Comparing Results of Three Treatments for Idiopathic Subglottic Stenosis

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ABSTRACT

Background: Idiopathic subglottic stenosis (iSGS) is a rare disease characterized by unexplained inflammation and localized fibrosis resulting in life-threatening blockage of the upper airway. It is a chronic and recurring disease whose hallmark symptom is breathlessness, which is the primary cause of morbidity and disability. However, the disease and its therapies also profoundly affect speaking. A variety of treatment algorithms have been advanced to manage iSGS but are generally categorized into (1) endoscopic dilation (ED); (2) endoscopic resection of the stenosis with adjuvant medical therapy (ERMT); and (3) open cricotracheal resection (CTR) of the affected subglottic segment with end-to-end anastomosis.

Objectives: Prospectively compare treatments in iSGS to determine how well each “works” and define the quality of life (QoL) trade-offs associated with each treatment approach.

Methods: Harnessing an engaged online community of affected patients, an international multi-institutional collaborative of airway surgeons, and an innovative digital clinical trial infrastructure, we conducted a 3-year, prospective multicenter cohort study that included newly diagnosed and untreated patients with iSGS as well as previously treated patients. We compared the effectiveness of the 3 most common treatments for iSGS. Effectiveness was defined as avoiding a recurrent surgical procedure. We investigated the primary treatment modality (1-3 in Background) in addition to the effect of any directed adjuvant medical therapies on need for recurrent surgical procedure. Secondary end points were the effect of treatment on breathing, swallowing, and voice. These were measured using validated patient-reported outcome measures (Clinical COPD Questionnaire [CCQ], Eating Assessment Tool [EAT-10], and Voice Handicap Index [VHI-10]). Adverse effects associated with each surgical approach were systematically collected.

Results: Patient characteristics and disease severity were similar across all 3 treatment arms. Overall, 185 of 810 patients (23%) required a subsequent procedure during the study period (mean follow-up, 1.43 years). In order, CTR had the lowest rate of recurrent procedure (1/86; 1%), followed by ERMT (15/121; 12%) and ED (169/603; 28%). These differences were all statistically significant and clinically important. Patient-reported breathing outcomes at 12 months (n = 444) were similar for ERMT and CTR, and worse in participants treated with ED (P = .001). Patient-reported voice outcomes at 12 months (n = 354) were significantly more impaired (higher scores) among those treated with CTR than either endoscopic treatment arm (P = .001). Patient-reported global QoL (n = 368) was significantly lower in the ED treatment arm (P = .015). Patient-perceived shared medical decision-making (n = 659) was consistently high and not significantly different between treatment arms (P = .56)

Conclusions: Of the 3 treatments evaluated, CTR had the lowest rate of recurrent procedure, but was also associated with the most adverse effects/events. ERMT was associated with better disease control than ED (based on lowered need for recurrent procedure) with minimal impact on voice function when compared with CTR.
**Limitations**: Given the observational study design, the inherent limitations of a nonrandomized assignment of treatment, and the impact of incomplete data, the effects observed should be considered association and require future confirmation based on comparative trials.
Idiopathic subglottic stenosis (iSGS) is a rare disease in which the trachea narrows for no known reason. Although uncommon (with an estimated incidence of 1:400 000 persons per year\(^1\)), it is life-threatening and its treatments potentially life-altering. Both the disease and its therapies profoundly affect patients’ ability to breathe,\(^2\) communicate,\(^3\) and swallow.\(^4\) Breathing difficulties (ie, dyspnea) are the hallmark symptom and the primary cause of disability.\(^5\) However, patients can also experience debilitating voice changes\(^3,6,7\) and swallowing problems\(^8\) (ie, dysphagia) due to the condition (see Figure 1) or its treatment.

**Figure 1. Diagram of normal airway (A), image of healthy airway (B), and iSGS patient with obstructive subglottic scar (C)**

Abbreviation: iSGS, idiopathic subglottic stenosis.
People with this chronic disease often require several surgeries per year. The various treatments that have been advanced to manage this condition are generally categorized as either (1) minimally invasive endoscopic approaches (accomplished with lasers, rigid instruments, or inflatable balloons) or (2) open surgery (ie, cricotracheal resection [CTR]). Patients may require repeated operations to keep their airway open, which increases the odds of treatment adverse effects and complications. All approaches have unique associated adverse effects, which can significantly affect the patient’s quality of life (QoL).

Because the disease is rare, prior to this project there was a lack of high-quality, reliable, and accessible data to inform individual patient treatment choices. Imperfect information on treatment outcomes was based on single-center case series and complicated patient decision-making as patients tried to balance survival, symptoms, and QoL considerations. Our prospective study was designed to fill this void, and leveraged our multi-institutional collaborative network of airway surgeons and pulmonologists, the North American Airway Collaborative (NoAAC). The NoAAC’s initial multicenter retrospective study of iSGS treatment outcomes (NoAAC RP-01) formed the background and impetus for our current PCORI-funded prospective study. This initial work identified the need for repeated operations as an important primary outcome measure. The published retrospective study centrally compiled clinical data from 10 NoAAC sites to characterize the iSGS patient population, describe modern management trends, and investigate treatment outcomes.

Specifically, this preliminary study demonstrated a striking similarity of affected individuals. Patients were almost exclusively female (98%; 95% CI, 96.1-99.6), white (95%, 95% CI, 92.2-98.8), and otherwise healthy (mean Charlson Comorbidity Index [CCI] 1.5; 95% CI, 1.44-1.69). The patients presented at a mean age of 50 years (95% CI, 48.8-51.1).

Yet, despite the similarity of patients, the NoAAC RP-01 study found significant variation in the standard of care for iSGS at expert centers. In total, 80.2% of iSGS patients were managed endoscopically, whereas 19.8% underwent open CTR. All centers used both approaches, but among expert centers there was substantial variability in use of endoscopic vs
open surgical approaches for these patients (Figure 2). The patient-specific selection criteria for the more invasive open surgical approaches were unclear.

Figure 2. Variation of therapeutic approach at each participating site

Overall, recurrences occurred at a mean 12.6 months after a procedure (95% CI, 11.4-13.8). Open approaches demonstrated a lower rate of disease recurrence (Figure 3A). However, within the category of minimally invasive endoscopic approaches there was an outlier in treatment effectiveness (Figure 3B). One approach (which was performed at 1 center and was technically quite distinct—endoscopic resection with adjuvant medical therapy [ERMT]) was associated with a much lower rate of disease recurrence. This preliminary study highlighted knowledge gaps and generated interest in unbiased prospective confirmation of the differential effectiveness of the ERMT approach used at one of our NoAAC sites compared with the more traditional endoscopic and open surgical approaches. Additionally, each approach has unique adverse effects, which can significantly affect the patient’s QoL. Before the present study, comparative data on trade-offs between approaches did not exist.
**Figure 3. Disease recurrence in open and endoscopic surgery**

(A) Kaplan-Meier curve depicting the percentage of patients avoiding disease recurrence after their initial procedure at 10 pooled centers. (B) When the subgroup of patients that underwent endoscopic surgery was stratified by center, there was 1 significant positive outlier (site 3; $P < .001$).

In contrast to the retrospective nature of the first NoAAC study, our prospective study directly compared the effectiveness of 3 contemporary treatments: (1) endoscopic dilation (ED) of the subglottic stenosis (accomplished with rigid instruments or inflatable balloons; (2) ERMT after surgery; and (3) open neck surgery (ie, CTR with end-to-end anastomosis) (Figure 4). Our study also assessed the QoL trade-offs associated with each approach, as these are key determinants in informed consent and patient medical decision-making. We recognized that to accomplish the study’s objectives it was critical that patients’ experience with the disease itself and its treatment be systematically characterized. This is imperative because patient and physician perspectives on health, surgical selection, and treatment outcomes are often discordant. To this end, across the cohort, the NoAAC collected longitudinal patient-reported outcome measures (PROMs). We also included an exploratory collection of patient-generated health data (PGHD; mobile peak expiratory flow [PEF] recording in a smartphone app).
Figure 4. Treatment approaches for iSGS

Abbreviation: iSGS, idiopathic subglottic stenosis.

1. Endoscopic Dilation

2. Endoscopic Resection

3. Open Anterior Neck Surgery

Clinical outcomes including need for and time to recurrent procedure (TTR) are important, but perhaps equally important are the health-related quality-of-life (HRQoL) concerns of patients with iSGS. Only a few small retrospective studies had considered these issues when we began the project in 2014.\(^5,13\) HRQoL considerations related to the disease and its treatment are critical determinants in management decision-making. Since project inception, several single-center retrospective studies have reinforced the impact of disease on QOL metrics in iSGS.\(^7,14-19\) For example, open CTR is a major surgery with immediate perioperative risks and has been associated with alterations in voice\(^3,6\) and swallowing.\(^4\) Yet despite the voice changes, the largest single-center series of patients undergoing CTR showed patient satisfaction surveys of 9.5/10.\(^20\) Open surgery appears to reduce the risk of disease recurrence, but the trade-offs associated with this approach, and patient perceptions of global HRQoL after CTR, are questions that required prospective study.

Paralleling the pace of treatment innovation seen in many common diseases in modern medicine, after the initiation of our trial a new treatment strategy for iSGS began to be explored by a subgroup of investigators. Office-based transcutaneous serial intralesional steroid
injection (SILSI) has been advocated by some physicians as a means to limit the process of recurrent subglottic scarring and reduce the need for repeated operations. Evidence of SILSI treatment efficacy is currently limited to small uncontrolled retrospective studies totaling 42 patients.\textsuperscript{21-23} However, the favorably perceived adverse effect profile (ie, tolerable adverse effects), the potential benefit to patient outcomes, and the facile translation of the treatment approach to clinical practice has led to rapid and significant provider uptake of the procedure. Although not a primary prespecified aim of our study, given the robust nature of the longitudinal data we collected, we were able to perform a secondary subgroup analysis of patients who underwent ED and then received SILSI. With this approach we could assess the ability of SILSI to reduce the rate of recurrent operative procedure in patients who have undergone ED. Additionally, using longitudinal PEF and PROMs, we could assess if SILSI modified objective measures of breathing and impacted patient-reported dyspnea.

Treatment outcomes from our retrospective multicenter study were helpful but did not represent a rigorous controlled approach to comparing the effectiveness of treatments in iSGS, and the study was not designed to systematically assess patient experience with the disease or its treatment(s). It did, however, identify a single center that was using a unique endoscopic surgical approach that showed better effectiveness than centers using more standard endoscopic approaches.\textsuperscript{24} These results were intriguing, but enthusiasm was tempered by the risk of selection bias and selective reporting that is common in retrospectives case-series studies. Therefore, we sought to independently validate these findings using a novel prospective study design that was structured for longer-term and systematic follow-up. Additionally, we believed longitudinal patient-centered data were of critical importance, as the patient survivorship experience is quite dynamic secondary to the recurring nature of iSGS. In this report we describe a 3-year prospective observational study that evaluated treatment outcomes in order to inform clinical and patient decision-making in iSGS. The proposed study was an international, multicenter prospective cohort study of iSGS patients that prospectively compared contemporary treatments of iSGS in order to determine how well each works and define the trade-offs associated with each treatment approach.
PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

Our patient-motivated and -centered investigation involved systematic iSGS patient and clinician stakeholder engagement, which was necessary to comprehensively understand and assess iSGS treatment options and their HRQoL trade-offs. Several core principles (delineated explicitly below) guided patient engagement in the design, execution, and results dissemination of our study.

- **Reciprocal relationships:** Patient input was involved at every level of study design. The 11-member NoAAC steering committee included a representative patient advocate, as well as co-principal investigator (PI) and online community support group director Catherine Anderson (herself an iSGS patient). Both positions had equal standing with other committee members.

- **Co-learning:** Formal planning sessions with active participation of all involved stakeholders enabled bidirectional dialogue between patients and clinicians and resulted in a more nuanced understanding of the patient experience. This helped define the critical questions that the disease experience has created for patients and led to the development of research methodology necessary to answer those questions.

- **Partnership:** Patients received compensation for their time and efforts during the study, which centrally also included direct funding for co-PI Catherine Anderson for her extensive time, energy, and contributions.

- **Trust, transparency, and honesty:** The fundamental ingredient to a multicenter study is trust between the participating centers, and between the study team and affected patients. This trust was evident in the relationships established in the formation of the NoAAC. The NoAAC study built on that foundation of open communication and honesty through its inclusion of patient-partner input in study planning, implementation, and results dissemination.

Building on the principles of reciprocation, co-learning, partnership, and trust, we engaged participants with a lived understanding of the disease at multiple levels throughout the study, an approach that we termed “discovery, data, and delivery” (Figure 5).
**Discovery—Planning the Study**

Clinicin stakeholders have long sought to answer the question of how best to treat iSGS. We began our project with the concept that dual processes were necessary to answer this question: a large-scale coordinated scientific collaboration, as well as a systematic approach to patient engagement. Both of these deficiencies were the focus of the present proposed study. Specifically, we seek to answer questions posed by patients (eg, which iSGS treatments work and what are their consequences, risk-benefit ratios, and trade-offs?). Answers to these fundamental questions would be transformative in improving patient experience through individualization of treatment and management decisions.

All member institutions and their associated patient partners were equal partners in planning the study. Dr. Gelbard (PI) from Vanderbilt University (the coordinating institution) was in frequent personal correspondence with each institution within the NoAAC at early meetings in the fall of 2014. These discussions informed study design, logistics, and eligibility requirements. Most important was direct input on the research questions and meaningful end points from patients with iSGS. A critical patient partner and co-investigator on this research proposal, Catherine Anderson, has performed groundbreaking work to engage the iSGS.

Abbreviation: iSGS, idiopathic subglottic stenosis.

*a*We called these phases *discovery, data, and delivery.*
community in which these questions are pervasive. She founded the Facebook iSGS support group and has used it as a platform to help understand patient needs and the patient perspective on therapy and subsequent adverse effects. The most pressing question voiced by iSGS patients in Catherine’s support groups (based on social media) is, “What can I expect with this disease?” This is followed closely by, “How do I get better?” Her work has illuminated how poorly patients typically understand which treatments they are choosing between.

Conversations with Catherine were central to study planning. The Facebook support group she founded and coordinated has served as a vehicle to understand the differential patient experience and given her a unique and nuanced view of iSGS from the patient perspective. A formal study-planning meeting was conducted in London, England, in August 2014 with Catherine in attendance. Her insights into the patient experience were an integral part of study design. She reported that iSGS patients consistently described alterations in their voice, and the frustrating nature of repeated operative interventions without a clear path to a definitive cure. She also reinforced the need for PROMs in order to more precisely understand the trade-offs inherent in each therapy (ie, ED, ERMT, and open CTR). This input was critical in formulating a prespecified study protocol.\textsuperscript{25}

Data—Conducting the Study

Recruitment

Prior to study initiation in July 2015, Catherine played a vital role in notifying her Facebook online community of the planned study. She also helped review participant materials for applicability, readability, and content. This led to remarkable alignment of patient and research goals, as well as comprehension across all stakeholders of the inclusion criteria and study procedures. In addition, Catherine’s engagement led to a large number of patients being ready and excited to consent and enroll quickly. This speed and momentum were critical to encouraging other participants to enroll. A high level of patient understanding of the study (obtained via the online support community) also served as a “push” to move the participating
centers to operationalize their workflows (ie, patients with iSGS would arrive at clinic appointments wanting to know if a center had begun enrolling patients yet).

Retention

Several formal and informal channels were available to patients who wished to provide input on study workflows. This ensured patient engagement and continual improvement of the protocol to optimize patient experience and information gleaned. Specifically, regional patient advocates reported on their experiences (as well as on that of patients within their region) directly to NoAAC steering committee members. Furthermore, our national study coordinating nurse (Cheryl Kinnard) became a vital advocate with whom patients could share questions or concerns relating to study workflows. Patients at local participating sites also met with the study leadership on a regular basis (we termed these sessions “engagement studios”). At these dedicated sessions, providers and patients interacted to share issues and concerns, as well as provide input on study design and execution and share their own personal experience with iSGS. This was an excellent forum for patients to describe their perceptions of their involvement in the study and confirm our belief (as investigators) that the patients were making meaningful contributions. All members of the study team (ie, consultants, regional patient advocates, and the NoAAC steering committee) and patient partners were also invited to attend an executive meeting once per year. The purpose of this yearly meeting was to report on study progress to date, identify any difficulties with implementing the intervention or outcome assessment, discuss strategies for communicating study results to the wider community and interested stakeholder groups, and review ideas for future iSGS investigations.

Delivery—Disseminating the Study Results

Team Meetings

Team meetings with members of the study team (eg, surgeons, regional patient advocates, and the NoAAC steering committee) and all interested patient partners focused on dissemination of overall study results. Further detailed discussions among the steering committee (with the input of Catherine Anderson) formalized unique strategies to disseminate
the study results to appropriate patient and scientific communities. Team composition was deliberately designed to include individual experts in and informants for each domain. After considering how the flow of information occurred in the online iSGS patient community, we will utilize infographics (both static images and short video summaries) of the results to allow rapid dissemination via social media. Results will also be published within academic journals and presented at national medical meetings to broaden the scope of dissemination to clinician providers who encounter iSGS. They will also be made publicly available through open access sources and directly through patient advocacy sources (eg, the Facebook online community and the National Organization for Rare Diseases).
METHODS

Study Overview

To provide high-quality data to inform individual patient decision-making in the rare disease iSGS, we designed a prospective international multicenter cohort study. Using an established protocol, we compared the effectiveness of the 3 most common surgical iSGS treatments for preventing recurrent airway stenosis and subsequent need for a repeat operation. In addition to the influence of treatment type on disease relapse, we compared the unique adverse effects associated with each surgical approach.

Study Design

The study followed a formalized prespecified protocol that used established criteria for the diagnosis of iSGS (Table 1). Once they had consented and enrolled, patients completed extensive baseline surveys (including sociodemographic, endocrinologic, and other medical history). They also completed traditional and nontraditional validated PROMs. A disease-specific medical history was obtained from the treating providers based on established common data elements. These included anatomic staging of disease (vocal fold mobility, % luminal compromise, distance of scar from vocal folds [mm], craniocaudal extent of scar [mm], and secondary airway lesions) and comorbid disease burden (using the CCI and select criteria from the European Laryngological Society consensus statement).
Table 1. Inclusion and Exclusion Criteria for Trial Enrollment

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<th>Inclusion Criteria</th>
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<tr>
<td>Greater than 18 years of age</td>
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<td>Obstructive airway lesion involving the subglottis</td>
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<table>
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<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Younger than 18 years of age</td>
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<tr>
<td>Patients without capacity to consent for themselves</td>
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<tr>
<td>History of significant laryngotracheal traumatic injury.</td>
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<td>History of endotracheal intubation or tracheotomy within 2 years of presentation.</td>
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<td>Major anterior neck surgery.</td>
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<td>History of neck irradiation.</td>
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<td>History of caustic or thermal injuries to the laryngotracheal complex.</td>
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<tr>
<td>History of either:</td>
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<tr>
<td>Clinically diagnosed vasculitis or</td>
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<td>Positive antinuclear cytoplasmic antibody (ANCA positive).</td>
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Both untreated and previously treated iSGS patients were enrolled. After establishing the date of the most recent standard-of-care operative treatment (their “index” procedure), we followed patients longitudinally to determine the need for further treatment, treatment-related complications, and symptom changes (ie, patient-reported outcomes [PROs] administered every 6 months). As a consequence of our decision to include previously treated patients, some patients’ index procedure preceded trial enrollment. Patients were also offered the ability to self-monitor their disease status via daily recording of PEF using a portable device and a smartphone application (this was not required for trial participation). Every 3 months patients received a “health status check.” This was an automatic query from the electronic data capture (EDC) system assessing their adjuvant medication use, inquiring if they had required a repeat procedure for their disease (recording both operative and clinic-based events), as well as investigating the presence of (prespecified) treatment-related complications (Figure 6). An affirmative response generated an automatic notification to the national trial coordinator, and the timing of the recurrent procedure was then verified via the clinical operative note. Negative responses were automatically recorded.
Both untreated and previously treated patients with idiopathic subglottic stenosis were included. Patients were also offered the option to self-monitor disease status via peak expiratory flow using a portable device and a smartphone application (although this was not required for trial participation). Every 3 months patients received an automatic query from the electronic data capture system assessing their adjuvant medication use, inquiring if they had required a repeat procedure for their disease (recording both operative and clinic-based events), and investigating the presence of (prespecified) treatment-related complications.

Study Setting

Study participants were recruited via several mechanisms. Direct recruitment was driven by participating NoAAC clinician providers. The NoAAC consists of 40 participating sites that contributed patients, including sites across all regions of the United States as well as those in Australia, France, Iceland, Norway, and the United Kingdom. All NoAAC sites are academic centers that function as tertiary referral centers for iSGS and thus have significant experience treating this rare condition. Nearly all patients with iSGS are ultimately referred for care and tend to cluster at such high-volume centers, which allowed us to create a representative patient cohort. Direct recruitment was also accomplished via partnered social media-based advocacy groups on Facebook and Yahoo.
Participants

All patients diagnosed with iSGS who presented to participating centers and met established diagnostic criteria were candidates for enrollment. Inclusion criteria were adults (>18 years of age) with no clinical or laboratory evidence of rheumatologic, immunologic, or infectious disease; no history of tracheostomy, trauma, or intubation within 2 years preceding symptoms; and no history of laryngeal surgery or tracheal surgery prior to symptom onset. Patients were excluded from the final analysis if they did not complete baseline sociodemographic surveys or if documentation of their index procedure was unobtainable. All candidate patients were counseled extensively about the objectives as well as risks and benefits of involvement in the study, and signed informed consent to be enrolled. Recruitment of patients from participating sites spanning a wide geographic area ensured that we captured a geographically diverse and representative racial/ethnic and socioeconomic iSGS cohort.

Interventions and Comparators

Patients with iSGS present to the health care system with symptoms of airway obstruction and respiratory distress. They require interventions to survive. Thus, we deemed a placebo or “no intervention” control clinically unethical and inappropriate. Our previous NoAAC study identified 3 basic treatment approaches used for iSGS. The 3 interventions compared in the current study include (1) ED, (2) endoscopic resection of the airway scar with subsequent long-term medical therapy (ERMT), and (3) CTR (Figure 2).

In ED the patient undergoes transoral exposure of the tracheal scar with dilation of the scar by either rigid instruments or controlled radial expansion device (ie, balloon dilation). Variations on this approach exist. Some surgeons simply dilate, whereas others may create radial relaxing incisions with a CO₂ laser prior to dilation. Adjuvant treatments during surgery are also used by some surgeons, which may include injecting intralesional steroids and applying mitomycin C to the scarred tracheal segment. Additionally, some surgeons utilize medical therapies postoperatively in an attempt to limit disease recurrence (ie, inhaled corticosteroids, proton pump inhibitors [PPIs]).
Somewhat similarly, in ERMT the patient undergoes transoral exposure of the tracheal scar; however, a CO\textsubscript{2} laser is then used to resect a significant portion of the scar, followed by long-term adjuvant medical therapy (anti-gastroesophageal reflux, antibacterial, and inhaled corticosteroid). The technical details of ERMT have been described previously.\textsuperscript{1} Specifically, the procedure begins with general mask anesthesia, with detailed attention to protecting the patient’s eyes and teeth. After establishing an effective mask airway, muscle relaxant is administered, and the larynx is exposed with the Kleinsasser C laryngoscope; if not accessible, then the Dedo laryngoscope is used (Figure 7). Intermittent endotracheal anesthesia with a cuffless endotracheal tube is used to maintain O\textsubscript{2} saturations and CO\textsubscript{2} levels. The laryngoscope is positioned to provide gentle lateral displacement of the arytenoid cartilages. Kenalog is then injected peripherally into the scar. A CO\textsubscript{2} laser is attached to a micromanipulator. The CO\textsubscript{2} laser is then used to resect scar tissue with the vaporization extended toward the conus elasticus/perichondrium, preserving small longitudinally oriented bridges of mucosa and underlying scar. The laser is delivered to the areas of scar by manually tilting the larynx or bed position to deliver the laser in a tangential fashion. The locations of the bridges vary but are typically at 2, 6, and 9 o’clock positions (Figure 8). Once the scar is vaporized, mitomycin 0.5 mg/mL is placed on pledgets and applied to the sites of vaporized tissue (typically for 2.5 minutes) with a saline rinse following pledget removal. Once completed, the patient is mask ventilated until spontaneously breathing and then transferred to the recovery room. Typically, one proceeds from a 4.0 cuffless endotracheal tube to a 5.0 cuffed tube to provide ventilation between interventions (alternatively, jet ventilation can be used throughout the procedure). Postoperatively, anti-gastroesophageal reflux medications (omeprazole 40 mg daily), inhaled corticosteroids (fluticasone inhaler 220 mcg twice a day), and trimethoprim/sulfamethoxazole ([TMP/SMX] 160/800 mg once daily) are initiated and maintained until the 12-month follow-up.
Figure 7. ERMT surgical technique

Abbreviation: ERMT, endoscopic resection with adjuvant medical therapy.

Figure 8. Endoscopic laryngeal exposure and manipulation, followed by laser mucosal resection with maintenance of mucosal bridges (6 o’clock depicted)

Surgical technique for open CTR has been detailed extensively in the literature. There are technical nuances unique to each surgeon (some of which may impact recurrence rates or voice outcomes). However, generally, CTR involves approaching the diseased subglottis/trachea via an external incision. The scarred segment of trachea is dissected, isolated, and then resected. The ends of the resection are then sewn back together or anastomosed in an airtight fashion.
Study Outcomes

We conducted interviews with participating providers and iSGS patients to reach consensus on the primary clinical outcomes to be compared across treatment modalities. Both groups were urged to select outcomes based on which data would be most critical and useful to patients and providers in decision-making. The critical clinical treatment outcome identified was time to repeat the operative procedure; thus, the primary outcome was the measured need for and timing of a recurrent procedure. Both expert consensus and published data demonstrated that this is a suitable surrogate measure for recurrence because patient-reported symptoms of respiratory distress correlated with additional treatment at these study sites.\textsuperscript{14}

The study’s primary end point was TTR, which was compared between the 3 treatment arms: (1) open CTR, (2) ED, and (3) ERMT.

Time Frame for the Study

Our preliminary study showed that recurrence occurred a median 8 months (95% CI, 7.2-11.3 months) following initial treatment. The timing of recurrence appeared to vary among the 3 modalities being prospectively compared in the proposed study.\textsuperscript{24} These results demonstrated the feasibility of capturing the critical treatment outcomes within the 3-year time frame of this study. Following the index procedure, patients were followed with serial status checks every 3 months. Every 6 months they completed validated PROMs related to voice, breathing, swallowing, and global QoL.

Data Collection and Sources

Data Sources

Multiple types of data were collected (Figure 9). These consisted of clinical data (eg, laboratory results, procedure notes, etc); PGHD (eg, surveys and PROMS); and safety data (eg, unanticipated adverse effects). Data were collected directly from patients via a digital interface or abstracted into the case report forms (CRFs) implemented in a custom EDC system. All data collection projects relied on a thorough, study-specific data dictionary. This was defined well in advance of our project launch by all members of the research team in an iterative, self-
documenting process. This iterative development and testing process resulted in a well-planned and individualized data collection strategy for our study.

**Figure 9. Data types collected during the study**

![Diagram showing data types collected during the study]

These consisted of clinical data (ie, laboratory results, procedure notes, and safety data) and patient-generated health data (surveys and patient-reported outcome measures). Data were collected directly from patients via a digital interface or abstracted into the case report forms implemented in a custom electronic data capture system.

**Baseline.** Baseline data included demographics, medical and surgical histories, physical examination findings, and relevant diagnostics obtained within the standard of care for each site (eg, computed tomography [CT] scan findings, gastrointestinal study values, and laboratory values). Relevant to this study and this disease process were reproductive, rheumatologic, and immunologic history.

**Procedure.** Details of the initial index surgical procedure were captured (eg, procedure type and disease severity: site and degree of narrowing within the trachea). This information, along with procedure-related complications, was abstracted from the operative note and clinical record into the EDC system.

**Recurrence.** At patient recurrence, information regarding the date of recurrent operative procedure was captured as for the initial procedure.
Patient-Generated Health Data

**PROMs.** It is critical that patients directly share their disease experience, so that treating physicians understand what it like to live with the disease. To facilitate this, we queried patients using established and valid PROMs focused on the domains that patients identified as most problematic for them in engagement studios. These related to voice (Voice Handicap Index [VHI-10][33]), swallowing (Eating Assessment Tool [EAT-10][34]), breathing (Clinical COPD Questionnaire [CCQ][13]), and global QoL (12-Item Short Form Survey [SF-12][35]). Additionally, 4 “nontraditional” PROMs that focused on social support,[36] participatory decision-making style,[37] disease anxiety and burden,[38] and fear of disease recurrence[39] were administered upon study enrollment (Table 2). “Traditional” PROMs were administered at routine intervals postprocedure (eg, every 6 months). For interval PROM completion, patients with internet access and email connectivity used the web-based data capture instrument; we sent automated email reminders to patients at each PRO interval. For patients without internet/email access (4% of total patients in our study), completion of PROMs occurred via paper forms; the research staff then transferred PRO data from paper to the EDC system.
### Table 2. PRO Tools Used in This Study

<table>
<thead>
<tr>
<th>PRO Instrument</th>
<th>Abbreviation</th>
<th>PMID</th>
<th>Functional Domain Assessed</th>
<th>MCID</th>
<th>PMID (for MCID)</th>
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<tr>
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<td></td>
<td></td>
<td></td>
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<td>Clinical Chronic Obstructive Pulmonary Disease Questionnaire</td>
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<td>Breathing</td>
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<td>VHI-10</td>
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<td>Speaking</td>
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<td>29219184</td>
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<td>Eating Assessment Tool</td>
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<td>19140539</td>
<td>Swallowing</td>
<td>unk</td>
<td></td>
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<td>12-Item Short Form Health Survey</td>
<td>SF-12</td>
<td>9817135</td>
<td>Global Physical Health</td>
<td>3.29</td>
<td>28658040</td>
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<td></td>
<td></td>
<td></td>
<td>Global Mental Health</td>
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<td>28658040</td>
</tr>
<tr>
<td><strong>Non-Traditional</strong></td>
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<tr>
<td>Medical Outcomes Study Social Support Survey</td>
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<td>Shared Decision Making Questionnaire</td>
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<td>19879711</td>
<td>Medical decision-making</td>
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<td>Brief Illness Perception Questionnaire</td>
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<td>Disease anxiety and burden</td>
<td>unk</td>
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<tr>
<td>Fear of Progression Questionnaire</td>
<td>FoP-Q</td>
<td>22021099</td>
<td>Fear of disease recurrence</td>
<td>unk</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MCID, minimal clinically important difference; PMID; PubMed identifier for the manuscript that established the MCID for a given instrument (when available); PRO, patient-reported outcome.

Note: MCIDs are the smallest differences in scores in the domain of interest that patients perceive as beneficial and that would mandate, in the absence of adverse effects and excessive cost, a change in the patient’s management.
**Patient-recorded physiologic data from mechanical devices.** An innovative method to learn directly from patients about their lived experience with iSGS was the collection of PGHD using wearable devices or smartphone apps. We captured patient self-reported PEF measurements longitudinally over time for a subset of patients (obtained with a handheld asthma peak-flow monitoring device supplied by the study and distributed following the index procedure). Participation and use of PEF monitoring was not mandated; it was completely voluntary and patient-driven.

**Data handling and record-keeping.** Our investigator team was responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to adequate source documentation, EDC data are housed on servers at a local data center at Vanderbilt, and all web-based information transmission is encrypted.

**Data management responsibilities.** All source documents and laboratory reports were reviewed by the study team and data entry staff, who ensured their accuracy and completeness. Unanticipated problems or ambiguous data were reviewed by the PI or designee and were followed up via direct communication with the patient or referring provider to resolve the discrepancy. When no data were available, we noted this in the EDC system.

**Data entry, collection, and quality control.** Data collection and management for the proposed project was performed via a custom web-based EDC system. Built on established HIPPA-compliant technology actively in use for more than 10 years, the system is structured on the Ruby on Rails (RoR) platform. RoR is an open-source web application development framework for creating rich internet applications that model complex data and reinforce data integrity through custom validations. The RoR framework for web-based data entry was linked to a MySQL database for the data storage component. All data entry interfaces used dropdown menus, radio buttons/checkboxes, and other structured variable formats whenever feasible, to enforce consistency of variable values in data entry. Also, to support data quality control, extensive automated validations checked records for internal consistency, conformity to any prespecified data ranges, and compliance with any known intervariable relationships. Support
for longitudinal data was provided through the use of a relational database architecture that models one-to-many relationships.

In addition to the use of structured variables and validations to prevent data entry errors, we used other mechanisms for data quality control.

- **Testing:** The EDC system was tested extensively in both the development/staging and production environments. Automated testing was performed via scripted tests, to verify that observed behavior of the system conforms to expected behavior. Manual testing of all system features was employed via the user interface and performed by dedicated testing personnel to identify bugs, suboptimal feature performance, and other issues that could negatively impact the user experience and/or integrity of the data collected. Testing results were documented via a standard operating procedure, in which bugs or other comments are posted to a web-based electronic board; each bug is then tracked on this board through the process of debugging, retesting in the staging environment, deployment to production, and final testing in the production environment; thus, a permanent audit trail of testing was maintained.

- **Access controls:** Access to the EDC system was restricted to authorized personnel. Data entry personnel and other users were provided secure access to the web-based application via standard internet technologies (ie, HTTPS), with tiered access permissions appropriate to their study role; such access was granted only when the following criteria were met: (1) request for access was authorized by a study PI or other designated key study personnel and accompanied by a designation of the user’s role, to ensure appropriate level of access; and (2) the user completed training on system use, which could include a live training provided by our group and/or documented completion of a prerecorded video training. This training helped ensure that all users understood the system and the data elements, to minimize potential for data entry errors. All requests for user access, with documentation of fulfillment of the above criteria, were recorded in the permanent system documentation.

- **User-facing validation feature:** In addition to automated data validations run upon submission of data, a user-facing validation feature was implemented to allow for electronic capture of the completion of manual data review for data monitoring purposes. This feature provided a “validate” button for each patient record, on a perform basis; a designated user with appropriate role permissions used this button to indicate that a form had passed manual review of data entry; the form was then date/time-stamped with the date and time of validation review. If a form was edited
postvalidation, the time stamp of previous validation was retained, but the record returned to an unvalidated state. An accompanying validation report could be generated from the system user interface to provide for rapid identification of which forms had completed validation, and which required validation or revalidation; links within the reports took the user directly to the annotated forms.

- **Review of datasets / interim analysis:** Datasets extracted from our EDC systems were reviewed at the prespecified interim analysis 1.5 years into the project. Results were reviewed, with evaluation of data distributions, for any outliers or unexpected values. Interim analysis reporting in December 2016 showed normal data distributions without outlier variables and without identification of other data integrity issues. Intake patient-facing sociodemographic surveys (88%) and PROMs (75%) also showed high levels of completion. We did observe that several patients completed the intake surveys and PROMs following their index procedure. Clinicians provided less information (i.e., anatomic staging of disease and comorbid disease; 65%). At the same time data review showed a high rate of completion of 3-month status checks (88%). Based on these results we worked aggressively to encourage intake data completion before the index procedure, as well as to obtain provider-specific history and follow-up on all status check reports.

**Analytical and Statistical Approaches**

This project tested 2 hypotheses: (1) There is variation in recurrence rates between different surgical approaches for iSGS, and (2) the different surgical approaches are associated with unique trade-offs in terms of voice, swallowing, breathing, and global QoL.

**Sample Size Considerations**

The primary end point of this trial was TTR. The sample size estimation was completed using the 95% CI method. Initially with a proposed sample size of 300 (180 ED, 60 CTR, and 60 ERMT), the margin of error of the 95% CI for the TTR function would be less than 0.25 SE for the ERMT and CTR arms and less than 0.15 SE for the ED arm. Over the course of the trial our methods for recruitment were surprisingly successful and ultimately, we achieved numbers that significantly surpassed these estimates.
Primary end point. The primary end point of this study was TTR between 3 possible treatment arms: (1) CTR, (2) ED, and (3) ERMT. Recurrence was defined as repeat procedure in the operating room or death due to airway obstruction.

Data analysis plan for the primary end point. Demographic information was tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, are presented in the Results section. For the primary objective analysis (ie, estimating the TTR with 95% CI), the TTR was estimated using the Kaplan-Meier method with the 95% CI. The Rothman CI (CI based on Greenwood variance) is reported. The log-rank test was used to compare the equality of survival curves. The generalized Wilcoxon and log-likelihood tests were also examined, as these tests weight the survival function differently from the log-rank test, which gives more weight to later occurring events. The Cox proportional hazards model was applied to investigate potential prognostic factors, such as age on the TTR data.

Secondary end points. The QoL trade-offs with each treatment approach were systematically assessed using validated traditional and nontraditional PROMs. Four traditional PROMs measure disability related to voice (VHI-10\textsuperscript{33}), swallowing (EAT-10\textsuperscript{34}), breathing (CCQ\textsuperscript{13}), and global QoL (SF-12\textsuperscript{35}). At trial enrollment, we also administered 4 nontraditional PROMs focused on social support,\textsuperscript{36} participatory decision-making style,\textsuperscript{37} disease anxiety and burden,\textsuperscript{38} and fear of disease recurrence\textsuperscript{39}. Responses to PROMs tend to change in chronic disease states because severity of the measured concept is time-variable. This is particularly true for iSGS patients whose symptoms markedly improve after treatment and revert and worsen before subsequent treatments. To better understand the breadth of patient experience with this condition, we employed PROMs at a priori determined intervals after initial treatment (ie, at 6-month intervals postintervention), to obtain an accurate portrait of the survivorship experience after different therapeutic modalities.

Data analysis plan for secondary end points. The secondary objective of this study was to evaluate the QoL scores (ie, SF-12, CCQ, EAT-10, and VHI-10) between 3 treatment
arms. The 95% CI method based on the normal distribution was applied to estimate the QoL scores between the 3 arms. A mixed-effects model was used to examine the correlation between PROM scores between treatment arms.

**Statistical strategy for addressing missing data.** Despite the enthusiasm of the iSGS population for this study, we entertained the possibility that bias could be introduced due to missing data. To account for this, we used 2 approaches in cases where participants are alive but are missing data. These approaches are based on the assumption of missingness at random: the multiple imputation model based on the Markov chain Monte Carlo method\(^{41}\) and a hierarchical hot-deck imputation approach.\(^{42,43}\) Sensitivity analyses comparing the 2 methods were performed to assess the validity of the 2 approaches. Inferences were based on the combined parameter estimates and appropriate covariance structure. Our group has used these methods successfully in previous studies.\(^{44,45}\)

**Strategy to address heterogeneity of treatment effect.** Subgroup analysis is the most commonly used analytic approach for examining heterogeneity of treatment effect,\(^{46}\) and we used an exploratory variant of this analysis in our approach. We used viSNE, a visualization technique based on t-Distributed Stochastic Neighbor Embedding algorithm,\(^{47}\) which allowed unbiased interrogation of all the measured covariates to detect subgroups. The following standard variables were measured: (1) demographic variables (eg, age); (2) pathophysiologic variables (eg, timing after recurrence and disease grade); (3) comorbidities (eg, presence of diabetes); and (4) concomitant exposures (eg, hormone replacement therapy and PPIs). To improve risk adjustment and increase individualization of the results, we added nontraditional characteristics that affect patient decision-making (eg, social support, patient decision-making style, disease-related anxiety, and baseline QoL) to the model.

**Strategy to address confounding by selection bias.** Our rare disease population is uniquely homogeneous (ie, nearly all patients are otherwise healthy, adult white women), and the surgeons providing treatment are not typically choosing between the 3 options under study; the treatment a patient receives at one of the centers within the NoAAC is likely
impacted by the surgeon’s views of differential treatment efficacy between approaches. Those caveats aside, observational studies (like ours) that lack random assignment of subjects into treatment groups must address selection bias to properly estimate the treatment effect. This becomes an interesting issue in rare disease, in which little solid information is available to delineate what important covariates are associated with treatment response.

To identify important covariates, we employed content expert opinion, extrapolated from the limited disease natural history we had established in our prior study, and incorporated clinical proxies for the inflammatory mediators observed in ongoing basic science investigations into iSGS. All measurable covariates and confounders were considered for planned propensity score modeling. Incorporation into the multivariate model was determined a priori based on a covariate’s hypothesized potential to confound or modify the association between treatment and time to recurrence, and covariates included the following: sociodemographics (age, sex, race, socioeconomic status, and marital status); health (CCI score and body mass index); endocrinologic history (number of pregnancies, onset of menopause, and use of hormone replacement therapy); and disease severity (number of prior procedures, duration of disease, and anatomic staging of disease). Provider-specific covariates included the type of subspecialty training program. In addition, the model included interaction terms for the associations of age with endocrinologic history and CCI score based on statistical evidence of effect modification and theoretical plausibility.

Our rare disease patient group is unique, with consistent sociodemographics among affected patients (likely as a consequence of a conserved genetic biology driving a singular disease). Despite the relatively balanced covariates between the 3 treatment arms, we also used propensity scoring to further address the impact of observed confounders. We then directly applied regression models using the measured covariates (Cox proportional hazards, mixed-effects models, and linear modes) to address observed confounding. Since time to recurrence was a continuous variable and there was only 1 recurrence in the CTR arm, the effect of treatment was estimated as the difference between the mean time for patients
receiving ED vs ERMT. Multivariate regression was used to reduce bias caused by any residual differences in observed baseline covariates between arms.

**Changes to Study Protocol**

We have none to report.
RESULTS

Participant Flow Through the Study

Potential participants (N = 1336) were screened from provider clinical practices; we also screened interested individuals recruited via social media outlets. Twenty-one were deemed ineligible (due to vasculitis, prolonged intubation, inability to speak English, or cognitive impairment limiting the ability to provide informed consent). Of the 1315 eligible participants, 50 declined to participate for various reasons and 209 did not respond to recruitment inquires.

In all, a total of 1056 patients consented to the study. Of these, 35 formally withdrew shortly after providing consent. A total of 211 patients consented but were unable to produce treatment data (relating to their index procedure) and were excluded from analysis. The 211 excluded patients did not differ from those included based on sociodemographic characteristics or disease severity. This left 810 patients for analysis: 121 in ERMT, 603 in ED, and 86 in open CTR. Participant flow including ineligibility, reasons for declining to participate, and reasons for withdrawal are noted in detail in the Appendix. Participant flow is also depicted in Figure 10.
In total, 1336 participants were screened, 1315 were eligible, 1056 consented, 35 formally withdrew, and 211 consented but were unable to produce treatment data (relating to their index procedure) and were excluded from analysis. A total of 810 patients were included for analysis (endoscopic resection with adjuvant medical therapy = 121, endoscopic dilation = 603, cricotracheal resection = 86).
Results From Aim 1: Building a Rare Disease Cohort

Patient recruitment and retention were major strengths of this study. We combined a broad network of providers (the NoAAC) with an engaged patient community (Living with iSGS, Facebook) to create a geographically diverse and ethnically representative iSGS disease cohort. As depicted in Figure 11 (and consistent with our prior report\textsuperscript{24}), the iSGS population shows similar demographics. Patients are a mean 50 years of age (interquartile range [IQR], 43-58), 97% white, and 98% female. They are otherwise healthy, with a CCI score of 0 (IQR, 0-0), and 40% of patients are college graduates. Anatomically, they presented with a subglottic scar arising 11 mm below the vocal cords (IQR, 8-17), with a length of 15 mm (IQR, 10-20), and a mean of 60% airway obstruction (IQR, 50-75).

Figure 11. iSGS population\textsuperscript{a}

Abbreviation: SES, socioeconomic status.
\textsuperscript{a}In the 810-patient cohort the median age was 50 years old (IQR,43-58), 97% white, and 98% female. Patients were otherwise healthy, with a median non-age-adjusted Charlson Comorbidity Index score of 0 (IQR, 0-0). Forty percent were college graduates, with 24% having completed graduate school. Patient education level was significantly higher than that of the median age-adjusted US female population ($P < .005$).
Dual methods of recruitment, both via the participating NoAAC institutions (centers of excellence [COE]) and the iSGS Facebook online community (OC), resulted in a patient cohort that was also geographically representative (Figure 12).

Figure 12A depicts the residence of enrolled patients (with labels distinguishing both COE and OC). The distribution of recruited patients was representative, as qualitative analysis demonstrates that it paralleled the population distribution of the United States (depicted in the heat map, Figure 12B). Preliminary qualitative analysis shows that recruitment from the OC played a large role in enrolling patients from lower-density population centers in the study.

Table 3 demonstrates the sociodemographics (sex, race, socioeconomic status, and marital status); health (CCI score); endocrinologic history (number of pregnancies, menopause status, and use of hormone replacement therapy); and anatomic disease characteristics (degree of luminal obstruction, scar length, and distance from the glottis) of patients. Measured covariates distinguishing treatment arms were age (ERMT patients were slightly older than patients in the other 2 treatment arms) and ethnicity (ERMT patients were exclusively white). The ERMT patients also had a greater degree of luminal obstruction when presenting for the treatment represented in the study results. The ED patients had shorter subglottic scars that occurred farther below the vocal cords. ERMT patients had a longer disease duration on enrollment, and CTR patients had a greater number of procedures prior to their index procedure. A greater percentage of ED patients had never had a full-term pregnancy. The median duration of patient follow-up (date of last follow-up to date of index procedure) in ERMT and ED patients was shorter than in CTR patients.
Figure 12. Geographic location of iSGS patient residence in the United States

Abbreviation: iSGS, idiopathic subglottic stenosis.

*Patients recruited from COE in blue dots, those recruited from OC in red. (A) Adjacent graph depicts geographic distribution of the US population (via 2016 census bureau data). Higher population density is shown in red, lowest density in white. (B). Qualitative comparison via analysis of overlaid images. (C) Overlay shows broad diversity in regions of enrolled participants.
Table 3. iSGS Patient Demographics, Disease Severity, and Health Status

<table>
<thead>
<tr>
<th>iSGS Patient Characteristics</th>
<th>ED (n=603)</th>
<th>ERMT (n=121)</th>
<th>CTR (n=86)</th>
<th>Total (n=810)</th>
<th>Significance (p)</th>
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<td><strong>Demographics</strong></td>
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<td>Race (% Caucasian)</td>
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<td><strong>Disease Morphology</strong></td>
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<td>% Stenosis (Median %, IQR)</td>
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<td>75 (64 - 80)</td>
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<tr>
<td>Stenosis Length (Median mm, IQR)</td>
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<td>15 (10 - 20)</td>
<td>17 (15 - 20)</td>
<td>15 (10 - 20)</td>
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<tr>
<td>Distance below glottis (Median mm, IQR)</td>
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<td>10 (5 - 15)</td>
<td>10 (5 - 15)</td>
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<td>Disease Duration (Median Years, IQR)</td>
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<td>8.6 (3.4 - 13.0)</td>
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<td>Total Number of Surgical Procedures</td>
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<td>GERD (% positive)</td>
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<td><strong>Followup Duration</strong></td>
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<tr>
<td>Years of Follow up (Median Years, IQR)</td>
<td>1.3 (0.39 - 2.16)</td>
<td>1.5 (0.2 - 3.6)</td>
<td>4.3 (1.7 - 6.1)</td>
<td>1.4 (0.4 - 2.5)</td>
<td>0.0131</td>
</tr>
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</table>

Abbreviations: CTR, cricotracheal resection; ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; GERD, gastrointestinal reflux disease; IQR, interquartile range; iSGS, idiopathic subglottic stenosis.

*Median (lower quartile to upper quartile) for continuous variables. Covariates distinguishing treatment arms were age (ERMT patients were slightly older than patients in the other 2 treatment arms) and ethnicity (ERMT patients were exclusively white). ERMT patients also had a greater degree of luminal obstruction. ED patients had shorter subglottic scars that occurred farther below the vocal cords. ERMT patients had a longer disease duration upon enrollment, and CTR patients had a greater number of procedures prior to their index procedure. A greater percentage of ED patients had never had a full-term pregnancy. The median duration of patient follow-up was longer in CTR patients. Tests used were as follows: 1, Kruskal-Wallis test; 2, Pearson test.*
Results From Aim 2: How Well Do the 3 Treatments Work?

The 3 treatment arms show differential effectiveness at avoiding a repeat surgical procedure over the follow-up period (median, 1.4 years): CTR had the lowest number of recurrences (1/86: 1%), followed by ERMT (15/121: 12%) and ED (169/603: 28%). Kaplan-Meier analysis of the 3 treatment arms depicts differential effectiveness of the treatment modalities (Figure 13). Log-rank comparisons show CTR vs ERMT ($P = .0019$), CTR vs ED ($P < .0001$), and ERMT vs ED ($P < .0001$). All patients were censored after a recurrent procedure. One patient in the ERMT arm died, while 2 patients in the ED arm died and were censored. Death occurred secondary to airway obstruction more than 30 days after the surgical procedure. Sensitivity analysis performed using a time interval derived from the index procedure to the last reported status check (compared with a time interval derived from the index procedure to the study end date) showed identical results.

We took several independent approaches to address the impact of multiple covariates on patient outcome after treatment. Because there was only 1 recurrent procedure among those receiving CTR, we did not compare adjusted recurrent procedure rates between CTR and the other 2 arms. Using multiple techniques, we did compare the effect of treatment for patients in the ED arm vs the ERMT arm. First, we used Cox regression modeling to estimate the effect of the prespecified covariates on the probability of a recurrent procedure between ED and ERMT; this showed a hazard ratio of 3.0355 (IQR, 1.78-5.17). When using the Cox model and adjusting for prespecified known covariates, we found that the hazard ratio between ED and ERMT remained elevated at 2.75 (IQR, 1.38-5.44). The results were similar when employing the Cox proportional hazards model with multiple imputation for missing values: ED vs ERMT; hazard ratio, 2.97 (IQR, 1.71-5.16) (Table 4).
Figure 13. Kaplan-Meier analysis of disease recurrence between the 3 treatment arms

Abbreviations: CTR, cricotracheal resection; ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy.

CTR had a significantly lower probability of recurrence at 3000 days than ERMT ($P = .0003$) or ED ($P < .0001$). ERMT also had a significantly lower probability of recurrence than ED ($P < .0001$).
Table 4. Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Hazard Ratio for Recurrence: Unadjusted Cox Proportional Hazards Model</th>
<th>Hazard Ratio</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Type - ED : ERMT</td>
<td>3.0355</td>
<td>1.7804</td>
<td>5.1751</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio for Recurrence: Adjusted Cox Proportional Hazards Model (without multiple imputation)</th>
<th>Hazard Ratio</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Type - ED : ERMT</td>
<td>2.7499</td>
<td>1.3882</td>
<td>5.4473</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio for Recurrence: Adjusted Cox Proportional Hazards Model (with multiple imputation)</th>
<th>Hazard Ratio</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Type - ED : ERMT</td>
<td>2.9678</td>
<td>1.7072</td>
<td>5.1592</td>
</tr>
</tbody>
</table>

Abbreviations: ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy.

*Unadjusted for covariates, adjusted, and adjusted with multiple Imputation.
We then employed a novel approach to search for confounding variables associated with need for recurrent procedure using variables captured but not designated for modeling a priori. viSNE is a technique used extensively in molecular biology to allow visualization of multidimensional datasets and rapidly assess for clustering of outcomes (or phenotypes). Within our dataset, it allowed us an unbiased interrogation of all the patient, disease, and provider covariates captured in order to inspect for subgroups of treatment response that might be associated with a confounding covariate (without requiring a priori selection of important variables for our model). In viSNE, each patient is represented as a point in high-dimensional space. Each dimension is 1 parameter (eg, demographic, physiologic, or PROM scores). An optimization algorithm searches for a projection of the points from the high-dimensional space into 2 or 3 dimensions such that pairwise distances between the points are best conserved between the high- and low-dimensional space. The resulting low-dimensional projection, termed a viSNE map, is visualized as a scatter plot, where a patient’s location in the plot represents information from all of the original dimensions.

As shown in Figure 14, viSNE showed no clustering of recurrence when incorporating all measured covariates. This effect was tested both with and without hot-deck imputation methods to account for incomplete data. viSNE results (showing no covariates associated with treatment response) were confirmed with the Kaplan-Meier curves of treatment outcome stratified by patient age (Figure 15). Log-rank testing confirmed our viSNE results showing no association ($P = .99$). The results of this rigorous and unbiased approach to detecting measured covariates associated with treatment response demonstrated that none of the measured covariates appeared to impact treatment response.
Figure 14. viSNE showed no clustering of treatment response when incorporating all measured covariates. 

*This effect was tested with and without hot-deck imputation methods to account for incomplete data.
Figure 15. Validation of viSNE findings showing no clustering of treatment response by any measured covariate

We used Kaplan-Meier analysis to validate the viSNE findings. Log-rank testing showed no association between age and treatment response ($P = .4$).

We used Kaplan-Meier analysis to validate the viSNE findings. Log-rank testing showed no association between age and treatment response ($P = .4$).
We also used propensity score matching (PSM) to further address the impact of observed confounders. iSGS is a rare disease with a limited evidence base. There are no variables that have been rigorously associated with disease recurrence or treatment failure. Nor are there comprehensive variables that are consistently used to allocate patients to a specific treatment. However, we created propensity score-matched cohorts of ED and ERMT patients using covariates determined a priori by expert consensus based on the hypothesized ability to affect the type of surgical treatment allocated or the outcome of treatment received. Logistic regression was used to create the propensity score, defined as the probability of receiving ED, conditional on covariates. Covariates included in the model were age, highest education level, marital status, non-age-adjusted CCI, Mucosal Atopy Index, gastrointestinal reflux disease (GERD) clinical diagnosis, number of previous surgeries, estrogen exposure, and age at first parturition. Nearest neighbor matching without replacement was used to select the patients in the ED cohort to include in the final data set. No caliper was used. After constructing the propensity score, we matched ERMT subjects with 3 ED subjects. We performed the analyses using R programming language and statistical software (R version 3.4.3; R Foundation) with package “MatchIt.”

We selected covariates we thought might impact treatment selection. These primarily included sociodemographics (age, highest education level [as a proxy for socioeconomic status], and marital status). These variables were hypothesized to impact patients’ ability to travel significant distances to specific medical centers, or to affect the severity of a patient’s disease at presentation. To reduce bias, we included variables thought to be related to the outcome but not necessarily to the treatment. Overall health as captured by the CCI score and specific comorbid conditions (as captured in the binary assessment of gastroesophageal disease, or the score of the airway Mucosal Atopy Index) were hypothesized to impact either treatment allocation or treatment outcomes. Similarly, estrogen exposure (time from menarche to menopause adjusted for the use of hormone replacement therapy, and number of pregnancies) and disease severity (number of prior procedures) were hypothesized to impact either treatment allocation or treatment outcomes.
Once our propensity score was calculated we ensured overlap in the range of propensity scores across treatment and comparison groups (ie, verified common support) by examining a graph of propensity scores across treatment and comparison groups (Figure 16). In addition to overlapping, the propensity score should have a similar distribution (“balance”) in the treated and comparison groups. We estimated this distribution by splitting the sample by quintiles, and then verified that the mean propensity score was equivalent in the treatment and comparison groups within each of the 5 quintiles. Unbalanced quintiles were split into smaller blocks, where balance was achieved (Figure 17).

Figure 16. Verification of common support in PSM demonstrates evenly matched scores in treated (ERMT) and comparison (ED) groups

Distribution of Propensity Scores

Abbreviations: ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; PSM propensity score matching.
We then verified successful matching of the covariates in our model to estimate the effect of treatment on disease outcomes (Table 5). Although imbalance in some covariates is expected, there is no rule regarding how much imbalance is acceptable in a propensity score.
Proposed maximum standardized differences for specific covariates range from 10% to 25%.\textsuperscript{52,53}

Thus, after assessment, we believe our PSM process to be suitable.

Table 5. Description of PSM Model Covariates in the Treated (ERMT) and Comparison (ED) Groups\textsuperscript{a}

<table>
<thead>
<tr>
<th>Table 5.2</th>
<th>ERMT ( N = 52 )</th>
<th>ED ( N = 307 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (at index)</td>
<td>52 (47-58)</td>
<td>48 (40-56)</td>
<td>( P=0.42 )</td>
</tr>
<tr>
<td>Marital Status</td>
<td>( P=0.87 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>88% (46)</td>
<td>88% (269)</td>
<td></td>
</tr>
<tr>
<td>non-Married</td>
<td>12% (6)</td>
<td>12% (38)</td>
<td></td>
</tr>
<tr>
<td>Highest education level</td>
<td>( P=0.93 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate school</td>
<td>19% (10)</td>
<td>20% (60)</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>46% (24)</td>
<td>50% (155)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>25% (13)</td>
<td>23% (70)</td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>10% (5)</td>
<td>7% (22)</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>( P=0.88 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>90% (47)</td>
<td>91% (278)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8% (4)</td>
<td>6% (18)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2% (1)</td>
<td>3% (10)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0% (0)</td>
<td>0% (1)</td>
<td></td>
</tr>
<tr>
<td>Mucosal Atopy Index</td>
<td>( P=0.18 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>63% (33)</td>
<td>43% (132)</td>
<td></td>
</tr>
<tr>
<td>0.17</td>
<td>27% (14)</td>
<td>33% (101)</td>
<td></td>
</tr>
<tr>
<td>0.33</td>
<td>4% (2)</td>
<td>16% (49)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>6% (3)</td>
<td>7% (21)</td>
<td></td>
</tr>
<tr>
<td>0.67</td>
<td>0% (0)</td>
<td>1% (4)</td>
<td></td>
</tr>
<tr>
<td>Estrogen Exposure (years)</td>
<td>26 (22-34)</td>
<td>27 (19-32)</td>
<td>( P=0.21 )</td>
</tr>
<tr>
<td>Full Term Pregnancy</td>
<td>( P=0.1 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8% (4)</td>
<td>20% (60)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4% (2)</td>
<td>14% (43)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>48% (25)</td>
<td>43% (133)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25% (13)</td>
<td>14% (42)</td>
<td></td>
</tr>
<tr>
<td>More than 3</td>
<td>15% (8)</td>
<td>9% (29)</td>
<td></td>
</tr>
<tr>
<td>Number of prior surgeries</td>
<td>3.5 (2.0-6.5)</td>
<td>3.0 (2.0-8.0)</td>
<td>( P=0.075 )</td>
</tr>
</tbody>
</table>

Abbreviations: ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; PSM, propensity score matching.

\textsuperscript{a} Successful matching of the covariates in our model is indicated by lack of statistical differences between covariates in each group.
When using PSM to compare the probability of recurrent procedure between the ED and ERMT groups, we saw consistent results with our previous standard models (Table 6). ED continued to have a hazard ratio of 2.77 (IQR, 1.4-5.5), and this effect persisted in PSM models using multiple imputation to adjust for missing data: ED vs ERMT hazard ratio, 3.16 (IQR, 1.8-5.5).

Table 6. PSM: Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Procedure Type - ED : ERMT</th>
<th>Hazard Ratio</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without multiple imputation</td>
<td>2.7799</td>
<td>1.402</td>
<td>5.5123</td>
</tr>
<tr>
<td>With multiple imputation</td>
<td>3.1646</td>
<td>1.8188</td>
<td>5.5062</td>
</tr>
</tbody>
</table>

Abbreviations: ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; PSM propensity score matching.

To further address the concern that the differential ability to avoid recurrent operative procedures may relate to an individual provider’s determination of disease severity (ie, all providers would not elect to perform a repeat operative procedure, our proxy for recurrent disease, for similar degrees of airway compromise), we used several mechanisms to investigate whether patients were evenly matched for disease severity at enrollment and also compared treatment criteria across providers.

The primary mechanism of clinical staging in airway disease relates to the anatomic characteristics of the observed airway scar. The 3 major variables that impact treatment decisions and are recorded by the majority of providers are (1) the distance between the vocal cords and the beginning of the subglottic scar, (2) the total length of the scar, and (3) the percentage of open airway lumen. The majority of airway surgeons define more severe disease as scar closer to the vocal cords, of longer length, and with more significant obstruction. As described in Table 3, ERMT patients had a greater degree of luminal obstruction. ED patients had shorter subglottic scars that occurred farther below the vocal cords than CTR and ERMT
patients. Based on these results the patients undergoing ERMT appeared to have more severe disease (based on commonly accepted surgical criteria for disease severity).

Although formal pulmonary function testing (PFT) in the pulmonary laboratory is often employed in the initial work-up and diagnosis of iSGS patients, it is not routinely employed longitudinally to influence treatment decisions by airway surgeons (although some surgeons have reported on its benefits). As a sensitivity analysis we used formal PFT to evaluate the subset of patients before their index procedure. As shown in Table 7, when using PEF rate as a measure of impaired ventilation, we observed that patients appeared evenly matched with a PEF rate of approximately 50% predicted before surgery in any of the 3 treatment arms.

Table 7. Percentage Normal Peak Expiratory Flow Rate Before Index Procedure

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>N</th>
<th>% PEFR @ Index</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic Resection w/ Adjuvant Medication</td>
<td>60</td>
<td>55</td>
<td>(43-70)</td>
</tr>
<tr>
<td>Endoscopic Dilation</td>
<td>57</td>
<td>50</td>
<td>(38-67)</td>
</tr>
<tr>
<td>Cricotracheal Resection</td>
<td>27</td>
<td>58</td>
<td>(37-60)</td>
</tr>
</tbody>
</table>

Abbreviations: %PEFR, percentage peak expiratory flow rate; IQR, interquartile range.

We also used longitudinal data derived from a portable PEF rate meter and entered into a smartphone application by a subgroup of enrolled patients. PEF was captured with an inexpensive portable handheld device (provided to the patients, which they then registered) and a smartphone app we created. In our cohort of 810 patients, 496 reported PEF (ED, 63%; ERMT, 50%; CTR, 59%), while 314 elected not to record data. The only characteristic that distinguished reporters and nonreporters was age (nonreporters were older). The remaining covariates were not statistically different (Table 8). These findings support the generalizability of the PEF results across the patient population.
Table 8. Characteristics of Patients Who Reported PEF and Those Who Did Not

<table>
<thead>
<tr>
<th>Patient Characteristics in PEF Reporting Subsets</th>
<th>Reporting (n=496)</th>
<th>Not Reporting (n=314)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Median years, 95% CI)</td>
<td>49 (42 - 56)</td>
<td>52 (43 - 59)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>98</td>
<td>98</td>
<td>ns</td>
</tr>
<tr>
<td>Marital Status (% Married)</td>
<td>76</td>
<td>78</td>
<td>ns</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>97</td>
<td>97</td>
<td>ns</td>
</tr>
<tr>
<td>Ethnicity (% Non-Hispanic or Latino)</td>
<td>98</td>
<td>97</td>
<td>ns</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate school</td>
<td>23</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>44</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>High School or less</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Morphology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Stenosis (Median %, 95% CI)</td>
<td>50 (42 - 60)</td>
<td>50 (42 - 58)</td>
<td>ns</td>
</tr>
<tr>
<td>Distance below glottis (Median mm, 95% CI)</td>
<td>15 (10 - 20)</td>
<td>15 (8 - 20)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Health / Endocrine Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson Index (Median, 95% CI)</td>
<td>0.00 (0 - 0)</td>
<td>0.00 (0-0)</td>
<td>ns</td>
</tr>
<tr>
<td>Menstrual Status (% premenopausal at Index Procedure)</td>
<td>71</td>
<td>72</td>
<td>ns</td>
</tr>
<tr>
<td>HRT (% no)</td>
<td>98</td>
<td>98</td>
<td>ns</td>
</tr>
<tr>
<td>Full Term Pregnancy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>39</td>
<td>ns</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
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<td></td>
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</tr>
<tr>
<td>Procedure Type (% total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERMT</td>
<td>14</td>
<td>22</td>
<td>ns</td>
</tr>
<tr>
<td>ED</td>
<td>72</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>CTR</td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CTR, cricotracheal resection; ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; HRT, hormone replacement therapy; PEF, peak expiratory flow.

Interestingly, Loess curves of mixed-effects model–fitted values for %PEF confirm the durability of excellent respiratory function for treated patients who did not experience recurrence during the study period (Figure 18). These data support the idea that patients who did not require a repeat procedure truly did not recur (regardless of surgeon’s algorithm for operative intervention). Similar results were seen when using raw PEF values (data not shown).
Figure 18. Longitudinal mean percentage of PEF rate in patients who did not experience recurrence in the 3 treatment arms

Abbreviation: PEF, peak expiratory flow.

*aThe Loess smooth curve of the mixed-effects model shows sustained PEF in patients after successful treatment.
In all, 185 of 810 patients required a recurrent airway procedure during the study period. We evaluated PROMs of breathing (CCQ), as well as objective measures of ventilation (%PEF), before retreatment in patients who recurred in order to determine if there were significant differences in retreatment criteria. Our results showed no difference between ED and ERMT treatment when comparing the CCQ scores of patients before recurrence: 2.4 (IQR, 1.6-3.4) vs 2.6 (IQR, 1.6-3.3), respectively.

In the subset of patients who reported longitudinal PEF and recurred, we investigated the %PEF before recurrence (Figure 19). Paralleling the CCQ scores, overall there was no difference between ED and ERMT treatments when comparing the %PEF scores of patients before recurrence: 56.5 (IQR, 44-69) vs 54.0 (IQR, 45-59), respectively. Although there was some variability between centers, overall the retreatment thresholds appeared comparable among centers with more than 5 data points.

Figure 19. Percentage of PEF rate before retreatment organized by center

Abbreviations: CTR, cricotracheal resection; ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; HRT, hormone replacement therapy; PEF, peak expiratory flow.

aPurple squares represent ED patients, blue circles represent ERMT patients, and the green triangle is a CTR patient.
Results From Aim 3: What Are the Trade-offs Associated With Each Approach?

Immediately following study initiation, we conducted engagement studios with iSGS patients to ensure that the trial QoL metrics and end points accurately reflected the issues and concerns of patients with a lived experience of the disease. Thirty interviews were conducted with participants diagnosed with clinically confirmed iSGS. Interviews were conducted by a trained qualitative researcher using a written interview guide. Questions included participants’ experiences living with iSGS, treatment experiences, and perceptions of treatment needs. Follow-up questions were asked to clarify responses and to facilitate detailed discussion. Data coding and analysis was conducted by following the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines, an evidence-based qualitative methodology. A hierarchical coding system was developed and refined using the interview guide and a preliminary review of 4 transcripts. Major categories included (1) diagnosis process, (2) QoL, (3) postdiagnosis treatment, (4) patient satisfaction, (5) suggestions, and (6) questions about iSGS condition.

Experienced qualitative coders first established reliability in using the coding system, then independently coded the transcripts. Coding of each transcript was compared, and any discrepancies were resolved to create a single coded transcript. Each statement was treated as a separate quote and could be assigned up to 5 different codes. Transcripts were combined and sorted by code. Analysis consisted of interpreting the coded quotes and identifying higher-order themes using an iterative inductive-deductive approach. Deductively, theoretical contributions to the analysis included (1) social cognitive theory, (2) research and theory in coping and emotional regulation, and (3) clinical experience. Inductively, the codes and themes from the focus groups were used to fill in the details of the conceptual framework.

Using the inductive-deductive approach, we developed a conceptual framework that expresses iSGS in terms of challenges, psychosocial responses, personal impacts, and proposed solutions. The left-hand side of Figure 20 represents the important iSGS challenges pertaining to the health care system, treatment, and physical symptoms. Psychosocial responses include a range of emotional responses, along with strategies that participants use to cope with their
condition. Impacts include changes in QoL, changes in interpersonal relationships, and significant financial challenges.

Figure 20. Qualitative analysis of patients’ lived experience with disease was used to create a cognitive-behavioral framework for the impact of iSGS.

Abbreviation: iSGS, idiopathic subglottic stenosis.
The results of our qualitative analysis confirmed that the end points selected during the trial (ie, the need for recurrent procedures, the complications associated with each treatment approach, and the patient-perceived impact on breathing, voice, swallowing, and overall quality of life) were in fact critically important to patients (Figure 20). Additionally, the results validated the significance of social support, medical decision-making, disease anxiety, and fear of disease in patients’ lived experience with the disease.

**Immediate Procedure-Specific Impact on HRQoL**

Although patients who underwent open CTR had the lowest recurrent procedure rate, even when performed at high-volume centers with significant expertise in open airway surgery, there were several complications associated with this more invasive procedure; namely, 3.5% (n = 3) had a leak at their anastomosis, 9.3% (n = 8) required an unplanned trip back to the operating room during their initial hospitalization, 9.3% (n = 8) required a temporary tracheostomy or T-tube, 8% (n = 7) had permanent paralysis of 1 vocal cord, and 1.2% (n = 1) had permanent paralysis of both vocal cords. None had a myocardial infarction, pulmonary embolus, or deep vein thrombosis. One patient developed a urinary tract infection secondary to their urinary catheter and one had postoperative pneumonia.

In patients who received ERMT, 35 of 121 reported an adverse reaction to TMP/SMX, with 27 patients (22%) stopping their adjuvant medication secondary to the reaction. Adverse reactions consisted of anorexia and nausea (n = 6), rash (n = 16), and fever (n = 2). Three adverse reactions to TMP/SMX leading to treatment cessation were not specified. There were no Stevens-Johnson reactions. No patients developed nephritis or hepatotoxicity. All adverse effects resolved after the medication was stopped. Additionally, there were transient complications related to the endoscopic surgical exposure in ERMT: 12% (n = 14) had temporary tongue paresthesia relating to direct laryngoscopy (although some patients had taste changes for more than 4 weeks before eventually returning to normal) and 3.3% (n = 4) had a dental injury. None had subcutaneous emphysema after the procedure.
Patients who underwent ED similarly had primarily mild procedure-related transient complications. These included 14% (n = 84) with temporary tongue paresthesia, 6% (n = 34) with a dental injury, and 0.5% (n = 3) with transient postoperative subcutaneous emphysema indicating a full thickness tracheal tear. All occurrences of subcutaneous emphysema resolved with conservative management.

**Long-Term Procedure-Specific Impact on HRQOL**

Speech, swallowing, breathing, and global QOL were followed longitudinally after the index procedure. In patients with a successful procedure (ie, they had not yet recurred) patient-reported HRQoL metrics showed differences between the treatment approaches 360 days after the index procedure (Figure 21).
Figure 21. Patient-reported functional outcomes at 12 months

Abbreviations: CCQ, Clinical COPD Questionnaire; CTR, cricotracheal resection; EAT-10, Eating Assessment Tool; ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; SF-12, 12-Item Short Form Survey; VHI-10, Voice Handicap Index.

aValidated instruments were used to compare breathing (CCQ), voicing (VHI-10), swallowing (EAT-10), and global quality of life (both physical and mental domains; SF-12) between 3 treatment approaches.
Even in successful procedures (where patients avoided recurrence), patients who underwent ED reported worse breathing outcomes (higher CCQ score) at 360 days when compared with either endoscopic resection (ED vs ERMT, 1.8 vs 1.25; \( P = .009 \)) or CTR (ED vs CTR, 1.8 vs 0.75; \( P < .0001 \)). Although the results differ by a statistically significant margin, the minimal clinically important difference (MCID) for the CCQ has been reported at 0.4 (Table 2). This would render the breathing outcomes after CTR both statistically and clinically better than ED and ERMT.

However, patient-reported voice outcomes were significantly more impaired (higher VHI-10 scores) in patients who underwent CTR when compared with ERMT (CTR vs ERMT, 13 vs 3.5; \( P = .002 \)). Interestingly, tracheal resection patients were not significantly different from patients who underwent ED (CTR vs ED, 13 vs 10; \( P = .135 \)) when evaluated at 360 days after their procedure. The best voice outcomes (lowest VHI-10 scores) were reported in the ERMT arm. This effect was significant both for comparisons with ED (\( P = .012 \)) and CTR (\( P = .002 \)). While the results differ by a statistically significant margin, the MCID for the VHI-10 has been reported at 4 (Table 2). This would render the voice outcomes after ERMT both statistically and clinically better than those for ED and CTR.

Swallowing outcomes overall were quite good regardless of surgical approach. However, there were subtle but significant higher scores on the EAT-10 (ie, worse function) in patients who underwent ED when compared with either ERMT (\( P = .03 \)) or CTR (\( P = .019 \)). Although an MCID has not yet been established for the EAT-10, consensus expert opinion among NoAAC providers suggests that it is unlikely these differences are clinically significant.

Global QoL was measured with the established SF-12v2 instrument.\(^3\) At 360 days, patients who underwent ED reported significantly lower physical health subscale scores (worse global QOL) when compared with ERMT (ED vs ERMT, 49 vs 53; \( P = .049 \)) or CTR (ED vs CTR, 49 vs 54; \( P = .03 \)). The MCID for the physical health subscale of the SF-12 is reported at 3.29 (Table 2). According to this MCID, patient-reported global QoL was both statistically and clinically worse after ED than after ERMT or CTR.
Although patient characteristics, the number of previous intervention(s), and a patient’s unique perception of the importance of breathing, speaking, swallowing, and overall QoL are clearly important determinants of medical decision-making, our qualitative study suggested that they may provide an incomplete signature of the patient’s lived experience with disease. With that in mind (and driven by the results of our qualitative study of iSGS patients) we included nontraditional measures we hoped would more fully capture subjective parameters that impact decision-making.\textsuperscript{59} Validated patient-centered scales were used to determine these unique previously unmeasured individual characteristics. The results of specific PROMs focusing on social support,\textsuperscript{36} shared decision-making,\textsuperscript{37} coping with disease anxiety and burden,\textsuperscript{38} and the perceived impact of illness on daily life\textsuperscript{39} are shown in Table 9.

### Table 9. Patient Scores for PROs Measuring Nontraditional Social Metrics\textsuperscript{a}

<table>
<thead>
<tr>
<th>PRO Instrument</th>
<th>Abbreviation</th>
<th>ED</th>
<th>ERMT</th>
<th>CTR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Outcomes Study Social Support Survey</td>
<td>MOS</td>
<td>93 (76-100)</td>
<td>89 (76-99)</td>
<td>94 (86-100)</td>
<td>ns</td>
</tr>
<tr>
<td>Shared Decision Making Questionnaire</td>
<td>SDM-Q9</td>
<td>84 (64-100)</td>
<td>80 (60-98)</td>
<td>88 (63-98)</td>
<td>ns</td>
</tr>
<tr>
<td>Brief Illness Perception Questionnaire</td>
<td>BIPQ</td>
<td>46 (39-54)</td>
<td>44 (32-53)</td>
<td>35 (21-47)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fear of Progression Questionnaire</td>
<td>FoP-Q</td>
<td>9 (6.9-11.5)</td>
<td>7.6 (6-9)</td>
<td>7 (5.8-9.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CTR, cricotracheal resection; ED, endoscopic dilation; ERMT, endoscopic resection with adjuvant medical therapy; ns, not significant; PROs, patient-reported outcomes.

\textsuperscript{a}Three treatment arms (ERMT, ED, and CTR) had similar scores for the MOS and SDM-Q9. The BIPQ score was significantly lower in CTR, while the FoP-Q score was significantly higher in ED.

Interestingly, social support was high across all treatment arms without observed differences. Similarly, there was a high (and comparable) level of shared decision-making between the 3 treatment approaches. Although we have previously demonstrated variability in the type of procedure that patients receive at the distinct centers\textsuperscript{24} (which we could not attribute exclusively to patient-specific covariates), our results suggest that overall patients felt a high degree of shared decision-making with their treating physicians.
Although patients in the 3 treatment arms appeared to have comparable social support and shared medical decision-making with their treating physicians, their perceptions of how the disease impacted their lives differed. Brief Illness Perception Questionnaire (BIPQ) scores (which capture the perceived impact of an illness on a patient’s life) were significantly lower (less impacted) in patients who underwent CTR ($P = .001$). Similarly, the fear of disease progression (FoP, measured by the Fear of Progression Questionnaire [FoP-Q]) differed between those receiving ED (9; IQR, 6.9-11.5), ERMT (7.6; IQR, 6-9), and CTR (7; IQR, 5.8-9.5), with the highest levels of fear seen in those receiving ED ($P = .001$). The magnitude of FoP demonstrated in ED patients is comparable to published reports in patients with cancer.\textsuperscript{60}

**Post Hoc Subgroup Analysis**

We sought to examine 3 additional questions that arose during the study, which we detail below.

**What is the role of the medical regimen in ERMT?** TMP/SMX is a standard postoperative medication that patients in the ERMT arm were prescribed. In all, 27 patients from the ERMT cohort stopped taking TMP/SMX due to adverse effects. We performed a Kaplan-Meier time-to-event analysis comparing those patients who continued to take TMP/SMX and those who stopped taking it within the ERMT arm. We found no difference in the recurrence rate of those who took full-course TMP/SMX and those who stopped taking it early due to adverse effects (Figure 22). The amount of time that patients took the medication before stopping is an open question that we are working to resolve.
What is the impact of adjuvant medical treatment after ED? Many patients are prescribed adjuvant medications even after ED. These are primarily PPIs and inhaled corticosteroids. Using robust data collected on the 603 patients in the ED arm, we performed post hoc analysis to investigate the effect of postoperative PPI (Figure 23) and inhaled corticosteroid (Figure 24) therapies. Need for and time to recurrent procedure did not differ based on postoperative PPI or corticosteroid therapy.
Figure 23. Kaplan-Meier plot of recurrence rates in patients who underwent ED (and never received SILSI) and then received adjuvant PPI treatment

Abbreviations: ED, endoscopic dilation; PPI, proton pump inhibitor; SILSI, serial intralesional steroid injection.
Figure 24. Kaplan-Meier plot of recurrence rates in patients who underwent ED (and never received SILSI) and then received adjuvant inhaled corticosteroid treatment

ED group with non-in-office steroids

Abbreviations: ED, endoscopic dilation; PPI, proton pump inhibitor; SILSI, serial intralesional steroid injection.

What is the impact of SILSI on treatment outcome after ED? To assess the impact of adjuvant SILSI after ED (measured via patient %PEF, subjective patient-reported breathing outcomes, and probability of avoiding a recurrent surgical procedure), we compared ED patients who never received SILSI with ED patients who did receive SILSI. Interestingly, the patients who did receive SILSI recurred more quickly and in higher numbers than those who did not receive it (Figure 25). This association should not be interpreted to mean that steroids hastened recurrence; rather, they might have been used by surgeons in patients who were
rapidly worsening as a potential salvage therapy in hopes of avoiding the need for recurrent surgical procedure. It is important to note that the sociodemographic characteristics, PEF (Figure 26), and patient-reported breathing (CCQ) scores (Figure 27) did not differ between those who did and did not receive SILSI in the ED arm.

**Figure 25. SILSI administration**

![Image of SILSI administration graph]

Abbreviations: ED, endoscopic dilation; SILSI, serial intralesional steroid injection.

aIntralesional steroids administered in the office did not lower the rate of recurrence after an ED index procedure. In fact, the opposite was true; patients who received SILSI had a higher rate of recurrence than patients who did not receive it (log-rank test, \( P = .0001 \)). In patients who did not recur during their study period and received SILSI, there were no significant differences in peak expiratory flow or patient-reported outcomes for breathing (Clinical COPD Questionnaire score) at 360 days (\( P = .34 \)).
Figure 26. Fifty-three ED patients with PEF data and SILSI vs 239 ED patients with PEF data and no SILSI\textsuperscript{a}

Abbreviations: ED, endoscopic dilation; iSGS, idiopathic subglottic stenosis; PEF, peak expiratory flow; SILSI, serial intralesional steroid injection.

\textsuperscript{a}ED+SILSI, mean %PEF, 68 (95% CI, 64-70), vs ED alone, mean %PEF, 71 (95% CI, 68-73). The overlay is shown to facilitate visual comparison.
Figure 27. CCQ scores at 12 months in 53 ED patients with SILSI vs 239 ED patients without SILSI\textsuperscript{a}

Abbreviations: CCQ, Clinical COPD Questionnaire; ED, endoscopic dilation; SILSI, serial intralesional steroid injection.
\textsuperscript{a}Analysis was restricted to patients who did not recur during the study period. There was no significant difference in CCQ score in patients who received SILSI and those who did not.

We also compared need for recurrent procedure among all 53 patients who underwent ED and then received SILSI. Of the 53 with %PEF, 28 recurred and 25 did not (Figure 28). Examining the individual longitudinal %PEF with indication of the timing of the series of injection showed persistent decline in %PEF in nonresponders, with some degree of apparent stabilization in the 25 who did not recur. Although these results are prospective and were collected objectively by an unbiased observer, the type of steroid, the timing of injections after the index procedure, and the number of injections are factors still being examined within our dataset. Based on the information we have collected (with the caveats mentioned), our analysis suggests that intralesional steroids injected in the office after ED did not lower the rate of recurrent procedure. In patients who did not experience recurrence, SILSI did not consistently improve ventilation (via %PEF) or subjective dyspnea (via CCQ scores).
Figure 28. Fifty-three patients who were treated with ED and then received SILSI with longitudinal %PEF values.

**Required Repeat Procedure (N=28)**

**Did NOT Require Repeat Procedure (N=25)**

Abbreviations: ED, endoscopic dilation; PEF, peak expiratory flow; SILSI, serial intralesional steroid injection.

*Twenty-eight patients required a recurrent procedure, and 25 did not recur. The small upright purple line on the x-axis corresponds to the initiation date of a series of SILSI.
DISCUSSION

Context for Study Results

We assembled a cohort of 810 patients with the rare disease iSGS, then performed an unbiased and objective measurement of the effectiveness of 3 current surgical treatments (ie, ED, ERMT, and CTR) at avoiding a recurrent procedure. We also defined the immediate perioperative risks, as well as longer-term (12 month) patient-reported functional outcomes after surgery.

Consistent with previous retrospective reports, the iSGS patients in our study were primarily adult, white, and female. They were otherwise healthy and highly educated. They presented with subglottic obstruction arising approximately 1 cm below the vocal cords extending downward for 1.5 cm, and obstructing 60% of their airway. The consistent demographics of affected patients in our geographically diverse cohort seem to suggest that a conserved biologic process is driving a singular disease. Supporting this concept is recent translational science conducted by investigators within the NoAAC that has begun to interrogate the biologic mechanisms responsible for recurrent airway scarring in iSGS. These results suggest that localized aberrant mucosal immune activation in the large airway plays a role in the disease process.

These scientific insights (ie, identifying localized derangement in mucosal inflammation) are also supported by our observation that removal of the offending mucosa via CTR offered the most durable treatment in our cohort. However, CTR clearly has more significant and severe perioperative risks than the less invasive endoscopic approaches. CTR also demonstrates worse patient-reported voice outcomes at 360 days than the other 2 approaches we studied. Yet the interplay between vocal function and overall QoL in patients who choose to undergo CTR appears nuanced and complex. The different techniques used to capture the lived experience with the disease in our study support the concept that despite more impaired voicing, patients who undergo CTR report high levels of overall QOL (via the SF-12), and believe the disease affects their lives less (via the BIPQ) than the other 2 approaches. Patients who choose to undergo CTR also show significantly lower levels of FoP than those who receive ED.
Although overall our results support efficacy and durability of CTR, they must be taken with a number of caveats. Several reports have identified a significant rate of recurrent disease (10%-30%) after CTR occurring at 5 to 10 years after surgery.\textsuperscript{20,63,64} These effects would not be observed in our cohort given the constrained temporal scope of our study. Longer-term follow-up of CTR patients from our cohort will continue to offer insight into this question. Additionally, given that CTR is preformed primarily in high-volume centers, the generalizability of our findings across centers is not clear. CTR requires special training, experience, and institutional infrastructure (eg, highly skilled anesthesiologists, nurses, respiratory therapists, critical care physicians, etc). Many physicians who manage this condition do not possess high-volume training in CTR or the advanced infrastructure required for successful patient care with these techniques. The degree to which outcomes for CTR in our cohort are transferable between centers is a critical question that demands further careful study.

An interesting finding in our study was the effectiveness of ERMT. In our cohort over the study duration, ERMT offered significantly improved disease control compared with ED. This effect was reproducible even when adjusting for observed confounders (with adjusted Cox proportional hazard models, as well as with PSM). Additionally, improved disease control with ERMT had minimal impact on voice function, particularly when compared with CTR.

Despite its efficacy, ERMT was performed primarily at 1 institution. Performing ERMT incorporates several technical details that differ significantly from the majority of endoscopic procedures for iSGS. Additionally, the postoperative medical regimen is a significant component and highly complex. It remains unclear if the reduced recurrence rate relates to the surgery, the postoperative medications, or both. Although it is difficult to disentangle the effects of training, experience, and institutional infrastructure, our post hoc subset analysis offers some insight. Of patients who received ERMT, 24% stopped the TMP/SMX component of the medical regimen secondary to medication adverse effects. These patients did not experience a higher rate of disease recurrence. However, the comparison of patients who tolerated TMP/SMX (n = 94) with those who stopped using it (n = 27) was likely significantly underpowered. Additionally, in patients who received ED, those who received postoperative PPIs or inhaled corticosteroids
also did not show differences in rates of disease recurrence. These results would suggest that the technical details of ERMT (i.e., lack of dilation coupled with selective CO$_2$ laser scar vaporization) are responsible for a significant portion of the treatment effect. It remains uncertain if ERMT outcomes will converge with ED outcomes when followed for 5 or 10 years. This question will be an area of continued study within our cohort.

Our study is not without limitations (which we elaborate on in the following section); however, we believe a strength of our work is the unbiased and objective nature of data collection for both treatment outcomes and QoL trade-offs in iSGS. Our results will help inform patient decision-making. They will also inform characteristics of future trial design and research methodology that will allow continued progress in the study of iSGS and other rare diseases.

**Generalizability of the Findings**

Patients with iSGS appear demographically similar in our geographically representative cohort and parallel disease demographics described in previous studies, supporting the generalizability of our findings. However, issues with generalizability do exist. One potential issue relates to treating surgeons. ERMT is primarily performed at a single institution. It is unclear if this approach will work as well when performed by another surgeon who is not as familiar with the technique. CTR also requires unique technical skills and dedicated infrastructure. It is not clear that either approach is transferable between centers. This question demands further study within the NoAAC consortium.

Another issue with generalizability relates to the number of procedures seen per year in our cohort. Our retrospective work demonstrated that 80% of endoscopically treated patients recurred by 1,000 days of initial surgery. This appears significantly greater than we observed in our prospective study (approximately 50%). These differences may stem from our inclusion of both centers of excellence and smaller centers in the current study. The retrospective work was based entirely on 10 high-volume centers of excellence. As patients with more severe disease that is recalcitrant to therapy cluster at high-volume centers, this might have skewed our retrospective results to a higher rate of recurrence.
Informed by our initial qualitative study, we sought to capture the iSGS disease experience in the less tangible, subjective parameters that are known to impact medical decision-making, including social support, shared decision-making, coping with disease anxiety and burden, and the perceived impact of illness on daily life. We viewed these domains all as previously unmeasured potential confounders that could influence treatment choice and outcome. Pilot data from other diseases supported this contention. In prostate cancer, higher scores on the participatory decision-making scale (odds ratio, 1.31; P = .013) and better self-reported overall health (odds ratio, 1.25; P < .001) were both significantly associated with selecting surgery rather than observation. We also felt that a collection of patient-initiated nontraditional data elements would improve risk adjustment and increase the individualization of the results.

Social support (measured via the validated Medical Outcomes Study survey) was high across all treatment arms without observed differences. The degree to which the established online Facebook community of affected patients contributes to this perception of support is unknown. Future research into the ability of online communities to provide social support to patients has the potential to impact individuals who have both common and rare diseases.

There was also a high (and comparable) level of shared decision-making between the 3 treatment approaches. The importance of this finding is significant. Previously we demonstrated variability in the type of procedure patients received at distinct centers that we could not attribute exclusively to patient-specific covariates. Yet our results demonstrate that patients with iSGS largely feel that their treatment options are not imposed on them externally by their surgeons. We believe that this high degree of shared decision-making is a testament to the informed nature of these patients, the commitment of doctors to optimal care, and the level of communication between doctors and patients.

Although patients in the 3 treatment arms appeared to have comparable social support and shared medical decision-making with their treating physicians, their perceptions of how their disease impacted their lives differed. The perceived impact of iSGS on daily life (measured via BIPQ scores) was significantly lower in patients who underwent CTR than in those who
underwent ED or ERMT. This suggests that the durability of the treatment response with CTR also translates to tangible psychological benefit for some patients.

Patients with myriad chronic disease suffer from fears related to the illness itself. These illness-related fears have been termed FoP. FoP is an adequate response to the real issues associated with diagnosis, treatment, and course of illness. Elevated levels of FoP can become dysfunctional and interfere with coping, treatment adherence, QoL or social functioning. Within our cohort, the FoP (as measured by the FoP-Q) was highest in the ED arm. The magnitude of the FoP-Q scores in ED patients is comparable with previous published reports in patients with cancer. Identification of a high FoP in patients with iSGS opens the door to incorporation of structured programs aimed at reducing FoP levels.

The results of the 4 nontraditional surveys (see Table 9) need to be tempered with the timing of survey completion. When patients were recruited from provider offices, they were typically in distress and seeking advice on surgical treatment. Although 679 members of the 810-member cohort completed the PROMS, frequently this occurred after their index procedure. Eighty-one ED, 61 ERMT, and 11 CTR patients completed these PROMS before their index procedure. Published studies in multiple alternate disease models report that responses to PROs often meaningfully change following diagnosis and treatment. This limitation aside, our dedicated qualitative study in 30 patients at study inception had findings that mirrored our PROM results. Ultimately, longitudinal follow-up of our 810-member cohort, with repeated nontraditional surveys, is planned and anticipated to offer additional insight into this question.

Dissemination of Study Results

The most common treatment in our iSGS cohort, ED, demonstrated the highest recurrence rate. We believe this affords an opportunity to improve patient outcomes through the delivery of the alternate techniques. Although the recurrence rate in ED is balanced by the limited side effect profile, both CTR and an alternate endoscopic procedure (ERMT) appeared to have a lower rate of disease recurrence and were associated with good long-term QoL. Additionally, rather than viewing CTR and ERMT as 2 competing alternate approaches, the study team believes they can function in complementary fashion to deliver personalized care to
patients with iSGS. CTR is a more intensive procedure with more discrete selection criteria and not all patients will be candidates for this technique. Patients who are not candidates for CTR, or who do not find the risk-benefit ratio favorable, can explore ERMT. However, to date, the ERMT procedure is not widely disseminated among providers, as it is only performed at 1 medical center. This is hampered by the fact that iSGS is a rare disease treated by specialty care surgeons, exposing evidence to informational bottlenecks, individual interpretation, and institutional intransigence. We hope to disseminate evidence about the study results to patients and treating surgeons with a long-term goal of promoting improved care. We plan to disseminate our results to patients via the Facebook group. We will disseminate the results to surgeons by leveraging established peer and mentorship networks. With these networks we can communicate the technical aspects of the procedure via traditional didactic lecture as well as via newer methods of surgical simulation.

We have active plans to promote widespread use of the study results via 3 engage-disseminate-evaluate cycles:

1. Engage patients and surgeons to capture the information and delivery approaches that best promote dissemination of and advocacy for the superior treatment (ie, CTR). A mixed methods needs assessment (surveys and interviews) will identify target behaviors, barriers/facilitators, and preferred dissemination modalities.
2. Disseminate evidence of treatment outcomes to patients (Facebook) and to surgeons (likely and unlikely to implement) via mentorship and peer networks using novel respondent-driven sampling methods to achieve network penetration.
3. Evaluate dissemination by assessing video metrics (unique views), surveying, and interviewing patients and surgeons about knowledge, motivation, and implementation of this treatment. Collected data about dissemination barriers/facilitators will inform process revisions.

Implementation of Study Results

Although adoption of new surgical techniques can improve patient care, our understanding of why such procedures come to be offered as treatment is still in its infancy. Neurosurgeon and medical innovator Charles Wilson has described factors that determine the adoption and diffusion of a new innovation in surgery. He reports that these factors
fall into two categories: characteristics of the technique itself and contextual factors that promote it. Surgeons are attracted to the new techniques if they can be passively observed, easily and quickly learnt, and added to their existing practice with minimal disruption. If the potential contribution to their practice is sufficiently great, surgeons are more likely to invest time and effort and tolerate disruption of their routine to gain the competitive advantage that a new technology offers.

There is a body of literature primarily from the social sciences that has explored the adoption and diffusion of technologies in general. Everett Rogers portrayed the diffusion of innovation with an S-curve. Malcolm Gladwell offered a kinetic concept to the process of social change. His work suggest that diffusions of innovation are the result of circumstances in which ideas, products, messages, and behaviors spread like viruses through “word-of-mouth epidemics” that are set in motion by 3 types of individuals: “mavens,” who gather information and pass it on to others; “connectors,” who are sociable and bring people together; and “salesmen,” who have a talent for persuasion. The speed of diffusion accelerates to a peak (ie, the tipping point), which occurs on average at 20% adoption. Rogers’ and Gladwell’s theories will be useful as we work to implement our findings across all the surgeons treating patients with iSGS.

Subpopulation Considerations

In clinical trials, subjects have variable responses to identical treatments. Heterogeneity in response can come from observable or unobservable sources. Heterogeneity is often anticipated in studies based on known patient groups and hence is a characteristic that is built into trial design. For our study in the rare disease iSGS, there were no established covariates previously demonstrated to influence treatment outcome. A priori, we selected several covariates that we anticipated would have an effect on response; however, analysis showed no treatment response subgroups within our cohort.

We used 2 main methods for interrogating heterogeneity in the study data. Using recurred/not-recurred definitions, we employed logistic regression to assess patient characteristics associated with each of these outcomes. Our second approach used a more
recent statistical method that allows patterns of heterogeneity to emerge from robust multidimensional data sources. That is, if subgroups of patients exist who are similar to one another but different from the main group of patients, these subgroups will emerge graphically during analyses and their characteristics can be explored. The advantage of this approach is that all recorded variables can be included, obviating the need for an a priori designation. Our innovative approach employs viSNE as an alternative to searching for confounding variables associated with treatment response (with variables captured but not designated a priori). Based on the t-distributed stochastic neighbor embedding (t-SNE) algorithm, viSNE enables visualization at single-patient resolution, preserves the geometry and nonlinearity of the data, represents both abundant and rare populations, and provides a robust, interpretable view of the data. The resulting viSNE map provides a visual representation of the single-patient data that is similar to a biaxial plot; however, the positions of patients on the map reflect their proximity in high-dimensional rather than 2-dimensional space. We used color as a third dimension to interactively visualize features of these patients. viSNE showed no clustering of patients that required a recurrent procedure for any of the known covariates. This effect was tested both with and without hot-deck imputation for incomplete data. The viSNE results were confirmed by testing Kaplan-Meier curves of treatment outcome stratified by patient age. Taken together, the iSGS population is strikingly homogeneous, and we found no confounding covariates measured that associate with treatment response.

Study Limitations

As with any nonrandomized study design, the issue of confounding can interfere with interpretation of results. We sought to mitigate this effect via several formal statistical mechanisms. We initially employed Cox proportional hazard models alone, then with adjustment for covariates, and then with adjustment coupled with multiple imputation to interrogate the effect of missing data. All techniques supported a significant lower risk of recurrent procedure in the ERMT arm when compared with the ED arm. We then used PSM to ensure balanced covariates between treatment arms, following Cox proportional hazard models (both with and without multiple imputation to account for missing data). As with the
previously listed techniques, PSM showed a significant lower risk of recurrent procedure in the ERMT arm when compared with the ED arm.

To address the possibility of unmeasured confounders influencing treatment outcome, we also attempted instrument variable analysis (IVA), with the institution performing index procedure as the instrument. This variable was selected based on 5 specific assumptions: (1) Potential outcomes for each patient are unrelated to treatment status of other patients; (2) the instrument affects receipt of the treatment of interest; (3) this effect is always in the same direction; (4) the instrument assigns treatment randomly; and (5) the instrument has an effect on the outcome only through the treatment assignment. However, when employing IVA, we found that the total number of performing institutions (considering study-enrolling centers of excellence as well as institutions reported by self-enrolled patient partners) was more than 80. This rendered imputation for missing values difficult and prevented reliable results using a Cox proportional hazard analysis with institution as instrument. Thus, our current analysis is limited in its inability to account for unmeasured confounding.

Missing data are common in clinical research and our study is not immune to this limitation. The distributed nature of our study, variability in diagnostic and monitoring protocols across centers, and our integration of PGHD contributed to missing data. However, despite these issues, we believe our robust primary end point data coupled with consistent findings when employing established statistical techniques for missingness, as well as validation of the results of our previous retrospective study, strongly support our primary outcome results.

Another potential limitation is the use of PGHD that were not objectively recorded by key study personnel. However, we believe the use of peak flow data generated remotely by patients is consistent with PCORI’s methodology standard to measure outcomes of interest identified by key stakeholders for which patients or people at risk of a condition are the best source of information.
Future Research

The next phase of study will include continued surveillance of our established cohort to determine if the differential effectiveness of the 3 approaches is durable over time (ie, Do the patients who received EMRT begin to recur at 5 years?). Continued longitudinal follow-up driven by an engaged patient population will be critical to realize this goal.

Our post hoc analysis suggests that adjuvant medical therapies do not significantly improve the treatment outcomes of the 3 approaches under study. Although SILSI has widespread support in the patient community, as well as among some treating surgeons, our results contradict the limited retrospective series available in the literature. A randomized placebo-controlled trial investigating the ability of SILSI to improve or slow the decline of PEF would be feasible with our cohort. Additionally, the emerging role of IL-17A in iSGS has made this an attractive target for dedicated study using FDA-approved biologics. Given the results of our study, we can employ the characterized clinical outcome measures and trial design elements to unambiguously assess treatment efficacy of these reagents in our population. We believe this approach will facilitate future progress in this disease.

We are also interested in investigating the process of disseminating and implementing the findings from this study. Key questions for future study include how to rapidly and effectively disseminate a novel procedure among surgeons. Then, once disseminated, what are key techniques and tools we can use to accelerate its adoption and implementation? Endoscopic resection appears to be more durable than dilation and poses significantly less risk or vocal impact than tracheal resection, but will the surgeons embrace it? How can we harness the power of an informed patient population to help drive this implementation?

Another component of future study will revolve around clinical trial methodology. Future analytical methods employing spatial epidemiology (ie, Lorenz curve and the Gini coefficient) will be used to assess the distribution of enrolled study patients across a geographic region and demonstrate how harnessing online patient communities can generate more representative patient cohorts in rare diseases. We will also be able to investigate the sensitivity of portable PEF, as well as the activity recorded on smartphones (eg, daily step
count) in predicting disease recurrence. We are also interested in more in-depth study of the viSNE technique for delineating important confounders from capture covariates in large clinical trial datasets. We believe this will prove to be a useful tool for future clinical investigations.

Additionally, we have several post hoc subgroup analyses planned to build robust hypotheses for future testing. Starting with comparisons of treatment outcomes between centers (restricted to a given approach), we hope to highlight differential effectiveness and allow for focused study delineating new technical or medical refinements to improve patient outcomes.

Finally, our project has created a large cohort of patients with iSGS linked with detailed demographic and disease outcome data. We plan to explore how individual genetics, when combined with powerful new genomic approaches, contribute to treatment outcomes. In doing so we hope to move the promise of personalized medicine to those who have a rare disease and are thus living on the margins of modern medicine.
CONCLUSIONS

iSGS is a rare disease characterized by unexplained inflammation and localized fibrosis resulting in life-threatening blockage of the upper airway. Harnessing an engaged online community of affected patients, an international multi-institutional collaborative of surgeons, and an innovative digital clinical trial infrastructure, we conducted a prospective cohort study to provide high-quality data to inform iSGS patient decision-making.

Patient sociodemographics and disease severity were similar across our cohort, yet patients received different surgical approaches across the participating institutions. However, despite different approaches to treatment, patients with iSGS voiced a high level of shared decision-making with their treating physicians. We believe this demonstrates that these patients largely feel their treatment options are not imposed on them externally by their surgeons. It is a testament to the informed nature of patients with iSGS, the commitment of doctors to optimal care, and the level of communication between doctors and patients.

Of the 3 treatments evaluated, CTR had the lowest rate of recurrent procedure, but was also associated with the most adverse effects/events. ERMT was associated with better disease control than ED (based on lowered need for recurrent procedure) with minimal impact on voice function when compared with CTR. The differing harms and benefits of the 3 treatments were also supported by PGHD. Patient-reported breathing outcomes (via CCQ) at 360 days were similar for ERMT and CTR, and worse in participants treated with ED. CTR patients report significant trade-offs with their voice over time (via VHI-10). Swallowing outcomes overall were quite good regardless of surgical approach. Despite the differences in functional outcomes between the 3 treatments (reflected in the CCQ, VHI-10, and EAT-10) at 360 days, patients who underwent CTR or ERMT reported significantly higher physical health subscale scores (better global QOL) when compared with patients who underwent ED.

We believe our study offers reliable data for patients to make individualized treatment decisions. However, equally as critical, our project created a sustainable, scalable infrastructure that can be applied more generally to comparative effectiveness research in iSGS and other rare
diseases. Although there is a wealth of literature showing several variables closely associated with outcomes for surgical treatment in multiple common diseases (ie, procedure volume,\textsuperscript{72,73} physician skill,\textsuperscript{74} and geographic region\textsuperscript{75-77}), there is a paucity of data available to understand what structure and process characteristics influence outcomes in rare diseases requiring surgical procedures. Our infrastructure will allow future investigations to explore which of these relationships apply to such procedures and, in the process, continue to pioneer their application in comparative effectiveness research addressing scientifically underserved patient populations.
REFERENCES


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We thank all the iSGS patients who generously contributed their time and input to this study. Their search for answers to their disease is driving us ever closer to a cure. We also recognize the physicians within the North American Airway Collaborative (NoAAC) who showed tremendous courage to freely share the outcomes of their patient care. This work also would not be possible without the unmatched scientific and technical resources of the NoAAC data coordinating center provided by the Center for Quantitative Science at the Vanderbilt School of Medicine.

Disclosures: None of the study investigators have financial relationships impacting their participation or the analysis of trial results. Additionally, there were no competing interests within the study team in assessment of treatment outcomes. Biostatistical analysis was performed independently of the principal investigators.
Screening of 1336 patients generated 1315 potentially eligible participants. Closer evaluation deemed 16 ineligible (due to vasculitis, prolonged intubation, non-English speaking, or cognitive impairment limiting informed consent). 50 eligible patients declined to participate for various reasons. 193 potentially eligible patients did not respond to further recruitment inquiries.

1056 total patients consented for the study. Of these 1056, 35 formally withdrew shortly after providing consent. 211 patients consented but were unable to produce treatment data (relating to their disease and index procedure) and were excluded from analysis. This left 810 patients for analysis. 121 in endoscopic resection, 603 in endoscopic dilation, and 86 in tracheal resection.

**Total Screened (N = 1336)**

**Total Eligible (N = 1315)**

- Screened and eligible but patient declined (50):
  - Reasons listed below

- Screened but actually ineligible (16):

- Screened and eligible but no response to recruitment (193):

**Total Enrolled (N = 1056)**

In the 1056 consented/enrolled patients

- Total Withdrawals (N) - 35
  - % Withdrawals - 3%

- No treatment-specific data (N) - 211
  - % no patient-specific data - 20%

810 Enrolled and subject to comparative analysis of primary & secondary endpoints

- 121 Endoscopic Resection
- 603 Endoscopic dilation
- 86 Open Tracheal Resection
Our systematic effort documenting eligible individuals who decline to enroll in the project. We had fifty eligible patients (of 1336) decline to participate. Some reasons cited are below:

“I feel like I have to make myself forget I have this and try to live my life between appointments. It decreases my stress and actually lets me enjoy each day.”

“I’ve had to have surgery not related to ISS and have other things going on at this time.”

“Last year I was diagnosed with ISS incorrectly. I was lucky that I had swallowed a foreign object 40 years ago.”

“I am heavily involved with the care of a relative (cancer patient).”

“Due to the verbiage in the consent form and I am currently on disability and don’t want anything to interfere with this I will decline being part of this study group...”

“I don’t think it would be suitable for me to take part.”

“After reading the guidelines for participation, I do not wish to participate.” “After reading the consent disclosures, I do not wish to participate.”

“I was diagnosed with Wegener’s.”

“I don’t think I am going to be able to participate in the study. I suffer from depression and anxiety disorder, and right now I am going through a very difficult time.”

“having problems with lymph nodes which is taking all my attention”

“After reading through the stipulations, I do not choose to participate in the study."

“Thank you for asking me to take part in your study but I will decline. It’s more than I feel like getting into at this time.”

“I have reviewed the details of the consent form and have decided not to participate in the survey.”

“I have changed my mind. Perhaps this study is not one I care to participate in.”

“I was not diagnosed with subglottic stenosis.”

“I really don’t think I have time to be in the study hon.”

“Not interested, my doctor said my throat was ok the last time he looked at it.”
“I don’t do surveys.”

not idiopathic per patient

“too busy, husband advised against it”

Pregnant, baby came early, feeling too overwhelmed

Made her nervous and mentally anxious

“changed my mind, I’m in a study already”

“husband and I are traveling the world for the next year, may have difficulty with internet in some countries. We also have limited packing space.

Now that I see what is involved in the study, I have decided that I do not wish to take part, but thank you for doing this, and for including me”.

“I am not interested at this time. Thank you.”

As much as I’d like to participate my treatment began over 15yrs ago & its just too difficult for me to get the data you want for your study. So sorry I won’t be participating but you’re doing a great job!

“I appreciate your email. I will absolutely participate at some point (although your study might well be over then). Perhaps, take me off for now since I have been a bit consumed with other health issues. Unfortunately, this was pushed down in priority. My apologies. I am having open heart surgery sometime in the next month or two.

declined to participate via voice message, it stated, “I don’t know how to complete the surveys and will send them back. She also stated she was 74 yrs old and doesn’t understand a lot of things in the survey.

“I was very much interested in being a part of this study until I found out that I have to release my medical records. I’m sure you would be careful with the information, but who knows where else they would end up floating around. So, I decided not to participate.

“I don't believe I am interested in participating. I have done fabulously since my tracheal resection so I don't visit regularly.

“I'm sorry, I was going to but I have a lot going on right now. Maybe next year.
“I'm so glad research is being done on this disease, however I have to decline participating. I'll be moving to California and can't obligate myself to the testing involved. “I do not wish to participate in your study, but thank you for your consideration”.

“Hi I’ve decided not to participate at this time.”

Although I really want to participate, I'm afraid I will not be able to commit to all the requirements. I think it’s important to be honest up front.”

Hello. Thank you for the follow-up. I haven't been well lately and haven't kept up with email. After reviewing the attached, I think it will be difficult for me to commit to this project at this time. Thank you and best of luck with the study”.

“ I have reviewed the consent as well as the PHI consent. I then reviewed this with a family member who is involved with research. I have decided that I am not comfortable with the release of personal health information consent parameters so am no longer able to participate in the study. I would like to thank you for taking the time to answer my questions and wish you the best with the study.

“after thinking about what is involved with the study, I have decided not to participate in it”. 

“Have decided not to participate, too much time involved. Sorry”
Our systematic effort documenting reasons for 35 formal withdrawals.
Withdrawals occurred after consent, but before initial intake questions were completed.

138- per email, stated she had tonsillitis during month of Feb 2016 and wasn’t able to complete surveys, so she didn’t want to pursue study.

280- per email, Due to family reasons, stated she was unable to continue participation

307- per email- “Apparently I am unable to complete the survey. Please forget about it.”

328- per email “ I’m sorry. Since I signed up for this, too many life changes have taken place and I no longer have the time to devoted to this study.”

341- Called to state she wanted to withdraw from the study, as her husband was not comfortable with the release of medical information.

392- per email, the day she signed the consent she was in “total overload,” states she would not have the daily commitment to complete short or long term

269a- per phone call, stated she didn’t want to perform the peak flow readings, I told her she could do at her convenience, she still opted out of the study.

151a- per email, “While I would like to assist, I will withdraw consent to participate. Will look forward to your results!”

575- no reason cited

414- “against my religion to use technology”

451- “ just too much right now, she is a diabetic with an infected foot and will be receiving 4-6 weeks of daily IV antibiotics, too overwhelmed at this time”.

418- receiving cancer treatments

320- withdrew due to vasculitis

245- “too much going on, right now”

495a- Sub-Investigator withdrew her due to medical reasons

482a- withdrew as she didn’t want to submit her social security number
408- problems with her computer, offered to mail or call

594- cited health reasons

653- no reason cited

556- “I am opting to no longer participate in this study. thanks”.

804- “We have had some bad health news for my husband, so I will need to pull out of this study”.

772- left me a voice message this morning withdrawing consent to participate in the study. She stated, “it took too much of her time”.

847- - “Sorry it has taken me so long to get back to you. Things here have been just a little busy. I’m sorry but I think that I really do want to withdraw from the study. I just have enough here to take care of that will keep me plenty busy. I really appreciate all the help you have given me. Thank you,”

935- I called to determine if she wanted the surveys mailed or if she had an email address and wanted to complete them online. Per the male who answered the phone as he said she was driving (she was talking to me in the background). She stated, “I don’t want to have anything to do with that study, besides I just saw my primary care doctor and they haven’t even done a blood test yet,” I’m not having any procedure or any of that stuff. I asked so does this mean you don’t want to participate in the study and she replied, “yes, just cancel everything”.

790- “I am so far overcommitted at this time that I can’t help with your study”.

944- – “Thank you for the info. I have changed my mind and decided not to participate in the study. Could you please remove my information from your system?”

684- “I attempted to participate in this study some time ago and in fact did do an initial survey. However, after that, there seemed to be problems with the technology that I had available working with the technology that your study was using. At this time, I think I will withdraw from the study so that we all have less frustration with my technology limitations!

968- “I am opting out of this study. Please remove my name from all correspondence. Thank you!

295- coordinator at Mayo withdrew participant due to patient request (no reason cited)

429- coordinator at Mayo withdrew participant due to patient request (no reason cited)

395- coordinator at Mayo withdrew participant due to patient request (no reason cited)
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