

Prospective Multi-arm Evaluation of Surgical Treatments for Vocal Fold Scar and Pathologic Sulcus Vocalis

Nathan V. Welham, PhD; Seong Hee Choi, PhD; Seth H. Dailey, MD; Charles N. Ford, MD;
Jack J. Jiang, MD, PhD; Diane M. Bless, PhD

Objectives/Hypothesis: The purpose of this study was to compare the clinical effectiveness of type I thyroplasty, injection laryngoplasty, and graft implantation for the treatment of vocal fold scar and pathologic sulcus vocalis.

Study Design: Prospective, multi-arm, quasi-experimental research design.

Methods: Twenty-eight patients with newly diagnosed vocal fold scar and/or pathologic sulcus vocalis were assigned to one of three treatment modalities: type I thyroplasty ($n = 9$), injection laryngoplasty ($n = 9$), and graft implantation ($n = 10$). Psychosocial, auditory-perceptual, acoustic, aerodynamic, and videostroboscopic data were collected pretreatment and at 1, 6, 12, and 18 months posttreatment.

Results: Type I thyroplasty and graft implantation both resulted in reduced voice handicap with no concomitant improvement in auditory-perceptual, acoustic, aerodynamic, or vocal fold physiologic performance. Injection laryngoplasty resulted in no improvement on any vocal function index. Patients who underwent graft implantation exhibited the slowest improvement trajectory across the 18-month follow-up period.

Conclusions: A persistent challenge in this area is that no single treatment modality is successful for the majority of patients, and there is no evidence-based decision algorithm for matching a given treatment to a given patient. Progress therefore requires the identification and categorization of predictive clinical features that can drive evidence-based treatment assignment.

Key Words: Larynx, phonosurgery, sulcus vocalis, treatment efficacy, vocal fold scar.

Level of Evidence: 2b.

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INTRODUCTION

Vocal fold scar and pathologic sulcus vocalis are related but challenging clinical entities characterized by fibrotic changes to the vocal fold mucosa,¹ an often irreversible loss of tissue viscoelasticity and vibratory potential,^{2–4} profound dysphonia,^{5,6} and significant voice handicap.^{7,8} Both conditions involve physical disruption of the vocal fold edge contour (due to scar contraction and/or the anatomic sulcus), disordered lamina propria extracellular matrix,^{1,9,10} and impaired glottal closure.⁵ The presentation and severity of these features can vary significantly between patients, and a certain subset of patients present with concomitant scar and sulcus

deformities.⁷ Treatment of these disorders is considered difficult, and complete voice restoration is highly unusual.^{11,12}

Current surgical approaches to the treatment of chronic vocal fold scar and pathologic sulcus focus on enhancing glottal closure/efficiency via medialization, and/or improving vocal fold vibratory potential by direct manipulation of the lamina propria.¹³ The classic medialization approaches of type I thyroplasty and injection laryngoplasty are familiar to most surgeons and generally considered robust.^{14–18} Approaches to treatment of the lamina propria are more challenging and include scar/sulcus excision,^{19–21} undermining and release,^{22,23} mucosal slicing,²⁴ superficial implantation of autologous fat, fascia, or other scaffold materials,^{25–34} superficial injection of steroids or regenerative biomaterials,^{35–37} and pulsed dye laser irradiation.³⁸

Each of these approaches, whether used individually or in combination, have demonstrated some degree of therapeutic benefit in retrospective case review and prospective, single-arm studies; however, there are currently no prospective, multi-arm comparisons of relative treatment efficacy for vocal fold scar or pathologic sulcus vocalis in the clinical literature. Such comparative studies are necessary to demonstrate relative treatment efficacy and provide data-driven guidance for clinical/surgical decision making. The purpose of this study, therefore, was to compare the clinical effectiveness of

From the Division of Otolaryngology, Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison Wisconsin, U.S.A.

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Send correspondence to Dr. Nathan V. Welham, K4/723 CSC, 600 Highland Avenue, Madison, WI 53792. E-mail: welham@surgery.wisc.edu
The National Institute on Deafness and Other Communicative Disorders
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TABLE I.
Patient Demographic, Diagnostic, and Treatment Information.

Treatment Group	Thyroplasty (n = 9)	Injection (n = 9)	Graft (n = 10)	Total (n = 28)
Sex				
Male	3	7	1	11
Female	6	2	9	17
Mean age, years (SD)	48.2 (6.6)	58.7 (12.8)	56.5 (12.2)	54.5 (10.6)
Diagnosis				
Vocal fold scar	2	2	1	6
Pathologic sulcus vocalis	2	3	3	7
Both	5	4	6	15
Treatment material				
ePTFE	9	—	—	9
Calcium hydroxyapatite	—	2	—	2
BDDE crosslinked HA	—	2	—	2
Micronized acellular dermal matrix	—	5	—	5
Acellular dermal matrix	—	—	7	7
Autologous fascia	—	—	3	3

SD = standard deviation; ePTFE = expanded polytetrafluoroethylene; BDDE = butanediol diglycidyl ether; HA = hyaluronic acid.

three treatment modalities (type I thyroplasty, injection laryngoplasty, and graft implantation) using a prospective, nonrandomized, quasi-experimental research design. We elected to compare these specific treatments because they represent the three most cited approaches to vocal fold scar and pathologic sulcus vocalis management in the clinical literature, and because they attempt to address the two primary aspects of voice impairment associated with these conditions: glottal incompetence (type I thyroplasty, injection laryngoplasty) and lamina propria extracellular matrix disruption (graft implantation).^{13,23} We focused on direct comparison of these treatment modalities irrespective of the implant or injectate material delivered to the larynx, and followed patients for 18 months posttreatment.

MATERIALS AND METHODS

Patients

Twenty-eight patients with a clinical diagnosis of vocal fold scar and/or pathologic (types II or III)²³ sulcus vocalis were enrolled in this study (Table I). All patients were enrolled during an initial diagnostic visit and had not undergone any form of intervention (surgical or behavioral) at the time of enrollment. The diagnosis and classification of sulcus vocalis were made by a laryngologist following videostroboscopic examination of the larynx performed by a speech-language pathologist, and confirmed or revised by the laryngologist during subsequent direct microlaryngoscopy. Vocal fold scar was diagnosed using the same procedures. For the purposes of this study, vocal fold scar concomitant with sulcus vocalis was defined as any degree of reduced tissue pliability and apparent fibrosis in a region distinct from the sulcus.

Interventions

Patients were assigned to one of three treatment modalities: Type I thyroplasty (n = 9), injection laryngoplasty (n = 9), and graft implantation (n = 10). Treatment assignment was not randomized but rather determined by the laryngologist based on clinical judgment of the pathology and major factors causing the dysphonia. Generally, injection laryngoplasty was used for relatively small volumetric deficiencies with limited scar contracture. Type I thyroplasty was used for larger deficiencies where preoperative manual compression of the thyroid alae yielded a perceptible improvement in voice quality, and graft implantation was reserved for large deficiencies associated with extensive scarring and/or deep sulci. Neither the laryngologist nor the patient was blinded to the treatment condition. The implant or injectate material administered to each patient was determined by the laryngologist and, with the exception of expanded polytetrafluoroethylene (ePTFE; GoreTex[®], Gore Medical, Flagstaff, AZ) thyroplasty, varied across patients within each treatment group (Table I). Patients with unilateral pathology received unilateral treatment; patients with bilateral pathology received bilateral treatments. All surgical interventions were administered by one of two laryngologists. Postoperative voice rest was 24 to 48 hours in all cases. All patients received routine perioperative behavioral voice therapy (1–3 sessions) consisting of vocal hygiene education, resonant voice and accent method instruction, and (in cases of presumed compensatory hyperfunction) extrinsic laryngeal muscle repositioning. In each case, all voice therapy was administered by a single speech-language pathologist.

Type I Thyroplasty Type I thyroplasty was performed as described by Isshiki et al.³⁹ with additional modifications according to McCulloch et al.⁴⁰ After confirmation of bilateral vocal fold mobility (prior to local or intravenous anesthesia), the soft tissues of the neck were infused at the level of the inferior border of the thyroid cartilage, where a 4- to 5-cm incision was made. Subplatysmal flaps were raised, and the strap muscles were split in the midline to expose the larynx. The sternohyoid and thyrohyoid muscles were separated, and an inferiorly based perichondrial flap was elevated. Next, a standard thyroid cartilage window was created, with its superior limit no higher than the midpoint between the thyroid notch and the inferior border of the thyroid cartilage at the midline. The anterior limit was no closer than 6 mm from the midline, the inferior limit was no closer than 3 mm from the inferior border, and the posterior limit was generally no farther than 10 mm from the anterior margin of the window. The cartilage window was incised with an oscillating saw, removed, and retained for later replacement. The strut of thyroid cartilage immediately inferior to the window was liberated from its surrounding soft tissues to allow wrapping and/or suturing of the implant to that region to prevent migration. The ePTFE implant was then inserted through the thyroid cartilage window with a bias toward placement at and below the level of the true vocal fold. Implant placement was fine-tuned via auditory-perceptual judgment of voice quality produced by the awake patient and visual-perceptual judgment of medialization obtained using simultaneous transnasal flexible endoscopy of the larynx. In cases of bilateral thyroplasty, implant placement was performed after the creation of both thyroid cartilage windows. Once satisfactory medialization was achieved, the cartilage window and perichondrial flaps were replaced and the wound closed in layers over a passive drain.

Injection Laryngoplasty All injection laryngoplasty procedures were performed in the clinic setting using a transoral approach and topical and/or local anesthesia. With the patient seated upright and leaning forward, the posterior oral cavity and oropharynx were lightly anesthetized using atomized 4%

topical lidocaine. Next, three doses of 0.5 to 1.0 mL 4% topical lidocaine were delivered to the supraglottis and glottis using an Abraham cannula while the patient produced a sustained [i] vowel, with simultaneous visualization using a 70° rigid endoscope attached to a light source and video monitoring system (RLS9100B; Kay Elemetrics, Lincoln Park, NJ). Vocal fold injections were performed using a curved orolaryngeal injector needle (Medtronic/Xomed, Minneapolis, MN) for the delivery of butanediol diglycidyl ether crosslinked hyaluronic acid (BDDE crosslinked HA; Restylane®, Medicis Aesthetics, Scottsdale, AZ; $n = 2$) and micronized acellular dermal matrix (Cymetra®, LifeCell, Branchburg, NJ; $n = 5$), and the manufacturer's proprietary needle (bent to accommodate the transoral approach) for the delivery of calcium hydroxyapatite (Radiess® Voice, BioForm, San Mateo, CA; $n = 2$). Each injection targeted the paraglottic space musculature at the junction of the posterior and middle thirds of the vocal fold, to avoid the possibility of either arytenoid rotation or anterior vocal fold overcorrection. The injectate material (0.2–0.8 mL per vocal fold) was delivered to both the infraglottic and glottic regions, and the procedure was terminated when mild overcorrection was achieved at the level of the glottis.

Graft Implantation Under adequate anesthesia, a Zeitels glottiscope (Endocraft, Boston, MA) was introduced to lateralize the false vocal folds to expose the true vocal fold superior surface. All subsequent vocal fold dissection and implantation procedures were performed using an operating microscope. A linear incision was placed laterally with a sharp sickle knife and extended parallel to the vocal fold edge, extending just beyond the length of the scar/sulcus deformity. This incision afforded the development of a lateral flap, identification of the vocal ligament, and placement of a securing suture away from the vocal fold medial edge. A sharp dissection technique was used to maintain flap integrity. The flap was developed by extending the dissection 2 to 3 mm inferior to the plane of the scar/sulcus. In each case, the intention was to create a sufficiently large pocket to allow straightforward placement of the graft followed by closure of the mucosal incision with minimal tension. Temporalis fascia, harvested from the retroauricular area ($n = 3$), and acellular dermal matrix (AlloDerm®, LifeCell, Branchburg, NJ; $n = 7$) graft materials were used. The implantation procedure was identical for both materials. The graft material was trimmed to fit inside the pocket without tension, and a single 6-0 catgut suture was employed to coapt the free edges of the flap.

Vocal Function Measures

Psychosocial, auditory-perceptual, acoustic, aerodynamic, and videostroboscopic data were collected less than 1 month prior to treatment and 1, 6, 12, and 18 months posttreatment. A single speech-language pathologist with doctoral-level training and 10 years of experience evaluating patients with voice disorders conducted all data collection sessions.

Psychosocial analysis The voice handicap index (VHI) was presented in the format described by Jacobson et al.⁴¹ The VHI total score was calculated and then recalculated to eliminate tallying errors. The VHI emotional, physical, and functional subscales were not employed.

Auditory-Perceptual Analysis Patients were instructed to produce a 3- to 4-second sustained [a] vowel token and the standard phrase “the blue spot is on the key again” at comfortable pitch and loudness levels. Voice samples were recorded using a unidirectional cardioid microphone (SM58; Shure, Niles, IL) placed 10 cm from the lips at a 45° angle, connected to a preamplifier (Bluetube DP; PreSonus, Baton Rouge, LA) and digital audio tape (DAT) recorder (Fostex D-5; Foster Electric,

Schaumburg, IL). Digitization was performed using a 44.1 kHz sampling rate and 16-bit quantization.

A digital copy of each sample was transferred from DAT to desktop computer, sample order was randomized, and sample identity was masked prior to analysis. Auditory-perceptual ratings were performed in a quiet room and samples (sustained vowels and connected speech) were presented at approximately 70 dB sound pressure level (SPL) using headphones (HD 238; Sennheiser, Old Lyme, CT). Ratings were performed using the using the Grade component of the GRBAS scale⁴² by a doctoral-level speech-language pathologist with seven years of experience evaluating patients with voice disorders. A second speech-language pathologist with 10 years of comparable experience performed reliability ratings on 10% of samples. Inter-rater agreement (Spearman's ρ) was 0.81.

Acoustic Analysis Pitch range was elicited using the recording setup reported above. Patients were instructed to produce both ascending and descending pitch glides beginning at a comfortable pitch. Each task was repeated until the speech-language pathologist was satisfied maximum performance was achieved. Maximum and minimum F_0 were measured using CSpeech 4.0 (Paul Milenkovic, Madison, WI). Maximum F_0 was defined as including falsetto register; minimum F_0 was defined as excluding pulse register. F_0 range was calculated and then converted to pitch range in semitones (ST).

Acoustic perturbation values (percent jitter, percent shimmer, signal-to-noise ratio [SNR]) were extracted from a 1-second steady-state portion of the same sustained [a] vowel used for auditory-perceptual analysis. Analyses were performed using CSpeech 4.0. The correlation dimension (D_2) acoustic parameter was also measured, based on recent work demonstrating the value of nonlinear dynamic analysis in the characterization of severely aperiodic voice signals.^{43–46} D_2 was measured using a previously reported algorithm.^{47,48}

Aerodynamic Analysis Phonation threshold pressure (P_{th}) data were collected using a custom-built aerodynamic measurement system. A 3-mm-bore pressure tube was placed inside the mouth perpendicular to the airstream (slightly past the front incisors), passed through a pneumotachograph mask, and attached to a narrow-band pressure transducer. A second (wide-band) pressure transducer was used to measure flow output from the mask. A microphone was positioned adjacent to the mask to record the acoustic voice signal.

Patients were trained to produce a series of repeated [pi] syllables on a single breath, starting at a whisper and gradually increasing subglottal pressure (P_s) until phonation was initiated. Once the speech-language pathologist was satisfied with patient training, the pneumotachograph mask was set in place and the [pi] syllable train task was performed five times. All productions occurred at a comfortable pitch level and were paced at approximately 1.5 syllables per second.

Pressure and flow calibration were performed before each data collection session. Signals were digitized at 8.33 Hz and 12-bit quantization using a desktop computer and CSpeech 4.0. Pressure peaks were investigated for suitable waveform morphology, and extremely sharp, shallow, or irregular-shaped peaks were eliminated from the analysis. The pressure peak in each train that corresponded with the initiation of phonation (as observed on the acoustic channel) was used for the analysis. Mean P_{th} was calculated by averaging the maximum pressure at this peak across the five trains.

Videostroboscopic Analysis Laryngeal imaging was performed using a Kay Elemetrics RLS 9100B system attached to a 70° rigid endoscope. Laryngeal maneuvers were observed using both halogen and stroboscopic light. Phonation was elicited at low, comfortable, and high pitches and with gradual

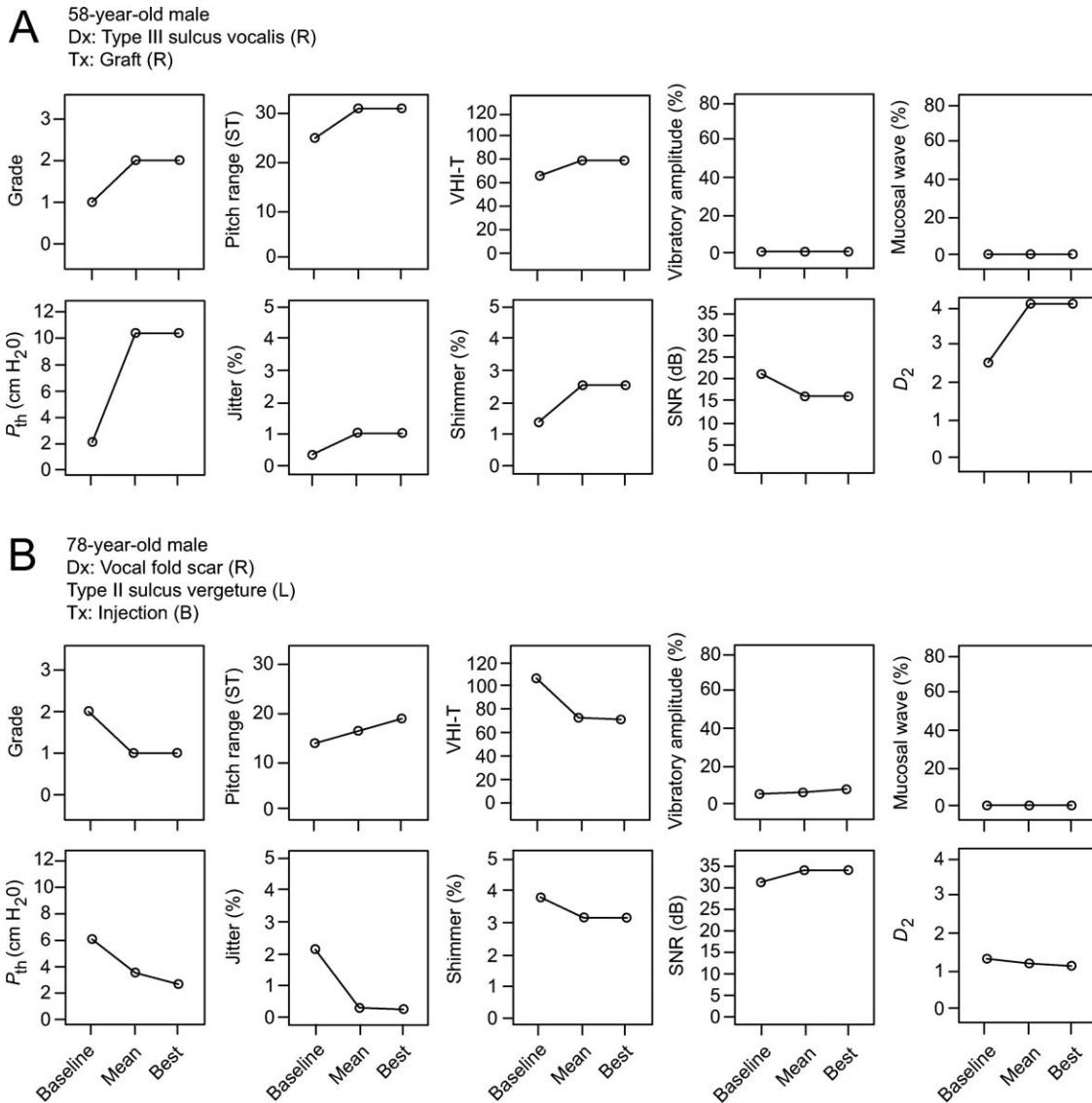


Fig. 1. Representative clinical cases illustrating negative and positive outcomes following treatment for vocal fold scarring and pathologic sulcus vocalis. Fig. 1A contains vocal function data collected from a 58-year-old male patient with right-sided type III sulcus vocalis treated with an acellular dermal matrix graft. This patient demonstrated improved pitch range and no change/deterioration on all other indices. Videostroboscopic closure pattern was spindle-shaped on both pretreatment and all posttreatment examinations. Fig. 1B contains vocal function data collected from a 78-year-old male patient with right-sided vocal fold scar and left-sided type II sulcus vergeture treated with bilateral calcium hydroxyapatite injections. This patient demonstrated improvement on all indices except mucosal wave excursion. Videostroboscopic closure pattern was spindle-shaped on both pretreatment and all posttreatment examinations. Vocal function data are graphed as pretreatment baseline value, mean posttreatment value across an 18-month period, and best posttreatment value at any time point within this 18-month period. B = bilateral; D_2 = correlation dimension; Dx = diagnosis; L = left; P_{th} = phonation threshold pressure; R = right; SNR = signal-to-noise ratio; ST = semitone; Tx = treatment; VHI-T = voice handicap index total score.

increases in loudness. The larynx was also observed at rest, during deep inspiration, and during inhalation phonation.

Videostroboscopic ratings were performed independently by the same two speech-language pathologists who performed the auditory-perceptual ratings. Patient identity and pre- or posttreatment time point were masked in all samples. Presentation order was randomized. To validate comparison across measurement points, all ratings were confined to phonation segments produced at comfortable pitch and loudness levels.

Ratings focused on vocal fold vibratory amplitude and mucosal wave excursion were performed using the SERF instrument.⁴⁹ These indices were selected because they are direct physiologic correlates of mucosal pliability and can be

expressed quantitatively as a percentage of vocal fold width in the medial-lateral plane. Percentage excursion for each parameter was rated using a scale resolution of 10% of total vocal fold medial-lateral width. Values were then averaged across left and right vocal folds. Inter-rater agreement (Spearman's ρ) was 0.85.

Statistical Analysis

Pretreatment baseline value, mean posttreatment value across an 18-month period, best posttreatment value within this 18-month period, number of vocal function indices showing posttreatment improvement/deterioration/no change,

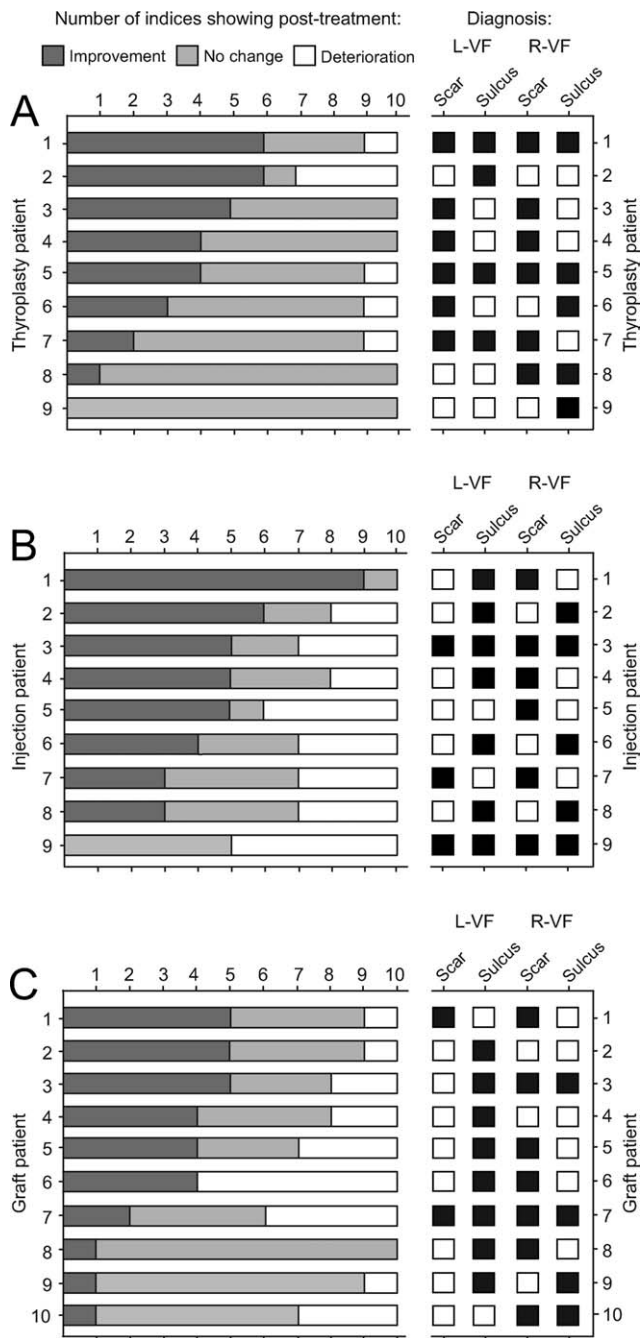


Fig. 2. Distribution of the number of vocal function indices showing mean posttreatment improvement, no change, or deterioration following type I thyroplasty (A; n = 9), injection laryngoplasty (B; n = 9) and graft implantation (C; n = 10) treatments for vocal fold scarring and pathologic sulcus vocalis. Data are presented by individual patient on the left; key diagnostic information for each patient is presented on the right. Mean posttreatment change reflects an 18-month follow-up period. L-VF = left vocal fold; R-VF = right vocal fold.

and duration to best posttreatment value were calculated for all indices to facilitate visual and statistical comparisons. Individual patient data were analyzed using graphing and visual inspection, and group data were analyzed using one-way ANOVAs with treatment modality as a fixed effect. An α -level of .05 was employed for all statistical testing; all *P* values were two-sided.

RESULTS

We observed a wide variation in treatment response across individual patients and treatment groups. Certain patients exhibited general deterioration reflected by the majority of vocal function indices (for a representative case, see Fig. 1A), whereas others experienced robust improvement across indices (for a representative case, see Fig. 1B). Eleven patients (three thyroplasty, five injection, three graft) demonstrated improvement in at least five of 10 indices; two patients (one injection, one graft) demonstrated deterioration in at least five of 10 indices; 21 patients (seven thyroplasty, 11 injection, three graft) demonstrated no change in at least five of 10 indices (Fig. 2). Overall positive or negative outcome did not appear to correspond to pathologic sulcus subtype, the presence of sulcus with or without concomitant scar, or the presence of unilateral versus bilateral pathology (Fig. 2).

Analysis of group data revealed statistically significant improvement in mean and best posttreatment VHI total scores for the thyroplasty group, and best posttreatment VHI total score for the graft group (Fig. 3). All other vocal fold function indices demonstrated non-significant posttreatment changes. Mucosal wave excursion and vibratory amplitude exhibited the greatest variance across patients.

Analysis of duration to best posttreatment value revealed clear differences between treatment modalities. Patients in the graft group exhibited the slowest trajectory of improvement across all vocal function indices: 100% of these patients obtained maximum improvement in eight of 10 indices at 18 months posttreatment (Fig. 4); the exceptional indices were pitch range and D_2 , which reached the 100% plateau at 12 months posttreatment. In contrast, 100% of patients in the injection group obtained maximum improvement in the majority of indices (eight of 10) by six months posttreatment, and 100% of patients in the thyroplasty group obtained maximum improvement in the majority of indices (seven of 10) by 12 months posttreatment. P_{th} demonstrated the most rapid course to stability of any outcome measure in any group, exhibiting maximum improvement in 100% of thyroplasty patients at 1 month posttreatment.

DISCUSSION

The purpose of this study was to compare the clinical effectiveness of type I thyroplasty, injection laryngoplasty, and graft implantation for the treatment of vocal fold scar and pathologic sulcus vocalis, using a prospective, quasi-experimental research design. To our knowledge, this study represents the first multi-arm treatment comparison for these disorders in the clinical literature. No single treatment modality demonstrated clear superiority across the majority of vocal function indices used. Type I thyroplasty and graft implantation both resulted in improved VHI with no concomitant improvement in auditory-perceptual, acoustic, aerodynamic, or vocal fold physiologic performance. Injection laryngoplasty resulted in no improvement on any vocal function index. Patients who underwent graft

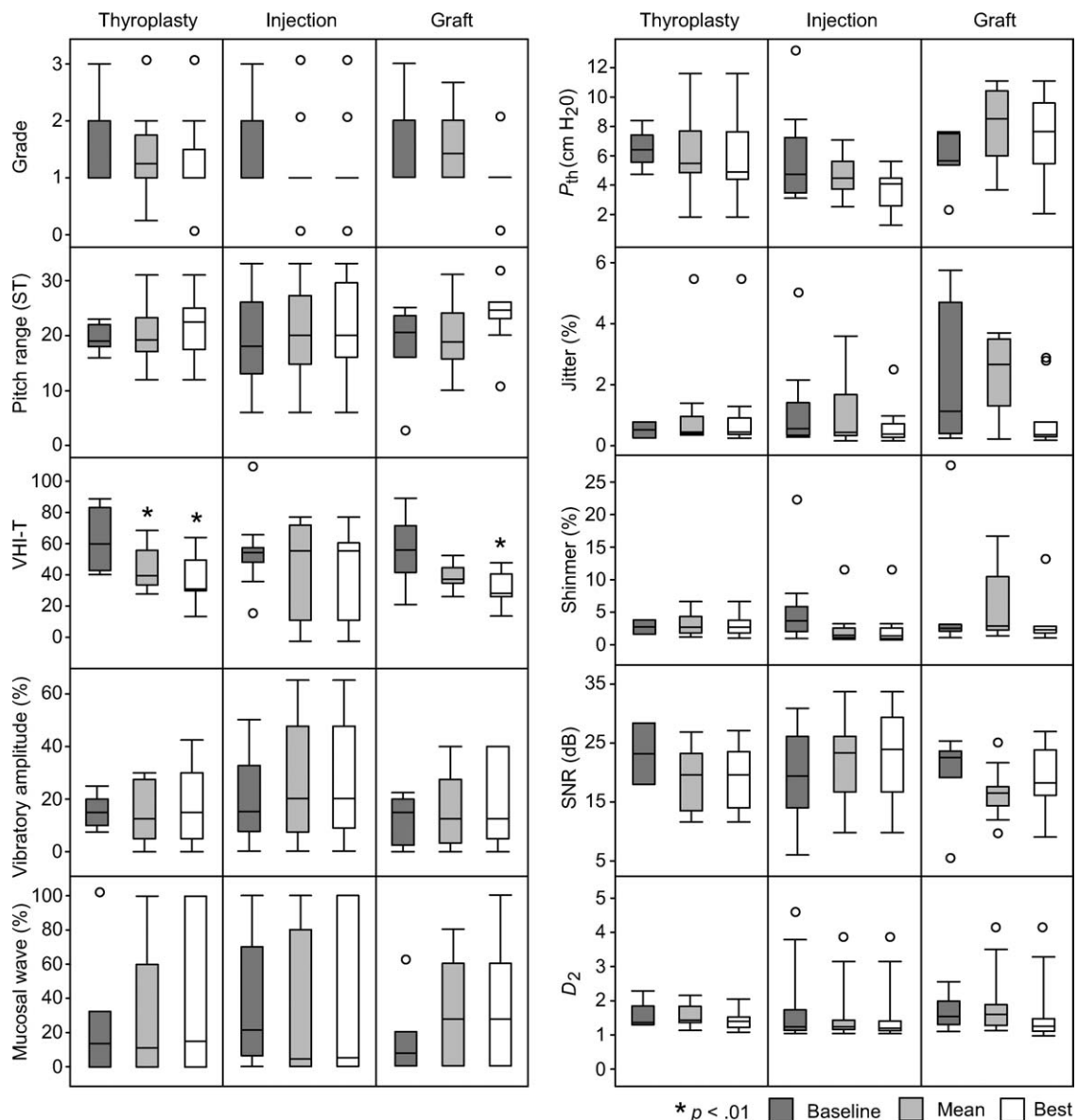


Fig. 3. Group analysis of outcomes following type I thyroplasty (n = 9), injection laryngoplasty (n = 9), and graft implantation (n = 10) treatments for vocal fold scarring and pathologic sulcus vocalis. Vocal function data are graphed as pretreatment baseline value, mean posttreatment value across an 18-month period, and best posttreatment value at any time point within this 18-month period. D_2 = correlation dimension; P_{th} = phonation threshold pressure; SNR = signal-to-noise ratio; ST = semitone; VHI-T = voice handicap index total score.

implantation exhibited the slowest trajectory of improvement across the 18-month follow-up period.

Type I thyroplasty resulted in improved mean and best posttreatment VHI total scores, whereas graft implementation resulted in improved best posttreatment score only. This discrepancy was most likely due to the relatively slow trajectory of improvement in the graft group, leading to significantly improved VHI scores at a smaller number of (later occurring) postoperative time points and a relatively smaller magnitude change in mean outcome. Given that VHI outcome at 18 months posttreatment was equivalent, but recovery trajectory was slower, our data do not support graft implantation over type I thyroplasty as a primary treatment modality for patients with vocal fold scar/sulcus. A prolonged and

gradual recovery period is well documented following graft implantation to the lamina propria,^{25,29,30,32} as such, it is possible that a number of patients in the graft group experienced meaningful improvement beyond 18 months posttreatment. If so, there may be therapeutic value with this approach that was not captured in our dataset.

Discordance between the VHI and other vocal fold function measures, as seen in our dataset, has been reported in a number of studies. Cheng and Woo⁵⁰ identified significant improvement in VHI total score after surgical removal of benign vocal fold lesions in 21 patients but no change in 12 of 13 acoustic and aerodynamic parameters. The majority of these instrumental parameters did not correlate with the VHI. Lau et al.⁵¹

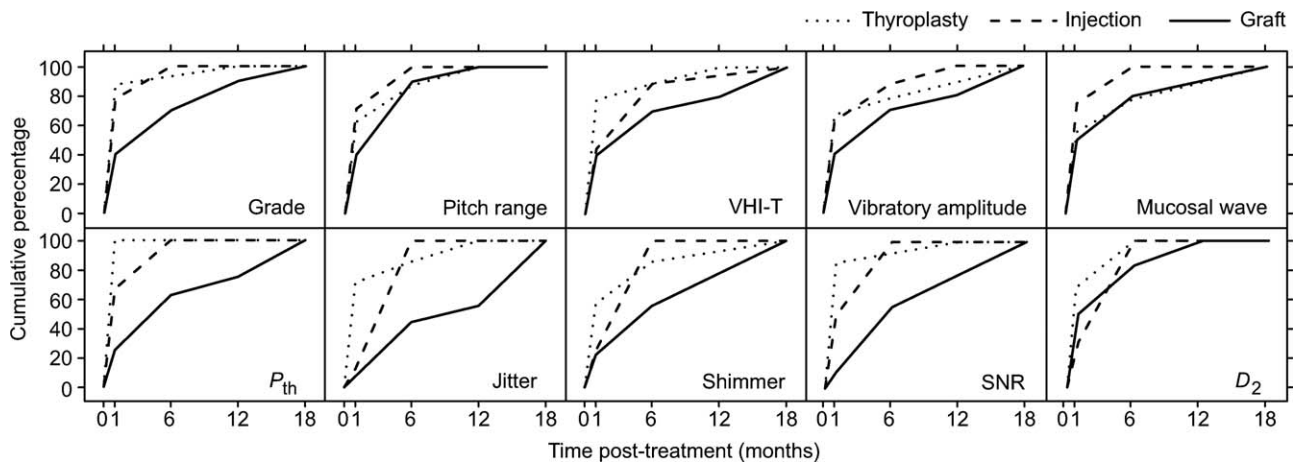


Fig. 4. Duration to best posttreatment value following type I thyroplasty (n = 9), injection laryngoplasty (n = 9), and graft implantation (n = 10) treatments for vocal fold scarring and pathologic sulcus vocalis. Best posttreatment value reflects an 18-month follow-up period. Data are presented as cumulative percentage of total patient number within each treatment group. D_2 = correlation dimension; P_{th} = phonation threshold pressure; SNR = signal-to-noise ratio; VHI-T = voice handicap index total score.

compared VHI total score and various videostroboscopic parameters in 28 patients before and after injection laryngoplasty for unilateral vocal fold paralysis. VHI total score exhibited a moderately strong correlation with closed phase duration and weak correlations with all other parameters. These findings align with the majority of descriptive (nontreatment) studies that have reported weak to moderately strong correlations between the VHI and commonly used acoustic and aerodynamic measures.^{52–55} It is intuitive that individuals with dysphonia have varying personalities, personal circumstances, social and occupational demands, and consequently perceive different degrees of voice-related handicap. Because of this, it has been suggested there is a nonlinear relationship between voice impairment, disability, and handicap.⁵⁴ Overall, the VHI captures a unique aspect of voice-related psychosocial function that is independent of (and complementary to) acoustic, aerodynamic, and physiologic voice function. In one sense, improved voice handicap represents one of the most meaningful aspects of treatment-induced change.

Our study design and implementation hold several limitations. First, we did not randomize patients to the three treatment groups. This allowed the laryngologist to assign patients to the presumed most-appropriate treatment based on presentation, therefore reflecting standard clinical practice; nevertheless, our findings do not carry the weight of a randomized clinical trial. Second, we did not control for implant or injectate material but rather focused exclusively on treatment modality. This may represent a source of intratreatment variability in the dataset. Third, we administered routine perioperative voice therapy to all patients, which again reflects standard of care but also may have influenced treatment outcome. Fourth, our recruitment success and associated sample size were limited by the decision to exclude patients who had undergone prior surgical or behavioral intervention. Due to our sample size, we were unable to delineate and categorize patient subgroups

based on potentially important variables such as scar/sulcus location, unilateral versus bilateral pathology, pathologic sulcus subtype, and the presence of aggravating factors and other comorbidities. This degree of patient heterogeneity, inherent to almost any clinical scar/sulcus study, represents another source of variability. Future research efforts in this area may benefit from multi-institutional recruitment, in addition to patient randomization and (although controversial) consideration of a placebo control (i.e., sham surgery) condition. Additional experimental precautions, such as single- or double-blinding of treatment group assignment, are difficult to implement, as in-office injection laryngoplasty does not require general anesthesia, and patients/researchers can easily identify the incision sites used for thyroplasty window creation and autologous fat/fascia harvest.

We focused on three singular treatment modalities in this study, primarily due to their prominence and reported value in the clinical literature. Consequently, it is unknown how type I thyroplasty, injection laryngoplasty, and graft implantation outcomes compare to other proposed approaches such as mucosal slicing,²⁴ pulsed dye laser irradiation,³⁸ steroid injection,³⁵ and superficial injection/implantation of hyaluronic acid-based biomaterials^{36,37} or autologous fat.^{27,28,33,34} Further, we did not include combinative treatments, such as CO₂ laser excision followed by collagen injection,^{19,20} fascia implantation followed by fat injection,³² or gelatin sponge implantation followed by fat injection;²⁶ each of which holds the conceptual appeal of simultaneously or sequentially tackling glottal incompetence and lamina propria issues, with possibly compounded benefit. Finally, a number of emerging therapies involving growth factors,^{56–60} phytochemical and pharmacologic agents,^{61,62} tunable biomaterials,^{63–70} and various cell types^{71–79} await future clinical translation. Appropriate evaluation of these treatment strategies requires careful investigation in appropriately powered clinical trials.

CONCLUSIONS

Our data suggest that type I thyroplasty and graft implantation lead to reduced voice handicap in patients with vocal fold scar and pathologic sulcus vocalis; however, the improvement trajectory for patients undergoing graft implementation is relatively slow. Although select patients exhibit benefit, none of the treatment approaches evaluated in this study reliably improve auditory-perceptual, acoustic, aerodynamic, or vocal fold physiologic function. A persistent challenge in this area is that no single treatment modality is successful for the majority of patients, and there is no evidence-based decision algorithm for matching a given treatment to a given patient. Progress therefore requires the identification and categorization of predictive clinical features that can drive evidence-based treatment assignment. In the meantime, the clinician must rely on careful assessment of the pathology so that the most critical aspects are addressed during initial treatment. Where there is extensive tissue loss and glottal incompetence, tissue replacement and medialization seem appropriate first steps. Additional gains may be seen as emerging therapies are translated to clinical practice.

BIBLIOGRAPHY

- Hirano S, Minamiguchi S, Yamashita M, Ohno T, Kanemaru S, Kitamura M. Histologic characterization of human scarred vocal folds. *J Voice* 2009;23:399-407.
- Thibeault SL, Gray SD, Bless DM, Chan RW, Ford CN. Histologic and rheologic characterization of vocal fold scarring. *J Voice* 2002;16:96-104.
- Rousseau B, Hirano S, Scheidt TD, et al. Characterization of vocal fold scarring in a canine model. *Laryngoscope* 2003;113:620-627.
- Welham NV, Montequin DW, Tateya I, Tateya T, Choi SH, Bless DM. A rat excised larynx model of vocal fold scar. *J Speech Lang Hear Res* 2009;52:1008-1020.
- Hirano M, Yoshida T, Tanaka S, Hibi S. Sulcus vocalis: functional aspects. *Ann Otol Rhinol Laryngol* 1990;99:679-683.
- Kishimoto Y, Hirano S, Tateya I, Kanemaru S, Ito J. Temporal changes in vocal functions of human scarred vocal folds after cordectomy. *Laryngoscope* 2010;120:1597-1601.
- Welham NV, Dailey SH, Ford CN, Bless DM. Voice handicap evaluation of patients with pathologic sulcus vocalis. *Ann Otol Rhinol Laryngol* 2007;116:411-417.
- Rosen CA, Lee AS, Osborne J, Zullo T, Murry T. Development and validation of the voice handicap index-10. *Laryngoscope* 2004;114:1549-1556.
- Hsiung MW, Woo P, Wang HW, Su WY. A clinical classification and histopathological study of sulcus vocalis. *Eur Arch Otorhinolaryngol* 2000;257:466-468.
- Sato K, Hirano M. Electron microscopic investigation of sulcus vocalis. *Ann Otol Rhinol Laryngol* 1998;107:56-60.
- Benninger MS, Alessi D, Archer S, et al. Vocal fold scarring: current concepts and management. *Otolaryngol Head Neck Surg* 1996;115:474-482.
- Hirano S. Current treatment of vocal fold scarring. *Curr Opin Otolaryngol Head Neck Surg* 2005;13:143-147.
- Dailey SH, Ford CN. Surgical management of sulcus vocalis and vocal fold scarring. *Otolaryngol Clin North Am* 2006;39:23-42.
- Koufman JA, Isaacson G. Laryngoplastic phonosurgery. *Otolaryngol Clin North Am* 1991;24:1151-1177.
- Zeitels SM, Mauri M, Dailey SH. Medialization laryngoplasty with Gore-Tex for voice restoration secondary to glottal incompetence: indications and observations. *Ann Otol Rhinol Laryngol* 2003;112:180-184.
- Su CY, Tsai SS, Chiu JF, Cheng CA. Medialization laryngoplasty with strap muscle transposition for vocal fold atrophy with or without sulcus vocalis. *Laryngoscope* 2004;114:1106-1112.
- Bjorck G, D'Agata L, Hertegard S. Vibratory capacity and voice outcome in patients with scarred vocal folds treated with collagen injections—case studies. *Logoped Phoniatr Vocol* 2002;27:4-11.
- Ford CN, Bless DM, Loftus JM. Role of injectable collagen in the treatment of glottic insufficiency: a study of 119 patients. *Ann Otol Rhinol Laryngol* 1992;101:237-247.
- Martinez Arias A, Remacle M, Lawson G. Treatment of vocal fold scar by carbon dioxide laser and collagen injection: retrospective study on 12 patients. *Eur Arch Otorhinolaryngol* 2010;267:1409-1414.
- Remacle M, Lawson G, Degols JC, Evrard I, Jamart J. Microsurgery of sulcus vergeture with carbon dioxide laser and injectable collagen. *Ann Otol Rhinol Laryngol* 2000;109:141-148.
- Welham NV, Rousseau B, Ford CN, Bless DM. Tracking outcomes after phonosurgery for sulcus vocalis: a case report. *J Voice* 2003;17:571-578.
- Bouchayer M, Cornut G, Witzig E, Loire R, Roch JB, Bastian RW. Epidermoid cysts, sulci, and mucosal bridges of the true vocal cord: a report of 157 cases. *Laryngoscope* 1985;95:1087-1094.
- Ford CN, Inagi K, Khidr A, Bless DM, Gilchrist KW. Sulcus vocalis: a rational analytical approach to diagnosis and management. *Ann Otol Rhinol Laryngol* 1996;105:189-200.
- Pontes P, Behlau M. Treatment of sulcus vocalis: auditory perceptual and acoustical analysis of the slicing mucosa surgical technique. *J Voice* 1993;7:365-376.
- Kishimoto Y, Hirano S, Kojima T, Kanemaru S, Ito J. Implantation of an atelocollagen sheet for the treatment of vocal fold scarring and sulcus vocalis. *Ann Otol Rhinol Laryngol* 2009;118:613-620.
- Zhang F, Sprecher AJ, Wei C, Jiang JJ. Implantation of gelatin sponge combined with injection of autologous fat for sulcus vocalis. *Otolaryngol Head Neck Surg* 2010;143:198-203.
- Hsiung MW, Woo P, Minasian A, Schaefer Mojica J. Fat augmentation for glottic insufficiency. *Laryngoscope* 2000;110:1026-1033.
- Paniello RC, Sulica L, Khosla SM, Smith ME. Clinical experience with Gray's minithyrotomy procedure. *Ann Otol Rhinol Laryngol* 2008;117:437-442.
- Tsunoda K, Baer T, Niimi S. Autologous transplantation of fascia into the vocal fold: long-term results of a new phonosurgical technique for glottal incompetence. *Laryngoscope* 2001;111:453-457.
- Tsunoda K, Kondou K, Kaga K, et al. Autologous transplantation of fascia into the vocal fold: long-term result of type-1 transplantation and the future. *Laryngoscope* 2005;115:1-10.
- Pinto JA, da Silva Freitas ML, Carpes AF, Zimath P, Marquis V, Godoy L. Autologous grafts for treatment of vocal sulcus and atrophy. *Otolaryngol Head Neck Surg* 2007;137:785-791.
- Hsiung MW, Kang BH, Pai L, Su WF, Lin YH. Combination of fascia transplantation and fat injection into the vocal fold for sulcus vocalis: long-term results. *Ann Otol Rhinol Laryngol* 2004;113:359-366.
- Sataloff RT, Spiegel JR, Hawkshaw M, Rosen DC, Heuer RJ. Autologous fat implantation for vocal fold scar: a preliminary report. *J Voice* 1997;11:238-246.
- Neuenschwander MC, Sataloff RT, Abaza MM, Hawkshaw MJ, Reiter D, Spiegel JR. Management of vocal fold scar with autologous fat implantation: perceptual results. *J Voice* 2001;15:295-304.
- Mortensen M, Woo P. Office steroid injections of the larynx. *Laryngoscope* 2006;116:1735-1739.
- Molteni G, Bergamini G, Ricci-Maccarini A, et al. Auto-crosslinked hyaluronan gel injections in phonosurgery. *Otolaryngol Head Neck Surg* 2010;142:547-553.
- Hertegard S, Hallen L, Laurent C, et al. Cross-linked hyaluronan used as augmentation substance for treatment of glottal insufficiency: safety aspects and vocal fold function. *Laryngoscope* 2002;112:2211-2219.
- Mortensen MM, Woo P, Ivey C, Thompson C, Carroll L, Altman K. The use of the pulse dye laser in the treatment of vocal fold scar: a preliminary study. *Laryngoscope* 2008;118:1884-1888.
- Isshiki N, Morita H, Okamura H, Hiramoto M. Thyroplasty as a new phonosurgical technique. *Acta Otolaryngol* 1974;78:451-457.
- McCulloch TM, Hoffman HT, Andrews BT, Karnell MP. Arytenoid adduction combined with Gore-Tex medialization thyroplasty. *Laryngoscope* 2000;110:1306-1311.
- Jacobson BH, Johnson A, Grywalski C, et al. The voice handicap index (VHI): development and validation. *Am J Speech Lang Pathol* 1997;6:66-70.
- Hirano M. *Clinical Examination of Voice*. New York, NY: Springer-Verlag; 1981.
- Jiang JJ, Zhang Y, MacCallum J, Sprecher A, Zhou L. Objective acoustic analysis of pathological voices from patients with vocal nodules and polyps. *Folia Phoniatr Logop* 2009;61:342-349.
- Jiang JJ, Zhang Y, McGilligan C. Chaos in voice, from modeling to measurement. *J Voice* 2006;20:2-17.
- Maccallum JK, Cai L, Zhou L, Zhang Y, Jiang JJ. Acoustic analysis of aperiodic voice: perturbation and nonlinear dynamic properties in esophageal phonation. *J Voice* 2009;23:283-290.
- Zhang Y, Jiang JJ. Acoustic analyses of sustained and running voices from patients with laryngeal pathologies. *J Voice* 2008;22:1-9.
- Zhang Y, McGilligan C, Zhou L, Vig M, Jiang JJ. Nonlinear dynamic analysis of voices before and after surgical excision of vocal polyps. *J Acoust Soc Am* 2004;115:2270-2277.
- Zhang Y, Jiang JJ, Wallace SM, Zhou L. Comparison of nonlinear dynamic methods and perturbation methods for voice analysis. *J Acoust Soc Am* 2005;118:2551-2560.
- Poburka BJ. A new stroboscopy rating form. *J Voice* 1999;13:403-413.
- Cheng J, Woo P. Correlation between the Voice Handicap Index and voice laboratory measurements after phonosurgery. *Ear Nose Throat J* 2010;89:183-188.
- Lau DP, Zhang EZ, Wong SM, Lee G, Chan YH. Correlating voice handicap index and quantitative videostroboscopy following injection laryngoplasty for unilateral vocal paralysis. *Otolaryngol Head Neck Surg* 2010;143:190-197.
- Hsiung MW, Pai L, Wang HW. Correlation between voice handicap index and voice laboratory measurements in dysphonic patients. *Eur Arch Otorhinolaryngol* 2002;259:97-99.

53. Schindler A, Mozzanica F, Vedroly M, Maruzzi P, Ottaviani F. Correlation between the Voice Handicap Index and voice measurements in four groups of patients with dysphonia. *Otolaryngol Head Neck Surg* 2009; 141:762–769.
54. Wheeler KM, Collins SP, Sapienza CM. The relationship between VHI scores and specific acoustic measures of mildly disordered voice production. *J Voice* 2006;20:308–317.
55. Woisard V, Bodin S, Yardeni E, Puech M. The Voice Handicap Index: correlation between subjective patient response and quantitative assessment of voice. *J Voice* 2007;21:623–631.
56. Hirano S, Bless DM, Rousseau B, et al. Prevention of vocal fold scarring by topical injection of hepatocyte growth factor in a rabbit model. *Laryngoscope* 2004;114:548–556.
57. Hirano S, Bless DM, Nagai H, et al. Growth factor therapy for vocal fold scarring in a canine model. *Ann Otol Rhinol Laryngol* 2004;113: 777–785.
58. Ohno T, Hirano S, Kanemaru S, et al. Drug delivery system of hepatocyte growth factor for the treatment of vocal fold scarring in a canine model. *Ann Otol Rhinol Laryngol* 2007;116:762–769.
59. Kishimoto Y, Hirano S, Kitani Y, et al. Chronic vocal fold scar restoration with hepatocyte growth factor hydrogel. *Laryngoscope* 2009;120: 108–113.
60. Luo Y, Kobler JB, Zeitels SM, Langer R. Effects of growth factors on extracellular matrix production by vocal fold fibroblasts in 3-dimensional culture. *Tissue Eng* 2006;12:3365–3374.
61. Rousseau B, Tateya I, Lim X, Munoz-Del-Rio A, Bless DM. Investigation of anti-hyaluronidase treatment on vocal fold wound healing. *J Voice* 2006;20:443–451.
62. Akdogan O, Selcuk A, Ozcan I, et al. Activation of vocal fold healing with topical vitamin A in rabbits. *Acta Otolaryngol* 2009;129: 220–224.
63. Hansen JK, Thibeault SL, Walsh JF, Shu XZ, Prestwich GD. In vivo engineering of the vocal fold extracellular matrix with injectable hyaluronic acid hydrogels: early effects on tissue repair and biomechanics in a rabbit model. *Ann Otol Rhinol Laryngol* 2005;114:662–670.
64. Duflo S, Thibeault SL, Li W, Shu XZ, Prestwich GD. Vocal fold tissue repair in vivo using a synthetic extracellular matrix. *Tissue Eng* 2006; 12:2171–2180.
65. Thibeault SL, Klemuk SA, Smith ME, Leugers C, Prestwich G. In vivo comparison of biomimetic approaches for tissue regeneration of the scarred vocal fold. *Tissue Eng Part A* 2009;15:1481–1487.
66. Jia X, Yeo Y, Clifton RJ, et al. Hyaluronic acid-based microgels and microgel networks for vocal fold regeneration. *Biomacromolecules* 2006;7: 3336–3344.
67. Hahn MS, Teply BA, Stevens MM, Zeitels SM, Langer R. Collagen composite hydrogels for vocal fold lamina propria restoration. *Biomaterials* 2006;27:1104–1109.
68. Munoz-Pinto DJ, Jimenez-Vergara AC, Gelves LM, McMahon RE, Guiza-Arguello V, Hahn MS. Probing vocal fold fibroblast response to hyaluronan in 3D contexts. *Biotechnol Bioeng* 2009;104:821–831.
69. Kutty JK, Webb K. Mechanomimetic hydrogels for vocal fold lamina propria regeneration. *J Biomater Sci Polym Ed* 2009;20:737–756.
70. Kutty JK, Webb K. Vibration stimulates vocal mucosa-like matrix expression by hydrogel-encapsulated fibroblasts. *J Tissue Eng Regen Med* 2009;4:62–72.
71. Krishna P, Rosen CA, Branski RC, Wells A, Hebda PA. Primed fibroblasts and exogenous decorin: potential treatments for subacute vocal fold scar. *Otolaryngol Head Neck Surg* 2006;135:937–945.
72. Chhetri DK, Head C, Revazova E, Hart S, Bhuta S, Berke GS. Lamina propria replacement therapy with cultured autologous fibroblasts for vocal fold scars. *Otolaryngol Head Neck Surg* 2004;131:864–870.
73. Long JL, Zuk P, Berke GS, Chhetri DK. Epithelial differentiation of adipose-derived stem cells for laryngeal tissue engineering. *Laryngoscope* 2009;120:125–131.
74. Long JL, Neubauer J, Zhang Z, Zuk P, Berke GS, Chhetri DK. Functional testing of a tissue-engineered vocal fold cover replacement. *Otolaryngol Head Neck Surg* 2010;142:438–440.
75. Johnson BQ, Fox R, Chen X, Thibeault S. Tissue regeneration of the vocal fold using bone marrow mesenchymal stem cells and synthetic extracellular matrix injections in rats. *Laryngoscope* 2010;120:537–545.
76. Hertegard S, Cedervall J, Svensson B, et al. Viscoelastic and histologic properties in scarred rabbit vocal folds after mesenchymal stem cell injection. *Laryngoscope* 2006;116:1248–1254.
77. Cedervall J, Ahrlund-Richter L, Svensson B, et al. Injection of embryonic stem cells into scarred rabbit vocal folds enhances healing and improves viscoelasticity: short-term results. *Laryngoscope* 2007;117:2075–2081.
78. Svensson B, Nagubothu RS, Cedervall J, et al. Injection of human mesenchymal stem cells improves healing of scarred vocal folds: analysis using a xenograft model. *Laryngoscope* 2010;120:1370–1375.
79. Kanemaru S, Nakamura T, Omori K, et al. Regeneration of the vocal fold using autologous mesenchymal stem cells. *Ann Otol Rhinol Laryngol* 2003;112:915–920.