The Utilization and Safety of Per Oral Endoscopic Myotomy (POEM) for Achalasia in the US

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Abstract

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Background: Clinical trials show that per oral endoscopic myotomy (POEM) has similar efficacy to pneumatic dilation (PD) and laparoscopic heller myotomy (LHM) for relief of achalasia symptoms. We describe the diffusion of POEM into clinical practice and evaluate unanswered questions regarding safety and the burden of healthcare utilization after POEM.

Methods: Retrospective cohort study of achalasia patients (18-63 years) initially treated with POEM, PD, or LHM (2010-2017) using the MarketScan® claims databases. Administrative codes used to measure POEM were validated in an institutional cohort using gold standard chart abstraction. We compared frequencies of perforation requiring intervention and healthcare utilization in the year following intervention.

Results: Among 1,921 patients (mean age 46 years, 49% women), 75.7%, 16.9%, and 7.4% underwent LHM, PD, and POEM, respectively. POEM increased from 1.1% of cases in 2010 to 18.9% in 2017. Perforation occurred in 0.3% (95% confidence interval [CI]: 0.1-0.7%)

undergoing LHM vs 0.9% (95%CI 0.2-2.7%) undergoing PD vs 0.0% (95%CI 0.0-2.6%) undergoing POEM. After POEM, 88.0% (95%CI 82.6-93.4) of patients underwent achalasia-related diagnostic testing, compared to 74.3% (95%CI 72.1-76.5) and 78.5% (95%CI 74.0-83.0) after LHM and PD, respectively. Reintervention was performed in 16.9% (95%CI 11.1-24.1) of patients after POEM, compared to 7.8% (95%CI 6.4-9.3) and 45.5% (95%CI 40.0-51.1) after LHM and PD, respectively.

Conclusions: Utilization of POEM has increased over time in the US, and comprised nearly a fifth of definitive procedures performed for achalasia in 2017. Perforation requiring intervention was rare for all procedures. POEM was associated with greater post-procedure diagnostic testing and reintervention compared to LHM. Compared to PD, POEM was associated with greater post-procedure diagnostic testing but less frequent reintervention.

Introduction

Achalasia is a rare, chronic condition (prevalence 10/100,000) characterized by progressive dysphagia, chest pain, regurgitation, and weight loss.[1] Definitive treatment requires mechanical disruption of the lower esophageal sphincter (LES), classically via endoscopic pneumatic dilation (PD) or laparoscopic heller myotomy (LHM). Randomized comparisons of the two approaches have shown similar proportions of symptom relief (90% at two years).[2] However, practice guidelines have been mixed in their recommended first-line therapy due to tradeoffs between the two approaches.[3-5]

In 2010, Inoue et al. published the first experience with per oral endoscopic myotomy (POEM), an incisionless approach to myotomy of the LES.[6] While PD may require multiple treatments to achieve lasting therapeutic effect, POEM achieves definitive myotomy similar to LHM but through an endoscopic approach.[7] In 2019, the POEMrct, the first RCT comparing POEM and LHM, published two-year results in which POEM was found to be no different from LHM with regard to relief of achalasia symptoms.[8] However, enthusiasm for POEM may be driving widespread adoption without a complete understanding of its safety, burden of additional care, and tradeoffs in symptoms requiring subsequent interventions.[9] Because of the rarity of achalasia, previous studies have been underpowered to detect differences in rare procedure-related adverse events, such as perforation and hemorrhage.[7,10] Further, the relationship between POEM and subsequent healthcare utilization, including the impact of symptomatic, post-procedural gastroesophageal reflux requiring surgical intervention has not been described.

The goal of this study was to describe temporal trends in the definitive treatment of achalasia with PD, LHM, and POEM. Additionally, we sought to describe the safety of POEM, in terms of the frequency of severe procedure-related adverse events relative to LHM and PD, as well as subsequent healthcare utilization in terms of subsequent diagnostic testing and reinterventions.

Methods

The data reporting in this study adheres to the standards described by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[11] This study was approved by the University of Washington Institutional Review Board (approval number: STUDY00009742).

Study Design, Data Source, and Study Population

This is a retrospective cohort study of adult patients, ages 18 to 63, with a diagnosis of achalasia and treated with LHM, PD, or POEM between July 1, 2010 and December 31, 2017 using the Truven MarketScan® Commercial Claims and Encounters Databases. MarketScan® data include both outpatient and inpatient claims information for more than 30 million employed United States (US) adults and their dependents enrolled in employer-based health insurance plans (ref). Diagnoses are catalogued using the International Classification of Diseases, 9th and 10th Revisions (ICD9/10), and procedures and services are codified using the Current Procedural Terminology (CPT) (American Medical Association, Chicago, IL), and Healthcare Common Procedure Coding System (HCPCS) codes (Appendix A). The study population consisted of patients with at least 12 months of enrollment (unless disenrollment was due to death) after initial definitive treatment in order to measure subsequent diagnostic testing and reinterventions using claims. Additionally, patients must have had at least six months of continuous enrollment prior to their date of procedure to allow for determination of comorbid disease. Patients 64 years of age and older were excluded to avoid potential underestimation of healthcare claims from enrollment in Medicare supplemental insurance. Patients with a prior diagnosis of an esophageal or gastric malignancy, any claims for prior gastric or esophageal surgery, including prior LHM were excluded. Patients treated prior to 2010 were excluded for two reasons: 1) dates prior 2010 predate the first POEM procedure in the US and 2) the specific CPT code for LHM was not introduced until 2008.

From 2010 to 2017, we identified 3,600 adult patients (age 18-63) with a diagnosis of achalasia who underwent definitive intervention with LHM, PD, or POEM (Figure 1). Of these, 528 were excluded because they had less than six months of enrollment prior to their index procedure; 17 were excluded due to prior esophageal or gastric surgery; 37 were excluded due to prior diagnosis of esophageal or gastric malignancy; and 1,097 were excluded due to incomplete follow-up (i.e. less than 12 months of continuous enrollment unless disenrollment due to death).

Treatment Cohorts

Patients were placed into one of three groups based on their index procedure. We used specific CPT codes to identify LHM (43249) and PD (43458, 43214, 43233) procedures. POEM procedures were measured using CPT code 43499 which corresponds to "unlisted procedure of the esophagus". There is a precedent for using CPT codes for unlisted procedures to study the utilization of a new technology. A similar approach was used to study lung-volume-reduction-surgery (LVRS) for bullous emphysema which ultimately inspired a randomized trial funded jointly by the Center for Medicare and Medicaid Services and the National Heart Lung Blood Institute and a national coverage decision [NETT trial].[12,13] To test the validity of our definition, we performed a retrospective chart review of all patients with diagnosis code for achalasia that underwent procedural intervention at the University of Washington from January 1st, 2015, through December 31st, 2019. Using clinical documentation as the gold-standard for identification of POEM procedures, we calculated a sensitivity and specificity for our definition of 100% (95% CI 69.2-100) and 98.7% (95% CI 96.6-100), respectively (Appendix A). This validation study was approved by the University of Washington Institutional Review Board (STUDY00009618).

Covariates

Available patient covariates included age, sex, health plan type (classified as Fee-For-Service vs Managed Care), date of claims, region of residence, and rurality of patient's

residence. Diagnosis codes for medical comorbidities were determined from the six month pre-intervention period and used to calculate an Elixhauser comorbidity index.[14] Prior diagnostic evaluations (esophagoduodenoscopy, esophagram, pH testing, or manometry) and non-definitive treatments for achalasia (i.e. dilation < 30mm, botox injection) were identified according to the procedure codes listed in Appendix B.

Outcomes

Safety

Relevant procedure-related adverse events included esophageal perforation, hemorrhage, pneumothorax, and death. We defined perforation as a claim for hospitalization linked to a diagnosis code for perforation and procedure code for intervention (i.e. surgical repair, esophagectomy, surgical drainage, or esophageal stent) that occurred within seven days of a procedure for achalasia.[15,16] Hemorrhage was defined by a diagnosis code for hemorrhage within 7 days of a procedure for achalasia and linked to a claim for intervention (i.e. surgical/endoscopic intervention or transfusion). Pneumothorax was similarly defined by a claim for pneumothorax within 7 days of procedure with procedure code for intervention (i.e. thoracostomy). MarketScan provides information on deaths occurring during hospitalizations. We defined death as occurring in the inpatient setting (either index hospitalization or unplanned hospitalization) following intervention.[16]

Subsequent Diagnostic Testing and Treatment

We measured achalasia-related utilization in the one year following initial therapy using claims for admission and subsequent procedures linked to a diagnosis code for achalasia or an achalasia procedure. Utilization outcomes included subsequent diagnostic testing (esophagogastroduodenoscopy [EGD], esophagram/upper GI series [UGI], pH testing, manometry), subsequent procedural intervention (myotomy via any incisional approach, POEM, dilation of any size, or botulinum toxin injection), length of stay, and unplanned hospitalization. Unplanned hospitalization was defined as those that occurred within 7 days of any (initial or

recurrent) PD; hospitalization after any LHM or POEM whose length exceeded 5 days; or any readmission to the hospital within 7 days after discharge for LM or POEM

Costs

Analysis of the direct total medical expenditures (henceforth referred to as "costs") was conducted from both the payer and patient perspective. Out-of-pocket expenses include all copayments, coinsurance, and deductibles paid by the patient at the time of initial treatment and in the subsequent one year. Payments were adjusted for inflation using the Consumer Price Index for Medical Care Services to 2018 United States dollars.[17]

Statistical Analysis

STATA/SE version 16.1 (Stata Corp LP, College Station, TX) was used for all analyses. Patient characteristics were summarized using frequency distributions for categorical variables, means for normally distributed continuous variables, and medians for non-normally distributed continuous variables. Cost data were summarized using both mean and median. Categorical variables were compared with Pearson's chi-square test. For continuous variables, medians were compared using a Kruskal-Wallis test and means were compared with an ANOVA that allowed for unequal variance. Multivariable regression with robust standard errors was used to determine the association between treatment type, healthcare utilization, and costs. These models were adjusted for age, sex, Elixhauser score, insurance type, region, calendar year, prior diagnostic testing, and prior intervention with botulinum toxin injection or dilation <30mm. Healthcare use measures were modelled as count variables, specifying a negative binomial distribution to account for overdispersion in the data. Total costs were modelled as a continuous variable using generalized linear models (GLM) specifying a gamma distribution with a log link to address heteroscedasticity in the data. Out-of-pocket costs were modelled using two-part models, consisting of a GLM conditional on a logit model of the probability of a non-zero outcome, to adjust for zero-inflation in the data. Model fit was assessed using Bayesian and Akaike information criterion and determined the above models to be superior to ordinary least

squares regression (Chakrabarti 2011). Adjusted mean cost differences were estimated using the delta method. Overall 3.9% of patients had missing covariate data. The proportion of patients with missing data was not different across treatment groups.

Results

Among 1,921 patients (median age 49 years, range 18-63, 49% women) 75.7%, 16.9%, and 7.4% underwent LHM, PD, and POEM, respectively (Table 1). On averaqe, patients who initially underwent LHM were younger than those who underwent PD (median 48 vs 51 years) and those that underwent POEM (median 48 vs 50 years). The Elixhauser comorbidity score was no different across groups (p=0.16). The majority of patients (77%) were enrolled in fee-for-service insurance plans and the distribution was similar between procedures (p=0.37). There was substantial regional variation in case mix, with LHM most often performed in the Southern and Western regions (79%) and least often performed in the Northeastern region (67%) (p<0.01). The frequency of POEM increased over time with POEM comprising 1.1% of cases in 2010 up to 18.9% in 2017 (Figure 2). Diagnostic testing was performed less often prior to PD (74%) compared to LHM (88%) and POEM (90%) (p<0.01). The frequency of prior non-definitive intervention did not differ appreciably across treatments (LHM 27%; PD 21%; POEM 21%, p=0.07).

Unadjusted Analysis

There were 11 (0.8%) severe procedure-related adverse events that required intervention among patients who underwent LHM, compared to five (1.5%) in those who underwent pneumatic dilation and four (2.1%) in those who underwent POEM. Perforation requiring intervention occurred in four (0.3%), three (0.9%), and zero patients, respectively. Pneumothorax requiring intervention occurred in two (0.1%) patients who received LHM. Bleeding requiring intervention occurred in two (0.1%) patients after LHM and two (1.4%)

patients after POEM. Hospital associated death occurred after LHM in three (0.2%) patients, in two (0.6%) after PD, and in one (0.7%) after POEM (Table 2).

After LHM, on average, patients underwent 1.77 (95% Confidence Interval [CI]: 1.67-1.86) achalasia-related diagnostic tests compared to 2.55 (95% CI 2.28-3.84) after PD and 3.87 (95%CI 3.38-4.36) after POEM. The most common diagnostic test was esophagram/UGI, with an average 1.15 tests (95%CI 1.08-1.21) after LHM, 1.63 (95%CI 1.42-1.84) after PD, and 2.06 (95%CI 1.80-2.31) after POEM. Esophageal manometry was performed most often after POEM (mean 0.60 [95%CI 0.43-0.76]) compared to LHM (0.06 [95%CI 0.04-0.08]) and PD (0.06 [95%CI 0.02-0.09]). Esophageal pH testing was also performed more frequently after POEM (mean 0.46 [95%CI 0.33-0.60]) compared to LHM (0.09 [95%CI 0.07-0.11]) and PD (0.20 [95%CI 0.13-0.26]). Procedural reinterventions were most frequent after PD (mean 0.78 procedures [95%CI 0.64-0.93]) relative to LHM (0.16 [95%CI 0.12-0.20]) and POEM (0.31 [95%CI 0.10-0.52]). The most commonly performed reintervention was non-pneumatic balloon dilation, with an average of 0.36 (95%CI 0.27-0.45) dilations after PD, 0.11 (95%CI 0.09-0.14) dilations after LHM, and 0.09 (95%CI 0.02-0.15) dilations after POEM. Subsequent pneumatic dilation was also more common after PD, with an average of 0.15 procedures (95%CI 0.11-0.20) compared 0.01 (95%CI 0.00-0.02) after LHM and 0.01 (95%CI 0.00-0.03) after POEM. Subsequent surgical myotomy was performed in 30 (9.2%) patients after PD, 11 (0.7%) patients after LHM, and two (1.4%) patients after POEM. No patients underwent POEM after their index procedure. Two patients underwent a subsequent anti-reflux procedure (i.e. fundoplication), one (0.1%) patient after LHM and one (0.7%) patient after POEM.

The average length of stay was 1.48 days (95%CI 1.17-1.34) after LHM, 0.36 days (95%CI 0.17-0.55) after PD, and 1.03 days (95%CI 0.78-1.28) after POEM. Unplanned hospitalization occurred in 77 (5.3%) patients after LHM, 43 (13.2%) patients after PD, and 10 (7.0%) after POEM. In the year following the index procedure, patients who underwent initial LHM spent, on average, 1.80 (95%CI 1.59-2.01) total days in the hospital compared to 1.25

(95%CI 0.73-1.77) days in those after PD, and 1.58 (95%CI 1.05-2.11) days in those after POEM. Patients who underwent PD had lower unadjusted total costs at one year (mean $22,975 [95%CI $17,359-$28,590] than LHM ($31,451 [95%CI $29,408-$33,494]) and POEM ($35,143 [95%CI $28,216-$42,607]). The average out-of-pocket costs in the year following treatment were similarly lower [???] for PD ($1,999 [95%CI $1,901-$2,097] compared to LHM ($1,588 [95%CI $1,404-$1,773) and POEM ($1,810 [95%CI $1,531-$2,088]).

Adjusted Analysis

The incidence rate ratio for reintervention after POEM was 1.9 (95%CI 1.1 to 3.3) when compared to LHM and 0.4 (95%CI 0.4 to 0.6) when compared to PD (Table 3). Subsequent diagnostic testing after POEM was 2.2 times (95%CI 1.9 to 2.6) more common compared to LHM and 1.5 times (95%CI 1.3 to 1.8) more common compared to PD. Patients who initially underwent POEM were 1.2 times [95%CI 0.6 to 2.3) as likely to experience an unplanned hospitalization relative to those who underwent LHM and 0.4 times [95%CI 0.2 to 0.8) as likely relative to those who underwent PD. Adjusted mean difference in one year payer costs (-$2,063 [95%CI -$7,792 to $3,665]) and one year out-of-pocket were no different (-$238 [95%CI -$564 to $89]) when comparing POEM to LHM. The mean difference in one year payer costs were higher ($7,674 [95%CI $657 to $14,692]) and one year out-of-pocket were no different ($133 [95%CI -$217 to $482]) when comparing POEM and PD.

Sequential addition of variables to the cost model demonstrated that total one-year payer cost differences were most influenced by patient factors (i.e. age, sex, elixhauser score, and region), length of stay, subsequent treatment, and unplanned hospitalization (Table 4). After adjusting for length of stay, subsequent testing, reintervention, unplanned hospitalization, and adverse events, the mean cost difference for POEM relative to LHM was -$902 (95%CI -$7,375 to $5,570) and for POEM relative to PD was $15,353 (95%CI $8,704 to $22,003). With each additional explanatory variable added to the model, the one-year payer costs of POEM remained no different to LHM and substantially higher than PD.

Discussion

To the best of our knowledge this is the largest comparative cohort study of outcomes and utilization after definitive intervention for achalasia to date. LHM remains the most frequently employed approach, representing nearly 76% of definitive interventions performed in the US from 2010-2017. While POEM accounted for just 7% of definitive interventions during the same interval, the use of POEM increased greatly during the study period. Severe procedure-related adverse events, including perforation and death, were rare for all procedures. POEM was associated with the highest likelihood of subsequent diagnostic testing and a higher likelihood of reintervention compared to LHM. Total health-related expenditures at one year were similar for POEM and LHM, but lower for PD. Out-of-pocket costs were not appreciably different between intervention groups.

Our findings indicate that POEM is being rapidly adopted into clinical practice. This is likely the result of enthusiasm among both patients and physicians for this new technology that allows effective, definitive management of achalasia through a less-invasive, natural-orifice approach. These findings are consistent with a recent study of achalasia using Medicare data that reported an annual percent increase in the occurrence of the CPT code 43499 (unlisted procedure of the esophagus) of 19.7% from 2008 to 2015.[18] This rise in the use of POEM has occurred despite a hesitancy among payers to reimburse for POEM, as evidenced by the lack of a specific CPT code. Recently published policy documents from Permera Blue Cross © continue to refer to POEM as an investigational procedure despite the growing body of evidence to support its use as a first-line intervention for achalasia.[19]

Current guidelines from the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) both recommend either POEM or LHM as first-line therapy for patients with type I and II achalasia and POEM as the preferred therapy for patients with type III achalasia.[20-22] These recommendations are based on two randomized trials that compared POEM to LHM and POEM

to PD as primary intervention for achalasia. The POEMA trial compared POEM and PD and found POEM to be superior to PD in achieving treatment success (i.e. Eckardt Score ≤ 3 and absence of severe complications or re-treatment) at two years (92% vs 54%).[23] The POEMrct trial compared POEM to LHM and found POEM to non-inferior to LHM in achieving clinical success (i.e. Eckardt Score ≤ 3 without re-treatment) at two years (83% vs 82%).[8] These trials confirmed the short-term efficacy of POEM in relieving achalasia symptoms but were underpowered to detect differences in uncommon procedure-related adverse events.

Establishing the safety of POEM has been challenging given the rarity of achalasia and the lack of a disease-specific registry. A 2017 systematic review that included nearly 1,300 procedures evaluated the safety of POEM and found that adverse events requiring procedural intervention were rare, occurring in only 11 patients.[24] A 2016 meta-analysis of non-randomized studies comparing POEM to LHM attempted to establish comparative safety and found that the frequency of complications did not differ between procedures (OR 1.53, 95% CI 0.65–3.59.[25] While these studies provide evidence for the safety of POEM, it is important to acknowledge the potential for publication bias among the studies included these reviews. Our study provides further evidence for the safety of POEM, as the frequency of adverse events requiring reintervention was low after POEM (2.1%) did not differ appreciably from the frequency following LHM and PD. It should be noted that, despite this being the largest comparative cohort to date, we could not exclude the possibility of there being true small differences in the frequency of adverse events among the three procedures.

The demonstrated and efficacy and safety of POEM, LHM, and PD, provide physicians and patients the flexibility to make individualized treatment decisions in managing achalasia. Patients should informed, however, of the important tradeoffs between the procedures. LHM is associated with higher one-year total costs relative to PD, typically requires an inpatient hospital stay, and requires surgical incisions may lead to more pain—all of which may prohibit those with less favorable insurance plans or less flexibility in their work schedule from assessing the

procedure.[26] LHM, however, is associated with the lowest risk for post-procedural diagnostic testing and reintervention, and less risk of post-procedural pathologic reflux.[27] PD is associated with the lowest one-year total costs, is performed as an outpatient procedure, and does not require surgical incisions. However, PD may require multiple, ongoing interventions to achieve the same therapeutic effect as LHM and POEM, with each subsequent intervention carrying a risk of complications and additional cost.[2,3] POEM is associated with similar one-year total costs compared to LHM but avoids surgical incisions and the associated pain. However, POEM is associated with more frequent post-procedural diagnostic testing and reintervention than LHM. This is likely due, in part, to the lack of an anti-reflux mechanism leading to more frequent symptomatic reflux.[28]

There are several limitations to this study. First, it is possible that we have inadvertently included patients who had previously undergone intervention for achalasia more than one year before their “index” procedure. This could have resulted in the inclusion of patients with more complex disease that could result in a higher frequency of adverse events. Second, due to the inaccuracy of diagnosis codes in claims data, we could not accurately measure less severe adverse events. However, by defining severe adverse events by the presence of an associated intervention, we believe we have captured clinically important events. Third, our utilization analysis is limited by a one-year time horizon and does not account for utilization and cost beyond one year. As a result, we likely underestimate future utilization associated with PD, which may require multiple reinterventions beyond one year. Fourth, Marketscan does not include provider-specific identifiers, and thus we were unable to adjust for physician experience in comparing outcomes. This may be especially important for POEM, for which it has been estimated a physician needs to treat 100 cases in order to decrease the risk of adverse events.[29] Finally, it is possible that the sensitivity and specificity of our administrative definition of POEM are lower in MarketScan than in our institutional cohort. Decreased sensitivity would lower our sample size of POEM patients, but would be unlikely to substantially bias our results.

Decreased specificity could be problematic as it could result in misclassification of other esophageal procedures, with different risk profiles, as POEM cases. However, to the best of our knowledge, the other esophageal procedures that utilized the unlisted procedure code during the study period where investigational anti-reflux procedures that would be contraindicated in patients with achalasia—thus this misclassification is unlikely to have occurred.

In conclusion, the use of POEM in the US is increasing rapidly. The diffusion of this new technology is occurring despite a hesitancy among payers to reimburse for POEM. Payers should consider the totality of evidence in making reimbursement decisions for this new technology. Finally , patients should be informed of the tradeoffs between the available treatment strategies, with POEM associated with more frequent subsequent diagnostic testing, and both POEM and PD associated with more frequent reintervention compared to heller myotomy.

References

1. Pandolfino JE, Gawron AJ. Achalasia: a systematic review. JAMA. 2015;313(18):1841-1852.

2. Boeckxstaens GE, Annese V, des Varannes SB, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med*. 2011;364(19):1807-1816.

3. Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. The Lancet. 2014;383(9911):83-93.

4. Vaezi MF, Pandolfino JE, Vela MF. ACG Clinical Guideline: Diagnosis and Management of Achalasia. Official journal of the American College of Gastroenterology | ACG. 2013;108(8):1238-1249.

5. Kahrilas PJ, Katzka D, Richter JE. Clinical Practice Update: The Use of Per-Oral Endoscopic Myotomy in Achalasia: Expert Review and Best Practice Advice From the AGA Institute. Gastroenterology. 2017;153(5):1205-1211.

6. Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. Endoscopy. 2010;42(4):265-271.

7. Inoue H, Sato H, Ikeda H, et al. Per-Oral Endoscopic Myotomy: A Series of 500 Patients. *J Am Coll Surg*. 2015;221(2):256-264.

8. Werner YB, Hakanson B, Martinek J, et al. Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia. New Engl J Med. 2019;381(23):2219-2229.

9. Cho YK, Kim SH. Current Status of Peroral Endoscopic Myotomy. Clin Endosc. 2018;51(1):13-18.

10. Bhayani NH, Kurian AA, Dunst CM, Sharata AM, Rieder E, Swanstrom LL. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. Ann Surg. 2014;259(6):1098-1103.

11. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806-808.

12. Huizenga HF, Ramsey SD, Albert RK. Estimated growth of lung volume reduction surgery among Medicare enrollees: 1994 to 1996. Chest. 1998;114(6):1583-1587. doi:10.1378/chest.114.6.1583

13. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348(21):2059-2073.

14. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998 Jan;36(1):8–27

15. Thornblade LW, Cheng AM, Wood DE, et al. A Nationwide Rise in the Use of Stents for Benign Esophageal Perforation. Ann Thorac Surg. 2017;104(1):227-233.

16. Ehlers AP, Oelschlager BK, Pellegrini CA, et al. Achalasia Treatment, Outcomes, Utilization, and Costs: A Population-Based Study from the United States. J Am Coll Surg. 2017;225(3):380-386.

17. U.S. Bureau of Labor Statistics, Division of Consumer Prices and Price Indexes. Consumer Price Index. Available at: http://www.bls.gov/cpi/. Accessed August 1st, 2020.

18. Gaber CE, Eluri S, Cotton CC, Strassle PD, Farrell TM, Lund JL, Dellon ES. Epidemiologic and Economic Burden of Achalasia in the United States. Clin Gastroenterol Hepatol. 2021 Feb 27:S1542-3565(21)00214-7.

19. Premera Blue Cross. (2021). Peroral Endoscopic Myotomy for Treatment of Esophageal Achalasia. Medical Policy [2.01.91]. https://www.premera.com/medicalpolicies/2.01.91.pdf

20. Khashab MA, Vela MF, Thosani N, Agrawal D, Buxbaum JL, Abbas Fehmi SM, Fishman DS, Gurudu SR, Jamil LH, Jue TL, Kannadath BS, Law JK, Lee JK, Naveed M, Qumseya BJ, Sawhney MS, Yang J, Wani S. ASGE guideline on the management of achalasia. Gastrointest Endosc. 2020 Feb;91(2):213-227.e6.

21. Kohn GP, Dirks RC, Ansari MT, et al. SAGES guidelines for the use of peroral endoscopic myotomy (POEM) for the treatment of achalasia. Surg Endosc. 2021;35(5):1931-1948.

22. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. Official journal of the American College of Gastroenterology | ACG. 2020;115(9):1393-1411.

23. Ponds FA, Fockens P, Lei A, et al. Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia: A Randomized Clinical Trial. JAMA. 2019;322(2):134-144.

24. Crespin OM, Liu LWC, Parmar A, et al. Safety and efficacy of POEM for treatment of achalasia: a systematic review of the literature. Surg Endosc. 2017;31(5):2187-2201.

25. Zhang Y, Wang H, Chen X, Liu L, Wang H, Liu B, Guo J, Jia H. Per-Oral Endoscopic Myotomy Versus Laparoscopic Heller Myotomy for Achalasia: A Meta-Analysis of Nonrandomized Comparative Studies. Medicine (Baltimore). 2016 Feb;95(6):e2736

26. Docimo S Jr, Mathew A, Shope AJ, Winder JS, Haluck RS, Pauli EM. Reduced postoperative pain scores and narcotic use favor per-oral endoscopic myotomy over laparoscopic Heller myotomy. Surg Endosc. 2017 Feb;31(2):795-800.

27. Schlottmann F, Herbella F, Allaix ME, Patti MG. Modern management of esophageal achalasia: From pathophysiology to treatment [published correction appears in Curr Probl Surg. 2019 Feb;56(2):91]. Curr Probl Surg. 2018;55(1):10-37.

28. Schlottmann F, Luckett DJ, Fine J, Shaheen NJ, Patti MG. Laparoscopic Heller Myotomy Versus Peroral Endoscopic Myotomy (POEM) for Achalasia: A Systematic Review and Meta-analysis. Ann Surg. 2018;267(3):451-460.
29. Liu Z, Zhang X, Zhang W, Zhang Y, Chen W, Qin W, Hu J, Cai M, Zhou P, Li Q. Comprehensive Evaluation of the Learning Curve for Peroral Endoscopic Myotomy. Clin Gastroenterol Hepatol. 2018 Sep;16(9):1420-1426.e2.

Figures

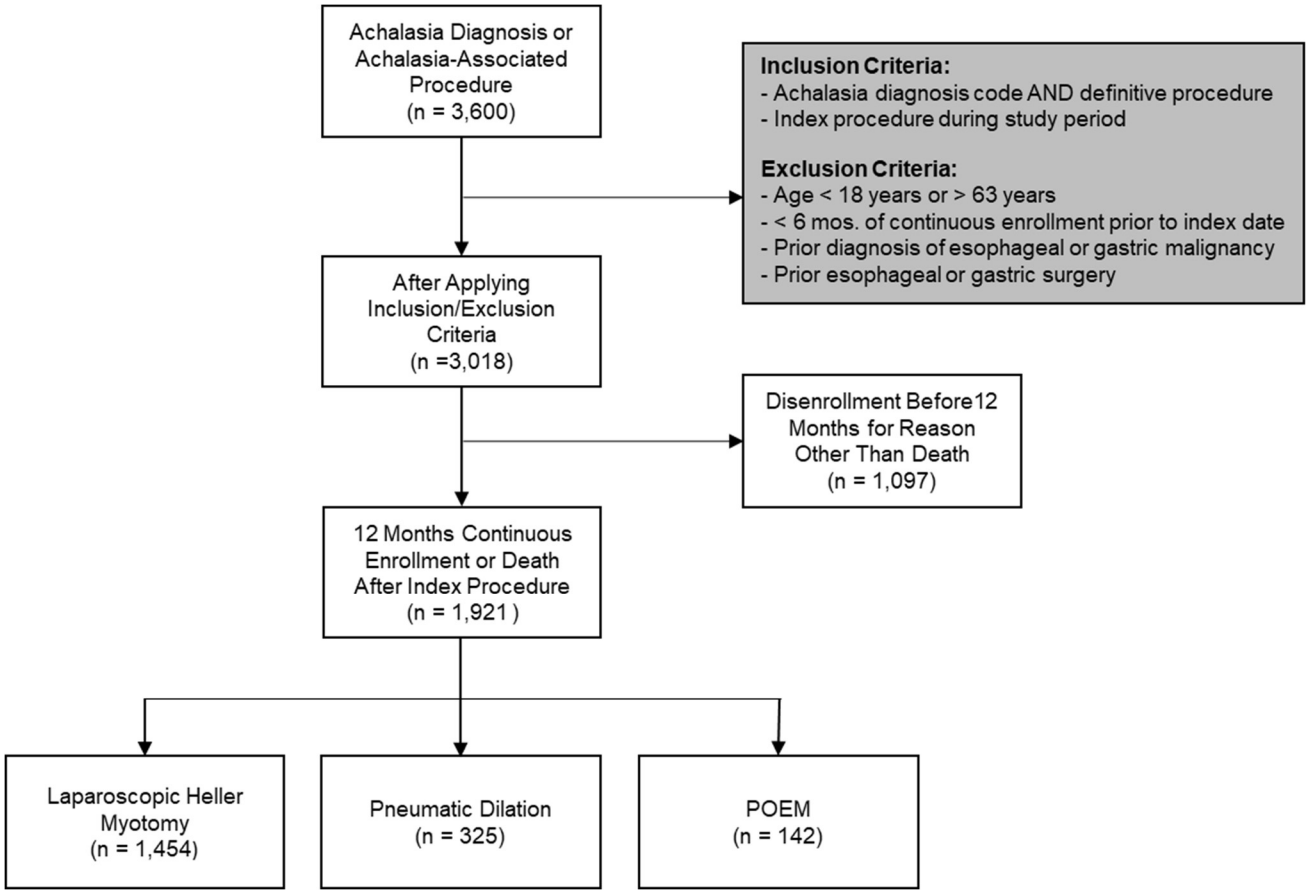

Figure 1. Study flow diagram of patients included in final analysis.

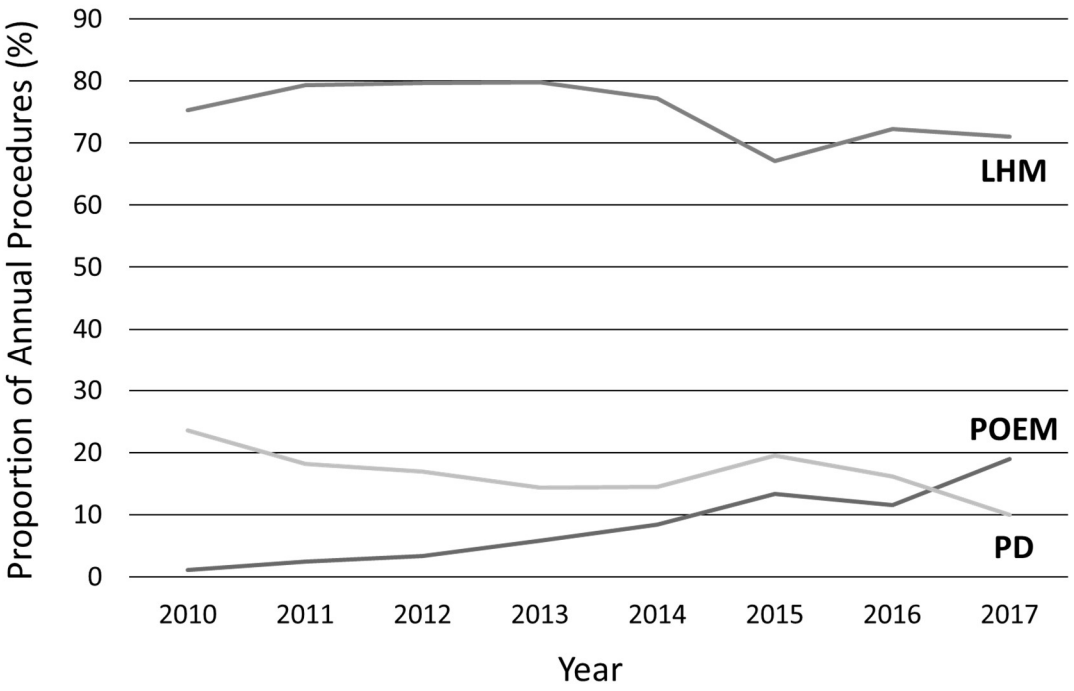

Figure 2. Definitive Procedures Performed For Achalasia Among Commercially-Insured US Adults From 2010-2017

Tables

Table 1. Patient Characteristics

	Laparoscopic Heller Myotomy (n=1,454)	Pneumatic Dilation (n=325)	POEM (n=142)	P value
Age, years, Median (IQR)	48 (37-56)	51 (41-58)	50 (40-57)	<0.01
Sex, female, n (%)	717 (49)	157 (48)	62 (44)	0.48
Elixhauser score, n (%)				0.17
0	539 (37)	121 (37)	49 (35)	
1	447 (31)	97 (30)	34 (24)	
2	209 (14)	47 (15)	20 (14)	
3+	259 (18)	60 (19)	39 (28)	
Mean (95% CI)	1.3 (1.2-1.4)	1.3 (1.2-1.5)	1.6 (1.2-1.5)	0.16
Insurance plan type, n (%)				0.37
Managed Care	304 (21)	56 (17)	34 (24)	
High Burden Fee-For-Service	178 (12)	35 (11)	21 (15)	
Low Burden Fee-For-Service	933 (64)	224 (69)	85 (60)	
Unknown	39 (3)	10 (3)	2 (1)	
Region, n (%)				<0.01
Northeast	268 (18)	85 (26)	45 (32)	
North Central	292 (19)	63 (19)	40 (28)	
South	600 (41)	131 (40)	29 (20)	
West	274 (19)	44 (14)	27 (19)	
Unknown	20 (1)	2 (1)	1 (1)	
Prior Diagnostic Evaluation, n (%)				
Manometry	1083 (75)	187 (58)	111 (78)	<0.01
EGD	352 (24)	51 (16)	37 (26)	<0.01
UGI/Esophagram	1147 (79)	211 (65)	114 (80)	<0.01
pH testing	355 (24)	57 (40)	55 (17)	<0.01
Any	1275 (88)	238 (74)	129 (90)	<0.01
Prior non-definitive intervention for achalasia, n (%)				
PD < 30mm	244 (17)	45 (14)	19 (13)	0.33
Botox Injection	180 (12)	29 (9)	13 (9)	0.15
Any	389 (27)	69 (21)	30 (21)	0.07

Includes Achalasia diagnoses after July 1, 2010. EGD, esophagogastroduodenoscopy; UGI, upper gastrointestinal series

Table 2. Unadjusted Safety, Health Care Use, and Cost Outcomes

	Laparoscopic Heller Myotomy (n=1,454)	Pneumatic Dilation (n=325)	POEM (n=142)
Severe procedure-related adverse events in one year following index procedure, n, (%) [95%CI]			
Perforation	4 (0.3) [0.08-0.7]	3 (0.9) [0.2-2.7]	0 (0.0) [0-2.6]
Pneumothorax W/ Intervention	2 (0.1) [0.01-0.5]	0 (0.0) [0-1.1]	0 (0.0) [0-2.6]
Bleeding W/ Intervention	2 (0.1) [0.01-0.5]	0 (0.0) [0-1.1]	2 (1.4) [0.2-5.0]
Hospital Associated Death	3 (0.2) [0.04-0.6]	2 (0.4) [0.08-2.2]	1 (0.7) [0.01-3.9]
Total Adverse Events	11 (0.8) [0.4-1.3]	5 (1.5) [0.5-3.6]	3 (2.1) [0.4-6.0]
Subsequent diagnostic tests in one year following index procedure, Mean [95%CI]			
EGD	0.48 (0.44-0.52)	0.68 (0.56-0.79)	0.79 (0.48-1.1)
UGI/Esophagram	1.15 (1.08-1.21)	1.63 (1.42-1.84)	2.06 (1.80-2.31)
pH Testing	0.06 (0.04-0.08)	0.06 (0.02-0.09)	0.60 (0.43-0.76)
Manometry	0.09 (0.07-0.11)	0.20 (0.13-0.26)	0.46 (0.33-0.60)
Any Diagnostic Test	1.77 (1.67-1.86)	2.55 (2.28-3.84)	3.87 (3.38-4.36)
Reintervention in one year following index procedure, Mean [95%CI]			
Dilation < 30mm	0.11 (0.09-0.14)	0.36 (0.27-0.45)	0.09 (0.02-0.15)
EGD with Botox	0.03 (0.01-0.05)	0.18 (0.10-0.27)	0.2 (0.01-0.40)
Pneumatic Dilation	0.01 (0.00-0.02)	0.15 (0.11-0.20)	0.01 (0.00-0.04)
Surgical Myotomy	0.01 (0.00-0.01)	0.09 (0.06-0.12)	0.01 (0.00-0.04)
POEM	0.00 (0.00-0.002)	0.00 (0.00-0.01)	0.00 (0.00-0.03)
Anti-reflux Procedure[a]	0.001 (0.00-0.002)	0.00 (0.00-0.01)	0.01 (0.00-0.04)
Esophagectomy	0.00 (0.00-0.002)	0.01 (0.00-0.02)	0.00 (0.00-0.03)
Any Intervention	0.16 (0.12-0.20)	0.78 (0.64-0.93)	0.31 (0.10-0.52)
Hospital use in one year following index procedure, Mean [95%CI]			
Length of Stay (days)	1.48 (1.17-1.34)	0.36 (0.17-0.55)	1.03 (0.78-1.28)
Unplanned Hospitalizations	0.06 (0.05-0.08)	0.17 (0.12-0.22)	0.07 (0.03-0.11)
Total Hospital Days[b]	1.80 (1.59-2.01)	1.25 (0.73-1.77)	1.58 (1.05-2.11)
Unadjusted direct health-related expenditures in one year following index procedure, 2018 USD[c]			
Total Costs[d]			
Mean (95% CI)	31,451 (29,408-33,494)	22,975 (17,359-28,590)	35,143 (28,216-42,607)
Median (IQR)	24,244 (15,593-36,032)	9,280 (5,022-20,002)	23,929 (15,295-35,617)
Out-Of-Pocket Costs[e]			
Mean (95% CI)	1,999 (1,901-2,097)	1,588 (1,404-1,773)	1,810 (1,531-2,088)
Median (IQR)	1,576 (608-2,884)	1,147 (428-2,086)	1,401 (634-2,795)

a. Laparoscopic fundoplication. No claims for LINX or other anti-reflux procedures.
b. Total hospital days is the sum of initial length of stay and length of stay of each unplanned hospitalizations.
c. US Dollars. Cost analysis limited to patients with fee-for-service insurance plans.
d. Total Costs = Payer Costs + Out-of-Pocket Costs
e. Out-Of-Pocket Costs = Copay + Coinsurance + Deductible

Table 3. Adjusted Risk of Selected Outcomes, Comparing Patients Who Underwent Initial Treatment with POEM Compared with Laparoscopic Heller Myotomy or Pneumatic Dilation

Variable	POEM vs LHM	POEM vs PD
Reintervention incidence rate ratio (95% CI)	1.9 (1.1 to 3.3)	0.4 (0.2 to 0.6)
Subsequent diagnostic testing incidence rate ratio (95% CI)	2.2 (1.9 to 2.6)	1.5 (1.3 to 1.8)
Unplanned hospitalization incidence rate ratio (95% CI)	1.2 (0.6 to 2.3)	0.4 (0.2 to 0.8)
Length of stay incidence rate ratio (95% CI)	0.7 (0.5 to 0.9)	3.1 (1.7 to 5.3)
Total cost difference, $, mean (95% CI)	-2,063 (-7,792 to 3,665)	$7,674 ($657 to $14,692)
Out-of-pocket cost difference, $, mean (95% CI)	-238 (-564 to 89)	$ 133 (-$217 to $482)

Adjusted for age, sex, Elixhauser comorbidity score, insurance type, region, year, previous diagnostic treatment, and previous intervention with pneumatic dilation <30 mm or botulinum toxin injection. Cost analysis limited to patients with fee-for-service health plans.

Table 4. Potential Explanatory Factors for Differences in Cost Between POEM Compared to Laparoscopic Heller Myotomy or Pneumatic Dilation

Absolute Difference in Cost (95% CI) Compared to Laparoscopic Heller Myotomy		
Model	**POEM vs LHM**	**POEM vs PD**
Unadjusted	$3,962 (-$3,417 to $11,341)	$12,437 (3,411 to $21,464)
Add patient factors[a] and year	-$2,146 (-$7,993 to $3,701)	$7,651 ($476 to $14,825)
Add health plan type	-$2,055 (-$7,823 to $3,713)	$7,712 ($703 to $14,7221)
Add prior testing[b] and non-definitive treatment[c]	-$2,063 (-$7,792 to $3,665)	$7,674 ($657 to $14,692)
Add length of stay	$229 (-$5,645 to $6,102)	$7,818 ($262 to $15,374)
Add subsequent testing[b]	-$511 (-$6,664 to $5,642)	$7,526 (-$40 to $15,091)
Add reintervention[d]	-$1,638 (-$7,914 to $4,639)	$12,978 ($6,393 to $19,563)
Add unplanned hospitalization[e]	-$902 (-$7,375 to $5,570)	$15,353 ($8,704 to $22,003)

Limited to patients with fee-for-service health plans.

a. Age, sex, region, comorbidity index
b. Esophagogastroduodenoscopy, manometry, pH testing, esophagram/upper GI series
c. Includes botox injection, dilation < 30mm
d. Botox injection, dilation < 30mm, pneumatic dilation, surgical myotomy, POEM, fundoplication, and esophagectomy
e. Admission with 7 days of PD, POEM or any reintervention, readmission within 7 days of discharge for LHM or POEM, or primary admission for LHM or POEM longer than 5 days
f. Perforation, pneumothorax, hemorrhage, and death

Appendix A:

Supplemental Table 1. Two-By-Two Table Evaluating POEM Definition Using UWMC Data

	Chart Abstracted (gold standard)		
	POEM Case	**Non-POEM Case**	**Total**
Definition Positive POEM	10	1	11
Definition Negative POEM	0	160	160
Total	10	161	171