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ORIGINAL ARTICLE

Retrospective Study

Severity of gastric mucosal atrophy affects the healing speed of post-endoscopic submucosal dissection ulcers

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Abstract

AIM

To investigate factors associated with the healing of endoscopic submucosal dissection (ESD)-induced ulcers.

METHODS

We enrolled 132 patients with gastric tumors scheduled for ESD. Following ESD, patients were treated with daily lansoprazole 30 mg or vonoprazan 20 mg. Ulcer size was endoscopically measured on the day after ESD and at 4 and 8 wk. The gastric mucosa was endoscopically graded according to the Kyoto gastritis scoring system. We assessed the number of patients with and without a 90% reduction in ulcer area at 4 wk post-ESD and scar formation at 8 wk, and looked for risk factors for slower healing.

RESULTS

The mean size of gastric tumors and post-ESD ulcers was 17.4 ± 12.1 mm and 32.9 ± 13.0 mm. The mean

reduction rates in ulcer area were 90.4% ± 0.8% at 4 wk and 99.8% ± 0.1% at 8 wk. The reduction rate was associated with the Kyoto grade of gastric atrophy at 4 wk (A0: 97.9% ± 0.6%, A1: 93.4% ± 4.1%, and A2: 89.7% ± 1.0%, respectively). In multivariate analysis, the factor predicting 90% reduction at 4 wk was gastric atrophy (Odds ratio: 5.678, 95%CI: 1.190-27.085, P = 0.029).

CONCLUSION

The healing speed of post-ESD ulcers was associated with the degree of gastric mucosal atrophy, and *Helicobacter pylori* eradication therapy is required to perform at younger age.

Key words: *Helicobacter pylori*; Gastric mucosal/AB; Endoscopic submucosal dissection; Gastric ulcer

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Core tip: It is important to investigate factors influencing the healing speed of endoscopic submucosal dissection (ESD)-induced ulcers to prevent gastrointestinal bleeding. Although previous studies have looked at many factors related to ESD-induced ulcer healing, such as location of the tumor, submucosal fibrosis, initial ulcer size, diabetes, and method of gastric acid suppression, this report showed that the severity of gastric atrophy is possible factor to affect speed of ESD-induced ulcer healing. Therefore, *Helicobacter pylori* (*H. pylori*) eradication therapy is required to perform at younger age before progression of gastric mucosal atrophy to prevent development of *H. pylori*-related diseases and bleeding from ESD-induced ulcer.

Otsuka T, Sugimoto M, Ban H, Nakata T, Murata M, Nishida A, Inatomi O, Bamba S, Andoh A. Severity of gastric mucosal atrophy affects the healing speed of post-endoscopic submucosal dissection ulcers. *World J Gastrointest Endosc* 2018; 10(5): 83-92 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i5/83.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i5.83

INTRODUCTION

The efficacies of endoscopic submucosal dissection (ESD) and surgical gastrectomy for early-stage gastric cancer are generally similar[1]. ESD, being less invasive, is the first-line treatment for early-stage gastric cancer. ESD allows en bloc resection and is associated with a lower recurrence rate than endoscopic mucosal resection (EMR)[2,3].

Gastrointestinal bleeding from ESD-induced ulceration is a common complication[4-7]. Factors associated with an increased risk of post-ESD gastrointestinal bleeding include the size, location, and histology of the gastric cancer; kinds of gastric acid suppressant; patient use of dialysis; and long procedure time[4-7]. The risk of bleeding is reduced by endoscopic coagulation of exposed vessels at the base of ESD-induced ulcers and potent acid inhibition over the first 24 h post-treatment[4-7]. When ESD is performed for gastric cancer, proton pump inhibitors (PPIs) are used to treat ESD-induced ulcers[7]. However, PPIs may not suppress gastric acid secretion over 24 h, especially at night. Administration is required over several days to maximize gastric acid inhibition. More recently, interindividual genetic variations (*e.g.*, CYP2C19 genotype)[8,9] have been linked to different metabolism rates of PPIs. Vonoprazan, a potassium-competitive acid blocker (P-CAB) with more potent and sustained acid inhibition than PPIs, has been approved in Japan[10-12]. Although vonoprazan inhibits gastric H^+/K^+-ATPase similarly to PPIs, its mechanism of acid inhibition involves inhibition of H^+, K^+-ATPase by binding reversibly and competitively with K^+[13]. It remains unclear whether vonoprazan is associated with improved ulcer healing speed and prevention of post-ESD bleeding, due to the low statistical power of the most recent studies[5,14].

Previous studies have looked at many factors related to ESD-induced ulcer healing, such as location of the tumor[15], submucosal fibrosis[16], initial ulcer size[17,18], diabetes[18], coagulation abnormality[18], electrocoagulation during ESD[18], and method of gastric acid suppression[19].

Concurrent *Helicobacter pylori* (*H. pylori*) infection has been found to influence the speed of peptic ulcer healing[20,21]. However, it is unclear whether current *H. pylori* infection and eradication therapy affect the healing of ESD-induced ulcers[22,23]. In addition, there may be an association with the severity of gastritis/gastric atrophy and post-ESD ulcer healing[23,24].

Rapid healing of ESD-induced ulcers is key to the prevention of delayed bleeding. We investigated factors that might be associated with healing of post-ESD ulcers, including *H. pylori* status, profile of the gastric tumor, kinds of acid inhibitory drugs, and severity of gastritis (*e.g.*, gastric atrophy and intestinal metaplasia).

MATERIALS AND METHODS

Patients

We enrolled 132 Japanese patients who underwent ESD for clinical early-stage gastric cancer and adenoma between March 2013 and October 2016 at our institution. Approval for the study protocol was given in advance by the Institutional Review Board of the Shiga University of Medicine Science (Number 27-36). This trial was registered in the University Hospital Medical Information Network, UMIN000018188.

ESD was performed if cases met the following criteria of early-stage gastric cancer and gastric adenoma according to the Union for International Cancer Control/American Joint Committee on Cancer stages: (1) Intramucosal intestinal-type neoplasm without ulceration, regardless of tumor size; (2) intramucosal

intestinal-type cancer with ulceration, ≤ 3 cm; (3) intestinal-type cancer invading the submucosa < 500 μm from the muscularis mucosa, ≤ 3 cm in size; and (4) intramucosal diffuse-type cancer without ulceration, ≤ 2 cm. Exclusion criteria were patients with advanced-stage gastric cancer, patients who refuse follow-up endoscopy at both 4 and 8 wk after ESD treatment and patients with lack of informed consent.

Although severity of anemia and oxygenation were expected to affect the healing speed of ESD-induced ulcer, there were no patients with severe anemia of less than 10 g/mL or hypoxemia.

Study protocol

For this study, we enrolled patients who had undergone ESD for resection of gastric tumor and provided blood samples for an anti-*H. pylori* IgG serological testing and *CYP2C19* genotyping. The endoscopic severity of gastritis was characterized by the Kyoto classification[25]. According to the Kyoto classification of gastritis, patients are scored according to atrophy (None: A0, atrophic patterns with a margin between the non-atrophic fundic mucosa and atrophic mucosa located in the lesser curvature of the stomach: A1, and atrophic patterns, whose margin does not cross the lesser curvature: A2), intestinal metaplasia (none: IM0, within antrum: IM1, and up to corpus: IM2), hypertrophy of gastric folds (negative: H0, positive: H1), and diffuse redness (negative: DR0, mild: DR1, severe: DR2)[25].

ESD was performed with a single-channel magnifying endoscope (GIF-H290Z or GIF-H260Z; Olympus, Tokyo, Japan). We used a fixed-length disc-tipped knife (Dual knife®, KD-650L/Q; Olympus, Tokyo, Japan) or an insulated-tip diathermic knife (IT knife 2®, KD-611L, Olympus, Tokyo, Japan) and applied electric current using an electrosurgical generator (VIO300D®; ERBE Elektromedizin GmbH, Tubingen, Germany). Visible vessels were heat-coagulated using hemostatic forceps (FD-412LR®; Olympus, Tokyo, Japan). After ESD, 73.5% of patients were dosed with lansoprazole 30 mg and 26.5% were dosed with vonoprazan 20 mg (Table 1) for 8 wk.

The major and minor axes of ESD-induced ulcers were endoscopically measured the day after ESD by measurement forceps (M2-4K®; Olympus Corporation, Tokyo, Japan), and at 4 and 8 wk post-ESD.

H. pylori infection

Infection status of *H. pylori* was evaluated based on findings from two tests: an anti-*H. pylori* IgG serological test (E plate Eiken *H. pylori* antibody®; Eiken Chemical Co. Ltd., Tochigi, Japan) and a rapid urease test (Helicocheck®; Otsuka Co., Tokyo, Japan). When either test was positive, the patient was diagnosed as positive for *H. pylori* infection.

CYP2C19 genotyping

Genomic DNA was extracted from the blood (DNA Extract All Reagents®, Applied Biosystems, Foster City CA, United States). Subsequently, genotyping was performed using a single-nucleotide polymorphism (SNP) genotyping assay (TaqMan®, Applied Biosystems) in a real-time polymerase chain reaction (PCR) system (Step One Plus®, Applied Biosystems). Genotyping for identifying the *CYP2C19* wild-type gene and two mutated alleles, *CYP2C19 *2* (rs4244285, A/G) and **3* (rs-4986893, G/A) were performed to classify each subject as belonging to one of the following four genotype groups: extensive metabolizers (EMs, * 1/ * 1), intermediate metabolizers (IMs; * 1/ * 2 or * 1/ * 3), or poor metabolizers (PMs; * 2/ * 2, * 2/ * 3 or * 3/ * 3).

Statistical analysis

Age, ESD procedure time and ESD-induced ulcer area are expressed as mean ± SD. The healing rates of ulcers were calculated as (1-ulcer area/ulcer area just after ESD) × 100 (%) and are expressed as mean ± SD. Statistical differences in these parameters among CYP2C19 genotypes; between *H. pylori* infection statuses; among degrees of atrophy, intestinal metaplasia, and diffuse redness according to the Kyoto classification; and among tumor locations were determined using one-way ANOVA with Scheffé multiple comparison and Fisher's exact tests. All *P* values are two-sided, and $P < 0.05$ was considered statistically significant. Calculations were performed using commercial software (SPSS version 20, IBM Inc; Armonk NY, United States).

RESULTS

ESD and ESD-induced ulcers

The mean procedure time was 76.4 ± 56.7 min and the mean resected ESD-induced ulcer area was 671.9 ± 720.9 mm^2 at Day 1. Procedure time for lesions in the lower third of the stomach (47.5 ± 3.2 min) was significantly shorter than those for the middle and upper thirds [*vs* middle (85.7 ± 6.6 min), $P = 0.001$, *vs* upper (131.3 ± 17.9 min), $P < 0.001$, respectively]. The initial ulcer area in the lower third (456.4 ± 265.2 mm^2) was significantly smaller than that of the middle third (822.0 ± 922.2 mm^2, $P = 0.008$).

After ESD, mean ESD-induced ulcer areas at 4 and 8 wk were 71.3 ± 135.6 mm^2 and 2.8 ± 15.6 mm^2, respectively, and mean healing rates were 90.4% ± 0.8% at 4 wk and 99.8% ± 0.1% at 8 wk (Figures 1A and 2A). At 8 wk, mean healing rate in the *H. pylori*-positive group (99.7% ± 0.1%) was significantly lower than that in the negative group (99.9% ± 0.0%, $P = 0.035$). There were no significant differences between mean healing rates for lansoprazole and vonoprazan treatment at 4 and 8 wk (Figures 1B and C, 2B and C).

Healing rate was associated with the severity of gastric atrophy at 4 wk (A0: 97.9% ± 0.6%, A1: 93.4% ± 4.1%, and A2: 89.7% ± 1.0%, respectively).

In patients with severe gastric atrophy, the healing

Table 1 Characteristics of enrolled patients with gastric tumor

Parameter	
Number	132
Age (yr)	71.0 ± 8.6
Gender (male/female)	100/32 (75.8%/34.2%)
H. pylori status (positive/negative)	68/64 (51.5%/48.5%)
Anti-coagulant administration (+/-)	22/110 (16.7%/83.3%)
Acid suppressant post-ESD (lansoprazole/vonoprazan)	97/35 (73.5%/26.5%)
CYP2C19 genotype (EM/IM/PM)	40/51/22 (35.4%/45.1%/19.5%)
Endoscopic background of gastric mucosa	
Atrophy (Kyoto A0+A1/Kyoto A2)	20/112 (15.2%/84.8%)
Intestinal metaplasia (none + mild/severe)	72/55 (56.7%/43.3%)
Diffuse redness (none/mild/severe)	65/62 (51.2%/48.8%)
Tumor	
Types (adenoma/cancer)	16/116 (12.1%/87.9%)
Depth (mucosa/submucosa)	118/14 (89.4%/10.6%)
Location of tumors (upper/middle/lower third)	15/67/50 (11.4%/50.8%/37.8%)
ESD	
Mean procedure time (min)	76.4 ± 56.7
Mean resected ulcer area (mm^2)	671.9 ± 720.9
ESD-induced ulcer area	
Reduction at 4 wk	90.4% ± 10.7%
Mean ulcer area at 4 wk (mm^2)	71.3 ± 135.6
Reduction at 8 wk	99.8% ± 0.6%
Mean ulcer area at 8 wk (mm^2)	2.8 ± 15.6

EM: Extensive metabolizer of *CYP2C19*; ESD: Endoscopic submucosal dissection; IM: Intermediate metabolizer of *CYP2C19*; PM: Poor metabolizer of *CYP2C19*.

rate was significantly lower than that in patients with mild or no atrophy (A0 + A1) ($P < 0.001$ and $P = 0.010$) (Figures 1D and 2E). In addition, at 4 wk, the mean healing rate in the lower third (92.8% ± 1.2%) was significantly delayed compared to the upper two-thirds (83.7% ± 5.3%, $P = 0.013$) (Figure 1E and 2F). After 8 wk, ESD-induced ulcers were scarred in 85.7% (12/14) in the upper third, 89.2% (58/65) of the middle third, and 83.3% (40/48) of the lower third ($P = 0.657$) of the stomach. There was no significant association of healing rates at 4 wk with CYP2C19 genotypes (Figure 2D).

Factors affecting ESD-induced ulcer healing

We investigated the healing rate of ESD-induced ulcers by setting up over 90% of ESD-induced ulcer area at 4 wk and 100% at 8 wk. ESD-induced ulcers with ⩾ 90% healing at 4 wk were associated with absence of atrophy ($P = 0.010$), depth of gastric tumor ($P = 0.004$), and procedure time $P = 0.026$) (Table 2). The mean procedure time in the ⩾ 90% healing group was significantly shorter than that in the < 90% healing group (65.6 ± 41.1 min *vs* 89.7 ± 64.0 min, $P = 0.026$). The prevalence of patients with open-type atrophic gastritis in the ⩾ 90% healing group was 78.0% (64/82), which was significantly lower than that in the < 90% healing group (96.0%, 43/45, $P = 0.01$).

In achievement of scar formation at 8 wk, the rates were associated with gender ($P = 0.021$) and age ($P = 0.047$), but not gastritis or tumor-related factors (Table 2).

In the univariate analysis to identify possible factors related to achievement of 90% healing at 4 wk, healing was associated with gastric atrophy (OR = 6.047, 95%CI: 1.334-27.403, $P = 0.019$), procedure time (OR = 1.009, 95%CI: 1.002-1.017, $P = 0.018$) and initial ESD-induced ulcer size (OR = 0.001, 95%CI: 1.000-1.001, $P = 0.032$) (Table 3). At 8 wk, gender and initial ESD-induced ulcer size significantly correlated with the achievement of scarring at 8 wk ($P = 0.021$ and $P = 0.013$, respectively) (Table 3).

In the multivariate analysis including gender, *H. pylori* infection, endoscopic severity of atrophy, tumor location, mean procedure time, and mean initial ESD-induced ulcer size, the factor associated with 90% healing at 4 wk was gastric atrophy (OR = 5.678, 95%CI: 1.190-27.085, $P = 0.029$) (Table 4). The factors associated with scarring at 8 wk were gender (female, OR = 4.438, 95%CI: 1.253-15.724, $P = 0.021$) and initial ESD-induced ulcer size (1.001, 1.000-1.002, $P = 0.023$) (Table 4).

ESD-related adverse events

Two patients (1.5%) experienced delayed bleeding with tarry stool and only one patient received transfusion treatment after ESD treatment. Although the prevalence of patients received anti-coagulants was 16.7% and no cases with hematologically abnormal coagulation ability were observed (Table 1), intake of aspirin of non-steroidal anti-inflammatory drug did not increase incidence of gastric bleeding after ESD. There were no other major ESD-related adverse events.

DISCUSSION

The healing speed of ESD-induced ulcers may be a

Table 2 Characteristics of patients who achieved early healing of artificial ulcer area after endoscopic submucosal dissection

Characteristic	Reduction rate over 90% at 4 wk			Reduction rate 100% at 8 wk		
	Achieved (n = 82)	Not achieved (n = 45)	P value	Achieved (n = 110)	Not achieved (n = 16)	P value
Age (yr)	70.9 ± 9.3	71.2 ± 7.3	0.831	70.4 ± 8.9	74.1 ± 6.2	0.047
Gender (male/female)	62/20 (75.6%/24.4%)	33/12 (73.3%/26.7%)	0.777	86/24 (78.2%/21.8%)	8/8 (50.0%/50.0%)	**0.021**
H. pylori (positive/negative)	42/40 (51.2%/48.8%)	24/21 (53.3%/46.7%)	0.82	54/56 (49.1%/50.9%)	12/4 (75.0%/25.0%)	0.053
Anti-coagulants	13 (15.9%)	8 (17.8%)	0.78	16 (14.5%)	4 (25.0%)	0.231
PPI or PCAB (post-ESD)	60/22 (73.2%/26.8%)	32/13 (71.1%/28.9%)	0.804	82/28 (74.5%/25.5%)	14/2 (87.5%/12.5%)	0.210
CYP2C19 type (EM/IM/PM)	27/28/15 (38.6/40/21.4)	12/20/7 (30.8/51.3/17.9)	0.522	35/39/19 (37.6/41.9/20.5)	4/9/1 (28.6%/64.3%/7.1%)	0.249
Gastric mucosa						
Trophy (Kyoto A0+A1/Kyoto A2)	18/64 (22.0%/78.0%)	2/43 (4.0%/96.0%)	0.01	19/91 (17.3%/82.7%)	1/15 (6.3%/93.7%)	0.233
Metaplasia (none-mild/severe)	51/31 (62.2/37.8)	21/24 (46.7/53.3)	0.091	64/46 (58.2/41.8)	8/8 (50.0/50.0)	0.537
Diffuse redness (none-mild/severe)	44/38 (53.7/46.3)	21/24 (46.7/53.3)	0.451	60/50 (54.5/45.5)	7/9 (43.8/56.2)	0.419
Tumor						
Depth (mucosa/submucosa)	78/4 (95.1/4.9)	35/10 (77.8/22.2)	0.004	101/9 (91.8 /8.2)	15/1 (93.8/6.2)	0.629
Location (upper/middle/lower third)	7/39/36/ (8.5/47.6/43.9)	7/26/12 (15.6/57.8/26.6)	0.124	12/58/40 (10.9/52.7/36.4)	2/7/7 (12.4/43.8/43.8)	0.797
ESD						
Mean procedure time (min)	65.6 ± 41.1	89.7 ± 64.0	0.026	73.9 ± 52.3	76.1 ± 41.4	0.872
Mean resected ulcer area (mm^2)	544.7 ± 387.1	809.8 ± 849.8	0.053	567.3 ± 435.2	1178.5 ± 1520.1	0.130

EM: Extensive metabolizer; ESD: Endoscopic submucosal dissection; IM: Intermediate metabolizer; PCAB: Potassium competitive acid blocker; PM: Poor metabolizer; PPI: Proton pump inhibitor; *H. pylori*: *Helicobacter pylori*.

Table 3 Univariate analysis of factors preventing healing of ulcers after endoscopic submucosal dissection

Variable	Reduction rate over 90% at 4 wk		Reduction rate 100% at 8 wk	
	Not achieved (n = 45)	P value	Not achieved (n = 16)	P value
Age (yr)	1.004 (0.963-1.048)	0.841	1.058 (0.987-1.135)	0.113
Gender (female *vs* male)	1.127 (0.491-2.588)	0.777	3.583 (1.218-10.545)	0.021
Helicobacter pylori	1.088 (0.525-2.255)	0.820	3.111 (0.945-10.244)	0.053
Lansoprazole *vs* vonoprazan	1.108 (0.493-2.488)	0.804	0.418 (0.089-1.956)	0.210
Anti-coagulants	1.148 (0.436-3.018)	0.780	1.958 (0.561-6.832)	0.231
CYP2C19 type (EM *vs* IM/PM)	1.084 (0.635-1.850)	0.768	0.921 (0.420-2.020)	0.838
Atrophy (Kyoto A0+A1 *vs* Kyoto A2)	6.047 (1.334-27.403)	0.010	3.132 (0.390-25.163)	0.233
Tumor located in upper and middle third (*vs* lower third)	0.465 (0.211-1.026)	0.055	1.361 (0.471-3.934)	0.568
Mean procedure time (min)	1.009 (1.002-1.017)	0.018	1.001 (0.991-1.011)	0.871
Mean resected ulcer area (mm^2)	1.001 (1.000-1.001)	0.032	1.001 (1.000-1.001)	0.013

EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

Table 4 Multivariate analysis of factors preventing healing of ulcers after endoscopic submucosal dissection

Variable	Reduction rate over 90% at 4 wk		Reduction rate 100% at 8 wk	
	Not achieved (n = 45)	P value	Not achieved (n = 16)	P value
Gender (male *vs* female)	1.833 (0.715-4.698)	0.207	4.438 (1.253-15.724)	0.021
Helicobacter pylori	1.012 (0.463-2.213)	0.976	3.340 (0.866-12.885)	0.080
Atrophy (Kyoto A0+A1 *vs* Kyoto A2)	5.678 (1.190-27.085)	0.029	2.764 (0.309-24.711)	0.363
Tumor located in upper and middle third (*vs* lower third)	0.698 (0.283-1.724)	0.436	1.848 (0.493-6.933)	0.362
Mean procedure time (min)	1.007 (0.997-1.017)	0.194	0.998 (0.982-1.015)	0.850
Mean resected ulcer area (mm^2)	1.000 (1.000-1.001)	0.443	1.001 (1.000-1.002)	0.023

key factor in preventing ESD-related bleeding. In this study, we investigated possible risk factors associated with healing of ESD-induced ulcers and found that of all possible factors, severe gastric atrophy at 4 wk post-ESD and initial ulcer size at 8 wk were independent risk factors in multivariate analysis. However, we found no significant association of healing of ESD-induced ulcers and tumor location[15], initial ulcer size[17,18], coagulation abnormality[18], electrocoagulation during ESD[18], or kind of gastric acid suppressant[19]. Because the healing rate of ESD-induced ulcers was affected by tumor size, post-ESD ulcer size and severity of gastritis (*e.g.*, gastric atrophy), attention should be paid to the incidence of complications (*i.e.*, bleeding and perforation) in patients with severe gastric atrophy and a large size of gastric tumor.

In this study, we focused on the influence of the severity of gastric atrophy on the healing rate of ESD-

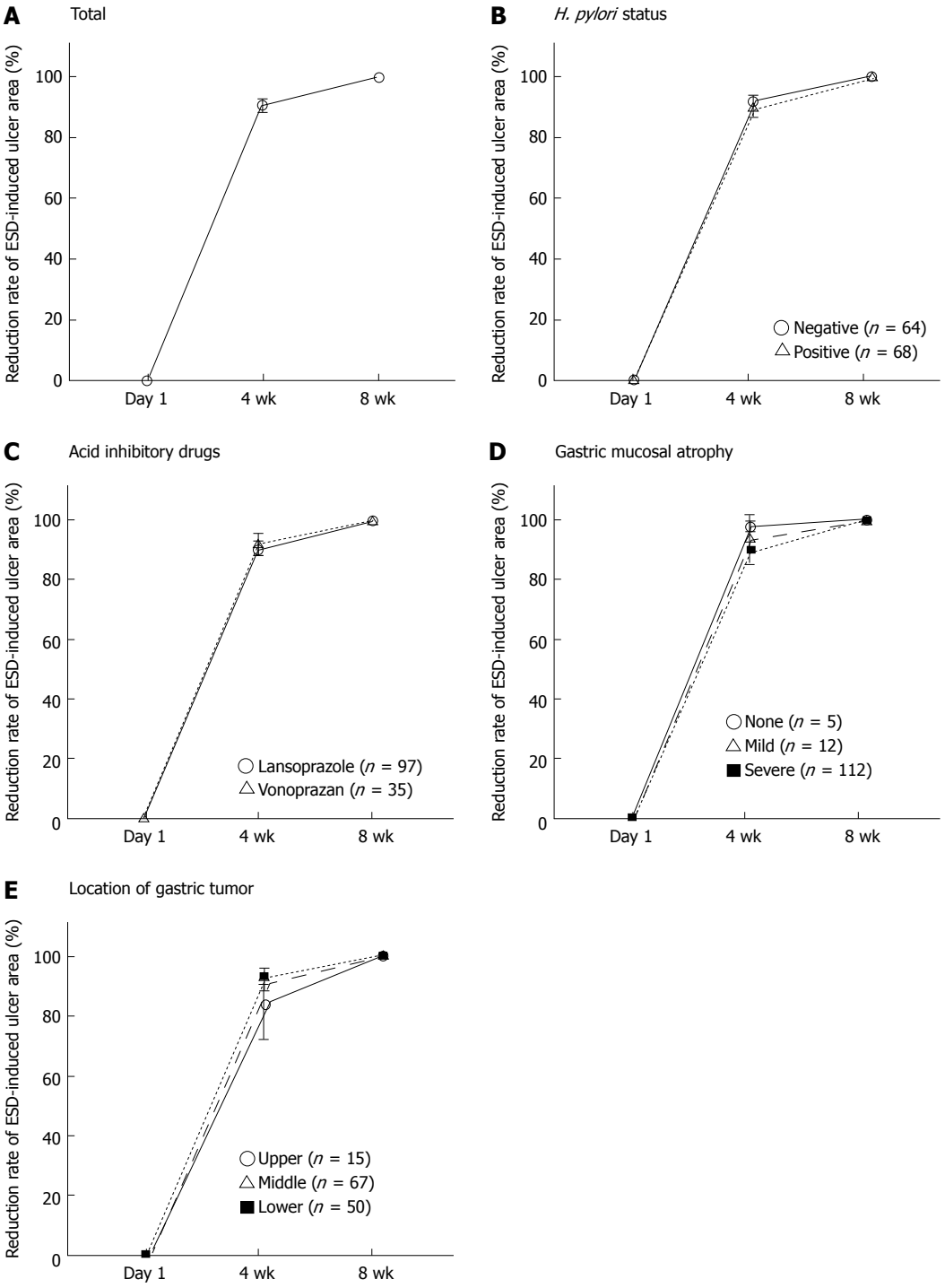

Figure 1 After endoscopic submucosal dissection endoscopic submucosal dissection, mean endoscopic submucosal dissection-induced ulcer areas at 4 and 8 wk in all patients (A), between *Helicobacter pylori*-positive patients and *Helicobacter pylori*-negative patients (B), between lansoprazole and vonoprazan (C), among patients with no atrophy, mild atrophy and severe atrophy (D), and among different locations of tumor (E). ESD: endoscopic submucosal dissection; *H. pylori*: *Helicobacter pylori*.

induced ulcers. Previously, Fujiwara *et al*[24] reported improved healing at 8 wk post-ESD for patients with severe atrophic gastritis when treated concomitantly with a PPI and rebamipide. In this study, at 4 wk after ESD, we revealed that severe gastric atrophy, especially of the A2 type according to the Kyoto classification, slowed healing speed. Kakushima *et al*[23] failed to show a significant association between the severity of gastric atrophy and ESD-induced ulcer healing with administration with omeprazole and sucralfate for 8 wk post-ESD; our study also did not demonstrate significant differences at 8 wk post-ESD. At 8 wk, mean reduction rates were 99.8% ± 0.1% and ESD-induced ulcers were scarred in 83.3% (110/132). We therefore hypothesize that the severity of gastric atrophy may influence healing of ESD-induced ulcers at 4 wk, but not at 8 wk.

Intestinal metaplasia is often observed in patients

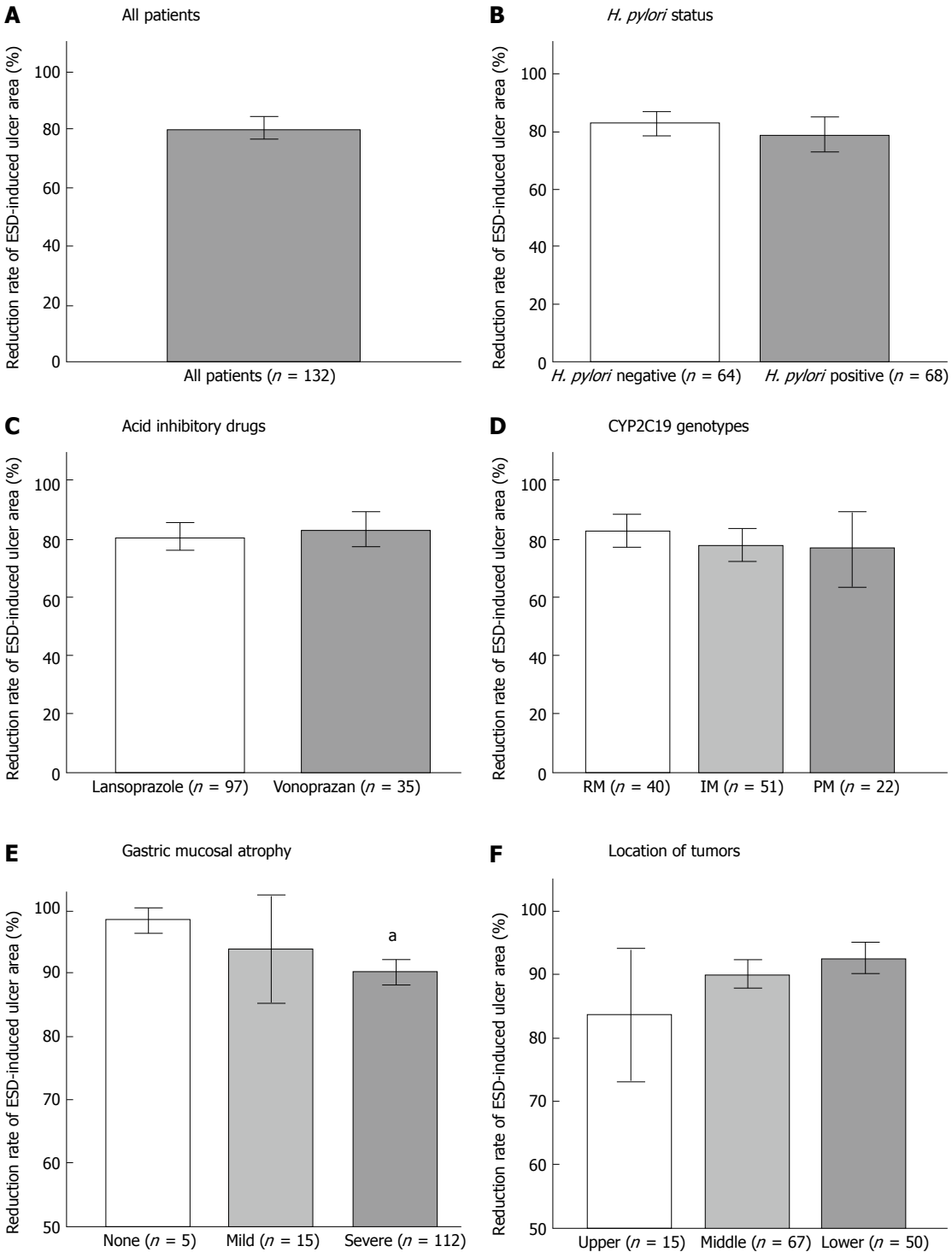

Figure 2 After endoscopic submucosal dissection, mean reduction rate of endoscopic submucosal dissection-induced ulcer area at 4 wk in all patients (A), between *Helicobacter pylori*-positive and *Helicobacter pylori*-negative patients (B), between lansoprazole and vonoprazan (C), among CYP2C19 genotypes (EM, IM and PM) (D), among non-atrophy, mild atrophy and severe atrophy (E), and among different locations of tumor (lower third, middle third and upper third) (F). *H. pylori*: *Helicobacter pylori*.

with severe gastric atrophy and is a well-known risk factor for gastric cancer, similar to severe gastric atrophy alone. The prevalence of intestinal metaplasia in *H. pylori*-positive patients is 57% in Japanese aged approximately 70 years[26]. Although we saw no significant association between the severity of intestinal metaplasia and ulcer healing speed in this study, Chen *et al*[27] reported that patients with intestinal metaplasia had a higher healing rate of gastric ulcers than those without intestinal metaplasia, suggesting that patients with severe gastric atrophy accompanied by intestinal metaplasia should be considered as likely candidates for ESD-related complication, due to delayed ulcer healing.

In general, peptic ulcer healing has been correlated with intragastric pH[28], *H. pylori* infection[20], gastric motility[29], microcirculation in gastric mucosa[30-32],

gastric mucosal levels of growth factors[33,34] and prostaglandins (PGs)[35]. The aggressive factors induced gastric mucosal injury resulting in loss of mucosal barrier can be quickly healed if adequate supply of PGE_2, epidermal growth factor and tumor growth factor (TGF) α takes place. Although it is unclear whether peptic ulcers and ESD-induced ulcers share a similar healing mechanism, because severity of gastric mucosal atrophy reduced microcirculation in gastric mucosa and gastric mucosal levels of prostaglandin and growth factors, resulted that advanced gastric atrophy perturbs the process of ulcer healing in the presence of these above factors.

Association with intragastric pH and speed of post-ESD ulcer healing

Vonoprazan has a longer half-life (7.7 h) than PPIs, due to its slow dissociation from H^+/K^+-ATPase[36]. In addition, vonoprazan inhibits H^+/K^+-ATPase activity with 400-fold greater potency than lansoprazole at pH 6.6[37]. Therefore, use of vonoprazan for treatment of ESD-induced ulcers is expected to confer an advantage over the conventional regimen with a PPI. This is despite the finding of Kagawa *et al*[5], who reported that the rates of ESD-related ulcer healing were 96.0% ± 6.7% at 6 wk with vonoprazan and 94.7% ± 11.6% at 8 wk with PPI, despite the fact the post-ESD bleeding incidence in the vonoprazan group (1.3%) was less than that in the PPI group (10.0%, $P = 0.01$). In a prospective randomized controlled trial, the rate of scar formation attained with vonoprazan at 8 wk was significantly higher than that for esomeprazole (94.9% *vs* 78.0%, $P = 0.049$), and in a multivariate analysis, only vonoprazan was correlated with scar formation (OR = 6.33; 95%CI: 1.21-33.20)[14]. However, although we have two kinds of clinical pathways scheduled to use lansoprazole or vonoprazan after ESD treatment for gastric tumors and investigated to analyze the healing speed of ulcer after ESD by use of only the two kinds of acid inhibitory drugs, lansoprazole and vonoprazan, there was no significant difference between vonoprazan and lansoprazole at 4 wk and 8 wk after ESD in this study. Given that one factor associated with healing of ESD-induced ulcers at 8 wk in multivariate analysis was initial ulcer size, this discrepancy may be due to differences in the size of lesions. Although potent acid inhibition is required to heal ESD-induced ulcers, a 90% reduction in ESD-induced ulcers was achieved at 28 d, irrespective of acid inhibitors. It is important to investigate whether the kind of acid inhibitor influences the speed of artificial ulcer reduction in an earlier phase (*i.e.*, within 2 wk).

Limitations

Several limitations of this study warrant mention. First, the sample size is not large. Second, we did not gather data regarding the reduction rate at 2 wk post-ESD. In this study, most ESD-induced ulcers had already healed by 4 wk post-ESD, which means evaluation at an earlier phase is required. Third, although we investigated the influence of CYP2C19 genotype, which impacts the pharmacodynamics of PPI, on the healing of ulcers, we did not clarify whether the CYP3A4/5 genotype, which is related to vonoprazan-dependent pharmacodynamics, influenced healing[38]. Forth, although minerals (*e.g.*, Zn) and vitamins (*e.g.*, Vitamin C) may affect the healing speed of ulcer after ESD, unfortunately, we have no data of minerals and vitamins in all patients[39,40].

In conclusions, we conducted a study to investigate factors influencing the healing speed of ESD-induced ulcers. Healing speed was affected by the severity of gastric atrophy, but not by *H. pylori* status, kinds of acid inhibitory drugs, or CYP2C19 genotype. These results suggest that eradication of *H. pylori* can be carried out at any time in terms of ulcer healing and that PPI or vonoprazan treatment for ESD-induced ulcers can be administrated at the standard dose irrespective of CYP2C19 genotype.

ARTICLE HIGHLIGHTS

Research background

The endoscopic submucosal dissection (ESD) for early-stage gastric cancer is first-line therapy in Japan, because of en bloc resection and a lower local recurrence rate of gastric cancer. However, bleeding from ESD-induced ulcer is a major complication of ESD treatment. When ESD is performed for gastric cancer, PPIs or vonoprazan are used to treat ESD-induced ulcers in Japan. It remains unclear whether vonoprazan with more potent and sustained acid inhibition than PPIs, *H. pylori* infection and characteristics of gastric mucosa (*e.g.*, inflammation and atrophy) are associated with improved ulcer healing speed and prevention of post-ESD bleeding. Rapid healing of ESD-induced ulcers is key to the prevention of delayed bleeding.

Research motivation

Of many possible factors related to ESD-induced ulcer healing, such as location of the tumor, submucosal fibrosis, initial ulcer size, diabetes, coagulation abnormality, electrocoagulation during ESD, and method of gastric acid suppression, it is unclear whether above parameters actually affect the healing of ESD-induced ulcers and the incidence of gastrointestinal bleeding after ESD treatment. Especially, there was no report investigated with the healing speed of ulcer after ESD and characteristics of gastric mucosa (*e.g.*, inflammation and atrophy).

Research objectives

The main objective was to clarify factors that might be associated with healing of post-ESD ulcers and bleeding, including *H. pylori* status, profile of the gastric tumor, kinds of acid inhibitory drugs, and severity of gastritis including of gastric atrophy and intestinal metaplasia.

Research methods

We retrospectively enrolled 132 patients with gastric tumors scheduled for ESD, irrespective to *H. pylori* infection. Following ESD, patients were treated with daily lansoprazole 30 mg or vonoprazan 20 mg for 8 wk. Ulcer size was endoscopically measured on the day after ESD and at 4 and 8 wk. The gastric mucosa was endoscopically graded according to the Kyoto gastritis scoring system. We assessed the number of patients with and without a 90% reduction in ulcer area at 4 wk post-ESD and scar formation at 8 wk, and looked for risk factors for slower healing.

Research results

After ESD, mean healing rates of ESD-related ulcer were 90.4% ± 0.8% at 4 wk and 99.8% ± 0.1% at 8 wk. The reduction rate was associated with the Kyoto grade of gastric mucosal atrophy at 4 wk and ESD-induced ulcers with ⩾ 90% healing at 4 wk were associated with absence of atrophy, depth of

gastric tumor, and procedure time. In the univariate analysis to identify possible factors related to achievement of 90% healing at 4 wk, healing was associated with gastric atrophy, procedure time and initial ESD-induced ulcer size. In the multivariate analysis, the factor associated with 90% healing at 4 wk was gastric mucosal atrophy (OR = 5.678, 95%CI: 1.190-27.085, *P* = 0.029).

Research conclusions

The healing speed of ESD-induced ulcers was affected by the severity of gastric atrophy, but not by *H. pylori* status, kinds of acid inhibitory drugs, or CYP2C19 genotype. Patients with severe gastric atrophy accompanied by intestinal metaplasia should be considered as likely candidates for ESD-related complication, due to delayed ulcer healing. Therefore, *H. pylori* eradication therapy is required to perform at younger age before progression of gastric mucosal atrophy to prevent development of *H. pylori*-related diseases and bleeding from ESD-induced ulcer.

Research perspectives

Eradication of *H. pylori* can be carried out at any time in terms of ulcer healing and that PPI or vonoprazan treatment for ESD-induced ulcers can be administrated at the standard dose irrespective of CYP2C19 genotype. However, because this is a preliminary small study, further study is required to plan whether the healing speed of ESD-induced ulcers was affected by the severity of gastric atrophy in prospective multicenter study. In addition, we will clarify the potential mechanism about association with the healing of ESD-induced ulcer and severity of gastric atrophy as further study.

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ORIGINAL ARTICLE

Observational Study

Endoscopic ultrasound-guided drainage of pancreatic walled-off necrosis using self-expanding metal stents without fluoroscopy

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Data sharing statement: Data set available from corresponding author braden@em.uni-frankfurt.de. Consent has not been obtained for sharing of this data but all data have been anonymised and the risk of identification is therefore low.

STROBE statement: Guidelines of the STROBE Statement have been adopted.

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Abstract

AIM

To investigate whether endoscopic ultrasound (EUS)-guided insertion of fully covered self-expandable metal stents in walled-off pancreatic necrosis (WOPN) is feasible without fluoroscopy.

METHODS

Patients with symptomatic pancreatic WOPN undergoing EUS-guided transmural drainage using self-expandable and fully covered self expanding metal stents (FCSEMS) were included. The EUS visibility of each step involved in the transmural stent insertion was assessed by the

operators as "visible" or "not visible": (1) Access to the cyst by needle or cystotome; (2) insertion of a guide wire; (3) introducing of the diathermy and delivery system; (4) opening of the distal flange; and (5) slow withdrawal of the delivery system until contact of distal flange to cavity wall. Technical success was defined as correct positioning of the FCSEMS without the need of fluoroscopy.

RESULTS

In total, 27 consecutive patients with symptomatic WOPN referred for EUS-guided drainage were included. In 2 patients large traversing arteries within the cavity were detected by color Doppler, therefore the insertion of FCSEMS was not attempted. In all other patients (92.6%) EUS-guided transgastric stent insertion was technically successful without fluoroscopy. All steps of the procedure could be clearly visualized by EUS. Nine patients required endoscopic necrosectomy through the FCSEMS. Adverse events were two readmissions with fever and one self-limiting bleeding; there was no procedure-related mortality.

CONCLUSION

The good endosonographic visibility of the FCSEMS delivery system throughout the procedure allows safe EUS-guided insertion without fluoroscopy making it available as bedside intervention for critically ill patients.

Key words: Necrotizing pancreatitis; Peripancreatic fluid collection; Therapeutic endoscopic ultrasound; Transmural drainage; Acute pancreatitis

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Core tip: The use of self-expanding and lumen-apposing metal stents for the drainage of walled-off necrosis has revolutionised the treatment options and outcome of this disease. Conventionally, these stents are placed by endoscopic ultrasound-guidance but under fluoroscopic control. We could demonstrate that all steps of the stent insertion are visible endosonographically which allows safe and controlled stent placement. Without the need for fluoroscopy and consequent radiation protection regulations, this procedure becomes available in the endoscopy unit and at the bedside of critically ill patients.

Braden B, Koutsoumpas A, Silva MA, Soonawalla Z, Dietrich CF. Endoscopic ultrasound-guided drainage of pancreatic walled-off necrosis using self-expanding metal stents without fluoroscopy. *World J Gastrointest Endosc* 2018; 10(5): 93-98 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i5/93.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i5.93

INTRODUCTION

Endoscopic management by endoscopic ultrasound (EUS)-guided drainage and endoscopic necrosectomy has become the preferred treatment of walled-off pancreatic necrosis (WOPN) after necrotizing pancreatitis as it is minimally invasive and has lower morbidity compared to surgery[1,2]. Pancreatic pseudocysts can be relatively easily drained by insertion of plastic stents but the drainage of WOPN requires large caliber drainage or multi-stenting to empty the necrotic debris and often the remaining necrotic material has to be extracted by endoscopic necrosectomy[3-5]. The use of conventional plastic stents has limitations when treating WOPN because their narrow lumen is often prematurely occluded by necrotic debris[3].

The development of large caliber, specially designed lumen apposing fully covered self-expanding metal stents (FCSEMS) has provided new options for the drainage of peripancreatic fluid collections and improved clinical outcome[4-7].

Previously Rana *et al*[8] demonstrated that transmural drainage of non-bulging WOPN using plastic stents and nasocystic drains can be safely and effectively achieved non-fluoroscopically by endoscopic ultrasound guidance. The EUS-visibility during EUS-guided placement of metal stents has not been studied previously. However, the avoidance of radiation exposure and fluoroscopy would improve the availability of this outcome changing procedure for critically ill patients as it could be performed at the bedside.

Therefore, in this two-center, single arm study we investigated whether the transmural insertion of FCSEMS for large caliber drainage of WOPN is safely possible by EUS guidance only, avoiding fluoroscopy. For this purpose, we aimed to assess the EUS-visibility of all procedural steps that are required for EUS-guided transmural insertion of FCSEMS.

MATERIALS AND METHODS

From May 2014 we started a prospectively maintained database to audit clinical outcome of EUS-guided therapy of pancreatic fluid collections. EUS-guided transmural drainage of walled-off necrosis by FCSEMS insertion performed between May 2014 and August 2017 were analysed. Participating centers were the John Radcliffe Hospital in Oxford, United Kingdom and the Caritas Hospital in Bad Mergentheim, Germany.

The observational nature of the study was established with the respective Health Research Authority and Trust R and D department. The study was therefore registered locally in accordance with Trust clinical governance guidelines. All authors had access to the study data and had reviewed and approved the final manuscript.

Patients underwent EUS-guided FCSEMS insertion only if computed tomography or MRCP had confirmed WOPN based on the revised Atlanta classification[9] and the patients were symptomatic due to gastric outlet obstruction or biliary obstruction, or ongoing infection and fever despite intravenous antibiotic therapy. EUS-guided transluminal drainage of the pancreatic collection

was performed at least four weeks after onset of pancreatitis to allow for sufficient demarcation of the necrotic tissue. Patients were informed in detail about the risks and benefits of the endoscopic treatment and surgical and endoscopic alternatives. Informed consent was obtained from all patients before the endoscopic procedure.

Using a linear scanning therapeutic echoendoscope (EG 3870 Pentax Inc., Tokyo, Japan) EUS-guided drainage was performed in the endoscopy unit under endotracheal intubation and monitoring by an anaesthetic team. Doppler guidance was used to avoid intervening blood vessels and the optimal site for transmural access was selected giving the closest distance between necrotic fluid collection and the gastroduodenal lumen. Transmural access into the WOPN was achieved using a cystotome (Cook Endoscopy, Winston-Salem, NC, United States) or directly the Hot Axios™ electrocautery system (Xlumena Inc., Mountain View, CA, United States).

A 0.035-inch guidewire was advanced under EUS-guidance and coiled at least twice into the cavity to stabilize the position. The new tract was enlarged using the diathermy of the cystotome or the Axios™ electrocautery system before the stent delivery system (Axios™ or NAGI™ stent, TaeWoong Medical, Gyeonggi-do, South Korea) was introduced over the guidewire. For correct positioning, the opening of the distal flange in the cavity and slow withdrawal of the entire delivery system until the distal flange was in contact with the wall was controlled by EUS while the opening of the proximal flange was then observed endoscopically.

The EUS visibility of each step involved in the transmural stent insertion was assessed by the operators as "visible" or "not visible": (1) Access to the cyst by needle or cystotome; (2) insertion of a guide wire; (3) introducing of the diathermy and delivery system; (4) opening of the distal flange; and (5) slow withdrawal until contact of distal flange to cavity wall.

Final correct position of the FCSEMS was confirmed endoscopically when the liquid content of the WOPN emptied through the stent into the gastric lumen. Fluoroscopy was not used at any time during the procedure.

As clinically indicated, endoscopic necrosectomy was performed through the large diameter metal stent[10]. When the collection had shrunk to less than 4 cm on ultrasound or computed tomography after at least 6 wk follow-up the metal stent was endoscopically removed. Additional pigtail plastic stents were not inserted during this study, neither through the FCSEMS to prevent stent migration nor after removal of the FCSEMS.

Further imaging after stent removal was reviewed to assess recurrence of pancreatic collections.

Primary outcome of this study was the technical feasibility of EUS-guided FCSEMS placement without fluoroscopy and the EUS visibility of the different steps during stent insertion. Technical success was defined as correct positioning of the transmural FCEMS without using fluoroscopy during the procedure. Secondary outcome parameters included adverse events and clinical outcome.

Statistical analysis

Continuous variables were reported in median and interquartile range. Categorical variables were described as frequencies. The technical success of EUS-guided stent insertion was reported according to intention-to-treat-analysis. Procedure-related adverse events are given as per-protocol.

RESULTS

From the prospective database, 27 consecutive patients with symptomatic walled-off necrosis after necrotizing pancreatitis were identified who were referred for EUS-guided insertion of FCSEMS to drain the fluid content and necrotic debris. Patient demographics and indications for endoscopic intervention are given in Table 1.

Technical feasibility

In 2 patients large diameter traversing arteries within the cavity were detected by Doppler during the orientating EUS, therefore the insertion of FCSEMS was not attempted to avoid possible erosion of the vessels by the stent edges with reducing collection size. In one patient a plastic stent was inserted instead, the other suffered a spontaneous haemorrhage into the necrotic cavity a week later and was found to have a necrotic tumour at surgery.

In all other patients, the EUS-guided insertion of the FCSEMS was technically successful achieving correct stent positioning without any fluoroscopy (92.6%) (Table 2).

EUS visibility

(1) Access to the cyst by needle or cystotome could be endosonographically visualized in all 25 patients; (2) insertion of a guide wire could be monitored on EUS in all patients, however, the visibility of the entire coiling of the wire was limited in 6 patients with large amounts of debris within the cavity (> 30%); (3) introduction of the diathermy and delivery system was clearly seen, both in all NAGI™ as well as all Hot Axios™ stents. The diathermy produces artefacts on EUS during transmural transition but the caliber difference between guidewire and diathermy/delivery system is clearly visible within the fluid filled cavity; (4) opening of the distal flange could be clearly observed using all stents; and (5) the slow withdrawal of the opened distal flange until reaching contact to the cavity wall could be continuously monitored with both stent types in all patients (Figure 1).

Adverse events and clinical outcome

In nine patients, endoscopic necrosectomy through the large diameter metal stent became necessary due to incomplete clearance of debris or stent occlusion by obstructing necrotic tissue and/or infection.

Overall procedure-related adverse events occurred in 3 of 25 patients (12.0%); one patient developed self-

Table 1 Patient demographics and baseline characteristics of 27 patients with walled-off necrosis after necrotizing pancreatitis

Characteristic	Value
Sex, male/female	21/6
Median age (interquartile range), yr	54 (45-63)
Median size of walled-off pancreatic necrosis (interquartile range), cm	14 (12-16)
Cause of pancreatitis	
Alcohol induced	9
Biliary	17
Idiopathic	1
Main indication	
Gastric outlet obstruction	15
Biliary obstruction	3
Infection/fever despite antibiotic therapy	9

Table 2 Performance characteristics of non-fluoroscopic endoscopic ultrasound-guided fully covered self expanding metal stents insertion in patients with walled-off necrosis

Characteristic	Patients, *n* = 27
Technical success	25 (92.6%)
Type of stent	
Axios™	8
NAGI™	17
Stent diameter, mm	
12	2
14	11
15	10
16	2
Transduodenal/transgastric/ transoesophageal approach	1/24/0
Adverse events	4 (in 3 patients)
Stent migration	1 (after WOPN resolved)
Self-limiting bleeding	1
Perforation/Pneumoperitoneum	0
Readmission with fever	2

FCSEMS: Fully covered self-expanding metal stent; WOPN: Walled-off pancreatic necrosis.

limiting bleeding, two patients were readmitted with fever and a blocked stent and subsequently underwent endoscopic necrosectomy. In one of the readmitted patients the stent migrated spontaneously after 4 wk but the WOPN had already resolved. There was no procedure-related mortality (Table 2).

After 8 wk the WOPN had resolved in all but one patient (96.0%) to a diameter of less than 4 cm. The patient with persistent WOPN had deep extensions of the inflammatory cavity into the retrocolic gutter requiring additional percutaneous drainage.

There were no adverse events at the time of stent removal. From the 24 patients with successful resolution of the WOPN, 20 had further imaging (ultrasound, CT or MRCP) after six months. None had reoccurrence of pancreatic collections indicating disconnected pancreatic tail syndrome. Four patients did not have follow-up of more than 8 wk available as they had been discharged back to the referring hospitals.

DISCUSSION

The endoscopic management of WOPN has been simplified by technical advances in EUS and the development of specially designed, dumbbell-shaped, fully covered large caliber stents which can be placed endoscopically in a few or even only one step[5,11-13]. In contrast to plastic stents, the radial expansive forces of FCSEMS and the lumen-apposing design avoid leakage of fluid along the newly created transmural tract. The wide flanges should prevent dislodgment and migration.

Usually, FCSEMS are placed under EUS-guidance with fluoroscopic control of guidewire insertion, tract enlargement and stent deployment. In these series, we could show that all the steps required for endoscopic transmural insertion of FCSEMS into a WOPN can be visualized and safely monitored by EUS without the need for fluoroscopy. Although we used different stents due to availability and preference in the different centres, the EUS visibility of both types during all steps of the procedure was excellent: The cystotome access, the insertion of the guidewire, the transmural advancing of the diathermy and delivery system, the opening of the distal flange and the correct positioning by withdrawal to the wall of the WOPN could be controlled and displayed by EUS in all patients.

On the other hand, the endosonographic visibility of access needle, guide-wire, cystotome and stent delivery system might depend on the debris content within the WOPN. None of the WOPNs in this series had debris of more than 50% but we only very rarely see WOPN with debris filling more than 50% of the cavity.

Fluoroscopy has not been applied in any of the transgastric stent insertions in this study. It might be argued that the availability of fluoroscopy is important should adverse events occur during the procedure. However, the most common complications related to EUS-guided transluminal stent insertion into pancreatic collections can be managed endoscopically or recognized endosonographically as well. In case of massive bleeding it might be helpful to inflate a balloon within the stent to achieve tamponade. Stent dislocation or incorrect positioning is recognized endoscopically and usually requires repeating the procedure.

Recently, an intra-channel release technique has been described for the hot axios stent which also enables a fluoroless placement[14]. However, it remains unclear whether fluoroscopy has been used additionally in these cases and the visibility of the deployment steps has not been reported. Another retrospective recent study reports on 25 selected patients in whom EUS-guided stent insertion was safely performed without fluoroscopy[15].

The strength of our study is the fact that we included consecutive patients and systematically assessed the visibility of all procedure steps. Another advantage is that we tested the EUS-visibility of two types of stents, a lumen apposing and another FCSEMs, the most commonly inserted metal stents for the purpose of

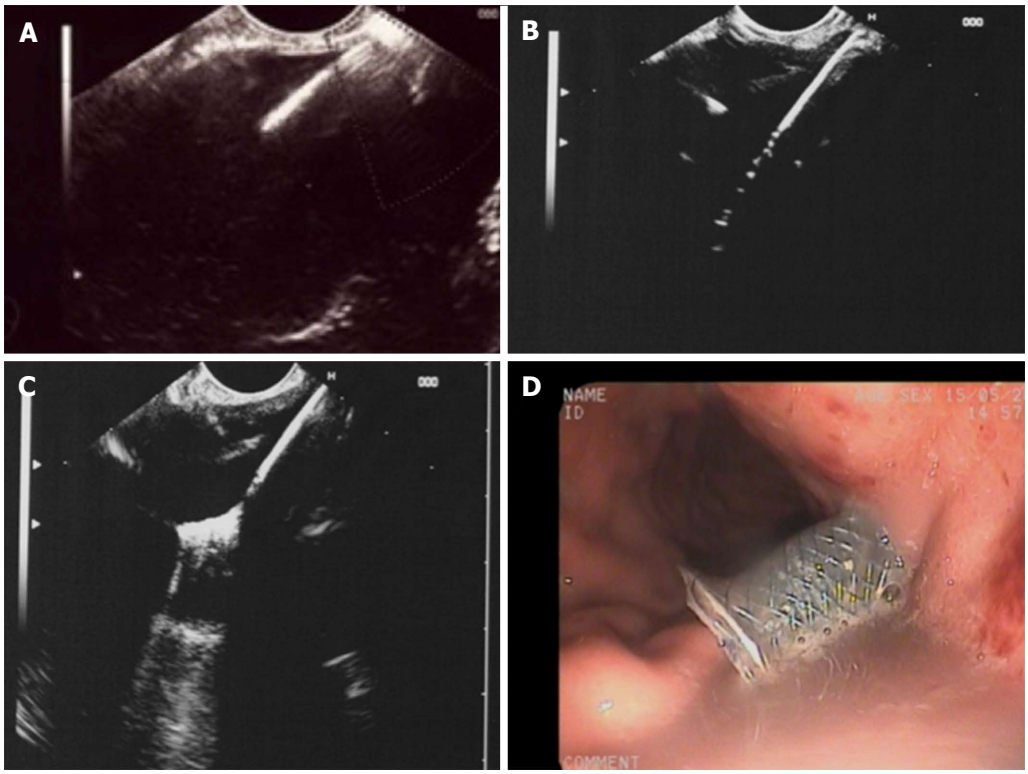

Figure 1 Endoscopic ultrasound-guided transgastric insertion of a fully covered self-expanding metal stent into a walled-off necrosis. A: Transmural access using the the cystotome; B: Insertion and coiling of the guidewire into the cavity; C: Opening of the distal flange; D: Endoscopic confirmation of correct positioning.

WOPN drainage.

In nine patients endoscopic necrosectomy to extract obstructing necrotic material from the stent was required. The large diameter of the stents allows the direct endoscopic access and the anchoring flanges prevent stent dislodgment during the endoscopic debridement of the necrotic cavity.

For 20 patients imaging follow-up after 6 mo was available. None of these patients had signs of re-occurrence of a peripancreatic collection after removal of the FCSEMS as would be expected in case of dis-connected pancreatic tail syndrome. The large diameter of the newly created track between pancreatic cavity and gastric lumen by the FCSEMS might facilitate persistence of a pancreaticogastric fistula if the pancreatic tail cannot drain *via* the papilla.

Our study has some limitations. The endoscopists evaluated the visibility of the different procedure steps themselves during the intervention. The procedures were not recorded and images were not evaluated by a second person. Also, we are tertiary centers practicing advanced endoscopic ultrasound procedures and our results may not be replicated in other centers. However, we believe that patients with complex WOPN should be treated in expert centers with multidisciplinary teams and expertise in pancreatic surgery. In addition, our study was not randomized or controlled and the sample size was relatively small. Ideally, a larger randomized study with a control arm using EUS and fluoroscopic imaging should be conducted.

In conclusion, all procedural steps during EUS-guided insertion of FCSEMS are well visualized by EUS. Non-fluoroscopic EUS-guided transmural insertion of FCSEMS for drainage of WOPN is feasible and appears to be safe and effective. Without the need for fluoroscopy and radiation exposure, EUS-guided drainage of WOPN with insertion of FCSEMS can become a bedside intervention for critically ill patients.

ARTICLE HIGHLIGHTS

Research background

Transluminal placement of specially designed fully covered self-expandable and lumen-apposing metal stents (FCSEMS) has improved the management and clinical outcome of walled-off pancreatic necrosis (WOPN). Most often this procedure is performed under fluoroscopy after EUS-guided access.

Research motivation

Without the need for fluoroscopy EUS-guided drainage using large diameter metal stents would also become available in endoscopy units and at the bedside of critically ill patients. This procedure is often crucial for the management of patients with complex pancreatic necrosis.

Research objectives

The principal aim of this study is to assess the feasibility and safety of fluoroless, purely EUS-guided insertion of self-expandable and lumen-apposing stents for the drainage of walled-off pancreatic necrosis.

Research methods

In 27 consecutive patients, we investigated the EUS-visibility of all procedural steps required to insert a fully covered self-expandable metal stent as transluminal drainage of walled-off pancreatic necrosis. EUS-visibility, technical

success, outcome and adverse events were analysed.

Research results

All procedural steps could be visualised by EUS alone. Fluoroscopy was avoided in all patients undergoing transmural stent placement. EUS-guided insertion of the FCSEMS was technically successful achieving correct stent positioning in 92.6%.

Research conclusions

Non-fluoroscopic EUS-guided transmural insertion of FCSEMS for drainage of WOPN is feasible and appears to be safe and effective.

Research perspectives

Large multi-center studies and prospective registries would provide more information on the use of EUS-guided WOPN drainage as bedside intervention, its safety and long-term outcome, the best time intervals when to remove the metal stents.

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ORIGINAL ARTICLE

Prospective Study

Different options of endosonography-guided biliary drainage after endoscopic retrograde cholangio-pancreatography failure

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Author contributions: Ardengh JC performed the procedures; Lopes CV designed the study and wrote the manuscript; Kemp R and dos Santos JS provided the collection of all human material.

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Informed consent statement: All study participants, or their legal guardians, provided informed written consent prior to study enrollment.

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Abstract

AIM

To investigate the success rates of endosonography (EUS)-guided biliary drainage (EUS-BD) techniques after endoscopic retrograde cholangiopancreatography (ERCP) failure for management of biliary obstruction.

METHODS

From Feb/2010 to Dec/2016, ERCP was performed in 3538 patients, 24 of whom (0.68%) suffered failure to cannulate the biliary tree. All of these patients were initially submitted to EUS-guided rendez-vous (EUS-RV) by means of a transhepatic approach. In case of failure, the next approach was an EUS-guided anterograde stent insertion (EUS-ASI) or an EUS-guided hepaticogastrostomy (EUS-HG). If a transhepatic approach was not possible or a guidewire could not be passed through the papilla, EUS-guided choledochoduodenostomy (EUS-CD) was performed.

RESULTS

Patients were submitted to EUS-RV (7), EUS-ASI (5), EUS-HG (6), and EUS-CD (6). Success rates did not differ among the various EUS-BD techniques. Overall,

technical and clinical success rates were 83.3% and 75%, respectively. Technical success for each technique was, 71.4%, 100%, 83.3%, and 83.3%, respectively (P = 0.81). Complications occurred in 3 (12.5%) patients. All of these cases were managed conservatively, but one patient died after rescue percutaneous transhepatic biliary drainage (PTBD).

CONCLUSION

The choice of a particular EUS-BD technique should be based on patient's anatomy and on whether the guidewire could be passed through the duodenal papilla.

Key words: Cholestasis; Drainage; Endosonography; Interventional procedures; Jaundice; Neoplasms

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Core tip: Endosonography-guided biliary drainage is an effective alternative in the failure of endoscopic retrograde cholangiopancreatography, with the potential to provide the least invasive and the lowest risk therapeutic modality for biliary drainage when compared to percutaneous transhepatic biliary drainage or surgery. For this procedure, access to the biliary tree can be obtained by transhepatic or transduodenal approaches. However, the transhepatic approach offers a good acoustic window for puncture of the biliary tree, a straight and easier to work with position of the echoendoscope, a better positioning of the guidewire, and a lower chance of bleeding or choleperitoneum.

Ardengh JC, Lopes CV, Kemp R, dos Santos JS. Different options of endosonography-guided biliary drainage after endoscopic retrograde cholangio-pancreatography failure. *World J Gastrointest Endosc* 2018; 10(5): 99-108 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i5/99.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i5.99

INTRODUCTION

Traditionally, endoscopic retrograde cholangiopancreatography (ERCP) is the standard approach to biliary drainage[1,2]. However, the procedure fails in up to 10% of patients, especially owing to anatomic variations, malignant duodenal obstructions and previous surgeries[3,4]. For these cases, percutaneous transhepatic biliary drainage (PTBD) or surgery has been used, despite the high morbidity and not negligible mortality caused by these procedures[5,6].

More recently, endosonography-guided biliary drainage (EUS-BD) has emerged as an effective alternative, with the potential to provide the least invasive and lowest risk therapeutic modality for biliary access and drainage[7,8]. A recent meta-analysis has reported technical and clinical success of 90% and 94%, respectively[9].

We aimed to evaluate the role of different EUS-BD techniques in case of ERCP failure, and to propose a systematic routine for EUS-BD according to the feasible access routes to the biliary tree.

MATERIALS AND METHODS

Study design

This was a retrospective study with prospective data collection about the role of EUS-BD conducted at two tertiary-referral centers. Between February 2010 and December 2016, 3528 ERCPs were performed at these centers. Eligible cases included patients older than 18 years with unresectable biliopancreatic neoplasia, and patients with benign conditions referred to EUS-BD when access to the biliary tree and internal biliary drainage by ERCP were not possible. ERCP failure was considered when biliary cannulation could not be achieved even after advanced techniques (cannulation in addition to a pancreatic guidewire or stent, needle-knife access papillotomy over a pancreatic stent, cannulation through a duodenal stent, and back-loading of the duodenoscope over a duodenal guidewire to pass a luminal stricture). Exclusion criteria were an international normalized ratio (INR) > 1.5 or platelet count < 50000/μL, ascites around the puncture area, absence of an adequate acoustic window for hepatic or choledochal puncture, total gastrectomy, and patient refusal. After EUS-BD, four follow-up visits were scheduled for each patient during the first 90 d, or until their death. The study was approved by the Institutional Review Board (Approval No. 2.191.319), and all patients gave written informed consent for ERCP and EUS-BD before enrollment.

Technical aspects

All EUS-BD procedures were performed by the same experienced endoscopist with Fujinon (FujiFilm Corporation, Nishiazabu 2-chome Minato, Ku, Tokyo) duodenoscopes (ED-530XT) and curvilinear array echoendoscopes (EG530UT2) coupled to SU-7000 or SU-8000 ultrasound units. The sequential EUS-BD procedures proposed for all patients were as follows: first, transhepatic puncture with a 19 gauge aspiration needle (EUSN-19 T, Cook, Winston Sallen, NC, United States) was tried. The EUS-RV technique was successful when the guidewire could be passed through the papilla and seized in the second portion of the duodenum. In case of papillary benign disease or absence of duodenal stenosis, retrograde treatment with a duodenoscope or echoendoscope was performed. An anterograde approach was attempted when tumoral duodenal infiltration or duodenal stenosis did not allow the capture of the guidewire in the duodenum. If the anterograde approach failed, Endosonography-guided hepatogastrostomy (EUS-HG) was the next alternative. In case of failure of the intrahepatic puncture due

to unfavorable anatomy, cirrhosis or difficulty in maintaining the adequate position of the guidewire, patients were submitted to endosonography-guided choledocoduodenostomy (EUS-CD). If all approaches for EUS-BD were unsuccessful, patients were submitted to PTBD. Duodenal self-expandable metallic stents (SEMS) were used in all stenoses obstructing access to the papilla.

The procedures were always performed with the patient in the left lateral decubitus position, under deep sedation with the assistance of an anesthesiologist. After the procedure, patients were monitored for two hours, and intravenous antibiotics (ciprofloxacin and metronidazole) were given for 7 d.

Routine for EUS-BD approaches

Endosonography-guided rendez-vous: When the duodenoscope could reach the major papilla, EUS-RV was tried and a curvilinear echoendoscope was used to obtain biliary access. The tip of the echoendoscope was positioned in the gastric fundus to access the intrahepatic bile duct. A 19 gauge EUS aspiration needle was used to puncture the bile duct close to the hepatic hilum, and to insert a large-caliber guidewire to deploy the stent. After fluoroscopic confirmation of the needle inside the bile duct, the guidewire was inserted through the obstruction and passed to the duodenum. Once the guidewire crossed the papilla, the guidewire was retrieved with a biopsy forceps or snare. Next, a metal stent was deployed by means of the over-the-wire technique[10].

Endosonography-guided anterograde stent insertion: In the presence of neoplastic duodenal stenosis, when the guidewire could not be seized in the duodenum, the stent was placed in an anterograde way. Access to the intrahepatic bile duct was obtained using a 19 gauge aspiration needle. Once puncture of the bile duct was confirmed by fluoroscopy, the guidewire was inserted through the duodenal major papilla and positioned in the second portion of the duodenum. At this point, a SEMS was inserted through the gastric wall across the papilla.

Endosonography-guided hepatogastrostomy: EUS-HG was tried after failure of the EUS-RV and EUS-anterograde stent insertion (EUS-ASI) techniques, in those cases whose hepatic puncture was successful but the guidewire could not be passed through the papilla. The dilated intrahepatic bile duct was punctured, and the guidewire was placed through the stenosis. The tract was dilated with a 6 Fr cystostome, and a fully covered metal stent was deployed, with care taken to leave more than 3 cm of the stent in the gastric lumen to avoid food obstruction.

Endosonography-guided Choledocoduodenostomy: In patients for whom a transhepatic approach was not feasible, EUS-CD was performed with the identification of the extrahepatic bile duct from the duodenal bulb. Once the insertion of the guidewire into the bile duct was confirmed by cholangiography, the tract was dilated with a 6 Fr cystostome, and a fully covered self-expandable metal stent was inserted.

Technical and clinical success

Technical success was defined as adequate positioning of the stent as shown by endoscopic and fluoroscopic images. Clinical success was defined as a decrease of at least 50% in serum total bilirubin levels.

Statistical analysis

A linear model was adjusted for the calculation of the technical success prevalence ratios, generalized by Poisson distribution and by the linking logarithmic function using the Proc Genmod of SAS 9.3 software (SAS Institute Inc., Cary NC, United States) to determine whether the different approaches had any impact on efficacy, compared to the EUS-RV technique ($P > 0.05$).

RESULTS

Patient demographics and technical aspects

During the study period, it was not possible to cannulate the biliary tree in 24 of 3528 (0.68%) patients submitted to ERCP. Thirteen men and 11 women with a mean age of 67.8 years old were included in the study. The most common symptom was jaundice in 96% of the patients, followed by abdominal pain and acute biliary pancreatitis in 21% and 8.3% of cases, respectively. The demographics, reasons for ERCP failure, indications for EUS-BD, as well as technical and clinical success are listed in Table 1.

Endosonography-guided rendez-vous

The EUS-guided transhepatic approach was tried in all patients (Figure 1). In 18/24 (75%) cases, puncture of the bile duct was possible, but the passage of the guidewire through the papilla occurred only in 12 (50%) cases. The guidewire could be recovered in 5/7 cases, and the passage of the stent was performed by means of an EUS-RV technique (Figure 2). The complication rate for these cases was 28% (2/7), consisting of an intracavitary hemorrhage and a choleperitoneum, both managed conservatively. In 5 other cases the guidewire could not be recovered in the duodenum owing to duodenal stenosis (3) or papillary infiltration (2). For these cases, an EUS-ASI technique was the next option. In 6 other cases, the guidewire did not cross the papilla, and was positioned in the proximal common bile duct (4), and in the right lobe (1) and left lobe of the liver (1). For these cases, an EUS-HG was the next alternative. The remaining 6 patients for whom transhepatic approaches were not possible underwent EUS-CD.

EUS-guided anterograde stent insertion

Even after passage of the guidewire in the second

Table 1 Demographics and treatment success of patients submitted to endosonography-guided biliary drainage due to endoscopic retrograde cholangiopancreatography failure

	EUS-BD	EUS-RV	EUS-ASI	EUS-HG	EUS-CD
***n* (%)**	**24 (100)**	**7 (29)**	**5 (21)**	**6 (25)**	**6 (25)**
Sex (M/F)	13/11	5/2	1/4	4/2	3/3
Age (range), yr	67.8 (42-91)	67.7 (42-84)	60.8 (42-70)	68.2 (50-81)	73.5 (52-91)
Reasons for ERCP failure (*n*)	-	-	-	-	-
Malignant duodenal stenosis	8	2	3	2	1
Malignant papillary infiltration	7	1	2	1	3
Impossibility of access to the common bile duct or intrahepatic duct	7	2	0	3	2
Giant duodenal diverticulum	1	1	0	0	0
Billroth Ⅱ gastrectomy without access to the duodenal papilla	1	1	0	0	0
Indications for EUS-BD	-	-	-	-	-
Malignant	20	3	5	6	6
Pancreatic cancer	13	3	4	2	4
Liver metastases of colon cancer	4	0	0	3	1
Cholangiocarcinoma	1	0	0	1	0
Duodenal lymphoma	1	0	1	0	0
Papillary cancer	1	0	0	0	1
Benign	4	4	0	0	0
Common bile duct stones	2	2	0	0	0
Biliary necrotizing acute pancreatitis	1	1	0	0	0
Recurrent acute pancreatitis due to sphincter of Oddi dysfunction	1	1	0	0	0
Technical success *n* (%)	20 (83.3)	5 (71.4)	5 (100)	5 (83.3)	5 (83.3)
Clinical success (%)	18 (75)	4 (57.1)	5 (100)	4 (66.7)	5 (83.3)
Complications (%)	3 (12.5)	2 (28.5)	0 (0)	1 (16.7)	0 (0)

EUS-BD: Endosonography-guided biliary drainage; EUS-RV: Endosonography-guided rendez-vous; EUS-ASI: Endosonography-guided anterograde stent insertion; EUS-HG: Endosonography-guided hepaticogastrostomy; EUS-CD: Endosonography-guided choledochoduodenostomy.

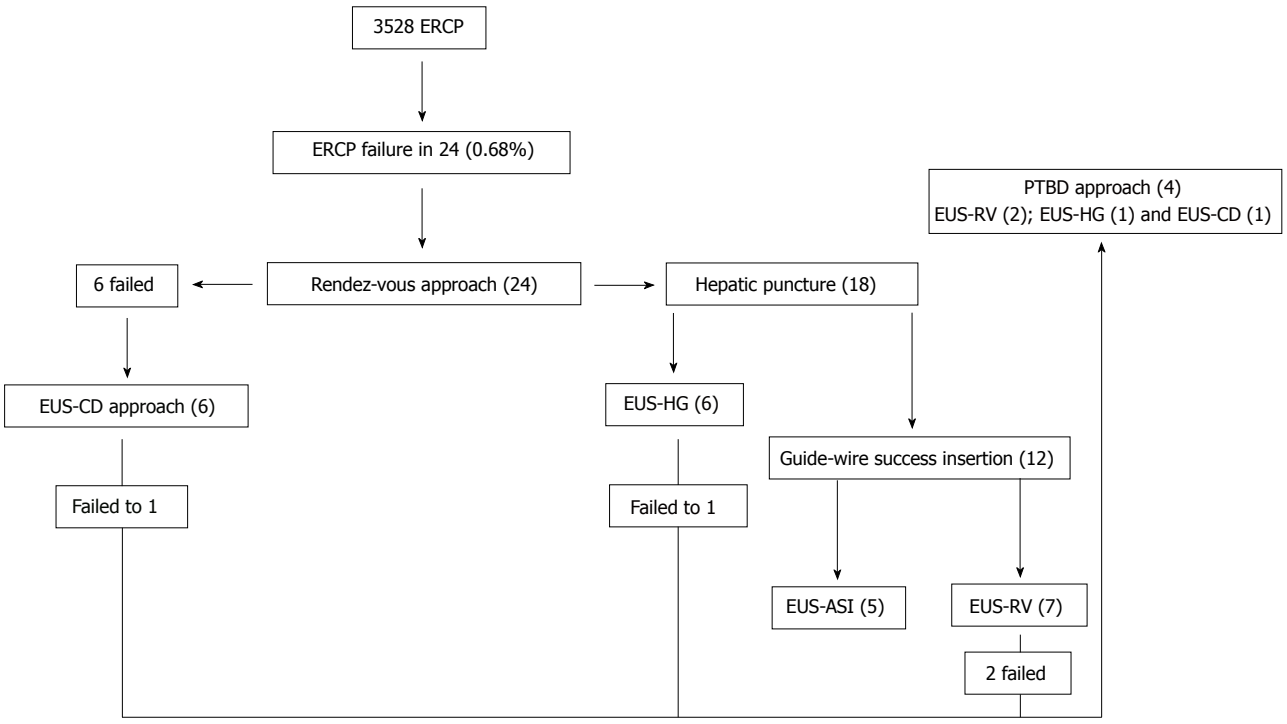

Figure 1 The systematic endosonography-guided biliary drainage approach for endoscopic retrograde cholangiopancreatography failure. PTBD: Percutaneous transhepatic biliary drainage; EUS-CD: Endosonography-guided choledochoduodenostomy; EUS-HG: Endosonography-guided hepaticogastrostomy; EUS-ASI: Endosonography-guided anterograde stent insertion; EUS-RV: Endosonography-guided rendez-vous.

duodenal portion, the recovery of the guidewire was not possible in 5 patients due to malignant duodenal stenosis (3) or papillary infiltration (2). For these cases, anterograde deployment of the biliary SEMS was performed (Figure 3). After passage of the biliary SEMS, a duodenal SEMS was delivered in 3 patients

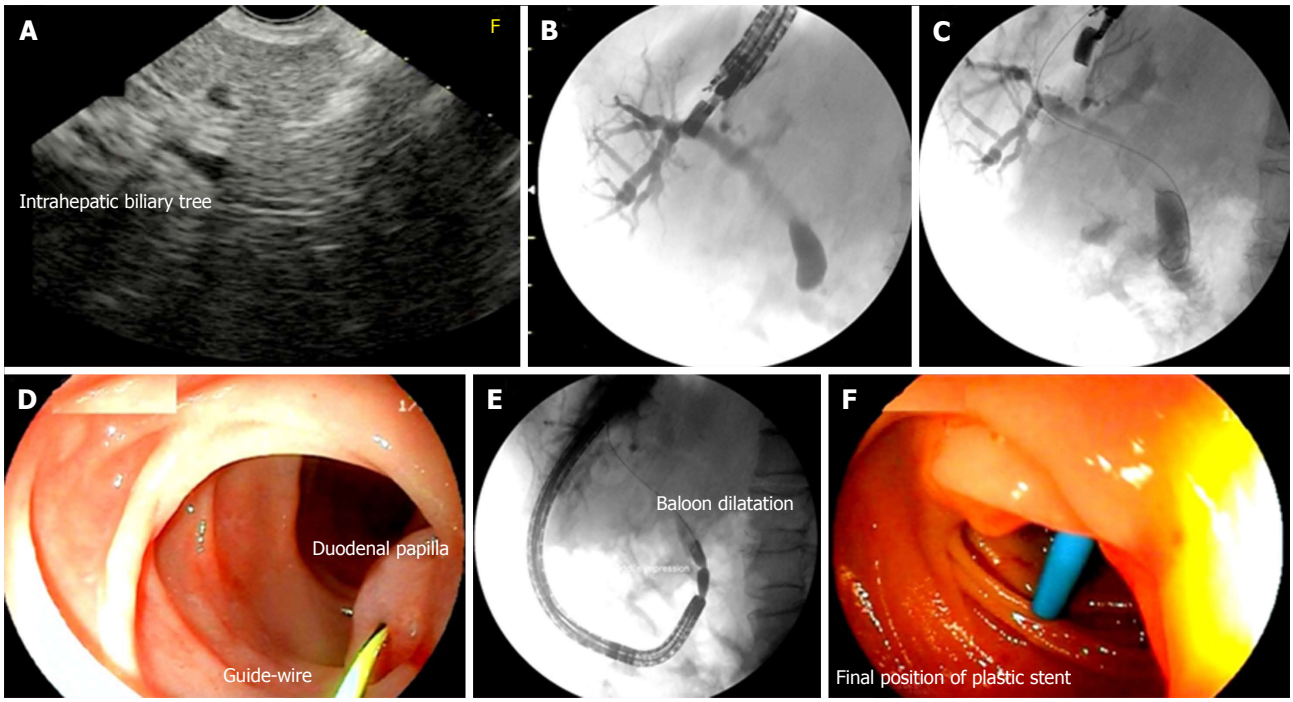

Figure 2 Patient with acute pancreatitis after cholecystectomy and Billroth Ⅱ gastrectomy. Endosonography (EUS)-guided rendez-vous technique. A: EUS image with dilation of the intrahepatic biliary duct; B: EUS-guided cholangiography; C: Insertion of the guidewire across the duodenal papilla and positioning in the duodenum; D: Capture of the guidewire with a frontal view endoscope; E: Balloon dilatation of the duodenal papilla; F: Insertion of a 10 Fr plastic stent.

with neoplastic duodenal stenosis. The overall technical success was 100%.

Endosonography-guided hepatogastrostomy

EUS-HG through transhepatic puncture was tried in 6 patients in whom the guidewire was positioned in the common bile duct (4), right lobe (1) and left lobe of the liver (1) (Figure 4). In 5/6 (83.3%) cases, an uneventful passage of the biliary SEMS was possible. For a single patient with recurrent liver metastasis from colon cancer after hepatectomy, the introduction of the transhepatic guidewire was impossible. The technical success rate was 83.3%, with one patient developing a pneumoperitoneum after the procedure.

Endosonography-guided choledochoduodenostomy

The insertion of the biliary stent through the duodenal puncture was tried in 6 patients as a rescue EUS-guided procedure for biliary drainage (Figure 5). All of these cases presented malignancies (Table 1). The correct positioning of the guidewire was achieved in 5/6 (83.3%), and one case was referred to PTBD. There was no complication.

Technical and clinical success

The overall technical success for EUS-BD was 83.3% (20/24). There was no significant difference among the various techniques (P = 0.81). Prior to EUS-BD, the mean levels of serum total and direct bilirubin were 13.3 mg/dL (5-29.9) and 9.1 (3-20.4) mg/dL, respectively. Ten days after EUS-BD, the mean levels were 2.3 (1.3-33) mg/dL, and 1.7 (0.6-22) mg/dL, respectively. The overall clinical success of EUS-BD was 75%.

Complications

Three (12.5%) complications occurred in patients submitted to EUS-BD: a pneumoperitoneum, a choleperitoneum, and an intracavitary liver hemorrhage. All of them were a consequence of the liver puncture in the hilum and were treated conservatively (Table 1). The patient with liver hemorrhage died three days after the PTBD due to acute respiratory and renal failure.

DISCUSSION

In our experience, an alternative to ERCP failure for biliary drainage was necessary in 0.68% of the cases, a finding similar to the rate of 0.62% in the experience of Holt *et al*[11]. Elderly people with malignant biliary obstruction are the most common candidates for the procedure[11], which was the case in our study, with patients at a median age of 68 years and with malignancies representing 83% of the cases. Endosonography-guided biliary drainage has been an alternative therapy to PTBD and surgery in ERCP failure[8,12]. PTBD, despite its satisfactory results, has a complication rate of about 30%, and surgery, although regarded as the definitive treatment for biliary drainage, is associated with high morbidity and mortality, especially for cases with terminal neoplastic disease[11,13,14].

Overall, the therapeutic success of EUS-BD ranges

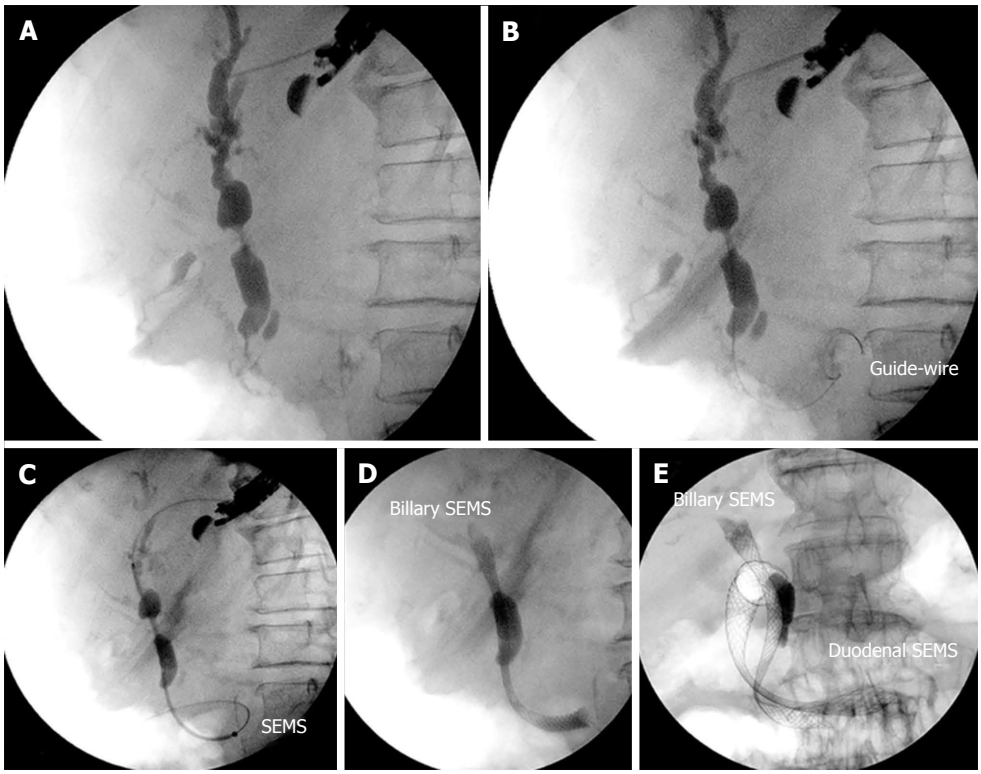

Figure 3 Patient with duodenal stenosis due to a pancreatic carcinoma. A: Endosonography (EUS)-guided cholangiography; B: Insertion of the guidewire through the duodenal major papilla and positioning in the duodenum; C: Anterograde insertion of the self-expandable metallic stents (SEMS) through the gastric wall across the duodenal major papilla and its positioning in the duodenum; D: Deployment of the SEMS; E: Insertion of the duodenal SEMS. SEMS: Self-expandable metallic stents.

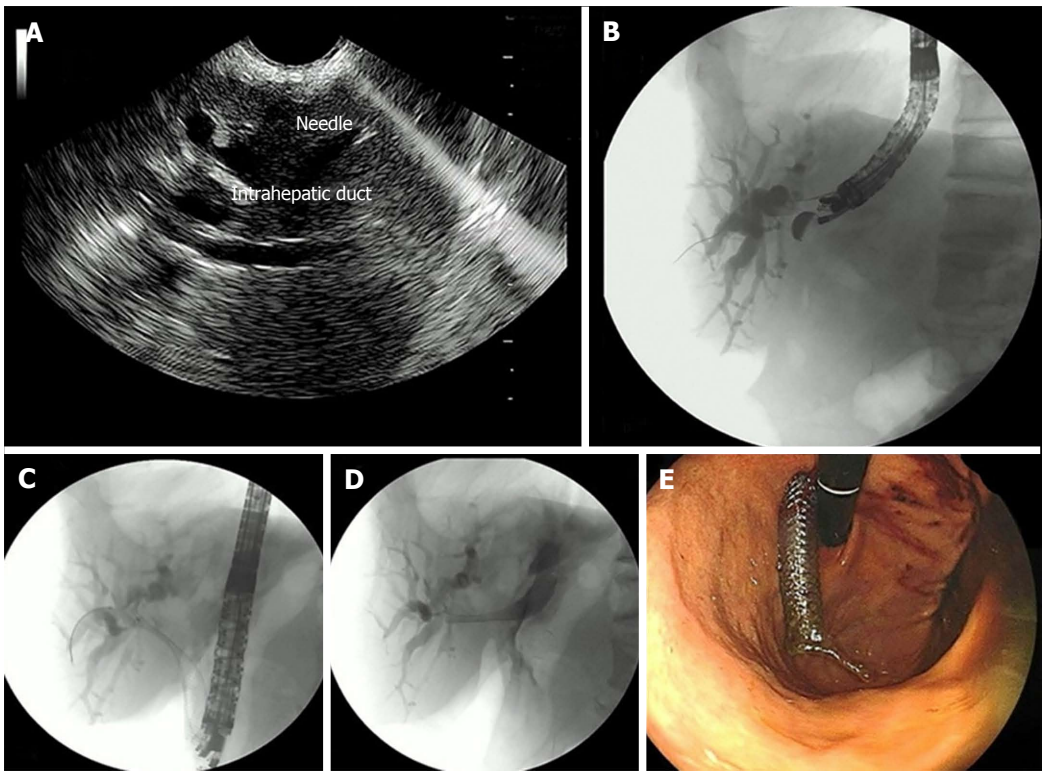

Figure 4 Endosonography-guided hepatogastrostomy. A: Endosonography (EUS) puncture of the dilated biliary intrahepatic duct; B: EUS-guided cholangiography; C and D: Deployment and positioning of the biliary self-expandable metallic stents (SEMS); E: Endoscopic view of the SEMS through the gastric wall.

from 73% to 100%[15-19]. However, there is no consensus about the best EUS-BD technique[9]. Regarding

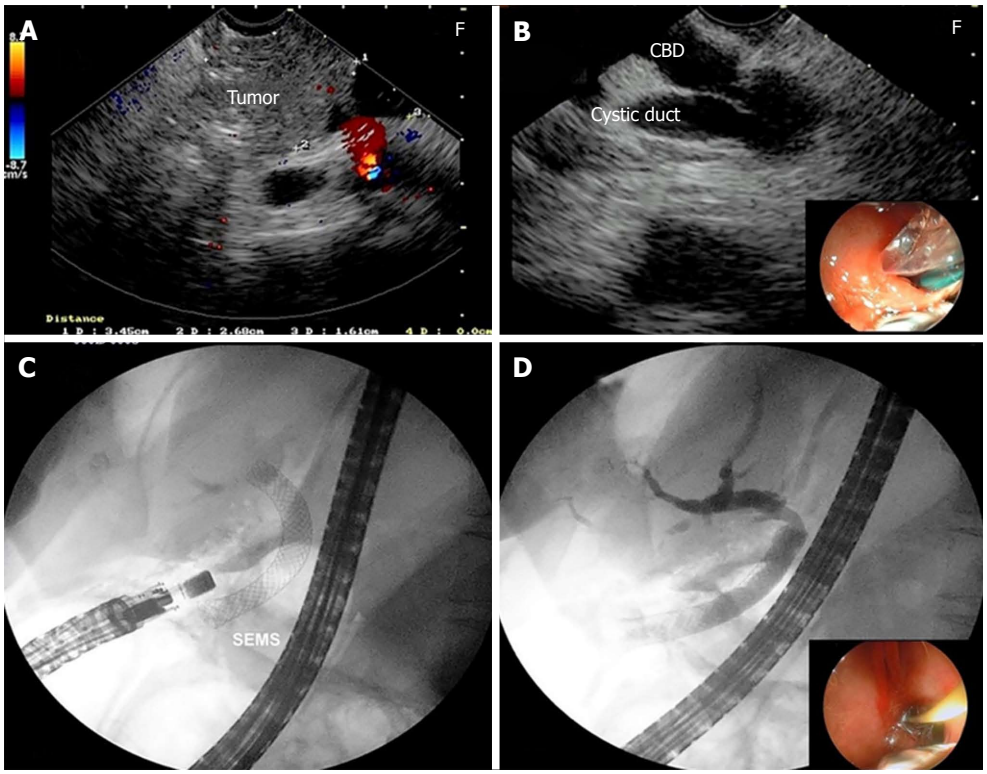

Figure 5 Endosonography-guided choledochoduodenostomy. A: Endosonography (EUS) image of the pancreatic carcinoma; B: Puncture of the common bile duct through the duodenum with a 19 gauge aspiration needle; C: Insertion of the self-expandable metallic stents after balloon dilation of the fistula; D: EUS-guided cholangiography through the choledochoduodenostomy.

particular EUS-BD techniques, there is a scarcity of comparative studies. Ogura *et al*[20] compared EUS-HG and EUS-CD for patients with jaundice and duodenal obstruction. Patients submitted to the transhepatic approach exhibited a longer patency of the biliary stent than those submitted to the transduodenal approach. In addition, the EUS-CD technique revealed a higher rate of complications, especially reflux cholangitis (OR = 10.285; 95%CI: 1.686-62.733; P = 0.012). Artifon *et al*[21] also evaluated the two techniques in a randomized clinical trial. There was no significant difference in effectiveness or safety between the two procedures. Technical and clinical success, as well as complications rates were 96%, 91%, and 20% for EUS-HG, respectively, and 91%, 77% and 12.5% for EUS-CD, respectively.

In an attempt to demonstrate the value of EUS-RV as the initial therapeutic option for biliary drainage in ERCP failure, Iwashita *et al*[22] performed the procedure using the transduodenal approach and using the transhepatic approach after failure of the transcholedochal approach. The authors concluded that EUS-RV is an effective and safe procedure, as also observed in our own experience. However, in contrast to the cited study, we began EUS-BD by the transhepatic approach, leaving the transduodenal approach only for the rescue option in the failure of the transhepatic approach.

In our experience, the transhepatic approach allows us to choose among three EUS-BD techniques according to the recovery or not of the guidewire, *i.e.*, the EUS-RV, EUS-ASI and EUS-HG techniques. Our group has adopted a systematic EUS-BD routine starting with the transhepatic access to initially perform the EUS-RV or EUS-ASI technique. This approach offers a good acoustic window for puncture of the biliary tree, a straight and easier to work position of the echoendoscope, a better positioning of the guidewire, and a lower chance of bleeding or choleperitoneum, with both complications amenable to tamponade by the liver parenchyma[19,23]. In our study, beginning with the transhepatic approach, the overall technical success was 83%, and the clinical success (intention-to-treat) was 75%, similar to literature results[23]. On the other hand, the transduodenal approach permits an easier execution of only the EUS-CD or, although more laborious and time-consuming, the EUS-RV. In the failure of this approach, the transhepatic approach should be the rescue therapy.

Nevertheless, despite the good results of EUS-BD when using the transhepatic approach, the literature still mentions some concern about the risk of complications with the intrahepatic access[18,20,24]. The needle must traverse the peritoneal cavity, a procedure that might increase the risk of pneumo- and choleperitoneum. This complication occurred in one of our patients and was managed conservatively. Another issue is the movement of the stomach and liver during breathing

and peristalsis, which might induce stent migration, trauma to the bilioenteric tract, and bile leakage. Finally, small-caliber intrahepatic ducts may not accommodate wider 8-mm to 10-mm metal stents, possibly predisposing to pneumoperitoneum and bile leakage due to incomplete sealing of the bilioenteric fistula[25,26]. For this reason, our goal during EUS-BD by means of the transhepatic approach is to obtain an intrahepatic duct of larger caliber as close as possible to the hepatic hilum.

In all of our cases in which the guidewire could not be reached in the duodenum due to stenosis or papillary infiltration, EUS-ASI succeeded without complications. The good performance and low complications rate of the EUS-ASI technique has been demonstrated in the literature[27].

On the other hand, if the patient has only a dilated biliary tree where the hepatic puncture is feasible but the guidewire could not reach the papilla, EUS-HG should be the next option. The greatest limitation in patients undergoing EUS-HG is the access to the right intrahepatic biliary tract and the progression of the guidewire to the common bile duct or its passage through the duodenal papilla. However, many authors justify selective drainage of the left intrahepatic biliary tract compared to the extrahepatic approach[7,28,29]. Both approaches have been shown to be effective and to involve low complications rates[21,26].

Nonetheless, EUS-BD by transhepatic approach may not be possible in some cases, depending on the patient anatomy[19,30]. We observed EUS-RV failure due to the impossibility of puncturing the liver or the inability to maintain the stability of the guidewire, and the difficulty to seize the guidewire in the duodenal lumen. In such cases, an extrahepatic approach must be adopted. The transcholedochal approach has the benefit of being feasible in patients whose papilla cannot be reached and has the advantage of being close to the duodenum[7,31,32]. In the current study, the technical success rates were the same (83.3%) for EUS-HG and EUS-CD, in agreement with published series[20,21]. Except for a pneumoperitoneum in the intrahepatic group, no difference in major complications was found between EUS-HG and EUS-CD (16.6% *vs* 0%; $P = 0.81$).

As a whole, EUS-BD is a safer technique than PTBD and surgery, with complication rates ranging from 10% to 20%, although the severity of most cases is mild to moderate[10,13]. Our complication rate also agreed with that reported in other studies[10,13]. Three of our cases developed complications, representing an overall rate of 12.5%. All of these cases were managed conservatively, but a patient with intracavitary bleeding was submitted immediately to PTBD after EUS-BD failure, and died three days later.

Despite the small number of our patients, this study did not demonstrate any significant difference in technical success or complication rates among different techniques of EUS-BD, in agreement with other studies[19,23].

In summary, a rational algorithm for EUS-BD in case of obstructive biliary diseases and ERCP failure might begin with the transhepatic approach, followed by particular EUS-BD techniques based on the patient's anatomy and feasibility to recover the guidewire.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard approach to biliary drainage, and, in the failure of the procedure, percutaneous transhepatic biliary drainage or surgery must be used. However, endosonography can guarantee the least invasive and lowest risk treatment for biliary drainage of these cases. This study presents the results of different techniques for endosonography-guided biliary drainage in case of ERCP failure.

Research motivation

In case of ERCP failure, patients must be submitted to surgery or percutaneous transhepatic biliary drainage at different places in the hospital and with a long delay in treatment, conditions which can increase the morbidity and risks for the patient. Endosonography-guided biliary drainage can be performed immediately after ERCP failure, decreasing the time and risk of definitive treatment of the patient.

Research objectives

The main objectives of the study were to evaluate the success rates of endosonography (EUS)-guided biliary drainage techniques after ERCP failure for the management of biliary obstruction, and to propose a rational approach based on the access to the biliary tree and feasibility to recover the guidewire.

Research methods

In our experience, an alternative to ERCP failure for biliary drainage was necessary in 24 of 3538 (0.68%) cases. Elderly people with malignant biliary obstruction were the most common candidates for the procedure. The sequential endosonography-guided biliary drainage (EUS-BD) procedures proposed for all patients were transhepatic puncture in order to perform the EUS-guided rendez-vous technique. An anterograde approach was attempted when the capture of the guidewire in the duodenum was not possible. If the anterograde approach failed, EUS-guided Hepatogastrostomy was the next alternative. In case of failure of the intrahepatic puncture, patients were submitted to EUS-guided choledochoduodenostomy (EUS-CD).

Research results

Patients were submitted to EUS-guided rendez-vous (7), EUS-guided anterograde stent insertion (5), EUS-guided hepaticogastrostomy (6), and EUS-CD (6). Success rates did not differ among the various EUS-BD technique. Overall, technical and clinical success rates were 83.3% and 75%, respectively. The technical success for each technique was 71.4%, 100%, 83.3%, and 83.3%, respectively ($P = 0.81$). Complications occurred in 3 (12.5%) patients. All of these cases were managed conservatively, but one patient died after a rescue percutaneous transhepatic biliary drainage. Regarding particular EUS-BD techniques, there is a scarcity of comparative studies, and a consensus about the best technique has not been established.

Research conclusions

A rational approach to EUS-guided biliary drainage in case of obstructive biliary disease and ERCP failure should begin with the transhepatic approach, followed by particular EUS-guided biliary drainage techniques based on the patient's anatomy and feasibility to recover the guidewire in the duodenum.

Research perspectives

EUS-guided biliary drainage should be included in the therapeutic arsenal for the management of malignant biliary obstruction in case of ERCP failure, and should be the choice rather than surgery or percutaneous transhepatic biliary drainage.

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