Voice Rehabilitation and Functional Outcomes Following Radiotherapy for Laryngeal Cancer

Lisa Tuomi

Department of Otorhinolaryngology

Institute of Clinical Sciences at the Sahlgrenska Academy

University of Gothenburg

UNIVERSITY OF GOTHENBURG

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lisa.tuomi@gu.se

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Department of Otorhinolaryngology, Institute of Clinical Sciences at the Sahlgrenska Academy
University of Gothenburg
Göteborg, Sweden

ABSTRACT

The overall aim of this thesis was to evaluate the effects of radiotherapy and voice rehabilitation on voice function and Health Related Quality of Life (HRQL) following treatment for laryngeal cancer.

Patients treated for laryngeal cancer were prospectively studied pre-radiotherapy and 1, 6 and 12 months post-radiotherapy. Patients were randomized into a voice rehabilitation group, in which they received voice rehabilitation between 1 and 6 months post-radiotherapy, or a control group. Patient Reported Outcome (PRO) measures included the S-SECEL (Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer), EORTC QLQ (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) and questions regarding hoarseness and vocal loudness. Acoustic, perceptual and temporal analyses were performed. The patients were also compared to a vocally healthy control group.

After radiotherapy, a general deterioration of HRQL was observed in all patients treated for laryngeal cancer, the supraglottic cohort generally had inferior scores compared to the glottic cohort. Regarding voice quality, the glottic cohort appeared inferior to the vocally healthy control group both pre- and post-radiotherapy, while the supraglottic cohort was comparable to the vocally healthy control group.

According to the S-SECEL results, improvement was seen in the voice rehabilitation group, results were maintained at the follow-up six months

later. The control group had no statistically significant change in S-SECEL results. No statistically significant changes regarding acoustically measured voice quality were present in the short- or long-term follow-up. HRQL measures according to the EORTC improved after voice rehabilitation and remained at follow-up 6 months later. The control group showed no statistically significant change except for the Social function domain, which improved from baseline to 6 months post radiotherapy. Perceptually assessed roughness did not change during voice rehabilitation, however, a statistically significant deterioration was present for the control group between 6 and 12 months post-radiotherapy. Factors increasing the likelihood of communication improvement 12 months post radiotherapy were voice rehabilitation, poor speech scores and experiencing less voice use one month post-radiotherapy compared to pre-radiotherapy. Smoking affected communication negatively.

In order to facilitate clinical interpretation of the S-SECEL, cut-off values as well as estimates of Minimum Clinically Important Differences (MCID) were identified for the instrument. Laryngeal cancer patients filled out the S-SECEL instrument and a question about acceptability of speech in a social context pre- and 12-months post oncologic treatment. Results at 12 months as well as the change between pre-treatment and 12-months follow-up were used for identification of cut-off values and estimates of MCID for each domain of the S-SECEL. When using the cut-off value, 36% of the participants scored above the value indicating the need for vocal rehabilitation at the 12-month follow-up.

The results of this thesis demonstrated that voice function and HRQL is affected after radiotherapy. A large proportion had communication functioning indicating the need for vocal rehabilitation. Voice rehabilitation prevented voice deterioration and improved the self-perceived communication function and HRQL. The effects remained in the long-term. The findings suggest that voice rehabilitation could be beneficial to patients after radiotherapy for laryngeal cancer. Additionally it raises the importance of monitoring the communication and voice function through self-assessment and voice recordings.

Keywords: voice quality, voice function, communication, voice rehablitation, laryngeal cancer, patient reported outcomes, health related quality of life, radiotherapy

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SAMMANFATTNING PÅ SVENSKA

Patienter som genomgått strålbehandling mot cancer i struphuvudet (larynx) upplever ofta röstbesvär som kan kvarstå i upp till 10 år efter avslutad behandling. Röstbesvären kan bero på att muskler i och kring struphuvudet, vårt röstorgan, blir stela efter behandling, vilket medför att stämbanden inte kan vibrera lika smidigt som innan sjukdomen. Trots att många studier visat att röstproblem är vanligt och att röstrehabilitering borde kunna hjälpa denna patientgrupp, har endast ett fåtal studier undersökt effekterna av röstrehabilitering. Dessa studier visar på positiva effekter både avseende patientens egen uppfattning av sin röst, hur rösten uppfattas av andra samt när det gäller akustiskt uppmätt röstkvalitet. De studier som genomförts har dock inkluderat få patienter och behöver kompletteras med studier med större patientmaterial. Kommande studier behöver också belysa patienternas röstfunktion och hälsorelaterad livskvalitet (Health Related Quality of Life, HRQL) utifrån tumörens lokalisation.

Det övergripande syftet med avhandlingen var att utvärdera effekterna av strålbehandling och röstrehabilitering gällande röstfunktion och HRQL efter avslutad strålbehandling mot larynxcancer.

Avhandlingens första studie belyser strålbehandlingens korttidseffekter på HRQL och röstkvalitet utifrån tumörlokalisation i larynx. De tumörlokalisationer som jämförs är tumörer på stämbanden (glottisk lokalisation) eller ovanför stämbanden (supraglottisk lokalisation), i relation till en röstfrisk kontrollgrupp. Resultaten visade en generell försämring av HRQL för larynxcancerpatienter efter strålbehandling, där den supraglottiska patientgruppen rapporterade sämre HRQL än den glottiska. Gällande röstkvalitet visade resultaten att den glottiska patientgruppen hade sämre röst än den röstfriska kontrollgruppen både före och efter strålbehandling. Den supraglottiska patientgruppen var jämförbar med den röstfriska kontrollgruppen vid dessa mättillfällen.

I avhandlingens tredje studie var syftet att ta fram riktlinjer för att underlätta användningen av frågeformuläret S-SECEL (svensk version av Self-Evaluation of Communication Experiences after Laryngeal cancer). I denna studie fyllde larynxcancerpatienter i S-SECEL och en fråga om patienten upplevde sin röst som acceptabel i ett socialt sammanhang. Förändringen i S-SECEL före och 12 månader efter onkologisk behandling jämfördes och gav värden som kan motsvara kliniskt relevant förändring av kommunikativ funktion. Resultaten för S-SECEL jämfördes också med resultat gällande

röstens acceptabilitet och gav gränsvärden för behov av röstrehabilitering, där 20 poäng eller mer för S-SECEL:s totalpoäng indikerar behov av röstrehabilitering.

I studie II och IV undersöktes effekterna av röstrehabilitering ur ett kort- och långtidsperspektiv. Efter röstrehabiliteringen förbättrades patientens uppfattning gällande kommunikationsförmåga samt röstkvalitet signifikant, medan röstkvalitet mätt med akustiska mått inte förändrades. Dessa resultat kvarstod även vid långtidsuppföljningen. I studie IV undersöktes också HRQL och resultaten visade att de patienter som erhållit röstrehabilitering förbättrades mest och att dessa förbättringar kvarstod 12 månader efter avslutad strålbehandling. När logopeder bedömde om patienternas röster lät skrovliga/skrapiga visade resultaten att det direkt efter röstrehabilitering inte fanns några skillnader mellan kontroll- och studiegruppen. Sex månader senare förelåg en försämring inom kontrollgruppen, men graden av skrovlighet var oförändrad i röstrehabiliteringsgruppen. Kontrollgruppen och röstrehabiliteringsgruppen delades också in i andel patienter över respektive under gränsvärdet för S-SECEL Total (20 poäng), som indikerar behov av röstrehabilitering. Resultaten visade att antalet patienter i behov av röstrehabilitering låg på en konstant nivå för kontrollgruppen (ca 50%), medan studiegruppens antal minskade från 80% till 50% efter avslutad röstrehabilitering och till 30% 6 månader efter röstrehabilitering. I studie IV undersöktes även möjliga prediktorer för förbättrad kommunikativ funktion 12 månader efter avslutad strålbehandling som visade att röstrehabilitering var den faktor som hade störst inverkan för kliniskt signifikant förbättring av kommunikationen. Fortsatt rökning påverkade utfallet negativt.

Sammanfattningsvis visade studierna att det är vanligt att patienter med larynxcancer får röstbesvär och nedsatt HRQL efter avslutad strålbehandling. Röstrehabilitering är effektiv, särskilt gällande självuppfattad funktion och HRQL, men även för att förhindra röstförsämring över tid. Vidare rekommenderas att patienternas röst och kommunikationsförmåga följs med såväl röstinspelningar som diagnosspecifika frågeformulär.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Tuomi, L*. Karlsson, T*. Johansson, M. Finizia, C. Health Related Quality of Life and Voice after Radiotherapy for Laryngeal Cancer: A Comparison Between Glottic and Supraglottic Tumours. Acta Oncologica 2014; Jun 10:1-7

II. Tuomi, L. Andréll, P. Finizia, C. Effects of Voice Rehabilitation After Radiation Therapy for Laryngeal Cancer: A Randomized Controlled Study. International Journal of Radiation Oncology Biology Physics 2014;89(5):964-72

III. Tuomi, L. Johansson, M. Andréll, P. Finizia, C. Interpretation of the Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer (S-SECEL): Cut-off levels and Minimum Clinically Important Differences. Submitted and under revision

IV. Karlsson, T*. Tuomi, L*. Johansson, M. Andréll, P. Finizia, C. Effects of Voice Rehabilitation after Radiotherapy for Laryngeal Cancer: A Longitudinal Study of Voice Quality and Health Related Quality of Life. Submitted

* Shared first authorship

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ABBREVIATIONS

ACE-27	Adult Comorbidity Evaluation-27
ANCOVA	Analysis of Covariance
CI	Confidence Interval
ELS	European Laryngological Society
EORTC	The European Organization for Research and Treatment of Cancer
F0	Fundamental frequency
GRBAS	Grade, Roughness, Breathiness, Asthenia, Strain
Gy	Gray
HNR	Harmonics-to-Noise Ratio
HRQL	Health Related Quality of Life
Hz	Hertz
ICC	Intraclass Correlation Coefficient
LOCF	Last Observation Carried Forward
MCID	Minimum Clinically Important Difference
MPT	Maximum Phonation Time
NHR	Noise-to-Harmonics Ratio
OR	Odds Ratio
PRO	Patient Reported Outcomes
QLQ-C30	The EORTC Quality of Life Questionnaire Core 30
QLQ-H&N35	The EORTC Quality of Life Questionnaire Head and Neck module
QOL	Quality Of Life
ROC	Receiver Operating Characteristic
S-SECEL	Swedish Self-Evaluation of Communication Experiences after Laryngeal Cancer
SD	Standard Deviation
SECEL	Self-Evaluation of Communication Experiences after Laryngectomy
SLP	Speech-Language Pathologist
TE	Tracheo-Esophageal
TLM	Transoral Laser Microsurgery
TNM	Tumor Node Metastasis
UICC	Union for International Cancer Control
VAS	Visual-Analogue Scale
VGR	Västra Götalandsregionen
VHI	Voice Handicap Index
VRQOL	Voice Related Quality Of Life
WHO	World Health Organization

INTRODUCTION

Voice production

The larynx is situated above the trachea and below the base of the tongue. It is shaped as a hollow tube and consists of the thyroid, cricoid, epiglottis and the arytenoid cartilages. The function of the larynx is three-fold: keep the airway open, seal off the airway when necessary (for example when swallowing) and to phonate, i.e. voice production. The larynx can be divided into three regions (Figure 1). The glottic region includes the true vocal folds and the anterior and posterior commisures. The supraglottic region consists of the false vocal folds, arytenoids, aryepiglottic folds and the epiglottis. The subglottic region is located below the glottis and ends at the level of the inferior border of the cricoid cartilage [1, 2].

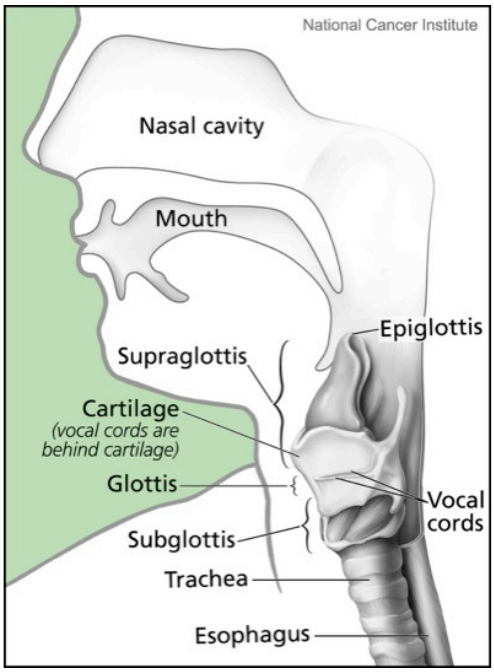

Figure 1. *Illustration of the anatomical regions of the larynx and nearby structures. Image by Alan Hoofring. Source: National Cancer Institute.*

The vocal folds are situated horizontally within the larynx. Anteriorly they attach to the thyroid cartilage and posteriorly to the arytenoid cartilages. The composition of the vocal fold is described as having three layers. The layer structure is essential to the vocal fold vibratory capacity, where the superficial layers are more elastic than the deeper structures [3]. The intermediate and deep lamina propria are often referred to as the vocal ligament or transition, and the vocalis muscle is often called the body of the vocal folds [3, 4]. The superficial lamina propria, or Reinke's space, is said to vibrate the most during phonation [5].

Voice can be referred to as the perceptually audible sound originating from the vocal folds [6]. Phonation is produced when adducing the vocal folds. Air from the lungs is pressed through the glottis and causes vocal fold vibration, which means that the airway is opened and closed in a rapid manner. The elastic tissue of the vocal folds forms a traveling, wave-like motion, which is referred to as the mucosal wave [7]. The vibrations chop the air into pulses, or changes of air pressure, which equals the sound waves [3, 8]. The vocal fold vibration frequency is measured in Hertz (Hz, vibrations per second). Vocal fold vibration frequency depends on the mass and length of the vocal folds, and this can be changed voluntarily by lengthening and/or changing the tension of the vocal folds [8].

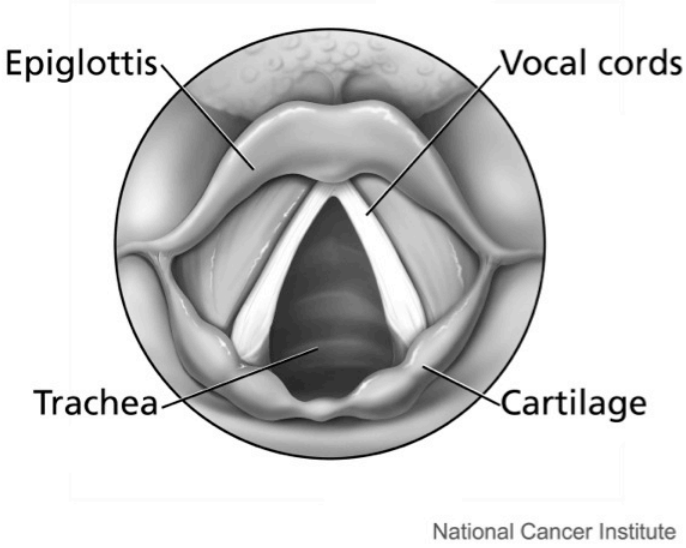

Figure 2. *Illustration of the larynx, superior view. Image by Alan Hoofring. Source: National Cancer Institute.*

The vibrations of the vocal folds are amplified, or resonated, by the shape of the vocal tract, including the pharynx, mouth and nasal cavity. The vocal fold vibrations and the vocal tract create the sounds we hear, giving different voice quality and speech sounds [9]. If there are structural deviations, voice production can be affected, giving a change of voice quality. Nodules [6], polyps [10] and laryngeal cancer [5, 11-16] are some examples of anomalies affecting the voice. Additionally, vocal abuse or misuse can affect the voice [5].

Laryngeal cancer

Laryngeal cancer constitutes about 11-17% of all head and neck tumors diagnosed in Sweden annually [17, 18]. In 2013, 135 newly diagnosed laryngeal tumors were reported in Sweden [17]. The incidence of laryngeal cancer is higher in males than females, with a male:female ratio of 5:1 [2]. A majority (~80%) of the patients diagnosed with laryngeal cancer are older than 60 years.

The tumor can be localized in the glottic, supraglottic, or subglottic region of the larynx (Figure 1). In Sweden, the most common localization is the glottis, where about 87% of the laryngeal tumors are located [18]. Hoarseness is a common symptom of glottic tumors, which often leads to early detection. In Sweden, approximately 11% of all laryngeal tumors are localized in the supraglottic region [18]. The supraglottic region has a robust lymphatic supply; therefore the risk of regional metastases is higher than for glottic tumors [2, 19]. Supraglottic tumors often present with pain and dysphagia and sometimes dysphonia. Subglottic tumors are rare, only about 2% of laryngeal tumors in Sweden are located in this region. Signs of subglottic tumors include dysphonia and sometimes trouble breathing. When all three levels are involved, the tumor is classified as transglottic. Tumor localization within the larynx varies worldwide. For example, in the USA, supraglottic tumors constitute 30-40% of all laryngeal tumors [20] while in Spain and Finland, supraglottic tumors are the most common laryngeal tumors [20, 21].

Risk factors

The largest independent risk factor reported for laryngeal cancer is smoking [2, 22]. Smoking in combination with heavy alcohol consumption [23], as well as gastro-esophageal reflux [24] and human papilloma virus are also potential risk factors for laryngeal cancer. However, a causal effect of the human papilloma virus has not been proved [23].

Table 1. TNM classification of laryngeal tumors according to the UICC [25].

Tumor size (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottic region	
T1	Tumor limited to one subsite, normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis. Without fixation of the larynx.
T3	Tumor limited to larynx with vocal cord fixation and/or invasion of post-cricoid area/pre-epiglottic space/paraglottic space, and/or thyroid cartilage.
T4a	Invades through the thyroid cartilage and/or invades tissues beyond the larynx.
T4b	Invades prevertebral space, encases carotid artery, or invades mediastinal structures.
Glottic region	
T1	Limited to the vocal cord(s) (may involve commissures) with normal mobility.
	T1a Limited to one vocal cord.
	T1b Involves both vocal cords
T2	Extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility.
T3	Limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage.
T4a	Invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx.
T4b	Invades prevertebral space, encases carotid artery, or invades mediastinal structures.
Subglottic region	
T1	Limited to the subglottis
T2	Extends to vocal cord(s) with normal or impaired mobility
T3	Limited to larynx with vocal cord fixation
T4a	Invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx
T4b	Invades prevertebral space, encases carotid artery, or invades mediastinal structures.
Regional lymph nodes (N) - All sites	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤ 3 cm
N2	a) Metastasis in a single ipsilateral lymph node 3-6 cm
	b) Metastasis in multiple ipsilateral lymph nodes ≤6 cm
	c) Metastasis in bilateral or contralateral lymph nodes ≤6 cm
N3	Metastasis in a lymph node >6 cm
Distant metastasis (M) – All sites	
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases present

Classification and staging

The staging and classification of tumors is performed in accordance with the Union for International Cancer Control (UICC) TNM-classification system (Table 1), where T (tumor) indicates the size of the primary tumor, N (node) refers to the involvement of lymph nodes and M (metastasis) indicates distant metastatic spread [25]. Tumor classification and staging is important in treatment planning and information on prognosis and allows for comparisons of outcomes since this classification system is used worldwide [1].

Staging of laryngeal cancer is performed by using the TNM-classification according to the listing in Table 2. The literature often refer to laryngeal cancer as early (stage I-II) or advanced (stage III-IV) [26].

Table 2. Staging (I-IV) of laryngeal cancer according to the UICC [25]

	N0	N1	N2-3	M1
T1	I	III	IV	IV
T2	II	III	IV	IV
T3	III	III	IV	IV
T4	IV	IV	IV	IV

Treatment

The primary goal for treatment of tumors is survival. However, since the larynx plays a crucial role in voice production and communication, functionality of the organ after treatment is also an important aspect when considering treatment options [27]. For laryngeal tumors, three different treatment approaches are generally applied: radiotherapy, surgery and chemotherapy, sometimes in combination.

Early glottic tumors are mainly treated with irradiation or transoral laser microsurgery (TLM). TLM is performed generally in T1 glottic tumors, particularly for midcord lesions, with local control rates comparable to the outcomes of radiotherapy [26, 28]. Supraglottic tumors are mainly treated with radiotherapy. Since there is greater risk of metastatic spread for supraglottic tumors, the lymphatic areas are also to a greater extent included in the irradiation field [18]. Subglottic tumors are rare, hence, the literature on treatment for this patient group is limited. However, treatment regimens are in general the same as those used to treat T2-T3 glottic tumors [1]. For advanced laryngeal tumors of all localizations, the choice of treatment differs.

T3 and some T4 tumors are treated with radiotherapy in combination with chemotherapy. Chemotherapy was formerly given as induction therapy, i.e. before start of radiotherapy, but is now generally given concomitant, i.e. simultaneously, with radiotherapy. T4 tumors with cartilage destruction are often treated surgically, with laryngectomy, with or without radiotherapy [26]. Total laryngectomy signifies removal of the whole larynx, which separates the upper and lower airways and a permanent tracheostoma is required.

Treatment in the region of Västra Götaland during the study period

During the study period, different fractionation schedules were used in the western part of Sweden (Västra Götalandsregionen, VGR), conventional or hyperfractionated-accelerated. Conventional radiotherapy was given with 34/26 fractions of 2.0/2.4 Gray (Gy), once daily, to a total dose of 68/62.4 Gy, respectively. The hyperfractionated-accelerated treatment was given using 38 fractions of 1.7 Gy, twice daily, to a total dose of 64.6 Gy. Lymph nodes were included in the irradiation fields for all sub- and supraglottic tumors as well as for T2 or larger glottic tumors. The patients in the study who received chemotherapy had all received induction chemotherapy.

Side effects

Common acute side effects of radiotherapy include dermatitis, mucositis, xerostomia, candida, pain and altered taste, which can result in impaired nutrition [29]. Additionally, it has been reported that voice quality and volume are often affected, especially at the end of the day [26]. Late side-effects include lymphedema, xerostomia, fibrosis, dysphagia, dental caries, infection, osteoradionecrosis and altered taste [29].

When treated surgically with laryngectomy, the formation of fistulas and aspiration are problems that might occur [30]. Additionally, the removal of the larynx results in a loss of voice. Different ways of communication can be achieved, such as esophageal speech or speech with an electrolarynx. However, the most common method during the past few decades is to create a tracheoesophageal (TE) puncture, in which a voice prosthesis is inserted. The prosthesis is a one-way valve, which lets air pass from the trachea to the esophagus when the tracheostoma is occluded. This enables phonation as the esophageal structures vibrate in a manner similar to the vocal folds.

Side effects from chemotherapy include nausea, vomiting, neurotoxicity and bone marrow toxicity. The reactions caused by chemotherapy most often resolve when treatment is completed [29].

Prognosis

The TNM-classification of the tumor in addition to other clinical factors such as tumor site and age can be used to predict the prognosis of local control rates [26]. For example, glottic tumors are highly curable, since the location is on the vocal fold, causing dysphonia; this often leads to early discovery and treatment. Additionally, the glottic tumors have a lower incidence of lymph node metastases. Tumors in the supraglottic and subglottic regions have a higher risk of lymph node involvement and the prognosis is worse [1].

The 5-year survival rate of laryngeal cancer patients in VGR between 1990 and 2009 was approximately 65-80% [18]. The 5-year survival rates for glottic tumors have been reported as follows: T1-T2 77-98%, T3-T4 36-65% [31-34].

Voice evaluation

Normal voice is difficult to define, since cultural and environmental factors contribute to how the voice is perceived, and depending on the speaker's age and gender it sounds differently. However, a description of normal voice from Aronson and Bless is summarized below [6]:

> Pleasant voice quality with little, or no noise, voice breaks, perturbation or atonality. The pitch is appropriate to age and gender. Vocal loudness is appropriate to the context in which the voice is being produced, adequate flexibility regarding pitch and loudness in order to express meaning and emphasis. The voice function meets the person's need in different social and occupational needs.

How a voice should be classified and evaluated is frequently discussed among experts. Voice includes quality and functionality, and in order to correctly describe and evaluate the voice, it needs to be investigated in a multidimensional approach. Leeper et al. stated in their study that both subjective and objective measures are necessary to capture changes over time [35]. Suggestions from the European Laryngological Society (ELS) have been made regarding which aspects could be included in a multidimensional assessment of pathological voices [36]. The proposed parameters include acoustic analysis, aerodynamic measures, perceptual evaluation, subjective evaluation and laryngeal visualization. The guidelines are formed in order to improve the assessments of the underlying physiological function as well as to determine how the voice function or dysfunction affects every-day life.

The extensive voice assessment also aims to aid intervention as well as predict the prognosis for change [37]. Despite these guidelines, a recent review over literature investigating the outcome after head and neck cancer found that most studies only rely on one of the several dimensions of the voice when reporting voice function [38]. Descriptions of the proposed parameters suggested by the ELS as well as some commonly used measures are reported in the following sections.

Acoustic analysis

Acoustics is the study of sound. Acoustic voice analysis can be performed on recordings of the voice; either connected speech or sustained vowels. It is a non-invasive method that can provide the clinician with objective information regarding vocal fold movement [5]. The acoustic measurements have been found to supplement the perceptual evaluation in detecting the presence or absence of voice disorders [37]. However, acoustic measurements should be interpreted with caution, since they are subject to variability from many factors, including the recording device used, microphone distance and the analysis method and do not necessarily reflect the patient or clinician perceived voice quality [39]. Table 3 lists some common acoustic measurements.

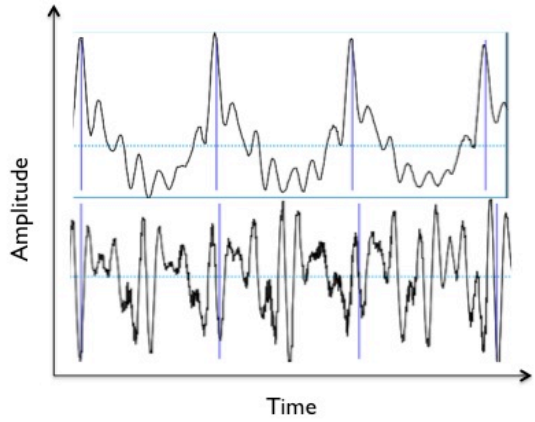

Figure 3. *Two different voices, sequences of 3 consecutive periods from phonation of a sustained vowel.*

Fundamental frequency

Fundamental frequency (F0) is the acoustic correlate of the perception of pitch [40]. It represents the rate of the vocal fold vibration, expressed in vibrations per second (Hz). The average F0 for male speakers have been reported as being from 111-134 Hz and from 188-204 Hz for female voices [41-44].

Table 3. Commonly used acoustic measures.

Acoustic measurement	What is measured
Fundamental frequency (F0)	Rate of vocal fold vibration, correlated to the perception of pitch
Jitter	Irregularity in frequency from one cycle to the next
Shimmer	Irregularity in amplitude from one cycle to the next
Harmonics-to-Noise Ratio (HNR)	The ratio between harmonics and noise in the voice signal, often caused by turbulence at the vocal folds
Noise-to-Harmonics Ratio (NHR)	The ratio between noise and harmonics in the voice signal
Normalized Noise Energy	Noise levels
Voice range profile/ phonetogram	Voice range measured in semitones and intensity

Perturbation

Perturbation measures irregularity of the vocal fold vibration where jitter measures differences in frequency, whereas shimmer measures differences in amplitude in one period compared to the next. High values are said to indicate a pathological voice. Harmonics-to-Noise Ratio (HNR) and Noise-to-Harmonics Ratio (NHR) both measure the ratio between harmonics and noise in the voice signal. HNR have been suggested to document voice quality, and changes correlated with aging [42]. NHR have been moderately correlated to the perception of hoarseness [45]. Another measurement is the normalized noise energy, which measures noise levels [44].

Some criticism has been directed at acoustic measures regarding the analysis of strongly aperiodic voices; generally, it is not recommended to perform perturbation measures on voice with perturbation levels above 5% [46]. Additionally, a review by Carding et al. reported that acoustic analysis only showed moderate test-retest reliability [39].

Voice range profile

Phonetograms or Voice Range Profiles can be used to measure voice range by combining the intensity and frequency [40]. A phonetogram could be performed by phonating for example an /a/ in different pitch and loudness. Each occurrence of a frequency in a specific intensity is marked on the phonetogram. The measured point becomes darker if it is phonated repeatedly. The phonetogram gives a direct visual representation of the voice range, which can facilitate the understanding and give a clearer feedback regarding therapy outcomes for the patient. Figure 4 shows an example of a phonetogram.

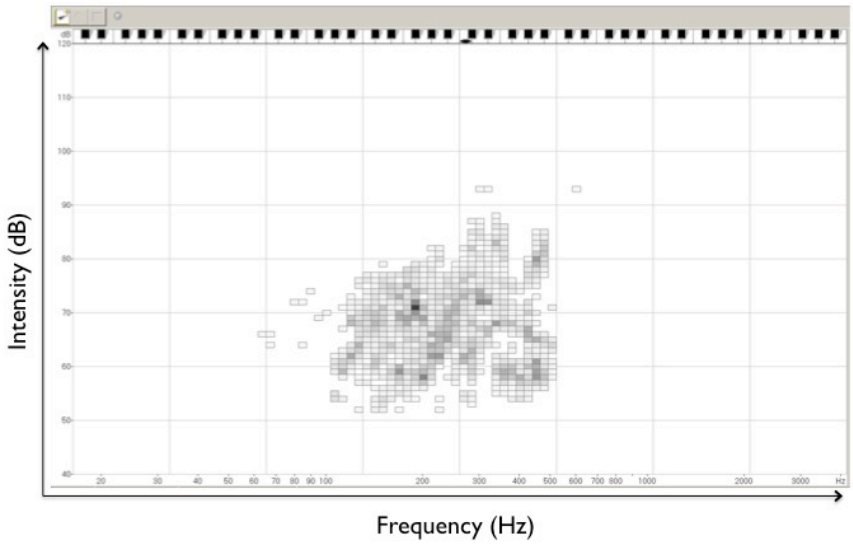

Figure 4. *Phonetogram. The Y-axis represents vocal intensity (loudness), and the X-axis represents the frequency (pitch). Darker points represent repeated recording of the marked intensity and frequency.*

Aerodynamic measures

A common aerodynamic measure is the Maximum Phonation Time (MPT). MPT is simply the time a person can sustain a vowel, often an /a/ in one exhalation at a comfortable pitch and loudness. It has been used to indirectly measure laryngeal function, assess dysphonia severity and changes after voice therapy [47]. It is often recorded three times, with the longest try being documented as the MPT. Normal values for adults above 61 years of age have been described as approximately 22 seconds [48]. However, even though

the MPT is a commonly used measure it does not distinguish between voice function and respiratory function [40].

Perceptual evaluation

Perceptual assessment of voice quality often includes pitch, vocal loudness and intelligibility in addition to specific voice quality parameters such as roughness, breathiness, strain, asthenia, vocal fry, diplophonia, tremor and register breaks [36, 39, 40, 49-51]. Commonly used protocols for perceptual ratings include a variety of these parameters in combination, rated by, for example, equal appearing interval scales or Visual Analogue Scales (VAS).

Internationally, the most commonly used instrument for perceptual voice evaluation, especially in the laryngeal cancer population [11, 16, 28, 52-57], is the GRBAS; Grade, Roughness, Breathiness, Asthenia, Strain, originally developed by the Japanese society of Logopedics and Phoniatrics [58]. It consists of the above-mentioned voice qualities rated on a 4-point categorical Likert scale, where 0 indicates normal and 4 indicates severe impairment. The G, overall Grade is rated as an overall score depending on the other four parameters. The GRB measures are the ones recommended by the ELS since they are the most robust and valid measures in this scale [36]. The GRBAS rating scale is attached in Appendix 1.

Examples of other perceptual voice assessment protocols are the Vocal Profile Analysis [59], the Perceptual Voice Profile (PVP) [51], the Consensus Auditory-Perceptual Evaluation – Voice (CAPE-V) [60], and the Stockholm Voice Evaluation Assessment (SVEA) [49]. These assessments are, similar to the GRBAS, clinician based and measure the severity of different voice qualities on different scales. The CAPE-V measures overall severity, roughness, breathiness, strain, pitch and loudness on a VAS and has proven to give high inter- and intra-rater reliability [61]. The SVEA is similar, with several qualities assessed on a VAS [49]. The PVP assesses pitch, loudness and several qualities on a 7-step scale ranging from normal to severe impairment [51].

Subjective evaluation

People with dysphonia have been reported to experience social difficulties in relation to their voice impairment [62]. Studies suggest that the patients' own perception of their voices or vocal function is one of the most important aspects to evaluate [63, 64]. The patients themselves are the ones most capable of judging the severity of their disability in their daily lives. The ELS recommends either using questionnaires for rating of voice function, or simply two questions where the patients rates their voice quality and how it

affects their everyday lives [36]. Different instruments evaluating voice function are further described in the section *Patient Reported Outcomes: Instruments.*

Laryngeal visualization

Laryngeal visualization through videolaryngoscopy makes it possible to assess the laryngeal structures including the free edge of the vocal folds. Vocal fold movement is assessed through stroboscopic evaluation or high-speed imaging of, for example, glottal closure, amplitude of vibration, regularity of vibration, symmetry and mucosal wave [5, 36].

Laryngeal cancer and voice

Voice function pre oncologic treatment

When a person is afflicted with glottic laryngeal cancer, the primary symptom is often dysphonia. Kazi et al. reported that T1-T2 glottic cancer patients pre-treatment presented with MPT, jitter, shimmer and noise measures significantly inferior to normal voices [43]. Additionally, 68 to 100% of laryngeal cancer patients were rated as having moderate or severe overall hoarseness as measured with the G-scale from GRBAS pre-treatment [54, 65]. The reason for the voice impairment when diagnosed with laryngeal cancer can depend on a variety of reasons. The tumor can prevent total closure when located on the vocal folds, which causes air leakage, which can result in shorter MPT [5, 65]. The size of the tumor can also be reflected in the voice quality. For example, Agarwal et al. found that patients with T2 tumors presented with lower minimum intensity as well as inferior perturbation measures than T1 tumors [66].

Biopsy is a common diagnostic tool in cancer. Few studies exist that investigate the relationship between the biopsy procedure used in laryngeal cancer and voice outcomes. Hocevar-Boltezar et al. mentions the possibility that the biopsy procedure might affect voice outcomes after radiotherapy, however, no associations were found in their study [67]. Another study found that stripping of the vocal fold (removal of the mucosa along the vocal fold) was associated with increased vocal fatigue after radiotherapy [68].

Voice function post oncologic treatment

A large proportion of laryngeal cancer patients experience voice problems after their oncologic treatment. Studies suggest that some degree of voice problem persist even for a long time after treatment is completed [53, 67, 69]. Morgan et al. described that the voices were rated as abnormal in all patients

after treatment for laryngeal cancer, up to 10 years post-radiotherapy [70]. One study reported that in 80% of laryngeal cancer patients treated with radiotherapy, some deviant voice quality persisted, while the functionality of the voice was restored [71]. Others reported that 40% of early glottic cancer patients perceived their voices as deviant up to 10 years post treatment [14], or 56% two years after oncologic treatment [72].

Voice in early laryngeal cancer following oncologic treatment

After radiotherapy the voice has been said to improve; however, several studies report that even though there is improvement, voices measured with acoustic measures are inferior to normal values [44, 66, 73-75]. Rovirosa et al. reported that F0, jitter, shimmer and HNR 1-2 years post radiotherapy for early laryngeal cancer were outside the normal range [55]. Niedzelska et al. reported in their study, that significant improvement was noticed for jitter, shimmer and noise measures. However, none of the measured values (perturbation, noise, F0, MPT) reached normal values 1-3 years after radiotherapy [54]. In line with these results, Adams et al. found, that in close connection to the radiotherapy, early laryngeal cancer patients showed deteriorated voice quality as measured with acoustic measures followed by improvements of the same measures up to 2 years after completion of oncologic treatment [15 35].

Similar patterns have been reported regarding voice function measured using self-perceived measures. These demonstrated that just after completion of radiotherapy laryngeal cancer patients scored high (bad) on the Voice Handicap Index (VHI), but improved to low (good) levels during the first year [15 76]. Similar results were reported by Johansson et al., where the Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer (S-SECEL) was used pre-treatment, 1 month and 12 months post start of oncologic treatment [77]. At one month, a statistically significant deterioration was noted for most domains of the S-SECEL, while at 12 months, a significant improvement compared to baseline was noted for all domains.

Krengli et al. found that 24-120 months post-radiotherapy for early glottic cancer 81% of the patients presented with reduced mucosal wave [78]. Twenty-six percent of the patients presented with severe glottic inadequacy [78]. Other studies also report stiff mucosal waves, inelasticity, and glottal incompetence [55, 68, 79]. Additionally, Hocevar-Boltezar et al. found in their study that 62% of the irradiated laryngeal cancer patients phonated with supraglottic activity [79]. However, the literature is inconclusive, since some suggest that the vibratory patterns of the vocal folds are normal or only mildly reduced [80].

Some studies report on differences in voice outcome with respect to tumor size. Agarwal et al. found that T2 glottic tumor patients had significantly inferior perturbation measures as well as perceptually evaluated hoarseness and harshness 3-6 months post radiotherapy compared to those with T1 tumors [66]. Similar results were presented by Al-Mamgani et al., where T2 tumors to a greater extent were correlated with inferior VHI outcomes than T1 tumors [81]. However, Adams et al. showed, using VHI and perceptual analysis, that those with larger tumors had statistically significant improvements of voice function from pre-treatment and 24 months post treatment. Smaller tumors did not improve to the same extent [15].

Studies regarding vocal outcomes after surgery for early laryngeal cancer show differing results. Sjögren et al. found when comparing laser surgery and radiotherapy for T1a glottic midcord lesions, that after surgery (mean 45 months), the laser cordectomy group had better voice quality regarding the perceptual quality breathiness compared to the radiotherapy group. However, no statistically significant differences were found for either perceptual, acoustic or videostroboscopic measures [28]. Peeters et al. found that one year post treatment, patients treated with laser surgery for T1 glottic tumors to a greater extent demonstrated normal self-perceived voice function than patients treated with radiotherapy [82]. Krengli et al. on the other hand, found superior outcomes for the radiotherapy group compared to a laser surgery group [78]. Additionally, two review articles have compared voice outcomes after radiotherapy or laser surgery for early glottic cancer. The outcome measures used in the studies reviewed differed, which hindered conclusions [83]. Some differences between the vocal outcomes existed; however, no certain differences in voice quality between the treatment modalities were identified [57, 83].

Voice in advanced laryngeal cancer following oncologic treatment

Voice function after radiotherapy in advanced laryngeal tumors follows the same trend as the early tumors; deterioration of voice function at the end of treatment that returns to pre-treatment values after 6 months. Values are almost comparable to normal voices after one year, as measured using the VHI [84]. Nguyen et al. reported that most patients experienced normal or near-normal voices allowing for adequate communication [85]. However, regarding acoustic measures, these remained outside normal values as reported by Woodson et al [86]. Van der Molen et al. reported that advanced laryngeal and hypopharyngeal tumors had more strained voices one year after chemoradiotherapy compared to 10 weeks post-treatment [87].

After laryngectomy the voice is altered. When compared to patients treated with radiotherapy for advanced laryngeal cancer, patients who have undergone total laryngectomy are said to demonstrate inferior voice quality, intelligibility and acceptability [13]. Additionally, other functional outcomes such as olfaction, taste and respiration are affected after laryngectomy. Voice rehabilitation is performed with the aid of speech-language pathologists. A review of voice rehabilitation by Singer et al. noted that active communication improves the chance of successful voice rehabilitation [88]. The most common way of restoring voice after laryngectomy is through using the voice prosthesis inserted through the TE-puncture. TE-speech often facilitate voice rehabilitation, since other options, such as learning esophageal speech, are time consuming, and speech with an electrolarynx results in a robotic sound [89].

Health Related Quality of Life and Patient Reported Outcomes

Quality of Life (QOL) is defined by the World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [90]. Health Related Quality of Life (HRQL) measures QOL in relation to health or functional status [91]. HRQL is subjective and multidimensional, and aims to measure a person's perception of his or her physical, functional, emotional and social well-being [92]. It is often measured through Patient Reported Outcomes (PRO), which refers to a report directly from the patient, without interpretation of a clinician or anyone else [93]. A PRO can consist of interviews or questionnaires, but the latter is less time consuming and is therefore the most commonly used method. PRO instruments consist of several questions, i.e. items, which are grouped together in scales or domains that all measure the same concept. Instruments can be generic or disease specific, where the generic instruments measure general health, disability and QOL, which provide a possibility to compare between groups of patients and norm populations. Diagnosis specific instruments measure symptoms, health and function relevant to the disease in question. Several HRQL instruments include both generic and disease specific domains [94].

Evaluation of Patient Reported Outcomes

In order to ensure the accuracy of an instrument, validation needs to be performed. Some central concepts of psychometric properties are explained in Table 4.

Clinical interpretation

PRO instruments are sometimes complemented with information aiming to improve the clinical interpretation, for example cut-off values developed to identify the need for rehabilitation measures or patients with suspected illness, or estimates representing the Minimum Clinically Important Difference (MCID).

There are some instruments for which guidelines regarding cut-off values have been provided. For example, cut-off values aiming to identify patients with probable depression or anxiety have been developed for the Hospital Anxiety and Depression Scale (HADS) [95]. For the Swedish Voice Handicap Index (VHI) there is a score used as a cut-off value indicating voice problems [96]. The Self-Evaluation of Communication Experiences after Laryngectomy (SECEL) has threshold values indicating the need for rehabilitation measures [97].

The MCID is a threshold value that represents a change that is considered important for the patient [98]. The MCID is a complement to statistical significance, since statistically significant differences in a large group of patients, could represent a very small difference, which would not be considered noticeable for the patients [99]. MCID can be obtained by several methods, either anchor based or distribution based. Anchor based methods utilize an external indicator, either clinical (laboratory measures, physiological measures or clinician ratings) or patient-based (other PRO measures), to establish groupings for no change and grades of improvements or deterioration. These groupings are then compared to actual changes in the intended PRO [100]. It has been recommended to use multiple anchors, and confirm the results across several samples. The anchors used should show sufficient correlation in order to be a relevant anchor for the intended measure. Revicki et al. recommends the use of Cohen's rule of thumb, i.e. 0.30-0.35 as the lowest correlation threshold to indicate relevance [100].

Common distribution based measures are one standard error of measurement and 0.5 Standard Deviation (SD) [101]. However, distribution based methods have been criticized to not necessarily reflect meaningful changes [100]. Guyatt et al. conclude that distribution based methods do not

suffice to independently establish the MCID, but a combined approach of primarily anchor based methods supported by distribution based methods could give relevant MCID estimates [100, 101].

Table 4. Psychometric concepts explained [102, 103]

Concept	Concept explained	How to analyze
Validity	If the instrument measures what it is intended to measure	
Content validity	If the items reflect what they are intended to reflect. High content validity means that the instrument covers all relevant aspects, but does not include any irrelevant items.	Literature review, expert and patient input. The patient input is a very important step, since the purpose of the PRO instrument is to capture the patient's experience.
Criterion validity	If the scale has association with external criteria or "gold standard".	Agreement between two methods (example: interview and instrument agreement).
Construct validity	If an instrument measures the theoretically intended constructs. Consists of convergent and discriminant validity.	
Convergent validity	How well constructs that should be related are related.	Correlations of the measured scale with the theoretical construct should demonstrate correlations > 0.40.
Discriminant validity	Tests whether supposedly unrelated concepts are, in fact, unrelated.	Low correlations should be demonstrated.
Reliability	Precision and stability of an instrument, i.e. the instrument gives consistent results in repeated measurement.	Test-retest through correlations (repeatability) or Cronbach's alpha, which measures internal consistency, how well items are correlated to each other. Alpha > 0.70 is considered acceptable.
Sensitivity	Ability to detect differences between patients or cohorts.	Can be evaluated in cross-sectional studies. If statistically significant differences are detected when comparing groups, the instrument is considered sensitive.
Responsiveness	Ability to detect within-patient changes over time.	Longitudinal studies required. Measured through e.g. Standardized Response Mean or Effect Sizes.

Patient Reported Outcomes: Instruments

Health Related Quality of Life instruments

Some common instruments reporting HRQL in cancer populations are described below.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) is a self-administered multidimensional instrument aiming to evaluate HRQL for cancer patients. It has been validated and translated into several languages [94, 104]. The EORTC QLQ consists of a core questionnaire, the EORTC QLQ-C30 and several disease specific modules for different cancer sites. The QLQ-C30 includes 30 questions divided into several functioning and symptom domains, and can be used in all cancer populations [94]. The module for head and neck cancer patients (QLQ-H&N35) [105] consists of 35 questions regarding symptoms more specific to the head and neck cancer population. This well established instrument has been found reliable with Cronbach's alpha above 0.70 for most domains of the QLQ-H&N35 [94]. However, the Speech and Senses domains have not shown as high reliability [106, 107]. The instrument has demonstrated acceptable construct validity since the instrument can differ between patient groups. Additionally, responsiveness over time has been presented for most domains [94]. There are also recommendations regarding the MCID, which aids interpretation [108-110]. However, this instrument is significantly longer than many other instruments and could therefore be more burdensome for patients [94]. Additional description is found in the section *Outcome measures*.

Functional Assessment of Cancer Therapy (FACT) is also an instrument developed for cancer patients. It includes a general questionnaire (FACT-G) and supplementary modules for different cancer populations including head and neck cancer (FACT-HN) [111]. The FACT-G consists of 27 items in four domains (physical, social/family, emotional, functional) [112]. The FACT-HN is a supplementary domain of the FACT-G with 11 items regarding head and neck specific symptoms [112]. Calculations for clinically significant differences have been performed for the FACT-instrument in a laryngeal cancer population [112]. It has proven to be valid and sensitive, with reliability scores (alpha) ranging from 0.59 to 0.89 [113].

The University of Washington Quality of Life questionnaire (UW-QOL) was developed primarily for patients undergoing surgery. It consists of 15 items. The UW-QOL has been criticized due to its lack of description on how the items were generated [94]. Reliability was measured with test-retest and gave

excellent results (correlation coefficient above 0.94). Internal validity measured with the Cronbach's alpha rendered alpha scores of 0.74-0.83. To establish concurrent validity, comparisons between the UW-QOL and other measures of well-being were made. These resulted in correlation coefficients of 0.79-0.96 [94].

Voice and communication instruments

Several PRO instruments for voice function have been developed. Some are commonly used in the laryngeal cancer population and are described below.

Self-Evaluation of Communication Experiences after Laryngectomy (SECEL) was originally developed to measure communicative dysfunction after laryngectomy [97]. Items were generated from the literature and patient interviews and the items were examined by both patients and experts. The instrument consists of 34 items in three domains as well as an additional question regarding the amount of voice use that is not included in the domain scores. Content validity is considered high, and reliability was found high through test-retest (87% agreement) and Cronbach's alpha>0.80. The SECEL has been translated into other languages [56, 114], including Swedish; *Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer (S-SECEL)* [77, 115, 116]. The S-SECEL is adapted to fit all patients undergoing oncologic treatment for laryngeal cancer. It has proved reliable and valid through adequate convergent and discriminant validity and it has satisfactory internal consistency [115, 116] and sensitivity [77]. However, the General domain has demonstrated inferior reliability outcomes in the Italian and Swedish versions, with Cronbach's alpha of 0.58-0.60 [56, 115]. An additional description of the S-SECEL is found in the section *Outcome measures.*

Voice Handicap Index (VHI) was developed to measure voice handicap for dysphonic patients [96, 117]. The items were generated from case histories of interviews with patients with voice disorders and its final form consists of 30 items in three domains. The structure with three domains has been criticized since factor analysis could only find two separate scales [118]. However, the reliability has been measured through Cronbach's alpha, with values varying between 0.91-0.97 for different languages [119]. The VHI was developed for voice complaints due to a variety of diagnoses [117]. VHI has been translated into several languages [96, 119]. There is also a short version of the VHI, *VHI-10* which was developed from the original VHI including the items that generated the largest discrepancies between dysphonic and non-dysphonic persons [120]. The VHI-10 demonstrated correlation coefficients greater than 0.90 when compared to the original VHI. However, additional testing for validity and reliability is lacking.

Voice Related Quality Of Life (VRQOL) [121] focuses more on quality of life in relation to voice than the VHI does. It was developed through clinician and patient input. The Cronbach's alpha was measured to 0.89 and correlations for test-retest were measured to be 0.92 and 0.93, indicating good reliability. The VRQOL is considered sensitive since it can differentiate between dysphonic and non-dysphonic people. Responsiveness was tested by using the instrument pre-and post-treatment for patients with voice-complaints. The change in scores for the VRQOL were correlated to the degree of change in perceptual voice quality, which gave statistically significant correlations, indicating responsiveness [121].

Communication Participation Item Bank is an instrument developed to measure communicative participation for adults with speech-related communication disorders [122, 123]. It has been studied in a head and neck cancer population and found to be valid through strong correlations with the VHI-10 [123].

Other PROs regarding voice function, include the *Voice Activity and Participation Profile* [124], *The Voice Symptom Scale* [125] and the *Voice Outcome Survey* [126]. However, these are not commonly used in laryngeal cancer populations.

Health Related Quality of Life and laryngeal cancer

Several studies report on HRQL for laryngeal cancer patients. Generally, most HRQL measures deteriorate during, or at the end of, treatment with improvement reaching pre-treatment levels or better after a year [76, 77, 81, 84, 127].

Health related quality of life in early laryngeal cancer

For early glottic tumors, reports say the HRQL is at its worst during, or at the end of treatment. Improvement starts soon thereafter [76, 81, 127]. Twelve months after the end of radiotherapy, most values have returned to pre-treatment values [76, 81, 127]. When looking at speech, measured using the EORTC QLQ-H&N35 or its previous version, speech appears to improve over time; values 1 year after oncologic treatment were significantly better than pre-treatment [77, 127, 128]. When comparing those with T1 and T2 tumors, patients with T2 tumors showed inferior HRQL-values compared to those with T1, at baseline (before radiotherapy) and both 6 and 12 months later measured using the EORTC QLQ-H&N35 [128]. Continued smoking after radiotherapy has also been reported to negatively impact HRQL [81].

Several studies compare the effects of surgery for early laryngeal cancer to the outcomes after radiotherapy, but the results are not conclusive. Arias et al. found that even a long time after treatment (mean 63 months) moderate limitations in several domains in both the patients who underwent cordectomy and radiotherapy were present [129]. However, emotional function and social contact showed statistically significant differences. The radiotherapy group showed superior values compared to the surgery group. Other studies reported no differences regarding HRQL for patients treated with radiotherapy or surgery [57, 130]. Similar to the progress of HRQL in patients treated with radiotherapy, patients treated with partial laryngectomy or cordectomy, demonstrated fairly good HRQL results [131].

Nordgren et al. demonstrated in a study with more than 60% early laryngeal cancer patients, that patients with glottic tumors had better pre-treatment scores than patients with supraglottic tumors. The one exception was the Speech domain of the EORTC QLQ-H&N35, where the glottic and supraglottic cohort presented with similar results [132]. However, one-year post oncologic treatment the supraglottic cohort presented with speech-scores worse than the glottic cohort, while the glottic cohort reported improved speech at one year.

Health related quality of life in advanced laryngeal cancer

Differing HRQL results have been reported for patients with advanced laryngeal tumors pre-treatment. Al-Mamgani et al. demonstrated HRQL values indicating normal function, with deterioration at the end of radiotherapy [84], while Hammerlid et al. reported values inferior to the results of early laryngeal cancer patients [127]. A majority of the HRQL domains returned to baseline function [127]. However, at one year, problems with dysphagia and dry mouth were still present [84].

Nordgren et al. reported that patients undergoing laryngectomy showed pre-treatment values similar to radiotherapy cohorts, but at the one-year follow-up, the laryngectomy cohort revealed inferior values for several domains [132]. Conversely, Finizia et al. showed in their cross-sectional study that patients who had undergone either radiotherapy or laryngectomy (with a voice prosthesis inserted through the TE fistula) at least 6 months before, had comparable results regarding functional limitations in everyday life [12].

Regarding long time effects, Nordgren et al. reported that from pre-treatment to 5 years post oncologic treatment, there was a clinically and statistically significant improvement in Speech measured with the EORTC QLQ-H&N35 [132]. However, Physical function, Role function, Sticky saliva

and Dry mouth showed statistically and clinically significant deterioration when comparing baseline values and 5-year follow-up. At the 5-year follow up, when comparing patients treated with radiotherapy to patients who had undergone laryngectomy, many domains showed comparable results.

Voice rehabilitation/therapy

The general goal of voice therapy is to restore a person's voice, in order to be functional in that person's everyday life, in their work and in general communication [5]. In a review on the effectiveness of voice therapy for functional dysphonia, voice therapy is said to include direct and indirect approaches [133]. The direct approach focuses directly on the voice production apparatus, for example, laryngeal relaxation, diaphragmatic breathing, coordination of breathing with phonation and elimination of glottal attack. The indirect approach refers to therapy focused on other mental or bodily structures or functions that influence voice production, such as patient education, general relaxation, vocal hygiene and environmental awareness. The direct and indirect approaches are often combined, and have been found to be effective, such as in improving the person's own perception of voice function [133]. Unfortunately, many studies are poorly described and have large discrepancies in their methods [47, 134]. Further studies where the methods and endpoints are carefully described are requested.

Several studies conclude that the patient's self-perceived voice function improves after voice therapy [135-139]. Mackenzie et al. found that this effect remained after 12-14 weeks post therapy [136]. Some have reported that acoustic measures improve, however, these improvements were not maintained long term [136, 138]. Perceptually measured voice quality has been described as either constant [138] or improved [137] after voice therapy. Additionally, voice range and MPT have been reported as improved after voice therapy [139].

Even though many studies have found persisting voice problems after treatment for laryngeal cancer, only a few studies have investigated the effects of voice rehabilitation, and further research in the field has been requested [75]. One study investigated the effects of concomitant voice- and radiotherapy. There was a tendency towards improvement; however, the voice therapy and endpoint measures used as well as patient compliance to the voice therapy in this study were not presented [140]. Van Gogh et al. included patients who experienced voice problems up to 10 years post-radiotherapy or laser surgery for early glottic cancer [14]. Twenty-three patients were assigned to either a

voice therapy group or a control group. This cross-sectional study resulted in improvement in some acoustic measures, perceptually rated vocal fry and self-perceived voice function, after voice therapy. However, in this study, the voice therapy differed in time and content. Most effects remained improved in the long term (13 months post voice therapy) [141]. However, in the long-term follow-up, no comparison with a control group was performed, which to some extent hampers a conclusion [141]. Jotic et al. found that early glottic tumor patients who received voice therapy during two weeks after the end of radiotherapy showed improvement in some acoustic measures [142]. A pilot study preceding the studies in this thesis reported the results of 20 male laryngeal cancer patients, where 10 patients received voice rehabilitation, and 10 patients formed a control group [143]. There was improvement in self-perceived voice quality, suggesting the effectiveness of voice rehabilitation.

AIM

The overall aim of this thesis was to evaluate the effects of radiotherapy and voice rehabilitation on voice function and health related quality of life following treatment for laryngeal cancer.

Specific aims

Study I

To provide information about the short-term effects on voice quality and health related quality of life following radiotherapy after laryngeal cancer, comparing the outcomes with respect to tumor localization.

Study II

To assess the effect of voice rehabilitation in terms of acoustic and temporal analysis as well as communication function after radiotherapy for laryngeal cancer and to investigate the impact of tumor localization.

Study III

To establish cut-off values to identify the need for vocal rehabilitation as well as minimum clinically important differences for the Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer in order to facilitate clinical interpretation.

Study IV

To study the long-term efficacy of voice rehabilitation in terms of effects on voice function and health related quality of life in patients treated for laryngeal cancer as well as identifying factors predicting the likelihood of voice improvements 12 months post-radiotherapy.

PATIENTS AND METHODS

Participants

All laryngeal cancer patients in the VGR are referred to a weekly conference at the Otorhinolaryngology clinic at the Sahlgrenska University Hospital. The conference includes professions involved in the care of the patient, for example head and neck surgeons, oncologists, radiologists and pathologists. At the conference, the cancer diagnosis and treatment are discussed and decided upon. All patients in this thesis were asked to participate in the studies during the conferences. Tables 5 and 6 give an overview of the participants and methods used in the four studies.

The vocally healthy control groups were recruited from accompanying friends or family of patients visiting the hospital.

Study I, II, IV

Eligibility for inclusion in studies I, II and IV were patients with primary laryngeal cancer treated with curatively intended radiotherapy. Inclusion criteria were good cognitive ability and sufficient knowledge of the Swedish language in order to independently complete the questionnaires as well as participate in voice rehabilitation sessions. In studies I and II, only male patients were included for analysis. Details of the included and excluded patients for studies I, II and IV are listed in Figure 5. Of the included patients, approximately 72% received conventionally fractionated radiotherapy and 28% hyperfractionated-accelerated radiotherapy. Three patients received induction chemotherapy.

In studies I and II a vocally healthy control group was included. Details are listed in Table 5.

The 77 patients eligible for analysis were compared to the patients fulfilling inclusion criteria, but not included in the analysis (n=86). There were no statistically significant differences between the groups regarding gender, comorbidity, tumor site, tumor size or chemotherapy treatment. Statistically significant differences were present for age and smoking habits. The patients not included in the analysis were significantly older (mean age 71 years, range 52-94 years, $p<0.001$) and more often non-smokers ($p<0.001$).

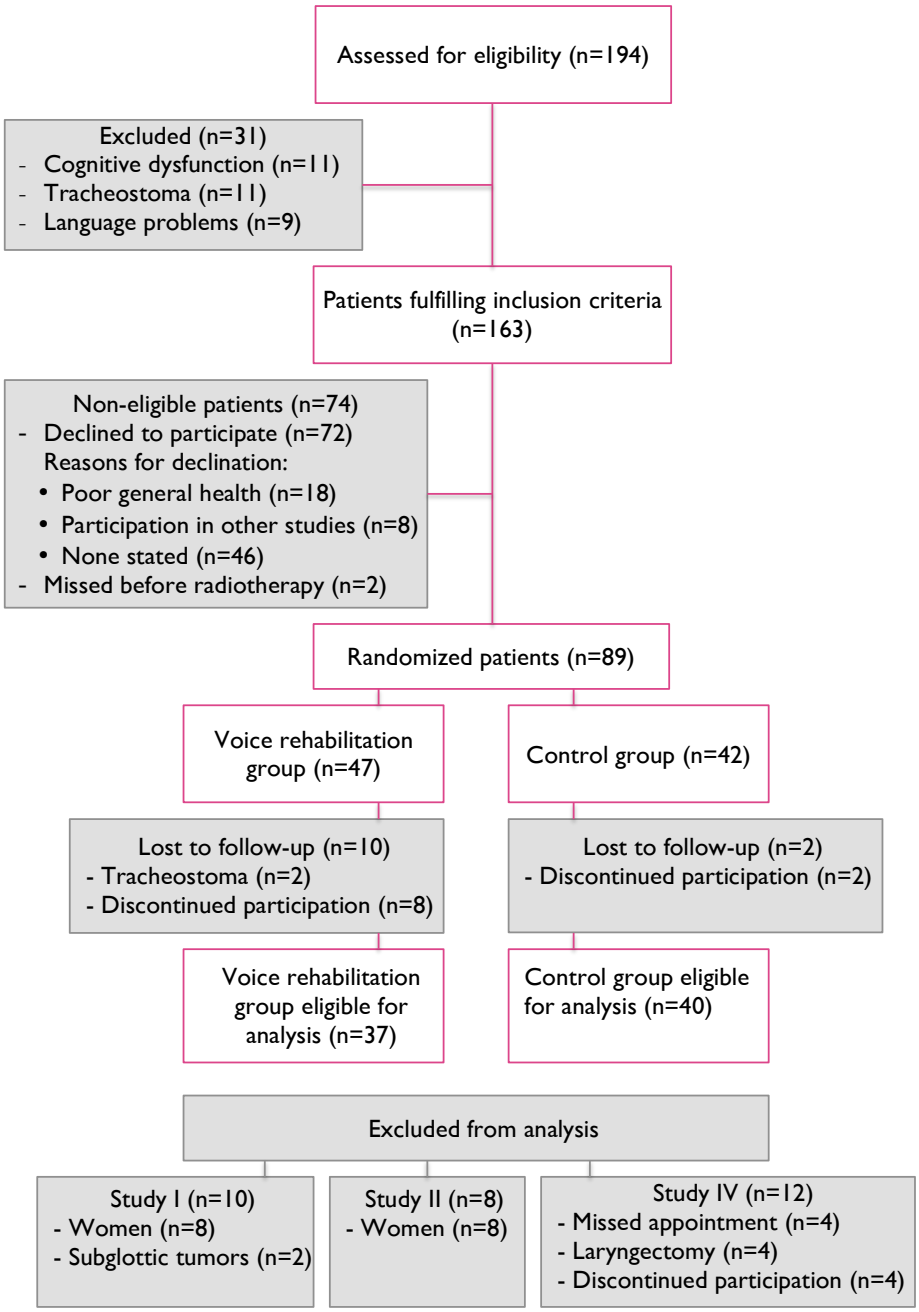

Figure 5. *Details regarding patient inclusion and exclusion in study I, II and IV.*

Study III

Patients eligible for inclusion in study III were newly diagnosed or recurrent laryngeal cancer patients referred to treatment with curative intent. Criteria for inclusion were sufficient cognitive ability and general health, and adequate knowledge of the Swedish language to be able to independently complete the questionnaires. Patients participating in other concurrent studies were excluded. Figure 6 lists the details regarding the included and excluded patients. Of the 119 analyzed patients 8 patients were treated with laryngectomy (2 laryngectomy only, 2 in combination with chemotherapy and 4 in combination with radiotherapy), 106 with radiotherapy only and 5 with chemoradiotherapy. A vocally healthy control group was included (n=35), details listed in Table 5.

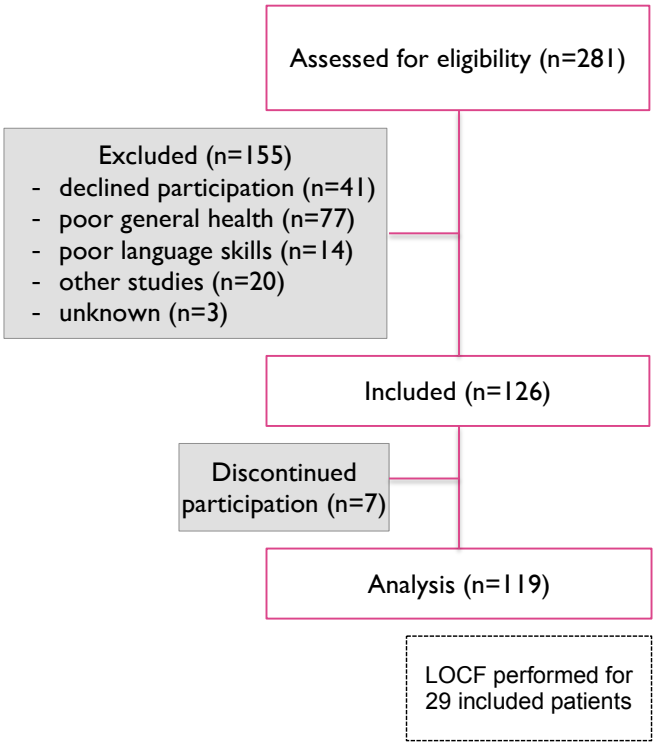

Figure 6. *Details regarding included and excluded patients in study III. LOCF=last observation carried forward.*

Table 5. Participant characteristics for study I-IV.

	Study I	Study II		Study I-II	Study III		Study IV	
		Voice rehab	Control	Vocally healthy control group	Laryngeal cancer patients	Vocally healthy control group	Voice rehab	Control
Age								
Mean	64.6	66.0	64.0	62.6	66.0	66.0	64.6	62.1
(median)	(65)	(65)	(66)	(63)	(66)	(67)	(64)	(63)
range	34-86	35-86	41-82	46-83	41-87	46-84	35-86	41-82
Gender	n (%)*	n (%)*	n (%)*	n (%)*	n (%)*	n (%)*	n (%)*	n (%)*
Male	67 (100)	33 (100)	36 (100)	23 (100)	102 (86)	29 (83)	29 (88)	28 (88)
Female	0	0	0	0	17 (14)	6 (17)	4 (12)	4 (12.5)
Smoking habits								
Smoker	25 (37)	12 (36)	18 (50)	8 (35)	39 (33)	13 (37)	13 (39)	16 (50)
Non-smoker	7 (10)	21 (64)	18 (50)	9 (39)	80 (67)	22 (63)	6 (18)	2 (6)
Previous smoker	35 (52)	**	**	6 (26)	**	**	14 (42)	14 (44)
Tumor localization								
Glottic	54 (81)	27 (82)	27 (75)	N/A	90 (76)	N/A	27 (82)	24 (75)
Supra-glottic	13 (19)	6 (18)	7 (19)		20 (17)		6 (18)	8 (25)
Sub-glottic	0	0	2 (6)		6 (5)		0	0
Trans-glottic	0	0	0		3 (3)		0	0
Tumor stage								
0	2 (3)	0	2 (6)	N/A	4 (3)	N/A	0	1 (3)
I	41 (61)	23 (70)	19 (53)		68 (57)		23 (70)	16 (50)
II	17 (25)	8 (24)	10 (28)		30 (25)		8 (24)	10 (31)
III	6 (9)	1 (3)	5 (14)		10 (8)		1 (3)	5 (16)
IV	1 (1)	1 (3)	0		7 (6)		1 (3)	0

** Percentages rounded – therefore does not always sum up to 100%.*

*** Participants divided into current smokers or non-smokers*

rehab=rehabilitation. N/A=not applicable

The patient population in the studies in this thesis were similar to those in other reports on the laryngeal cancer population regarding age, gender and tumor localization within the larynx. Tumor stage differ, where this thesis included a somewhat larger proportion of patients with early stage tumors [14, 18, 73, 127, 132].

Design

In studies I, II and IV, PRO as well as voice recordings were performed pre-radiotherapy and 1, 6 and 12 months post-radiotherapy. Voice recordings and completion of PRO were performed at the speech-language pathology (SLP) departments at four different hospitals in the VGR (Sahlgrenska University hospital, Norra Älvsborgs läns sjukhus, Skaraborgs sjukhus and Södra Älvsborgs läns sjukhus). Computerized randomization was performed after radiotherapy through optimal allocation using Pocock's sequential randomization method regarding age, smoking habits, tumor site, tumor size and patient's self-evaluation of communication pre-radiotherapy [144]. The patients were randomized into either a voice rehabilitation group or a control group. Sample size was determined by an 80% power calculation with dysphonia as the main variable. Recordings and PRO completion were performed at parallel time-points in both groups. Voice rehabilitation started after the occasion one month post-radiotherapy (baseline). All patients completed the S-SECEL, EORTC QLQ-C30, QLQ-H&N35 and study specific questions regarding hoarseness and vocal loudness on a VAS at all study occasions.

Table 6. Timing of measurement and outcome measures in study I-IV.

	Study I	Study II	Study III	Study IV
Timing of measurement	Pre-RT 1 month post-RT	Post-RT: 1 month 6 months	Pre-RT 12 months post start of RT	Post-RT: 1 month 6 months 12 months
Outcome measures	Acoustic S-SECEL EORTC QLQ-C30, H&N35	Acoustic S-SECEL Environmental Hoarseness Loudness	S-SECEL Acceptability of speech	Acoustic S-SECEL EORTC QLQ C30, H&N35 ** Perceptual: Roughness*
*RT=radiotherapy, * Roughness in GRBAS, ** Selected domains: Role function, Social function, Global QOL, Speech and Social contact*				

Study IV is a follow-up study based partly on the HRQL outcomes previously documented in a short-term study of the cohort [145]. The domains of the EORTC QLQ-C30 and QLQ-H&N35 that demonstrated statistically significant differences between the control group and voice

rehabilitation group were chosen to be included in the analysis of this study (Role function, Social function, Global QOL, Speech and Social contact) [145].

In study III, data were recorded pre-oncologic treatment and 1, 2, 3, 6 and 12 months post start of oncologic treatment. All patients completed the S-SECEL and a study specific question regarding acceptability of speech in a social context. The instruments were sent by mail, and the patients returned their completed instruments by mail in a pre-paid envelope. Patients who had not returned their questionnaires within 2-3 weeks were reminded once. The vocally healthy control group completed the instruments once.

Voice recordings

The recordings consisted of reading of a standard passage, spontaneous speech and maximum phonation time for the sustained vowel /a/ at a comfortable pitch and loudness. This was performed three times and the longest recording was documented as the MPT. Voice recordings were performed in a soundproof booth with a Panasonic Professional Digital Audio Tape (DAT) recorder SV-3800 at a sampling frequency of 44.1 kHz, using a headset microphone (Sennheiser MKE 2-p) at 12 cm from the corner of the mouth. The recordings were transferred from DAT to a computer hard drive as an audio file (.wav) using the program Swell Soundfile Editor version 4.5 (Electronix Hitech).

Voice rehabilitation

Voice rehabilitation commenced after the recording one month post-radiotherapy, and was conducted by a SLP at the hospital nearest to the patient's home. The voice rehabilitation protocol was established through consensus by SLPs within the research group. It consisted of 10 sessions over the course of 10 weeks. The sessions are described in Table 7. Each session lasted approximately 30 minutes, and between sessions, the patients were encouraged to practice at home. The voice rehabilitation consisted of a combination approach of indirect and direct treatment techniques [133]. Indirect techniques included vocal hygiene advice, general relaxation and patient education. The direct treatment focused on physiological changes needed to improve the voice technique. It included, for example, laryngeal relaxation, diaphragmatic breathing, resonance, voice projection and maintaining phonatory control.

Table 7. Specification of structured voice rehabilitation sessions.

Session	Content
1	Voice physiology education Foundation exercises consisting of indirect and direct techniques: - education and training of relaxation and posture - education and training of diaphragmatic breathing, vocal techniques and coordination of breathing and phonation
2	Review patient understanding and mastery of session 1 techniques Patient specific feedback and continued training to consolidate techniques Phonation with correct vocal techniques to a greater extent; voiced sounds and syllables
3	Review foundation exercises Expand on vocal techniques and phonation exercises: - repeated syllables, short words - commence generalization with short phrases
4	Review, provide feedback and continue training Expand on session 3: focus on intonation and stressed syllables
5	Review, provide feedback and continue training Expand on session 4 and begin generalization of phonation with correct vocal techniques with a focus on: - longer phrases - with simultaneous physical movement
6	Review and feedback Repetition of most patient-relevant techniques Continue generalization exercises with a focus on resonance and also phrases of increasing length
7	Review and feedback Generalization exercises - maintaining optimal phonatory control in reading of dialogues and also in conversation Review appropriate pausing, eye contact (holistic communication)
8	Repetition of most patient-relevant techniques. Focus on volume and voice projection
9	Repetition of most patient-relevant techniques
10	Repetition of most patient-relevant techniques
The sessions took place 2 times/week during the first 2 weeks, once a week during week 3-6, and once every second week for the last 2 sessions. The patients were encouraged to exercise at home with focus on the techniques taught.	

Outcome measures

Voice analysis

Acoustic analysis was performed with the program Voxalys, a plug-in program to Praat. Mean F0 was measured from the reading of the standard passage. Jitter, shimmer and HNR were analyzed from two seconds from the middle of the second sustained vowel /a/. MPT was documented as the longest of the three sustained /a/.

The perceptual analysis was performed using the GRBAS rating scale developed by Hirano [58]. The protocol consists of ratings of four voice qualities: Roughness, Breathiness, Asthenia and Strain. Grade is an overall score depending on the ratings of the aforementioned qualities. Each of these five variables are rated on a 4-point scale where 0=normal, 1=mildly impaired, 2=moderately impaired and 3=severely impaired (Appendix 1). Two-speech-language pathologists (SLP) conducted the perceptual ratings and a third SLP was used for the consensus rating. The raters attended a half-day consensus training. For the rating, each sound file consisted of two sentences from the reading and the sustained vowel for each recording. Anchor samples were interspersed every 20 samples. Random samples of twenty percent were reduplicated for intra-rater reliability. The raters were blinded to patient status. A prior study by Karlsson et al. revealed that roughness was the voice quality that changed over time after radiotherapy for laryngeal cancer, and was therefore the perceptual quality used in study IV [146].

Swedish Self-Evaluation of Communication Experiences after Laryngeal Cancer

The S-SECEL is, to our knowledge, the only communication instrument developed and validated specifically for laryngeal cancer patients [77, 115, 116]. The S-SECEL consists of 35 questions concerning communication dysfunction, divided into three domains (General, Environmental, Attitudinal) and a Total score. The General domain (5 items) assesses attitudes about being relaxed and calm as well as acknowledgement of the disease and treatment. “Do you think that your speech improves with practice?” is one of the items in the General domain. The Environmental domain (14 items) focuses on a person’s use of his or her voice in different environments, such as speaking in a large room or to a group of people. An example is “Do you have trouble speaking in a large room?” The Attitudinal domain (15 items) covers aspects of speech attitudes, for example “Do you

avoid speaking because of your voice?" Each item is answered on a 4-point Likert scale from 0 (never) to 3 (always) and addresses the last 30 days. Domain scores are calculated by addition, summary scores range from 0-15 for General, 0-42 for Environmental, 0-45 for Attitudinal, and 0-102 for the Total score. A higher score indicates a worse perceived communication function. The last question, "Do you talk the same amount now as before your laryngeal cancer?" is answered as Yes/More/Less and is not included in the scoring system.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

The EORTC questionnaires are validated questionnaires often used in the laryngeal cancer population and were therefore chosen as HRQL measures in the studies. The EORTC QLQ-C30 consists of 30 items divided into a Global QOL domain, five functional domains, three symptom domains and six single items. The QLQ-H&N35 comprises of 35 questions in seven domains and 10 single items regarding the last week. The scores of each domain of the QLQ-C30 and H&N35 are linearly transformed to a scale of 0-100. A higher score indicates a better level of functioning or Global QOL, or a higher (worse) level of symptoms or problems. A change of ≥10 points can be considered a clinically relevant change [110].

Adult Comorbidity Evaluation-27

Comorbidity was classified using the Adult Comorbidity Evaluation 27 (ACE-27) [147]. It is a validated scale that originates from the Kaplan-Feinstens Comorbidity Index [148]. It consists of 27 items divided into ten body areas: cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, immunological disorders, previous malignancy, obesity or excessive alcohol intake. Each comorbid condition is graded on a four-grade level of severity (none, mild, moderate, severe).

Study specific questionnaires

Questionnaires consisting of the questions "Do you have a hoarse or unclear voice?" and "Is your vocal loudness adequate (can you raise your voice/shout if needed)?" were used. Responses were made on a 100 mm VAS ranging from "always" to "never" and "never adequate loudness" to "always adequate loudness" respectively. A higher value indicates better-perceived function.

A question regarding acceptability of speech was used as the anchor in study III. The question "Is your speech acceptable in a social context?" was

answered on a Likert scale ranging from 0-3, where 3 indicated always good acceptability and 0 never good acceptability.

Ethical considerations

The studies were conducted in accordance with the Declaration of Helsinki and approved by the Regional Ethical Review Board in Gothenburg, Sweden. Before inclusion, all participants gave their informed consent.

Statistical analysis

Due to the skewness of data, mainly non-parametric statistics were used. For comparisons between two groups Fisher's exact test was used for dichotomous variables, the Chi square for non-ordered categorical data, the Mantel-Haenszel chi square test for ordered categorical variables and the Mann Whitney U-test for continuous variables. For changes within groups the Sign test was used for ordered categorical variables and the Wilcoxon Signed test for continuous variables. All significance tests were two-tailed and conducted at the 5% significance level. Descriptive statistics were provided as means with SD and 95% confidence intervals (CI) for the mean according to standard procedures.

In study III, correlations between the anchor question and the S-SECEL domains as well as change within these parameters were calculated with the Spearman rank correlation. The responses of the anchor question regarding acceptability of speech were dichotomized for the logistic regression analysis. Responses 0-1 were determined to indicate the need for vocal rehabilitation, and 2-3 were determined to indicate no need of vocal rehabilitation. Logistic regression with the dichotomized acceptability score as dependent variable and the S-SECEL domains as predictors was performed to create Receiver Operating Characteristic (ROC) curves for the cut-off calculations. The cut-off score was set to be the score where the sum of sensitivity and specificity was the greatest. Correct classification of the vocally healthy control group was calculated for each S-SECEL domain. If the S-SECEL score was below the cut-off score, and the acceptability rating was 2-3 (often-always good acceptability), it was considered to be a correct classification. If the acceptability rating and the S-SECEL score were inconsistent it was considered an incorrect classification.

For calculations of the MCID estimates using an anchor-based method, the change from pre-treatment to 12 months post start of oncologic treatment

was used. Participants who improved or deteriorated zero or one step on the acceptability score were divided into three groups. For each of these three groups the mean, SD and p-value for change on the S-SECEL domains were calculated. Distribution based methods for MCID using 0.3 SD and 0.5 SD at the 12-month follow-up were used as a complement.

In cases of missing items in a domain, imputation was performed if less than 50% of the items were missing. Imputation was performed by replacing the missing value with the mean of the domain. In study III, if a patient did not complete the instruments at the 12-month occasion, last observation carried forward (LOCF) after start of treatment was applied.

In studies I and IV, besides statistical significance, clinical significance for the EORTC QLQ-C30 and H&N35 were used, represented by a mean score change of ≥10 points. MCID for the S-SECEL from study III was used in the predictive analysis in study IV.

In study IV, the intraclass correlation coefficient (ICC) was used for calculation of the inter- and intra-rater reliability.

In study IV, patients in the voice rehabilitation group and control group were divided into groups according to the cut-off level of the S-SECEL indicating the need for vocal rehabilitation. Descriptive calculations within the groups were carried out. Bivariate logistic regression analysis was performed to find factors influencing the odds of a clinically significant communication improvement, results were presented as odds ratio (OR) with 95% confidence interval in a forest plot.

In study IV, in order to adjust for differences between the groups in baseline values, Analysis of Covariance (ANCOVA) was used for comparison of change between the two randomized groups.

RESULTS

Study I

Post-radiotherapy, deterioration of HRQL occurred for both the glottic and supraglottic cohort (Figure 7). The glottic cohort demonstrated acoustic and temporal measures that were statistically different from healthy controls pre-radiotherapy (MPT, jitter, shimmer, HNR, F0). Post-radiotherapy the glottic cohort had statistically significant differences regarding some acoustic measures when compared to the healthy control group. However, no statistically significant changes between pre- and post-radiotherapy were present. The patients with supraglottic tumors and the healthy control group had mostly comparable voice measures both pre- and post-radiotherapy.

The changes regarding HRQL within the glottic cohort showed only a few statistically and clinically significant differences (changes ≥10 points) however, there were trends toward general deterioration. The supraglottic cohort demonstrated several clinically significant deteriorations, however, not all were statistically significant. When comparing the glottic and supraglottic cohorts, the supraglottic cohort demonstrated statistically significant inferior HRQL following radiotherapy for Physical function, Social function, Cognitive function, Nausea/vomiting, Appetite loss, Swallowing and Social eating.

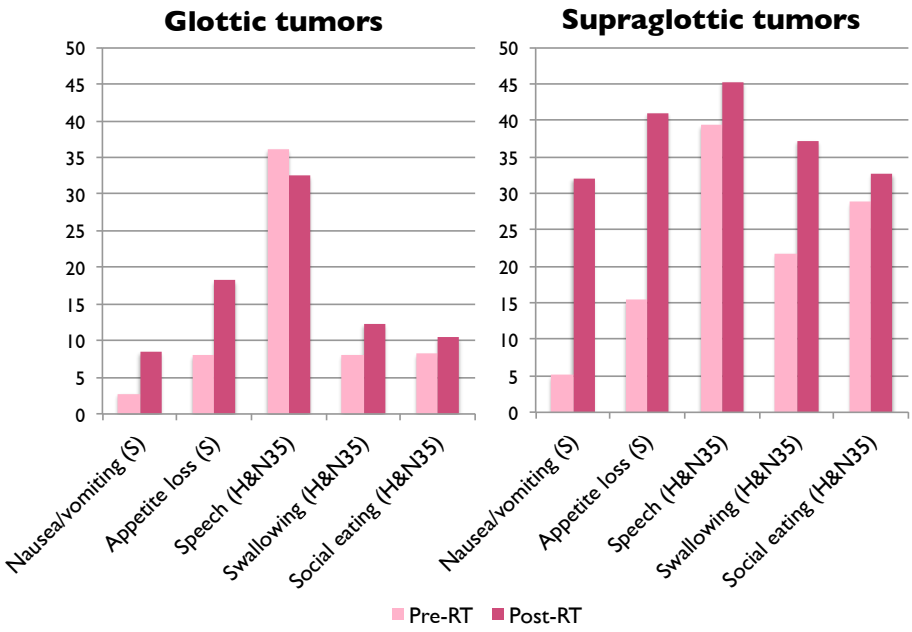

Figure 7. *Selected EORTC QLQ-C30 and H&N35 results pre- and post-radiotherapy for the glottic and supraglottic cohorts. Higher values for the symptom domains and single item (S) as well as the H&N35 domains indicate worse symptoms. All domains range from 0-100.*

Study II

The patients in the voice rehabilitation group experienced improved self-rated vocal function post rehabilitation, using the S-SECEL Environmental domain and the study specific questions regarding hoarseness and vocal loudness (Figure 8). No statistically significant differences were found between the voice rehabilitation group and control group regarding acoustic or temporal measures. However, the voice rehabilitation group had several values comparable to the voices of the healthy control group at baseline and follow-up, while the control group differed from the healthy control group regarding HNR, jitter, shimmer and MPT at follow-up.

Analysis of the patients with supraglottic tumors who received voice rehabilitation revealed statistically significant improvements of acoustically measured voice quality. The supraglottic cohort of the control group deteriorated or remained constant regarding the acoustic measures.

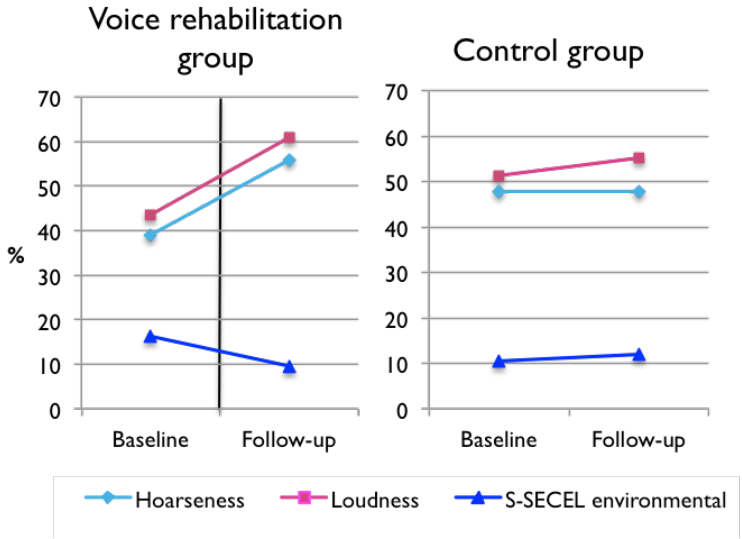

Figure 8. *Results of the S-SECEL environmental domain and questions about hoarseness and vocal loudness. The S-SECEL environmental domain ranges from 0-42 points, where a higher score represents worse communication function. The questions regarding hoarseness and vocal loudness range from 0-100, where 100 represents best possible. Vertical line indicates occurrence of voice rehabilitation.*

Study III

In this study, cut-off values indicating the need for voice rehabilitation were calculated for all domains of the S-SECEL (Total 20; General 4; Environmental 16; Attitudinal 5). These cut-off values had high sensitivity and specificity values (Table 8). Correct classification was performed for over 94% of the vocally healthy control group for the Total, Environmental and Attitudinal domain. The General domain cut-off score resulted in correct classification in approximately 40% of the vocally healthy control group. When using the cut-off score for the Total domain, 71 patients (60%) were above the cut-off, i.e. in need of rehabilitation at the start of the study and 43 patients (36%) were above the cut-off at the 12-month follow-up.

Additionally, MCID estimates were obtained for all domains. Improvement of -13 points (p<0.0001) or a deterioration of +8.7 points (p=0.035) were identified as MCID for the Total domain. Improvement/deterioration for the General, Environmental and Attitudinal domains were -2.0/1.1; -7.0/2.5; -4.0/5.1 respectively. Distribution based methods with fractions of a standard deviation showed similar results.

Table 8. Cut-off values of the S-SECEL when compared to the anchor question regarding acceptability of speech

Domain	Cut-off value	Sensitivity	Specificity	Area under the curve
Total	20.0	0.86	0.79	0.892
General	4.0	0.89	0.60	0.825
Environmental	16.0	0.75	0.93	0.887
Attitudinal	5.0	0.75	0.76	0.842

Study IV

The effects of voice rehabilitation regarding communication function and HRQL in the short-term remained 12 months post-radiotherapy measured using the S-SECEL Environmental domain and Total score as well as the selected EORTC QLQ-C30 and H&N35 domains Role function, Social function, Global QOL, Speech and Social contact. Perceived roughness deteriorated in the control group between 6 and 12 months (p=0.041), while the intervention group remained unchanged. Additionally, the difference in the proportion of patients with normal-mild perceived roughness between the control group (29%) and intervention group (60%) was statistically significant at 12 months (p=0.021).

Regarding the proportion of patients scoring above the cut-off score indicating the need for rehabilitation, the subjects in the control group remained at a constant level (approximately 50%). At baseline (1 month post-radiotherapy), approximately 20% of the subjects in the intervention group demonstrated S-SECEL values not indicating the need for vocal rehabilitation. At 12 months post-radiotherapy, the corresponding figure was 70% (Figure 9).

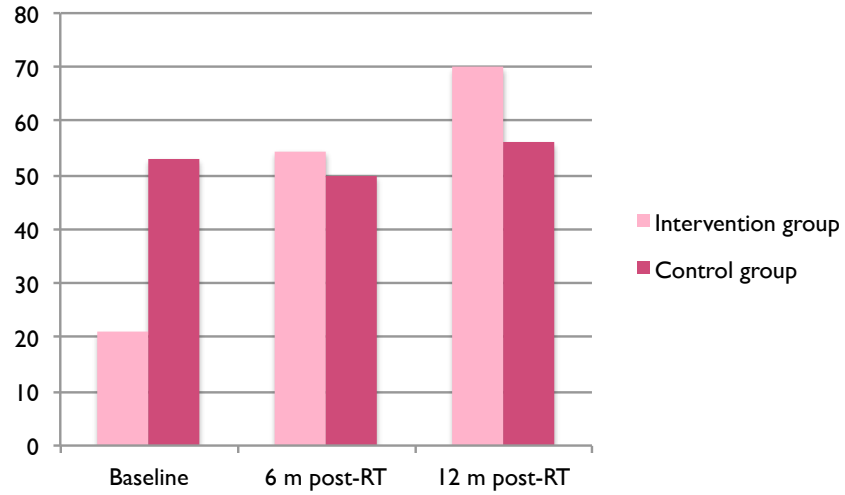

Figure 9. *Proportion of patients scoring below the S-SECEL cut-off score indicating the need for vocal rehabilitation*

Factors affecting the likelihood (Odds Ratio, OR) of improvement in communication function at the 12-month follow-up, measured with the S-SECEL Total domain were voice rehabilitation (OR 6.94 p=0.0013), high (bad) Speech scores (QLQ H&N35) post-radiotherapy (OR 1.38 p=0.0095), and less voice use one month post-radiotherapy compared to pre-radiotherapy (OR 3.6, p=0.03). Smoking affected the outcome negatively (OR 0.09 p=0.011). Tumor localization, size or stage, gender, radiotherapy regime or comorbidity did not affect the odds of improved communication function.

DISCUSSION

Voice, speech and communication are important factors for the laryngeal cancer population. Since voice and communication are affected after treatment, there is a need to add focus to the symptoms that the patients experience, and rehabilitation should be aimed at improving the reported symptoms [27]. This thesis showed that patients treated with radiotherapy for laryngeal cancer experienced a deterioration in HRQL. Voice rehabilitation improved HRQL and communication function as well as prevented deterioration of voice quality.

Impact of tumor localization

Tumor localization and its impact on functional outcomes regarding laryngeal tumors has been scarcely addressed in previous studies. In studies I and II, the tumor localization appears to impact the outcomes after treatment. Pre- and post-radiotherapy, the glottic cohort revealed voice quality inferior to the voices of vocally healthy controls, while the supraglottic cohort showed results comparable to vocally healthy controls. However, no statistically significant differences were found between the glottic and supraglottic cohort. This is in accordance with results presented by Oridate et al., where no statistically significant differences were found when comparing early glottic and supraglottic tumors regarding VRQOL and VHI-10 outcomes [149]. Sessions et al. demonstrated the 5-year outcome for patients treated for supraglottic tumors, where 85.7% reported good voices [150]. Regarding self-perceived communicative function in study I, both the glottic and supraglottic cohort demonstrated values similar to the other, but both were inferior to the vocally healthy control group, indicating worse communication function. However, with regard to HRQL, the supraglottic cohort revealed values inferior to the glottic cohort pre-, and to a greater extent, post-radiotherapy. These results are similar to those demonstrated by Nordgren et al. with the difference that their follow-up occasion was one-year post treatment [132]. The supraglottic cohort did to a greater extent require a feeding tube during radiotherapy when compared to the glottic cohort, a difference that was statistically significant. The need for a feeding tube is expected to have a negative impact on HRQL. Additionally, the supraglottic tumors were larger, also a statistically significant difference in comparison to the glottic cohort. These results are similar to a study by Langius et al. where malnutrition during radiotherapy was found to be associated with larger tumors and supraglottic localization of the tumor [151].

After voice rehabilitation, the supraglottic cohort of the voice rehabilitation group demonstrated improvement regarding acoustic measures and self-perceived communication function, while deterioration in acoustic measures were demonstrated for the control group. Supraglottic tumors in this study were larger than the glottic tumors. Voice quality in patients with glottic tumors has been found to be correlated with tumor size, where larger tumors present with inferior voice quality than smaller tumors [152]. Additionally, larger tumor size at diagnosis has been correlated to phonation with supraglottic activity, resulting in hoarseness [67]. One explanation as to why the supraglottic cohort demonstrated improvement after voice rehabilitation could be that the voice rehabilitation itself included relaxation of the larynx, therefore decreasing phonation with supraglottic activity. However, stroboscopic evaluation of phonation would be needed to draw proper conclusions.

Voice rehabilitation

Effect of voice rehabilitation

Voice rehabilitation following radiotherapy for laryngeal cancer resulted in improved self-perceived communication function, both in the short-term and in the follow-up study (II and IV). This is in line with results from Van Gogh et al., who found that VHI-improvements after voice therapy remained 13 months later [14, 141]. Additionally, voice rehabilitation appears to prevent the deterioration of perceived roughness, possibly due to the fact that voice rehabilitation aims to prevent development of hyperfunctional behavior. The normal progress after radiotherapy has been said to include fibrosis, which could give increased laryngeal tension, resulting in a hyperfunctional voice behavior [73]. This possibly explains the deterioration of perceived roughness in the control group. Voice rehabilitation also appear to impact on HRQL, since some parameters from the EORTC QLQ-C30 and H&N35 improved after voice rehabilitation, with patterns similar to the effects seen in self-perceived communication function, where results also remained at follow-up.

Patients suitable for rehabilitation

The next issue would be to determine which patients should receive voice rehabilitation. The prediction model in study IV showed that patients who experience voice problems, and speak less after treatment than before, are more prone to have improved communication function 12 months post radiotherapy. Additionally, efforts should be made on motivating patients to

quit smoking, since continued smoking negatively affected the chances of communication improvement. These results are in line with the literature, where continued smoking has repeatedly been associated with poor voice outcomes [66, 67, 76, 81]. Study II found that voice rehabilitation improved voice function and quality for patients with supraglottic tumors receiving voice rehabilitation. Meanwhile, localization was not found to be a predictor of communicative improvement according to the S-SECEL in study IV. This could be due to the study not examining localization as a predictor of acoustically measured voice improvement, but only self-reported improvement.

Timing of voice rehabilitation

Few studies exist concerning the timing of voice rehabilitation. The studies that do exist for the laryngeal cancer population report either on voice therapy concomitant with radiotherapy [140] or 6-120 months post oncologic treatment [14, 141]. Fex et al. concluded that voice therapy probably is helpful, but conclusions are difficult to draw, since the voice therapy itself and the outcome measures are insufficiently described [140]. Van Gogh et al. offered voice rehabilitation with different timings, which therefore could offer insight. However, the relatively small sample size hampers assessment of the most appropriate timing [14, 141]. The present studies demonstrated positive effects on how the patients perceived their communication and HRQL, which indicates that the timing, i.e. close to radiotherapy cessation, appears appropriate. However, optional timings were not explored, so no firm conclusion may be drawn as to whether this is optimal.

In conclusion, voice rehabilitation after radiotherapy for laryngeal cancer could be implemented in clinical practice. Focus should be on patients with supraglottic tumors, as well as patients who are experiencing deterioration of speech and decreased usage of their voice after radiotherapy. Additional efforts should be on helping with smoking cessation in order to improve the chances of communication recovery. In order to identify the patients in need of voice rehabilitation, PRO measures as well as documentation of voice quality through voice recordings before and after radiotherapy could be incorporated in the clinical management of the patients.

Patient Reported Outcomes

A complement to instrumental and perceptual measures as well as survival outcomes, is the patient's own opinion, which is helpful when evaluating treatment or intervention outcomes. PRO measures come in different

varieties, both generic and disease or symptom specific. Metcalfe et al. found that for early as well as advanced laryngeal cancer, speech is of utmost importance [27]. Additionally, Müller et al. concluded that instruments concerning the voice are necessary for the laryngeal cancer population in addition to general HRQL instruments [153].

Symptom specific instruments

Several instruments measuring vocal function exist, however, to our knowledge, only one is developed and adapted for the laryngeal cancer population. The S-SECEL has previously been found to be sensitive to change [77]. Symptom specific instruments such as the S-SECEL could be of use in clinical practice, in order to survey communication function post-treatment, and also to identify patients in need of rehabilitation by using the applied cut-off values suggested in study III. Wissinger et al. drew similar conclusions in their review of 130 longitudinal studies on PRO in head and neck cancer patients [154]. They suggested that PRO should be incorporated both in research and clinical practice in order to better inform the patients and clinicians in treatment decisions as well as help provide early intervention.

Measuring vocal outcome

What is the most effective and precise way to measure vocal outcome? The ELS suggests using a multidimensional approach based on the literature on which measures are the most reliable [36]. The different dimensions of the voice assessments complement each other, and give a more complete picture of the voice problem, which could aid the decision making regarding for example, intervention [37]. In the present studies several dimensions were used to assess voice and communication function. Acoustic measurements in this thesis did not prove associated with the patients' own perceptions of their voices nor of communication function, since no significant changes were detected by acoustic outcomes, while the self-perceived and perceptual measures did present changes. Woodson et al. stated that acoustic measures do reflect the sound of the voice, but not necessarily the ability to communicate [86]. Bhuta et al. found that only 3 of 19 acoustic measures correlated with perceptually measured voice quality [52]. Additionally, Ma et al. recommend that one should not over-rely on instrumental voice measures when evaluating voice, since the associations between acoustic and perceptual measures are inconsistent [155]. These results indicate that the acoustic measures do not always reflect what can be perceived.

One can speculate on whether the results for rehabilitation outcomes would have differed had voice rehabilitation been offered only to patients scoring above the threshold value indicating the need for voice rehabilitation. This would be similar to the method in the Van Gogh-studies, who offered voice therapy only to patients experiencing voice problems [14, 141]. In their studies there were improvements regarding not only the self-perceived voice function, but also acoustically measured voice quality. This design could possibly have given different outcomes. However, in study IV, the supplementary material suggests that no statistically significant differences regarding acoustic outcomes exist for patients scoring above or below the threshold.

When evaluating vocal outcomes, after for example voice rehabilitation or a medical treatment, the most important aspects to consider would, rather than the acoustic measures, be the patient's own perception of his or her voice or communication, as well as other people's perception. Benninger et al. stated that the subject's own opinion is the most important aspect to focus on, which further supports the use of PRO in measuring vocal outcome [63]. Killguß et al. found correlations between quality of life and self-perceived voice function, and recommended both aspects to be included in evaluation of treatment outcome [64]. In order to capture possible changes and to be able to demonstrate for the patients that changes have occurred, both PRO instruments and voice recordings are probably needed.

The ELS recommendations include stroboscopic evaluation of phonation, however, this was not performed in the present studies, which could be named a limitation [36]. Stroboscopic evaluations would add to the results in this study, particularly regarding the discussion on hyperfunctional voice behavior.

Clinical implications

The results documented in this thesis indicate that voice rehabilitation is effective, and could therefore to a greater extent be offered to patients after radiotherapy. Surprisingly, patients with supraglottic tumors seem to benefit more from voice rehabilitation than the glottic cohort, since improvement was documented not only concerning self-perceived communication function, but also regarding acoustic measurements and could more systematically be offered voice rehabilitation.

Additionally, the results indicated that the self-perceived communication function and perception of speech affects the likelihood of communicative

improvement. Therefore, voice rehabilitation could also be offered to patients who themselves experience difficulties in addition to patients with supraglottic tumors. However, in order to identify the patients experiencing communication problems, or deteriorated voice quality, all laryngeal cancer patients should be monitored regarding self-perceived communication function and HRQL as well as voice quality. The patients that are found to have inferior communication function or voice quality could then be offered voice rehabilitation. Communication instruments such as the S-SECEL could be of great importance in the planning of patient care after radiotherapy, and can hopefully be implemented as a part of the patient care after oncologic treatment.

The voice rehabilitation performed in this study, i.e. the 10 specified sessions, resulted in improvement of self-perceived communication function as well as HRQL, results that also persist at follow-up. The voice rehabilitation also appears to prevent deterioration of perceived voice quality. This specified voice rehabilitation protocol also leave some room for individual adaptation since the last three sessions include exercises that are most relevant for the individual patient.

Routines including voice recording and PRO-instruments regarding communication could preferably be managed at SLP departments, coordinated with follow-up visits at the oncology clinic. If the voice is recorded and communication instruments are filled in pre-radiotherapy, and at follow-up after radiotherapy, when the patient is seeing an SLP, rehabilitation efforts could be directed instantly if problems are identified. Voice therapy is part of the SLP's work, and could be implemented for the laryngeal cancer population. However, in order to add routine follow-up with SLPs, additional resources would be needed.

Limitations

- A limitation to the randomized studies (II and IV) is the fact that the randomization was performed partly using S-SECEL data from pre-radiotherapy, which gave differences of PRO measures at baseline, limiting the possibility for clear conclusions. However, in study IV, data were adjusted for these differences, and results still remained positive.
- Stroboscopic evaluation of laryngeal function is lacking, addition of this is suggested in further studies.

- The conclusions concerning the supraglottic cohort indicated vocal improvement for this group after voice rehabilitation, as well as inferior HRQL outcomes compared to a glottic cohort. However, the supraglottic cohort in this thesis was quite small, and in order to draw clear conclusions, a larger cohort would be preferred.
- Compliance to the voice training between the sessions was not assessed. Information on the amount of home-exercise could possibly provide insight in the matter of success of voice rehabilitation.

Future perspectives

Future studies planned within the study cohorts include follow-up on voice function and HRQL 2, 5 and 10 years post radiotherapy in order to establish whether rehabilitation outcomes persist for a long time. The aim is also to survey the natural course of voice and HRQL in the long-term after radiotherapy for laryngeal cancer.

The timing of voice rehabilitation needs to be evaluated. For example, a structured prophylactic voice rehabilitation program during radiotherapy compared to a voice therapy program after radiotherapy would provide important insight for improved rehabilitation.

Additionally, in this thesis, the compliance to the home exercise of the rehabilitation program was not measured. This could be an important aspect to study, as well as studying the patient's motivation to voice rehabilitation and its effect on rehabilitation outcomes.

Few studies have investigated the cost-effectiveness of rehabilitation programs for the head and neck cancer populations. There is one, providing information on the health-economic aspects regarding swallowing intervention [156]. When resources in health-care are limited, it is important that given treatment is evidence-based and effective. Subsequently, the next step would be to evaluate if the rehabilitation is cost-effective, which would be an interesting addition to the effectiveness studies in this thesis.

Factors affecting improvement of communication function were identified, but more information regarding what factors are associated with deterioration of communication function is equally important, in case there is a possibility to prevent the deterioration.

CONCLUSION

The thesis demonstrates that a large proportion of laryngeal cancer patients experience voice problems indicating the need for vocal rehabilitation following radiotherapy. For over a third of the patients this need persisted one year after treatment. Voice rehabilitation has beneficial short- and long-term effects on self-perceived communication function and HRQL, and prevents deterioration of perceived roughness. Patients with supraglottic tumors appeared to improve more than patients with glottic tumors when receiving voice rehabilitation, especially for acoustic measures.

Voice function needs to be monitored for the laryngeal cancer patients pre- and post-radiotherapy. Suggestions regarding PRO measurements on communication as well as voice recordings are recommended for incorporation in clinical care.

Summarizing points

- Voice problems are common after radiotherapy for laryngeal cancer
- Voice function and voice quality should be measured pre and post oncologic treatment through PRO and voice recording
- Supraglottic tumors present with inferior HRQL after radiotherapy
- Voice rehabilitation improves communication function and HRQL
- Voice rehabilitation prevents voice deterioration in terms of roughness
- The S-SECEL is an instrument suitable for measuring therapy outcomes as well as screening for the presence of communication problems

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APPENDIX

Appendix 1: GRBAS-rating scale

Sample no._____

Listen to the 2 sentences and long vowel /a/.
Please circle the most appropriate rating.

Scoring	Not present 0	Mild 1	Moderate 2	Severe 3	
Roughness	0	1	2	3	☐Continuous ☐Intermittent
Breathiness	0	1	2	3	☐Continuous ☐Intermittent
Asthenia	0	1	2	3	☐Continuous ☐Intermittent
Strain	0	1	2	3	☐Continuous ☐Intermittent
Overall Grade	0	1	2	3	

Appendix 2: S-SECEL

INSTRUKTION: Här följer 35 påståenden om Dina rösterfarenheter vid struphuvudtumör. Läs varje fråga noga och var vänlig kryssa i rutan för det svarsalternativ som bäst beskriver Dig och Din situation ***den senaste månaden***.

		Alltid	**Ofta**	**Ibland**	**Aldrig**
1.	Känner Du Dig avslappnad och väl till mods i samtalssituationer med andra människor?	☐$_0$	☐$_1$	☐$_2$	☐$_3$
2.	Skulle Du beskriva Dig själv som en lugn, stillsam person?	☐$_0$	☐$_1$	☐$_2$	☐$_3$
3.	Är Du en aktiv, utåtriktad, pratsam person?	☐$_0$	☐$_1$	☐$_2$	☐$_3$
4.	Kan Du tala om för en person Du pratar med att Du fått behandling för struphuvudtumör?	☐$_0$	☐$_1$	☐$_2$	☐$_3$
5.	Tycker Du att Ditt tal förbättras ju mer Du använder det?	☐$_0$	☐$_1$	☐$_2$	☐$_3$
6.	Har Dina möjligheter att delta i möten, föreningsliv eller andra sammankomster varit begränsade på grund av Ditt tal?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
7.	Tycker Du att det är svårt att få andra människors uppmärksamhet när Du pratar?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
8.	Har Du svårt att höja rösten eller ropa?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
9.	Märker Du att andra människor har svårt att förstå vad Du säger?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
10.	Behöver Du upprepa samma sak flera gånger för att bli förstådd?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
	Har Du problem med att tala:				
11.	- i stora grupper?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
12.	- i små grupper?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
13.	- med en person?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
14.	- i hemmiljö?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
15.	- i bullrig miljö?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
16.	- i telefon?	☐$_3$	☐$_2$	☐$_1$	☐$_0$
17.	- när Du åker bil eller buss?	☐$_3$	☐$_2$	☐$_1$	☐$_0$

	Gör Ditt tal att:	Alltid	Ofta	Ibland	Aldrig
18.	- Du har svårigheter att vara med på fester eller andra sociala tillställningar?	☐3	☐2	☐1	☐0
19.	- Du pratar i telefon mindre ofta än Du skulle vilja?	☐3	☐2	☐1	☐0
20.	- Du känner Dig utanför tillsammans med andra människor?	☐3	☐2	☐1	☐0
21.	- Ditt privatliv eller sociala liv begränsas?	☐3	☐2	☐1	☐0
	Får Ditt tal Dig att känna Dig:				
22.	- deprimerad?	☐3	☐2	☐1	☐0
23.	- frustrerad när Du pratar med Din familj eller Dina vänner och de inte förstår Dig?	☐3	☐2	☐1	☐0
24.	- annorlunda eller egendomlig?	☐3	☐2	☐1	☐0
25.	- tveksam inför att möta nya människor?	☐3	☐2	☐1	☐0
26.	- utelämnad i diskussioner?	☐3	☐2	☐1	☐0
27.	Undviker Du att prata med andra människor på grund av Ditt tal?	☐3	☐2	☐1	☐0
28.	Brukar folk fylla i ord eller avsluta meningar åt Dig?	☐3	☐2	☐1	☐0
29.	Blir Du avbruten när Du pratar?	☐3	☐2	☐1	☐0
30.	Talar folk om för Dig att de inte förstår vad Du säger?	☐3	☐2	☐1	☐0
31.	Blir folk Du pratar med irriterade (på Dig) på grund av Ditt tal?	☐3	☐2	☐1	☐0
32.	Undviker folk Dig på grund av Ditt tal?	☐3	☐2	☐1	☐0
33.	Pratar folk annorlunda med Dig på grund av Ditt tal?	☐3	☐2	☐1	☐0
34.	Har Din familj och Dina vänner liten förståelse för hur det är att kommunicera med den här typen av tal?	☐3	☐2	☐1	☐0
35.	Pratar Du lika mycket nu som innan Du fick Din struphuvudtumör?	Ja ☐	Mer ☐		Mindre ☐

TACK FÖR DIN MEDVERKAN !

Appendix 3: EORTC QLQ-C30

EORTC QLQ C30 **(version 3.0.)**

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig.
Det finns inga svar som är "rätt" eller 'fel'.
Den information Du lämnar kommer att hållas strikt konfidentiell.

	Inte alls	**Lite**	**En hel del**	**Mycket**
1. Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska ?	1	2	3	4
2. Har Du svårt att ta en lång promenad ?	1	2	3	4
3. Har Du svårt att ta en kort promenad utomhus ?	1	2	3	4
4. Måste Du sitta eller ligga på dagarna ?	1	2	3	4
5. Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten ?	1	2	3	4

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
6. Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter ?	1	2	3	4
7. Har Du varit begränsad i Dina möjligheter att utöva Dina hobbies eller andra fritidssysselsättningar ?	1	2	3	4
8. Har Du blivit andfådd ?	1	2	3	4
9. Har Du haft ont ?	1	2	3	4
10. Har Du behövt vila ?	1	2	3	4
11. Har Du haft svårt att sova ?	1	2	3	4
12. Har Du känt dig svag ?	1	2	3	4
13. Har Du haft dålig aptit ?	1	2	3	4
14. Har Du känt dig illamående ?	1	2	3	4
15. Har Du kräkts ?	1	2	3	4
16. Har Du varit förstoppad ?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
17. Har Du haft diarré ?	1	2	3	4
18. Har Du varit trött ?	1	2	3	4
19. Har Dina dagliga aktiviteter påverkats av smärta ?	1	2	3	4
20. Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV ?	1	2	3	4
21. Har Du känt Dig spänd ?	1	2	3	4
22. Har Du oroat Dig ?	1	2	3	4
23. Har Du känt Dig irriterad ?	1	2	3	4
24. Har Du känt Dig nedstämd ?	1	2	3	4
25. Har Du haft svårt att komma ihåg saker ?	1	2	3	4
26. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt familjeliv ?	1	2	3	4
27. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina sociala aktiviteter ?	1	2	3	4
28. Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska ? svårigheter ?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått ?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått ?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

Appendix 4: EORTC QLQ-H&N35

Patienter uppger ibland att de har följande symptom eller problem.
Var vänlig och ange i vilken grad Du har haft dessa besvär under veckan som gått.
Sätt en ring runt den siffra som stämmer för Dig.

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
31. Har Du haft smärtor i munnen ?	1	2	3	4
32. Har Du haft smärtor i käken ?	1	2	3	4
33. Har Du haft sveda i munnen ?	1	2	3	4
34. Har Du haft smärtor i svalget ?	1	2	3	4
35. Har Du haft problem med att svälja flytande ?	1	2	3	4
36. Har Du haft problem med att svälja mosad mat ?	1	2	3	4
37. Har Du haft problem med att svälja fast föda ?	1	2	3	4
38. Har Du ”satt i halsen” när Du svalt ?	1	2	3	4
39. Har Du haft problem med tänderna ?	1	2	3	4
40. Har Du haft problem med att gapa ?	1	2	3	4
41. Har Du varit torr i munnen ?	1	2	3	4
42. Har saliven varit seg ?	1	2	3	4
43. Har Du haft problem med luktsinnet ?	1	2	3	4
44. Har Du haft problem med smaksinnet ?	1	2	3	4
45. Har Du hostat ?	1	2	3	4
46. Har Du varit hes ?	1	2	3	4
47. Har Du känt Dig sjuk ?	1	2	3	4
48. Har Ditt utseende besvärat Dig ?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
49. Har Du haft problem med att äta ?	1	2	3	4
50. Har Du haft svårt att äta inför familjen ?	1	2	3	4
51. Har Du haft svårt att äta inför andra människor ?	1	2	3	4
52. Har Du haft svårt att njuta av måltiderna ?	1	2	3	4
53. Har Du haft svårt att prata med andra människor ?	1	2	3	4
54. Har Du haft problem med att prata i telefon ?	1	2	3	4
55. Har Du haft svårt att umgås med Din familj ?	1	2	3	4
56. Har Du haft svårt att umgås med Dina vänner ?	1	2	3	4
57. Har Du haft svårt för att gå ut offentligt bland andra människor ?	1	2	3	4
58. Har Du haft svårt för fysisk kontakt med Din familj eller Dina vänner ?	1	2	3	4
59. Har Du känt Dig mindre intresserad av sex ?	1	2	3	4
60. Har Du känt mindre sexuell njutning ?	1	2	3	4

Under veckan som gått:	**Nej**	**Ja**
61. Har Du använt smärtstillande mediciner ?	1	2
62. Har Du tagit något näringstillskott (förutom vitaminer) ?	1	2
63. Har Du haft matsond ?	1	2
64. Har Du gått ner i vikt ?	1	2
65. Har Du gått upp i vikt ?	1	2

Appendix 5: Study specific questions

Patient nr:.....

Här följer en fråga om hur Du upplever din röst. Markera med en cirkel runt det alternativ Du tycker passar bäst på Dig.

	Alltid	Ofta	Ibland	Aldrig
Är Ditt tal acceptabelt i ett socialt sammanhang?	3	2	1	0

Här följer nu frågor om hur Du själv upplever Din röst. Du skall markera med ett kryss på linjen.

Har Du hes eller oklar röst?

Inte alls Mycket

Är Din röststyrka tillräcklig (kan Du höja rösten som Du vill)?

Alltid bra styrka Aldrig bra styrka