopping the bleeding [38]. The patient was followed up for more than a year with no complications recorded. Roberts et al. in their brief report demonstrated successful EUS-guided treatment of visceral pseudoaneurysm by injecting a mixture of Histoacryl glue and lipiodol directly into the lesion [39]. Levy et al. described a patient with a big pseudoaneurysm of the superior mesenteric artery (SMA) that was previously unsuccessfully treated with coiling and injection therapy during angiography. After visualization, a 2 mm wide branch of the SMA communicating with the pseudoaneurysm was injected with 7 mL of 99% alcohol, through a 22-gauge FNA needle, and cessation of blood flow was confirmed by Doppler. There were no complications, and no rebleeding occurred during 16-month followup [16].

Roach et al. appear to be the first to describe the use of thrombin for the EUS-guided management of visceral pseudoaneurysm. A 32-year-old man with a superior mesenteric artery (SMA) pseudoaneurysm after pancreatitis and recurrent bleeding episodes was considered for selective embolization during angiography and percutaneous US/CT-guided injection therapy, but these were rejected due to unsuccessful selective catheterization and anatomic positioning. Under the EUS guidance the pseudoaneurysm was punctured with a 22-gauge needle, and 500 IU of thrombin was injected immediately obliterating the sac of pseudoaneurysm leaving the SMA patent, which was confirmed by Doppler. At computed tomography 12 weeks later partial recanalization was verified, but no further treatment was undertaken, and spontaneous rethrombosis of the pseudoaneurysm was detected by computed tomography 28 and 42 weeks after the treatment [40]. Chaves et al. reported a case of a 29-year-old man with a big pseudoaneurysm of the splenic artery at the level of the pancreatic body. The sac of pseudoaneurysm was punctured with a 22-gauge needle under EUS guidance, and 500 IU of thrombin was injected. Obliteration occurred instantly. A week later CT detected a small local splenic infarction, probably due to distal embolization. Four months later CT angiography and EUS confirmed the persistence of the occlusion. The authors hypothesized that the presence of a vascular stalk forming communication between the artery and pseudoaneurysm in this patient was facilitating, increasing the probability of successful obliteration, and reducing the possibility of distal embolization [41]. Robinson et al. also reported the successful treatment of a splenic artery pseudoaneurysm with a 2 mm stalk. Thrombin (500 IU) was injected via a 22-gauge needle into the sac of pseudoaneurysm under the EUS guidance, and occlusion occurred, which was confirmed on an immediate CT angiography and repeatedly one and six weeks later [42]. In their case record Lameris et al. reported the successful EUS-guided injection of 7 mL of thrombin-collagen compound into a splenic artery pseudoaneurysm through a 22-gauge needle, confirming complete pseudoaneurysm obliteration by Doppler, leaving the pseudoaneurysm obliterated at CT angiographies six weeks and ten months after [43].

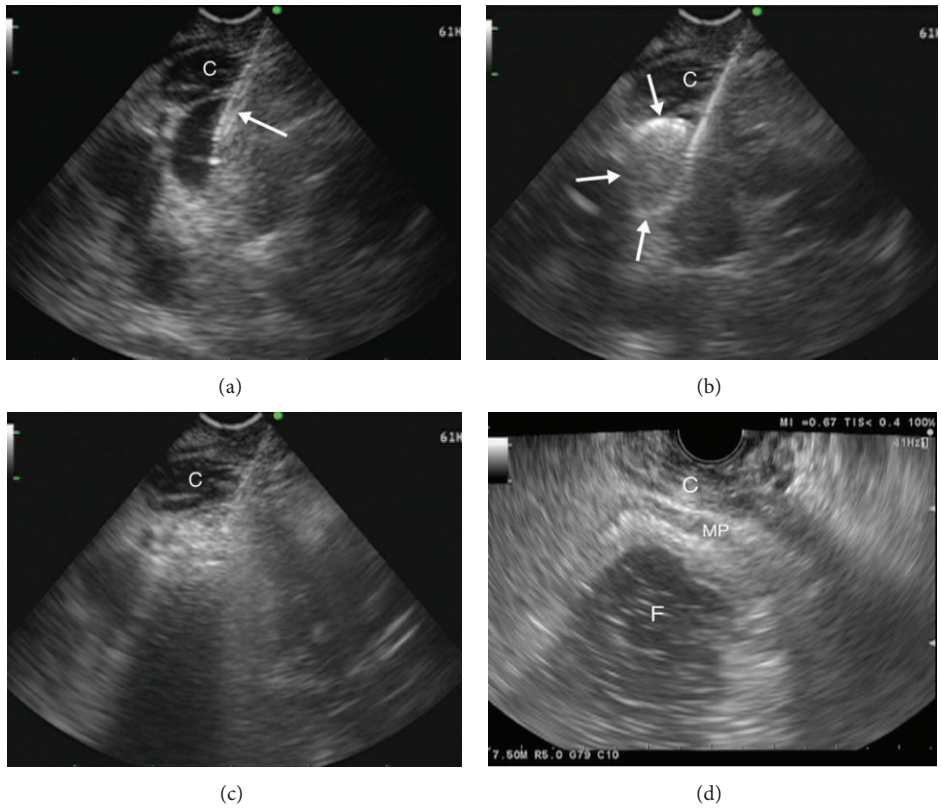

Figure 1: (a) Endosonographic transesophageal view—a 19-gauge needle inserted into the varix (arrow). (b) Coil delivery (arrows) through the 19-gauge needle. (c) Injection of 1 mL of cyanoacrylate. (d) Fundal varices obliterated. C: crus muscle, F: fundus; MP: muscularis propria of stomach wall. (Images curtsey of [32]).

Publications of rather anecdotal cases of EUS-guided treatment of visceral pseudoaneurysms demonstrated the feasibility and technical ease of performing such procedures and, together with the theoretical benefits over traditional methods, are promising. However, theoretical disadvantages such as bleeding, introduction of infections, unwanted thrombotic events, and efficacy and safety issues, in comparison to standard treatment modalities, should be further robustly evaluated in order to potentially set these methods as the standard.

3.4. EUS-Guided Embolization of Portal Venous System. There is some evidence (studies on animal models) that EUS-guided portal vein pressure measurement is feasible, suggesting the EUS-guided transhepatic puncture of portal vein to be safer [44–47]. Additionally, in a study on animal model, the EUS-guided puncture of all major abdominal vessels (arteries and veins) appeared to be feasible and safe [48, 49]. Matthes et al. in their animal model study showed that the EUS-guided embolization of portal vein with ethylene vinyl alcohol is feasible [50], and the same authors in another animal model study demonstrated the feasibility of embolization of splenic vein with ethylene vinyl alcohol (published as abstract). Selective embolization of portal veins can be useful to achieve selective hepatic atrophy before major hepatic surgery [49, 50]. The described EUS-guided procedures offer theoretical therapeutic benefits, but the feasibility and safety issues of such procedures have not been evaluated in humans as of now.

3.5. EUS-Guided Creation of Portosystemic Shunt. Portal hypertension of any etiology is associated with substantial complications. Lowering portal vein pressure, thus reducing complication rates, can be achieved with drugs, transjugular intrahepatic portosystemic shunt (TIPSS) placement, or surgical shunts. TIPS is a widely used and effective technique but with a number of possible periprocedural complications, such as pneumothorax formation, cardiac arrhythmias, and injury to the blood vessels in the liver resulting in hemorrhage. The proximity of the portal and hepatic veins to the scope of the EUS offers a potentially more favorable route for shunt formation under EUS guidance, avoiding some of the complications such as pneumothorax and cardiac arrhythmias. However, some potential disadvantages of this approach have to be acknowledged, such as introduction of infection and potentially higher bleeding complications, in comparison to TIPSS.

Recently Buscaglia et al. in their animal model study demonstrated the feasibility of EUS guided creation of an intrahepatic portosystemic shunt (IPSS). After positioning in the plane where both portal and hepatic veins were endosonographically visualized, transhepatic puncture of selected

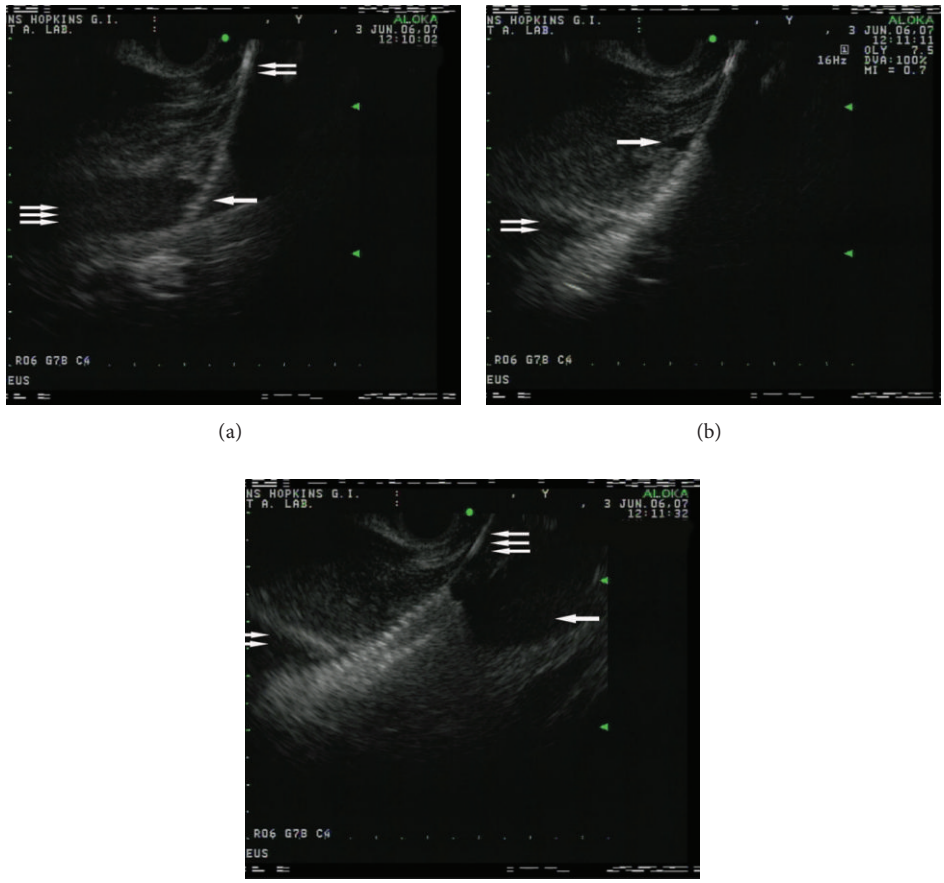

Figure 2: Endosonographic views during the stent deployment. (a) The stent (one arrow) delivery over the guidewire (two arrows) into the hepatic vein (three arrows). (b) Deployment of the stent; the proximal end of the stent inside the hepatic vein (one arrow) and the distal end of the stent inside the portal vein (two arrows). (c) The stent fully deployed with its proximal end inside the hepatic vein (one arrow) and the distal end inside the portal vein (two arrows); the guidewire (three arrows) (images curtsey of [51]).

hepatic vein was performed firstly and then advanced to intrahepatic branch of the portal vein with a 19-gauge needle under EUS-guidance aided by fluoroscopy. Hereafter, the stylet was withdrawn following guidewire insertion in the portal vein through the needle, and the needle was withdrawn out from endoscope. After measuring the distance between selected veins, an appropriate uncovered biliary metal stent was inserted over the guidewire, bridging the selected hepatic and portal veins, therefore forming a portosystemic shunt (Figure 2). The authors stated that the procedure was feasible, easy to perform, and effective, without major complications [51]. Further evaluation in humans is needed to evaluate the feasibility, efficacy, and safety, as well as comparison of this theoretically promising alternative to the conventional TIPSS.

4. Conclusion

The paucity of the studies undertaken to date and their quality cannot give answers to the questions posed by clinicians and healthcare policy makers. However, papers published to date can give directions for future research that needs, in a more robust scientific manner, to address technical feasibility, efficacy, and safety of the procedures, as well as cost benefits in this rather young therapeutic arena.

Standard treatment modalities for the management of variceal and nonvariceal GI bleeding as well as for management of visceral pseudoaneurysms and TIPS creation are relatively effective and safe, and as such, are being used worldwide. However, unsuccessful treatment in a percentage of patients and recurrent bleeding episodes, together with theoretical benefits of EUS-guided interventions over standard treatment, as well as feasibility and technical ease demonstrated in the papers summarized in this review, calls for future research.

Further development of EUS-guided access to the vessels could potentially replace the interventional radiology vascular interventions in the abdomen and provide more efficient and precise, as well as safer local application of drugs (chemotherapeutics, fibrinolytics, etc.), vascular embolization (sclerotherapy, coiling, etc.), endoprostheses placement, and creation of portosystemic shunts [48, 49].

We all witnessed the "transformation" of ERCP from a purely diagnostic procedure at its beginnings to a mainly therapeutic procedure nowadays [52, 53]. Considering the continuous evolvement of various noninvasive diagnostic modalities and the technical development of EUS, can we expect the same for endoscopic ultrasound in the future?

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Clinical Study

Prospective Study about the Utility of Endoscopic Ultrasound for Predicting the Safety of Endoscopic Submucosal Dissection in Early Gastric Cancer (T-HOPE 0801)

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Background. Intraoperative bleeding is an important determinant for safety of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). This study aimed to prospectively evaluate the usefulness of endoscopic ultrasound (EUS) for predicting ESD safety. *Methods*. A total of 110 patients with EGC were divided into two groups based on EUS findings: group P, almost no blood vessels in submucosa, or ≤4 small vessels per field of view; group R, remaining patients. Primary endpoint was the decrease in Hb after ESD. Secondary endpoints included procedure time and the incidence of muscle injury and clip use. *Results*. A total of 89 patients were evaluated. Fifty were classified into group P and 39 into group R. Mean decrease in Hb was 0.27 g/dL in group P and 0.35 g/dL in group R, with no significant difference. Mean procedure time was significantly longer in group R (105.4 min) than in group P (65.5 min) ($P < 0.001$). The incidence of muscle injury and clip use were significantly higher in group R (25.6%/48.7%) than in group P (8.0%/20.0%) ($P = 0.02$/$P = 0.004$). *Conclusion*. Preoperative EUS can predict procedure time and the incidence of muscle injury and clip use and is thus considered useful for predicting gastric ESD safety.

1. Introduction

The advance from endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) has enabled *en bloc* endoscopic resection of lesions, regardless of their location and size or the presence or absence of scar formation [1–3]. While ESD is now widely used for endoscopic treatment of early gastric cancer, there are several unsolved problems associated with its use, such as prolonged procedure time and high incidence of perforation, bleeding, and other complications [4]. In particular, intraoperative bleeding during gastric ESD significantly affects the safety of the procedure and can result in extra time for hemostasis and injury or perforation of the muscle layer due to loss of clear surgical field of view.

We have previously reported the use of endoscopic ultrasonography (EUS) to identify vasculature in the submucosa beneath the lesion and thereby predict the risk of intraoperative bleeding during ESD [5]. In this paper, we present the results of our prospective clinical study on the usefulness of EUS for predicting the intraoperative bleeding and safety of gastric ESD (Toranomon Hospital Prospective Study of Endoscopy: T-HOPE 0801).

2. Materials and Methods

2.1. Patients. This study was commenced after obtaining approval from the Ethics Committee at Toranomon Hospital in June 2008. Inclusion criteria were (1) age ≥20 years, (2) gastric tumor treated by ESD, (3) having received EUS prior to ESD, and (4) having provided written informed consent. Patients were excluded if they (1) had multiple resectable gastric lesions, (2) had undergone any surgical procedure involving the stomach or esophagus, (3) had a lesion that extended to the esophagogastric junction or pyloric ring,

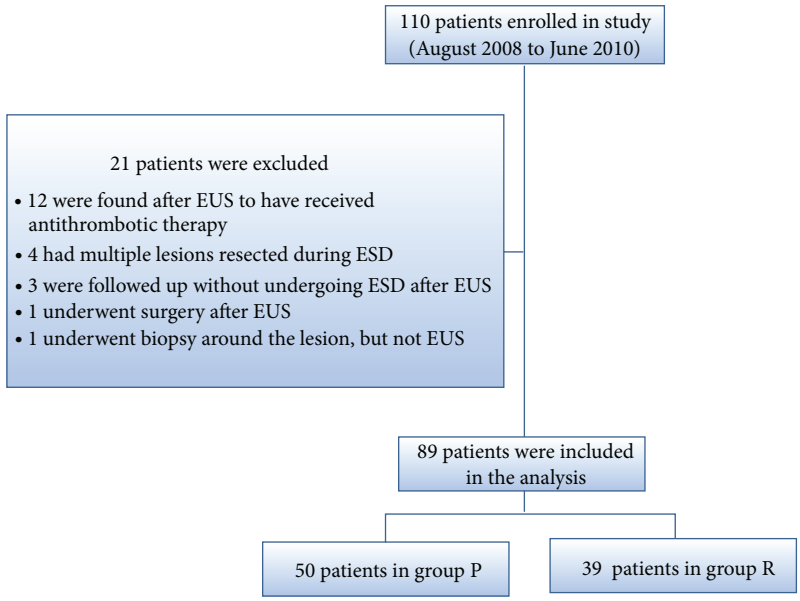

Figure 1: Flow of patients through this study.

(4) had a ulcer scar that made it difficult to identify the layer structure of the gastric wall by EUS, (5) had serious liver/kidney dysfunction or hematological disorder, (6) were receiving antiplatelet or anticoagulation therapy, or (7) were considered inappropriate for participation in this study by the attending physician.

A total of 110 patients were enrolled in this study between August 2008 and June 2010. Of them, 89 were included for analysis, and the following were excluded: 12 who were found after entry to be receiving antithrombotic therapy, 4 in whom multiple lesions were resected during ESD, 3 who were followed up without treatment after EUS, 1 who underwent surgery after EUS, and 1 who underwent stepwise biopsy, but not EUS, due to an irregularly bordered lesion (Figure 1).

2.2. EUS. EUS was performed to determine the invasion depth of the lesion prior to ESD. During EUS, a deaerated water-filling method was used for the observation using a 20 MHz miniature probe (Olympus Optical, Tokyo, Japan). The gastric wall was visualized as consisting of 5 layers. A hyperechoic line observed in the third layer was identified as the submucosa and a hypoechoic line observed in the fourth layer was identified as the muscularis propria. Lesions were classified into the following two groups according to the vascular structure identified by EUS in the third layer: group P, lesions with almost no hypoechoic areas likely to represent blood vessels or with ≤4 vessels of 50 μm in diameter per field of view in the third layer (Figures 2 and 3); group R, lesions not classified as group P (Figures 4, 5, 6, and 7). In EUS, blood vessels were defined as structures visualized as hypoechoic, circular, or band-like areas in the third layer that could be recognized as vasculature. A structure was considered a ulcer scar when the third layer gradually disappeared or tapered off. During EUS, a single endoscopist (D. Kikuchi) classified each lesion into group P or R.

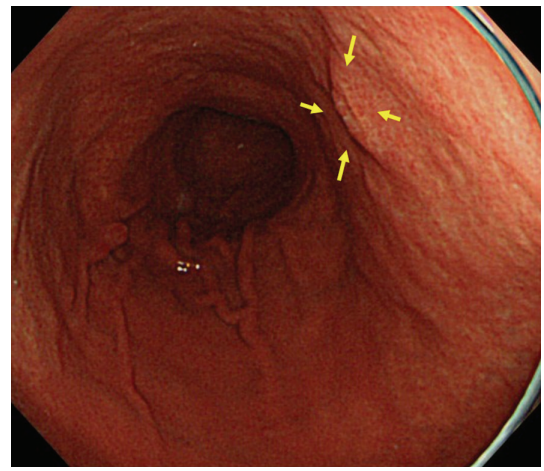

Figure 2: Endoscopic image of a patient in group P showing a flat elevated lesion on the posterior wall of the middle gastric body (yellow arrow).

2.3. ESD. ESD was performed by skilled endoscopists who had experienced more than 100 cases of gastric ESD. Endoscopists under training were also allowed to perform the procedure under the guidance and supervision of the skilled endoscopists, who was blinded to EUS findings when performing ESD. ESD was performed using a GIF Q260J or 2TQ 260 M endoscope (Olympus Optical, Tokyo, Japan), a Flex or Dual knife (Olympus Optical, Tokyo, Japan) in all cases, plus a Hook knife (Olympus Optical, Tokyo, Japan) in some cases at the discretion of the operator, and an ICC 200 or VIO 300D high-frequency apparatus (ERBE, Tübingen, Germany).

Some marks were placed around the lesion, Glyceol (Chugai Pharmaceutical, Tokyo, Japan) was injected locally,

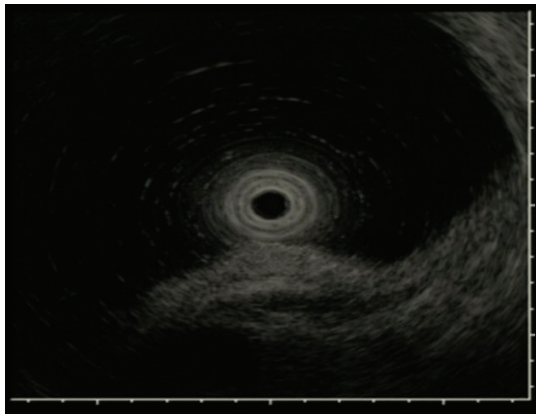

Figure 3: EUS image of the lesion of Figure 2. EUS showing no hypoechoic area suggestive of blood vessels in the third layer.

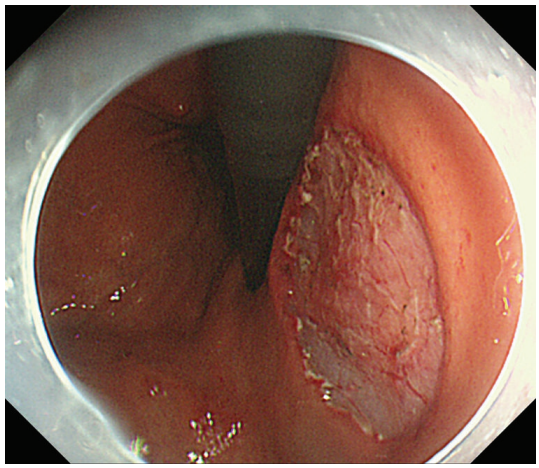

Figure 4: Post-ESD image of the lesion of Figure 2. There is no carbide on ESD ulcer.

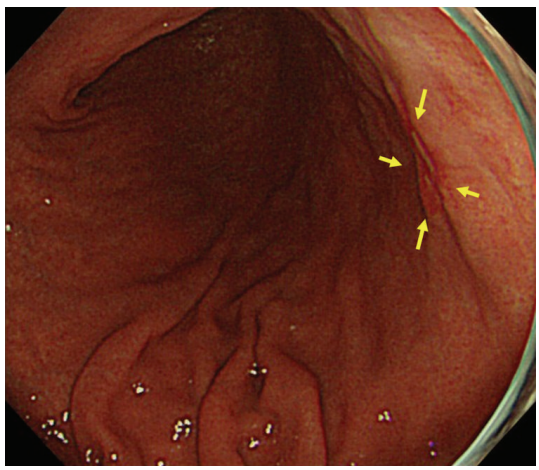

Figure 5: Endoscopic image of a patient in group R showing a depressed lesion on the posterior wall of the lower gastric body (yellow arrow).

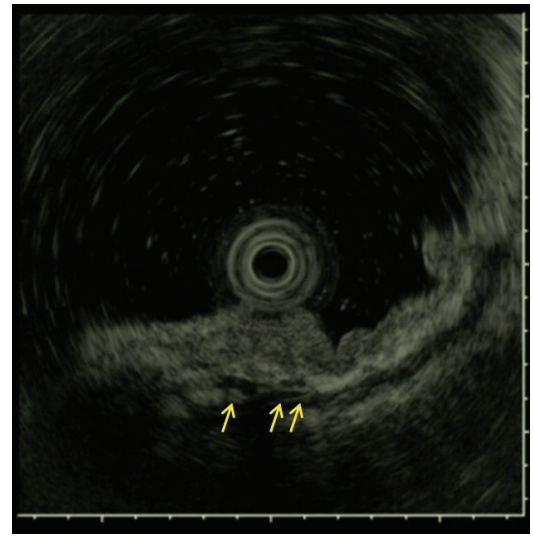

Figure 6: EUS image of the lesion of Figure 5. EUS showing some large vessels approximately 1000 μm in diameter in the third layer (yellow arrow).

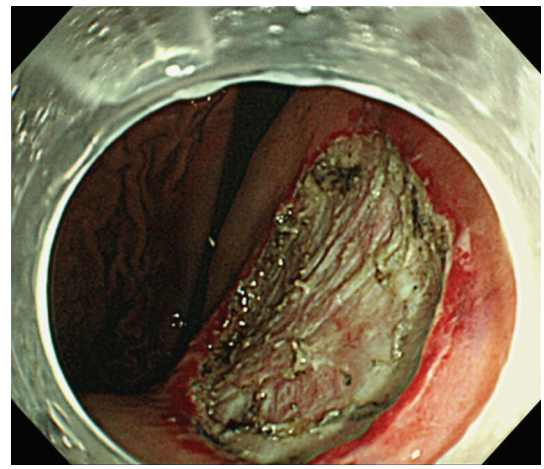

Figure 7: Post-ESD image of the lesion of Figure 5. A lot of carbide by hemostatic forceps and muscle injury were recognized on ESD ulcer.

and an incision was made around the lesion. With the submucosa identified under direct view, the lesion was separated from the submucosa to obtain *en bloc* resection. Intraoperative bleeding was managed by coagulation hemostasis with the tip of the knife (swift coagulation, effect 4, 40 W) for mild bleeding or with hemostatic forceps (Pentax, Tokyo, Japan; soft coagulation, effect 4, 50 W) for moderate bleeding. For arterial bleeding or bleeding that could not be stopped with hemostatic forceps, clips (Olympus Optical, Tokyo, Japan) were used for hemostasis at the discretion of the operator. In cases of suspected injury or perforation of the muscle layer, a suture was made with clips at the discretion of the operator. On the day of ESD, the patient was fasted and given fluid replacement. On the day after ESD, abdominal, blood, and X-ray examinations were performed, and the

operator decided when to resume eating based on the results of the examinations. One week after ESD, endoscopic examination was performed to confirm the absence of bleeding or exposed vessels. Patients who developed symptoms such as hematemesis or melena underwent urgent endoscopic examination, and those who required a hemostatic procedure for a post-ESD ulcer were considered to have developed postoperative bleeding.

2.4. Evaluation Items. This study was performed as a prospective observation study. The primary endpoint was the decrease in Hb after ESD compared with before ESD. The secondary endpoints were (1) total procedure time, (2) incidence of injury or perforation of the muscle layer during ESD, (3) incidence of clip use during ESD, (4) incidence of postoperative fever of ≥38°C, (5) incidence of postoperative bleeding, and (6) percentage of patients who resumed eating on the day after ESD. The total procedure time was defined as the interval from the start of marking to completion of resection. Perforation was defined as the presence of free air or mediastinal emphysema on postoperative X-ray. Muscle layer injury was defined as exposure and partial tearing of the muscularis propria, without perforation, during ESD.

2.5. Histological Evaluation. Pathological examination of the resected specimen was performed using parallel 2 mm thick sections stained with hematoxylin and eosin in accordance with the Japanese classification of gastric carcinoma [6].

2.6. Statistical Analysis. Data were analyzed using the unpaired t-test, chi-squared test, or Mann-Whitney's U-test as appropriate. A P value <0.05 was considered significant.

3. Results

En bloc resection was achieved by ESD in all cases. Of the 89 patients, 50 were classified into group P and 39 into group R. Patients background in each group is summarized in Table 1. No significant intergroup difference was observed in mean age, gender, macroscopic findings, mean maximum diameter of tumor, or mean maximum diameter of specimen. The proportion of patients with lesions in region L was significantly higher in group P while that of patients with lesions in region U was significantly higher in group R ($P < 0.001$). In terms of invasion depth, the proportion of patients with submucosal cancer was significantly higher in group R than in group P ($P = 0.004$).

The mean decrease in Hb, the primary endpoint, was 0.27 g/dL in group P and 0.35 g/dL in group R, with no significant difference between groups. Perforation occurred in only 1 (1.1%) patient in group R, and therefore no significant difference was found in the incidence of perforation between groups. The total procedure time was significantly longer in group R (105.4 min) compared with group P (65.5 min) ($P = 0.002$). The incidence of postoperative bleeding and postoperative fever was not significantly different between groups, whereas the incidence of muscle layer injury was significantly higher in group R (25.6%) than in group P (8.0%) ($P = 0.02$). The incidence of clip use was also significantly higher in group R (48.7%) than in group P (20.0%) ($P = 0.004$).

The incidence of muscle layer injury and that of clip use were not significantly different depending on the location of lesions, but tended to be higher in regions U/M and L in group R, respectively. The procedure time for lesions in region U/M was longer in group R, but not significantly (Table 3). The procedure time for lesions in region L was significantly longer in group R (120.5 min) than in group P (58.0 min) (Table 4). All group P patients with lesions in region L (37/37) resumed eating on the day after the operation; the proportion of such patients was significantly lower in group R (81.8%) (see Table 2).

4. Discussion

Invasion depth is an important criterion for selecting an appropriate treatment in early gastric cancer. Thus, prior to ESD, the invasion depth of a lesion is determined by various modalities, such as EUS. However, the diagnostic accuracy of EUS is controversial; some studies clearly demonstrate the usefulness of EUS for determining invasion depth in early gastric cancer [7] while others show the opposite [8]. When performing EUS to determine invasion depth, we sometimes see hypoechoic areas in the submucosa that are likely to represent blood vessels. Then, during ESD, we encounter blood vessels that appear to correspond to the hypoechoic areas on EUS. Based on these experiences, we retrospectively analyzed EUS images and demonstrated their predictive value for determining the risk of intraoperative bleeding and safety of ESD [5]. However, since the presence or absence of blood vessels may not be precisely determined by retrospective analysis, we decided to conduct the current prospective study to eliminate possible bias. This prospective study used a new definition of blood vessels identified by EUS. In the retrospective studies, lesions with ≥10 vascular structures per field of view or with vessels of ≥500 μm in diameter were defined as "Rich" lesions and others as "Non-rich" lesions. In the present study, the definition of group P was changed to those with almost no hypoechoic areas likely to represent blood vessels in the submucosa or with 4 or fewer small vessels per field of view, and all other lesions not classified as group P were defined as group R. This change was based on our experience that higher reproducibility and credibility of diagnosis can be ensured by demonstrating the absence of blood vessels in the submucosa beneath the lesion.

The results of the present study revealed that the procedure time was significantly longer and that the incidence of clip use and muscle layer injury was significantly higher in group R than in group P, whereas no significant difference was seen in the decrease in Hb after ESD, the primary endpoint. A significant intergroup difference was observed in decrease in Hb in a previous retrospective study, but not in the present study. The most likely reason for this discrepancy is the operator's improved skill in performing ESD. In other words, in the previous study, the operator was less skillful, and bleeding was more likely to occur from vessel-rich lesions

Table 1: Clinical characteristics of two groups.

	Group P	Group R	*P* value
Number of patients	50	39	
Gender (male/female)	37/13	33/6	0.23
Mean age (years ± SD†)	67.0 ± 8.9	66.2 ± 10.7	0.90
Location (U/M/L)	3/10/37	16/12/11	<0.001
Gross type (elevated/others)	15/35	13/26	0.74
Mean maximum diameter of tumor (mm ± SD)	20.2 ± 12.6	25.4 ± 19.7	0.18
Mean maximum diameter of specimen (mm ± SD)	41.0 ± 13.5	47.6 ± 19.2	0.06
Tumor depth (mucosal cancer/submucosal cancer)	47/3	28/11	0.004

†SD: standard deviation.

Table 2: Overall results of this study.

	Group P (n = 50)	Group R (n = 39)	*P* value
Mean decrease in Hb† (g/dL ± SD‡)	0.26 ± 0.08	0.34 ± 0.10	0.56
Mean procedure time (min ± SD)	65.2 ± 39.9	105.4 ± 50.2	<0.001
Incidence of perforation, % (n)	0.0 (0)	2.6 (1)	0.25
Incidence of clip use, % (n)	20.0 (10)	48.7 (19)	0.004
Incidence of muscle injury, % (n)	8.0 (4)	25.6 (10)	0.023
Incidence of postoperative fever, % (n)	4.0 (2)	7.7 (3)	0.45
Incidence of postoperative bleeding, % (n)	4.0 (2)	7.7 (3)	0.45
Percentage of patients who resumed eating on the day after ESD, % (n)	84.0 (42)	82.1 (32)	0.81

†Hb: hemoglobin. ‡SD: standard deviation.

Table 3: Results for lesions in region U/M.

	Group P (n = 13)	Group R (n = 28)	*P* value
Mean decrease in Hb† (g/dL ± SD‡)	0.21 ± 0.66	0.37 ± 0.67	0.55
Mean procedure time (min ± SD)	87.5 ± 51.3	99.5 ± 46.1	0.28
Incidence of perforation, % (n)	0.0 (0)	3.6 (1)	0.49
Incidence of clip use, % (n)	38.5 (5)	57.1 (16)	0.27
Incidence of muscle injury, % (n)	15.4 (2)	28.6 (8)	0.36
Incidence of postoperative fever, % (n)	7.7 (1)	10.7 (3)	0.76
Incidence of postoperative bleeding, % (n)	0.0 (0)	3.6 (1)	0.49
Percentage of patients who resumed eating on the day after ESD, % (n)	76.9 (10)	82.1 (23)	0.81

†Hb: hemoglobin. ‡SD: standard deviation.

Table 4: Results for lesions in region L.

	Group P (n = 37)	Group R (n = 11)	*P* value
Mean decrease in Hb† (g/dL ± SD‡)	0.28 ± 0.57	0.27 ± 0.43	0.56
Mean procedure time (min ± SD)	58.0 ± 32.7	120.5 ± 58.8	0.002
Incidence of perforation, % (n)	0.0 (0)	0.0 (0)	
Incidence of clip use, % (n)	13.5 (5)	27.3 (3)	0.28
Incidence of muscle injury, % (n)	5.4 (2)	18.2 (2)	0.18
Incidence of postoperative fever, % (n)	2.7 (1)	0.0 (0)	0.58
Incidence of postoperative bleeding, % (n)	5.4 (2)	18.2 (2)	0.18
Percentage of patients who resumed eating on the day after ESD, % (n)	100 (37)	81.8 (9)	0.008

†Hb: hemoglobin. ‡SD: standard deviation.

during ESD, while in the present study, improved skills in hemostasis and prophylactic hemostasis might have led to a decreased intraoperative bleeding volume. At the same time, this might have led to an increased time required for hemostatic procedures and subsequent significant increases in total procedure time and frequency of clip use. Another possible reason for the absence of significant difference in decrease in Hb after ESD is the major influence of factors other than intraoperative bleeding, such as patient physique and fluid replacement volume.

Given that ESD for lesions in region L has been associated with a lower volume of intraoperative bleeding than lesions in other regions [9], it is important to examine bleeding volume during ESD for lesions in each region. In the present study, each parameter was analyzed separately for regions L and U/M. Although no significant difference was observed for some endpoints due to small sample size, the procedure time tended to be longer and the incidence of muscle layer injury and clip use during ESD tended to be higher in group R than in group P, regardless of lesion location. In particular, the procedure time for lesions in region L was significantly longer in group R (120.5 min) than in group P (58.0 min). This finding indicates that ESD for lesions with many blood vessels in the submucosa by EUS is more likely to cause muscle layer injury and clip use, as well as requiring a longer procedure time. This is probably because for vessel-rich lesions, a longer time is required for hemostatic procedures, such as clip hemostasis, and because the incidence of complications, such as muscle layer injury, is increased due to reduced visibility of the surgical field by bleeding.

Ideally, ESD safety should be assessed on the basis of bleeding volume and incidence of perforation, and bleeding volume should be based on the actual amount of bleeding. However, since it is difficult to measure the actual amount of bleeding during ESD, the decrease in Hb was used as a surrogate measure for safety. In addition, the fact that perforation occurred in only 1 patient in group R demonstrates the safety of the procedure. Thus, other parameters, such as the incidence of muscle layer injury, incidence of clip use, and the proportion of patients who resumed eating on the day after ESD were also used as surrogate measures for safety. Overall, the incidence of muscle layer injury and clip use was significantly higher in group R than in group P. These parameters tended to be higher in group R regardless of the location of lesions, suggesting that the safety of ESD can be predicted by using EUS to some extent.

When performing ESD on lesions with abundant blood vessels in the submucosa, the operator should (1) carefully identify blood vessels under clear surgical field, (2) perform prophylactic hemostasis after identifying blood vessels, and (3) try to dissect the lesion at a deep layer of the submucosa [10]. In addition to these technical issues, EUS also provides important information for determining the treatment schedule and for selecting an appropriate operator. Specifically, when a lesion was found to be rich in blood vessels by EUS, a more skilled operator should perform the procedure in good time. For lesions expected to require a longer procedure time, the use of general anesthesia should also be considered.

There are several limitations to the present study. The first is that a single examiner evaluated EUS findings; multiple examiners may improve diagnostic objectivity and reliability. Second, the variability in skill levels of operators may also significantly affect the outcome of ESD [11]. We believe that the consistency of outcome was ensured in the present study, as ESD was performed by or under the supervision of a skilled endoscopist who had experienced more than 100 cases of gastric ESD. The third limitation is that frequency of submucosal cancer was significantly different. There is a possibility that ESD of submucosal cancer may be more difficult and danger than that of mucosal cancer. The last limitation is that we were not completely sure that the hypoechoic areas identified by EUS were truly blood vessels. It would have been ideal if the miniature probe had included a Doppler function. However, the miniature probe was our only option, as dedicated EUS systems with a Doppler function are unlikely to scan target lesions accurately because target lesions of this study were small. Development of more sophisticated instruments is another issue that needs to be addressed.

5. Conclusions

In conclusion, identifying blood vessels in the submucosa by EUS does not help in predicting the risk of worsening of anemia or occurrence of perforation, but may be helpful for predicting procedure time, risk of muscle layer injury, and use of clips. The preoperative use of EUS was effective for predicting the safety of ESD and procedure time and is thus considered useful for determining ESD treatment strategy.

Conflict of Interests

The authors declare that they have no conflict of interests in this research.

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Methodology Report

Therapeutic Endoscopic Ultrasonography: Intratumoral Injection for Pancreatic Adenocarcinoma

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Pancreatic adenocarcinoma is an aggressive disease that has poor outcomes despite maximal traditional therapies. Thus, treatment of this cancer demands innovative strategies to be used in addition to standing therapies in order to provide new avenues of care. Here, we describe the technique of using endoscopic ultrasound in order to directly inject both novel and conventional therapies into pancreatic tumors. We detail the rationale behind this strategy and the many benefits it provides. We then describe our technique in detail, including our experience injecting the AdV-tk adenoviral vector to create an in situ vaccine effect.

1. Rationale

Pancreatic adenocarcinoma is the 11th most common cause of cancer, but the 5th leading cause of cancer deaths [1]. The vast majority of patients present with cancer untreatable by surgical excision owing to locally advanced or metastatic disease; even those who are able to undergo resection almost always succumb to this disease with 94% dying within 5 years [1]. Thus, novel treatment methods are desperately needed in order to improve outcomes. Here, we present one such technique, the injection of AdV-tk into the pancreatic tumor using endoscopic ultrasonography (EUS) prior to resection. AdV-tk is a replication defective adenoviral vector expressing the Herpes simplex virus thymidine kinase gene that renders tumor cells susceptible to the cytotoxic effects of antiherpetic prodrugs, such as valacyclovir, and more importantly induces a potent local and systemic antitumor immune response [2].

Besides the novelty of this therapy, EUS injection of pancreatic tumors provides an advantage over other treatment modalities in that it can overcome the anatomical constraints inherent to gaining access to the pancreatic parenchyma. Located in the retroperitoneum and adjacent to large mesenteric vessels, the pancreas is not easily accessed by other minimally invasive techniques such as computed tomography (CT) guided injection. Other techniques, such as laparoscopic or open surgical techniques, are much more invasive, bringing with them potential morbidity and longer hospital stays. An additional theoretical advantage of direct injection over intravenous or oral administration of medications is that pancreatic adenocarcinoma is relatively hypovascular and creates an extensive desmoplastic reaction [3], thus impeding the access of traditional chemotherapy to tumor cells. Tissue-specific targeting of agents, such as viral vectors, can be accomplished easily by direct tumoral injection without having to overcome pancreatic tumor hypovascularization or evade systemic antiviral immunity to get the vector to its target tissue.

Several recent studies have shown initial success with injection of various medications and therapies into pancreatic tumors using this technique. Such examples include the allogenic mixed lymphocyte culture cytoimplant [4], the replication-selective adenovirus ONYX-015 [5],

an adenovector encoding tumor necrosis factor TNFerade [6], the traditional systemic chemotherapeutic agent gemicitabine [7], and tumor antigen loaded dendritic cells [8]. All have shown some initial degree of success, showing this technique to be of practical therapeutic value. Herein we describe our institution's method of performing intratumoral injection into pancreatic tumors.

2. Procedural Details

As part of a phase I clinical trial (NCT00638612), a replication-defective adenoviral vector (AdV-tk, Advantagene, Inc, Auburndale, MA) was injected prior to surgery for resectable (Arm A) or prior to and during chemoradiation for locally advanced (Arm B) pancreatic cancer. The results of this trial will be reported separately. After cytologic confirmation of pancreatic cancer, tumors were injected with AdV-tk under EUS guidance.

The process of intratumoral injections under the guidance of EUS, when performed by an experienced endosonographer, is fairly straightforward. The required equipment includes a curvilinear echoendoscope, an endoscopic ultrasound processor with Doppler technology, and a 22-gauge fine needle aspiration (FNA) needle. The procedure is performed in the endoscopy unit and typically does not require fluoroscopy. If initial sampling is not required, the procedure time is approximately 15–30 minutes.

Most patients tolerate standard conscious sedation utilizing a narcotic, such as fentanyl or meperidine, and a benzodiazepine, typically midazolam. However, in our experience, patients who are young, have a history of chronic narcotic or alcohol use, or have previous anxiolytics usage require higher levels of sedation to maintain comfort during the procedure. Thus, monitored anesthesia care or general anesthesia may also be required. Especially in cases of conscious sedation, a topical anesthetic is often utilized, as the intubation of the esophagus with the larger caliber echoendoscope can be uncomfortable. Since precise needle placement is required to insure good distribution of vector in the tumor, adequate anesthesia is crucial.

For initial identification and characterization of the pancreatic mass lesion, either a radial or curvilinear echoendoscope can be utilized. Both echoendoscopes can be used for identification, characterization, measurements, and evaluation for surrounding vasculature. However, these are the limitations of the radial echoendoscope. Sampling and fine-needle injection requires the use of the curvilinear echoendoscope.

EUS guided fine needle injection is performed in a similar fashion to standard EUS with FNA. The esophagus is carefully intubated and the echoendoscope is passed into the stomach and duodenum where the pancreatic examination occurs. Echoendoscope position in the stomach allows for visualization of the pancreas genu, body, and tail. It is from this location that the celiac axis can be evaluated for lymphadenopathy and the left liver lobe can be evaluated for evidence of metastatic lesions. Echoendoscope position in the duodenum bulb allows for visualization of the pancreas head and genu, as well as the extrahepatic biliary tree. Finally, echoendoscope position in the second portion in the duodenum allows for visualization of the pancreas head, uncinate process, and distal common bile duct, as well as endoscopic visualization of the major and minor papilla.

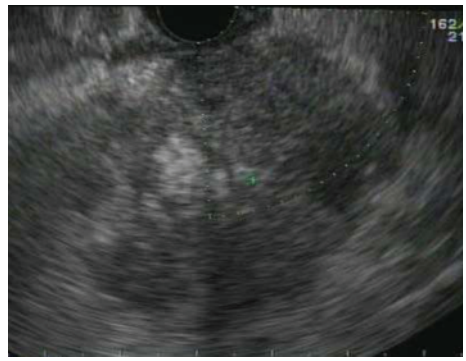

Figure 1: Endoscopic ultrasound image of a tumor in the head of the pancreas prior to intratumoral injection.

Once the mass has been identified (Figure 1), it is important to obtain an accurate measurement of the largest plane. In our trial, this measurement was utilized to estimate tumor volume in order to calculate volume of AdV-tk for injection. Based on previous preclinical data and treatment with previous tumors, we chose to inject approximately 20–40% of the total tumor volume. AdV-tk was administered by dividing the tumor into up to 4 quadrants and then injecting 1 mL into each quadrant. For tumors with estimated volumes greater than 20 cm^3, an accessible region where the sum of the major and minor axis was approximately 6 cm was chosen and this area was divided into 4 quadrants for injection. Use of the installed Doppler technology also assures there are no arterial or venous structures that may interfere with the needle passage into the tumor. If such interference is present, the scope may need to be repositioned to obtain a similar view from another angle or the procedure may need to be aborted. Once the tumor size and subsequent injection volume has been calculated, the appropriate volume is drawn into a syringe. The 22-gauge FNA needle is primed with approximately 0.5 cc of injection solution and passed into the working channel of the echoendoscope. Under ultrasound guidance, the needle is passed into the tumor (Figure 2). In order to distribute vector throughout the tumor, a total of four passes were used in a fanning technique along the single largest plane of the tumor with 1/4 volume injected at each pass. The needle tip was first passed into the back of the tumor. As the needle was slowly withdrawn, 1/4 of the solution is injected into the tunnel created by the needle. Patients were monitored in the recovery suite as per standard protocol and then discharged to home.

The EUS and needle passage procedures tend to be very safe with a less than 1% risk of immediate and delayed complication. These include perforation, bleeding, and aspiration, in addition to standard risk associated with sedations, such as hypoxia, arrhythmia, and hypotension. The risk of bleeding is minimal due to the use of Doppler technology, as well

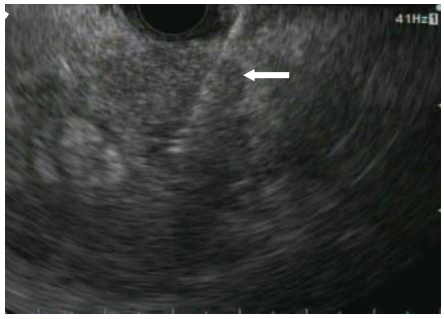

Figure 2: The same pancreatic tumor from Figure 1 being injected with intratumoral therapy. The white arrow indicates the hyperechoic shadow of the fine needle entering the tumor.

as the small 22G needle caliber, and our experience has yet to produce bleeding serious enough to require transfusion. The risk of infectious complications related to needle passage is minimal, and prophylactic antibiotics are not typically recommended. Risks related to the injection solution ultimately depend on the solution or chemotherapeutic agent and are usually related to inflammatory complication, such as pancreatitis. No procedure-related complications occurred in this trial with AdV-tk (to be reported separately).

3. Conclusions

Pancreatic cancer is a highly lethal form of cancer, and standard therapies provide minimal long-term benefit. Thus, novel strategies are vitally important in order to improve outcomes. Here we have described intratumoral injection of pancreatic masses via endoscopic techniques. This technique provides the ability to treat the pancreas in a direct and relatively minimally invasive manner, with a very low incidence of procedural-related complications. It bypasses the poor parenchymal penetration of systemic chemotherapy and the morbidities inherent to laparoscopic or open surgical procedures, as well as giving the ability to administer therapies that would be prohibitive to give systemically. Giving innovative treatments in such a specific and novel manner could provide hope in treating this otherwise overwhelming disease.

Conflict of Interests

The authors L. K. Aguilar and E. Aguilar-Cordova are employees of Advantagene, Inc., the makers of AdV-tk.

Acknowledgment

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Review Article

Outcomes of Endoscopic-Ultrasound-Guided Cholangiopancreatography: A Literature Review

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Endoscopic retrograde cholangiopancreatography (ERCP) can fail in 3–10% of the cases even in experienced hands. Although percutaneous transhepatic cholangiography (PTC) and surgery are the traditional alternatives, there are morbidity and mortality associated with both. In this paper, we have discussed the efficacy and safety of endoscopic-ultrasound-guided cholangiopancreatography (EUS-CP) in decompression of biliary and pancreatic ducts. The overall technical and clinical success rates are around 90% for biliary and 70% for pancreatic duct drainage. The overall EUS-CP complication rate is around 15%. EUS-CP is, however, a technically challenging procedure and should be performed by an experienced endoscopist skilled in both EUS and ERCP. Same session EUS-CP as failed initial ERCP is practical and may result in avoidance of additional procedures. With increasing availability of endoscopists trained in both ERCP and EUS, the role of EUS-CP is likely to grow in clinical practice.

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard procedure for decompression of biliary and pancreatic ducts. Although the success rate is very high, it can fail in 3–10% of cases even by an experienced endoscopist [1, 2]. Percutaneous transhepatic cholangiography (PTC) [3, 4] and surgery [5, 6] have been the traditional alternatives. However, there is morbidity and mortality associated with both. PTC has a complication rate of up to 30% [4]. Although surgery offers long-term patency, it is also associated with increased morbidity as well as mortality [6]. Since first reported by Wiersema et al. [7], endoscopic ultrasound guided cholangiopancreatography (EUS-CP) is now increasingly being employed at expert centers as an alternative to surgery or PTC.

An online pubmed search was conducted to review the published case reports and series on EUS-CP. The key words used were endoscopic-ultrasound-guided cholangio-pancreatography, endoscopic-ultrasound-guided cholangiography, endoscopic-ultrasound-guided pancreatography, failed endoscopic retrograde cholangio-pancreatography, endoscopic-ultrasound-guided therapeutic interventions, endoscopic-ultrasound-guided biliary drainage, and endoscopic-ultrasound-guided pancreatic drainage. All studies and case series involving at least 5 patients were included for the present review. The purpose of this paper was to analyze the published data on EUS-CP and assess its overall efficacy and safety in decompression of biliary and pancreatic ducts. First the indications and techniques of EUS-CP will be discussed, followed by efficacy, safety, and role in clinical practice.

2. Indications of EUS-CP

The first case series of EUS-guided cholangiogram was reported by Wiersema et al. in 1996 [7]. Biliary drainage has been performed for both malignant as well as benign indications. The reported malignant biliary indications were pancreatic cancer, metastatic cancer, cholangiocarcinoma, gallbladder cancer, ampullary cancer, and duodenal cancer. Following were the benign biliary indications: bile leak, benign strictures (PSC or iatrogenic), choledocholithiasis, and papillary stenosis. The reported pancreatic indications were pancreas divisum, benign pancreatic duct strictures (chronic pancreatitis, postsevere acute pancreatitis), postsurgical (Whipple) pancreaticojejunostomy stricture, pancreatic

stone with obstruction, pancreatic leak ± fistula, and papillary stenosis. The pancreatic duct was dilated (>4 mm in diameter) in most of the studies. However, the nondilated duct was also accessed in recent studies [8]. Initially, EUS-CP was performed on a subsequent day after failed initial ERCP. However, there was a trend towards same day/session EUS-CP with recent studies [9].

In general, EUS-CP can be considered in patients with native papilla after failed initial ERCP or inaccessible papilla due to either obstructed gastrointestinal tract lumen or surgically altered anatomy. The procedure is especially helpful in altered anatomy cases after failed initial ERCP like post-Whipple, Billroth II gastrojejunostomy, hepaticojejunostomy, gastric bypass, and duodenal switch. The bile duct can be accessed by either an extrahepatic or intrahepatic approach. The decision between the extrahepatic and intrahepatic approach is based on the following factors: presence of intrahepatic dilation, presence of gastric outlet obstruction, and ability to reach the second part of duodenum.

3. Technique

3.1. Patient Selection and Preparation. All such cases should be performed in a tertiary care center by an experienced endoscopist who is proficient in both ERCP and EUS. Repeat ERCP should be attempted on patients referred to the tertiary care center before resorting to EUS-CP. The failed ERCP was defined as failed deep access to bile or pancreatic duct despite the use of advanced cannulation techniques including precut sphincterotomy [10]. The procedure should be done in a dedicated interventional endoscopy room equipped with both fluoroscopy and EUS capability. An informed consent explaining the risk and benefits of EUS-CP versus PTC and surgery needs to be explained to the patient. Prophylactic antibiotics should be administered. Since EUS-CP is a longer procedure, anesthesia assistance should be sought. In the published data, all such cases were done either under intravenous sedation or general anesthesia. It is also important to have back up of both surgical and interventional radiology services.

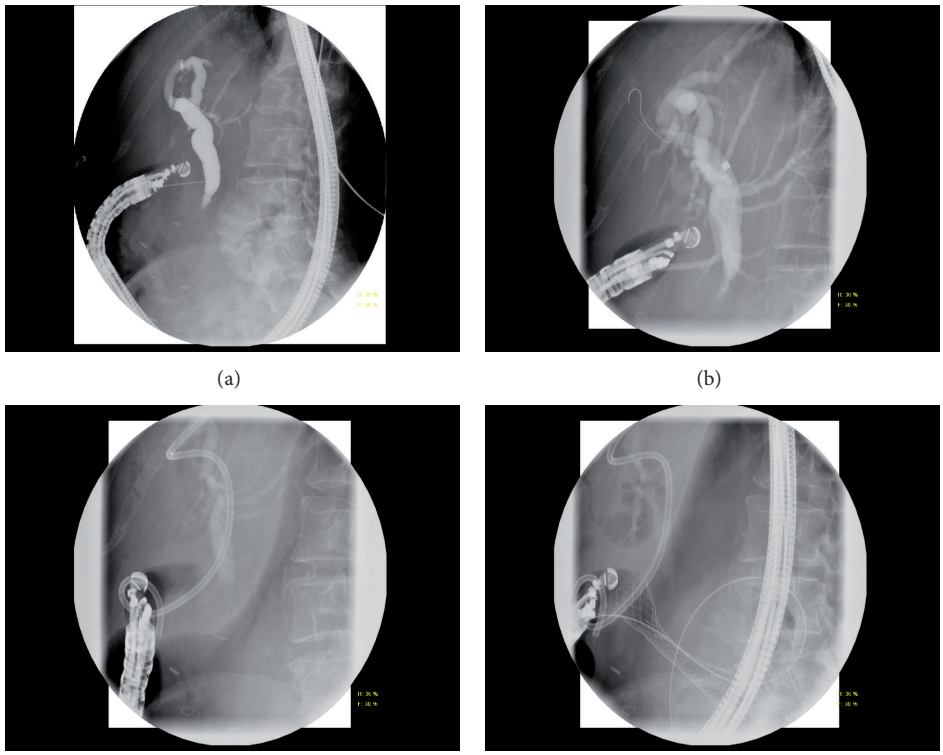
Table 1: Instruments and accessories needed for EUS-CP.

Purpose	Devices
Echoendoscopes	Preferably therapeutic (>3 mm working channel): (i) GF-UCT140 (Olympus America Inc, Center valley, PA, USA): 3.7 mm (ii) EG-3870UTK (Pentax of America Inc, Montvale, NJ, USA): 3.8 mm
Puncture devices	(i) 19- or 22-gauge fine needle aspiration needles (ii) 19-gauge fistulotome (iii) 5 Fr needle knife
Guidewires	Long (450 or 480 cms): 0.018 inch, 0.021 inch, 0.025 inch, or 0.035 inch
Dilation devices	Needed for transluminal and antegrade techniques: (i) 6–10 Fr bougie (SBDC; (Cook Medical Inc, Bloomington, IN, USA) (ii) 4–6 mm dilation balloon (Boston Scientific, Natick, MA, USA) (iii) ERCP 3.9–4.9 Fr sphincterotome (Boston Scientific, Natick, MA, USA) (iv) 5.5 Fr needle knife cautery (Boston Scientific, Natick, MA, USA)* (v) 6–8.5 Fr cystotome (EndoFlex, Voerde, Germany).
Stent types (as needed)	Biliary: Plastic (6–10 Fr; straight, single, or double pigtail) Metal (8–10 mm; uncovered, partially fully covered)# Pancreatic: Plastic (5–10 Fr; straight, single, or double pigtail)

EUS-CP: endoscopic-ultrasound-guided cholangiopancreatography. *Needle knife cautery is associated with increased risk of postprocedure complications. #Either plastic or covered (partially/fully) metal stents are used for transluminal stenting.

3.2. Instruments and Accessories Selection. The procedure is done using a curvilinear array echoendoscope, preferably therapeutic with working channel of over 3 mm. The following therapeutic echoendoscopes are commonly used in the United States: GF-UCT140 (Olympus America Inc, Center valley, PA, USA) and EG-3870UTK (Pentax of America Inc, Montvale, NJ, USA) with working channels of 3.7 and 3.8 mm, respectively. These allow placement of stents up to 10 Fr (French) in diameter (Table 1).

A 19- or 22-gauge FNA (fine needle aspiration) needle is used for initial duct puncture. A 5 Fr needle knife or 19-gauge fistulotome can also be used for duct puncture. One of the following long (450 or 480 cms) guidewires are then passed into the duct: 0.018 inch, 0.021 inch, 0.025 inch, or 0.035 inch. The 19-gauge FNA needle allows passage of all guidewires, while 22-gauge one allows only 0.018 and 0.021 inch guidewires. It is technically easier to deploy a subsequent stent over a wider diameter guidewire. However, the maneuverability is relatively better with smaller diameter guidewire. The following accessories are used for dilation of newly created fistula in selected cases (especially in transluminal and antegrade stenting): 6–10 Fr bougie (SBDC; (Cook Medical Inc, Bloomington, IN, USA)), 4–6 mm dilation balloon (Boston Scientific, Natick, MA, USA), ERCP 3.9-4.9 Fr sphincterotome (Boston Scientific, Natick, MA, USA), 5.5 Fr Needle Knife cautery (Boston Scientific, Natick, MA, USA), or 6–8.5 Fr Cystotome (EndoFlex, Voerde, Germany). The use of needle knife cautery should be avoided if possible as it was shown to be associated with postprocedure complications in a multivariate analysis by Park do et al. [11]. The rest of the accessories (including stone retrieval balloon and stents) are the same as those for conventional ERCP.



(a) (b) (c) (d)

Figure 1: Transluminal stenting in a patient with metastatic breast cancer with extrahepatic biliary and duodenal obstruction. (a) Initial Cholangiogram using 22-gauge needle via transduodenal approach. (b) Choledochoduodenostomy tract dilation with 7–10 Fr dilating catheter. (c) Placement of a 10 Fr × 6 cm double-pigtail plastic stent. (d) Placement of a 22 × 60 mm uncovered enteral stent.

3.3. Technical Methods

3.3.1. Biliary EUS-CP. As mentioned before, the bile duct can be accessed by either extrahepatic (transenteric-transcholedochal) or intrahepatic (transgastric-transhepatic) approach. According Maranki et al. [12], the extrahepatic approach is less challenging and should be preferred when second part of duodenum is accessible.

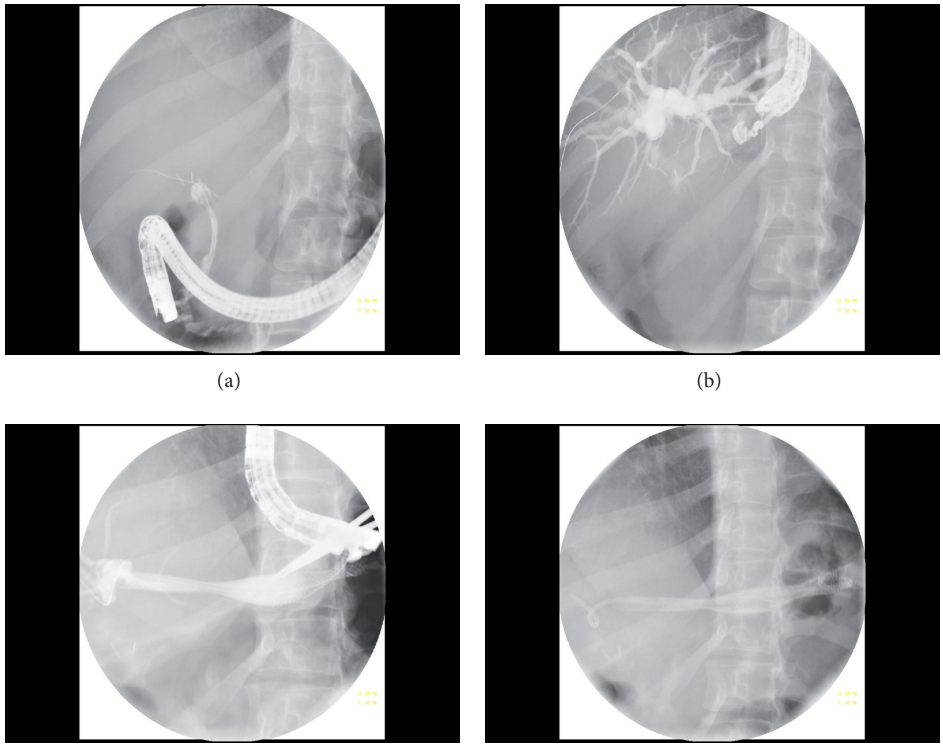
3.3.2. Extrahepatic Biliary Tree. The echoendoscope is positioned either in the duodenal bulb or distal antrum for extrahepatic approach. Color-Doppler US is used to confirm lack of vascular structures. One of the EUS-FNA needles (as mentioned previously) is used to puncture the extrahepatic bile duct. Upon removal of stylet, the fluid is aspirated to confirm entrance of needle tip inside the duct. Contrast is injected under fluoroscopic guidance to obtain a ductogram. A long (450 or 480 cms) guidewire is passed into the bile duct. EUS-CP is then completed by one of the following techniques: ductography, rendezvous with transpapillary stenting, antegrade tract dilation/stenting, and transluminal tract dilation/stenting.

(1) Ductography: after EUS-FNA needle has been passed into the bile duct, contrast is injected. The opacified duct is then used as a guide for retrograde cannulation by a duodenoscope. It may facilitate cannulation by causing visible ampullary bulge in cases with flat intradiverticular papilla [13].

(2) Rendezvous: the EUS-FNA needle tip is oriented in a caudal direction, and attempts are made in passing the guidewire across the papilla. If successful, the echoendoscope is removed leaving the guidewire in place, with the upper end securely held near patient's mouth. A duodenoscope is passed beside the guidewire into the second part of duodenum. The guidewire is caught with a rat tooth forceps or snare and pulled through the operating channel of the duodenoscope. The rest of the procedure is completed in a retrograde ERCP fashion. Instead of catching the guidewire, biliary cannulation can also be done alongside the guidewire by passing another guidewire or sphincterotome next to it.

(3) Antegrade: if transpapillary guidewire passage is unsuccessful or papilla is not accessible, antegrade approach can be attempted. The fistula tract is first dilated (with one or a combination of previously mentioned dilation accessories), followed by antegrade placement of stent across the stricture (and possibly transpapillary, if possible). Antegrade clearance of stones can also be achieved in selected cases.

(4) Transluminal: the EUS-FNA needle tip is oriented in upward direction, and the guidewire is passed in an upward direction of the puncture. The fistula tract is dilated (with one or a combination of the previously mentioned dilation accessories), followed by transenteric-transcholedochal



(a) (b) (c) (d)

Figure 2: Transluminal stenting in a patient with common hepatic duct transection post-cholecystectomy. (a) Complete iatrogenic CHD obstruction at the site of cholecystectomy clips. (b) Initial cholangiogram with a 19-gauge needle via transgastric approach with passage of 0.025″ guidewire. (c) Placement of two 10 × 80 mm partially covered SEMS. (d) Placement of a 7 Fr × 12 cm double-pigtail plastic stent inside metal stents to prevent outmigration.

placement of stent(s). Unlike pancreatic pseudocyst drainage, it is important to focus on EUS and fluoroscopic views rather than endoscopic view during tract dilation and stenting. Only for the final part of stent placement, the echoendoscope is withdrawn to get endoscopic view. For metal stents, sufficient (about 2 cms) intraluminal length is needed to compensate for foreshortening postdeployment. It is our expert opinion that transluminal stenting is more technically challenging than other EUS-CP techniques. However, in cases where the guidewire does not cross papilla and antegrade stenting is not possible due to acute angulation, transluminal stenting is the only possibility (Figure 1).

3.3.3. Intrahepatic Biliary Tree. The echoendoscope is positioned in the cardia or lesser curvature of stomach for intrahepatic (left liver) approach. The intrahepatic tree can also be accessed through distal esophagus [14]. One of the EUS-FNA needles (as mentioned previously) is used to puncture the left intrahepatic biliary tree. The rest of the procedure is similar to that described for extrahepatic approach. During transluminal technique, attempts should be made to advance the guidewire either into the right intrahepatic ducts (if possible) or to make few intrahepatic loops in order to provide stability for subsequent tract dilation and stenting (Figure 2).

3.3.4. Pancreatic EUS-CP. The echoendoscope is positioned either in the gastric body or duodenal bulb [13, 15]. The EUS-CP techniques are similar to those of biliary tree. During ductography, 1% methylene blue can be mixed in 1 : 4 ratio with full strength contrast. Methylene blue acts as guide to the location of pancreatic duct orifice in the small intestine. The guidewire is advanced antegrade towards the papilla for rendezvous or antegrade techniques. If not possible, the guidewire is advanced retrograde and looped in the pancreatic duct for transluminal approach (Figure 3).

4. Efficacy and Safety of EUS-CP

4.1. Definitions. All the published case reports and series were reviewed, and studies involving at least 5 patients were included for the present review. The data was separated into extrahepatic biliary, intrahepatic biliary, and pancreatic duct drainage. The technical success was defined as the decompression of the pancreatobiliary tree with placement of a stent and/or stone extraction [13]. The clinical success was defined as resolution of jaundice, pain relief [13], or major improvement of symptoms (like resolution of pancreatic fistula) [16]. Kahaleh et al. [17] measured mean pancreatic duct size, pain scores, and weight before and after the procedure as clinical success parameters.

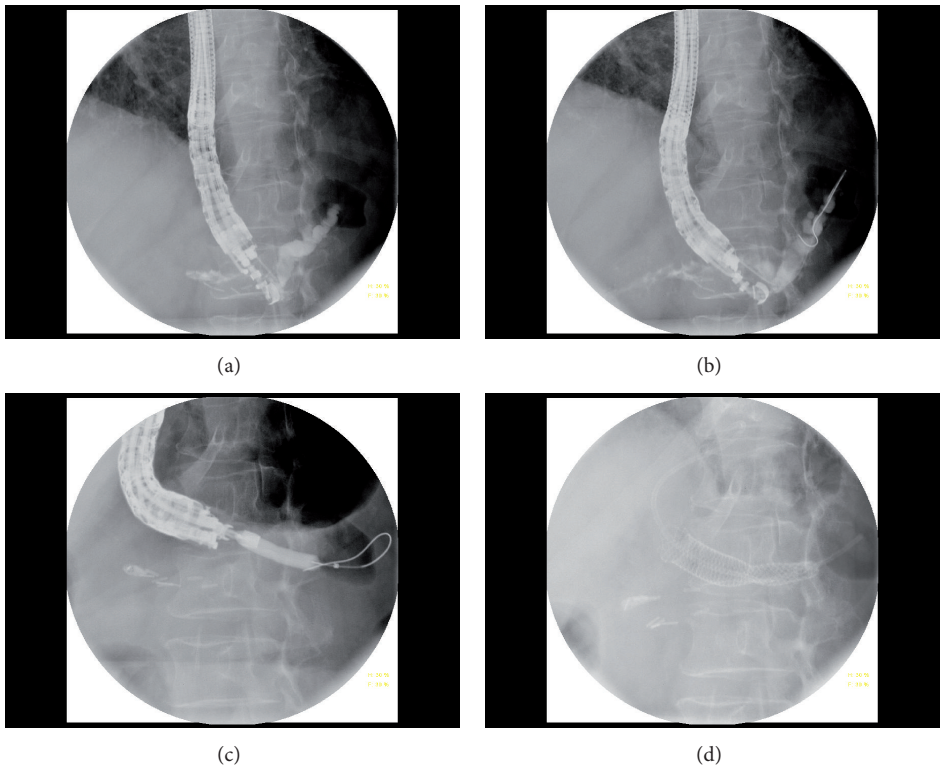


Figure 3: Transluminal stenting in a patient s/p central pancreatectomy with pancreaticogastrostomy obstruction. (a) Initial pancreatogram. (b) Passage of a 0.025″ guidewire. (c) Pancreaticogastrostomy tract dilation with 6 mm dilation balloon. (d) Placement of a 8 × 60 mm fully covered SEMS followed by 7 Fr × 7 cm single-pigtail plastic stents placement.

4.2. Extrahepatic Biliary Tree. Table 2 presents the published data on extrahepatic biliary drainage. There are 21 studies involving 360 on extrahepatic biliary drainage via EUS-CP. The first case series of EUS-guided cholangiogram was reported by Wiersema et al. in 1996 [7]. Later, Giovannini et al. [18] reported the first case of transluminal stenting, followed by common bile duct stone removal by Püspök et al. [19]. Plastic stents were first placed transluminally to create a fistula, followed by stone removal in 3 weeks. Overall, the procedure was technically successful in 325/360 cases (90%; range 70–100%).The overall clinical success (if reported) was achieved in 254/258 (98%; range 60–100%). The overall complication rate was 51/360 cases (14%, range 0–47%). These included pneumoperitoneum, bile leak/peritonitis, hemobilia, bacteremia, pancreatitis, abdominal pain, and cardiopulmonary failure due to fluid overload [13].

4.3. Intrahepatic Biliary Tree. The published data for intrahepatic biliary drainage is listed in Table 3. There are 8 published studies involving 123 cases. The overall technical and clinical success rates were 109/23 (88.6%, range 44–100%) and 103/109 (94.5%, range 83–100%), respectively. The overall complication rate was 19/123 (15%, range 7.7–36%). These included pneumoperitoneum, cholangitis, bile leak, minor bleed, stent dysfunction (occlusion/migration), aspiration pneumonia, and even death from bile peritonitis due to stent migration in one patient [8].

The procedure timing was not reported by most of the studies. Kim et al. [20] reported a median procedure time of 19.5 minutes (range 14–35) for transluminal approach. In a case series of 6 patients with gastric bypass, the procedure time ranged from 66–78 minutes for antegrade and 100–144 minutes for rendezvous approaches. The stent types placed were both plastic (6–10 Fr, straight, single or double pigtail), and metal (8–10 mm, uncovered, partially fully covered). Either plastic or covered (partially/fully) metal stents were placed transluminally. Stent dysfunction in the form of either occlusion or migration was encountered more frequently with transluminal approach. Stent dysfunction was noted in 16 out of 55 patients (29%) in the study by Park do et al. [11], with reintervention successful in all patients with fully covered metal and in half with plastic stents. The mean stent patency was 133 days (range 18–433).

4.4. Pancreatic Duct. Table 4 shows the published data on drainage on pancreatic duct via EUS-CP. There are 6 published studies involving 115 cases. Wiersema et al. [7] reported the first case on pancreatic ductography in 1996, followed by injection of methylene blue-contrast solution by DeWitt et al. in 2004 [21] to localize minor papilla in a patient with pancreas divisum. The largest pancreatic case series of 36 patients was reported by Tessier et al. in 2007 [22]. The overall technical and clinical success (if reported) rates were 90/115 (78%, range 48–91.7%) and 51/68 (75%,

Table 2: Published EUS-CP series on Extrahepatic biliary tree drainage (involving ≥5 patients).

Year	Author	*N*	Indication	Initial ERCP	Techniques	Technical success	Clinical success	Complication
1996	Wiersema et al. [7]	10	B	Both	D	7/10 (70%)	n/a	1/10 (10%)
2005	Püspök et al. [19]	5	M	Sb	T	5/5 (100%)	5/5 (100%)	No
2006	Kahaleh et al. [28]	10	Both	Sb	8 R; 2 T	9/10 (90%)	9/10 (90%)	3/9 (33%)
2008	Yamao et al. [29]	5	M	Sb	T	5/5 (100%)	5/5 (100%)	1/5 (20%)
2008	Tarantino et al. [30]	9	Both	Sb	4 T; 4 R; 1 D	9/9 (100%)	9/9 (100%)	No
2009	Maranki et al. [12]	14	Both	Sb (mostly)	8 R; 4 T	12/14 (86%)	12/12 (100%)	3/14 (21%)
2009	Brauer et al. [13]	12	Both	Sb	4 R; 4 T; 3 D	11/12 (92%)	11/11 (100%)	2/12 (16.7%)
2009	Horaguchi et al. [14]	8	M	Sb	T	8/8 (100%)	8/8 (100%)	1/8 (12.5%)
2010	Kim et al. [10]	15	Both	Sm (mostly)	R	12/15 (80%)	11/12 (91.7%)	2/15 (13.3%)
2010	Iwamuro et al. [27]	7	M	Sb	T	7/7 (100%)	7/7 (100%)	2/7 (28%)
2011	Siddiqui et al. [31]	8	M	Sb	T	8/8 (100%)	8/8 (100%)	2/8 (25%)
2011	Komaki et al. [32]	15	M	n/a	14 T; 1 R	15/15 (100%)	15/15 (100%)	7/15 (47%)
2011	Hara et al. [33]	18	M	n/a	T	17/18 (94%)	17/17 (100%)	3/18 (17%)
2011	Park do et al. [11]	26	Both	Sm	T	24/26 (92%)	22/24 (92%)	5/26 (19%)
2011	Ramírez-Luna et al. [34]	9	M	Sb	T	8/9 (89%)	8/8 (100%)	1/9 (11%)
2011	Fabbri et al. [35]	16	M	Sm	13 T; 3 R	12/16 (75%)	12/12 (100%)	1/16 (6.25%)
2012	Dhir et al. [26]	58	Both	Sm	R	57/58 (98.3%)	57/57 (100%)	2/58 (3.4%)
2012	Iwashita et al. [36]	31	Both	Sm	R	25/31 (81%)	25/25 (100%)	4//31 (13%)
2012	Kim et al. [20]	9	M	Sb	T	9/9 (100%)	9/9 (100%)	3/9 (33%)
2012	Shah* et al. [9]	70	Both	Sm	46 R; 20 A (or T); 2 D	60/70 (85.7%)	n/a	6/70 (8.5%)
2012	Maluf-Filho et al. [37]	5	M	Sm	T	5/5 (100%)	3/5 (60%)	2/5 (40%)
	Total	360			178 R; 141 T; 20 A; 16 D	325/360 (90%)	254/258 (98%)	51/360 (14%)

EUS-CP: endoscopic-ultrasound-guided cholangiopancreatography, *N*: number of patients, B: benign, M: malignant, Sb: subsequent day, Sm: same day/session, D: ductography, T: transluminal, R: rendezvous, A: antegrade, n/a: not applicable/mentioned. *The biliary tree was accessed at extra- as well as intrahepatic levels. However, the exact puncture site was not specified in the paper.

Table 3: Published EUS-CP series on intrahepatic (left) biliary tree drainage (involving ≥5 patients).

Year	Author	*N*	Indication	Initial ERCP	Techniques	Technical success	Clinical Success	Complication
2006	Kahaleh et al. [28]	13	Both	Sb	11 R*; 1 T	12/13 (92.3%)	12/12 (100%)	1/13 (7.7%)
2007	Bories et al. [38]	11	Both	Sb	T	10/11 (91%)	10/10 (100%)	4/11 (36%)
2007	Will et al. [7]	10#	Both	Sb	T	9/10 (90%)	8/9 (88.9%)	1/8 (12.5%)
2009	Maranki et al. [12]	35	Both	Sb (mostly)	24 R; 3 T; 2 A	29/35 (83%)	29/35 (83%)	5/35 (14.3%)
2009	Horaguchi et al. [14]	7	M	Sb	T	7/7 (100%)	6/7 (86%)	1/7 (14.3%)
2011	Park do et al. [11]	31	Both	Sm	T	31/31 (100%)	27/31 (87%)	5/31 (16%)
2011	Weilert et al. [39]	6	B	n/a	4 A; 2 R	6/6 (100%)	6/6 (100%)	1/6 (17%)
2012	Iwashita et al. [36]	9	Both	Sm	R	4/9 (44%)	4/4 (100%)	1/9 (11%)
	Total	123			63 T; 46 R; 6 A	109/123 (88.6%)	103/109 (94.5%)	19/123 (15%)

EUS-CP: endoscopic-ultrasound-guided cholangiopancreatography, *N*: number of patients, B: benign, M: malignant, Sb: subsequent day, Sm: same day/session, D: ductography, T: transluminal, R: rendezvous, A: antegrade, n/a: not applicable/mentioned. *In few cases stents might have been placed antegrade. #10 interventions in 8 patients.

range 50–100%), respectively. The overall complication rates were 19/115 (16.5%, range 10–42.9%). These included pancreatitis (mild), abdominal pain, bleed, perforation, fever, severe pancreatitis, and even peripancreatic abscess [8]. Although there was no procedure-related mortality, severe complications (as previously mentioned) were noted with pancreatic drainage via EUS-CP. It is believed that EUS-guided pancreatic drainage is usually successful with dilated PD (≥4 mm), and complications are more likely with nondilated PD [8, 23]. The total procedure timings were reported by François et al. [24] in four cases: average 81.25 minutes (range 40–180). In the largest single-operator and single-session EUS-CP study by Shah et al. [9], the mean procedure time including failed ERCP was only 97 minutes (range 36–210) for both biliary and pancreatic cases. Pancreatic stent types used were plastic (5–10 Fr, straight, single or double pigtail). In the largest reported pancreatic series by Tessier et al. [22], stent dysfunction was noted in 22/36 (55%) cases. The median stent patency was 195 days (range 10–780).

Table 4: Published EUS-CP series on pancreatic duct drainage (involving ≥5 patients).

Year	Author	*N*	Indication	Initial ERCP	Techniques	Technical success	Clinical success	Complications
2007	Will et al. [16]	12*	B	Sb	5 T; 4 R	8/12 (67%)	4/8 (50%)	6/14 (42.9%)
2007	Tessier et al. [22]	36	B	Sb	T	33/36 (91.7%)	25/36 (69%)	5/36 (13.8%)
2007	Kahaleh et al. [40]	13	B	Sb	5 R; 5 T	10/13 (77%)	10/10 (100%)	2/13 (15.4%)
2009	Brauer et al. [13]	8	B	Sb	4 T; 3 R	7/8 (88%)	4/8 (50%)	No
2010	Barkay et al. [8]	21	B	Sb	6 D (mb injection); 4 R	10/21 (48%)	8/8# (100%)	2/21 (10%)
2012	Shah et al. [9]	25	B	Sm	10 A or T; 9 R; 3 D	22/25% (88%)	n/a	4/25 (16%)
	Total	115			46 T; 25 R; 10 A; 9 D	90/115 (78%)	51/68 (75%)	19/115 (16.5%)

EUS-CP: endoscopic-ultrasound-guided cholangiopancreatography, *N*: number of patients, B: benign, Sb: subsequent day, Sm: same day/session, D: ductography, T: transluminal, R: rendezvous, A: antegrade, mb: methylene blue, n/a: not applicable/mentioned. *14 attempts in 12 patients. #Long-term data was available in 8 patients only.

5. Clinical Role of EUS-CP

At present, EUS-CP is increasingly been used at expert centers as an alternative to surgery or PTC. It should be considered in patients in whom ERCP has failed by an experienced endoscopist, and there is a need for pancreatobiliary drainage. Unlike PTC, EUS-CP can also be performed in patients with ascites [25]. However, only the left intrahepatic biliary tree can be accessed. For isolated right-sided biliary obstruction, PTC is still needed. Although suggested by Dhir et al. [26] in a retrospective nonrandomized study that EUS-guided rendezvous was a low-risk alternative to precut sphincterotomy for biliary cannulation, EUS-CP is a technically challenging procedure with a significant learning curve. The endoscopist should be proficient in both EUS and ERCP. Unlike pancreatic pseudocyst drainage, there is possibility of displacement between the puncture site and obstructed ducts with resultant failure and complications. The creation or dilation of fistula tract may be difficult due to fibrosis as in chronic pancreatitis. Care should be taken to avoid major vessels in the vicinity, like portal vein, hepatic artery, and splenic vessels. However, with increasing availability of endoscopists trained in both ERCP and EUS, the role of EUS-CP is likely to grow in clinical practice.

Same session EUS-CP as failed initial ERCP is practical and may result in avoidance of additional procedures. Combined duodenal and EUS-guided biliary stenting has also been shown to be practical [27]. Although nondilated ducts have been accessed, the puncture can be risky in such cases. The diameter of the working channel of the linear echoendoscopes is still limited, allowing small-caliber stents or delivery systems. There are no dedicated EUS-CP accessories. Commercially available one-step devices are needed. There are no studies directly comparing EUS-CP versus PTC.

6. Summary

EUS-CP is safe, efficacious, and a viable alternative to PTC or surgery in failed ERCP cases by an experienced endoscopist. It can be accomplished in one of the four ways: ductography, rendezvous, antegrade, or transluminal stenting. The overall technical and clinical success rates are around 90% for biliary tree and 70% for pancreatic duct drainage. The technical success rate is relatively low for pancreatic as compared to biliary cases. The overall EUS-CP complication rate was around 15%. Most of the complications are minor. However, severe complications can be encountered during pancreatic drainage. EUS-CP should be performed by an experienced endoscopist skilled in both EUS and ERCP. EUS-CP has a potential application in benign biliary cases. Same session EUS-CP as failed initial ERCP is practical and may result in avoidance of additional procedures. Since it tends to be a longer procedure, anesthesia support should be sought. Prophylactic antibiotics should be administered to all patients. Future research will be needed to improve instruments and accessories.

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Research Article

Combined EUS-Guided Abdominal Cavity Drainage and Cystogastrostomy for the Ruptured Pancreatic Pseudocyst

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Background. Endoscopic-Ultrasonography- (EUS-) guided puncture and drainage of pancreatic pseudocyst is currently one of the most widely accepted nonsurgical treatments. To date, this technique has only been used for pancreatic pseudocysts adhesive to the gastric wall. This study introduces the technique of EUS-guided pseudocyst drainage and additional EUS-guided peritoneal drainage for the ruptured pseudocyst. *Methods*. Transmural puncture and drainage of the cyst were performed with a 19 G needle, cystotome, and 10 Fr endoprosthesis. Intraperitoneal drainage was performed with a nasobiliary catheter when rupture of pseudocyst occurred. The entire procedure was guided by the echoendoscope. *Results*. A total of 21 patients, 8 men and 13 women, with a mean age of 36 years, were included in this prospective study. All of the pseudocysts were successfully drained by EUS. Peritoneal drainage was uneventfully performed in 4 patients. There were no severe complications. Complete pseudocyst resolution was established in all patients. *Conclusion*. The technique of EUS-guided transmural puncture and drainage, when combined with abdominal cavity drainage by a nasobiliary catheter, allows successful endoscopic management of pancreatic pseudocysts without adherence to gastric wall.

1. Introduction

Endoscopic-Ultrasonography- (EUS-) guided pancreatic pseudocyst puncture and drainage are a widely accepted nonsurgical intervention [1–5].

Recent advances in understanding of the pathophysiology of pancreatic pseudocysts (PPs) allow the selection of optimal candidates for minimally invasive treatment approaches [6]. To date, the EUS-guided drainage approach has been limited to those cysts adherence to gastric wall, where it has been proven to be safe and effective. EUS-guided drainage of cysts without adherence to gastric wall can cause cyst collection leakage or even rupture, and for these patients a transpapillary or other approach is usually chosen [7].

A review of the literature indicates that this paper is the first to demonstrate the use of combined EUS-guided pseudocyst drainage for ruptured pancreatic pseudocyst and to provide an evaluation of the safety and effectiveness of this method.

2. Materials and Methods

2.1. Patients. Inclusion criteria for this study are as follows: (1) pancreatic pseudocyst without adherence to gastric wall confirmed by CT and EUS; (Figures 1(a), and 1(b)) (2) pancreatic pseudocyst presenting with severe symptoms, such as abdominal pain, abdominal distension, duodenal obstruction, or biliary obstruction; (3) asymptomatic patient with pancreatic pseudocyst larger than 5 cm (considered a relative indication for drainage therapy in order to avoid serious complications, such as disruption or infection, in the future). Exclusion criteria were (1) thin, irregular pseudocyst wall; (2) coagulopathy; (3) unconfirmed diagnosis. All patients provided informed consent for the procedure. Complete blood counts, prothrombin time, and partial thromboplastin time were normal for all patients.

2.2. Devices. Longitudinal echoendoscope (PENTAX EG3830UT, Pentax Corporation, Japan) with a working channel of 3.8 mm accessible to a 10 Fr stent is used.

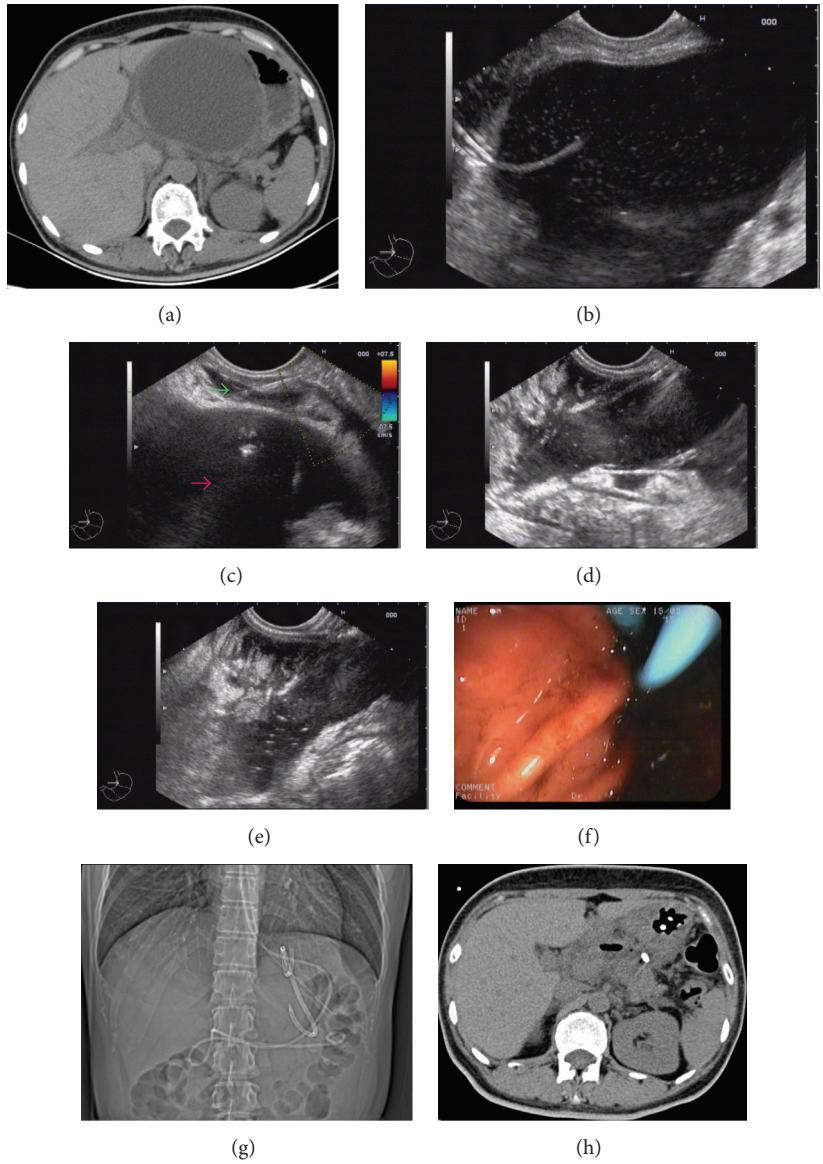

FIGURE 1: (a) CT shows a large cyst in the upper abdominal area. (b) EUS shows the cyst wall was 3 mm. The wall was not adhered to the gastric wall, as relative movement was observed. (c) After the needle puncture, cyst (red arrow) fluid will leak into the omental bursa. After cystotome dilation and stent placement, fluid leak (green arrow) begins to increase. (d) A large collection of fluid, measuring 3 cm, is seen below the cyst. (e) Transmural approach by a cystotome. (f) Intraperitoneal drainage by a 7 Fr nasobiliary catheter. (g) Drainage catheters seen on X-ray. (h) Pancreatic pseudocyst size is diminished, as confirmed by CT.

Echo-Tip Ultra needle (19-G, Wilson-Cook Medic, USA) with a lumen of 0.8 mm in diameter is fitted to a 0.035 inch guidewire. Cystotome (10-Fr, Wilson-Cook Medic) is used to dilate the tract and create a large fistula. A nasobiliary drainage catheter (7-Fr, Wilson-Cook Medic) is used for peritoneal drainage or infected cyst drainage. A double pigtail stent (10 Fr, Endo-Flex GmbH, Germany) facilitates the cyst drainage.

2.3. Method. The patient candidate for our study is following the steps shown in the chart in Figure 2. The echoendoscope-guided drainage procedure is described as below. The echoendoscope is introduced to scan for the pseudocyst and mark the puncture point. The contact zone (i.e., the closest approximation of the region between the gastric wall and the cyst wall) was identified. Color Doppler then is applied to identify the interposing vessels and thus avoid them during puncture. An Echo Tip Ultra endoscopic needle is then introduced via the working channel of the echoendoscope, and the cyst was punctured under EUS guidance. A sample of the cyst is aspirated for biochemical, cytological, and tumor marker analysis. If the cyst is very small, this sample should be limited to avoid rapid cyst deflation, which can cause increased difficulty during stent placement. The guidewire is inserted through the needle lumen into the cyst and coiled into 2-3 loops, and the needle is removed. The needle path is then

Table 1: Patient characteristics in this study.

Patients details	
Patients, total	21
Male : Female	8 : 13
Age, mean, years (range)	36 (10–45)
Location of cyst	
Head	2
Body	18
Tail	1
The distance from the cyst to the gastric wall, cm	2.1 (1.5–3)
Diameter of cyst, cm	7.6 (7–10)
Cause of the cyst	
Trauma	3
Severe pancreatitis	16
Postoperative	2

Table 2: Patients results of EUS-guided cystogastrostomy.

Patient details	
Completely recovery	21
Cyst rupture during the procedure	4/21
Symptoms after EUS drainage	
Fever	1
Abdominal pain	0
Others	0
Decompression tube in place, days	2-3
Postoperative hospital stay, days	4–10 (4.3)

dilated by the cystotome and a balloon dilator. A double pigtail (10 Fr) then is introduced for the drainage. The dilation is repeated when possible before placing stents to enhance efficacy.

If the cyst is ruptured with a large amount of fluid rush into the abdominal cavity, EUS-guided abdominal cavity drainage is introduced (Figures 1(c), 1(d), 1(e), 1(f), and 1(g)). The needle is again introduced via the working channel. Guided by EUS, the needle was punched into the abdominal cavity. The puncture site used in the cyst drainage procedure is preferentially considered. Guidewire was inserted through the needle lumen into the abdominal cavity. Deploy the 7 Fr nasobiliary drainage catheter via the guidewire. The nasobiliary drainage catheter with continuous aspiration was placed to complete the abdominal drainage. After the procedure, a tube remains in the stomach for decompression.

3. Results

A total of 86 patients with pancreatic pseudocyst treated at Shengjing hospital between May 2005 and June 2011 were enrolled in this study. 21 patients (13 women, 8 men) with pancreatic pseudocyst without adherence to gastric wall were selected for this procedure (Table 1).

All patients resumed regular diets after three days. Within one week of treatment, there was a reduction in cyst diameter of at least 50% in 19/21 patients, as measured by abdominal CT scan. Cysts in both of the patients in whom reduction of cyst diameter was less than 50% had an etiology of trauma.

4 patients had cyst ruptured, with intraperitoneal drainage kept for 3 days, and the gastric decompression tube for 2 days. No further infections were found in these patients.

Cyst infection was found in 2 patients in our study. EUS-guided secondary dilation of fistula was performed with an additional 10 Fr stent placement.

Stents were to be removed by endoscopy once cyst diameter was <3 cm, as measured by CT or EUS; this goal was achieved in 18 patients at 3-month followup. In the three remaining patients, stents were removed at six-month followup. At one year, no recurrence was found in any of the patients.

There were no severe procedure-related complications resulting from this technique; no bleeding, no perforation, no pneumoperitoneum. The postprocedure fever that developed in 2 patients was successfully managed by a secondary EUS-guided dilation. Results are reviewed in Table 2.

4. Discussion

A pancreatic pseudocyst is a collection of pancreatic fluid occurring within the pancreas or adjacent to it and surrounded by nonepithelialized tissue. It can occur after an episode of acute pancreatitis, trauma, or surgery, or in the setting of chronic pancreatitis. The cysts result from liquefaction of necrotic pancreatic tissue or from pancreatic duct obstruction or disruption [8]. Analysis of cyst fluid obtained during EUS should distinguish pancreatic pseudocyst from other cystic neoplasm. A high amylase or lipase content is typically seen in pseudocysts [9].

Management options available for pancreatic pseudocysts include endoscopic, radiologic (percutaneous), surgical (open surgery or Laparoscopic drainage), and conservative (medical) treatment [10]. The traditional treatment for pancreatic pseudocyst has been surgical, which has proven to be therapeutically effective, but is accompanied by high complication and mortality rates [11]. In recent years, there have been rapid gains in less invasive interventional techniques. CT and US-guided transcutaneous puncture and drainage have been widely applied. However, when the source of pancreatic pseudocyst is pancreatic fistula, simple aspiration therapy may result in recurrence rates of over 70% [12]. Transcutaneous external drainage may reduce this recurrence rate, but it can also greatly increase complication rates, from 5% to 60%, mainly due to perforation and hemorrhage [11]. Endoscope-guided transmural drainage is a recent intervention that provides continuous drainage via an endoprosthesis stent or a nasobiliary tube placed in a fistulous tract between the upper GI tract and the pseudocyst. This is only applied in cases of well-defined compression resulting from the cyst [13, 14]. If the cyst involves the gastric wall (e.g., the mucosa in the prominence emerges with a dark color or "Mosaic" sign), this treatment will be even more efficient. However, because it is a blind procedure, the risk of complication remains elevated. With the application of

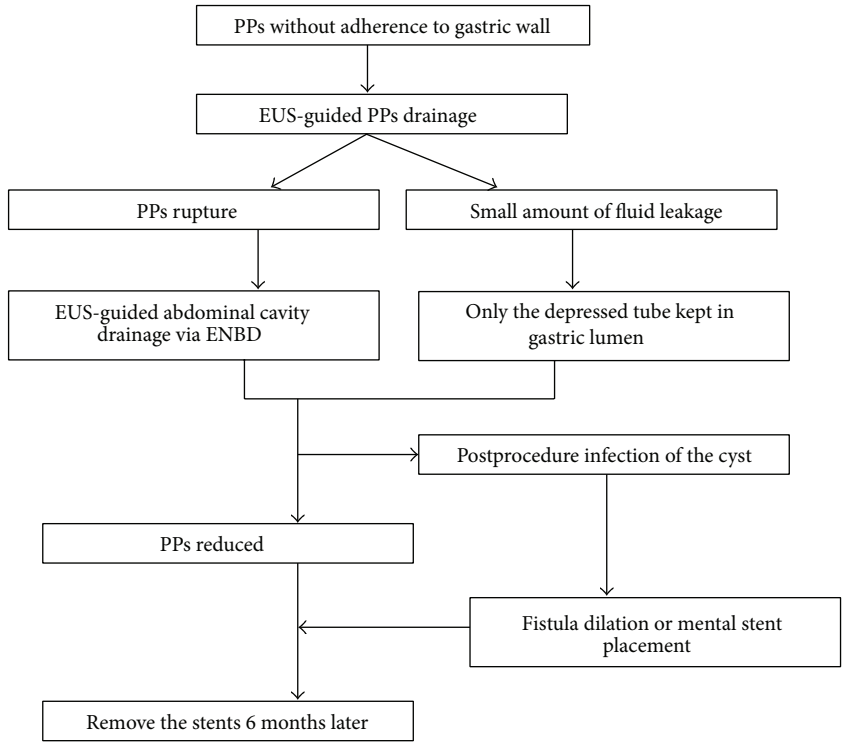

Figure 2: The patient candidate for our study is following the steps in chart.

EUS guidance, blind puncture procedures should be phased out. Transpapilla drainage is another endoscopic treatment. Current consensus holds that cyst drainage through a stent placed in the pancreatic duct is insufficient because of the small lumen of the stent. Further, the long-term placement of a stent in the pancreatic duct is likely to induce morphological changes of the pancreatic duct and its surrounding tissues.

During the past decade, it has gradually been recognized that echoendoscopic treatment is a preferred approach in management of pancreatic pseudocysts [15–19]. Therefore, EUS-guided pancreatic pseudocyst drainage via cystoenterostomy should be considered as the first-line therapy [20]. With the addition of EUS guidance, selection of puncture points can be precise. As this minimally invasive technique matures, more patients should benefit from decreased trauma and fewer complications.

Pseudocysts may be classified according to anatomic location in relation to the omental bursa. Pseudocysts inside the omental bursa often have a common wall with the GI tract, and retroperitoneal perforation is rare when there is close apposition of the pseudocyst to the gastric wall. EUS-guided cystoenterostomy in this type of cyst usually has a low risk of complications and short recovery period. Over the past ten years, there have been numerous reports of successful treatment by this method, and it has become the recommended therapy for these cysts.

The other type of pseudocyst is located without adherence to gastric wall. This type of cyst usually has a wall that is separate from the gastric wall. Relative motion between the cyst wall and the gastric wall may be seen during EUS, particularly if the patient is instructed to take a deep breath. These cysts may be situated 2 cm or further from the GI wall as shown in our study. A transmural approach may cause cyst rupture or large leak of cyst fluid, resulting in ascites or infection. We think adequate drainage was effective to reduce the risk of infection. So, needle path dilation by cystotome or balloon was needed even they may have the higher risk of cyst rupture. Simple EUS-guided drainage of these ruptured cysts is usually not adequate. In the past, drainage by transpapillary placement of a stent in the pancreatic duct was considered if the cyst wall was behind omental bursa, but, as noted above, this approach has limited efficacy due to the smaller diameter of the stent.

This study proposes that cysts without adherence to gastric wall can be safely and effectively drained by EUS-guided cystoenterostomy accompanied by nasobiliary tube drainage of the abdominal cavity. To demonstrate this, the technique and the results of the procedure in 21 patients have been reported.

For surgeons, abdominal drainage for peritoneal infection or fistula in the abdominal cavity has been a routine [21, 22]. In this study, this method is successfully adapted to allow the echoendoscopic transmural drainage of pancreatic pseudocysts outside the omental bursa. A search of the literature has not revealed any other reports of this technique. Therefore, placement of the 7 Fr nasobiliary drainage catheters continuous abdominal drainage following cyst puncture and cystoenterostomy is the cornerstone concept in this treatment. The catheter allows the direct drainage of the leaked fluid from the abdominal cavity and prevents peritonitis.

No infection was found in our 4 patients that performed abdominal cavity drainage. All this cavity drainage catheters were kept in place for 3 days. When we observed that no fluid was found from the catheters, patients had no symptoms including fever, and CT scan 3 days after the procedure shows the disappear of the leakage; catheters were removed. Since this is the first pilot study about EUS-guided abdominal cavity drainage, further studies focus on the efficiency of this method and the time to remove the abdominal catheters is still needed.

The main complications expected of this therapy are hemorrhage and infection. Hemorrhage can be avoided by using color Doppler for the detection and avoidance of interposing vessels during the puncture. Some studies are considered performing the povidone-iodine washing of gastrointestinal mucosa to prevent the infection [23]. In our study antibiotic drugs were taken after the procedure to prevent the infection caused by the needle puncture. We only observed cyst infection in one patient. Cyst infection was successfully treated with a secondary EUS-guided dilation. Placement of covered metal stent with larger lumen can also be considered [19].

5. Conclusion

The technique of EUS-guided transmural drainage of pancreatic pseudocysts without adherence to gastric wall combined with drainage of the abdominal cavity by a nasobiliary catheter allows for successful endoscopic management with a low risk of complications. This should lead to expanded application of EUS-guided pancreatic pseudocyst drainage.

Results from larger series will be necessary to learn more about this procedure and its ultimate role in the treatment of pancreatic pseudocysts without adherence to gastric wall.

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