Radiotherapy and Voice Rehabilitation in Laryngeal Cancer

Effects on Health-Related Quality of Life and Voice Function

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ABSTRACT

The overall aim of the thesis was to describe the effects of radiotherapy following laryngeal cancer on health-related quality of life (HRQL) and voice function as well as to assess the efficiency of voice rehabilitation.

Patients treated by radiotherapy for laryngeal cancer were included in the study and randomised into two groups, one intervention group receiving voice rehabilitation and one control group. Patients were assessed prospectively pre-radiotherapy and one, six and 12 months post-radiotherapy completion. Voice rehabilitation took place between one and six months post-radiotherapy. Endpoints included patient-reported outcomes, such as HRQL measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ) as well as communication function according to Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer (S-SECEL). Perceptual, acoustic and temporal analyses of voice recordings were also performed. Additionally, a vocally healthy control group was included for comparison.

Results demonstrated that although HRQL deteriorated for both glottic and supraglottic tumours one month post-radiotherapy, the latter group reported the largest deteriorations. In terms of voice quality, acoustic measures revealed that glottic tumours deviated significantly from vocally healthy controls pre-radiotherapy with some parameters improving post-radiotherapy. Supraglottic tumours however, demonstrated no difference compared to the vocally healthy control group at either time-point.

Twelve months post-radiotherapy, laryngeal cancer patients demonstrated no significant difference when compared to pre-treatment in terms of HRQL, communication dysfunction or voice quality, albeit still had abnormal values. HRQL declined immediately post-radiotherapy and recovered to pre-treatment values at six months post-radiotherapy. All patients presented with perceptually perceived dysphonia, with only the variable "roughness" changing significantly during the study period. Roughness improved post-radiotherapy but deteriorated again between six and 12 months post-radiotherapy.

The intervention group receiving voice rehabilitation demonstrated more improvements in HRQL and communication function domains compared to the control group, which remained static during the study period. The improvements were maintained up to six months post-voice rehabilitation (12 months post-radiotherapy). Voice rehabilitation also appeared to prevent the

perceptual deterioration observed in the control group between six and 12 months. Lastly, the likelihood of experiencing a clinically significant communication improvement at 12 months post-radiotherapy was positively influenced by undergoing voice rehabilitation and negatively influenced by smoking continuation.

This thesis concludes that the majority of laryngeal cancer patients have impaired voice quality, communicative function and HRQL prior to radiotherapy with no significant improvements seen 12 months post-radiotherapy. Voice rehabilitation has positive effects on HRQL and communication function as well as seems to hinder a perceived deterioration of the voice quality roughness. These beneficial effects are maintained up to six months following voice rehabilitation completion. Voice rehabilitation could be offered to patients who experience voice and communication problems as well as to risk patients identified by speech-language pathologists.

SAMMANFATTNING PÅ SVENSKA

Strålbehandling är en vanlig behandlingsform för cancer i struphuvudet (larynx). Både sjukdomen och dess behandling kan resultera i röstpåverkan, där en undermålig funktion kan ha en negativ inverkan på patienternas hälsorelaterade livskvalitet (HRQL). Många studier rekommenderar röstrehabilitering för denna patientgrupp, men här finns det en kunskapslucka att fylla eftersom det saknas longitudinella randomiserade röstrehabiliteringsstudier. Avhandlingens övergripande syfte var därför att beskriva strålbehandlingens effekt på HRQL, kommunikationsförmåga och röstfunktion samt att utvärdera effekten av röstrehabilitering efter avslutad strålbehandling hos larynxcancerpatienter.

Resultaten visade att patienter med tumören lokaliserad ovanför stämbanden (supraglottiska tumörer) i högre grad rapporterade sämre HRQL efter strålbehandling jämfört med de patienter vars tumörer var lokaliserade på stämbanden (glottiska tumörer). Avseende röstkvalitet visade resultaten att patienter med glottiska tumörer hade sämre röst enligt akustiska mätningar än den röstfriska gruppen både före och efter strålbehandling, medan patienter med supraglottiska tumörer var jämförbara med den röstfriska gruppen vid båda mättillfällena.

Resultaten från HRQL- och kommunikationsinstrument, logopeders mätning (perceptuell analys) samt utifrån akustisk mätning visade att larynxcancerpatienter före strålbehandling hade sämre HRQL, kommunikationsförmåga och röstkvalitet jämfört med röstfrisk normalpopulation. Tolv månader senare förelåg ingen signifikant förändring med undantag av hur logopederna uppfattade patienternas röstkvalitet (röstskrovlighet), vilken försämrades mellan sex och 12 månader efter avslutad strålbehandling.

Patientgruppen som erhöll logopedisk röstrehabilitering uppvisade signifikant bättre HRQL och kommunikationsförmåga jämfört med kontrollgruppen, vilket även kvarstod sex månader efter avslutad röstrehabilitering. Den försämring i röstkvalitet som noterades i kontrollgruppen, uteblev i interventionsgruppen. Avhandlingen visar även att den viktigaste faktorn för patientupplevd förbättrad kommunikativ funktion 12 månader efter strålbehandling var erhållen röstrehabilitering. Fortsatt rökning påverkade utfallet negativt.

Vi konkluderar att strålbehandlade larynxcancerpatienter rapporterar sämre livskvalitet, kommunikationsförmåga och röstkvalitet före strålbehandling jämfört med en röstfrisk kontrollgrupp samt att dessa försämringar kvarstår 12 månader senare. Röstrehabilitering är effektiv och bidrar till förbättrad HRQL och kommunikativ funktion samt förhindrar en röstförsämring över tid och skulle kunna erbjudas till de patienter som efter strålbehanding upplever röstproblem samt till riskgruppspatienter.

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 following radiotherapy for laryngeal cancer – a comparison between glottic and supraglottic tumours.

   Acta Oncologica 2015; 54 (1) 73-9.

II. Karlsson, T. Bergström, L. Ward, E. Finizia, C.

   A prospective longitudinal study of voice characteristics and health-related quality of life outcomes following laryngeal cancer treatment with radiotherapy.

   Submitted.

III. Karlsson, T. Johansson, M. Andréll, P. Finizia, C.

   Effects of voice rehabilitation on health-related quality of life, communication and voice in laryngeal cancer patients treated with radiotherapy: A randomised controlled trial.

   Acta Oncologica 2015. E-pub ahead of print.

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 function and health-related quality of life.

   Submitted.

* Shared first authorship

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CONTENT

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ABBREVIATIONS

ACE-27	Adult Comorbidity Evaluation-27
ANCOVA	Analysis of Covariance
CI	Confidence Interval
CT	Computed Tomography
EORTC	European Organisation for Research and Treatment of Cancer
F0	Fundamental frequency
GORD	Gastro-Oesophageal Reflux Disease
GRBAS	Grade, Roughness, Breathiness, Asthenia, Strain
Gy	Gray
HART	Hyperfractionated Accelerated Radiotherapy
HNC	Head and Neck Cancer
HNR	Harmonics-to-Noise Ratio
HPV	Human Papilloma Virus
HRQL	Health-Related Quality of Life
MCID	Minimum Clinically Important Difference
MPT	Maximum Phonation Time
PRO	Patient-Reported Outcome
PVP	Perceptual Voice Profile
QLQ-C30	The EORTC Quality of Life Questionaire Core 30
QLQ-H&N35	The EORTC Quality of Life Questionnaire Head and Neck Module
QOL	Quality of Life
RCT	Randomised Controlled Trial
SCPL	Supracrichoid Partial Laryngectomy
SD	Standard Deviation
SECEL	Self-Evaluation of Communication Experiences after Laryngectomy
S-SECEL	Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer
TEP	Tracheoesophageal Puncture
TL	Total Laryngectomy
TLM	Transoral Laser Microsurgery
TNM	Tumour Node Metastasis
VGR	Västra Götalandsregionen/Västra Götaland county
VHI	Voice Handicap Index
WHO	World Health Organisation

1 INTRODUCTION

1.1 Laryngeal cancer

Laryngeal cancer is the second most common head and neck cancer (HNC) and constitutes 30% of all head and neck malignancies [1]. With an incidence of 157 000 cases world-wide, it accounts for 1% of all cancer diagnoses [2]. Incidence is related to socioeconomic factors, where it has been shown to increase with decreasing income, education levels, social class and lack of cohabitating status [3]. Additionally, geographical differences have been observed with highest incidence rates occurring in southern Europe, Brazil and western Asia, whilst lower rates are found in Africa, eastern Asia, Oceania and most northern European countries [4].

In Sweden, approximately 200 new cases are diagnosed annually of which 35 are found in Västra Götaland county (VGR) [5]. The majority of patients are male (85%) and 80% are 60 years of age or older at diagnosis [6].

Site
The larynx serves three main functions, namely airway protection as well as respiration and phonation.

It is found above the trachea, in the neck anterior to the level of cervical vertebrae three to six and is subdivided anatomically into a supraglottic, glottic and subglottic compartment (Figure 1). The supraglottic larynx encompasses the epiglottis, the false vocal cords, the arytenoids and the ventricles, whereas the glottic larynx consists of the true vocal cords including the anterior and posterior commissures and extends approximately one cm below the vocal cords into the paraglottic space. The subglottic larynx starts below the glottic larynx and extends to the trachea inferiorly [7]. The larynx is lined by squamous epithelium, whereby 95% of the tumours are squamous cell carcinomas [8].

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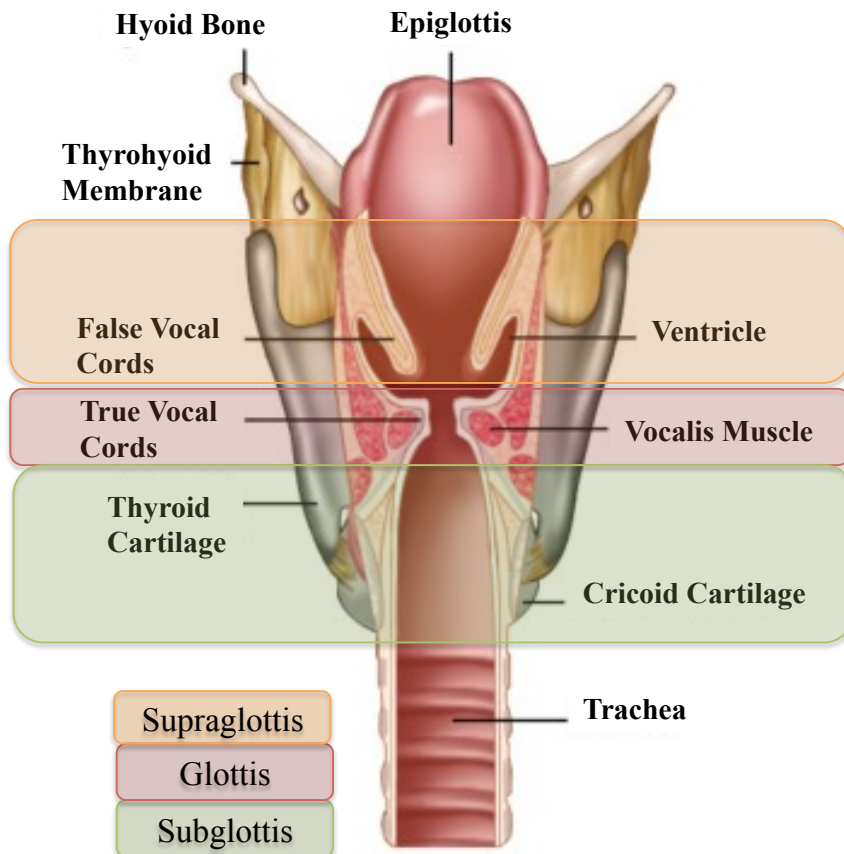
Figure 1. Anatomical subdivision of the larynx and its compartments.
Reproduced with permission from www.vocaltips.net.

If a tumour encompasses all three compartments it is termed transglottic. However, the vast majority of laryngeal cancer in Sweden presents as glottic (87%) tumours, followed by supraglottic (11%) and rarely as subglottic malignancy (2%) [5].

Aetiology

Risk factors for laryngeal cancer can be subdivided into social, occupational, inflammatory and infectious factors (Figure 2). Social factors include smoking and alcohol use, of which the former is the most predominant of all

aetiological agents. Frequency (cigarettes/day) and smoking duration are strongly associated with the carcinogenic process and although smoking cessation decreases risk, it is still elevated 20 years post-cessation when compared to non-smokers [9]. Moderate to high alcohol intake (12.5-50 g/day and ≥50 g/day of ethanol respectively) has been shown to increase risk up to 2.5 fold [10].

The role of gastro-oesophageal reflux disease (GORD) as an inflammatory factor predisposing to laryngeal cancer has been debated, but is now gaining increasing foothold [11]. Additionally, viral-induced DNA mutations possibly caused by the presence of Human Papilloma Virus (HPV) have been reported in up to 24% of cases and being of particular importance in younger patients, whilst other studies find no such association [12,13].

Moreover, occupational exposure including asbestos, polycyclic aromatic hydrocarbons, engine exhaust, textile dust and rubber industry employment have all been implicated in increasing risk of laryngeal cancer [14,15].
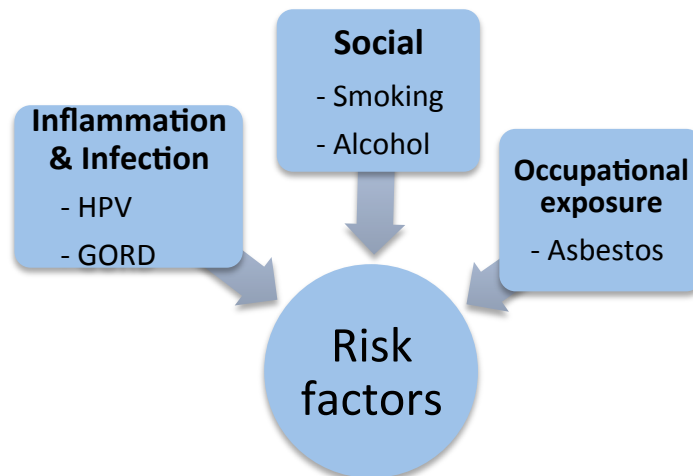
Figure 2. Classification of risk factors for laryngeal cancer. HPV=Human Papilloma Virus, GORD=gastro-oesophageal reflux disease.

Staging and classification

Staging is the process of classifying a primary tumour depending on the extent of cancer in the body, including the presence or absence of metastases. It aids in treatment planning, prognosis determination and communication between healthcare centres. In Sweden, laryngeal tumours are staged according to the International Union against Cancer. This classification stages malignancies according to three criteria, namely depending on the primary tumour site (T), regional (N) as well as distant spread (M):

T: Takes into account the size and local penetration of primary tumour as well as evidence of invasion into adjacent organs and structures. It is graded on a scale of X-4 (Table 1) [16].

N: Describes regional spread to neck lymph nodes and is graded on a scale of X-3 (Table 2) [16].

M: Establishes if distant metastasis is present and is graded as 0 or 1 (Table 2).

These three variables are then combined according to Table 3, resulting in tumour stages I-IV.

Table 1. TNM-classification: T-stage.

	Supraglottic	**Glottic**	**Subglottic**
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
Tis	Carcinoma-in-situ		
T1	One subsite, normal vocal cord mobility	Limited to vocal cords(s), normal mobility (a) one cord (b) both cords	Limited to subglottis
T2	Mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis; wthout larynx fixation	Into supraglottis, subglottis or impaired cord mobility	Extends to vocal cord(s) with normal or impaired mobility
T3	Cord fixation or invades postcricoid area, pre-epiglottic tissue, paraglottic space or thyroid cartilage erosion	Cord fixation, thyroid cartilage erosion or invasion into paraglottic space	Cord fixation
T4a	Through thyroid cartilage or tissue invasion beyond larynx		
T4b	Prevertebral space, mediastinal structures or carotid artery		

Table 2. TNM-classification: N- and M-stage.

N-stage: Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, ≤ 3 cm
N2 a	Metastasis in a single ipsilateral node between 3-6 cm
b	Metastasis in multiple ipsilateral nodes, all ≤ 6 cm
c	Metastasis in bilateral or contralateral nodes, all ≤ 6 cm
N3	Metastasis in a lymph node > 6 cm
M-stage: Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	Distant metastasis absent
M1	Distant metastasis present

Table 3. Combinations of Tumour (T), Regional lymph nodes (N) and Metastasis (M)-classifications forming tumour stages (I-IV).

	N0	N1	N2	N3	M1
T1	I	III	IV	IV	IV
T2	II	III	IV	IV	IV
T3	III	III	IV	IV	IV
T4	IV	IV	IV	IV	IV

Treatment

Oncologic treatment for laryngeal cancer is primarily aimed at survival, but due to the important communicative aspects of voice, organ preservation is increasingly desirable.

Early stage disease

In the western part of Sweden, an organ-sparing approach for early stage disease (stages I and II) using radiotherapy is employed [5]. The amount of radiation absorbed by the tissue is referred to as the absorbed dose, which is measured in joules per kilogram or Gray (Gy). Prior to radiotherapy

administration, a plastic mask is fitted along with a vacuum cushion, aiming to keep the head in the same position for each treatment session. A Computed Tomography (CT) scan is then performed in treatment position and a dosimetric plan established whereafter treatment can commence. Therapeutic treatment of laryngeal cancer employs fractionated radiotherapy protocols. This implies that the total radiation dose is subdivided into smaller doses given over a certain period of time. Because the total radiation dose, number of fractions and overall treatment time all affect the tumour and adjacent tissue, several fractionation protocols exist and can be subdivided into [5]:

- Conventional fractionation: where 2.0 Gy (most commonly) is administered as a fraction once daily, five days per week.
- Modified fractionation
    - Hyperfractionation: Involves a reduced fraction size to < 1.8 Gy. This spares healthy tissue but in order to achieve a similar total dose, treatment time is prolonged, which can have negative effects. Administering fractions twice daily often compensates for this.
    - Accelerated fractionation: implies delivering the same total dose in a shorter period of time and can be achieved by increasing the number of daily fractions or by administering fractions up to six or seven times per week.

A summary of radiotherapy fractionation protocols in use during the study period in VGR for HNC is presented in Table 4.

Table 4. Examples of fractionation protocols used in VGR during the study period.

Fractionation protocols	Total dose (Gy)	Gy/fraction	Daily fractions	Fractions per week
Conventional	68.0	2.0	1	10
Hyperfractionated Accelerated (HART)	64.6	1.7	2	10

However, because healthy tissue is also affected in the radiation process, side effects of the treatment are unavoidable. These can be classified as acute if appearing during or immediately following treatment completion, or late, which can manifest months or years post-radiotherapy. Acute effects are often reversible whilst late side effects tend to remain chronic. Examples of

side effects include mucositis, which arises due to cell depletion in the mucosa combined with fibrin leakage resulting in pain, dysphagia and hoarseness. Erythema is also common along with injuries to the salivary glands causing a dry mouth (xerostomia). Finally, hypothyroidism results in 10% of patients where the thyroid has received a significant radiation dose [5].

An alternative option to radiotherapy does exist, namely transoral laser microsurgery (TLM). However, this is more frequently used in other parts of Sweden than in VGR. Systematic reviews and randomised controlled trials (RCT) have not yet been able to show one treatment as convincingly superior in terms of survival, Health-Related Quality of Life (HRQL) or voice function [17-19].

Advanced stage disease

In contrast to early stage disease, patients suffering from more advanced stages (stages III and IV) often require a combination of treatments for optimal results. For nearly 100 years, total laryngectomy (TL) was considered the only option for advanced disease. However, in 1991 the Veterans Affairs Study was published, which was an RCT comparing induction chemotherapy + radiotherapy versus surgery. It demonstrated no survival difference between treatment arms at two years, thus highlighting the possibility of organ preservative approaches even for advanced disease [20]. Chemotherapy can be administered as induction, i.e. given prior to radiotherapy, or as concurrent, where it is administered simultaneously as radiotherapy. Although induction chemotherapy was administered initially, practice changed to concurrent chemotherapy following the study by Forastiere et al. [21] demonstrating superior loco-regional control and higher rates of intact larynxes using the latter approach.

The benefits of chemoradiotherapy must however be balanced by its increased toxicity, especially amongst patients with medical comorbidities and reduced performance status. When contra-indications for chemotherapy exist, cetuximab is a viable alternative [5]. Cetuximab is a monoclonal antibody against epidermal growth factor, which becomes pathologically activated in squamous cell carcinomas. The RCT by Bonner et al. concluded that by combining cetuximab with radiotherapy versus radiotherapy alone, loco-regional control and overall survival was significantly increased without an increase in toxicity [22].

However, organ preservation does not equal functional preservation. Subsequently, there is increasing support for operative management of

advanced laryngeal cancer and a shift away from chemoradiotherapy for selected patients [23]. Two examples of this include TLM and supracrichoid partial laryngectomy (SCPL). A retrospective study by Canis et al. employed TLM in 391 patients with T2-T3 tumours of the aero-digestive tract and achieved laryngeal conservation in 80-90% of patients with five-year survival rates comparable to those of TL or chemoradiotherapy. In addition, SCPL has demonstrated superior functional outcomes in terms of speech and swallowing compared to TL and has in some areas replaced near-TL as an organ-sparing surgical option [23].

Total laryngectomy and adjuvant radiotherapy is still in use but reserved for T4 tumours with cartilage invasion as well as for salvage surgery following failed primary radiotherapeutic treatment [5].

Prognosis

Prognosis is influenced by tumour stage at presentation, i.e. size of the primary tumour and the presence of regional or metastatic spread. In addition, tumour site holds a vital role as glottic tumours often carry better prognostic rates compared to supraglottic or subglottic tumours. This is due to the fact that a glottic lesion often presents with hoarseness, prompting an early help-seeking behaviour. Additionally, the true vocal cords lack lymphatic drainage hampering the spread of regional and distant metastatic disease, thereby improving survival. For glottic tumours, the five year loco-regional control rates world-wide are 80-94%, 70-80%, 65-75% and 50-80% for T1, T2, T3 and T4-disease respectively [5].

Many deaths of patients with early laryngeal cancer are no longer attributed to acute effects of therapy or therapy failures, but rather to second primary tumours or intercurrent disease [24].

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1.2 Voice

Although laryngeal cancer survival is high and organ preservation rates are increasing, organ preservation is not synonymous with function preservation as previously mentioned. Both the tumour and radiotherapy can affect voice and speech negatively.

The pathophysiological vocal fold effects of radiotherapy have been documented and include altered microcirculation, acute oxidative responses, fibrosis, chronic inflammation as well as oedema of the cords and surrounding tissues [25,26]. Additionally, the invasive nature of the tumour can cause neuromuscular vocal fold weakness. Subsequent structural effects include impaired vocal fold mobility, decreased tissue elasticity, irregular vocal fold vibration and glottic incompetence due to structural abnormalities [27]. Studies have also suggested that radiation-induced xerostomia and thickened secretions can adversely influence voice quality [28-30]. Hence, these factors can all contribute to deteriorations in phonation ability.

Vocal function measures
Vocal function can be measured using patients' experiences (described in chapter 1.3) and by acoustic, temporal as well as by perceptual analysis.

Acoustic analysis and temporal measures
Acoustic analysis yields a numeric output of specific properties of the sound waveform produced by the patient (Figure 3). It is a computerised process performed on a voice recording and can be based on a sustained vowel or continuous speech [31]. A multitude of variables can be measured but those most frequently reported in literature and recommended by the European Laryngological Society for functional assessment of voice pathology include fundamental frequency (F0), jitter, shimmer, harmonics-to-noise ratio (HNR) and maximum phonation time (MPT) and are defined below [32,33].

F0	Rate of vocal fold vibration, correlated to the perception of pitch
Jitter	Irregularities in frequency from one cycle to the next
Shimmer	Irregularities in amplitude from one cycle to the next
HNR	The ratio between harmonics and noise in the voice signal, often caused by turbulence at the vocal folds
MPT	A temporal measure that reflects the longest time a person can sustain a vowel using one breath

Most acoustic studies performed on laryngeal cancer patients agree on the fact that abnormal vocal measures are obtained pre-radiotherapy when compared to vocally healthy controls. Agarwal et al. found deviant F0, jitter, shimmer and HNR both at baseline and three months post-radiotherapy in their cohort of 50 early stage laryngeal cancer patients despite a significant intra-group improvement [34]. This is supported by Bibby et al. where jitter, shimmer and HNR significantly improved from pre-treatment to 12 months post-radiotherapy yet, could not be considered normal [35]. Finally, van Gogh et al. demonstrated in their prospective study with 106 patients undergoing TLM or radiotherapy that although all acoustic measures were abnormal pre-treatment only jitter significantly remained so two year post-treatment when compared to a vocally healthy control group [36].

In sum, there appears to be a spontaneous recovery post-radiotherapy exceeding pre-treatment values albeit these values are still of pathological nature. Long-term follow-up studies have shown that, although some acoustic measures normalise, jitter, shimmer and HNR can remain abnormal up to five years later [26,37,38].
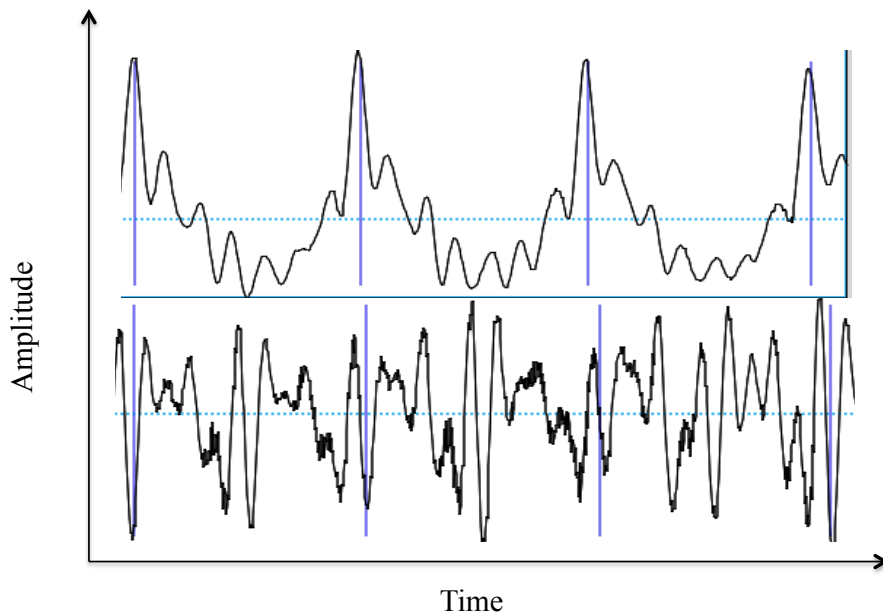

Figure 3. Sequence of three consecutive periods in a waveform produced by two different voices during phonation of a sustained vowel.

Perceptual analysis

Perceptual voice analysis involves the judgement of a voice sample by either an expert or a naïve listener. The listener judges voice characteristics and often relates them to degree of deviancy from what is perceived as normal [32]. The European Laryngological Society proposed that the term dysphonia could encompass "any kind of perceived voice pathology: the deviation may concern pitch or loudness as well as timbre or rhythmic or prosodic features" [33]. Hoarseness on the other hand should be limited to deviant voice quality and is a combination of breathiness and roughness. The former is the "audible impression of turbulent air leakage through an insufficient glottic closure", and the latter the "audible impression of irregular glottic pulses and abnormal fluctuations in F0" [33]. Rating tools can be employed of which several exist and some are summarised in Table 5.

Niedzielska et al. demonstrated that all of their 45 male patients with T1-T2 laryngeal cancer had moderate to severe dysphonia pre-treatment of which 50% demonstrated roughness and strain [38]. These findings are in line with those of Bibby et al. where patients according to the Perceptual Voice Profile (PVP) also had breathy, strained and rough voices pre-radiotherapy [35]. Although perceptual qualities mostly improve during the first 12 months, they do not return to normal. These abnormal voice qualities appear to persist in many patients up to 10 years post-treatment completion [28,39-41].

Table 5. Summary of some available instruments for perceptual voice analysis.

Abbreviated title	Explained abbreviation	Author	Perceptual qualities (examples)	Rating scale
BVP	Buffalo Voice Profile	Wilson, 1987 [42]	Pitch, loudness, nasality, resonance, hypo-/hypertensiveness rate, speech intelligibility	5-point Likert scale
CAPE-V	Consensus Auditory-Perceptual Evaluation of Voice	ASHA, 2001[43]	Roughness, breathiness, strain, pitch, loudness	VAS
GRBAS	Grade-Roughness-Breathiness-Asthenia-Strain	Hirano, 1981[44]	Overall grade, roughness, breathiness, asthenia, strain	4-point Likert scale
LSE	London Speech Evaluation Scale	Dwivedi, 2012 [45]	Intelligibility, articulation, nasality, rate, asthenia	4-point Likert scale
PVP	Perceptual Voice Profile	Oats and Russell, 1998 [46]	Pitch, loudness, breathy, strain, roughness, glottal fry, pitch/phonation breaks, falsetto, tremor, diplophonia	6-point Likert scale
SVEA	Stockholm Voice Evaluation Approach	Hammarberg and Gauffin, 1995 [47]	Aphonia, diplophonia, hoarseness, hyperfunction, vocal fry, breathy, register breaks	VAS
VPA	Vocal Profile Analysis Scheme	Laver, 1991 [48]	Breathiness, roughness, vocal fry, strain, asthenia, aphonia, falsetto, diplophonia, tremor	4-point Likert scale
ASHA = American Speech-Hearing Association, VAS=Visual Analogue Scale.				

GRBAS is the most commonly used perceptual rating instrument for laryngeal cancer pathology and three of its components (Grade, Roughness and Breathiness) are recommended for voice evaluation by the European Laryngological Society [33].

1.3 Patient-Reported Outcome

Patient-Reported Outcome (PRO) encompasses any report stemming from the patients themselves regarding his or her condition and should hence, be free from interpretation by relatives or clinicians. Observers often underestimate or make incorrect judgements of patients' experiences [49]. Several studies have shown that perceived experiences rated by clinicians or relatives as well as by objective measures clearly deviate from those reported by patients completing PRO instruments [49-51]. It can therefore be argued that the patient is the only reliable source of information for this purpose and also most free from bias.

PRO can be measured in open interviews, semi-structured interviews or using questionnaires, where the latter is the most frequently employed method. These instruments commonly consist of a set of statements or questions that form domains, with several domains being measured in each instrument. They measure the impact of an intervention, injury or illness on patients' health status, ranging from symptoms to more advanced concepts including impact on activities of daily living or HRQL.

PRO instruments can be further subdivided into generic, disease-specific, diagnosis-specific and symptom-specific (Figure 4) [52]. Generic instruments measure general health, overall disability and HRQL and are intended for general use by patients irrespective of disease but are often applicable to healthy populations as well. Their advantage is that scores across patients with different diseases can be compared with each other as well as with the general population. However, they may fail to identify symptoms specific for certain diagnoses and risk lacking sensitivity to measure change for specific patient cohorts, which has highlighted the need for both disease-specific (e.g. cancer) and diagnosis-specific instruments (e.g. HNC). Further symptom-specific questionnaires exist for examining specific issues or symptoms in greater depth [49].

Generic	• Short Form 36/Short Form 12 (SF-36/SF-12) • European QoL 5 dimensions (EQ-5D) • Sickness Impact Profile (SIP)
Disease-specific → Cancer	• European Organisation for Research and Treatment of Cancer C30 (EORTC QLQ-C30) • Functional Assessmen of Cancer Therapy – General (FACT-G)
Diagnosis-specific → HNC	• EORTC Head and Neck 35 (EORTC QLQ-H&N35) • FACT-Head and Neck (FACT-HN) • University of Washington Quality of Life (UW-QOL)
Symptom-specific	• Swedish Self-Evaluation of Commuication Experiences after Laryngeal cancer (S-SECEL) • Gothenburg Trismus Questionnaire (GTQ) • MD Anderson Dysphagia Inventory (MDADI)

Figure 4. Examples of some of the PRO instruments in use today. HNC=Head and Neck Cancer.

1.4 Interpreting PRO scores

The increasing use of PRO instruments during the past two decades have resulted in difficulties in terms of meaningful interpretation of score changes. Historically, clinical experience has aided the assessment of significant instrument score change over time, but is today hampered as the majority of PRO measures are used for research rather than clinical purposes. A statistically significant observed difference between interventions or within patients over time does not equate to that change being meaningful to or noticeable by the patient [53]. Hence, the concept of clinical significance or minimum clinically important difference (MCID) has been developed as a complement to statistical significance and was first defined by Jaeschke et al. [54] as the "smallest difference in a score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of

troublesome side effects and excessive cost, a change in the patient's management".

The MCID can be established using anchor-based or distribution-based approaches. The former approach employs an external indicator and analyses any association between the specific PRO instrument and the closely related concept measured by the independent external anchor. Any change observed in the PRO instrument is compared to changes in the external indicator, which can be either patient-based or clinically based [53,55]. Distribution-based approaches on the other hand, estimate the magnitude of meaningful change in PRO score using statistical parameters such as effect size or standard error of the mean [53,55]. However, no consensus exists as to which is the optimal method for approaching the issues of clinical significance.

1.5 Health-Related Quality of Life

PRO has gained importance, which is emphasised by the fact that the American Food and Drug Administration now urge pharmaceutical companies to incorporate PRO in clinical trials [56]. The principle underlying HRQL is not novel and was mentioned by Aristotle, whereas the concept of "Quality of life" (QOL) was created by economists in the 1950s when John Kenneth Gailbraith stated that "what counts is not the quantity of our goods but the quality of life" [57]. Nevertheless, QOL is a term difficult to define. In order to separate general QOL from that measured in clinical trials as a result of injury, illness or treatment, the term HRQL is used [49]. The World Health Organisation (WHO) defines health as "a state of complete physical, mental, and social well-being not merely the absence of disease" [58]. There is no current consensus on what aspects HRQL instruments should measure but generally HRQL constitutes four main domains, namely physical, functional, emotional and social well-being [59].

The use of HRQL instruments is increasing with over 1000 different questionnaires in use today [52]. With better survival rates and a plethora of treatments resulting in various acute and delayed side effects, HRQL is now one of the most important outcome measures in cancer studies alongside survival and recurrence rates [59].

HRQL can be used to differentiate between treatment options when survival outcome is similar. Furthermore, it emphasises the move toward patient-centred care, which highlights the individual's particular health care needs. To incorporate HRQL is a novel medical approach that empowers patients to become active participants in their own care [60]. Furthermore, HRQL pre-

treatment has also been shown to be predictive for survival and adds prognostic information that is additive over clinical and sociodemographic variables [61].

1.6 Patient-reported voice function after radiotherapy

The majority of HRQL instruments used in laryngeal cancer contain only a few questions regarding speech and voice and as such might not be sensitive enough to fully assess problems or change in these domains [62]. Hence, voice and communication-specific instruments have been developed to complement HRQL questionnaires in this population. To date, more than 10 instruments exist for use in adults but worldwide the Voice Handicap Index (VHI) is most often recommended and utilised although Self-Evaluation of Communication Experiences after Laryngectomy (SECEL) has been gaining increasing interest in Europe during the last five years [32,63-66]. The latter instrument has also been translated to Swedish and adapted for use following other laryngeal cancer treatments, such as radiotherapy and is then called Swedish Self-Evaluation of Communication Experiences after Laryngeal cancer (S-SECEL) [67].

Adams et al. reported a VHI score of 39 by their 15 patients with T1-T2 laryngeal cancer prior to treatment, which significantly improved to 16 points 24 months later [51]. A more recent study by Al-Mamgani et al. supported these figures, where 233 patients reported mean VHI scores of 37 pre-treatment, improving to 18 points 48 months later [68]. Similar trends have been demonstrated by Bibby et al., Johansson et al. and Finizia et al. albeit employing the Voice-Related Quality of Life-questionnaire and S-SECEL respectively which demonstrated pathological voice usage pre-treatment that despite improvement never normalised [35,67,69]. Additionally, Rinkel et al. found that 56-63% of their 79 patients reported clinically relevant speech and voice problems long-term as measured by both VHI and the Speech Handicap Index [70].

With a cut-off score for S-SECEL of ≥ 20 points indicating need for voice rehabilitation and ≥ 15 points for VHI [70-72], patients clearly experience voice problems both prior to and following oncologic treatment. Although a subjective communication improvement occurs after radiotherapy, subnormal function has still been reported up to five years post-treatment completion irrespective of measuring instrument used [71,73-75].

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1.7 Voice function after laryngectomy

Prior to organ-preserving treatment, laryngectomy was a debilitating but often life-saving procedure, which left the patient mute. However, voice rehabilitative measures have existed for the past 40 years allowing speech production in laryngectomees and include oesophageal speech, an artificial larynx and tracheoesophageal puncture prosthesis (TEP).

Oesophageal speech was the first technique used and relies on the ability to swallow air in the upper oesophagus. The release of air then produces sound resonance in the pharynx, mouth and nose, albeit only permits short sentences with techniques that can be difficult to master. An alternative is the artificial larynx, which is an electronic device placed against the side of the throat. Vibrations are transmitted from the device through the tissue and into the oral cavity, producing a voice with a mechanical quality [76]. However, nowadays the most widely used rehabilitative approach is the TEP, which relies on a surgically created passage of airflow from the trachea to the oesophagus. The vibratory segment of the pharynx is the source of sound production as in oesophageal speech. However, compared to oesophageal speech, success rates of speech production with TEP are much higher at 50-90%, yielding a speech that is stronger and more sustainable due to the larger air reservoir [23,76].

Despite speech function, laryngectomees tend to perceive more communication problems compared to laryngeal cancer patients undergoing organ-sparing procedures. This was emphasised by Finizia et al. where laryngectomees reported higher S-SECEL scores compared to those treated with radiotherapy. It must however be kept in mind that the majority of the laryngectomees in the study underwent laryngectomy as a salvage procedure and not as a primary treatment [67].

1.8 Voice impact on HRQL

Laryngeal cancer patients prioritise speech and communicative function more highly compared to other HNC patients [77]. Hoarseness is by far the problem experienced most frequently and troublesome by this patient cohort (72%), followed by mucus production (26%) [77,78]. This is further emphasised as one study showed that 63% of patients when given a choice would consider preserving the larynx even if this meant compromising survival [79].

As established, laryngeal cancer patients report abnormal voice quality and communicative function both before and after treatment. However, the consequences of this on HRQL were until recently unexplored. A limited number of studies report subjective voice problems in combination with HRQL (Table 6), yet do not correlate voice and communication with HRQL measures. The overall trends observed in Table 6 could suggest that as voice improvement is perceived, HRQL also improves albeit does not normalise. Nevertheless, the studies are hampered by limitations. Firstly, the majority are retrospective in design resulting in lacking baseline or pre-treatment values [40,70,75,80-82]. Secondly, scores presented occasionally deviate from conventional established scoring guidelines, hampering inter-study comparisons [75,81]. Furthermore, some lack raw data presentation [68,70] whilst others give no reference to normative values making interpretation difficult.

However, the recently published study by Rinkel et al. does suggest that speaking impairment as measured by VHI is associated with and negatively influences Global quality of life [70]. This is also supported by a previous study by Wang et al. in which speaking impairment was related to lower functional well-being [59]. Hence, there is increasing evidence suggesting that subnormal vocal function and usage negatively influences the HRQL of patients. In order to investigate this more in-depth, a communication-specific PRO can be used to complement the HRQL instruments.

Table 6. Summary of studies that combine voice PRO and HRQL in laryngeal cancer.

Author (year)	Patients (n)	Cohort	Design	Voice pre-treat (PRO)	Follow-up score* (m)	HRQL compared to norms
Rinkel (2014) [70]	88	T1-T4	R	N/A (VHI30)	25/120 (3-60)	Data not shown
Laoufi (2014) [81]	95	T1a	R	N/A (VHI30)	13-29/120 (48-96)	Conclusion cannot be drawn
Arias (2014) [80]	91	T1-T2	R	N/A (VHI10)	8.5/40 (63)	Inferior
Robertson (2013) [82]	147	T1-T4	R	N/A (VoiSS)	22/120 (36)	Superior
Olthoff (2009) [75]	10	Stage III-IV	R	N/A (VHI)	Conclusion cannot be drawn (43)	Conclusion cannot be drawn
Loughran (2005) [40]	36	T1a	R	N/A (VHI30)	22-25/120 (28-31)	Inferior
Al-Mamgani (2013) [68]	233	T1-T2	P	37/120 (VHI30)	18/120 (48)	Data not shown
Johansson (2008) [69]	100	Tis-T4	P	25/102 (S-SECEL)	15/102 (12)	Improved, but inferior
Finizia (2002) [83]	26	T1-T4	P	29/102 (S-SECEL)	15/102 (12)	Improved, but inferior

HRQL= Health-Related Quality of Life, N/A= non applicable, VHI=Voice Handicap Index, S-SECEL=Swedish Self-Evaluation of Communication Experiences after Laryngeal Cancer, R=Retrospective, P=Prospective, treat=treatment, PRO= patient-reported outcome, XX/XXX= score on PRO instrument/total achievable score.
* PRO score at the follow-up time-point in each study, (m) = mean number of months post-treatment when PRO score was measured.

1.9 HRQL and laryngeal cancer

During the past 15 years, HNC patients have been shown to report inferior HRQL compared to normal reference populations at diagnosis [84,85]. Studies have repeatedly demonstrated deteriorations in HRQL during and immediately after treatment completion followed by a recovery with the return of pre-treatment values at one year [85-87]. The same is true for the laryngeal cancer population [68,73,77,87]. The long-term follow-up however for laryngeal cancer and HNC, is relatively scarce with two three-year studies by Hammerlid et al. [74,84], a four-year follow-up by Al-Mamgani et al. [68] as well as two five-year studies by Nordgren et al. [73] and Abendstein et al. [88], all using the EORTC QLQ-C30 and QLQ-H&N35. In general, the majority of score dynamics can be seen during the first 12 months, with little change thereafter. Three to five years post-treatment completion, the QLQ-C30 scores are comparable to those of the general population whereas the QLQ-H&N35 scores still deviate significantly with respect to dry mouth and sticky saliva. This may hence be a reflection of the permanent treatment-specific side effects.

Although voice and communication can influence HRQL, so can other factors. More advanced tumour stage at diagnosis can for instance result in inferior HRQL [89]. The radiotherapy regimen may also impact HRQL as highlighted by Hammerlid et al. [89], where laryngeal cancer patients receiving hyperfractionated accelerated radiotherapy demonstrated improvements in more domains compared to at diagnosis, as opposed to those treated by conventional radiotherapy 12 months post-treatment. At 12 months, the hyperfractionated group reported scores superior to the conventionally fractioned group in the majority of the domains.

Besides voice problems, typical symptoms reported by laryngeal cancer patients following radiotherapy include dry mouth (xerostomia), sticky saliva and coughing [62]. These symptoms have been shown to affect functional domains, diet normalcy as well as pain perception in laryngeal and HNC populations and their impact on HRQL may increase with time [90-92].

1.10 Effects of voice rehabilitation

Following the established effects of radiotherapy on voice function, as measured by both objective measures and PRO, with its subsequent negative influence on HRQL, many studies recommend voice rehabilitation [28,93].

Despite this, evidence for the efficacy of voice rehabilitation in the laryngeal cancer population is scarce.

In 1969, Fex and Henriksson concluded that voice training given concomitantly with radiotherapy was effective for their 15 patients. However, the study had few patients, no control group and it is unclear what variable was used to measure improvement [94]. An attempt at an RCT was made by van Gogh et al., who on the other hand, did utilise a control group but still only included 23 patients, where the time from treatment (radiotherapy or laser surgery) to voice rehabilitation ranged from six to 120 months [95]. The study demonstrated an improvement in VHI and acoustic parameters jitter as well as in vocal fry. A recently published RCT by Tuomi et al. included 69 male patients and reported acoustic analyses as well as subjective voice ratings, which improved but lacked any mention of HRQL [96]. A final study by Zwirner et al. found vocal improvement in their 13 patients treated by laser surgery for T1-T3 carcinomas yet again did not measure HRQL. Fundamental frequency improved significantly but did not normalise [97].

In sum, findings from the few studies available all suggest positive effects on voice function following voice rehabilitation yet are hampered by several factors. The studies often have small cohorts, non-randomised designs, lacking control groups, pre-treatment values or structured reproducible voice rehabilitation protocols. However, most importantly no study to date investigates the voice rehabilitative effects of HRQL.

2 AIMS

2.1 Overall aim

The overall aim of the thesis was to describe the effects of radiotherapy following laryngeal cancer on HRQL and voice function as well as to assess the efficiency of voice rehabilitation.

2.2 Specific aims

Study I: The study aimed to investigate the short-term effects on voice quality and HRQL following radiotherapy in laryngeal cancer, comparing glottic and supraglottic tumours.

Study II: The study aimed to assess longitudinal results during the first 12 months following radiotherapy completion with regard to vocal deficits, voice changes over time and impact on HRQL outcomes for laryngeal cancer patients treated with radiotherapy.

Study III: The primary aim of this randomised controlled trial was to assess the effect of voice rehabilitation on perceived communication function and HRQL six months post-radiotherapy.

Study IV: The longitudinal study was aimed at investigating effects of voice rehabilitation on HRQL and voice function in patients treated for laryngeal cancer six months post voice rehabilitation completion (12 months post-radiotherapy). A secondary aim was to identify factors that predict significant communication improvement.

3 PATIENTS AND METHODS

3.1 Study design

All studies employed quantitative methodology and data was retrieved from a prospective longitudinal randomised controlled trial (Table 7).

All patients diagnosed with a laryngeal cancer in VGR were referred to a weekly tumour conference at the Otorhinolaryngology department at Sahlgrenska University Hospital in Gothenburg. This conference was of multidisciplinary nature and included head and neck clinicians, oncologists, radiologists and pathologists all aiming to create patient-centred treatment approaches. Patient participation was sought at this conference during the period 2000-2011 from all whom were to receive curatively intended radiotherapy.

Table 7. Studies included in the thesis.

	Study I	**Study II**	**Study III**	**Study IV**
Design	Descriptive, prospective		Prospective, randomised	
Subjects	Pat = 67 HC = 23	Pat = 40	Pat = 74	Pat = 65
Male/Female	Pat = 67/0 HC = 23/0	36/4	66/8	57/8
Time frame	Pre-RT, 1 m post-RT	Pre-RT, 1, 6, and 12 m post-RT	1 and 6 m post-RT	1, 6 and 12 m post-RT
Outcome measures				
EORTC QLQ				
C30	X*	X*	X	X*
H&N35	X*	X*	X	X*
S-SECEL	X	X*	X	X*
Perceptual		X		X**
Acoustics	X	X		X
RT=radiotherapy, m=month, Pat=patients, HC=vocally healthy controls. * selected domains and items. ** Roughness from the GRBAS-scale.				

Following participation acceptance, computerised randomisation was performed into two groups: an intervention group undergoing voice rehabilitation and a control group receiving only vocal hygiene advice, according to current standard practice. Patients were followed prior to radiotherapy, one, six and 12 months post-radiotherapy completion as outlined in Figure 5. At each time-point, data was collected from PRO instruments and voice recordings. Voice rehabilitation for the intervention group occurred between the one and six months post-radiotherapy time-point.
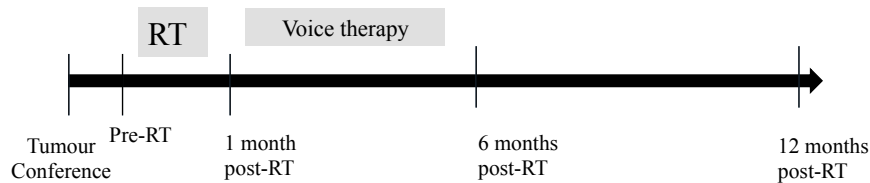
Figure 5. Overall outline of the study time-points. RT=radiotherapy.

3.2 Study participants

A total of 194 patients intended to receive curative radiotherapy were identified at the weekly tumour conference, of which 31 patients were excluded due to a tracheostoma, insufficient cognitive abilities or inadequate Swedish language competency enabling the patient to independently answer the questionnaires and partake in the rehabilitative measures. Of the remaining 163, 74 patients were non-eligible due to declined participation (n=72) or were missed prior to radiotherapy (n=2), yielding 89 patients available for randomisation into a voice rehabilitation group (n=47) and a control group (n=42). During the time frame for voice rehabilitation, 12 patients were lost to follow-up, resulting in 37 and 40 patients available for analysis in the voice rehabilitation and control group respectively. A detailed outline of patient inclusion is provided in Figure 6.
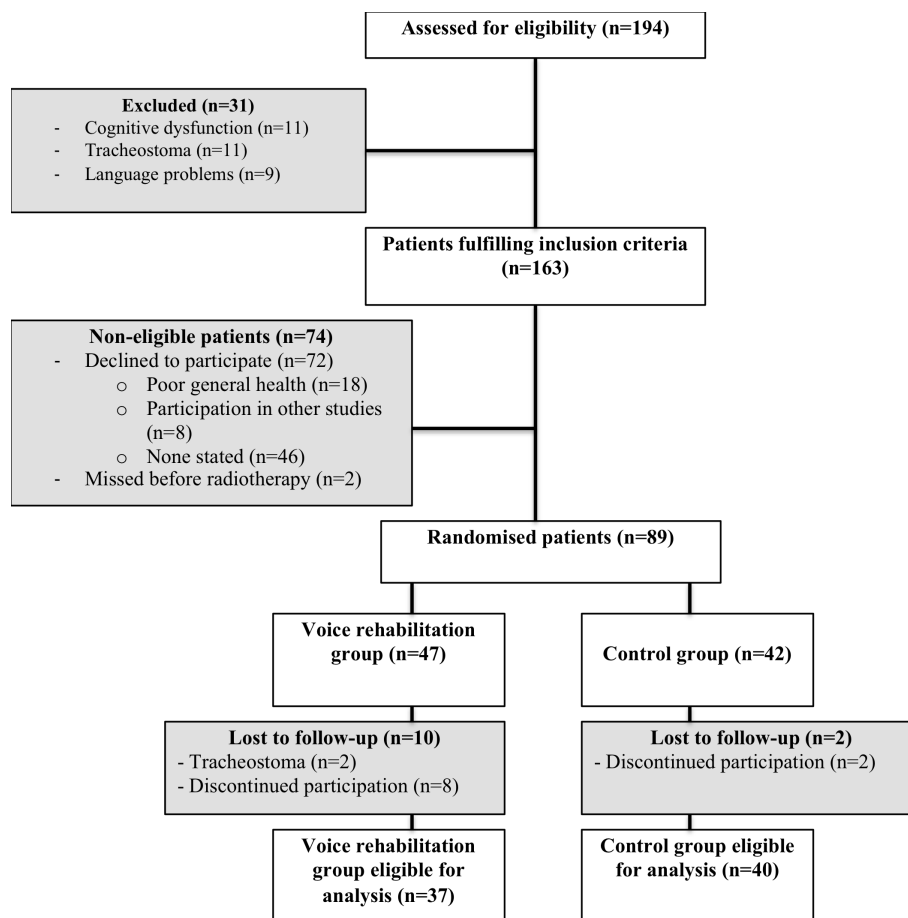
Figure 6. Outline of included and excluded patients.

In Study I, eight women and the only two subglottic tumours in the cohort were excluded from analysis due to the scarce number naturally occurring in these populations. In Study II, only the control group was analysed. In study III, three patients were excluded due to lacking all data both pre- and post-voice rehabilitation. In study IV, 12 patients were excluded due to missed appointments (n=4), discontinued participation (n=4) and being laryngectomised (n=4) (Figure 7).
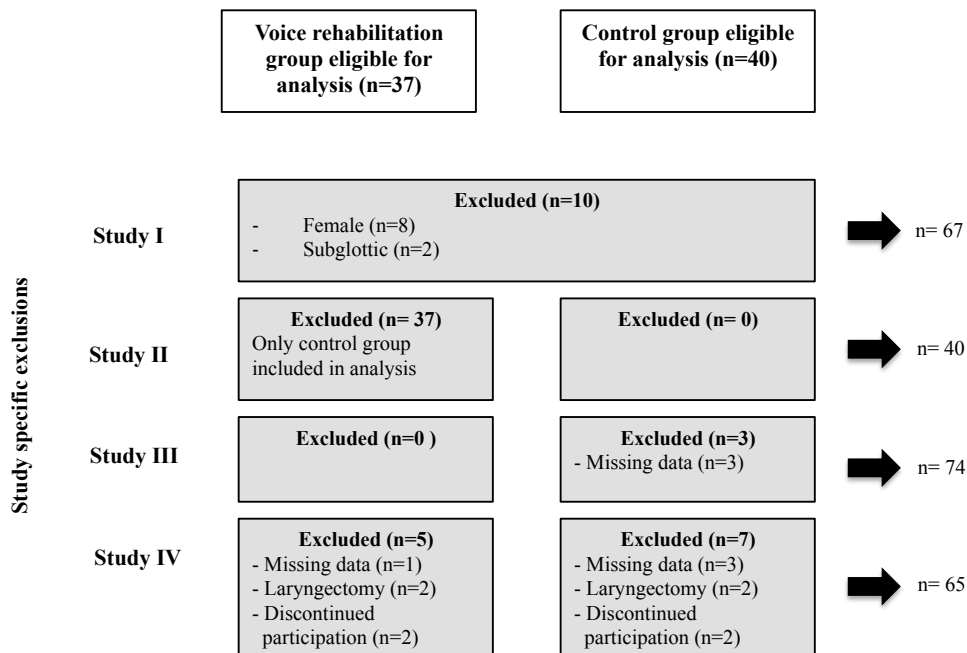

Figure 7. Summary of reasons for study-specific patient exclusions.

The 74 non-eligible patients and the 12 patients lost to follow-up during voice rehabilitation did not differ from the included patients in terms of gender, tumour site, comorbidity or tumour stage but significantly more were older and non-smokers (Table 8).

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Table 8. Clinical characteristics of the included versus excluded patients.

	Included (n=77)	Excluded* (n=86)	Excluded vs included patients p-value
Gender			
Male	69 (90%)	68 (79%)	
Female	8 (10%)	18 (21%)	0.09
Age			
Mean (SD)	64 (11)	71 (10)	
Median (range)	65 (34-86)	72 (52-94)	< 0.001
Tumour size/stage**			
0	2 (3%)	2 (2%)	
T1/I	45 (58%)	45 (52%)	
T2/II	23 (30%)	23 (27%)	
T3/III	6 (8%)	11 (13%)	
T4/IV	1 (1%)	5 (6%)	0.12
Tumour site			
Glottic	60 (78%)	59 (68%)	
Supraglottic	15 (19%)	16 (19%)	
Subglottic	2 (3%)	6 (7%)	
Transglottic	0 (0%)	5 (6%)	0.09
Comorbidities			
0 – None	31 (40%)	25 (29%)	
1 – Mild	30 (39%)	39 (45%)	
2 – Moderate	16 (21%)	20 (23%)	
3 - Severe	0 (0%)	2 (3%)	0.13
Smoking status			
Non-smoker	9 (12%)	26 (30%)	
Smoker	37 (48%)	48 (56%)	
Quit smoking >12 m	31 (40%)	12 (14%)	< 0.001
* Excluded patients encompass those non-eligible and those who dropped out during the voice rehabilitation period. ** Tumour stage and tumour size are the same due to all patients have a nodal stage (N) of 0.		

A vocally healthy control group comprising of 23 male volunteers were recruited from relatives of patients or visitors at Sahlgrenska University Hospital. The vocally healthy control subjects did not perceive any voice problems and showed normal vocal fold status when examined by an otolaryngology specialist. Voice and PRO data were recorded in the same

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manner as for the study group. However, only 20 out of the 23 vocally healthy controls completed the PRO instruments.

3.3 Oncologic treatment

During the study period, traditional radiotherapy treatment was administered. Oncologic treatment was given as conventional or hyperfractionated-accelerated radiotherapy according to regional guidelines, which varied slightly during the study period but not between the intervention groups. The former was administered as 34/26 fractions of 2-2.4 Gray (Gy) fractions daily totalling 62.4-68 Gy. The latter regimen encompassed 1.7 Gy fractions given twice daily, resulting in 38 fractions and a total of 64.6 Gy. Lymph nodes, levels II-IV, were irradiated in all patients with subglottic and supraglottic tumours as well as those with T2 or larger glottic tumours totalling 40.8-46 Gy. T3 and T4-tumours also received induction chemotherapy unless contraindicated.

3.4 Randomisation

Computerised randomisation was performed by optimal allocation using Pocock's sequential randomisation method [98] applied to age, smoking habits, tumour site, tumour size and patient's self-evaluation of communication as assessed by S-SECEL pre-radiotherapy. Patients were randomised into two groups: an intervention group receiving voice rehabilitation or a control group.

3.5 Voice rehabilitation intervention

Voice rehabilitation was conducted in line with a structured protocol at the hospital in closest proximity to the patient's residence. It commenced approximately one month following radiotherapy completion and was given by trained speech-language pathologists in the research group. The protocol was developed according to Swedish standard voice training prior to the study starting. Voice rehabilitation consisted of ten 30-minute sessions over ten weeks and included relaxation, respiration, posture and phonation exercises as outlined in Table 9 [96]. The patients were asked to conduct voice training daily at home in between sessions. The control group did not receive any voice rehabilitation but were followed with recordings and PRO instruments in parallel with the study group. The control group received vocal hygiene advice, according to standard practice.

Table 9. Voice rehabilitation protocol.

Session	Time	Exercise
1	Week 1	Voice physiology education including relaxation, posture, diaphragmatic breathing, vocal techniques and co-ordination of breathing and phonation.
2	Week 1	Review patient understanding and mastering of session 1 techniques. Patient specific feedback and continued training to consolidate techniques.
3	Week 2	Review foundation exercises. Expand on vocal techniques and phonation exercises such as repeated syllables, short words and commence generalisation with short phrases.
4	Week 2	Review, provide feedback and continue training.
5	Week 3	Review, provide feedback and continue training.
6	Week 4	Review and feedback.
7	Week 5	Review and feedback. Generalisation exercises and maintaining optimal phonatory control in reading of dialogues and also in conversation.
8	Week 6	Repetition of most patient-relevant techniques. Focus on volume and voice projection.
9	Week 8	Repetition of most patient-relevant techniques.
10	Week 10	Repetition of most patient-relevant techniques.

3.6 Outcome measures

EORTC QLQ-C30

In 1986, the European Organisation for Research and Treatment of Cancer initiated the development of a research programme designed to develop a self-administered modular approach aimed at measuring HRQL in cancer patients participating in clinical trials [99]. This resulted in the Quality of Life Questionnaire Core 30 (QLQ-C30), which consists of 30 items incorporated into five functional domains (Physical, Role, Cognitive, Emotional and Social), one Global QOL domain, three symptom domains and six single items that describe the patients' symptoms and functional levels during the last week [100,101].

Response options consist of a four-point Likert scale ranging from "none at all" (1) to "very much" (4), except the Global QOL domain, which is comprised of a seven-point Likert scale. All domains and single items scores

are linearly transformed to a 0-100 scale. Higher scores for the Functional domains and Global QOL represent better function, whereas higher scores for symptom domains and single items indicate a higher symptom burden [102]. A change of ≥ 10 points could be considered as a clinically significant difference [103,104] (Appendix 1).

It is one of the most widely used quality of life instruments in cancer research today [102,105] and has been shown to be reliable, valid and responsive over time in large multinational cancer populations [100,101].

EORTC QLQ-H&N35

A disease-specific HNC module has been developed to complement the Core 30 questionnaire, addressing specific symptoms caused by the tumour or the oncologic treatment as well as additional QOL domains, which can be affected by the aforementioned [106]. This 35-item questionnaire, EORTC QLQ-H&N35, consists of seven symptom scales (Pain, Swallowing, Senses, Speech, Social eating, Social contact and Sexuality) and 11 single items assessing problems with teeth, mouth opening, sticky saliva, coughing, feeling ill, use of analgesics, nutritional supplements, feeding tube, weight loss and weight gain. The module has a recall period of one week.

Response options consist of a four-point Likert scale ranging from "none at all" (1) to "very much" (4), except five of the single items, which consist of the two response options "no" (1) and "yes" (2). All symptom and single items scores are linearly transformed to a 0-100 scale. Higher scores indicate a higher symptom burden [102] (Appendix 2). Although no guidelines exists for interpretation of clinical significance, a change of ≥ 10 points is often used for this purpose [73].

This complementary module has been used in over 136 studies, demonstrating high reliability, validity and responsiveness over time except for the domains Speech and Senses, which are hampered by lower internal consistency [101,107]. An updated revision of the instrument, QLQ-H&N43 has recently been proposed partially to address this problem with psychometric evaluation underway [108].

SECEL and S-SECEL

The original Self-Evaluation of Communication Experiences after Laryngectomy (SECEL) is a self-administered questionnaire developed to evaluate patients' communicative dysfunction following laryngectomy and demonstrated satisfactory psychometric properties [109]. In 1999, SECEL was translated to the Swedish Self-Evaluation of Communication Experiences

after Laryngeal cancer (S-SECEL) and adapted for use in patients receiving varying oncologic treatments. This resulted in two items being reworded as they specifically addressed post-laryngectomy experiences [67].

The instrument encompasses 35 items of which 34 items are divided into three domains; General, Environmental and Attitudinal. The General domain assesses attitudes regarding being relaxed and calm as well as acknowledgement of sickness and treatment. The Environmental domain focuses on efficiency of voice usage in different environments such as in a large room or with groups of people, whereas the Attitudinal domain addresses attitudes about speech. Items are rated on a four-point Likert scale ranging from "never" (0) to "always" (3) and have a recall period of 30 days. Scoring of domains, including a Total score domain, is accomplished by simple addition yielding summary domain scores ranging from 0-15, 0-42, 0-45 and 0-102 for the General, Environmental, Attitudinal and Total score domains respectively. A higher score indicates a greater perceived communication dysfunction. The last question "Do you talk the same amount now as before your laryngeal cancer" has three response options (Yes/Less/More) and is not included in the scoring system (Appendix 3). Guidelines for score changes that may be considered clinically significant along with cut-off scores representing the need for voice rehabilitation are shown in Table 10 [72].

Table 10. S-SECEL scores used for interpretation of clinical significant difference and need for voice rehabilitation.

S-SECEL domain	Δ score improvement	Cut-off score need for voice therapy
General	-2	≥ 4
Environmental	-7	≥ 16
Attitudinal	-4	≥ 5
Total Score	-13	≥ 20

Psychometric properties of the S-SECEL have been investigated and found satisfactory with the exception of the General domain, which consistently demonstrates lower internal consistency and validity [67,69].

Adult Comorbidity Evaluation-27 (ACE-27)

The Adult Comorbidity Evaluation-27 is a 27-item instrument developed by Piccirillo and colleagues at the Barnes Jewish Hospital in Washington [110]. It measures patient comorbidity and was developed following modification of the Kaplan-Feinstein Comorbidity Index [111]. ACE-27 assesses comorbidity on an organ decompensation basis, where each category has four grades; none (0), mild (1), moderate (2) or severe (3). The highest-ranking single organ score defines the overall score.

3.7 Voice recordings

Voice recordings included reading of a standard passage of text and the maximum sustained vowel /a/ repeated three times. A headset microphone (Sennheiser MKE 2-p) was set at a distance of 12 cm from the corner of the mouth. Recordings were made at a sampling frequency of 44,1 kHz with a Panasonic Professional Digital Audio Tape Recorder SV-3800. Prior to analysis, all recordings were transferred from a digital audio tape to a computer hard drive as an audio file (.wav) using the program Swell Soundfile Editor, version 4.5 (Saven Hightech).

Acoustic analysis and temporal measure

Acoustic analysis was performed using Voxalys, a plug-in programme to Praat and yielded five parameters.

F0	Analysed from reading of the standard text passage
Jitter Shimmer HNR	Analysed from a two-second excerpt in the middle of the second sustained /a/
Maximum phonation time	Measured from the sustained vowel /a/ where the highest value from three repetitions was used

Perceptual voice analysis

Excerpts from the voice recordings were cut using Swell Soundfile Editor (4.5). These excerpts, i.e., rating samples, included the first two sentences of the standard passage and the second recorded prolonged vowel /a/ and were saved as audio files (.wav). Samples were compiled from each patient across

study-specific time-points. Twenty percent of samples were randomly reduplicated for intra-rater reliability calculations. All samples were then randomly compiled with anchor samples interspersed at every 20 voice samples, into the final rating file for perceptual analyses.

Perceptual ratings were conducted by two speech-language pathologists, with a third clinician used for consensus rating. All raters attended a half-day's consensus training based on the format of Iwarsson and Petersson [112]. The raters were blinded to patient status and voice sample information.

The rating protocol used the GRBAS scale [44] which consists of five voice qualities: Grade, Roughness, Breathiness, Asthenia, and Strain (Appendix 4). Each voice quality is rated on a four-point scale, where 0 = normal, 1 = mildly impaired, 2 = moderately impaired and 3 = severely impaired. The GRBAS scale was chosen since it is recommended for voice evaluation by the European Laryngological Society [33]. It has been shown to be reliable, valid[32] and is one of the instruments most frequently reported in literature, thereby facilitating inter-study comparisons. The parameter of vocal fry (also rated on a four-point scale mirroring the GRBAS) was added to the rating protocol as it has also been reported to exist in irradiated voices [39,95].

3.8 Statistical analysis

All analyses were performed using SPSS version 20.0 for Mac and SAS 9.3. Sample size was determined by an 80 % power calculation with dysphonia as defined by Stoicheff et al. [113] as the main variable.

Descriptive statistics were provided as means with standard deviation (SD) and 95% confidence intervals (CI) for the mean for continuous variables whilst number and percent were used for categorical variables. Non-parametric two-tailed tests were used and the significance level was set at 5%. For comparisons between two groups Fisher's exact test was used for dichotomous variables, the Chi square test for non-ordered categorical data, the Mantel-Haenszel Chi square for ordered categorical variables and the Mann Whitney U-test for continuous variables. For paired analyses of changes over time within groups the Sign test was used for ordered categorical variables and the Wilcoxon Signed test for continuous variables was used in studies I, III and IV. In study II, repeated measures tests for overall significant differences within groups, over time, were conducted using Friedman's test and post-hoc paired analyses performed where significance was found.

Clinical significance, as a complement to statistical significance, for the EORTC QLQ-C30 and QLQ-H&N35 was used in studies I-IV, represented by a mean score change of ≥10 points.

Magnitude of group differences were further analysed using effect sizes in studies II and III. Effect size of within-group change was calculated as mean change between assessment time-point divided by the standard deviation of change and was interpreted according to Cohen's standard criteria where size is classified as trivial (0 to <0.2), small (0.2 to <0.5), moderate (0.5 to <0.8) or large (≥ 0.8) [114]. This method complements standard significance testing and yields standardised effect levels regardless of sample size and scaling properties.

Inter- and intra-rater reliability was calculated using percent exact agreement, percent close agreement and Weighted Kappa for study II and IV.

In study III, Spearman correlation coefficient was used for all correlation analyses.

In study IV, patients in the voice rehabilitation group and control group were divided into groups according to the cut-off level of S-SECEL Total score domain representing the need for vocal rehabilitation (≥20 p). Descriptive calculations within the groups were carried out. Univariable logistic regression analysis was performed to find factors influencing the odds of a clinically significant communication improvement. Results were presented as odds ratio with 95% confidence intervals in a forest plot.

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

3.9 Ethical considerations

All studies were conducted in accordance with the Declaration of Helsinki and were approved by the Regional Ethical Review Board in Gothenburg, Sweden. Written informed consent for study participation was obtained from all participants.

4 RESULTS

4.1 Study I

The supraglottic cohort reported inferior HRQL compared to the glottic cohort pre-radiotherapy. Although the HRQL for both groups deteriorated post-radiotherapy, supraglottic tumours reported the largest deteriorations. Both groups reported communication dysfunction, which remained unchanged post-radiotherapy yet was inferior compared to the vocally healthy control group. In terms of voice quality, acoustic measures revealed that glottic tumours deviated significantly form vocally healthy controls pre-radiotherapy with some parameters improving post-radiotherapy. Supraglottic tumours however, demonstrated no difference compared to the vocally healthy control group at either time-point (Figure 8).
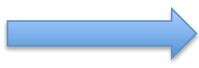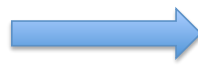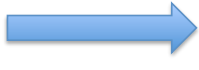
	HRQL Pre-RT Post-RT	S-SECEL communication dysfunction Pre-RT Post-RT	Acoustic analysis Pre-RT Post-RT
Supraglottic tumours			
Glottic tumours			

Figure 8. Summary of findings in supraglottic and glottic patients in Study I. RT=radiotherapy.

4.2 Study II

Study II investigated the effects of radiotherapy on the control group up to 12 months post-radiotherapy, with findings summarised in Figure 9.

Twelve months post-radiotherapy laryngeal cancer patients demonstrated no significant difference when compared to pre-treatment in terms of HRQL, communication dysfunction or voice quality. HRQL declined immediately post-radiotherapy and recovered to pre-treatment values at six months post-radiotherapy. All patients presented with perceptually perceived dysphonia, with only the variable "roughness" changing significantly during the study period. Roughness improved post-radiotherapy but deteriorated again between six and 12 months post-radiotherapy.

	HRQL	S-SECEL communication dysfunction	Acoustic analysis	Perceptual analysis
	Pre-RT 1m 6m 12m	Pre-RT 1m 6m 12m	Pre-RT 1m 6m 12m	Pre-RT 1m 6m 12m
Control Group				

Figure 9. Summary of findings in the control group in Study II. RT=radiotherapy, m=months post-radiotherapy.

4.3 Studies III and IV

Studies III and IV investigated the effects of voice rehabilitation in the control group and intervention group up to 12 months post-radiotherapy completion, with findings summarised in Figure 10.

	HRQL			S-SECEL communication dysfunction			Acoustic analysis			Perceptual analysis		
	1m	6m	12m	1m	6m	12m	1m	6m	12m	1m	6m	12m
Intervention Group												
Control Group												

Figure 10. Summary of findings in the intervention and control group in Studies III and IV. Changes in one group are shown in comparison to changes in the other group. m=months post-radiotherapy.

The intervention group receiving voice rehabilitation demonstrated more improvements in HRQL and communication function domains compared to the control group, which remained static during the study period. The improvements were maintained up to six months post-voice rehabilitation (12 months post-radiotherapy) as seen in Figures 11 and 12.

Voice rehabilitation also appeared to prevent the perceptual deterioration of roughness observed in the control group between six and 12 months. Lastly, the odds ratio of having a clinically significant communication improvement at 12 months post-radiotherapy, i.e. a decrease of ≥ 13 points in S-SECEL Total score domain was positively influenced by undergoing voice rehabilitation, experiencing voice dysfunction following radiotherapy and negatively influenced by smoking continuation.
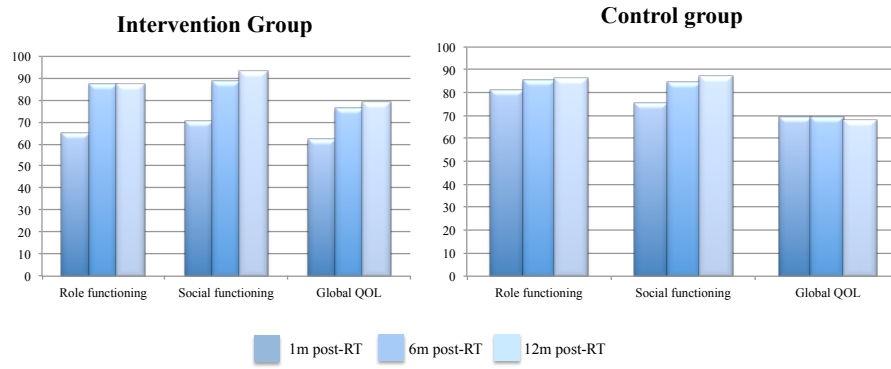
Figure 11. Selected EORTC QLQ-C30 domains one, six and 12 months post-radiotherapy for the intervention and control group. All domains range from 0-100. Higher scores indicate better function. RT=radiotherapy, QOL=quality of life.
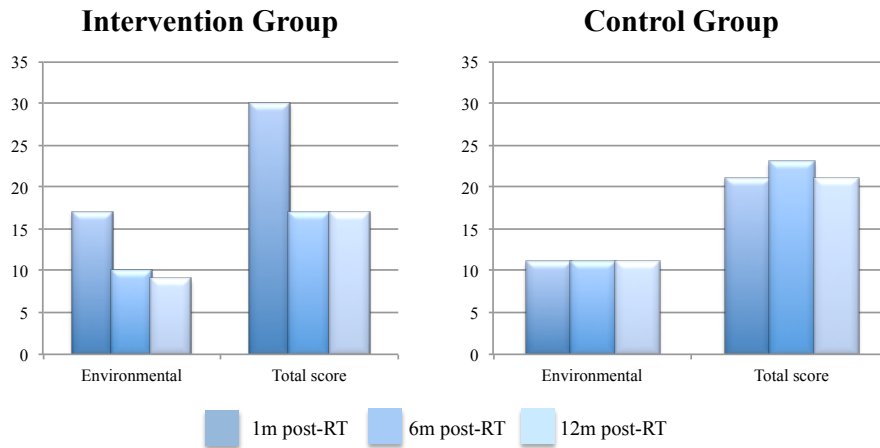

Figure 12. Selected S-SECEL domains one, six and 12 months post-radiotherapy for the intervention and control group. The Environmental domain ranges from 0-42 and the Total score domain ranges from 0-102. Higher scores indicate worse communication function. RT=radiotherapy.

5 DISCUSSION

Generally, very few studies exist that report voice and HRQL in a randomised manner and this is the first randomised controlled study with a main focus on effects of voice rehabilitation on HRQL and communication function.

5.1 HRQL, communication and voice related to tumour site

Supraglottic tumours reported trends of inferior HRQL pre-radiotherapy, albeit few differences compared to glottic tumours were statistically significant. Similar but significant findings were demonstrated by Nordgren et al. in their cohort of 86 laryngeal cancer patients of which 24 were supraglottic tumours. At diagnosis, glottic carcinomas scored better in nearly all functional domains and single items, which were maintained up to 12 months post-radiotherapy [73]. In Study I, the supraglottic tumours also reported greater deteriorations immediately post-radiotherapy compared to glottic tumours, particularly in EORTC QLQ-C30 domains Role and Social functioning. This may be explained by a more thorough examination of the symptom scales, where the supraglottic cohort reported more nausea and vomiting, increased appetite loss and dysphagia compared to the glottic cohort. Hence, swallowing problems appear to be a contributing factor to the deterioration in HRQL. This is supported by Roh et al., where their supraglottic patients treated with partial laser supraglottic resection all demonstrated increased dysphagia post-surgery as measured by both PRO and videoflouroscopic swallowing studies. These problems could perhaps be caused by the removal or alteration of protective supraglottic barriers including the epiglottis, aryepiglottic folds and false vocal folds [115]. Additionally, the supraglottic tumours in this study were larger and would therefore more often have received additional lymph node irradiation, a larger radiation volume as well as required a feeding tube during radiotherapy to a greater extent than did the glottic tumours. Apart from the expected negative effects on HRQL of a feeding tube, Langius et al. demonstrated that malnutrition during radiotherapy was most accurately predicted by neck node irradiation and thusly, specifically associated with both supraglottic tumours and increasing tumour size [116].

In terms of voice quality however, glottic tumours were found to have consistently inferior acoustic and temporal measures compared to vocally

healthy controls pre-radiotherapy. The majority of parameters improved and normalised following treatment. The supraglottic cohort, on the other hand, presented with values comparable to vocally healthy controls both pre- and post-radiotherapy. This is not a controversial finding as a lesion on the vocal folds probably would impact voice quality to a greater extent than lesions above the vocal folds. The only other study investigating acoustic parameters in a supraglottic cohort was published by Roh et al., who also failed to demonstrate any statistically significant changes from pre- to post-treatment [115]. Patient-perceived communication dysfunction revealed no differences dependent on glottic or supraglottic tumour site, yet both were significantly inferior to scores reported by the vocally healthy control group.

In sum, HRQL and voice quality appear to differ dependent on tumour site post-radiotherapy, whereas subjective communication dysfunction does not.

5.2 HRQL and voice over time following radiotherapy

The dynamics in HRQL scores from pre- to 12 months post-radiotherapy found in Study II suggest that laryngeal cancer patients deteriorate in most domains immediately post-radiotherapy but then recover to pre-treatment levels at six to 12 months, with the exception of treatment-specific side effects such as sticky saliva and xerostomia. This is in line with other published studies [69,87]. However, although recovery to pre-radiotherapy values was observed, these scores are still abnormal when compared to reference data published for Swedish and Norwegian normative populations [117,118].

Voice quality measured by perceptual evaluation revealed no significant change at 12 months post-radiotherapy compared to pre-radiotherapy in any of the GRBAS or vocal fry parameters. Nevertheless, findings were far from normal with 95%, 61% and 64% of patients presenting with roughness, breathiness and strain respectively pre-treatment. These deviant voice characteristics in laryngeal cancer populations have also been observed by others [50].

Interestingly, three vocal parameters did demonstrate significant changes during the 12 months following radiotherapy and included perceptually perceived roughness and vocal fry as well as the acoustic measure F0. Roughness improved from pre-treatment to immediately post-radiotherapy and then deteriorated between six and 12 months. The initial improvement

was also noted subjectively and is most likely explained by removal of tumour burden with similar findings noted in other studies [89]. Roughness is the result of unsynchronised vocal fold vibration and the noted late deterioration could be attributed to the delayed radiotherapy effects, including fibrosis, oedema and inflammation, which impair vocal fold mobility [25,27,119]. Additionally, xerostomia post-radiotherapy has also been shown to negatively influence voice quality, furthering the perception of roughness [28,30].

Although some dynamic can be observed in voice quality, communication dysfunction and HRQL over time, scores at 12 months post-radiotherapy are similar to pre-treatment values – values that cannot be considered normal.

5.3 Effects of voice rehabilitation on HRQL, communication and voice

Voice rehabilitation appears beneficial as positive effects could be discerned in selected HRQL domains, communication dysfunction as well as perceived roughness. Firstly, the intervention group reported clinically significant improvements in all S-SECEL domains except for the General domain in Study III. The improvements were statistically significantly greater when compared to the control group. Additionally, the number of patients in need of voice rehabilitation, as determined by the threshold value of the S-SECEL Total score domain, decreased from 80% prior to voice rehabilitation to 30% six months post-voice rehabilitation (12 months post-radiotherapy) in the intervention group. These results are strengthened by Tuomi et al. [96] and van Gogh et al. [95] where similar significant patient-reported communication improvements were found in their voice rehabilitation groups but lacking in the control groups.

The patient-reported communicative improvements were also mirrored in the HRQL domains Speech and Social contact, which was expected and revealed moderate correlations with S-SECEL domains. However, only weak correlations were observed between S-SECEL and EORTC QLQ-C30 domains Role and Social functioning. This could be explained by acute effects of radiotherapy such as fatigue, inflammation, xerostomia and dysphagia having a larger impact in these areas compared to communication function at this point in time. Alternatively the EORTC instruments might not be sensitive enough to measure such specific communication symptoms in depth. Most importantly, however, was the finding that the intervention group reported clinically and statistically significant improvements in Global

QOL on EORTC QLQ-C30. This domain also showed the strongest correlations with S-SECEL domains, thereby indicating that voice rehabilitation can improve patients' quality of life. A similar correlation between VHI and EORTC QLQ-C30 Global QOL was recently demonstrated by Rinkel et al. [70]. Nevertheless, that study investigated effects of radiotherapy on voice and HRQL whilst no corresponding study for voice rehabilitation existed until now.

Besides positive effects on HRQL and communicative function, the observed perceptual deterioration of roughness did not occur in the intervention group and was possibly prevented by voice rehabilitation. As the larynx is a muscular organ and voice rehabilitation provides active stimulus following radiotherapeutic damage, it could be hypothesised that voice rehabilitation to some extent hinders or alleviates the effects of fibrotic progression.

5.4 Acoustic and perceptual measures versus patient-reported tools to measure communication

As a result of the complex nature of voice, multimodal assessment approaches are often advocated [33]. These include acoustic and perceptual measures as well as patient-reported experiences. However, objective and subjective measures do not always agree [49], tendencies of which have also been observed in the thesis studies. Firstly, in Study I acoustic values for glottic tumours were found to improve following radiotherapy but such an improvement was not reflected in S-SECEL. The perceptual deterioration of roughness noted between six and 12 months post-radiotherapy in Study II was not seen in either S-SECEL or the acoustic measurements. Additionally, no intra- or inter-group change was observed in acoustic measures in Study IV despite voice rehabilitation taking place, which may question the sensitivity of acoustic analysis in a laryngeal cancer population.

Literature in this area is conflicting where some studies demonstrate associations between variables, whilst others do not. Dejonckere et al., for instance, found that jitter correlated with roughness, whilst shimmer correlated with grade and breathiness [120]. Bhuta et al., on the other hand, found no such relationship and instead demonstrated significant correlations between a different three out of 19 acoustic parameters with the GRBAS scale, namely voice turbulence index, noise harmonics ratio and soft phonation index [121]. These varying findings have resulted in questioned reliability and sensitivity of acoustic measures [32,122], which may be explained

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by a number of factors. Acoustic analysis can for instance be influenced by recording equipment, mouth-to-microphone distance, the software used for analysis as well as choice of vowel, thereby hampering inter-study comparisons [123,124]. Although perceptual voice analysis is considered the gold standard when assessing voice function [31,121], it too can be biased by the listener's profession [125], type of grading instrument used and the severity of dysphonia [31].

Nevertheless, the discrepancies between measurement methods are not truly controversial as each tool measures a slightly different aspect of voice. Acoustic analysis reflects the sound of voice, perceptual analysis the voice quality as perceived by others and PRO mirrors the patients' viewpoint stemming from their needs and surroundings. Ultimately, we advocate the use of PRO as successful treatment in this situation is determined by patient satisfaction. However, continued perceptual evaluation by speech-language pathologists is vital because it can identify patients in need of voice rehabilitation and tailor it according to individual needs.

5.5 Clinical implications of voice rehabilitation

Why should it be offered?

As seen in Study II, despite the improvements that occur post-radiotherapy, HRQL, communication and voice quality still remain abnormal 12 months after treatment completion. Impaired voice quality and communication dysfunction can in itself result in negative effects on HRQL [30,59,126]. Consequently, others have advocated voice rehabilitation but with lacking evidence of its effectiveness [28,93]. However, Study III highlighted that voice rehabilitation is effective and improves both selected HRQL domains as well as communication dysfunction. Based on these positive findings, we suggest that voice rehabilitation post-radiotherapy could be offered to patients who experience voice problems particularly since it can be administered in a simple setting at all Ear, Nose and Throat clinics. The most prominent deviant voice characteristics found in the study population in Study II both prior to and following radiotherapy were roughness, breathiness and strain. These parameters have also been highlighted in laryngeal cancer populations in other studies [35,38] and therefore, it can be argued that the rehabilitation itself should aim to target these voice qualities.

Timing of rehabilitation

Optimal timing is a complicated matter of discussion due to the limited published data available. Irradiation fibrosis progression has been shown to cause more collagen deposition and severe morphological changes after 12-24 months [25,28]. Hence, earlier implementation of voice rehabilitation may help to hinder effects of fibrosis progression and decrease risk of developing mal-adaptive compensatory vocal behaviours [35]. However, effectiveness of voice rehabilitation on voice quality and patient-reported vocal function has been demonstrated even when performed as long as 10 years after radiotherapy [95]. Declines in HRQL, functioning and increased symptom burden observed immediately post-radiotherapy may impact patient engagement in voice rehabilitation. However, as these were all found to improve again by six months, patients will have greater capacity, in time, to take on more active rehabilitation. In Study III, voice rehabilitation took place between one and six months post-radiotherapy and yielded positive effects that were maintained six months post-rehabilitation completion. This may be an adequate starting point considering other studies are lacking.

Patient selection for rehabilitation

Voice rehabilitation is however unlikely to be suitable for all patients. Study IV identified important factors increasing the likelihood of patients experiencing a clinically significant communication improvement as measured by S-SECEL Total score domain at 12 months post-radiotherapy. Receiving voice rehabilitation was the single most important parameter, further emphasising the efficacy of the intervention. Additional factors increasing chance of success were higher (impaired) EORTC QLQ-H&N35 Speech scores one month post-radiotherapy and experiencing less vocal use post-radiotherapy compared to pre-disease. It has been established that laryngeal cancer patients prioritise voice function highly post-treatment and thus, perceived inferior function may increase motivation for rehabilitative measures. Finally, continued smoking negatively influenced the odds ratio of significant communication improvements, which is in line with studies reporting deteriorated voice quality in smokers post-radiotherapy, why smoking cessation should be encouraged [28,34].

Factors such as tumour stage or site were not significant predictors of clinical communication improvement in this thesis. Similar to others, Study II found that although T2 tumours reported more problems pre-treatment, they did not remain inferior at endpoint and should perhaps not be the guiding factor [34]. Additionally, S-SECEL also failed to discriminate between tumour site in Study I in terms of communication dysfunction. The reason for these discrepancies probably lie in the fact that the present study compared clinical

predictors with improvement of self-perceived communication function, whilst others compare it to deterioration of acoustic measures. Moreover, only few advanced stage tumours were included, which hampers conclusions regarding the influence of tumour size.

5.6 Limitations

This thesis was limited by several factors. Firstly, the number of women included is small due to their low prevalence in the laryngeal cancer population. Secondly, videostroboscopic measurements to assess voice function are lacking, but was not feasible within the scope of the study. Additionally, as patients were randomised pre-radiotherapy, several PRO measures differed between the intervention and control group one month post-radiotherapy. This was addressed by adjusting the magnitude of inter-group change and significant findings were still observed. Also, when patients were subgrouped into above and below the 20 point threshold for S-SECEL Total score domain, although some patients initially scored lower, they still experienced a score change of similar magnitude to those that scored higher (worse) one month post-radiotherapy. Moreover, patients were encouraged to practice at home, but this was not formally assessed and could perhaps provide further insight into the effectiveness of voice rehabilitation. Finally, patients excluded from the study were significantly older, thereby slightly hampering generalisation of the results as older individuals often report lower HRQL scores [127].

6 CONCLUSIONS

➢ The vast majority of laryngeal cancer patients have impaired voice quality, communicative function and HRQL prior to radiotherapy with no significant improvements seen 12 months later.

➢ Patients with supraglottic tumours experience greater deteriorations in HRQL post-radiotherapy compared to glottic tumours.

➢ Voice rehabilitation has positive effects on HRQL and communication function as well as seems to hinder a perceived deterioration of roughness 12 months post-radiotherapy.

➢ Voice rehabilitation could be offered to patients who experience voice and communication problems as well as to those identified by speech-language pathologists.

7 FUTURE PERSPECTIVES

In order to strengthen the results and conclusions of this thesis, further long-term studies are required to evaluate if the observed beneficial effects of voice rehabilitation are maintained. A second purpose of such longitudinal studies is to investigate if the differences between tumour sites, in terms of HRQL noted immediately post-radiotherapy, still exist further down the line as evidence in this field is scarce. Only one study including five supraglottic tumours has been published and suggests that no significant difference exist at five year post-radiotherapy compared to glottic tumours [73].

Moreover, it would be interesting to document the effects of radiotherapy and voice rehabilitation on mental health (e.g. depression and anxiety) from both a short-term and long-term perspective.

In this thesis factors contributing to an increased likelihood of experiencing a clinically significant communication improvement were identified. In the future, this needs to be supplemented with factors that can increase the likelihood of a communicative deterioration.

Finally, the timing of voice rehabilitation is currently difficult to optimise due to the limited published data available. One possible future aspect could be to investigate the effects of offering voice rehabilitation prophylactically, i.e. commencing during radiotherapy. This could for instance be complemented by videostroboscopy and/or subglottic pressure measurements in order to evaluate anatomic effect.

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APPENDIX

**Appendix 1:
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 <u>lång</u> promenad ?	1	2	3	4
3. Har Du svårt att ta en <u>kort</u> 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 <u>familjeliv</u> ?	1	2	3	4
27. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina <u>sociala</u> 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 <u>hälsa</u> 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 <u>livskvalitet</u> under den vecka som gått ?

      1   2   3   4   5   6   7

Mycket dålig   Utmärkt

EORTC QLQ-H&N 35

Patienter uppger ibland att de har följande symptom eller problem.
Var vänlig och ange i vilken grad Du har haft dessa besvär <u>under veckan som gått</u>.
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

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

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?	$\square_0$	$\square_1$	$\square_2$	$\square_3$
2.	Skulle Du beskriva Dig själv som en lugn, stillsam person?	$\square_0$	$\square_1$	$\square_2$	$\square_3$
3.	Är Du en aktiv, utåtriktad, pratsam person?	$\square_0$	$\square_1$	$\square_2$	$\square_3$
4.	Kan Du tala om för en person Du pratar med att Du fått behandling för struphuvudtumör?	$\square_0$	$\square_1$	$\square_2$	$\square_3$
5.	Tycker Du att Ditt tal förbättras ju mer Du använder det?	$\square_0$	$\square_1$	$\square_2$	$\square_3$
6.	Har Dina möjligheter att delta i möten, föreningsliv eller andra sammankomster varit begränsade på grund av Ditt tal?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
7.	Tycker Du att det är svårt att få andra människors uppmärksamhet när Du pratar?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
8.	Har Du svårt att höja rösten eller ropa?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
9.	Märker Du att andra människor har svårt att förstå vad Du säger?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
10.	Behöver Du upprepa samma sak flera gånger för att bli förstådd?	$\square_3$	$\square_2$	$\square_1$	$\square_0$

Har Du problem med att tala:

		Alltid	Ofta	Ibland	Aldrig
11.	- i stora grupper?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
12.	- i små grupper?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
13.	- med en person?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
14.	- i hemmiljö?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
15.	- i bullrig miljö?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
16.	- i telefon?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
17.	- när Du åker bil eller buss?	$\square_3$	$\square_2$	$\square_1$	$\square_0$

	Gör Ditt tal att:	**Alltid**	**Ofta**	**Ibland**	**Aldrig**
18.	- Du har svårigheter att vara med på fester eller andra sociala tillställningar?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
19.	- Du pratar i telefon mindre ofta än Du skulle vilja?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
20.	- Du känner Dig utanför tillsammans med andra människor?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
21.	- Ditt privatliv eller sociala liv begränsas?	$\square_3$	$\square_2$	$\square_1$	$\square_0$

	Får Ditt tal Dig att känna Dig:				
22.	- deprimerad?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
23.	- frustrerad när Du pratar med Din familj eller Dina vänner och de inte förstår Dig?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
24.	- annorlunda eller egendomlig?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
25.	- tveksam inför att möta nya människor?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
26.	- utelämnad i diskussioner?	$\square_3$	$\square_2$	$\square_1$	$\square_0$

27.	Undviker Du att prata med andra människor på grund av Ditt tal?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
28.	Brukar folk fylla i ord eller avsluta meningar åt Dig?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
29.	Blir Du avbruten när Du pratar?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
30.	Talar folk om för Dig att de inte förstår vad Du säger?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
31.	Blir folk Du pratar med irriterade (på Dig) på grund av Ditt tal?	$\square_3$	$\square_2$	$\square_1$	$\square_0$

32.	Undviker folk Dig på grund av Ditt tal?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
33.	Pratar folk annorlunda med Dig på grund av Ditt tal?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
34.	Har Din familj och Dina vänner liten förståelse för hur det är för Dig att kommunicera med den här typen av tal?	$\square_3$	$\square_2$	$\square_1$	$\square_0$
35.	Pratar Du lika mycket nu som innan Du fick Din struphuvudtumör?	$\square_3$	$\square_2$	$\square_1$	$\square_0$

TACK FÖR DIN MEDVERKAN !

Appendix 4:
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**	