Annals of Gastroenterology (2014) **27,** 346-351

Anti-reflux mucosectomy for gastroesophageal reflux disease in the absence of hiatus hernia: a pilot study

Haruhiro Inoue[a], Hiroaki Ito[a], Haruo Ikeda[a], Chiaki Sato[a], Hiroki Sato[a], Chainarong Phalanusitthepha[a], Bu'Hussain Hayee[b], Nikolas Eleftheriadis[a], Shin-ei Kudo[c]

Digestive Diseases Center, Showa University Koto-Toyosu Hospital, Tokyo, Japan; King's College Hospital NHS Foundation Trust, London, UK; Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama, Japan

Abstract

Background In our previous case report of circumferential mucosal resection for short-segment Barrett's esophagus with high-grade dysplasia, symptoms of gastro-esophageal reflux disease (GERD) were significantly improved. This observation suggests that anti-reflux mucosectomy (ARMS) could represent an effective anti-reflux procedure, with the advantage that no artificial devices or prostheses would be left *in situ*.

Methods In this pilot study, 10 patients with treatment-refractory GERD received ARMS, 2 of whom circumferential, and the remaining 8 crescentic.

Results Key symptoms of GERD improved significantly after ARMS. In the DeMeester score, mean heartburn score decreased from 2.7 to 0.3 (P=0.0011), regurgitation score from 2.5 to 0.3 (P=0.0022), and total score from 5.2 to 0.67 (P=0.0011). At endoscopic examination, the flap valve grade decreased from 3.2 to 1.2 (P=0.0152). In 24-h esophageal pH monitoring the fraction of time at pH <4 improved from 29.1% to 3.1% (P=0.1). Fraction time absorbance more than >0.14 of bile reflux was controlled from 52% to 4% (P=0.05). In 2 cases of total circumferential resection, repeat balloon dilation was necessary to control stenosis. In all cases, proton pump inhibitor prescription could be discontinued with no ill effects.

Conclusion This initial case series demonstrated the potential anti-reflux effect of ARMS, with a crescentic mucosal resection appearing adequate. Further longitudinal study of patients without sliding hiatus hernia will be required to establish ARMS as an effective technique to control GERD in this setting.

Keywords Gastroesophageal reflux disease, endoscopic treatment, anti-reflux mucosectomy

Ann Gastroenterol 2014; 27 (4): 346-351

Introduction

As a treatment for gastroesophageal reflux disease (GERD), proton pump inhibitors (PPIs) are the mainstay of medical therapy [1,2]. Laparoscopic fundoplication is generally advised when symptoms are poorly controlled with PPIs and is regarded as a gold standard of treatment, with excellent control in the short- and midterm [3,4]. Long-term results, however, remain equivocal [5,6]. Following on from the principles of surgical fundoplication, a variety of endoscopic procedures for GERD have been proposed to achieve non-surgical control. Literature data at the date support that the delivery of radiofrequency energy to the gastroesophageal junction (Stretta) is safe, effective, durable, and repeatable if necessary and serves an unmet need for many GERD sufferers. The SAGES guidelines for GERD published in early 2013 gave for this procedure high grade of evidence and strong recommendation for treating GERD in well-selected patients [7].

Commonly employing tissue-approximating devices (staple- or suture-based), a range of response rates have been demonstrated with these techniques [7-13]. To date, however, no endoscopic procedure has been widely accepted

[a]Digestive Diseases Center, Showa University Koto-Toyosu Hospital, Tokyo, Japan (Haruhiro Inoue, Hiroaki Ito, Haruo Ikeda, Chiaki Sato, Hiroki Sato, P. Chainarong, Nikolas Eleftheriadis); [b]Department of Gastroenterology, King's College Hospital NHS Foundation Trust, London, UK (Bu'Hussain Hayee); [c]Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama, Japan (Shin-ei Kudo)

Conflict of Interest: None

Correspondence to: Haruhiro Inoue, MD, Professor and Director, Digestive Disease Center, Showa University Koto-Toyosu Hospital, Tokyo, Japan, e-mail: haruinoue777@yahoo.co.jp

Received 18 July 2014; accepted 08 August 2014

as a standard treatment of GERD, either (primarily) due to insufficient symptom control or the requirement of costly proprietary devices.

In 2003, we reported a case of circumferential mucosal resection of the distal esophagus and cardia for high-grade dysplasia (HGD) in a short segment of Barrett's esophagus [14]. In this case, the primary objective was complete excision of Barrett's mucosa with HGD. The patient happened also to present with repeat chest pain and regurgitation (DeMeester score 5) with significant hiatal hernia (flap valve Grade 3). A circumferential mucosal resection extending to include a 2 cm wide portion of the gastric cardia was completed to ensure an adequate distal margin to the Barrett's mucosa. We postulated that this would also reduce reflux symptoms by creating a relative stricture at gastric cardia. As expected, excellent control of reflux was indeed obtained by scar formation at the level of gastric cardia, associated with normalization of 24-h pH monitoring [15]. The unobstructed passage of food through the gastroesophageal junction was preserved, although multiple balloon dilatations were required to control initial stricture formation. Eventually, the Barrett's mucosa was totally replaced by new squamous epithelium in the healing process [15]. After more than 10 years of follow up, the patient still remains asymptomatic, without requiring PPI prescription and no recurrence of Barrett's epithelium.

This case series suggests that endoscopic anti-reflux mucosectomy (ARMS) may represent an effective anti-reflux procedure, with the added advantage of requiring no additional devices and leaving no artificial prostheses *in situ*.

Patients and methods

Patient selection

PPI-refractory GERD without sliding hernia seems the most appropriate indication for this procedure, regardless of the presence or absence of Barrett's esophagus. We selected 10 consecutive such patients presenting to the outpatient clinics at our institution for this procedure (Table 1).

Table 1 Patient background

Age	56.3 (22-81) years
Female: Male	2:8
Duration of GERD symptom	2.8 (1-10) years
Esophagitis Los none: Los A: Los B	7:2:1
Barrett's esophagus	+2 cases, –8 cases
Dysplasia	+2 cases, –8 cases
PPI resistance	All cases
Mucosal flap valve grade	All in Grade 3
Major symptoms	Regurgitation - 10 cases Respiratory symptoms - 3 cases Chest pain - 8 cases Esophageal distention - 2 cases Belching - 1 case

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor

Examinations before ARMS

To evaluate the severity of GERD symptoms, the DeMeester score [16] was applied. Upper gastrointestinal endoscopy was used to evaluate the size/grade of hiatal hernia, grade of esophagitis if present, and to detect and characterize Barrett's esophagus with or without HGD). Esophageal function tests (esophageal manometry, 24-h pH monitoring, and Bilitec) were mandatory. The gastro-esophageal flap valve grading [17] was used to describe the size/grade of hiatal hernia.

In 24 h, esophageal pH monitoring in our early six cases was carried out using Digitrapper MK III (Synectics Medical) and Bilitec 2000 (Medtronic, Minnesota, USA) wherein for the last 4 cases GMMS-4000 (Star Medical Inc., Tokyo, Japan) was used.

Institutional review board (IRB) approval and National registration

This pilot study was approved by IRB of Showa University (approved number: 1205-06) and registered to the University Hospital Medical Information Network (registered number UMIN000013565).

ARMS

In the first two cases, a circumferential ARMS was performed to remove a short segment Barrett's esophagus with HGD. In the subsequent 8 cases crescentic ARMS of the esophagogastric junctional (EGJ) mucosa was conducted with the now standardized techniques of endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD), of at least 3 cm length (1 cm in the esophagus and 2 cm in the stomach), with the length of mucosal resection at the cardia measured in retroflexion from the gastric side. ARMS was conducted along the side of the lesser curve of the stomach, thus preserving a sharp mucosal valve at gastric cardia.

Step 1: marking of scheduled reduction area on the mucosa. Mucosal reduction is scheduled along lesser curve of gastric cardia in hemi-circumferential ARMS. This preserves mucosal flap valve at greater curve side which is expected to become sharp edged and robust mucosal valve.

Markings on the mucosa were placed along the expected margin of mucosal resection using an electrocautery knife (Dual knife, KD-650L, Olympus Co., Tokyo, Japan) connected to the electrocautery generator (VIO300DERBE Electromedizin, Tübingen, Germany), in soft coagulation mode, 50 W, effect 3 in esophagus and in forced coagulation mode 30 W, effect

3 in stomach. At crescentic ARMS in retroflex view from the stomach, the length of preserved mucosa on the side of the greater curve was estimated at approximately twice the diameter of the endoscope when viewed in retroflexion.

Step 2: EMR and ESD. Both techniques were, and can be, applied to resect the mucosa. In our first [14] and last two clinical cases, a cap-EMR method was used [18]. In the case of cap-EMR, a large hard cap with oblique cut (MAJ-296, Olympus) was used together with thin diameter crescent snare (SD-221L-25, Olympus). Saline with indigo carmine dye was injected into submucosa along the markings using a 4 mm tip, 25-Gauge needle. Correct submucosal saline injection was confirmed by lifting of the mucosal surface. Cap-EMR was carried out repeatedly until the marked mucosal area was completely resected. The technical aspects are identical to the original description of Cap-EMR [14,18].

For ESD, submucosal injection was carried out along the marking. Marginal incision was made along the markings using the Dual knife with the ERBE Endocut Q setting at 6-1-2. A tapered hood (Short ST hood, DH-28GR, Fujifilm Co., Tokyo, Japan) was mounted on the endoscope (GIF-H240, H260J or H290, Olympus). Submucosal dissection was completed using electrocautery knives (Dual knife, KD-650L, and IT-nano knife, KD-612L, Olympus). For this, the ERBE setting was forced coagulation mode 40 W, effect 3. Hemostasis was carried out using coagulating forceps (Coagrasper, FD-410LR, Olympus) with soft coagulation 80 W effect 5.

Management and follow up after ARMS

Patient started drinking clear water on the morning following the procedure. The patient was started on a soft diet from the second day and was on normal diet from the third day. PPI therapy was continued for 40 days after ARMS and then stopped. A complete set of follow-up studies (as conducted pre-treatment) was carried out 2 months after the procedure.

Statistical analysis

Regarding the changes in DeMeester score [16] before and after ARMS, a non-parametric Wilcoxon exact test was used because the data was not normally distributed. In order to compare flap valve grade [17], the flap valve Grades 1, 2, 3, and 4 received a score of 0, 1, 2, and 3 points, respectively . Then, non-parametric Wilcoxon exact test was used to identify the difference.

Results

In all cases, mucosal reduction of the scheduled area was completed without any immediate complications (bleeding or perforation).

GERD symptoms were significantly improved after ARMS (DeMeester score: heartburn 2.7-0.3, P=0.0022; regurgitation 2.5-0.3, P=0.0022; total, 5.1-0.8, P=0.0022) (Fig. 1). The flap valve score was also significantly improved after ARMS from 3.2 to 1.2 (P=0.0152) (Fig. 2).

In this series, the initial 2 patients underwent circumferential ARMS, removing short-segment Barrett's esophagus also including HGD. In one patient (case no. 1) circumferential ARMS was carried out in multi-fragment EMR manner. In the other patient (case no. 2) circumferential ARMS was completed by ESD technique. In both cases, 2 cm-wide circumferential mucosal resection at the gastric cardia was completed and visually confirmed in the retroflexed view (Fig. 3A). Endoscopic balloon dilatation was repeated several times in the subsequent 3 months due to stricture formation. Further dilatation was not required once re-epithelialization was complete. In these cases, almost all reflux symptoms disappeared after mucosal healing (DeMeester score 0).

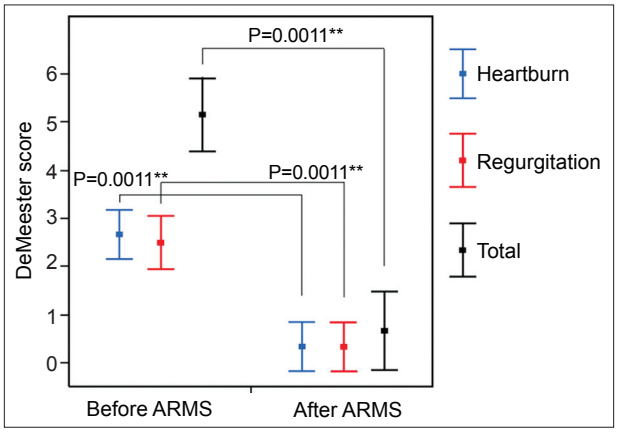

Figure 1 DeMeester score before and after anti-reflux mucosectomy (ARMS). The upper and lower bars show the standard deviation. The square indicates mean value. The DeMeester scores significantly improved after cardiac mucosal reduction (heartburn, P=0.0011; regurgitation, P=0.0011; total, P=0.0011)

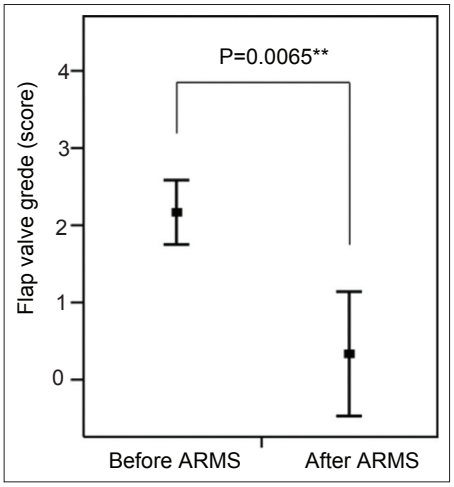

Figure 2 Flap valve grade before and after anti-reflux mucosectomy (ARMS). The flap valve grade score significantly improved after cardiac mucosal reduction (P=0.0065)

Retroflex view from stomach at this stage demonstrated a tight and robust junction with the procedure having created mucosal fold convergence at the lesser curve of the stomach (Fig. 3B). After 10 and 3 years of follow up respectively, neither patient has experienced recurrence of symptoms or recurrence of endoscopic evidence of esophagitis or Barrett's esophagus (Fig. 3C, D). Although circumferential ARMS resulted in very good long-term control of GERD symptoms , it was related to stricture formation necessitating repeat balloon dilation. Hence, we considered these initial two cases as "anecdotal" in attendance of further studies.

The remaining 8 consecutive patients underwent crescentic ARMS; 6 received ESD, and 2 multi-fragment EMR. In all cases, hemi-circumferential ARMS was completed with approximately 2 cm cardia mucosal resection.

Before treatment, endoscopic retroflexed view demonstrated substantial opening of EGJ (flap valve Grade 2 or 3) but no sliding hernia was identified (Fig. 4A). Half- to two-thirds circumferential ARMS was carried out (Fig. 4B). The standard dose PPI was prescribed for the subsequent 40 days and then discontinued. These patients were started on a soft diet the morning after the procedure and were switched to a regular diet after the 2nd day. Follow-up endoscopy was scheduled at 2 months after ARMS. The EGJ in retroflex view demonstrated a significantly improved appearance (flap valve Grade 1) (Fig. 4C, D). Reflux symptoms were absent, with no medication. The DeMeester score fell to 0 in 7 cases and to 1 in 1 case.

Fraction time absorbance (>0.14) was controlled from 52% to 4% in Bilitec (P=0.05). In 24-h esophageal pH monitoring the fraction of time at pH <4 improved from 29.1% to 3.1% (P=0.01), (Fig. 5). Fraction time absorbance (>0.14) of bile reflux was controlled from 52% to 4% (P=0.05) (Fig. 6).

Operating time on average was 76 min (42-124, N=3) in the group of piecemeal EMR and 127 min on average (98-176, N=7) in the group of ESD, EMR is faster than ESD (P=0.05). In all cases, PPI prescription could be discontinued with no ill effects.

Discussion

Our results suggest a potential anti-reflux effect of ARMS. The mechanism is presumed to be due to scar formation after healing of the mucosal defect [14,15]. On the gastric side, this induces narrowing of the gastric cardia opening, while preserving and/or re-creating a robust his angle. We also postulate some remodeling of mucosal flap valve as an effective antireflux mechanism at this anatomical level.

As demonstrated in Fig. 4, after ARMS, the lesser curve of the gastric cardia takes on an almost "mechanically-stitched" appearance. The mucosal flap is rebuilt and looks well-defined. Furthermore, the lesser curve side of the EGJ is shortened with scar formation, and greater curve of EGJ (his angle side) is kept non-scarred and therefore retains its flexibility as a mucosal flap valve. Another major advantage of this procedure is that it requires no proprietary equipment and leaves no artificial prostheses *in situ* (which could generate a foreign body reaction in the future).

Although possible complications may include perforation or bleeding, the techniques of EMR/ESD used in this procedure

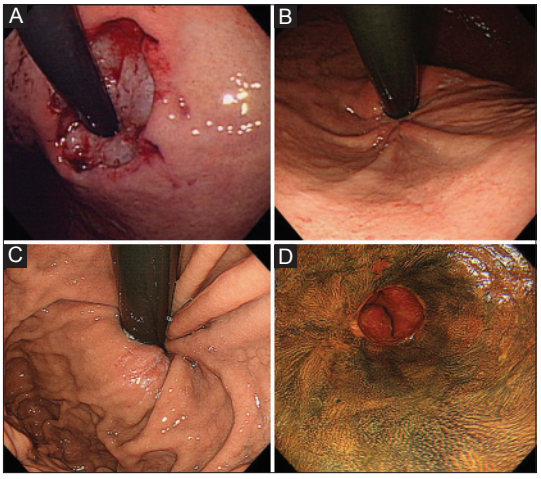

Figure 3 Endoscopic follow up of circumferential anti-reflux mucosectomy (ARMS) (retroflexed views). (A) Immediately after circumferential ARMS. Approximately 2 cm-wide gastric cardia mucosa was circumferentially resected by cap-endoscopic mucosal resection method [18]. (B) Appearance at 3 years. A tight gastro-esophageal junction. Convergence of three gastric folds was observed along the lesser curve of the stomach. (C) More than 10 years after circumferential ARMS. Appearance is similar to Fig. 3B. (D) More than 10 years after circumferential ARMS (forward view). Chromoendoscopy with Lugol's solution demonstrated well-stained squamous epithelium with neither recurrence of esophagitis nor Barrett's esophagus

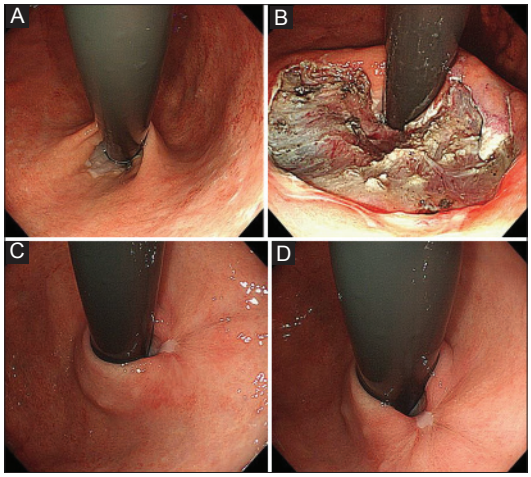

Figure 4 Endoscopic follow up of crescentic anti-reflux mucosectomy (ARMS). (A) Before ARMS. Endoscopy in retroflexion demonstrated significant hiatal hernia (Flap valve score 3) but no sliding component. Chest pain and regurgitation were prominent in this case (DeMeester score 5) and symptoms were not controlled by double dose proton pump inhibitor. (B) Immediately after procedure. Endoscopy in retroflexion showed two-thirds circumferential artificial ulcer. ARMS was centered at lesser curve and the mucosal flap valve at greater curve was preserved. (C) Appearance at 2 months. Mucosal valve was re-shaped and well-defined (Mucosal flap valve Grade 1). (D) Alternative endoscopic view at 2 months. Mucosal valve as appeared as though "stitched" at the lesser curve of gastric cardia

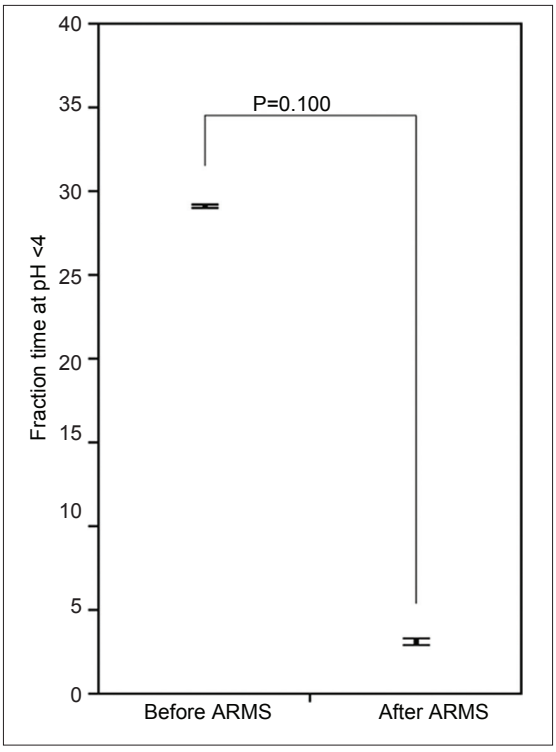

Figure 5 Changes of acid reflux after anti-reflux mucosectomy (ARMS). The fraction of time at pH <4 was improved from 29.1% to 3.1% (P=0.05)

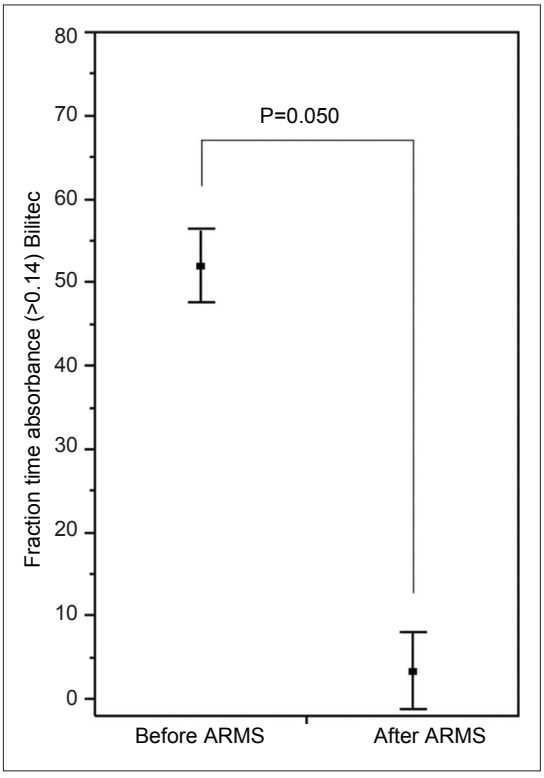

Figure 6 Changes of bile reflux after anti-reflux mucosectomy (ARMS). Fraction time absorbance (>0.14) was controlled from 52% to 4% in Bilitec (P=0.05)

have become standardized and popularized. These risks are likely to be minimal in "expert" hands and, even if experienced, can be resolved using standardized endoscopic recovery techniques such as coagulation forceps or clips for bleeding and perforation [18-20]. Furthermore, piecemeal EMR could be a less time-consuming and acceptable (sole) technique in this procedure, particularly if the specimen involves no dysplasia.

The limitation of this pilot study is that, in almost half of cases, pH monitoring was not accepted by the patients after procedure. In order to demonstrate efficacy, the results of this pilot study need to be confirmed by larger ones with long-term follow up. For this perspective, manometric studies before and after the procedure are highly recommended, and pH-impedenzometry might be used as the only measurement for reflux so ameliorating the compliance to instrumental studies after the procedure.

The quantity of mucosa to be resected to induce appropriate ("not too tight and not too loose") scar formation is a key issue in this procedure. Our two cases seem to indicate that total circumferential resection causes too tight a junction, which requires repeat endoscopic dilation [21,22], while subtotal dissection, which we have termed crescentic, produces better results in this regard, while still resulting in symptom control. In the initial 2 cases circumferential ARMS was eventually done because of multiple HGD in short-segment Barrett's, but circumferential ARMS should be avoided from the point of post-procedural stricture. In this latter technique, the remaining mucosal area should be estimated as twice the width of the endoscope circumference when viewed in retroflexion from stomach. The ideal range of mucosal reduction may be altered by several factors such as the extent of laxity at the EGJ as well as esophageal contractile function. In the case of hypomotility of the esophageal body, for instance, half circumferential mucosal reduction may be recommended.

In this pilot study, the crescentic ARMS was centered on the lesser curve. As this kept the mucosa on the angle side intact, but greater curve ARMS is also technically possible. A prospective study is necessary to clarify which ARMS technique produces the best results.

Furthermore, the length of ARMS may also influence outcomes. In this series, mucosal reduction was carried out in 1 cm esophageal site and 2 cm gastric side as this followed from the first successful clinical case. As the major antireflux contribution may be from the mucosal resection on the gastric side, the overall length could also vary.

Finally, the long-term results of ARMS warrant close attention. Excellent control of GERD in our first clinical case of ARMS even after more than 10 years suggests that this technique may achieve long-lasting results.

Case selection is important, and we have not extended the study at this stage as most GERD in Japanese population is generally mild and can be easily controlled by PPI medication, whereas most refractory cases have a substantial hiatal hernia. This is well-treated by laparoscopic Nissen fundoplication [4,5]. We feel that the most appropriate indication for ARMS is intractable GERD with no sliding hernia. Patients with PPI-refractory GERD without a sliding hiatal hernia and possibly

Summary Box

What is already known:

- Proton pump inhibitor (PPI)-refractory reflux patients are mostly treated by laparoscopic fundoplication
- Many endoscopic procedures were attempted but no procedure has been widely accepted as standard endoscopic treatment, either due to insufficient symptom control or the requirement of costly proprietary devices

What the new findings are:

- Anti-reflux mucosectomy (ARMS) is a novel endoscopic procedure to rebuild mucosal flap valve at gastric cardia
- Patients with PPI-refractory gastroesophageal reflux disease without a sliding hiatal hernia seem to be the best candidates for ARMS treatment
- Although this pilot study showed promising results, larger studies with long-term follow up are warranted to assess control of intractable GERD by ARMS

short-segment Barrett's esophagus seem to be the best candidates for the ARMS treatment.

In conclusion, this first clinical series of ARMS for GERD with no sliding hernia showed excellent short- and midterm control of GERD. Future, larger studies with objective assessment and long follow up are warranted.

References

1. Cook MB, Wild CP, Forman D. A systematic review and meta-analysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. *Am J Epidemiol* 2005;**162**:1050-1061.
2. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 2011;**305**:1969-1977.
3. Cicala M, Emerenziani S, Guarino MP, Ribolsi M. Proton pump inhibitor resistance, the real challenge in gastro-esophageal reflux disease. *World J Gastroenterol* 2013;**19**:6529-6535.
4. Kellokumpu I, Voutilainen M, Haglund C, Färkkilä M, Roberts PJ, Kautiainen H. Quality of life following laparoscopic Nissen fundoplication: assessing short-term and long-term outcomes. *World J Gastroenterol* 2013;**19**:3810-3818.
5. Rickenbacher N, Kötter T, Kochen MM, Scherer M, Blozik E. Fundoplication versus medical management of gastroesophageal reflux disease: systematic review and meta-analysis. *Surg Endosc* 2014;**28**:143-155.
6. Lødrup A, Pottegård A, Hallas J, Bytzer P. Use of proton pump inhibitors after antireflux surgery: a nationwide register-based follow-up study. *Gut* 2014;**63:**1544-1549.
7. Mahmood Z, Byrne PJ, McMahon BP, et al. Comparison of transesophageal endoscopic plication (TEP) with laparoscopic Nissen fundoplication (LNF) in the treatment of uncomplicated reflux disease. *Am J Gastroenterol* 2006;**101**:431-436.
8. Triadafilopoulos G. Stretta: a valuable endoscopic treatment modality for gastroesophageal reflux disease. *World J Gastroenterol* 2014;**20**:7730-7738.
9. Feretis C, Benakis P, Dimopoulos C, et al. Endoscopic implantation of Plexiglas (PMMA) microspheres for the treatment of GERD. *Gastrointest Endosc* 2001;**53**:423-426.
10. Cicala M, Gabbrielli A, Emerenziani S, et al. Effect of endoscopic augmentation of the lower oesophageal sphincter (Gatekeeper reflux repair system) on intraoesophageal dynamic characteristics of acid reflux. *Gut* 2005;**54**:183-186.
11. Wong RF, Davis TV, Peterson KA. Complications involving the mediastinum after injection of Enteryx for GERD. *Gastrointest Endosc* 2005;**61**:753-756.
12. Chuttani R, Sud R, Sachdev G, et al. A novel endoscopic full-thickness plicator for the treatment of GERD: a pilot study. *Gastrointest Endosc* 2003;**58**:770-776.
13. Cadière GB, Buset M, Muls V, et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. *World J Surg* 2008;**32**:1676-1688.
14. Satodate H, Inoue H, Yoshida T, et al. Circumferential EMR of carcinoma arising in Barrett's esophagus: case report. *Gastrointest Endosc* 2003;**58**:288-292.
15. Satodate H, Inoue H, Fukami N, Shiokawa A, Kudo SE. Squamous reepithelialization after circumferential endoscopic mucosal resection of superficial carcinoma arising in Barrett's esophagus. *Endoscopy* 2004;**36**:909-912.
16. DeMeester TR, Johnson LF. The evaluation of objective measurements of gastroesophageal reflux and their contribution to patient management. *Surg Clin North Am* 1976;**56**:39-53.
17. Hill LD, Kozarek RA, Kraemer SJ, et al. The gastroesophageal flap valve: *in vitro* and *in vivo* observations. *Gastrointest Endosc* 1996;**44**:541-547.
18. Inoue H, Takeshita K, Hori H, Muraoka Y, Yoneshima H, Endo M. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. *Gastrointest Endosc* 1993;**39**:58-62.
19. Fujishiro M, Yahagi N, Kakushima N, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. *Clin Gastroenterol Hepatol* 2006;**4**:688-694.
20. Sato H, Inoue H, Ikeda H, et al. Clinical experience of esophageal perforation occurring with endoscopic submucosal dissection. *Dis Esophagus* 2013.
21. Giovannini M, Bories E, Pesenti C, et al. Circumferential endoscopic mucosal resection in Barrett's esophagus with high-grade intraepithelial neoplasia or mucosal cancer. Preliminary results in 21 patients. *Endoscopy* 2004;**36**:782-787.
22. Sato H, Inoue H, Kobayashi Y, et al. Control of severe strictures after circumferential endoscopic submucosal dissection for esophageal carcinoma: oral steroid therapy with balloon dilation or balloon dilation alone. *Gastrointest Endosc* 2013;**78**:250-257.