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**ORIGINAL ARTICLE****Retrospective Study**

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

*Otsuka T, Sugimoto M, Ban H, Nakata T, Murata M, Nishida A, Inatomi O, Bamba S, Andoh A*

**Observational Study**

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

*Braden B, Koutsoumpas A, Silva MA, Soonawalla Z, Dietrich CF*

**Prospective Study**

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

*Ardengh JC, Lopes CV, Kemp R, dos Santos JS*

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## 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  $17.4 \pm 12.1$  mm and  $32.9 \pm 13.0$  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.

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## INTRODUCTION

The efficacies of endoscopic submucosal dissection (ESD) and surgical gastrectomy for early-stage gastric cancer are generally similar<sup>[1]</sup>. 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)<sup>[2,3]</sup>.

Gastrointestinal bleeding from ESD-induced ulceration is a common complication<sup>[4-7]</sup>. 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<sup>[4-7]</sup>. 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<sup>[4-7]</sup>. When ESD is performed for gastric cancer, proton pump inhibitors (PPIs) are used to treat ESD-induced ulcers<sup>[7]</sup>. 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)<sup>[8,9]</sup> 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<sup>[10-12]</sup>. Although vonoprazan inhibits gastric H<sup>+</sup>/K<sup>+</sup>-ATPase similarly to PPIs, its mechanism of acid inhibition involves inhibition of H<sup>+</sup>, K<sup>+</sup>-ATPase by binding reversibly and competitively with K<sup>+</sup><sup>[13]</sup>. 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<sup>[5,14]</sup>.

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

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

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,  $\leq 3$  cm; (3) intestinal-type cancer invading the submucosa  $< 500$   $\mu\text{m}$  from the muscularis mucosa,  $\leq 3$  cm in size; and (4) intramucosal diffuse-type cancer without ulceration,  $\leq 2$  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<sup>[25]</sup>. 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)<sup>[25]</sup>.

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<sup>®</sup>, KD-650L/Q; Olympus, Tokyo, Japan) or an insulated-tip diathermic knife (IT knife 2<sup>®</sup>, KD-611L, Olympus, Tokyo, Japan) and applied electric current using an electrosurgical generator (VIO300D<sup>®</sup>; ERBE Elektromedizin GmbH, Tübingen, Germany). Visible vessels were heat-coagulated using hemostatic forceps (FD-412LR<sup>®</sup>; 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<sup>®</sup>; 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<sup>®</sup>; Eiken Chemical Co. Ltd., Tochigi, Japan) and a rapid urease test (Helicocheck<sup>®</sup>; 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<sup>®</sup>, Applied Biosystems, Foster City CA, United States). Subsequently, genotyping was performed using a single-nucleotide polymorphism (SNP) genotyping assay (TaqMan<sup>®</sup>, Applied Biosystems) in a real-time polymerase chain reaction (PCR) system (Step One Plus<sup>®</sup>, 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  $\pm$  SD. The healing rates of ulcers were calculated as (1-ulcer area/ulcer area just after ESD)  $\times$  100 (%) and are expressed as mean  $\pm$  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  $76.4 \pm 56.7$  min and the mean resected ESD-induced ulcer area was  $671.9 \pm 720.9$  mm<sup>2</sup> at Day 1. Procedure time for lesions in the lower third of the stomach ( $47.5 \pm 3.2$  min) was significantly shorter than those for the middle and upper thirds [vs middle ( $85.7 \pm 6.6$  min), *P* = 0.001, vs upper ( $131.3 \pm 17.9$  min), *P*  $<$  0.001, respectively]. The initial ulcer area in the lower third ( $456.4 \pm 265.2$  mm<sup>2</sup>) was significantly smaller than that of the middle third ( $822.0 \pm 922.2$  mm<sup>2</sup>, *P* = 0.008).

After ESD, mean ESD-induced ulcer areas at 4 and 8 wk were  $71.3 \pm 135.6$  mm<sup>2</sup> and  $2.8 \pm 15.6$  mm<sup>2</sup>, respectively, and mean healing rates were  $90.4\% \pm 0.8\%$  at 4 wk and  $99.8\% \pm 0.1\%$  at 8 wk (Figures 1A and 2A). At 8 wk, mean healing rate in the *H. pylori*-positive group ( $99.7\% \pm 0.1\%$ ) was significantly lower than that in the negative group ( $99.9\% \pm 0.0\%$ , *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:  $97.9\% \pm 0.6\%$ , A1:  $93.4\% \pm 4.1\%$ , and A2:  $89.7\% \pm 1.0\%$ , 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%)
<i>H. pylori</i> 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 <sup>2</sup> )	671.9 ± 720.9
ESD-induced ulcer area	
Reduction at 4 wk	90.4% ± 10.7%
Mean ulcer area at 4 wk (mm <sup>2</sup> )	71.3 ± 135.6
Reduction at 8 wk	99.8% ± 0.6%
Mean ulcer area at 8 wk (mm <sup>2</sup> )	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 ( $92.8\% \pm 1.2\%$ ) was significantly delayed compared to the upper two-thirds ( $83.7\% \pm 5.3\%$ ,  $P = 0.013$ ) (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  $\geq 90\%$  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  $\geq 90\%$  healing group was significantly shorter than that in the  $< 90\%$  healing group ( $65.6 \pm 41.1$  min vs  $89.7 \pm 64.0$  min,  $P = 0.026$ ). The prevalence of patients with open-type atrophic gastritis in the  $\geq 90\%$  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%)	<b>0.021</b>
<i>H. pylori</i> (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 <sup>2</sup> )	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
<i>Helicobacter pylori</i>	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 <sup>2</sup> )	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.

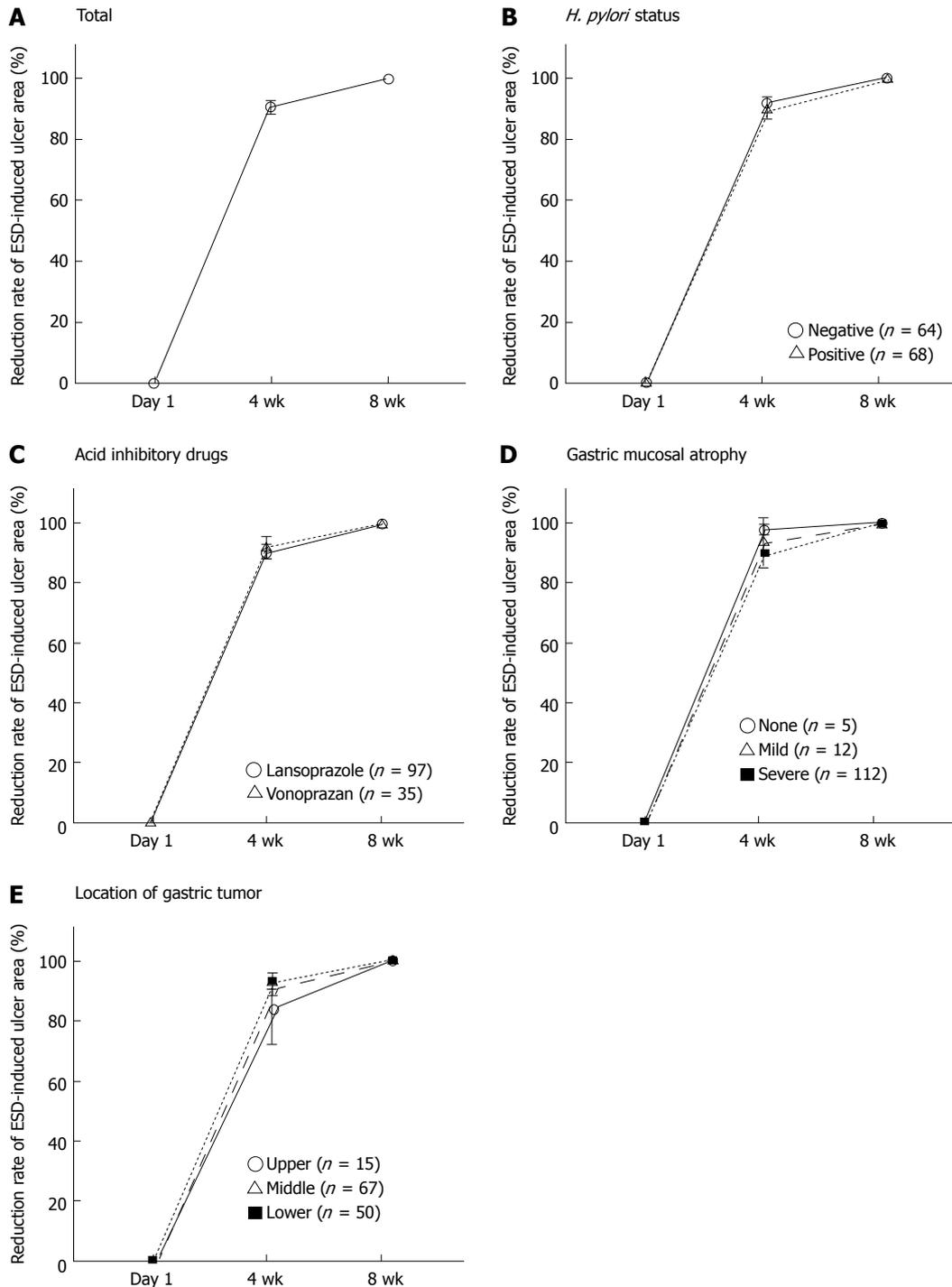
**Table 4 Multivariate analysis of factors preventing healing of ulcers after endoscopic submucosal dissection**

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
<i>Helicobacter pylori</i>	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 <sup>2</sup> )	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<sup>[15]</sup>, initial ulcer size<sup>[17,18]</sup>, coagulation abnormality<sup>[18]</sup>, electrocoagulation during ESD<sup>[18]</sup>, or

kind of gastric acid suppressant<sup>[19]</sup>. 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-

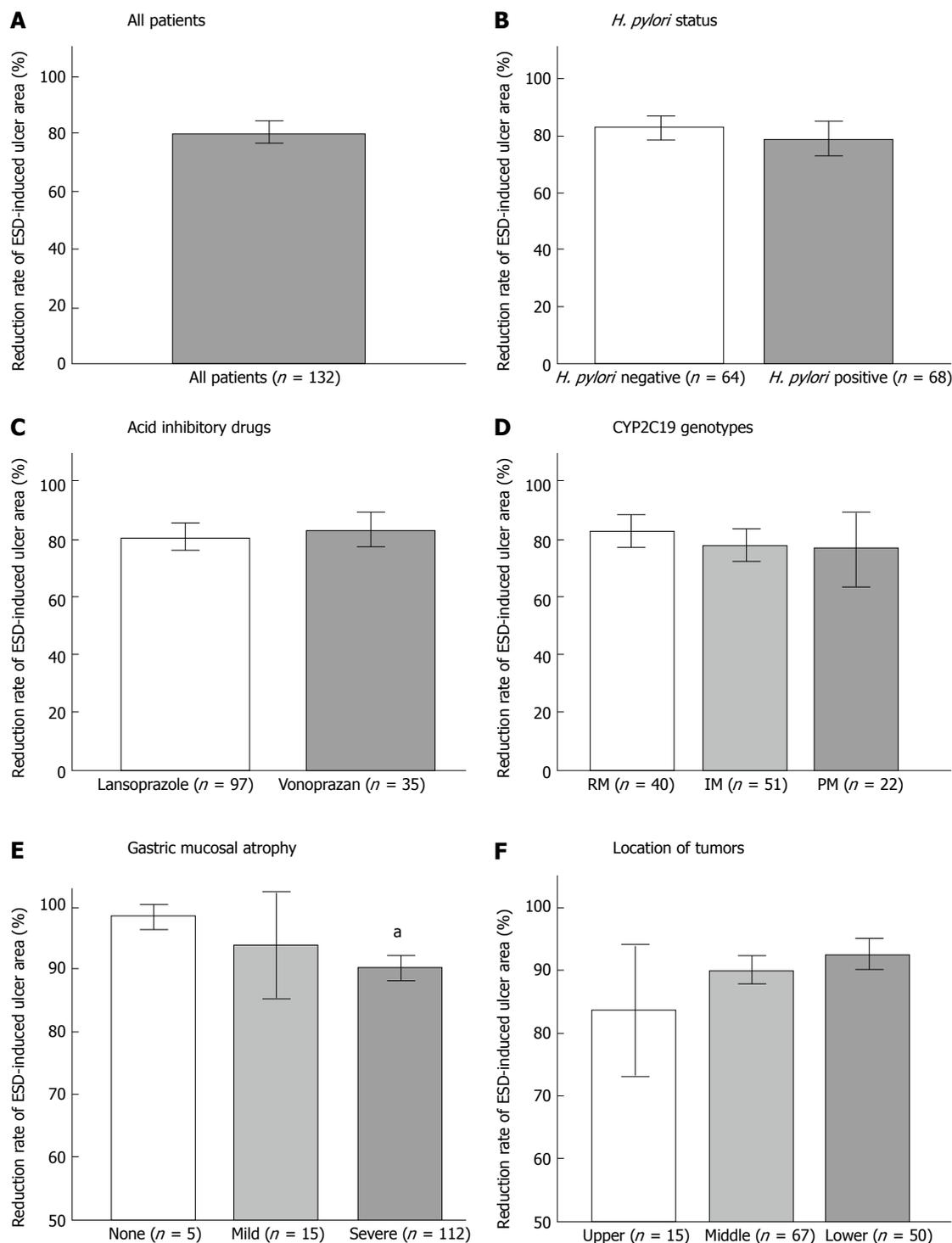


**Figure 1** After endoscopic submucosal dissection, mean endoscopic submucosal dissection-induced ulcer areas at 4 and 8 wk in all patients (A), between *Helicobacter pylori*-positive patients and *Helicobacter pylori*-negative patients (B), between lansoprazole and vonoprazan (C), among patients with 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*<sup>[24]</sup> 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*<sup>[23]</sup> 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<sup>[26]</sup>. Although we saw no significant association between the severity of intestinal metaplasia and ulcer healing speed in this study, Chen *et al.*<sup>[27]</sup> 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<sup>[28]</sup>, *H. pylori* infection<sup>[20]</sup>, gastric motility<sup>[29]</sup>, microcirculation in gastric mucosa<sup>[30-32]</sup>,

gastric mucosal levels of growth factors<sup>[33,34]</sup> and prostaglandins (PGs)<sup>[35]</sup>. The aggressive factors induced gastric mucosal injury resulting in loss of mucosal barrier can be quickly healed if adequate supply of PGE<sub>2</sub>, epidermal growth factor and tumor growth factor (TGF)  $\alpha$  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<sup>+</sup>/K<sup>+</sup>-ATPase<sup>[36]</sup>. In addition, vonoprazan inhibits H<sup>+</sup>/K<sup>+</sup>-ATPase activity with 400-fold greater potency than lansoprazole at pH 6.6<sup>[37]</sup>. 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.*<sup>[5]</sup>, who reported that the rates of ESD-related ulcer healing were 96.0%  $\pm$  6.7% at 6 wk with vonoprazan and 94.7%  $\pm$  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)<sup>[14]</sup>. 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<sup>[38]</sup>. 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<sup>[39,40]</sup>.

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%  $\pm$  0.8% at 4 wk and 99.8%  $\pm$  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  $\geq 90\%$  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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