Published in final edited form as:

Clin Gastroenterol Hepatol. 2015 February ; 13(2): 263–271.e1. doi:10.1016/j.cgh.2014.07.010.

Esophageal Anastomotic Strictures: Outcomes of Endoscopic Dilation, Risk of Recurrence and Refractory Stenosis, and Effect of Foreign Body Removal

Aaron H. Mendelson, MD^{*,1}, Aaron J. Small, MD^{*,2,3}, Anant Agarwalla, BS⁴, Frank I. Scott, MD, MSCE^{2,3}, and Michael L. Kochman, MD, AGAF^{1,2,5}

¹Department of Internal Medicine, University of Pennsylvania Perelman School of Medicine

²Gastroenterology Division, University of Pennsylvania Perelman School of Medicine

³Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine

⁴University of Pennsylvania Perelman School of Medicine

⁵Wilmott Center for Endoscopic Innovation, Research, and Training

Abstract

Background & Aims—Esophageal anastomotic strictures often require repeat dilation to relieve dysphagia. Little is known about factors that affect their remediation. We investigated long-term success and rates of recurrence or refractoriness following dilation, and factors associated with refractory stenosis.

Methods—We performed a retrospective study of 74 patients with an anastomotic stricture that had been dilated over a 5-year period (564 dilations; median follow-up period, 8 months). A

© 2014 The American Gastroenterological Association. Published by Elsevier Inc. All rights reserved.

Address for Correspondence: Michael L. Kochman, M.D., AGAF, Gastroenterology Division, Perelman School of Medicine at the University of Pennsylvania, 9th Floor Penn Tower, 1 Convention Center Avenue, Philadelphia, PA, U.S.A., Telephone: 215-662-4279, Fax: 215-349-5915, michael.kochman@uphs.upenn.edu.

*Drs. Mendelson and Small contributed equally to this article.

Disclosure: Dr. Kochman is a consultant for Boston Scientific Company, Cook Medical Inc., and Olympus Inc. The authors have no financial interest in any products mentioned in this manuscript.

Contributions of the authors were as follows: Aaron H. Mendelson*- study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. Aaron J. Small*- study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; and administrative, technical, or material support.

Anant Agarwalla- acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and administrative, technical, or material support; study supervision

Frank I. Scott- analysis and interpretation of data and statistical analysis

Michael L. Kochman- study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

stricture was refractory if luminal patency could not be maintained after 5 dilation sessions over 10 weeks.

Results—Of the 74 patients, 93% had initial relief of dysphagia. The stricture recurred in 43% of patients, and 69% were considered refractory. Removal of sutures/staples protruding into the lumen did not accelerate time to initial patency (median 37 days; interquartile range [IQR], 20–82 days) or lengthen the dysphagia-free interval (37.4 days; IQR 8–41 weeks), compared to patients who did not undergo removal (initial patency, median 55 days; IQR, 14–109 days; $P=.66$ and median dysphagia-free interval, 21.7 days; IQR, 9–64 weeks; $P=.8$). Use of fluoroscopy during dilation (odds ratio=8.92; 95% confidence interval, 1.98–40.14) was positively associated with development of refractory strictures, whereas neoadjuvant chemotherapy (odds ratio=0.28; 95% confidence interval, 0.07–0.97) was inversely associated. Female sex and distal location of strictures increased risk of refractoriness as effect modifiers in multivariate analysis.

Conclusions—Endoscopic dilation is highly successful in achieving luminal remediation, yet anastomotic strictures are often refractory and frequently recur. Removal of sutures/staples within the lumen does not help achieve patency. Need for fluoroscopic guidance indicates a high likelihood of refractoriness to dilation, whereas prior neoadjuvant chemotherapy indicates a lower risk.

Keywords

Esophageal anastomotic strictures; recurrence; refractory; foreign body removal

Introduction

Proton pump inhibitor therapy has effectively eliminated easy-to-treat peptic related esophageal strictures, and currently the remaining esophageal strictures by definition tend to include more complex strictures.¹ Benign esophageal strictures that develop after surgery for primary esophageal or head and neck malignancies can be particularly difficult to manage by non-surgical measures. These anastomotic strictures are often refractory to endoscopic dilation and require multiple dilation sessions to remediate.^{2,3,4,5,6,7,8,9,10,11,12,13,14,15} Strictures are typically amenable to antegrade endoscopic dilation using a variety of endoscopic tools (Savary-Gilliard dilators or through-the-scope (TTS) balloon dilators) and carry a low complication rate.¹³ However, the risk of recurrence after dilation is considerable for these complex, non-peptic strictures.^{1,16,17}

Cardiovascular risk factors, such as diabetes and obesity, and prior chemoradiation are associated with anastomotic stricture development after esophagectomy.³ Shorter time of dysphagia onset after surgery, smaller luminal diameter at index dilation, presence of anastomotic leak, type of transthoracic approach, intraoperative hemorrhage, poor vascularization of the gastric tube, and type of anastomosis (staples worse than hand-sewn) are factors associated with stricture recurrence.^{2,3,7,8} While these few reports describe factors affecting stricture formation and recurrence based on surgical factors, studies on the clinical and endoscopic factors associated with refractory strictures are lacking. Risk stratifying patients prone to have strictures refractory to traditional endoscopic therapies may help determine the appropriate timing and relative benefit of endoprosthetics or surgical

revision. Furthermore, the prevalence of recurrent and refractory strictures using standardized criteria is not well-characterized.

Lastly, endoscopic findings that influence remediation (reestablishing of patency of a luminal stenosis) and duration of relief of dysphagia in these patients are not well delineated. A common endoscopic finding in patients with anastomotic strictures is the presence of suture material or staples from the surgical field protruding into the esophageal lumen. Presence of a foreign body may contribute to inflammation and scarring, thereby impairing stricture remediation.¹

This study was designed to determine the long-term clinical success of endoscopic dilation and the rates of recurrent and refractory esophageal anastomotic strictures. A secondary aim was to identify clinical and endoscopic factors associated with refractory strictures.

Methods

A retrospective analysis was performed on patients who underwent endoscopic dilation for esophageal stenosis by a single provider from October 2007 - October 2012. The study population included patients who developed dysphagia after formation of an esophageal anastomosis. Some patients had prior chemoradiation. Only patients who had an anastomotic esophageal stricture, clinical dysphagia, and at least one month of follow-up after dilation were included. Patients who died before achieving luminal remediation were excluded. Only patients in whom initial remediation was achieved were included in the *a priori* analysis of the staples/suture removal and retention groups. The institutional review board approved this protocol.

Dilation Procedures

All patients with a stenosis underwent antegrade dilation (Figure 1). Patients who had a complete stenosis requiring retrograde dilation, (i.e. a guidewire was unable to be passed through the residual lumen or a residual lumen was not visualizable either via endoscope or fluoroscopy), were excluded from the study (4 patients during the study period).¹ Dilation technique was at the discretion of the operator. Patients underwent serial dilation until successful stricture remediation was achieved. Re-intervention was performed if they developed recurrent dysphagia.

Stricture Characteristics

Size of stenosis was estimated based on diameters of the endoscope and dilators used (TTS or Savary). Inability to traverse the stricture using an adult upper endoscope [Olympus GIF-H180 in the majority or GIF-160 in the remainder] implied stricture diameter <9 mm. Endoscopic injection of Kenalog into the stricture (four 1-mL aliquots of 10 mg/mL triamcinolone acetonide in a four-quadrant pattern, for a total of 40 mg) using a standard sclerotherapy needle was used in selected patients. Endoscopic steroid injection was used in patients who had early significant stricture recurrence in the absence of inflammation. The degree of stenosis recurrence and lack of response to dilation (e.g. stricture dilated up to 15 mm and promptly returned with dysphagia and a luminal diameter 8 mm) guided the determination to use Kenalog as adjunctive therapy. Suture/staples removal was performed

after endoscopic visualization of the protruding foreign body in the lumen after technical success of dilation was achieved. Synthetic nylon suture material or staples that were visible within the lumen and located within the proximal end of the stricture were cut and removed in entirety. Forceps [FG-47L-1, Olympus] or endoscopic scissors [straight FB3L-1 or sickle shape scissors 38B-130, Olympus] were used for retrieval.

Definitions of Variables

Technical success was defined as the ability to traverse the stricture with the chosen dilator and subsequent completion of dilation (increasing luminal diameter by at least 3 mm). Clinical success was defined as resolution of dysphagia and achieving luminal patency for 1 month. Luminal patency was defined as 14 mm diameter and inferred if the patient remained dysphagia free after the patient had undergone dilation with a CRE balloon dilator or Savary dilation preceding relief of dysphagia. The length of time required to achieve clinical success (or reestablish patency after recurrence) was determined, and referred to as a dilation cycle. The number of dilation sessions needed to achieve luminal patency 14 mm was determined for each dilation cycle. The days between dilation cycles were calculated to identify treatment time intervals.

A stricture was considered refractory if luminal patency of 14 mm could not be achieved after 5 dilation sessions within 10 weeks.¹⁸ Dysphagia-free intervals and number of dilation sessions within each dilation cycle were used to determine if a stricture was refractory. A stricture was considered recurrent if after a luminal patency of 14 mm was achieved, the stricture was found to be <14 mm on repeat endoscopic evaluation for dysphagia within 4 weeks. The total refractory and recurrence rates were determined. A recurrent stricture was also considered refractory if refractory criteria were met when repeat dilations were initiated for recurrence. A stricture that was amenable to endoscopic dilation but had late recurrence of stenosis (after 4 weeks) was not classified as a recurrent stricture based on our predetermined definition. Patients who required endoprosthesis or operative revision after failure to achieve sustained luminal patency from repeated dilations were also considered refractory.

We analyzed the effect of endoscopic foreign body removal using two cohorts among patients in whom remediation was achieved. One cohort had suture and/or staples removed during the initial dilation, while the suture/staples remained *in situ* in the comparative cohort.

Covariates and Data Analysis

Review of electronic medical charts that included office visits, radiologic studies, and operative and endoscopic reports were performed to identify baseline patient and stricture characteristics for analysis. Results were either expressed as median with IQR for non-parametric data or mean with standard deviation for parametric data. Wilcoxon rank-sum tests were used to compare quantitative differences between groups with non-parametric data. Potential risk factors for refractory strictures were assessed by univariate analysis with the chi-square statistic in the case of categorical variables and simple logistic regression in the case of continuous variables. Significant predictors ($P < 0.20$) in the univariate analysis

were then included in a backward, stepwise elimination multiple-regression model to identify the most important risk factors for developing a refractory stricture. Variables that no longer had a $P < 0.20$ in the regression model were excluded to make the model parsimonious. Type of operation, location of stricture and female sex were included in the model regardless of the P-value to test for effect modification of both of these factors on the outcome (refractory stricture) within the model. Patients for whom relevant data were missing were excluded from multivariate analysis. All statistical analysis was performed using the Stata System for Macintosh, version 12 (StataCorp LP, College Station, TX).

Results

Patient Characteristics

74 patients underwent 564 dilations for remediation (Table 1). Median follow-up time was 8 months (IQR 3, 33), and median number of dilations per patient was 6 (IQR 3, 11) during the treatment and follow-up period. Of these patients, 62% developed distal strictures as a result of prior esophagectomy, while 38% developed proximal strictures from prior total laryngectomy. 28 strictures were dilated between 15-30 days after surgery, whereas the majority (62%) of strictures were identified after 30 days.

Dilation Techniques

Patients were remediated with TTS balloons (57%), Savary dilators (8%) or both (35%) (Table 1). Two patients were instructed to self-dilate with a 13 mm Maloney after initial success was achieved. These two were highly motivated and opted for self-dilation. One was an elderly man who wanted to avoid a far commute to our center, and the other was a 20 year-old who did not want to miss additional time away from school for additional dilations. The stenosis precluded passage of the endoscope in 32 patients (43%). Fluoroscopy was utilized in 65% of patients during the procedure. Steroids were injected into 22% of strictures.

Clinical Outcomes

Technical success was accomplished in all cases (Table 2). Initial clinical success was achieved in 93% (69/74) with a median of 3 dilations (IQR 2, 6) over a median of 40 days (IQR 10, 103). Four patients had esophageal endoprosthesis placed after initial dilation did not achieve satisfactory stricture remediation and were therefore considered refractory. These four patients had strictures that demonstrated a high degree of ineffective expansion of the luminal diameter despite repeated dilation. One death occurred prior to remediation and was unrelated to endoscopic therapy. Only 4% of patients encountered a complication, all of which were self-limited bleeding events that did not require transfusion or surgical intervention. No perforations occurred and none underwent surgical revision for a refractory stricture.

Recurrence and Refractory Strictures

Recurrence after primary remediation of a stricture occurred in 43% of patients who had initially achieved clinical success (Table 3). This occurred at a median of 152 days (IQR 49, 312). In patients with recurrent strictures, the median number of dilations needed to

reestablish patency was 2 (IQR 1, 3). Refractory strictures were identified in 69% (51/74 strictures). Patients who had a laryngectomy (proximal) had a higher proportion of refractory strictures than those after esophagectomy (distal), although this difference was not statistically significant (82% vs. 61%, $p=0.07$). Proximal anastomotic strictures required more dilation sessions over a longer period of time to achieve initial remediation [median 3 (IQR 2, 6) dilations over 60 (IQR 20, 173) days vs. 2 (1, 5) dilations over 33 (1, 81) days; $p=0.13$, $p=0.1$] (Appendix, Table 7).

Suture Material and Staples

For the suture/staples removal analysis, only patients who achieved initial patency were included: 66 patients (8 had an endoprosthesis, death, or were lost to follow-up after initial dilation). Sutures/staples were removed at the time of initial dilation in 11 and left in place in the remaining 55. Six patients had only sutures that were visibly protruding and subsequently removed, 3 with only staples, 2 with removal of both sutures and staples. All patients in the suture/staples removal group had an anastomosis from prior esophagectomy. In the suture/staples retention group, 28 patients had a prior esophagectomy and 27 a prior laryngectomy. Median follow-up time in the suture/staple group was 12 months (IQR 3, 49) and 8 months (IQR 3, 28) in the group with suture/staples left in. Further cohort demographics are described in Table 4.

In this cohort, removal of suture/staples appears to potentially accelerate time to initial patency and required similar dilation sessions to achieve relief [median 37 (IQR 20, 82) days, median 3 (IQR 2, 7) dilations] as compared to patients who did not undergo suture or staple removal at time of initial dilation [median 55 (IQR 14, 109) days ($p=0.66$), median 3 (IQR 2, 5) dilations ($p=0.77$)], though these findings were not statistically significant (Table 4). Recurrence following primary remediation of a stricture was not significantly different in the retained suture/staple group as compared to the group with suture material or staples removed [43.6% (24) at median 21.7 (IQR 9, 64) weeks vs. 63.6% (7) at median time to recurrence 37.4 (IQR 8, 41), ($p=0.19$) and ($p=0.8$)]. There were no complications in the group with suture/staples removed; none had an anastomotic leak after removal and dilation. Self-limited bleeding occurred in 2 patients in the retention group.

Risk Factors for Refractory Stricture

Of the 11 hypothesized risk factors, only 5 variables with $P < 0.20$ or with evidence of effect modification or confounding were included in the final multivariate model. Three factors were significant by univariate analysis and 2 remained significant in multivariate analysis ($P < 0.20$) (Table 5). These factors included use of fluoroscopy during dilation (adjusted OR (aOR)= 8.92; 95% CI, 1.98 – 40.14) and neoadjuvant chemotherapy (aOR= 0.28; 95% CI, 0.07 – 0.97). Targeted steroid injection (aOR= 3.33; 95% CI, 0.56 – 19.76) appeared to be associated with refractory anastomotic strictures in the univariate analysis but was not statistically significant in the multivariate model. Female sex and stricture location in the distal esophagus were identified as effect modifiers and further increased the risk of having a refractory stricture when fluoroscopy was used. Conversely, patients with neoadjuvant chemotherapy had an even greater reduced risk of developing a refractory stricture if they were male and the stricture was localized to the proximal esophagus. Race, prior radiation

therapy, type of cancer, age, and removal of staples or suture material were not found to be significant predictors associated with refractory strictures.

Discussion

The prevalence of esophageal stenosis after esophagectomy ranges from 9%-48%.² These benign strictures may develop as a result of collagen deposition and fibrin production from deep ulceration or chronic inflammation.¹ Medical therapy (i.e. proton pump inhibitors) can be limited in the absence of active, reflux-induced inflammation. Endoscopic dilation can achieve initial patency for patients with anastomotic strictures with low complication rates.^{11,12,12,15,15} Dilation requires a commitment to compliance by both the patient and the endoscopist, as evident by the frequent number of dilation sessions (median 3) over an extended period of time (median 40 days) to achieve initial patency seen in our cohort. Furthermore, while the majority of patients achieved initial patency and symptomatic relief (93%), many had stenosis recurrence after one month (up to 43%), although recurrence occurred later (average of 5 months), and required less dilations to re-establish patency (median 2 vs. 3 to achieve initial patency). This high recurrence rate is similar to other studies.² Moreover, there was a high rate of refractory strictures (69%) in our cohort based on previously mentioned criteria.¹⁸ Recurrent and refractory anastomotic strictures may be the consequence of cicatricial luminal compromise or fibrosis without evidence of inflammation on endoscopy.¹⁸ The high prevalence of recurrence and refractory strictures supports the idea that the likely underlying mechanism for these strictures (deep ulceration or chronic inflammation) is not easily remediated with expansile and transient radial forces.

There were no major complications in this study. Apart from self-limited bleeding, our low complication rate (0%) was comparable to previous studies, including our larger series of endoscopic dilation for all benign strictures that reported an overall complication incidence of 0.4%.¹⁹ It is our institutional practice not to perform dilation within the early post-operative period (within the first 14 days) since the majority of those strictures are either i) inflammatory and will resolve with time, or ii) due to early ischemia, with the concern that early dilation may result in anastomotic dehiscence. The majority of strictures in this series were identified after 30 days. We do not support endoscopic dilation for strictures that develop within 14 days post-operatively, and did not note any anastomotic dehiscence in the 28 patients who were dilated between post-op days 15-30.

Stricture characteristics, cost, and operator preference play a role in determining the type of dilator and device used. A variety of dilators were used in this study, although the majority of patients were treated with TTS balloons. Prior studies have shown little difference in outcomes when comparing balloon dilators to rigid Savary dilators.^{1,20,21,22,23} It is therefore unlikely that the heterogeneity of dilators used have affected outcomes in our study. In our practice, balloon dilators offer the advantages of direct visualization and controlled application of expansile radial forces at the level of the stricture as opposed to longitudinal shear forces proximal to the stricture, which is seen with bougies. As such, balloon dilation was often the dilator of choice. Savary dilators were the only dilator type used in a small fraction of patients (8%) or in combination with balloon dilators in 35% in our series, particularly in patients who had esophagectomy strictures that were 15 mm or larger.

Luminal remediation can be temporarily achieved using endoprosthetics for benign refractory strictures. Stent insertion was considered a treatment endpoint in this study to properly evaluate the efficacy of balloon dilation and uniformly identify refractory strictures. In select candidates, endoprosthetics can be placed temporarily as a bridge to more definitive therapy or be inserted for long-term therapy of recurrent strictures. The four patients who had a stent placed in our series had strictures that were not only refractory to endoscopic dilation but demonstrated a high degree of ineffective expansion of the luminal diameter despite repeated dilation. It is important to note while endoprosthetics may provide a temporizing maneuver for highly select patients, this does not appear to definitively remediate the stricture.^{24,25,26} Further studies are needed to determine the appropriate timing and relative benefit of stent placement for refractory esophageal strictures.

Endoscopic factors accelerating luminal remediation of anastomotic strictures are not well defined. A common endoscopic finding in patients with an esophago-gastric anastomosis is the presence of suture and/or staples protruding into the esophageal lumen. Presence of a foreign body may contribute to inflammation and scarring, thereby making remediation more difficult.¹ Anecdotally, while removal of staples and suture seemed to accelerate time to initial patency and result in a longer dysphagia-free interval, these findings were not statistically significant. Furthermore, staple/suture removal did not reduce the risk of having a refractory stricture in the multivariate model. Further studies with larger sample size are implicit to validate the impact of this intervention.

Location of the anastomotic stenosis appears to affect dilation outcomes. Time to remediation, the number of dilations needed for remediation, and the rate of refractory strictures was higher in those who underwent laryngectomy. Strictures near the upper esophageal sphincter are more technically challenging to dilate given the proximity of the site of intervention to the airway. Also, many of these patients had a transesophageal prosthesis placed, which could contribute to persistent inflammation and scarring.

There is substantial heterogeneity in the literature as to what defines successful remediation and recurrence of an esophageal stricture using endoscopic dilation.^{2,9,10,11,12,14,15} One of the strengths of this study was the application of definitive criteria for refractory and recurrent strictures.¹⁸ Application of these easy-to-use criteria in future studies can ensure uniform endpoints for the study of dilation outcomes and stricture management.

We also identified certain patient and intra-procedural characteristics as independent risk factors for developing refractory anastomotic strictures. Interestingly, patients who had undergone prior neoadjuvant chemotherapy preceding dilation were less likely to develop a refractory stricture, an effect that was further influenced by the sex of the patient and stricture location. Prior exposure to chemotherapy reduced the likelihood of having a refractory stricture by nearly 70%. One postulation is that chemotherapy attenuates the post-operative inflammatory response (fibrosis and intimal hyperplasia) that leads to luminal stricturing. A similar phenomenon was not seen with local steroid injection, which seemed to have a positive association with refractory strictures though not statistically significant. Perhaps this is because endoscopic injected steroids are used after the chronic inflammatory cascade has already resulted in scar formation. Thus, while focal steroid injection has been

reported to increase the symptom-free interval to the next required dilation and can result in an increase in the maximum achieved diameter of dilation, injected steroids did not appear to reduce the risk of developing a refractory stricture.^{1,27,28}

Finally, the use of fluoroscopy during initial dilation predicted a high (ten-fold) likelihood that the anastomotic stricture would be refractory, and female sex and distal location potentiated this positive correlation. This association is likely multifactorial but may be related to the endoscopist's decision to use contrast guidance under conditions when the stricture was felt to be more complex (i.e. long, angulated, and severely narrowed), and thus, these inherently more complicated strictures have a higher probability of being refractory.

There are several limitations to this study. This data is based on an expert provider at a single tertiary care center, which may preclude generalizability to community practice. However, anastomotic stricture patients often have multiple co-morbidities and are typically managed at large referral centers. For example, the widespread availability and decision to use endoscopic scissors to remove suture material or staples in the lumen should not be cavalier. Second, this was a retrospective cohort study, which consequently lends itself to confounding, including selection bias and reverse causation. As such, the recurrence and refractory rates may be inflated given the scope of the provider's quaternary academic referral practice. However, this descriptive analysis still provides insight on an estimated prevalence of recurrent and refractory strictures. Finally, while this is the first study to investigate risk factors of esophageal strictures refractory to dilation, this study may be underpowered to achieve precise and significant point estimates of effect for some of our variables (i.e. steroid injection), which had wide confidence intervals. Furthermore, although there were a small number of events of interest (refractory strictures), our final multivariate model is within the accepted constraints to avoid bias from overfitting (number of covariates per events >10).^{29,30}

In conclusion, this study demonstrates the following: 1] endoscopic dilation can achieve luminal remediation with a high degree of technical success and a low complication rate; 2] anastomotic strictures require frequent dilation at short intervals and carry a high recurrence rate; 3] many anastomotic strictures are refractory to endoscopic dilation; 4] removal of suture material and staples at the anastomosis at time of initial dilation did not accelerate luminal remediation nor affect time to recurrence; 5] need for fluoroscopic guidance appears to indicate a high likelihood of refractoriness to dilation, while prior neoadjuvant chemotherapy is associated with a reduced risk; 6] alternative and adjunctive strategies may be considered for treatment of refractory anastomotic strictures. Future investigation should validate the factors that influence rates of recurrence and refractoriness to better risk stratify which patients will most benefit from endoscopic dilation rather than early escalation of therapy, such as endoprosthesis placement or surgical revision.

Acknowledgments

#This work was supported by the NIH/NIDDK T32 DK007740 (Clinical Epidemiology Training in Gastroenterology) and the NIH/NIDDK P30DK050306 Center for Molecular Studies in Digestive and Liver Diseases.

This work was supported by the Wilmott Center for Endoscopic Innovation, Research, and Training.

Appendix – Other Factors Affecting Remediation

(Only those who achieved clinical success were included for analysis)

Table 6
Intralesional Steroid Outcomes

	Steroids (N=16)	No Steroids (N=53)	P-value
Dilations to achieve patency ⁱ , median	5 (IQR 4, 8)	2 (IQR 1, 4)	0.001
Days to initial patency ⁱ , median	83 (IQR 25, 240)	35 (IQR 1, 80)	0.02
Recurrence ⁱⁱ , no (%)	9 (56%)	24 (45%)	0.98
Weeks to recurrence, median	16.9 (IQR 8, 27)	22.1 (IQR 7, 69)	0.55
Refractory, no (%)	14 (88%)	34 (64%)	0.08

ⁱPatency defined as luminal diameter >14 mm, before any recurrence

ⁱⁱRecurrence defined as inability to maintain luminal diameter >14 mm

Table 7
Outcomes By Location of Anastomosis

	Proximal (N=28)	Distal (N=41)	P-value
Dilations to achieve patency ⁱ , median	3 (IQR 2, 6)	2 (IQR 1, 5)	0.13
Days to initial patency ⁱ , median	60 (IQR 20, 173)	33 (IQR 1, 81)	0.1
Recurrence ⁱⁱ , no (%)	12 (43%)	21 (51%)	0.5
Weeks to recurrence, median	22.7 (IQR 5, 58)	19 (IQR 8, 45)	0.89
Refractory, no (%)	20 (71%)	28 (68%)	0.78

Table 8
Radiation Outcomes

	Prior XRT (N=18)	No XRT (N=51)	P-value
Dilations to achieve patency ⁱ , median	3 (IQR 1, 5)	3 (IQR 2, 5)	0.63
Days to initial patency ⁱ , median	33 (IQR 1, 95)	42 (IQR 18, 103)	0.8
Recurrence ⁱⁱ , no (%)	8 (44%)	25 (49%)	0.74
Weeks to recurrence, median	31.3 (IQR 10, 109)	19.1 (IQR 7, 38)	0.31
Refractory, no (%)	11 (61%)	37 (73%)	0.37

Table 9
Chemotherapy Outcomes

	ChemoRx (N=26)	No ChemoRx (N=43)	P-value
Dilations to achieve patency ⁱ , median	3 (IQR 1, 6)	3 (IQR 2, 5)	0.85
Days to initial patency ⁱ , median	33 (IQR 1, 82)	42 (IQR 20, 116)	0.39
Recurrence ⁱⁱ , no (%)	13 (50%)	20 (47%)	0.78

	ChemoRx (N=26)	No ChemoRx (N=43)	P-value
Weeks to recurrence, median	21.7 (IQR 7, 48)	16.6 (IQR 6, 38)	0.81
Refractory, no (%)	16 (62%)	35 (81%)	0.07

ⁱ Patency defined as luminal diameter >14 mm, before any recurrence

ⁱⁱ Recurrence defined as inability to maintain luminal diameter >14 mm

References

1. Lew RJ, Kochman ML. A review of endoscopic methods of esophageal dilatation. *J Clin Gastroenterol.* 2002; 35:117–26. [PubMed: 12172355]
2. Park JY, Song HY, Kim JH, et al. Benign anastomotic strictures after esophagectomy: long-term effectiveness of balloon dilation and factors affecting recurrence in 155 patients. *Am J Roentgenol.* 2013; 198:1208–13. [PubMed: 22528915]
3. van Heijl M, Gooszen JA, Fockens P, et al. Risk factors for development of benign cervical strictures after esophagectomy. *Ann Surg.* 2010; 251:1064–9. [PubMed: 20485137]
4. Williams VA, Watson TJ, Zhovtis S, et al. Endoscopic and symptomatic assessment of anastomotic strictures following esophagectomy and cervical esophagogastrostomy. *Surg Endosc.* 2008; 22:1470–6. [PubMed: 18027040]
5. Chen PC. Endoscopic balloon dilation of esophageal strictures following surgical anastomoses, endoscopic variceal sclerotherapy and corrosive ingestion. *Gastrointest Endosc.* 1992; 38:586–9. [PubMed: 1341884]
6. Zieren HU, Muller JM, Pichlmaier H. Prospective randomized study of one- or two-layer anastomosis following oesophageal resection and cervical esophagogastrostomy. *Br J Surg.* 1993; 80:608–11. [PubMed: 8518900]
7. Law S, Fok M, Chu KM, et al. Comparison of hand-sewn and stapled esophagogastric anastomosis after esophageal resection for cancer: a prospective randomized controlled trial. *Ann Surg.* 1997; 226:169–73. [PubMed: 9296510]
8. Chung WC, Paik CN, Lee KM, et al. The findings influencing restenosis in esophageal anastomotic stricture after endoscopic balloon dilation: restenosis in esophageal anastomotic stricture. *Surg Laparosc Endosc Percutan Tech.* 2009; 19:293–7. [PubMed: 19692876]
9. Ikeya T, Ohwada S, Ogawa T, et al. Endoscopic balloon dilation for benign esophageal anastomotic stricture: factors influencing its effectiveness. *Hepatogastroenterology.* 1999; 46:959–66. [PubMed: 10370646]
10. Chiu YC, Hsu CC, Chiu KW, et al. Factors influencing clinical applications of endoscopic balloon dilation for benign esophageal strictures. *Endoscopy.* 2004; 36:595–600. [PubMed: 15243881]
11. Kim HC, Shin JH, Song HY, et al. Fluoroscopically guided balloon dilation for balloon dilation for benign anastomotic stricture after Ivor-Lewis esophagectomy: experience in 62 patients. *J Vas Interv Radiol.* 2005; 16:1699–1704.
12. Pereira-Lima JC, Ramieres RP, Zamin I Jr, et al. Endoscopic dilation of benign esophageal strictures: report on 1043 procedures. *Am J Gastroenterol.* 1999; 94:1497–1501. [PubMed: 10364013]
13. Hernandez LV, Jacobson JW, Harris MS. Comparison among the perforation rates of Maloney, balloon, and Savary dilation of esophageal strictures. *Gastrointest Endosc.* 2000; 51:460–2. [PubMed: 10744819]
14. Honkoop P, Siersema PD, Tilanus HW, et al. Benign anastomotic strictures after transhiatal esophagectomy and cervical esophagogastrostomy: risk factors and management. *J Thoracic Cardiovasc Surg.* 1996; 111:1141–6.
15. Ahlawat SK, Al-Kawas FH. Endoscopic management of upper esophageal strictures after treatment of head and neck malignancy. *Gastrointest Endosc.* 2008; 68:19–24. [PubMed: 18355822]

16. Said A, Brust DJ, Gaumnitz EA, et al. Predictors of early recurrence of benign esophageal strictures. *Am J Gastroenterology*. 2003; 98:1252–6.
17. de Lange EE, Shaffer HA Jr. Anastomotic strictures of the upper gastrointestinal tract: results of balloon dilation. *Radiology*. 1988; 167:45–50. [PubMed: 3347744]
18. Kochman ML, McClave SA, Boyce HW. The refractory and the recurrent esophageal stricture: a definition. *Gastrointest Endosc*. 2005; 62:474–5. [PubMed: 16111985]
19. Kochman ML. Minimization of risks of esophageal dilation. *Gastrointest Endosc Clin N Am*. 2007; 17:47–58. [PubMed: 17397776]
20. Lew RJ, Ginsberg GG, Long WB, et al. Esophageal dilation is safe despite increasing complexity of strictures [abstract]. *Gastrointest Endosc*. 2001; 53:AB77.
21. Scolapio JS, Pasha TM, Gostout CJ, et al. A randomized prospective study comparing rigid to balloon dilators for benign esophageal strictures and rings. *Gastrointest Endosc*. 1999; 50:13–7. [PubMed: 10385715]
22. Saeed ZA, Winchester CB, Ferro PS, et al. Prospective randomized comparison of polyvinyl bougies and through-the-scope balloons for dilation of peptic strictures of the esophagus. *Gastrointest Endosc*. 1995; 41:189–195. [PubMed: 7789675]
23. Cox JG, Winter RK, Maslin SC, et al. Balloon or bougie for dilatation of benign oesophageal stricture? An interim report of a randomised controlled trial. *Gut*. 1988; 29:1741–1747. [PubMed: 3065156]
24. Oh YS, Kochman ML, Ahmad NA, et al. Clinical outcomes after self-expanding plastic stent placement for refractory benign esophageal strictures. *Dig Dis Sci*. 2010; 55:1344–8. [PubMed: 20155322]
25. Kochman ML. Removable endoprosthetics in the management of esophageal pathology: all strictures and fistulae are not created equal.... *Gastrointest Endosc*. 2008; 67:26–7. [PubMed: 18155421]
26. Holm AN, de la Mora Levy JG, Gostout CJ, et al. Self-expanding plastic stents in treatment of benign esophageal conditions. *Gastrointest Endosc*. 2008; 67:20–5. [PubMed: 17945227]
27. Kochhar R, Ray JD, Sriram PVJ, et al. Intralesional steroids augment the effects of endoscopic dilation in corrosive esophageal strictures. *Gastrointest Endosc*. 1999; 49:509–13. [PubMed: 10202068]
28. Hirdes MM, van Hooft JE, Koornstra JJ, et al. Endoscopic corticosteroid injections do not reduce dysphagia after endoscopic dilation therapy in patients with benign esophagogastric anastomotic strictures. *Clin Gastroenterol Hepatol*. 2013; 11:795–801. [PubMed: 23376318]
29. Cepeda MS, Boston R, Farrar JT. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol*. 2003; 158:280–87. [PubMed: 12882951]
30. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996; 49:1373–79. [PubMed: 8970487]

Figure 1.

Endoscopic images showing nylon suture removal with endoscopic scissors (A), Savary dilation (B) TTS balloon dilation next to a diverticulum (C) CRE balloon dilation and suture removal (D), staples left *in situ* after serial Savary dilation (E).

Table 1
Patient And Dilation Characteristics

Patient Characteristics	
Total Number of Patients	74
Sex, no. (%)	
Male	52 (70%)
Female	22 (30%)
Age, yrs., median (range)	65 (24-85)
Type of Prior Operation [#] , no. (%)	
Esophagectomy	46 (62%)
Laryngectomy	28 (38%)
Prior Radiation	20 (27%)
Strictures >30 days post-op, no. (%)	46 (62%)
Follow-up after 1 st dilation, median in months (IQR)	8 (IQR 3, 33)
Size of stenosis at first dilation, no. (%)	
<9mm	32 (43%)
>9mm	42 (57%)
Dilation Factors	
Total Dilations, no.	564
Initially unable to traverse with adult upper endoscope, no. (%)	32 (43%)
Savary	6 (8%)
TTS Balloon [*]	42 (57%)
Both	26 (35%)
Fluoroscopy utilized, no. (%)	48 (65%)
Intralesional Steroids, no. (%)	16 (22%)

[#]Type of operation reflects the procedure that immediately proceeded onset of dysphagia

^{*}TTS = Through-the-scope

Table 2
Clinical Outcomes

Factors	Number (% or IQR)
Technical Success ⁱ	74 (100%)
Clinical Success ⁱⁱ	69 (93%)
Reasons for failure (5 total)	4 stent, 1 unrelated death
Follow-up Time, median	8 (3, 33)
Total Dilations per patient, median	6 (3, 11)
Dilations to achieve initial patency ⁱⁱⁱ , median	3 (2, 6)
Days to achieve initial patency ⁱⁱⁱ , median	40 days (10, 103)
Complications	3 (4%) ^{iv}

ⁱ Stricture was able to be dilated by at least 3 mm during initial procedure

ⁱⁱ Dilation to 14 mm maintained for at least 4 weeks

ⁱⁱⁱ Patency defined as 14 mm, before any recurrence

^{iv} All self-limited bleeding

Table 3
Recurrent and Refractory Strictures

Recurrent and Refractory Strictures	Number, (%)	
Patients with Recurrence *	32 (43%)	
Time to recurrence, median (IQR)	152 days (49, 312)	
Dilations to reestablish patency, median (IQR)	2 (1, 3)	
Stents used	4 (5%)	
Refractory Strictures **	51 (69%)	
In pts. who received Radiation	11 (15%)	
In pts. who underwent Esophagectomy	28 (61%)	} p = 0.07 ***
In pts. who underwent Laryngectomy	23 (82%)	

* Among those with clinical success

** Among all strictures

*** Comparing patients who underwent esophagectomy vs. laryngectomy

Table 4
Foreign Body Removal Outcomes

Suture/Staples Data			
Category	Removed	Retained	
Number of Patients	11	55	
Age (median)	66 (IQR 62, 69)	62.5 (IQR 55, 68)	
Gender (M)	3 (27%)	21 (38%)	
Type of Prior Operation			
Esophagectomy	11 (100%)	28 (51%)	
Laryngectomy	None	27 (49%)	
Prior Radiation	1 (9%)	18 (33%)	
Prior Chemotherapy	4 (36%)	22 (40%)	
Unable to traverse with upper adult endoscope	4 (36%)	27 (49%)	P-Value
Dilations to achieve patency ⁱ , median	3 (IQR 2, 7)	3 (IQR 2, 5)	0.77
Days to initial patency ⁱ , median	37 (IQR 20, 82)	55 (IQR 14, 109)	0.66
Recurrence ⁱⁱ , no (%)	7 (63.6%)	24 (43.6%)	0.19
Weeks to recurrence ⁱⁱ , median	37.4 (IQR 8, 41)	21.7 (IQR 9, 64)	0.8
Complications	None	2 (4%) ⁱⁱⁱ	0.7

ⁱ Patency defined as luminal diameter >14 mm, before any recurrence

ⁱⁱ Recurrence defined as inability to maintain luminal diameter >14 mm

ⁱⁱⁱ All were self-limited bleeding

Table 5

Risk Factors for Anastomotic Refractory Stricture After Dilation in the Univariate and Multivariate Analyses*.

Risk Factor	Unadjusted Odds Ratio (95%CI)[¶]	Adjusted Odds Ratio (95% CI)[¶]
<u>Significant in multivariate analysis</u>		
Use of Fluoroscopy	8.67 (2.70 – 27.85)	8.92 (1.98 – 40.14)
Targeted Steroid Injection ^a	3.75 (0.77 – 18.21)	3.33 (0.56 – 19.76)
Prior Chemotherapy	0.37 (0.13 – 1.08)	0.28 (0.07 – 0.97)
Female Sex ^b	2.18 (0.63 – 7.52)	3.56 (0.68 – 18.66)
Type of Operation/Proximal Stenosis ^b	0.74 (0.33 – 1.64)	0.31 (0.28 – 3.29)
<u>Not significant in univariate or multivariate analysis</u>		
African-American Race	0.38 (0.02 – 6.33)	
Prior Radiation	0.57 (0.19 – 1.76)	
History of Extrinsic Cancer	1.23 (0.43 – 3.52)	
Middle Age (age 45 to 64 years old) [#]	2.67 (0.33 – 21.87)	
Older Age (>64 years old) [#]	3.11 (0.38 – 25.38)	
Staple or Suture Removal	1.13 (0.31 – 4.07)	

* Only 5 candidate factors with p values below 0.20 in the univariate analysis or with evidence of effect modification or confounding were included in the final multivariate analysis. Type of operation and female sex were both included in the model regardless of the p value to test for effect modification. Factors with p values below 0.20 in the multivariate analysis were considered significant. There were no candidate predictors with missing data on subjects included in this study. CI denotes confidence interval.

[¶]Unadjusted odds ratio as compared to respective referent: no fluoroscopy used during initial dilation, no intralesional steroid injected into focal stricture, no exposure to neoadjuvant chemotherapy, male sex, prior laryngectomy/proximal stenosis as compared to esophagectomy/distal stenosis, Caucasian or other race/ethnicity apart from African-American, no prior radiotherapy, head and neck cancer or other (breast or lung metastases) as compared to esophageal (intrinsic) cancer, middle or older age as compared with a patient age 44 or younger, staples or suture material protruding into lumen not removed.

[#] Odds ratio as compared with a patient age 44 or younger; there was no significant difference when age categorized as binary variable (less than or greater than age 65).

** Odds ratios have been adjusted for the effect of the other variables in the model.

^a CI was statistically significant in univariate analysis but not in multivariate model.

^b Female sex and location in proximal esophagus were effect modifiers on fluoroscopy and refractoriness.