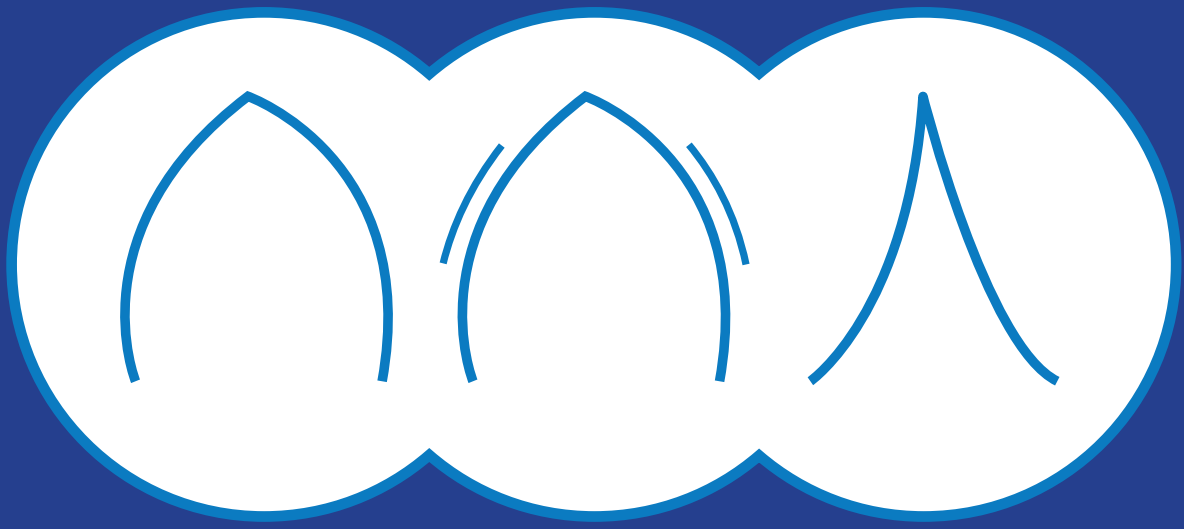
Glottic insufficiency in patients with vocal fold atrophy with or without sulcus

treatment modalities and outcome



Emke van den Broek

GLOTTIC INSUFFICIENCY IN PATIENTS WITH VOCAL FOLD ATROPHY WITH OR WITHOUT SULCUS; TREATMENT MODALITIES AND OUTCOME

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GLOTTIC INSUFFICIENCY IN PATIENTS WITH VOCAL FOLD ATROPHY WITH OR WITHOUT SULCUS; TREATMENT MODALITIES AND OUTCOME

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Voor papa “doe ze de boks op”

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General introduction

Insufficient closing of the vocal folds during phonation (glottic insufficiency) in patients with mobile vocal folds is a pathological condition which can lead to varying degrees of dysphonia, vocal fatigue and reduced quality of life. There are several causes of glottic insufficiency. In this thesis we focus on glottic insufficiency caused by vocal fold atrophy and/or sulcus and surgical treatment.

In the last decades surgical treatment options for these pathologies have expanded. There are endoscopic and external medialization procedures using different injection materials and implants. There are microphonosurgical approaches for sulcus using different excision techniques. And more recently the use of techniques from regenerative medicine have been introduced. With all these different surgical treatment modalities to choose from, in addition to variations in the underlying pathology, it is challenging to compare outcome results.

In this thesis, we focus on reporting our treatment outcomes of two surgical modalities: vocal fold injection (VFI) and laryngeal framework surgery (LFS) with bilateral medialization thyroplasty and we compare our results to other surgical techniques. We also investigate the use of outcome measurement instruments (OMIs) in this specific patient group. With our results we hope to attribute to the ultimate goal to identify the best treatment for individual patients with glottic insufficiency caused by vocal fold atrophy and/or sulcus.

In this general introduction causes of glottic insufficiency with mobile vocal folds, overview of surgical treatments and OMIs for voice quality will be further described.

ANATOMY AND PHYSIOLOGY OF THE LARYNX

To be able to understand dysfunction, one must first be familiar with normal function. Anatomy and physiology of the larynx (voice box) will therefore be briefly described.

Anatomy of the larynx

Structurally, the larynx has a cartilaginous framework consisting of the cricoid, thyroid, two arytenoids and epiglottis (Figure 1). The arytenoids are crucial for voicing. They are paired pyramidical cartilages anchored to the posterior lamina of the cricoid through the cricoarytenoid joints. Each arytenoid has a vocal process medially to which the vocal ligament is attached, and a muscular process laterally which is the attachment for the intrinsic laryngeal muscles. Through the cricothyroid joint the arytenoid has a broad reach of movement that involves rotation, sliding and tilting. The movement of the arytenoid and its vocal process outwards - abduction - is important for breathing, and the movement of the arytenoid and its vocal process moving inwards - adduction - is important for voicing (Figure 2). Between

the inferior horn of the thyroid and the posterolateral aspect of the cricoid articulates the cricothyroid joint, which allows for a change in angle between the thyroid and cricoid cartilages.

Figure 1. Cartilaginous framework of the larynx

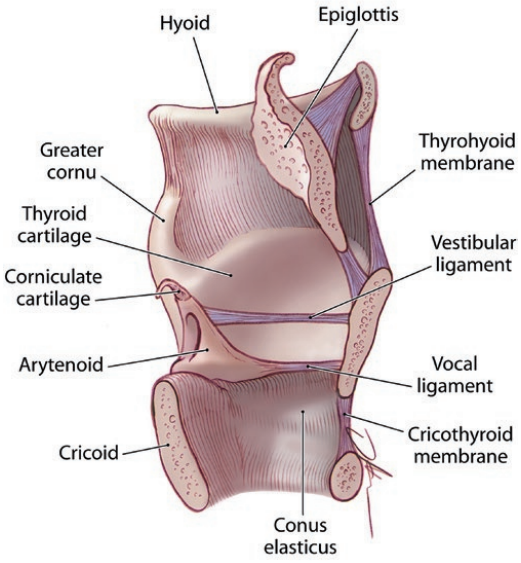

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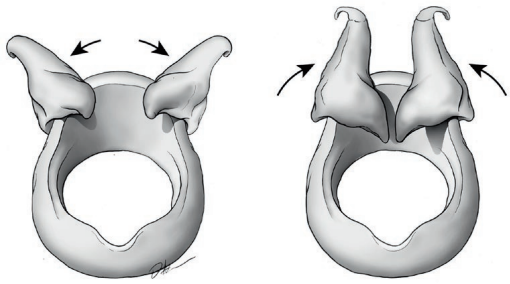
Figure 2. Cricoid, arytenoid, and cricoarytenoid joint; abduction, adduction



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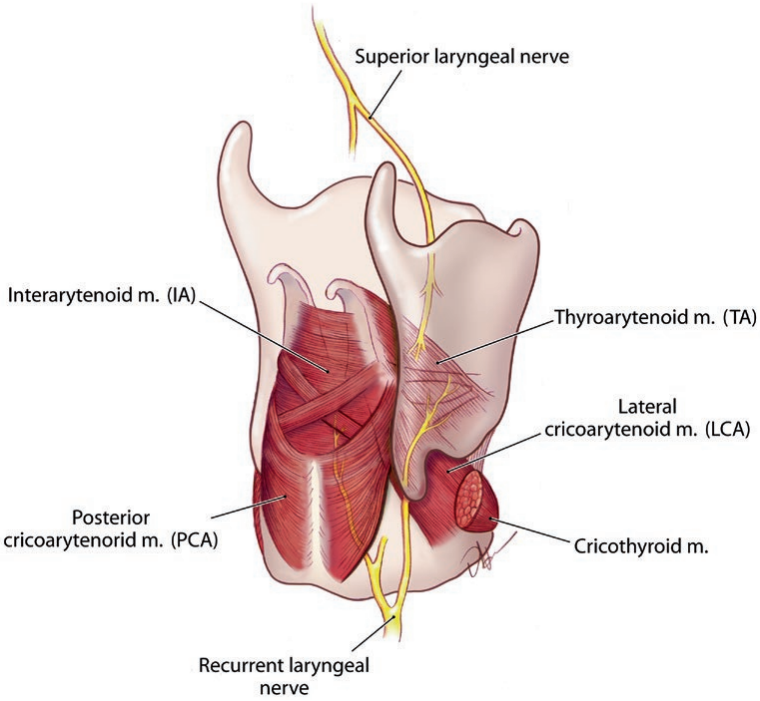
The laryngeal muscles attach to the cartilaginous framework. The extrinsic laryngeal muscles are mostly located on the outside of the larynx and move the framework as a unit upwards and downwards. They include the infrahyoid muscles (sternothyroid, sternohyoid, thyrohyoid and omohyoid muscle) and suprahyoid muscles (mylohyoid, geniohyoid, stylohoid, and

digastric muscle) and stylopharyngeus muscle. The intrinsic laryngeal muscles are smaller muscles, mostly located on the inside of the larynx, that move the separate cartilages relative to each other. There are three adducting muscles, the paired lateral cricoarytenoid (LCA) muscles and thyroarytenoid (TA) muscles, and the unpaired interarytenoid (IA) muscle. There is one abducting muscle, the posterior cricoarytenoid (PCA) muscle, and one tensor muscle, the cricothyroid (CT) muscle (Figure 3).

Figure 3. Intrinsic laryngeal muscles and nerve innervation



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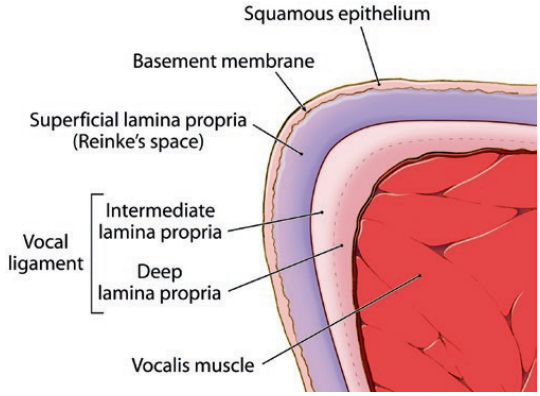
The main nerve responsible for sensory and motor input to the larynx is the vagal nerve (the Xth cranial nerve). It has three major branches: the pharyngeal branch, the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN) (Figure 3). The SLN provides sensatory innervation to the supraglottis and glottis and motor input to the cricothyroid muscle which controls vocal fold lengthening and pitch (falsetto voice). The RLN provides sensatory innervation to the subglottis and innervates all remaining intrinsic laryngeal muscles. If there is no innervation of the RNL this will result in an ipsilateral vocal fold immobility.

Anatomy of the vocal fold

The vocal fold extends from the anterior commissure to the vocal processes of the arytenoid. The true vocal fold consists of multiple (micro)layers. From the surface inwards these are the squamous epithelium, superficial lamina propria (SLP) also known as Reinke's space, intermediate (ILP) and deep lamina propria (DLP) and vocalis muscle (Figure 4). The three layers of the lamina propria - SLP, ILP and DLP - each display increasing rigidity. The SLP is gelatinous with loosely arranged collagen and elastin. In the ILP and DLP the elastin and collagen fibers are more densely organized with the deepest layer (DLP) consisting of tightly arranged collagen fibers. Together the ILP and DLP form the vocal ligament.

Figure 4. Microanatomy of the vocal fold



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Physiology of the larynx

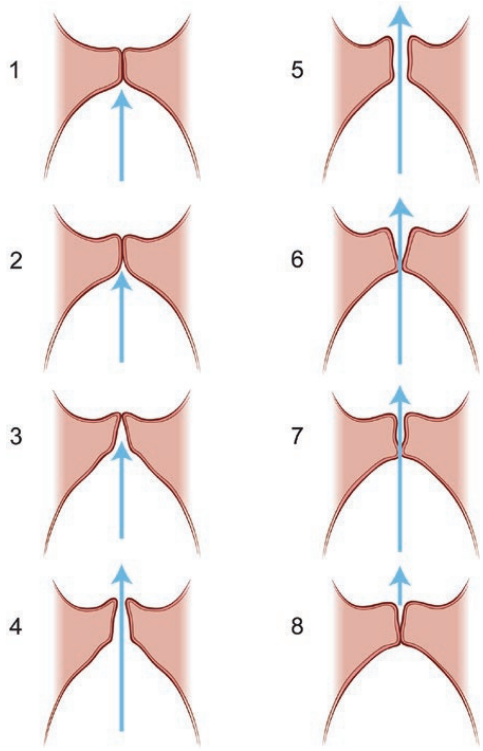
The larynx is crucial for three basic functions: breathing, swallowing and voicing. The most primitive function of the larynx is to protect the airway; opening of the glottis to breath and closing the glottis to prevent aspiration during swallowing and to allow for airway clearance during coughing. The most complex function is voicing. Voicing is based on two basic physiological principles: (1) closure of the vocal folds followed by (2) vibration of the vocal folds. For vocal fold closure, as described in anatomy of the larynx, innervation, intrinsic laryngeal muscles, arytenoids and cricoarytenoid joints play important roles. Immobility or hypomobility of a vocal fold can be caused by (partial) denervation (neurological) or by fixation of the joint (mechanical).

The second condition for voicing is vibration of the vocal fold. This phenome is described as the glottic cycle, in which short bursts of air are released through the closed vocal folds. These cyclical changes in airflow, amplified by the vocal tract consisting of the pharyngeal

wall and oral cavity are what we perceive as voice. In this process the layered microanatomy of the vocal folds (biomechanics) and pressure changes (aerodynamics) come together.

As described the vocal fold consists of layers with different stiffness. This allows the superficial layer (the cover), consisting of epithelium and SLP, to move freely over the deep layers (the body), consisting of the ILP/DLP and muscle. This is known as the body-cover-theory [2]. The underlying force for this movement is the airflow from the lungs passing through the glottis. When vocal folds are closed, the subglottal pressure builds up until it surpasses the holding pressure of the loose, superficial layers of the vocal folds, forcing the cover to move over the body. First the lower lips separate, and as a burst of air passes, the vocal folds separate completely. As airflow continues through the narrow tract between the vocal folds, air pressure will drop (Bernoulli's law) and the lower lip will draw inward and close. As long as phonation is taking place, this glottic cycle will keep on repeating (Figure 5). This fluent "wave-like" movement of superficial layer is called the mucosal wave. A regular mucosal wave will result in a clear voice, but disruption of this wave, by tension variation or disruption of the layered composition, will affect voice quality.

Figure 5. Glottic cycle



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GLOTTIC INSUFFICIENCY

Glottic insufficiency, incomplete closure of the vocal folds, leads to dysphonia. There are several underlying causes, which can be divided into two main categories: glottic insufficiency with unilateral immobile vocal fold or glottic insufficiency with mobile vocal folds. The unilateral vocal paralysis (UVFP) is a well-recognized condition and much has been written about its etiologies and treatment [1]. As this entity is not the subject of this thesis, and the same goes for the unilateral hypomobile vocal fold or vocal fold paresis, they will not be further discussed. This thesis focusses on glottic insufficiency caused by atrophy with or without sulcus in patients with normal mobility of the vocal folds.

Vocal fold atrophy

There are several forms of vocal fold atrophy. A well-known form of vocal fold atrophy is presbylaryngis. It is characterized by atrophy of the lamina propria and the

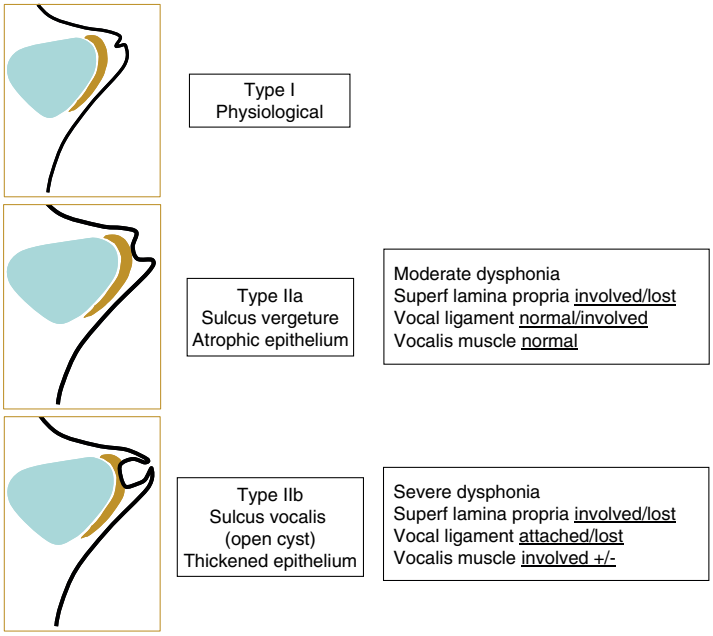
vocal fold muscles, as well as degeneration of the cartilaginous framework due to the aging process [3]. Presbyphonia is the symptomatic dysphonia resulting from presbylaryngis. Voice complaints consist of hoarseness, voice fatigue and difficulty in singing. Clinical evaluation with videolaryngostroboscopy shows bowed vocal folds with incomplete glottic closure and prominence of the vocal processes.
We have also described a form of adolescent atrophy [4]. This is seen in the younger patient population in their 2nd to 4th decade of life with main complaints of hoarseness and vocal fatigue dating back to adolescence. Laryngoscopy shows atrophy of the entire larynx, with wide supraglottic ventricles, a rounded aspect of the anterior commissure and atrophy of the true vocal folds. Interestingly, although encountered regularly at our voice clinic, it has only rarely been described in literature - although some authors have mentioned it [5]. Lastly there is atrophy in combination with sulcus as discussed below.

Sulcus
A sulcus is a groove in the vocal fold running parallel to the free edge. This groove is the result of an invagination of the outer epithelial layer onto the ligament or even onto the vocalis muscle due to atrophy and scaring of the underlying layers. This disturbance of the layered structure will lead to both stiffness and loss of volume of the vocal fold, affecting both closure and mucosal wave. It counteracts the mechanism of the “body and cover” by obstructing the formation of the mucosal wave.

Histologically sulcus vocalis interrupts the superficial layers of the lamina propria on the free edge of the vocal fold with an increase in density of collagen fibers around the sulcus. Sato and Hirano investigated the histopathologic findings of sulcus vocalis under electron microscopy and found sulcus confined to the squamous epithelium and situated in the superficial layer of lamina propria which was thin around the bottom of the sulcus. They found an increased thickness of basement membrane, dense collagenous fibers, decreased elastic fibers in numbers and with altered composition, degeneration of fibroblasts and abnormal fibrogenesis in the macula flava, the cell reservoir of the vocal folds [6].

There are several types of sulcus and these have been described in different classifications. The most used are the classifications according to Bouchayer and Cornut and according to Ford [7,8](Figure 6). Ford type I sulcus is limited to the superficial portion of the lamina propria and is considered physiological with no functional impact. Ford Type IIa sulcus, or a sulcus vergeture according to Bouchayer, is characterized by loss of superficial lamina propria resulting in an area of atrophy with epithelium being attached directly on the vocal ligament. Ford Type IIb, or a sulcus vocalis/open cyst according to Bouchayer, is a narrow invagination of the epithelium extending into the vocal ligament or even into the muscle.

Figure 6. sulcus classification (figure printed with permission [9])



Two different scenarios regarding the etiology of sulcus have been described [9]. First is the congenital origin as postulated by Bouchayer and Cornut. They propose that a sulcus is the result of a ruptured epidermoid cyst originating from the fourth or sixth branchial arch. To support their hypothesis, they used the following findings: early onset of dysphonia in childhood, absence of recurrence after excision, existence of familial cases [7]. The other scenario is that sulcus is acquired due to local trauma and/or chronic inflammatory processes. It may be well possible that congenital and acquired etiologies are complementary [9]. Contrary to sulcus, vocal fold scar is always acquired, most often after laryngeal surgery (iatrogenic), but also after trauma or chronic inflammation as reflux, smoking, or radiotherapy.

Dysphonia in patients with sulci can vary from limited to severe, including hoarseness, strain, voice fatigue and loss of voice control. Both glottic closure and mucosal wave are impaired; there is incomplete closure because of atrophy and tissue loss caused by sulcus and mucosal wave is interrupted by the fibrosis and interruptions in the lamina propria caused by sulcus. Videolaryngostroboscopy can be used for clinical evaluation of these patients, but the sulcus is not always visible which makes it challenging to diagnose. Other findings on laryngostroboscopy can be vocal fold bowing, compensatory hypertonia of the false vocal folds or associated lesions such as hypervascularity or oedema. For definite diagnosis close inspection by in-office endoscopy or suspension laryngoscopy in operating room is often needed.

THE CONCEPT OF SURGICAL TREATMENT

The treatment of glottic insufficiency caused by atrophy and/or sulcus is challenging. On the one hand, vocal fold closure needs to be corrected and on the other hand, mucosal wave needs restoring and rebuilding. This “double pathology” of atrophy/thinning of the vocal folds, but also disrupted layered structure, is more outspoken in sulcus. When treating this pathology, one has the conceptual choice of focusing on improving closure or focusing on improving vibration and mucosal wave.

Improving closure by reducing the glottic gap can be done in a procedure that approximates the vocal folds, a so-called medialization procedure. The techniques are mostly the same as in glottic insufficiency caused by UVFP, but obtaining optimal results can be more difficult in patients with mobile vocal folds.

Correction of the interrupted layered structure of the vocal fold is one of the greater challenges in laryngology. The difficulty is to find surgical techniques that (1) restore the delicate layered structure of the vocal fold and (2) replace the missing lamina propria. Many different surgical procedures have been developed and described, but series are usually small and consisting of mixed pathologies, and outcomes are not reported uniformly. New solutions are continuously being sought, for instance in the field of regenerative medicine, but unfortunately the “perfect” surgical technique has yet to be found. These constraints make it difficult to compare treatments and to decide which modalities are the most effective.

These challenges are discussed in the European Laryngological Society (ELS) consensus statement on vocal fold scarring, which states to always start with the least traumatizing procedure whenever possible, because of the unpredictability of the results of the surgical intervention. From the surgical perspective, optimizing closure is less traumatizing than improving vibration and therefor the consensus statement advices to first consider VFI techniques using a re-absorbable material.

They also emphasize that an optimal result does not only require a skilled surgeon with a broad armamentarium of surgical techniques and procedures, but also a multidisciplinary treatment approach with combining of various (non-)surgical methods [10].

SURGICAL TECHNIQUES

Management of patients with atrophy and/or sulcus can vary from no treatment to speech language therapy (SLT) and surgical procedures often in combination with each other. This

introduction gives a short overview of surgical treatment options. As already mentioned, treatment can be divided in (1) medialization procedures to improve glottic closure (2) microphonosurgical procedures to improve mucosal wave by removing/replacing disrupted tissue in case of sulcus and (3) surgery using techniques from regenerative medicine. These different options can also be used in combination.

MEDIALIZATION PROCEDURES

Vocal fold injection

There is a long history of vocal fold injection, with the first injection performed and described by Brünings in 1911 using a self-shaped syringe, the now well-known Brünings' syringe, with paraffin as the injection material [11]. At present there are several techniques for VFI with a variety of injection materials or "fillers". Procedures are performed both in general anesthesia and in-office for a range of indications from UVFP to sulcus. Injectables can be classified based on historical use, material (alloplastic, autologous, xenogenic) and lifespan. In the past, several permanent alloplastic injectables have been used such as Teflon® and silicon (polydimethylsiloxane, PDMS, Vox Implant®). With current knowledge that some of these permanent, inert materials can cause local inflammation with granulation and with the availability of more forgiving alternatives, they are now considered to be obsolete or are used sparingly [12]. Historically, a range of temporary injectables have been available both short and longer term acting. Short-term injectables that have been used in the past are bovine gelatine (Gelfoam, Surgifoam) and bovine collagen (Zyplast), both with a lifespan of about one month. Homologous collagen (Cosmoplast®, Cosmoderm® and Micronized Acellular Derma Compound (Cymetra®) with a longer lifespan of 6-9 months have also frequently been utilized.

Nowadays injectables are easier to use, are available in a variety of consistencies, have a far smaller risk of allergic reactions and don't need skin testing. In the short-term range there are the hyaluronic acid gels (Juvederm ®, Restylane®) and the sodium carboxymethylcellulose gels (Radiesse voice gel®, Renu voice gel®, Prolaryn gel®) with a lifespan from weeks up to several months [1,12]. In the mid to long-term range there are calciumhydroxylapatite (CaHa) compounds (Radiesse®, Renu®, Prolaryn plus®) in addition to autologous fat, both with a lifespan from 9-18 months [1]. In the studies in this thesis, hyaluronic acid is used as a temporary injectable for trial VFI, and autologous abdominal fat harvested with liposuction as a long-term injectable.

VFI under general anesthesia is performed with the patient in larynx suspension and the vocal folds visualized through a microscope or alternatively through an endoscope. Injection of the

material is performed using a syringe for which various options are available. The preferred injection site is lateral in the thyroarytenoid muscle at a level of the vocal process. Depending on the material used, specific preparation can be necessary, for example liposuction and preparation of autologous fat. Some degree of overcorrection is needed to compensate for early absorption of carrier materials, but the amount varies between injectables, vocal fold pathology, and preference of the performing surgeon.

Thyroplasty

Thyroplasty was first described by Isshiki in 1975 for UVFP and atrophy [13]. Over time this technique has been used for glottic insufficiency in patients with mobile vocal folds [14]. Modulations have been introduced such as bilateral medialization thyroplasty with Gore-tex® (GORE-TEX® Soft Tissue Patch, Gore Medical, Flagstaff, Arizona) as described by McCulloch [15]. The main surgical steps during thyroplasty with Gore-tex® are (1) positioning of the cartilage window at the level of the vocal fold and (2) adequate medialization, including overcorrection, of the vocal fold by placing the Gore-tex® implant through the cartilage window into the paraglottic space. The advantage of using Gore-tex®, which is a malleable material, is that suboptimal window position can be partly corrected with manipulation of the material within the paraglottic space. Finding the ideal amount of medialization, including overcorrection, is the most challenging aspect of the surgery. Because the patient is awake, she/he can vocalize perioperatively and the surgeon can therefore determine the optimal amount of implant based on perceptual and videolaryngoscopic findings, patient feedback and surgeon's own experience.

MICROPHONOSURGICAL PROCEDURES

In case of sulcus, procedures improving mucosal wave by freeing the epithelium lining and restoring the subepithelial space can be used.

Microphonosurgery: flap with/or without grafting

The main principal in microphonosurgery for sulcus is to improve voicing, by restoring mucosal wave, by repairing the layered structure of the vocal fold. Ideally, this means rebuilding the transitional layer formed by the superficial lamina propria between the epithelium ("cover"), and the vocal ligament ("body"). There are several techniques to free the epithelium and to remove disrupted tissue. The technique broadly used by laryngologists is the formation of the microflap followed by excision of the subepithelial fibrosis and repositioning of the flap with tissue glue or sutures [16,17,18]. A more aggressive form of epithelium freeing is the slicing technique described by Pontes et al. making transvers incisions through the epithelium into the muscle to interrupt the longitudinal fibrosis [19].

Many implant materials have been used to restore the superficial lamina propria. Examples are fibrin glue, gelatine sponge, subepithelial fat graft and subepithelial fascia graft of which the last has been the most reported in the literature [10,20-26].

Angiolytic lasers

A newer technique that has been described is the use of angiolytic lasers, PDL (pulse dye laser) and KTP (potassium-titanyl phosphate), for softening of fibrosis. The use of these lasers was first described by Mortensen et al. in 2008, but also by others [27,28,29]. The working mechanism of angiolytic lasers is based on the concept of selective photothermolysis. The light is selectively absorbed by hemoglobin leading to photocoagulation of microvascular lesions with minimal damage to surrounding tissues, supposedly resulting in softening of fibrosis, leading to more pliable vocal folds, improvement of mucosal wave and, ultimately, improving of voicing [10,28]. Although lasers, as pulsed dye lasers, have shown to be effective for scar treatment f.e. in skin, the mechanism has not been fully elucidated yet. Photothermolysis, but also neo-collagenesis, a process of collagen fiber heating and realignment, have been proposed [28].

TECHNIQUES FROM REGENERATIVE MEDICINE

In the last decade, there has been increasing interest in regenerative medicine for treating vocal fold atrophy, sulcus and scar, because these techniques may have the potential to rebuild and restore vocal fold structure. Regenerative medicine is an umbrella term for techniques that use growth factors, stem cell techniques and scaffolding systems, often in combination. Combining all three techniques is referred to as tissue engineering [30].

For growth factors, the most used is basic fibroplast growth factor (bFGF) [31-35]. Basic FGF stimulates fibroblast proliferation and modulation. Fibroblasts are responsible for maintaining the extracellular matrix (ECM), including the endogenous production of hyaluronic acid, reducing collagen depositions and increasing matrix metalloproteinase (MMP)(collagenase). In 2021 Hirano et al. published a serie of 100 human cases treated with intracordal injection of bFGF [31].

The implantation of stem cells, such as adipose-derived mesenchymal stem cells or bone marrow-derived mesenchymal stem cells, with or without growth factors, may be another approach. Stem cell trials have been mainly performed in animals and an overview of this topic has been giving by Svistushkin et al. [36]. There are only a spare some numbers of human clinical trials [37,38,39]. Future directives for the treatment of vocal fold scarring and

atrophy using regenerative medicine techniques will focus on optimizing ECM restoration, retaining longer lasting effects and, ultimately, replacing the entire cover layer.

OUTCOME MEASUREMENT INSTRUMENTS FOR DYSPHONIA

In this thesis we present and compare different surgical treatment outcomes, but to be able to meaningfully reflect on outcome, it is even so important to compare and reflect on the outcome measurement instruments themselves.

Outcome measurement instruments are tools to measure quality or quantity of outcome. An OMI can be a single question, a questionnaire, a score obtained through physical examination, a laboratory measurement, a score obtained through observation of an image, etc.[40]. OMIs are helpful to monitor outcome before and after treatment for patients and health professionals. Monitoring treatment outcome is not only important for the individual patient, but also for a cohort of patients. It can be used for scientific purpose, but also for public and political decision making within our health care system, which is increasingly based on the principles of evidence-based and value-based medicine.

In a consensus statement on the functional assessment of dysphonia, published in 2001 by the European Laryngological Society and recently updated in 2023, authors proposed that the OMIs used for dysphonic patients are divided into five categories. These are subjective, perceptual, aerodynamic, acoustic and videolaryngostroboscopic evaluation [41,42].

Subjective evaluation can be measured with self-assessment tools. Frequently used questionnaires for dysphonia are the Voice Handicap Index (VHI) and Voice related Quality of Life (VRQOL), which both have reasonable good psychometric properties [43–46]. There are also questionnaires developed specifically for glottic insufficiency such as the glottal function index (GFI)[47], the Vocal Fatigue Index (VFI) [48] and the Vocal Fatigue Handicap Questionnaire (VFHQ) [49].

Perceptual evaluation is done by listening to and grading of the dysphonic voice. A widely used scale for this purpose is the GRBAS scale proposed by Hirano in which the dysphonic voice is evaluated in the domains of overall grade, roughness, breathiness, asthenia, and strain [50]. Another voice evaluation tool is the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V), which evaluates the grade of dysphonia, including roughness, breathiness and strain, but also pitch and loudness (Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) Special Interest Division 3, Voice and Voice Disorders. Available at: http://www.asha.org. Accessed June 18, 2010).

Aerodynamic parameters include the maximum phonation time (MPT) in seconds, phonation quotient (PQ) (vital capacity (ml)/MPT (s)), and mean airflow rate (MFR (ml/s)) [41]. Acoustic parameters are jitter (perturbation of frequency), shimmer (perturbation of amplitude) and fundamental frequency (F0), including F0-range (highest to lowest frequency) and softest intensity.

The highest frequency and softest intensity seem to be the most sensitive to changes in voice quality [41]. The use of these parameters depends on the availability of measuring equipment. A pneumotachograph (Phonatory Aerodynamic System (PAS), KayPENTAX, Montvale, NJ) is needed to measure MFR, but also to measure subglottic pressure and aerodynamic resistance. If no pneumotachograph is available PQ can be used as an alternative to MFR.

For acoustic parameters voice program software is needed. These programs are commercially available, for example PRAAT or MDVP (multidimensional voice program software, Computerized Speech Laboratory (KayPENTAX, Montvale, NJ)). These voice programs have their own extensive sets of parameters, often visualized in a phonetogram, from which parameters can be extracted or calculated.

Videolaryngostroboscopy is a standard investigation in dysphonic patients. The two most important aspects are glottal closure and mucosal wave; the last can be assessed for regularity, symmetry and quality, as stated in the ELS-protocol [41]. Comprehensive rating system for assessing videostroboscopy in a systematic and detailed manner have been developed. One example is the VALI (Voice-Vibratory Assessment with Laryngeal Imaging) [51]. For glottic insufficiency there are also specific videolaryngostroboscopic assessment tools, for instance Frame-by-frame analysis (FBFA) in which subject's average percentage of closed frames per glottic cycle is recorded [52].

The ELS protocol was formulated for general dysphonic patients. This may be a limitation when used in a specific population of patients. Therefor Core Outcome Sets (COSs) are being developed for specific conditions [53]. There is no COS yet for patients with glottic insufficiency due to atrophy with or without sulcus.

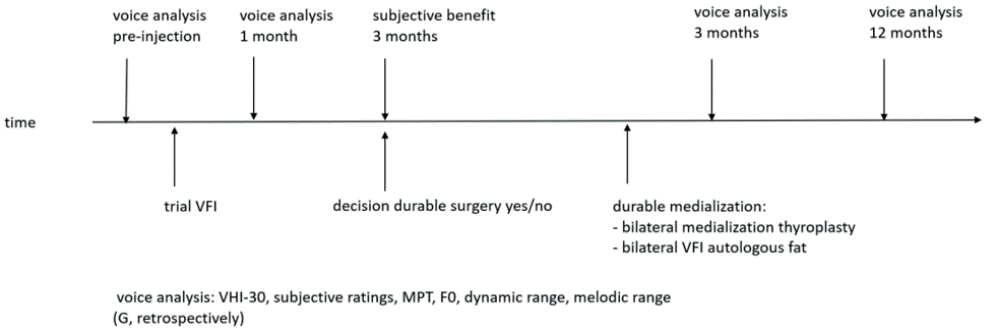
THESIS OUTLINE

LUMC strategy

From 2012, based on the ELS consensus statement [10], all patients presenting at the LUMC (Leiden University Medical Center) with glottic incompetence due to atrophy or atrophy with sulcus have been treated according to the concept of primary correction of closure with a predetermined scheme and timeline with collection of voice outcome data at pre-established time points according to a set prospective protocol.

According to this treatment scheme, patients were offered trial VFI with hyaluronic acid (HA). Voice date were collected preoperative and 1 month postoperative. At 3 months postoperative patients' subjective outcome was evaluated and patients were asked whether they experienced enough benefit from trial VFI to continue to a more durable form of surgery. If yes, patients underwent either VFI with autologous fat or bilateral medialization thyroplasty, depending on patient's and surgeon's preference. Preoperative, 3- and 12-month postoperative voice data were collected (Figure 7). If patients benefit from trial injection was insufficient, they were offered possible other treatment options (microphonosurgery, corticosteroid injections, additional voice therapy) or no further treatment.

Figure 7. timeline treatment glottic insufficiency with mobile vocal folds



The protocol included patients' self-assessment using the VHI-30. In the Dutch version of the VHI-30, a score of 15 points or more identifies patients with voice problems in daily life, a change in pre- and postoperative score of 10 points or more in the individual patient and 15 points or more for a group can be considered clinically relevant [54,55]. In addition, a subjective 10-point rating scale on four domains (quality of voice, effort of voicing, possibility or limitation in voicing, voice influence on life) was collected.

Patient's phonetogram was recorded with the Voice profiler ((Alphatron, Rotterdam, the Netherlands, 2007) in standardized settings. Fundamental frequency (F0, hertz (Hz)) and melodic range (MR, semitones (ST)) were extracted as acoustic outcome measurements. For aerodynamic outcome dynamic range (DR, decibel (dB)) was extracted. Maximum phonation time (MPT) was measured on /a/ at a comfortable pitch and loudness, using the longest MPT from 2 attempts.

For perceptual outcome voices were retrospectively rated by experienced listeners, using the overall grade score of the GRBAS. The cohort of patients treated in this scheme and timeline have been analyzed for this thesis.

Thesis outline

This is a thesis on glottic insufficiency caused by vocal fold atrophy and/or sulcus and the outcome after surgical treatment. We will focus on (1) patient selection, (2) surgical treatment, and (3) outcome measurements.

Chapter 2 shows voice outcome after trial VFI with hyaluronic acid, retrospectively analyzed from data collected according to a prospectively administered voice outcome protocol. It also describes the clinical relevance of trial VFI and the predictive value of trial VFI on the outcome of durable medialization procedure. Chapter 3 reports on voice outcome 3 and 12 months after VFI with autologous fat. Outcome parameters are subjective VHI-30 scores, perceptual evaluation (grade (G)), aerodynamic evaluation, including MPT and dynamic range, and acoustic analysis, including F0 and melodic range. Chapter 4 evaluates voice outcome 3 and 12 months after bilateral medialization thyroplasty with Gore-tex® using the same study design and outcome parameters as in chapter 3. Chapter 5 retrospectively describes the long-term outcome (> 1 year, median follow-up 6.7 years) after bilateral medialization thyroplasty. Chapter 6 contains a systematic review of OMIs for treatment outcome, both surgical and non-surgical, in patients with atrophy and/or sulcus. Strengths and weaknesses of the most frequent used OMIs are discussed. This review may be a first step in developing a COS. In chapter 7, general discussion, we reflect on the importance of using appropriate OMIs and how to define them and we reflect on the surgical techniques investigated in this thesis, discussing future improvements and treatment options for patients with glottic insufficiency caused by vocal fold atrophy with or without sulcus.

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2

Bilateral trial vocal fold injection with hyaluronic acid in patients with vocal fold atrophy with or without sulcus

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ABSTRACT

Purpose: To evaluate the outcome of bilateral trial vocal fold injection (VFI) with hyaluronic acid in patients with vocal fold atrophy ± sulcus and to assess the predictive value of trial VFI on the outcome of durable medialization procedure.

Methods: Voice data collected according to a standardized protocol before and one month after trial VFI of 68 patients with vocal fold atrophy (30) and atrophy with sulcus (38) were analyzed. Voice Handicap Index (VHI)-30 was compared to the outcome of a durable medialization at 3 and 12 months.

Results: The overall VHI-30 improvement was 16.8 points (from 49.9 to 33.1), which was statistically significant and clinically relevant. 57.8% of the patients experienced enough subjective benefit after trial VFI to undergo durable medialization. Of the patients that experienced subjective benefit 62% had a clinically relevant improvement in VHI-30. There was no relevant change in other parameters and no difference between ± sulcus. After durable medialization 90-94% of the patients had VHI-30 scores similar to or better than post-trial VFI.

Conclusion: The majority of patients experience subjective improvement after bilateral trial VFI indicating that medialization is a valid treatment option for patients with vocal fold atrophy ± sulcus. The VHI-30 only partially overlaps with patients' subjective evaluation and does not predict which patients will experience subjective improvement. It is, however, predictive for VHI-30 outcome after durable medialization. The aerodynamic and acoustic parameters showed no relevant change. Further identification of voice assessment parameters accurately reflecting the subjective experience of these patients is warranted.

INTRODUCTION

Vocal fold atrophy is defined as loss of muscle bulk and tone of the thyro-aytenoid/lateral cricoarytenoid complex in a vocal fold with a normal range of motion [1]. It is a common cause of dysphonia in non-paralytic glottic insufficiency. There are several forms of vocal fold atrophy. (1) In presbyphonia atrophy of both the lamina propria and the vocal fold muscles, and degeneration of the cartilaginous framework occur due to the aging process [2]. Because of the growth of the elderly population this problem is seen more frequent in daily laryngological practice [2,3,4]. (2) Atrophy can also be found in younger patients who report similar complaints from childhood or early adolescence and have a comparable clinical presentation, suggesting a young adolescent form of vocal fold atrophy. This phenomenon has been observed by others [5]. Finally, (3) atrophy can also be associated with congenital forms of vocal fold scar such as sulcus [6]. In these patients, in our experience, there is often loss of muscle bulk in addition to the abnormalities found in the upper vibratory layers of the vocal fold. The treatment options for improving glottic closure in patients with vocal fold atrophy are speech therapy and/or medialization of the vocal folds. For presbyphonia improvement in vocal function after speech therapy has been observed, but is influenced by degree of atrophy, glottis closure pattern and patient's burden of medical problems [7].

Medialization can be achieved either by bilateral vocal fold injection (VFI) with a durable injectable such as autologous fat or calcium hydroxyapatite, or by bilateral medialization thyroplasty. In patients with additional vocal fold scar there is also the option of microphonosurgery on the upper vibratory layers of the vocal fold. A recent consensus report on vocal fold scar by the European Laryngological Society (ELS) presents an overview of treatment options for these patients. These include classic medialization and epithelium freeing techniques as well as novel approaches such as the use of angiolytic lasers to soften the scar tissue, tissue engineering and stem cell techniques. Although no definite recommendations are made, because of the unpredictability of the results, the advice of the consensus committee is to start with the least traumatizing procedure, which is usually VFI [6].

The results of treatment of vocal fold atrophy with or without vocal fold scar are less predictable than those of glottic insufficiencies caused by hypomobility or paresis [8]. Therefore trial VFI with a short acting substance can be used to predict the outcome of a durable medialization procedure [1].

Since 2012 we have been performing trial VFI using hyaluronic acid (HA) in patients with vocal fold atrophy. Due to the varying and sometimes disappointing results of microphonosurgery in patients with vocal fold scar, trial VFI has been our first approach in this patient cohort as well. Depending on the degree of subjective benefit after trial VFI, through a shared

decision making process, it is decided whether or not to move on to a durable medialization procedure. For this we prefer bilateral VFI with autologous fat or bilateral medialization thyroplasty depending on patient and/or surgeon's preference. Our treatment strategy is in line with the algorithm for treatment for scar and glottic incompetence as proposed by Carroll et al. [9].

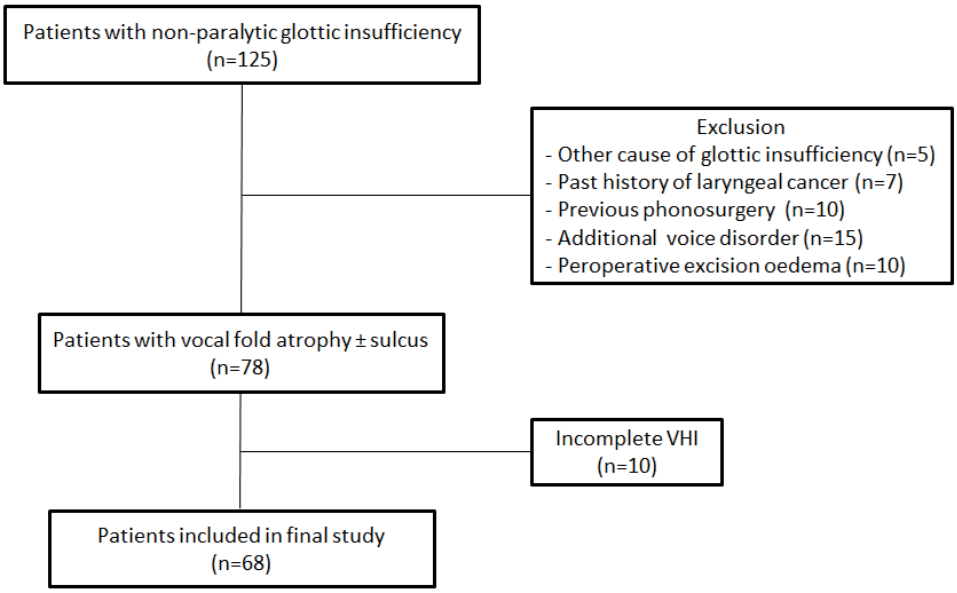
The purpose of this study was to evaluate the outcome of bilateral trial VFI with HA in our patients with vocal fold atrophy with or without sulcus and to assess the predictive value of trial VFI on the outcome of durable medialization procedure.

METHODS

Patients

Institutional review board approval for the publication of this data was obtained from the Leiden University Medical Center Ethics Committee. All patients with non-paralytic glottic insufficiency who underwent bilateral trial VFI with HA under general anesthesia (*n*=121) or as an in-office procedure (*n*=4) from September 2011 to April 2017 (*n*=125) were retrospectively reviewed (Figure 1). 47 patients were excluded because of another cause of glottic insufficiency (e.g., paresis or glottic insufficiency post intubation (*n*=5), a past history of laryngeal cancer (*n*=7), previous phonosurgery (*n*=10), an additional voice disorder (e.g., vocal tremor, cyst) (*n*=15) or peroperative excision of oedema (*n*=10)). The remaining 78 patients had been diagnosed with vocal atrophy based on the clinical features of glottic incompetence (atrophic appearance of the vocal folds with or without sulcus while retaining a normal range of motion). Of these 78 remaining patients, 68 had pre- and postoperative voice data with at least a complete Voice Handicap Index (VHI)-30 questionnaire and were included in the definitive analysis. These 68 patients had undergone trial VFI under general anesthesia between June 2012 and April 2017. Patients routinely started speech therapy within a week of the injection and continued as long as deemed necessary by the speech-language therapist. The outcome was evaluated based on two criteria: (1) voice analysis data collected routinely at one month after trial VFI and (2) patients' subjective perception of benefit during their return visit at 3 months after trial VFI. If the voice analysis data did not match the patient's own appraisal, the patient's subjective perception was leading both in determining the final result of the trial VFI and the decision regarding a durable medialization procedure. Therefore, patients that experienced enough subjective benefit to be motivated for a durable medialization procedure were considered good responders.

Figure 1. Patient selection, inclusion and exclusion criteria



Voice data

Voice outcome data was collected according to a standardized voice analysis protocol implemented preoperatively and at one month postoperatively. This protocol included patients' self-assessment using the VHI-30, aerodynamic evaluation with maximum phonation time (MPT) and dynamic range and acoustic analyses including fundamental frequency (F0) and melodic range. Voice outcome data for the durable medialization procedure was collected using the same protocol preoperatively as well as 3 and 12 months postoperatively. In this study the VHI-30 was the primary outcome parameter of the voice analysis protocol. It is a patient based self-assessment tool consisting of 30 items, which are distributed over three domains: functional, physical and emotional [10]. In the Dutch version of the VHI-30 a score of 15 points or more identifies patients with voice problems in daily life [11,12]. Furthermore, a change in pre- and postoperative score of 10 points or more in the individual patient and 15 points or more for a group can be considered clinically relevant [12]. The MPT was measured on /a/ at a comfortable pitch and loudness. The longest MPT from two attempts was included for analysis. Fundamental frequency in hertz (Hz), dynamic range in decibel (dB) and melodic range in semitones (ST) were extracted from the patient's phonetogram recorded with the voice profiler ((Alphatron, Rotterdam, the Netherlands, 2007) in standardized settings.

Procedure

All procedures were performed by an experienced laryngologist and/or a fellowship trained laryngologist. The trial VFI was performed in general anesthesia as this allows for the palpation of the vocal folds to distinguish between atrophy and atrophy with sulcus. Also, the extent of a sulcus can be assessed as part of the work-up for possible future microphonosurgery with sulcus excision. In our study sulcus was defined as a pathological type 2 sulcus and/or type 3 sulcus according to the Ford classification [13]. This corresponds to a sulcus vergeture and/or sulcus vocalis in the classification by Bouchayer [14]. The material used for the trial VFI was hyaluronic acid (Juvéderm® ULTRA SMILE, Allergan, Dublin, Ireland). The injection was bilateral in all cases. The standard practice was to inject in the lateral part of the thyroarytenoid muscle at the level of the vocal fold process. If necessary a second injection point was chosen at the level of the midcord. Injection was continued until adequate medialization was achieved according to the clinical experience of the surgeon. Typically 0.15-0.25 cc per vocal fold was used. Durable VFI was performed in general anesthesia using autologous fat harvested by abdominal liposuction. Bilateral medialization thyroplasty was performed in local anesthesia using Gore-tex® (GORE-TEX® Soft Tissue Patch, Gore Medical, Flagstaff, Arizona) as implant material as described by Isshiki and McCulloch with some modifications [15,16].

Statistical analysis

All data were analyzed using SPSS for windows (IBM SPSS Statistics for Windows, Version 21.0, released 2012. IBM Corp, Armonk, NY). Data showed a normal distribution. The pre- and postoperative voice data for the overall patient group were analyzed using a linear mixed model. A linear regression model was used to analyze the association between various factors (age, gender and pathology) and voice outcome. The chi-squared test was used to compare the dichotomous variables ”clinically relevant VHI improvement” and “durable medialization”. For all statistical tests a *p* value smaller than 0.05 was considered significant.

RESULTS

Demographic details at baseline of the 68 patients with vocal fold atrophy (*n*=30) or atrophy with sulcus (*n*=38) that underwent bilateral trial VFI with HA and the type of durable medialization according to patients' choice are shown in Table 1. 27 did not experience enough subjective benefit to want to undergo a durable medialization procedure. Three of these were patients with sulcus who elected to undergo microphonosurgery (data not shown).

Table 1. Demographic details of patients with vocal fold atrophy ± sulcus who underwent bilateral trial vocal fold injection and their choice of durable medialization

Characteristics	Total	Atrophy	Atrophy with sulcus
	n = 68 (100%)	*n* = 30 (44.1%)	*n* = 38 (55.9%)
Trial VFI			
Mean age, years at baseline (SD)	40 (18.5)	42 (19.5)	39 (17.7)
Gender, *n* (%)			
Male	18 (26.5)	7 (23.3)	11 (28.9)
Female	50 (73.5)	23 (76.7)	27 (71.1)
Postoperative voice outcome timing, *n* (%)			
At 1 month	53 (77.9)	24 (80)	29 (76.3)
At other time (range 2-8 weeks)	15 (22.1)	6 (20)	9 (23.7)
Durable medialization			
Bilateral VFI with autologous fat	19 (27.9)	8 (26.7)	11 (28.9)
Bilateral medialization thyroplasty	18 (26.5)	10 (33.3)	8 (21.1)
No durable medialization procedure	27 (39.7)	10 (33.3)	17 (44.7)
Undecided	4 (5.9)	2 (6.7)	2 (5.3)

VFI vocal fold injection, *SD* standard deviation

The pre- and post-injection voice outcome data for the overall patient group are shown in Table 2. The mean VHI-30 for the overall group decreased by 16.8 points from 49.9 to 33.1. This improvement was both statistically significant and clinically relevant (improvement ≥ 15 points). Melodic range improved from 16.5 to 19.6 ST, which was also statistically significant. For the other voice parameters changes in pre- and post-trial outcomes were not statistically significant.

Table 2. Pre-and post-trial vocal fold injection voice outcome data of patients with vocal fold atrophy ± sulcus

Voice outcome	Mean pre-trial VFI value (95% CI)	Mean post-trial VFI value (95% CI)	Mean difference (95% CI)	*p* value
VHI-30	49.9 (45.6; 54.2)	33.1 (28.8; 34.4)	-16.8 (-21.5; -12.1)	<0.001*
MPT (sec)	12.4 (10.8; 14.0)	12.5 (10.9; 14.1)	0.1 (-1.5; 1.6)	0.932
F0 (Hz) Male	158 (140; 176)	149 (131; 167)	-9 (-21; 3)	0.135
F0 (Hz) Female	202 (192; 212)	205 (195; 215)	3 (-3; 9)	0.358
Dynamic range (dB)	30.1 (27.2; 33.1)	32.9 (29.9; 35.9)	2.7 (-0.2; 5.6)	0.069
Melodic range (ST)	16.5 (14.5; 18.6)	19.6 (17.5; 21.6)	3.0 (1.1; 4.9)	0.002*

VFI vocal fold injection, *CI* confidence interval, *VHI* voice handicap index, *MPT* maximum phonation time, *F0* fundamental frequency, *Hz* hertz, *dB* decibel, *ST* semitone

*p value < 0.05 was considered significant

Table 3 shows the influence of various patient factors on voice outcome after trial VFI with HA in an univariate linear regression model. There was no association between gender or sulcus and the post-trial change in any of the voice parameters. For age a significant association was found with two of the five voice parameters showing an improvement in outcome with increasing age (VHI-30 and dynamic range).

Table 3. Patient factors age, gender and pathology, and their influence on voice outcome parameters

Covariance	**Age**	**Gender**	**Pathology**
	(continue)	**(male/female)**	**(vocal fold atrophy ± sulcus)**
	B (95%CI), *p* value	B (95%CI), *p* value	B (95%CI), *p* value
VHI-30	- 0.301 (- 0.55; - 0.05), 0.018*	1.156 (- 9.6; 11.9), 0.830	4.663 (- 4.8; 14.1), 0.329
MPT	0.056 (- 0.03; 0.14), 0.183	0.146 (- 3.4; 3.7), 0.934	- 1.094 (- 4.2; 2.0), 0.482
F0 Male	0.137 (- 0.66; 0.94), 0.720	NA	- 5.106 (- 11.7; 1.5), 0.120
F0 Female	- 0.473 (- 1.1; 0.11), 0.109	NA	0.528 (- 4.3; 5.4), 0.828
Dynamic range	0.169 (0.01; 0.32), 0.033*	2.111 (- 4.5; 8.7), 0.524	- 4.009 (- 9.8; 1.8), 0.174
Melodic range	- 0.954 (- 4.9; 2.9), 0.62	- 0.710 (- 5.1; 3.6), 0.745	0.058 (- 0.05; 0.16). 0.277

B Beta coefficient, *CI* confidence interval, *VHI* voice handicap index, *MPT* maximum phonation time, *F0* fundamental frequency, *NA* not applicable

*p value < 0.05 was considered significant

40 of the 68 patients (58.8%) had a clinically relevant improvement in their VHI-30 score after trial VFI (improvement ≥ 10 points). Their mean improvement was 29.1 points (SD 14.6). 28 patients (41.2%) did not have a clinically relevant improvement (improvement < 10 points or a deterioration of the VHI-30 score). Their mean improvement was - 0.8 points (SD 8.8) (data not shown).

Table 4 shows clinically relevant VHI-30 improvement (yes/no) according to patients' choice regarding a durable medialization procedure (yes/no). There was only a partial overlap between these two parameters. Of the 37 patients that chose to undergo a durable medialization procedure only 23 (62.2%) had a clinically relevant improvement in their VHI-30 score. This means that 14 patients (37.8%) chose to undergo a durable medialization procedure because they experienced a subjective benefit of the trial VFI that was not reflected in their VHI-30 score. 15 (55.6%) of the 27 patients that did not chose to continue to a durable medialization procedure because they did not experience enough subjective benefit, still had a clinically relevant improvement in their VHI-30 score. The reasons they did not want to continue to a durable procedure was prolonged improvement in voice outcome after the bilateral trial VFI (*n*=6), lack of motivation to undergo a second procedure (*n*=5) or no self-reported improvement after the trial VFI despite a clinically relevant improvement in VHI-30 score (*n*=4). This pattern of partial overlap was seen in both patients with and without sulcus. Statistically, there was no significant difference in the proportions between these subgroups (data not shown).

Table 4. Patients' choice for durable medialization procedure according to clinically relevant VHI-30 improvement

Durable medialization	**Total = 64**	
	Yes = 37 (57.8%)	**No = 27 (42.2%)**
Clinically relevant VHI-30 improvement[a]		
Yes	23 (62.2)[b]	15 (55.6)
No	14 (37.8)	12 (44.4)

[a]VHI-30 improvement ≥ 10 points in individual patient

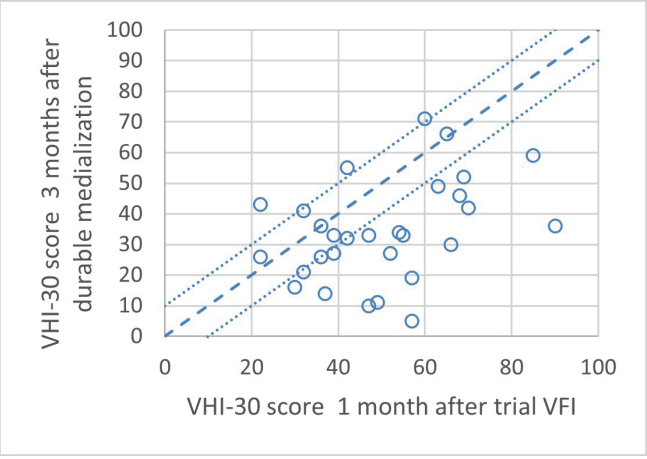
[b]No sign. difference was found for clinically relevant VHI-30 improvement and durable medialization (p = 0.595)

As stated earlier 37 patients initially chose to have a durable medialization procedure, of which 31 have been carried out to date (5 patients have had second thoughts and cancelled their procedure for unknown reasons and 1 patient is still on the waiting list). Of the 31 patients that have had a durable medialization procedure 2 were lost to follow up between 0 and 3 months. Therefore, voice analyses data was available for 29 patients at 3 months after long-term medialization. At the 12-month interval voice analyses was available for 18 of the 31 patients; 3 patients were lost to follow up between 3 and 12 months, 1 patient underwent revision thyroplasty within 12 months and 9 patients were still short for their 12 month follow up period. The mean VHI-30 score was 34.2 (± 16.5) at 3 months and 25.2 (± 14.6) at 12 months after the durable procedure.

Figure 2 shows the individual VHI-30 score 1 month after bilateral trial VFI plotted against the VHI-30 score 3 months after durable medialization (bilateral VFI with autologous fat

n=11; bilateral medialization thyroplasty *n*=18). In 26 patients (90%) the VHI-30 score after the durable procedure was either comparable to (within a 10-point range, *n*=7) or better than (> 10 points improved, *n*=19) the VHI-30 score after trial injection. Three patients had a deterioration of more than 10 points in their VHI-30 scores 3 months after durable medialization procedure compared to the trial VFI.

Figure 2.

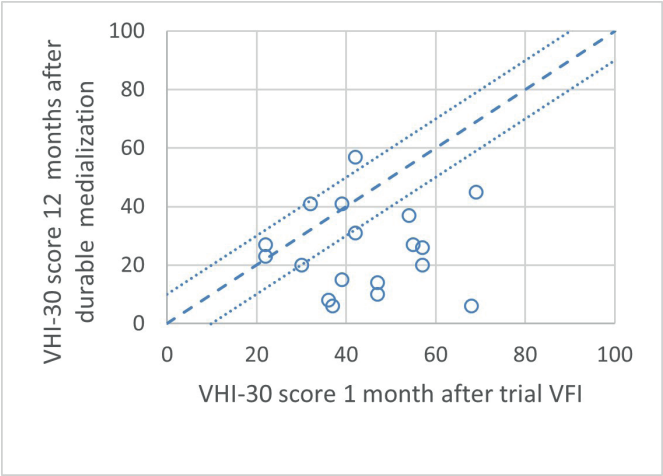


VHI-30 score 3 months after durable medialization compared to VHI-30 score 1 month after bilateral trial vocal fold injection (*n*=29)

VHI voice handicap index, *VFI* vocal fold injection

Figure 3 shows the individual VHI-30 score 1 month after trial VFI plotted against the VHI-30 score 12 months after durable medialization (bilateral VFI with autologous fat *n*=11; bilateral medialization thyroplasty *n*=7). In 17 patients (94%) the VHI-30 score for the durable procedure was either comparable to (within a 10-point range, *n*=5) or better than (> 10 points improved, *n*=12) the VHI-30 score after bilateral trial VFI. One patient had a deterioration of 15 points in VHI-30 12 months after durable procedure compared to the trial VFI.

Figure 3.



VHI-30 score 12 months after durable medialization compared to VHI-30 score 1 month after bilateral trial vocal fold injection (*n*=18)

VHI voice handicap index, *VFI* vocal fold injection

DISCUSSION

In this study we evaluated the outcome of bilateral trial VFI with HA in 68 patients with vocal fold atrophy (atrophy only (*n*=30) and atrophy with sulcus (*n*=38)) and assessed the predictive value of trial VFI on the outcome of a durable medialization procedure. To our knowledge this is the largest study on trial VFI to date.

We found that the majority of patients reported a good response to the trial VFI, which was defined as enough subjective benefit to want to undergo a durable medialization procedure. The proportion of patients with a good response was not influenced by the type of pathology. We also found a statistically significant and clinically relevant improvement in the overall VHI-30 score. Looking at individual patients, the majority (58.8%) showed a clinically relevant improvement in the VHI-30.

These results demonstrate that the majority of patients with atrophy with or without sulcus experience less voice handicap after trial VFI, indicating that medialization is a valid treatment option in both these patient groups. However, the group of patients that chose to undergo a durable medialization procedure only partially corresponded to the group with a clinically relevant improvement in the VHI-30. Therefore, our findings show that even though the VHI-30 is indicative for voice improvement in this overall patient group, it does

not adequately identify the subgroup of "true" good responders who will be motivated for a durable medialization procedure based on their subjective benefit of the trial VFI.

The concept of trial vocal fold injection was defined in 2010 [1]. Since then at least five studies have looked at the change in voice parameters after trial injection, with study populations ranging from 19 to 35 patients [1,9,17,18,19]. The study by Young et al. was done in patients with atrophy, excluding patients with hypomobility, paresis or paralysis [17]. The other studies did include patients with hypomobility or paresis. One study also included one patient with a vocal fold paralysis [19]. Our proportion of patients with a good subjective response (57.8%) is comparable with those found by Carroll. He found a good response in 32%-75% of patients in his three studies [1,9,19]. When including partial responses this proportion increased to 76%-83% [1,9,19].As for the VHI, it is not possible to compare our findings directly to those of other studies as they used either the VHI-10 version [1,17,19] or an alternative self-assessment tool [18]. However, when considering the proportion of patients with a clinically relevant change in the VHI in the different studies, our study (58.8%) has a relatively high percentage compared to earlier reports by Young (42%) and Carroll (30.4%) [17,19]. Although the VHI scores improve it is important to realize that all studies show that the VHI does not normalize after trial VFI. Even the subgroups of good responders show elevated scores indicating an on-going burden on voice use in these patients. In our study good responders had a mean post-injection VHI-30 score of 26.7 (normal value VHI-30 Dutch version < 15) [12]. The mean post-injection VHI-10 score in good responders in the study by Young et al. was 12 and 20.5 in the study by Carroll et al. [17,19] (normal value VHI-10 English version ≤ 11) [20].

Finally, the discrepancy that we found between the patients' subjective experience and the VHI outcome has also been noted by others; a recent study showed that although 65% of the patients reported a subjective good response only five out of 15 (33%) had a clinically relevant improvement in their VHI-10 score (≥ 5 points improvement) [19]. The value of the VHI for assessing voice improvement in patients with glottic incompetence due to atrophy with or without sulcus is therefore unclear and needs to be further explored.

As for the acoustic and aerodynamic parameters, we found a statistically significant improvement in the melodic range from 16.5 to 19.6 ST. However, this would still classify as a limited range according to values for healthy subjects found by Wuyts. In this publication healthy subjects showed a melodic range between 22 and 44 ST [21]. Also, it is unclear what the clinical relevance of this increase in melodic range would actually mean to the patients. We found no statistically significant changes in the other voice parameters. The limited effect seen in acoustic and aerodynamic parameters in our study are reflected in other studies [17,19].

As the effect of bilateral trial VFI is not reflected in the objective voice measures as described above and is only partially reflected in a clinically relevant VHI improvement two questions arise: (1) are the voice parameters used in these publications sufficiently valid and precise and (2) is the timing of the voice data acquisition optimal? The VHI is proven to be a reliable tool for measuring the general impact of a voice disorder and patient burden [10]. Also, as vocal effort is reflected in aerodynamic parameters, we expected these to change after trial VFI. However, some authors are currently pointing out that disease specific outcome tools may be needed to accurately reflect voice impairment and to measure outcome of intervention [22,23], which is in line with our findings. Alternative voice outcome measurements that better represent the voice problems of this patient group need to be identified. Two questionnaires for analyzing subjective voice change in patients with glottal insufficiency are mentioned in the literature: the glottal function index (GFI) and the vocal fatigue index (VFI) [24,25]. The GFI is a 4-item symptom index, which can be used in the evaluation and treatment in patients with glottal dysfunction [24]. Although the questionnaire has not been designed for a specific clinical disease entity it has been used in several studies on non-paralytic glottic incompetence and its treatment [8,18,26,27]. The VFI is a questionnaire designed specifically for detecting vocal fold fatigue and assessing the impact of treatment these patients [25].

These questionnaires could be of added value when assessing subjective voice change in patients with glottic incompetence, but validated Dutch versions have not yet been developed. Alternative aerodynamic parameters more suited for atrophy patients could be the phonation threshold pressure (PTP) and phonation threshold flow (PTF) reflecting the minimum pressure and flow required to sustain phonation. These parameters may better mirror the ease of phonation [28] [personal communication S. Thibeault and D. Phyland]. Frame-by-frame analysis (FBFA) of laryngovideostroboscopy in which subject's average percentage of closed frames per glottic cycle is recorded may be another option [29]. The use of 2D digital kymography using laryngeal high-speed video-endoscopy allowed Bae to identify vibratory changes after VFI in patients with paresis and after speech therapy in patients with atrophy [30]. The benefit of these and other alternative voice outcome parameters as well as their clinical implications need to be further explored for patients with atrophy with or without sulcus. For now, we agree with the decision to continue to a definitive procedure is mainly based on the patient's subjective experience and that additional voice data are of limited contribution [1].

Next to selecting suitable voice outcome parameters, the timing of evaluation is of great importance when evaluating the success of trial VFI. In our study post-trial injection data were collected at 1 month, with a spread from 2 to 8 weeks for a minority of patients. As the different substances used in the studies described have different lifespans it is difficult to compare results, although these other studies also raise concerns about the optimal

timing of data collection. In our experience the window of benefit varies per patient even if the same substance is used and depends on factors such as the amount injected, possible oedema or temporary stiffness of the vocal folds and patient compliance with speech therapy. Due to these variations we assume that the voice outcome data in our study will not have been collected at the optimal time point in all patients. Interestingly some of the patients reported noticing a subjective benefit only after the effect of the injection had worn off. The confrontation with their "old" voice made them realize that the injection had been helpful. This subjective effect will therefore not have been captured in the VHI-30 filled in during voice analysis at 1 month. Ideally, evaluation should be done frequently to capture voice data at the time of patients' optimal benefit from the trial VFI. However, for practical reasons we chose to evaluate at 1 month as (1) patients in our experience generally undergo an adjustment period the first few weeks when the voice is not optimal and (2) HA has an average lifespan of 3 months. We do agree that further studies are warranted determining the optimal timing for data collecting post-trial injection [19].

In our study we found that neither gender, nor the additional presence of a sulcus had any influence on voice outcome. We did find an association between age and two of the five voice parameters (VHI and dynamic range) showing an improvement in their outcome with increasing age. This influence of age has not been reported before. We hypothesized that a lower voice demand in the absence of work-related voice use may be underlying cause for increased VHI improvement with increasing age. In the literature, although the data are limited, poorer results after medialization procedures in patients with vocal fold scar have been reported [8,27]. This poorer result may be well explained by the "double" pathology, not only affecting the glottic closure, but also affecting the vibratory potential of the layered anatomy of the vocal fold. However, although we conceptually agree with this assumption, these findings were not confirmed in our study for patients with sulcus undergoing trial VFI with HA. Our results may have been influenced by the fact that we included only patients with sulcus (Ford type II and III), which is a specific form of vocal fold scar. Further studies on patients with vocal fold scar and specifically with sulcus are needed to determine the value of (trial) medialization in this subcategory.

In this study the VHI-30 outcome did not always correspond to the patients' subjective experience of the trial VFI. However, we did demonstrate the ability of the VHI-30 outcome after trial VFI to predict the VHI-30 outcome of a durable medialization procedure. 3 months after durable medialization procedure 90% of patients had a similar or better VHI-30 score compared to after trial VFI. This increased to 94% at 12 months. This is in line with previous studies that also have found a predictive value of trial VFI. In 2010 Carroll and Rosen described that all patients with a good subjective result after their trial VFI also had a good result after the durable medialization procedure [1]. In the study by Young et al. 75% of the patients with

a good response to trial VFI (VHI-10 improvement of ≥5 points) also had a good response to the durable medialization procedure. 55% of patients with a poor response to trial VFI also had a poor response after the durable medialization procedure. Conversely 45% of patients had a good response after the durable procedure despite failing the trial VFI, indicating that the predictive value of a failed trial VFI might be lower than an successful one [17]. As theirs is the only study in which all patients with trial VFI underwent a durable medialization procedure this information cannot be compared to other studies. Interestingly, a recent study also showed the predictive value for trial VFI in patients with vocal fold scar. In this study 80% of good responders to trial VFI also showed clinically significant improvement after durable augmentation [9]. Dumberger et al. reported on predictability of trial VFI in 35 patients with non-paralytic glottic incompetency, including patients with paresis, who underwent trial VFI followed by type 1 medialization with Gore-Tex. They concluded that trial VFI is a useful tool, showing a good correlation (r=0.55) with change in VRQOL, a strong correlation with change in GFI (r=0.74) and excellent correlation with change in GRBAS (r=0.90) [18].

Our study had some limitations. Firstly, although the data was collected using a standardized protocol at set time-points as part of routine voice outcome registration, the study design was retrospective. This possibly led to more missing data than if the study had been prospective. We corrected for this where possible by using a linear mixed model for analysis of change in pre- and post-trial VFI voice data. Additionally, there was missing data at the 12-month interval after the durable medialization procedure, mainly because 9 patients were still not 12 months out from their operation. Second, the size of the patient group is a limitation. Although with 68 patients it is the largest series in this patient group to date, the isolated atrophy (n=30) and atrophy with sulcus groups (n=38) are still relatively small. A third limitation is that two different long-term procedures were used. It is still unclear which durable medialization procedure is the most beneficial for this patients group. We consider the current sample size too small to investigate the difference between the two procedures and this question was also beyond the scope of this study. Also, we did not investigate a possible difference for patients with atrophy versus atrophy with sulcus for the long-term procedure. Furthermore, the definition of a good responder in this study was based on the patient's motivation to continue to a durable medialization procedure, which was in turn based on their subjective experience of the trial VFI. We recognize that there were 5 patients who initially opted for a durable procedure who had second thoughts and chose to cancel their procedure. As we had thorough discussions with each patient before consenting them for a long-term procedure, to make sure that the effect of the trial VFI was sufficient, and as we do not know the reason for their cancellation we have included them as good responders in analysis. Furthermore, a few patients with a good response did not opt to continue to a permanent procedure. Therefore, our estimation of good responders may be slightly over or under valued. We do not expect this deviation to be significant as in the group of poor

responders the joint decision was always to refrain from a durable medialization procedure. Finally, we already mentioned our concerns about validity of the voice outcome parameters used and the timing of data collection. Further studies and consensus guidelines on the optimal voice outcome parameters for this patient group are warranted.

CONCLUSION

This study shows that a majority of patients (57.8% in this study) with non-paralytic glottic incompetence due to atrophy with or without sulcus experienced subjective improvement in voice after trial VFI. Patients showed a statistically significant and clinically relevant improvement in overall VHI-30 score. This indicates that vocal fold medialization is a valid treatment option in patients with vocal fold atrophy and atrophy with sulcus. However, the VHI-30 score and patients' subjective experience only partially overlapped and the VHI-30 is therefore not able to adequately predict patients' subjective experience. However, in patients with a good response to trial VFI who choose to undergo a durable medialization procedure the VHI-30 score is predictive for a similar or better VHI-30 outcome after durable medialization procedure. Aerodynamic and acoustic parameters in our study showed no relevant change. Therefore, in line with previous publications, this study suggests that the general voice parameters used may not be suitable for this patient population and further exploration to find specific voice assessment tools is necessary. To our knowledge this is the largest study on trial VFI to date.

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3

Bilateral vocal fold injection with autologous fat in patients with vocal fold atrophy with or without sulcus

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ABSTRACT

Purpose: To evaluate voice outcome after bilateral vocal fold injection with autologous fat in patients with non-paralytic glottic insufficiency due to vocal fold atrophy with or without sulcus.

Methods: This is a retrospective cohort study from September 2012 to December 2017 including 23 patients undergoing bilateral vocal fold injection with autologous fat (24 procedures) for vocal fold atrophy (15 procedures) or atrophy with sulcus (Ford type II or III) (9 procedures). Voice data were collected and analyzed for the preoperative and the 3- and 12-month postoperative time point according to a standardized protocol, including Voice Handicap Index (VHI)-30 and perceptual, acoustic and aerodynamic parameters. Failure rate was defined as non-relevant improvement (< 10 points) in VHI-30 at 12 months and number of revisions within 12 months.

Results: There was a clinically relevant (≥ 15 points) and statistically significant improvement in the VHI-30 (preoperative: 49.1 points; postoperative at 12 months: 29.7 points). Change in dynamic range was also statistically significant over time (p=0.028). There were no differences in voice parameters between patients with atrophy only and atrophy with sulcus, although grade tended to be lower in patients with atrophy only over all time points.

Conclusion: This study shows that bilateral vocal fold injection with autologous fat is a beneficial treatment not only for patients with atrophy but also for patients with sulcus. A comparison of the results with those reported from other forms of sulcus surgery confirmed this finding. However, there is a need for further prospective studies comparing the short- and long-term effects of different techniques.

INTRODUCTION

Non-paralytic glottic insufficiency is a common cause of dysphonia. There are several underlying causes, including vocal fold atrophy. In our clinic, we routinely encounter three forms of vocal fold atrophy: vocal fold atrophy in presbyphonia, an adolescent form, and atrophy associated with congenital vocal fold scar in the form of sulcus [1]. If a sulcus is present it can be further classified as a physiologic sulcus (Ford type I) or pathologic sulcus vocalis (Ford type II and III) with Ford type II and III corresponding to a sulcus vergeture and a sulcus vocalis in the classification by Bouchayer and Cornut [2,3].

The main surgical treatment for atrophy without sulcus is vocal fold medialization, which can be achieved either by bilateral vocal fold injection (VFI) with a durable injectable such as autologous fat or calcium hydroxyapatite, or by bilateral medialization thyroplasty. For vocal fold atrophy with sulcus, several surgical techniques are used that are broadly divided into phonosurgical epithelium freeing techniques such as microflap formation, hydrodissection, angiolytic laser treatment and tissue engineering techniques on one hand and medialization techniques on the other. In their consensus report on vocal fold scar, the European Laryngological Society (ELS) considered medialization to be the least traumatizing procedure to the vocal fold and, therefore, suggested that it be used as the initial treatment for vocal fold scar, including sulcus [4]. However, it is also known that the results of medialization for vocal fold atrophy with scar, including sulcus, are less predictable than the results for glottic insufficiencies caused by atrophy alone, hypomobility, or paresis [5]. In this study, we evaluated the prospectively collected voice outcome data after bilateral VFI with autologous fat in patients with vocal fold atrophy with or without sulcus and compared our findings with those reported in the literature.

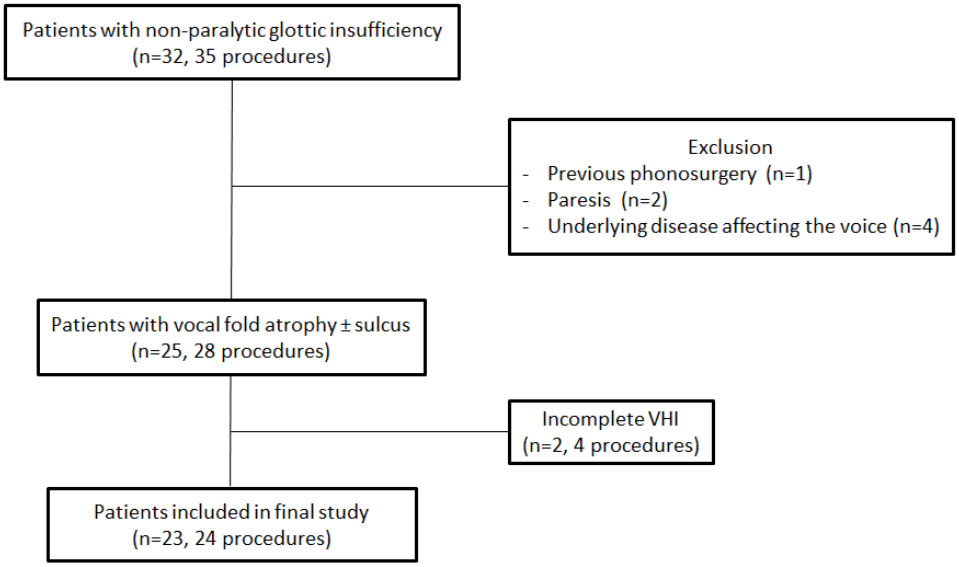
METHODS

Patients

This study was approved by the Leiden University Medical Centre Ethics Committee. All patients with non-paralytic glottic insufficiency who underwent bilateral VFI with autologous fat under general anesthesia (*n*=32, procedures= 35) from September 2011 to December 2017 were retrospectively reviewed. Seven patients were excluded because of previous phonosurgery for sulcus (*n*=1), paresis as another cause of glottic insufficiency (*n*=2), or an underlying disease affecting the voice (*n*=4) including Parkinson's disease (*n*=2), laryngeal dystonia (*n*=1), and laryngeal papillomatosis (*n*=1). Of the 25 remaining patients (28 procedures), 23 (24 procedures) had pre- and postoperative voice data with at least a complete Voice Handicap Index (VHI)-30 questionnaire and were included in the definitive

analysis (Figure 1). These patients had undergone bilateral VFI with autologous fat between September 2012 and December 2017.

Figure 1.



Patient selection and inclusion and exclusion criteria

Voice data

Voice outcome data were collected according to a standardized voice analysis protocol implemented preoperatively and at 3 and 12 months postoperatively. This protocol included patients' self-assessments using the VHI-30, perceptual evaluation using the overall grade score of the GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale, aerodynamic evaluation with maximum phonation time (MPT) and dynamic range, and acoustic analyses including fundamental frequency (F0) and melodic range. The VHI-30 was the primary outcome parameter of the voice analysis protocol. It is a patient-based self-assessment tool consisting of 30 items, which are distributed over three domains: functional, physical, and emotional [6]. In the Dutch version of the VHI-30, a score of 15 points or more identifies patients with voice problems in daily life [7,8]. Furthermore, a change in pre- and postoperative score of 10 points or more in the individual patient and 15 points or more for a group can be considered clinically relevant [8]. The voice was perceptually graded using the grade of the GRBAS scale ranging from zero to three [9]. Running speech samples in random order were graded by experienced listeners (two senior speech language therapists and one laryngologist) and a consensus was reached through (re)evaluation and

discussion. The MPT was measured on /a/ at a comfortable pitch and loudness. The longest MPT from two attempts was included in the analysis. The fundamental frequency in hertz (Hz), dynamic range in decibels (dB), and melodic range in semitones (ST) were extracted from the patient's phonetogram recorded with the Voice profiler (Alphatron, Rotterdam, the Netherlands, 2007) using standardized settings.

Procedure

All procedures were performed under general anesthesia by an experienced laryngologist and/or a fellowship-trained laryngologist. Bilateral VFI was performed with autologous fat, harvested by abdominal liposuction. In a minority of patients using anticoagulants, a periumbilical incision was made to ensure hemostasis, and fat lobules were harvested and separated from the underlying connective tissue. Subsequently, the fat was centrifuged and separated from blood and its liquid component. The standard practice was injection of fat lateral in the vocal fold (thyroarytenoid muscle) at a level just anterior of the vocal fold process using a Brünings syringe until medialization was achieved, with an anticipated overcorrection of between 1/3 and 1/4 of the vocal fold width at the free edge. The final amount on overcorrection was based on the clinical experience of the surgeon. In some cases, a second injection point at the level of the midcord was needed to obtain the intended result. All patients had absolute voice rest for 24 hours after the procedure. Subsequently, they received voice therapy by an experienced speech-language therapist, starting within the first week postoperatively, including resonant voice therapy and vocal hygiene advice.

Statistical analysis

All data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 21.0, released 2012. IBM Corp, Armonk, NY, USA). Demographic details were presented as the mean with standard deviation (SD) or as proportions using percentages. The effect of time on the different voice parameters was assessed with the linear mixed model and was adjusted for diagnosis (atrophy versus atrophy with sulcus). The linear mixed model was chosen because it applies a correction for missing data. This correction is based on the observed data and uses all available data, without the need to censure a patients' entire data, when one or more data points are missing or the need for imputation of measurements [10]. For all statistical tests, a p value < 0.05 was considered significant.

RESULTS

Table 1 shows the preoperative demographic details of the 23 patients undergoing 24 procedures. These were all female patients. Fifteen injections were performed in patients with vocal fold atrophy, two of these were performed consecutively in the same patient within

5 months. Nine injections were performed in patients with atrophy and sulcus (Ford type II or III). The pre- and post-VFI voice outcome data for the overall patient group are shown in Table 2. The changes in VHI-30 ($p < 0.001$) and dynamic range ($p = 0.028$) were statistically significant over time. The change in the VHI-30 from baseline to 12-months postoperative was also clinically relevant (Δ19.4). The improvement in postoperative outcomes in the other voice parameters was not statistically significant (Table 2).

Table 1. Demographic details of the patients undergoing bilateral vocal fold injection with autologous fat

Characteristics	**Total = 24 (100%)**
Mean age, years at baseline (SD)	39.5 (18.2)
Gender, *n* (%)	
Female	24 (100)
Etiology, *n* (%)	
Atrophy	15 (62.5)
Atrophy with sulcus	9 (37.5)

SD standard deviation

Table 2. Pre- and postoperative voice outcome data of patients with vocal fold atrophy ± sulcus undergoing bilateral VFI with autologous fat

	Preoperative	**3 months postoperative**	**12 months postoperative**	***p* value**
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	
VHI-30	49.1 (41.4; 56.8)	34.8 (27.0; 42.6)	29.7 (21.5; 37.9)	<0.001*
Grade	1.58 (1.3; 1.9)	1.20 (0.9; 1.5)	1.18 (0.8; 1.6)	0.071
MPT (s)	11.0 (9.2; 12.9)	12.4 (10.5; 14.3)	12.2 (10.0; 14.4)	0.384
Dynamic range (dB)	32.3 (27.5; 37.0)	33.8 (29.1; 38.5)	41.1 (35.4; 46.8)	0.028*
F0 (Hz)	198 (187; 209)	201 (190; 212)	196 (184; 209)	0.730
Melodic range (ST)	17.0 (14.1; 19.8)	17.4 (14.5; 20.3)	19.7 (16.2; 23.2)	0.428

VFI vocal fold injection, *CI* confidence interval, *VHI* voice handicap index, *MPT* maximum phonation time, *F0* fundamental frequency, *Hz* hertz, *dB* decibel, *ST* semitone

*p value < 0.05 was considered significant

Table 3 shows the results stratified for patients with vocal fold atrophy only and patients with vocal fold atrophy and sulcus. The overall change in the VHI-30 was statistically significant in both groups ($p < 0.001$, $p = 0.002$). The change in the VHI from the preoperative time point to the 12-month postoperative time point was clinically relevant in both groups (Δ21.2 atrophy; Δ 17.7 sulcus). There was no significant improvement in any of the other voice parameters for the two groups. Finally, there was no significant difference between the two groups in the severity of the scores for the various voice parameters, although the grade

of dysphonia tended to be lower in patients with atrophy (mean difference over all time points 0.47, $p = 0.057$, data not shown in table).

Table 3. Pre- and postoperative voice outcome data stratified for patients with vocal fold atrophy and vocal fold atrophy with sulcus

	Etiology	Preoperative	3 months postoperative	12 months postoperative	*p* value
		Mean	Mean	Mean	
VHI-30	Atrophy	47.5	33.0	26.3	<0.001*
	Sulcus	51.8	38.0	34.1	0.002*
Grade	Atrophy	1.5	0.9	1.0	0.078
	Sulcus	1.8	1.6	1.5	0.602
MPT (s)	Atrophy	11.2	13.4	12.4	0.292
	Sulcus	10.7	10.9	11.8	0.825
Dynamic range (dB)	Atrophy	30.6	33.3	41.6	0.051
	Sulcus	35.0	34.6	40.6	0.449
F0 (Hz)	Atrophy	191	199	194	0.513
	Sulcus	210	205	200	0.642
Melodic range (ST)	Atrophy	15.7	17.5	19.8	0.363
	Sulcus	19.1	17.2	19.6	0.743

VHI voice handicap index, *MPT* maximum phonation time, *F0* fundamental frequency, *Hz* hertz, *dB* decibel, *ST* semitone

**p* value < 0.05 was considered significant

Looking at individual procedures, 12-month data was available in 18 out of 24 procedures. Six procedures did not have 12-month data: in four procedures the patients (*n*=4) had already undergone or opted for a revision procedure (repeat VFI with fat (*n*=2) or medialization thyroplasty (*n*=2)) and in two procedures the patients (*n*=2) were lost to follow up. Out of the 18 procedures were 12 month data was available improvement at 12 months could be calculated; 15 procedures had a clinically relevant improvement (≥ 10 points) in the VHI-30. Three out of 18 had a non-relevant improvement (< 10 points). We, therefore, estimate the failure rate within 12 months for individual procedures to be somewhere between 16.7% (4/24 procedures) if considering only procedures requiring revision as failures, and 37.5% (9/24 procedures) if considering procedures requiring revision and procedures without clinically relevant VHI improvement as failures and hypothesizing that the two procedures lost to follow up were also failures.

DISCUSSION

In this study, we evaluated the voice outcome data after bilateral VFI of autologous fat in patients with vocal fold atrophy with or without sulcus. We found a statistically significant and clinically relevant improvement in the VHI-30 for the study group as a whole. This improvement was consistent in both patient groups (atrophy alone and atrophy with sulcus). Therefore, our results show that bilateral VFI with autologous fat is a beneficial treatment for patients with vocal fold atrophy with or without sulcus. Additionally, our results suggest that it is equally beneficial in both these patient groups. Although our results demonstrated voice improvement, there was no normalization of the voice and/or voice use based on the 12-month postoperative VHI-30 score remaining above 15 points, which indicates an elevated patient-perceived voice related handicap.

The improvement in the VHI is supported by a statistically significant improvement in the dynamic range. Although there are no clear definitions as to what constitutes a clinically meaningful improvement in this parameter, we believe that this improvement in volume range from 32.3 dB to 41.1 dB is most likely meaningful to the patient, taking into account that range of 46 dB is considered acceptable for a normal voice [11]. Functionally, this reflects the likelihood that patients will notice that less effort is required to produce a softer or louder voice. Effort, and not the quality of the voice, is often the main complaint of patients with atrophy with or without sulcus and the primary aim when performing these procedures is most often to improve their voice function.

Several studies have shown a beneficial effect of autologous fat injection on glottic insufficiency from both paralytic and non-paralytic causes [12-20]. Autologous fat injection is known to be safe [21], but the long-term (>1 year) benefits are less consistent [12,19,22,23]. The effectiveness of autologous fat injection in patients with non-paralytic glottic insufficiency caused by atrophy with or without sulcus has been studied to a lesser extent, with generally positive subjective results [19,22,24,23]. Chen et al. reported excellent results in 62.5% of their patients based on subjective patient ratings, together with an overall significant improvement in the perceptual rating of grade, roughness, and breathiness, and videolaryngostroboscopic rating [22]. Although Chen and others suggest that the results of fat injection are better in patients with atrophy alone than atrophy with sulcus [14,22], this was not confirmed in our study. Recently, Dominguez et al. reported good results for patients with vocal atrophy and/or paresis treated with fat injection or bilateral medialization thyroplasty [19]. However, they found that only the thyroplasty group maintained this effect during the whole follow-up period (19 months for fat injection, 16.3 months for thyroplasty). Although the reabsorption of fat is a well-acknowledged downside of the procedure, which we anticipated, we did not see this when looking at our overall VHI-30 scores at 12 months. However failure rate in the

first 12 postoperative months in this study was estimated to be between 17% and 37.5%. A longer follow-up is required to more definitely establish the life span of fat injections in our population. Possible explanations for the discrepancies in literature on this topic can be the amount of overcorrection or the technique of fat preservation used and the timing of postoperative measurements. It is important to establish firmly if long-term results do indeed favor thyroplasty over VFI as medialization technique.

To determine the optimal treatment for sulcus, we compared our results from bilateral VFI with autologous fat with those from other forms of sulcus surgery. The main alterative is microphonosurgery to free the epithelium and many different techniques have been described, mostly retrospectively and with varying effects.

Stuut et al. found no improvement in VHI (preoperative 48.8, postoperative 47.1) in their patients with sulcus glottidis (*n*=17) using solely the epithelium freeing technique as described by Bouchayer [25]. Therefor it has been suggested by them and by others to not only dissect the sulcus, but to restore the layered structure of the vocal folds to improve treatment outcome. Positive results have been achieved using transplantation of autologous temporalis fascia into the vocal fold (ATFV). In a study showing long-term results of ATFV in 21 patients, the VHI-10 decreased by 8.35 points after 6 months and 13.53 points after 44 months. These improvements were both statistically ($p < 0.001$) and clinically relevant (≥ 5 points on the VHI-10 [26]) [27]. However, the mean VHI-10 at last follow-up was still just above 11 points, which is considered abnormal [26]. A recent cohort of ten patients with sulcus vocalis (*n*=6) and vocal fold scar (*n*=4) confirmed the beneficial effect of ATFV with significant improvements in the VHI-10, perceptual grading, as well as aerodynamic (MPT, s/z ratio) and stroboscopic findings 6 months after the operation [28].
There are also studies that combine the excision of the sulcus with medialization of the vocal fold [29,30,31]. Yilmaz reported on 44 patients with sulcus who underwent excising of the sulcus followed by injection medialization with hyaluronic acid or calcium hydroxyapatite (*n*=42) or bilateral type 1 thyroplasty (*n*=2). The VHI-30 improved significantly (90.5 to 39.1 points) at a mean follow-up of 30 months. There was also significant improvement in the grade, roughness and breathiness of the GRBAS score, glottal closure and mucosal wave amplitude of the stroboscopic findings, and in most of the aerodynamic and acoustic parameters [29]. Miaskiewicz recently showed an improvement in the VHI-30 of 10.2 points (preoperative 44.36 versus postoperative 34.12) at 12 months after combined sulcus excision and VFI, using a short acting filler in 29 cases, a long acting filler in 2, a combination of fillers in 2, and no filler in 3 cases [30].

The use of angiolytic lasers for sulcus vocalis is a relatively new treatment option conceptually based on using selective photothermolysis to soften scar tissue [32,33,34]. A recently

published series of 79 patients showed an improvement in the VHI-30 of 19.76 points, to a score close to 40 points after 6 months, as well as an significant improvement in the GRBAS by 1.07 points. Several objective voice parameters (noise to harmonic ratio, jitter, shimmer, MPT) also improved significantly in this study [34].

Despite their different surgical approaches to treat sulcus, the studies above show statistically significant and clinically relevant improvements in VHI scores; although, these are still above normal [27,29,30,34]. It is important to note that these results are in line with our results from treating sulcus with autologous fat injection only. Therefore, at the moment these techniques can be considered equal as to short-term (12 months) treatment effect. This is supported by the findings of Welham in his prospective trial comparing three types of surgery for sulcus: type I thyroplasty, VFI with synthetic filler, and graft implantation. They concluded that no single treatment option is completely successful and there is no evidence-based decision algorithm available to identify the optimal treatment for an individual patient with sulcus [35]. Therefore, at this stage, our findings support the recommendation in the ELS consensus report to start with the least invasive technique for sulcus [4], i.e. VFI. We emphasize the importance of larger prospective studies comparing the different surgical techniques to establish optimal treatment algorithms for these patients.

Our study has some limitations. Our patient population was relatively small, although it was one of the larger study cohorts on this subject. We advocate a prospective study with a larger cohort. Also, our follow-up at this time was limited to 12 months. As stated above, a longer follow-up would better establish the life-span of fat injections in our population.

CONCLUSION

This study shows a statistically significant and clinically relevant subjective improvement up to 12 months after VFI with autologous fat in patients with vocal fold atrophy with or without sulcus. This improvement was reflected in the dynamic capabilities of the patients' voices. The degree of improvement was similar in patients with or without sulcus. This indicates that bilateral VFI with autologous fat is a beneficial treatment option not only for patients with atrophy but also for patients with sulcus. Comparing our results with those from other forms of sulcus surgery in the literature confirms this finding; although we emphasize the need for further prospective studies comparing the short and long-term effects of different techniques.

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4

Bilateral medialization thyroplasty in patients with vocal fold atrophy with or without sulcus

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ABSTRACT

Purpose: To evaluate voice outcome after bilateral medialization thyroplasty in patients with non-paralytic glottic insufficiency due to vocal fold atrophy with or without sulcus.

Methods: Retrospective cohort study on 29 patients undergoing bilateral medialization thyroplasty for vocal fold atrophy (14 procedures) or atrophy with sulcus (15 procedures) between October 2012 and November 2017. Voice data were collected and analyzed for the preoperative and the 3- and 12-month postoperative time point according to a standardized protocol, including Voice Handicap Index (VHI)-30 and perceptual, acoustic and aerodynamic parameters. Failure rate was based on number of revisions within 12 months and non-relevant improvement (< 10 points) in VHI-30 at 12 months.

Results: There was a clinically relevant (≥ 15 points) and statistically significant improvement ($p < 0.0001$) in the VHI-30 (preoperative: 55.8 points; postoperative at 12 months: 30.9 points). Fundamental frequency for male subjects decreased significantly from 175 Hz to 159 Hz ($p=0.0001$). The pre- and postoperative grade of dysphonia was significantly lower in patients with atrophy compared to atrophy and sulcus (mean difference 0.70, $p = 0.017$).

Conclusion: Bilateral medialization thyroplasty is a valid treatment option for patients with atrophy with or without sulcus. Outcomes are comparable to other methods reported in literature. However, there is a great need for larger, prospective studies with long-term follow-up to gain more insight into the comparative voice outcomes for the different forms of surgery for patients with glottic incompetence due to atrophy with or without sulcus.

INTRODUCTION

Non-paralytic glottic insufficiency is a common cause of dysphonia affecting both voice quality as vocal function and causing substantial patient's burden. There are several underlying etiologies, including hypomobility, paresis and vocal fold atrophy. In our practice we distinguish three forms of vocal fold atrophy: (1) vocal fold atrophy in presbyphonia, (2) an adolescent form of vocal fold atrophy, and (3) atrophy associated with congenital vocal fold scar in the form of sulcus [1, 2]. In our patient population pathological sulcus is defined as type II and III according to Ford, and/or sulcus vergeture and sulcus vocalis according to Bouchayer and Cornut [3, 4].

The main surgical treatment for atrophy is vocal fold medialization. This can be achieved by vocal fold injection (VFI) with short acting injectables such as hyaluronic acid, or with durable injectables such as autologous fat or calcium hydroxylapatite. Alternatively, medialization can be accomplished by bilateral medialization thyroplasty. For the treatment of atrophy associated with sulcus epithelium freeing techniques can be used as an alternative or in addition to medialization [5]. At this moment there is no evidence-based decision algorithm available to identify the optimal treatment for an individual patient with sulcus [6]. In their consensus report, the European Laryngological Society (ELS) has suggested medialization as the initial treatment, as it is the least traumatizing to the vocal fold [5]. Several studies have however shown the results of medialization to be less predictable for patients with atrophy associated with sulcus or vocal fold scar compared to those for patients with hypomobility/paresis and atrophy alone. This is thought to be due to the "double pathology" affecting both glottic closure and vibratory potential of the vocal fold in patients with sulcus or vocal fold scar [7].

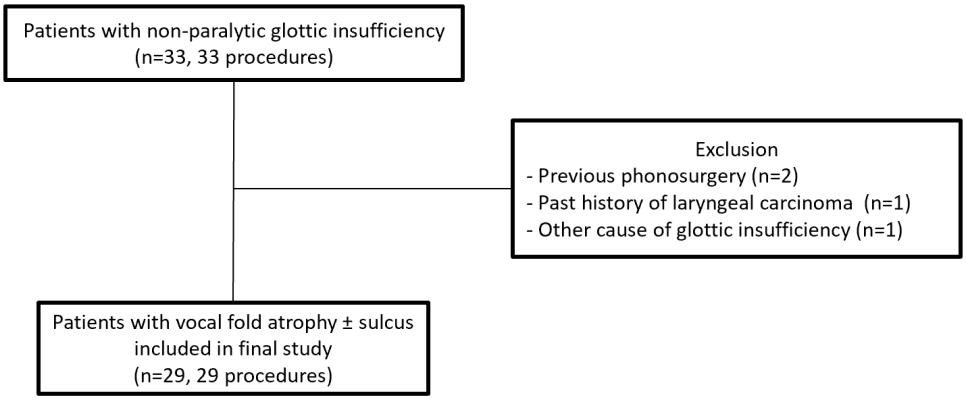
In a previous study we showed that VFI with autologous fat resulted in equivalent subjective voice improvements for up to 12 months in patients with atrophy and patients with atrophy associated with sulcus [2]. In this study we evaluated the results after bilateral medialization thyroplasty in patients with vocal fold atrophy with or without sulcus. The aim of this and previous studies on this topic is to contribute to the ongoing attempts to identify the optimal, evidence-based treatment for an individual patient with atrophy or atrophy with sulcus.

METHODS

Patients

All patients with non-paralytic glottic insufficiency who underwent bilateral medialization thyroplasty under local anesthesia (*n*=33) from December 2011 to November 2017 were retrospectively reviewed. Four patients were excluded because of previous phonosurgery (*n*=2), past history of laryngeal carcinoma (*n*=1), or another cause of glottic insufficiency (bilateral paresis, *n*=1). All of the 29 remaining patients had a complete Voice Handicap Index (VHI)-30 questionnaire pre- and postoperatively and were included in the definitive analysis (Figure 1). These patients had undergone bilateral medialization thyroplasty between October 2012 and November 2017. The study was approved by Leiden University Medical Center Ethics Committee.

Figure 1. Patient selection and inclusion and exclusion criteria



Voice data

Voice outcome data were collected according to a standardized voice analysis protocol implemented preoperatively and at 3 and 12 months postoperatively. This protocol including patients' self-assessments using the VHI-30, perceptual evaluation by experienced raters using the overall grade score (G) of the GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale, aerodynamic evaluation with maximum phonation time (MPT) and dynamic range, and acoustic analyses including fundamental frequency (F0) and melodic range, has been extensively described in previous publications [1,2]. A score of 15 points or more in VHI-30 was used to identify patients with voice problems in daily life [8,9]. A change in pre- and postoperative score of 10 points or more in the individual patient and 15 points or more for a group was considered clinically relevant [9].

Procedure

All procedures were performed by an experienced laryngologist. Bilateral medialization thyroplasty with Gore-tex® (GORE-TEX® Soft Tissue Patch, Gore Medical, Flagstaff, Arizona) was performed under local anesthesia in the operating room. The operation technique used was as described by Isshiki and McCulloch with some modifications [10,11]; starting with a horizontal skin incision at the level of the thyroid, raising subplatysmal flaps, dividing the strap muscles in the midline and visualizing the thyroid alas. The outer perichondrium was incised and a superiorly based flap was raised. The position and the size of the first cartilage window was determined. The window was shaped using a drill and the Kerrison ronguer. The position of the window was checked endoscopically and a similarly positioned window was made in the other ala. Using a 4 mm Gore-tex® patch, cut as a ribbon, optimal medialization was achieved based on three factors: the perceptual evaluation of the voice by the patient and the surgical team, the ease of phonation as evaluated by the patient and the visual evaluation of vocal fold closure and vibration using intraoperative videolaryngostroboscopic guidance. The implant was stabilized with a fixation plate. The wound was closed in layers, leaving a drain in situ. All patients had absolute voice rest the first four days postoperatively. Subsequently, they received speech therapy by an experienced speech-language therapist, starting in the second postoperative week. This included resonant voice therapy and vocal hygiene advice.

Statistical analysis

All data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 21.0, released 2012. IBM Corp, Armonk, NY, USA). Demographic details were presented as the mean with standard deviation (SD) or as proportions using percentages. The effect of time on the different voice parameters was assessed with the linear mixed model and was adjusted for diagnosis (atrophy versus atrophy with sulcus). For all statistical tests, a p value < 0.05 was considered significant.

RESULTS

Table 1 shows the preoperative demographic details of the 29 patients; 14 patients had atrophy and 15 patients had atrophy with sulcus.

Table 1. Demographic details of the patients undergoing bilateral medialization thyroplasty

Characteristics	Total = 29 (100%)
Mean age, years at baseline (SD)	50.5 (17.9)
Gender, *n* (%)	
Male	12 (41.4)
Female	17 (58.6)
Etiology, *n* (%)	
Atrophy	14 (48.3)
Atrophy with sulcus	15 (51.7)

SD standard deviation

Table 2 shows the changes in voice parameters for the overall patient group. The mean VHI-30 score improved from 55.8 to 30.9 in 12 months (Δ24.9), which was a clinically relevant and a statistically significant improvement ($p < 0.0001$). Fundamental frequency for males decreased from 175 Hz to 159 Hz ($p = 0.0001$) (normal value male: 100-130 Hz). Postoperative changes in other voice parameters were not significant.

Table 2. Pre- and postoperative voice outcome data of patients with vocal fold atrophy ± sulcus undergoing bilateral medialization thyroplasty

	preoperative	3 months postoperative	12 months postoperative	*p* value
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
VHI-30	55.8 (48.4-63.1)	33.0 (25.6-40.3)	30.9 (22.8-38.9)	<0.0001*
Grade	1.9 (1.6-2.3)	1.6 (1.3-1.9)	1.7 (1.4-2.1)	0.059
MPT (s)	11.3 (9.2-13.3)	12.8 (10.8-14.9)	12.6 (10.5-14.8)	0.221
Dynamic range (dB)	30.2 (25.3-35.2)	36.2 (31.4-41.1)	32.3 (27.1-37.5)	0.065
F0 male (Hz)	175 (137-213)	152 (114-190)	159 (121-198)	0.0001*
F0 female (Hz)	224 (167-252)	200 (172-228)	221 (191-251)	0.284
Melodic range (ST)	17.8 (14.9-20.7)	17.7 (14.8-20.5)	18.7 (15.6-21.8)	0.784

CI confidence interval, *VHI* voice handicap index, *MPT* maximum phonation time, *F0* fundamental frequency, *Hz* hertz, *dB* decibel, *ST* semitone

*p value < 0.05 was considered significant

Table 3 shows the results stratified for patients with vocal fold atrophy versus patients with vocal fold atrophy and sulcus. At baseline the preoperative values of the different voice parameters were comparable between the patient groups except for grade of dysphonia. VHI-30 showed significant improvement for both patient groups and this improvement was also clinically relevant in both groups (Δ29.9 atrophy; Δ19.0 sulcus). The perceptive rating of the grade of dysphonia showed no significant improvement, but was significantly lower both pre- and postoperatively in patients with atrophy, with a grade corresponding to mild dysphonia (1.6-1.4) compared to patients with atrophy and sulcus, with a grade corresponding to moderate dysphonia (2.3-2.1) (mean difference 0.70, $p = 0.017$). Dynamic range in the atrophy group showed a significant improvement at three months, but this effect had disappeared at 12 months. Finally, fundamental frequency for males in both groups showed significant lowering postoperatively (atrophy $p = 0.001$, sulcus $p = 0.015$).

Table 3. Pre- and postoperative voice outcome data stratified for patients with vocal fold atrophy and vocal fold atrophy with sulcus

	Etiology	Preoperative	3 months Postoperative	12 months Postoperative	*p* value
		Mean	Mean	Mean	
VHI-30	Atrophy	56.9	29.9	27.0	<0.0001*
	Sulcus	54.4	34.9	35.4	0.002*
Grade	Atrophy	1.6	1.3	1.4	0.284
	Sulcus	2.3	1.9	2.1	0.204
MPT (s)	Atrophy	11.5	13.7	13.6	0.221
	Sulcus	11.0	12.0	11.7	0.769
Dynamic range (dB)	Atrophy	29.0	38.6	31.1	0.028*
	Sulcus	31.4	34.1	33.4	0.732
F0 male (Hz)	Atrophy	160	133	139	0.001*
	Sulcus	190	172	179	0.015*
F0 female (Hz)	Atrophy	234	197	212	0.263
	Sulcus	215	203	230	0.548
Melodic range (ST)	Atrophy	17.1	19.5	19.6	0.446
	Sulcus	18.5	16.0	17.9	0.482

VHI voice handicap index, *MPT* maximum phonation time, *F0* fundamental frequency, *Hz* hertz, *dB* decibel, *ST* semitone

*p value < 0.05 was considered significant

All 29 procedures had complete follow-up at 3 months and 24 procedures had complete follow up at 12 months. Five procedures did not have 12-month data: three patients (n=3) had already undergone or opted for a revision thyroplasty and 2 patients (n=2) were lost to follow up. Out of the 24 procedures of which voice outcome at 12 months could be

calculated, 19 had a clinically relevant improvement (≥ 10 points) in VHI-30. Five out of 24 had a non-relevant improvement (< 10 points). One of the patients with non-relevant improvement opted to undergo revision thyroplasty at the 12-month visit, bringing the total number of revisions to four.

We estimate the failure rate within 12 months for individual procedures to be somewhere between 13.8% (4/29 procedures) if considering only procedures requiring revision thyroplasty as failures and 27.6%% (8/29 procedures) if considering procedures requiring revision thyroplasty and procedures without clinically relevant VHI improvement at 12 months as failures. If, additionally, the two procedures lost to follow-up are included as failures, the rate would be 34.5%. Looking at the revisions in more detail the VHI significantly improved at 12 months after revision in two patients, one with atrophy and one with sulcus. In two patients, both with sulcus, the VHI 12 months after revision was similar to the values before the primary intervention.

DISCUSSION

In this study we present our results after bilateral medialization thyroplasty in patients with atrophy with or without sulcus. We found a statistically significant and clinically relevant subjective improvement in both patient groups. Based on this, we conclude that bilateral medialization thyroplasty is an effective treatment option for both atrophy and atrophy with sulcus. Although VHI-scores improved significantly they remained above normal limits, implying a diminished but ongoing voice burden for these patients after surgery. It is important to incorporate this information in patient counselling.

As stated, VHI outcome was similar for patients with atrophy with or without sulcus. In the perceptual grading and in dynamic range there were some differences between the two groups. Postoperatively, patients with atrophy only had an overall lower grade score, which corresponded to mild dysphonia, compared to patients with atrophy and sulcus, which corresponded to moderate dysphonia. This difference was already present preoperatively and could be well explained by the more complex “double pathology” in the latter group, resulting in a more severe perceptual dysphonia. For dynamic range the results showed a significant improvement at 3-months postoperatively in patients with atrophy, but this effect had dissolved at 12 months. We have no solid explanation for this temporary improvement in dynamic range. It may be related to characteristics of the Gore-Tex and could possibly be explained by the malleability of the material. In time, this could cause it to change shape, position or volume. The fact that this increase was not seen in the patients with sulcus could be because of the earlier mentioned “double pathology”. Lastly, we found a lowered,

but still higher than normal fundamental frequency in males after bilateral medialization thyroplasty, both for atrophy and atrophy with sulcus. This may be an interesting aspect for further research as gender specific outcomes after medialization thyroplasty for non-paralytic glottic incompetence has gained more attention recently, showing female having greater subjective improvement compared to male after surgery [12]. We would also consider to include this aspect in the preoperative counselling of male patients by informing them that their voices may still be higher pitched after surgery.

Thyroplasty as surgical treatment for vocal fold atrophy, with or without sulcus, became more popular after Isshiki et al. reported promising results in the mid-1990's [13]. Shortly after, Gore-tex® medialization thyroplasty was introduced [11,14]. Since then several studies have reported on bilateral medialization thyroplasty in patients with glottic incompetence as a result of atrophy and sulcus, as well as paralysis, paresis, and other causes [6,7,14-23]. The largest patient group (total *n*=75, hypomobility *n*=27, paresis *n*=16, scarring *n*=18, atrophy *n*=14), which also has the longest follow-up (up to 10 years), showed overall improvement in voice-related quality of life (VRQOL). This improvement was statically significant in most subgroups. Notably however, for the scar subgroup there was no statistically significant improvement in VRQOL [7].

Only a few additional studies have reported specifically on bilateral medialization thyroplasty in patients with atrophy or atrophy with sulcus/scar [6,18,20]. Sachs et al. showed significant improvement in self-rating measures (VRQOL, Glottal Function Index (GFI)) and a "best voice" Visual Analogue Scale (VAS)) in their patients with age-related atrophy treated with bilateral medialization thyroplasty [18]. Allensworth et al. found a significant improvement in the VHI-30 (59.4 to 31.5) in 10 patients, which was very similar to the improvement found in our study (55.8 to 30.9) [20]. Contrary to our study where we only found an impact on fundamental frequency (males) and a transient effect in the dynamic range (patients with atrophy only), both Sachs and Allensworth showed improvements in several of the (semi-) objective parameters they analyzed [18,20]. As for patients with sulcus/scar, Welham et al. showed a significant improvement in VHI-30 after treatment with thyroplasty in his series which did include unilateral procedures. The median VHI-30 in thyroplasty group improved from 59.0 to 39.3 (average post-treatment value at 18 months) or 31.0 (best post-treatment value in 18 months)(personal communication with author) [6].

Several studies have reported less promising results after medialization thyroplasty for patients with scar compared to other causes of nonparalytic glottic incompetence in the past and more recently [7,13,17,21]. Although we did anticipate more negative results for our sulcus patients, we did not see this in our own series [1,2], including this study. This may be due to our inclusion criteria, as we have only included sulcus and not iatrogenic

scar. From assessing the revision thyroplasties in this study (*n*=4), which occurred in both atrophy and atrophy with sulcus patients, we concluded that there are probably different reasons for disappointing results. Some failures may be due to an inadequate procedure, such as too little or too much medialization, which can be corrected, but that some failures are also likely due to the inherent limitations of this technique in treating this patient cohort.

Concerning the duration of the effect of thyroplasty, we did not have data beyond twelve months. However, Dominguez et al. showed that the results of medialization thyroplasty in her patients with non-paralytic glottic incompetence were stable at a median follow up of 16.3 months [19]. We conclude from the above that there is evidence in literature to support our finding that bilateral medialization thyroplasty provides long-term, subjective improvement in patients with vocal fold atrophy and atrophy with sulcus. The relationship between the relatively constant improvement in subjective parameters, and the varying improvement in the multitude of the (semi-)objective parameters studied so far is still not clear [1]. With "(semi-)objective" parameters we mean all stroboscopic, aerodynamic and acoustic voice outcome measurements described in the literature. We added "semi-" because these measurements are not entirely objective, as patient performing factors and investigator interpretation factors may influence the outcome. If (semi-)objective voice parameters should be used, and if so, which parameters are suitable, needs further investigation.

Several studies have compared medialization thyroplasty in patients with glottic incompetence to other treatments modalities such as VFI medialization and alternatively microphonosurgery in the case of sulcus/scar. In their earlier mentioned study, Dominguez et al. compared medialization thyroplasty (*n*=20) to VFI with autologous fat injections (*n*=15) in patients with atrophy, although their series did include patients with paresis [19]. It showed improved subjective voice outcome with clinical relevant and statistically significant VHI-10 improvements for both techniques; even showing a normalization of the VHI-10 in thyroplasty patients at 7 months (decrease from 30.5 to 9.1; normal value VHI-10 English version ≤ 11 [24]). Moreover, as stated earlier, the thyroplasty group maintained this effect during the whole follow-up period in contrast to the VFI group, in which values had regressed to pretreatment scores at around 16 months. In accordance with Dominguez, we also found the subjective outcome of our bilateral thyroplasty patients to be comparable to a similar cohort of our patients treated with bilateral VFI with autologous fat [2]. VHI-30 scores for our VFI patients decreased from 49.1 (pretreatment) to 27.9 (12 months posttreatment) which is very similar to VHI-30 outcomes in our present study. In a prospective trial performed by Welham et al., comparing three types of surgery for sulcus (type I thyroplasty (*n*=9), injection laryngoplasty (*n*=9), and graft implantation (*n*=10)) both thyroplasty and graft implantation yielded significant improvement in VHI-30, although graft implantation only showed significant VHI-improvement in best post-treatment score and had a slow and long

recovery period. No significant changes were found in perceptual, acoustic, aerodynamic and vocal fold physiology outcomes. Although subjective improvement after thyroplasty was clinically relevant and statistical significant, authors advised caution in their conclusions, because of the wide variation in response seen across individual patients and different treatment groups [6].

Finally, several studies have published results for microphonosurgical techniques in treating sulcus/scar [25-38]. Techniques vary and include: microflap with or without prosthesis (fibrin glue, fascia, fat), slicing techniques, superficial steroid injections and fat injections as well as laser procedures with PDL and KTP lasers. The mean decrease in VHI-30 in the publications from which this could be extracted [27,29,33,36,37,38]; ranges from 1.7 [29] to 30.6 [38] points with an average decrease of 20.1 points. Although this does not constitute a qualified systematic review or meta-analysis, when comparing it to the average VHI-30 decrease in this study (24.9 points) it gives a rough indication that bilateral medialization thyroplasty may be as effective in treating sulcus/scar as performing microphonosurgery.

There were some limitations of this study. One was the retrospective study design. Although missing data were limited and corrected for, the retrospective study design implied selection bias. Other limitations were the size of the subgroups of our patient population and the limited follow-up time of 12 months, as already mentioned above.

CONCLUSION

This study together with a review on this topic shows that bilateral medialization thyroplasty is a valid treatment option for patients with atrophy with or without sulcus. Outcomes are comparable to other methods although there are indications that they may be more stable than in VFI medialization. In the case of sulcus/scar results are reached more quickly, and potentially with less risk of permanent deterioration than in microphonosurgery. However, there is a great need for larger, prospective studies with long-term follow-up to gain more insight into the comparative voice outcomes for the different forms of surgery for patients with glottic incompetence due to atrophy with or without sulcus. Also, more data are needed on which subjective and (semi-)objective voice parameters are reliable and meaningful in the evaluation of these outcomes.

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5

Long-term outcomes of bilateral medialization thyroplasty in patients with vocal fold atrophy with or without sulcus

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ABSTRACT

Purpose: Evaluate long-term voice outcome after bilateral medialization thyroplasty in glottic insufficiency due to vocal fold atrophy with or without sulcus

Methods: Patients after medialization thyroplasty for vocal fold atrophy with or without sulcus were identified. Long-term postoperative subjective voice outcomes (> 1 year) using Voice Handicap Index-30 (VHI-30), subjective ratings on voice aspects and study-specific questionnaire were compared to preoperative and shorter term (1 year) values.

Results: Thirty-six patients were identified, of which 26 were included (16 atrophy, 10 sulcus) with median follow-up of 6.7 years. Mean VHI-30 score at > 1 year (40.0) showed clinically relevant (≥ 15 for groups) and statistically significant improvement compared to preoperative score (58.1) and remained stable compared to postoperative score (35.7) at 1 year. Ten patients (56%) reported clinically relevant improvement (≥ 10) after more than 5 years.

Conclusion: Long-term improvement in subjective voice outcomes are attainable in a significant proportion of patients undergoing bilateral medialization thyroplasty for atrophy with or without sulcus.

INTRODUCTION

Patients suffering from non-paralytic glottic insufficiency with or without sulcus have complaints of deteriorated voice quality, increased effort to speak, and reduced vocal load, leading to a negative impact on health-related quality of life and functional health status [1,2]. Several treatment options for non-paralytic glottic insufficiency caused by vocal fold atrophy with and without sulcus are known from the literature and our own clinical experience [3-6]. Treatment options can be grossly categorized three ways: (1) procedures improving glottic closure such as vocal fold injection (VFI) with different materials or laryngeal framework surgery (LFS) in the form of (bilateral) medialization thyroplasty; (2) in case of sulcus, procedures improving mucosal wave by removing or replacing scar tissue such as microlaryngeal phonosurgery involving the subepithelial space with or without grafting; and (3) VFI using techniques from regenerative medicine. The different options can also be used in combination.

Regarding LFS the most used material for bilateral medialization with mobile vocal folds is Gore-Tex® (GORE-TEX® Soft Tissue Patch, Gore Medical, Flagstaff, Arizona) because it is not absorbed and is considered the most permanent treatment option for improving glottic closure. To our knowledge, available literature consists of only a few studies that have reported on long-term results for medialization thyroplasty in this patient population [4,7,8]. In this study, we evaluate the results in our own cohort in order to further investigate the longevity of bilateral medialization thyroplasty in voice outcome. These results will contribute to the challenging task of identifying the optimal, evidence-based treatment for patients with atrophy or atrophy with sulcus and will serve to support patients' counselling in this specific patient group.

METHODS

Patients

Patients with non-paralytic glottic insufficiency who underwent bilateral medialization thyroplasty with Gore-Tex® implantation between October 2012 and January 2020 under local anesthesia were retrospectively identified and asked to participate in this cohort study. For further description of the surgical technique we refer to our previous publication on this subject [6]. All patients received speech language therapy, including resonant voice therapy and vocal hygiene advice, in their first postoperative year. To be included, surgery should have been performed at least 1 year earlier. The study was approved by the local medical ethical committee of the Leiden University Medical Center (N21.013).

Data collection

As a part of routine clinical care in our center, multidimensional voice outcome data were collected according to a standard protocol at three time points: preoperatively and at 3 and 12 months postoperatively. As part of this protocol patients' perceived voice handicap is evaluated by the Voice Handicap Index-30 (VHI-30) and supplemented by four subjective ratings on voice aspects that were used for this study. For the long-term follow-up in this study (> 1 year postoperative) subjective data were collected with the use of a digital survey, including a repeat of the routine VHI-30 questionnaire and four subjective ratings on voice aspects supplemented by a study-specific questionnaire.

Voice Handicap Index

Patient self-assessment was performed using the Dutch validated version of the VHI-30 [9]. The VHI-30 is considered a reliable and valid method to assess the impact of voice impairments and gives a score between 0 and 120 points. The questionnaire comprises 30 items, with a grading from 0 to 4 points (0=never and 4=always) [10]. A score of 15 points or more in VHI-30 was used to identify patients with voice problems in daily life [9,11]. A change in pre- and postoperative score of 10 points or more in the individual patient and 15 points or more for a group was considered clinically relevant [11].

Patient rating of voice aspects

In addition, patients were asked to rate their voice on four domains: (1) quality of voice, (2) effort of voicing, (3) possibility or limitation in voicing, (4) voice influence on life. These subjective ratings were based on a 10-point scale. In this numeric rating scale, 1 is considered very poor, 10 outstanding, 6 and above is considered a pass, 5 and below a fail [12].

Study specific questionnaire

In order to gain more details about the long-term effect of surgery a study specific questionnaire was used to gain more in-depth information. The questionnaire contained the five questions. (1) Has your voice remained stable after the last check-up at the outpatient clinic, 1 year postoperatively? (Yes/No) (if no, go to question 2, if yes, go to question 4). (2) After how many months/years after the last checkup, did your voice start to change? How many months / years? (3) Try to describe as precisely as possible what has changed after this period (in general, quality, effort, vocal load). (4) Is your voice stable now? (Yes/No). (5) Is your voice better than before surgery? (Yes/No).

Statistical analysis

All data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 21.0, released 2012. IBM Corp, Armonk, NY, USA). Demographic details were presented as median and range or as proportions using percentages. The effect of time on voice parameter was assessed

with the linear mixed model and was adjusted for diagnosis (atrophy versus atrophy with sulcus) and for duration of follow-up (1-5 years, >5-7.5 years, >7.5 years). The linear mixed model was chosen because it applies a correction for missing data. For all statistical tests, a p value < 0.05 was considered significant.

RESULTS

Patient characteristics

Patients' characteristics are presented in Table 1. Thirty-six patients were retrospectively identified. Ten patients were excluded: five patients could not be reached (e.g. patient died, incorrect address), no consent was obtained for four patients, for one patient consent was obtained, but with no availability of any of the voice data. In total 26 patients were included. There were some cases of missing data (one-year VHI score n=2, one-year and long-term VHI score n=1, long-term VHI score and study specific questionnaire n=2). These patients were therefore excluded in the descriptive statistics of the various modalities. In the analysis of the effect of time on voice the missing data was corrected for by the linear mixed model.

Table 1. Patient characteristics

Characteristics	Total = 26 (100%)
Median age, years [range]	60 [20-77]
Gender, *n* (%)	
Male	7 (26.9)
Female	19 (73.1)
Etiology, *n* (%)	
Atrophy	16 (61.5)
Atrophy with sulcus	10 (38.5)
Years since operation, median [range]	6.7 [2.4-9.0]
Revision surgery, *n* (%)	4 (15.4)

Voice Handicap Index

The mean VHI score was 58.1 preoperatively, 35.7 at 1 year follow-up and 40.0 at more than 1 year follow-up. Improvement from preoperative to 1 year (Δ22.4), and from preoperative to > 1 year (Δ18.1) was clinically relevant (≥ 15 points, as defined for groups) and statistically significant (p < 0.001) for both time frames. The change in VHI from 1 year to > 1 year (Δ4.3) was neither clinically relevant nor statistically significant (p = 0.328). Improvement in VHI was similar in patients with atrophy only and with sulcus (p = 0.908) (Table 2).

Table 2. Voice Handicap Index results overall and atrophy or sulcus

	Preoperative	Postoperative1 year	Postoperative > 1 year
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**
Total (*n*=25)	58.1 (50.1-66.0)	35.7 (27.4-43.9)	40.0 (31.9-48.2)
Atrophy (*n*=16)	57.7 (48.6-66.8)	35.3 (26.1-44.4)	39.7 (30.3-49.0)
Sulcus (*n*=9)	58.4 (47.0-69.8)	36.0 (24.3-47.8)	40.4 (29.0-51.9)

Table 3 shows the VHI change grouped according to the length of follow-up: 1-5 years, >5-7.5 years, and >7.5 years. These results are in line with the results in Table 2, except for the group of 1-5 years. In this group the VHI score at > 1 year was 50, which, although lower than the preoperative score, did not reach the threshold for statistical significance or clinical relevance.
Looking at individual patients, in the two groups with the longest follow-up (> 5 years, *n*=18) there were 10 patients (56%) with a long-term clinical improvement in VHI of ≥ 10 points as defined for individuals. Three patients had a clinical improvement that did not reach the threshold for clinical relevance and 3 patients had a deterioration compared to preoperative values, of which only one was clinically relevant (data not shown).

Table 3. Voice Handicap Index results stratified in length of follow-up

	Preoperative	Postoperative 1 year	Postoperative > 1 year
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**
Follow-up 1-5 y (*n*=7)	63.7 (48.2-79.2)	35.9 (20.3-51.4)	50.0 (34.5-65.5)
Follow-up >5-7.5 y (*n*=9)	53.8 (41.7-65.9)	26.6 (13.8-39.5)	26.0 (13.1-38.8)
Follow-up >7.5 y (*n*=9)	57.7 (43.8-71.5)	45.5 (31.3-59.6)	45.1 (30.9-59.3)

Patient rating of voice aspects

Preoperative ratings of voice aspects were available in 26 patient and long-term ratings for 24 patients. Ratings for the different time points are shown in Table 4. Ratings preoperatively ranged from 4.0 to 5.0, which could be considered unsatisfactory. The 1 year postoperative rating and the best postoperative rating ranged from 6.0 to 7.5. At > 1 year the ratings could be considered satisfactory ranging from 5.5 to 6.0.

Table 4. Voice rating, numeric rating scale 1-10 (1 = poor, 10 = outstanding)

	Rating (0-10)	Median (IQR)
Quality	preoperative (*n*=26)	4.0 (2)
	postoperative 1 year (*n*=23)	7.0 (3)
	postoperative best (*n*=24)	7.0 (2)
	postoperative > 1 year (*n*=24)	6.0 (4)
Effort	preoperative (*n*=26)	4.0 (3)
	postoperative 1 year (*n*=23)	7.0 (3)
	postoperative best (*n*=24)	7.0 (2)
	postoperative > 1 year (*n*=24)	5.5 (5)
Possibilty	preoperative (*n*=26)	4.5 (3)
	postoperative 1 year (*n*=23)	6.0 (3)
	postoperative best (*n*=24)	7.0 (3)
	postoperative > 1 year (*n*=24)	6.0 (5)
Influence	preoperative (*n*=26)	5.0 (4)
	postoperative 1 year (*n*=23)	7.0 (4)
	postoperative best (*n*=24)	7.5 (5)
	postoperative > 1 year (*n*=24)	6.0 (5)

IQR interquartile range

Study specific questionnaire

Two of the 26 patients had not answered the questionnaire and were excluded from further analysis (*n*=24). Fifteen patients rated their present voice as being better than their preoperative voice (62.5%). Regarding the stability of the voice, 10 patients (42%) reported no voice change since last follow-up at 1 year postoperatively. Fourteen (58%) of the patients did report voice deterioration after the 1 year follow-up, consisting mostly of voice fatigue and hoarseness, and occurring at different time points between 1 and 9 years after surgery (median 3 years). Of these 14 patients, 6 rated their voice as stable at present, and 8 rated their voice as instable at present.

DISCUSSION

In this study we evaluated the long-term results (> 1 year) of bilateral medialization thyroplasty in patients with atrophy with and without sulcus. We also compared these long-term data to data collected routinely before the procedure and at 1 year after the procedure.

The average long-term postoperative VHI scores in our cohort showed enduring improvement that was clinically relevant and statistically significant both in patients with and without sulcus.

This is in accord with our earlier studies in which we also found no difference between the results of patients with atrophy and atrophy with sulcus [5,6].

For individual patients with more than 5 years of follow-up (*n*=18), 56% still reported a clinically relevant improvement compared with preoperative state. This shows that on average, stable and long-term VHI improvement after bilateral medialization can be achieved and that this long-term improvement is applicable to about half of the patients. As has been reported earlier, the VHI scores from this study also show that although voices improve they do not normalize and that some voice burden is still to be expected [6].

When stratifying for length of follow-up, this same general effect was seen in the groups with longer follow-up lengths of >5-7.5 years and >7.5 years, but not in the follow-up period of 1-5 years. In this group, after having shown an initial significant improvement at 1 year, the VHI score deteriorated in the long-term follow-up to scores that were in range of the preoperative values. The underlying cause for this observation in the youngest follow-up group remains unclear. Possible explanations could be sought in a change in the case-mix, an unconscious change in operative technique, or just chance in these small number of patients. However, these speculations cannot be proven or disproven by the current data.

An additional challenge when working with Gore-Tex® is the risk of change in implant volume or position due to the compression of the malleable material over time. It has been speculated that this may require some degree of overcorrection [13]. However, this effect would be present in all groups and would not be expected to have affected one group specifically. Nevertheless, we have started a pilot study to capture these possible volume and position changes on serial postoperative MRIs with the aim to better predict the optimal amount of overcorrection during surgery.

The subjective ratings were designed to mirror the grading system in Dutch schools, with 1 being the poorest score, 10 being the best score and a 6 being the lowest “passing score”. Using this approach, the preoperative voice scores (range 4-5) can be considered unsatisfactory whereas the scores at 1 year (range 6-7.5) can be considered satisfactory or in some cases even good. Although the long-term scores showed a decline (range 5.5-6), they can still be considered around the satisfactory threshold and therefore better than the preoperative scores. Although 2 out of 3 patients did report voice some deterioration in the long-term follow-up in the study specific questionnaire, most patients (62.5%) rated their present voice as being better than their preoperative voice.

In summary, the subjective voice parameters used in this study (VHI scores, subjective ratings and the specific questionnaire) show the same trend: significant voice outcome improvement

after surgery that remains stable in the first year and then shows some deterioration in the long-term although voices remain satisfactory on average.

Only a limited number of studies report on subjective, long-term voice outcome (> 1 year) after medialization thyroplasty in patients with atrophy with or without sulcus [4,7,8]. The study by Overton et al., which is the only study with follow-up longer than 1.5 year, included patients with glottic insufficiency of the mobile vocal folds (total *n*=75; atrophy *n*=14, scar *n*=18). The long-term follow-up was divided into 1.5-3 years (total *n*=23, atrophy *n*=4, scar *n*=4), 3-5 years (total *n*=13, atrophy *n*=3, scar *n*=2) and 5-10 years (total *n*=12, atrophy *n*=1, scar *n*=3). Although significant improvements were maintained in the long-term for the study group as a whole, this did not apply to the atrophy and scar subgroups. For atrophy, the initially significant improvements in VRQOL (Voice Related Quality of Life) and GFI (Glottal Function Index) were not maintained after > 1 year follow-up. For scar, no statistically significant improvement was seen at any of the tested time points [7]. In the study by Welham et al., dedicated specifically to patients with sulcus or scar, significant improvement in long-term VHI-30 scores after medialization thyroplasty was noted (*n*=9). Reported in a graph form, the VHI scores can be estimated at around 60 points preoperatively and 30 points at 18 months [4]. Finally, Dominguez et al. showed significant improvement in long-term subjective outcomes (VHI-10 and GFI) after medialization thyroplasty in a mixed cohort of patients (*n*=20, 20% atrophy, 30% paresis, and 50% atrophy and paresis). In this study the VHI-10 decreased from 30.5 to 15.0 at 16.3 months (normal value English version VHI-10 ≤ 11 [14]) [8].

In view of the above we conclude that several studies, including our own study, show that (bilateral) medialization thyroplasty can offer significant, long-term voice improvement in patients with atrophy and sulcus, but that not everyone will benefit [4,8]. This individual variation is supported by the large variations around the mean of outcomes in most studies. Also, because voices do not generally normalize, there is a persisting voice burden and possibly the need for revision surgery, additional treatment, or both. This raises the question: how satisfying are the long-term results of LFS compared to other techniques, taking into regard the surgical procedure, surgical time and patient burden?

As mentioned in our introduction there are grossly three groups of operative techniques to treat vocal fold atrophy with or without sulcus. Firstly, there are the procedures to improve glottic closure: VFI and LFS. In addition to the results of LFS that have already been discussed, long-term results after VFI techniques have also been reported ranging from 1 to 5 years [4,8,15,16,17]. In their study from 2011, using hyaluronic acid (HA), micronized acellular dermal matrix or calcium hydroxylapatite (CaHA), Welham et al. reported no significant changes in VHI score in patients with sulcus and/or scar (*n*=9) at any time point post injection

up to 1.5 years post injection, with scores remaining close to pretreatment values [4]. This could partially have been due to the short life-span of two of the substances used for injection (HA or micronized acellular dermal matrix). Dominguez et al. compared their results after medialization thyroplasty, as discussed previously, to those of VFI with autologous fat in a mixed cohort of patients (*n*=15, 35.7% atrophy, 14.3% paresis, and 50% atrophy and paresis). The results of VFI showed a significant improvement in VHI-10 at 3 months, but then a decrease with a score close to the preoperative level at 19 months (pre-treatment 27.8, post-treatment 23.5) [8]. In a recent study Lahav et al. found long-lasting improvement up to 3 years for VFI with autologous fat in a mixed patient group (50% UVFP (unilateral vocal fold paralysis) and 50% atrophy or scar) [17]. The results show an average decrease in VHI-30 for the whole group from 73.5 preoperatively to 52.8 at 3 months with further decreases in time ending at 44.9 at 3 years. This trend was seen in both the UVFP and the atrophy or scar group. Finally, Cantarella et al. and Zelenik et al. both reported long-lasting improvement after VFI with autologous fat or CaHA, but the relevance of their studies for our purpose are difficult to assess due to very small proportions of patients with atrophy or scar without stratifications of the results [15,16]. In summary, we conclude that extent of long-term benefit of VFI in this patient group is still unclear, with the two largest study in this field showing conflicting results [8,17]. Again, the large outcome variations around the mean also suggest that results will vary individually.

Secondly, there is microlaryngeal phonosurgery for scar and sulcus involving the subepithelial space. The longest follow-up reported for this type of surgery is 1.5 and 3 years from two studies, both using fascia temporalis implantation in patients with vocal fold scar or sulcus [4,18]. In the study by Welham et al., which also reported results for VFI and LFS, only the best postoperative VHI, which was not attained until 18 months after the procedure, showed significant improvement compared to pretreatment values. Reported in a graph form, the VHI scores can be estimated at around 60 points preoperatively and just below 30 at 18 months. Given that the ultimate result at 18 months for graft implantation was equivalent to that of their LFS group, but that the recovery trajectory was slower, authors concluded that their data did not support graft implantation as a primary treatment modality for patients with vocal fold scar or sulcus [4]. Tsunoda et al. used MPT (Mean Phonation Time) and laryngostroboscopic findings to report on voice outcome, with postoperative MPT being significantly improved up to 3 years after graft implantation [18]. Because the study lacks subjective (self-evaluation) voice outcomes, it is however difficult to compare their results with our findings.

Lastly, in recent years, more and larger in-vivo studies in the field of regenerative medicine have been published. The largest series to date, with an average follow-up of 1 year, reported on injection of basic fibroblast growth factor (bFGF) in 100 patients with atrophy, scar or

sulcus [19]. Improvements in VHI-10 were statistically significant in all groups (atrophy 22.7 to 12.2; scar 24.7 to 12.5; sulcus 24.4 to 17.7), but an intergroup comparison showed that improvement in the atrophy group was significantly higher than in the scar and sulcus groups. Nevertheless, both the atrophy and the scar group can be considered to reach near normal values (normal value English version VHI-10 ≤ 11 [14]). As in other studies, the variation in the post-procedure scores was large, ranging from 6.4 to 9 points for the different subgroups.

The longest follow-up reported until now is 2-3 years [20,21]. Although the series are small (19 and 6 patients, respectively), the results are promising. The largest series, 19 patients (9 atrophy, 8 sulcus and 2 UVFP), showed significant improvement up to 36 months in perceptual GRBAS score, MPT, and endoscopic findings (minimal glottal area and minimum distance between focal folds) [20]. Unfortunately, subjective voice outcomes were not included in this study. The study by Sueyoshi et al. did include subjective voice outcome, in addition to acoustic, aerodynamic and endoscopic outcomes. The VHI-10 showed not only significant improvement, but also close to normal VHI-10 scores at 2 years (data estimated from graph), indicating high patient satisfaction [21]. These three studies therefore carefully suggest that with regenerative surgery it might be possible to obtain long-lasting nearly normal voice outcomes.

Our study is subject to a number of limitations. The retrospective study design and a portion of non-responders (10 of 36 patients) may have led to non-respons bias which could mean either over- or underestimation of our results. However, because our data are in line with data from literature, we judge this bias to be small. Although there were also some missing data under the responders, these were limited and corrected. In this study we used different subjective voice parameters, and in line with our study on trial VFI, we noticed only a partial overlap in these subjective voice parameters [22]. Therefor the question remains if the VHI, the main Outcome Measurement Instrument (OMI) used in this study, is valid and precise enough for this specific population of patients and what OMI would be the best alternative. We therefore again stress the need for further research on the most appropriate voice outcome measurement instruments in this group of patients. Developing a predictive model to forecast long-term outcomes can be of supplemental value to the decision-making process of these procedures.

CONCLUSION

Our study shows that long-term improvement in subjective voice outcomes are attainable in a significant proportion of patients undergoing bilateral medialization thyroplasty with

Gore-Tex® for atrophy with or without sulcus, although voices will not normalize and not every patient will benefit.

The results are comparable to other treatment options such as VFI, microlaryngeal phonosurgery and regenerative medicine procedures since residual voice handicap and large variations in outcomes are seen in all of the small number of studies in this area, although the sparse data available so far suggest that the residual voice handicap may be limited after regenerative procedures. The benefit of medialization thyroplasty currently seems to be that results are attained quicker than after microlaryngeal phonosurgery and that there is more of evidence available of a long-lasting effect than for VFI in this patient population. We do however stress the need for larger series with longer follow-up for all these treatment modalities.

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6

Glottic insufficiency caused by vocal fold atrophy with or without sulcus: systematic review of outcome measurements

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ABSTRACT

Purpose: Identifying outcome measurements instruments (OMIs) to evaluate treatment efficacy in patients with vocal fold atrophy and/or sulcus.

Methods: Systematic review of records published before March 2021 by searching Pubmed and EMBASE. Included studies reported on adults (>18 year) with dysphonia caused by glottic insufficiency due to vocal fold atrophy with or without sulcus, who were enrolled into a randomized controlled trial, a non-randomized controlled trial, a case-controlled study or a cohort study. All included studies described an intervention with at least one outcome measurement.

Results: A total of 5456 studies were identified. After removing duplicates, screening title and abstract and full text screening of selected records, 34 publications were included in final analysis. From these 50 separate OMIs were recorded and categorized according to the ELS protocol by DeJonckere [1]. With most OMIs being used in multiple studies the total number of OMIs reported was 265. Nineteen (19) individual OMIs accounted for 80% of reports. The most frequently used OMIs according to category were: VHI-30 and VHI-10 (subjective evaluation); G of GRBAS (perceptual evaluation); F0, Jitter and Shimmer (acoustic evaluation); MPT and MFR (aerodynamic evaluation) and glottic closure and mucosal wave (endoscopic evaluation). Of these OMIs VHI had a high percentage of significance of 90%.

Conclusion: This systematic review identifies the most used OMIs in patients with glottic incompetency due to vocal fold atrophy and/or sulcus as a step toward defining a Core Outcome Set (COS) for this population.

INTRODUCTION

Vocal fold atrophy, with or without sulcus, can lead to both reduced vocal fold closure and reduced vibration during phonation. There is however a great heterogeneity in presentation among patients, varying from mild to severe dysphonia with a similarly large variation in patient's disease burden and findings during laryngostroboscopy. There is also a wide variation in treatment options for the glottic incompetence caused by these entities varying from speech language therapy (SLT) to different forms of laryngeal surgery. Vocal fold injection (VFI) with different injection material or laryngeal frame surgery (LFS) are often performed to improve glottic closure and for patients with sulcus there is also the option of microphonosurgery of the upper vibratory layers of the vocal fold using cold steel, lasers or tissue engineering techniques [2,3]. Finally, there is also variation in outcome measurement instruments (OMIs) used to assess the severity of the condition and/or treatment outcome. These OMIs can be divided into subjective (self-assessment), perceptual, aerodynamic and acoustic measurements in addition to videolaryngostroboscopic findings according to the guidelines on voice quality assessment published and recently updated by the European Laryngological Society [1,4].

Taking all of the above into account, evaluating treatment outcome in this patient group in a consistent way is challenging. To reliably evaluate and compare treatment outcomes it is important to formulate a core outcome set (COS). A COS is a consensus-based agreed minimum set of outcomes that should be evaluated and reported in clinical trials in a specific disease or population. For unilateral vocal fold paralysis (UVFP) such a COS has been formulated by Desuter et al., but up until now this is lacking for patients with non-paralytic glottic insufficiency [5, 6]. The protocol for developing a COS in an evidence-based multi-step process has been described in the COSMIN guidelines (consensus-based standards for the selection of health measurement instruments) [7,8,9]. In the first step, a definition for the construct to be measured is created. In the second step, the existing OMIs for the defined construct are determined through a systematic review of the literature. In the third step, quality assessments of the included studies and the OMIs are performed. Finally, in the fourth step minimal outcome measures to be included in the COS are selected, often in a Delphi type procedure [10].

The definition of the construct of voice (step 1) has already been achieved through the work of the European Laryngological Society guidelines described earlier [1]. The aim of this review is to establish a systematic overview of the frequency and type of OMIs used in literature for patients with non-paralytic glottic insufficiency caused by vocal fold atrophy with or without sulcus as a further step towards formulating a COS for this patient population.

MATERIALS AND METHODS

The design of this study was modeled on earlier studies such as by Desuter et al. in patients with vocal fold paralysis [5]. The construct to be measured in this review was determined to be “treatment effect in patients with dysphonia caused by vocal fold atrophy and/or sulcus”. A systematic review was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [11]. With assistance of a clinical librarian a search was performed in two databases Pubmed and EMBASE.

The search in Pubmed was constructed with following terms:
("Glottis"[MeSH Terms] OR "Glottis"[Title/Abstract] OR "glottic"[Title/Abstract] OR "glottal"[Title/Abstract] OR "vocal fold"[Title/Abstract] OR "vocal folds"[Title/Abstract] OR "vocal cord"[Title/Abstract] OR "vocal cords"[Title/Abstract]) AND ("incompetence"[Title/Abstract] OR "incompetency"[Title/Abstract] OR "insufficience"[Title/Abstract] OR "insufficiency"[Title/Abstract] OR "Atrophy"[MeSH Terms:noexp] OR "Atrophy"[Title/Abstract] OR "atrophic"[Title/Abstract] OR "Cicatrix"[MeSH Terms] OR "scar"[Title/Abstract] OR "scars"[Title/Abstract] OR "scarring"[Title/Abstract] OR "scarred"[Title/Abstract] OR "sulcus"[Title/Abstract] OR "paresis"[Title/Abstract] OR "pareses"[Title/Abstract] OR "hypomobil*"[Title/Abstract] OR "hypo mobil*"[Title/Abstract])
The search in EMBASE was constructed with the following terms:
('glottis'/exp OR 'glottis' OR 'glottis':ti,ab,kw OR 'glottic':ti,ab,kw OR 'glottal':ti,ab,kw OR 'vocal fold':ti,ab,kw OR 'vocal folds':ti,ab,kw OR 'vocal cord':ti,ab,kw OR 'vocal cords':ti,ab,kw) AND ('incompetence':ti,ab,kw OR 'incompetency':ti,ab,kw OR 'insufficience':ti,ab,kw OR 'insufficiency':ti,ab,kw OR 'atrophy'/exp OR 'atrophy' OR 'atrophy':ti,ab,kw OR 'atrophic':ti,ab,kw OR 'scar'/exp OR 'scar':ti,ab,kw OR 'scars':ti,ab,kw OR 'scarring':ti,ab,kw OR 'scarred':ti,ab,kw OR 'sulcus':ti,ab,kw OR 'paresis':ti,ab,kw OR 'pareses':ti,ab,kw OR 'hypomobil*':ti,ab,kw OR 'hypo mobil*':ti,ab,kw)

Records published before March 2021 were identified. Included studies reported on adults (> 18 year) with dysphonia caused by glottic insufficiency due to vocal fold atrophy with or without sulcus, who were enrolled into a randomized controlled trial, a non-randomized controlled trial, a case-controlled study or a cohort study. All included studies described an intervention with at least one outcome measurement. Studies including other etiologies of glottic incompetence, with vocal fold atrophy and/or sulcus included as a subgroup, were not included. Pre-clinical studies, including animal and laboratory studies, were also excluded, as were case reports.

Title and abstract of the identified studies were screened by two independent reviewers (EB and SM). This was followed by full-text evaluation by one reviewer (EB). Baseline

characteristics of the included studies were extracted (publication date, study type, diagnosis, number of patients, gender, mean age, treatment, follow up). Treatment was categorized in three groups: speech language therapy (SLT), surgery and regenerative therapy. The surgery group included microlaryngeal surgery (MLS) with cold steel instruments - labelled as “direct”- and with the use of laser - labelled as “laser”- and medialization technique vocal fold injection (VFI) and laryngeal framework surgery (LFS). All reported OMIs were extracted and listed according to frequency of use. Cumulative percentages were calculated to identify the OMIs accounting for 80% of the total of reported OMIs and outcomes were displayed in a Pareto diagram. Subsequently these OMIs were also subdivided in categories based on the ELS protocol for functional assessment of dysphonia consisting of: subjective parameters, perceptual parameters, acoustic and aerodynamic parameters and videolaryngostroboscopic findings (henceforth endoscopic findings) [1]. In this last category we included the assessment of glottic closure and mucosal wave in accordance with a recent review on vocal fold scar [3]. OMIs on respiratory function were separately collected. OMIs that did not fit this category, nor the categories of the ELS protocol were reported as “additional” parameters. Finally, the percentage of significance for the most frequently used OMIs, defined as the number of studies with a significant post-treatment improvement divided by the total number of studies using this OMI, was calculated [5].

RESULTS

A total of 173 articles were full text assessed. Fifty-eight (58) studies were excluded for the following reasons: population not clearly described (*n*=11), no atrophy and/or sulcus included (*n*=12), no therapy (*n*=2), no relevant outcome (*n*=2, complication, duration), no pre- and posttreatment outcome (*n*=9), language other than English (*n*=10, 1 Slovenic, 1 Polish, 1 Serbian, 2 Japanese, 2 Chinese, 3 Portuguese), abstract only (*n*=10), duplicate (*n*=2). Another 81 studies were excluded, because they included a mixed study populations of glottic insufficiencies including atrophy and/or sulcus but also scar, paresis, hypomobility, paralysis or other causes. Thirty-four (34) studies, only including atrophy and/or sulcus, were included in final qualitative synthesis (Figure 1).

Figure 1. Flow chart of study inclusion process

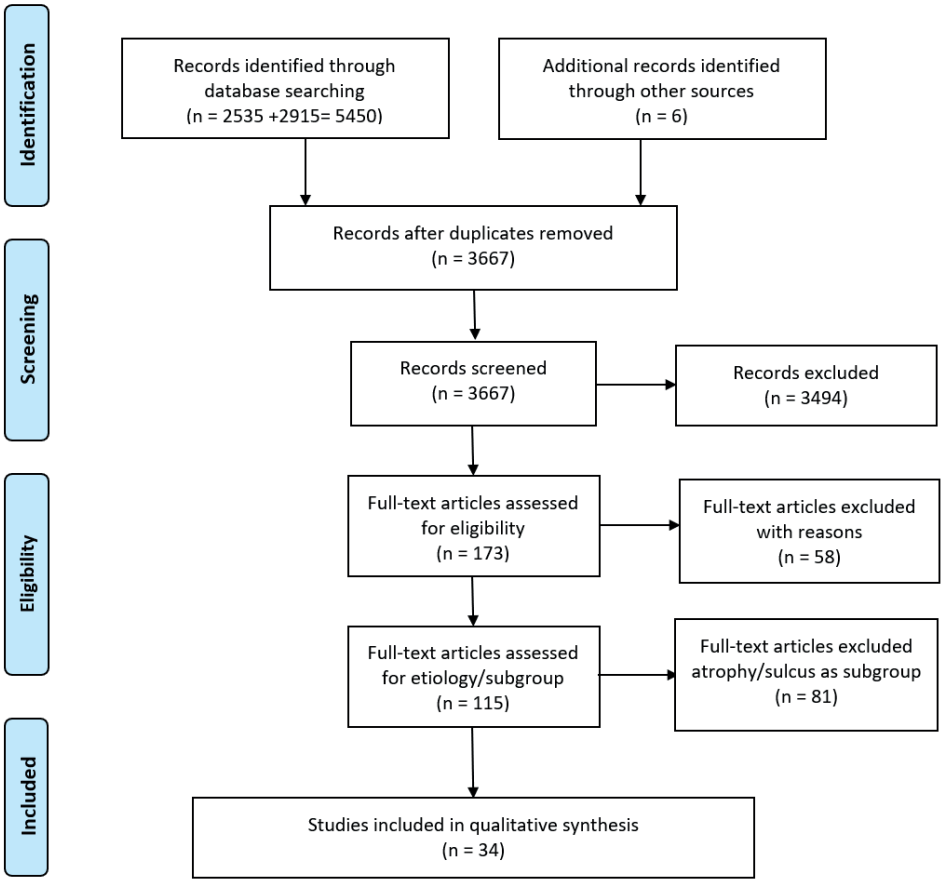


Table 1 shows the baseline characteristics and OMIs of the included studies [2, 12–44]. Two studies were randomized clinical trials [13,16]; of which one was a double blind randomized controlled trial (RCT)[16]. All other reports were cohort studies of which 7 were prospective, 25 were retrospective; 11 studies included atrophy patients, 14 included sulcus, and 9 studies atrophy and sulcus. Two studies included a control group; one study with sulcus in a prospective cohort and one study with atrophy and sulcus in a RCT, mentioned above [16,33].
In 3 studies treatment consisted of SLT, in 3 studies SLT or surgery, in 24 surgical treatments and in 4 regenerative therapy. The studies with surgical treatment were divided into "direct" microlaryngeal surgery (MLS), including microphonosurgical cold steel procedures invading subepithelial space with or without grafting (*n*=6), MLS with laser surgery, including KTP, PDL and CO2 laser (*n*=2), different types of medialization both VFI with different fillers (hyaluronic acid (HA), calcium hydroxylapatite (CaHA), carboxymethylcellulose (CMC)) and LFS (*n*=10) or a combination of above described technics (*n*=6). Follow-up varied from 1 to 36 months (median of 8 months). In Table 2 an overview is presented of the included studies and their OMIs.

A total of 50 different OMIs were reported in the 34 selected studies. With most OMIs being used in multiple studies the total number of OMIs reported was 265. The frequencies of the different OMIs are shown in Table 3 and additionally as a Pareto diagram in Figure 2. Nineteen (19) OMIs accounted for 80% of reports. Table 4 shows an overview of these top 19 OMIs identified from the Pareto diagram divided into the ELS subcategories, together with the percentage of studies that find a significant impact after treatment. Five of these OMIs show a significant change after treatment in more than half of the studies that reported on them.

Table 1. Overview included studies and their baseline characteristics

Reference		Study type	Diagnosis	Patients (*n*)	atrophy/ sulcus/(con)	Gender (m:f)	Age (SD)	Treatment category	Treatment	Follow up
Bick[12]	2021	Cohort (retrospective)	atrophy	197	197/0	111:86	70.9±10.15	SLT / surgery	SLT / SLT+surgery / surgery / no treatment	-
Desjardins[13]	2020	Clinical trial	atrophy	12	12/0	7:5	71.83±7.76	SLT	VFE / VFE+IMST / VFE+EMST	1 m
Andreadis[14]	2020	Cohort (retrospective)	sulcus	13	0/13	5:8	28.9	surgery (direct)	MLS excision	6,3 m (mean)
Okui[15]	2020	Cohort (retrospective)	atrophy	53	53/0	41:12	69.0±9.5	regenerative	VFI bFGF	6 m
Ma[16]	2020	Clinical trial	atrophy, sulcus,	21	7/8/(6)	15:6	64	regenerative	VFI ACF	12 m
Van den Broek[17]	2020	Cohort (retrospective)	atrophy, sulcus	29	14/15	12:17	50.5±17.9	surgery	LFS bilateral medialization	12 m
Hu[18]	2019	Cohort (retrospective)	atrophy, sulcus	23	19/4	7:16	39.2	surgery	VFI autologous fat	6 m
Allensworth[19]	2019	Cohort (retrospective)	atrophy	21	21/0	17:4	76	surgery	VFI CaHA / LFS bilateral medialization	1.6 m (mean)
González-Herranz[20]	2019	Cohort (retrospective)	sulcus	10	0/10	-	-	surgery (direct)	MLS autologous fascia graft	6 m
Park[21]	2019	Cohort (retrospective)	sulcus	79	0/79	55:24	41	surgery (laser)	MLS laser (PDL/KTP)	6 m
Van den Broek[22]	2019	Cohort (retrospective)	atrophy, sulcus	24	15/9	0:24	39.5±18.2	surgery	VFI autologous fat	12 m
Van den Broek[2]	2019	Cohort (retrospective)	atrophy, sulcus	68	30/38	18:50	40±18.5	surgery	VFI HA	1 m
Miaśkiewicz[23]	2018	Cohort (retrospective)	sulcus	36	0/36	13:23	44.17±11.95	surgery (combination)	MLS excison + VFI HA/CaHA	12 m
Kanazawa[24]	2018	Cohort (prospective)	sulcus	12	0/12	6:6	51.6	regenerative	VFI bFGF	3 m
Kaneko[25]	2015	Cohort (retrospective)	atrophy	22	22/0	13:3	72.9±	SLT	VFE	2 m
Miaśkiewicz[26]	2015	Cohort (retrospective)	sulcus	24	0/24	11:13	38.7±	surgery (direct)	MLS excision, subepithelial HZ(*)	8 m
Young[27]	2015	Cohort (retrospective)	atrophy	19	19/0	10:9	72±11	surgery	VFI CMC; subsequent VFI autologous fat / VFI CaHA / LFS bilateral medialization	3 m
Hwang[28]	2013	Cohort (retrospective)	sulcus	25	25/0	17:8	37.6	surgery (laser)	MLS PDL	12 m

Table 1. *(Continued)*

Reference		Study type	Diagnosis	Patients (*n*)	atrophy/ sulcus/(con)	Gender (m:f)	Age (SD)	Treatment category	Treatment	Follow up
Yilmaz[29]	2012	Cohort (prospective)	sulcus	44	0/44	18:26	37	surgery (combination)	MLS excision, suture + VFI / LFS bilateral medialization	12 m
Hirano[30]	2012	Cohort (prospective)	atrophy	10	10/0	6:4	70.1±5.3	regenerative	VFI bFGF	12 m
Gartner-Schmidt[31]	2011	Cohort (retrospective)	atrophy	275	275/0	133:142	71.8±9.6	SLT / surgery	SLT / SLT+surgery / surgery / no treatment	-
Mau[32]	2010	Cohort (retrospective)	atrophy	67	67/0	33:34	71	SLT / surgery	SLT / SLT+surgery / surgery	-
Zhang[33]	2010	Cohort (prospective)	sulcus,	24	0/12/(12)	7:5	-	surgery (combination)	MLS gelatine sponge + VFI autologous fat	3 m
Pinto[34]	2007	Cohort (prospective)	sulcus	34	0/34	15:19	34.8	surgery (direct)	MLS autologous graft (fat or fascia)	12 m
Hsiung[35]	2006	Cohort (retrospective)	atrophy, sulcus	101	31/70	45:56	51.2	surgery (combination)	MLS autologous fat graft +VFI autologous fat	17 m (mean)
Tsunoda[36]	2005	Cohort (prospective)	sulcus	10	0/10	8:2	46.5	surgery (direct)	MLS autologous fascia graft	36 m
Hsiung[37]	2004	Cohort (retrospective)	sulcus	22	0/22	10:12	33.1	surgery (combination)	MLS autologous fascia graft +VFI autologous fat	16.6 m (mean)
Su[38]	2004	Cohort (retrospective)	atrophy, sulcus	27	17/10	16:11	41.5	surgery	LFS strap muscle transposition	4 m
Hsiung[39]	2003	Cohort (retrospective)	atrophy	21	21/0	9:12	46	surgery	VFI autologous fat	9.5 m (mean)
Chen[40]	2003	Cohort (retrospective)	atrophy, sulcus	24	16/8	-	-	surgery	VFI autologous fat	19.5 m (mean)
Hsiung[41]	2003	Cohort (retrospective)	atrophy, sulcus	16	14/2	7:9	51.3	surgery	VFI autologous fat	10 m (mean)
Ramig[42]	2001	Cohort (prospective)	atrophy	3	3/0	2:1	-	SLT	LSVT	-
Remarcle[43]	2000	Cohort (retrospective)	sulcus	45	0/45	7:38	36	surgery (laser, combination)	MLS CO2, collagen graft	5 m
Pontes[44]	1993	Cohort (retrospective)	sulcus	10	0/10	7:3	-	surgery (direct)	MLS slicing mucosa	-

SLT speech language therapy, *VFE* vocal function exercise, *IMST* inspiratory muscle strength training, *EMST* expiratory muscle strenght training, *MLS* microlarygeal surgery, *VFI* vocal fold injection, *bFGF* basic fibroblast growth factor, *ACF* autologous cultured fibroblast, *LFS* laryngeal framework surgery, *CaHA* calciumhydroxylapatite, *PDL* pulsed dye laser, *KTP* potassium titanyl phosphate, *HA* hyaluronic acid, *CMC* carboxymethylcellulose, *LSVT* Lee Silverman voice therapy
(*) 2 patients adjuvant VFI HA

Table 2. Overview included studies and their OMIs

Reference		OMI subjective	OMI perceptual	OMI acoustic	OMI aerodynamic	OMI endoscopic	OMI respiratory	OMI additional
Bick[12]	2021	VRQOL**, GFI**	GRBAS**	F0**, SPI	MPT**			
Desjardins[13]	2020	VHI-10, GFI, CPIB	CAPE-V (overall severity)	CPPS, NHR, APQ	MFR, Psub, AR, SPL	GC*, MW	MIP, MEP, FVC, FEV1, FEV1/FVC	
Andreadis[14]	2020	-	-			MW*		
Okui[15]	2020	VHI-30*	-	F0*, Jitt*, Shim*, HNR†, MR*	MPT*, MFR†			
Ma[16]	2020	VHI-30†, subjective rating (own questionnaire)† VAS**	G*			MW*		
Van den Broek[17]	2020	VHI-30*	G†	F0**, MR†	MPT†, DR†			
Hu[18]	2019	VHI-10*	G*B*R*A*S†	Jitt*, Shim†, NHR*	MPT†			
Allensworth[19]	2019	VHI-30*	CAPE-V*, G*		MPT*	GC*, MW*		
González-Herranz[20]	2019	VHI-10*	G*R*B† A†S*	Jitt†, Shim†, HNR†, MR	MPT*, s/z ratio*	GC, MW		
Park[21]	2019	VHI-10*	GRBAS*	F0†, Jitt*, Shim*, NHR*	MPT*, MFR†	GC, MW		
Van den Broek[22]	2019	VHI-30*	G†	F0†, MR†	MPT†, DR*			
Van den Broek[2]	2019	VHI-30*	-	F0†, MR*	MPT†, DR†			
Miaśkiewicz[23]	2018	VHI-30*	G*R*B*A*S*	F0†, Jitt†, RAP†, PPQ†, sPPQ†, vF0†, Shim*, APQ*, sAPQ†, vAm†, NHR†, SPI†		GC*, MW*		
Kanazawa[24]	2018	VHI-30*	-	F0*, Jitt†, Shim†, NHR*, MR*	MPT*, MFR†, SPL†			
Kaneko[25]	2015	VHI-10	GRBAS*	Jitt*, Shim†	MPT*, DR†, MFR†	GC*, MW*		
Miaśkiewicz[26]	2015	-	GR*B*AS*	F0, Jitt†, Jita*, PPQ, vF0, Shim†, ShdB†, APQ†, vAm†, NHR†, SPI†		GC†, MW†		
Young[27]	2015	VHI-10**	-	CPP, CSID	MFR, Psub, SPL,			

Table 2. *(Continued)*

Reference		OMI subjective	OMI perceptual	OMI acoustic	OMI aerodynamic	OMI endoscopic	OMI respiratory	OMI additional
Hwang[28]	2013	VHI-30*	G*R*B*AS	F0*, Jitt*, Shim†, NHR†	MPT†, MFR*, Psub*	GC, MW*		QxM†, CFx*, CAx† (EEG)
Yilmaz[29]	2012	VHI-30*	G*R*B*A†S†	F0†, Jita*, RAP*, PPQ*, sPPQ*, vF0*, Shim*, APQ*, sAPQ*, vAm*, NHR*, MR*, SPI†, VTI*	MPT*, MFR*, resistance†, power†, efficiency*, pressure*	GC*, MW*		
Hirano[30]	2012	-	-	Jitt*, PPQ*, Shim*, APQ*, NHR*	MPT*, MFR**			
Gartner-Schmidt[31]	2011	VHI-10	-					
Mau[32]	2010	-	-					FCMs in NOMS*
Zhang[33]	2010	-	-	F0*, Jitt*, Shim*,NNE*	MPT*	GC, MW		
Pinto[34]	2007	subjective rating (5-point scale)*	subjective rating (5-point scale)*	F0†, Jitt†, Shim†		GC, MW		
Hsiung[35]	2006	subjective rating (3-point scale)**	subjective rating (3-point scale)	F0, Jitt, Shim, NHR	MPT			
Tsunoda[36]	2005	-	-		MPT*	GC, MW		
Hsiung[37]	2004	subjective rating (3-point scale)	G*R*B*	F0†, Jitt†, Shim†, HNR†	PT*	GC, MW*		
Su[38]	2004	-	G*R*B*A†S*, subjective rating (improvement yes/no)	F0†, Jitt*, Shim†, NHR†	MPT*, MFR*	GC, MW		
Hsiung[39]	2003	subjective rating (3-point scale)	G*R*B*	Jitt†, Shim†, HNR†	PT†	GC, MW*		
Chen[40]	2003	subjective rating (3-point scale)	G*R*B*	F0†, Jitt†, Shim†, HNR†	PT†	GC, MW*		
Hsiung[41]	2003	subjective rating (2-point scale)	GRB	Jitt, Shim, HNR	PT			MRI**

Table 2. *(Continued)*

Reference		OMI subjective	OMI perceptual	OMI acoustic	OMI aerodynamic	OMI endoscopic	OMI respiratory	OMI additional
Ramig[42]	2001	-	CAPE-V (overall severity, loudness)	F0, MR	Psub, SPL	GC, MW		laryngeal EMG
Remarcle[43]	2000	subjective rating	-	F0†, own spectral analysis *	MPT*, DR†, PQ*	MW	VC	
Pontes[44]	1993	subjective rating (vocal fatique)	subjective rating (breathiness, harshness)	F0, own spectral analysis		GC, MW		

VRQOL voice related quality of life, *GFI* glottal function index, *VHI* voice handicap index, *CPIB* communicative participation item bank, *VAS* visual analog scale, *GRBAS* grade roughness breathiness asthenic strain, *CAPE-V* consensus auditory-perceptual evaluation of voice, *F0* fundamental frequency, *Jitt* jitter, *Jita* absolute jitter, *RAP* relative average perturbation, *PPQ* pitch perturbation quotient, *sPPQ* smoothed pitch perturbation quotient, *Shim* shimmer, *ShdB* absolute shimmer, *APQ* amplitude pertubation quotient, *sAPQ* smoothed amplitude pertubation quotient, *vAm* peak-to-peak amplitude, *NHR* noise to harmonic ratio, *HNR* harmonic to noise ratio, *SPI* soft phonation index, *VTI* voice turbulence index, *NNE* normalized noise energy, *MR* melodic range, *CPPS* smoothed cepstral peak prominence, *CPP* cepstral peak prominence, *CSID* cepstral spectral index of dysphonia, *MPT* maximum phonation time, *PT* phonation time, *PQ* phonation quotient, *DR* dynamic range, *MFR* mean flow rate, *Psub* subglottal pressure, *AR* aerodynamic resistance, *SPL* sound pressure level, *MV* mucosal wave, *GC* glottic closure, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure, *FVC* forced vital capacity, *FEV1* forced expiratory volume, *QxM* mean closed quotient, *CFx* irregularity of frequency, *CAx* irregularity of amplitude, *FCMs* functional communication measures, *NOMS* national outcomes measurement system, *MRI* magnetic resonance imaging, *EMG* electromyography

*significant difference, **significant difference in subgroup, †not significant

Table 3. Frequency of OMIs, overall percentage (%), cumulative percentage (%)

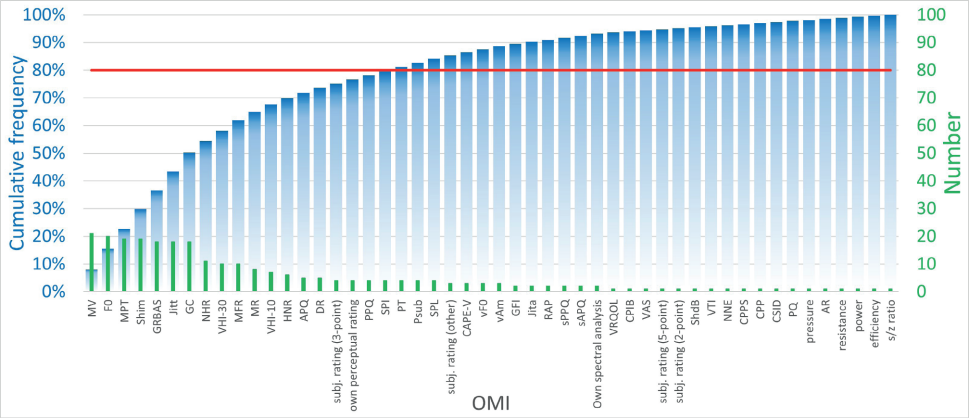
OMI	Frequency	Percentage (%)	Cumulative percentage (%)
MV	21	7,9%	7,9%
F0	20	7,5%	15,5%
MPT	19	7,2%	22,6%
Shim	19	7,2%	29,8%
GRBAS	18	6,8%	36,6%
Jitt	18	6,8%	43,4%
GC	18	6,8%	50,2%
NHR	11	4,2%	54,3%
VHI-30	10	3,8%	58,1%
MFR	10	3,8%	61,9%
MR	8	3,0%	64,9%
VHI-10	7	2,6%	67,5%
HNR	6	2,3%	69,8%
APQ	5	1,9%	71,7%
DR	5	1,9%	73,6%
subj. rating (3-point)	4	1,5%	75,1%
own perceptual rating	4	1,5%	76,6%
PPQ	4	1,5%	78,1%
SPI	4	1,5%	79,6%
PT	4	1,5%	81,1%
Psub	4	1,5%	82,6%
SPL	4	1,5%	84,2%
subj. rating (other)	3	1,1%	85,3%
CAPE-V	3	1,1%	86,4%
vF0	3	1,1%	87,5%
vAm	3	1,1%	88,7%
GFI	2	0,8%	89,4%
Jita	2	0,8%	90,2%
RAP	2	0,8%	90,9%
sPPQ	2	0,8%	91,7%
sAPQ	2	0,8%	92,5%
own spectral analysis	2	0,8%	93,2%
VRQOL	1	0,4%	93,6%
CPIB	1	0,4%	94,0%
VAS	1	0,4%	94,3%

Table 3. *(Continued)*

OMI	Frequency	Percentage (%)	Cumulative percentage (%)
subj. rating (5-point)	1	0,4%	94,7%
subj. rating (2-point)	1	0,4%	95,1%
ShdB	1	0,4%	95,5%
VTI	1	0,4%	95,8%
NNE	1	0,4%	96,2%
CPPS	1	0,4%	96,6%
CPP	1	0,4%	97,0%
CSID	1	0,4%	97,4%
PQ	1	0,4%	97,7%
pressure	1	0,4%	98,1%
AR	1	0,4%	98,5%
resistance	1	0,4%	98,9%
power	1	0,4%	99,2%
efficiency	1	0,4%	99,6%
s/z ratio	1	0,4%	100,0%
	265	100	

MV mucosal wave, *F0* fundamental frequency, *MPT* maximum phonation time, *Shim* shimmer, *GRBAS* grade roughness breathiness asthenic strain, *Jitt* jitter, *GC* glottic closure, *NHR* noise to harmonic ratio, *VHI* voice handicap index, *MFR* mean flow rate, *MR* melodic range, *HNR* harmonic to noise ratio, *APQ* amplitude perturbation quotient, *DR* dynamic range, *PPQ* pitch perturbation quotient, *SPI* soft phonation index, *PT* phonation time, *Psub* subglottal pressure, *SPL* sound pressure level, *CAPE-V* consensus auditory-perceptual evaluation of voice, *vF0* fundamental frequency coefficient variation, *vAm* peak-to-peak amplitude, *GFI* glottal function index, *Jita* absolute jitter, *RAP* relative average perturbation, *sPPQ* smoothed pitch perturbation quotient, *sAPQ* smoothed amplitude perturbation quotient, *VRQOL* voice related quality of life, *CPIB* communicative participation item bank, *VAS* visual analog scale, *ShdB* absolute shimmer, *VTI* voice turbulence index, *NNE* normalized noise energy, *CPPS* smoothed cepstral peak prominence, *CPP* cepstral peak prominence, *CSID* cepstral spectral index of dysphonia, *PQ* phonation quotient, *AR* aerodynamic resistance

Figure 2. Pareto diagram of OMIs



MV mucosal wave, *F0* fundamental frequency, *MPT* maximum phonation time, *Shim* shimmer, *GRBAS* grade roughness breathiness asthenic strain, *Jitt* jitter, *GC* glottic closure, *NHR* noise to harmonic ratio, *VHI* voice handicap index, *MFR* mean flow rate, *MR* melodic range, *HNR* harmonic to noise ratio, *APQ* amplitude perturbation quotient, *DR* dynamic range, *PPQ* pitch perturbation quotient, *SPI* soft phonation index, *PT* phonation time, *Psub* subglottal pressure, *SPL* sound pressure level, *CAPE-V* consensus auditory-perceptual evaluation of voice, *vF0* fundamental frequency coefficient variation, *vAm* peak-to-peak amplitude, *GFI* glottal function index, *Jita* absolute jitter, *RAP* relative average perturbation, *sPPQ* smoothed pitch perturbation quotient, *sAPQ* smoothed amplitude perturbation quotient, *VRQOL* voice related quality of life, *CPIB* communicative participation item bank, *VAS* visual analog scale, *ShdB* absolute shimmer, *VTI* voice turbulence index, *NNE* normalized noise energy, *CPPS* smoothed cepstral peak prominence, *CPP* cepstral peak prominence, *CSID* cepstral spectral index of dysphonia, *PQ* phonation quotient, *AR* aerodynamic resistance

Table 4. Percentage of studies per OMI showing significant results between pre- and post-treatment

	OMI	*p* value ≤ 0.05	Percentage of significance (%)
Subjective	VHI-30	9/10 (1 NS, - NA)	90.0*
	VHI-10	4/7 (- NS, 3 NA)	57.1*
	subjective rating (3-point)	1/4 (- NS, 3 NA)	25.0
Perceptual	GRBAS	13/18 (2 NS, 3 NA)	72.2*
	own perceptual rating	1/4 (-NS, 3 NA)	25.0
Acoustic	F0	6/20 (10 NS, 4 NA)	30.0
	Shimmer	6/19 (11NS, 2 NA)	31.6
	Jitter	8/18 (8 NS, 2 NA)	44.4
	NHR	5/11 (4 NS, 2 NA)	45.5
	HNR	0/6 (5 NS, 1 NA)	0.0
	MR	4/8 (2 NS, 2NA)	50.0
	APQ	3/5 (1 NS, 1NA)	60.0*
	PPQ	2/4 (1 NS, 1NA)	50.0
	SPI	0/4 (3 NS, 1 NA)	0.0
Aerodynamic	MPT	13/19 (5 NS, 1 NA)	68.4*
	MFR	4/10 (4 NS, 2 NA)	40.0
	DR	1/5 (4 NS, - NA)	20.0
Endoscopic	MV	10/21 (1 NS, 10 NA)	47.1
	GC	5/18 (1 NS, 12 NA)	27.8

VHI voice handicap index, *GRBAS* grade roughness breathiness asthenic strain, *F0* fundamental frequency, *NHR* noise to harmonic ratio, *HNR* harmonic to noise ratio, *MR* melodic range, *APQ* amplitude perturbation quotient, *PPQ* pitch perturbation quotient, *SPI* soft phonation index, *MPT* maximum phonation time, *MFR* mean flow rate, *DR* dynamic range, *MV* mucosal wave, *GC* glottic closure

NS not significant, *NA* not available

* > 50% "percentage of significance

DISCUSSION

In this review we identified the OMIs most used to evaluate treatment effect in patients with non-paralytic glottic insufficiency caused by vocal fold atrophy with and without sulcus. A total of 50 different OMIs were identified with 19 of these accounting for 80% of total reported OMIs. Of these 19 OMIs, five showed a significant change after treatment in more than half of the studies where they were used.

Interestingly, of the top ten most used parameters most were acoustic, aerodynamic or stroboscopic. Only one patients' self-evaluation parameter was included in the top ten which

was the VHI-30 ranked as 9th most used while self-evaluation is one of the most clinically relevant tools for measuring treatment outcome in daily practice. Additionally, several studies have proposed that it is the one most reliable tool for evaluating treatment response in this patient population [2,45,46]. This review shows it has a much higher percentage of significance than the acoustic or endoscopic parameters.

It is well known that assessing voice outcome after treatment is complex and that multidimensional evaluation is necessary. With the large body of OMIs available, choosing representative and reliable parameters is challenging and much evidence points to the fact that disease specific core outcome sets of OMIs are needed [10]. Before formulating such a COS a basic overview of parameters used in literature is required. It is important to emphasize that the parameters found to be the most frequently used for patients with non-paralytic glottic insufficiency caused by vocal fold atrophy with or without sulcus in this review may not necessarily be the most appropriate for this cohort. To properly assess the usefulness of an OMI, not only frequency of use, but also clinical relevance, applicability and psychometric validity are important factors to consider [10].

However, as a starting point, it is valuable to have insight into the choices that are currently being made by clinicians. The findings of this review can guide further initiatives on the route to a COS by indicating which parameters should be prioritized going forwards. The top OMIs revealed by this review as well as the factors for determining the ultimate relevance of an OMI are discussed below.

Subjective OMIs

The VHI-30 was the most frequently used subjective OMI (n=10, 9th rank) and had a very high percentage of significance at 90%. The VHI-10 was the second most used (n=7, 12th rank) with a lower percentage of significance of 57%. Around 75% of the studies in this review (26 out of 34) used a form of subjective rating. Subjective evaluation is one of the most clinically relevant tools in the communication with patients. The VHI is a robust questionnaire with translations and validations in many languages and it has the most sufficient psychometric construct based on COSMIN taxonomy [47,48]. One may argue that VHI is designed for dysphonic patients in general and not specifically for patients with glottic insufficiency and that a questionnaire especially designed for glottic insufficiency may be preferred above VHI. More focused questionnaires for a future COS could be the glottal function index (GFI) [49], vocal fatigue index (VFI)[50] or vocal fatigue handicap questionnaire (VFHQ)[51] with the GFI having the advantage above the other disease specific questionnaires being the only OMI with moderate positive rating on psychometric ratings [48].

However, it is also important to consider that instead of incorporating ever more detailed disease specific PROMs (Patient-reported Outcome Measurement), there is also a countercurrent in literature supporting the development and use of generic PROMs focusing on general health aspects such as physical, mental and social health including quality of sleep or ability to work. An initiative to develop and measure generic PROMs is PROMIS (Patient-reported Outcomes Measurement Information System) which is an innovative, intelligent system for measuring generic PROMs to be used for different health problems and diseases. A generic, non-disease specific health survey may be also of interest as a quality of life measurement instrument which can be used for cost-utility analysis by measuring quality-adjusted life years (QALYs) such as the EQ-5d (EuroQol 5D)[52].

Perceptual OMIs

The GRBAS was the most frequently used perceptual OMI (n=18, 5th rank), with a percentage of significance of 72%. GRBAS is a widely used perception scale. The G, general grade, has a satisfactory inter- and intra-rater reliability and is therefore suitable as a single OMI. In the latest ELS proposal the use of complete GRBAS scale is preferred [4]. A main disadvantage of using perceptual OMIs in patients with non-paralytic glottic insufficiency is that structural defects, such as sulcus, are not always addressed in treatments, such as medialization procedures, where the primary goal of treatment is to improve endurance and not perceptual quality of the voice [17,22].

Acoustic OMIs

Interestingly, our review showed that studies relied heavily on acoustic OMIs such as fundamental frequency (F0) (n=20, 2nd rank), shimmer (n=19, 4th rank), jitter (n=18, 6th rank) and noise to harmonic ratio (NHR) (n=11, 8th rank), even though none of these acoustic parameters achieved a percentage of significance above 50%. Their high frequency of use is likely due to them being automatically provided by most voice programs, but their clinical usefulness may be less defined. They are less intuitive in communications with patients, in our and other's experience, and have been shown not to correspond to more clinically relevant parameters [2,17,22,45].

Nevertheless, acoustic OMIs could potentially aid in detecting differences in the regularity of phonation that may be missed with more broad spanning parameters such as perceptual evaluation. The challenge would be to find the appropriate ones for this specific patient population from the large number of parameters available. Despite its low ranking and lack of significance in our review, one example could be the soft phonation index (SPI) (n=4, 19th rank, 0% percentage of significance) which reflects the approximation of vocal folds [52]. It's possible usefulness has been shown in unilateral nodules, but, to our knowledge, has not been clarified in atrophy and/or sulcus [54]. Inconsistency in normal values and increased

SPI for pressed phonation have been seen [53,54]. This may hamper the interpretation of SPI in atrophy and sulcus.

Aerodynamic OMIs

Of the top 19 OMIs used, three were aerodynamic; maximum phonation time (MPT) (n=19, 3th rank), mean flow rate (MFR) (n=10, 10th rank), and dynamic range (DR) (n=5, 15th rank). MPT is a well-known voice parameter; it is simple, reliably obtainable, but with the disadvantage that normative data will differ in sub-populations depending on gender or age [55,56]. MPT has been found to be the most used and most significant OMI for UFVP (90% percentage of significance) [5]. Our results indicated a less prominent role in our patient group (68% percentage of significance), possibly due to the difference in underlying pathology, including the degree of glottal gap that needs correction. Aerodynamic OMIs that require a pneumotachograph are less easy to obtain, f.e. MFR or phonation quotient ((PQ)(vital capacity/MPT)) as alternative. MFR may be of value for glottic insufficiency with mobile vocal folds, as it is for immobile vocal fold in UVFP, stated by Desuter et al., with relatively high ranking and percentage of significance (86% percentage of significance) [5].

Another measurement of interest is the phonation threshold pressure (Pth). It reflects the minimum subglottic pressure needed to reach phonation onset and sustain phonation [57]. It may be more appropriate to capture the subtle changes in subglottic pressure when comparing pre- and posttreatment effect. It has found only limited use up till now, although a preliminary study in 2021 showed that measuring Pth in UVFP is feasible [58]. Attributing factors for this may be variations in procedural methodology for task elicitation as well as environmental and participant inconsistencies that might affect phonation threshold pressure values [59].

Endoscopic OMIs

Mucosal wave was the most used OMI (n=21, 1th rank) followed by glottic closure (n=18, 7th rank), although both had a relative low percentage of significance (47% and 28% respectively). It is therefore debatable if endoscopic parameters are the most suitable OMIs for this patient population due to the inherent inter-observer bias associated with this form of assessment and the combined pathology of atrophy and sulcus leading to further difficulties in assessing exams [4,60].

However, as endoscopy is broadly used in this patient group, more systematic and detailed videolaryngostroboscopic assessment protocols should be investigated, f.e. as described in VALI (Voice-Vibratory Assessment with Laryngeal Imaging)[61]. Frame-by-frame analysis (FBFA) could also be useful [62]. Another possibility would be to use disease specific laryngoscopic assessments. For vocal fold atrophy, the reliability of laryngoscopic features

have been investigated with satisfying results and recently a validated classification of presbylarynx based on laryngoscopic findings has been published [63,64].

As stated in the introduction, to properly assess the usefulness of an OMI, before it can be included in a COS, quality assessment has to be performed. In doing so, not only frequency of use, but also clinical relevance, applicability and psychometric validity are important factors to consider [10].

To address the issue of the relevance we calculated the "percentage of significance" for the most frequently used OMIs, defined by Desuter et al. as the percentage of number of studies with a significant change in a specific OMI, divided by total number of studies using this OMI [5]. We found the VHI-30 to be the only OMI with a percentage of significance higher than 80% and the VHI-10, GRBAS, MPT and the APQ to be the only parameters of 50% or more. Interestingly, Desuter et al. found percentages of significance higher than 80% for MPT (90%), mean airflow (86%) and the G of the GRBAS (85%) in his review on unilateral vocal fold paralysis. We hypothesize that this difference may reflect the pathophysiological difference between glottic insufficiency with mobile vocal folds and UVFP, supporting the notion that the relevance of OMIs may differ from disease to disease.

Studies tend to report mainly on the statistical significance of a change in an OMI, which does not necessarily correspond to a difference that is clinically relevant. But for patients and health professionals clinically relevant changes in outcome are of great importance. Until now, the clinical relevance of a certain outcome has often been consensus based [31]. However, values for clinically relevant changes have been suggested for some of these OMIs. Van Gogh et al. defined what constitutes a clinically relevant change for the VHI-30 based on a selected Dutch population with dysphonia after treatment for early glottic cancer or benign voice disorders and a normal population [65]. More recently Young et al. formulated the MCID (minimal clinically important difference) for VHI-10 in patients with vocal fold paralysis. The authors highlight that not only the numerical change within a parameter that represents a minimal clinically relevant change is important, but also that this value may be disease specific [66]. Therefore, some OMIs may not be as valuable for a specific disease as traditionally assumed.

Applicability, whether a test can be performed or not, depends on logistic, technical and financial possibilities and limitations. For acoustic, aerodynamic, but also endoscopic OMIs this can be a limiting factor. For acoustic measurements special voice program software is needed to record and store a phonetogram, and to extract, calculate and store various voice parameters. These programs are commercially available, f.e. MDVP (multidimensional voice program software, computerized speech laboratory (KayPENTAX, Montvale, NJ)) and have

their own set of parameters. For aerodynamic parameters as MFR a pneumotachograph is needed (phonatory aerodynamic system (PAS), KayPENTAX, Montvale, NJ).

The last important factor is psychometric validity. Psychometric validity has been only investigated for subjective OMIs [48,67]. In the study of Francis et al. 32 PROMs were reviewed on development and validation and showed gross psychometric weaknesses as lack of patient involvement, lack of robust construct validity and lack of interpretability and scaling [67]. Speyer et al. reported on psychometric properties of 15 PROMs and concluded that many psychometric data were missing or indeterminate, with VHI seeming to be the most promising questionnaire [48].

This study has some several weaknesses. First of all, no formal Risk of Bias (RoB) was performed. We found this of limited added value, because most studies, 32 out of 34 were cohort studies of which 25 retrospective, with a comparable risk of bias. Of the 2 clinical trials, there was only one double blind RCT, which has a low RoB. Secondly, no formal meta-analysis was performed. As statically significance does not always correspondent with clinically relevancy we chose “percentage of significance” to capture relevancy, although this may not be the most thorough way of doing this. Lastly, we would like to emphasize that the most frequently used OMIs, collected in this review, do not defacto represent the most appropriate OMIs for this patient group, and that besides frequency of use, also clinical relevance, applicability, and psychometric validity are important factors to consider.

CONCLUSION

In this systematic review we identified the most used OMIs to evaluate treatment effect in patients with non-paralytic glottic insufficiency caused by vocal fold atrophy with and without sulcus as a second step towards developing a COS for this population. The need for a COS is further demonstrated by the fact that studies in this review rely heavily on parameters that have a low percentage of significance in this population, with the exception of VHI-30 with a high percentage of significance of 90%. Future steps in this process will include a quality analysis of the identified OMIs for this specific use and final inclusion through a Delphi process.

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7

General discussion

SUMMARY THESIS

This thesis focuses on surgical treatment to improve glottic closure in patients with glottic insufficiency due to vocal fold atrophy and sulcus and how to demonstrate this improvement. With the results we hope to attribute to the optimal counseling and treating of these patients by obtaining more insight into (1) patient selection, (2) voice outcome after surgical treatment, (3) voice outcome measurements.

In **chapter 2** we evaluated the outcome of bilateral trial vocal fold injection (VFI) with hyaluronic acid (HA) and assessed the predictive value of trial VFI on the outcome of durable medialization. It is a retrospective cohort study including 68 patients (30 atrophy, 38 atrophy and sulcus) in which voice data were analyzed comparing pre- with post-trial VFI outcome and comparing post-trial VFI outcome with postoperative outcome after durable treatment.
Overall Voice Handicap Index (VHI)-30 improvement (from 49.9 to 33.1) after trial VFI was statistically significant and clinically relevant. 58% of the patients (37 out of 64) experienced enough subjective benefit after trial VFI to undergo durable medialization. There was only a partial overlap between subjective benefit and VHI outcome; 62% of the patients (23 out of 37) who continued to durable treatment had a clinically relevant improvement in VHI-30. After durable medialization 90-94% of the patients had VHI-30 scores similar to or better than post-trial VFI.
We concluded that medialization could be considered a valid treatment option for vocal fold atrophy and for sulcus. And, although VHI-30 only partially overlapped with patients' subjective benefit, it could predict outcome after durable medialization.

Chapter 3 is a retrospective cohort study evaluating voice outcome after bilateral VFI with autologous fat including 23 patients undergoing 24 procedures for vocal fold atrophy (*n*=15) or atrophy with sulcus (*n*=9). Voice data were analyzed comparing preoperative data with 3 and 12-month postoperative data, including subjective VHI-30, perceptual outcome (Grade of GRBAS), acoustic parameters (fundamental frequency (F0), melodic range (MR)) and aerodynamic parameters (mean phonation time (MPT), dynamic range (DR)). There was a clinically relevant and statistically significant improvement in VHI-30 (from 49.1 to 29.7 at 12 months). Change in dynamic range was statistically significant over time. There were no significant differences in voice parameters between patients with atrophy and atrophy with sulcus. Based on these results, we concluded that bilateral VFI with autologous fat is a valid treatment option for patients with atrophy as well as atrophy with sulcus.

In **chapter 4** voice outcome after bilateral medialization thyroplasty including 29 patients (14 atrophy, 15 atrophy with sulcus) was evaluated in a similar study design used in chapter 3. There was also a clinically relevant and statistically significant improvement in VHI-30

(from 55.8 to 30.9 at 12 months) in this patient cohort. Fundamental frequency for male subjects decreased significantly from 175 Hz to 159 Hz. The pre- and postoperative grade of dysphonia was significantly lower in patients with atrophy compared to atrophy and sulcus. In this study we concluded that bilateral medialization thyroplasty is a valid treatment option for patients with atrophy with or without sulcus. In both chapter 3 and 4, we emphasized the need for larger prospective studies with long-term follow-up to gain more insight into voice outcomes for the different forms of surgery for patients with glottic incompetence due to atrophy with or without sulcus.

Chapter 5 is a retrospective questionnaire-based follow-up study on the long-term outcomes (>1 year) after bilateral medialization thyroplasty including 26 patients (16 atrophy, 10 atrophy with sulcus). A sustained long-term improvement in VHI scores was found, which was statistically significant and clinically relevant, with a median follow up of 6.7 years (mean VHI-30 preoperative 58.1, postoperative 1 year 35.7, postoperative > 1 year 40.0). There were 10 out of 18 patients (56%) (follow-up > 5 years) with a long-term clinically relevant improvement in VHI-30. This study showed that long-term improvement is attainable in a significant proportion of patients undergoing bilateral medialization thyroplasty for atrophy with or without sulcus, but voices will not normalize and not every patient will benefit.

Lastly, in **chapter 6**, a systematic literature review was performed to identify outcome measurements instruments (OMIs) to evaluate treatment in patients with vocal fold atrophy and/or sulcus. From the 5456 studies identified, 34 articles were included in final analysis and screened for OMIs; 50 OMIs were collected and were ordered in Pareto diagram and percentage of significance was calculated. Most used OMIs were VHI-30 andVHI-10 for subjective outcome; G of GRBAS for perceptual; F0, Shimmer and Jitter for acoustic; MPT, MFR (mean airflow rate) and DR for aerodynamic outcome and glottic closure and mucosal wave for endoscopic findings. This review, identifying the most used OMIs and their percentage of significance, is a first step toward defining a Core Outcome Set (COS) for this specific patient population.

DISCUSSION AND FUTURE DIRECTIONS

In this discussion we reflect on lessons learnt in this thesis and discuss future directions and improvements for this patient group of atrophy and atrophy with sulcus.

RELEVANCY

With growing elderdom across the (world)population, dysphonia due to presbylaryngis with vocal fold atrophy will increase in prevalence. The dysphonia related patient burden may also increase, as a result of elderly people being more and longer socially active. In the Netherlands the elderly population (above > 65 years) will grow from 3.4 million in 2020 to 4.8 million in 2040. A significant part of these elderly participate in community activities, for instance as volunteers, caregivers, babysitters etc. This thesis contributes to the surgical management of presbyphonia. It will be of guidance in counselling and treating presbyphonic patients and contributes to the growing number of literature on this subject [1,2].

Sulcus is more prominent in the younger population and, although it is relatively rare, the social and work related impact is significant. In general, it has been shown that work-related voice complaints are becoming more prevalent [3]. Moreover, the surgical treatment of sulcus is challenging and an ongoing theme within the laryngological literature [4,5,6]. Outcome studies, such as performed in this thesis, are needed to obtain the full picture of current treatments and to further improve physicians' and patients' choice of treatment and counseling.

PATIENT SELECTION

In chapter 2 we focused on patient selection and advocated the use of trial VFI to select patients who will benefit from durable medialization. Our results and conclusions are in line with earlier studies [7–10]. Caroll was the first to introduce and publish over trial VFI for patients with atrophy, sulcus or scar [7].

Two important points to consider for future research are (1) timing: what is the optimal timing for voice data acquisition? and (2) outcome measurement: what are the preferred voice parameters to capture treatment effect?

The timing of evaluation is of great importance when evaluating the success of trial VFI due to the short-acting nature of fillers which are used as injection material for such trials. In our

cohort study post-trial injection data were collected at four weeks (spread 2-8 weeks) and the decision to continue to durable treatment was after 3 months, based on retrospective subjective experience of the patients. Carroll et al. evaluated a shorter follow-up time of two weeks to capture benefit after trial, but also found a mismatch in subjective improvement and VHI(-10) outcome [11].

In our experience the window of maximum benefit varies per patient and collecting voice outcome data at one fixed time point will not capture this optimal voice outcome [12]. Ideally voice evaluation should be done frequently to capture patient's optimal benefit after trial VFI. Proposed investigation should focus on repeated voice outcome measurement after trial VFI. A possible future subject of investigation could be the value of home-monitoring, with the use of an app-based voice data collecting system, to monitor patient's individual optimal time point and to collect voice data at exactly this time point.

OUTCOME MEASUREMENT INSTRUMENTS

Maybe as important as timing of evaluation of voice quality, may be the evaluation parameters themselves. In chapter 6 most used OMIs for patients with atrophy and sulcus, and their estimated clinical relevancy, expressed in percentage of significance, were presented and divided into ELS subcategories of subjective, perceptual, acoustic, aerodynamic and endoscopic approach [13]. Chapter 6 forms a first step towards a COS. The final step will be formulating a COS with use of Delphi Method for this specific patient population [14]. The introduction of this consensus based COS will be of great benefit for comparing pre- and post-treatment outcome, monitoring individual patient outcome and for research purposes within (multi-center) studies. As we discussed in chapter 6, in order to select a minimal set of outcome parameters, quality assessments of the included OMIs need to be performed. Quality of an OMI depends on clinical relevance, psychometric validity and applicability [14]. Future research should focus on these quality assessments.

In chapter 6 we concluded that the psychometric validity studies for OMIs in dysphonic patients are lacking, with the exception of subjective outcome (patient-reported outcome measurements (PROMs)) [15,16]. PROMs are, in our opinion, the most clinically relevant tool in the communication with patients. Although the VHI-30 is a robust questionnaire with translations and validations in many languages and with the most sufficient psychometric construct based on the COSMIN taxonomy [15,17], we did raise the question in chapter 2 and 6 whether VHI is sufficiently valid as subjective outcome measurement in this specific patient population. We discussed disease specific PROMs (Chapter 2 and 6) and generic PROMs focusing on general health aspect (Chapter 6) as possible alternatives. A future direction of research

should be to validate and compare these different PROMs for this specific patient group. We would also recommend to include clinical relevance and not only statistical significance, when reporting on voice outcome in future research. With the insight that subjective clinical relevance may be disease specific [18], we would suggest to formulate a minimal clinically important difference (MCID) in VHI for patients with atrophy and/or sulcus.

FUTURE COS

Based on our findings in chapter 6, a future COS should include at least one subjective OMI. We would suggest VHI, preferably with disease specific MCID. A second disease specific or generic questionnaire may be of added value and we would suggest to use GFI (glottal function index [19]), which is a disease specific questionnaire with better psychometric properties compared to other disease specific subjective OMIs [15].
Perceptual grading should be included. In accordance with the latest ELS proposal, the use of complete GRBAS scale is preferred [20]. We do acknowledge the limitations of perceptual grading in this specific patient group, because structural defects are not always addressed and main treatment goal is improving endurance of voicing and not perceptual quality of the voice [21,22].
In our opinion, the value of acoustic OMIs is very limited and therefore only a minimum, if any, acoustic OMIs should be included. Most often used OMIs are F0, jitter and shimmer. A possible interesting parameter may be SPI (soft phonation index) [23], but its usefulness in atrophy and/or sulcus needs to be proven first.
For acoustic parameters, we would suggest MPT because it is simple and reliably obtainable [24]. It's main disadvantage is not to reflect subtle differences in glottic closure. A measurement of interest may be the phonation threshold pressure (Pth). This reflects the minimum subglottic pressure needed to reach phonation onset and sustain phonation [25]. This parameter may capture changes in subglottic pressure, caused by subtle changes in glottic closure, but at this point in time it has only limited clinical use (Chapter 6).
Lastly, endoscopic evaluation should be included in a future COS. We would recommend the use of systematic videolaryngostroboscopic assessment protocols, as described in chapter 6, to maximize clinical usefulness and minimize inter- and intra-observer variations.

THE LUMC STRATEGY

Since 2012 all patients with glottic insufficiency in LUMC have been treated following a fixed strategy, based on the concept of correction of closure, with a predetermined scheme and timeline and with collection of a pre-established set of voice outcome data (Chapter 1).

The results over the past decade, collected in this thesis, may suggest some alternations of this strategy.

We recommend voice data collection after trial VFI to be performed at multiple time points in order to capture best voice outcome, this may be at 1, 2, and 3 months postoperative. Furthermore, the question “Do you experience enough benefit to continue to a durable intervention?” should be formally added, as well as overall numerical (1-10) rating of voice, in addition to the four separate domains, as this is more practical to work with in the clinical – as opposed to the scientific – setting. For future cost-effectiveness studies, it is advised to introduce a questionnaire which can be used for calculation of QUALYs (quality-adjusted life years), f.e. EuroQol 5D. Finally, we would update the present used OMIs according to the, previously described, proposed future COS.

In this thesis, atrophy and sulcus, consisting of sulcus type II (vergeture) and sulcus type III (sulcus vocalis), were analyzed in total and for atrophy and sulcus, but with no further division in different types of sulcus [26,27]. However, sulcus type II and III, and atrophy are separate entities with specific terminology, different underlying disease processes and different treatments. Sulica and his research group emphasized the importance of recognizing the different entities of sulcus I and II and III, supported by their observation of inflammatory component in sulcus type III, which was not observed in type II and I (physiological sulcus) [28,29]. However, taking into account the limiting factor of small numbers of patients with sulcus, we felt justified in analyzing atrophy and sulcus subtypes together, but we do recognize this was suboptimal and hope this will be encountered in a future multicenter study with larger patient numbers.

With the lessons learned from chapter 3, 4 and 5, we have improved patient counseling with realistic management of expectation on voice outcome, including a possible need for revision surgery. We can state that voice will improve, but will not normalize, and we can inform patients what fraction of patients benefit from surgery and for how long. Lastly, with data from this thesis, we are now in a better position to initiate a multicenter study cohort on the treatment of vocal fold sulcus and atrophy.

VFI WITH AUTOLOGOUS FAT

There is a long history of VFI and different injectables have been used over time. Nowadays most used durable injectables are autologous fat and calcium hydroxylapatite (Radiesse®, Renu Voice®) with a lifespan estimated around 12-18 months [30,31]. There are some great advantage of autologous fat; availability of donor sites, low costs, small risk to inflammatory reaction and its viscosity is similar to the superficial lamina propria. Important disadvantages are graft absorption and the precarious preservation of fat to diminish the decay of viable adipocytes. Preservation of fat is important for voice outcome and several processing techniques have been described to enhance survival of fat, including preparation with saline-, steroid- or insulin-washings [32]. It may be that processing methods used in other types of surgery are less effective in microlaryngeal surgery. A future direction would be to look for new fat processing techniques to optimize fat survival. Various methods of enriching autologous fat grafts are currently being investigated, f.e. with use of growth factors, adipose-derived stromal cells, or angiogenic cells (E4+ endothelial cells)[33].

VFI WITH OTHER INJECTABLES

There is also the development of new injectables. One injectable of interest may be sil-hyaluronic acid [34]. This injectable suspension with silk microparticles and HA as carrier will potentially be an easy to use, durable, possible permanent, injectable with low inflammation or migration risks. The first preliminary results with three months follow-up of 58 patients showed improvement in subjective and perceptual voice outcomes. Complications, including dyspnea and hemi-laryngeal edema, have been reported (3.4%). Fourteen (25%) patients underwent a repeat silk-HA injection. At this point in time, with no long-term data available, there is no proof of longevity or possible permanent effect, but it may be an alternative long-term material for the future [34].

MEDIALIZATION THYROPLASTY

Window placement in the thyroid cartilage and implant position are crucial for optimal voice outcome in thyroplasty. This has been investigated for unilateral thyroplasty with pre-carved implants and with implants of varying stiffness in a simulation study [35,36], but not for bilateral medialization thyroplasty with malleable/soft implants as Gore-tex® in larynges with mobile vocal folds.

In bilateral medialization thyroplasty with mobile vocal folds and soft implants, it is challenging to obtain perfect position and optimal amount of overcorrection, because these implants may change in form and position over time. In a current pilot study, change in volume and position of implant material (Gore-Tex®) after bilateral medialization thyroplasty will be measured using Magnetic Resonance Imaging (MRI) at 1 day and 3 months postoperative. With the results of this study we hope to improve implant position and amount of overcorrection during surgery to obtain better voice outcome.

Besides surgical effects, the effect of natural aging of the larynx may be of importance. Presbylaryngis is characterized by atrophy of the lamina propria, the vocal muscles and degeneration of the cartilaginous framework due to the aging process [37]. Despite corrective surgery, atrophy of the vocal fold and the vocal muscle will progress, possibly leading to further voice decline. An observational study following the aging processes of the larynx may be of future interest. Having more in-depth knowledge of the aging process of the human larynx, both physiological and (micro)anatomical, may also be of value for regenerative medicine techniques.

A last future direction may be the combination of thyroplasty with laryngeal reinnervation, in which a nerve-muscle pedicle (NMP) implant is placed in the vocal muscle complex through a thyroplasty window. This technique is based on the principle of reinnervation to restore tonus in an immobile vocal fold and has been applied in unilateral vocal fold paralysis [38]. With growing experience with this technique in our clinic, this may be of future interest for vocal fold atrophy.

MICROPHONOSURGERY

Also for microphonosurgical procedures further developments have to be expected. Several techniques have been published, including microphonosurgery with excision [29,39,40], with the use of graft implants such as autologous fat grafts [41,42] or fascia grafts [43,44,45], and laryngeal laser surgery [46–49]. In chapter 6 an overview is given in Table 1a.

An additional search on Pubmed (September 2023) showed one new publication on laser-assisted sulcus release (LASR) with VHI-10 scores improving from 25.3 to 9.9, together with significant improvements in GRBAS and MPT [50]. With LASR deep cuts are made with CO2 laser at 90 degrees to the medial and lateral lips of a sulcus, it is a combination of slicing mucosa technique and radiate laser cuts in subglottic stenosis [51]. With LASR the epithelium is not elevated of the sulcus bed, possibly achieving a relatively faster healing [50].

Another publication described the use of in-office blue laser [52]. The blue laser is a relatively new angiolytic laser. Its working mechanism, although not fully understood yet, is comparable to other angiolytic lasers and involves the process of photothermolysis (Chapter 1). The development of in-office procedures for atrophy and sulcus is of future interest. With the avoidance of general anesthesia, it may be of potential benefit for (elderly) patients and overall healthcare costs. It may also be possible to combine techniques as in-office laser techniques with injection techniques.

A limited number of review articles evaluating treatment for atrophy, sulcus and vocal fold scar have been published [5,6,53,54]. The two most recent reviews, published in 2024, included meta-analyses [6,54]. One review focused on sulcus vocalis and included 15 studies with meta-analysis of subjective, acoustic and aerodynamic outcomes comparing different techniques. It concluded that surgical treatments significantly improved subjective, aerodynamic and acoustic outcomes and that dissective and combined dissective/injective techniques appeared to yield better perceptual and phonatory outcomes compared to injective techniques alone [6].

A second review, including 43 studies for scar and sulcus with meta-analysis of subjective, perceptual, acoustic, aerodynamic and endoscopic parameters, showed different effectiveness on different parameters comparing different techniques, including medialization, microphonosurgery with graft interposition, laser surgery and regenerative medicine [54]. In its discussion the authors underline the limited availability of RCTs and high-quality comparative studies in the literature and emphasize the need for more rigorous research in the future.

Concluded from above systematic reviews and our own publications, future development will be to initiate large (multicenter) studies, preferably prospective randomized trails, comparing different types of surgical treatment with uniform reporting on outcome [6,12,21,22,54].

REGENERATIVE MEDICINE

The surgical techniques described in this thesis all show clinically relevant and statistically significant improvement in subjective voice outcome, but without normalization of voice and with persistent patient burden. In recent years, more and larger in-vivo studies in the field of regenerative medicine have been published, showing subjective improvement with near normal postoperative scores [55,56,57].

Investigations in the field of regenerative therapy in the larynx have been ongoing for the last decades. This has led to a better understanding of the microstructure and physiology

of the vocal folds and the development of therapies based on regenerative medicine [58]. The essential cell types are stratified squamous epithelium and collagen in the epithelium and basement membrane; proteoglycans and hyaluronan in the superficial lamina propria; elastin and hyaluronan in the intermediate lamina propria; collagen (type 1,3) in the deep lamina propria; and myocytes in the thyroarytenoid muscle [59]. Based on the body-cover model, the epithelium, basement membrane and superficial lamina propria - the vocal mucosa - are the cover; the intermediate and deep lamina propria and vocalis muscle/ thyroarytenoid muscle are the body [58]. The vocal mucosa is mostly involved in scarring, sulcus and atrophy, and therefore the main target for regenerative medicine therapies [58].

Regenerative medicine therapy aims to restore normal function by replacing, engineering, or regenerating human tissues. It may be a very potent treatment for patients with vocal fold atrophy and atrophy with sulcus by restoring the biochemical properties of the native tissue, rebuilding the extracellular matrix, and restoring the vibratory behavior of the vocal folds [58]. Regenerative medicine contains (1) stem/progenitor cell therapy, (2) scaffolding techniques, and (3) use of growth factors (biological active factors). These components are often used in combination [58,59]. The combination of all 3 approaches is known as tissue engineering [58]. In vocal fold scar, including sulcus, regenerative therapy aims to modify wound healing processes by reducing scar formation, improving healing and restoring function. In atrophy, regenerative therapy aims to regenerate new tissue and restoring function.

Stem/progenitor cell therapy

Regenerating and rebuilding layers of a vocal fold can be done with the use of stem cells. This can be endogenous stem cells within the vocal fold (stellate cells from the macula flava, vocal fold fibroblasts, laryngeal mucosa mesenchymal stem cells) or exogenous stem cells (mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), human embryonic stem cells, or induced pluripotent stem cells) [58]. Most studies with endogenous or exogenous stem cells are in-vitro or animal studies [58,60]. There are only limited human trials [60].

Hertegård et al. reported on 16 patients with vocal fold scar injected with autologous mesenchymal stromal cells (MSCs) with one year follow-up. No serious or minor adverse events were reported, laryngoscopic findings (vocal fold vibration, high-speed laryngoscopy) and phonation pressure threshold improved in 62-75% of the patients, VHI-30 improved in 8 patients [61]. Mattei et al. reported on 8 patients, 6 with scar and 2 with sulcus, injected with autologous adipose tissue-derived stromal vascular fraction (ADSVF) with one year follow-up. VHI-30 score improved in all patients and seven patients improved with ≥ 18 points which was considered clinically relevant, based on the minimum clinically important difference as formulated by Jacobsen et al. [62,63].

Two clinical trials have used autologous cultured fibroblasts (ACFs) in scar, sulcus and atrophy patients [64,65]. Ma et al. performed a randomized, double-blinded, placebo-controlled study (*n*=21) injecting ACFs in 15 patients with atrophy or sulcus with a follow-up of one year. The median VHI consistently decreased; however, it did not achieve statistical significance. Mucosal wave during videostroboscopy significantly improved compared to baseline in complete ACF group, but compared to control group, mucosal waves only significantly improved in the atrophy group at 4 and 8 months. Perceptual outcome in the ACF treated sulcus group was associated with better voice grade compared to control group at one year. No adverse events occurred [65].

All above studies reported no serious adverse events [61,63,64,65], but more evidence is needed to prove long-term safety of the use of stem cells. Moreover, the patient numbers are small and the voice outcomes show contradicting results. Further studies involving stem cell therapy reporting on voice outcome in patients with atrophy and sulcus are needed. Possible other future directions would be choice of cell type, injection mode (timing and doses), non-invasive techniques and the use of spheroidal self-organizing cell structures [60]. In addition to choice of cell type, possible further research on the stellate cells within the macula flava, being stem cell niche of the human vocal fold mucosa, may be of interest [66].

Growth factors

In recent years more and larger studies about the use of basic fibroblast growth factor (bFGF) have been published. Basic FGF stimulates the migration and proliferation of vocal fold fibroblasts, it stimulates the secretions of proteins inducing viscoelasticity (f.e. hyaluronic acid) and reduces fibrosis in the superficial lamina propria (SLP). Basic FGF is relatively inexpensive and can be used in in-office-procedures [67].

A recent meta-analysis on the use of bFGF included 15 studies with a total of 390 patients with atrophy, vocal fold scar, sulcus, and paralysis, with the largest series including 100 patients [55,67]. The meta-analysis showed a significant improvement in MPT, VHI, GRBAS, glottic closure and mucosal wave. The mean VHI-30 score (6 out of 14 studies) changed from 54.6 pre-injection to 26.7 at 6 months post-injection. VHI-10 (5 out of 14 studies) changed from 21 pre-injection to 10 at 12 months post-injection [67]. This last score can be considered as normal [68]. In chapter 5 of this thesis, we discussed three of the studies included in this meta-analysis, confirming close to normal VHI-10 scores at respectively one, two and three years [55,56,57]. In the subgroup analysis in the study of Hirano et al. VHI-10 improvement was significantly higher in atrophy compared to scar/sulcus group and within in the scar/sulcus subgroup the VHI-10 improved in mild-moderate scarring was better compared to severe scarring [55]. In summary, there is literature, including a review with meta-analysis,

showing that bFGF may be an effective treatment for patient with glottic insufficiency caused by atrophy and/or sulcus.

Other growth factors have been investigated, but to a lesser extent. There is a phase I/II exploratory clinical trial on the use of hepatocyte growth factor (HGF) in scar and sulcus (*n*=18) and a study investigating the use of platelet-rich plasma (PRP)[69,70].

Future directions focusing on bFGF therapy should include larger subgroups analysis and meta-analysis, reducing risk of bias by improving study design including a placebo arm, and improving outcome measurement [67]. Hirano et al. also suggest further research options, including the long-term effect of bFGF on (the absence of) recurrence of atrophy of the vocal fold mucosal. They hypothesized that autocrine effects, after stimulation by exogenous growth factors, possibly upregulate the endogenous production of growth factor resulting long-term benefits [55]. Furthermore, Hirano et al. suggest to focus on the epithelial lining at the bottom of the sulcus and its histological alterations. Basic FGF only improves SLP , but these epithelial alterations at the bottom of the sulcus may interfere with the regeneration of mucosa. Strategies to replace this pathologic epithelium with healthy tissue should be further investigated. Lastly, they suggest the implantation of stem cells, with or without added growth factor, in (severe) scar [55].

In our opinion, significant steps forward have been made in the field of regenerative medicine in the last decade. Still there are many questions to be answered; what is the exact pathophysiologic mechanism in atrophy, sulcus and scar? What are the working mechanisms of different forms of regenerative medicine? Although first clinical results of regenerative medicine with growth factor are promising, there is a lack of placebo controlled studies, as well as long-term (>3 years) outcome data and there are no comparing studies with surgical techniques proving superiority.
At this point in time, it is premature to conclude that regenerative medicine is the better treatment option compared to surgical treatment options, but we can conclude that regenerative therapy is the only treatment option which has the potential to fully restore the vocal fold anatomy and function and development in this field will be of future interest.

NON-SURGICAL TECHNIQUES

The main focus of this thesis is on surgical treatment, but non-surgical methods for voice improvement are an essential part of treatment of patients with atrophy or atrophy with sulcus. Speech language therapy (SLT) plays an important role in managing and counselling of these patients. SLT is used as supportive treatment alongside surgery, but can also be

used as primary therapy. Research publications on outcome after SLT are limited and consist mostly of retrospective cohort studies [37, 71–74]. There is a slowly increasing number of prospective randomized-controlled clinical trials [75,76,77]. A very recent systematic review of SLT for presbyphonia showed evidence that voice therapy for presbyphonia results in significant improvement in subjective, perceptual, aerodynamic and acoustic voice outcomes, although there was uncertainty of internal validity because of the inclusion of a wide range of study designs [78]. Future direction would be to initiate studies, preferably randomized prospective trails with longer (> 4 weeks) follow-up time, on the effect of SLT on voice outcome in patient with atrophy and/or sulcus.

Another non-surgical intervention that could be of interest is the use of speech computers and/or amplifiers with the use of artificial intelligence (AI). These “new” voice amplifiers give higher voice quality and are easier to use in daily life compared to “old” voice amplifiers. A recent development are the text-to-speech generators with use of AI. But of greater interest are the speech-to-speech generators with the use of AI, also called “smart voice amplifiers”. These techniques seem promising, but have no formal role in medical care for dysphonic patients at this moment. Possible applications in patients with dysphonia, including atrophy and/or sulcus, could be of interest for future developments.

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8

Nederlandse samenvatting

Dit proefschrift richt zich op patiënten met onvolledige glottissluiting, met beiderzijds beweeglijke stembanden, als gevolg van stemband atrofie of atrofie met sulcus. De eerste hoofdstukken richten zich op de chirurgische behandeling, het laatste deel richt zich op uitkomstmaten binnen deze patiënten groep.

In de afgelopen decennia zijn er verschillende chirurgische technieken ontwikkeld en toegepast voor stemband atrofie en atrofie met sulcus. Deze zijn te verdelen in 3 groepen; (1) ingrepen gericht op verbetering van glottissluiting, zoals injectieaugmentatie en bilaterale medianisatie thyroplastiek, (2) ingrepen gericht op verbetering van stemband trilling bij sulcus, waaronder verschillende vormen van microlarynxchirurgie met verschillende technieken van excisie, met of zonder gebruik van verschillende grafts, zoals vet of fascie, als ook microlarynxchirurgie met gebruik van lasers. Tenslotte zijn er (3) technieken vanuit de regeneratieve geneeskunde, zoals injectie van groeifactoren. Ook combinatie van technieken is mogelijk.

In dit proefschrift wordt dieper ingegaan op de volgende chirurgische technieken ter verbetering van de glottissluiting: injectieaugmentatie met hyaluronzuur als proefbehandeling, injectieaugmentatie met autoloog vet en bilaterale medianisatie thyroplastiek. Tenslotte bevat dit proefschrift een systematische review over uitkomstmaten, zoals deze nu gebruikt worden in deze patiënten groep. Met dit proefschrift hopen wij bij te dragen aan het vinden van de meest passende behandeling voor patiënten met glottische insufficiëntie veroorzaakt door atrofie en sulcus.

Hoofdstuk 1 bevat de algemene inleiding. In **hoofdstuk 2** evalueren we de uitkomsten van bilaterale injectieaugmentatie met hyaluronzuur als proefbehandeling (trial VFI) bij patiënten met stemband atrofie met of zonder sulcus en beoordelen we de voorspellende waarde van trial VFI op de uitkomst van duurzame medianisatie. Het is een retrospectieve cohortstudie met 68 patiënten (30 atrofie, 38 atrofie en sulcus) waarbij stem uitkomsten voor en na trial VFI werden geanalyseerd en waarbij de uitkomsten na trial VFI vergeleken werden met de postoperatieve uitkomsten na duurzame medianisatie (injectieaugmentatie met autoloog vet of bilaterale medianisatie thyroplastiek).
De algehele verbetering na trial VFI was statistisch en klinisch relevant (van 49,9 naar 33,1). 58% van de patiënten (37 van 64) ervoer voldoende subjectief voordeel na trial VFI om duurzame medianisatie te ondergaan. Er was een gedeeltelijke overlap tussen subjectieve patiënt beoordeling en VHI-uitkomst; 62% van de patiënten (23 van 37) die doorgingen naar duurzame medianisatie hadden een klinisch relevante verbetering in VHI-30. Na duurzame medianisatie had 90 tot 94% van de patiënten VHI-30 scores die vergelijkbaar waren of beter waren dan na trial VFI. We concludeerden dat, aangezien de meerderheid van de patiënten subjectieve verbetering ervoer na trial VFI, medianisatie van toegevoegde waarde

is als behandeling voor patiënten met atrofie en atrofie met sulcus. Ook concludeerden wij dat VHI-30, hoewel deze slechts gedeeltelijk overlapte met het subjectieve oordeel van patiënten, voorspellend was voor VHI-30 uitkomst na duurzame medianisatie.

Hoofdstuk 3 is een retrospectieve cohortstudie die de uitkomsten evalueert na bilaterale injectieaugmentatie met autoloog vet, bestaande uit 23 patiënten die 24 procedures ondergingen voor atrofie (*n*=15) of atrofie met sulcus (*n*=9). Uitkomsten werden geanalyseerd door preoperatieve gegevens te vergelijken met postoperatieve gegevens van 3 en 12 maanden, bestaande uit subjectieve parameter VHI-30, perceptuele parameter maat van dysfonie (Grade van GRBAS score)), akoestische parameters (fundamental frequency (F0), melodic range (MR)) en aerodynamische parameters (mean phonation time (MPT), dynamic range (DR)). Er werd een klinisch relevante en statistisch significante verbetering gevonden van VHI-30 (van 49,1 naar 29,7) na 12 maanden. Verandering in dynamisch bereik (DR) was statistisch significant in de loop van de tijd. Er waren geen significante verschillen in parameters tussen patiënten met alleen atrofie en atrofie met sulcus. Op basis van deze resultaten concludeerden we dat bilaterale injectieaugmentatie met autoloog vet een valide behandeling is voor patiënten met atrofie en atrofie met sulcus.

In **hoofdstuk 4** werd in een vergelijkbare studie als hoofdstuk 3, de uitkomsten na bilaterale medianisatie thyroplastiek geëvalueerd, bestaande uit 29 patiënten (14 atrofie, 15 atrofie met sulcus). Ook in deze patiëntengroep was er een klinisch relevante en statistisch significante verbetering in de VHI-30 (van 55,8 naar 30,9) na 12 maanden. De fundamentele frequentie (F0) voor mannelijke patiënten daalde significant van 175 Hz naar 159 Hz. De pre- en postoperatieve graad van dysfonie was significant lager bij patiënten met atrofie in vergelijking met atrofie en sulcus. In deze studie concludeerden we dat bilaterale medianisatie thyroplastiek, net als injectieaugmentatie met autoloog vet, een geschikte behandeling is, vergelijkbaar met andere chirurgische methoden, maar dat grotere prospectieve studies met langdurige follow-up nodig zijn om meer inzicht te krijgen.

Hoofdstuk 5 is een retrospectieve, op vragenlijst gebaseerde, follow-up studie over de lange termijn uitkomsten (> 1 jaar) na bilaterale medianisatie thyroplastiek met 26 patiënten (16 atrofie, 10 atrofie met sulcus). Er werd een aanhoudende verbetering op lange termijn in VHI-scores gevonden, die zowel statistisch significant als ook klinisch relevant was, met een gemiddelde follow-up van 6,7 jaar (gemiddelde VHI preoperatief 58,1; postoperatief 1 jaar 35,7; postoperatief > 1 jaar 40,0). In de groep met een follow-up >5 jaar (*n*=18) waren er 10 patiënten (56%) met een langdurig klinisch relevante verbetering in VHI. Deze studie toonde aan dat verbetering op lange termijn haalbaar is bij een aanzienlijk deel van de patiënten met atrofie met en zonder sulcus na bilaterale medianisatie thyroplastiek, maar dat de stem niet normaliseert en dat niet elke patiënt verbetert.

Ten slotte werd in **hoofdstuk 6** een systematische literatuurstudie uitgevoerd om uitkomstmaten (outcome measurement instrument (OMIs)) te identificeren om de uitkomsten van behandeling bij patiënten met stemband atrofie of atrofie met sulcus te evalueren. Van de 5456 studies die werden geïdentificeerd na doorzoeken van Pubmed en EMBASE, werden 34 artikelen opgenomen in de uiteindelijke analyse en gescreend op OMIs. Er werden 50 OMIs gevonden en samengevoegd in een Pareto-diagram. Van de meest gebruikte OMIs werd "percentage van significantie" berekend als maat voor klinische relevantie. De meest gebruikte OMIs waren VHI-30 en VHI-10 voor subjectieve uitkomst; G van GRBAS voor perceptuele uitkomst; F0, Shimmer, Jitter voor akoestisch; MPT, MFR (mean flow rate) en DR voor aerodynamische uitkomst; en "glottic closure" en "mucosal wave" voor endoscopische bevindingen. Deze review is een eerste stap richting een Core Outcome Set (COS) voor patiënten met stemklachten op basis van onvolledige glottissluiting bij stemband atrofie en atrofie met sulcus.

In **hoofdstuk 7** volgt de discussie van het proefschrift. Hierin wordt gereflecteerd op voorgaande hoofdstukken. Mogelijke verbeteringen in patiënten selectie, operatie technieken en uitkomstmaten worden besproken. Er wordt dieper ingegaan op nieuwe ontwikkelingen, zoals ontwikkelingen vanuit de regeneratieve geneeskunde, aangevuld met voorstellen tot verder toekomstig onderzoek.

Appendices

List of publications

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LIST OF PUBLICATIONS

Glottic insufficiency caused by vocal fold atrophy with or without sulcus: systematic review of outcome measurements. Van den Broek EMJM, Mes SD, Heijnen BJ, Langeveld APM, van Benthem PPG, Sjögren EV. Eur Arch Otorhinolaryngol. 2024 Jul; online ahead of print. doi: 10.1007/s00405-024-08751-5.

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LIST OF ABBREVIATIONS

ACF	autologous cultured fibroblast
ADSC	adipose-derived stem cell
ADSVF	adipose tissue-derived stromal vascular fraction
AI	artificial intelligence
APQ	amplitude perturbation quotient
AR	aerodynamic resistance
bFGF	basic fibroblast growth factor
B	beta coefficient
CaHA	calcium hydroxylapatite
CAPE-V	consensus auditory-perceptual evaluation of voice
CAx	irregularity of amplitude
CFx	irregularity of frequency
CI	confidence interval
CMC	carboxymethylcellulose
COS	core outcome set
CPIB	communicative participation item bank
CPP	cepstral peak prominence
CPPS	smoothed cepstral peak prominence
CSID	cepstral spectral index of dysphonia
CT	cricothyroid
dB	decibel
DLP	deep lamina propria
DR	dynamic range
Δ	delta
ECM	extracellular matrix
ELS	European laryngological society
EMG	electromyography
EMST	expiratory muscle strength training
EQ-5d	EuroQol 5D
FBFA	frame-by-frame analysis
FCM	functional communication measure
FEV1	forced expiratory pressure

FVC	forced vital capacity
F0	fundamental frequency
GC	glottic closure
GFI	glottal function index
GRBAS	grade roughness breathiness asthenic strain
HA	hyaluronic acid
HGF	hepatocyte growth factor
HNR	harmonic to noise ratio
Hz	Hertz
IA	interarytenoid
ILP	intermediate lamina propria
IMST	inspiratory muscle strength training
IQR	interquartile range
Jita	absolute jitter
Jitt	jitter
KTP	potassium-titanyl phosphate
LASR	laser-assisted sulcus release
LCA	lateral cricoarytenoid
LFS	laryngeal framework surgery
LSVT	Lee Silverman voice therapy
LUMC	Leiden university medical center
MCID	minimal clinically important difference
MDVP	multidimensional voice program
MFR	mean airflow rate
MEP	maximum expiratory pressure
MIP	maximum inspiratory pressure
MLS	microlaryngeal surgery
MMP	matrix metalloproteinase
MPT	mean phonation time
MR	melodic range
MRI	magnetic resonance imaging
MSC	mesenchymal stromal cell
MV	mucosal wave
NHR	noise to harmonic ratio

NNE	normalized noise energy
NOMS	national outcomes measurement system
NPM	nerve-muscle pedicle
OMI	outcome measurement instrument
PAS	phonatory aerodynamic system
PCA	posterior cricoarytenoid
PDL	pulse dye laser
PPQ	pitch perturbation quotient
PQ	phonation quotient
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROM	patient reported outcome measurement
PRP	platelet-rich plasma
Psub	subglottal pressure
PT	phonation time
Pth	phonation threshold pressure
PTF	phonation threshold flow
PTP	phonation threshold pressure
QUALY	quality-adjusted life year
QxM	mean closed quotient
RAP	relative average perturbation
RCT	randomized controlled trial
RLN	recurrent laryngeal nerve
RoB	risk of bias
s	second
sAPQ	smoothed amplitude perturbation quotient
SD	standard deviation
ShdB	absolute shimmer
Shim	shimmer
SLN	superior laryngeal nerve
SLP	superficial lamina propria
SLT	speech language therapy
SPI	soft phonation index
SPL	sound pressure level
sPPQ	smoothed pitch perturbation quotient

ST	semitones
TA	thyroarytenoid
UVFP	unilateral vocal fold paralysis
VALI	voice-vibratory assessment with laryngeal imaging
vAm	peak-to-peak amplitude
VAS	visual analogue scale
vF0	fundamental frequency coefficient variation
VFE	vocal function exercise
VFHQ	vocal fatigue handicap questionnaire
VFI	vocal fold injection
VFI	vocal fatigue index
VHI	Voice handicap index
VRQOL	voice related quality of life
VTI	voice turbulence index

CURRICULUM VITAE

Emke van den Broek was born on the 4th of January 1980 in Geldrop, the Netherlands. In 1998 she finished her secondary education, VWO Carolus Borromeus College in Helmond. She studied Medicine at Utrecht University from 1999 until 2005. In 2009 she started her residency of otorhinolaryngology, head- and neck surgery at LUMC in Leiden, which she completed in 2014. From 2014 to 2015 she did a fellowship laryngology in Auckland, New Zealand. After returning to the Netherlands she worked as otorhinolaryngologist with subspecialism laryngology, at the ENT department in LUMC and started her PhD research under supervision of Elisabeth Sjögren, resulting in this thesis. In 2018 she took on the position of staff-member, laryngologist, at the department of otorhinolaryngology, head- and neck surgery in UMC Utrecht. Besides her clinical work, she is actively involved in the training of medical students and ENT registrars in UMC Utrecht. In her role as chairman and member of laryngological workgroup of the Dutch scientific ENT Association, she contributes to improve laryngologic care in the Netherlands.
Emke is married to Michiel Jaarsveld, they have two sons Jan and Ties, and live in the old city center of Utrecht.

DANKWOORD

In de wetenschap dat met de snelle ontwikkeling van AI (artificiële intelligentie) met programma's zoals chatGPT, computers het mensenbrein kunnen evenaren, vervult het mij met trots dat elke zin in dit proefschrift door een mensenhoofd en vingers is gevormd. Mijn promotie traject, dat liep van 2018 tot 2024, heb ik gecombineerd met mijn werk als KNO-arts/ laryngoloog en met thuis een uitbreidend gezin. Ik ben veel mensen dankbaar voor hun steun.

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[1] Dikkers FG, Remacle M, Karagama, Y. In memoriam: Nobuhiko Isshiki 1930–2022. Eur Arch Otorhinolaryngol 279(.):4653-4654