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Evaluation of Treatment Effect using Timed Barium Esophagography in Patients with Peroral Endoscopic Myotomy for Achalasia

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Abstract: Peroral endoscopic myotomy (POEM) is one of the standard treatment modality for achalasia. This study was to evaluate the usefulness of timed barium esophagography (TBE) in the evaluation of treatment effect of POEM for achalasia. A total of 36 patients (M:F=22:14) underwent pre- and post-POEM TBE (3 groups according to lower esophageal sphincter (LES) caliber, A: < 5 mm, B: 5~8 mm, C: > 8 mm). On pre and post-POEM TBE, the rate of area changes of barium column and the changes of LES caliber were investigated. All data were statistically analyzed using the Kruskal-Wallis test or Mann-Whitney U test. The mean rate of area change of the barium column at 5 minutes between pre- and post-POEM TBE were -51.7%, -28.8% and -11.6% in group A (n=10), B (n=18), and C (n=8), respectively, statistically significant ($p < 0.001$). The rate difference of the barium column area changes between group A and group B only showed the statistical significance ($p < 0.001$). The mean increased caliber of LES after POEM was 5.5 mm, 2.9 mm, and 3.3 mm in group A, B, and C, respectively. Group A and bird′s beak type showed a statistically significant treatment effect ($p < 0.001$). In conclusion, TBE was useful in the evaluation of the treatment effect of POEM for achalasia and the narrowest LES group and bird′s beak esophageal type on TBE showed statistically significant treatment effects.

Keywords: Achalasia; Peroral endoscopic myotomy; Timed barium esophagography; Lower esophageal sphincter

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Introduction

Achalasia is an uncommon motility disorder of the esophagus characterized by a loss of esophageal peristalsis, incomplete relaxation of the lower esophageal sphincter (LES) in response to deglutition, increased resting LES pressure, and increased intraesophageal pressure (1, 2).

Timed barium esophagography (TBE) is known as one of the useful modalities in assessing esophageal emptying and responses to treatment in patients with achalasia [3-5]. Compared to esophageal transit scintigraphy (ETS) and endoluminal functional lumen imaging probe(EndoFLIP), TBE is simple, noninvasive, and convenient (3-6). ETS has been shown to correlate well with lower esophageal sphincter (LES) pressure and achalasia symptom score (1, 5), but is not commonly available recently. EndoFLIP provides real-time measurements of the esophageal diameter through a specific catheter with a balloon attached at the distal end, using specific algorithms and impedance planimetry (7, 8).

Surgical myotomy has been the treatment of choice for treating esophageal achalasia since the first report by Heller in 1913 (9). Other management methods include medication, endoscopic pneumatic dilatation (10, 11), and botulinum toxin injection (12, 13). In 2010, Inoue et al. (14) introduced peroral endoscopic myotomy (POEM) as a non-surgical treatment method for esophageal achalasia in humans. Since then, POEM has been one of the standard treatments for esophageal achalasia and related esophageal motility diseases, such as diffuse esophageal

spasm and jackhammer esophagus (15, 16). Until now, the evaluation of response to achalasia treatment has been performed by symptom improvement (Eckardt scores) (11), ETS, high-resolution esophageal manometry (HRM), EndoFLIP or conventional barium esophagography; however, symptom scores lack standardized criteria for treatment response (17), ETS has some radiation hazards, and HRM and EndoFLIP are relatively invasive and not simple. By contrast, TBE is known to assess the esophageal motility function based on time-series images with low radiation hazards and invasiveness (5). Therefore, the purpose of this study was to evaluate the efficacy of POEM for achalasia by the ratio of change of barium column area and the change of LES caliber using TBE before and after POEM.

Materials and methods

This retrospective study was approved by our institutional review board, and the requirement for informed consent was waived due to the retrospective nature of this study. The authors declare no conflict of interest.

Patients and Imaging Studies

We retrospectively reviewed the electronic medical records according to diagnostic codes of all patients who had both POEM and clinical diagnosis of achalasia for 4 years. The diagnosis of achalasia was based on clinical symptoms,

endoscopy, TBE, ETS, and/or HRM. Initially, 43 patients were included, but seven patients were later excluded due to absence of TBE (n=4), short interval (less than 30 days) between POEM and post-POEM TBE (n=2), and presence of epiphrenic diverticulum (n=1). As a result, a total of 36 patients (M:F=22:14, mean age: 43 years) were enrolled in this study and underwent pre- and post-POEM TBE for achalasia.

All 36 patients were arbitrarily divided into three groups according to LES caliber (A: < 5 mm, B: 5~8 mm, C: > 8 mm) on TBE before POEM, because it was reported that effective LES diameter of 8-10 mm correlated well with improved clinical response (18). And, the patients were classified into 2 types based on esophageal type: bird's beak type and sigmoid type. Bird's beak type showed a dilated esophageal lumen and tapered narrowing of the distal esophagus. Sigmoid type showed severe dilatation and subsequent tortuous angulation of the esophageal lumen, resulting from longstanding aperistalsis and lack of LES relaxation (19).

TBE was performed with the patient standing both before and after 30 days of POEM treatment. Anteroposterior, left posterior oblique, and left anterior oblique fluoroscopic projections (Shimavision 2000HG; Shimadzu) were taken after barium ingestion (150 mL barium sulfate with a concentration of 45 % w/v) over a period of 30 seconds to 1 minute (3-5, 20).

We used the area of barium column at 5 minutes to determine completeness of emptying. This was based on the previous report that barium completely empties from esophagus in 1 minute in most and in 5 minutes in all healthy individuals (21).

To assess the area of the esophageal barium column, the product of height times width has been considered to be an estimate parameter of the area of the esophageal barium column, rather than using height and width as separate parameters (20). Therefore, we compared the area change of the esophageal barium column at 5 minute before and after POEM to evaluate the esophageal emptying, as determined by the measurement of height times width and by the qualitative estimate.

The caliber of the LES on the anteroposterior view was also measured at 1, 2, and 5 minutes after barium ingestion on both pre- and post-POEM TBE, among which the largest caliber was chosen for comparison (Fig. 1). The interval changes in LES calibers between both pre- and post-POEM TBE were compared for evaluation of treatment effect of POEM. All measurements including LES diameter and area of barium column were reviewed by two gastrointestinal radiologists together to achieve consensus and interobserver agreement on picture-archiving and communication system images.

Eckardt scores measure frequency of dysphagia, regurgitation, chest pain, and amount of weight loss. Each of these parameters is rated on a scale of 0-3, resulting in a total score of 0-12; higher Eckardt scores indicate more severe disease. Eckardt scores (11) were recorded before and after POEM in each group, the differences of which were compared and statistically analyzed. The history of pre-POEM pneumatic dilatation (n=14) was also compared in each group.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 25.0 for Windows (IBM Corp.). For comparing three groups, Kruskal-Wallis test was first used for evaluation of the statistical difference of Eckardt scores changes and the area change of barium column at 5 minute before and after POEM. If the Kruskal-Wallis test yielded $p < 0.001$, Mann-Whitney U test with Bonferroni correction were additionally used to compare the values of each two groups (group A and B, group A and C, group B and C). Bonferroni correction for multiple comparisons was applied to assess possible significance with p value of $< 0.05 \times 2/n(n-1)$, where n was the number of groups. The difference of LES caliber on TBE before and after POEM and the effect of previous pneumatic dilatation on POEM were statistically analyzed using Mann-Whitney U test.

Results

All of 36 patients were divided into three groups according to LES caliber: 10 patients (27.8%) in group A (< 5 mm), 18 (50.0%) in group B (5~8 mm), and 8 (22.2%) in group C (> 8 mm), among whom 29 patients (80.6%) showed a bird's beak type and 7 patients (19.4%) showed a sigmoid type (Table 1).

Of 10 patients in group A (Fig. 2), 8 (80.0%) showed a bird's beak esophageal type and 2 (20.0%) showed a sigmoid type. Of 18 patients in group B (Fig. 3), 15 (83.3%) showed a bird's beak type and 3 (16.7%) showed a sigmoid type. Of remaining 8 patients in group C (Fig. 4), 6 (75.0%) showed a bird's beak

type and 2 (25.0%) showed a sigmoid type.

The interval between pre-POEM TBE and POEM was an average of 26 days and that between POEM and post-POEM TBE was an average of 64 days.

The area of barium column at 5 minutes showed the statistically significant difference ($p < 0.001$) between three groups before and after POEM by Kruskal-Wallis test. To further verify this result, Mann-Whitney U test with Bonferroni correction was used to compare each pair of three groups: group A and B, group B and C and group A and C, in which the area difference of the barium column showed the statistical significance ($p < 0.001$) only between group A and group B (Fig. 5).

The mean increased caliber of the LES after POEM was 5.5 mm in group A, 2.9 mm in group B, and 3.3 mm in group C. Group A only showed a statistically significant treatment effect ($p < 0.001$) on Mann-Whitney U test, compared with group B. No statistically significant difference ($p > 0.001$) between group A and group C or between group B and group C was observed.

Comparing to sigmoid type, bird's beak type showed a statistically significant treatment effect ($p < 0.001$) on Kruskal-Wallis test in all three groups.

The mean Eckardt score of pre-POEM patients was 5.8, and that of post-POEM patients was 1.1. Eckardt score improved in all three groups, but there was no statistical significance (p value = 0.970) in the change of Eckardt scores between three groups before and after POEM by Kruskal-Wallis test.

The history of pneumatic dilatation in 16 patients (44.4%) showed no statistical significance ($p > 0.05$) in the LES changes between three groups on

Mann-Whitney U test.

Discussion

Evaluation of responses to achalasia treatment has generally been based on symptom improvement. Clinical symptoms of dysphagia, regurgitation, retrosternal pain, and weight loss are used to calculate the Eckardt score to assess disease severity (11). However, symptom scores lack standardized criteria for treatment response (17). Earlier reports indicated that achalasia patients with chronic symptoms could mistake minimal improvements for dramatic change in esophageal emptying, highlighting the need for more objective assessment (22). The degree of esophageal dilation noted on post-POEM esophagography was not helpful for predicting patient outcomes, because symptoms of achalasia are primarily related to the degree of distensibility of the distal esophagus in the LES region rather than the degree of proximal esophageal dilatation (23). Vaezi et al. reported that they found a correlation between improvement in patient symptom scores and esophageal barium column height after pneumatic dilatations in 37 achalasia patients and concluded that TBE was a valuable clinical tool for assessing esophageal emptying (19). Esophageal manometry, TBE, and EndoFLIP are thus performed as objective tests.

An LES pressure less than 10 mmHg determined by manometry is the most effective predictor of long-term achalasia treatment success (24). Manometry is the

most accurate method of achalasia diagnosis and evaluation, enabling both quantitative and qualitative assessments of esophageal motility function (25, 26). A previous report suggested that the impedance bolus height on HRM correlates better with manometric variables than barium column height on TBE (27). However, repetitive manometric tests have disadvantages; invasiveness and difficulty inserting the catheter, especially in a sigmoid-type esophagus, make manometry a poor choice for evaluating treatment efficacy during long-term follow-up (20).

The EndoFLIP uses impedance planimetry and a pressure sensor to measure the distensibility and cross-sectional area of hollow organs in real time. In achalasia patients, the EndoFLIP provides a dynamic assessment of distensibility of the LES, which is valuable for evaluation and treatment (6, 7). LES distensibility measurements performed during myotomy, either laparoscopic or endoscopic, can reveal whether distensibility has been appropriately increased by the treatment. Even though EndoFLIP can provide a more direct measurement of LES function than TBE, it is more invasive and inconvenient rather than TBE. TBE provides information on esophageal anatomy and bolus retention. In fact, EndoFLIP, HRM, and TBE may be complementary modalities; therefore, the combined use of these modalities will provide more detail and more accurate information for predicting the clinical outcomes, after POEM (8).

By contrast, TBE can be easily performed and measures barium height, distance from the distal esophagus to the top of a distinct retained barium column, and barium width, the maximal esophageal width, at 1, 2, and 5 minutes after barium ingestion (19, 22). TBE is a noninvasive and effective method in both the

diagnosis and evaluation of response to achalasia treatment due to the correlation between improvement of symptoms and esophageal barium emptying (3, 4, 28, 29). A decrease in the height of the barium column at 1 min of more than 50% is a favorable predictor of treatment success and is associated with symptomatic improvement (4). Therefore, TBE is recommended both before and after POEM in patients with achalasia for evaluation of treatment effect.

While many authors have used height and width of barium column in sequential images to assess the emptying, others have used the area of the barium column (3, 20, 30). The TBE is a reproducible technique for estimating esophageal empting with almost perfect inter-observer agreement (20).

TBE helps to easily confirm anatomical structure of the esophagus and characteristics of achalasia (e.g., Bird's beak sign) and assess the esophageal motility function based on time-series images (3, 19). Clinicians usually expect achalasia treatment to be successful when the LES is greater than 8 mm in caliber on TBE (18, 31). Therefore, we arbitrarily divided all patients into three groups according to LES caliber (A: < 5 mm, B: 5~8 mm, C: > 8 mm) on TBE before POEM, based on the previous reports that effective LES diameter of 8-10 mm correlated well with improved clinical response (18) and Levy et al interpreted their results according to 2 groups, 5 mm or less and greater than 5 mm of distal esophageal width (32).

In our study, the narrowest LES group (LES: < 5 mm, group A) on pre-POEM TBE only showed a statistically significant treatment effect of POEM (p <

0.001), compared with group B (LES: 5~8 mm). But, Eckardt score showed no statistical significance in the treatment effect between two groups. This may mean that the increased caliber did not show improvement in symptoms. It was reported that there was no association between the esophageal caliber on post-POEM esophagography and the clinical response to treatment (32). Levy et al. also reported that a mean distal width of 5 mm or less on post-POEM esophagography was more likely to be associated with a suboptimal clinical response to POEM, i.e., treatment failure (32).

Why the narrowest LES group showed the most effective response to POEM in our study is not well explained, but we thought that this narrowest group rather showed better response to POEM treatment due to effective submucosal tunneling and transection myotomy of the circular muscle of the LES. Our study revealed that bird's beak type showed the statistically significant treatment effect, comparing to sigmoid type, which means the sigmoid type is not easy to recover normal LES function by POEM because of its chronic pathologic process and longstanding aperistalsis, comparing to bird's beak type (19).

The main benefit of POEM is its decreased invasiveness, leaving no scar. POEM also provides quicker relief of dysphagia. POEM is also typically performed in an outpatient setting and is associated with less post-procedural pain than surgery (33, 34). The main shortcoming of POEM is the increased risk of reflux compared to surgery, but reflux can be easily managed with a once-daily proton pump inhibitor (33, 35).

The variable complications of POEM include subcutaneous emphysema, pneumothorax, pneumoperitoneum, pneumomediastinum, gastroesophageal reflux, mediastinitis, bleeding, and esophageal and gastric cardia perforation (22, 36). In a study by Inoue et al. (35), the incidence of adverse events related to the POEM procedure was less than 3.2%; and all patients with these complications recovered with conservative treatment. No procedure-related deaths were reported. Another recent publication reported that POEM, pneumatic dilatation, and Heller myotomy were all effective in improving esophageal function in achalasia, and no difference in efficacy was noted among the three treatments (34).

Other researchers suggested that both TBE and ETS were effective for diagnosis and follow-up assessment of achalasia patients (19, 28). However, ETS has disadvantages; detailed anatomical structures, such as esophageal mucosal lesion or the calibers of the esophagus or the esophagogastric junction cannot be verified (5). Moreover, ETS has not been widely used in clinics; neither its testing method nor analyses of the resulting data have been standardized. Conventional esophagography can detect structural abnormality well but is limited in functional diagnosis of achalasia. TBE has the advantage of measuring changes in barium column height across time to assess esophageal emptying (3). Therefore, TBE might be the best modality for follow-up of achalasia patients after treatment.

Our study has some limitations. First, our study is retrospective in nature, and the single institutional setting may lead to selection bias. Second, the interval periods between pre-POEM TBE and POEM had a relatively wide range. Third, 16 patients (44.4%) had a history of pre-POEM pneumatic dilatation, which can affect

the treatment effect of POEM presented by the area change of barium column due to post-procedure scarring changes in the circular muscles of the LES area. Finally, correlation between the change of Eckardt score and the area change of barium column or increase of LES caliber on pre- and post-POEM TBE was not compared in each patient.

In conclusion, POEM was the most effective for treatment of achalasia in group A based on both the area change of barium column at 5 minutes on TBE and the LES change among three groups before and after POEM and bird's beak type showed a statistically significant treatment effect.

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Table 1. Summary of 32 Patients in Three Groups.

Group No	Sex	Age	Esoph shape	Pnem dilat	E-score change	Initial LES (mm)	Pre-post LES change (mm)	Pre-post area change (cm^2)
A-1	M	49	B	N	3	4.4	8.5	31.4
A-2	M	15	S	Y	7	4.6	5.4	30.8
A-3	F	15	B	Y	3	4.8	1.5	35.6
A-4	F	56	B	N	11	3.2	5.3	55.0
A-5	F	48	B	N	3	3.3	6.9	59.8
A-6	F	35	B	N	8	4.0	1.4	48.8
A-7	M	71	B	N	3	3.2	6.1	219.4
A-8	M	44	B	Y	3	3.8	6.0	99.0
A-9	M	35	B	Y	3	4.0	9.3	72.7
A-10	F	66	S	N	4	4.4	7.6	82.9
B-1	F	63	B	Y	4	6.7	2.6	19.9
B-2	F	58	B	Y	6	6.4	1.1	32.4
B-3	M	56	B	N	4	7.5	3.5	35.6
B-4	F	44	S	Y	6	7.4	1.6	13.9
B-5	M	20	B	Y	5	5.9	4.7	- 40.0
B-6	M	84	B	N	2	7.5	3.8	4.7
B-7	M	37	B	Y	5	5.8	4.1	52.5
B-8	M	28	B	N	5	6.2	3.0	104.6
B-9	M	76	S	N	2	6.3	1.0	9.3
B-10	M	29	B	N	4	5.6	0.5	7.3
B-11	M	23	B	Y	2	6.0	3.4	7.9
B-12	M	50	B	N	6	6.0	3.8	- 7.9
B-13	M	58	B	N	3	6.0	4.6	0.1
B-14	M	28	B	N	10	5.6	4.6	11.2
B-15	F	52	B	N	10	5.2	3.8	16.3
B-16	F	23	B	N	3	7.3	1.9	74.5
B-17	M	45	S	N	6	7.7	1.9	19.8
B-18	M	56	B	N	2	5.2	2.9	12.3
C-1	F	39	B	Y	5	8.7	3.5	60.2
C-2	M	16	B	Y	5	8.2	3.9	- 6.8
C-3	M	41	B	Y	3	8.3	4.2	12.5
C-4	F	23	B	Y	4	8.5	1.6	- 17.7
C-5	M	47	B	N	6	8.4	2.6	14.7
C-6	M	37	S	Y	3	8.3	3.2	5.9
C-7	F	38	S	Y	4	8.5	1.9	- 6.3
C-8	F	50	B	N	5	8.2	3.4	39.2

Esoph shape: Esophageal shape, B: Bird's beak, S: Sigmoid

Pneum dilat: Pneumatic dilatation, Y: Yes N: No

E-score change: Change of Eckardt score between pre- and post-POEM

LES: Lower esophageal sphincter

Pre-post LES change: LES change on TBE between pre- and post-POEM

Pre-post area change at 5 minute: Area change of TBE barium column between pre- and post-POEM

Figure Legends

Fig. 1. Measurement of the LES.

Figure 1. The caliber of the LESs were measured on the anteroposterior view at 1, 2, and 5 minutes after barium ingestion when the largest volume of barium contrast passed through the narrowest point of LES on both pre- and post-POEM TBE, among which the largest caliber was chosen for comparison.

Fig. 2. A 66-year-old female patient in group A with sigmoid type and an Eckardt score of 4.

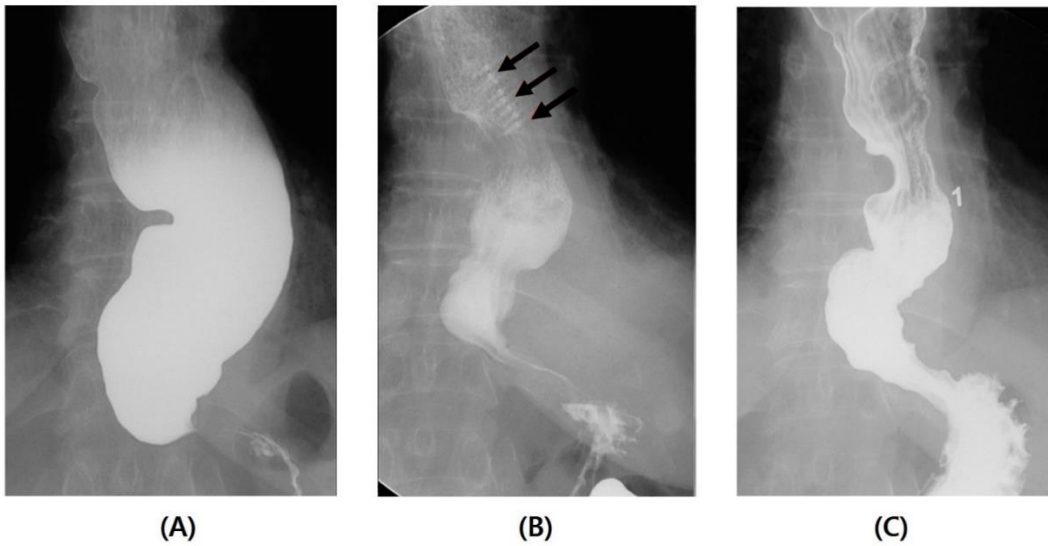

Figure 2. The LES caliber on pre-POEM TBE (A) was 4.4 mm, and that of post-POEM TBE (C) was 12.0 mm. Several endoscopic clips (arrows) are seen in the entry site of the submucosal tunnel at the mid esophagus (B).

Fig. 3. A 52-year-old female patient in group B with bird's beak type and an Eckardt score of 10.

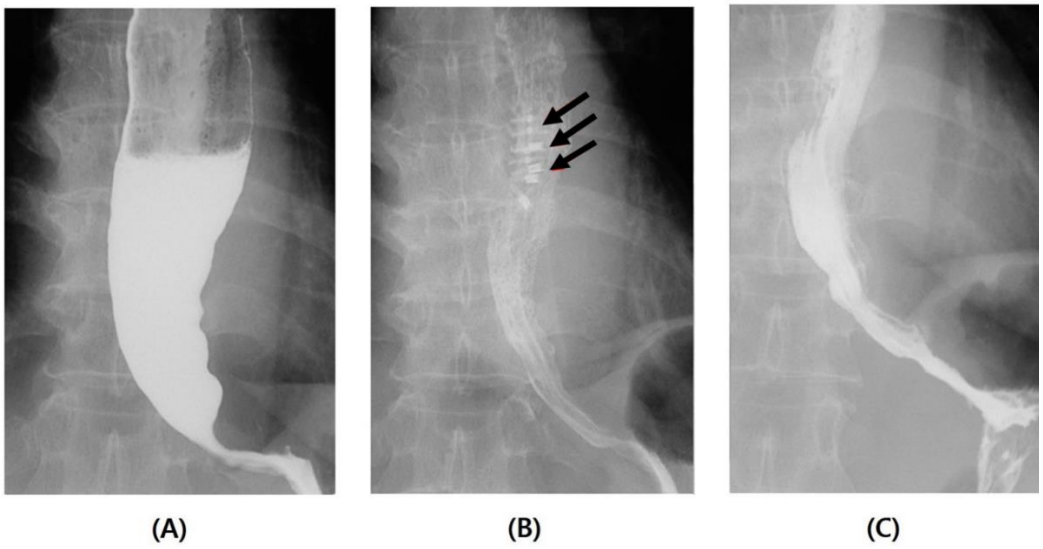

Figure 3. The LES caliber on pre-POEM TBE (A) was 5.2 mm, and that of post-POEM TBE (C) was 9.0 mm. Several endoscopic clips (arrows) are seen in the entry site of the submucosal tunnel at the mid esophagus (B).

Fig. 4. A 39-year-old female patient in group C with bird's beak type and an Eckardt score of 5.

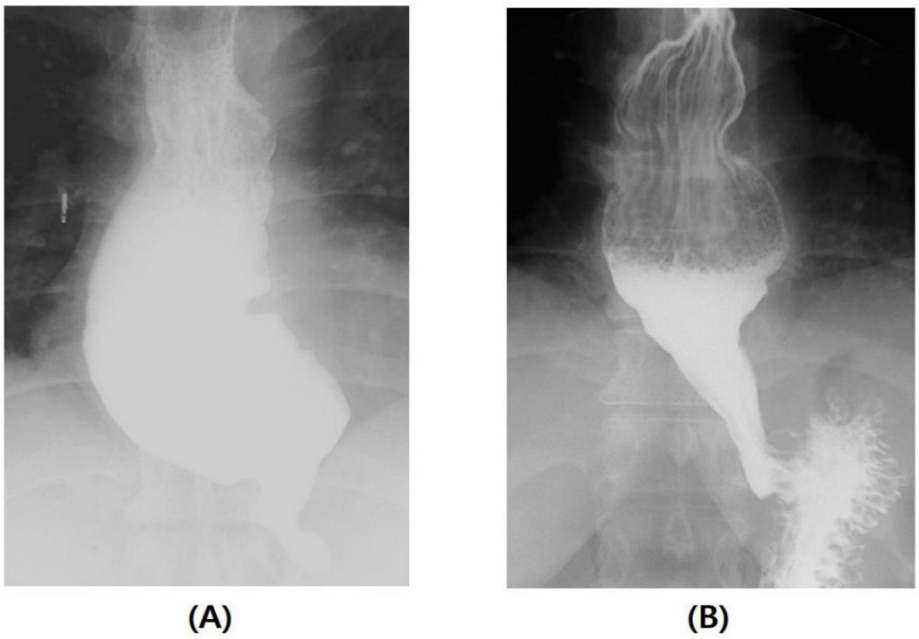

Figure 4. The LES caliber on pre-POEM TBE (A) was 8.7 mm, and that of post-POEM TBE (B) was 12.2 mm.

Fig. 5. A 66-year-old female patient with sigmoid type in group A.

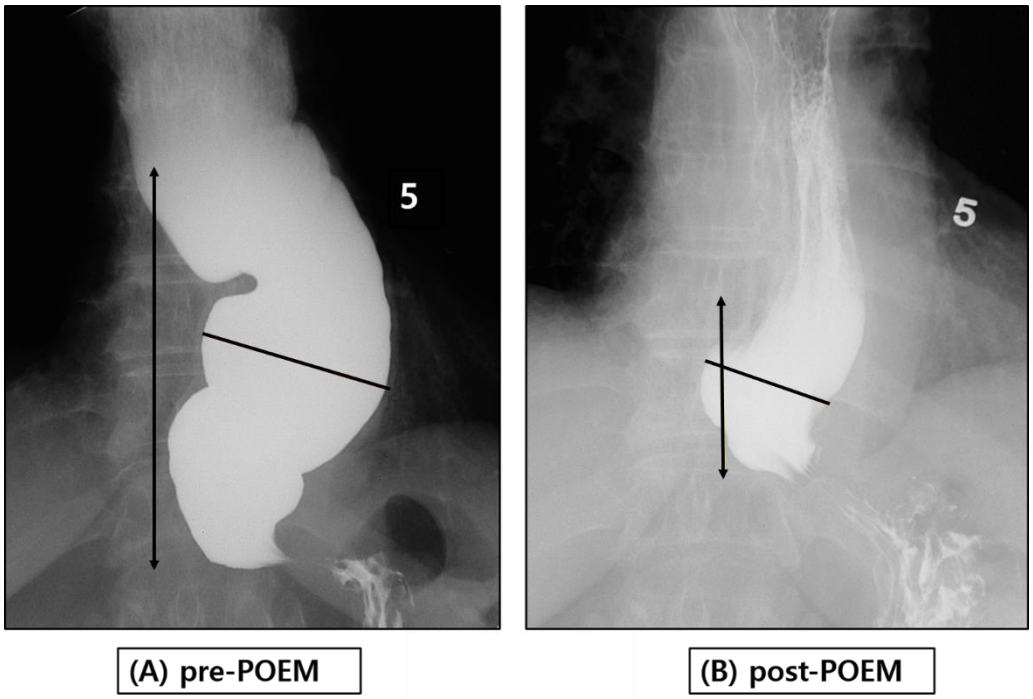

Figure 5. The height (bidirectional arrows) and the width (straight lines) of barium column at 5 minutes on TBE of pre-POEM (A) were 16.3 cm and 6.5 cm, respectively and those of post-POEM (B) were 5.5 cm and 4.2 cm, respectively. The area change of esophageal barium column on TBE between pre- and post-POEM showed the statistically significant treatment effect.