Journal of Pediatric Surgery 58 (2023) 2375–2383

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.sciencedirect.com/journal/journal-of-pediatric-surgery

Original Article

Surgical Treatment of Esophageal Anastomotic Stricture After Repair of Esophageal Atresia

Ali Kamran [a,1], Charles J. Smithers [a,b,1], Shawn N. Izadi [a], Steven J. Staffa [a,c], David Zurakowski [a,c], Farokh R. Demehri [a], Somala Mohammed [a], Hester F. Shieh [b], Peter D. Ngo [d], Jessica Yasuda [d], Michael A. Manfredi [e], Thomas E. Hamilton [f], Russell W. Jennings [b], Benjamin Zendejas [a,*]

[a] Department of Surgery, Boston Children's Hospital, Boston, MA, USA
[b] Department of Surgery, Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA
[c] Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Boston, MA, USA
[d] Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston, MA, USA
[e] Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[f] Department of General, Thoracic and Fetal Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA

A R T I C L E I N F O

Article history:
Received 10 April 2023
Received in revised form
17 July 2023
Accepted 24 July 2023

Keywords:
Esophageal atresia
EA
Anastomotic stricture
Esophageal stricture
Esophageal anastomotic stricture
Stricture surgical repair

A B S T R A C T

Background: Anastomotic strictures (AS) after esophageal atresia (EA) repair are common. While most respond to endoscopic therapy, some become refractory and require surgical intervention, for which the outcomes are not well established.
Methods: All EA children with AS who were treated surgically at two institutions (2011–2022) were retrospectively reviewed. Surgical repair was performed for those with AS that were either refractory to endoscopic therapy or clinically symptomatic and undergoing surgery for another indication. Anastomotic leak, need for repeat stricture resection, and esophageal replacement were considered poor outcomes.
Results: 139 patients (median age: 12 months, range 1.5 months–20 years; median weight: 8.1 kg) underwent 148 anastomotic stricture repairs (100 refractory, 48 non-refractory) in the form of stricturoplasty (n = 43), segmental stricture resection with primary anastomosis (n = 96), or stricture resection with a delayed anastomosis after traction-induced lengthening (n = 9). With a median follow-up of 38 months, most children (92%) preserved their esophagus, and the majority (83%) of stricture repairs were free of poor outcomes. Only one anastomotic leak occurred in a non-refractory stricture. Of the refractory stricture repairs (n = 100), 10% developed a leak, 9% required repeat stricture resection, and 13% required esophageal replacement. On multivariable analysis, significant risk factors for any type of poor outcome included anastomotic leak, stricture length, hiatal hernia, and patient's weight.
Conclusions: Surgery for refractory AS is associated with inherent yet low morbidity and high rates of esophageal preservation. Surgical repair of non-refractory symptomatic AS at the time of another thoracic operation is associated with excellent outcomes.
Level of Evidence: Level III.

1. Introduction

Anastomotic stricture (AS) is a common occurrence after the repair of esophageal atresia (EA), with a reported incidence of up to 80% [1]. The majority of strictures can be managed with endoscopic dilation; however, some fail to respond and are termed refractory [1–5]. Unfortunately, a widely accepted definition of what constitutes a refractory stricture does not exist. Hence, the threshold at which a stricture is deemed refractory is likely dependent upon

Abbreviations: AS, Anastomotic Stricture; EA, Esophageal Atresia; ISI, Intralesional Steroid Injections; EIT, Endoscopic Incisional Therapy; GERD, Gastroesophageal Reflux Disease; LGEA, Long-gap Esophageal Atresia; mFOIS, Modified Functional Oral Intake Scale; GEJ, Gastroesophageal Junction; IQR, Interquartile Range; HR, Hazard Ratio; CI, Confidence Interval; AUC, Area Under Curve; IRB, Institutional Review Board; BCH, Boston Children's Hospital; JHACH, John Hopkins All Children's Hospital.

* Corresponding author. Surgery Esophageal and Airway Treatment (EAT) Center, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115, USA. Tel.: +617 355 9871.
E-mail address: benjamin.zendejas@childrens.harvard.edu (B. Zendejas).

[1] Contributed equally to the article (co-first authors).

https://doi.org/10.1016/j.jpedsurg.2023.07.014
0022-3468/

both local resources and the treating provider's experience. Nonetheless, repeated dilations [6], intralesional steroid injections (ISI) [7], endoscopic incisional therapy (EIT) [8], and stenting [9–11] can be successful, yet some strictures persist and require surgical treatment [2,5,12–14].

Given that the outcomes of surgical therapy are not well known and generally perceived as morbid, many children with refractory strictures undergo repeated endoscopic treatments, accepting the risks of countless anesthetic exposures with limited and often short-lived symptomatic relief. Furthermore, it is not uncommon for patients with refractory AS to also have medically refractory gastroesophageal reflux disease (GERD) with or without a hiatal hernia. In such cases, children may require both AS surgical repair and anti-reflux surgery. The decision regarding which procedure to perform first and how long to wait between procedures poses a unique challenge, with no published evidence for guidance. An initial repair of AS can create or worsen a hiatal hernia, making the subsequent anti-reflux procedure more challenging. On the other hand, performing the anti-reflux procedure first may result in temporary ischemia and increased tension on the lower esophagus while it is mobilized and drawn down into the abdomen, potentially making a subsequent esophageal stricture resection more challenging if collateral blood flow and/or esophageal growth fails to develop appropriately.

To clarify the surgical risks and help guide management in these challenging circumstances, we sought to review our collective experience with the surgical treatment of esophageal anastomotic strictures after EA repair, focusing on esophageal preservation and examining predictors of poor outcomes.

2. Methods

2.1. Study design

With Institutional Review Board (IRB) approval, we conducted a retrospective review of the electronic medical records of all children diagnosed with esophageal atresia (any type) who underwent surgical treatment for esophageal anastomotic stricture at the Esophageal and Airway Treatment Center at Boston Children's Hospital (BCH) between July 2011 and January 2022. Similar patients treated at Johns Hopkins All Children's Hospital (JHACH) in Florida by two of our former surgeons (CJS, HFS) from June 2020 to January 2022 were also included, given that they were managed with a similar treatment strategy. Non-anastomotic strictures (e.g., distal congenital strictures) or those caused by caustic or peptic injury were excluded.

2.2. Data collected

The collected data included patient demographics, stricture characteristics, preoperative findings, operative details, and postoperative outcomes. Preoperative variables included the original type of EA according to the Gross classification and the presence or absence of long-gap EA (LGEA), history of primary or rescue (after failed attempt elsewhere) traction-induced esophageal lengthening process (Foker), prior endoscopic or surgical stricture management, and history of fundoplication. LGEA was defined as any type of EA where the esophageal gap length precluded the ability to complete a primary one-stage surgical repair. The diameter and length of the esophageal anastomotic stricture were measured endoscopically at the time of the last endoscopy prior to surgical therapy, using the known diameter of the endoscope and dimensions of opened and closed biopsy forceps [6]. The last in-person or telehealth clinic visit was considered the date of the last follow-up. The feeding status was determined at the last follow-up using the modified Functional Oral Intake Scale (mFOIS, range 1–6, with 1–3 being entirely dependent on tube feedings, 5–6 being fully orally fed, and 4 and 4.5 being primarily orally fed but remaining partially dependent on tube feedings) [15]. Endoscopy data collected included therapeutic endoscopic maneuvers after the stricture repair. Anastomotic leak, need for repeat stricture resection, and esophageal replacement were considered poor outcomes. Perioperative esophagrams and endoscopies were reviewed to determine the presence or absence of a hiatal hernia based on the location of the gastroesophageal junction (GEJ) with respect to the diaphragm pinch, and if a hiatal hernia was present before stricture repair whether it had increased in size after stricture repair.

2.3. Patient selection for surgical management of anastomotic strictures

The decision for surgical repair of an AS was made on a case-by-case basis and with a multidisciplinary approach after a thorough gastrointestinal and airway assessment using flexible esophagogastroduodenoscopy with fluoroscopic contrast esophagram, together with diagnostic laryngoscopy and dynamic rigid 3-phase tracheobronchoscopy [16] (Fig. 1).

A refractory stricture was defined as one that showed recurrence despite multiple attempts at endoscopic treatments or failure of dilation to improve esophageal luminal diameter to the age-appropriate caliber. For strictures that our team had treated since inception (anastomosis), we generally considered a stricture refractory when it had not effectively responded to 7–10 dilation sessions that included advanced endoscopic maneuvers [6]. Patient symptoms, the trend of improvement over time, and the frequency of dilations were also factored into the equation. In cases referred to us from other institutions, the decision to pursue immediate or delayed surgical stricture management over endoscopic therapy was made by a multidisciplinary review of prior endoscopic attempts, existing comorbid conditions (e.g., tracheomalacia), and overall clinical status. Non-refractory strictures were surgically repaired for children that required thoracic operative intervention for airway problems such as severe tracheobronchomalacia or recurrent tracheoesophageal fistula (TEF). These patients would have had further endoscopic attempts at stricture management, rather than operations, had the airway and respiratory concerns not warranted operative intervention.

Our surgical preference is to avoid a gastric pull-up to limit the challenges associated with gastroesophageal reflux disease (GERD) [17–19]. In settings where a significant (>2–3 cm) hiatal hernia coexists with a refractory esophageal stricture, as long as there was healthy lower esophageal tissue between the stricture and the GEJ, we considered hiatal hernia repair with fundoplication either before or after the management of the stricture (spacing out procedures by a timeframe of at least 9 weeks) [15]. Generally, we prefer to pursue hiatal hernia repair and/or fundoplication prior to surgical stricture management, yet in certain circumstances (e.g., complete esophageal obstruction, recurrent TEF, or other severe airway problems) it was performed afterward. Furthermore, despite our emphasis on esophageal preservation, in settings without good quality lower esophagus between the stricture and the GEJ, these patients were considered for upfront esophageal replacement with a supercharged jejunal interposition [20].

2.4. Surgical techniques

The techniques employed included Heineke-Mikulicz type stricturoplasty, segmental resection with primary anastomosis, or resection with a delayed anastomosis after the traction-induced

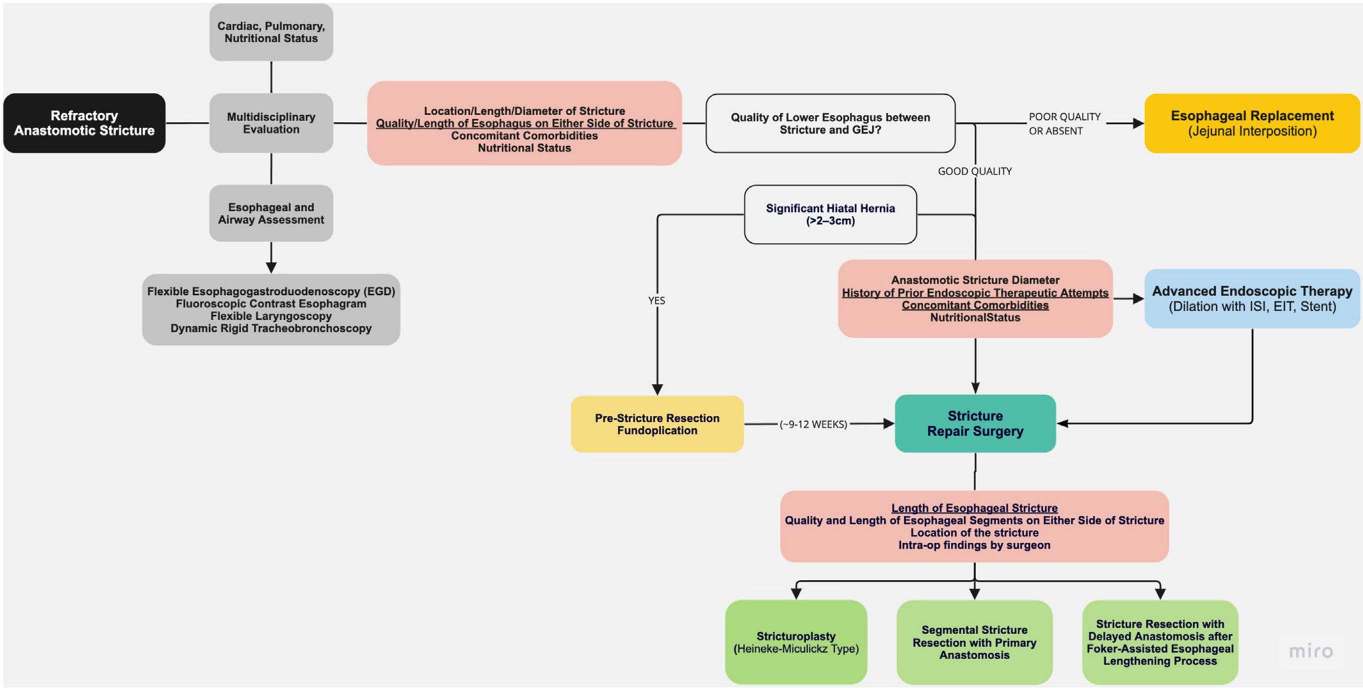

Fig. 1. Treatment Algorithm.

esophageal lengthening process (i.e., Foker-assisted) [21]. The surgical technique performed was chosen based on preoperative evaluations as well as various intra-operative factors, such as the length of the esophageal stricture, the quality and length of esophageal segments on either side of the stricture, the location of the stricture, and the existence of concomitant comorbidities. For segmental resections, the type of anastomosis (end-to-end, single Cheatle slit, or double opposing Cheatle [slide]) depended similarly on stricture characteristics and surgeon preference. Still, whenever possible, we aimed to perform a slide anastomosis to increase the potential luminal diameter [22]. We have previously reported our technique and outcomes of hiatal hernia repair and fundoplication in children with esophageal atresia [19].

2.5. Postoperative surveillance

All patients underwent contrast esophagram 1–2 weeks after the operation to assess anastomotic patency and integrity. An endoscopy was performed 3–4 weeks after surgery, and subsequent endoscopic surveillance was tailored based on the size of the initial anastomotic diameter [23]. Endoscopic dilation was performed if the patient was found to have a stricture. In such cases, a series of additional endoscopies with dilation and other adjunct maneuvers (such as ISI (intralesional steroid injections), EIT (endoscopic incisional therapy), and/or stenting was also performed, each spaced 1–3 weeks apart. In our standard practice, we first perform lower-risk endoscopic therapeutic maneuvers such as balloon dilation and/or ISI, assess the endoscopic response, and then attempt EIT and/or stenting [8,11]. The decision to apply stenting or EIT is typically limited to patients who have had multiple prior attempts of balloon dilation (and ISI) and still had residual dysphagia and an unacceptable esophageal luminal diameter at the level of the stricture. EIT is most commonly performed in cases of a stricture that appears asymmetric with a thick scar band component that can be incised. Stenting is preferred for longer strictures or circumferentially symmetric strictures not amenable to EIT that fail to respond to balloon dilation (and ISI). As a last resort, we consider repeating stricture resection or esophageal replacement in patients who still have significant dysphagia and an unacceptable esophageal luminal diameter at the level of the stricture even after maximal endoscopic therapy.

2.6. Statistical analysis

Descriptive or summary statistics are provided. Continuous variables are reported as the median and interquartile range (IQR), and categorical variables are reported as frequency and percentage. Univariate comparisons were done using the Chi-square test or Fisher's exact test for categorical data and the Kruskal–Wallis test and the Wilcoxon rank-sum test for continuous data. Univariate and multivariable analyses were based on the Cox regression model for time-to-event outcomes to determine predictors of poor outcomes, with hazard ratios (HR), 95% confidence intervals (CI), and p-values. If a subject's anastomosis underwent repeated surgical resection (poor outcome), the new anastomosis was considered a separate anastomosis. Subgroup analyses of outcomes and time intervals in patients with fundoplication were performed using Fisher's exact test and the Wilcoxon rank sum test. Nonparametric Spearman correlation coefficients were implemented for comparing continuous variables. Receiver operating characteristic (ROC) curve analysis was implemented to determine the discriminatory ability of weight and weight-for z-score to distinguish between patients with and without leak. Results from ROC analysis are presented as the area under the curve (AUC) with corresponding 95% confidence intervals. The optimal cut-point for weight was determined using Youden's J index to maximize the combination of sensitivity and specificity. Statistical analyses were performed using Stata (version 16.1, StataCorp LLC., College Station, Texas). A two-tailed alpha level of 0.05 was used to determine statistical significance.

3. Results

During the study period, 139 children underwent surgical management of esophageal anastomotic stricture (AS) after EA

Table 1
Patients demographics, characteristics of anastomotic strictures, operative details.

Patient Demographics	
Total number of patients	**N=139**
Gender: male, n (%)	76 (55)
Age, median (IQR), months	12 (6–23)
Weight, median (IQR), kg	8.1 (6.2–12.2)
Weight-for-age Z-score, median (IQR)	−1.59 (−0.55 to −2.44)
EA type, n (%)	
A	19 (14)
B	10 (7)
C	105 (76)
D	3 (2)
E	2 (1)
Long-gap EA, n (%)	30 (22)
Initial EA repair at our institutions, n (%)	21 (15)
EA repair using Foker process at our institutions[a], n (%)	14 (10)
Primary repair using Foker process, n (%)	9 (6)
Rescue repair using Foker process, n (%)	5 (4)
History of prior AS resection at other institutions, n (%)	4 (3)
Characteristics of Anastomotic Strictures (pre-op)	
Total number of AS	**N=148**[b]
Refractory AS, n (%)	100 (68)
Non-refractory AS, n (%)	48 (32)
History of fundoplication, n (%)	40 (27)
History of AS endoscopic therapy at our institutions, n (%)	65 (44)
# Dilations, median (IQR; range)	
Initial anastomosis at our institutions (n = 26)	7 (5–10; 1–17)
Initial anastomosis at other institutions (n = 39)	2 (1–4; 1–17)
Advanced endoscopic therapy, n (%)	30 (20)
EIT, n (%)	14 (10)
Stent, n (%)	11 (7)
Both, n (%)	5 (3)
AS location	
1/3 upper, n (%)	23 (15)
1/3 middle, n (%)	118 (80)
1/3 lower, n (%)	7 (5)
AS endoscopic measurement, n	126[c]
Diameter, median (IQR; range), mm	
Refractory AS	3 (2–5; 0–13)
Non-refractory AS	9 (7–10; 3–14)
Length, median (IQR; range), cm	
Refractory AS	1 (1–1.5; 0.3–5)
Non-refractory AS	1 (0.8–1; 0.2–3)
GEJ location: above diaphragm before AS repair surgery, n (%)	31 (21)
Operative Details	
Operative indication:	
Refractory AS ± airway procedures, n (%)	100 (68)
Airway procedures + Non-refractory AS, n (%)	48 (32)
Surgical technique:	
Stricturoplasty, n (%)	43 (29)
Refractory AS, n (%)	29 (67)
Non-refractory A, n (%)	14 (33)
Segmental resection, n (%)	96 (65)
Refractory AS, n (%)	78 (81)
Non-refractory AS, n (%)	18 (19)
Staged repair (Foker-assisted), n (%)	9 (6)
Refractory AS, n (%)	9 (100)
Non-refractory AS, n (%)	0
Type of anastomosis[d]**, n**	105
End-to-End, n (%)	71 (68)
Slide, n (%)	30 (28)
Other, n (%)	4 (4)
Concomitant airway procedures	
TEF repair, n (%)	48 (32)
Tracheal diverticulectomy, n (%)	78 (53)
Posterior tracheopexy, n (%)	101 (68)

EA: esophageal atresia; AS: anastomotic stricture; GEJ: gastroesophageal junction; TEF: tracheo-esophageal fistula.

[a] Of the 14 patients with EA repair using the Foker process that later required surgical therapy for AS, seven had a poor outcome (4 of 9 primary Foker, 3 of 5 rescue Foker).
[b] Nine patients had 2 stricture resections.
[c] Endoscopic measurements were documented for 126 of 148 AS (91 refractory strictures, 35 non-refractory strictures).
[d] For segmental resection or staged repair.

repair at our institutions (128 from Boston Children's Hospital and 11 from Johns Hopkins All Children's Hospital) (Table 1). Of the study cohort, 55% of children were male, 76% had a history of EA type C, 22% had LGEA, 16% had their primary EA repaired at our institutions, and 14 (10%) had a staged EA repair after a period of esophageal traction process (Foker-assisted) at our institutions (primary Foker = 9; rescue Foker = 5). At the time of surgical repair of the AS, children had a median (IQR) age of 12 months (6–23), weight of 8.1 kg (6.2–12.2), and weight-for-age Z-score of −1.59 (−0.55 to −2.44). Sixty-five patients (44%) received some extent of endoscopic therapy before their surgical stricture repair at our institutions, with the median (IQR) number of 7 (5–10) balloon dilations for those anastomoses that we treated since inception at our institutions (n = 26) and 2 (1–4) balloon dilations for those who came from another institution (n = 39) (Table 1). No significant correlations were found between the number of pre-stricture repair balloon dilations and the patient's age (correlation = −0.19, p = 0.133), weight (correlation = −0.24, p = 0.06), or weight-for-age Z-score (correlation = −0.18, p = 0.158).

Nine children had two separate stricture resections. In total, 148 cases of AS (refractory = 100, non-refractory = 48) underwent surgical repair (Table 1). These represent 27% of the total EA-related anastomoses performed at our centers during the study timeframe (N = 547; 134 primary EA repairs (BCH = 118, JHAC = 16), 181 staged EA repairs (BCH = 165, JHAC = 16), and 84 esophageal replacements (BCH = 83, JHAC = 1). The majority of AS cases were located in the middle third of the esophagus (n = 118, 80%). Based on the endoscopic measurements, strictures had a median (IQR) diameter of 3 mm (2–5) and length of 1 cm (1–1.5) for refractory cases, and 9 mm (7–10) by 1 cm (0.85–1) for non-refractory cases. Surgical procedures performed for stricture management included stricturoplasty (n = 43, 67% refractory), segmental resection with primary anastomosis (n = 96, 81% refractory), or resection with a delayed anastomosis after the traction process (Foker-assisted; n = 9, all refractory).

The median duration of hospital stay was 31 days (IQR: 16–62). Of note, 34 (25%) children had more than one surgical procedure (i.e., hiatal hernia repair/fundoplication = 17, esophageal leak repair = 7) during the same hospitalization. Following esophageal stricture repair, the median duration of intubation was five days (IQR: 3–8), excluding 7 children, who had a tracheostomy. A new vocal fold movement impairment (VFMI, paralysis/paresis) was identified in five (4%) children. In three children VFMI was unilateral (resolved in one), while in two children VFMI was bilateral requiring tracheostomy. No cases of prolonged air leak or chylothorax occurred.

With a median (IQR) length of postoperative follow-up of 38 months (18–63), 123 out of 148 cases (83% overall; 76% refractory, 98% non-refractory) had favorable anastomotic outcomes (no anastomotic leak, need for repeat stricture resection, or esophageal replacement) (Table 2). The native esophagus was preserved in 128 of 139 (92%) cases. Esophageal preservation was achieved in 7 of the 9 patients who required repeat stricture resection. At the time of the last follow-up, most children were orally fed (median [IQR] mFOIS of 6 [3–6]). Overlap between the different types of poor anastomotic outcomes is depicted in Fig. 2.

Table 2
Postoperative outcomes.

Total number of surgically repaired AS	N = 148
Length of Hospital stay, median (IQR; range), days	**31 (16–62; 4–496)**
Length of follow-up, median (IQR), months	38 (18–63)
Endoscopic balloon dilation, n (%)	98[a] (66)
# Dilations, median (IQR; range)	
Refractory AS	4 (2–7; 1–19)
Non-refractory AS	2 (1–4; 1–9)
[+] advanced therapeutic maneuver (EIT, Stent)	28 (19)
Refractory AS, n (%)	22 of 100 (22)
Non-refractory AS, n (%)	6 of 48 (12.5)
Poor outcomes, n (%)	25 (17)
AL: anastomotic leak, n (%)	11 (7.4)
Time to AL, median (IQR; range), days	13 (8–25; 3–40)
Leak management:	
Only conservative (NPO, Abx, Drain), n (%)	2 (18)
EVAC (successful trial), n (%)	4 (36)
Operative, n (%)	5 (45)
No EVAC trial, n	3
Failed EVAC trial, n	2
RSR: repeat stricture resection, n (%)	9 (6.1)
Time to RSR, median (IQR; range), months	5.5 (4–6; 1.5–8.5)
ER: esophageal replacement, n (%)	13 (8.8%)
Time to ER, median (IQR; range), months	16 (8.5–24.5; 6.5–62.5)
Poor outcome rates by operative indications:	
Refractory AS, n	100
AL, n (%)	10 (10)
RSR, n (%)	9 (9)
ER, n (%)	13 (13)
Non-refractory AS, n	48
AL, n (%)	1 (2)
RSR, n (%)	0
ER, n (%)	0
Poor outcome rates by surgical techniques:	
Stricturoplasty, n	43
AL, n (%)	1 (4.7)
RSR, n (%)	0
ER, n (%)	0
Segmental resection, n	96
AL, n (%)	8 (8.3)
RSR, n (%)	7 (7.3)
ER, n (%)	9 (9.4)
Staged repair (Foker-assisted), n	9
AL, n (%)	1 (11.1)
RSR, n (%)	2 (22.2)
ER, n (%)	3 (33.3)
GEJ location:	
Above diaphragm after AS repair surgery, n (%)	42 (28)
Worsening of GEJ with AS repair surgery, n (%)	28 (19)

AS: anastomotic stricture; EIT: endoscopic incisional therapy; AL: anastomotic leak; RSR: repeat stricture resection; ER: esophageal replacement; GEJ: gastroesophageal junction.
[a] 98 of 148 anastomotic strictures received endoscopic balloon dilation after surgery (68 refractory strictures, 30 non-refractory strictures).

3.1. Anastomotic leak

An anastomotic leak occurred in 10 cases (10%) of the refractory strictures, while only one anastomotic leak occurred in a child with a non-refractory stricture (2%). Leaks were detected at a median (IQR) time of 13 days (8–25) postoperatively (Table 2). Of the 11 leaks, two were successfully managed conservatively, four were successfully treated endoscopically using esophageal VAC therapy, and five required a surgical repair. Significant predictors of developing an anastomotic leak by univariate regression included the patient's age (older) and weight (heavier), history of LGEA, preoperative advanced endoscopic therapy, postoperative location of the GEJ (above the diaphragm), and worsening of the GEJ location (increase in the size of the hiatal hernia) with AS repair. A concomitant posterior tracheopexy was found protective (HR 0.17, 95% CI 0.05–0.56, $p = 0.004$). Based on multivariable analysis, only two factors were statistically significant: the patient's body weight (HR 1.11, 95%CI 1.04–1.18, per each increase of 1 kg, $p = 0.001$), and the worsening of the GEJ location (HR 9.63, 95%CI 1.06–87.4, $p = 0.044$) (Table 3). In ROC analyses, weight and leak demonstrated an AUC of 0.678 (95% CI: 0.532, 0.824) with a cut-point of weight >8.75 kg (64% sensitivity, 58% specificity), while weight-for-age Z-score and leak had an AUC of 0.664 (95% CI: 0.559, 0.769) with a cut-point of Z-score > -1.2 (64% sensitivity, 64% specificity).

3.2. Recurrent stricture and need for repeat stricture resection

Ninety-eight cases (66% overall; 68% refractory vs. 63% non-refractory) underwent at least one balloon dilation of an anastomotic stricture that developed after surgical stricture-repair, with a median (IQR) number of 3 (2–6) dilations (Table 2). Advanced endoscopic therapeutic maneuvers (EIT and/or stenting) were performed in 28 cases (19%). Despite this, only nine cases (9%, all in the refractory category) required a repeat stricture resection at a median (IQR) interval of 5.5 (4–6) months and after a median (IQR) of 7 (4–8) therapeutic endoscopic procedures performed at our institutions. On univariate analysis, only the history of EA repair (primary or reoperative) at our institutions was significantly associated with the need for repeat stricture resection (Table 3).

3.3. Need for esophageal replacement

Thirteen cases (13% of the refractory group, 9% overall) required an esophageal replacement (jejunal interposition) at a median (IQR) interval of 16 months (8.5–24.5) following a prior stricture resection (Table 2). On univariate analysis, several factors were significantly associated with the need for esophageal replacement, including the need for repeat stricture resection, age (older), stricture length (longer), prior anastomotic leak, history of Foker procedure for primary EA repair, preoperative location of the GEJ (above the diaphragm), postoperative location of the GEJ (above the diaphragm), and worsening of the GEJ location with AS repair. A concomitant posterior tracheopexy was found protective (HR 0.25, 95% CI 0.07–0.87, $p = 0.029$). On multivariable analysis a history of Foker procedure for EA repair (HR 7.37, 95%CI 2.61–20.8, $p < 0.001$), anastomotic leak (HR 6.03, 95%CI 1.73–21, $p = 0.005$), length of the stricture (HR 1.71, 95%CI 1.16–2.54, per each increase of 1 cm, $p = 0.007$), and worsening of the GEJ location (HR 5.84, 95%CI 1.84–18.4, $p = 0.003$) were significant (Table 3).

3.4. Subgroup analysis: perioperative fundoplication

Fifty-two cases (35%) had a history of at least one fundoplication and/or hiatal hernia repair performed before ($n = 40$) and/or after ($n = 20$) AS repair. The majority of fundoplications (62%) were performed within 3 months of AS repair (perioperative fundoplication), with a median interval of nine weeks between the two procedures. Of this cohort which had perioperative fundoplications, 17 (32%) had a poor anastomotic outcome(s): anastomotic leak ($n = 6$), need for repeat stricture resection ($n = 5$), and/or need for esophageal replacement ($n = 8$). Analyses of subgroups in this cohort did not indicate a statistically significant association between fundoplication before or after AS repair and poor anastomotic outcomes. However, there was a significant association between the time interval between fundoplication and AS repair and the need for repeat stricture resection (Table 4). The median time interval between these two procedures was significantly shorter in children who subsequently required a repeat stricture resection (25 vs. 65 days; $p = 0.005$).

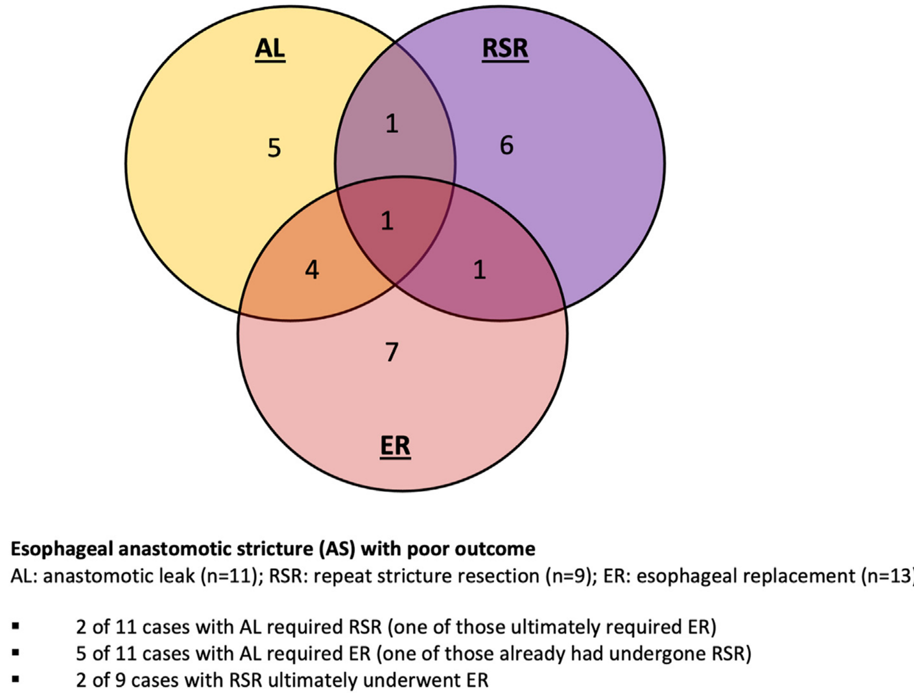

Fig. 2. Overview of poor anastomotic outcomes.

4. Discussion

This study reports the largest series of children requiring surgical intervention for esophageal anastomotic strictures following EA repair. Surgical therapy of refractory strictures is inherently challenging, yet when performed at centers with experienced thoracic teams, excellent rates of esophageal preservation (>90%) with low morbidity can be achieved. Strictures with inadequate response to repeated endoscopic therapy, particularly when the patient is approaching seven or more dilations, should be considered refractory since the odds of success with continued endoscopic attempts diminish significantly [6]. Continuing to dilate a refractory stricture without an apparent threshold or surgical plan needlessly exposes the child to the harms of repeated anesthetics [24–28], risks of endoscopic dilations, and can delay their oral independence [29], while also ultimately compromising their chance for an eventual satisfactory outcome. Our results help to clarify the risk profile of surgical therapy for esophageal AS and should be considered when counseling families of children with refractory strictures.

Our strategy for the treatment of esophageal anastomotic strictures starts with the goal of understanding the problem. Tissue

Table 3
Univariable and multivariable cox regression analysis of poor surgical outcomes.

Variables	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Anastomotic Leak				
Age (per year)	1.15 (1.03–1.29)	**0.012***		
Weight (per kg)	1.07 (1.02–1.13)	**0.005***	1.11 (1.04–1.18)	**0.001***
History of long-gap EA	4.18 (1.45–12.1)	**0.008***		
Preoperative advanced endoscopic intervention:				
Stent	6.26 (1.69–23.9)	**0.006***		
EIC and Stent	14.4 (2.72–76.0)	**0.002***		
Posterior tracheopexy	0.17 (0.05–0.56)	**0.004***		
GEJ above diaphragm after AS repair surgery	4.97 (1.69–14.6)	**0.004***		
GEJ location worsened with AS repair surgery	4.06 (1.42–11.6)	**0.009***	9.63 (1.06–87.4)	**0.044***
Repeat Stricture Resection				
History of EA repair at our institutions	3.87 (1.13–13.3)	**0.031***		
Esophageal Replacement				
Age (per year)	1.13 (1.03–1.23)	**0.007***		
Stricture length (per cm)	1.55 (1.16–2.06)	**0.003***	1.71 (1.16–2.54)	**0.007***
History of Foker-assisted EA repair	3.71 (1.38–9.95)	**0.009***	7.37 (2.61–20.8)	**<0.001***
Anastomotic leak	5.51 (1.71–17.8)	**0.004***	6.03 (1.73–21)	**0.005***
2nd Stricture resection event	3.04 (1.01–9.20)	**0.049***		
Posterior tracheopexy	0.25 (0.07–0.87)	**0.029***		
GEJ above diaphragm before AS repair surgery	4 (1.17–13.7)	**0.027***		
GEJ above diaphragm after AS repair surgery	3.27 (1.24–8.65)	**0.017***		
GEJ location worsened with AS repair surgery	3.29 (1.26–8.57)	**0.015***	5.84 (1.86–18.4)	**0.003***

EA: esophageal atresia; GEJ: gastroesophageal junction; AS: anastomotic stricture; HR: hazard ratio.

Table 4
Subgroup Analysis for Children with Fundoplication Before and/or After AS Repair (n = 52).

Poor outcome rates by fundoplication before and after AS repair surgery				
	Poor Outcome (Overall)	Anastomotic Leak	Repeat Stricture Resection	Esophageal Replacement
Fundoplication before AS repair surgery:				
No, n (%)	1/12 (8.3)	0/12 (0)	0/12 (0)	1/12 (8.3)
Yes, n (%)	16/40 (40)	6/40 (15)	5/40 (12.5)	7/40 (17.5)
p-value	0.076	0.316	0.578	0.663
Fundoplication after AS repair surgery:				
No, n (%)	13/32 (40.6)	5/32 (15.6)	4/32 (12.5)	5/32 (15.6)
Yes, n (%)	4/20 (20)	1/20 (5)	1/20 (5)	3/20 (15)
p-value	0.143	0.387	0.637	0.999
Fundoplication within 3 months to/from AS repair surgery:				
Yes, within 3 months, n (%)	12/32 (37.5)	4/32 (12.5)	5/32 (15.6)	4/32 (12.5)
Yes, not within 3 months, n (%)	5/20 (25)	2/20 (10)	0/20 (0)	4/20 (20)
p-value	0.383	0.999	0.143	0.695

Temporal relationship between fundoplication and AS repair surgery vs. Poor outcomes	**Fundoplication–AS repair surgery Time Interval** median (IQR), days	**p-value**
Fundoplication before AS repair surgery (n = 40)	9 (6–21)	1.00
Fundoplication after AS repair surgery (n = 20)	9 (4–28)	
Poor outcome (overall):		
No	65 (35–219)	0.18
Yes	50 (27–122)	
Anastomotic leak:		
No	58 (30–148)	0.87
Yes	64 (49–126)	
Repeat stricture resection:		
No	65 (45–158)	**0.005***
Yes	25 (14–29)	
Esophageal replacement:		
No	58 (27–158)	0.68
Yes	70 (50–126)	

AS: anastomotic stricture.

quality, perfusion, and tension at the time of anastomosis are key factors for effective anastomotic healing [30]; and these elements must be optimized when performing an initial anastomosis and/or following surgical stricture repair. Once an esophageal anastomotic stricture develops, it is important to evaluate all aspects of the problem in detail: diameter, length, pliability of the anastomosis vs. density and configuration of scar tissue, esophageal wall integrity (e.g., diverticula above the stricture), and entrapment of the esophagus by other mediastinal structures. Some strictures represent a portion of the esophagus with a mucosal-lined scar tube without a good muscular wall; these will often fail endoscopic-based treatment, especially if longer than 1 cm. Nonetheless, endoscopic dilation remains the first line and mainstay of stricture management; but we also have to recognize that dilations cause traumatic injury to the tissue, which is scarred and stenotic from the primary tissue insult. Hence, there will always be limits to obtaining a successful long-term anastomotic outcome from the balloon or other types of dilation, despite how technically simple they are to perform.

Multiple other surgical factors are important to consider. Airway problems are almost invariably present in EA patients. We think it is important to thoroughly evaluate and address these concerns when indicated during operative esophageal stricture management. The degree of these potential airway issues, tracheobronchomalacia being the most common, will also impact the threshold for operative intervention, as was generally the case for the non-refractory strictures in this study. Our results suggest that surgical therapy of non-refractory yet symptomatic esophageal anastomotic strictures in the setting of a concomitant thoracic operation (e.g., tracheopexy) is appropriate as it yields excellent results with minimal morbidity. Stricture resections will involve reoperative thoracic surgery, and the risks should not be underestimated; inadvertent injury to the lungs, esophagus, airway, and critical nerves will not only bring their own morbidity but also impact the esophageal anastomotic outcomes.

We examined several predictors of poor anastomotic outcomes after surgical therapy for esophageal anastomotic strictures. Interestingly, older age and weight were associated with an increased risk of poor outcomes. We hypothesized that younger/smaller patients may have greater healing potential or have been exposed to fewer endoscopic therapies that could lead to cumulative esophageal injury. However, our analyses did not yield a statistically significant correlation between age or weight and the number of prior endoscopic balloon dilations. However, due to the lack of accurate historical data on endoscopic dilation therapies for anastomoses performed outside our institutions, we cannot make a definitive statement about this association. Further research is necessary to clarify this age/weight association.

Unique patient and stricture characteristics warrant special considerations, given they represent greater challenges. Patients with a history of long-gap EA and those undergoing the Foker procedure for their EA repair (more likely to have been repaired at our institutions) appear to carry an increased risk of poor outcomes after stricture resection. This patient population is inherently challenging as their esophagus has often already undergone significant strain from multiple prior operations. An abnormal GEJ location or hiatal hernia is also common in this cohort with its attendant need for fundoplication consideration. Strictures at the cervical location may need combined cervical and thoracic esophageal mobilization, along with recurrent laryngeal nerve identification, monitoring, and preservation [31–33]. It is important to define the distance from the cricopharyngeal muscle to the proximal extent of the stricture, as strictures that involve the cricopharyngeal muscle require careful exposure of the pharynx, which is a skill set not common to general pediatric surgeons. Similarly, it is important to define the distance between the GEJ and the distal end of a stricture located in the lower third of the esophagus, as strictures involving the GEJ should prompt consideration of a concomitant anti-reflux procedure or a Roux-en-Y reconstruction with jejunum to prevent GERD. For patients with long-segment (>3 cm) esophageal strictures or a history of a prior stricture resection, one needs to be prepared to consider a staged approach with segmental resection and either internal or external esophageal traction process (Foker-assisted). Though patients with this staged approach were few, and the rate of poor outcomes was significant, it was still possible to achieve esophageal preservation in most instances. Our results include outcomes on the largest number of EA patients to require a second or repeat stricture resection in the literature. Although we use repeat stricture resection as a measure of poor outcome in this study, it is important to note that only 2 of 9 (22%) of these patients went on to require esophageal replacement. Despite this, it is important to consider that esophageal preservation does not always lead to adequate esophageal function, and one must be prepared to consider an esophageal replacement if significant damage to the esophagus already exists despite its potential for preservation.

The surgical technique appears to play a role, which is likely influenced by the stricture length and characteristics. Less severe strictures amenable to a strictureplasty appear to have excellent outcomes. For strictures that require segmental resection, we have previously shown that a slide-type anastomosis can lead to a wider lumen and less risk for stricture formation [22]. While the data in this study did not show significance statistically, a slide-type anastomosis remains our preferred approach whenever possible. Our data also suggest that the location of the GEJ plays a significant role in outcomes for stricture resection. Patients in whom the GEJ was above the diaphragm prior to resection were more likely to experience a poor anastomotic outcome, particularly the need for esophageal replacement. Hence, efforts to avoid a hiatal hernia and to adequately address it if present (by bringing the GEJ back into the abdomen at the time of hiatal hernia repair/fundoplication), are critical for esophageal preservation. With respect to which procedure to perform first, our data suggest that anastomotic outcomes are similar with either strategy, yet one should allow at least a nine-week interval between procedures, as children with a shorter time interval fared worse. It is important to note that our data does not address the role of GERD in stricture formation. We believe that while it is possible that GERD may contribute to a refractory stricture, it is not the only factor, and with optimal acid suppression, the role of GERD in stricture formation is likely not as significant as it was once thought, yet data on this topic is controversial [34,35].

Limitations of this study include its retrospective nature, which relies on the accuracy and completeness of the medical record, including those patients that are referred to us with an incomplete medical record from their outside institution. Another significant limitation is a potential lack of generalizability, as our patient referral population is inherently complex, with a large proportion of children with a history of LGEA. Though our study does not explicitly examine a volume/outcome relationship, given the challenging nature of these refractory strictures and potential morbidity with surgical therapy, early referral to a high-volume center with expertise in advanced endoscopic therapy and reoperative esophageal surgery should be strongly considered.

5. Conclusion

Surgical therapy for refractory strictures has an inherent but low risk of anastomotic leak, need for repeat stricture resection, and/or eventual need for esophageal replacement. However, when performed at centers with experience in reoperative esophageal surgery, excellent rates of esophageal preservation with acceptable morbidity can be achieved. Surgical therapy should thus be considered in the setting of refractory esophageal strictures. Children with co-existent refractory anastomotic stricture and a hiatal hernia are at an increased risk of poor anastomotic outcomes. In these circumstances, hiatal hernia repair with fundoplication before or after surgical stricture management should be considered, ideally with at least a nine-week interval between the two procedures. In the setting of a non-refractory stricture, surgical stricturoplasty for symptomatic children at the time of another primary thoracic operation carries little risk and provides an excellent outcome.

Funding

The authors have no sources of financial support.

Conflicts of interest

None declare.

Acknowledgment

The authors express their gratitude to Dr. Robert Shamberger for his invaluable guidance and meticulous review of the manuscript, and to Dori Gallagher and all members of the Esophageal and Airway Treatment (EAT) Center at Boston Children's Hospital for their support and contributions.

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