國立臺灣大學公共衛生學院流行病學與預防醫學研究所

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病灶內類固醇注射用於治療良性聲帶病變：比較性效果與成果研究

Intralesional Steroid Injection for Benign Vocal Fold Lesions: Comparative Effectiveness and Outcome Researches

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論文中文題目：**病灶內類固醇注射用於治療良性聲帶病變：比較性效果與成果研究**

論文英文題目：**Intralesional Steroid Injection for Benign Vocal Fold Lesions: Comparative Effectiveness and Outcome Researches**

本論文係 王榮德 君（學號 D99849018）在國立臺灣大學流行病學與預防醫學研究所完成之博士學位論文，於民國 103 年 5 月 26 日承下列考試委員審查通過及口試及格，特此證明。

口試委員：賴美淑（簽名）

（指導教授）

中文摘要

目的:本論文應用臨床流行病學之研究方法，探討聲帶類固醇注射於良性聲帶病變之治療成果。主要之研究方向包括:1)比較聲帶類固醇注射與保守治療(嗓音保健與衛教)、侵入性治療(喉顯微手術)之優劣與臨床應用時機；2)多面向研究聲帶類固醇注射用於治療良性聲帶病變之成果與可能之預後因子、副作用發生率及其危險因子、以及治療後之長期成效追蹤。

方法:本研究收錄自 2009 年 1 月至 2013 年 12 月間就診並接受治療之良性聲帶病變患者。所有患者均於初診時記錄相關之嗓音症狀、抽菸喝酒習慣、職業與用聲程度、其他內科疾病，並填寫 10 項聲音障礙指標(voice handicap index, VHI-10)與胃酸逆流症狀量表(reflux symptom index, RSI)。治療成果於治療後 1 及 2 個月間進行測量，項目包括喉閃頻內視鏡檢查、聽覺音質評估(使用 GRB 量表)，電腦化嗓音分析、以及病患主觀評分（0-10 分）。聲帶類固醇注射於門診局部麻醉下以經口或經鼻內視鏡進行治療，定義術後 VHI-10<=10 分，或 GRB<=1 分為治療成功，並藉由單變項與多變項分析探討相關之預後因子與發生副作用之可能危險因子。治療後之長期成效則依據病歷記載及每半年電話追蹤之結果，將症狀復發且 VHI-10 ＞10 分，或接受後續治療者定義為治療失敗。

結果:相較於保守治療，聲帶類固醇注射於治療後 1、2 個月皆有較佳之成效(p 值 <0.05)。對聲帶結節之患者而言，聲帶注射之效果在術後 1 個月比音聲衛教好(p 值 <0.05)；至於聲帶息肉之患者，接受聲帶注射後 1 個月及 2 個月，病灶皆顯著變小(p 值<0.01)，但接受音聲衛教的組別則沒有明顯改善。對於聲帶息肉或黏液囊腫之病患，接受聲帶類固醇注射或喉顯微手術後皆有顯著之進步，惟男性、有抽菸喝酒習慣、病灶較大、出血性息肉、嗓音品質較差等患者多傾向接受顯微手術。在應用 propensity score 移除極端值之後，比較兩種治療方式顯示喉顯微手術在治療聲帶

息肉與囊腫上仍有較佳之成效(p 值<0.05)。

雖然聲帶類固醇注射可有效應用於治療聲帶結節、息肉、與黏液囊腫，但礙於收案數之限制，對於黏膜下水腫(Reinke’s edema), 皮下纖維組織增生(fibrous mass)與偽囊腫(pseudocyst)之治療成效並不明確。接受經鼻內視鏡治療之患者之不適感較經口治療來的高(p 值=0.01)，但兩者之治療成效則無顯著差異。職業上頻繁用聲與纖維化之”硬”結節，在接受聲帶類固醇注射後之臨床治療成效較差(p 值<0.05)。聲帶息肉之患者如嗓音症狀大於一年或同時合併有胃食道逆流，接受聲帶類固醇注射後之臨床成效較差(p 值<0.05)。治療後常見之副作用包括局部出血(27%)、藥物沉積(4%)、與聲帶萎縮(1%)，於 1-2 個月內可自行恢復，無不可逆之後遺症。其中，聲帶微血管異常與用聲程度較高之患者，較易於治療後發生聲帶出血之症狀。

長期追蹤顯示接受聲帶類固醇注射兩年內，有 28% 之個案症狀復發或接受後續治療，聲帶結節、息肉、囊腫之治療失效比率並無明顯差異。後續分析顯示，病患自覺症狀較嚴重者，治療失效之比率較高(p 值<0.01)。對於聲帶結節與囊腫之患者，症狀發生一年以上始就醫之患者，治療後失效之比率較低 (p 值<0.05)。

結論: 聲帶類固醇注射可有效應用於聲帶結節、息肉、與黏液囊腫。對於聲帶結節之患者，聲帶類固醇注射可較快達成臨床成效；對於息肉與囊腫，則仍以喉顯微手術之成效較佳。職業用聲程度、結節軟硬度、病程長短、與胃食道逆流皆會影響聲帶類固醇注射之治療成果。治療後之副作用包括局部出血、藥物沉積、與聲帶萎縮，於 1-2 個月內可自行恢復。聲帶類固醇注射後症狀復發或需要後續治療之情況並不罕見，有賴後續研究探索個人之行為與心理因素之潛在關聯性與影響。

關鍵字: 聲帶結節、息肉、囊腫、喉顯微手術、胃食道逆流、嗓音、職業

Abstract

Objective: This thesis conducted series of epidemiological studies focusing on the application of vocal fold steroid injection (VFSI) for treating benign vocal fold lesions. First, we compared the clinical effectiveness of VFSI with non-invasive intervention (i.e. vocal hygiene education, VHE) and invasive procedure (i.e. phonomicrosurgery). Additionally, we investigated treatment outcomes, including prognostic factors, side effects, and long-term surveillance of treatment failures following VFSI.

Methods: This study recruited patients with benign vocal fold lesions treated from January 2009 to December 2013. A detailed history was recorded using a self-completing questionnaire, including age, gender, duration of symptoms, smoking, alcohol consumption, occupational vocal demand, medical comorbidity, 10-item voice handicap index (VHI-10), and reflux symptom index (RSI).

VFSI was performed under local anesthesia in the office setting through trans-oral or trans-nasal approaches. Treatment outcomes were evaluated 1 and 2 months after the procedure, including endoscopic evaluation of lesion regression and vibratory capacity of vocal folds, perceptual voice quality (GRB: grade, roughness, and breathiness), acoustic analysis, and 10-item voice handicap index (VHI-10). “Responder” of VFSI was defined by: 1) post-operative VHI-10 score <=10 points or 2) GRB score <=1 point. Prognostic factors for VFSI treatment outcomes and risk factors for side effects following VFSI were evaluated via univariate and multivariate analyses. Long-term treatment results were investigated by reviewing medical charts and structured telephone interviews semi-annually. Treatment failure after VFSI was defined as 1) subjective report of recurring dysphonic symptoms with VHI-10 score more than 10 points or 2) receiving

secondary procedures.

Results: Compared with vocal hygiene education (VHE), VFSI was associated with a higher lesion reduction rate ($p<0.05$). In vocal nodules, VFSI achieved a higher lesion regression rate than VHE at 1 month ($p<0.05$). In vocal polyps, the lesion reduction rate after VFSI was higher than that following VHE at 1 and 2 months ($p<0.01$). Crude treatment outcomes measured at 1 and 2 months demonstrated significant improvements from baseline following both VFSI and phonomicrosurgery for vocal polyps and cysts. Male, smokers, patients with larger or hemorrhagic vocal polyps and worse voice quality tended to receive phonomicrosurgery. After controlling baseline heterogeneity by trimming patients with extreme propensity scores, phonomicrosurgery remains more effective than VFSI in patients with both vocal polyps and cysts.

Although treatment outcomes of VFSI in patients with vocal nodules, polyp and mucus retention cysts revealed significant improvements from baseline, the treatment outcomes for Reinke's edema, fibrous mass and pseudocyst were unclear. Higher occupational vocal demands and fibrotic vocal nodules were significantly associated with poorer clinical responses as measured by the VHI-10 and GRB scores, respectively. For vocal polyps, dysphonia for more than 1 year was significantly associated with lower VHI-10 scores, whereas patients with laryngopharyngeal reflux (LPR) showed significantly poor postoperative voice quality. Trans-oral and trans-nasal injection approaches revealed similar treatment results, whereas more discomforts were experienced during trans-nasal approach ($p=0.01$). Side effects following VFSI included hematoma (27%), triamcinolone deposits (4%), and vocal atrophy (1%), which resolved spontaneously within 1-2 months. Presentation with vocal fold ectasias/varicosities and higher vocal demands were significantly correlated with postoperative vocal hematoma.

Long-term survey demonstrated the cumulative failure rates (symptomatic recurrence plus secondary treatment) following VFSI were 28% (for up to 24 months), without significant difference between vocal nodules, polyp and cyst. Time-to-event analysis documented that patients with higher subjective disease severity were significantly associated with more treatment failures after VFSI ($p<0.01$). Prognostic analyses noted that longer symptoms durations (> 12 months) tended to present with less treatment failures after VFSI, for vocal nodules and cysts ($p<0.05$).

Conclusions: VFSI was effective for vocal nodules, polyp and cysts. Comparative effectiveness researches demonstrated that VFSI resulted in more rapid lesion regression than subjects receiving vocal hygiene education in vocal nodules, whereas phonomicrosurgery remains more effective than VFSI in patients of vocal polyps and cysts. Occupational vocal demand, subtypes of vocal nodules, chronicity of clinical symptoms, and the presence of LPR were potential prognostic factors for short-term treatment outcomes of VFSI. Side effects following VFSI were self-limited, including vocal hematoma, triamcinolone deposits, and vocal atrophy. Treatment failure after VFSI were not infrequent, which necessitate further study to explore the potential influence of personal behavioral and psycho-emotional factors on benign vocal lesions.

Keywords: nodules, polyp, cyst, triamcinolone, dexamethasone, laryngopharyngeal reflux, voice, occupation

Abbreviations

(a)OR	(adjusted) Odds ratio
ANOVA	Analysis of variance
CI	Confidene intervals
GRB	Grade, roughness, breathiness
HR	Hazard ratio
LPR	Laryngopharyngeal reflux
MPT	Maximal phonation time
NGGA	Normalized glottal gap area
NHR	Noise to harmonic ratio
RSI	Reflux symptom index
VAS	Visual analogue scale of subjective voice qaulity
VFSI	Vocal fold steroid injection
VHE	Vocal hygiene education
VHI-10	10-item Voice handicap index
VLS	Videolaryngostroboscopy

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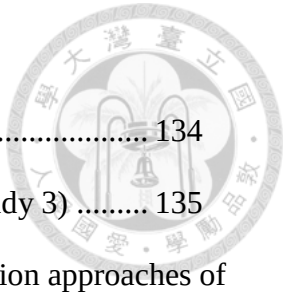


I. Background

Benign vocal fold lesions, such as vocal nodules, polyp, cyst and Reinke's edema, refer to unilateral or bilateral lesions of the mid-membranous portion of vocal fold that lie deep to the normal epithelium (Rosen, et al., 2012). Common clinical presentations of these lesions include dysphonia (i.e., pain or discomfort while speaking), voice fatigue, dryness or tightness of voice, narrowed vocal range, and deteriorated voice quality (husky or breathy character). Most of these patients were related to occupational dependence on voice, noisy working environment, or inappropriate phonation habits, (e.g., hyper-talkative, shouting, etc.). Although pathological examination reveals subtle differences, most of these lesions present as chronic inflammation, and subsequent remodeling of the superficial lamina propria of the vocal folds (i.e., Reinke's space)(Johns, 2003). Management options include a list of conservative and surgical modalities. Generally, clinical treatment initiates with behavioral modifications such as vocal hygiene education (Bailey, et al., 2006), while more active voice/speech therapy conducted via professional therapist may have better treatment outcomes (Leonard, 2009). Medical prescriptions, such as mucolytic and anti-inflammatory agents, may help to relieve clinical symptoms, despite curative effects are seldom achievable. For lesions refractory to conservative managements, phonomicrosurgery can be performed to directly remove the

structural lesions of vocal folds under general anesthesia. However, when compliance with conservative management is poor, when the risk from general anesthesia is high, when the patient is unwilling to have an operation, or in case of recurrence after surgery, clinicians not infrequently encounter with a clinical dilemma where very few options remain for patients.

II. Literature Review

Epidemiology of benign vocal fold lesions

Increasing trend in modern society

Early epidemiology study had reported varying estimates on the prevalence of dysphonia, ranging from 0.65% to 15% (Morley, 1952; Laguaite, 1972). Later report had estimate the prevalence among US to be around 3 to 9% (Ramig & Verdolini, 1998). Recently, another regional telephone survey of 1326 random subjects revealed a current voice disorder of 6.6% and a lifetime prevalence of 29.9% in adults aged less or equal to 65 years (Roy, et al., 2005). Another study based on primary care physicians had demonstrated similar result on life time prevalence of dysphonia (4.3% to 29.1%) and 7.5% of current voice disorders (Cohen, 2010). More recently, two large-scaled claim data-based epidemiological studies had revealed the prevalence rate of voice disorders ranging from 0.26% to 0.98% (Best & Fakhry, 2011; Cohen, et al., 2012). Such wide-ranged estimates on the prevalence of dysphonia may be explained by 1) methodological differences (active telephone/questionnaire survey vs. passive claims data analysis; primary care physician vs. voice specialists); 2) most of the dysphonic event tends to spontaneously regressed over several weeks and therefore, only 5.9% to 22.1% of

dysphonic subjects actually seek medical intervention (Roy, et al., 2005; Cohen, 2010). Although the precise incidence and prevalence of dysphonia may not be concluded based on current knowledge, it is undoubtedly that voice-related disorders account for a considerable part of healthy issue in modern society.

Populations at risk

Human voice is produced by expiratory airflow which creating a periodically vibration of the elastic tissue known as the vocal folds. With cumulative voice loads, vibration overdose results in vocal fold injuries (Titze, 1994). Herein, the most recognized risks for dysphonia are occupational voice overuse, such as salespeople, industrial/factory workers, teachers, clergy, lecturers, singers, etc. (Titze, et al., 1997; Williams, 2003). Among these occupations, teachers are well known to possess higher risk of developing voice disorders and had drawn the most attentions of academic researches (Miller & Verdolini, 1995; Simberg, et al., 2000; Sliwinska-Kowalska, et al., 2006; Chen, et al., 2010; Bermudez de Alvear, et al., 2011). Compared with other occupations, teachers were more likely to report voice problems and negative effects of dysphonia on work performance (e.g. missed work days) (Smith, et al., 1998). Large-scaled studies had revealed the prevalence of current voice disorders was significantly higher in teachers (11%) compared to

non-teachers (6.2%), as was their lifetime prevalence of dysphonia (57.7% in teachers vs. 28.8% in non-teachers) (Roy, et al., 2004).

Female gender is another well-identified risk factor for developing voice disorders, for both general population and occupational voice users (Coyle, et al., 2001; Preciado-Lopez, et al., 2008; Van Houtte, et al., 2010; Bermudez de Alvear, et al., 2011; Best & Fakhry, 2011). Except for the higher pitch of feminine voice (fundamental frequency around 220Hz, in contrast with 120 Hz in male) due to the shorter vocal folds, which associates with more rapid vocal fold vibration; anatomical studies had also reveal a significant difference of the composition of hyaluronic acid, which serve as a primary damper of the oscillatory force upon voice production (Butler, et al., 2001; Ward, et al., 2002). Another study focusing on menopause women had also noted more frequent voice related symptoms, highlighting the potential influence of estrogen on voice production (Schneider, et al., 2004).

Environmental factors may also play roles in the development of voice disorders. Noise is one of the most common-recognized risk factors for developing dysphonia due to the involuntary louder voice compensating the background noise (i.e. the Lombard effect)(Lane & Tranel, 1971). A recent study documented a significant correlation between the indoor noise and the subjective report of voice

disorders (van Houtte, et al., 2012). Investigation had also noticed poor air quality and exposure to dust/chemicals/mold can be related to the occurrence of laryngitis and other voice-related symptoms (Sala, et al., 1996; Patovirta, et al., 2004; Geneid, et al., 2009; Rantala, et al., 2012).

Psycho-emotional factors may also contribute to the development of voice disorders. A nation-wide study had revealed a significant correlation between the presence of voice disorders and the comorbidity of major depression, anxiety, or phobia (Nerriere, et al., 2009). Personal traits (e.g., stress-reactive, aggressiveness, socially dominant) is reported to be closely related to functional dysphonia or vocal nodules, compared with vocal fold paralysis and control subjects (Roy, et al., 2000). Another study had also noticed a strong correlation between certain personality traits (e.g., rush, impatient, nervous) with the presence of voice disorders (van Houtte, et al., 2012). Mild to severe anxiety scores were significantly higher in dysphonic patients, compared with control subjects (Siupsinskiene, et al., 2011); while female subjects seem to be more susceptible to psychological distress (Dietrich, et al., 2008).

Laryngopharyngeal reflux (LPR) had long been recognized to cause chronic injury to the larynx (Koufman, 1991), which usually presented as hoarseness, voice fatigue, throat clearing, globus/lumping sensation. Not only the acidity, but also the

presence of pepsin act synergistically in the inflammation of postcricoid laryngeal mucosa (Ylitalo, et al., 2004), probably via similar mechanism as altered epithelial permeability following hypertonic challenges to the vocal folds epithelium (Sivasankar, et al., 2010). In fact, several studies had pointed out that LPR is one of the most common laryngeal diseases among treatment-seeking population (Coyle, et al., 2001; Van Houtte, et al., 2010). In a recent study using 24-hout pH monitor for definite diagnosis of LPR, a strong relationships between LPR and vocal fold disorders are documented (Chung, et al., 2009), with higher scores of both reflux symptom index (Belafsky, et al., 2002) and reflux finding score (Belafsky, et al., 2001) among patients of Reinke's edema and vocal polyps than subjects without structural lesions, suggesting that LPR might play a role in the pathogenesis of vocal lesions.

Other frequently reported risk factors of developing voice disorders include a list of tobacco smoking (Garrett & Ossoff, 1999; Preciado-Lopez, et al., 2008), caffeinated beverage (Akhtar, et al., 1999; Preciado-Lopez, et al., 2008), drying medications (Verdolini-Marston, et al., 1990; Verdolini-Marston, et al., 1994; Miller & Verdolini, 1995; Witt, et al., 2011), cold air with low humidity (van Houtte, et al., 2012), aging, and frequent upper airway infections (Roy, et al., 2005).

In summary, the development of benign vocal fold disorder shall better be

regarded as combined effects resulting from physiological, psychological, behavioral, and environmental factors. Herein, clinicians shall always consider all dimensions for pathogenesis for tailored management strategies.

Consequences and disease burden

In modern society, more and more occupational professions relied on personal communication. Formal estimates had conservatively estimated that 25% or more working populations rely on voice in their jobs (Speech, 1993), while other researches had indicated a 5 to 20% of the workforce rely on vocal communication (Speech, 1993; Titze, et al., 1997; Roy, et al., 2004; Cohen, et al., 2012). Titze, et al. had further estimated that around 3% of the voice dependent occupations are related to public safety (e.g., police officer, air pilot/navigators) (Titze, et al., 1997). In Spain, vocal nodules in teachers and other professional voice users had been included in the list of occupational diseases since 2006 (Bermudez de Alvear, et al., 2011), and in Poland, voice disorders in teachers accounted for over 25% of all occupational diseases (Sliwinska-Kowalska, et al., 2006). From the society point of view, several studies had pointed out that dysphonia may cause missed work days (Roy, et al., 2004; Van Houtte, et al., 2011), which in turns creat a considerable financial lost and insurance reimbursement (Cohen, et al., 2012). Economic study

had also estimated a $2.5 billion cost of dysphonia related lost works days and treatment expenses (Verdolini & Ramig, 2001).

Voice, as a determinant of a person's well-being, correlates significantly with the patient's quality of life (Merrill, et al., 2011), which can be measured by several psychometrically sound tools (Zraick & Risner, 2008). Recent study subsequently demonstrated that patients with voice-related symptoms correlates with a significantly lowered scores on subscales of physical functioning, general health, bodily pain, fatigue, and role limitation (Merrill, et al., 2011; Merrill, et al., 2013). A meta-analysis on non-neoplastic laryngeal disorders had specifically demonstrated depressed quality of life among neurotic, inflammatory and traumatic laryngeal disorders (Cohen, et al., 2006).

Taiwan studies

Most of the studies in Taiwan focused on occupational vocal users, for example, singing students (張昭明, 1979). Later on, a large study from 5218 teachers of junior high schools had noticed a prevalence rate of vocal nodules to be 7.8% to 11%, which was far more common than the general population (盛華, et al., 1985). This study imply a 2-steps screening method by first introducing questionnaires, followed by professional otolaryngologists examination among teachers with frequent

dysphonic symptoms (e.g., hoarseness and voice fatigue). Except for estimating prevalence, this study had also noticed several risk factors for developing voice disorder among teachers, such as female gender, noise level of the classroom, and workloads (current and cumulative). Compared with age- and gender-matched healthy subjects, teachers were more likely to suffer from voice disorders (30% vs. 10%) and dysphonic symptoms (dry and tight throat, 12% vs. 1%)(董貞吟, et al., 2002). Another study had noticed that teachers from noisy schools (background noise larger than 65dB) were more likely to experience vocal fatigue dysphonic and apply microphone during class than teachers from quite school (background noise less than 55dB)(董貞吟 & 黃乾全, 民國 89 年). More recently, study of 1400 elementary school teachers noted that 35.8% of teachers frequently experienced dysphonic symptoms, while 8.9% of the teachers suffered from persistent hoarseness. (廖國翔, et al., 2005). Around 10.9% of the teachers were diagnosed as structural vocal lesions, such as nodules or polyp. Risk factors for developing dysphonia include cumulative workloads, noise of the classrooms, psychological characters of personality, and poor vocal hygiene. Among these elementary and high school teachers, nearly half of them routinely use microphones in the class and nearly 80% of the teacher had never learned the knowledge of vocal hygiene (王淑俐, 2003), which signify the lack of population awareness of dysphonia in Taiwan.

Preventive strategies on benign vocal fold lesions

Primary & secondary prevention

The key method of prevention the development of vocal disorders relies on awareness of voice dependence with sufficient knowledge for maintaining optimal phonation habit for overall vocal health (Roy, et al., 2001; Thomas & Stemple, 2007; Behlau & Oliveira, 2009). Vocal hygiene education, as the cornerstone for primary preventive strategies, is targeted to reduce speech- and non-speech related risk factors which contribute to the subsequent phonotrauma and the development of benign vocal fold disorders (Behrman, et al., 2008). Principal concepts of vocal hygiene education contain a list of sufficient hydration (Verdolini-Marston, et al., 1990; Verdolini-Marston, et al., 1994; Witt, et al., 2011; Nakagawa, et al., 2012); voice rest (van der Merwe, 2004); avoidance of caffeine-contained drinks (Maughan & Griffin, 2003); cessation of tobacco smoking; avoid misuse of voice such as loud speech, shouting and screaming; treat LPR if presence; avoid frequent throat clearing; voice amplification at work (Roy, et al., 2002); and regular physical exercise (Thomas & Stemple, 2007). Early study had demonstrated significant improvement in kindergarten teachers receiving vocal hygiene education for 2 months, in comparison with control subjects (Chan, 1994). One similar study had also revealed

some benefits of vocal hygiene education among professional voice users (Timmermans, et al., 2003). Another randomized study demonstrated that after 3 months of voice program including lectures on vocal hygiene and a short course of group therapy, experimental group demonstrated significant improvement in various acoustic parameters, compared with control groups (Bovo, et al., 2007). However, other studies had noticed that indirect vocal hygiene education may be less effective than active vocal training programs (Carding, et al., 1999; Roy, et al., 2001; Duffy & Hazlett, 2004; Timmermans, et al., 2004; Behrman, et al., 2008); whereas some studies had failed to discover beneficial effects following vocal hygiene education (Broaddus-Lawrence, et al., 2000; Holmberg, et al., 2001). In summary, despite that vocal hygiene education remains fundamental for primary prevention of benign vocal fold disorders, overall treatment effectiveness can be quite variable and influenced by several contributing factors (e.g., content of educating materials, treatment setting, patient's adherence and motivation, duration of treatment) (Roy, et al., 2001; Ruotsalainen, et al., 2007; Behrman, et al., 2008).

Despite the reported effectiveness of primary prevention using various conservative management, unfortunately, public awareness can be quite low. It has been reported that nearly half of the 237 teachers from kindergarten to high school did not aware that there may be a doctor that can help or a therapy program is

available (Da Costa, et al., 2012). Similar results were obtained in another study which revealed that dysphonic patients scores less on voice care knowledge than healthy voice users (Fletcher, et al., 2007). Even among professional vocalist, reluctance to seek medical intervention is frequent (Gilman, et al., 2009).

Herein, secondary prevention through early screening of voice disorders represents another significant clinical issue, especially for existing structural lesions that necessities more active interventions. Simberg, et al. had proposed a screening method consisting perceptual assessment of voice quality and questionnaire for subjective vocal symptoms (Simberg, et al., 2001), which revealed a 76% positive referral rate for active structural vocal fold disorders. Several recent studies had investigated the potential usefulness of voice handicap index (VHI)(Jacobson, et al., 1997), originally designed as a specific questionnaire to screen voice disorders. A recent study comparing 165 patients of benign vocal pathologies with 65 normal controls had suggested using 12 points as a cutoff point of VHI (polish version) with 98% of sensitivity and 95% of specificity (Niebudek-Bogusz, et al., 2011). A similar study using Persian version of VHI showed similar cut-off value of 14.5 points with 92% of sensitivity and 95% of specificity (Moradi, et al., 2013). Another screening index for voice disorder which comprising 12 symptoms had also demonstrated a good results of 94% sensitivity (specificity: 39%), if the patients had scored more

than 5 symptoms that were always or almost always encountered (Ghirardi, et al., 2013).

Except for the above-mentioned subjective and objective modalities, novel studies tried to detect voice disorders using acoustic signals with automatic computerized calculating algorithms, including 3 main categories (i.e., temporal, frequency and cepstral features) (Muhammad, et al., 2012). Accordingly, numerous studies are published in the recent decade, demonstrating 56% to 93% of accuracy in differentiating normal vs. pathological voices by different measurements parameters (e.g., fundamental frequency, pitch and amplitude perturbation from sustained vowel (Parsa & Jamieson, 2000; Moran, et al., 2006); time-frequency analysis in continuous speech (Umapathy, et al., 2005); first and second derivatives from cepstral vectors (Godino-Llorente, et al., 2006); and automated speech recognition system (Muhammad, et al., 2011).

Tertiary prevention

Once the structural vocal fold disorders are present, modern treatment modalities include a list of conservative and interventional managements, which is helpful to reduce disability, workday loss, and improve life quality. For example, since the development of vocal nodules is closely related to excessive voice use,

voice therapy remains the first-line treatment in most circumstances (Sulica & Behrman, 2003; Bailey, et al., 2006; Schwartz, et al., 2009). Despite the varying techniques across therapists (Leonard, 2009), three main categories of hygienic, symptomatic, and physiologic approaches had been summarized (Thomas & Stemple, 2007). Common symptomatic approaches of voice therapy include pushing exercise to increase vocal loudness, humming method to train relaxed phonation, yawn-sigh approach, auditory and visual feedback, etc. (Colton & Casper, 1996; Laukkanen, et al., 2004). Physiologic approaches for voice therapy focus on holistic consideration of the voice (Thomas & Stemple, 2007); common protocols include confidential voice(Colton & Casper, 1996), functional exercise(Stemple, 1993), resonant therapy(Verdolini, et al., 1998; Chen, et al., 2007), etc. Clinically, numerous studies had documented clinical effectiveness of voice therapy among vocal nodules (Holmberg, et al., 2001; Chen, et al., 2007; Chernobelsky, 2007), while voice therapy can sometimes be effective for other vocal pathologies such as polyps and cysts (Cohen & Garrett, 2007; Nakagawa, et al., 2012; Schindler, et al., 2012).

Most physicians may prescribe medications to relieve dysphonic symptoms, despite the lack of scientific evidence and not routinely recommened by the practice guideline (Schwartz, et al., 2009). A recent sudy on the prescription pattern had demonstrated higher odds of receiving antibiotics when dysphonic patients visting

primary care physicians (Best & Fakhry, 2011; Cohen, et al., 2013); while some laryngologists may prescribe oral or inhaled corticosteroid for for acute dysphonia, especially for professional voice users (Sataloff, et al., 2001; Watts, et al., 2001; Souza, et al., 2013) with several different regimens (Spiegel, et al., 2000; Franco & Andrus, 2007). Other frequent prescriptions from otolaryngologists to dysphonic patients include proton pump inhibitor, mucolytics, muscle relaxant, and histamine 2 antagonists (Best & Fakhry, 2011; Cohen, et al., 2012).

When conservative managements fails, phonomicrosurgery are usually indicated to remove structural vocal fold disorders and restore the layred structure of vocal fold epitehelium and lamina propria. Various instruments and techniques had been gradually evolved over the past centrury (Zeitels, 2001; Rosen & Simpson, 2008); nowadays, it is one of the most common surgical procedures for all otolaryngologists (Wang, et al., 2010). With continual refinements, the clinical effectiveness of phonomicrosurgery had been well-documented in the literatures (Bouchayer & Cornut, 1988; Sataloff, et al., 1995; Bastian, 1996; Zeitels, et al., 2002; Chang & Chang, 2003; Lee & Chiang, 2009).

Limitations

Despite the widely reported effectiveness of voice therapy, the long treatment

course had lowered the patient's adherence, with up to 48% of patients droppped during the treatment course in a recent report (Portone, et al., 2008). Similar drop out rates had also been reported in another study that 43.8% of patients refuse voice therapy, while the remaining patients failed to complete the eight sessions of voice therapy (Woo, et al., 2011). It has been suggested that such higher dropout rates may negatively influence the overall treatment effectiveness of voice therapy (Murry & Woodson, 1992; Franco & Andrus, 2007). In the other way, although short-term corticosteroids are generally safe, prolonged administration (> 2 weeks) might cause systemic side effects(Campagnolo, et al., 2008). Therefore, recent clinical guidelines for hoarseness had recommended against the routine prescription of oral steroids to dysphonic patients (Schwartz, et al., 2009).

From clinical perspectives, phonomicrosurgery had long represented the only available treatment option when conservative managements fail. However, potential adverse effects following laryngeal suspension include injury to the teeth or cervical spine, or tongue paresthesia (Corvo, et al., 2007). Besides, violation of the layered structure of the vocal fold during careless surgery can also result in fibrosis or scarring of the lamina propria (Woo, et al., 1994; Benninger, et al., 1996). Furthermore, it is well known that vocal disorders are prone to recurrence when post-operative vocal hygiene is poorly maintained. Most importantly, it is not infrequently for clinicians to

encounter situations when the risk for general anesthesia is high (e.g. poor cardiopulmonary function), when the patient's will to receive operation is low, when difficult exposure of larynx is anticipated (e.g. retrognathia, short neck, etc.), when the patients cannot tolerate the voice rest period after the surgery (usually 7 days)(Behrman & Sulica, 2003), or when the lesion has recurred after preceding surgeries. In such circumstance, a therapeutic gap existed that nearly no optimal treatment option remains for patients, which remains a dilemma for modern laryngologists.

Vocal fold steroid injection (VFSI) as a tertiary preventive modality

Evolving history

Yanagihara et al. first proposed the concept of direct intralesional steroid injection for benign vocal fold disorders (Yanagihara, et al., 1964). In the original protocol, 2-3 injections of corticosteroid in the office setting using indirect mirror for visual guidance were performed at an interval of 3 days. The authors reported 62.5%~79.6% effective rates among 64 and 49 patients receiving prednisolone or dexamethasone, respectively. Later on, studies had applied percutaneous intralesional injection of triamcinolone on laryngeal stenosis and subglottic stenosis with good results (Rosen & Vered, 1975; Gnanapragasam, 1979). Moreover, intralesional steroid injection has been advocated in the management of inflammatory laryngeal diseases, such as sarcoidosis, systemic lupus erythematosus, and Wegener's granulomatosis (Krespi, et al., 1987; Teitel, et al., 1992; Gulati, et al., 1997). In addition, steroid injection after microsurgical removal of benign vocal fold structural lesions had also been suggested to reduce scar formation during the healing process of microflap (Bouchayer & Cornut, 1988; Courey, et al., 1995).

However, VFSI as an office-based procedure to treat benign vocal fold disorders had not been widely accepted until the past decade, when Tateya et al. made 2 major

refinements to the procedure: 1) enhanced precision of needle placement by flexible fiberscope guidance and 2) triamcinolone, a depot solution with longer effective duration, as the injected regimen.(Tateya, et al., 2003) Since then, a number of published studies have demonstrated that VFSI can be applied to treat many structural vocal fold disorders, such as vocal nodules, polyp, cyst, scar, granuloma and Reinke's edema (Tateya, et al., 2004; Mortensen & Woo, 2006; Hsu, et al., 2009). Meanwhile, compared with surgeries in the operating room under general anesthesia, office-based procedures can be cost-effectiveness(Rees, et al., 2007; Kuo & Halum, 2012), especially under health insurance programs(Bove, et al., 2007; Fang, et al., 2013). Preliminary estimation of the medical cost from Taiwan's medical conditions was provided in Appendix I, which also pointed out potential cost-saving of VFSI than microsurgeries.

Pathophysiology and mechanisms

According to the updated definition and diagnostic guide (Rosen & Murry, 2000), benign vocal fold lesions can be categorized as diffuse or focal, where diffuse lesion refers to Reinke's edema and focal lesions include vocal nodules, cyst, fibrous mass, reactive lesion, and pseudocyst (Rosen, et al., 2012). The development of vocal nodules usually starts from persist voice overuse, which cause edematous, focal

hyperemia and inflammation of vocal folds among the mid-membranous portion, where the maximal shearing and collision forces during phonation occurs (Altman, 2007). Without adequate rest, focal inflammatory reactions, hyperkeratosis of vocal fold vibratory edges may ensue with the resultant mass lesion perceived on clinical endoscopic examinations. Histologically, vocal nodules generally show thickened epithelium, proliferation of fibroblast with abundant fibrin and organized collagen (Kotby, et al., 1988; Wallis, et al., 2004). Immunohistochemical staining also noted rich staining of type IV collagen and fibronectin over the basement membrane zone (Courey, et al., 1996). Molecular study had also demonstrated significant increased messenger RNA expression of interleukin 1beta (IL-1β), transforming growth factor beta-1 (TGFβ1), and cyclooxygenase-2 (COX-2) in rabbits following 30 minutes of raised intensity phonation (Swanson, et al., 2010).

The developments of vocal polyps are mostly resulted from phonotrauma, triggered by aggressive cough during viral illness, shouting, or screaming (Woo, 2009). The pathogenesis are generally considered a preceding capillary rupture with blood accumulation within the Reinke's space, which contributes to the clinical picture of hemorrhagic vocal polyps (Altman, 2007). Following the absorption of oxyhemoglobin, "non-hemorrhagic polyps" with hyalinized stroma may be subsequently observed. Histologically, vocal polyps may present with similar features

as vocal nodules (i.e. fibrin deposition, inflammation, and amyloid-like material accumulation)(Wallis, et al., 2004), with increased level of hypoxia inducible factor-1α and vascular endothelia growth factor (Fang, et al., 2013), probably as a consequences of raise intravascular pressure caused by overvibration of vocal folds (Czerwonka, et al., 2008).

Vocal fold cysts are epithelial-lined lesions with either mucus- or keratin-filled content, usually located at the subepithelial plane of the vocal folds (Woo, 2009). Mucus-retention cyst are more commonly encountered, which represented an obstructed excretory duct with retained mucus of the affected gland. Histologically, mucus retention cyst usually consists of an outer layer of cuboidal cells with an internal layer of ciliated columnar cells (Bouchayer & Cornut, 1988). In the other hand, keratin (epidermoid) cyst may be resulted from congenital ectopic squamous epithelium within the lamina propria, or from the secondary vocal trauma (Martins, et al., 2011). In contrast, pseudocyst represent superficial translucent bleb of vocal fold, which composed of semisolid fluid accumulation (Rosen, et al., 2012). Although clinical diagnoses can sometime be confused by fusiform, non-hemorrhagic polyp; histologically, pseudocyst present with distinguished features of incomplete cyst wall with thinned and atrophic mucosa (Bouchayer & Cornut, 1988).

Reinke's edema is clinically interchangeably nominated with "polypoid corditis",

which illustrating the bilateral, diffuse polypoid appearance of vocal folds (Yonekawa, 1988). The clinical triad of developing Reinke's edema include smoking, acid reflux, and vocal abuse with more than 90% of Reinke's edema are heavy smokers (Rosen & Simpson, 2008). Histopathological features of Reinke's edema featured abundant extruded plasma from the thin-walled, fragile subepithelial neovascularization (Sato, et al., 1999), probably share similar pathogenesis as nasal polyps, which can be cause by fibroblast-producing VEGF to promote angiogenesis under hypoxic conditions (Lin, et al., 2008). Although early disease may be managed by smoking cessation of life style modification, most of the cases requires interventions due to the irreversible changes among the lamina propria.

It is well known that the pharmacological effects of corticosteroids are quite complex (e.g., carbohydrate, protein, and lipid metabolism; increased hepatic capacity for gluconeogenesis; enhanced catabolic actions upon muscle, skin, lymphoid, adipose and connective tissues; immunomodulation via various cytokines on lymphocytes and macrophages, etc.)(Campagnolo, et al., 2008); herein, the mechanism of corticosteroid on benign vocal lesions are commonly attributed to its "anti-inflammatory effects" without detailed investigation. Tracing back the history, Coleman, et al. first conducted laboratorial works in 1999. The authors analyzed the healing process of lateral microflap treated by triamcinolone layered on the operative

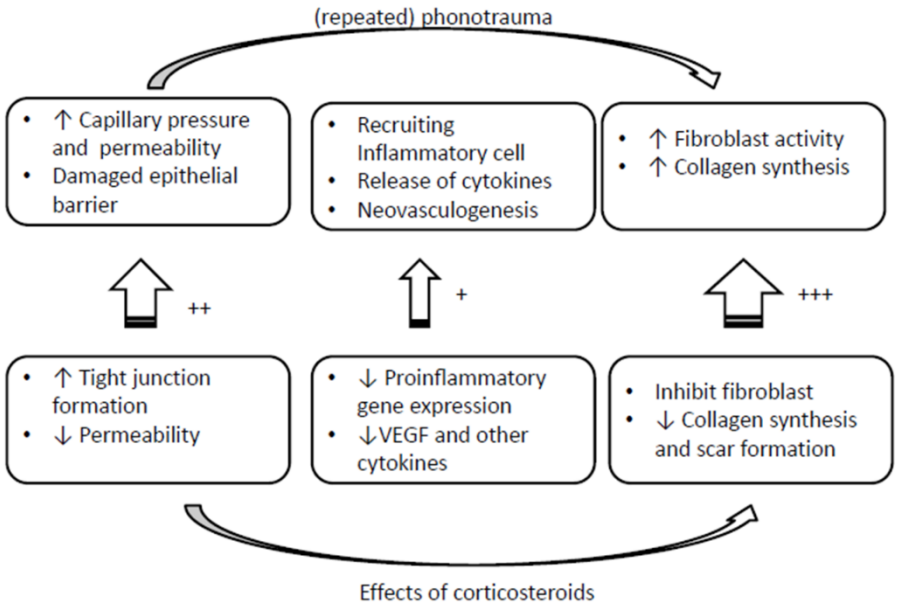
wounds of 15 dogs. In this study, the authors noted a histological 12-day delay in inflammatory responses and a 21-day delay in neovascular responses, measured by hematoxylin and eosin stain and movat's stain, respectively. Subsequent study demonstrated a trend of decreased COX-2 gene expression by prophylactic triamcinolone after acute phonotrauma (Hall, et al., 2012), despite the result did not reach statistical significance. Similar study targeted on the regulatory effects of glucocorticoid on vascular endothelial growth factor in nasal polyposis may also help to explain the potential mechanism of intralesional steroid injection (Yazici, et al., 2013).

According to the studies from keloid and granulation tissue (Meisler, et al., 1997; Wu, et al., 2006), the significant effects of corticosteroid on fibroblast and collagen synthesis may also explain the mechanism of vocal fold steroid injection. In the histological study conducted by Campagnolo, et al., rabbits treated by dexamethasone revealed significantly decreased rates and amount of collagen deposition during the acute healing process (within 7 days) of surgically injured vocal folds (Campagnolo, et al., 2010). Later study had also demonstrated that exogenous dexamethasone can significantly reduce fibroblast proliferation and TGF-ß induced collagen synthesis, in a dose-dependent fashion (Zhou, et al., 2011).

Epithelial barrier function of vocal folds may also accounts for the observed

effects of intralesional steroid injection. Previous study had demonstrated significant obliteration, desquamation, microhole formation, dilated intercellular morphology, decreased occludin and beta-catenin gene expression, after 30-minuted of raised-intensity phonation in the rabbit vocal folds (Rousseau, et al., 2011). Accordingly, it has been proposed that repeated phonotrauma may alter the normal epithelial barrier via altered integrity of intercellular tight junction. Therefore, it may hypothesized that intralesional corticosteroids may reduce inflammatory effects by decreasing cellular permeability, either through its effects on epithelial cell tight junction formation (Zettl, et al., 1992) or through the regulation of proinflammatory cytokines (Aveleira, et al., 2010).

Although the actual mechanism of VFSI are not fully understood by the published literature, it can be proposed that intralesional corticosteroid take effects across the whole inflammatory stages (i.e. reduce capillary permeability immediate after phonotrauma; down-regulate the cytokines during the recruitment of inflammatory cells; and reduced collagen synthesis fibroblast activity to prevent scar/fibrosis formation). Following diagram summarized the current understanding of the mechanism of intralesional corticosteroid on benign vocal fold lesions.



Note: "+, ++, +++" represent strength of evidences

Systematic review and meta-analysis

The literature search was conducted during December, 2011 by searching the electronic databases of PubMed, using the following keywords: vocal fold, vocal cord, larynx, corticosteroid, and injections. After limiting to English literature and human subjects, 78 relevant articles were identified. The inclusion criteria for study recruitment were (1) benign vocal fold lesion, (2) office-based approach for VFSI with endoscopic guide. Studies that applied steroids in other parts of the larynx except for vocal folds, combined steroid injection with other laryngeal microsurgeries, or evaluated chronic inflammatory disorders of the larynx or laryngeal manifestations of systemic diseases were excluded. Review articles and case reports were also excluded. After screening for titles and abstracts, 64 papers were discarded. Full texts of the

remaining articles were retrieved and a further 10 articles were excluded. Another 2 articles were identified using a hand-searching process. Finally, 6 articles were included in the final analysis (Tateya, et al., 2003; Tateya, et al., 2004; Mortensen & Woo, 2006; Hsu, et al., 2009; Lee, et al., 2011; Woo, et al., 2011). Appendix II summarizes the process for literature search and study recruitment, which comprising a total of 321 patients (Wang, et al., 2013).

According to the PRISMA Statement (Moher, et al., 2009), 2 reviewers extracted the data from each study, including authorship, year of publication, study subject, diagnosis, steroid regimen, time points for outcome measurement, follow-up period, side effects and recurrence in a systemic fashion. Reported disease entities suitable for VFSI included Reinke's edema, vocal nodules, polyp/cyst, granuloma and vocal scar. Except for one study using methylprednisolone for VFSI (Mortensen & Woo, 2006), all the other studies injected triamcinolone acetonide into the vocal folds, mostly due to its depot nature and long-standing effects (Tateya, et al., 2004; Hsu, et al., 2009). Suggested voice rest after VFSI ranged from one day to 7 days.

Treatment outcome were clustered into 5 categories, i.e. subjective, aerodynamic, acoustic, perceptual, and endoscopic (Dejonckere, 2000), as detailed in Appendix III. Since all the recruited studies were conducted in a non-randomized fashion with one treatment group only; therefore, study reporting qualities were assessed by the

methodological index for non-randomized studies (MINORS) (Slim, et al., 2003), which constitutes 8 items, rated from 0 to 2 points. The follow-up periods between studies were inconsistent (ranging from 3 weeks to 6 months); therefore, for easier interpretation, extracted outcome measurements were based on information obtained between 3 weeks to 1 month after VFSI. All 6 studies demonstrated subjective improvement after VFSI and the effective rate ranged from 82% to 98%. Specifically, 3 studies used voice handicap index (VHI) to evaluate subjective treatment response, which all demonstrated a significant difference after VFSI ($p<0.05$). Four out of 5 studies measuring aerodynamic outcome showed significant improvements in maximal phonation time (MPT, $p<0.05$), with only one study failing to demonstrate improvement in MPT after VFSI (Woo, et al., 2011). Although this study did not investigate such discordance, a possible explanation might be the inclusion of multiple centers and various disease entities. Three studies conducted complete acoustic analysis and reported significant improvements in jitter and/or shimmer. Two studies demonstrated improved noise to harmonic ratio (NHR), while another study reported non-significant changes in harmonic to noise ratio (HNR). Inclusion of vocal scar in the study population might explain this insignificant result. Two studies compared fundamental frequency (F0) before and after VFSI, with only one significant difference noted among female subjects with Reinke's edema (from 168 to 181 Hz,

$p<0.05$). Three studies had demonstrated significant improvements in perceptual ratings of voice quality (GRBAS scale). Endoscopic evaluation among all 6 studies showed that in 89% to 100% of the patients, the primary lesions had either disappeared or improved after VFSI. Two studies reported details of stroboscopic parameters, including edges of vocal folds, amplitude/propagation of mucosal wave and glottis closure.

Considering different disease entities, in the 2 studies of vocal nodules (Tateya, et al., 2004; Lee, et al., 2011), endoscopic exams revealed that 93% to 100% of the lesions either disappeared or improved after VFSI. Objective measurements using VHI, MPT, MFR, or acoustic analysis also revealed significant improvements (Table I). Tateya et al. performed VFSI on 42 patients of Reinke's edema and demonstrated improvements on subjective, aerodynamic, acoustic and endoscopic evaluations (Tateya, et al., 2003). In the study of vocal polyp (Hsu, et al., 2009), significant treatment effects of VFSI were revealed in all 5 categories of outcome measurements. Subjective improved voice were reported in 12 patients of vocal scar receiving VFSI (Mortensen & Woo, 2006), while quantitative outcome analysis was pooled with other disease entities in another study (Woo, et al., 2011).

Whitish deposition of the injected steroid (triamcinolone) after VFSI was reported in 2 studies (Lee, et al., 2011; Woo, et al., 2011), which mentioned that such

whitish plaques had no effects on vocal fold vibration and that spontaneous resolution usually occurred after 1 to 2 months. Another common complication after VFSI is vocal fold hematoma, as mentioned in 2 studies (Hsu, et al., 2009; Woo, et al., 2011). Four patients (out of 80 subjects) displayed signs of mild vocal fold atrophy with breathy voice 1 month after VFSI (Lee, et al., 2011). Stroboscopy demonstrated decreased amplitude of the mucosal wave and vocal fold bowing. All the patients showed improvement after 2-month follow up.

Recurrence after VFSI was commonly reported in all studies except the study by Mortenson and Woo, and the overall recurrence rate was between 4% and 31%. Time to recurrence ranged from 4 weeks to 9 months after VFSI (Hsu, et al., 2009; Lee, et al., 2011). The predominant reason for recurrence was persistent vocal abuse (Lee, et al., 2011), which can be managed by administering repeated steroid injections with adjuvant voice therapy (Tateya, et al., 2004; Lee, et al., 2011).

The reporting quality of the 6 studies was assessed using MINORS (Slim, et al., 2003), which constitutes 8 items, rated from 0 to 2 points (Appendix IV). Study endpoints were regarded adequate if both objective and subjective measurements were applied (item-4). Unbiased assessment of study endpoints shall be conducted by raters who are blind to the clinical status of the patients (item-5). Owing to the considerable recurrence rate after VFSI, a follow-up period longer than 1 month was

regarded as adequate (item-6). In summary, most of the studies revealed moderate methodological quality, ranging from 6 to 12 points.

Five studies with available numerical results were included in the meta-analysis (Tateya, et al., 2003; Tateya, et al., 2004; Hsu, et al., 2009; Lee, et al., 2011; Woo, et al., 2011). Specifically, maximal phonation time (MPT) was selected as the representative parameter for objective outcome measurements while voice handicap index (VHI) was selected as the representative parameter for subjective outcome measurements. Pooled estimate using random effects model demonstrated a significant increase in MPT after VFSI by 2.04 seconds (95% confidence interval (CI): 0.41 ~ 3.67 seconds). Significant heterogeneity between studies was noticed (I-square=99.7%), most likely derives from the study of Woo et al. Examination of publication bias was performed by Egger's test, which revealed a non-significant result (p=0.81). Pooled analysis of VHI showed a significant decrease of 26.7 points (95% CI: 16.4 ~ 37.0 points). Although significant heterogeneity between studies existed (I-square=99.8%), the directions of VHI changes were the same. We did not perform further subgroup and publication bias analyses because of the limited study numbers.

Modified trans-nasal injection approach of VFSI

Three different approaches for performing VFSI have been introduced in the published literature, including: 1) trans-oral approach with flexible fiberscope (Tateya, et al., 2003; Tateya, et al., 2004); 2) trans-oral injection with rigid telescope (Mortensen & Woo, 2006); and 3) trans-cutaneous via cricothyroid membrane using flexible fiberscope (Hsu, et al., 2009; Lee, et al., 2011; Woo, et al., 2011). Although trans-oral injection avoids penetration of skin and airway mucosa, handling a long and curved needle can be difficult. Besides, the gag reflex tends to be stronger since the needle has to pass through sensitive oropharynx (Tateya, et al., 2003; Tateya, et al., 2004; Mortensen & Woo, 2006). Alternatively, trans-cutaneous approach might offer the advantage of less irritation of pharynx with reduced gag reflex, but penetrating subglottic mucosa may sometimes cause bothersome bleeding intraoperatively (Hsu, et al., 2009). Although subepithelial needle migration through the cricothyroid membrane may avoid mucosal injury, indirect visualization of the needle tip requires significantly greater surgical skills (Lee, et al., 2011; Woo, et al., 2011).

To overcome the drawbacks of exiting transoral and transcutaneous injection approaches, we modified the injection technique using the operating channel of a transnasal flexible laryngoscope (trans-nasal endoscopic steroid injection, TESI). The

original series was conducted between January 2010 and December 2011. We preliminarily performed TESI on 30 outpatients with vocal nodules and polyps. With an experienced resident doctor operating the transnasal flexible laryngoscope (PENTAX, VNL-1570 STK), which was connected to a high-definition video processor (PENTAX EPK-i), the patient was instructed to phonate a sustained "ee" sound when 5ml of 2% lidocaine solution was dripped into the laryngeal introitus. TESI was performed using a specially designed endoscopic injection apparatus (Olympus NM-101C-0427), which includes a reusable metallic external sheath (MAJ-655) and a disposable flexible needle tract with a 27G rigid tip (MAJ-656). Precise placement of needle tip can be assured by the formation of a subepithelial translucent bleb over the Reinke's space (Fig. 1). The duration of the procedure was approximately 10 to 15 minutes. All patients underwent voice rest for 3 days following the procedure to prevent leakage of the injected material.

The original series enrolled 9 men and 21 women. The mean age was 38.2 years, ranging from 24 to 70 years. Vocal nodules and vocal polyps were present in 13 and 17 patients, respectively. All the patients tolerated the procedure well under local anesthesia in an office setting. Vocal fold lesions were completely resolved or much improved in 10 and 19 patients, respectively, 3 months after TESI. MPT measurements significantly increased from 11.0 ± 4.2 seconds before treatment to

13.0 ± 4.7 seconds at 1 month post-treatment ($p<0.05$). MPT measurements at 3 months also revealed significant increases (13.2 ± 4.0 seconds, $p<0.05$, compared with baseline). VHI-10 assessments showed a significant reduction from 22.5 ± 7.3 before injection to 16.4 ± 10.0 points at 1 month post-treatment ($p<0.01$). VHI-10 measurements at 3 months post-treatment remained significantly lower (14.5 ± 13.6 points, $p<0.05$). Acoustic analysis revealed significant improvements in jitter (%) and shimmer (%) for both 1- and 3-month measurements after the procedures. Decreases in NHR values after TESI treatment were not statistically significant from those before treatment ($p>0.05$). Perceptual evaluation of voice quality using the GRB scale also indicated significant improvements after TESI ($p<0.01$). Appendix V summarize the treatment outcomes of transnasal endoscopic steroid injection in our original series (Wang, et al., 2013).

Knowledge gaps

According to the literature review, several knowledge gaps of VFSI are recognized. First, all the published studies of VFSI were conducted in a pre-post study design in the treatment group only, neglecting the possibility of spontaneous lesions regression following voice conservation or phonation habit modification (McCrory, 2001; Cohen & Garrett, 2007; Nakagawa, et al., 2012). Without a control group, these

studies might overestimate the treatment effectiveness of VFSI, since a portion of the vocal lesions tended to regress gradually following conservative management. (McCrory, 2001; Cohen & Garrett, 2007) Similarly, no existing studies had compared the treatment outcomes between VFSI and phonomicrosurgery, which represents the most wide-accepted gold standard treatment of structural vocal lesions, especially for vocal polyp and cyst (Bouchayer & Cornut, 1988; Bastian, 1996; Bailey, et al., 2006; Rosen & Simpson, 2008).

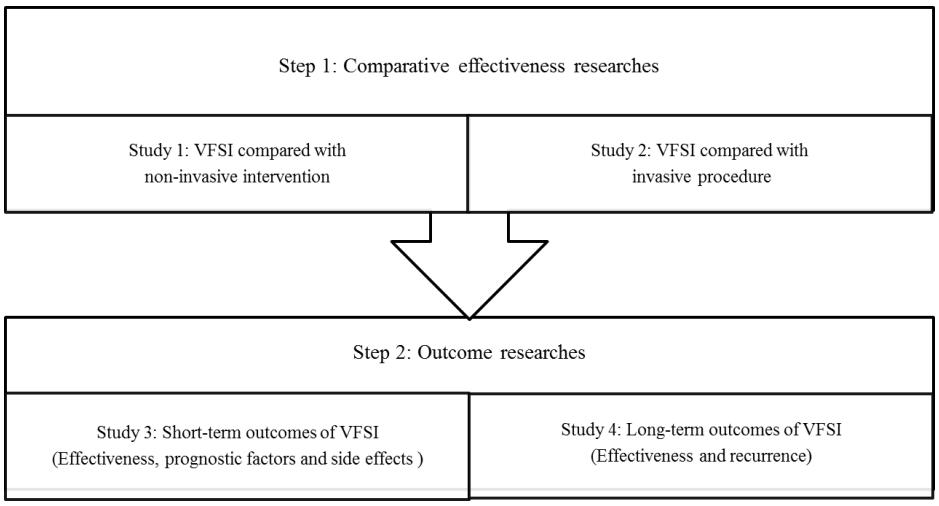
A number of studies have advocated the potential role of VFSI for the treatment of benign vocal fold lesions.(Tateya, et al., 2004; Mortensen & Woo, 2006; Hsu, et al., 2009) However, few studies have investigated the treatment outcomes between different disease entities. Moreover, the prognostic factors of VFSI, such as the duration of clinical symptoms, laryngopharyngeal reflux (LPR), and occupational vocal demands, were not investigated before. Treatment outcomes for other vocal fold lesions (e.g. mucus retention cyst and fibrous mass) had rarely been reported in details. Despite adverse effects were reported in the previous studies (i.e. deposit of the material (triamcinolone), vocal fold hematoma, and vocal atrophy), the incidence rates varied widely and no study had investigate the associated risk factors so far. Finally, since most of the vocal fold diseases are closed related to personality and occupational vocal demand, such lesions had a strong tendency for recurrence.

However, the longest follow-up period in published literatures was 6 months (Appendix III), and no study had systematically evaluated the long-term results following VFSI so far.

Purposes of studies

The primary purpose of this thesis is applying evidence-based, epidemiological methods to fulfill the knowledge gaps on existing literatures of VFSI. Specifically, this study intends to:

1) Compare the clinical effectiveness of VFSI with non-invasive intervention (i.e. vocal hygiene education) and invasive procedure (i.e. phonomicrosurgery) respectively;
2) Investigate the treatment outcomes following VFSI, with specific focus on short-term effectiveness for various diagnostic groups, prognostic factors, side effects, and long-term effectiveness and recurrence.



III. Methods and Results

[Study 1] Comparative effectiveness research: VFSI vs. non-invasive intervention

In previous meta-analysis, we have documented objective and subjective improvements following vocal fold steroid injections (VFSI) in benign vocal fold lesions (Wang, et al., 2013). However, all these published studies of VFSI were conducted in a pre-post study design that included only one treatment group, neglecting the possibility that part of the vocal lesions may resolve spontaneously following voice conservation or phonation habit modification. Therefore, this study intends to objectively quantify and compare the regression rates of vocal lesions in patients receiving vocal fold steroid injection (VFSI) with patients who received non-invasive intervention (i.e. vocal hygiene education (VHE)).

Materials and Methods

In this study, we retrospectively collected data on patients with benign vocal lesions (i.e. vocal nodules and polyps) treated at Far Eastern Memorial Hospital from January 2009 to December 2011. A detailed history concerning dysphonia was recorded using a self-completing questionnaire during the first clinical visit of the patient (Appendix VI). After detailed explanation of the currently available

management modalities, all the patients chose their own treatment. The recorded data included age, gender, duration of clinical symptoms, and 10-item voice handicap index (VHI-10, Mandarin Chinese version, Appendix VII) (Rosen, et al., 2004; 王南梅, et al., 民100). Clinical diagnoses of vocal pathology were based on videolaryngostroboscopic (VLS) exams. The diagnostic criteria for vocal nodules are bilateral symmetric mid-membranous lesions with minimal reduction of mucosal wave (Rosen & Murry, 2000). Vocal polyps are categorized as hemorrhagic and non-hemorrhagic. Patients who had received phonomicrosurgery previously within 1 year and patients with a follow-up period less than 2 months were excluded.

VFSI was performed after adequate local anesthesia of the pharynx and larynx, by spraying 2% lidocaine over soft palate, posterior pharyngeal wall, tongue base, and vallecula, followed by laryngeal gargling using 5 ml of 2% lidocaine (Wang, et al., 2012). Afterward, the patient was instructed to pull out and hold the tongue, while the surgeon uses the non-dominant hand to operate the rigid laryngoscope (Mortensen & Woo, 2006). Under visual guidance, 0.1 ml, 1:1 mixture of triamcinolone acetonide (10 mg/mL) and dexamethasone sodium phosphate (5mg/mL) was injected by curved injection needle (Model 16-50050, Medtronix, Xomed) into the Reinke's space of the vocal lesions. For patients intolerable to the above transoral procedure, transnasal injection via the working channel of a flexible nasopharyngoscope can be applied

instead (Wang, et al., 2013). All the patients received post-operative voice rest for 3 days.

Vocal hygiene education were conducted by medical doctors with a printed document handed to the patients (Appendix VIII), including phonation habit modification, microphone amplification at work, regular physical exercise, adequate hydration, avoidance of throat-clearing, and sufficient rest. These concepts were highlighted, and reviewed repeatedly during each of the following clinical visits.

Objective measurement of the lesion size was based on pre- and post-treatment VLS exams before, 1, and 2 months after the treatment. Still images of the lesions were captured with identical sizes (1366 X 768 pixels), and the lesion area was circumscribed using ImageJ software (National Institute of Health, Bethesda, USA). To correct for the variability of lesion size based on the distance from the endoscope tip to the vocal cords, adjusted lesion sizes were calculated (circumscribed lesion area divided by the length of the vocal fold, which was defined by the distance between anterior commissure and the posterior end of vocal process)(Mallur, et al., 2011). To ensure the consistency of the vocal fold length, the open angle between bilateral vocal folds were measured, and an angle of more than 40˚ was considered adequate (Mallur, et al., 2011). Fig. 2 demonstrates the measurements of the lesion area, vocal fold length, and the open angle of bilateral vocal folds.

Treatment effectiveness was evaluated by comparing the adjusted lesion sizes of pre- and post-treatment measurements using paired *t*-tests. Sizes and reduction rates between patients receiving either VFSI or VHE were compared using Student's *t*-test. A p value < .05 was considered statistically significant. All statistical analyses were conducted by SAS software, version 9.2 (SAS Institute, Inc. Cary, NC).

Results

This study recruited 176 patients with benign vocal lesions, including 39 men and 137 women. The mean age was 40 years (standard deviation 12 y; range 19 – 70 y). Vocal nodules were diagnosed in 76 patients, whereas polyps were diagnosed in the other 100 patients, including hemorrhagic polyps in 28 and non-hemorrhagic polyps in 72. Ninety-two patients received VFSI, and the other 84 patients received VHE. High occupational vocal demands were reported in 75 patients, consisting mainly of teachers (39%), sales people (18%), customer service agents (17%), and performing artists (7%). Comparisons of the underlying characteristics of the VFSI and VHE groups demonstrated non-significant differences in the distributions of age, gender, duration of clinical symptoms, occupational voice dependence, pre-treatment lesion sizes, and VHI-10 scores (Table 1).

For patients who received VFSI, the mean reduction rate of vocal lesions

measured at 1 month was 39% (95% confidence interval [CI]: 30% ~ 49%); as compared with 6% in those who received VHE (95% CI: -4% ~ 17%, the negative value representing lesion enlargement), the difference was statistically significant (Table 1, $p<0.01$, Student's *t*-test). Although the mean reduction rate in the VHE group at 2 months increased to 24% (95% CI: 9% ~ 39%), it was still significantly lower than the regression rate of the VFSI group at 2 months (46%, 95% CI: 34% ~ 58%, Table 1, $p=0.02$, Student's *t*-test). Ten (11%) out of the 92 patients who initially received VFSI underwent an additional treatment modality, including angiolytic laser (Wang, et al., 2013) in 3 and phonomicrosurgery in 7. In contrast, 36 (43%) out of the 84 patients who were initially treated by VHE received another management, including angiolytic laser in 3, VFSI in 18, and phonomicrosurgery in 15.

The records of VHI-10 scores were available in 49 patients receiving VFSI, which demonstrated a significant reduction from 24.4 points (95% CI: 22.3 ~ 26.6) preoperatively to 14.9 points (95% CI: 12.2 ~ 17.5) at 2 months postoperatively ($p<0.01$, paired *t*-test). Although the VHI-10 scores among the 47 patients receiving VHE had also revealed a significant decrease from 23.0 points (95% CI: 21.0 ~ 24.9) before to 20.4 points (95% CI: 17.8 ~ 22.9), 2 months after the treatment ($p=0.04$, paired *t*-test); the improvement of VHI-10 scores following VHE was significantly lower than that after VFSI ($p<0.01$, Student's *t*-test).

In the 33 patients with vocal nodules treated by VFSI, the adjusted lesion sizes reduced significantly at 1 month and 2 months (Fig. 3, $p<0.01$, paired *t*-test, compared with baseline). In contrast, for 43 patients with vocal nodules treated by VHE, lesion sizes did not regress significantly 1 month after VHE ($p=0.10$, paired *t*-test); however, a significant reduction in lesion sizes was noted at 2 months ($p=0.01$, paired *t*-test). A comparison of the reduction rate between VFSI and VHE groups revealed a significant difference at 1 month (Fig. 3, 42% vs. 9%, $p=0.01$, Student's *t*-test). At 2 months, the reduction rates for both groups were similar, without a statistically significant difference (Fig. 3, 37% vs. 26%, $p=0.51$, Student's *t*-test).

In 100 patients with vocal polyps, 59 received VFSI and the treatment outcomes demonstrated a significant reduction of lesion sizes at 1- and 2-month follow-ups (Fig. 3, $p<0.01$, paired *t*-test). Although the lesion sizes also reduced in the other 41 patients with vocal polyps following VHE, the difference from baseline was not statistically significant at 1- and 2-month follow-ups ($p>0.05$, paired *t*-test). Comparison of the reduction rates revealed significantly greater therapeutic effects following VFSI than VHE at both 1- and 2-month follow-ups (Fig. 3, 38% vs. 4% and 50% vs. 22% for 1- and 2-month results, respectively; $p<0.01$, Student's *t*-test).

[Study 2] Comparative effectiveness research: VFSI vs. invasive procedures

Previous studies primarily focused on providing reliable evidential support of VFSI, based on the comparison of benign lesion regression following VFSI and vocal hygiene education (VHE) (study 1). In reality, vocal hygiene education denotes the minimal requirement of medical care for dysphonic patients and are mostly recommended for patients of vocal nodules.(Bailey, et al., 2006) Since non-invasive management alone is less effective for structural lesions such as vocal polyps and cyst, phonomicrosurgery remains the primary treatment modality applied by most otolaryngologists (Bouchayer & Cornut, 1988; Rosen & Simpson, 2008). Therefore, this study intends to compare the effectiveness between VFSI and phonomicrosurgery in patients of vocal polyp and cyst.

Materials and Methods

Subjects

This study recruited consecutive dysphonic patients who had received VFSI or phonomicrosurgery as the primary treatment modality for benign vocal fold lesions from January 2012 to December 2013. The inclusion criteria include vocal polyp and mucus retention cyst. Patients with keratin cyst, pseudocyst, and patients who

received previous phonomicrosurgery were excluded. Other exclusion criteria include previous radiotherapy to the neck and systemic autoimmune diseases. Clinical diagnoses were based on the appearance of vocal fold edge and the vibratory property of mucosa (i.e. the mucosa wave) revealed by videolaryngostroboscopy (VLS), based on the published nomenclature and diagnostic paradigm (Rosen, et al., 2012). Vocal polyps were further classified as hemorrhagic (vascular), fusiform (wide-based), pedunculated and fibrous (Woo, 2009). For patients receiving phonomicrosurgery, operative findings retrieve from medical records denote the definite diagnosis.

Data collection

A detailed history concerning dysphonia was recorded using a self-completing questionnaire during the first clinical visit of the patient (Appendix VI). The collected data include age, gender, duration of dysphonia, smoking, alcohol consumption, occupational vocal demand, medical comorbidity (i.e. Diabetes Mellitus, hypertension, and cardiovascular disease), 10-item voice handicap index (VHI-10)(Appendix VII), and Reflux Symptom Index (王仲祺，民國 98 年 7 月), Appendix IX). Subjects with RSI scores more than 13 points were defined as positive for laryngopharyngeal reflux (LPR) (Belafsky, et al., 2002). For subjects without retrievable RSI scores, we define the presence of LPR by the presence of

self-reported heartburn during the initial clinical visits. We reviewed the occupations of each patient and classified them into 1) professional (i.e. singers, actor/actress, radio broadcast, and singing student); 2) high (teachers, clergy, lecturer, sales, tour guide, aerobic exercise coach, and patients who work in noisy environment; or 3) routine (others), as suggested in the literature (Behrman, et al., 2004). Professional voice users and patients with high occupational vocal demands who subjectively reported “always” on a 4-point Likert scale (always, often, occasional, and no need, Appendix VI) of vocal usage were defined as “high” occupational vocal demand, while the others were clustered as “routine” occupational vocal demand.

Interventions

The details of injection procedures were illustrated previously in study 1. For the patients received phonomicrosurgery, the procedures were conducted under general anesthesia after the data of routine blood tests, chest radiograph and electrocardiograph were evaluated. The patients were admitted 1 day prior to the procedure and discharged on the same day of surgery, or the operation was performed on an out-patient basis. General anesthesia was conducted using a small-caliber endotracheal tube (#5.0/5.5 for female subjects, #5.5/6.0 for male subjects). Under direct suspension laryngoscopy with operating microscopic magnification, grasping and cutting of the exophytic vocal polyps were performed bimanually (Woo, 2009).

For lesions with involvement of the Reinke's space (e.g. larger vocal polyps and mucus retention cyst) of vocal folds, surgery was conducted using a microflap technique followed by careful dissecting of the lesion without damaging the layered structure of vocal folds (Bouchayer & Cornut, 1988; Zeitels, 2001; Rosen & Simpson, 2008). Cystic capsule, if identifiable, were dissected and removed (Bouchayer & Cornut, 1988). The goal of phonomicrosurgery is to leave the free margins of the vocal folds straight, while avoiding injury to the vocal ligament and excessive removal of the mucosal cover and lamina propria. Complete voice rest for 7 days was prescribed after the surgery (Behrman & Sulica, 2003).

Outcome evaluation

Treatment outcomes were evaluated before, 1 month and 2 months after the procedure, including (1) perceptual rating of voice quality; (2) acoustic measurement of the speech signal; (3) patient reported outcomes; (4) aerodynamic measurement of phonation efficiency, and (5) endoscopic evaluation of VF appearance and mucosal wave propagation (Dejonckere, 2000; Carding, et al., 2009). Perceptual evaluation of voice quality was performed using the GRB scale and scored as 0: normal, 1: slightly deviated, 2: moderately deviated, and 3: extremely deviated (Hirano, 1981). In details, G (grade) represents the overall voice quality; R (roughness) denotes the irregularity of speaking voice, usually resulted from over-contact of bilateral vocal

folds; and B (breathiness) illustrates the airy/breathy character of voice, usually resulted from incomplete glottic closure. The three scores were summed for easier statistical computation subsequently.

Acoustic analysis was conducted by recording a 3-s sample of the sustained vowel sound /a:/ at a comfortable level of loudness, with a microphone-to-mouth distance of approximately 15-20 centimeters, using a high-quality microphone (Model: SM58, SHURE) with a digital amplifier (Model: X2u, SHURE). Computerized multidimensional voice program (MDVP, Model 4500, Kay Elematrics Corp. Lincoln Park, NJ) was used to analyze parameters including jitter (i.e. cycle-to-cycle frequency perturbation), shimmer (i.e. cycle-to-cycle amplitude perturbation), and noise-to-harmonic ratio (NHR).

Aerodynamic measurement was performed by instructing the patient to produce the /a:/ sound for as long as possible after deep inspiration and at a spontaneous, comfortable pitch and loudness level. We recorded the longest time from three consequent trials (i.e. the maximal phonation time, MPT).

The patient-reported outcome included a visual analogue scale of voice quality (ranged from 0(worst) to 10(best))(Aaby & Heimdal, 2013; Carroll, et al., 2013), subjectively perceived resolution of clinical symptoms (categorized as complete remission, more than 50% improvement, 50% improvement or less, no effect or

worsening), and Mandarin-Chinese version of VHI-10. (Rosen, et al., 2004; Lam, et al., 2006; 王南梅, et al., 民 100)(Appendix VII).

Vibratory capacity of vocal fold were evaluated using videolaryngostroboscopy (VLS), which was conducted by instructing the patient to phonate a sustained /ee/ sound with habitual pitch and intensity, using a 70° rigid endoscope and a 3-chip CCD camera (Model 2706CA and 20222120, KARL STORZ, Germany) or a digital laryngoscope with the corresponding video processor (VNL-1590 STi and EPK-i, PENTAX). Each session of the VLS test was digitally recorded onto a portable hard disk using a computerized video processor (NHX-B10, Grass Valley Inc., USA). We objectively measured the mobile part of the membranous vocal fold by capturing video clips of maximally opened and closed phases during phonation, and we measured the glottal gap area with correction to the vocal fold length (i.e., normalized glottal gap area (NGGA, Fig. 4), Image J software, version 1.44, National Institute of Mental Health, Bethesda, Maryland, USA.); we then subtracted the open phase from the closed phase NGGA (i.e., dynamic NGGA) (Omori, et al., 1996; Ivey, et al., 2008). Subsequently, improvements to the mucosal wave could be calculated by comparing the pre- and post-treatment dynamic NGGAs (Pei, et al., 2014).

Comparison between the treatment groups

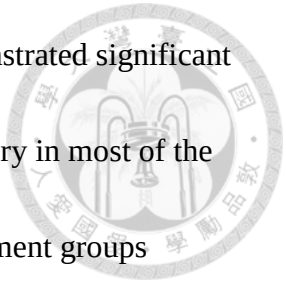
Since the treatments of VFSI and phonomicrosurgery were not randomly allocated, the existence of heterogeneity between the two groups of patients was inevitable. Considering the potential influence of baseline factors on the treatment outcomes (e.g. size of lesion, subjective disease severity, endoscopic appearance), we calculated the propensity score, which represents the probability of assignment to a particular treatment option based on the observed covariates (Rosenbaum & Rubin, 1983; D'Agostino, 1998). The procedure began with a multiple logistic regression model to determine the likelihood of receiving phonomicrosurgery (i.e. the propensity score, ranging from 0 to 1), as a function of all the recruited confounding factors (i.e. age, gender, pre-treatment lesion sizes, duration of clinical symptoms, DM, hypertension, and cardiovascular disease, reflux symptom index, sum of GRB scores, VHI-10, occupational voice dependence, and the size of vocal lesion). In order to decrease the biases due to the uneven distribution of the confounding factors and to obtain a more reliable comparative results, we trimmed the cases with extreme, non-overlapped values of the propensity scores, which represents removing those subjects who are always or never treated by certain modality, in order to approximate baseline equivalence of patients (Glynn, et al., 2006; Patorno, et al., 2013).

Statistics

Missing values of maximal phonation time and visual analogue scale (VAS) were managed by filling the median values from patients with similar VHI scores. Missing values of GRB scores were filled by the median of the corresponding diagnosis and treatment groups. A comparison of the baseline characteristics and treatment outcomes in the two treatment groups was conducted using Student's t-test and trend test for continuous and ordinal parameters, respectively. Pre- and post-treatment measurements were evaluated using paired t-tests. A p value < .05 was considered statistically significant. All statistical analyses were conducted by SAS software, version 9.3 (SAS Institute, Inc. Cary, NC).

Results

This study recruited 107 patients of vocal polyps, including 47 patients receiving VFSI while the other 60 patients received phonomicrosurgery. Baseline characteristics among patients of vocal polyps were illustrated in Table 2, which demonstrated significant heterogeneity between the 2 treatment groups, including gender, cigarette smoking, alchohol consumption, type of vocal polyp, lesion size, and GRB scores. In short, male patients, smokers, patients with larger hemorrhagic vocal polyps and worse voice quality tend to receive phonomicrosurgery than VFSI.



Crude treatment outcomes measured at 1 and 2 months demonstrated significant improvements from baseline following VFSI and phonomicrosurgery in most of the measuring parameters (Table 3). Comparing between the two treatment groups demonstrated higher lesion regression on endoscopic evaluation, and more improvements from baseline on MPT and GRB scores in phonomicrosurgery than VFSI, 1 months post-operatively ($p<0.05$, Table 3, middle column). Two months after the procedures, phonomicrosurgery also demonstrated higher lesion regression, lower VHI scores, and better voice quality (GRB scores, jitter and shimmer) than subjects receiving phonomicrosurgery, as well as higher change values from the baseline measurements ($p<0.05$, Table 3, right column).

As mentioned earlier, since the composition of patient characteristics, disease severity, and lesion morphologies are quite different between the two groups (Table 2), direct comparison of the crude treatment outcomes may yield biased results. In order to decrease the heterogeneity at baseline, we calculate the propensity scores between the two treatment groups and remove the patients with extreme, non-overlapped values (Appendix X). Table 4 demonstrated balanced baseline composition between the two groups. Among the propensity score-trimmed subjects of vocal polyps, 1-month treatment outcome showed higher improvement of GRB scores from the baseline measurements among subjects receiving microsurgery than

VFSI ($p<0.05$, Table 5, middle column). Similarly, 2-month results also revealed significant lower GRB scores, as well as more improvement from the baseline among subjects receiving microsurgery than VFSI ($p<0.05$, Table 5, right column). Endoscopic evaluation of lesion regression also demonstrated more favorable recovery of microsurgery than VFSI ($p<0.01$, trend test).

In the 51 patients of vocal fold mucus retention cyst, comparison of the baseline characteristics also revealed significant differences on MPT, VHI-10, self-rating of voice quality, GRB scores and jitter (Table 6). Crude treatment outcomes demonstrated significant improvements following either VFSI or phonomicrosurgery in most measured parameters (Table 7). Comparing between the two treatments demonstrated more improvements on endoscopic evaluation and higher change values of VHI-10 and GRB scores from the baseline measurements among patients receiving microsurgery than VFSI, 1 month after the procedures (Table 7, middle column). Two months later, microsurgery also demonstrated significant higher change values of self-rating voice quality and VHI-10 scores from baseline, compared with patients receiving VFSI (Table 7, right column, $p<0.05$).

In order to decrease baseline heterogeneity and improve the clinical equipoise between the two treatment groups, we also trimmed the patients with extreme, non-overlapped values of propensity scores (Appendix X). Table 8 demonstrated the

recomposed groups of patients with only slight differences remained on the baseline values of jitter. Subsequent analyses demonstrated significantly higher improvements on endoscopic evaluation and the vibratory properties of vocal folds (dynamic NGGA), as well as higher change values of MPT, 1 month post-operatively (Table 9, middle column). Two months after the procedures, no significant differences existed between the two treatment groups of vocal cysts receiving VFSI or phonomicrosurgery (Table 9, right column).

[Study 3] Short-term outcomes of VFSI

Study 1 and 2 had compared the treatment effectiveness between VFSI and non-invasive modality (patients receiving vocal hygiene education) and invasive modality (patients receiving phonomicrosurgery). This study intends to further explore the treatment outcomes between different disease entities, and the prognostic factors, such as subtypes of vocal lesion, duration of clinical symptoms, laryngopharyngeal reflux (LPR), and occupational vocal demands. Furthermore, the other objective of this study is to investigate the incident rates and risk factors for side effects after VFSI, which had not been thoroughly reported before.

Materials and Methods

Subjects

The study populations in this study are patients who received VFSI from January 2012 to December 2013 at Far Eastern Memorial Hospital. The inclusion criteria include vocal nodules, polyp, mucus retention cyst, Reinke's edema, fibrous mass and pseudocyst. Clinical diagnoses and subtypes of vocal polyps were illustrated previously in study 2. Vocal nodules were further classified as 1) soft (i.e., mid-membranous thickening without fibrotic change of the epithelium or limitation of the mucosal wave) or 2) hard (i.e., hyperkeratosis of the epithelium, fibrotic

appearance with some limitation of mucosal wave propagation) (Allen, et al., 1991; Shah, et al., 2008). Secondary lesions (e.g. reactive nodules, anterior commissure microweb, sulcus vocalis, etc), if present, was recorded as well. Patients who were lost right after the treatments (without any available follow-up records) were also excluded. All the clinical and demographical factors had been collected in the initial clinical visit, as illustrated in study 2.

Treatment outcomes and prognostic factors of VFSI

In order to investigate the prognostic factors on short-term treatment outcomes, we defined "responder" of VFSI as: 1) post-operative VHI-10 scores <=10 points, which denoted the upper limit from normal population (Lam, et al., 2006; 王南梅, et al., 民 100) and 2) GRB scores <=1, which represents objective rating of normal voice quality (Lee & Chiang, 2009). We selected the first clinical follow-up within one month post-operatively as the primary outcome to avoid the influence of lost subjects. For subjects who missed the first clinical follow-up, the results from the second follow-up between 1 to 2 months were applied instead. Analyzed prognostic factors include gender, duration of clinical symptoms (>12 months vs. ≤ 12 months), occupational vocal demand (high vs. routine), cigarette smoking (active smoker vs. ever/non-smokers), laryngopharyngeal reflux (LPR), and subtypes of vocal lesions. (Behrman, et al., 2004; Yun, et al., 2007; Nakagawa, et al., 2012)

Numerical treatment outcome measured at 1 and 2 months post-operatively (e.g. MPT and VHI-10) were analyzed using paired t tests. Comparative effectiveness between different diagnoses was evaluated via one-way analysis of variance (ANOVA). Since each disease entity represents different etiology and disease course, we analyzed the prognostic factors separately. Univariate analysis was conducted between the responding vs. non-responding groups, using chi-square test. Multivariate analyses were subsequently conducted via multiple logistic regression to verify the significance of prognostic factors. A p value less than 0.05 indicated statistical significance. All statistical analyses were conducted by SAS software, version 9.3 (SAS Institute, Inc. Cary, NC).

Risk factors for developing post-operative side effects

Side effects following VFSI were identified by reviewing video recordings post-operatively, including 1) vocal fold hematoma surrounding the injection sites; 2) deposit of injected material (triamcinolone), which was defined as the presence of whitish plaque over the Reinke's space, with minimal to moderate influence of the vibration of mucosal wave; and 3) vocal fold atrophy, which was defined as "bowing" of vocal fold(s) with the presence of glottic gap and atrophic thyroarytenoid muscle.

According to the literatures, microvascular lesions such as ectasias and varices can cause repeated vocal fold hematoma with resulting hemorrhagic vocal polyps

(Hsiung, et al., 2003; Hirano, et al., 2006; Zeitels, et al., 2006). Herein, we reviewed the videolaryngostroboscopy (VLS) recordings to identify the presence of ectasias (defined as spheroidal, tangible subepithelial hemangioma) and varices (defined as enlarged, aberrant, and tortuous vessels.). Other potential significance of risk factors for developing side effects following VFSI were investigated in similar fashions as illustrated earlier.

Results

Short-term outcomes

This study recruited 148 patients receiving VFSI, including 49 nodules, 47 polyps, 30 cyst, 12 Reinke's edema, 5 fibrous mass and 5 pseudocyst. The mean age was 40 years (standard deviation: 10 year; range: 18 – 69 year). Subtypes of vocal nodules include soft nodules in 32 patient and hard, fibrotic nodules in the other 17 patients. Subtypes of vocal polyps consisted hemorrhagic polyp in 3, fusiform (wide-based) in 35, pedunculated in 3, and fibrotic in 6. Secondary lesions were presented in 37 patients, including reactive nodules in 29, anterior commissure microweb in 1, sulcus vocalis in 3, and vocal atrophy in 4 patients. High occupational vocal demands were reported in 75 patients, consisting mainly of teachers (26%), sales people (7%), customer service agents (25%), performing artists

(6%), and others. Clinical duration of dysphonic symptoms are 15 months (mean value, standard deviation: 25 months).

More than 80% of the patients of vocal nodules reported subjective improvements of clinical symptoms 1 month and 2 months after receiving VFSI (Table 10, left column). Similarly, subjective improvements of dysphonia had been reported in up to 90% of the patients of vocal polyps and cysts (middle and right column). VLS exams had also revealed decreased lesion sizes for more than 80% of the vocal nodules, polyp and cyst, as well as significantly improved vibratory capacities as measured by dynamic NGGA ($p<0.01$, paired t test, Table 10).

Treatment outcomes demonstrated significant improvements of VAS, VHI-10, and GRB scores following VFSI in all 3 diagnoses ($p<0.01$, paired t test, Fig. 5). Comparing the change values from the baseline measurements showed non-significant differences of both 1 and 2-month measurements ($p>0.05$, ANOVA tests, Table 10). Although significant improvements in MPT 1 month post-operation were revealed in all three disease categories ($p<0.05$, paired t test), the 2-month results did not reach statistical significance (Table 10). Other parameters, including jitter, shimmer and NHR, showed more universal improvements upon vocal cysts, followed by partial improvements for vocal polyps and minimal improvements for vocal nodules (Table 10). Comparing the change values of all the acoustic parameters from

the baseline measurements all demonstrated similar effectiveness without significant differences ($p>0.05$, ANOVA tests).

The treatment outcome of VFSI for Reinke's edema, fibrous mass, and pseudocyst were less significant (Table 11), and further comparison of treatment effectiveness were not performed, due to limited case numbers.

Side effects following VFSI

Following VFSI, the most common side effects was hematoma (37 out of 148 patients, 25%), followed by deposits of triamcinolone (7 cases, 5%) (Fig. 6a and 6b). Both conditions generally presented with dysphonia, increased phonation effort, and occasionally, decreased voice quality compared with preoperative status. VLS tended to reveal decreased amplitude and asymmetry of mucosal waves. Clinical observation showed that all side effects resolved spontaneously within 2 months, leaving no sequel. We observed one case of pseudocyst with a breathy voice and increased phonation effort after VFSI. VLS showed bowing of the vocal folds with prominent glottic gap and ventricles. Two months afterward, her symptoms resolved, and follow-up endoscopy showed recovery of her baseline vocal fold mass (Fig. 6c). The overall incidence rates for developing postoperative side effects are 32 %, with no significant differences between the 3 main disease entities. We also compared the treatment outcomes between subjects present and absent with post-VFSI side effects (Table 12), which demonstrated that subjects with side effects present with shorter phonation time,

2 months post-operatively (10.0 ± 2.9 vs. 12.3 ± 4.9, $p<0.01$, Student's t test), while the other parameters showed non-significant differences.

Univariate and multivariate analyses revealed that presentation with vocal fold ectasias and varicosities was significantly correlated with post-operative vocal hematoma ($p<0.05$, Table 13). Meanwhile, multivariate analysis also identified that subjects with high occupational vocal demands were also more likely to develop vocal hematoma following VFSI ($p<0.05$). Other clinical factors, including gender, smoking, hypertension, and LPR, all showed non-significant correlation with post-operative vocal hematomas (Table 13). Subsequent analyses of the potential risk factors for triamcinolone deposits and vocal atrophy were not performed because of the limited sample.

Comparison between trans-oral and trans-nasal injection approaches

Among the 148 patients receiving VFSI, trans-oral approach with rigid telescope guidance was performed in 117 patients, wheras trans-nasal approach via the working channel of flexible nasopharyngoscope was performed in the other 31 patients. Baseline characters between the two treatment groups did not reveal significant differences ($p>0.05$, Table 14). The mean duration for both injection approaches are similarly around 10 minutes, and the treatment processes also revealed similar precision. However, available records of the discomfort level (in 82 patients) during

the injection procedures were significantly higher in trans-nasal approach, compared with trans-oral approach (p=0.01, trend test). Treatment outcomes following VFSI showed non-significant differences between the two injection approaches, including the incidence rates of post-operative side effects (Table 14).

Prognostic factors

Because the etiology and contributing factors for developing different vocal lesions are different, we subsequently compared the prognostic factors for better clinical responses following VFSI between each different disease entity (i.e., nodules, polyp, and cyst). For vocal nodules, patients with higher occupational vocal demands were associated with a poorer clinical response as measured by the VHI-10 (p=0.032, chi-square test, Table 15). Multivariate analyses also demonstrated significant correlation between vocal demand and treatment outcomes (adjusted odds ratio (aOR):4.32, 95% confidence interval (CI):1.06~17.6, multiple logistic regression). Additionally, hard and fibrotic vocal nodules, compared with soft nodules, had a lower chance of recovering normal perceptual voice quality as measured by GRB scores (p=0.010, Chi-square test). Multivariate analyses also validated this significant correlation (aOR: 9.3, 95% CI: 1.40 ~ 61.3).

Univariate analyses of the prognostic factors for vocal polyps following VFSI showed significantly lower VHI-10 scores among the subsets of patients with

dysphonia for more than 1 year (p=0.030, Table 16), Subsequent multivariate analyses also demonstrated this association with borderline significance (aOR: 4.20, 95% CI: 0.91 ~ 19.3). Alternatively, we observed that patients who presented with LPR showed significantly poor post-operative voice quality based on univariate and multivariate analyses (p=0.014, Chi-square test; aOR: 14.5, multiple logistic regression). Subsequent univariate and multivariate evaluations of vocal fold cysts did not reveal a significant correlation between clinical, endoscopic or interventional factors and the treatment outcomes (Table 17).

[Study 4] Long-term outcomes of VFSI

According to the systematic review and meta-analysis, various studies had already demonstrated clinical improvements following VFSI. Despite most of these studies had recognize the potential recurrence after primary VFSI, only 1 study had reported the follow-up results for up to 6 months in the literatures (Woo, et al., 2011)(Appendix III), while the other studies reported only short-term treatment outcomes of VFSI. Up to date, no study had investigated the treatment effectiveness, the recurrence rates, and whether the patients require further interventions following VFSI on a long-term basis.

Materials and Methods

In order to investigate the long-term treatment results, we investigated the patients of vocal nodules, polyps and cysts, who received VFSI between August 2011 and September 2013. We reviewed the medical chart at the outpatient department and record the date from treatment to the last follow-up clinic, VHI-10 scores at each clinical visits, presence of recurring dysphonic symptoms, and the date of subsequent procedures (e.g. VFSI or phonomicrosurgery). Treatment failure of VFSI was defined by 1) subjective report of recurring dysphonic symptoms (Laccourreye, et al., 2003) with VHI-10 score more than 10 points (which denotes

the upper normal limit)(Lam, et al., 2006; 王南梅, et al., 民 100); and 2) receiving secondary procedures.

For patients without recurring vocal symptoms or receiving secondary treatments, and for those patients who were lost from clinical appointments, we contacted the subjects via structured telephone interview on March 2013, September 2013, and April 2014 (Appendix XI). All the patients were first inquired the improvement of clinical symptoms and whether the dysphonic symptoms had recurred. For patients who reported recurring dysphonic symptoms after the procedure, we further inquire the approximate time (year and month) of recurrence and whether he/she had visited medical doctors or receive any further interventions. Subsequently, we asked the patient to rate their voice quality in a 0-10 point scale and answer the 10 items of voice handicap index. As mentioned earlier, treatment failure of VFSI was defined as 1) subjective reporting of symptoms recurrence plus VHI-10 score more than 10 points or 2) receiving secondary procedures at any medical facilities.

Time-to-event analysis was applied to analyze the long term effectiveness following VFSI. In case of treatment failure following VFSI (i.e. “event”), effective duration was calculated by subtracting the date of recurring symptoms (or secondary procedures) by the date of initial VFSI (i.e. “time”). For patients without recurring symptoms, we censored the case at the latest date of follow-up or telephone contact

(Wen, et al., 2013). Kaplan-Meier method was applied to evaluate the failure rates after VFSI. In order to examine the association between clinical factors and subsequent treatment failure following VFSI, Cox proportional hazard regression model was used to provide the directions and strength of association, while Log-rank test was applied for calculating the p value for statistical significance.

Results

Long term surveillance recruited 139 patients, including 116 female and 23 male patients. Vocal nodules were diagnosed in 50, polyps in 57 and mucus retention cyst in 32 patients. The mean follow-up periods are 15.3 months (ranged from 1 to 33 months, median 14.9 months). Three patients were not achievable during the three courses of telephone interview and were censored at 1.1, 1.4, and 4.6 months post-operatively. Treatment outcomes demonstrated that VHI-10 scores had gradually improved from the baseline value of 22.9 points to 13.1 points, 6 months post- operatively, and remained below 10 points from 12 to 24 months (Fig. 7). Subjective rating of voice quality also revealed a gradual improvement from 3.5 point preoperatively to 6.6 point, 6 months post-operatively, which also sustained in the subsequent follow-up periods.

Treatment failure of VFSI was recorded in 29 patients, including symptomatic recurrence (with VHI-10 score higher than 10 points) in 15 patients (3 identified by chart review while the other 12 by telephone contact), and secondary treatment in 14 patients (repeated VFSI in 10, angiolytic laser in 1 and phonomicrosurgery in 3 patients). The cumulative symptomatic recurrence rates at 6, 12, 18, and 24 months were 5%, 8%, 15% and 16%, respectively, and the mean failure time for symptomatic recurrence was 9.3 ± 6.6 months (median: 9.4 months). The cumulative rates for receiving secondary treatments at 6, 12, 18, and 24 months were 6%, 8%, 12%, and 14%, respectively. The mean failure time for receiving secondary treatment was 8.1 ± 6.6 months (median: 4.5 months). The overall cumulative failure rates (symptomatic recurrence plus secondary treatment) at 6, 12, 18, and 24 months were 11%, 15%, 24%, and 28%, respectively, with a mean failure time of 8.7 ± 6.5 months (median: 6.5 months). Fig. 8 illustrated the rates for symptomatic recurrence, secondary treatment, and the overall cumulative failure rate following VFSI. Although the cumulative failure rate gradually elevated among patients of vocal cyst than patients of vocal nodules and polyp, further analyses revealed non-significant differences between the three diagnostic groups (p=0.744, Log-rank test, Fig. 9).

We subsequently investigated the potential prognostic factors for long-term treatment outcomes of VFSI. First, we compared the clinical factors and disease

severity between subjects with and without subsequent treatment failure. Table 18 demonstrated significantly higher VHI-10 scores and lower subjective rating of voice quality in failed subjects. Subsequent time-to-event analysis also documented that patients with initial VHI-10 scores higher than 25 points and initial VAS scores equal or lower than 3 points were significantly associated with more treatment failures after VFSI (Fig. 10, $p<0.01$, Log-rank tests). Prognostic analyses for all the 3 diseases noted that longer symptoms durations (> 12 months) tended to present with lower treatment failures after VFSI (HR(hazard ratio): 0.57, 95% CI: 0.25 ~1.3, univariate analysis by Cox model, Table 19). Subgroup analyses noted that patients of vocal nodules and cysts with symptom duration longer than 12 months were less likely to report treatment failure following VFSI (Table 19, $p<0.05$, Log-rank test), similar to the results obtained in vocal cyst. In contrast, patients of vocal polyp tended to present a different direction of association (longer symptoms duration, higher failures after VFSI), despite statistical significance was not achieved. Otherwise, patients with LPR were more likely to experience treatment failures after VFSI (HR: 1.45, 95% CI: 0.67 ~ 3.21), with similar trends across all 3 diseases (Table 19).

Among the 139 patients, 20 were lost from clinical follow-up right after the procedure of VFSI (i.e., without any follow-up records). In order to examine the potential heterogeneity between lost and adherent patients and its impact on the

treatment outcomes, we analyzed the demographic factors, disease severity and treatment outcomes between the two groups. The results showed only slight younger ages among the lost subjects than the adherent subjects (35 ± 9 vs. 40 ± 10 years, p=0.044, Student's t test), without significant differences on the initial severity and subsequent long-term treatment outcomes (Table 20).

IV. Discussion

Comparative effectiveness between VFSI, non-invasive and invasive procedures

In order to examine the clinical effectiveness of VFSI, we demonstrated the 1- and 2-month lesion reduction rates following VFSI to be 39% and 46%, respectively, which were significantly higher than the reduction rates with VHE (6% and 24 %, respectively, Table 1). Furthermore, the obtainable data of VHI-10 scores (49 and 47 patients receiving VFSI and VHE, respectively) had also demonstrated a significantly higher improvement in patients receiving VFSI than VHE ($p<0.01$). However, since VHE was provided by otolaryngologist in study 1, the strength may be lower than VHE conducted by experienced voice therapist, who may have more time and better skills to discuss such issues with the patients. Because the follow-up period was shorter than the reported resolution time of vocal polyps (5 months)(Yun, et al., 2007; Nakagawa, et al., 2012), we cannot rule out the possibility of underestimating the resolution rate of vocal polyps by VHE (Fig. 3). Therefore, we proposed that VFSI may result in more rapid lesion regression than VHE (within 1 month), while VHE might have a chance to reach similar effectiveness following a longer period of time, especially for vocal nodules and adherent patients (Behrman, et al., 2008).

In study 2, we subsequently compared the effectiveness between VFSI and phonomicrosurgery in the patients of vocal polyp and cyst to further explore the clinical roles of VFSI. Grossly, patients of vocal polyps and cysts demonstrated much better recovery profiles following microsurgery than VFSI (Table 3 and 7); however, such results may not be adapted directly since the heterogeneous composition between two groups can pose significant influence on the interpretation of the treatment outcomes (Table 2 and 6), as well as the improvements form the baseline measurements.

Although a randomized head-to-head comparison shall provide the most solid evidence, such study may require a long time before collecting enough patients who are willing to receive such experimental arrangement. Alternatively, we applied propensity score, which represents the probability of assignment to a particular treatment option based on the observed covariates (Rosenbaum & Rubin, 1983), to reduce such heterogeneity associated with treatment allocation and to approximate baseline equipoise. Propensity scores have been widely used to compare the effectiveness and associated risks of medical interventions (Glynn, et al., 2006; Ray, et al., 2009). Several otolaryngological studies have already applied propensity scores to compare survival outcomes and treatment effectiveness (Patel, et al., 2002; Goldenberg, et al., 2009; Wen, et al., 2013).

In study 2, we noticed that patients with large hemorrhagic polyp were almost always treated by microsurgery (Table 2). Similarly, patients of vocal cysts were more likely to undergo microsurgery if they experienced more profound dysphonic symptoms (Table 6). After removing these patients who were very likely/unlikely to receive VFSI or microsurgery by trimming the extreme (non-overlap) values of propensity scores (Sturmer, et al., 2010), as illustrated in Appendix X, later results showed a much more balanced compositions between patients receiving VFSI or microsurgery (Table 4 and 8). Accordingly, significantly higher lesion regression and better voice quality revealed by subsequent analyses were persuasive that microsurgery remained the treatment of choice for vocal polyp and cyst (Table 5 and 9).

Interestingly, we noticed that significant differences between VFSI and microsurgery were more prominent in the second month post-operatively (Table 3, 5, and 7). A possible explanation is that during the first clinical visit (usually between 2 to 3 weeks post-operatively in our protocol), patients might perceive more discomforts associated with direct suspension laryngoscopy (e.g., endotracheal intubation, neck extension, tongue numbness and stretching/laceration of the soft palate)(Benninger, et al., 1996; Franco & Andrus, 2007) and report lower rates of subjective satisfaction with the treatment outcome (higher VHI-10 score and lower

VAS, Table 5, middle column), despite the significantly improved objective measurements (MPT and acoustic analyses). Further study may record the treatment outcomes at a later time point (e.g. 4 weeks post-operatively), to avoid such potential influences.

According to study1 and 2, the clinical roles of VFSI can be more clearly defined. For medical diseases such as vocal nodules, phonation habit modification is generally the first-line recommendation (Schwartz, et al., 2009), typically taking effect after 2–3 months and with potentially longer-lasting effects in adherent cases (Chen, et al., 2007; Behrman, et al., 2008). However, for noncompliant cases, as well as those who desires more rapid symptom relief, VFSI may be applied first and offers a positive chance of improvements within 1 month. For surgical diseases such as vocal polyps and cysts, microsurgery remains the first-line recommendation in most circumstances. However, if there are concerns about the risk of general anesthesia, the potential adverse effects of direct suspension laryngoscopy (e.g., injury to the teeth or cervical spine, tongue paresthesia) or postoperative scarring after exploring Reinke's space (Chang & Chang, 2003), VFSI may be applied instead to postpone or avoid surgery with minimal risk of causing permanent, irreversible adverse effects (Mortensen & Woo, 2006). However, clinicians should always inform patients that complete resolution following VFSI is not always achievable (Fig. 5). Prognostic factors of

VFSI treatment outcomes, potential adverse effects and risk factors, as well as the long-term recurrence rates following VFSI, which are also essential during pre-operative consultation, will be discussed in the following sections.

Short-term outcomes of VFSI

In study 3, we investigated the multidimensional treatment outcomes among the most common pathologies of vocal folds. For vocal nodules, we demonstrated that VFSI can resulted in significant subjective and objective improvements (Table 10, left column), which was comparable with previously published results.(Tateya, et al., 2004; Lee, et al., 2011) Moreover, we investigated the prognostic factors of vocal nodules following VFSI, which had not previously been done. The study results demonstrated that patients with higher vocal demand were more likely to perceive higher phonation discomforts as measured by their post-operative VHI-10 scores (Table 15, upper half). Because vocal nodules are closely related to occupational overuse of the voice, without adequate modification of phonation habits, the therapeutic effects of corticosteroids on vocal folds may gradually be countered by persistent voice overloads; if that is the case, dysphonic symptoms may persist. (Behrman, et al., 2008). This study also found that subjects with thick, fibrotic nodules were less likely to regain normal voice quality following VFSI (Table 15, lower half).

The histological features of vocal nodules may help to explain these findings. In soft nodules, which present with stroma edema, dilation and the increased permeability of microvasculature among the superficial lamina propria (Campagnolo, et al., 2008), VFSI can be more effective than it is for fibrotic or thick nodules, which feature a thickened epithelium and the proliferation of fibroblasts with abundant fibrin and organized collagen(Kotby, et al., 1988; Wallis, et al., 2004).

For patients with vocal polyps, this study demonstrated significant improvements in most of the outcome parameters (Table 10, middle column), comparable with results from a previous study (Hsu, et al., 2009). Subsequent analyses revealed that patients with dysphonic symptoms lasting for more than 1 year were more likely to have higher VHI-10 scores post-operation (Table 16, upper half). It is likely that chronic vocal polyps may present with a higher degree of fibrin deposition, inflammation, and amyloid-like material accumulation in Reinke's space, (Wallis, et al., 2004) which may be less reversible following one course of VFSI. Meanwhile, chronic vocal polyps may also more likely to cause reactive nodules on the contralateral vocal folds, which can also contribute to the less favorable postoperative recovery. A recent study found a 6% coexistence rate of vocal polyps with sulcus vocalis, which may negatively affect surgical outcomes.(Byeon, et al., 2013) In this study, we also identified 2 cases of vocal polyps with underlying sulcus; both patients

presented with symptom duration longer than 12 months and a less favorable response to VFSI. These comparable findings may also help to explain the association between the chronicity of diseases and treatment outcomes.

Our study results found that patients with vocal polyp comorbid with LPR tended to present with poorer voice quality following VFSI compared with the patients without LPR (Table 16, lower half). Although a previous study had already recognized the strong relationship between LPR and vocal fold disorders,(Koufman, 1991) this study provides additional clinical association of LPR and the treatment outcomes. Persistent inflammation surrounding the glottis caused by LPR (e.g., laryngeal edema and increased phlegm) may explained the fair recovery of normal voice quality following VFSI. (Belafsky, et al., 2001; Chung, et al., 2009)

Mucus retention cysts are epithelial-lined lesions, typically located at the subepithelial plane of the vocal folds, (Woo, 2009) that indicate an obstructed excretory duct with retained mucus of the affected gland. Histologically, mucus retention cysts tend to consist of an outer layer of cuboidal cells with an internal layer of ciliated columnar cells.(Bouchayer & Cornut, 1988) Except for a small number of reported cases,(Mortensen & Woo, 2006) this is the first clinical series to document the treatment effectiveness of VFSI for mucus retention cysts of vocal folds. Beyond the inflammatory effects of corticosteroids on vocal lesions, direct puncture of the cyst

wall during the injection process, if applicable, may help to drain the serous content of vocal fold cyst and result in a higher concentration of steroid in the residual cystic capsule, which could have contributed to the favorable observed effects (Table 10 and Fig. 5).

Although previous studies had reported clinical improvements following VFSI in Reinke's edema (Tateya, et al., 2003), the treatment outcomes revealed in Table 11 may not confirm such results, probably due to scares samples (12 cases only). Similarly, we cannot conclude the therapeutic effect of VFSI for pseudocyst and fibrous mass since only 5 cases in each category were recruited. Further studies gathering more samples shall provide further evidences of applying VFSI on these disease entities.

Previous studies had already reported potential adverse events following VFSI, with a highly variable range of incident rates (Wang, et al., 2013). For example, although triamcinolone's depot nature can result in longer duration of effectiveness within the injected site, (Hsu, et al., 2009) transient impairment of vocal fold vibration might occur following thick plaque formation of the injected triamcinolone, with incidence rates varying from 2.5% to nearly 100%.(Andrade Filho & Rosen, 2003; Lee, et al., 2011; Woo, et al., 2011). Such inconsistent results might be explained by different time frames for post-operative visits. Because the triamcinolone is mostly

absorbed gradually, it is likely that subjects returning to the clinic earlier might be more likely to notice such adverse effects than will subjects who return to the clinic after 1 to 2 months. In order to reduce the incidence rates of whitish plaque formation while maintaining the effectiveness of corticosteroid, we modified the steroid regimen by mixing triamcinolone with dexamethasone by half (50:50). Our study results demonstrated outcomes comparable with the findings in the literature, (Wang, et al., 2013) with the incidence rate of triamcinolone deposits limited to 3.9 %. These distinctions between benefits and harm may help to validate the rationale of applying the modified corticosteroid regimen used in this study.

Another common complication after VFSI is vocal fold hematoma, as noted in 2 studies with very low incidence rates (~ 1 %).(Hsu, et al., 2009; Woo, et al., 2011) In comparison, this study found a much higher rate of postoperative vocal fold hematoma (37 cases, 25%). Compared with the transcutaneous approach applied in previous studies,(Lee, et al., 2011; Woo, et al., 2011) in which the needle migrates subepithelialy without direct puncture through the epithelium of the vocal folds, the transoral and transnasal injection approaches performed in this series require direct puncture of the injection needle through the upper epithelial cover of the vocal fold, which may explain the higher rates of postoperative hematoma. Similarly, time between interventions to clinical follow-up might also have altered the incidence rates

of vocal hematoma because these adverse effects tended to regress spontaneously within 1 to 2 months. We noticed that the presence of vocal varices was the most significant risk factor for post-operative hematoma (Table 13) otolaryngologists may thus consider controlling varices prior to VFSI in order to prevent injury to these fragile neovasculatures during the injection process, especially for those with minimal tolerance of postoperative side effects (e.g., singers).(Hsiung, et al., 2003; Zeitels, et al., 2006) Another potential risk factor for post-VFSI vocal hematoma is high occupational vocal demand (Table 13). Although this study did not investigate the compliance rate of voice rest following VFSI (3 days), it is reasonable to suspect that patients with high occupational vocal demands may be less able to maintain 3 days of voice rest following VFSI than are patients with routine vocal demands, (Wang, et al., 2014) which might result in oozing before the re-epitheliazation and sealing of the injection wound is completed.

A previous study observed a 5% incidence rate of vocal fold atrophy after VFSI.(Lee, et al., 2011) In contrast, this study revealed a much lower incident rate (only 1 out of 148 cases). One reasonable explanation for this discrepancy is the different injection approaches. As noted earlier, the transcutaneous approach requires subepithelial needle migration without a directly visible needle tip; (Lee, et al., 2011) therefore, misplacement of the steroid around the vocal ligament and vocalis muscle

could occur. In contrast, transoral and transnasal needle placements were guided by direct, magnified endoscopic view; thus, surgeons could be more confident about the precise placement of the needle tip into the targeted Reinke's space, which might reduce the rate of vocal atrophy as found in this study and previous studies. (Tateya, et al., 2004; Mortensen & Woo, 2006) However, because the improvement of MPT in this series was less prominent than were other parameters, one should be cautious that some patients with subclinical atrophic change might not be adequately detected by the routine VLS exams.

According to our study results, the effectiveness of VFSI via trans-oral or trans-nasal approaches were non-significantly different (Table 14), and both were comparable with proposed results using trans-cutaneous injection approaches in the literature (Appendix III). However, trans-nasal approach requires passing fiberscope through nasal cavity, via pharynx to larynx, subjects tended to perceive higher discomfort level than trans-oral approach (Table 14). Since trans-cutaneous approach also require trans-nasal endoscopy for visual guidance, additional skin puncture might result in higher discomforts than trans-oral approach. In contrast, trans-cutaneous approach less frequently results in vocal fold hematoma, since it avoid direct puncture of the vocal fold mucosa as trans-oral and trans-nasal approaches. However, submucosal migration of needle tip via trans-cutaneous

approach might increase the risk of subsequent vocal atrophy following VFSI. In summary, the pros and cons between the different injection approaches seemed to counteract with each other, clinicians may select the most optimal method according to personal familiarity and each patient's tolerability.

Long-term outcomes of VFSI

Recurrence after VFSI had long been recognized in previous studies of VFSI, with the reported incidence rates ranging from 4% to 31% (Wang, et al., 2013). However, none of the studies had mentioned how such recurrent cases were identified, neither had they stated the follow-up rate and the criteria to define recurrence. Assuming that previous studies had identified the recurrent cases in patients who returned to the out-patient clinic and neglected the others who were lost to follow-up, a lower estimates of the recurrence rates might be reported (Lee, et al., 2011; Woo, et al., 2011). Likewise, considering only the patients who were adherent to the clinical follow-up, 17 cases recurred after VFSI in this series (3 symptomatic recurrence plus secondary treatment in 14 patients), consisting a similar, probably underestimated, recurrence rates.

In order to avoid such bias, this study assessed the long-term treatment outcomes of VFSI by: 1) setting a clear criteria of symptomatic recurrence using the validated

VHI-10 questionnaire (Lam, et al., 2006; 王南梅, et al., 民 100), and 2) approaching the patients via structured telephone interview regularly (Appendix XI). For subjects with available medical records, the timing for treatment failure was defined by the follow-up date in which the patients reported symptomatic recurrence or by the date for receiving secondary treatment. For subjects without medical records, 3 consecutive telephone interviews at an interval of 6 months shall decrease potential bias for the patients to recall the approximate time for symptom recurrence. As a results, we identified another 12 patients of symptomatic recurrence in the follow-up period for up to 33 months. The overall cumulative failure rates (symptoms recurrence plus secondary treatment) was 28%, similar to the original report (Tateya, et al., 2004).

Owing to the high responding rates (118 out of 122 patients without treatment failure during the clinical follow-up were successfully contacted via telephone interviews) of the long-term surveillance, we were able to investigate the potential influence of follow-up status on the treatment outcomes of VFSI. In the 20 patients who were lost right after VFSI, only age distribution was significantly different from adherent patients (Table 20). Since a 5 year difference (35 vs. 40 years) is not clinically significant, subsequent treatment outcomes revealed similar results between the two groups, for up to 24 months. In the other hand, considering the 3 cases absent from telephone interviews, we conducted a sensitivity analysis by

assuming that all the 3 patients had symptomatic recurrence at the median failure time of 9.4 months. Such estimation would increase the cumulative failure rates at 6, 12, 18, and 24 months to 10%, 16%, 25%, and 30%, respectively (Appendix XII). Meanwhile, one may concern about the definition of symptomatic recurrence by subjective report plus VHI-10 scores. Therefore, we performed another sensitivity analysis by changing the definition of treatment failure using only the VHI-10 scores (>10 points). Accordingly, additional 15 patients were assigned as symptomatic recurrence (mean effective duration for 8.3 months, median 5.7 months). Re-estimated failure rates at 6, 12, 18 and 24 months were 15%, 25%, 32%, and 40%, respectively (Appendix XII). However, such results might over-estimate the failure rates since 55% of these patients reported more than 50% of improvements compared with pre-treatment condition, with a mean VAS scores of 6.4 ± 1.7 points. Herein, depending on different criteria for treatment failure, the estimation of the failure rates shall fall between those receiving secondary treatments and those who present with post-operative VHI-10 scores larger than 10 points (Appendix XII).

The last recruited patients for long-term surveillance received VFSI by September 31th, 2013; herein, during the last telephone interview by April 30th 2014, all the subjects had been treated for at least 6 months (the shortest follow-up period). Considering the mean (median) follow-up period for the overall cohort was 15 months,

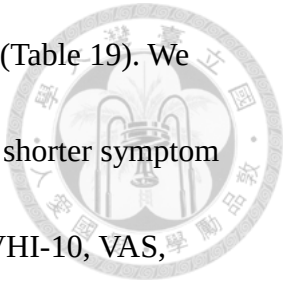
estimation of treatment failure after 15 months shall be interpreted with caution, because a lot of patients had been right-censored. A previous study had already noticed that vocal lesions can occur over a period of 5 years post-operatively (Bequignon, et al., 2013), further follow-ups of the study cohort are mandatory to rule out possible underestimate of the recurrence rates following VFSI.

In study 3, we noticed that despite significant improvement from the baseline measurements, the mean value of VHI-10 at 2 months post-operatively were still higher than the normal upper limit of 10 points (Fig. 5). However, in study 4, long-term surveillance had revealed that VHI-10 and VAS scores gradually fell within normal limit between 6 to 12 months (Fig. 7) Since the biological effects of injected corticosteroid cannot be so long-lasting, and the patients who had received secondary treatment had been discarded from the list of telephone interview; long-term improvement following VFSI might result from self-modification of phonation habit and life styles, following repeated vocal hygiene education during the clinical visits (Appendix VIII). Or, for patients with only partial improvements with residual diseases, they might adapted an adequate coping strategy with insights to accept such "imperfect" status leaving no further active complaints (de Jong, et al., 2003).

The most significant prognostic factors for long-term treatment outcomes in the overall cohort was the subjective perceiving of disease severity (VHI-10 and VAS

scores, Table 19). Patients with poorer self-reported voice quality (VAS scores) and higher voice-related symptoms (VHI-10) recorded at the initial clinical visit were associated with more treatment failures during the follow-up periods (Fig. 10). Such results were consistent with a recent study by Ng. et al., which noticed that patients with higher VHI-10 scores improved less after the treatment for benign vocal lesions (Ng, et al., 2013). Interestingly, we noticed that subjective disease severity measured by VHI -10 and VAS scores were not in accord with the objective measurements (i.e. MPT and GRB scales, Table 18). Such results were compatible with a recent article indicating that patients' perception of dysphonia severity is independent from other objective or clinician's assessment (Behrman, et al., 2004). Because treatment failure defined in the long-term surveillance was primarily based on subjective report of symptomatic recurrence, and the decision of receiving secondary treatment was also left to the patients' own decisions; it may be assumed that higher subjective severities (higher VHI-10, lower VAS) may represent a lower threshold to tolerate dysphonic symptoms (Siupsinskiene, et al., 2011; Meulenbroek, et al., 2012), and were therefore more likely to report symptomatic recurrence or request 2nd treatment than the other patients with lower subjective severity.

In the other hand, we also noticed that patients of with longer symptom durations (>12 months) were less likely to report symptomatic recurrence or receive secondary



treatment following VFSI, especially among vocal nodules and cyst (Table 19). We examine the objective disease severity between patients of longer or shorter symptom duration, which revealed a non-significant differences among size, VHI-10, VAS, MPT or GRB scores. Therefore, it is likely that psycho-emotional perspectives, rather than biological derangement of vocal folds itself, shall be accounted for the long term prognosis VFSI. In the psychological cascade model proposed by de Jong, et al., the authors noticed 3 phases of psychological adaptation following the development of benign voice disorders (de Jong, et al., 2003). In phase 1, patients might experience anxiety, threatened, and afraid of loss. Afterward, patients may proceed to the 2nd and 3rd phase, featured by acceptance of real scenario and establish a new goal, respectively. Although the transition from phase 2 to 3 is mostly uneventfully, the transition from phase 1 to phase 2 can sometimes be struggling and the patients might experience a "dead-locked" situation, depending on the presence of maintaining factors (i.e., physiological lesions, functional phonation techniques, and socioeconomic status) and inadequate coping strategies (e.g., externalization and unawareness). According to this model, we proposed that patients with symptom durations longer than 12 months might have already gone through the psychological transition from phase 1 to 3; herein, they may be more willing to accept a slight abnormal/imperfect voice quality following VFSI without further intervention and

more willing to accept modification of phonation behavior with a lower chance of symptoms recurrence thereafter.

Study limitations

This thesis possessed several limitations resulting from data collection and the study design. For example, clinical diagnoses of vocal lesions relied on morphological appearance and the vibratory pattern of VLS. Without confirmation by direct observation under operative microscope, we cannot exclude the possibility of misclassified lesion types (e.g., tiny mucus retention cyst vs. fusiform polyp). Similarly, the presence of simultaneous or reactive lesions (e.g. subepithelial fibrous mass or microweb of anterior commissure) could have been missed, which might have reduced the favorability of treatment outcomes. Additionally, although the injection process can sometimes provide texture feedback (e.g. soft vs. firm), the exact cystic content (serous vs. mucoid) cannot be always confirmed unless a direct cordotomy is performed. Recent study had noticed that 6% of vocal polyps coexist with underlying sulcus vocalis, which can resulted in less improvements and higher recurrence rates following surgical removal (Byeon, et al., 2013). In this study, we had identified 2 sulcus in the 47 patients of vocal polyp receiving VFSI (4.3%). Without direct examination under operating microscope, it is likely that a few cases of underlying

sulcus might be missed.

The quality of measuring prognostic factors might also result in paradoxical study results. For example, the duration of clinical symptoms was significantly correlated with VFSI outcomes in vocal polyps, but not for vocal nodules (Table 15 and 16). A probable explanation is that vocal polyps were frequently resulted from an acute insult (e.g., shouting, severe cough after URI); therefore, patients might recall the onset and duration of symptoms more accurately than vocal nodules, which generally took a longer, on-and-off, and insidious courses before gross voice deterioration was noted. Similarly, smoking status was simply classified as active vs. ever/non-smoker without details on the cumulated dosage of tobacco consumption, which might also contributes to the non-significant correlation with VFSI outcomes (Table 15 – 17).

The other limitation in this thesis is the sample size. For example, although a previous study had proposed an association between smoking and treatment outcomes,(Yun, et al., 2007) no correlation was established in this study (Table 16). Similarly, the different morphological features of vocal polyps, and the potential prognostic factors of vocal cysts following VFSI (Table 17), cannot be ascertained until further studies with larger sample sizes are available. Likewise, multivariate analyses of long-term prognostic factors within each diagnostic groups were not

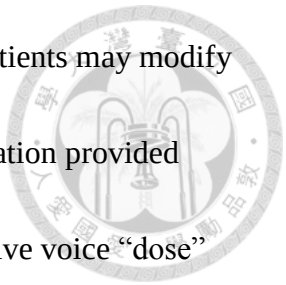
performed, mainly due to the lack of sufficient samples (Table 19).

Except for the limitation of subgroup analyses, small sample sizes gather in this study might also represent the lack of sufficient statistical power, especially when the follow-up records were incomplete. For example, although subjects of vocal polyp receiving microsurgery demonstrated more prominent improvements on dynamic NGGA and VHI-10 scores, 2 months post-operatively (Table 5, right column); such difference did not reach statistical significance. According to our estimation based on available clinical data of sample size and data distribution, the achieved post- hoc statistical power of dynamic NGGA and VHI-10 were only 22% and 40%, respectively (G-power software, version, 3.1)(Faul, et al., 2007). Similarly, although VHI-10 scores for vocal cysts measured 2 months after microsurgery were lower than VFSI (Table 9, right column), the calculated post-hoc statistical power was only 29%. In order to obtain adequate statistical power (80%), further study shall collect at least 50 patients at each treatment groups.

In study 2, treatment allocation between VFSI and phonomicrosurgery was left for the patients' self-choices without randomization; herein, study results demonstrated that patients with larger lesion sizes and higher disease severities tended to received surgery than VFSI (Table 2 and 6), which is mostly likely a bias from "confounding by indication". Although trimming extreme values of propensity scores

helped to eliminate most of the baseline heterogeneities between the 2 treatments (Table 4 and 8), such maneuver may raise the consideration of removing “typical” cases for VFSI or surgery (Appendix X), which may in turns decrease the external validity of our study results. Another way to control baseline heterogeneity using propensity scores is to match the subjects from each treatment groups(Patorno, et al., 2013). Despite excellent balance between treatment groups, such maneuver would result in a net loss of nearly 60% of the subjects, leaving scares samples for further statistical analyses (Appendix XIII). Early study of propensity scores had proposed that stratified analysis with 5 strata is sufficient to remove more than 90% of biases (Rosenbaum & Rubin, 1983). However, limited by small sample sizes, we can only stratify vocal polyps and cysts into 3 and 2 groups, respectively, leaving residual unbalanced heterogeneity between treatment groups (Appendix XIV and XV).

In long-term surveillance of treatment outcome following VFSI (study 4), only the initial VHI-10 and VAS scores were significantly related to subsequent treatment failure (Table 18). Other significant prognostic factors revealed in study 3 (e.g. occupational vocal demand and the presence of LPR, Table 15 and 16) did not revealed such relationships. Although the measurement of vocal demand and LPR were based on literature supports (Behrman, et al., 2004) (Belafsky, et al., 2002), using measurement at the first clinical visit may not adequately represent the varying



conditions during the follow-up periods after VFSI. For example, patients may modify their phonation habit or reduce voice loads after vocal hygiene education provided during the treatment course. Objective quantification of the cumulative voice "dose" over a certain period of time may be applied for more sensitive measurements (Titze, et al., 2003; Nix, et al., 2007). Similarly, after receiving education to modify the diet and lifestyles, with optional anti-reflux medications, severity of LPR can also be varied during the treatment courses, which may resulted in a non-significant correlations to the long-term treatments (Table 19). Future studies may apply repeated measurements of these time-dependent variables for more reliable results (Rothman, et al., 2008).

In Table 20, we showed that the patients lost from the clinic after VFSI had similar treatment outcomes than those who were regularly followed at the clinic. In contrast, the association between follow-up status and treatment outcomes of phonomicrosurgery cannot be established due to the lack of corresponding information on the lost subjects. Considering that complete follow-up records only in 60% of patients receiving microsurgery (Table 3 and 7), further studies shall contact patients receiving microsurgery in similar ways as Appendix XI to eliminate potential under- or over-estimation of the treatment effectiveness of phonomicrosurgery.

Based on the general concept from epidemiology (Fletcher & Fletcher, 2005), the

observed effects of any medical interventions represent a sum of natural history, Hawthorne effect, placebo effect, and the specific treatment itself. In study 1, we had eliminated the potential influence from natural history and Hawthorne effect by incorporating patients receiving VHE. However, whether the treatment outcome of VFSI were resulted from placebo effect remained unsolved. Further study comparing cases receiving VFSI with sham injection (normal saline) shall solve the last puzzle of this clinical dilemma, as well as exploring the possible mechanism of VFSI by dissociation the vocal lesions from the underlying Reinke's space and vocal ligaments, which might resulted in ischemia with spontaneous resolution.

Future perspectives

In this study, most of the outcome parameters demonstrated significant improvements following VFSI, except for MPT (Table 10.) Theoretically, MPT represents the conversion of energy from trans-glottic pressure to audible sounds produced by intermittent closure of vocal folds. Although it has been widely used as a proxy for phonatory ability (Sataloff, 2005), measured results can be inconsistent due to difficult standardization of measuring conditions (e.g. pulmonary supports, loudness of produced sounds, background noise, and the adherence to instructions). Herein, further evaluation shall focus on a more direct measurement of the phonation

threshold pressure, which indicates the minimum subglottal pressure required for the maintenance of vocal fold vibration (Wang, et al., 2010). Numerous studies had already documented the significant correlations between phonation threshold pressure with physiological and environmental conditions (Titze, 2009), and it can represents the ease of phonation more reliably (Lucero, 1998), which is the major concern for most dysphonic patients.

Previous studies had demonstrated that office-based laryngeal procedures may cause significant elevation of blood pressure and heart rate, as well as lowered oxygen saturation (Yung & Courey, 2010). Although such changes may be subtle with limited impact on the hemodynamic profiles (Ongkasuwan, et al., 2012), researchers had suggested monitoring vital signs in patients over 50 years of age (Morrison, et al., 2012). In this thesis, we did not experience any symptomatic alternations of vital signs, probably due to a relative young cohort (75% of the patients are under 50 years old). Subsequent studies shall incorporate peri-operative hemodynamic monitors to assure adequate patient safety and understand the potential influence of office-based laryngeal procedures in Asian populations.

Except for patient's convenience, previous studies had demonstrated that office-based procedures can save a great amount of financial expenses (up to USD $2000~5000 per case) for the third party payer, when comparing with direct

laryngoscopic surgery under general anesthesia during admission.(Rees, et al., 2007) Similarly, Bove et al. demonstrated that office-based injection larygoplasty had similarly clinical effectiveness comparing with operating room-based procedures, while preserving more than $2000(USD) of medical cost.(Bove, et al., 2007) Another article by Kuo, et al. also demonstrated that the medical cost of operative direct laryngeal laser surgery cost 10-times than similar procedure performed at the clinician's offices,(Kuo & Halum, 2012) which was similar in a recent research from Taiwan (Fang, et al., 2013). Based on the preliminary estimation of medical cost and failure rates following VFSI (Fig. 8 and Appendix I), subsequent study may proceed to investigate the cost effectiveness of VFSI and compared it with other treatment modalities.

In this thesis, we applied VHI-10 instead of the original version of VHI (Jacobson, et al., 1997), primarily because it take much less time for the patients to complete (Rosen, et al., 2004). Lacking the different subscales designed originally in VHI (functional, physical, and emotional), we were not able to explore the potential influence of emotional characteristics on the long-term treatment outcome of VFSI. Since psycho-emotional distress, as well as different personal traits may have significant influence on the pathogenesis and treatment effectiveness of benign vocal fold lesions (Yano, et al., 1982; Roy & Bless, 1999; Ng, et al., 2013), further studies

combined with psychiatrist may proceed to delineate the complex relationship between personal traits, psychometric measurement of dysphonia, and the treatment outcomes of benign vocal fold lesions.

In long-term surveillance, the primary outcome (treatment failure) was relied on subjective perception and willingness for symptom recurrence and secondary intervention, respectively. For more reliable and objective evaluation, further study may apply endoscopic evaluation to investigate “lesion” recurrence instead of “symptom” recurrence, by means of corrected lesion size or dynamic NGGA, as illustrated in Fig. 2 and 4, respectively. Thereafter, researches can adapt objective criteria for lesion recurrence (e.g., regrowth of more than 50% the initial size).

Previous study had noticed that lacking of voice therapy following phonosurgery for vocal nodules was significantly associated with higher recurrence rate of dysphonia (Zeitels, et al., 2002; Bequignon, et al., 2013). In this study, although patients received VHE during the clinical visits (Appendix VIII), only a few patients completed voice therapy either before or after VFSI. Such low attendance rate might probably due to the lack of interdisciplinary approach combining otolaryngologist and speech therapist, as suggested in the recent literate (Starmer, et al., 2014). Since vocal hygiene with voice therapy is the standard care for benign vocal lesions, (Schwartz, et al., 2009) further practice shall combine otolaryngologist with speech therapist to

investigate the potential superiority of additional voice therapy on the treatment outcomes of phonosurgery and VFSI.

V. Conclusion

Comparative effectiveness researches demonstrated that VFSI resulted in more rapid lesion regression than vocal hygiene education in vocal nodules, whereas phonomicrosurgery remained more effective than VFSI in vocal polyps and cysts. Short-term treatment outcomes demonstrated significant improvements in subjective, perceptual, endoscopic, and acoustic evaluations following VFSI in vocal nodules, polyp and mucus retention cyst; though treatment outcomes for Reinke's edema, fibrous mass, and pseudocyst were unclear. Occupational vocal demand and the subtypes of vocal nodules were closely related to the treatment outcomes following VFSI; whereas chronicity of clinical symptoms and LPR were significant prognostic factors for VFSI treatment outcomes in vocal polyps. Common side effect following VFSI were vocal hematoma, f triamcinolone deposits and vocal atrophy, which might vary by injection approaches and the concurrence of vascular abnormalities. Long-term surveillance revealed a 28% rate of treatment failure, 2 years after VFSI, without significant differences between vocal nodules, polyp and cysts. Patients with higher subjective symptoms severity were significantly associated with more treatment failures, which necessitate further studies to understand the potential influence of behavioral and psycho-emotional factors on benign vocal fold lesions.

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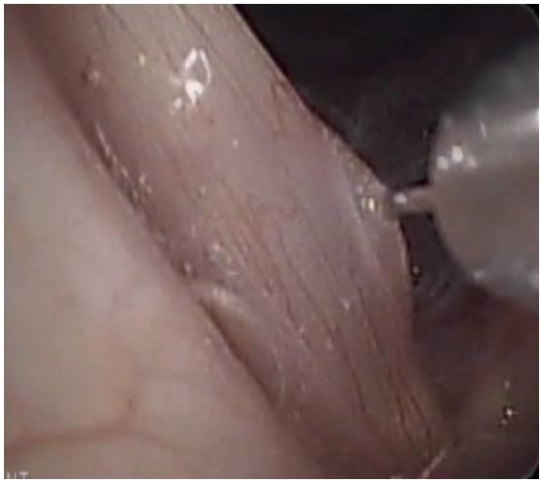
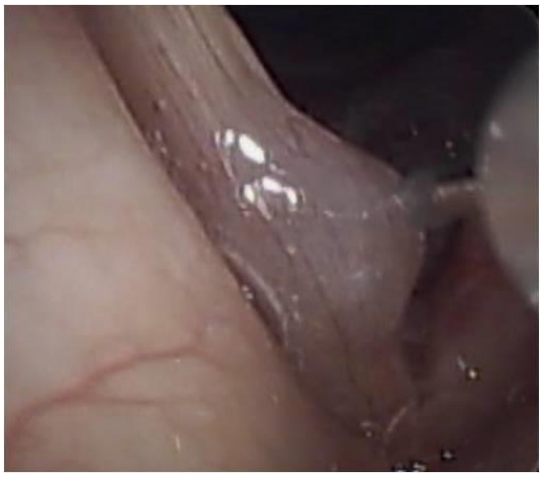
VII. Figures



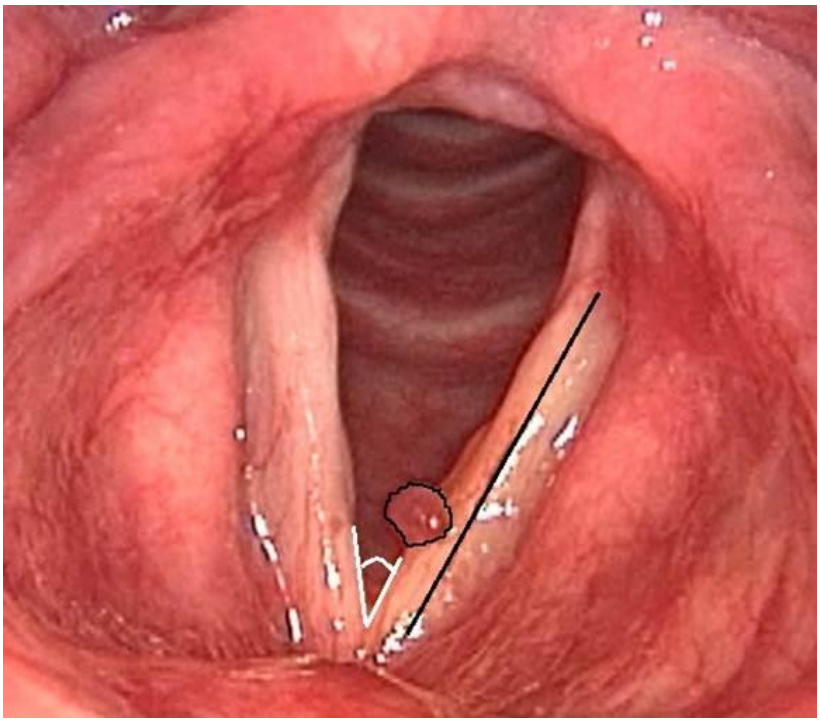
(a)



(b)

Note: Flexible injection needle is inserted thorough the working channel of a flexible nasopharyngoscope (a). Accurate placement of injection material can be identified by the formation of a subepithelial translucent bleb immediately after the procedure (b).

Fig. 1. Transnasal endoscopic injection approach for VFSI.



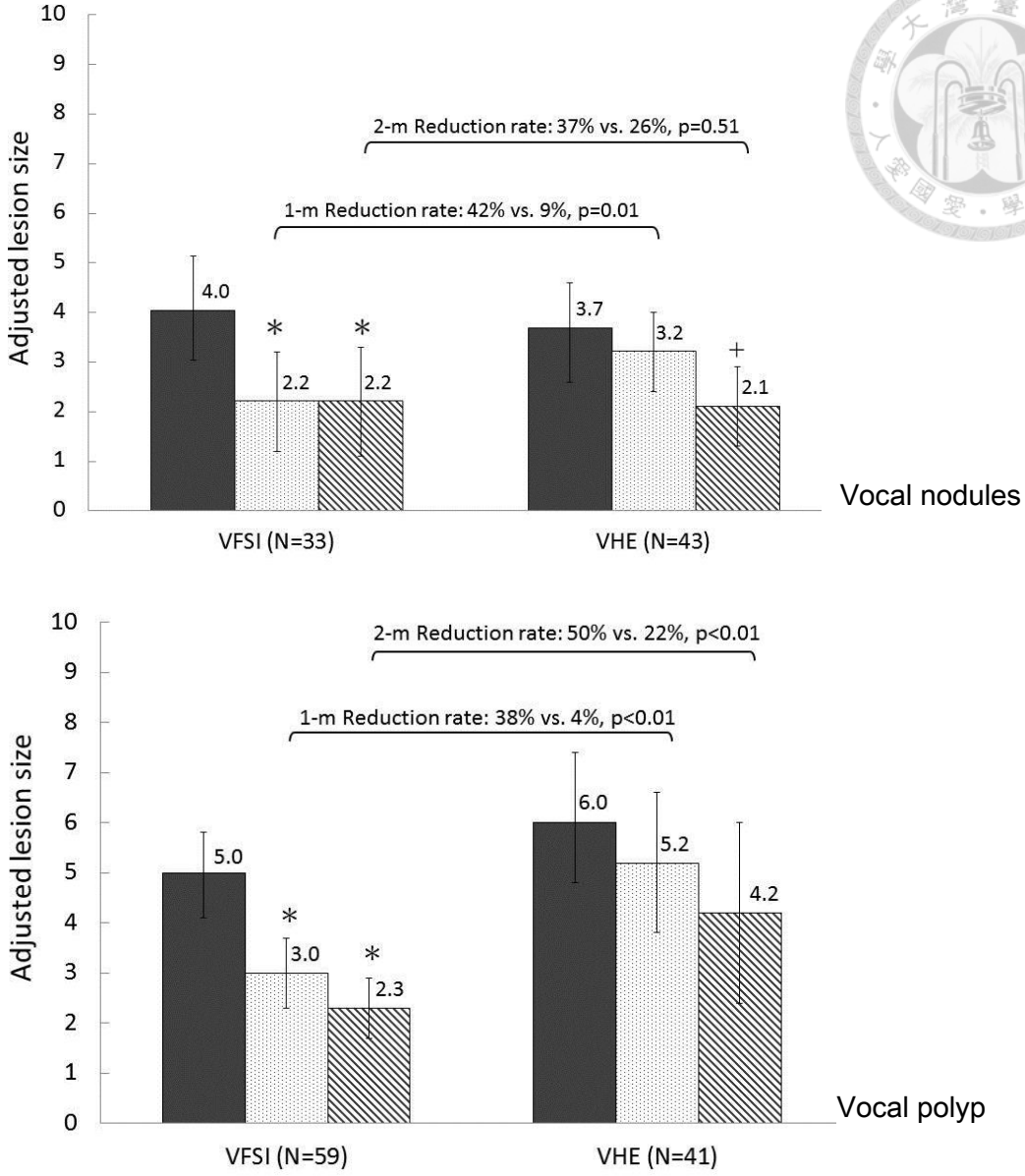
Note:

Lesion size: circumscribed area in black

Vocal fold length: black line

Open angle of bilateral vocal folds: white lines

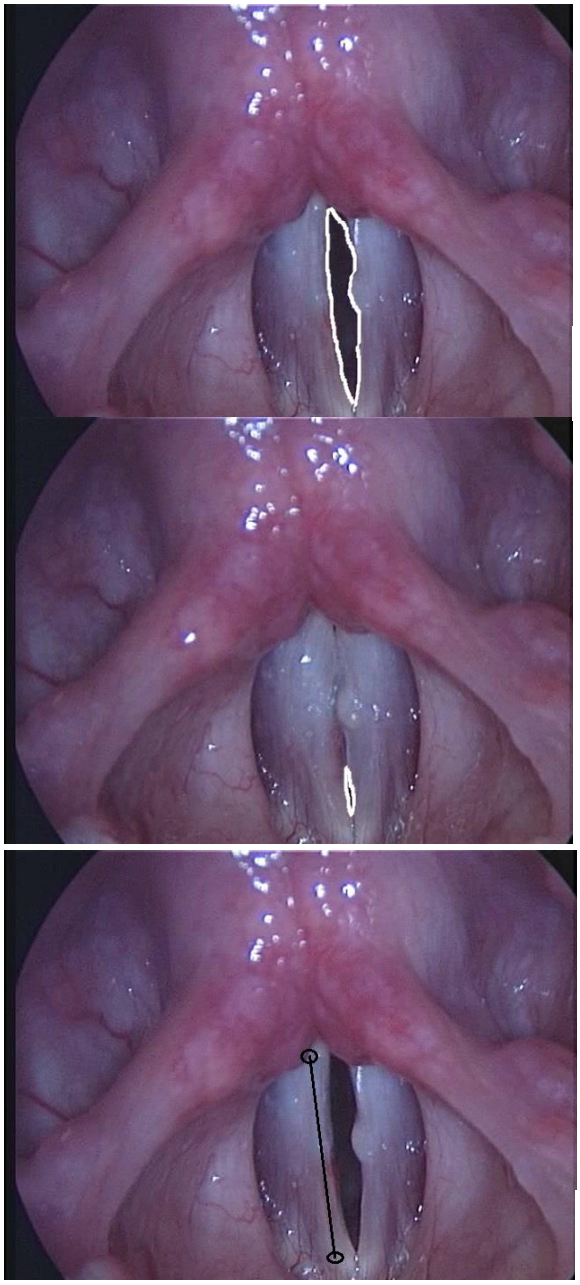
Fig. 2. Measurements of lesion size, vocal fold length, and open angle of bilateral vocal folds using Image J software. (study 1)



Note: ■:baseline, ▩:1 month, ▨:2 months;

*: $p<0.01$, $^{+}$: $p<0.05$, paired *t*-test, compared with baseline.

Fig. 3. Comparisons of adjusted lesion sizes and lesion reduction rates of vocal nodules and polyps treated by VFSI or VHE. (study 1)



(a)

(b)

(c)

Note: NGGA is calculated by subtracting the maximally opened glottic area (a) by the maximally closed glottic area (b) during the phonation cycle, and corrected by the length of vocal fold, measured from anterior commissure to the vocal process (c).

Fig. 4. Normalized glottal gap area (NGGA). (study 2 and 3)

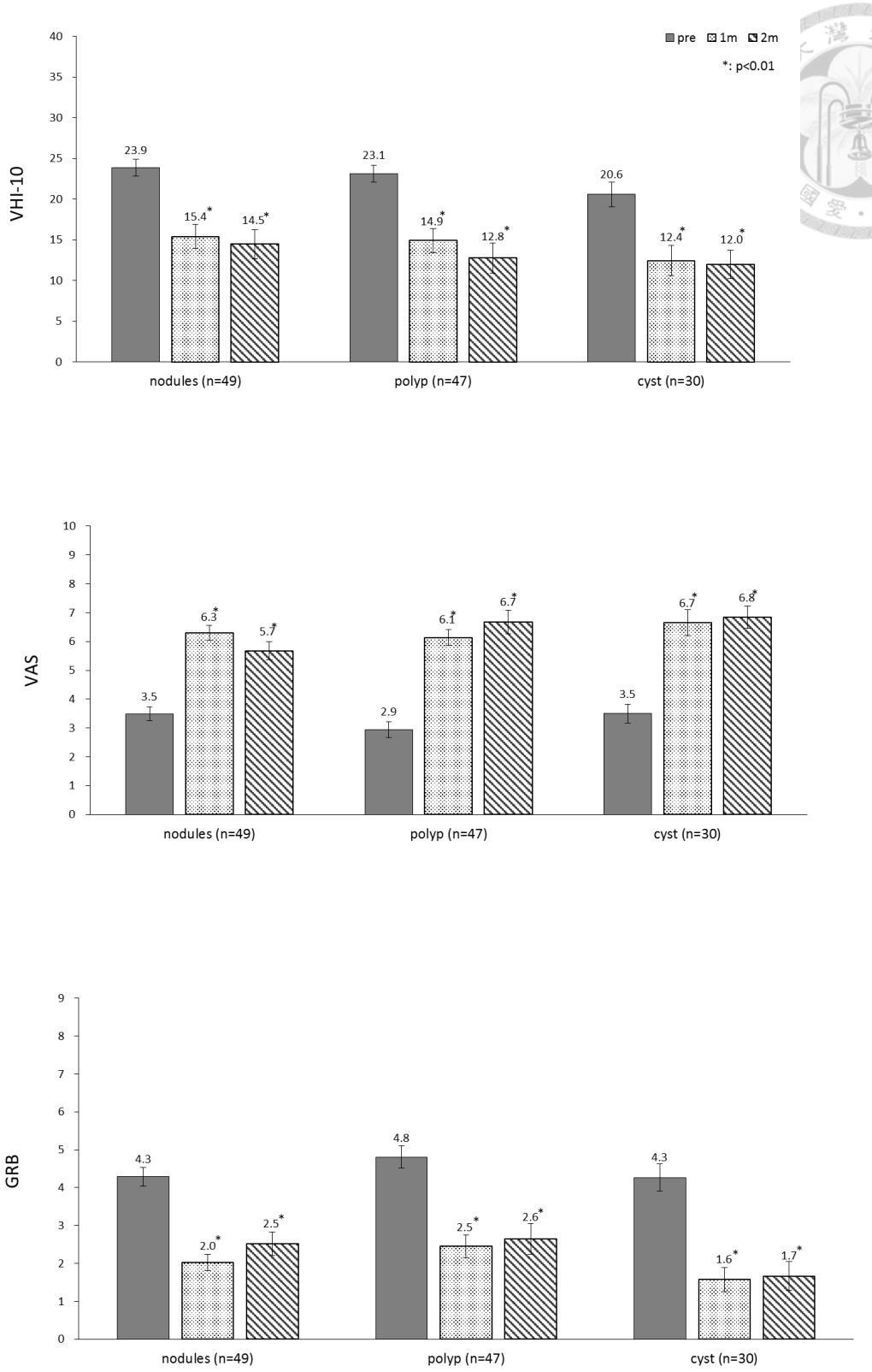
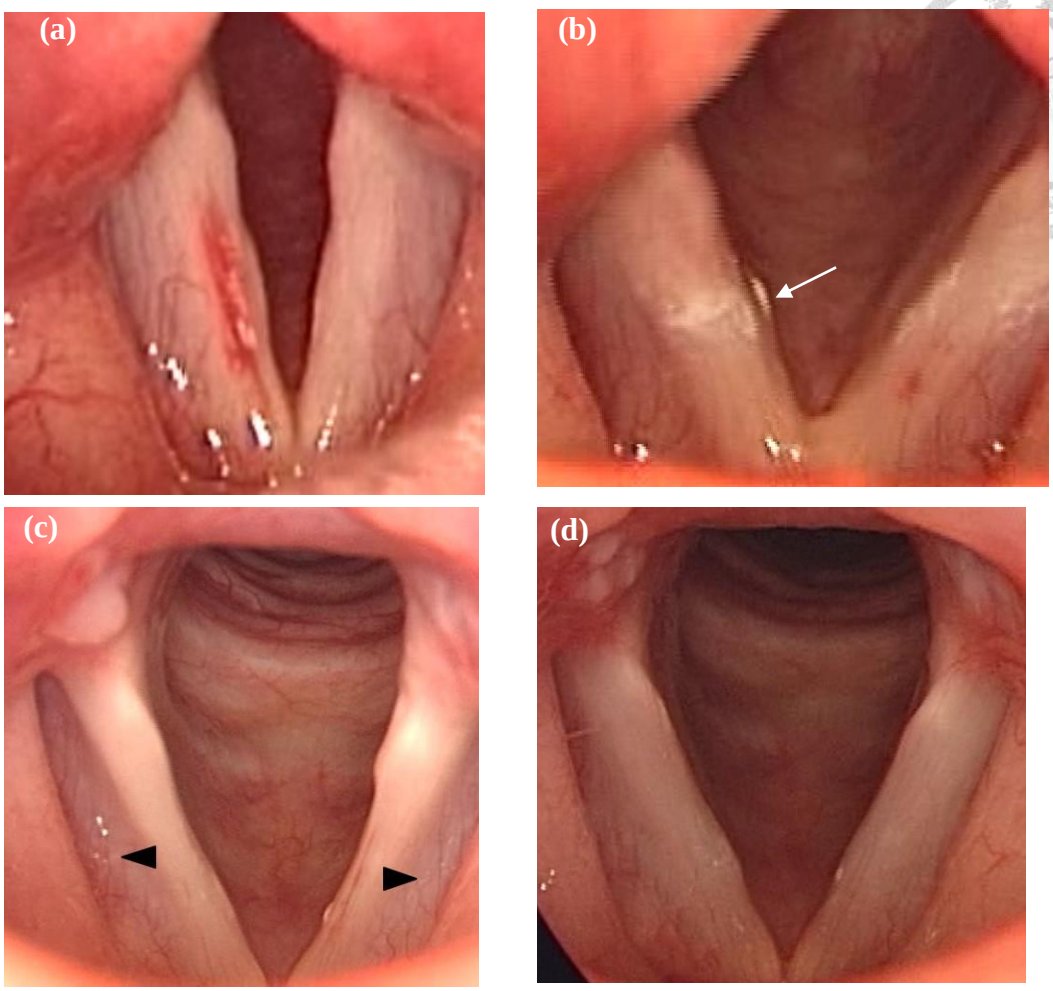
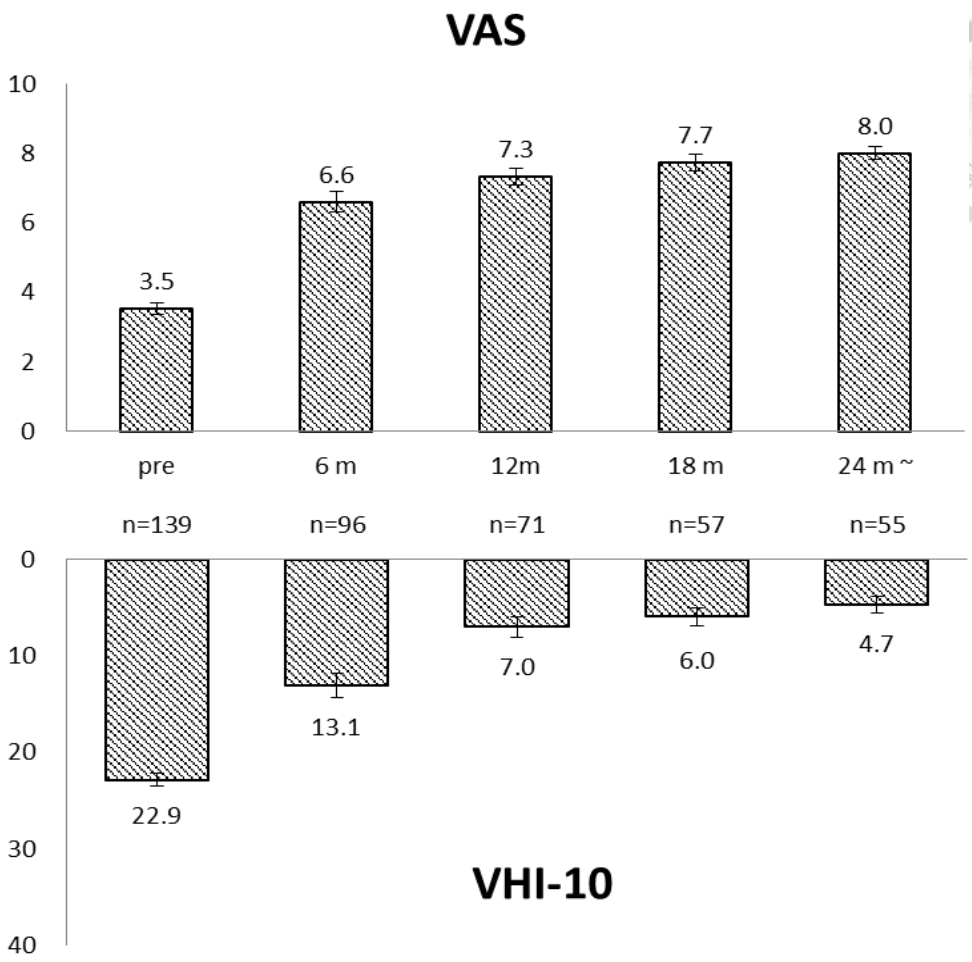


Fig. 5. Short-term treatment outcomes of VFSI in vocal nodules, polyp and cyst. (study 3)



Note: Hematoma (a), deposit of triamcinolone (b, white arrow) and bowing atrophic vocal folds following VFSI (c, black arrowhead: decreased bulk of vocalis muscle). Atrophic vocal folds recovered completely after 2 months (d).

Fig. 6. Side effects following VFSI. (study 3)



Note: VAS: visual analogue scale of subjectively evaluated voice quality,

VHI-10: 10-item voice handicap index

Fig. 7. Long-term treatment outcomes following VFSI. (study 4)

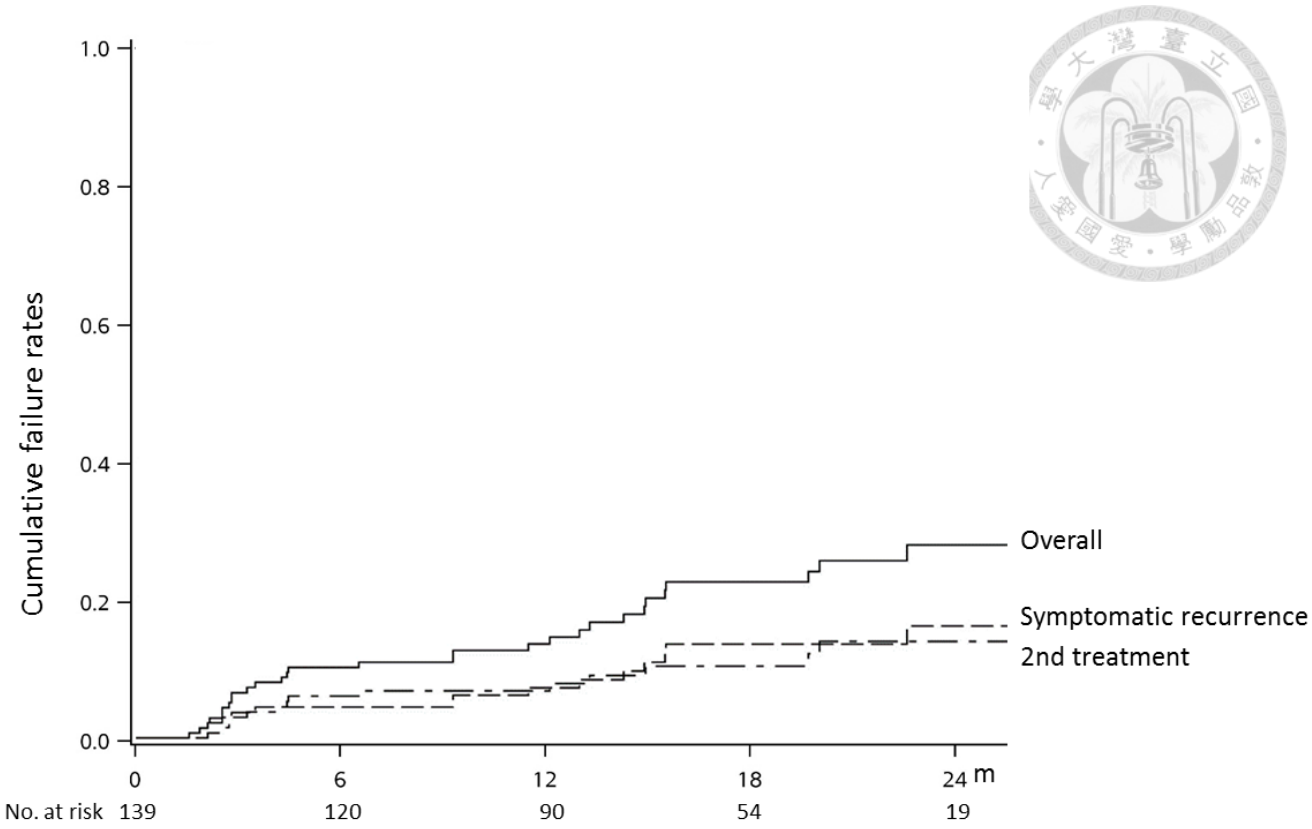


Fig. 8. Cumulative failure rates (symptomatic recurrence plus secondary treatment) after VFSI. (study 4)

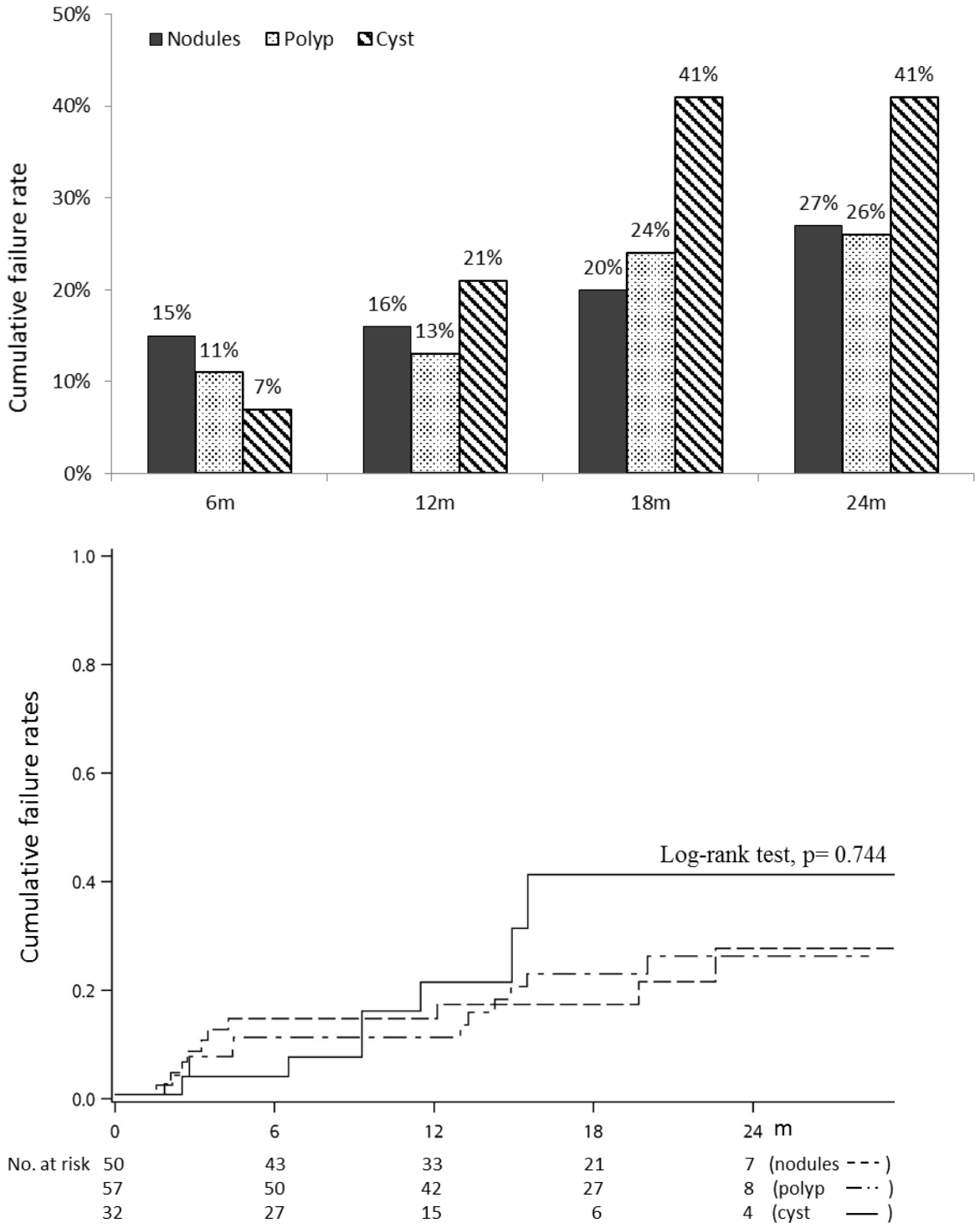
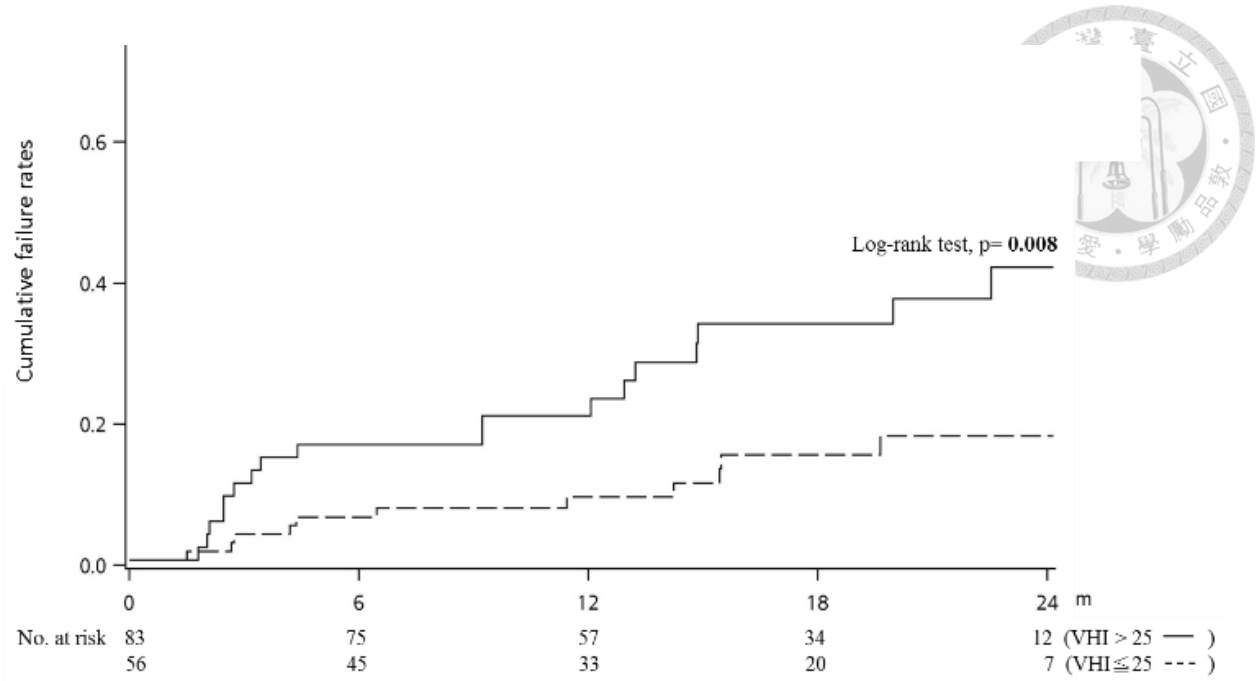


Fig. 9. Cumulative failure rates after VFSI in vocal nodules, polyp and cyst. (study 4)



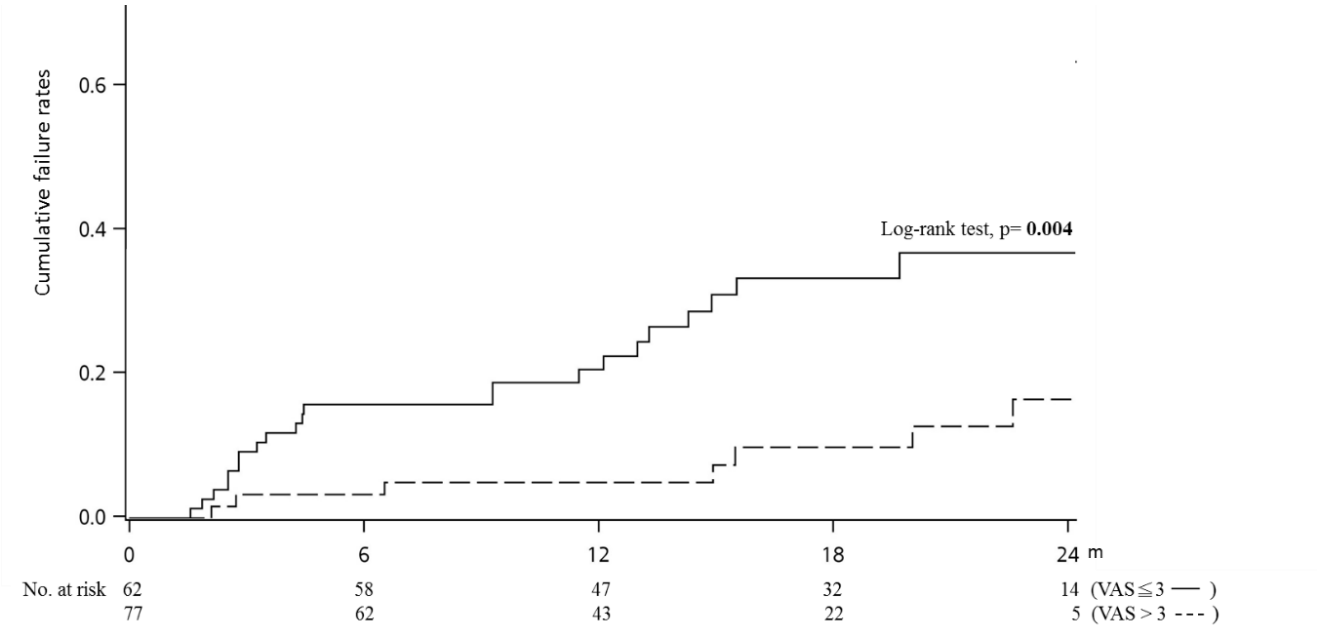


Fig. 10. Cumulative failure rates following VFSI, separated by initial VHI-10 and VAS scores. (Study 4)

VIII. Tables

Table 1. Demographics and lesion regression rates of patients receiving VFSI or VHE for vocal nodules and polyps (study 1).

	VFSI	VHE	p value
N	92	84	
Gender (M/F)	24 / 68	15 / 69	0.19
Occupational voice demands (high / ordinary)	38 / 54	37 / 47	0.71
Age (years)*	40 (38 ~ 43)	39 (37 ~ 42)	0.69
Duration of symptoms (months)*	12 (9 ~ 16)	11 (6 ~ 15)	0.58
Pre-treatment adjusted lesion size (pixels)*	4.7 (4.0 ~ 5.3)	4.8 (4.0 ~ 5.7)	0.75
VHI-10*†	24 (22 ~ 27)	23 (21 ~ 25)	0.32
1-m lesion regression rate (%)	39 (30 ~ 49)	6 (-4 ~ 17)	**<0.01**
2-m lesion regression rate (%)	46 (34 ~ 58)	24 (9 ~ 39)	**0.02**

*: Data are expressed as mean (95% of confidence interval)

†**:** VHI-10 scores are available in 49 and 47 patients of the VFSI and VHE groups, respectively.

Table 2. Comparison of the baseline characters of the 107 patients of vocal polyp receiving VFSI or phonomicrosurgery (study 2)

Parameters	VFSI n=47	Phonomicrosurgery n=60	p value
Age	39 ± 10	43 ± 11	0.085
Gender (male / female)	6 / 41	23 / 37	**0.003** *
Duration (>1 year / ≤ 1 year)	20 / 27	23 / 37	0.710
Smoking (active / nil)	6 / 41	22 / 38	**0.005** *
Alcohol (+/-)	1 / 46	17 / 43	**0.002** *
Hypertension (+/-)	2 / 45	5 / 55	0.397
Diabetes Mellitus (+/-)	1 / 46	3 / 57	0.437
Cardiovascular disease (+/-)	1 / 46	1 / 59	0.861
Vocal demand			0.063
professional	4	0	
high	26	30	
routine	17	30	
Polyp type			**0.001** *
hemorrhagic	3	29	
fusiform	35	19	
pedunculated	3	4	
fibrous	6	8	
Reflux symptom index	15.5 ± 8.5	13.5 ± 8.1	0.278
Max. phonation time	9.9 ± 4.6	9.3 ± 4.4	0.500
VHI-10	23.1 ± 7.1	24.0 ± 8.7	0.573
Self-rating of voice quality	2.9 ± 1.8	2.7 ± 1.8	0.446
Size of vocal lesions (pixels)	2.6 ± 2.3	7.6 ± 11	**0.001** †
Acoustic analysis			
GRB scores (sum)	4.8 ± 2.0	5.6 ± 1.9	**0.042** †
Jitter	1.9 ± 1.4	2.4 ± 2.0	0.170
Shimmer	4.5 ± 2.8	6.0 ± 4.3	0.050
NHR	.14 ± .06	.16 ± .09	0.103

*:chi-square test

†:Student's t-test

Table 3. Crude treatment outcomes following VFSI and phonomicrosurgery in patients of vocal polyps. (study 2)

Outcome parameters	Baseline			1 month			2 months		
	VFSI (n=47)	Surgery (n=60)	p value†	VFSI (n=42)	Surgery (n=49)	p value†	VFSI (n=29)	Surgery (n=38)	p value†
Subjective evaluation						0.824			**0.009**
complete remission				6 (14%)	2 (4%)		4 (14%)	13 (34%)	
much improve (>50%)				24 (57%)	35 (71%)		16 (55%)	21 (55%)	
some improve (≤50%)				7 (17%)	10 (20%)		8 (28%)	3 (8%)	
no effect				5 (12%)	2 (4%)		1 (3%)	1 (3%)	
Endoscopic evaluation						**0.017**			**<0.001**
complete remission				8 (19%)	16 (33%)		4 (14%)	23 (61%)	
much improve				23 (55%)	29 (59%)		14 (48%)	12 (32%)	
some improve				10 (24%)	4 (8%)		9 (31%)	3 (8%)	
no effect				1 (2%)	0 (0%)		2 (7%)	0 (0%)	
Dynamic NGGA	10.3 ± 7.9	7.2 ± 5.0	**0.027**	15.6 ± 10.8 **	12.9 ± 7.5 **	0.182	12.1 ± 7.7 **	14.9 ± 8.0 **	0.198
(change from baseline)				4.7 ± 5.9	6.4 ± 7.4	0.255	3.9 ± 6.4	7.9 ± 7.8	0.048
Self-rating of voice quality	2.9 ± 1.8	2.7 ± 1.8	0.446	6.1 ± 1.7 **	6.3 ± 1.6 **	0.657	6.7 ± 1.8 **	7.4 ± 1.8 **	0.155
(change from baseline)				3.5 ± 2.0	3.7 ± 2.3	0.625	3.9 ± 2.2	4.5 ± 2.3	0.316
VHI-10	23.1 ± 7.1	24.0 ± 8.7	0.573	14.9 ± 9.4 **	13.9 ± 8.2 **	0.612	12.8 ± 9.8 **	7.5 ± 8.9 **	**0.033**
(change from baseline)				8.2 ± 10.4	10.3 ± 10.9	0.359	11.2 ± 9.6	15.4 ± 12.2	0.131
Acoustic analysis									
Max. phonation time	9.9 ± 4.6	9.3 ± 4.4	0.500	11.5 ± 4.9 **	12.8 ± 4.6 **	0.225	11.4 ± 4.5	11.9 ± 4.5 **	0.651
(change from baseline)				1.7 ± 3.5	3.7 ± 4.9	**0.026**	1.2 ± 4.2	2.4 ± 4.5	0.283
GRB scores (sum)	4.8 ± 2.0	5.6 ± 1.9	**0.042**	2.4 ± 1.9 **	1.5 ± 1.8 **	0.533	2.6 ± 2.2 **	1.5 ± 1.8 **	**0.030**
(change from baseline)				2.3 ± 2.0	4.0 ± 2.0	**<0.001**	2.1 ± 2.0	3.9 ± 1.8	**<0.001**
Jitter	1.9 ± 1.4	2.4 ± 2.0	0.170	1.4 ± 0.9 *	1.3 ± 0.9 **	0.668	1.4 ± 1.3	1.1 ± 0.7 *	0.299
(change from baseline)				0.6 ± 1.5	1.3 ± 2.3	0.091	0.2 ± 1.2	1.2 ± 1.8	**0.017**
Shimmer	4.5 ± 2.8	6.0 ± 4.3	0.050	3.1 ± 1.2 *	3.1 ± 1.4 **	0.971	3.8 ± 2.5	3.0 ± 1.7 **	0.152
(change from baseline)				1.5 ± 2.9	3.1 ± 4.6	0.063	0.4 ± 3.3	2.7 ± 3.1	**0.007**
NHR	.14 ± .06	.16 ± .09	0.103	.13 ± .12	.12 ± .02 **	0.554	.15 ± .15 **	.12 ± .02 **	0.286
(change from baseline)				.002 ± .14	.05 ± .10	0.100	-.03 ± .15	.03 ± .07	0.052

*: p<0.05, paired t test, compared with baseline

**: p<0.01, paired t test, compared with baseline

†: Student's t test, compared between the two treatment groups

Table 4. Baseline characteristics after trimming extreme propensity scores in patients of vocal polyps. (study 2)

Parameters	VFSI n=32	Phonomicrosurgery n=29	p value
Age	41 ± 10	42 ± 11	0.641
Gender (Male / Female)	6 / 26	8 / 21	0.413
Duration (>1 year / ≤ 1 year)	14 / 18	10 / 19	0.459
Smoking (active / nil)	6 / 26	8 / 21	0.413
Alcohol (+/-)	1 / 31	3 / 26	0.255
Hypertension (+/-)	2 / 30	1 / 28	0.613
Diabetes Mellitus (+/-)	1 / 31	0 / 29	0.337
Cardiovascular disease (+/-)	1 / 31	0 / 29	0.337
Vocal demand			0.130
professional	4	0	
high	15	14	
routine	13	15	
Polyp type			0.893
hemorrhagic	3	5	
fusiform	22	15	
pedunculated	1	3	
fibrous	6	6	
Reflux symptom index	16.4 ± 9.4	13.8 ± 9.9	0.365
Max. phonation time	10.3 ± 4.8	9.7 ± 4.5	0.565
VHI-10	23.3 ± 7.6	24.3 ± 8.6	0.625
Self-rating of voice quality	2.5 ± 1.7	2.5 ± 1.7	0.911
Size of vocal lesions (pixels)	3.0 ± 2.6	3.9 ± 2.5	0.209
Acoustic analysis			
GRB scores (sum)	5.0 ± 2.1	5.3 ± 2.0	0.475
Jitter	1.9 ± 1.6	2.1 ± 1.8	0.717
Shimmer	4.5 ± 3.2	4.5 ± 3.0	0.955
NHR	.14 ± .07	.14 ± .09	0.977

Table 5. Comparative effectiveness of vocal polyps receiving VFSI or phonomicrosurgery, after trimming extreme propensity scores. (study 2)

Outcome parameters	Baseline			1 month			2 months		
	VFSI (n= 32)	Surgery (n= 29)	p value†	VFSI (n= 29)	Surgery (n= 23)	p value†	VFSI (n= 21)	Surgery (n= 20)	p value†
Subjective evaluation						0.594			0.273
complete remission				4 (14%)	0 (0%)		4 (19%)	8 (40%)	
much improve (>50%)				18 (62%)	18 (78%)		10 (48%)	9 (45%)	
some improve (≤50%)				5 (17%)	4 (17%)		7 (33%)	2 (10%)	
no effect				2 (7%)	1 (4%)		0 (0%)	1 (5%)	
Endoscopic evaluation				0%		0.348			**0.001**
complete remission				6 (21%)	9 (39%)		3 (14%)	14 (70%)	
much improve				19 (66%)	10 (43%)		12 (57%)	4 (20%)	
some improve				3 (10%)	4 (17%)		5 (24%)	2 (10%)	
no effect				1 (3%)	0 (0%)		1 (5%)	0 (0%)	
Dynamic NGGA	9.3 ± 6.1	7.6 ± 5.1	0.252	14.6 ± 8.2 **	11.8 ± 5.1 **	0.145	11.5 ± 8.0 *	14.3 ± 6.9 **	0.316
(change from baseline)				4.6 ± 5.8	4.5 ± 5.8	0.988	3.4 ± 6.4	6.5 ± 6.3	0.201
Self-rating of voice quality	2.5 ± 1.7	2.5 ± 1.7	0.911	6.6 ± 1.6 **	5.7 ± 1.8 **	0.088	6.7 ± 2.0 **	7.3 ± 2.1 **	0.346
(change from baseline)				4.2 ± 2.0	3.2 ± 2.4	0.160	4.4 ± 2.2	4.5 ± 2.5	0.895
VHI-10	23.3 ± 7.6	24.3 ± 8.6	0.625	14.6 ± 9.8 **	15.5 ± 7.5 **	0.713	14.0 ± 10.2 **	8.4 ± 10.3 **	0.107
(change from baseline)				8.6 ± 10.3	9.1 ± 10.9	0.872	9.8 ± 9.6	14.6 ± 13.1	0.205
Acoustic analysis									
Max. phonation time	10.3 ± 4.8	9.7 ± 4.5	0.565	12.1 ± 5.4 *	12.2 ± 4.8 **	0.954	11.3 ± 4.9	12.9 ± 5.3 **	0.328
(change from baseline)				1.7 ± 4.1	3.2 ± 3.9	0.182	1.0 ± 4.5	3.1 ± 4.3	0.159
GRB scores (sum)	5.0 ± 2.1	5.3 ± 2.0	0.475	2.7 ± 2.1 **	1.8 ± 2.0 **	0.084	3.1 ± 2.4 **	1.4 ± 1.8 **	**0.019**
(change from baseline)				2.4 ± 2.2	3.6 ± 1.9	**0.044**	2.1 ± 2.2	3.8 ± 1.6	**0.008**
Jitter	1.9 ± 1.6	2.1 ± 1.8	0.717	1.2 ± 0.9 *	1.5 ± 0.8	0.183	1.2 ± 1.2	1.2 ± 0.9	0.999
(change from baseline)				0.8 ± 1.6	0.7 ± 2.0	0.910	0.2 ± 1.3	0.4 ± 0.9	0.630
Shimmer	4.5 ± 3.2	4.5 ± 3.0	0.955	2.8 ± 0.9 **	3.2 ± 1.2 *	0.246	3.6 ± 2.7	3.4 ± 2.1 *	0.868
(change from baseline)				1.8 ± 3.3	1.4 ± 3.0	0.634	0.5 ± 3.7	0.9 ± 1.2	0.696
NHR	.14 ± .07	.14 ± .09	0.977	.14 ± .15	.12 ± .03	0.410	.16 ± .18	.13 ± .02	0.384
(change from baseline)				-.004 ± .17	.03 ± .10	0.468	-.04 ± .17	-.004 ± .03	0.330

*: p<0.05, paired t test, compared with baseline

**: p<0.01, paired t test, compared with baseline

†: Student's t-test, comparison between the two treatment groups

Table 6. Comparison of the baseline characters of the 51 patients of vocal fold cyst receiving VFSI or phonomicrosurgery (study 2)

Parameters	VFSI n= 30	Phonomicrosurgery n= 21	p value
Age	44 ± 12	41 ± 12	0.276
Gender (male / female)	10 / 20	8 / 13	0.726
Duration (>1 year / ≤ 1 year)	13 / 17	13 / 8	0.233
Smoking (active / nil)	6 / 24	3 / 18	0.598
Alcohol (+/-)	5 / 25	3 / 18	0.942
Hypertension (+/-)	5 / 25	1 / 20	0.194
Diabetes Mellitus (+/-)	2 / 28	1 / 20	0.776
Cardiovascular disease (+/-)	0 / 30	0 / 21	1.000
Vocal demand			0.140
professional	0	0	
high	9	9	
routine	21	12	
Reflux symptom index	13.6 ± 6.3	17.4 ± 9.7	0.154
Max. phonation time	12.0 ± 4.6	8.9 ± 5.6	**0.045** †
VHI-10	20.6 ± 8.4	27.6 ± 7.3	**0.003** †
Self-rating of voice quality	3.5 ± 1.8	2.4 ± 1.6	**0.022** †
Size of vocal lesions (pixels)	4.3 ± 5.1	2.8 ± 2.4	0.164
Acoustic analysis			
GRB scores (sum)	4.3 ± 2.0	5.4 ± 1.9	**0.042** †
Jitter	1.8 ± 1.2	2.5 ± 1.0	**0.041** †
Shimmer	4.6 ± 3.1	5.0 ± 3.6	0.679
NHR	.14 ± .08	.15 ± .07	0.915

†:Student's t-test

Table 7. Crude treatment outcomes following VFSI and phonomicrosurgery in patients of vocal fold cyst. (study 2).

Outcome parameters	Baseline			1 month			2 months		
	VFSI (n= 30)	Surgery (n= 21)	p value†	VFSI (n= 28)	Surgery (n= 18)	p value†	VFSI (n= 21)	Surgery (n= 13)	p value†
Subjective evaluation						0.288			0.639
complete remission				6 (21%)	3 (17%)		6 (29%)	4 (31%)	
much improve (>50%)				14 (50%)	14 (78%)		9 (43%)	7 (54%)	
some improve (≤50%)				6 (21%)	1 (6%)		6 (29%)	1 (8%)	
no effect				2 (7%)	0 (0%)		0 (0%)	1 (8%)	
Endoscopic evaluation						**0.011**			0.075
complete remission				6 (21%)	8 (44%)		6 (29%)	7 (54%)	
much improve				16 (57%)	10 (56%)		10 (48%)	5 (38%)	
some improve				3 (11%)	0 (0%)		4 (19%)	1 (8%)	
no effect				3 (11%)	0 (0%)		1 (5%)	0 (0%)	
Dynamic NGGA	9.2 ± 5.1	9.8 ± 5.5	0.681	11.5 ± 6.1 **	14.4 ± 5.4 **	0.650	11.9 ± 7.2	11.9 ± 6.0	0.988
(change from baseline)				2.9 ± 4.4	4.3 ± 4.5	0.320	2.7 ± 5.9	2.1 ± 5.7	0.826
Self-rating of voice quality	3.5 ± 1.8	2.4 ± 1.6	**0.022**	6.7 ± 2.3 **	7.1 ± 1.2 **	0.453	6.8 ± 2.2 **	7.2 ± 1.6 **	0.566
(change from baseline)				3.3 ± 2.5	4.4 ± 1.9	0.098	2.9 ± 2.7	4.8 ± 2.0	**0.025**
VHI-10	20.6 ± 8.4	27.6 ± 7.3	**0.003**	12.4 ± 9.8 **	11.7 ± 6.4 **	0.769	12.0 ± 8.1 **	9.7 ± 8.3 **	0.444
(change from baseline)				8.0 ± 9.3	16.4 ± 10.7	**0.010**	8.0 ± 8.4	18.0 ± 11.5	**0.013**
Acoustic analysis									
Max. phonation time	12.0 ± 4.6	8.9 ± 5.6	**0.045**	13.8 ± 12.1 *	13.1 ± 9.6 **	0.692	13.4 ± 4.6	13.0 ± 7.1 **	0.854
(change from baseline)				1.8 ± 4.2	4.0 ± 5.1	0.142	2.0 ± 4.9	4.3 ± 3.4	0.124
GRB scores (sum)	4.3 ± 2.0	5.4 ± 1.9	**0.042**	1.6 ± 1.8 **	1.3 ± 1.4 **	0.533	1.7 ± 1.8 **	1.9 ± 1.7 **	0.696
(change from baseline)				2.8 ± 2.2	4.2 ± 1.9	**0.028**	2.5 ± 1.8	3.7 ± 2.0	0.112
Jitter	1.8 ± 1.2	2.5 ± 1.0	**0.041**	1.3 ± 0.9 *	1.8 ± 1.1	0.120	1.1 ± 0.9 *	1.1 ± 0.4 *	0.839
(change from baseline)				0.5 ± 1.2	0.8 ± 1.4	0.583	0.8 ± 1.3	1.5 ± 1.0	0.126
Shimmer	4.6 ± 3.1	5.0 ± 3.6	0.679	3.5 ± 2.4 *	3.5 ± 1.9	0.976	3.3 ± 2.1 *	2.6 ± 1.4	1.993
(change from baseline)				1.2 ± 2.5	1.1 ± 3.4	0.911	1.5 ± 2.7	1.1 ± 2.0	0.640
NHR	0.1 ± 0.1	0.1 ± 0.1	0.915	.13 ± .06	.13 ± .03	0.577	.12 ± .04	.12 ± .03	0.563
(change from baseline)				.02 ± .05	.02 ± .07	0.978	.03 ± .10	.01 ± .08	0.422

*: p<0.05, paired t test, compared with baseline

**: p<0.01, paired t test, compared with baseline

†: Student's t test, compared between the two treatment groups

Table 8. Baseline characteristics after trimming extreme propensity scores in patients of vocal cysts. (study 2)

Parameters	VFSI n= 19	Phonomicrosurgery n= 16	p value
Age	42 ± 12	42 ± 11	0.899
Gender (Male/ Female)	8 / 11	5 / 11	0.508
Duration (>1 year / ≤ 1 year)	9 / 10	11 / 5	0.203
Smoking (active/nil)	3 / 16	2 / 14	0.782
Alcohol (+/-)	4 / 15	3 / 13	0.865
Hypertension (+/-)	2 / 17	1 / 15	0.653
Diabetes Mellitus (+/-)	1 / 18	1 / 15	0.900
Cardiovascular disease (+/-)	0 / 19	0 / 16	1.000
Voice dependence			0.678
Professional	0	0	
High	7	7	
Routine	12	9	
Reflux symptom index	15.1 ± 6.4	19.3 ± 9.4	0.168
Max. phonation time	12.0 ± 4.7	8.8 ± 5.5	0.072
VHI-10	24.7 ± 5.8	28.3 ± 6.7	0.103
Self-rating of voice quality	3.1 ± 1.1	2.5 ± 1.3	0.152
Size of vocal lesions (pixels)	3.6 ± 3.1	2.8 ± 1.8	0.103
Acoustic analysis			
GRB scores (sum)	4.6 ± 1.8	5.5 ± 2.1	0.178
Jitter	1.7 ± 0.8	2.5 ± 1.1	**0.035** †
Shimmer	3.9 ± 1.8	4.4 ± 2.6	0.577
NHR	.12 ± .03	.14 ± .08	0.402

†:Student's t-test

Table 9. Comparative effectiveness of vocal cysts receiving VFSI or phonomicrosurgery after trimming extreme propensity scores. (study 2)

Outcome parameters	Baseline			1 month			2 months		
	VFSI (n= 19)	Surgery (n= 16)	p value†	VFSI (n= 18)	Surgery (n= 15)	p value†	VFSI (n= 12)	Surgery (n= 9)	p value†
Subjective evaluation						0.082			0.810
complete remission				1 (6%)	2 (13%)		3 (25%)	2 (22%)	
much improve (>50%)				12 (67%)	12 (80%)		5 (42%)	6 (67%)	
some improve (≤50%)				3 (17%)	1 (7%)		4 (33%)	0 (0%)	
no effect				2 (11%)	0 (0%)		0 (0%)	1 (11%)	
Endoscopic evaluation						**0.022**			0.287
complete remission				3 (17%)	6 (40%)		3 (25%)	4 (44%)	
much improve				10 (56%)	9 (60%)		6 (50%)	4 (44%)	
some improve				3 (17%)	0 (0%)		3 (25%)	1 (11%)	
no effect				2 (11%)	0 (0%)		0 (0%)	0 (0%)	
Dynamic NGGA	8.7 ± 5.7	9.9 ± 6.1	0.547	10.4 ± 4.6 **	14.7 ± 5.9 **	**0.029**	9.2 ± 5.0	10.9 ± 6.5	0.588
(change from baseline)				2.3 ± 2.9	4.3 ± 4.4	0.156	0.7 ± 2.9	0.4 ± 5.2	0.895
Self-rating of voice quality	3.1 ± 1.1	2.5 ± 1.3	0.152	6.2 ± 2.4 **	7.1 ± 1.1 **	0.175	6.4 ± 2.0 **	7.1 ± 1.1 **	0.303
(change from baseline)				3.2 ± 2.6	4.6 ± 1.9	0.097	2.9 ± 2.7	4.4 ± 1.5	0.132
VHI-10	24.7 ± 5.8	28.3 ± 6.7	0.103	14.5 ± 10.1 **	12.3 ± 6.1 **	0.441	14.3 ± 8.5 **	11.0 ± 5.5 **	0.301
(change from baseline)				10.2 ± 10.3	16.9 ± 9.2	0.060	11.2 ± 8.2	17.0 ± 8.2	0.124
Acoustic analysis									
Max. phonation time	12.0 ± 4.7	8.8 ± 5.5	0.072	13.8 ± 4.2	13.6 ± 7.2 **	0.913	13.5 ± 4.2	14.2 ± 7.8 **	0.807
(change from baseline)				1.7 ± 4.0	5.1 ± 4.8	**0.042**	2.2 ± 4.2	5.0 ± 3.4	0.107
GRB scores (sum)	4.6 ± 1.8	5.5 ± 2.1	0.178	1.7 ± 1.9 **	1.6 ± 1.4 **	0.838	1.7 ± 1.6 **	2.0 ± 1.4 **	0.615
(change from baseline)				2.8 ± 2.5	4.1 ± 2.1	0.100	2.8 ± 1.5	3.6 ± 2.1	0.397
Jitter	1.7 ± 0.8	2.5 ± 1.1	**0.035**	1.2 ± 1.0 *	1.9 ± 1.2	0.077	1.0 ± 0.9	1.1 ± 0.4 **	0.705
(change from baseline)				0.5 ± 1.0	0.8 ± 1.6	0.538	0.6 ± 1.2	1.5 ± 1.0	0.085
Shimmer	3.9 ± 1.8	4.4 ± 2.6	0.577	3.1 ± 1.9 *	3.3 ± 2.0	0.742	3.1 ± 1.2	2.1 ± 0.9 *	0.061
(change from baseline)				0.8 ± 1.6	1.5 ± 3.4	0.524	0.7 ± 1.7	1.6 ± 1.7	0.285
NHR	.12 ± .03	.14 ± .08	0.402	.12 ± .03	.13 ± .03	0.219	.11 ± .02	.12 ± .03	0.838
(change from baseline)				.003 ± .03	.02 ± .08	0.533	.00 ± .03	.01 ± .09	0.808

*: p<0.05, paired t test, compared with baseline

**: p<0.01, paired t test, compared with baseline

†: Student's t-test, comparison between the two treatment groups

Table 10. Short-term treatment outcomes of VFSI among vocal nodules, polyp and cyst. (study 3)

Outcome parameters	Nodules			Polyp			Cyst			ANOVA test†	
	Pre (n=49)	1 m (n= 43)	2m (n=33)	Pre (n=47)	1 m (n=42)	2m (n=29)	Pre (n= 30)	1 m (n=28)	2m (n=21)	1 m	2 m
Subjective evaluation											
complete remission		0 (0%)	2 (6%)		6 (14%)	4 (14%)		6 (21%)	6 (29%)		
much improve (>50%)		23 (54%)	17 (52%)		24 (57%)	16 (55%)		14 (50%)	9 (43%)		
some improve (≤50%)		15 (34%)	10 (30%)		7 (17%)	8 (28%)		6 (21%)	6 (29%)		
no effect		5 (12%)	4 (12%)		5 (12%)	1 (3%)		2 (7%)	0 (0%)		
Endoscopic evaluation											
complete remission		6 (14%)	4 (12%)		8 (19%)	4 (14%)		6 (21%)	6 (29%)		
much improve		28 (65%)	15 (46%)		23 (55%)	14 (48%)		16 (57%)	10 (76%)		
some improve		7 (16%)	8 (24%)		10 (24%)	9 (31%)		3 (11%)	4 (14%)		
no effect		2 (5%)	6 (18%)		1 (2%)	2 (7%)		3 (11%)	1 (14%)		
Dynamic NGGA	10.5 ± 4.7	13.4 ± 5.2 **	14.9 ± 6.5 **	10.6 ± 8.1	15.3 ± 10.7 **	12.0 ± 7.9 **	9.2 ± 5.1	11.5 ± 6.1 **	11.9 ± 7.2		
(change from baseline)		2.5 ± 4.3	4.0 ± 5.6		4.7 ± 5.9	3.9 ± 6.4		2.9 ± 4.4	2.7 ± 5.9	0.134	0.767
Self-rating of voice quality	3.5 ± 1.7	6.3 ± 1.7 **	5.7 ± 2.0 **	2.9 ± 1.8	6.1 ± 1.7 **	6.7 ± 1.8 **	3.5 ± 1.8	6.7 ± 2.3 **	6.8 ± 2.2 **		
(change from baseline)		3.0 ± 2.1	2.3 ± 2.7		3.5 ± 2.0	3.9 ± 2.2		3.3 ± 2.5	2.9 ± 2.7	0.555	0.066
VHI-10	23.9 ± 7.4	15.4 ± 9.6 **	14.5 ± 9.7 **	23.1 ± 7.1	14.9 ± 9.4 **	12.8 ± 9.8 **	20.6 ± 8.4	12.4 ± 9.8 **	12.0 ± 8.1 **		
(change from baseline)		9.5 ± 9.9	8.5 ± 11.2		8.2 ± 10.4	11.2 ± 9.6		8.0 ± 9.3	8.0 ± 8.4	0.771	0.454
Max. phonation time	10.2 ± 4.1	12.6 ± 5.1 **	10.8 ± 4.2	9.9 ± 4.7	11.5 ± 4.9 **	11.4 ± 4.5	12.0 ± 4.7	13.8 ± 4.3 *	13.4 ± 4.6		
(change from baseline)		2.3 ± 3.8	0.9 ± 3.4		1.5 ± 3.6	1.0 ± 4.4		1.4 ± 5.0	1.8 ± 5.2	0.731	0.602
Acoustic analysis											
GRB scores (sum)	4.3 ± 1.8	2.0 ± 1.6 **	2.5 ± 1.8 **	4.8 ± 2.0	2.5 ± 1.9 **	2.6 ± 2.2 **	4.3 ± 2.0	1.6 ± 1.8 **	1.7 ± 1.8 **		
(change from baseline)		2.3 ± 2.2	1.6 ± 2.3		2.3 ± 2.0	2.1 ± 2.0		2.8 ± 2.2	2.5 ± 1.8	0.577	0.285
Jitter	1.6 ± 1.0	1.4 ± 0.7	1.3 ± 0.9 **	1.9 ± 1.4	1.4 ± 0.9 *	1.4 ± 1.3	1.8 ± 1.2	1.3 ± 0.9 *	1.1 ± 0.9 *		
(change from baseline)		0.2 ± 1.1	0.5 ± 0.9		0.6 ± 1.5	0.2 ± 1.2		0.5 ± 1.2	0.8 ± 1.3	0.313	0.219
Shimmer	3.2 ± 1.5	2.9 ± 1.0	3.6 ± 3.4	4.5 ± 2.8	3.1 ± 1.2 **	3.8 ± 2.5	4.6 ± 3.1	3.5 ± 2.4 *	3.3 ± 2.1 *		
(change from baseline)		0.3 ± 1.8	0.2 ± 2.1		1.5 ± 2.9	0.4 ± 3.3		1.2 ± 2.5	1.5 ± 2.7	0.251	0.386
NHR	0.2 ± 0.6	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.1 ± .04		
(change from baseline)		.11 ± .67	.15 ± .77		.00 ± .14	-.03 ± .15		.02 ± .05	.03 ± .10	0.071	0.452

Data are expressed as mean ± standard deviation

*: p<0.05, **: p<0.01, paired t test, compared with baseline

MPT: maximal phonaiton time

NHR: Noise to harmonic ratio

Table 11. Short-term treatment outcomes of VFSI among Reinke's edema, fibrous mass and pseudocyst. (study 3)

Outcome parameters	Reinke's edema			Fibrous mass			Pseudocyst		
	Pre (n= 12)	1 m (n= 11)	2m (n= 5)	Pre (n= 5)	1 m (n= 4)	2m (n-=2)†	Pre (n= 5)	1 m (n= 5)	2m (n= 2)†
Subjective evaluation									
complete remission		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)
much improve (>50%)		3 (27%)	3 (60%)		1 (25%)	1 (50%)		2 (40%)	1 (50%)
some improve (≤50%)		6 (55%)	0 (0%)		3 (75%)	1 (50%)		3 (60%)	0 (0%)
no effect		2 (18%)	2 (40%)		0 (0%)	0 (0%)		0 (0%)	1 (50%)
Endoscopic evaluation									
complete remission		0 (0%)	0 (0%)		1 (25%)	0 (0%)		1 (20%)	0 (0%)
much improve		5 (45%)	4 (80%)		2 (50%)	2 (100%)		2 (40%)	1 (50%)
some improve		4 (36%)	0 (0%)		1 (25%)	0 (0%)		1 (20%)	0 (0%)
no effect		2 (18%)	1 (20%)		0 (0%)	0 (0%)		1 (20%)	1 (50%)
Dynamic NGGA	15.7 ± 7.0	13.0 ± 5.3	12.7 ± 7.2	11.1 ± 3.4	10.1 ± 5.6		9.6 ± 6.4	11.9 ± 6.0	
(change from baseline)		-1.6 ± 5.9	1.4 ± 2.4		0.4 ± 5.9			2.3 ± 5.4	
Self-rating of voice quality	3.4 ± 2.2	4.4 ± 2.5	5.6 ± 1.9	3.6 ± 1.3	5.3 ± 1.2		2.6 ± 1.5	7.0 ± 1.6	
(change from baseline)		0.7 ± 3.3	2.8 ± 2.6		2.0 ± 1.7			5.0 ± 1.8	
VHI-10	24.2 ± 7.9	23.5 ± 11.2	24.0 ± 9.8	27.8 ± 4.7	26.3 ± 8.5		26.6 ± 7.1	12.2 ± 4.8	
(change from baseline)		1.0 ± 11.7	3.5 ± 5.7		3.5 ± 8.4			14.4 ± 8.4	
Acoustic analysis									
Max. phonation time	7.9 ± 4.0	8.9 ± 4.2	8.8 ± 2.5	10.6 ± 3.4	8.3 ± 1.7		13.6 ± 8.6	15.4 ± 5.8	
(change from baseline)		1.1 ± 2.9	1.5 ± 1.9		-1.3 ± 2.6			1.8 ± 3.3	
GRB scores (sum)	4.2 ± 1.6	3.2 ± 1.3	2.8 ± 2.2	4.8 ± 0.4	4.5 ± 1.7		5.4 ± 1.8	1.8 ± 2.7	
(change from baseline)		1.0 ± 1.7	1.8 ± 1.7		0.3 ± 1.3			3.6 ± 3.0	
Jitter	2.3 ± 1.3	1.7 ± 1.1	4.2 ± 4.1	2.1 ± 0.7	2.2 ± 0.7		3.1 ± 2.8	1.9 ± 1.1	
(change from baseline)		0.8 ± 1.2	-2.3 ± 3.4		0.0 ± 0.9			1.2 ± 2.2	
Shimmer	4.7 ± 2.7	4.1 ± 2.0	6.9 ± 3.4	5.2 ± 1.5	2.8 ± 0.4		9.6 ± 10.4	3.3 ± 1.2	
(change from baseline)		1.2 ± 2.5	-2.0 ± 3.7		2.1 ± 2.0			6.2 ± 9.7	
NHR	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.0		0.2 ± 0.1	0.1 ± 0.0	
(change from baseline)		-.01 ± .08	-.01 ± .10		.03 ± .05			.07 ± .09	

†: numeric values not provided due to scarse samples.

Table 12. Short-term treatment outcomes of VFSI between patients with and without post-operative side effects. (study 3)

Outcomes	1 month			2 months		
Presence of side effects	No (n= 90)	Yes (n= 43)	p value†	No (n= 66)	Yes (n= 26)	p value†
Subjective evaluation			0.652			0.160
complete remission	8 (9%)	4 (9%)		10 (15%)	2 (8%)	
much improve (>50%)	44 (49%)	23 (53%)		32 (48%)	15 (58%)	
some improve (≤50%)	27 (30%)	13 (30%)		21 (32%)	4 (15%)	
no effect	11 (12%)	3 (7%)		3 (5%)	5 (19%)	
Endoscopic evaluation			0.739			0.893
complete remission	14 (16%)	8 (19%)		10 (15%)	4 (15%)	
much improve	52 (58%)	24 (56%)		33 (50%)	13 (50%)	
some improve	17 (19%)	9 (21%)		16 (24%)	5 (19%)	
no effect	7 (8%)	2 (5%)		7 (11%)	4 (15%)	
Dynamic NGGA	13.7 ± 8.6	13.2 ± 6.1	0.710	13.2 ± 7.4	13.0 ± 6.5	0.921
(change from baseline)	2.7 ± 5.5	3.5 ± 4.8	0.393	3.7 ± 6.4	3.2 ± 3.9	0.679
Self-rating of voice quality	6.2 ± 2.0	6.1 ± 2.0	0.787	6.3 ± 2.0	6.0 ± 2.1	0.572
(change from baseline)	3.0 ± 2.6	3.1 ± 2.0	0.995	3.1 ± 2.8	2.8 ± 2.0	0.595
VHI-10	15.2 ± 9.8	15.3 ± 9.7	0.927	13.5 ± 9.9	15.3 ± 9.3	0.423
(change from baseline)	8.2 ± 10.6	7.8 ± 9.2	0.813	9.8 ± 10.5	7.0 ± 8.1	0.186
Acoustic analysis						
Max. phonation time	12.5 ± 5.3	11.5 ± 4.0	0.277	12.3 ± 4.9	10.0 ± 2.9	**0.007**
(change from baseline)	1.5 ± 4.1	2.4 ± 2.4	0.113	1.4 ± 4.3	1.2 ± 2.9	0.770
GRB scores (sum)	2.2 ± 1.9	2.3 ± 1.8	0.698	2.4 ± 2.1	2.3 ± 1.8	0.863
(change from baseline)	2.1 ± 2.2	2.5 ± 2.1	0.401	2.0 ± 2.3	2.0 ± 1.8	0.973
Jitter	1.5 ± 0.9	1.3 ± 0.7	0.096	1.4 ± 1.5	1.4 ± 1.2	0.769
(change from baseline)	0.3 ± 1.3	0.7 ± 1.2	0.136	0.4 ± 1.6	0.4 ± 1.1	0.897
Shimmer	3.3 ± 1.7	3.0 ± 1.1	0.153	3.7 ± 3.1	4.0 ± 2.0	0.553
(change from baseline)	1.2 ± 3.6	1.4 ± 2.0	0.563	1.0 ± 4.2	0.1 ± 2.4	0.200
NHR	.12 ± .04	.13 ± .13	0.526	.13 ± .06	.16 ± .16	0.408
(change from baseline)	.06 ± .46	.01 ± .13	0.320	.08 ± .54	-.02 ± .16	0.187

†: Student's t test, compared between the two groups

Table 13. Risk factors for vocal fold hematoma after VFSI. (study 3)

Analyses		Univariate			Multivariate	
Parameters		**Hematoma (n=37)**	**No hematoma (n=111)**	p value*	**aOR (95% CI)**	p value
Gender	(male / female)	3 (8%) / 34 (92%)	19 (17%) / 92 (83%)	0.182	1.74 (0.44 ~ 6.84)	0.431
Smoking	(active / nil)	2 (5%) / 35 (95%)	21 (19%) / 90 (81%)	0.065	0.21 (0.04 ~ 1.06)	0.058
Hypertension	(presence / absence)	4 (11%) / 33 (89%)	9 (8%) / 102 (92%)	0.615	1.33 (0.35 ~ 5.04)	0.671
Vocal demand	(high / routine)	19 (51%) / 18 (49%)	39 (35%) / 72 (65%)	0.080	2.32 (1.03 ~ 5.26)	**0.043**
Reflux	(presence / absence)	13 (35%) / 24 (65%)	46 (41%) / 65 (59%)	0.473	0.63 (0.27 ~ 1.48)	0.290
Ectasia/varicosity	(presence / absence)	14 (38%) / 23 (62%)	22 (20%) / 89 (80%)	**0.027**	3.39 (1.39 ~ 8.29)	**0.007**

*: Chi-square tests

aOR (95% CI): Adjusted odds ratio (95% confidence intervals) by multiple logistic regression model

Table 14. Comparison between trans-oral and trans-nasal injection approaches of VFSI. (Study 3)

Injection appraoches	Trans-oral	Trans-nasal	
Parameters	n=117	n=31	p value
Baseline			
Age	40 ± 11	41 ± 8	
Gender (Male/ Female)	18 / 99	4 / 27	0.729
Size of vocal lesions (pixels)	2.6 ± 3.2	2.1 ± 2.5	0.393
Max. phonation time	10.6 ± 4.4	9.6 ± 4.7	0.303
VHI-10	23.8 ± 7.4	21.2 ± 7.0	0.083
Self-rating of voice quality	3.3 ± 1.8	3.2 ± 1.4	0.650
GRB scores (sum)	4.4 ± 1.8	4.9 ± 1.9	0.159
Dynamic NGGA	10.7 ± 6.5	9.5 ± 5.1	0.290
Procedure			
Duration (min)	10.4 ± 7.9	10.2 ± 4.7	0.889
Precision			0.082
Good	70 (61%)	15 (48%)	
Acceptable	36 (31%)	9 (29%)	
Poor	11 (9%)	7 (23%)	
Discomfort level*			**0.01†**
No discomfort	29 (45%)	5 (28%)	
Slight discomfort	34 (53%)	9 (50%)	
Much discomfort	1 (2%)	3 (17%)	
Intolerable	0 (0%)	1 (6%)	
Outcome			
Max. phonation time	12.5 ± 5.1	10.7 ± 3.8	0.097
VHI-10	15.9 ± 9.9	12.4 ± 8.5	0.067
Self-rating of voice quality	6.2 ± 2.1	6.3 ± 1.2	0.764
GRB scores (sum)	2.2 ± 1.9	2.1 ± 1.6	0.694
Dynamic NGGA	14.0 ± 8.4	11.9 ± 4.8	0.141
Postoperative side effects			0.591
Hematoma	31 (27%)	6 (19%)	
Deposition	4 (3%)	3 (10%)	
Atrophy	1 (1%)	0 (0%)	

*: incomplete records

†: trend test

Table 15. Short-term prognostic factors of VFSI in vocal nodules. (study 3)

Outcomes parameters		Univariate			Multivariate	
VHI-10		**Responder (<=10)**	**Non-responder (>10)**	p value*	**aOR (95% CI)**	p value
Gender	(male / female)	2 (10%) / 19 (90%)	1 (4%) / 27 (96%)	0.390	14.3 (0.50 ~ 411)	0.121
Duration of symptoms	(>12m / ≤ 12m)	9 (43%) / 12 (57%)	8 (29%) / 20 (71%)	0.299	0.25 (0.05 ~ 1.16)	0.076
Vocal demand	(high / routine)	7 (33%) / 14 (67%)	18 (64%) / 10 (36%)	**0.032**	4.32 (1.06 ~ 17.6)	**0.042**
Smoking	(active / nil)	2 (10%) / 19 (90%)	2 (7%) / 26 (93%)	0.763	2.27 (0.18 ~ 28.1)	0.522
Reflux	(presence / absence)	6 (29%) / 15 (71%)	13 (46%) / 15 (54%)	0.204	1.76 (0.45 ~ 6.92)	0.422
Nodular type	(hard / soft)	6 (29%) / 15 (71%)	11 (39%) / 17 (61%)	0.436	1.99 (0.47 ~ 8.43)	0.348
		Univariate			**Multivariate**	
GRB scores		**Responder (<=1)**	**Non-responder (>1)**	p value*	**aOR (95% CI)**	p value
Gender	(male / female)	1 (6%) / 16 (94%)	2 (6%) / 30 (94%)	0.959	0.64 (0.02 ~ 17.6)	0.793
Duration of symptoms	(>12m / ≤ 12m)	6 (35%) / 11 (65%)	11 (34%) / 21 (66%)	0.949	1.30 (0.26 ~ 6.45)	0.753
Vocal demand	(high / routine)	9 (53%) / 8 (47%)	16 (50%) / 16 (50%)	0.845	0.45 (0.11 ~ 1.87)	0.274
Smoking	(active / nil)	3 (18%) / 14 (82%)	1 (3%) / 31 (97%)	0.114	0.09 (0.01 ~ 1.56)	0.099
Reflux	(presence / absence)	5 (29%) / 12 (71%)	14 (44%) / 18 (56%)	0.327	3.37 (0.72 ~ 15.7)	0.122
Nodular type	(hard / soft)	2 (12%) / 15 (88%)	15 (47%) / 17 (53%)	**0.010**	9.27 (1.40 ~ 61.3)	**0.021**

*: Chi-square test

aOR (95% CI): Adjusted odds ratio (95% confidence intervals) by multiple logistic regression model

Table 16. Short-term prognostic factors of VFSI in vocal polyp. (study 3)

Outcomes parameters		Univariate			Multivariate	
VHI-10		**Responder (<=10)**	**Non-responder (>10)**	p value*	**aOR (95% CI)**	p value
Gender	(male / female)	3 (20%) / 12 (80%)	3 (9%) / 29 (91%)	0.309	1.52 (0.19 ~ 11.9)	0.692
Duration of symptoms	(>12m / ≤ 12m)	3 (20%) / 12 (80%)	17 (53%) / 15 (47%)	**0.030**	4.20 (0.91 ~ 19.3)	0.066
Vocal demand	(high / routine)	6 (40%) / 9 (60%)	15 (47%) / 17 (53%)	0.659	1.55 (0.38 ~ 6.26)	0.542
Smoking	(active / nil)	3 (20%) / 12 (80%)	3 (9%) / 29 (91%)	0.309	0.46 (0.06 ~ 3.64)	0.458
Reflux	(presence / absence)	6 (40%) / 9 (60%)	14 (44%) / 18 (56%)	0.809	0.88 (0.21 ~ 3.70)	0.863
Polyp type	(Fibrous / others)	1 (7%) / 14 (93%)	5 (16%) / 27 (84%)	0.391	3.70 (0.29 ~ 47.9)	0.317

		Univariate			Multivariate	
GRB scores		**Responder (<=1)**	**Non-responder (>1)**	p value*	**aOR (95% CI)**	p value
Gender	(male / female)	3 (27%) / 8 (73%)	3 (8%) / 33 (92%)	0.131	3.00 (0.25 ~ 35.5)	0.384
Duration of symptoms	(>12m / ≤ 12m)	3 (27%) / 8 (73%)	17 (47%) / 19 (53%)	0.242	1.33 (0.22 ~ 8.21)	0.756
Vocal demand	(high / routine)	5 (45%) / 6 (55%)	16 (44%) / 20 (56%)	0.953	1.79 (0.33 ~ 9.68)	0.502
Smoking	(active / nil)	2 (18%) / 9 (82%)	4 (11%) / 32 (89%)	0.539	0.31 (0.01 ~ 6.83)	0.458
Reflux	(presence / absence)	1 (9%) / 10 (91%)	19 (53%) / 17 (47%)	**0.014**	14.5 (1.33 ~ 157)	**0.028**
Polyp type	(Fibrous / others)	0 (0%) / 11 (100%)	6 (17%) / 30 (83%)	0.312	>1 (unavailable†)	-

*: Chi-square test

aOR (95% CI): Adjusted odds ratio (95% confidence intervals) by multiple logistic regression model

†: Unable to estimate due to the presence of 0 subjects

Table 17. Short-term prognostic factors of VFSI in vocal cysts. (study 3)

Outcomes parameters		Univariate			Multivariate	
VHI-10		**Responder (<=10)**	**Non-responder (>10)**	p value*	**aOR (95% CI)**	p value
Gender	(male / female)	6 (46%) / 7 (54%)	5 (29%) / 12 (71%)	0.602	1.45 (0.28 ~ 7.45)	0.660
Duration of symptoms	(>12m / ≤ 12m)	6 (46%) / 7 (54%)	6 (35%) / 11 (65%)	0.547	0.54 (0.11 ~ 2.79)	0.466
Vocal demand	(high / routine)	1 (8%) / 12 (92%)	4 (24%) / 13 (76%)	0.249	2.83 (0.22 ~ 36.4)	0.424
Smoking	(active / nil)	2 (15%) / 11 (85%)	4 (24%) / 13 (76%)	0.581	1.64 (0.21 ~ 13.0)	0.641
Reflux	(presenc / absence)	2 (15%) / 11 (85%)	8 (47%) / 9 (53%)	0.119	4.11 (0.64 ~ 26.3)	0.136
		Univariate			**Multivariate**	
GRB scores		**Responder (<=1)**	**Non-responder (>1)**	p value*	**aOR (95% CI)**	p value
Gender	(male / female)	6 (38%) / 10 (63%)	4 (29%) / 10 (71%)	0.605	1.77 (0.30 ~ 10.5)	0.529
Duration of symptoms	(>12m / ≤ 12m)	9 (56%) / 7 (44%)	3 (21%) / 11 (79%)	0.072	0.20 (0.03 ~ 1.21)	0.080
Vocal demand	(high / routine)	3 (19%) / 13 (81%)	2 (14%) / 12 (86%)	0.743	0.37 (0.03 ~ 4.31)	0.427
Smoking	(active / nil)	4 (25%) / 12 (75%)	2 (14%) / 12 (86%)	0.464	0.66 (0.08 ~ 5.36)	0.698
Reflux	(presenc / absence)	4 (25%) / 12 (75%)	6 (43%) / 8 (57%)	0.301	3.37 (0.52 ~ 21.7)	0.201

*: Chi-square test

aOR (95% CI): Adjusted odds ratio (95% confidence intervals) by multiple logistic regression model

Table 18. Demographics and disease severities between subjects with or without treatment failures following VFSI.

Treatment outcome	Effective	Failure	p value
	n=110	n= 29	
Demographics			
Age	39 ± 10	39 ± 10	0.914
Gender (Male/ Female)	18 / 92	5 / 24	0.910
Duration (>1 year / ≤ 1 year)	51 / 59	20 / 9	0.138
Smoking (active/nil)	16 / 94	4 / 25	0.918
Alcohol (+/-)	16 / 94	4 / 25	0.918
Hypertension (+/-)	10 / 100	4 / 25	0.454
Diabetes Mellitus (+/-)	2 / 108	1 / 28	0.591
Cardiovascular disease (+/-)	2 / 108	1 / 28	0.591
Reflux symptom index	14.2 ± 7.6	15.9 ± 8.7	0.332
Voice dependence			0.761
Professional	6	2	
High	54	16	
Routine	50	11	
Disease severity			
Max. phonation time	10.5 ± 4.2	10.5 ± 5.3	0.981
VHI-10	22.0 ± 8.1	26.1 ± 6.2	**0.005**
Self-rating of voice quality	3.7 ± 1.8	2.8 ± 1.4	**0.016**
Size of vocal lesions (pixels)	2.5 ± 2.5	1.9 ± 1.6	0.103
GRB scores (sum)	4.6 ± 1.9	5.0 ± 2.1	0.359

Table 19. Prognostic factors of long-term treatment failure after VFSI. (study 4)

Diseases		Overall (n=139)		Nodules (n=50)		Polyp (n=57)		Cyst (n=32)	
Factors		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Gender	(male / female)	0.98 (0.34 ~ 2.8)	0.943	3.05 (0.36 ~ 26)	0.274	0 ~ 1 (unavailable†)	0.109	2.10 (0.45 ~ 9.8)	0.320
Duration of symptoms	(>12m / ≤ 12m)	0.57 (0.25 ~ 1.3)	0.167	0.13 (0.02 ~ 1.1)	**0.023**	2.60 (0.76 ~ 8.9)	0.106	0 ~ 1 (unavailable†)	**0.038**
Vocal demand	(high / routine)	1.05 (0.49 ~ 2.3)	0.993	1.27 (0.35 ~ 4.6)	0.716	0.72 (0.22 ~ 2.3)	0.577	2.70 (0.43 ~ 16.8)	0.254
Smoking	(active / nil)	0.95 (0.31 ~ 2.9)	0.841	1.88 (0.38 ~ 9.2)	0.420	0.46 (0.06 ~ 3.7)	0.443	0.72 (0.08 ~ 6.3)	0.760
Reflux	(presence / absence)	1.45 (0.67 ~ 3.2)	0.346	1.64 (0.39 ~ 6.9)	0.492	1.35 (0.42 ~ 4.3)	0.601	1.62 (0.35 ~ 7.5)	0.522

HR (95% CI): Hazard ratio (95% confidence intervals), calculated by Cox regression model (univariate, unadjusted value)

†: Unable to estimate due to the presence of zero event within strata

p value: Claculated using Log-rank test

Table 20. Long-term treatment outcome of VFSI between patients with different follow-up status. (study 4)

Follow-up status	Adherent n=119	Lost n= 20	p value
Demographics			
Age	40 ± 10	35 ± 9	**0.044**
Gender (Male/ Female)	17 / 102	6 / 14	0.080
Duration (>1 year / ≤ 1 year)	50 / 69	10 / 10	0.505
Smoking (active/nil)	16 / 103	4 / 16	0.440
Alcohol (+/-)	16 / 103	4 / 16	0.440
Voice dependence			0.837
Professional	7	1	
High	61	9	
Routine	51	10	
Residence			0.272
Taipei / New Taipei city	101 (85%)	15 (75%)	
Others	18 (15%)	5 (25%)	
Disease severity			
Max. phonation time	10.3 ± 4.4	11.7 ± 4.3	0.208
VHI-10	22.6 ± 7.5	24.5 ± 10.0	0.522
Self-rating of voice quality	3.6 ± 1.8	3.4 ± 1.9	0.759
Size of vocal lesions (pixels)	2.4 ± 2.3	1.7 ± 0.5	0.586
GRB scores (sum)	4.7 ± 2.0	4.2 ± 1.9	0.322
Treatment outcomes			
6 months			
Self-rating of voice quality	6.5 ± 2.1	7.3 ± 2.5	0.517
VHI-10	13.3 ± 9.5	12.0 ± 10.4	0.817
12 months			
Self-rating of voice quality	7.3 ± 2.0	7.5 ± 2.2	0.727
VHI-10	7.3 ± 9.4	4.6 ± 7.0	0.375
18 months			
Self-rating of voice quality	7.8 ± 1.7	6.8 ± 2.5	0.212
VHI-10	6.1 ± 7.7	5.7 ± 5.8	0.889
24 months			
Self-rating of voice quality	8.1 ± 1.0	8.5 ± 0.7	0.566
VHI-10	4.5 ± 5.8	4.5 ± 5.6	0.984

IX. Appendices

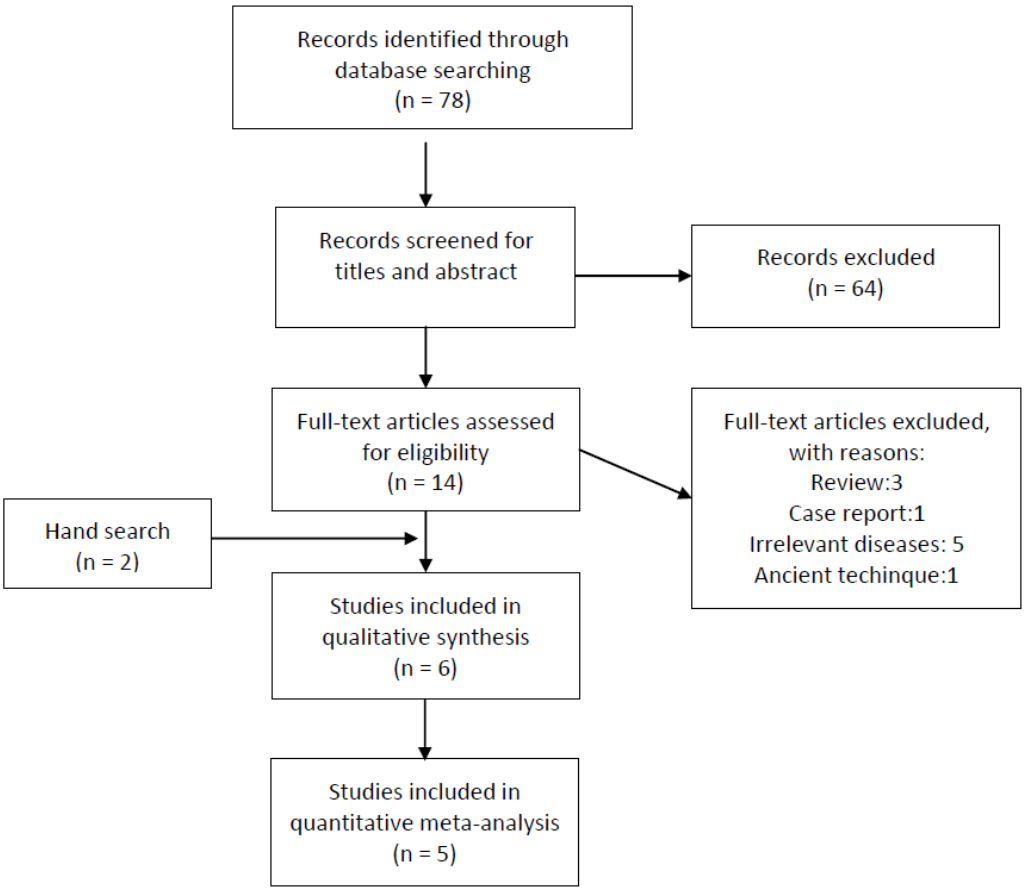
Appendix I: Cost analysis of VFSI, VHE, voice therapy, and phonomicrosurgery for benign vocal fold lesions

Item	$ (NTD)	Note
Vocal hygiene		
Outpatient clinic	$ 1, 380	ENT * 3 (Unit price $ 460)
Endoscopy	$ 2, 580	Laryngoscope * 1 ($ 500) Stroboscope * 1 ($ 2,080)
Productivity loss	$ 1, 253 ($835 ~ $1, 671)	OPD visits: (0.25~0.5) day/ * 3 = 0.75 ~ 1.5 days Work days: 20 days/ month Average wage: $ 40, 114 Labor participation rate: 0.58 Unemployment rate: 0.04 $ 40,114 * (0.75~1.5/20)*0.58*(1-0.04) = $835 ~$1, 671
Sum	**$ 5, 213 ($ 4, 795 ~$ 5, 631)**	
Voice therapy		
Outpatient clinic	$ 1, 380	ENT * 2 + Rehab * 1 (Unit price $ 460)
Endoscopy	$ 2, 580	
Therapy sessions	$ 2, 760	$ 460 * 6 = $ 2,760
Productivity loss	$ 3, 760 ($2,506~ $5,013)	Therapy sessions: (0.25~0.5) day/ * 6 = 1.5~3 days OPD visits: (0.25~0.5) day/ * 3 = 0.75 ~ 1.5 days $ 40,114 * (2.25~4.5/20)*0.58*(1-0.04) = $2,506 ~$5,013
Sum	**$ 10,480 ($ 9,226 ~ $ 11, 733)**	

Vocal fold steroid injection		
Outpatient clinic	$ 1, 380	ENT * 3 (Unit price $ 460)
Endoscopy	$ 2, 580	
Injection needle	$ 700	Disposable needle
Procedure	$ 6, 349	66003B (vocal fold injection)
Productivity loss	$ 2, 646 ($1, 949 ~ $ 3,342)	OPD visits: (0.25~0.5) day/ * 3 = 0.75 ~ 1.5 days Procedure: 0.5 day Voice rest: 1 day * weight (0.5~1) (3 days – 2 days of weekend) $ 40,114 * (1.75~ 3/20) *0.58*(1-0.04) = $1, 949 ~ $ 3,342
Sum	**$ 13,655 ($ 12, 958 ~ $ 14, 351)**	

Phonomicrosurgery		
outpatient clinic	$ 1, 380	ENT * 3 (Unit price $ 460)
Endoscopy	$ 2, 580	
Admission+Surgery	$ 26, 171	DRG package (05506 耳鼻咽喉手術無併發症者)
Productivity loss	$ 6, 545 ($ 4, 177 ~ $ 8, 912)	OPD visits: (0.25~0.5) day/ * 3 = 0.75 ~ 1.5 days Procedure: 0.5 days Admission (Optional): 0~1 days Voice rest: 5 days * weight (0.5~1) (7 days – 2 days of weekend) $ 40,114* (3.75 ~ 8/20) *0.58*(1-0.04) = $ 4, 177 ~ $ 8, 912
Sum	**$ 36, 676 ($ 34,308 ~ $ 39,043)**	

Appendix II. Flow diagram in the systematic literature review.



Appendix III. Systematic review of VFSI in benign vocal fold lesions.

Authors (Year)	Diagnosis	N	Steroid†	F/u	Outcome measurement					Recur
					Subjective	Aerodynamic	Acoustic	Perceptual	Endoscopy	
Tateya, et al.[16] (2003)	Reinke's edema (R.E.)	42	T	4 wk	Disappear: 16(38%) Improved: 25(60%) No change: 1(2%)	MPT: 9.0 → 11.4s*	F0: M: 86 → 130Hz F: 168 → 181Hz*		Disappeared: 14(33%) Improved: 27(64%) No change: 1(3%)	13 (31%)
Tateya, et al.[17] (2004)	Nodules	28	T	3 wk	Disappear: 14(61%) Improved: 8(35%) No change: 1(4%)	MPT: 10.9 → 13.9s* MFR: 236 → 166 mL/s*			Disappeared: 17(63%) Improved: 10(37%)	8 (29%)
Mortensen & Woo[18] (2006)	Scar Nodules Polyp/cyst Granuloma	34	M	1 m	Improvement: 82%			GRBS*	Improvement of edge, amplitude, wave, vibration*	NA
Hsu, et al.[19] (2009)	Polyp	22	T	3 m	VHI: 54.3 → 38.2*	MPT: 10.67 → 13.55* MFR: 177 → 168 mL/s	Jt: 3.77 → 2.09* Sm: 8.44 → 3.84* NHR: 0.24 → 0.14*	GRBAS*	Disappeared: 5(23%) Improved: 15(68%) No change: 2(9%)	2 (9%)
Lee, et al.[20] (2011)	Nodules	80	T	4 wk	VHI: 57.1 → 18.9*	MPT: 10.32 → 12.79*	F0: 198 → 201Hz Jt: 2.46 → 0.93* Sm: 6.41 → 8.20 NHR: 0.52 → 0.27*		Disappeared: 35(44%) Improved: 39(49%) No change: 6(7%)	6 (8%)
Woo, et al.[21] (2011)	R.E. Nodules Polyp Scar	115	T	6 m	VHI: 49.2 → 36.8*	MPT: 12.67 → 12.27	Jt: 2.03 → 1.41* Sm: 4.14 → 3.31* HNR: 22.54 → 23.65	Sum of GRBAS 4.60 → 1.90*	Mucosal wave 1.86 → 2.23* Glottis closure 1.89 → 2.34*	5 (4%)

†T: Triamcinolone; M: Methylprednisolone.
*Indicate of statistical significance ($p<0.05$).
VHI: Voice handicap index.
MPT: Maximal phonation time; MFR: Mean flow rate.
F0: Fundamental frequency; Jt: Jitter (%); Sm: Shimmer (%).
NHR: Noise to harmonic ratio; HNR: Harmonic to noise ratio.

Appendix IV. Quality assessment in the systematic review.

TABLE II.
Quality Assessment Using the MINORS*

Study (Year)	Tateya, et al. (2003)	Tateya, et al. (2004)	Mortensen & Woo (2006)	Hsu, et al. (2009)	Lee, et al. (2011)	Woo, et al. (2011)
1. A clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	0	0	0	0	0	0
3. Prospective collection of data	0	0	0	2	0	2
4. Endpoints appropriate to the aim of the study	2	2	1	2	2	2
5. Unbiased assessment of the study endpoint	1	1	1	1	1	2
6. Follow-up period appropriate to the aim of the study	1	1	1	2	1	2
7. Loss to follow up less than 5%	1	1	1	2	2	2
8. Prospective calculation of the study size	0	0	0	0	0	0
SUM	8	8	6	11	8	12

*The items are scored as 0: not reported, 1: reported but inadequate or 2: reported and adequate.

MINORS: Methodological index for non-randomized studies.

Appendix V. Treatment outcomes of transnasal endoscopic steroid injection in the original series of 30 patients

Measurement Parameters	Mean (Standard Deviation)		
	Baseline	1 Month	3 Months
MPT	11.0 (4.2)	13.0 (4.7)*	13.2 (4.0)*
VHI-10	22.5 (7.3)	16.4 (10.0)†	14.5 (13.6)*
Jitter, %	1.98 (1.43)	1.40 (0.93)*	1.05 (0.54)*
Shimmer, %	4.08 (3.86)	2.78 (1.59)*	2.51 (0.86)*
NHR	0.13 (0.06)	0.12 (0.04)	0.10 (0.03)
Sum of GRB scale	3.43 (1.89)	1.83 (1.84)†	1.15 (1.17)†

*$P < .05$, paired t test, compared with baseline.
†$P < .01$, paired t test, compared with baseline. GRB = grade, roughness, breathiness; MPT = maximal phonation time; NHR = noise-to-harmonic ratio; VHI-10 = 10-item voice handicap index.

Appendix VI. Self-filled questionnaire during the first clinical visit

姓名：_____ 病歷號碼：_____ 性別：男 ／ 女 年齡：_____

日期：_____ 連絡電話：_____

1. 今天就診的主要問題為何？_____

2. 這樣的症狀持續多久？_____

3. 如何發生的？（1）突然_____（2）逐漸變差_____（3）時好時壞_____（4）從小開始____

4. 您是否曾至其他醫療機構就診？ 是（院所名稱）_____／否

   就診時診斷為何？_____

5. 您是否有以下症狀或習慣？（✔請勾選有的部分即可）

   ☐ 聲音沙啞 ☐ 說話久了容易累 ☐ 喉嚨有異物感

   ☐ 音域變窄 ☐ 說話多了喉嚨痛 ☐ 胸口有灼熱感

   ☐ 說話音量變小 ☐ 喉嚨常覺得乾 ☐ 時常吃宵夜

   ☐ 吞東西容易嗆到 ☐ 眼睛乾澀 ☐ 鼻涕倒流

   抽菸 ☐ 無 ☐ 已戒 ☐ 有 一天抽_____包

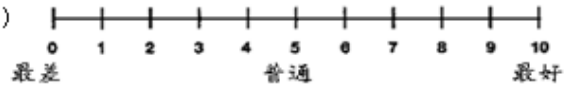
   喝酒 ☐ 無 ☐ 已戒 ☐ 有 偶爾喝 _____ 每周喝 _____ 幾乎每天 _____

6. 一天之中，聲音最差(1）早上_____（2）下午/ 晚上_____（3）都一樣_____（4）不一定___

7. 您的工作為何？ _____ 是否需要經常說話（下列請選擇一項）

   （1）一直說話 _____（2）經常需要 _____（3）偶而需要_____（4）不需要_____

8. 請您為自己的聲音品質打分數 （圈選）



9. 請問您是否有內外科之重要疾病？_____

   ☐ 糖尿病 ☐ 高血壓 ☐ 心臟病 是否有服藥控制？ 是 ／ 否

10. 您是否曾經接受過聲帶或喉部之手術？ 是（請列出）_____

Appendix VII. Mandarin Chinese version of 10-item voice handicap index (VHI-10).

聲音障礙自我評量表

MPT_____,_____,_____

下述問題請 **依照目前個人經驗** ，包含針對別人提及您的聲音，以及聲音問題所造成對您生活的影響....等，再下列欄位中，勾選您的感受。

	從來沒有	很少	有時候	經常	總是如此
1. 我的聲音沙啞很難讓人聽清楚	0	1	2	3	4
2. 在吵雜室內，別人更難聽懂我說什麼	0	1	2	3	4
3. 聲音沙啞限制了我的個人與社交活動	0	1	2	3	4
4. 聲音沙啞使我無法與人順利交談	0	1	2	3	4
5. 發出聲音或是說話使我覺得很吃力	0	1	2	3	4
6. 我無法預測何時不會再沙啞	0	1	2	3	4
7. 我的聲音沙啞困擾著我	0	1	2	3	4
8. 我的聲音沙啞使我覺得有障礙	0	1	2	3	4
9. 別人常問"你的聲音怎麼了"	0	1	2	3	4
10. 我的聲音問題影響我的收入	0	1	2	3	4

總分_____

Appendix VIII: Printed document of vocal hygiene education (VHE)

1 多喝水

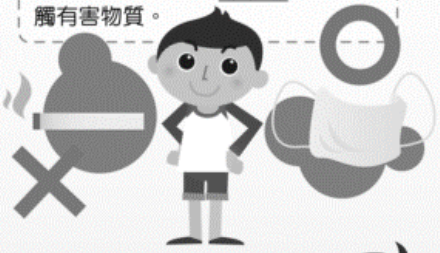
時常喝水或吸入濕蒸汽可以讓話說得輕鬆，減少振動聲帶的傷害。另外，市售感冒藥常會減少呼吸道黏液的分泌，請記得多喝溫開水來舒緩口乾舌燥的副作用。

2 飲食控制

避免食用油炸或刺激性食物，如烈酒、辣椒、濃茶、咖啡、冰品等。甜食或宵夜（睡覺前4小時內）則容易誘發胃酸逆流並導致逆流性咽喉炎（喉嚨卡卡、有異物感），應盡量節制。

3 減少抽菸或接觸二手菸

抽菸會造成聲帶慢性發炎與水腫，使得音質變得低沉與粗啞，長久下來會演變成白斑甚至喉癌，可說是百害而無一利。此外，台灣地區空氣品質不佳，騎機車或在馬路上行走時可以儘量戴口罩以減少接觸有害物質。



4 調整說話方式

『四不』原則如下：不用力，不大聲，不長舌，不急躁。在吵雜環境中說話應使用麥克風，或盡可能拉近說話的距離。時時提醒自己放慢說話速度，不要一口氣說太長的句子。如果您時間許可，請參加音聲復健療程，由專業的語言治療師來指導您發聲的技巧。

5 充分的休息

如果您工作上需要一直說話，下班後請讓聲帶徹底休息，減少非必要的使用（如聊天、唱卡拉OK）。當音質出現變化或說話容易累的時候，則應該徹底休息二至三天，以免聲帶發生不可回復之病變。

6 不可用力『清喉嚨』

當咽喉的異物感難以忍受時，請多喝溫開水來緩解。若您為逆流性咽喉炎的患者，除了調整飲食習慣外，睡覺時可以把枕頭墊高以減少胃液逆流的發生。

7 多運動

每周兩至三次、持續20分鐘以上的有氧運動（如游泳、爬山、健走等等），可以有效提升肺活量，減緩聲帶肌肉及韌帶的自然老化，讓您中氣十足，聲如洪鐘！

Appendix IX: Reflux Symptom Index (RSI).

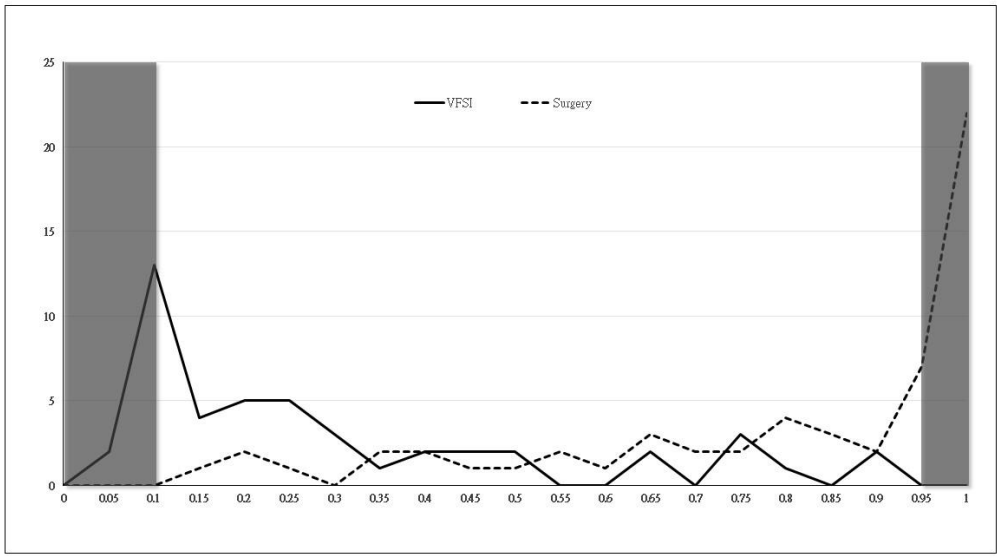
胃酸逆流症狀評量表

為了解您是否有胃酸逆流症狀及症狀的嚴重程度，煩請您對下表的九個症狀 **依照目前個人經驗**，勾選您的嚴重度謝謝！

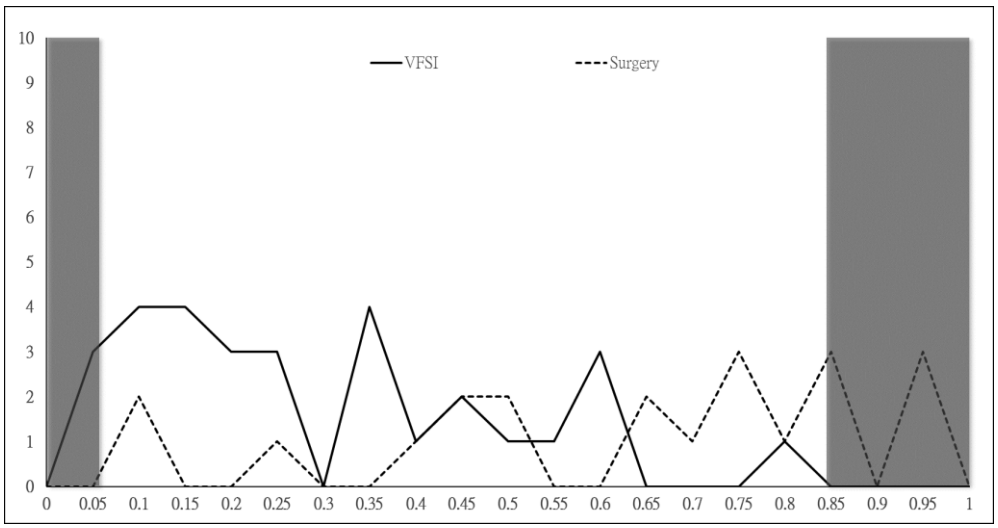
		沒有	很輕微	輕度	中度	重度	很嚴重
1	聲音沙啞或嗓音有問題	0	1	2	3	4	5
2	想清喉嚨的症狀	0	1	2	3	4	5
3	喉部有過多的黏液或有鼻涕倒流	0	1	2	3	4	5
4	吞嚥食物、液體或藥丸時有困難	0	1	2	3	4	5
5	在用餐後或平躺時有咳嗽現象	0	1	2	3	4	5
6	呼吸困難或有陣發性的嗆到感	0	1	2	3	4	5
7	嚴重惱人的咳嗽	0	1	2	3	4	5
8	喉嚨有東西卡住或有腫塊現象	0	1	2	3	4	5
9	胸口灼熱、疼痛、消化不良或胃酸跑上來的感覺	0	1	2	3	4	5

總分_____

Appendix X. Distribution of propensity scores between patients of vocal polyp and cyst receiving VFSI or phonomicrosurgery.



Vocal polyp



Vocal cyst

Note: Shaded area indicated patients with extreme, non-overlapped values of propensity scores, which were removed from further comparative analyses.

Appendix XI. Structured telephone interview for long-term treatment outcomes following VFSI.

問題一: 請問您治療後到目前為止，發聲困難的症狀是否有復發的情況？
有_____ 無_____
有: 大概甚麼時間（_____年/_____月）
是否有再就醫? 或接受治療/手術 ？
____ 門診吃藥 / _____醫院 _____手術 / ____語言治療 / 其他_____

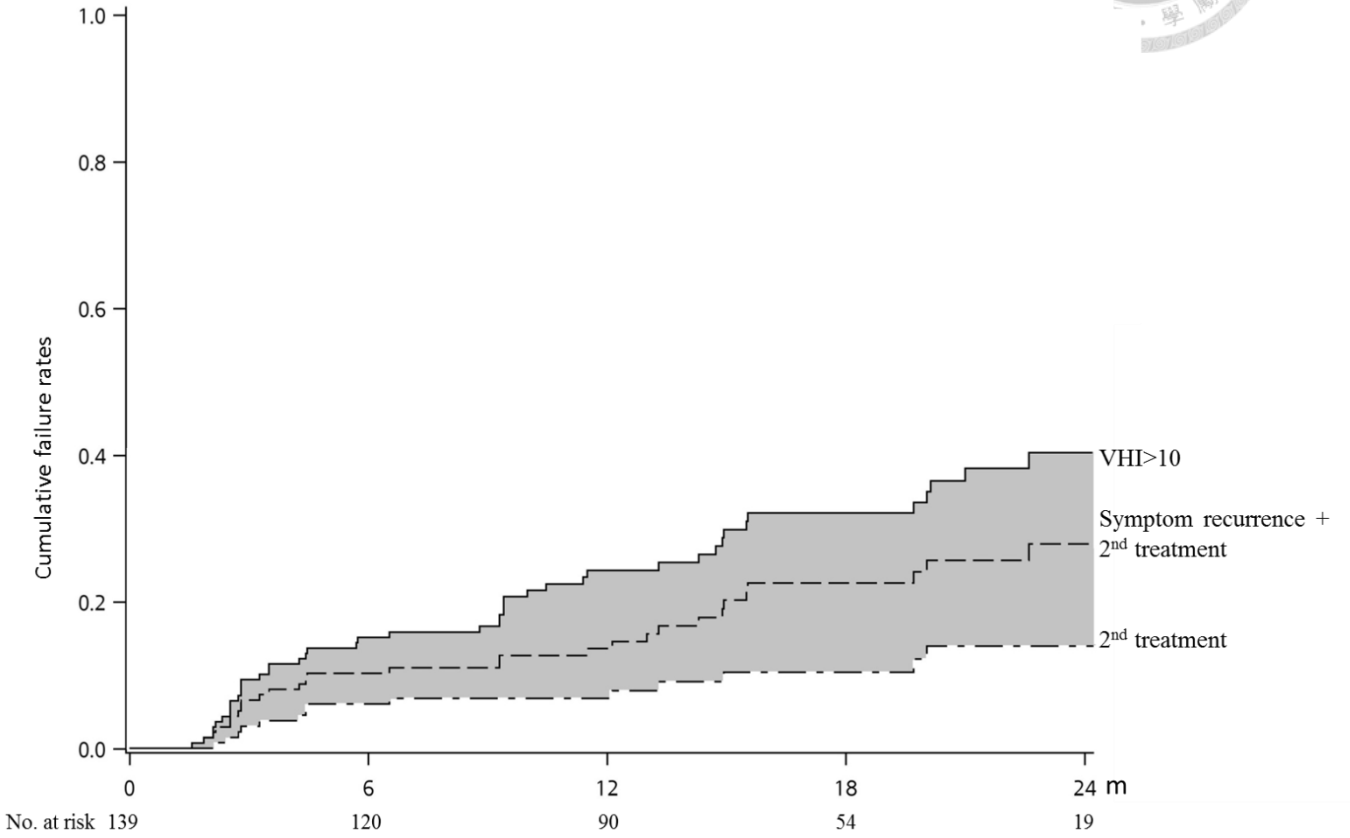
問題二: 請問您跟治療前比較起來，情況改善

1. (幾乎)完全好了
2. 好很多(進步一半以上)
3. 好一點(進步一半以下)
4. 沒改善，跟治療前一樣
5. 比治療前更差

問題三: 打分數 _____ (0:最差 10 :最好)

問題四: VHI 問卷（見 Appendix VII）

Appendix XII. Sensitivity analyses for the estimation of treatment



failures after VFSI using different criterias.

Appendix XIII. Controlling baseline heterogeneity between treatments by matching propensity scores

Diseases	Vocal polyp			Vocal cyst		
Parameters	VFSI n=21	Surgery n=21	p value	VFSI n= 13	Surgery n= 13	p value
Age	41 ± 8	43 ± 10	0.346	45 ± 10	44 ± 10	0.938
Gender (male / female)	6 / 15	5 / 16	0.729	5 / 8	5 / 8	1.000
Duration (>1 year / ≤ 1 year)	5 / 16	7 / 13	0.437	4 / 9	8 / 5	0.123
Smoking (active / nil)	6 / 15	6 / 15	1.000	3 / 10	2 / 11	0.626
Alcohol (+/-)	1 / 20	2 / 19	0.824	2 / 11	2 / 11	1.000
Vocal demand			0.142			0.429
professional	3	0		0	0	
high	9	9		6	4	
routine	9	12		7	9	
Reflux symptom index	18.6 ± 9.0	15.3 ± 10.7	0.969	13.1 ± 6.2	18.7 ± 10.7	0.481
Max. phonation time	10.2 ± 4.9	11.0 ± 4.9	0.558	10.8 ± 4.0	10.3 ± 6.5	0.725
VHI-10	24.2 ± 8.2	24.9 ± 9.0	0.793	22.2 ± 7.5	26.3 ± 7.2	0.229
Self-rating of voice quality	2.4 ± 1.7	2.3 ± 1.6	0.803	2.7 ± 1.4	2.9 ± 1.6	0.513
Size of vocal lesions (pixels)	3.7 ± 3.0	3.4 ± 2.2	0.612	6.3 ± 7.2	2.9 ± 2.5	0.156
GRB scores (sum)	5.3 ± 2.2	5.4 ± 1.6	0.938	4.8 ± 1.6	4.7 ± 1.6	0.781

Appendix XIV. Statified analysis by 3 groups of propensity scores in patients of vocal polyps receving VFSI or phonomicrosurgery.

Propensity score groups	**group 1**			**group 2**			**group 3**		
Treatments	**VFSI (n=18)**	**Surgery (n=20)**	p value	**VFSI (n=18)**	**Surgery (n=20)**	p value	**VFSI (n=17)**	**Surgery (n=20)**	p value
Age	33 ± 7	42 ± 10	**0.003**	39 ± 2	46 ± 3	**0.042**	47 ± 9	41 ± 12	0.089
Gender (male / female)	0 / 18	4 / 16	0.113	4 / 14	7 / 13	0.245	4 / 11	12 / 8	0.050
Duration (>1 year / ≤ 1 year)	8 / 10	7 / 13	0.202	6 / 12	7 / 13	0.877	5 / 12	8 / 12	0.686
Smoking (active / nil)	0 / 18	5 / 15	0.053	2 / 16	6 / 14	0.257	5 / 12	11 / 9	0.094
Alcohol (+/-)	0 / 18	2 / 18	0.492	0 / 18	2 / 18	0.193	2 / 15	7 / 13	**<0.001**
Vocal demand			**0.031**			**0.022**			0.266
professional	2	0		3	0		0	0	
high	#	9		8	#		8	9	
routine	4	#		5	8		9	11	
Polyp type			**0.017**			**<0.001**			**<0.001**
hemorrhagic	0	2		0	#		3	16	
fusiform	#	#		#	4		9	2	
pedunculated	3	2		2	2		1	0	
fibrous	0	3		2	3		4	2	
Reflux symptom index	13.4 ± 7.0	14.0 ± 9.1	0.839	14.4 ± 8.6	13.9 ± 9.0	0.889	20.6 ± 9.4	12.6 ± 6.6	**0.018**
Max. phonation time	9.7 ± 4.0	10.1 ± 5.0	0.815	10.3 ± 1.4	8.8 ± 0.9	0.336	9.7 ± 4.4	9.1 ± 4.5	0.686
VHI-10	21.3 ± 5.5	24.3 ± 8.1	0.216	23.1 ± 8.4	25.7 ± 9.2	0.401	25.0 ± 7.0	22.0 ± 8.7	0.272
Self-rating of voice quality	3.5 ± 1.8	2.8 ± 1.8	0.226	2.8 ± 1.9	2.2 ± 2.0	0.366	2.5 ± 1.7	3.1 ± 1.5	0.305
Size of vocal lesions (pixels)	1.6 ± 1.0	3.0 ± 1.7	**0.006**	2.3 ± 1.3	5.6 ± 2.8	**<0.001**	3.9 ± 3.4	13.8 ± 16.7	**0.018**
GRB scores (sum)	4.6 ± 1.9	5.0 ± 2.0	0.618	4.6 ± 2.1	6.0 ± 2.1	0.059	5.3 ± 2.2	5.9 ± 1.3	0.332

Appendix XV. Statified analysis by 2 groups of propensity scores in patients of vocal cysts receving VFSI or phonomicrosurgery.

Propensity score groups	group 1			group 2		
Treatments	**VFSI (n=15)**	**Surgery (n=10)**	**p value**	**VFSI (n=15)**	**Surgery (n=11)**	**p value**
Age	45 ± 11	44 ± 11	0.803	44 ± 14	38 ± 9	0.251
Gender (male / female)	3 / 12	5 / 5	0.194	7 / 8	3 / 8	0.428
Duration (>1 year / ≤ 1 year)	4 / 11	5 / 5	0.397	7 / 8	4 / 7	0.701
Smoking (active / nil)	4 / 11	1 / 9	0.615	2 / 13	2 / 9	0.386
Alcohol (+/-)	2 / 13	2 / 8	0.374	3 / 12	1 / 10	0.614
Vocal demand			0.374			0.220
professional	0	0		0	0	
high	2	2		7	7	
routine	13	8		8	4	
Reflux symptom index	12.7 ± 6.9	16.5 ± 12.2	0.382	14.5 ± 5.9	18.2 ± 7.8	0.203
Max. phonation time	13.3 ± 4.2	11.1 ± 7.3	0.338	10.6 ± 4.8	7.1 ± 2.3	**0.022**
VHI-10	17.0 ± 8.6	23.3 ± 6.4	0.060	24.1 ± 6.7	31.5 ± 5.8	**0.007**
Self-rating of voice quality	3.9 ± 2.1	3.5 ± 1.3	0.631	3.1 ± 1.2	1.4 ± 1.1	**0.001**
Size of vocal lesions (pixels)	4.5 ± 6.6	3.6 ± 2.7	0.627	4.1 ± 3.4	2.1 ± 1.8	0.082
Acoustic analysis						
GRB scores (sum)	3.8 ± 1.9	4.7 ± 2.2	0.283	4.7 ± 2.0	6.1 ± 1.5	0.070