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Original Article

Utility of repeated therapeutic endoscopies for pediatric esophageal anastomotic strictures

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SUMMARY. **Anastomotic stricture is a common complication of esophageal atresia (EA) repair. Such strictures are managed with dilation or other therapeutic endoscopic techniques such as steroid injections, stenting, or endoscopic incisional therapy (EIT). In situations where endoscopic therapy is unsuccessful, patients with refractory strictures may require surgical stricture resection; however, the point at which endoscopic therapy should be abandoned in favor of repeat thoracotomy is unclear. We hypothesized that increasing numbers of therapeutic endoscopies are associated with increased likelihood of stricture resection. We retrospectively reviewed the records of patients with EA who had an initial surgery at our institution resulting in an esophago-esophageal anastomosis between August 2005 and May 2019. Up to 2 years of post-surgery endoscopy data were collected, including exposure to balloon dilation, intralesional steroid injection, stenting, and EIT. Primary outcome was need for stricture resection. Receiver operating characteristic (ROC) curve analysis and univariate and multivariable Cox proportional hazards regression analyses were performed. There were 171 patients who met inclusion criteria. The number of therapeutic endoscopies was a moderate predictor of stricture resection by ROC curve analysis (AUC = 0.720, 95% CI 0.617–0.823). With increasing number of therapeutic endoscopies, the probability of remaining free from stricture resection decreased. By Youden's J index, a cutoff of ≥7 therapeutic endoscopies was optimal for discriminating between patients who had versus did not have stricture resection, though an absolute majority of patients (≥50%) remained free of stricture resection at each number of therapeutic endoscopies through 12 endoscopies. Significant predictors of needing stricture resection by univariate regression included ≥7 therapeutic endoscopies, Foker surgery for long-gap EA, fundoplication, history of esophageal leak, and length of stricture ≥10 mm. Multivariate analysis identified only history of leak as statistically significant, though this regression was underpowered. The utility of repeated therapeutic endoscopies may diminish with increasing numbers of endoscopic therapeutic attempts, with a cutoff of ≥7 endoscopies identified by our single-center experience as our statistically optimal discriminator between having stricture resection versus not; however, a majority of patients remained free of stricture resection well beyond 7 therapeutic endoscopies. Though retrospective, this study supports that repeated therapeutic endoscopies may have clinical utility in sparing surgical stricture resection. Esophageal leak is identified as a significant predictor of needing subsequent stricture resection. Prospective study is needed.**

KEY WORDS: **esophageal atresia, esophageal dilation, esophageal stricture, therapeutic endoscopy.**

INTRODUCTION

Repaired esophageal atresia (EA) is a common reason for pediatric esophageal stricture. Often these anastomotic strictures are managed with endoscopic dilation.[1–3] In situations where endoscopic therapy is unsuccessful, patients with refractory strictures may require surgical stricture resection. Some literature suggests that repeated endoscopic dilations can relieve dysphagia symptoms and improve esophageal luminal diameter;[4–11] however, in patients who require frequent ongoing dilations, the optimal point at which endoscopic therapy should be abandoned in favor of taking on the risks associated with repeat thoracotomy is unclear. Moreover, existing literature is limited to study of repeated dilations without

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examining the utility of newer adjunct techniques such as intralesional steroid injection (ISI), stenting, or endoscopic incisional therapy (EIT) in avoiding repeat surgery.[1–3,12–14]

As a high-volume referral center for EA that routinely applies advanced complementary endoscopic techniques beyond endoscopic dilation, we were interested in understanding the utility of repeated therapeutic endoscopies utilizing a wider array of maneuvers (including dilation, ISI, stenting, and EIT) in sparing surgical stricture resection. We hypothesized that the increasing number of therapeutic endoscopies (as a proxy for increasing degree of 'refractoriness' of a stricture) is associated with diminishing freedom from stricture resection. In this retrospective study of 171 repaired EA patients at a tertiary care referral center, we examined our experience with repeat attempts at endoscopic therapy with primary outcome of odds of eventual need for surgical stricture resection.

METHODS

This study was approved by our institutional review board. We retrospectively reviewed the electronic medical records of all patients with EA who had a surgical procedure resulting in an esophago-esophageal anastomosis performed by one of our four EA-specialized surgeons at our tertiary care referral center between August 2005 and May 2019. Long-gap esophageal atresia (LGEA) was defined as any EA where the size of the gap length precluded the ability to complete a primary, one-stage surgical repair regardless of the presence or absence of an associated tracheoesophageal fistula (TEF).[15,16] In cases of referrals from outside facilities who underwent immediate stricture resection resulting in their qualifying esophago-esophageal anastomosis at our institution, decision to pursue immediate surgical stricture resection over endoscopic therapy was made by multidisciplinary (surgeon and gastroenterologist) review of outside facility endoscopic attempts at dilations and patient's endoscopic, radiographic, and clinical response; in addition, surgical plan for other procedures requiring thoracotomy and esophageal mobilization (e.g. posterior tracheopexy to address tracheomalacia) was taken into account.

Either up to 2 years of follow-up endoscopy data or follow-up endoscopy data until the primary endpoint of stricture resection occurred was included for each patient. Endoscopy data collected included diagnostic endoscopies and therapeutic endoscopic maneuvers such as dilation, ISI,[14] stenting,[12] and EIT.[13] Our typical practice is to first attempt lower risk endoscopic therapeutic maneuvers such as balloon dilation and/or ISI and assess endoscopic response prior to attempting EIT and/or stenting, as EIT is higher risk for perforation and stenting obligates additional repeat endoscopy to replace or remove a stent. The decision to apply stenting or EIT at our institution is typically limited to patients who have had multiple prior attempts of simple balloon dilation (and most often, multiple prior attempts of ISI) and still had residual dysphagia and an unacceptable esophageal luminal diameter at the level of the stricture. EIT is performed in cases of a stricture which appears asymmetric with a thick scar band component that can be incised.[13] Stenting is preferred for longer strictures or circumferentially symmetric strictures not amenable to EIT that fail to respond to dilation and/or ISI.[12]

We focused on 2 years of follow-up data because all but one of the patients meeting the primary endpoint criteria for clinical failure (defined as needing a stricture resection or esophageal replacement) at our institution occurred within the first year following the initial surgical procedure, and all of the failures occurred within the first 2 years. The decision to pursue a repeat surgical procedure for refractory stricture was determined on a case-by-case basis by a multidisciplinary team of gastroenterologists and surgeons using primarily endoscopic and/or radiographic information. Such information included continued regression of the stricture despite multiple attempts at dilation or failure of improvement in esophageal luminal diameter to age-appropriate diameters.[13] The esophageal diameter and length were measured at endoscopy estimated using the known diameter of the endoscope and dimensions of opened and closed biopsy forceps.

All endoscopies were performed by one of two pediatric gastroenterologists using either Olympus XP-190N or Olympus GIF-H190 under general anesthesia. Our protocol for anastomotic evaluation and surveillance is summarized in Figure 1. Our center practice has been to perform dilations with radial expansion balloons, and none of our patients received bougie dilations.

In the overall and stratified cohorts of patients with and without surgery or stricture resection, continuous data are presented as median (interquartile range), and categorical data are presented as frequency (percentage). Univariate comparisons were done using the Chi-square test or Fisher's exact test for categorical data and the Kruskal-Wallis test and Wilcoxon rank sum test for continuous data. Univariate and multivariable Cox proportional hazards regression was used to determine the independent associations between risk factors and need for stricture resection, with results presented as hazard ratios, 95% confidence intervals, and P values. Receiver operating characteristic (ROC) curve analysis was used to determine the discriminatory ability of the number of therapeutic endoscopies in predicting need for surgery or stricture resection, with Youden's J index assessed to determine the optimal cut-point for the number of dilations criteria

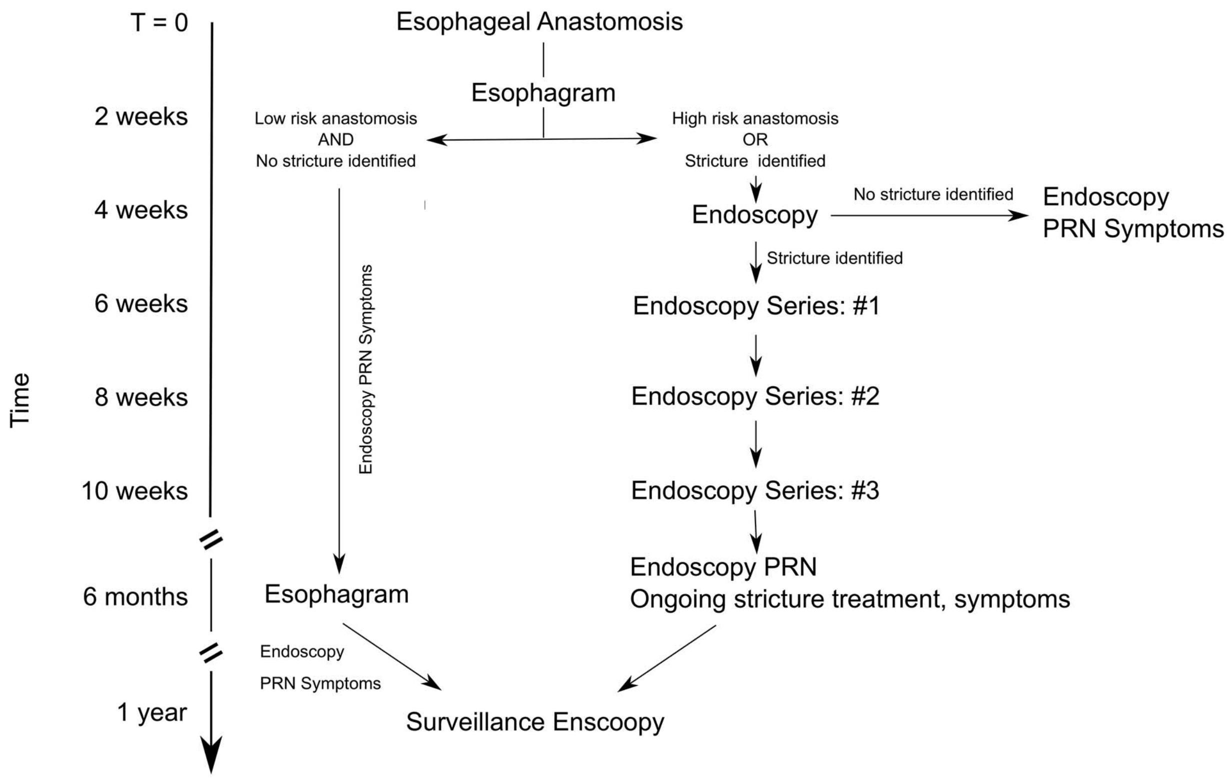

Fig. 1 Our typical practice for post-repair anastomotic surveillance and treatment of anastomotic stricture. All patients undergo contrasted-enhanced esophagram at 1–2 weeks after their anastomosis creation to assess for anastomotic leak. For 'low risk' patients who have uncomplicated surgeries, short gaps with low anastomotic tension, and no leak or evidence of stricture on esophagram, clinical surveillance of symptoms with repeat esophagram at 6 months is performed. For patients who do not meet low risk criteria, endoscopy is performed at the 3–4 week post-operative mark. If stricture is identified, dilation is performed and a series of additional planned endoscopies with dilations and other adjunct maneuvers as needed (including intralesional steroid injection, EIT, and/or stenting) each spaced 1–3 weeks apart is performed. At any point for any patient, development of obstructive symptoms prompts repeat investigation with esophagram and/or endoscopy. All patients undergo surveillance endoscopy 1 year post-operatively to assess for long-term sequelae of EA including but not limited to stricture, esophagitis, etc.

in identifying patients at a higher probability for stricture resection. Results of ROC analyses are summarized using the area under the ROC curve (AUC) with corresponding 95% confidence intervals. Logistic regression modeling was used to estimate the probability of need for stricture resection by the number of therapeutic endoscopies with 95% confidence bands. Multivariable logistic regression was used to identify independent factors associated with tube feeding (feeding score ≤ 3), with results presented as adjusted odds ratios, 95% confidence intervals, and *P* values. All statistical analyses were performed using Stata (version 16.0, StataCorp LLC., College Station, Texas). A two-tailed alpha level of 0.05 was used to determine statistical significance.

Table 1 Demographics of cohort

Demographics ($N = 171$)	
Variable	*N* (%) or median (IQR)
Male gender	83 (48.5%)
Diagnosis	
• Long-gap EA	94 (55.0%)
• Non-long gap EA	77 (45.0%)
Type of surgery leading to E-E anastomosis	
• Primary EA repair	45 (26.3%)
• Foker procedure	75 (43.9%)
• Stricture resection	51 (29.8%)
Age at initial surgery, months	4 (2–8)
• Primary EA repair	0 (0–2)
• Foker procedure	4 (2–7)
• Stricture resection	10 (5–18)
Fundoplication	74 (43.3%)

E-E, esophago-esophageal.

RESULTS

Cohort characteristics

There were 171 patients who met inclusion criteria (Table 1). While LGEA represents approximately 10% of the EA population,[17] this condition is over-represented in our cohort (55%) due to our large volume of EA referrals. As surgical practice can vary considerably, only surgeries resulting in an esophago-esophageal anastomosis performed by one of four surgeons who specialize in EA at our institution were included in this study; these consisted of primary EA repairs ($N = 45$), repairs after a period of esophageal traction or Foker procedure

Table 2 Summary of exposure to therapeutic maneuvers in patients who had at least one exposure to a therapeutic endoscopic maneuver

Therapeutic endoscopic interventions		
Therapeutic maneuver	Unique patients ($N = 149$)	Median number of episodes of maneuver per exposed patient (IQR)
Balloon dilation	148	4 (3–7)
Intralesional steroid therapy	96	2 (1–4)
Stenting	23	2 (2–3)
Endoscopic incisional therapy	25	1 (1–2)

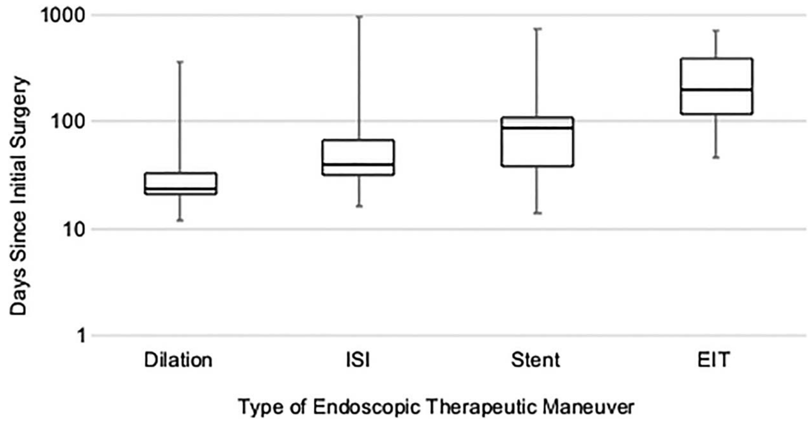

Fig. 2 Timing of first incidence of therapeutic maneuvers is presented as a box (quartile 1 to quartile 3; black horizontal line through box represents median) and whisker (lines extend to minimum and maximum values) plot.

($N = 75$), and stricture resections in patients with a history of attempted repaired EA ($N = 51$). There were 26 patients (15%) who met the primary endpoint of requiring subsequent stricture resection at a median of 153 days (interquartile range (IQR) 112–229 days) from the date of initial anastomosis (Supplemental Table 1). Of patients who met the primary endpoint of requiring subsequent stricture resection, the estimated esophageal luminal diameter at the time of most recent endoscopy preceding the surgical endpoint was a median 3 mm (IQR 2–4 mm). Patients who did not meet the primary endpoint had a median 12 mm diameter at the time of most recent follow-up endoscopy (IQR 10–15 mm).

Therapeutic endoscopy

Exposure to therapeutic maneuvers per patient is provided in Table 2. The most common therapeutic maneuver was balloon dilation ($N = 148$ patients exposed to dilation; median 4 dilations per patient exposed), followed by ISI ($N = 96$ patients; median 2 ISI episodes per patient exposed).[14] EIT was performed in 25 patients (median 1 episode of EIT per patient exposed), and stents were placed in 23 patients (median 2 stent placements per patient exposed). The timing of the first incidence of each therapeutic maneuver (in patients who experienced that respective maneuver) is presented in Figure 2. Median day of the first dilation (in patients who experienced dilation) was 23 days after anastomosis creation (IQR 21–33 days); median day of the first ISI exposure was 40 days (IQR 31–66 days); median day of the first stent exposure was 86 days (IQR 38–109); and median day of the first EIT exposure was 195 days (IQR 118–391 days).

The median number of therapeutic endoscopies per patient during the study period was 5 (IQR 3–9). Of patients who avoided stricture resection, the median number of therapeutic endoscopies was 4 (IQR 2–6); patients who required stricture resection underwent a median of 7 therapeutic endoscopic attempts prior to surgery (IQR 4–11).

The first endoscopy following the initial surgical procedure was performed a median of 22 days following esophago-esophageal anastomosis creation (IQR 20–28 days). The interval between therapeutic endoscopies tended to increase with increasing numbers of therapeutic endoscopies; by Friedman's test, there was a significant relationship between the time interval size as the number of endoscopies increased ($P < 0.001$; Supplemental Figure 1). Median length of follow-up time between initial and final endoscopy within the 2-year study timeframe was 413 days (IQR 151–655 days).

Predictors of failure of therapeutic endoscopic management

The number of therapeutic endoscopies during the study period was a moderate predictor of stricture resection by ROC curve analysis (Fig. 3;

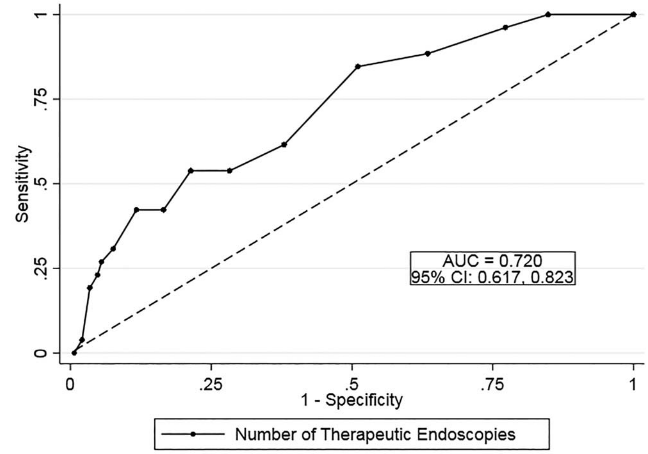

Fig. 3 ROC analysis of the number of therapeutic endoscopies as a predictor of need for stricture resection. Sensitivity is defined as the percentage of patients who had X or more dilations of the patients with stricture resection. Specificity is defined as the percentage of patients who had fewer than X dilations of the patients without stricture resection.

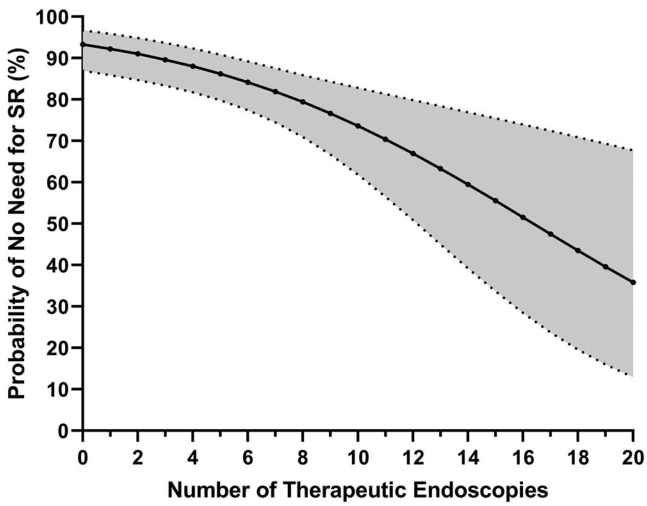

Fig. 4 Logistic regression modeling predicting the probability of not needing stricture resection (SR) per number of therapeutic endoscopies. The gray shaded region represents 95% confidence interval.

AUC = 0.720, 95% CI 0.617–0.823). With an increasing number of therapeutic endoscopies, the probability of remaining free from stricture resection decreased (Fig. 4). By Youden's J index, a cutoff of ≥7 therapeutic endoscopies was optimal for discriminating between patients who had versus did not have stricture resection, though an absolute majority of patients (≥50%) remained free of stricture resection at each number of therapeutic endoscopies through 12 endoscopies (Supplemental Table 1).

Exposure to any advanced therapeutic maneuver beyond dilation (ISI, stent, EIT) was significantly associated with increased hazard for stricture resection (hazard ratio (HR) 5.15; 95% confidence interval (CI): 1.55, 17.16; $P = 0.008$); moreover, exposure to increasing numbers of advanced therapeutic maneuvers (ISI, stent, EIT) was also significantly associated with increased hazard for stricture resection (HR per 1-unit increase in number of therapeutic maneuvers 1.15; 95% CI: 1.07, 1.23; $P < 0.001$).

Significant predictors of having stricture resection by univariate regression included ≥7 therapeutic endoscopies, LGEA and Foker surgery, fundoplication, history of esophageal leak, and length of stricture ≥10 mm (Table 3). Multivariate analysis identified only history of leak as statistically significant (Table 4; hazard ratio 3.64, $P = 0.005$). From clinical experience, we suspected there may be multicollinearity between our predictor variables used in this multivariate analysis; pairwise Fisher's exact tests were performed and confirmed multicollinearity between all of our predictor variables ($P < 0.05$; Supplemental Table 2), thereby limiting the power of our multivariate analysis to detect significant hazard ratios.

As leak is a well-described, strong predictor of stricture formation and because of the known multicollinearity between our variables, subgroup multivariable regression analyses of patients who did and did not have leak were performed. Within the

Table 3 Hazard ratios with 95% confidence intervals and *P* values were obtained using univariate Cox proportional hazards regression modeling

Univariate regression of need for stricture resection			
Variable	Hazard ratio	95% CI	*P* value
≥7 therapeutic endoscopies	2.88	(1.33, 6.23)	**0.007***
Type of surgery			
• Foker	3.48	(1.18, 10.23)	**0.024***
• Primary EA repair	Reference	—	—
• Stricture resection	0.68	(0.15, 3.02)	0.609
Fundoplication	2.62	(1.17, 5.87)	**0.020***
History of leak	6.56	(3.00, 14.32)	**<0.001***
History of erosive esophagitis	1.78	(0.70, 4.72)	0.248
Type of EA			
• Long-gap	2.78	(1.12, 6.93)	**0.028***
• Non-long-gap	Reference	—	—
Length of stricture			
• <10 mm	Reference	—	—
• ≥10 mm	3.57	(1.65, 7.72)	**0.001***

Statistically significant results are denoted by bold face type and an asterisk (*).

Table 4 Variables with P value < 0.05 in univariate analysis were included in the multivariable model. Statistically significant results are denoted by bold face type and an asterisk (*).

Multivariable regression of need for stricture resection			
Variable	Hazard ratio	95% CI	*P* value
≥7 therapeutic endoscopies	1.47	(0.65, 3.36)	0.356
Type of surgery			
• Foker	1.36	(0.29, 6.28)	0.695
• Primary EA repair	Reference	—	—
• Stricture resection	0.48	(0.10, 2.29)	0.361
Fundoplication	1.26	(0.49, 3.22)	0.626
History of leak	3.64	(1.49, 8.93)	**0.005** *
Long-gap EA	0.91	(0.25, 3.28)	0.881
Length of stricture ≥10 mm	2.32	(0.96, 5.62)	0.062

Variables with *P* value <0.05 in univariate analysis were included in the multivariable model.
Statistically significant results are denoted by bold face type and an asterisk (*).

subgroup of patients without a history of leak, exposure to ≥7 therapeutic endoscopies was significantly associated with need for stricture resection by multivariable regression (Table 5; HR 3.68; $P = 0.048$). In patients who had leak, long strictures (≥10 mm) were significantly more likely to go on to stricture resection regardless of the number of therapeutic endoscopies.

There were 22 patients who required no therapeutic endoscopies following their initial surgical repair. These patients had median 432 days of endoscopic follow-up (IQR 152–503), and none of these patients required subsequent stricture resection or esophageal replacement. Cases that required no therapeutic endoscopies included 4 Foker repairs, 6 primary EA repairs, and 12 stricture resections. Compared to patients who needed at least one therapeutic endoscopy, a smaller fraction of patients had LGEA (32 vs. 60%, $P = 0.019$; Supplemental Table 3) and underwent the Foker procedure in the group that required no therapeutic endoscopy (18 vs. 48%, $P = 0.011$). Patients who required no therapeutic endoscopies were also significantly less likely to have experienced esophageal leak (5 vs. 23%, $P = 0.05$). All patients who required no therapeutic endoscopy had strictures of lengths <10 mm (100 vs. 77%, $P = 0.008$). Age, gender, history of erosive esophagitis, and fundoplication were not significantly associated with undergoing no therapeutic endoscopies.

First versus second esophageal surgery

The subset of patients whose initial surgery at our institution was a stricture resection (and therefore at least a second esophageal surgery in the patient's lifetime) consisted of 36 patients with initial diagnosis of type C EA, 14 patients with LGEA, and 1 patient with type D EA. The most common reason for referral for stricture resection at our institution was refractory stricture ($N = 29$), refractory stricture with recurrent TEF ($N = 16$), or chronic leak/abscess following an outside hospital attempt at primary EA repair ($N = 2$) or previously failed Foker repair ($N = 4$). Patients who underwent stricture resection as their initial surgery at our institution were significantly older (median age 10 months; IQR 5–18 months) compared to patients whose initial surgery was a primary EA repair

Table 5 Adjusted hazard ratios with 95% confidence intervals and P values were obtained using Cox proportional hazards regression modeling. Statistically significant results are denoted by bold face type and an asterisk (*).

Variable	Hazard ratio	95% CI	*P* value
(a) Multivariable regression of need for stricture resection among patients who had leak			
≥7 therapeutic endoscopies	0.84	(0.30, 2.39)	0.749
Type of surgery			
• Foker	0.69	(0.08, 6.16)	0.737
• Primary EA repair	Reference	—	—
• Stricture resection	0.35	(0.02, 6.76)	0.488
Length of stricture ≥10 mm	4.35	(1.34, 14.14)	**0.014** *
(b) Multivariable regression of need for stricture resection among patients who did not have leak			
≥7 therapeutic endoscopies	3.68	(1.01, 13.37)	**0.048** *
Type of surgery			
• Foker	2.36	(0.56, 9.99)	0.242
• Primary EA repair	Reference	—	—
• Stricture resection	0.93	(0.14, 6.35)	0.941
Length of stricture ≥10 mm	0.66	(0.12, 3.49)	0.621

Adjusted hazard ratios with 95% confidence intervals and *P* values were obtained using Cox proportional hazards regression modeling. Statistically significant results are denoted by bold face type and an asterisk (*).

(median age 0 months; IQR 0–2 months) or Foker procedure (median age 4 months; IQR 2–7 months) ($P < 0.001$). Thirty-nine of 51 patients required at least one therapeutic endoscopy for stricture. Three of these thirty-nine patients with re-development of stricture required a second surgical stricture resection for refractory stricture. Initial stricture resection at our institution was not associated with a statistically significant difference in need for subsequent stricture resection compared to primary EA repairs performed at our institution (Table 3).

DISCUSSION

While our data supported our hypothesis that increasing numbers of therapeutic endoscopies (as a marker for increasing degree of 'refractoriness' of a stricture) are associated with diminishing freedom from stricture resection, we found that a majority of patients are able to avoid stricture resection even when the number of repeated therapeutic endoscopies reached 12. The true ability to remain free of stricture resection may even extend beyond 12 endoscopies but is not detected in this study due to low numbers of patients who experienced greater numbers of therapeutic endoscopies at our institution; indeed, there were 3 patients who had 19–20 therapeutic endoscopies within the study period and remained free of stricture resection. Our global stricture resection rate of 15% is greater than other reported centers (Supplemental Table 4) likely in part due to our greater volume of referrals, greater proportion of patients with LGEA, and a lower threshold to pursue stricture resection given our surgical experience and outcomes with reoperative esophageal surgery.

The single most important factor in predicting need for stricture resection identified by our study was history of esophageal leak. Leak has been previously described to be associated with reduced success of endoscopic therapy, regardless of definition of endoscopic success or patient population studied.[18,19] Because the predictor variables used in our multivariate regression model were confirmed to be collinear, our multivariate model is limited in its power to detect significant hazard ratios due to multicollinearity's effect on inflating the variance of each affected predictor. To investigate beyond the strong effect of leak, subgroup analysis was performed and found that among patients without history of leak, ≥7 therapeutic endoscopies was a significant predictor of need for stricture resection. It is possible that other clinical variables identified as significant in our univariate analysis such as length of stricture ≥10 mm, LGEA, and Foker repair also reflect more clinically significant 'difficult strictures' despite failure to achieve statistical significance in the multivariable regression or subgroup analysis in patients without leak. In-depth exploration of these effects is beyond the scope or capabilities of the current study.

Comparing studies of endoscopic management of refractory anastomotic strictures is difficult due to the lack of consensus around endoscopic or clinical success metrics, but the available evidence appears to support repeated dilation for anastomotic strictures in pediatric EA.[4–11] Most of the available literature is limited to small cohorts of largely non-long-gap EA patients who on average require 3–4 repeat dilations over varying time periods (Supplemental Table 4). Our study, unique in its large and complex referral patient base with a large number of LGEA cases, also supports the practice of repeated endoscopic therapy to manage anastomotic stricture even in highly complex cases. Even accounting for our high volume of long-gap and complex referral patients, patients in our cohort experienced a median of only 5 therapeutic endoscopies during the study period of 2 years, and the time interval between endoscopies became significantly less frequent over time.

Our study is the first to incorporate other advanced therapeutic maneuvers beyond dilation such as ISI, EIT and stenting. Exposure to these advanced maneuvers was significantly associated with increased need for stricture resection; however, selection bias certainly affects interpretation of this finding as patients who undergo advanced maneuvers are only those who fail to respond adequately to our first-line attempts at straightforward balloon dilation by our stricture treatment algorithm. Due to limitations inherent in our retrospective design, it is impossible to know from our data if exposure to advanced therapeutic maneuvers itself leads to increased need for stricture resection, though clinical intuition would suggest that exposure to these maneuvers more likely reflects some quality of 'refractoriness' of the stricture. Additional prospective study is needed.

Previous studies of mostly non-long-gap EA patients have shown that when using a symptom-based approach, the interval between balloon dilations tends to increase over time with more durable symptom-free periods in between.[4,9,10] Our practice is a hybrid approach, with screening endoscopy performed on most of our surgically repaired patients at the 4-week post-surgery mark to identify stricture, and to perform a series of 3 planned dilations with ISI, EIT, and/or stenting for those patients found to have stricture; following the series of endoscopies, we perform therapeutic endoscopy guided by stricture response to therapy and symptoms. Our practice is skewed toward referrals of long-gap and complex EA patients, which may not reflect the experience of most centers; however, our study also observed a statistically significant trend toward ability to space out endoscopies over time. This is consistent with previous studies as well as our anecdotal observation that less ongoing intervention is needed with time, possibly due to maturation or stabilization of the scar tissue component of the stricture that occurs in the remodeling phase of wound healing, which lasts several months to years.[20,21]

Our study is limited by its retrospective, single center design. We are not powered nor designed to identify optimal timing and sequence of endoscopic therapies. There is a wide range of institutional variability in surgical and endoscopic practice that merits exploration with multicenter investigation of practices and outcomes. As noted, many centers perform stricture dilation in a reactive fashion only once obstructive symptoms have developed,[10,22] whereas our practice, derived from our high volume experience with complex and long-gap EA referrals, includes the option of a proactive approach starting 1 month post-operatively for patients identified to have stricture. In our anecdotal experience, even repaired infants who develop severe strictures are frequently still able to tolerate their naturally liquid (milk) diets, and waiting to treat until symptoms develop may result in waiting until the esophagus has nearly or fully occluded. Understanding risk factors for development of severe or refractory strictures is therefore critical in better stratifying patients who may benefit from early therapeutic endoscopy.

An additional limitation is multicollinearity between our predictor variables, which reduces our power to detect significant effects in our multivariable regression model. As leak remained significant in the multivariable model despite this limitation of multicollinearity, leak is identified to be a robust predictor of eventual need for stricture resection. Indeed, 15 of 34 patients (44%) who experienced leak went on to stricture resection in our cohort. Patients with history of leak are therefore identified to comprise an 'at-risk' patient population who would benefit from future study to understand potential risks and benefits of various endoscopic practice patterns, such as utility of specific advanced therapeutic maneuvers or symptom-based versus proactive endoscopy.

In conclusion, the need for greater numbers of repeated therapeutic endoscopies within 2 years of an esophageal surgery was associated with reduced freedom from stricture resection, with a cutoff of $\geq$7 endoscopies identified by our single center experience as our statistically optimal discriminator between having stricture resection versus not (especially in patients without leak); however, a majority of patients remained free of stricture resection well beyond 7 therapeutic endoscopies. Though retrospective, this study supports that repeated therapeutic endoscopies may have clinical utility in sparing surgical stricture resection even in complex cases. Prospective study is critical in defining optimal endoscopic therapeutic approaches and understanding risk factors for failure of endoscopic management.

SUPPLEMENTARY DATA

Supplementary data mentioned in the text are available to subscribers in *DOTESO* online.

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