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ORIGINAL ARTICLE—ALIMENTARY TRACT

Autofluorescence imaging videoendoscopy in the diagnosis of chronic atrophic fundal gastritis

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Abstract
Purpose Diagnosis of chronic atrophic fundal gastritis (CAFG) is important to understand the pathogenesis of gastric diseases and assess the risk of gastric cancer. Autofluorescence imaging videoendoscopy (AFI) may enable the detection of mucosal features not apparent by conventional white-light endoscopy. The purpose of this study was to estimate the diagnostic ability of AFI in CAFG.
Methods A total of 77 patients were enrolled. Images of the gastric body in AFI and white-light mode were taken to assess the extent of gastritis, and biopsies were taken from green ($n = 119$) and purple ($n = 146$) mucosa in AFI images. The diagnostic accuracy of green mucosa for CAFG was investigated according to the Sydney system.
Results In per-patient analysis, the accuracy of green mucosa in patients with activity, inflammation, atrophy and intestinal metaplasia was 64, 93, 88 and 81%, respectively. In per-biopsy analysis, the accuracy for activity, inflammation, atrophy and intestinal metaplasia was 55, 62, 76 and 76%, respectively. Green areas in the gastric body exhibited more inflammation ($p < 0.001$), atrophy ($p < 0.001$) and intestinal metaplasia ($p < 0.001$), whereas purple areas rarely contained atrophy or intestinal metaplasia. The kappa statistics for inter- and intra-observer agreement of AFI on assessing the extent of CAFG were 0.66 and 0.47, while those for white-light endoscopy were 0.56 and 0.39.
Conclusions AFI could diagnose the extent of CAFG as a green area in the gastric body, with higher reproducibility compared with white-light endoscopy. Therefore, AFI may be a useful adjunct to endoscopy to identify patients at high risk of developing gastric cancer.

Keywords Atrophic gastritis · *Helicobacter pylori* · Autofluorescence endoscopy · Image-enhanced endoscopy

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Introduction

Chronic atrophic fundal gastritis (CAFG) is related to the development and incidence of various gastric diseases, including malignancy. Therefore, evaluating the prevalence and state of gastritis is important to understand the pathogenesis of gastric diseases and assess the risk of gastric cancer [1]. Currently, histological diagnosis of biopsy specimens from certain parts of the gastric mucosa, i.e., the updated Sydney system, is the most widely accepted method for evaluating CAFG [2]. Aside from the limitation of biopsy histology in providing only focal diagnosis, one reason why biopsy is still a standard method to assess the grade of gastritis is related to its low

accuracy and poor observer agreement in terms of conventional white-light endoscopy for the diagnosis of gastritis [3, 4]. We previously developed the endoscopic Congo red test to evaluate the development and extent of CAFG in terms of a pH-dependent color change reaction of the Congo red dye [5]. We have reported that the extent of CAFG evaluated by this test is related to the risk of gastric cancer development [6], location and healing of gastric ulcer [7], gastric emptying [8] or types of polyp [9]. However, despite recent attempts to refine the method [10, 11], it is not widely used in clinical practice because it may be associated with substantial prolongation of routine endoscopic examinations, possible adverse effects and a general underestimation of the potential benefits of this method.

Autofluorescence imaging (AFI) videoendoscopy produces real-time pseudocolor images based on natural tissue autofluorescence emitted by light excitation from endogenous fluorophores such as collagen, nicotinamide, adenine dinucleotide, flavin and porphyrins [12]. Because AFI enables the detection of mucosal features not visible with conventional endoscopy, it might improve the identification and characterization of the premalignant status in gastric mucosa. During observation of the gastric body by AFI, we noticed that the mucosa of patients who were not infected with *H. pylori* appeared purple, whereas the mucosa of patients with infection and CAFG exhibited green areas that were predominantly located in the lesser curvature [13]. Therefore, we suspected that the green areas in the gastric body in AFI images represented changes in CAFG. Based on these considerations, the aims of the present study were to estimate the diagnostic accuracy of AFI for CAFG, and to determine how colors in the AFI images relate to histological changes in gastritis.

Methods

Participants

This was a case series study performed in a cancer referral center. Patients who visited an outpatient clinic in our center to receive esophagogastroduodenoscopy (EGD) and who gave written informed consent after explanation of the study were enrolled. Patients were excluded if they had severe symptoms, including >10% weight loss within 3 months, anemia (hemoglobin < 10 g/dl), vomiting or symptoms suggestive of acute bleeding, obstruction or perforation of the gastrointestinal tract; advanced gastric cancer; history of gastric surgery; previous *H. pylori* eradication therapy; major organ failure; anticoagulation therapy or coagulopathy; use of aspirin or non-steroidal anti-inflammatory drugs within 30 days; or pregnancy. The study protocol was approved by the ethical committee of our institution.

Endoscopy system

The AFI system used in this study consisted of a light source (CLV-260SL; Olympus Medical Systems Co. Ltd., Tokyo, Japan), a processor (CV-260SL, Olympus), a video monitor and a high-resolution videoendoscope (EVIS-FQ260Z, Olympus) equipped with two charged-coupled devices (CCDs) that were available for autofluorescence and white-light modes. In the autofluorescence mode, the light source emits blue excitation light (395–475 nm) to induce autofluorescence and green light (540–560 nm) to capture green reflection images sequentially through a rotation filter [14]. A cut filter was placed with the lens to permit only light with wavelengths between 490 and 625 nm to intensify the CCD for the AFI mode. The modes were changed within 3 s by pressing a small button on the control head of the endoscope.

Endoscopic procedure

All examinations were performed by an endoscopist (N.U.) who had 4 years of experience in performing autofluorescence endoscopy in more than 2,000 cases and 14 years of conventional endoscopy in 15,000 cases. The patients ingested a mixture consisting of a mucolytic agent (20,000 U pronase, Pronase MS; Kaken Pharmaceutical Co. Ltd., Tokyo, Japan), a defoaming agent (80 mg dimethylpolysiloxane syrup, Gascony Drops; Kissei Pharmaceutical Co. Ltd., Matsumoto, Japan) and 1 g sodium bicarbonate diluted in 100 ml of tap water 5 min before the examination. After topical anesthesia, the endoscope was gently inserted into the stomach. During routine observation of the entire stomach, at least two corresponding images of downward and retroflex views of the gastric body under white light and in the AFI mode were taken to evaluate the extent of CAFG. For the evaluation, the lumen of the gastric body was adequately distended with sufficient air insufflations to obtain good images. After all of the endoscopic observations had been completed, biopsy specimens were taken from areas at 2 and 0.5 cm from the border of the green and purple area of the gastric body under AFI observation. In cases in which the entire gastric body was purple, two biopsy specimens were taken 2 cm proximal to the gastric angle, and in cases in which the entire gastric mucosa appeared green, two biopsies were taken from the greater curvature in the middle portion of the gastric body.

Histology

All biopsy specimens were placed in separate labeled small pots filled with 10% buffered formalin. Each specimen was processed, embedded in paraffin, sectioned into 4-μm-thick slices and stained with hematoxylin and eosin (H&E). These preparations were reviewed by a single pathologist (Y.T.) who was blinded to the endoscopic findings. The pathologist had more than 15 years of experience in general pathology. Based on the updated Sydney system [2], all specimens were classified as none, mild, moderate or severe for the following four features: activity (polymorphonuclear cell infiltration), inflammation (mononuclear cell infiltration), glandular atrophy and intestinal metaplasia.

Assessment of the diagnostic accuracy of AFI for CAFG

For per-biopsy analysis, each histological feature of gastritis was defined as present if the grade was greater than mild and absent if the grade was classified as none. In per-patient analysis, the individual was defined as having a particular feature of gastritis when it was present in any of the biopsy specimens, and without gastritis when none of the biopsy specimens had the particular feature of gastritis. Therefore, in per-biopsy analysis, the diagnostic accuracy of the green areas in the gastric body for histologically proven gastritis was evaluated. In per-patient analysis, the accuracy of the green mucosa in the gastric body for diagnosing patients with histological finding of gastritis was evaluated.

Inter- and intra-observer variability

Reproducibility of the diagnosis of CAFG by AFI was assessed by an experienced endoscopist (N.U.) and by a resident who was less familiar with AFI (T.I.), and was compared with the reproducibility of the diagnosis by white-light imaging. One downward and one retroflex view image of the gastric body was obtained by AFI and white-light imaging in each patient, and they were randomly arranged and reviewed by the two endoscopists twice, at an interval of at least 2 weeks. In the AFI images, the extent of CAFG was considered to be the green areas in the gastric body and was classified into six categories based on the Kimura–Takemoto classification (Fig. 1) [15]: AF-C-I, the entire gastric body looked purple to dark green; AF-C-II, a color border on the lesser curvature was observed at a lower part of the gastric body; AF-C-III, a color border on the lesser curvature was observed at an upper part of the gastric body; AF-O-I, a color border was observed between the lesser curvature and the anterior wall; AF-O-II, a color border was observed between the anterior wall and the greater curvature; and AF-O-III, a color border on the greater curvature was observed proximal to the lower gastric body. In the white-light images, the extent of CAFG corresponded to areas of whitish mucosa, increased

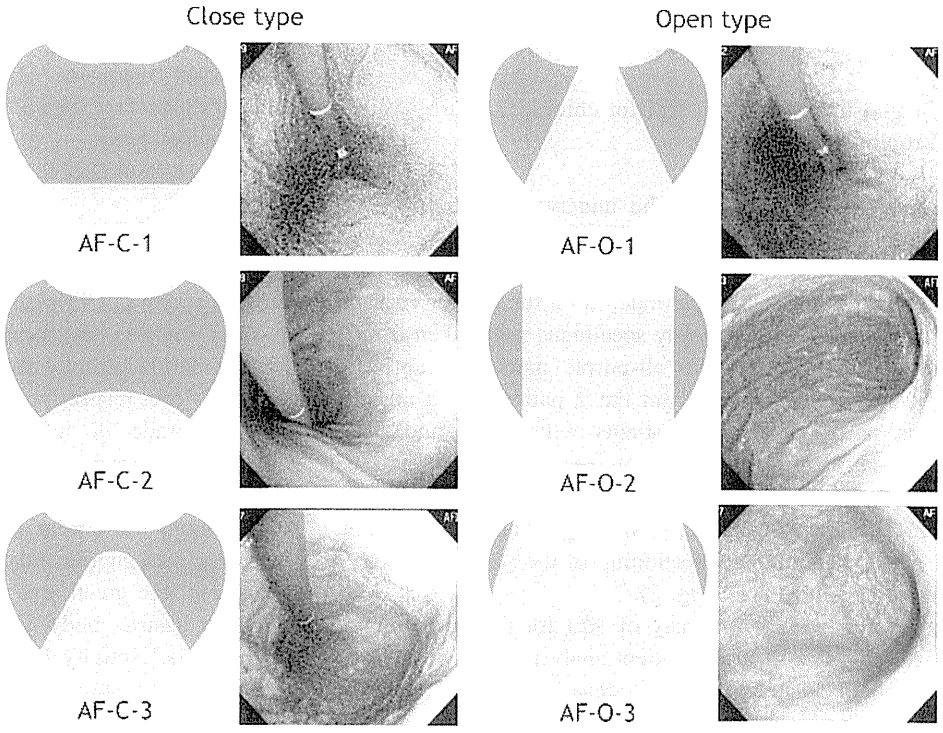

Fig. 1 Classification of the extent of atrophic fundal gastritis according to AFI color

visibility of mucosal vessels and loss of gastric rugae, and was classified into C-I to O-III according to the Kimura–Takemoto classification.

Statistical analysis

All statistical analyses were performed using JMP version 6.0 (SAS Institute Inc., Cary, NC). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of AFI for diagnosis of CAFG in per-patient and per-biopsy analyses were calculated. The grade of gastritis at each biopsy site, 0.5 and 2 cm from the color border in both green and purple mucosa, was compared by Friedman's test. The kappa (κ) values for the inter- and intra-observer agreement of the extent of CAFG in each AFI and white-light image was calculated. Agreement was considered poor if $\kappa < 0.2$, fair if $\kappa < 0.4$, moderate if $\kappa < 0.6$, substantial if $\kappa < 0.8$ or good if $\kappa > 0.8$.

Results

Participants

A total of 79 patients were enrolled between November 2006 and April 2007. We excluded one patient who had previously unknown diffuse advanced gastric cancer in the gastric body and another who had a large amount of food residue because of antral deformation that resulted from a scar after endoscopic resection of early gastric cancer. Finally, a total of 77 patients underwent AFI observation. Their demographics are shown in Table 1.

Table 1 Subject characteristics

Median age (range, years)	67 (63–75)
Sex	
Male	48
Female	31
H. pylori infection	
Positive	48
Negative	27
Not examined	4
Indication for esophago-gastro-duodenoscopy	
Follow-up examination	
Post endoscopic treatment for early gastric cancer/adenoma	35
Post-chemoradiation therapy for esophageal cancer	2
Esophageal varices	2
Gastric ulcer	1
Gastric polyp	1
Post-operation for laryngeal cancer	1
Pre-treatment evaluation	
Early gastric cancer or adenoma	9
Esophageal cancer	2
Abnormality in barium study	10
Symptoms	
Bloating	7
Epigastralgia	5
Chest discomfort	2
Dysphagia	2
Localized lesions in the stomach	
Post EMR/ESD scar	37
Early gastric cancer/adenoma	10
Gastric polyp	10
Malignant lymphoma	2
Gastric ulcer/ulcer scar	2
Submucosal tumor	2
Advanced gastric cancer	1
None	15

Diagnostic accuracy of AFI for chronic atrophic fundal gastritis

Among the 77 patients who underwent AFI, for 17 the entire mucosa in the gastric body was purple, 2 had all-green mucosa, and 58 had green mucosa on the lesser curvature side and purple mucosa on the greater curvature side (Fig. 2). Thirty biopsy specimens were taken from 15 of the 17 patients with all-purple mucosa; four biopsy specimens were taken from the 2 patients with all-green mucosa. From the 58 patients with green and purple mucosa, 115 biopsy specimens were taken from the green mucosa and 116 from the purple mucosa (Fig. 2). Of a total of 265 biopsy specimens, 15 were not evaluable for atrophy because of horizontal sectioning of the surface mucosa or small specimen size (Fig. 2).

The diagnostic accuracy of AFI for CAFG is summarized in Table 2. In per-patient analysis, we found that the diagnostic accuracy of green areas in the gastric body for patients with activity, inflammation, atrophy and intestinal metaplasia was 64, 93, 88 and 81%, respectively. In per-biopsy analysis, the accuracy of AFI for areas of activity, inflammation, atrophy and intestinal metaplasia was 55, 62, 76 and 76%, respectively.

The grade of inflammation, atrophy and intestinal metaplasia at 0.5 and 2 cm from the border of the green area was significantly more severe than that at 0.5 and 2 cm from the border of the purple area. The grade of atrophy was significantly more severe at 2 cm from the border of the green area than at 0.5 cm. The purple areas in the gastric body had little atrophy and intestinal metaplasia. Activity (polymorphonuclear cell infiltration) did not differ significantly between the green and purple areas (Fig. 3).

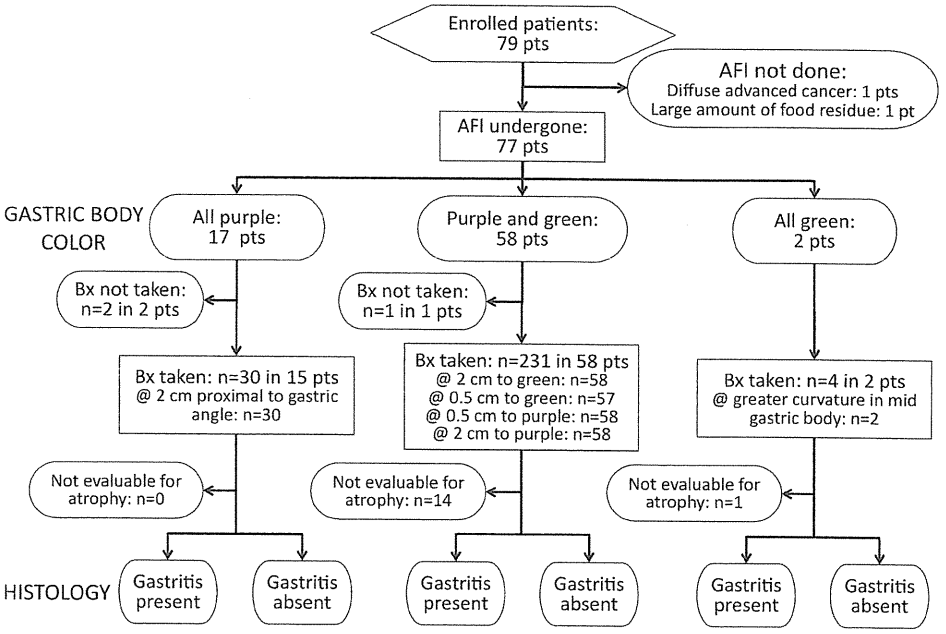

Fig. 2 Flow diagram of study samples

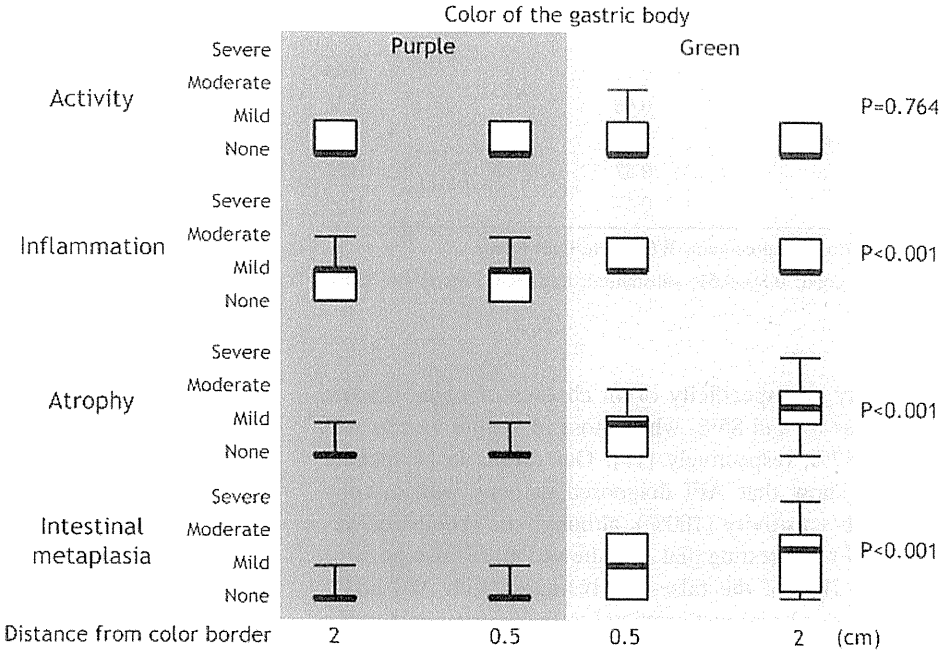

Fig. 3 Histological findings of biopsy specimens in relation to distance from AFI color border. Box plot indicates maximum, 75% percentile, median, 25% percentile and minimum. *P* values by Friedman's test

Reproducibility of AFI for the diagnosis of atrophic fundal gastritis

A total of 156 AFI images and 156 white-light images were obtained in 77 patients to evaluate reproducibility. For assessment of the extent of CAFG, the intra-observer agreement was substantial ($\kappa = 0.67$, 95% CI 0.55–0.80) for AFI, but only moderate ($\kappa = 0.56$, 95% CI 0.42–0.70) for the white-light images. The inter-observer agreement between the experienced endoscopist and the resident was moderate ($\kappa = 0.47$, 95% CI 0.37–0.57) for AFI and fair ($\kappa = 0.39$, 95% CI 0.29–0.49) for the white-light images (Table 3).

Discussion

Although gastritis is a histological entity, attempts have been made to diagnose the disease macroscopically during EGD. Redeen et al. investigated the diagnostic ability of conventional white-light endoscopy for patients with moderate-to-severe atrophy, and they demonstrated that the

Table 2 Diagnostic accuracy of green mucosa in the gastric body for gastritis

	%Sensitivity [95% CI]	%Specificity [95% CI]	%PPV [95% CI]	%NPV [95% CI]	%Accuracy [95% CI]
Per patient					
Activity	97 [92–100]	35 [20–50]	57 [44–69]	93 [81–100]	64 [53–75]
Inflammation	98 [95–100]	78 [59–97]	93 [87–100]	93 [81–100]	93 [88–99]
Atrophy	100 [100–100]	63 [43–82]	85 [76–94]	100 [100–100]	88 [81–95]
Intestinal metaplasia	100 [100–100]	52 [34–70]	77 [66–70]	100 [100–100]	81 [73–90]
Per biopsy					
Activity	50 [40–60]	57 [50–65]	38 [30–47]	68 [61–76]	55 [49–61]
Inflammation	55 [48–62]	86 [77–94]	93 [88–97]	37 [29–45]	62 [56–68]
Atrophy	72 [64–81]	78 [71–85]	70 [62–79]	80 [73–86]	76 [70–81]
Intestinal metaplasia	77 [69–85]	75 [68–82]	67 [58–75]	83 [77–89]	76 [71–81]

PPV positive predictive value, *NPV* negative predictive value

Table 3 Agreement for the diagnosis of the extent of atrophic gastritis

	Method	
	AFI	WLI
Intra-observer		
Pa	0.74	0.65
κ	0.66	0.56
Inter-observer		
Pa	0.57	0.51
κ	0.47	0.39

Pa proportion of agreement, *WLI* white-light image

κ: >0.80, good; 0.80–0.61, substantial; 0.60–0.41, moderate; 0.40–0.21, fair

sensitivity and specificity of an absence of rugae (gastric folds) was 67 and 85%, while those of visible vessels was 48 and 87%, respectively [16]. Our results in per-patient analysis show that AFI diagnosed patients with atrophy with high sensitivity (100%), although the specificity was low (63%), suggesting that AFI showed more false-positive findings. Half of the false-positive cases with AFI had a small area (<2 cm) just proximal to the gastric angle in the lesser curvature of the lower gastric body. Therefore, we suspect that a small green area in this region is unlikely to be related to CAFG and may be excluded from the diagnostic criteria. In the reminder of the false-positive cases, although atrophy was diagnosed as none in all of the biopsy specimens, moderate-to-severe inflammation or intestinal metaplasia was found in many of the biopsy specimens, so histological diagnosis in small biopsy specimens might underestimate the presence of atrophy, causing a discrepancy between endoscopic diagnosis and histology.

Kaminishi et al. assessed the accuracy of endoscopic findings for diagnosing chronic gastritis. They found that ash-colored nodular changes were specific (98–99%), but not sensitive (6–12%), for identifying histological intestinal metaplasia, and concluded that conventional endoscopy is unsuitable for diagnosing intestinal metaplastic gastritis [17]. The low specificity of white-light endoscopy for diagnosing intestinal metaplasia is because it usually appears in flat mucosa and has few morphological changes [18]. In our study, AFI recognized areas of intestinal metaplasia in the gastric body with a sensitivity of 77% and specificity of 75%. Intestinal metaplasia is commonly distributed in a scattered pattern, or regionally; however, AFI only showed homogeneous green areas in which intestinal metaplasia was prevalent. Therefore, the actual distribution of intestinal metaplasia could not be evaluated, and this might have lowered the sensitivity and PPV of AFI for the diagnosis of intestinal metaplasia. The current AFI system works tri-modally, so it can easily switch to a narrow-band imaging (NBI) mode, and the scope is equipped with a zoom function. In magnified NBI images, intestinal metaplasia can be identified by the specific finding of the light blue crest, which represents the presence of a histological brush border [19]. Thus, the system can reveal areas of intestinal metaplasia by AFI, and subsequently specify the location and evaluate the micro-morphological features by the magnifying NBI. If the findings of this endoscopic imaging technique offer an alternative to histology of biopsy specimens, it would provide a convenient indicator of the extent/grade of CAFG during endoscopic examination.

According to the histology of the biopsy specimens, the green areas in the gastric body were associated with a higher grade of inflammation, atrophy and intestinal metaplasia. Because these histological features usually coexist with each other, the main cause of the green color could not be determined in this study. In AFI images, areas with strong autofluorescence appear bright green, and those with weak autofluorescence are purple or dark green. Although the

fluorophores exist in both the mucosa and submucosa, collagen in the submucosa discharges strong green autofluorescence [14]. When we investigated the color patterns of early gastric cancer in AFI images, the tumor color was strongly associated with morphology, irrespective of whether it was elevated or depressed, rather than histologic type [20]. In other words, elevated tumors appeared purple because of their thickness, which reduced autofluorescence from the submucosa, while most depressed tumors did not affect autofluorescence intensity because they were thin and appeared green. Likewise, we speculate that the presence of thick fundic mucosa reduces autofluorescence and appears purple in AFI images, and the decreased height of the fundic mucosa, caused by glandular atrophy, permits autofluorescence from the submucosa to penetrate the thin mucosa, which results in a green color similar to the intestinal mucosa. Accordingly, we suspect that the green mucosal color in the gastric body is mainly due to atrophy of the fundic mucosa.

This study has several limitations to be considered. In this study, we found that the inter- and intra-observer agreement in AFI for diagnosis of the extent of CAFG was higher than that of white-light images. However, the diagnostic accuracy of AFI was not compared with that of white-light images in relation to the histology. Therefore, whether the accuracy of AFI was superior to that of white-light images is unknown. Moreover, because our study included many patients with gastric cancer or a history of endoscopic resection of early gastric cancer, which is associated with a high prevalence of atrophy or intestinal metaplasia, we may have overestimated the accuracy of this test. In fact, we experienced a few patients whose gastric body appeared greenish, even though they were not infected with *H. pylori* and had no atrophy in the gastric fundus. Consequently, a good indication for this method is the identification of patients with extensive CAFG or intestinal metaplasia who have a higher risk for developing gastric cancer among those with *H. pylori* infection.

In conclusion, AFI diagnosed the extent of CAFG as a green area in the gastric body more precisely compared with white-light endoscopy. Because this method is easier and associated with fewer adverse effects than chromoendoscopy, it may facilitate its application in clinical practice or studies that assess CAFG. Thus, AFI may be a useful adjunct to identify patients at high risk for developing gastric cancer.

Conflict of interest statement There are no conflicts of interest to disclose.

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Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve*

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Please see the accompanying editorial by J. J. G. H. M. Bergman on page 988.

Background and aim: Endoscopic submucosal dissection (ESD) is feasible as a treatment for early gastric cancer (EGC) when it is performed by an experienced endoscopist. We investigated whether it was feasible for novice endoscopists to perform ESD for EGC, and how difficult it was to learn the procedure.

Methods: This case series study was performed in a cancer referral center. Three resident endoscopists, who had already learned basic procedures, performed ESD under supervision for 30 consecutive lesions, and their procedures were analyzed. The procedure was divided for assessment into (i) mucosal incision and (ii) submucosal dissection by completion of the circumferential mucosal cut. An insulated-tip knife was used for mucosal incision and submucosal dissection. A total of 90 mucosal EGCs (≤ 2 cm) without ulcers or scars in 87 patients were included. Outcomes were: rates of complete resection, complications, and self-completion; operation time; learning curve; and reasons for change of supervisor as an indicator of difficulty.

Results: Among the 90 procedures, there was a good overall complete resection rate of 93 %, with an acceptable complication rate of 4.4 %; the complications were delayed hemorrhage in two patients, and perforations in another two patients that were repaired successfully by endoscopic clipping. The self-completion rate and operation time were significantly worse for submucosal dissection than for mucosal incision. Two of the three operators showed a flat learning curve for submucosal dissection. Difficulty with the procedure was related mainly to uncontrollable hemorrhage.

Conclusions: With appropriate supervision, gastric ESD by residents is feasible, with equivalent complete resection rates and acceptable complication rates compared with those of experienced endoscopists, although there was difficulty in achieving sufficient self-completion rates in submucosal dissection. Better control of bleeding during submucosal dissection may be a key to improving the procedure.

Introduction

Endoscopic submucosal dissection (ESD) was developed as an advanced technique of endoscopic resection for early gastric cancer (EGC) [1,2]. It yields a higher complete resection rate than do conventional methods of endoscopic mucosal resection [3,4], and enables en bloc removal of previously unresectable lesions, such as large mucosal tumors [5] or tumors with scars [6]. Although effective, the technique of ESD is complicated and requires considerable expertise and a prolonged operation time [7].

Previous studies have indicated that ESD for EGC is technically feasible when performed by experienced endoscopists [5]; however, its practicability for novice endoscopists and the difficulty of learning this advanced endoscopic procedure are still unclear. If we can identify the difficulties involved, we can establish a way to overcome these and reduce the time required to learn the ESD procedure.

The present study investigated the practicability of supervised residents performing ESD for EGC, and the difficulty of learning the procedure.

* Note: The article's guarantor is N. U. The authors contributed to the study as follows: S. Y., analysis of the data, and drafting of the article; N. U., conception and design, analysis and interpretation of the data, drafting and final approval of the article; R. I., final approval of the article; N. K., H. O. and Y. F., provision of study materials and patients, and collection and collation of data; S. Y., Y. T. and K. H., provision of study materials and patients; H. I. and M. T., final approval of the article.

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Table 1 Profiles of three operating endoscopists.

Endoscopist	A	B	C
Years since graduation	7	10	5
Number of EGDs performed	2000	3200	1500
Number of EMRs performed for EGC	22	18	10
Number of colonoscopies performed	800	800	250
Number of ERCPs performed	20	65	10

EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; EGC, early gastric cancer; ERCP, endoscopic retrograde cholangiopancreatography.

Table 2 Characteristics of the lesions treated by ESD.

Endoscopists	A	B	C	Total
Number of lesions	n = 30	n = 30	n = 30	n = 90
Median tumor size, mm (IQR)	15 (8.5)	15 (10.25)	13.5 (5.75)	15 (10)
Location of gastric lesions, n (%)				
Upper third	1 (3.3)	5 (17)	1 (3.3)	7 (7.8)
Middle third	13 (43)	11 (37)	14 (47)	38 (42)
Lower third	16 (53)	14 (47)	15 (50)	45 (90)
Type of tumors, n (%)				
Elevated	14 (47)	11 (37)	14 (47)	39 (43)
Depressed	16 (53)	19 (63)	16 (53)	51 (57)

IQR: interquartile range

Table 3 Devices and settings of electrical surgical unit for each procedure.

Procedure	Device	ICC200	PSD60
Marking	Needle knife	Forced 20 W	Forced 30 W, effect 1
Mucosal incision	IT knife	Endo Cut 80 – 120 W, effect 3	Endo Cut 120 W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Submucosal dissection	IT knife	Forced coagulation 50 W	Forced coagulation 55 W, effect 2
	IT knife (fibrous submucosal tissue)	Endo Cut 80 – 120 W, effect 3	Endo Cut 120 W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Hemostasis	IT knife (small vessel)	Forced coagulation 50 W	Forced coagulation 55 W, effect 2
	Hemostatic forceps (large vessel)	Soft coagulation 80 W	Soft coagulation 80 W, effect 6

Patients and methods

This case series was performed in the endoscopic training and learning center of a tertiary cancer referral center.

Participants

A total of three endoscopists were involved in this study. They had experience of at least 1500 regular esophagogastroduodenoscopy procedures and more than 10 endoscopic mucosal resections by the strip biopsy or cap methods (**Table 1**). Before starting ESD, the operators participated in pre- and postoperative conferences with surgeons, gastroenterologists, radiologists, and pathologists to learn about the diagnosis and management of gastric cancer. They attended ESD procedures performed by senior doctors, as assistants, for at least 1 year, and then attended a lecture about ESD techniques, using a manual and videos, by an experienced endoscopist.

We investigated the records of 30 consecutive ESD procedures performed by each of the three endoscopists, between June 2003 and February 2005, in 87 patients (68 men, 19 women, mean age 67 years). The lesions were allocated to the three endoscopists irrespective of tumor location and size. Lesion characteristics are shown in **Table 2**. The indication for ESD in this study was differentiated-type mucosal EGC, without ulcers or scars, smaller than 2 cm, as described in the gastric cancer treatment guidelines issued by the Japanese Gastric Cancer Association [8]. Before treatment, anticipated results, possible risks and complications, and alternative treatments including surgery and no treatment, were explained by the operator to all the patients, who gave their written informed consent. Patients who had severe organ failure or coagulopathy were excluded. The study protocol was approved by the institutional review board at our center.

ESD procedure

All procedures were performed with a videoendoscope (GIF-Q240; Olympus Medical Systems Co., Ltd., Tokyo, Japan) that was fitted with a disposable attachment (D-201 – 11 804; Olympus) on its tip. A needle knife (KD-1L-1; Olympus), an insulated-tip (IT) knife (KD-610L; Olympus), and hemostatic forceps (Coagrasper, FD-410LR; Olympus) were used in the procedure. The Intelligent Cut and Coagulation 200 (ICC-200; Erbe Elektromedizin GmbH, Tübingen, Germany) or Power Supply Diathermy 60 (PSD-60; Olympus) was used as an electrical surgical unit; the output settings are summarized in **Table 3**. A solution of 2% epinephrine (Bosmin; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) with 20% concentrated glycerin–fructose (Glyceol; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) was used for submucosal injection.

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With the patient under sedation, the ESD procedure was performed as follows [6]. *Marking for removal:* The endoscope was inserted into the stomach, and the extent of the tumor was estimated under chromoendoscopic observation to determine the resection area. Marking dots were drawn circumferentially 3 mm from the tumor boundary by a needle knife. *Mucosal incision:* The epinephrine and glycerol solution was injected into the submucosa just outside the marking dots to elevate the lesion. The procedure was performed with a downward view in the antrum and a retroflex view in the corpus. A precut hole to insert the tip of the IT knife was made outside the region to be resected with the needle knife. The hole was made at the distal side of the lesion in an endoscopic view, and it needed to be sufficiently deep to reach the submucosa. The tip of the IT knife was inserted fully into the submucosa through the precut hole, and the proximal mucosa was cut continuously outside the marking dots using an Endo Cut mode. During mucosal incision, the ceramic tip was in contact with the gastric wall and was pulled with some tension. *Submucosal dissection:* Submucosal dissection was started after completion of the circumferential mucosal cut. The epinephrine and glycerol solution was injected into the submucosa to obtain sufficient mucosal elevation. The IT knife was moved laterally, with the tip continuously touching the gastric wall. Lateral movement was achieved by torquing the scope rather than by using the scope angle. Submucosal dissection was performed with the IT knife using the coagulation mode, or the Endo Cut mode if the submucosa was fibrous. *Hemostasis:* When hemorrhage was noted from small vessels, the bleeding point was coagulated with the blade of the IT knife, using forced coagulation. When hemorrhage from larger vessels was observed, the bleeding point was stopped with the hemostatic forceps using the soft coagulation mode. *Retrieval of the specimen and prevention of delayed hemorrhage:* After removal of the mucosal area, it was retrieved by grasping forceps (FG-47L-1; Olympus). The ulcer base was washed out repeatedly and any adherent clots or suspicious protrusions were coagulated by the hemostatic forceps to avoid delayed hemorrhage. Resected specimens were sent to the department of pathology for histological assessment of completeness of resection and curability.

Assistant policy

The entire procedures were performed under the supervision of an experienced endoscopist (N.U.). The supervisor was changed under the following circumstances: (1) overtime: when time for each mucosal incision and submucosal dissection exceeded 1 hour; (2) inability to achieve hemostasis: when spurting hemorrhage could not be stopped; (3) perforation; and (4) inability to continue the procedure: when the procedure could not be continued for reasons other than inability to achieve hemostasis, or perforation. If an operator changed supervisor, the procedure was regarded as not "self-completed."

All procedures were recorded digitally on video and all events relating to the procedure were recorded on dedicated operation records.

Measured outcome parameters

Complete resection and complication rates were evaluated for assessment of feasibility. Self-completion rate, operation time, learning curve, and reasons for incompletion were analyzed to elucidate procedural difficulties. For assessment the ESD procedure was divided into (i) mucosal incision and (ii) submucosal dissection by completion of the circumferential mucosal cut.

Complete resection was defined as en bloc resection without cancer involvement to the lateral and vertical margin of the resected specimen, as shown by histology. Complications included delayed hemorrhage and perforation, which were classified as grade 3 or 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [9]. Operation time was measured from the start of the mucosal incision until the end of tumor removal. "Self-completion" referred to a

Table 4 Evaluated parameters for feasibility of ESD.

Endoscopist	A	B	C	Total	*P*-value*
Complete resection, n (%)	28 (93)	28 (93)	28 (93)	84 (93)	
Complication, n (%)					
Delayed hemorrhage	1 (3.3)	1 (3.3)		2 (6.7)	
Perforation	1 (3.3)	1 (3.3)		2 (6.7)	
Self-completion, n (%)					
Mucosal incision	30 (100)	20 (67)	27 (90)	77 (86)	0.000
Submucosal dissection	23 (77)	15 (50)	16 (53)	54 (60)	
Median procedure time, minutes (IQR)					
Mucosal incision	19 (13)	23 (19)	33 (26)	23 (20)	0.000
Submucosal dissection	26 (33)	34 (28)	57 (59)	39 (38)	

**P*-value for total mean procedure time and total self-completion rate of mucosal incision vs. submucosal dissection.

Table 5 Reasons for change of supervisor.

Procedure	A	B	C	Total (%)
Mucosal incision				
Overtime			2	2 (2)
Inability to achieve hemostasis		1	1	2 (2)
Perforation		1		1 (1)
Inability to continue procedure		8		8 (9)
Submucosal dissection				
Overtime	2	2	6	10 (11)
Inability to achieve hemostasis	1	2	2	5 (6)
Perforation	1			1 (1)
Inability to continue procedure	3	11	6	20 (22)

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procedure that was finished without a change of supervisor. The learning curve was assessed as the change in self-completion rate and required operation time for each 10 procedures of each operator. Reasons for a change of supervisor during each mucosal incision and submucosal dissection were analyzed with reference to the operation record and video recordings, and were categorized according to the above-mentioned assistant policy.

Statistical analysis

JMP version 6.0 (SAS Institute, Cary, North Carolina, USA) was used for data analysis. Summarized numerical data were expressed as medians (interquartile ranges). The Mann–Whitney U-test was used for comparison of procedure time between mucosal incision and submucosal dissection. The χ^2 test was used for comparison of self-completion rates between mucosal incision and submucosal dissection. Significant differences were taken to be indicated by a *P*-value below 0.05.

Results

Assessment of feasibility

The overall complete resection rate was 93% (84 of 90 procedures). A total of four complications were experienced (4.4%), comprising two cases of delayed hemorrhage and two perforations. The perforations were repaired successfully with endoscopic clips as soon as the operators changed. The distribution of complete resection and complication rates was similar between operators (**Table 4**).

Analysis of difficulty

The self-completion rate for submucosal dissection was significantly lower than that for mucosal incision, and operation time was significantly longer (**Table 4**).

Concerning the learning curve, the self-completion rate for mucosal incision for all operators exceeded 80% in the third group of 10 cases, whereas for submucosal dissection two of three operators stayed around 50%, even for the final 10 cases (**Fig. 1**). Median operation time for mucosal incision did not change markedly and remained around 30 minutes for all operators. Median operation time for submucosal dissection became shorter than 30 minutes for one operator whose self-completion rate increased, but did not improve for the other two operators (**Fig. 2**).

The reasons for incompletion of the procedures are listed in **Table 5**. For mucosal incision, "inability to continue the procedure" was the most frequent reason for a change of supervisor. According to the video recordings, this was mainly an inability to achieve a mucosal incision owing to unfamiliarity with use of the IT knife. For submucosal dissection, "overtime," "inability to achieve hemostasis," and "inability to continue the procedure" led to discontinuation of the procedure for about 40% of the lesions. Video recordings revealed that "overtime" was usually caused by spending too long on hemostasis, and "inability to continue the procedure" was largely the result of interference with the procedure and loss of orientation caused by hemorrhage and clotting: in other words, the main difficulty for completion of submucosal dissection was uncontrollable hemorrhage.

Discussion

In the present case series study, we found that ESD for EGC measuring less than 2 cm, performed by supervised residents, was practicable, with a complete resection rate of 93% and a complication rate of 4%, which is similar to findings in previous studies of experienced endoscopists [10]. Difficulties arose more frequently during submucosal dissection than mucosal incision, and most of these were related to uncontrollable hemorrhage.

It has been reported that closely supervised trainees can perform advanced surgery such as esophagogastrectomy, hepatectomy [11], or pancreatectomy [12] with similar outcomes to consultant surgeons. In these studies, surgeons with a large workload encouraged trainees to be accept more opportunities to participate in such complex operations, with appropriate supervision, because this improved their learning of the surgical methods and did not jeopardize patient care. We believe that this concept can be applied to endoscopic procedures, and our results support this conclusion. Needless to say, this cannot be achieved without the availability of a highly experienced supervisor, because a significant number of cases were not completed by the resident alone and complications such as perforations were generally managed by the supervisor.

The requirements and criteria for starting to perform ESD have not been clarified to date. In our center, endoscopists who intend to start ESD should attend the pre- and post-treatment conference, and take part in actual ESD procedures as an assistant for at least 1 year before beginning the procedure themselves. In addition to gastroenterologists, surgeons and pathologists participate in these conferences, and thus new endoscopists can learn how to diagnose the extent and depth of the tumor, establish the optimum treatment strategy, and manage the patients appropriately according to the histopathological findings in resected specimens. By assisting experienced endoscopists, trainees acquire the skills needed to troubleshoot various situations. Moreover, obtaining expertise in hemostasis before starting ESD is recommended since most of the difficulties surrounding the procedure were related to uncontrollable hemorrhage.

In the present study, patients with small EGCs were selected. We suspect that if a novice endoscopist performs ESD for large lesions, it could involve an extremely long operation time, and it is too difficult for them to acquire the basic techniques during their restricted time in clinical practice. For this reason, we recommend that supervision should be started with small lesions, so that trainees have the opportunity to learn the entire ESD procedure. After this, it is easier to move on to larger lesions, because the procedure for large lesions consists of repeating certain basic procedures.

Choi et al. [13] have investigated the learning curve for ESD, and reported an increase in the en bloc resection rate from 45% to 85% after experience of 40 cases. They have concluded that trainees need to perform 20–40 procedures to be able to use the technique effectively, although their method consisted of mucosal incision and snaring rather than ESD. Gotoda et al. [14] have found that experience of at least 30 cases is required for a beginner to gain early proficiency in this technique. In our study, two of the three operators could not achieve a sufficient self-completion rate for submucosal dissection after 30 cases. The fact that two of the three operators could not achieve a sufficient self-completion rate for ESD by the 30th case suggests that more extensive experience is required before endoscopists can be considered to be proficient. Our study did not include hands-on training

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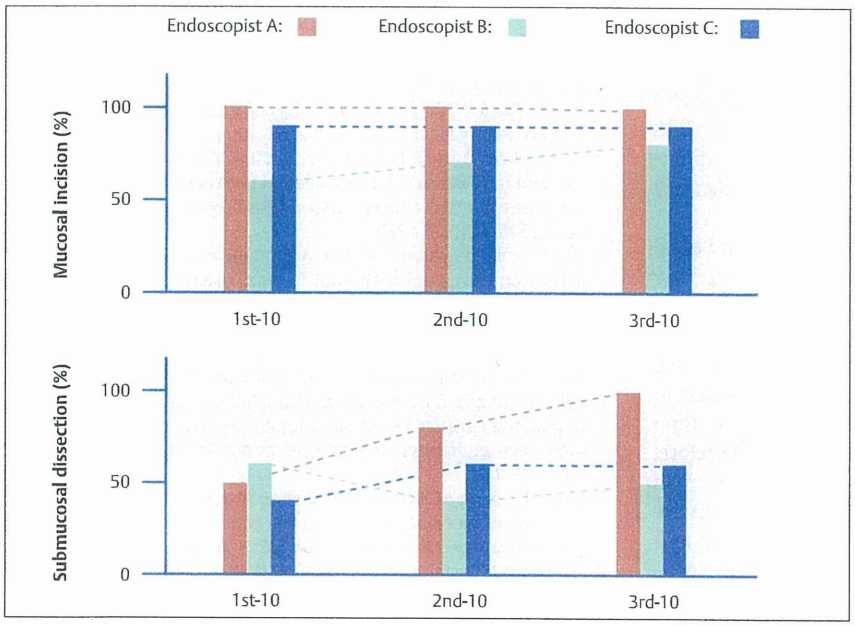

Fig. 1 Learning curves for self-completion rate for mucosal incision and endoscopic submucosal dissection.

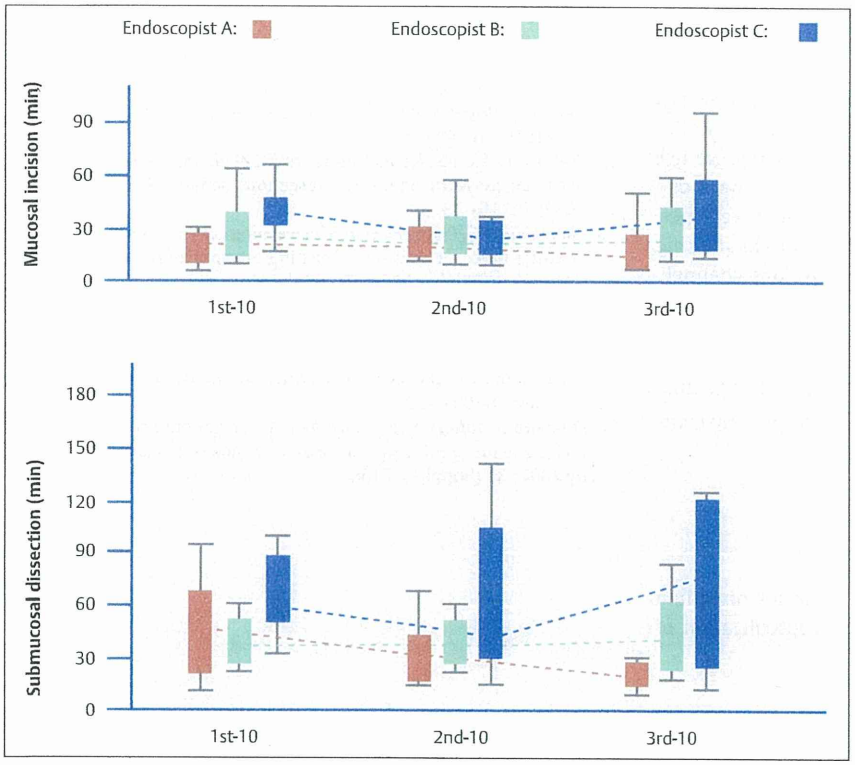

Fig. 2 Learning curves for operation time for mucosal incision and endoscopic submucosal dissection.

on ex vivo animal models such as the Erlangen Active Simulator for Interventional Endoscopy (EASIE) or living animals, which might have improved the learning curve of our three endoscopists. Nevertheless, we feel that incorporation of supervised clinical procedures is imperative.

The baseline profile of our operators, such as graduation year or number of cases experienced, was not associated with learning speed. Kakushima et al. [15] have indicated that a change in en bloc complete resection and complication rates did not represent operator proficiency with ESD under supervision, but that a decrease in operation time is a marker of proficiency. We evaluated self-completion rate as a parameter of expertise and it was associated with a decrease in procedure time, and as a result it may be a marker of proficiency. Differences in learning speed have been attributed to variations in individual talent. However, clarifying the objective parameters that reflect the actual expertise of a trainee and setting up relevant acquisition conditions are important for the establishing of a training system for advanced therapeutic procedures. Because our data are limited by the number of participating endoscopists and procedures, further investigations using common evaluation parameters are required.

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The three residents in this study had different profiles in terms of their endoscopic experience. The allocation of the lesions was not randomized and we therefore cannot exclude the possibility that some lesions may have been allocated on the basis of differences in profile between the residents. We attempted to avoid such bias as much as possible and found no statistically significant differences in the size of lesions or their locations, suggesting that any bias due to residents' profiles may have been minor.

Our results suggest that improving the process of submucosal dissection, especially the controllability of hemorrhage, may have contributed to the decrease in completion rate and shortening of operation time. To facilitate hemostasis during submucosal dissection, we attempted to improve the following. Firstly, we tried to dissect a deeper layer of the submucosa. The vessels in the gastric wall penetrate the muscularis propria and then branch in the submucosa toward the superficial layer. Therefore, when we dissect the superficial layer of the submucosa, small branched vessels are disrupted and more bleeding occurs. Dissection of deeper layers causes spurting hemorrhage but its frequency becomes less, and it can be stopped more easily because bleeding from the stump of the vessel trunk can be observed at a single point. Secondly, during submucosal dissection, we prefer to use the coagulation mode of the electrosurgical unit, e.g., a forced coagulation mode of 50 W for the ICC200 (Erbe) or swift coagulation of 100 W, for the VIO300D (Erbe). Dissection in the coagulation mode can cut and prevent bleeding, especially in loose submucosal tissue, but sometimes it cannot cut fibrous submucosal tissue in the gastric body; therefore, we alternated an Endo Cut mode with the coagulation mode in such cases. Thirdly, we use an endoscope with waterjet function for ESD [16]. The scope was developed originally to clean out mucus or food residues, but it can be used for washing out of shed blood or clots during ESD without withdrawing the device from the working channel.

In conclusion, with appropriate supervision, gastric ESD by residents is practicable, with equivalent clinical outcomes to those of experienced endoscopists, although there is a difficulty with self-completion of submucosal dissection. Better control of bleeding during submucosal dissection may be the key to improving completion rates and procedure times.

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Competing interests: None

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S. Abe, H. Kondo, T. Sumiyoshi, T. Mizushima, M. Sugawara, Y. Shimizu, S. Okushiba:

Treatment strategy for early gastric cancer with the risk of pyloric stenosis after endoscopic resection

We read with great interest the study by Dr. Coda and his colleagues, "Risk factors for cardiac or pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment," regarding early gastric cancer (EGC) [1].

At our center, endoscopic submucosal dissection (ESD) was performed for 433 EGCs (185 located in the lower third of the stomach, 146 in the middle third, and 102 in the upper third) from July 2000 to October 2008, and post-ESD stenosis occurred in five of the 185 pyloric resections. Four of the five had risk factors for post-ESD stenosis, that is a circumferential extent of the mucosal defect of more than ¾ or longitudinal extent of more than 5 cm, as described in the paper of Coda et al. [1].

The authors concluded that endoscopic balloon dilation was useful for pyloric stenosis after ESD. However, we think that balloon dilation is not always appropriate, considering the frequency of procedures needed, and risk of adverse events to the patient. In our series, four patients suffered from nausea and vomiting for a mean of 38 days (range 31–70), although the stenoses finally resolved with frequent balloon dilations. Furthermore, one patient sustained a perforation during her first balloon dilation, requiring an emergency operation (**Fig. 1**).

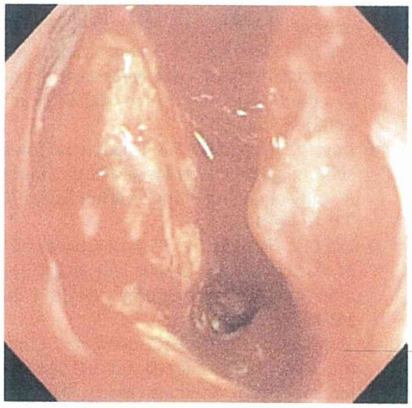


Fig. 1 Endoscopic image of perforation caused by balloon dilation for pyloric stenosis after endoscopic submucosal dissection (ESD). Omental fat tissue was seen in the anterior side of the pyloric ring.

We believe, therefore, that balloon dilation is not always a safe treatment for post-ESD pyloric stenosis.

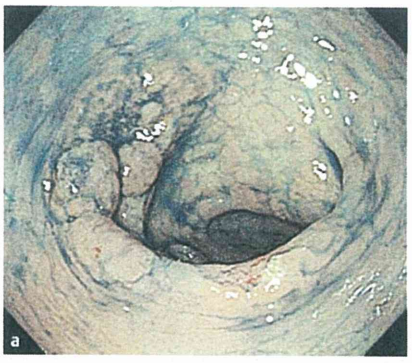
Coda and colleagues also reported that one of eight patients with pyloric stenosis had to undergo an additional distal gastrectomy with lymph node dissection following balloon dilation. Since the risk of lymph node metastasis is pathologically evaluated from the resected ESD specimens, the indication for ESD with high risk factors for pyloric stenosis should be decided carefully from the viewpoint of minimizing invasiveness.

Considering the above, we have started to recommend laparoscopic distal gastrectomy (LDG) including lymph node dissection for EGC with high risk of post-ESD pyloric stenosis. LDG for EGC is considered less invasive than open distal gastrectomy and is widely accepted in Korea and Japan. Long-term clinical outcome and survival have not been found to be different for the two surgical methods [2–4]. Our recent cases of EGC with high risk of pyloric stenosis have been successfully resected by LDG without complication, and with a median hospitalization of 20 days (**Fig. 2a,b**).

We agree that EGC near the cardia should be treated by ESD although this has high risk factors for cardiac stenosis. The standard operation for EGC near the cardia is total gastrectomy, which often makes the quality of life of patients worse because of weight loss, anorexia, dysphagia, and so forth [5–7]. ESD for cardiac lesions could avoid total gastrectomy if resection is curative, and consequently could preserve gastric function, although balloon dilation is required for cardiac stenosis [8].

ESD for EGC with a negligible risk of lymph node metastasis has been recognized as less invasive and more economical than conventional surgery. However, we should take into consideration the benefits and risks of ESD and LDG when deciding upon treatment strategies for EGC, especially in patients with lesions at high risk of post-ESD stenosis.

Competing interests: None



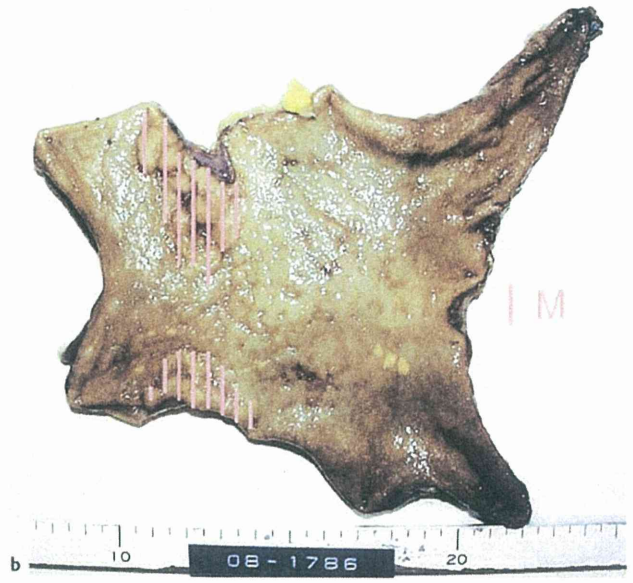


Fig. 2 **a** Antral 0 IIa + IIc lesion with ⅔ circumferential extent. Given the risk of pyloric stenosis after ESD, this lesion was resected by laparoscopic distal gastrectomy (LDG). **b** The resected specimen revealed an intramucosal well-differentiated adenocarcinoma without lymphatic or venous invasion.

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Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment

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Background and study aims: Bleeding and perforation are major complications of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC), but post-ESD stenosis represents a severe delayed complication that can result in clinical symptoms such as dysphagia and nausea. The aims of this study were to determine the risk factors and evaluate the clinical treatment for post-ESD stenosis.

Methods: A total of 2011 EGCs resected by ESD at our institution between 2000 and 2005 were reviewed retrospectively. Resection was defined as cardiac when any mucosal defect was located in the squamocolumnar junction, and as pyloric when any mucosal defect was located < 1 cm from the pylorus ring. Post-ESD stenosis was defined when a standard endoscope could not be passed through the stenosis. We examined the incidence of post-ESD stenosis, its relationship with relevant factors, and the clinical course of post-ESD stenosis patients.

Results: Post-ESD stenosis occurred with seven of 41 cardiac resections (17%) and eight of 115 pyloric resections (7%). Circumferential extent of the mucosal defect of > 3/4 and longitudinal extent > 5 cm were each significantly related to occurrence of post-ESD stenosis with both cardiac and pyloric resections. All 15 affected patients were successfully treated by endoscopic balloon dilation.

Conclusions: A circumferential extent of the mucosal defect of > 3/4 or longitudinal extent of > 5 cm in length were both demonstrated to be risk factors for post-ESD stenosis, in both cardiac and pyloric resections, and endoscopic balloon dilation was shown to be effective in treating post-ESD stenosis.

Introduction

Currently, endoscopic resection is a widely accepted treatment for early gastric cancer (EGC) when the risk of lymph node metastasis is diagnosed as being very low or negligible [1–3]. Endoscopic submucosal dissection (ESD) is a new endoscopic resection method that facilitates one-piece resection even in patients with large or ulcerative lesions, thereby reducing local recurrence [4–9].

Although bleeding and perforation remain the most common complications, post-ESD stenosis represents a severe delayed complication that may result in clinical symptoms such as dysphagia and nausea. It is thought that post-ESD stenosis is caused by the removal of a large area when lesions are located near either the cardia or the pylorus, but only one case series about post-ESD stenosis in gastric ESDs has been reported so far [10]. The aims of this study were to determine the risk factors for post-ESD stenosis and evaluate the clinical treatment of post-ESD stenosis patients.

Patients and methods

We performed ESD with curative intent on 2011 EGCs in 1819 consecutive patients at the National Cancer Center Hospital in Tokyo between January 2000 and December 2005. Written informed consent was obtained from all patients before their ESD procedures. The median age of patients was 68 years (range 27–94) and the male/female ratio was 3.92 (1449/370). The ECG lesions were located in the upper third of the stomach in 326 instances, the middle third in 887, and the lower third in 798. Resection was defined as cardiac when any mucosal defect was located in the squamocolumnar junction, and as pyloric when any mucosal defect was located < 1 cm from the pylorus ring.

Table 1 Characteristics of patients with cardiac and pyloric resections.

	Cardiac resection n = 41	Pyloric resection n = 115
Age, median years (range)	68 (41 – 85)	70 (37 – 90)
Gender, n (%)		
Male	36 (88)	75 (65)
Female	5 (12)	40 (35)
Concomitant disease, n (%)		
Diabetes mellitus	4 (10)	8 (7)
Liver cirrhosis	0 (0)	5 (4)
Chronic heart failure	2 (5)	3 (3)
Autoimmune disease	0 (0)	3 (3)
Chronic renal failure	0 (0)	2 (2)
Circumferential extent of mucosal defect, n (%)		
≤ 1/2	28 (68)	81 (70)
1/2 – 3/4	6 (15)	16 (14)
> 3/4	7 (17)	18 (16)
Longitudinal extent of mucosal defect, n (%)		
≤ 5 cm	39 (95)	109 (95)
> 5 cm	2 (5)	6 (5)
Location of mucosal defect (center), n (%)		
Lesser curve	32 (78)	32 (28)
Anterior wall	3 (7)	32 (28)
Greater curve	2 (5)	22 (19)
Posterior wall	4 (10)	29 (25)
Perforation*, n (%)		
No	37 (90)	113 (98)
Yes	4 (10)	2 (2)
Lesion macroscopic type, n (%)		
Elevated	14 (34)	32 (28)
Depressed	24 (59)	65 (56)
Elevated and depressed	3 (7)	18 (16)
Depth of invasion, n (%)		
Mucosal	29 (71)	99 (86)
Submucosal	12 (29)	16 (14)
Ulcer finding, n (%)		
Absence	37 (90)	94 (82)
Presence	4 (10)	21 (18)

*All patients with perforations were successfully treated by endocopic clipping.

ESD procedures were performed with sedation using midazolam and pentazocine and began with identification of the lesion margins which were then marked with a needle knife. Submucosal injections were used to lift the mucosa followed by a circumferential mucosal incision around the lesion. Finally, submucosal dissection of the lesion was performed with an insulation-tipped knife (Olympus Medical Systems, Tokyo, Japan) [5]. The curative success of the ESDs was subsequently determined pathologically. As a general rule, we performed an additional gastrectomy with lymph node dissection after a noncurative ESD in which a resected specimen was diagnosed as indicating a possible risk of nodal metastasis, such as showing submucosal deep invasion or positive lymphatic invasion. [11] When a resected specimen was diagnosed as showing a curative resection, we usually performed an endoscopy to check the healing progress of the ESD mucosal defect 2 – 3 months later. If patients had undergone cardiac or pyloric resection or had any clinical symptoms, we carried out endoscopy earlier than 2 – 3 months after ESD. We then followed up the patients every 6 months or annually.

Post-ESD stenosis risk factors

Post-ESD stenosis was diagnosed by endoscopy and defined as existing when a standard 10-mm diameter endoscope could not be passed through an existing stenosis.

We reviewed the clinical records, endoscopic images, and endoscopic and pathological reports for all patients. Patients with cardiac and pyloric resection lesions were divided into two groups, that is, with and without post-ESD stenosis. The two groups were compared with regard to age, gender, concomitant disease that might affect ESD ulcer healing, circumferential extent of the mucosal defect, longitudinal extent of the mucosal defect, gastric location of the center of the mucosal defect, occurrence of perforation during ESD, macroscopic type of the lesion, depth of invasion, and finding of the presence of an ulcer.

The extent of the circumferential mucosal defect was classified into ≤ 1/2, 1/2 – 3/4 or > 3/4. The extent of the longitudinal mucosal defect was divided into ≤ 5 cm and > 5 cm. The gastric location of the center of the mucosal defect was categorized as lesser curve, anterior wall, greater curve, or posterior wall. These classifications were made by an experienced endoscopist who reviewed endoscopic images without being aware of the clinical outcomes.

Table 2 Risk factors for post-ESD stenosis following cardiac resection.

	Post-ESD stenosis		*P* value
	None n = 34	Present n = 7	
Age, mean years (range)	68 (41 – 85)	73 (54 – 80)	n. s.
Gender, n (%)			
Male	31	5 (14)	n. s.
Female	3	2 (40)	
Concomitant disease, n (%)			
Diabetes mellitus	3	1 (25)	n. s.
Chronic heart failure	2	0 (0)	n. s.
Circumferential extent of mucosal defect, n (%)			
≤ 3/4	34	0 (0)	< 0.01
> 3/4	0	7 (100)	
Longitudinal extent of mucosal defect, n (%)			
≤ 5 cm	34	5 (13)	0.03
> 5 cm	0	2 (100)	
Location of mucosal defect (center), n (%)			
Lesser curve	26	6 (19)	n. s.
Anterior wall	3	0 (0)	
Greater curve	2	0 (0)	
Posterior wall	3	1 (25)	
Perforation*, n (%)			
No	30	7 (19)	n. s.
Yes	4	0 (0)	
Lesion macroscopic type, n (%)			
Elevated	12	2 (14)	n. s.
Depressed	19	5 (21)	
Elevated and depressed	3	0 (0)	
Depth of invasion, n (%)			
Mucosal	24	5 (17)	n. s.
Submucosal	10	2 (17)	
Ulcer finding, n (%)			
Absent	31	6 (16)	n. s.
Present	3	1 (25)	

n. s., not significant.
*All patients with perforations were successfully treated by endocopic clipping.

Macroscopic lesion types were classified endoscopically as elevated type, depressed type, or elevated and depressed type, based on data collected from the endoscopic reports. Depth of invasion and the presence of an ulcer were determined pathologically, according to the findings from the pathological reports.

Clinical treatment of post-ESD stenosis patients

The clinical treatment of post-ESD stenosis patients was also investigated in our study. Endoscopic balloon dilation was indicated for post-ESD stenosis patients complaining of any clinical symptoms. A 15 – 18-mm or 18 – 20-mm wire-guided balloon dilator (CRE Wire-Guided Balloon Dilation Catheter; Boston Scientific, Natick, Massachusetts, USA) was used without fluoroscopic guidance. Endoscopic balloon dilation was performed once or twice a week as necessary whenever the degree of post-ESD stenosis was severe. The interval was extended gradually to every 2 weeks and then every month as the patient's condition improved, and endoscopic balloon dilation was continued until the patient's post-ESD stenosis and clinical symptoms were resolved completely.

Data were analyzed using the chi-squared test, Fisher's exact test or the Student *t* test as appropriate (Statview; Abacus Concepts, Berkeley, California, USA). Value differences of $P < 0.05$ were considered statistically significant.

Results

Post-ESD stenosis risk factors

Post-ESD stenosis was associated with 15 of the 2011 lesions (0.7%) previously treated by ESD, in 15 of the 1819 patients. Of the other 1804 patients, 209 underwent gastrectomies because the ESDs were noncurative, while 84 received their first follow-up endoscopy examinations at other hospitals with no subsequent referrals to our hospital. None of the remaining 1511 patients showed signs of post-ESD stenosis, either at the first follow-up endoscopy after ESD at our hospital to check the healing progress of the mucosal defect or at any of their subsequent follow-up examinations.

All 15 post-ESD stenosis cases were induced by ESDs involving either the cardiac or pyloric resections that had comprised 41 of the 326 upper third lesions (13%) and 115 of the 798 lower third lesions (14%), respectively (**Table 1**). Post-ESD stenosis occurred following seven of the 41 cardiac resections (17%) and eight of the 115 pyloric resections (7%). All of the post-ESD stenosis patients were diagnosed before undergoing a routine first follow-up endoscopy examination, because each of the seven stenosis patients who had undergone cardiac resection experienced dysphagia while all eight of the pyloric resection stenosis patients suffered from severe nausea, with six of them actually vomiting due to the large amount of residual food in their stomachs.

Table 3 Risk factors for post-ESD stenosis following pyloric resection.

	Post-ESD stenosis		*P* value
	None n = 107	Present n = 8	
Age, mean years (range)	70 (37–90)	74 (51–83)	n.s.
Gender, n (%)			
Male	70	5 (7)	n.s.
Female	37	3 (8)	
Concomitant disease, n (%)			
Diabetes mellitus	8	0 (0)	n.s.
Liver cirrhosis	5	0 (0)	n.s.
Chronic heart failure	3	0 (0)	n.s.
Autoimmune disease	3	0 (0)	n.s.
Chronic renal failure	2	0 (0)	n.s.
Circumferential extent of mucosal defect, n (%)			
≤ 3/4	97	0 (0)	< 0.01
> 3/4	10	8 (44)	
Longitudinal extent of mucosal defect, n (%)			
≤ 5 cm	107	2 (2)	< 0.01
> 5 cm	0	6 (100)	
Location of mucosal defect (center), n (%)			
Lesser curve	29	3 (9)	n.s.
Anterior wall	29	3 (9)	
Greater curve	21	1 (5)	
Posterior wall	28	1 (3)	
Perforation*, n (%)			
No	105	8 (7)	n.s.
Yes	2	0 (0)	
Lesion macroscopic type, n (%)			
Elevated	28	4 (13)	n.s.
Depressed	62	3 (5)	
Elevated and depressed	17	1 (6)	
Depth of invasion, n (%)			
Mucosal	93	6 (6)	n.s.
Submucosal	14	2 (13)	
Ulcer finding, n (%)			
Absent	88	6 (6)	n.s.
Present	19	2 (10)	

n.s., not significant.
*All patients with perforations were successfully treated by endocopic clipping.

The median period from ESD to the diagnosis of post-ESD stenosis was 22 days (range 16–33) in the cardiac resection patients and 27 days (range 15–46) in the pyloric resection patients.

The data for post-ESD stenosis following cardiac and pyloric resections are shown in ● **Table 2** and ● **Table 3**, respectively. A circumferential mucosal defect > 3/4 in extent and a longitudinal mucosal defect > 5 cm in extent were each significantly related to the development of post-ESD stenosis in both cardiac and pyloric resections.

Clinical treatment of post-ESD stenosis patients

Each of the 15 post-ESD stenosis patients required endoscopic balloon dilation treatment. The clinical symptoms related to the stenosis were completely resolved in every patient in response to either single (one patient) or repeated (14 patients) endoscopic balloon dilation sessions. The median number of dilations and the median period from the first to the last dilation are shown in ● **Table 4**. No complications were observed after any endoscopic balloon dilation treatments.

Two patients, one each with post-ESD stenosis following cardiac resection and pyloric resection, underwent an additional gastrectomy with lymph node dissection following endoscopic balloon dilation treatment because their resected ESD specimens were subsequently pathologically diagnosed as showing a possible risk of lymph node metastasis. Those two patients were excluded from the analysis of follow-up data after repeated endoscopic balloon dilation treatment. During the median follow-up period of 36 months (range 2–63 months) for the other 13 post-ESD stenosis patients, the patency of the cardiac and pyloric lumens was well maintained and there were no further symptoms. The patient with the 2-month follow-up period subsequently received medical care at another institution with no further referral to our hospital.

Discussion

In the past, the accepted indications for conventional endoscopic mucosal resection (EMR) of EGC were a small intramucosal cancer ≤ 2 cm in size, of a differentiated histological type, and without an ulcer finding. This was because of technical limitations associated with the EMR procedure [4]. More recently, however, indications for the endoscopic resection of EGC have been expanded, based on a very low or negligible risk of lymph node metastasis

	Cardiac resection	Pyloric resection	*P* value
Number of dilations, median (range)	5 (1 – 14)	9 (7 – 40)	n. s.
Period of dilation treatments, median days (range)	42 (1 – 120)	50 (28 – 198)	n. s.

n. s., not significant

Table 4 Endoscopic balloon dilation treatment in patients with post endoscopic submucosal dissection (ESD) stenosis following cardac and pyloric resections.

as determined from a large number of surgical EGC cases [3,4,12]. The expanded indications include lesions > 20 mm and ulcerated lesions that would otherwise be difficult to resect by means of conventional EMR. Both kinds of lesions were previously resected by surgery, but the relatively new ESD technique has been developed to achieve the one-piece resection of even large and ulcerated lesions [4 – 9].

The number of EGC patients who undergo endoscopic resection is increasing in Japan because of the expanded indications and technical improvements mentioned above. Consequently, the number of endoscopic resection-related complications has also increased, so endoscopists must be aware of both the risk factors and the incidence of complications as well as knowing how to effectively treat such complications. Although cases of bleeding and perforation related to ESD of EGC have previously been reported [5,13,14], so far only one case series about post-ESD stenosis in gastric ESDs has been published [10].

This is the first study to determine the incidence of post-ESD stenosis in EGC lesions and the associated risk factors. The present study has shown that a circumferential mucosal defect of extent > 3/4 and a longitudinal mucosal defect of extent > 5 cm were each significantly related to the development of post-ESD stenosis in both cardiac and pyloric resections. Similar results have been reported in a study investigating esophageal stenosis after EMR of superficial esophageal cancer [15]. Knowledge of the risk factors associated with the subsequent development of post-ESD stenosis will allow endoscopists to better anticipate the likelihood of this complication.

Bleeding and perforation are complications that usually happen during ESD or within 24 hours after the procedure [5,13,14] so immediate treatment is normally required in such cases. In contrast, however, it is thought that post-ESD stenosis manifests itself several weeks after ESD, during the actual healing process. In this study, the median period from ESD to the diagnosis of post-ESD stenosis was 22 days in cardiac resection stenosis cases and 27 days in pyloric resection stenosis cases. Appropriate endoscopic follow-up to check for the subsequent presence of post-ESD stenosis, therefore, is recommended for patients with either of the identified risk factors for this complication. In order to minimize or prevent post-ESD stenosis-related symptoms from occurring, however, it may be advisable to start balloon dilation before the stenosis actually develops in such patients.

The clinical significance of post-ESD stenosis is that it decreases a patient's quality of life. In the present study, all 15 post-ESD stenosis patients developed a clinical symptom that was successfully relieved by either single (one patient) or repeated (14 patients) endoscopic balloon dilation treatment, and the patency of the cardiac and pyloric lumens was well maintained during a sufficiently lengthy follow-up period. Based on our findings, endoscopic balloon dilation can be regarded as an effective therapy for post-ESD stenosis although the number of patients was limited in this study. Similar effectiveness of endoscopic balloon dilation for the treatment of esophageal stenosis after EMR of superficial esophageal cancer has also been reported [15]. Patients with stenosis following pyloric resection required more balloon dilation procedures over a longer period compared with those with cardiac resections, although there was no significant difference between the two groups, probably once again because of the small number of patients involved (**Table 4**). In our study there were no complications after any of the balloon dilations, but the number of patients was limited and perforations related to endoscopic balloon dilation have been reported [10], so enhanced efforts should be made to preclude the development of post-ESD stenosis in the first place. In this regard, there is a recent case report of a biodegradable esophageal stent effective for patients with esophageal stenosis after ESD [16] that may be useful in preventing post-ESD stenosis from developing in patients with cardiac or pyloric resections.

In conclusion, the results of this retrospective study demonstrate that cardiac or pyloric resections in which the extent of the mucosal defect is > 3/4 circumferentially or > 5 cm longitudinally carry a risk for the occurrence of post-ESD stenosis, and that endoscopic balloon dilation can be an effective treatment for such post-ESD stenosis.

Competing interests: None

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