

# Evaluation of timed barium esophagram after per-oral endoscopic myotomy to predict clinical response



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## ABSTRACT

**Background and study aims** The aim of this study was to evaluate whether timed barium esophagram within 24 hours post-per-oral endoscopic myotomy (POEM) (TBE-PP) could predict clinical outcomes.

**Patients and methods** This was a single-center retrospective study of prospectively collected data on consecutive patients with  $\geq 6$ -month follow-up who underwent POEM followed by TBE-PP. Esophageal contrast retention 2 minutes after TBE-PP was assessed as Grade 1 (<10%), 2 (10%–49%), 3 (50%–89%) or 4 (>90%). Eckardt score, esophago-gastroduodenoscopy (EGD), high-resolution manometry (HRM) and function lumen imaging probe (FLIP) of the esophagogastric junction (EGJ) were obtained at baseline. These tests along with pH testing of antisecretory therapy were repeated 6 and 24 months after POEM. Clinical response by Eckardt score  $\leq 3$ , EGJ-distensibility index (EGJ-DI)  $> 2.8 \text{ mm}^2/\text{mm Hg}$ , and integrated relaxation pressure (IRP)  $< 15 \text{ mm Hg}$  and incidence of gastroesophageal reflux disease (GERD) were compared by transit time.

**Results** Of 181 patients (58% male, mean  $53 \pm 17$  yr), TBE-PP was classified as Grade 1 in 122 (67.4%), Grade 2 in 41 (22.7%), Grade 3 in 14 (7.7%) and Grade 4 in 4 (2.2%). At 6 months, overall clinical response by ES (91.7%), IRP (86.6%), EGJ-DI (95.7%) and the diagnosis of GERD (68.6%) was similar between Grade 1 and Grade 2–4 TBE-PP. At 24 months, Grade 1 had a higher frequency of a normal IRP compared to Grades 2–4 (95.7% vs. 60%,  $P=0.021$ ) but overall response by ES (91.2%), EGJ-DI (92.3%) and the diagnosis of GERD (74.3%) were similar.

**Conclusions** Contrast emptying rate by esophagram after POEM has limited utility to predict clinical response or risk of post-procedure GERD.

## Introduction

Idiopathic achalasia is a primary esophageal motor disorder characterized by aperistalsis and incomplete relaxation of the lower esophageal sphincter [1]. Treatment focuses on disruption

of the lower esophageal sphincter by pneumatic dilation, Heller myotomy, or most recently, peroral endoscopic myotomy (POEM). Recent randomized trials demonstrate that symptom relief with POEM is superior to pneumatic dilation [2] and noninferior to Heller myotomy [3]. Therefore, where available,

POEM has become the preferred primary management for patients with idiopathic achalasia.

Because POEM involves multiple steps including mucosal incision, submucosal dissection, myotomy and incision closure, fluoroscopic esophagram with oral contrast [4–7] or computed tomography (CT) scan (with [8] or without [9] oral contrast) is frequently performed to evaluate for procedure-related adverse events (AEs). Previous studies report that esophagram [5–7] and CT scans [8–9] after POEM often describe findings such as pneumoperitoneum or pneumomediastinum which are not usually clinically relevant or require repeat intervention. Furthermore, these tests are associated with increased cost, radiation exposure and may lead to unnecessary procedures for incidental findings [6, 7]. However, imaging may demonstrate contrast leaks within the wall (termed intramural dissection or contained leaks) or extravasation and it remains unclear whether intervention is required for contained leaks.

Timed barium esophagram (TBE) is often used to evaluate the efficacy of interventions in patients with achalasia, particularly after pneumatic dilation [10–12] or surgical myotomy. TBE after dilation can identify patients who may require repeat intervention [11] and is more effective than patient reported outcomes to predict treatment response [12]. Despite these findings, delay in esophagram contrast passage after POEM does not appear to predict clinical outcomes [4, 13, 14] thus raising questions about its utility in this setting.

Given its apparent limited utility in predicting clinically relevant AEs or patient outcomes, some authors have suggested that post-POEM imaging may not be warranted [5, 6, 9]. However, studies evaluating the role of esophagram after POEM are often retrospective [4–7, 9, 13, 14] or use non-standardized or unspecified esophagram protocols [5, 7, 13] to report clinical outcomes. Therefore, precise determination of the utility of imaging after POEM to determine clinical response or need for post-procedure intervention remains inconclusive.

In this retrospective, single-center study, we sought to determine the utility of 2-minute timed post-POEM barium esophagram (TBE-PP) transit speed to predict relevant short-term (6-month) and long-term (24-month) clinical outcomes. Our secondary aim was to evaluate the safety of conservative management in patients with intramural dissection after POEM in whom no other worrisome clinical signs were present. We hypothesized that delayed TBE-PP would not predict assessed clinical outcomes and reintervention was not required for contained submucosal leaks in stable patients.

## Patients and methods

### Patient selection and study design

This IRB-approved study (ClinicalTrials.gov ID NCT02770859) enrolled consecutive patients who underwent POEM for achalasia or esophagogastric outlet obstruction (EGJOO) at Indiana University Health Hospital in Indianapolis between 2016 and December 2019. All data were collected prospectively and analyzed retrospectively. TBE-PP within 24 hours of POEM was performed in all patients as standard of care. Patients with follow-up Eckardt scores or any objective testing (esophageal pH mon-

itoring, EGD, high-resolution esophageal manometry [HRM] or functional luminal impedance planimetry [FLIP]) performed  $\geq 6$  months after POEM comprised the study population. Patients were excluded for any of the following reasons: 1) baseline Eckardt score  $< 3$  or IRP  $< 15$  mm Hg; 2) follow-up  $< 6$  months; or 3) follow-up  $\geq 6$  months but no objective testing or Eckardt score completed. Written informed consent was obtained from all patients to participate in the study. All authors had access to the study data and reviewed and approved the final manuscript.

### Pre-procedure evaluation

Prior to POEM, key demographic information including gender, body mass index (BMI), age, and prior therapy (botulinum toxin injection, pneumatic dilation or surgical myotomy) for the esophageal motility disorder was recorded. Baseline patient reported frequency of dysphagia, chest pain, regurgitation, and weight change were recorded and an Eckardt score (range: 0–12, with higher score indicating more severe disease) was calculated [15]. Baseline EGD, HRM and beginning in 2017, FLIP of the esophagogastric junction (EGJ) was performed.

### High-resolution esophageal manometry

High-resolution esophageal manometry (HRM) studies were performed in the left lateral position with 30-degree head-elevation. A 4.2-mm, solid-state, manometry-impedance catheter with 36 circumferential pressure sensors at 1-cm intervals and 18 impedance channels (Medtronic, Minneapolis, Minnesota, United States) was placed transnasally and positioned with the pressure sensors spanning a length extending from the hypopharynx through the esophagus and 3 to 5 cm into the stomach. Once the catheter was in position and following an acclimation period, baseline resting EGJ morphology and pressure was assessed during normal respiration without swallows. Ten 5-mL liquid swallows were performed in the supine position. Study swallows were analyzed using the ManoView version 3.0 analysis software (Medtronic Minneapolis, Minnesota, United States) and Chicago Classification version 3.0 [16].

### EGD and FLIP procedures

EGD and FLIP were performed in the left lateral position under propofol sedation. The 16-cm FLIP (EndoFLIP EF-100, EF-322N or EF-325N, Medtronic, Inc, Shoreview, Minnesota, United States) was initially calibrated to atmospheric pressure and subsequently (with the endoscope withdrawn) passed transorally across the EGJ to ensure that at least 2 sensors were in the stomach. Endoscope visualization and rarely forceps assistance was required to facilitate catheter passage into the stomach. Endoscope insertion was done to confirm the balloon had traversed the EGJ and was positioned at the midpoint of the impedance sensors prior to inflation. Following endoscope removal, controlled, stepwise volumetric distensions of 20, 30, and 40 mL and beginning in July 2017, 50 mL were performed, maintaining each for at least 30 seconds while measurements were obtained. With each distention, the EGJ cross-sectional area, intrabag pressure, and EGJ diameter were assessed. If bag migration was suspected or peristalsis occurred, the bag was repositioned and the measurement repeated. The EGJ dis-

tensibility index (EGJ-DI) at each distension volume was calculated by dividing the EGJ cross sectional area by the intra-bag pressure and reported as  $\text{mm}^2/\text{Hg}$  [17].

### POEM procedure

All POEM procedures were performed by two gastroenterologists with patients in the supine position under general anesthesia. EGD was first performed to clear the esophagus and stomach of any debris. A total of 120 mL of dilute gentamicin solution (160 mg/100 mL of normal saline) was then instilled in the lower half of the esophagus and completely suctioned. A transparent cap was inserted on the distal end of the endoscope. Approximately 8 to 10 cm proximal to the EGJ, a mixture of saline with methylene blue was injected into the submucosa. After adequate lift, a longitudinal 2 to 3 cm mucosal incision (ENDO CUT Q, Effect 3, Cut Duration 2, Cut Interval 1) was made with a Hybrid T knife (Erbe USA, Inc., Marietta, Georgia, United States) using an electrosurgical generator (Erbe VIO 300D, Erbe USA, Inc., Marietta, Georgia, United States) to allow entrance to the submucosal space. A submucosal tunnel was created and through careful dissection extended (using Forced Coag, Effect 2, maximum 50 watts or ENDO CUT Q as above) for 2 to 3 cm into the gastric cardia. Bleeding or potentially bleeding sites were treated with Coagulation hemostatic forceps (Olympus America, Center Valley, Pennsylvania, United States) using soft coagulation (Effect 5, 80 Watts) current. A myotomy was performed using both ENDO CUT Q as above or Spray Coagulation (Effect 2, 35 Watts) in a proximal-to-distal direction and extended approximately 2 cm into the gastric cardia. After myotomy, the entry of the tunnel was then closed with endoscopic clips (Resolution, Boston-Scientific, Inc., Marlborough, Massachusetts, United States) and/or endoscopic suturing (Overstitch, Apollo Endosurgery, Austin Texas, United States). The orientation of the submucosal tunnel (i. e., anterior vs. posterior), myotomy type (circular alone vs. full thickness), and total myotomy length were recorded.

### Esophagram protocol

TBE-PP was performed by a registered radiologist assistant within 24 hours of POEM. The exam started with upright ingestion of 100 mL of water-soluble contrast (Gastrografin, EZ-EM Canada, Inc., Anjou Quebec). If an extramural leak was excluded, 100 mL of barium suspension (EZ-EM Canada, Inc., Anjou Quebec) was given immediately thereafter to complete the exam and confirm absence of extravasation. The quantity of contrast remaining in the esophagus 2 minutes after ingestion of barium was estimated prospectively by a gastrointestinal radiologist as: Grade 1 (<10%), Grade 2 (10%–49%), Grade 3 (50%–89%) or Grade 4 (>90%) transport. If no contrast remained after one minute, then no further images were obtained. An esophageal lumen diameter midway between the upper and lower sphincter was measured and topography assessed for sigmoid configuration. A sigmoid esophagus was considered dilation to  $\geq 10$  cm in diameter and/or a tortuous lumen towards the EGJ [18]. The presence of any intramural dissection (contained leak) or extramural leakage (non-contained leak) of contrast was also noted. Repeat endoscopic intervention was

considered for extramural leak but only for a contained leak if symptoms of severe chest pain, fever or odynophagia were present. If no extramural leak was identified with both contrast agents, then a clear or full liquid diet was started within four hours. Incidental findings such as subcutaneous emphysema, gastric pneumatosis, pneumoperitoneum or a pleural effusion were only tracked if additional interventions were required to manage suspected complications based on these results. After POEM, patients were instructed to take a proton-pump inhibitor twice daily for only 2 weeks and asked to restart only for recurrent symptoms or heartburn.

### Follow-up after POEM

Six and 24 months after POEM, patients returned to our hospital for one or more of the following: Eckardt score calculation, esophageal pH testing, HRM, EGD, and FLIP of the EGJ. Evaluations and diagnostics were performed after patients discontinued all anti-secretory therapy for at least one week. Patients were also queried about the presence of any heartburn and frequency of any use of proton pump inhibitors (PPIs). If patients were unable or unwilling to return for objective testing then information about Eckardt scores, PPI use, and heartburn were made by telephone call by a research nurse blinded to TBE-PP results. The severity of any endoscopic evidence of esophagitis was classified by the Los Angeles Classification [19].

### Esophageal pH testing

Measurement of esophageal acid exposure (Bravo, Medtronic, Minneapolis, Minnesota, United States) for 48 hours was obtained 6 months and 24 months after POEM by wireless ambulatory pH monitoring [20]. Prior to placement, the Bravo pH capsule was calibrated according to the manufacturer's protocol. The Bravo delivery system was passed orally, positioned 6 cm proximal to the EGJ and deployed in standard fashion. The diagnosis of conclusive, inconclusive, or absent GERD was determined using the Lyon consensus criteria [21]. Inconclusive or absent GERD for the current study was considered absence of GERD.

### Definitions of clinical response

Clinical response after POEM was defined by three independent metrics: Eckardt Score  $\leq 3$  [22] in absence of repeat intervention for treatment failure, EGJ-DI  $> 2.8 \text{ mm}^2/\text{mm Hg}$  at any balloon distention [23], and IRP  $< 15 \text{ mm Hg}$  [16].

### Statistical analysis

Patients were compared by speed of transport on TBE-PP: a) Grade 1 vs. Grades 2–4; and b) Grades 1 and 2 vs. Grades 3 and 4. Continuous variables are described as means  $\pm$  standard deviations or medians with ranges. Dichotomous variables are described as proportions. Two sample *t*-tests for continuous outcomes and Fisher's exact test for categorical variables to test for differences in patient reported outcomes and objective testing between the two groups. A logistic regression was used to determine if dichotomous clinical response outcomes differed by TBE-PP grade adjusting for esophageal motility disorder, esophageal width, presence of a sigmoid esophagus and

any pre-procedure therapy. Analysis of covariance (ANCOVA) models were used to compare continuous outcome measures by TBE-PP grade adjusting for type of esophageal motility disorder, esophageal width, presence of a sigmoid esophagus and any pre-procedure therapy.  $P < 0.05$  was used to determine significance. All analyses were performed using SAS v9.4 (Cary North Carolina, United States).

## Results

### Study population

During the study period, 228 patients underwent POEM for achalasia or EGJOO and 47 (21%) were excluded due to refusal to return phone calls or for follow up exams ( $n = 32$ ), failure to sign consent ( $n = 6$ ) or severe comorbidities preventing testing ( $n = 9$ ). The baseline characteristics of the 181 consecutive patients (58% male, mean  $53 \pm 17$  yrs.) who underwent POEM are shown in ► **Table 1**. Mean Eckardt score was  $7.9 \pm 1.8$  and the most common esophageal motor disorder was type 2 achalasia (62.4%). Previous therapy was performed in 52.5% of patients. Overall, 24 (13.4%) had a sigmoid configuration. TBE-PP was classified as Grade 1 in 122 (67.4%), Grade 2 in 41 (22.7%), Grade 3 in 14 (7.7%) and Grade 4 in 4 (2.2%). Mean esophageal width was larger in the Grade 2 to 4 group ( $4.0 \pm 1.8$  cm) compared to Group 1 ( $3.1 \pm 1.0$  cm;  $P < 0.001$ ); otherwise, the two groups were similar.

Intramural dissection was found in seven patients (3.8%) either at the site of the tunnel mucosotomy clip closure ( $n = 4$ ) or GE junction ( $n = 3$ ). In one patient with intramural dissection, POEM was also complicated intraoperatively by pneumothorax requiring chest tube insertion. Based on the subsequent finding of a contained leak on esophagram, a fully covered stent was inserted the day following POEM. In the other six patients with intramural dissection, no further intervention was performed for the contained leak and a clear or full liquid diet was started within 24 hours of POEM. In the remaining 174 patients, no findings on esophagram prompted change in clinical care.

### Six-month follow-up

At 6 months after POEM, follow-up was available for Eckardt scores ( $n = 181$ ), HRM ( $n = 127$ ), FLIP ( $n = 140$ ), EGD ( $n = 146$ ) and pH testing ( $n = 121$ ). Overall clinical response by Eckardt score (91.7%), IRP (86.6%) and EGJ-DI (95.7%) was similar between patients with Grade 1 transport and those with Grades 2 to 4 transport (► **Table 2**). Furthermore, there was no difference in post-POEM mean IRP, mean EGJ-DI  $> 2.8$  mm<sup>2</sup>/mm Hg, or mean EGJ-DI and at any (20–50 mL) balloon distention. Overall, GERD was diagnosed in 68.6% of the 127 patients who had EGD, pH testing, or both but the frequency was similar between the two groups. Esophagitis was present in 69.9% of the 146 patients who had follow up EGD, including 11.0% with LA Grade C and 4.1% with LA Grade D esophagitis. Heartburn was reported in 31.6% of patients and 31.2% were taking PPIs either daily or weekly. The overall rate of esophagitis, patient reported heartburn and PPI use were similar between the two groups.

### Twenty-four month follow-up

At 24 months after POEM, follow-up was available for at least one variable in 73 (40%) patients. TBE-PP was Grade 1 in 50 (68.4%), Grade 2 in 15 (20.5%), Grade 3 in 6 (8.2%), and Grade 4 in 2 (2.9%). Follow-up was available for Eckardt scores ( $n = 68$ ), HRM ( $n = 33$ ), FLIP ( $n = 39$ ), EGD ( $n = 39$ ), and pH testing ( $n = 33$ ). Overall clinical response by Eckardt score, IRP and EGJ-DI was 91.2%, 84.9% and 92.3%, respectively (► **Table 3**). Group 1 had a higher frequency of a normal IRP compared to Groups 2 to 4 (95.7% vs. 60%,  $P = 0.021$ ) but response by Eckardt score and EGJ-DI were similar between the two groups. There was no difference in post-POEM mean IRP, EGJ-DI  $> 2.8$  mm<sup>2</sup>/mm Hg or mean EGJ-DI and at any (20–50 mL) balloon distention. GERD was diagnosed in 74.3% of the 35 patients who had EGD, pH testing or both but the frequency was similar between the two groups. Esophagitis was present in 77.9% of 39 patients who had follow up EGD, including 7.7% with LA Grade C or and 5.1% with LA Grade D esophagitis. Heartburn was reported in 42.6% of patients and 25.5% reported taking a PPI at least daily or weekly. The overall rate of esophagitis, patient reported heartburn, and PPI use was likewise similar between the two groups.

Multivariate analysis results comparing grade 1 with grades 2 to 4 are presented in **Supplemental Table 4**. After adjusting for baseline IRP and other clinical characteristics, patients with TBE-PP grades 2 to 4 have higher IRP scores at 24 months than patients with grade 1. Increasing baseline IRP was also significantly associated with increasing IRP at 24 months. No other clinical outcomes differed significantly between grade 1 and grade 2 to 4 patients after adjusting for clinical characteristics.

### Comparison between Groups 1 and 2 versus Groups 3 and 4

Mean esophageal width was larger in the Grades 3 to 4 ( $4.6 \pm 2.0$  cm) compared to Group 1 group ( $3.3 \pm 1.2$  cm;  $P < 0.001$ ); otherwise, the two groups were similar (**Supplemental Table 1**). At 6 months after POEM (**Supplemental Table 2**), clinical response by EGJ-DI was higher in the Grade 1 to 2 group compared to the Grade 3 to 4 group (97.6% vs. 81.2%,  $P = 0.02$ ). At 24 months after POEM (**Supplemental Table 3**), clinical response by IRP was higher in the Grade 1 to 2 group compared to the Grade 3 to 4 group (95.7% vs. 81.2%,  $P = 0.02$ ). Otherwise, clinical response by Eckardt score, EGJ-DI or IRP or the incidence of GERD, heartburn, esophagitis and PPI use were similar between the two groups.

Multivariate analysis results comparing grade 1,2 with grades 3,4 are presented in **Supplemental Table 5**. After adjusting for clinical characteristics, DI at 20, 30, 40 and 50 at 6 months are no longer significantly different between the grade categories. Only one comparison between grades 1 and 2 versus grades 3 and 4 remained significant after adjustment. Any DI  $> 2.8$  at 6 months was significantly lower for grade 3 to 4 patients than grade 1 to 2 patients.

► **Table 1** Demographics, baseline features and results of POEM procedure in 181 consecutive patients with achalasia or EGJOO and at least 6-month follow-up with Grade 1 (<10% contrast retention) or Grade 2–4 (>10% contrast retention) post-POEM timed barium esophagram (TBE-PP) transit.

	Overall (n = 181)	Grade 1 TBE-PP (n = 122)	Grade 2–4 TBE-PP (n = 59)	P value
Male (n, %)	104/181 (57.5)	71 (58.2)	33 (55.9)	0.873
Mean (SD) age (n = 181)	53.2 (17.4)	53.3 (17.8)	53.0 (16.5)	0.905
Mean (SD) BMI (n = 181)	28.4 (7.7)	28.6 (7.4)	28.2 (8.2)	0.776
Mean (SD) HRM LES length (n = 168) <sup>1</sup>	3.3 (1.1)	3.4 (1.1)	3.2 (1.1)	0.454
Mean (SD) Eckardt score (n = 181)	7.9 (1.8)	8.0 (1.9)	7.5 (1.7)	0.063
Mean IRP (SD) (n = 181)	29.1 (13.2)	28.6 (13.5)	30.1 (12.4)	0.471
Motility disorder (n, %) (n = 181)				0.266
▪ Type 1 achalasia	30/181 (16.6)	16 (13.1)	14 (23.7)	
▪ Type 2 achalasia	113/181 (62.4)	77 (63.1)	36 (61.0)	
▪ Type 3 achalasia	10/181 (5.5)	8 (6.6)	2 (3.4)	
EGJOO	28/181 (15.5)	21 (17.2)	7 (11.9)	
Previous therapy (n, %) (n = 181)	95/181 (52.5)	65 (53.3)	30 (50.9)	0.874
▪ Botox	44/181 (24.3)	32 (26.2)	12 (20.3)	0.462
▪ Pneumatic Dilation	11/181 (6.1)	6 (4.9)	5 (8.5)	0.342
▪ Heller myotomy	8/181 (4.4)	7 (5.7)	1 (1.7)	0.277
EGJ-DI (n, %) <sup>2</sup>				
▪ 20 mL distension (n = 168)	1.6 (1.0)	1.5 (1.0)	1.7 (1.1)	0.224
▪ 30 mL distension (n = 169)	1.5 (1.4)	1.4 (1.6)	1.5 (1.0)	0.666
▪ 40 mL distension (n = 168)	1.2 (1.1)	1.2 (1.2)	1.3 (0.8)	0.831
▪ 50 mL distension (n = 143)	1.1 (1.0)	1.1 (1.1)	1.0 (0.7)	0.663
Sigmoid esophagus (n, %) (n = 179) <sup>3</sup>	24/179 (13.4)	12/120 (10.0)	12/59 (20.3)	0.065
Mean (SD) esophageal width (n = 181)	3.4 (1.3)	3.1 (1.0)	4.0 (1.8)	<0.001
Myotomy (n, %)				
▪ Mean length (SD) (n = 181)	9.8 (2.5)	9.8 (2.7)	9.8 (2.2)	0.999
Intended depth of incision (n = 181)				0.530
▪ Circular only	95/181 (52.5)	62 (50.8)	33 (55.9)	
▪ Full thickness	86/181 (47.5)	60 (49.2)	26 (44.1)	
Orientation (n = 181)				0.279
▪ Anterior myotomy	33/181 (18.2)	19 (15.6)	14 (23.7)	
▪ Posterior myotomy	130/181 (71.8)	92 (75.4)	38 (64.4)	
▪ Other	18/181 (9.9)	11 (9.0)	(11.9)	

BMI, body mass index; LES, lower esophageal sphincter; IRP, integrated relaxation pressure; EGJOO, esophagogastric outlet obstruction; TBE-PP, timed barium esophagram post-POEM; FLIP, function lumen imaging probe.

<sup>1</sup> Results of LES length by HRM available in 168 patients.

<sup>2</sup> Use of FLIP started after POEM in our population and distention to 50 mL after use of FLIP started. Therefore, results not available in all patients.

<sup>3</sup> Results for sigmoid esophagus available in 179 patients.

**► Table 2** Clinical response, diagnosis of GERD and results of esophageal manometry and functional luminal impedance planimetry (FLIP) 6 months after POEM stratified by Grade 1 (< 10% contrast retention) or Grade 2–4 (> 10% contrast retention) post-POEM timed barium esophagram (TBE-PP).

	Overall (n = 181)	Grade 1 TBE-PP (n = 122)	Grade 2–4 TBE-PP (n = 59)	P value
Clinical response				
▪ Eckardt Score ≤ 3 (n = 181)	166/181 (91.7)	110/122 (90.2)	56/59 (94.9)	0.392
▪ IRP < 15 mm Hg (n = 127) <sup>1</sup>	110/127 (86.6)	74/85 (87.1)	36/42 (85.7)	1.000
▪ EGI DI > 2.8 at any distention (n = 141) <sup>2</sup>	135/141 (95.7)	92/94 (97.9)	43/47 (91.5)	0.095
Esophageal manometry and FLIP				
▪ Mean (SD) ESM IRP (n = 127) <sup>3</sup>	9.1 (6.3)	8.6 (5.9)	10.1 (6.8)	0.205
▪ EGI DI > 2.8 mm <sup>2</sup> /mm Hg at 20 mL (n = 140)	119/140 (85.0)	78/93 (83.9)	41/47 (87.2)	0.803
▪ EGI DI > 2.8 mm <sup>2</sup> /mm Hg at 40 mL (n = 140)	128/140 (91.4)	87/93 (93.6)	41/47 (87.2)	0.218
▪ EGI DI > 2.8 mm <sup>2</sup> /mm Hg at 40 mL (n = 140)	128/140 (91.4)	87/93 (93.6)	41/47 (87.2)	0.218
▪ EGI DI > 2.8 mm <sup>2</sup> /mm Hg at 50 mL (n = 137)	119/137 (86.9)	81/92 (88.0)	38/45 (84.4)	0.595
▪ Mean (SD) EGJ-DI at 20 mL (n = 140)	3.6 (2.4)	3.5 (1.6)	3.8 (3.5)	0.470
▪ Mean (SD) EGJ-DI at 30 mL (n = 140)	5.0 (2.4)	5.1 (2.3)	4.9 (2.7)	0.775
▪ Mean (SD) EGJ-DI at 40 mL (n = 140)	5.6 (2.5)	5.6 (2.5)	5.5 (2.6)	0.846
▪ Mean (SD) EGJ-DI at 50 mL (n = 137)	4.9 (2.2)	4.9 (2.2)	5.0 (2.2)	0.901
GERD by Lyon Criteria (n = 127) <sup>4</sup>	87/127 (68.6)	61/85 (71.8)	26/42 (61.9)	0.311
Esophagitis grade (n = 146) <sup>5</sup>				0.191
▪ None	44/146 (30.1)	23/96 (24.0)	21/50 (42.0)	
▪ LA Grade A	33/146 (22.6)	22/96 (22.9)	11/50 (22.6)	
▪ LA Grade B	47/146 (32.2)	34/96 (35.4)	13/50 (26.0)	
▪ LA Grade C	16/146 (11.0)	13/96 (13.5)	3/50 (6.0)	
▪ LA Grade D	6/146 (4.1)	4/96 (4.2)	2/50 (4.0)	
Heartburn (n = 174) <sup>6</sup>	55/174 (31.6)	36/119 (30.3)	19/55 (34.6)	0.601
Taking PPIs (n = 176) <sup>7</sup>				0.086
▪ % No (n)	121/176 (68.8)	87/119 (71.0)	34/57 (59.6)	
▪ % Weekly (n)	28/176 (15.9)	14/119 (11.8)	14/57 (24.6)	
▪ % Daily (n)	27/156 (15.3)	18/119 (15.1)	9/57 (15.8)	

IRP, integrated relaxation pressure; TBE-PP, timed barium esophagram post-POEM; EGJ-DI, esophagogastric junction distensibility index.

<sup>1</sup> HRM 6 months after POEM was available in 127 patients.

<sup>2</sup> FLIP 6 months after POEM was available in 140 patients. Use of FLIP started after POEM in our population and distention to 50 mL after use of FLIP started. Therefore, results at 50 mL were not available in all patients.

<sup>3</sup> HRM 6 months after POEM was available in 127 patients.

<sup>4</sup> GERD diagnosed 6 months after POEM was classified by the Lyon Criteria based on the availability of EGD, wireless pH testing or both. pH testing was available in 121 patients.

<sup>5</sup> EGD 6 months after POEM to evaluate for esophagitis was done in 146 patients.

<sup>6</sup> Patient reported symptoms of heartburn 6 months after POEM were available in 174 patients.

<sup>7</sup> Patient reported use of PPIs 6 months after POEM were available in 176 patients.

## Discussion

In this, single center study of 181 patients with achalasia or EG-JOO treated with POEM, we found that rapid esophageal emptying (< 10% contrast retention) 2 minutes after a timed barium

esophagram (TBE-PP) within 24 hours of the procedure does not predict short-term (6 month) clinical response by Eckardt score, IRP or EGJ-DI. Two years after POEM, patients with rapid emptying were more likely to achieve a normalized IRP compar-

**► Table 3** Clinical response, diagnosis of GERD and results of esophageal manometry and functional luminal impedance planimetry (FLIP) 24 months after POEM stratified by Grade 1 (<10% contrast retention) or Grade 2–4 (<10% contrast retention) post-POEM timed barium esophagram (TBE-PP).

	Overall (n = 73)	Grade 1 TBE-PP (n = 50)	Grade 2–4 TBE-PP (n = 23)	P value
Clinical Response				
▪ Eckardt Score ≤ 3 (n = 73)	67/73 (91.2)	47/50 (94.0)	20/23 (87.0)	0.37
▪ IRP < 15 mm Hg (n = 33) <sup>1</sup>	28/33 (84.9)	22/23 (95.7)	6/10 (60.0)	0.02
▪ EGI DI < 2.8 at any distention (n = 39) <sup>2</sup>	36/39 (92.3)	24/26 (92.3)	12/13 (92.3)	1.0
Esophageal Manometry and FLIP				
▪ Mean (SD) IRP (n = 33) <sup>3</sup>	10.3 (5.7)	8.2 (3.5)	15.2 (6.8)	<0.001
▪ EGI DI < 2.8 mm <sup>2</sup> /mm Hg at 20 mL (n = 39)	24/39 (61.5)	17/26 (65.4)	7/13 (53.9)	0.51
▪ EGI DI < 2.8 mm <sup>2</sup> /mm Hg at 30 mL (n = 39)	33/39 (84.6)	21/26 (66.7)	12/13 (92.3)	0.64
▪ EGI DI < 2.8 mm <sup>2</sup> /mm Hg at 40 mL (n = 39)	34/39 (87.2)	22/26 (84.6)	12/13 (92.3)	0.65
▪ EGI DI < 2.8 mm <sup>2</sup> /mm Hg at 50 mL (n = 39)	31/39 (79.5)	21/26 (80.8)	10/13 (76.9)	1.0
▪ Mean (SD) EGJ-DI at 20 mL (n = 39)	3.5 (1.5)	3.6 (1.5)	3.3 (1.6)	0.68
▪ Mean (SD) EGJ-DI at 30 mL (n = 39)	4.7 (1.7)	4.8 (1.8)	4.7 (1.7)	0.89
▪ Mean (SD) EGJ-DI at 40 mL (n = 39)	5.1 (1.9)	5.1 (1.9)	5.2 (1.9)	0.88
▪ Mean (SD) EGJ-DI at 50 mL (n = 39)	4.7 (1.7)	4.7 (1.6)	4.7 (1.8)	0.92
GERD by Lyon Criteria (n = 35) <sup>4</sup>	26/35 (74.3)	18/24 (75.0)	8/11 (72.7)	1.0
Esophagitis Grade (n = 39) <sup>5</sup>				0.37
▪ None	9/39 (23.1)	6/26 (23.1)	3/13 (23.1)	1.0
▪ A	11/39 (28.2)	5/26 (19.2)	6/13 (46.2)	0.13
▪ B	14/39 (35.9)	10/26 (38.5)	4/13 (30.8)	0.73
▪ C	3/39 (7.7)	3/26 (11.5)	0/13 (0.0)	0.54
▪ D	2/39 (5.1)	2/26 (7.7)	0/13 (0.0)	0.54
Heartburn (n = 47) <sup>6</sup>	20/47 (42.6)	17/32 (53.1)	3/15 (20.0)	0.056
Taking PPIs (n = 47) <sup>7</sup>				0.29
▪ % No (n)	35/47 (74.5)	22/32 (68.8)	13/15 (86.7)	
▪ % Weekly (n)	12/47 (25.5)	10/32 (31.2)	2/15 (13.3)	
▪ % Daily (n)	0/47 (0.0)	0/32 (0.0)	0/15 (0.0)	

IRP, integrated relaxation pressure; TBE-PP, timed barium esophagram post-POEM; EGJ-DI, esophagogastric junction distensibility index.

<sup>1</sup> HRM 24 months after POEM was available in 33 patients.

<sup>2</sup> FLIP 24 months after POEM was available in 39 patients.

<sup>3</sup> HRM 24 months after POEM was available in 33 patients.

<sup>4</sup> GERD diagnosed 24 months after POEM was classified by the Lyon Criteria based on the availability of EGD, wireless pH testing or both. pH testing was performed in 33 patients.

<sup>5</sup> EGD 24 months after POEM to evaluate for esophagitis was done in 39 patients.

<sup>6</sup> Patient reported symptoms of heartburn 24 months after POEM were available in 47 patients.

<sup>7</sup> Patient reported use of PPIs 24 months after POEM were available in 47 patients.

ed to those with mild-severe delayed emptying ( $\geq 10\%$  contrast retention). After adjusting for baseline IRP and other clinical characteristics, patients with rapid esophageal transit after POEM had lower IRP scores at 24 months than patients with slower transit ( $>10\%$  contrast retention). However, clinical response at 24 months by Eckardt score and EGJ-DI and the inci-

dence of GERD, heartburn, esophagitis and PPI use were similar between the two groups.

Timed barium esophagram (TBE) is used to estimate esophageal emptying either before or after intervention for esophageal motility disorders. It is typically administered with a large volume of barium (i.e., 200–250 mL) and measurements of contrast column height or quantity remaining are taken at two

► **Table 4** Previous studies reporting the frequency of contrast leaks identified on CT scan or fluoroscopic esophagram by after per-oral endoscopic myotomy.

Author (yr)	N	Study settings	Method of esophagram	Extramural leaks n, (%)	Contained leaks n, (%)	Frequency esophagram findings altered management	Notes
Pannu (2016)	84	Single-center prospective	CT scan	1 (1.2%)	0 (%)	1 (1.2%). Repeat EGD in this patient showed ulcer, unsuccessfully treated with OTSC. Required surgical myotomy	Extensive coagulation of gastric cardia vessels done during POEM in this patient
Levy (2016)	25	Single-center, retrospective	Fluoroscopy	0 (0%)	7 (28%)	NA	
El Khoury (2016)	78	Single-center, retrospective	Fluoroscopy	0 (0%)	1 (2%)	2 (4%)	Clinical findings would have prompted these two esophagrams
Nast (2018)	114	Single-center, retrospective	Fluoroscopy	0 (0%)	2 (1.7%)	2 (1.7%)	1/2 was false positive esophagram
Reddy (2021)	170	Multicenter, retrospective	Fluoroscopy (n = 139) and CT (n = 31)	0 (%)	5 (2.9%)	2 (1.2%). Repeat EGD and clipping in these two leaks. These were considered true positive leaks.	2/4 leaks occurred with inadvertent mucosotomy (1) or thermal injury (1). 2/4 found after patient decompensation and were considered false-negative PPEs
Current study	181	Single-center, retrospective	Fluoroscopy	0 (0%)	7 (3.8%)	1/181 (0.6%) Fully covered stent inserted in 1 patient who also had intraprocedural pneumothorax requiring chest tube.	
Total	652		Fluoroscopy (n = 537), CT scan (n = 115)	1 (0.15%)	22 (3.4%)	8/652 (1.2%)	

CT, computed tomography; EGD, esophagogastroduodenoscopy; POEM, per-oral endoscopic myotomy; OTSC, over-the-scope clip.

or three intervals up to 5 minutes [10,24]. For this study, we used a timed esophagram protocol with gastrograffin followed by barium (total about 200 mLs contrast) with measurements up to only 2 minutes as we anticipated most patients would have little contrast remaining after POEM and evaluation for esophageal leaks could be adequately completed during this time period. Furthermore, we used a novel grading scale to quantitate the contrast retention to predict clinical response after POEM to patient-reported outcomes (Eckardt scale) or objective measurements (IRP, EGJ-DI or development of GERD).

Previous studies have reported that TBE following pneumatic dilation may identify patients who require repeat intervention [11] and is more effective than patient-reported outcomes to predict treatment response [12]. Furthermore, wider esophageal diameter, higher barium column height or poor emptying

from TBE following Heller myotomy for achalasia reportedly may predict risk of procedure failure or lack of symptom relief [24–28]. However, previous studies suggest that delay in contrast passage after POEM does not predict clinical outcomes [4, 13, 14] and often reports findings that are clinically irrelevant in stable patients and may lead to unnecessary post-procedure interventions [6–9]. We found that 2 years after POEM, after adjusting for baseline IRP and other clinical characteristics, rapid (<10% retention) predicted a lower IRP compared to those with mild-severe contrast delay but did not predict a normalized Eckardt score or other variables assessed. It is important to note that the value of TBE after interventions for achalasia are difficult to correlate due to a paucity of prospective studies with standardized esophagram protocols. Furthermore, studies after pneumatic dilation and POEM are usually per-



formed in the immediate post-procedure period to assess for complications whereas studies after Heller myotomy are performed usually months to years after myotomy to test esophageal emptying function and evaluate for need for reintervention. These findings after various interventions also underscore the disparity that often occurs between patient-reported symptoms in achalasia and results of esophageal physiology and radiographic studies [12, 29–31].

Our study also found that contained submucosal leaks on post-POEM esophagrams in clinically stable patients may not require intervention with repeat endoscopy. In six of seven patients with this finding, a liquid diet was started within 24 hours of POEM with no adverse effects. In the only unstable patient who had an intraprocedural pneumothorax during POEM, a fully-covered esophageal stent was placed after esophagram showed a contained leak. In the remaining 174 patients, there were no findings on esophagram that prompted change in clinical care in the immediate post-procedure period. Thus, results of one of 181 (0.6%) TBE-PP exams in the current study caused a change in clinical management and only in a clinically unstable patient. When our data is combined with four other studies [4–6, 8] with 652 patients (537 fluoroscopic esophagrams or 115 CT scans), contained (intramural) leaks are noted in 3.4% of studies after POEM and results of these changed management in only 1.2% of patients (► **Table 4**). As other studies have suggested [5, 6, 9] these findings collectively suggest that CT or esophagram may not be warranted in the immediate postoperative period in patients who clinically stable and did not incur iatrogenic mucosal injuries or insecure mucosotomy closures [5, 32]. Similarly, some authors have questioned the value of post procedure manometry to evaluate response to myotomy [33].

The current study represents the largest study to date evaluating the correlation between the rate of post-procedure esophagram contrast transport and clinical outcomes after POEM. Furthermore, a strict esophagram protocol was used to compare transit times to important patient-reported outcomes (Eckardt scores), lower esophageal sphincter measurements (IRP, EGJ-DI) and incidence of heartburn, PPI use and GERD. However, our study does have several weaknesses. First, follow-up short- and long-term objective testing was not available in all patients. Second, TBE protocol limited testing to a maximum of 2 minutes and the contrast grading scale used has not been validated by other authors. Third, the low frequency of contained leaks limits generalizations about the safety of conservative management of these patients. Finally, no pre-POEM TBE was available to compare findings from post-POEM esophagram.

## Conclusions

In conclusion, rapid contrast transit by timed fluoroscopic esophagram within 24 hours of POEM for achalasia or EGJOO predicts long-term normalization of IRP after POEM. Rapid emptying does not predict other short-term or long-term clinical responses, patient-reported outcomes, PPI use, or risk of post-procedure GERD. In clinically stable patients after POEM con-

tained leaks may be managed conservatively without intervention. These findings suggest that esophageal imaging after POEM may not be necessary in clinically stable patients or those in whom the procedure was completed without transmural mucosal injuries or possible incomplete submucosal tunnel closure. We recommend this instead should be reserved for signs of clinical deterioration or refractory symptoms in the perioperative period.

## Competing interests

Dr. DeWitt is a consultant for Boston Scientific, Inc. Dr. Al-Haddad is a consultant for Boston Scientific Inc.

## Clinical trial

clinicaltrials.gov  
NCT02770859  
TRIAL REGISTRATION: Single-Center, Retrospective Trial  
NCT02770859 at clinicaltrials.gov

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