# A comparison of voice quality following radiotherapy or transoral laser microsurgery of T1a laryngeal carcinomas

Andrew Jon Kinshuck

MBChB, DOHNS, FRCS ORL-HNS

‘Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Medical Doctorate’

30th June 2016

## Contents


Contents ..... 2

Table of Figures ..... 7

Tables ..... 10

Acknowledgments ..... 15

Author's Declaration ..... 16

Abstract ..... 17

Glossary of acronyms ..... 22

1. Introduction ..... 24

1.1 Laryngeal anatomy ..... 24

1.1.1 Laryngeal cartilages ..... 26

1.1.2 Joints of the larynx ..... 34

1.1.3 Muscles of the larynx ..... 35

1.1.4 Ligaments and membranes of the larynx ..... 42

1.1.5 Vasculature ..... 42

1.1.6 Lymphatics ..... 43

1.1.7 Innervation ..... 44

1.1.8 Vocal folds ..... 45

1.2 Laryngeal Physiology ..... 46

1.2.1 Vocal fold movement ..... 47

1.2.2 Variations in phonation ..... 48

1.2.3 Voice disorders ..... 49

1.3 Epidemiology of laryngeal carcinoma ..... 50

1.4 Management of early laryngeal carcinoma ..... 55

1.4.1 Endolaryngeal surgery ..... 56
1.4.2 Radiotherapy ..... 67
1.4.3 Comparison of laser and radiotherapy ..... 72
1.5 Measurements of voice quality ..... 85
1.5.1 Self-evaluation of voice ..... 86
1.5.2 Acquisition of a voice sample for analysis ..... 89
1.5.3 Perceptual rating of voice ..... 91
1.5.4 Electroglottography ..... 93
1.5.5 Acoustic analysis ..... 97
1.5.6 Videolaryngostroboscopy ..... 115
1.5.7 Aerodynamics ..... 116
1.6 Health related quality of life ..... 117
2. Aims and Objectives ..... 121
3. Methods ..... 122
3.1 Describing acoustic parameters of ‘normal’ voice ..... 122
3.1.1 Study design ..... 122
3.1.2 Study population ..... 122
3.1.3 Materials and methods ..... 123
3.1.4 Outcome measures ..... 125
3.1.5 Data collection and analysis ..... 126
3.2 Voice outcomes in patients treated with TLM with those treated with RT for T1a SCC of the glottis ..... 126
3.2.1 Study design ..... 126
3.2.2 Study population ..... 126
3.2.3 Materials and methods ..... 128

3.2.4 Outcome measures ..... 128
3.2.5 Data collection and analysis ..... 129
3.3 Longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of the glottis ..... 129
3.3.1 Study design ..... 129
3.3.2 Study population ..... 130
3.3.3 Material and methods ..... 130
3.3.4 Outcome measures ..... 131
3.3.5 Data collection and analysis ..... 131
4. Results ..... 133
4.1 Describing acoustic parameters of ‘normal’ voice ..... 133
4.1.2 Acoustic analysis ..... 134
4.2 Voice outcomes in patients treated with TLM with those treated with RT for T1a SCC of the glottis ..... 139
4.2.1 Patient demographics ..... 139
4.2.2 Subjective voice questionnaires ..... 141
4.2.3 QoL questionnaire: UW-QoLv4 ..... 142
4.2.4 Perceptual rating ..... 145
4.2.5 Acoustic analysis ..... 146
4.3 Longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of glottis ..... 153
4.3.1 Patient demographics ..... 153
4.3.2 Subjective voice questionnaires ..... 155
4.3.3 QoL questionnaire: UW-QoLv4 ..... 156
4.3.4 Perceptual rating ..... 159

4.3.5 Acoustic analysis ..... 159
5. Discussion ..... 166
5.1 Acoustic parameters of a ‘normal’ voice ..... 166
5.1.1 Acoustic analysis of sustained vowels in ‘normal’ subjects ..... 167
5.1.2 Acoustic analysis of connected speech in ‘normal’ subjects ..... 172
5.1.3 Study limitations ..... 174
5.2 Voice outcomes in patients treated with TLM with those treated with RT for T1a SCC of the glottis ..... 176
5.2.1 Self-reported questionnaire TLM and RT ..... 176
5.2.2 Perceptual rating of voice comparing TLM and radiotherapy ..... 180
5.2.3 Acoustic analysis comparing TLM and radiotherapy ..... 182
5.2.4 Study limitations ..... 189
5.3 Longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of glottis ..... 192
5.3.1 Self-reported questionnaires pre and post TLM ..... 192
5.3.2 Perceptual rating of voice pre and post TLM ..... 193
5.3.3 Acoustic analysis comparing pre and post TLM ..... 194
5.3.4 Study limitations ..... 195
5.4 Clinical implications ..... 198
5.5 Future areas of research ..... 199
6. Conclusion ..... 201
7. References ..... 203
8. Appendices ..... 216
Appendix 1: The ‘Grandfather passage’ ..... 216
Appendix 2: VHI-10 questionnaire ..... 217

Appendix 3: VoiSS questionnaire ..... 218
Appendix 4: UW-QoLv4 Questionnaire ..... 220
Appendix 5: Consent form and information sheet..... 227
Appendix 6: Complete data set: for sustained vowels for 'normal' voice .. 232
Appendix 7: Complete data set: voice questionnaires for RT and TLM patients..... 236
Appendix 8: Complete data set: UW-QoLv4 questionnaire for RT and TLM patients..... 240
Appendix 9: Complete data set: perception rating for RT and TLM patients ..... 251
Appendix 10: Complete data set: sustained vowels for RT and TLM patients ..... 253
Appendix 11: Complete data set: voice questionnaires for pre- and post-TLM patients..... 257
Appendix 12: Complete data set: UW-QoLv4 questionnaire for pre- and post-TLM patients..... 261
Appendix 13: Complete data set: perception rating for pre- and post- TLM patients..... 274
Appendix 14: Complete data set: sustained vowels for pre- and post-TLM patients..... 275
Appendix 15: Comparison of quality of life and voice outcome in patients included and excluded from pre- and post- TLM comparison..... 279

## Table of Figures

Figure 1: Location of the larynx ..... 24

Figure 2: Laryngeal cartilages ..... 26

Figure 3: Posterior view of larynx ..... 27

Figure 4: Posterior view of thyroid cartilage ..... 29

Figure 5: Cricoid cartilage ..... 31

Figure 6: Arytenoid, corniculate and cuneiform cartilages ..... 32

Figure 7: Endoscopic view of larynx ..... 33

Figure 8: Extrinsic laryngeal muscles ..... 36

Figure 9: Intrinsic laryngeal muscles ..... 37

Figure 10: Posterior Cricoarytenoid (labelled crycoarytenoideus posterior) ... 39

Figure 11: Thyroarytenoid muscle (labelled as thyro-arytenoideus) ..... 41

Figure 12: Endoscopic image of vocal folds ..... 45

Figure 13: Laryngeal cancer (C32), European age-standardised mortality rates, UK, 1971-2012 ..... 51

Figure 14: Microlaryngoscope with $C0_2$ laser attached ..... 62

Figure 15: Tumour divided with laser to evaluate depth ..... 63

Figure 16: Example of sequence of TLM incisions ..... 64

Figure 17: Classification of Cordectomy (Type I-IV illustrated) ..... 65

Figure 18: Thermoplastic shell ..... 70

Figure 19: Simulator film showing lateral portals in relation to bony landmarks before and after spinal cord shielding ..... 71

Figure 20: Electrolaryngograph (A: neck strap, B: ring electrodes, C: microprocessor, D: cable to microphone) ..... 94

Figure 21: Electrodes are placed on either side of thyroid cartilage.....95
Figure 22: Lx waveform and corresponding vocal fold cycle and contact .....96
Figure 23: Screenshot illustrating section of sustained vowels on SpeechStudio™ .....102
Figure 24: DFx 1&2 (DFx1 in red).....110
Figure 25: CFx scatter plot.....111
Figure 26: DQx1 and DQx1&2 .....112
**Figure 27: CQx scatter plot**.....112
Figure 28: DAx1 and DAx1&2.....114
Figure 29: Amplitude Scatter graph (CAx) .....114
Figure 30: Box plot of physical function for RT and TLM patients.....144
Figure 31:.....144
Figure 32: Example of DFx1&2 on connected speech in a RT and a TLM patient.....150
Figure 33: Example of DAx1&2 on connected speech in a RT and a TLM patient.....151
Figure 34: Example of CQx on connected speech in a RT and a TLM patient .....152
Figure 35: Study flow chart: outline of patient follow up.....155
Figure 36: Box plot of physical function for pre- and post-TLM patients .....158
Figure 37: Box plot of social function for pre- and post-TLM patients.....158
Figure 38: Example of DFx1&2 on connected speech in a pre and post TLM patient.....162
Figure 39: Example of DAx1&2 on connected speech in a pre and post TLM patient.....163

Figure 40: Example of CQx on connected speech in a pre and post TLM patient.....164

## Tables

Table 1: TNM Staging of Glottis carcinoma ..... 54

Table 2: Staging of Laryngeal Carcinoma ..... 55

Table 3: Power Density and tissue effects ..... 59

Table 4: Publications summarising costs of RT and TLM for early laryngeal carcinoma ..... 84

Table 5: Average Fundamental Frequencies with age ..... 103

Table 6: Summary of characteristics for ‘normal’ voice ..... 133

Table 7: Mean and range of acoustic analysis of sustained vowels for ‘normal’ voice ..... 135

Table 8: Summary table of DFx1&2 connective speech for ‘normal’ subjects ..... 136

Table 9: Summary table of DAx1&2 connective speech for ‘normal’ subjects ..... 137

Table 10: Summary table of DQx1&2 connective speech for ‘normal’ subjects ..... 138

Table 11: Summary table of AxFx1&2 connective speech for ‘normal’ subjects ..... 138

Table 12: Baseline demographics for RT and TLM patients ..... 140

Table 13: Voice handicap index–10 for RT and TLM patients ..... 141

Table 14: VoiSS questionnaire for RT and TLM patients ..... 142

Table 15: Summary table for UW-QoLv4 domain scores for RT and TLM patients ..... 142

Table 16: UW-QoLv4 composite quality of life scores of physical and social function for RT and TLM patients ..... 143
Table 17: Summary table for UW-QoLv4 global questions for RT and TLM patients ..... 145
Table 18: Combined mean GRBAS scores for RT and TLM patients ..... 146
Table 19: Acoustic analysis of both sustained vowels for RT and TLM patients ..... 148
Table 20: Summary table of DFx1&2 connective speech for RT and TLM patients ..... 149
Table 21 : Summary table of DAx1&2 connective speech for RT and TLM . 150
Table 22: Summary table of DQx1&2 connective speech for RT and TLM .. 151
Table 23: Summary table of AxFx1&2 connective speech for RT and TLM . 152
Table 24: Baseline demographics for prospective TLM patients ..... 154
Table 25: Voice handicap index–10 pre and post TLM ..... 156
Table 26: VoiSS questionnaire for pre-TLM and TLM patients ..... 156
Table 27: Summary table UW-QoLv4 domain scores for pre- and post-TLM patients ..... 157
Table 28: UW-QoLv4 composite scores of physical and social function for pre- and post-TLM patients ..... 157
Table 29: Combined mean GRBAS scores for pre- and post-TLM patients. 159
Table 30: Acoustic analysis of both sustained vowels for pre- and post-TLM patients ..... 161
Table 31: Summary table of DFx1&2 connective speech for pre- and post-TLM patients ..... 162

Table 32: Summary table of DAx1&2 connective speech for pre- and post-TLM patients ..... 163
Table 33: Summary table of DQx1&2 connective speech for pre- and post-TLM patients ..... 164
Table 34: Summary table of AxFx1&2 connective speech for pre- and post-TLM patients ..... 165
Table 35: 'Normal' males sustained vowel /i/ (complete data set) ..... 232
Table 36: 'Normal' male sustained vowel /a/ (complete data set) ..... 233
Table 37: 'Normal' female sustained vowel /i/ (complete data set) ..... 234
Table 38: 'Normal' female sustained vowels /a/ (complete data set) ..... 235
Table 39: VHI-10 for RT patients (complete data set) ..... 236
Table 40: VHI-10 for TLM patients (complete data set) ..... 237
Table 41: VoiSS for RT patients (complete data set) ..... 238
Table 42: VoiSS for TLM patients (complete data set) ..... 239
Table 43: UW-QoLv4 for RT patients (complete data set) ..... 240
Table 44: UW-QoLv4 for TLM patients (complete data set) ..... 241
Table 45: UW-QoLv4 domain scores for RT patients (complete data set) ... 242
Table 46: UW-QoLv4 domain scores for TLM patients (complete data set). 243
Table 47: UW-QoLv4 rank within past 7 days for RT patients (complete data set) ..... 244
Table 48: UW-QoLv4 rank within past 7 days for TLM patients (complete data set) ..... 245
Table 49: UW-QoLv4 global question scores for RT patients (complete data set) ..... 246

Table 50: UW-QoLv4 global question scores for TLM patients (complete data set) ..... 247
Table 51: UW-QoLv4 global questions for RT patients (complete data set) 248
Table 52: UW-QoLv4 global questions for TLM patients (complete data set) ..... 249
Table 53: UW-QoLv4 domain issue seen as most important in past seven days for RT and TLM patients (complete data set) ..... 250
Table 54: GRBAS scores for RT patients (complete data set) ..... 251
Table 55: GRBAS scores for TLM patients (complete data set) ..... 252
Table 56: Sustained vowel /i/ for RT patients (complete data set) ..... 253
Table 57: Sustained vowel /i/ for TLM patients (complete data set) ..... 254
Table 58: Sustained vowel /a/ for RT patients (complete data set) ..... 255
Table 59: Sustained vowel /a/ for TLM patients (complete data set) ..... 256
Table 60: VHI-10 for pre-TLM patients (complete data set) ..... 257
Table 61: VHI-10 for post-TLM patients (complete data set) ..... 258
Table 62: VoiSS for pre-TLM patients (complete data set) ..... 259
Table 63: VoiSS for post-TLM patients (complete data set) ..... 260
Table 64: UW-QoLv4 for pre-TLM patients (complete data set) ..... 261
Table 65: UW-QoLv4 for post-TLM patients (complete data set) ..... 262
Table 66: UW-QoLv4 domain scores for all pre-TLM patients (complete data set) ..... 263
Table 67: UW-QoLv4 domain scores for included pre-TLM patients (complete data set) ..... 264
Table 68: UW-QoLv4 domain scores for post-TLM patients (complete data set) ..... 265

Table 69: UW-QoLv4 rank within past 7 days for pre-TLM patients (complete data set).....266
Table 70: UW-QoLv4 rank within past 7 days for post-TLM patients (complete data set).....267
Table 71: UW-QoLv4 domain issue seen as most important in past seven days for pre- and post- TLM patients (complete data set).....268
Table 72: UW-QoLv4 global question scores for pre-TLM patients (complete data set).....269
Table 73: UW-QoLv4 global question scores for post-TLM patients (complete data set).....270
Table 74: UW-QoLv4 global questions for all pre-TLM patients (complete data set).....271
Table 75: UW-QoLv4 global questions for included pre-TLM patients (complete data set).....272
Table 76: UW-QoLv4 global questions for post-TLM patients (complete data set).....273
Table 77: GRBAS scores for pre and post-TLM patients (complete data set) .....274
Table 78: Sustained vowel /i/ for pre-TLM patients (complete data set) .....275
Table 79: Sustained vowel /i/ for post-TLM patients (complete data set).....276
Table 80: Sustained vowel /a/ for pre-TLM patients (complete data set) .....277
Table 81: Sustained vowel /a/ for post-TLM patients (complete data set).....278
Table 82: Comparison of quality of life and voice outcome in patients included and excluded from pre- and post- TLM comparison.....279

# Acknowledgments

The work undertaken in this thesis was performed at Aintree University Hospital NHS Foundation Trust, Longmoor Lane, Liverpool. The thesis was supervised by Professor Terry M Jones and Professor Richard Shaw at the Department of Molecular and Clinical Cancer Medicine at the University of Liverpool. I am extremely grateful for their patience, encouragement and support.

I would like to thank Professor Paul Carding, Professor of Speech Pathology at the Australian Catholic University, Brisbane, Australia who provided advice and guidance. Thank you to the speech and language therapists in the Freeman Hospital, Newcastle upon Tyne and in Aintree University Hospital who kindly provided their time to help in the research. Thank you to Fotis Polydoros, Medical Statistician at the University of Liverpool who provided support and guidance with the statistics.

I would like to express my gratitude to the laryngectomy support group the 'Happy Larrys'. This charitable organisation's donation allowed the purchase of the electrolaryngograph equipment which was invaluable for my research.

I would like to thank my colleagues in the Head & Neck department in Aintree University Hospital for their support and assistance whilst undertaking this research and all the patients who gave up their time to take part in this study.

A special thank you goes to my family who have always been there to help and support me. Merav's encouragement and wisdom has been invaluable and along with Zac have helped me reach the finish line.

## Author's Declaration

I declare that this thesis represents my own work. The research was carried out in the Head & Neck department in Aintree University Hospital NHS Foundation Trust, Liverpool. The Speech and Language therapists at Freeman Hospital, Newcastle upon Tyne and in Aintree University Hospital, Liverpool provided voice ratings. I received statistical support from Fotis Polydoros, at the University of Liverpool. All images used in this document are my own, have permission for reprint or free from copyright.

I declare that this thesis does not include work forming part of a thesis presented successfully for another degree

Andrew Jon Kinshuck

29th June 2016

# Abstract

**Introduction:**

Patients with laryngeal carcinoma often present early due to the change in their voice. The treatment for T1aN0M0 carcinoma varies throughout the world, but whether radiotherapy (RT) or endolaryngeal laser excision is performed both result in excellent local control of the tumour and five year survival rates. There are advantages and disadvantages of either treatment but there are no appropriately powered randomised controlled trials comparing them. Over recent decades external beam RT has become the more popular choice and this is partly due to a perception of poor voice outcomes from surgical excision. However with the development of technology allowing surgical precision, transoral laser microsurgery (TLM) has resulted in low morbidity and good voice outcomes.

**Objective:**

This research has three main objectives:

a. To describe acoustic parameters of 'normal' voice;
b. To compare voice outcomes in patients treated with TLM with those treated with radiotherapy for T1a SCC of the glottis;
c. To investigate longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of the glottis.

**Methods**:

The research was divided into three main parts. The first part was to analyse the acoustic parameters of 'normal' voice. To describe the parameters of 'normal' voice, adults with no history of voice disorders who scored zero on the voice questionnaire (Voice Handicap Index - 10) were included. The second part comprised a comparative cohort study of 40 patients with T1aN0M0 laryngeal carcinoma, treated with either TLM (20 patients) or RT (20 patients) to compare voice outcomes at least one year following treatment. The third part involved a prospective cohort study of 30 patients with T1aN0M0 laryngeal carcinomas who were treated with TLM, comparing voice qualities before and after treatment. All patients were recruited from those attending the regional Head and Neck centre in Aintree University Hospital.

The same methodology was adopted for voice recordings for all three parts of the study. Participants were asked to read a phonetically balanced passage and produce a prolonged vowel sound. In a sound proof room the voice recording included simultaneous audio and electrolaryngograph readings. The voice recordings were scored according to the GRBAS voice scale by an experienced rater. Acoustic analysis was performed form the electrolaryngograph recording using the SpeechStudio$^{TM}$ software. Several objective acoustic parameters were calculated from both sustained vowels and connected speech. These include: fundamental frequency (Fx), jitter, shimmer, harmonics to noise ratio (HNR) and normalized noise energy (NNE). In the comparative study of TLM versus RT and the prospective TLM study, patients were asked to complete voice-specific and quality of life

questionnaires. The voice-specific questionnaires were the Voice Symptom Scale (VoiSS) and the Voice Handicap Index-10 (VHI-10). The quality of life questionnaire adopted was the University of Washington Quality of Life (UWQoL) version 4.

**Results:**

In the acoustic analysis of sustained vowels in normal speech, females have a statistically significantly higher Fx than males (adjusted p=<0.05). There is no other statistically significant difference across the domains for sustained vowels in normal speech. In the analysis of connected speech, Fx is again higher in females (p<0.001). There is no statistically significant difference in amplitude (Ax) or contact quotient (Qx).

In the comparison of voice post TLM and RT, there is no statistical difference in voice-specific questionnaires between the groups. The UW-QoL4 found a statistically significantly higher QoL score in the TLM compared with the RT group for appearance (p=0.003), recreation (p=0.048), chewing (p=0.015) and saliva (p=0.016), however these are not statistically significant when adjusted for age. Overall for QoL, the RT group have a statistically significantly lower median score compared to TLM in physical function (p=0.004) and this remains statistically significant when adjusted for age (p=0.036). There is no statistically significant difference for social function (p=0.441). There is no statistically significant difference in perceptual rating (GRBAS score) between RT and TLM groups (total mean 5.49 vs. 5.12, p=0.254). Most domains as part of the acoustic analysis of sustained vowels show no statistically significant difference between RT and TLM. The mean Fx analysis on

connective speech is statistically significantly higher in the TLM group (161.2Hz vs. 131.1Hz, adjusted p=0.001). Coherence of frequency is statistically significantly higher in the TLM group (48.6% vs. 36.0%, adjusted p=0.027) and pitch irregularity is statistically significantly higher in the RT group (26.7% vs. 14.9%, adjusted p=0.013). There is no statistically significant difference in mean amplitude between the two groups. Coherence of amplitude is statistically significantly higher in the TLM group (adjusted p=0.006) and amplitude irregularity is statistically significantly higher in the RT group, (12.4% vs. 6.3%, adjusted p=0.005). There is no statistically significant difference in mean contact quotient (p=0.368), coherence (p=0.236) or irregularity (p=0.125) when comparing TLM and RT.

In the comparison of voice pre and post TLM, there is no statistical difference in voice-specific questionnaires between the groups. There is no statistically significant difference in the UW-QOLv4 domain scores or composite scores in patients pre- and post- TLM. There was no statistically significant difference in mean score for ‘G’,’R’,’B’ and ‘S’ indicators as part of perceptual rating between pre and post TLM patients, although asthenia was statistically significantly lower post-TLM (0.97 vs. 0.94, adjusted p=0.015). There is no statistically significant difference in any of the domains in the acoustic analysis of sustained vowels pre and post TLM. In the acoustic analysis of connected speech, the mean DFx is statistically significantly higher in the post TLM group (adjusted p=0.001). There is no statistically significant difference in the coherence of frequency or pitch irregularity when comparing pre and post TLM. There is no statistically significant difference in the mean DAx (p=0.121), coherence (p=0.472) or irregularity of amplitude (p=0.184) when comparing

pre and post TLM. There is no statistically significant difference in the mean DQx (adjusted p=0.904), coherence (adjusted p=0.293) or irregularity of the contact quotient (adjusted p=0.400) when comparing pre and post TLM.

**Conclusion:**

The treatment of T1a laryngeal carcinoma with either TLM or RT has been shown to have comparably good local control. There are advantages and disadvantages of both treatments, however TLM is often preferred by patient and clinician as it is a day case procedure, can provide histological clearance and leaves the option to use RT in the future. However voice outcomes of the procedures have been debated with various reports in the literature. There are challenges when comparing the two treatment modalities due to a number of tumour, patient and surgical factors. It is not surprising that the voice is affected by whatever treatment is performed to treat the glottic carcinoma. This study shows that voice quality is good, however it is measured, for after both TLM and RT.

## Glossary of acronyms

- AUH Aintree University Hospital, NHS Foundation Trust
- CPP Cepstral peak prominence
- DAx Distribution of amplitude
- DFx Distribution of frequency
- DQx Distribution of closed quotient
- EGG Electroglottography
- ENT Ear, Nose and Throat
- ELS European Laryngological Society
- Fx Fundamental frequency
- GRBAS Grade, Roughness, Breathiness, Asthenia, Strain
- HNR Harmonics to noise ratio
- IMRT Intensity modulated radiotherapy
- IQR Interquartile range
- Laser Light amplification by stimulated emission of radiation
- Lx Laryngograph waveform
- LPR Linear predictive coding
- MDVP Mulit-dimensional voice programme
- MPT Maximum phonation time
- NBI Narrow band imaging
- NHS National Health Service
- NNE Normalized noise energy
- ORL-HNS Otorhinolaryngology - Head & Neck Surgery

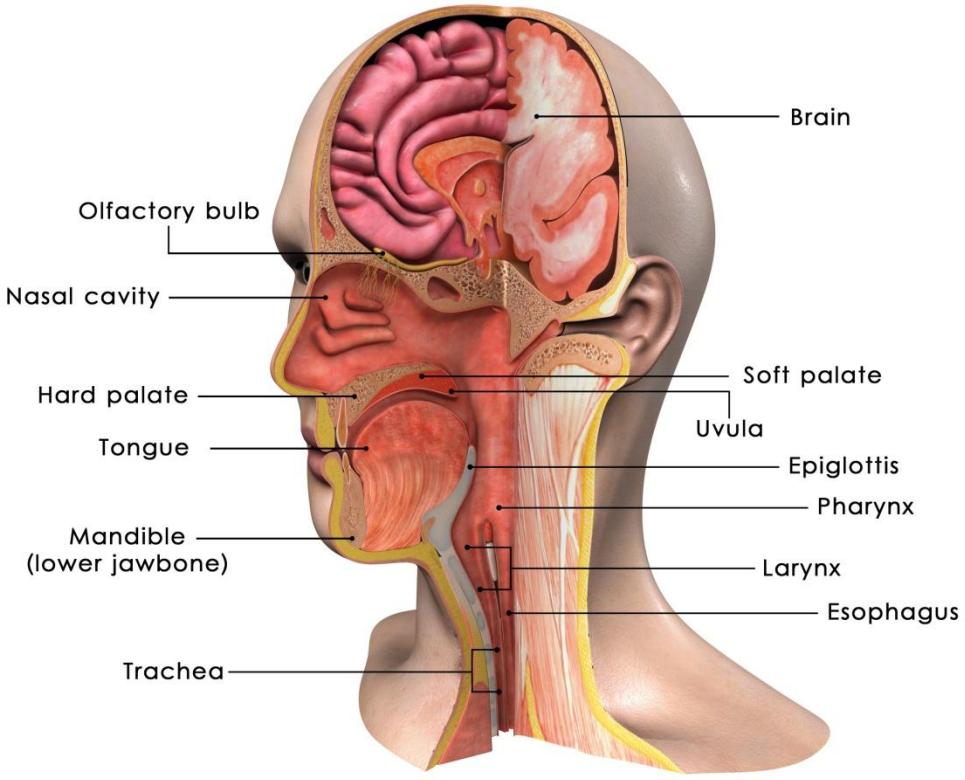
- QoL Quality of life
- RAP Relative Average Perturbation
- RT Radiotherapy
- SCC Squamous cell carcinoma
- SD Standard deviation
- SPL Sound pressure level
- TNM Tumour, Node, Metastasis
- TL Total laryngectomy
- TLM Transoral laser microsurgery
- UW-QoLv4 University of Washington quality of life version 4
- VHI Voice handicap index
- VoiSS Voice symptom scale

# 1. Introduction

## 1.1 Laryngeal anatomy

The larynx is a complex structure in the neck consisting of a framework of cartilages connected by ligaments, membranes and muscles. It is in a midline position in the anterior neck and its role is to provide voice as well as protecting the airway from the digestive tract. Figure 1 demonstrates the position of the larynx in the anterior neck.

**Figure 1: Location of the larynx**




*Source: Adobe stock images*[1]

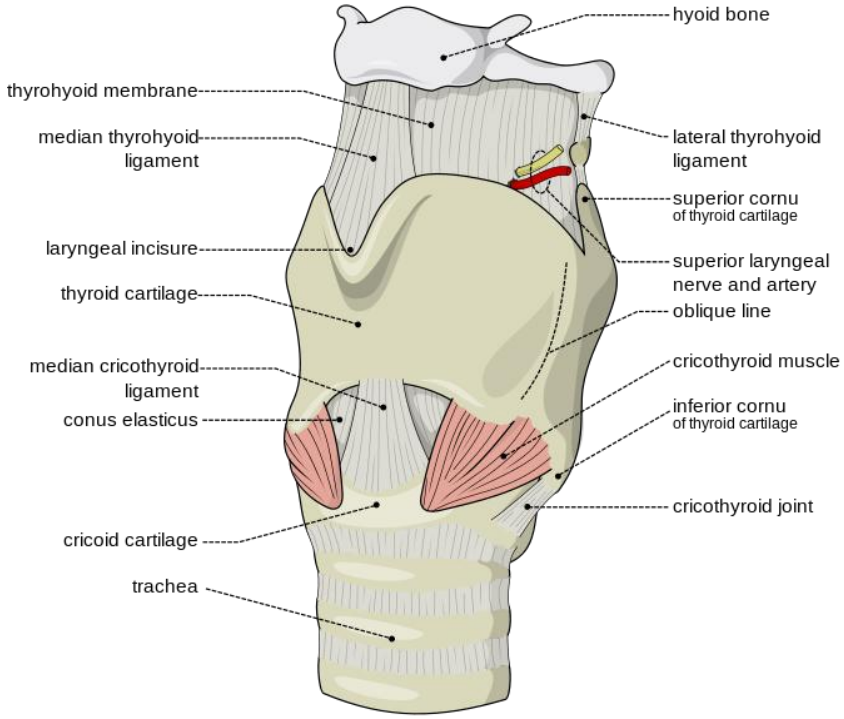
Embryologically the larynx develops from the ectodermal, endodermal and mesodermal tissues from the third, fourth and sixth pharyngeal arches and pouches. At the fourth week of intra-uterine life the laryngotracheal groove appears at the ventral wall of the larynx. This eventually deepens and the edges fuse to form the laryngotracheal tube which separates it from the pharynx and oesophagus. The laryngotracheal tube is lined with endoderm from which the epithelium of the airway develops. In the fifth to sixth week the primordial epiglottis and arytenoids arise from the third and fourth pharyngeal arches.[2] The thyroid cartilage develops from the fourth and the cricoid from the sixth pharyngeal arch after the eighth week. The laryngeal muscles develop from the fourth and sixth pairs of pharyngeal arches and are innervated by branches of the vagus nerves (recurrent and superior laryngeal nerves).[2]

The growth of the larynx and epiglottis is rapid during the first 3 years after birth, following which the epiglottis has reached its adult form. There is gradual descent of both structures during early childhood. The lower postion of the larynx in an adult enables a greater range of vocalization. The postion of the larynx also decreases the risk of aspiration and allows enough space for the vocal cords to lengthen.[3] The laynx is higher in the neck in adult humans compared to non-human primates. The extra space in adult humans allows improved tongue movements and a greater frequency range in humans compared to other primates.[4]

### 1.1.1 Laryngeal cartilages

The larynx is formed by three unpaired cartilages (epiglottic, thyroid and cricoid) and four paired cartilages (arytenoids, cuneiform, corniculate and tritiate). Figure 2 illustrates the position of the thyroid and cricoid cartilage in relation to the trachea and hyoid bone.

**Figure 2: Laryngeal cartilages**




*Source: Modified image of larynx from Gray's Anatomy*[6]

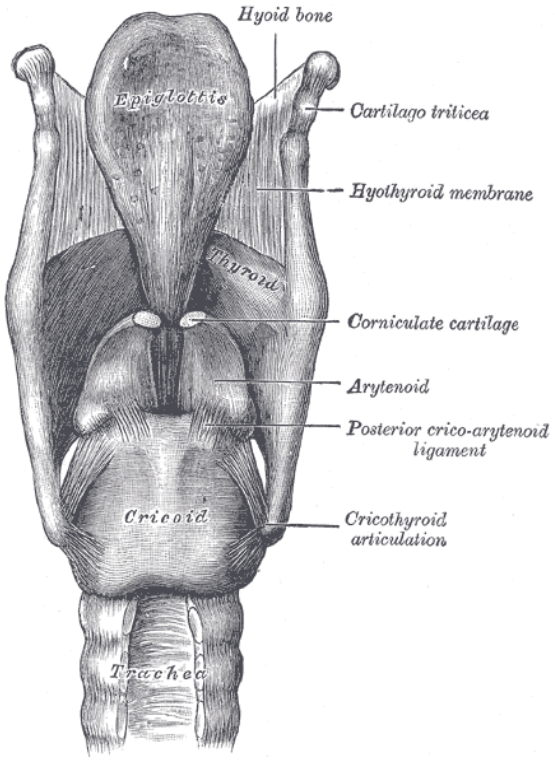
The thyroid, cricoid and the greater part of the arytenoid cartilages consist of hyaline cartilage whilst the epiglottic, cuneiform and corniculate cartilages and the apices of the arytenoid are composed of elastic fibrocartilage. Elastic cartilage contains elastin fibres giving it greater flexibility compared to hyaline cartilage and allowing it to return to its normal shape. This is important due to

the movement of the larynx during swallowing and speech. Hyaline cartilage contains high levels of collagen, which provides added strength and structure to the larynx. There is progressive mineralization and ossification of the laryngeal cartilages with age.[5]

*Epiglottic cartilage*

The epiglottis is a thin leaf-like plate of elastic fibrocartilage which protects the airway by diverting food and drink away from the laryngeal inlet and into the oesophagus. The epiglottic cartilage projects upwards behind the tongue and is attached anteriorly to the hyoid bone, posteriorly to the arytenoids (see figure 3) and inferiorly to the thyroid cartilage.

**Figure 3: Posterior view of larynx**




*Source: Anatomy of the human body, Gray.*[7]

Inferiorly the epiglottic cartilage has a long and narrow stalk known as the petiole. It is connected to the thyroid cartilage by the thyroepiglottic ligament. The sides of the petiole are connected to the arytenoid cartilage by aryepiglottic folds whilst the superior portion of the cartilage remains unattached. Anteriorly, the lingual surface is covered by a non-keratinised, stratified, squamous mucosa. The lingual surface is attached anteriorly to the hyoid bone by the hyoepiglottic ligament.

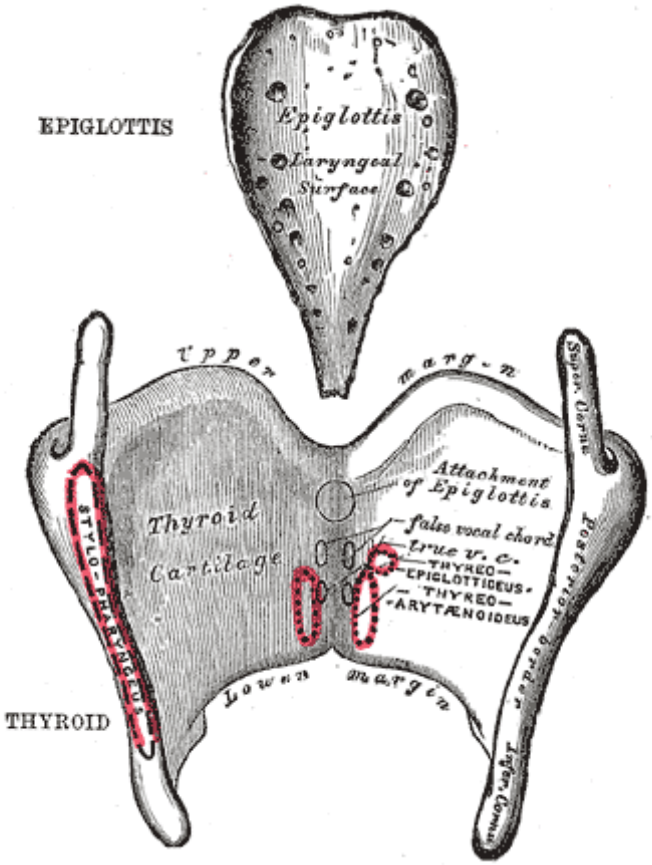
Posteriorly, the laryngeal surface of the epiglottic cartilage is smooth and covered by ciliated pseudostratified respiratory epithelium. In this posterior part of the epiglottis there are numerous small mucous glands which help lubricate the larynx. This is important for voice production as the vocal folds do not have any mucous glands.

*Thyroid cartilage*

The thyroid cartilage is the largest cartilage in the larynx and acts to protect the internal anatomy of the larynx. [8] The thyroid cartilage is located inferior to the hyoid bone and superior to the cricoid cartilage. The thyroid cartilage consists of two quadrilateral laminae (or alae) fused at the midline and opening posteriorly. In males, anterior borders of each lamina are at an approximate right angle, forming the laryngeal prominence or ‘Adam’s apple’. In females, this angle is about 120 degrees and therefore the laryngeal prominence is much less pronounced.[9] The more acute angle in men allows for a greater length of the vocal folds which, amongst other factors, results in

a deeper pitch of the voice. Thus the length of the vocal folds in female adults is 13-17mm compared to male adults of 15-23mm.[10]

**Figure 4: Posterior view of thyroid cartilage**




*Source: Anatomy of the human body, Gray.*[7]

The thyroid laminae are separated superiorly by the thyroid notch. A cadaveric study demonstrated that the midline vertical distance from the thyroid notch to the inferior border of the thyroid cartilage ranges from 23.8mm (+/- 3.9mm) in males and 15.0mm (+/-2.1mm) in females.[11] The anterior commissure is found at the midpoint between these landmarks and is defined as the anterior point where the vocal folds meet.[8]

The laminae of the thyroid cartilage continue posteriorly to form the superior and inferior horn or cornu as demonstrated in figure 4. The inferior cornu articulates with the cricoid cartilage to form the cricothyroid joint. This synovial joint allows rotation of the cricoid cartilage with respect to the thyroid cartilage. The movement at this joint enables the vocal fold tension to be varied. The superior cornu attaches to the greater cornu of the hyoid bone through the lateral thyrohyoid ligament. The thyroid cartilage is also attached to the hyoid bone by the thyrohyoid membrane. The thyrohyoid membrane is thicker in the middle to make up the median thyrohyoid membrane.

There is an oblique line that passes along the external surface of each lamina of the thyroid cartilage. This is where the thyrohyoid, sternothyroid and inferior constrictor muscles insert into the thyroid cartilage.

A perichondrium layer lines the thyroid cartilage except at the inner surface at the anterior commissure. At the commissure there are ligamentous attachments to the laryngeal folds, the thyroepiglottic ligament, bilateral vestibular ligaments (false cords) and bilateral vocal ligaments (vocal folds). [12] Broyle's ligament is where the vocal folds meet anteriorly at the anterior commissure and the fibres pass to the thyroid cartilage. This is a potential route for malignancy to spread from the larynx.[13]

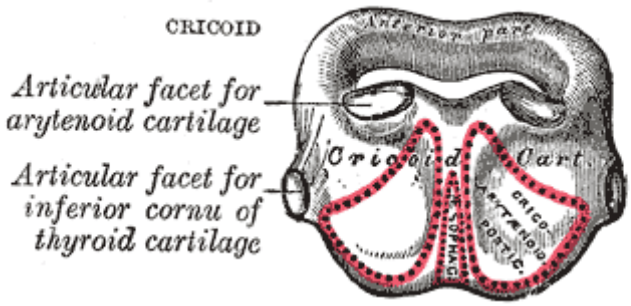
*Cricoid cartilage*

The cricoid cartilage forms a complete ring around the airway resembling a signet ring, with a broad posterior lamina and a thinner anterior arch.[14] It forms the base for the entire larynx and also supports the arytenoid cartilages. It provides attachments for the cartilages, ligaments and muscles involved in

opening and closing the airway and controlling voice production. Figure 5 illustrates the location of the muscular attachments to the posterior aspect of the cricoid.

The cricoid is attached to the thyroid cartilage through the median cricothyroid ligament and postero-laterally by the cricothyroid joints. The cricoid cartilage also articulates superiorly to the arytenoid cartilage via the synovial cricoarytenoid joint. Inferiorly, the cricoid cartilage is attached to the trachea via the cricotracheal ligament.

**Figure 5: Cricoid cartilage**



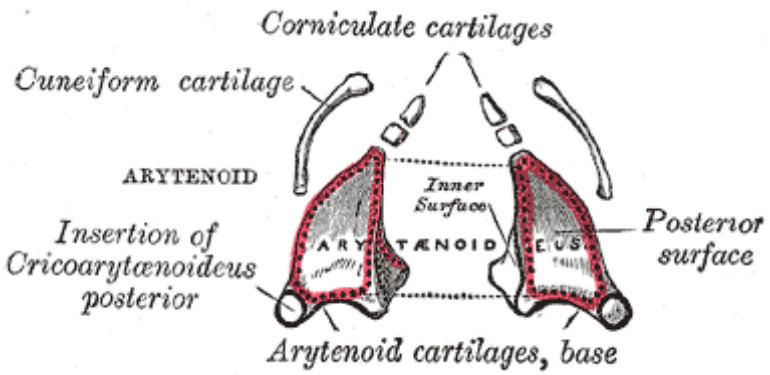

*Source: Anatomy of the human body, Gray.* [7]

*Arytenoid cartilages*

The paired arytenoid cartilages are small, pyramidal structures which allow the vocal folds to be tensed or relaxed. Figure 6 illustrates the pyramidal shape of the arytenoid cartilage. The arytenoids are located at the posterior, superior border of the cricoid cartilage. The arytenoid cartilage has two processes: the vocal and the muscular process. The vocal process projects forward, and attaches to the vocal ligament. The muscular process projects

laterally, and gives attachment to the posterior cricoarytenoid muscles and the lateral cricoarytenoid muscles.

**Figure 6: Arytenoid, corniculate and cuneiform cartilages**




*Source: Anatomy of the human body, Gray.* [7]

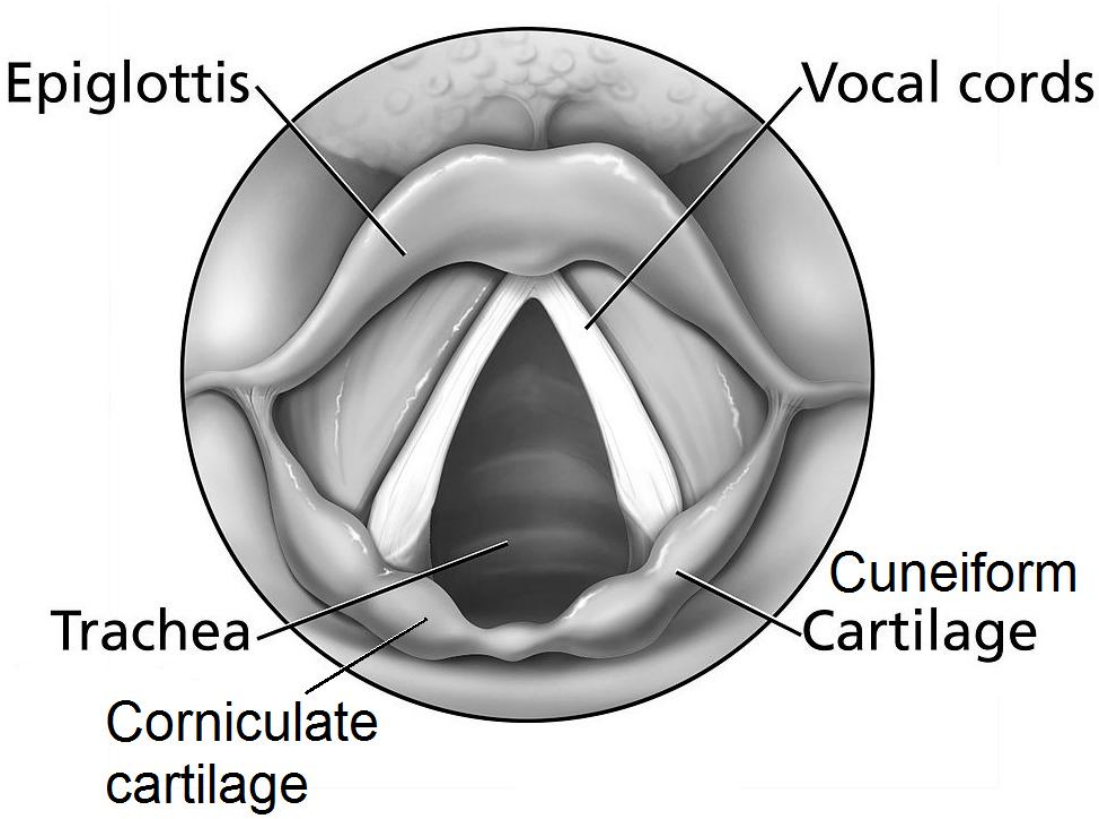
*Corniculate cartilage*

The corniculate cartilages are two small conical cartilages which articulate with the apices of the arytenoid cartilages. Figure 7 demonstrates how they are situated in the posterior parts of the aryepiglottic mucosal folds, and form the posterior aspect of the laryngeal inlet.

*Cuneiform cartilage*

The cuneiform cartilages are two small, elongated, nodules of elastic fibrocartilage. They sit on either side of the aryepiglottic fold, anterosuperior to the corniculate cartilages, and form the lateral aspect of the laryngeal inlet. The corniculate and cuneiform cartilages result in small bulges on the surface of the mucous membrane (see figure 7) and help prevent collapse of the larynx during inspiration and swallowing.

**Figure 7: Endoscopic view of larynx**




*Source: National Cancer Institute (2010).*[15]

*Tritiate cartilage*

The tritiate cartilages are two small nodules situated within the thyrohyoid membrane and help to strengthen the thyrohyoid membrane.

### 1.1.2 Joints of the larynx

The joints in the larynx include the cricothyroid, cricoarytenoid and arytenocorniculate joints. The joints help stabilize the larynx but also allow movement to assist in swallowing, vocalizing and breathing.

*Cricothyroid joints*

The cricothyroid joints are synovial joints situated between the inferior cornu of the thyroid cartilage and the sides of the cricoid cartilage. Each joint is enveloped by a capsular ligament, strengthened posteriorly by fibrous bands. Both capsule and ligaments are rich in elastin fibres. The primary movement at the joint is rotation around a transverse axis, moving the lamina of the thyroid cartilage and the arch of the cricoid cartilage closer together. This movement is important to allow changes in voice pitch by permitting elongation of the vocal folds.[16]

*Cricoarytenoid joint*

The cricoarytenoid joints are a pair of synovial joints between the lateral parts of the upper border of the cricoid cartilage and the bases of the arytenoids. There are two main movements at this joint: rotation of the arytenoid cartilages at right angle to the long axis of the cricoid; and gliding of the arytenoids towards or away from each other, in an anterior and posterior direction. By their movements, the joints facilitate alteration of the distance

between the vocal processes of the two arytenoids, and between each vocal process and the anterior commissure. This movement of the arytenoid cartilage changes the shape and tension of the vocal folds thereby changing voice quality. Rheumatoid arthritis causes inflammation in the synovium of joints. The rheumatoid arthritis can involve the cricoarytenoid joint and cause an abnormal voice (dysphonia) as well as airway obstruction.[17]

*Arytenocorniculate joints*

The arytenocorniculate joints are very small and link the arytenoid and corniculate cartilages. They are of no clinical significance.

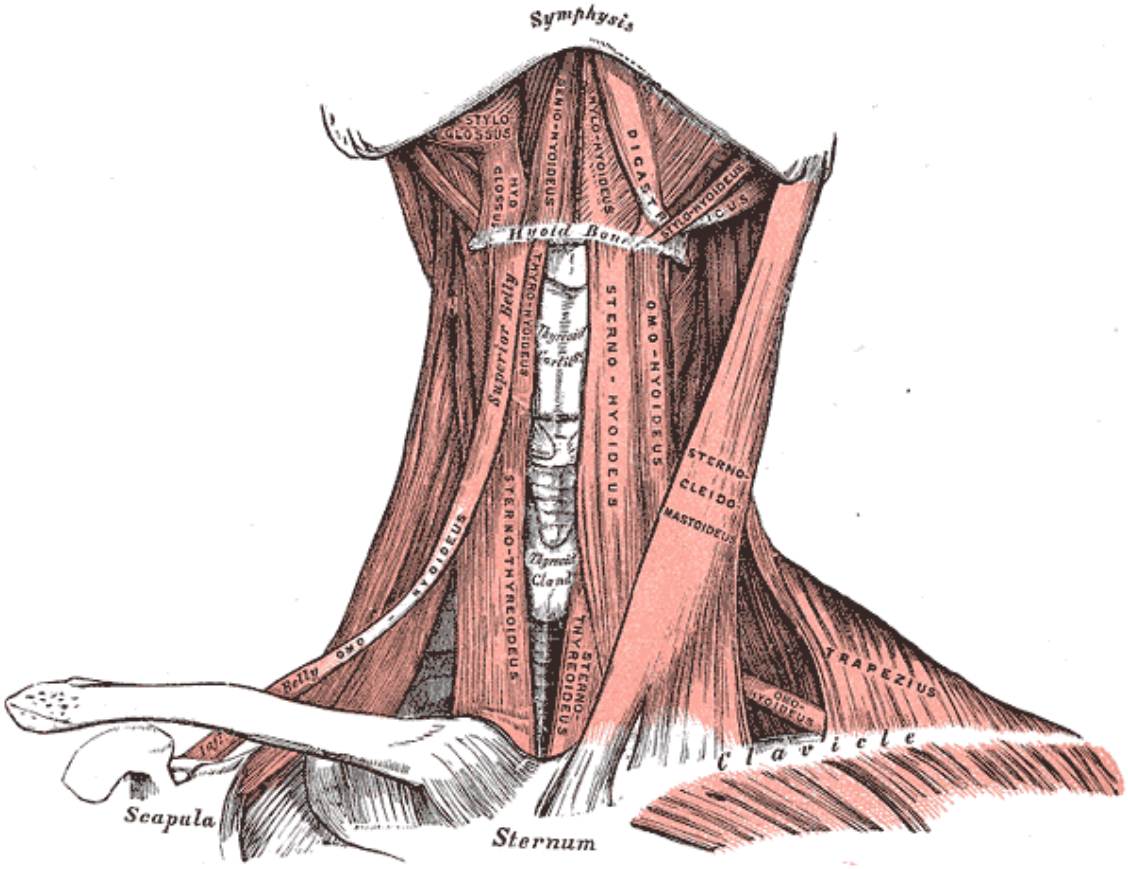
### 1.1.3 Muscles of the larynx

The muscles of the larynx may be divided into extrinsic or intrinsic groups.

*The Extrinsic laryngeal muscles*

The extrinsic muscles connect the larynx to the neighbouring structures and are responsible for moving it vertically during phonation and swallowing. The muscles that suspend the larynx and elevate it during swallowing are: thyrohyoid; stylohyoid; digastric; geniohyoid; mylohyoid; and stylopharyngeus muscles (illustrated in figure 8). Opposing muscles pull the larynx down and include: omohyoid; sternothyroid; and sternohyoid muscles. The middle constrictor, inferior constrictor, and cricopharyngeus muscles are important in the swallowing reflex. The extrinsic muscles of the larynx have little impact on voice production and will therefore not be described in further detail.

**Figure 8: Extrinsic laryngeal muscles**

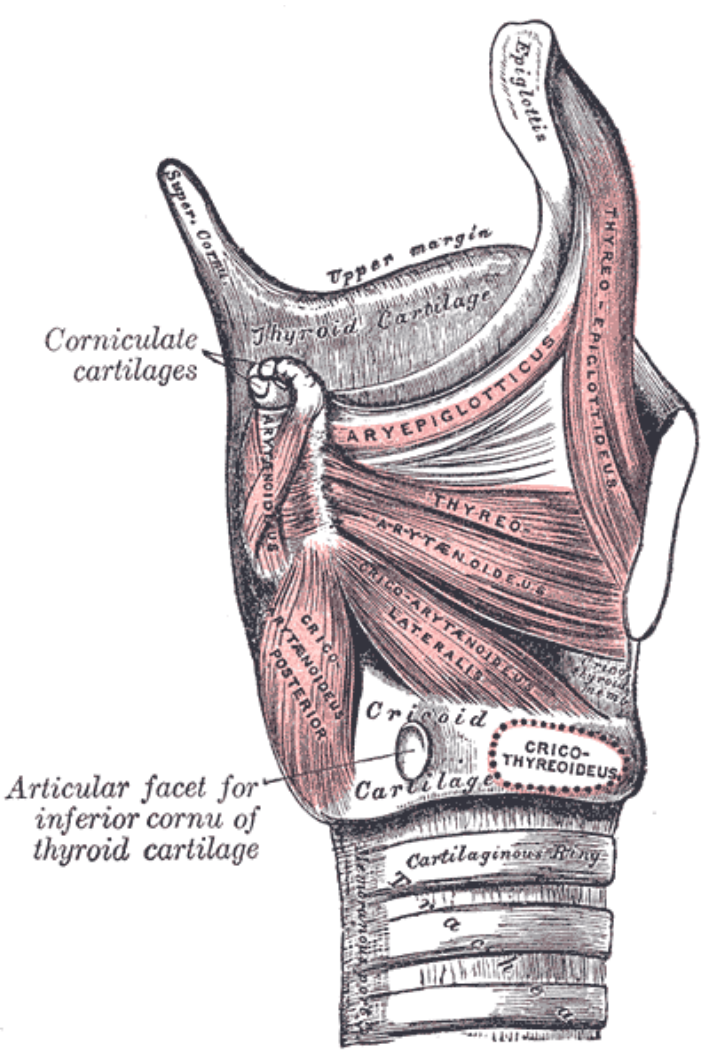



*Source: Anatomy of the human body, Gray.* [7]

*The Intrinsic laryngeal Muscles*

The intrinsic muscles of the larynx are confined to the larynx in their attachments and their function is to modify the size of the glottic opening (rima glottidis) along with changing the length and tension on the vocal folds. The intrinsic muscles include: cricothyroid; posterior and lateral cricoarytenoid; transverse and oblique arytenoid; aryepiglottic; thyroarytenoid; vocalis; and thyroepiglotticus muscles (illustrated in figure 9). All the intrinsic muscles, except the transverse arytenoid muscle, are paired, and work synchronously.

**Figure 9: Intrinsic laryngeal muscles**




*Source: Anatomy of the human body, Gray.*[7]

*Cricothyroid muscle*

The cricothyroid muscle is attached anteriorly to the external surface of the arch of the cricoid cartilage. Its fibres pass backwards and diverge into two portions, lower oblique and straight. On contraction of the cricothyroid muscle the cricoid rotates at the cricothyroid joint. This brings the anterior arch of the

cricoid superiorly towards the inferior border of the thyroid laminae. Whilst, at the same time causing the posterior cricoid lamina and the arytenoid cartilages to move inferiorly. This inferior displacement increases the distance between the vocal processes and the anterior commissure. This approximation of the thyroid and cricoid cartilage has been referred to the 'closing of the visor'.[18] The results of this are to lower, elongate, and thin the vocal folds while bringing them into a paramedian position. The stretching of the vocal fold tightens the edge of the vocal fold and passively stiffens the component layers of the vocal fold. This results in a sound of higher frequency produced by the vocal folds.

*Posterior cricoarytenoid muscle*

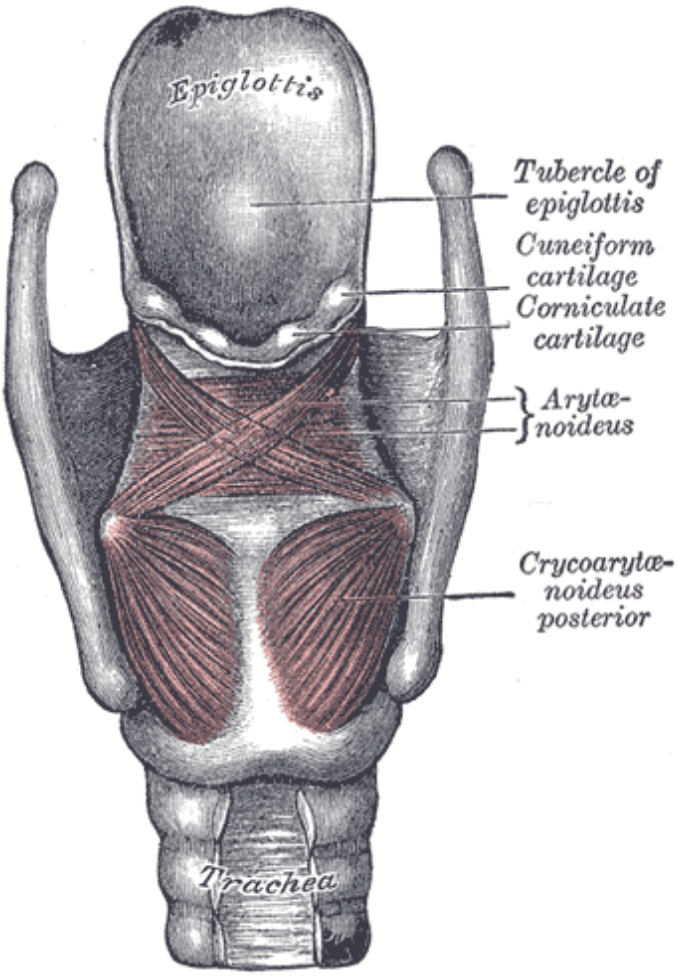
The posterior cricoarytenoid muscle (illustrated in figure 10) arises from the posterior surface of the cricoid lamina. The posterior cricoarytenoid muscles are the only laryngeal muscles that abduct the vocal folds. Its fibres run laterally and converge to insert on the upper and posterior surfaces of the muscular process of the ipsilateral arytenoid cartilage. The muscles also elongate, and thin the vocal folds while causing the vocal fold edge to be rounded.

*Lateral cricoarytenoid muscles*

The lateral cricoarytenoid muscles are attached anteriorly to the upper border of the cricoid arch. They run obliquely backwards to be attached to the front of the muscular process of the ipsilateral arytenoid cartilage. The lateral cricoarytenoid rotates the arytenoid cartilage in a direction opposite to that of

posterior cricoarytenoid and so closes the rima glottidis (space between the vocal folds).

**Figure 10: Posterior Cricoarytenoid (labelled crycoarytenoideus posterior)**




*Source: Anatomy of the human body, Gray.*[7]

*Oblique and transverse arytenoid muscles*

The oblique and transverse arytenoid muscles aid the adduction of the vocal folds. The oblique arytenoid muscles lie superficial to the transverse arytenoid and aryepiglotticus muscles. The muscles cross each other obliquely at the

back of the larynx, each extending from the posterior surface of the muscular process of one arytenoid cartilage to the apex of the opposite one. Some fibres continue laterally round the arytenoid apex into the aryepiglottic fold, forming the aryepiglotticus muscle. The oblique arytenoids and aryepiglotticus muscles act as a sphincter of the laryngeal inlet by adducting the aryepiglottic folds and approximating the arytenoid cartilages to the tubercle of the epiglottis.

*Transverse arytenoid muscle*

The transverse arytenoid muscle is a single unpaired muscle deep to the oblique arytenoid muscle. It bridges the gap at the back of the larynx between the two arytenoid cartilages. It attaches to the back of the muscular process and adjacent lateral borders of both arytenoids. The transverse arytenoid muscle moves the arytenoid cartilages towards each other, closing the posterior portion of the vocal folds.

*Thyroarytenoid muscles*

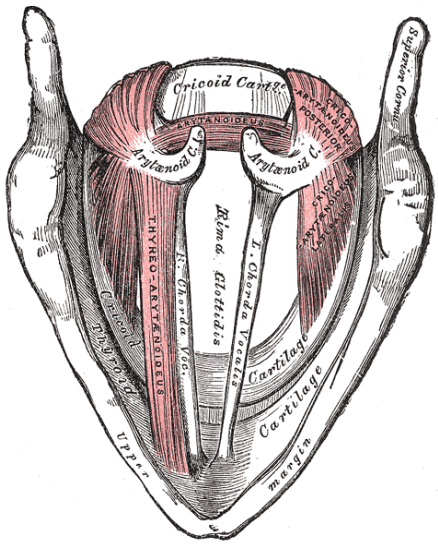
The thyroarytenoid muscles are broad and thin and lie lateral to the vocal folds as shown in figure 11. These muscles can be divided into the thyroarytenoid internus and externus muscles. The more developed internus muscles lie deep to the externus muscle. The thyroarytenoid internus are also known as the vocalis muscle. It attaches at the anterior commissure and inserts onto the vocal process. The thyroarytenoid internus contracts to adduct, shorten, thicken, and lower the vocal fold while rounding its edge. The thyroarytenoid externus arises from the anterior commissure and inserts onto

the lateral surface of the arytenoid cartilage. On contraction it contracts to bring the vocal process and anterior commissure closer to each other. The majority of fibres in internus are slow-twitch and those in externus fast-twitch. The structure of the thyroarytenoid muscle varies between mammals and the ratio of different fibres in humans helps to create a unique speech function.[19] In the elderly there is muscle atrophy and change of the ratio of slow and fast-twitch fibres which contributes to a change in voice with age.[20]

*Thyroepiglotticus muscle*

A few muscle fibres of the thyroarytenoid externus muscle run through the quadrangular membrane to establish the thyroepiglotticus muscle. The thyroepiglotticus muscle narrows the rima glottitis and can widen the inlet of the larynx by their action on the aryeplgottic folds.

**Figure 11: Thyroarytenoid muscle (labelled as thyro-arytenoideus)**




*Source: Anatomy of the human body, Gray.*[7]

### 1.1.4 Ligaments and membranes of the larynx

There are extrinsic and intrinsic ligaments of the larynx which support the laryngeal superstructure and enable movement. The extrinsic ligaments include: the thyrohyoid membrane, hyoepiglottic ligament and the cricotracheal ligament. The intrinsic ligaments include: the quadrangular membrane of the supraglottic larynx, conus elasticus and the vocal ligaments. The quadrangular membrane and the overlying mucosa form the aryepiglottic folds, constituting the medial wall of each of the piriform sinuses. It attaches to the lateral side of the epiglottis anteriorly, and attaches posteriorly to the arytenoid and corniculate cartilages. The conus elasticus is a thick elastic structure, which attaches inferiorly at the superior border of the cricoid cartilage, and superiorly to the anterior commissure of the thyroid cartilage and the vocal process of the arytenoid. Between the two superior attachments, it forms the vocal ligament. Anteriorly the conus elasticus forms the cricothyroid membrane, in the midline becomes the cricothyroid ligament, and superiorly extends to become the thyroglottic membrane. This thyroglottic membrane lies parallel to the superior surface of the true vocal fold. It is usually incomplete, and so forms an incomplete barrier to prevent extension of transglottic cancers.

### 1.1.5 Vasculature

The arterial supply to the larynx is from the superior and inferior laryngeal arteries. The superior laryngeal artery is formed from the superior thyroid artery, a branch of the external carotid artery, at the level of the hyoid. The

superior laryngeal artery runs alongside the internal branch of the superior laryngeal nerve and enters the thyrohyoid membrane inferior to the nerve. The artery enters the mucosa of the piriform sinus before being branching to perfuse other internal laryngeal structures.

The inferior laryngeal artery is formed from the inferior thyroid artery, a branch of the thryocervical trunk from the subclavian artery. The inferior laryngeal artery runs alongside the recurrent laryngeal nerve to the posterior of the cricothyroid joint. The artery then supplies the remainder of the internal larynx, forming multiple anastomoses with the superior laryngeal artery. The venous supply runs parallel to the arterial system.

### 1.1.6 Lymphatics

Understanding the lymphatic system in the neck aids diagnosis and treatment of cancer of the larynx. It is divided into superficial intramucosal and deep submucosal networks. The deep submucosal network is a key factor in the spread of cancer. It comprises of a right and left half, with limited communication between them. Each half is divided into: supraglottic, glottic, and subglottic regions. The drainage of the supraglottic structures follows the superior laryngeal and superior thyroid vessels, from the piriform sinus through the thyrohyoid membrane to the deep jugular chain at the carotid bifurcation. The ventricle in the supraglottic region drains into the paraglottic space, through the cricothyroid membrane and into the ipsilateral lobe of the thyroid, hence it requires resection during laryngectomy. The true vocal folds are not drained by a lymphatic network, and therefore there is a good

treatment success for cancers in this area.[18] The epiglottis is drained by the glottis network, and drains bilaterally.

The subglottic area comprises of two systems: one follows the inferior thyroid vessels to the deep jugular, subclavian, paratrachial and tracheoesophageal chains; and the other travels through the cricothyroid membrane to bilateral middle deep cervical nodes and prelaryngeal nodes, receiving lymphatics from both sides of the larynx.

### 1.1.7 Innervation

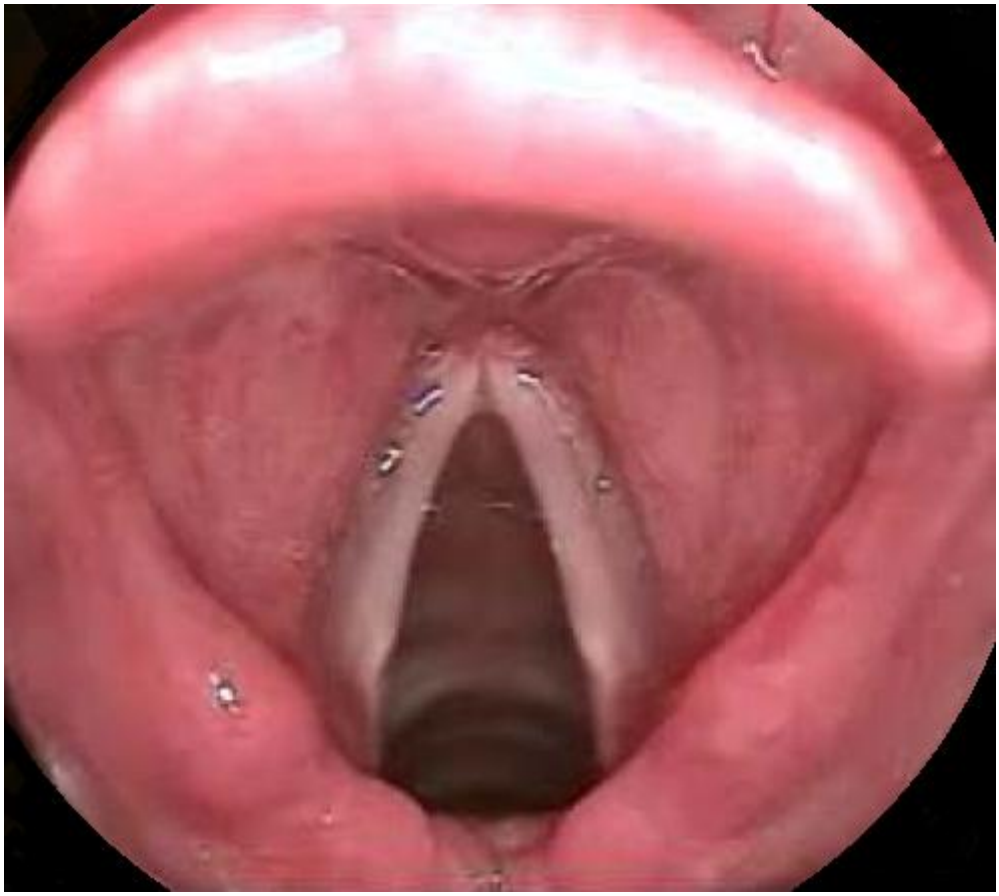
The larynx is innervated by the superior and inferior laryngeal nerves which are branches of the vagus nerve. The superior laryngeal nerve branches from the vagus high in the neck and divides into internal and external branches. The internal branch runs alongside the superior laryngeal artery through the thyrohyoid membrane, providing the sensory supply to the supraglottis. The external branch innervates the cricothyroid and inferior constrictor muscles.

The inferior laryngeal nerve originates from the recurrent laryngeal nerve and runs within the tracheoesophageal groove. It passes posteriorly to the cricothyroid joint before entering the larynx. It supplies motor innervation to all the intrinsic muscles of the larynx except the cricothyroid muscle. The recurrent laryngeal nerve also contains sensory and secretomotor fibres to the glottis and subglottis.

### 1.1.8 Vocal folds

There are two pairs of vocal folds: false (vestibular) and true vocal folds. The false (vestibular) folds are formed by mucosa overlying the vestibular ligament. The true folds are formed by mucosa overlying the vocal ligament and the vocal process of the arytenoid. Clinically, the true vocal folds are referred to as the vocal cords although the terms are often used synonymously with no consensus on terminology. Figure 12 shows an endoscopic image of the vocal folds.

**Figure 12: Endoscopic image of vocal folds**



*Source: Endoscopic image taken by author*

Each fold consists of five layers: the mucosa, three layers of lamina propria and the vocalis muscle. The mucosa overlying the vocal fold is thin and gives the vocal fold a pearly white appearance. It is attached to the underlying lamina propria by a basement membrane. The most superficial layer of the lamina propria consists of loose collagen and elastic fibres, loosely attached to the underlying vocal ligament.

This produces a potential space (Reinke's space) extending along the length of the free margin of the vocal ligament and a little way onto the superior surface of the cord. Fluid readily collects in this space when disease is present causing swelling or oedema of the vocal folds. The intermediate layer of the lamina propria consists of elastic fibres and the deep layer is formed of collagen fibres. These two layers collectively form the vocal ligament. Fibres of the vocalis muscles form the fifth layer of the vocal folds.

The free edge of the vocal folds is covered with stratified squamous epithelium whilst the supraglottis and posterior glottis is lined with pseudostratified ciliated epithelium. The ciliated epithelium contains mucous producing cells and allows for adequate lubrication of the vocal folds. Surgery or RT of this area, causing scarring (fibrosis), can disturb this layer and resulting in a lack of mucous to the vocal folds.

## 1.2 Laryngeal Physiology

The larynx has three primary functions: protection of the airway; respiration; and phonation. Phonation occurs when air is directed against the vocal folds, causing them to vibrate and produce sounds through columns of air in the

pharynx, nose and mouth. Phonation is not simply reliant on laryngeal movement, but also relies on lips, tongue, jaw, and nasal passages.

### 1.2.1 Vocal fold movement

The vibrations of the vocal folds are passive and represent the basis of the aerodynamic theory of sound production. Vibration of the vocal folds changes direct current airflow into alternating airflow, converting aerodynamic to acoustic energy. This is aided by movement of intrinsic and extrinsic laryngeal muscles, which shape and change the tension of the glottis during phonation. The laryngeal muscles are capable of a great degree of control, due to a high number of nerve cells. The laryngeal muscles contract around 100 to 200ms before the onset of phonation.[12]

The vibratory cycle is described as having three phases: opening, closing, and closed. The cycle begins with the vocal folds closed. The lateral cricoarytenoids and intercartilaginous muscles are contracted, which keep the folds closed (adducted). During the opening phase, the subglottic pressure increases, overcoming the muscular adduction, and forces the vocal folds apart from inferior to superior edges until the glottis opens. Air escapes and releases the subglottic pressure. Contraction of the posterior cricoarytenoid muscles aids the vocal folds to move apart (abduction).

The vocal folds will close if the adductive tension of the folds is sustained. In addition the rapid closure is aided by the physical process known as the ‘Bernoulli Effect’. This is the forcing of air from a region of high to low pressure through a narrow space. This creates a kinetic energy at the edge of the

space causing a negative pressure which brings the folds together.[18] This subsequently leads to a rise in the subglottal pressure and the cycle is repeated. The effect is to cause the release of a series of small amounts of air into the supralaryngeal vocal tract at a frequency of many times per second.[18]

### 1.2.2 Variations in phonation

The sound that results from phonation is due to: frequency of air release, perceived as pitch; pressure of air release, perceived as loudness; and timbre, perceived as voice quality.[18]

The frequency (pitch) depends on: vibratory mass of the vocal folds; tension of the folds; changing the size of the glottal opening; and subglottic pressure. The fundamental frequency is determined by the resting length of the vocal cords, which varies with age and sex. The frequency range of humans is from 60 to 500Hz, with an average of 120Hz in males, 200Hz in females and 270Hz in children.[21] Variations in frequency are determined by the relationship of the length, tension and thickness of the vocal cords. An increase in the length of the vocal cords, or an increase in tension in the cords causes the frequency (pitch) to rise. The actions of the cricothyroid, posterior cricoarytenoid and vocalis muscles lead to changes in length of the vocal cords. Inflamed and swollen vocal cords are thicker than normal and result in a hoarse voice. At puberty, growth of the thyroid cartilage in males lengthens the vocal cords and lowers the fundamental frequency. During panic the vocal cords may be tensed causing a high pitched squeek.

The greater the pressure of air against the vocal cords, the louder the sound. This is performed by changing the opening period of the glottis. The energy from the airstream is then used by other parts of the vocal tract to generate sound, normally by constricting or stopping the airflow. The perceived character of sound created is largely related to resonation through the supraglottic vocal tract, including the pharynx, tongue, palate, oral cavity, and nose.

### 1.2.3 Voice disorders

'Voice' is the acoustic output from the vocal tract that is characterized by their dependence on vocal fold vibration [22]. Voice disorders or dysphonia refer to breakdowns of phonation, which may be due to difficulties with: the air pressure system; the vibratory system; or the resonating system (vocal tract). A problem with the air pressure system would include an ineffective expulsion of air out of the lungs. This would lead to a weak voice and can be further affected by shortness of breath. This may be caused by lung disease, such as asthma, lung cancer or emphysema leading to difficulties in speaking loudly or for long periods of time. Changes to the vibratory system leading to compromise in vocal fold vibration can cause hoarseness or other problems with voice production. For example, swelling of vocal folds due to common cold or other respiratory viruses can lead to hoarseness and air leak due to nerve damage to the vocal folds, preventing them from adducting, can lead to a 'breathy' voice. Further dysphonia can be caused by problems with the resonating tract including pathology of the pharynx, oral and nasal cavity.

## 1.3 Epidemiology of laryngeal carcinoma

Laryngeal cancer accounts for 1% of all new cases of cancer in males and 0.2% in females.[23] It accounts for 0.5% of deaths from cancer in the UK and is the 18th most common cause of cancer death among males in the UK. There were 2,315 new laryngeal carcinomas in 2013, 83% of these were in males. This calculates as 6.1 new laryngeal cancers for every 100,000 males and 1.2 for every 100,000 females in the UK.

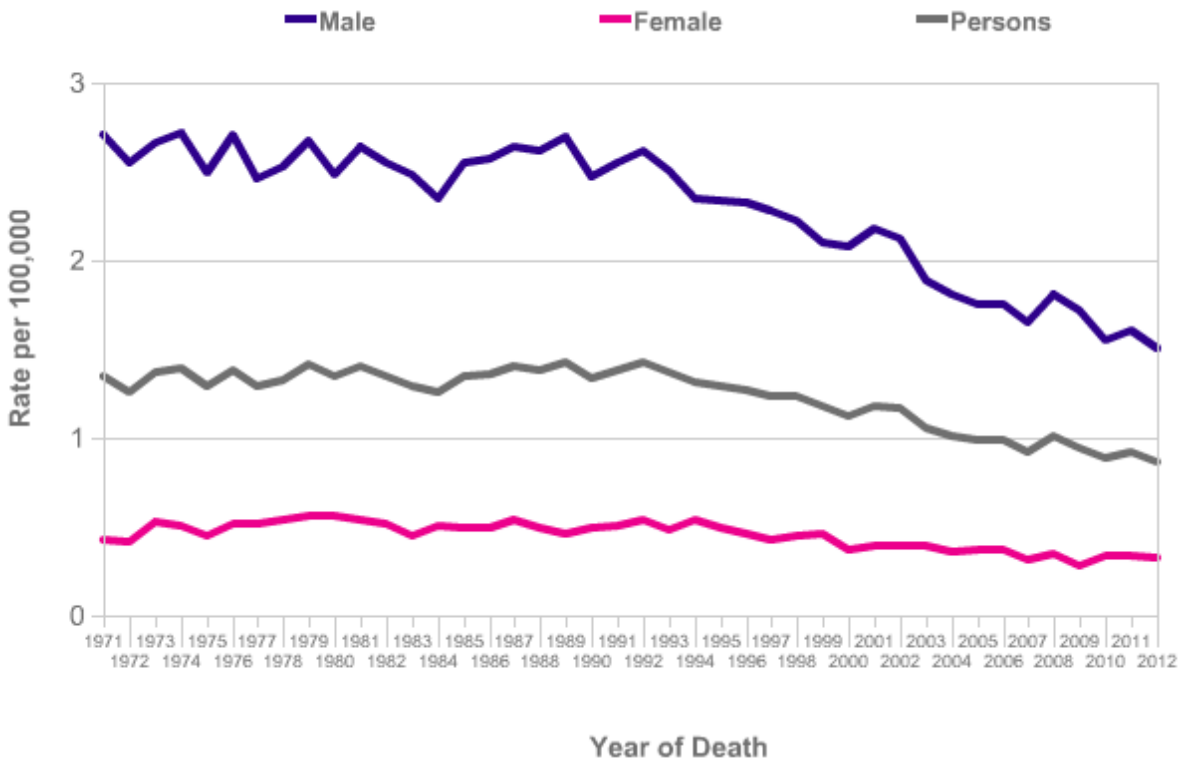
In the UK the highest rates are in parts of Scotland and northern England with the lowest rates being in southern England.[24] Throughout Europe laryngeal carcinomas are more common in males than in females although there are wide variations in the ratio of male to female. This variation is likely to reflect the differences in prevalence of smoking and alcohol consumption. There is a higher incidence of laryngeal carcinoma as age increases. In the UK between 2010 and 2012, 40% of laryngeal cancer mortality were in adults over 75 years.[23]

In the UK over the past 40 years the incidence rates have decreased in males but remained stable in females (see figure 13). The reasons for the decline in males are thought to be due to several reasons including decrease in smoking prevalence and improved diet. [25,26]

The mortality rate shows that there are 2 laryngeal cancer deaths for every 100,000 males in the UK and 0.5 for every 100,000 females.[23] The mortality rate is related to age with the highest mortality in older males and females. However there has been an overall decrease laryngeal cancer mortality rates in the UK over the past 40 years. Along with the majority of cancers the

relative survival for laryngeal caner is improving. This can be generally attributed to faster diagnosis and improvements in treatment. In general the improvements have been slow and increasing cancer survival remains a priority and there are national strategies to improve this including a national awareness campaign.[27]

**Figure 13: Laryngeal cancer (C32), European age-standardised mortality rates, UK, 1971-2012**




*Source: Cancer Research UK*[23]

More than 90% of laryngeal cancers are squamous cell carcinomas (SCC). There are a number of risk factors for squamous cell carcinoma. It is

associated with tobacco and excess alcohol use. Cigarette smoke in particular is the major risk factor but alcohol excess has been demonstrated to have an additional carcinogenic effect [25,28]. Other risk factors have been identified, including human papilloma virus (HPV)[29], gastro-oesophageal reflux and toxic inhalations (such as asbestos and mustard gas)[30]. There is a wide range in the reported incidence of HPV positive patients in the larynx. A systematic review of 1712 cases(by Isayeva et al. in 2012) has shown it to be up to 23.6%.[31] Although a study in our region (by Upile et al. 2014) assessing the rate of HPV positive patients in tumours outside the oropharynx showed the HPV rate to be only 3.2% in the larynx compared to 70% of tumours in the oropharynx.[32] SCC has been found to be more prevalent in low socioeconomic groups, likely due to these risk factors.[33]

The presenting features of laryngeal carcinoma include dysphonia, impairment in swallowing (dysphagia), coughing of blood originating from the respiratory tract (haemoptysis), neck mass, aspiration (inhalation of gastric or oropharygneal contents into the lower airway), pain when swallowing (odynophagia), ear pain (otalgia) and airway compromise.

Laryngeal cancers most commonly arise from the true vocal folds or the glottis. The majority of these patients present early with normal vocal cord movement, no lymph node involvement or extension beyond the larynx.

Due to the fact that minimal change in the vocal cords will result in voice change, patients often seek attention in a timely manner and laryngeal cancers are often picked up at an earlier stage. Up to three quarters of patients present early, with mobile vocal folds, no nodal involvement or extension beyond the larynx.[34] Early stage laryngeal SCC is characterised

by low tumour volume and low rate of regional metastasis. This is partly due to the poor lymphatic drainage from this area. For these reasons early laryngeal SCC has a relatively high chance of cure and low chance of metastatic spread.

The TNM (tumour, node, and metastasis) classification is used for the staging of laryngeal carcinoma (see table 1). This has been classified by the American Joint Committee on Cancer (AJCC, seventh edition, 2010).[35] The larynx is subdivided into three anatomical regions for classification of the tumour site: supraglottis, glottis and subglottis. The glottis includes the true vocal cords as well as the anterior and posterior commissure. According to the AJCC the superior boundary of the glottis is a horizontal line through the apex of the laryngeal ventricle and the inferior boundary is 1cm below this line.[35] Glottic T1aN0M0 are tumours confined to one vocal cord with normal mobility, no metastases to cervical lymph nodes and no distant metastases. T1bN0M0 involves both vocal cords but there is still normal mobility. In T2N0M0 the tumour extends to the subglottis and/or supraglottis and/or with impaired vocal cord mobility.

**Table 1: TNM Staging of Glottis carcinoma**

| Glottis | |
|---|---|
| **T1** | Tumour limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility. |
| **T1a** | Tumour limited to one vocal cord. |
| **T1b** | Tumour involves both vocal cords. |
| **T2** | Tumour extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility. |
| **T3** | Tumour limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage. |
| **T4a** | Moderately advanced local disease. |
| | Tumour invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or oesophagus). |
| **T4b** | Very advanced local disease. |
| | Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures. |

*Source: Reproduced from AJCC, seventh edition, 2010.*[35]

The laryngeal cancers can also be classified into stages, with Stage I relating to T1N0M0 and Stage II relating to T2N0M0 (table 2).

**Table 2: Staging of Laryngeal Carcinoma**

| Stage | T | N | M |
|---|---|---|---|
| **0** | Tis | N0 | M0 |
| **I** | T1 | N0 | M0 |
| **II** | T2 | N0 | M0 |
| **III** | T3 | N0 | M0 |
| | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| **IVA** | T4a | N0 | M0 |
| | T4a | N1 | M0 |
| | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N2 | M0 |
| | T4a | N2 | M0 |
| **IVB** | T4b | Any N | M0 |
| | Any T | N3 | M0 |
| **IVC** | Any T | Any N | M1 |

*Source: Reproduced from AJCC, seventh edition, 2010.*[35]

## 1.4 Management of early laryngeal carcinoma

The aim of the treatment of early laryngeal carcinoma is to achieve survival through local control, avoiding total laryngectomy, and maintaining voice quality. In addition, quality of life, cost-effectiveness and convenience are other key aims of treatment.

The UK head and neck cancer multidisciplinary management guidelines (2011) state that early stage laryngeal carcinoma (stage I and II) can be

treated with open surgery (an external approach via a neck incision), endolaryngeal excision (removal using a scope through the mouth) or RT.[36] Endolaryngeal excision can be undertaken using cold steel resection or laser excision. There is much variation and conflict between centres and countries as to which is the optimal treatment [37], nowadays, all are accepted modalities and the reported five-year-survival following any form of treatment exceeds 85%.[34,38] However historically RT was the main treatment with good control rates and low morbidity and there was some controversy as transoral laser microsurgery (TLM) became more popular.[39]

Voice quality, cost-effectiveness and convenience are also key indicators that may influence decisions regarding optimal treatment options.

Open surgery is not commonly used in the UK for early laryngeal carcinomas due to the increased morbidity of the treatment, temporary requirement for tracheostomy and aspiration and significant dysphonia. Due to these reasons open surgery has been excluded from further discussion.

### 1.4.1 Endolaryngeal surgery

#### *1.4.1.1 Cold Steel*

Endolaryngeal surgery involves excision of the laryngeal carcinoma through access via the mouth. This can be performed with or without the use of lasers. The procedure is performed in a similar way to the laser but using cold steel dissection for removal of the tumour. Kleinsasser in Germany published a large series of his work in 1974 on endoscopic cordectomies that were performed using cold instruments.[40] However since the development and

wider availability of lasers, cold steel dissection has become a less popular amongst surgeons.

*1.4.1.2 Trans-oral laser microsurgery*

Laser is an acronym for Light Amplification by stimulated Emission of Radiation and the first working laser was built by Maiman in 1960[41]. C.K.N Patel[42] developed the carbon dioxide laser in 1963 and it was introduced into surgery soon after. In 1972, Strong and Jako in America first described using the carbon dioxide ($CO_2$) laser for resection of laryngeal cancers.[43]

Light is part of the electromagnetic spectrum and can act as an electromagnetic wave and as particle radiation (photons).[44] The energy released by electromagnetic process is known as electromagnetic radiation. This electromagnetic radiation can be classified by its wavelength into radio, microwave, visible, ultraviolet, X-rays and gamma rays. For a laser beam to produce a thermal effect, the energy contained must be converted into heat. The shorter the wavelength of an electromagnetic disturbance the more energy each photon contains.

$$E=hc / s$$

This is where energy (E) equates to the speed of the electromagnetic field (c) multiplied by the constant (h) divided by the electromagnetic wavelength (s).

The high intensity power of the laser is generated through light amplification which is made possible by forcing a large group of atoms in the optical cavity of the laser.[45] This optical cavity is created with mirrors and the atoms are

stimulated along this cavity into an excited state. Amplification of these visible light particles (photons) are reflected off the mirrors and can be emitted.

The total energy of the laser beam equates to the sum of all the single-photon energy in Joules (J). The power of a laser (watts, W) is calculated when delivering the laser beam to an area for 1 second (s).[44]

$$P=J/s$$

When the area (metres, m) the laser beam is targeting is included in the equation then the power density and energy density can be calculated. The laser power density in a single pulse = $W/m^2$ and energy density = $J/m^2$.[44]

The visible spectrum includes light visible to the human eye 390 to 700nm (nanometres). A laser emits light through amplification, however this includes not only visible light but also infrared and ultraviolet. The longer the wavelength the lower its frequency and the lower the energy of the individual photons, the $CO_2$ laser is the most commonly used in ORL-HNS surgery and has a wavelength of 10,600nm which is invisible. An aiming beam is therefore required; accordingly, a red beam from a helium-neon laser is commonly used. This wavelength (10,600nm) is at the peak of water absorption and as soft tissues are 90% water it enables concentration of energy and vaporising of tissues with minimal collateral damage. For example the AcuPulse™ (model 30 UltraPulse SurgiTouch™ $CO_2$ laser system, produced by Lumenis® Surgical, USA) has a user-defined penetration depth of 0.2 to 2.0 mm.[46]

Thus by controlling power density the surgeon can control the effects of the laser. For an accurate incision a small spot size is used with a high power density. To minimise thermal damage of surrounding tissues pulsing of the

laser can be performed which still allows a high density delivery.[47] The effects of surrounding tissues will also depend on the wavelength, power, duration and spot size of the laser (see table 3).

**Table 3: Power Density and tissue effects**

| Power Density | Effect on Tissues |
|---|---|
| 0-500 | Heating |
| 500-1500 | Contracture, denaturing |
| 1500-5000 | Ablation, partial vaporisation |
| 5000-20,000 | Incision, complete vaporisation |
| 20,000-100,000 | Rapid deep incision |

*Source: Fagan et al., TLM of cancers of and other pathology of the upper aerodigestive tract (open access atlas of otolaryngology, head & neck operative surgery [48]*

The smaller and sharper the target red spot indicates that the laser is more accurately focused. Spot sizes of 0.5mm to 0.8mm allows a good compromise between depth of focus and cutting ability.[49] Newer lasers and micromanipulators enable this to be as small as 200µm. For coagulation the laser power density is adjusted so that the tissues are heated and not vaporised. The spot size can be altered to become more diffuse and thus reducing the power density. A monopoloar suction diathermy is an alternative for haemostasis without using the laser.

Continuous wave (CW) laser creates a laser output range of energy whilst pulsed laser is the energy of a single pulse. The units of the energy are stated

in Joules (J). Super pulse (SP) is when several thousand energy bursts of high peak power laser pulses emitted per second while the foot pedal is depressed. The bursts are spaced apart and this enables cooling to reduce thermal damage to surrounding tissues.

In laryngeal surgery the laser beam is delivered from the laser via an articulated arm to a micromanipulator mounted on an operating microscope. This allows the helium-neon aiming beam (and therefore the CO2 laser beam) to be accurately focused on the target. The operating microscope also provides illumination, magnification and frees up both hands for operating. The working distance is the distance from the microscope lens to the focus point on the larynx. At a distance of 400mm there is enough space for both hands to work under the microscope. The surgery is performed at high magnification for maximum control and precision. The operating microscopes have a variable magnification and a zoom control for optimizing the view of the surgical field.

Since lasers have been introduced into surgery it has increased in popularity and is well suited for use with a microscope, allowing accurate resection and causing minimal collateral damage to normal tissue [50]. The $CO_2$ laser is commonly used in ORL-HNS for other conditions including benign laryngeal disease such as laryngeal papillomata. Papillomata regularly require numerous laser microlarynogoscopy procedures and therefore the ORL-HNS surgeon is often familiar and confident at using the laser.[47] This has improved the learning curve of TLM with many transferable skills.

Between 1979 to 1991 Otolaryngologist Wolfgang Steiner successfully demonstrated the use of lasers for endolaryngeal resection of laryngeal

tumours, rather than more traditional open surgery.[51] This has been repeated in a number of studies showing overall 5 year survival rate of more than 85% with low rates of recurrence.[51-53] There is published data, from our own department, of early and moderately advanced laryngeal cancers treated with TLM.[54] The respective 3-year local control, overall survival, disease-specific survival and disease-free survival for the cohort as a whole, were 92%, 92%, 98%, and 86 % for glottic carcinomas.

*1.4.1.2.1 Patient selection for TLM*

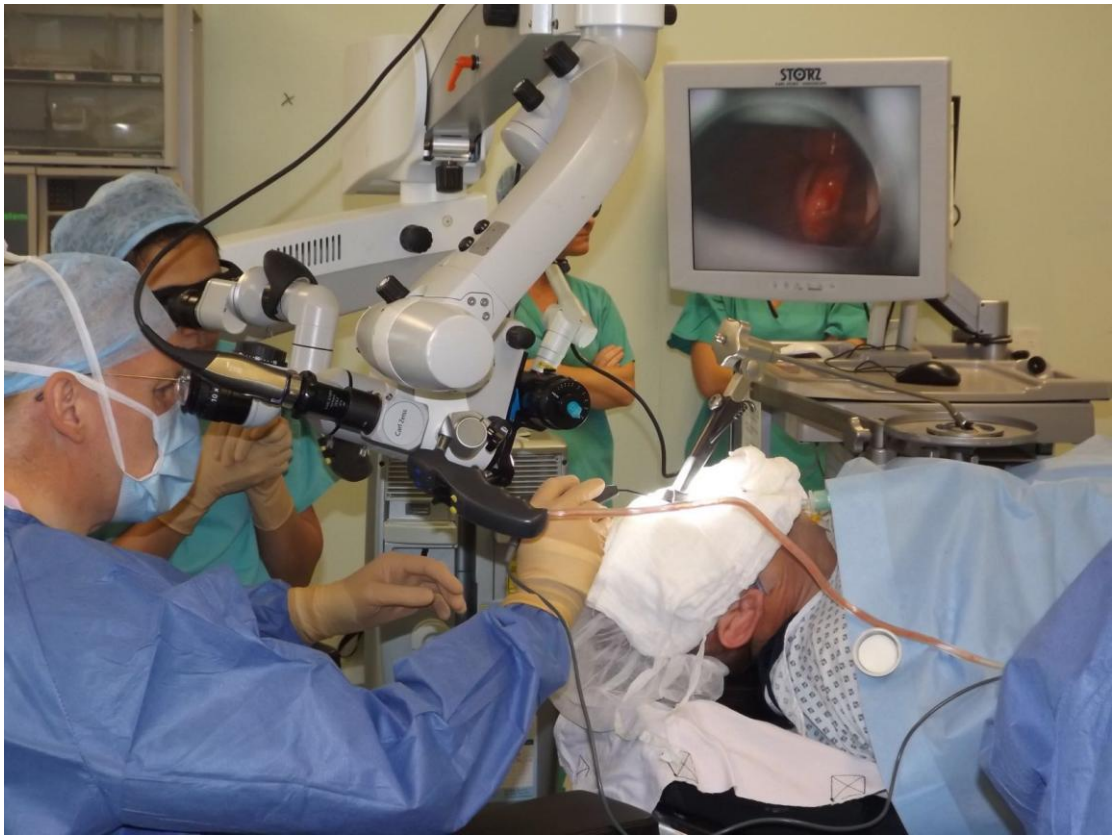
There are patient and/or tumour reasons why TLM may be contraindicated in any given patient. A general anaesthetic is required and the individual may not be suitable for surgery due to co-morbidities. Poor endoscopic access may also be a contraindication for TLM and may result from a combination of poor extension of the cervical spine, prominent incisor teeth or trismus.

Tumour-related contraindications to TLM include a tumour with poorly-defined edges. Although this may technically be possible to excise it would lead to an extensive resection which would have significant adverse effects for the patient. When the tumour is positioned at certain areas such as the anterior commissure then the access may be difficult. Also the contralateral vocal fold can be damaged if the tumour is at the anterior commissure. There is an increase risk of recurrence at the anterior commissure and for these reasons an alternative treatment may be preferred rather than laser excision. [55]

*1.4.1.2.2 The procedure of trans-oral laser microsurgery*

The procedure is performed under general anaesthesia with the patient in the supine position. Under direct laryngoscopy a conical metal endoscope, such as Steiner laryngoscope is inserted, as demonstrated in figure 14. Once the scope is in position, with a view of the larynx and the tumour, it is placed in suspension using a suspension platform which is attached to the operating table. This allows fine manoeuvres to be performed bimanually under the microscope.

**Figure 14: Microlaryngoscope with $C0_2$ laser attached**

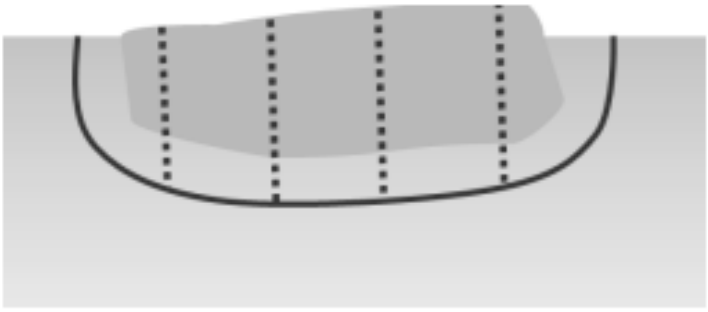



*Source: Photograph taken by author in operating theatre in AUH*

Surgical exposure is important and the patient is in the supine position with the neck extended. The operating microscope can then be focused and the laser attached so that the resection may begin. The laser settings are selected depending on the type of tissue being resected, the depth and haemostasis.

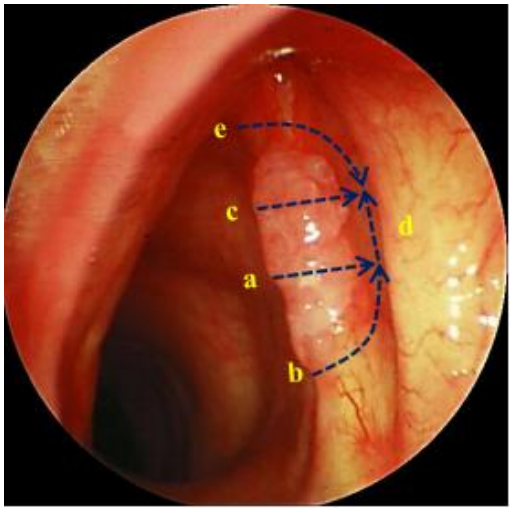
Although TLM was first described by Strong and Jako [43] in the 1970s, it was not until the work by Steiner in the 1980s and 1990s, that the laser gained popularity in the treatment of laryngeal carcinoma.[51] Rather than an en bloc resection the tumour is divided with the laser to assess the depth and the extent of invasion (see figures 15 and 16). This technique enables a minimal resection,[49] thus removing only the required amount of tissue and minimising effect on adjacent structures that may affect the voice outcome. Each individual section can be removed and pinned out. There is a constant challenge to balance adequate resection with preservation of structures. High magnification is used and where possible, the epithelium is retracted and dissected off the vocal ligament. Narrow margins (1mm) or the width of the laser have been used for many years to help preserve vocal function.[56]

**Figure 15: Tumour divided with laser to evaluate depth**



*Source: Fagan J, Open access atlas of otolaryngology, head & neck operative surgery*[48]

**Figure 16: Example of sequence of TLM incisions**



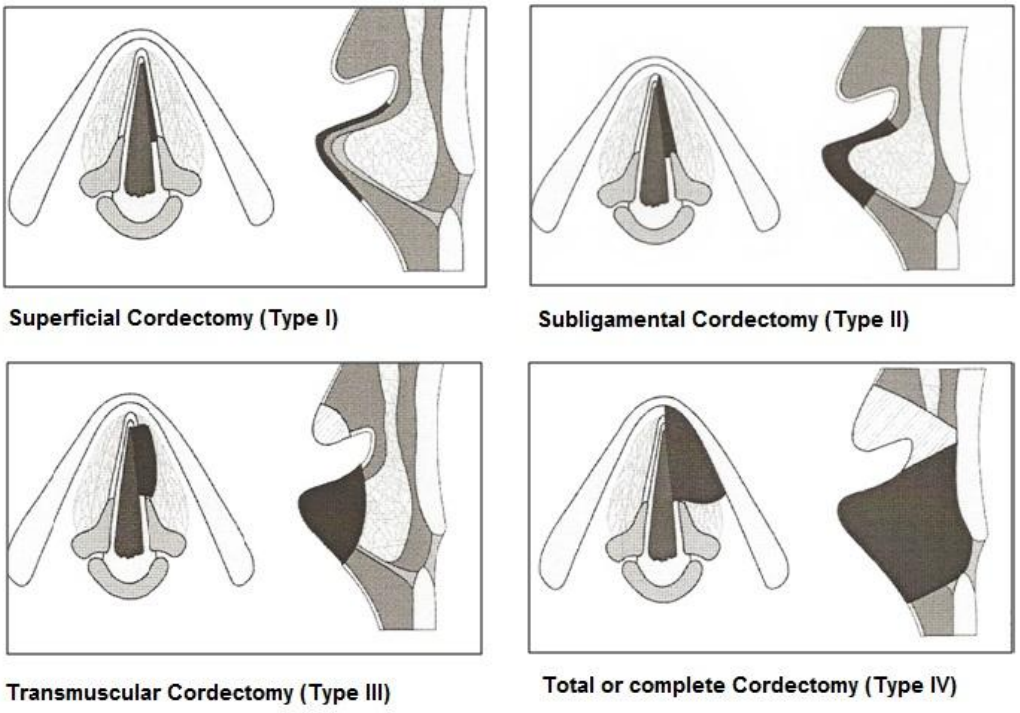

*Source: Fagan J, Open access atlas of otolaryngology, head & neck operative surgery*[48]

The European Laryngological Society has produced a classification for endolaryngeal microsurgery [57]. The classification comprises eight types of cordectomy (excision of part or all of the vocal cords, figure 17):

- subepithelial cordectomy (type I), resection of the epithelium;
- subligamental cordectomy (type II), resection of the epithelium, Reinke's space and vocal ligament;
- transmuscular cordectomy (type III), resection of above and vocalis muscle;
- total cordectomy (type IV);
- extended cordectomy (type Va), including the contralateral vocal fold and the anterior commissure;
- extended cordectomy (type Vb), including the arytenoids;
- extended cordectomy (type Vc), including the subglottis;
- extended cordectomy (type Vd), including the ventricle.

The commonest cordectomy types used for an early glottic carcinoma are types I-IV. In a study by Bocciolini et al.[58], 64 T1a glottic carcinomas were treated by TLM. The commonest type cordectomy performed was a Type III with 34 cases (53%). This was followed by 17 (27%) type IV, 11 (17%) type II and two cases (3%) requiring type V.

**Figure 17: Classification of Cordectomy (Type I-IV illustrated)**




*Source: Remarcle M et al., European Laryngological Society proposed classification of endoscopic cordectomy (2000).* [57]

The more extensive resections will be associated with more morbidity for the patient, particularly with respect to voice. The anterior commissure is another challenging area. Involvement of this area can make wide margin resection difficult and there is also the concern of cartilage invasion. The anterior

commissure may heal with scarring bridging the vocal cords (webbing). This is associated with a poor voice and can be difficult to treat. One option is to operate in a two-stage procedure. This would require a unilateral resection of the tumour and once this has re-reepithelialised to return for contralateral resection. However this generally applies to T1b laryngeal tumours which were not included in this research.

Once excised the lesion must be orientated properly and mounted to allow the histopathologist to interpret the specimen and make a comments on malignancy and completeness of excision. This is one of the advantages of TLM over RT in that the histological sample can be analysed and margins discussed in the MDT. The Glasgow technique is to mount the orientated resected tumour on dehydrated cucumber. This allows accurate assessment of histological margins by enabling the entire specimen to be processed intact.[59] There is a risk of residual disease in patients with close (<1mm) or involved margins.[60] The consensus document on TLM in early glottic cancer states that if the surgical margins are clear but the histological margins are involved then a repeat microlaryngoscopy is recommended in 6-8 weeks.[61] Peretti et al. [62] argued that surveillance post treatment may be easier following TLM due to decrease in oedema and mucousitis associated with RT. More recently narrow band imaging (NBI) has been performed to improve detecting early mucosal lesions as well as delineating the tumour intraoperatively.[63] NBI is an optical technique that adds narrow band spectrum filters onto the endoscope to enhance the mucosal abnormalities. Along with a high definition screen this will continue to improve diagnosis of early glottis carcinomas and assess for recurrence.[64]

Normally the patient is discharged the same day but occasionally requires an overnight stay. This may depend on co-morbidities and the effects from the general anaesthesia.

Following surgery the pathology is reviewed in the multidisciplinary team (MDT) Head & Neck meeting. If there are involved margins or marginal biopsies then a decision will be made for either a second look in 6-8 weeks time or further excision.[61]

There are possible complications from TLM. Early complications of laser surgery include dental/gum injury, sore throat and lingual nerve injury. This is due to pressure and traction from the endoscope to gain good visualization of the larynx. A mouth guard is used as standard to protect the teeth and sore throat usually settles after a few days. There is the risk of voice change and this will be covered further in section 1.4.3.2 (comparison of voice outcomes between the two modalities) and voice rest is advised for 48 hours post surgery. Although rare there is also a risk of bleeding, airway obstruction, aspiration, laser burns and airway fire. Later complications include incomplete resection, granuloma, webbing and chondronecrosis. Granuloma and chondronecrosis may occur when cartilage has been exposed.

### 1.4.2 Radiotherapy

Following the discovery of x-rays by Wilhelm Röntgen in 1895 and radium by Marie Curie in 1898, speculation began as to whether radiation could be used as a treatment or therapy for many different ailments from tuberculosis to

malignancies.[65] A French radiation oncologist Henri Coutard pioneered the use of fractionated RT in a variety of tumours. In 1934, Coutard published a paper including a series of 126 patients with laryngeal cancer treated from 1920 until 1930 with RT.[66]

By the 1950s advances in radiation therapy allowed less advanced laryngeal tumours to be cured without sacrificing the voice.[67] A review of the literature in 1970 by Vermund[67] showed the 5 year survival to be about 80% with either RT or surgery (including laryngofissure or cordectomy surgery) for T1N0 glottic carcinomas. Due to the preservation of voice, RT became the preferred choice across the Developed World for the treatment of early laryngeal tumours.[68,69]

There have been many advances in the delivery of RT since its inception. Recently it has greatly improved due to advances in cancer imaging, treatment planning computer software and developments in radiation delivery technology.[36] The treatment is delivered by computer driven linear accelerators with sub-millimetre accuracy and therefore minimising radiation to healthy tissue. The development of intensity modulated radiation (IMRT) over the past decade has continued to improve RT. IMRT matches the dose to the target in 3 dimensions and thus reducing the volume of normal tissues receiving high doses and the potential side effects.

RT works by damaging DNA of cancerous cells and this damage is caused by energy from photons or charged particles. Radiation-induced apoptosis also results from radiation damaging the plasma membrane. The three separate pathways that may result from DNA damage are cell cycle arrest, DNA repair and apoptosis. This outcome depends on the time of the cell division and the

tissue structure. Cancer cells which divide more rapidly will thus show more effects than cells with a slower division.[22]

RT traditionally has been delivered in divided doses. A single delivered dose of radiation is known as a fraction. Traditionally, RT is delivered in daily fractions, five days a week. Although this fits the typical working week there is evidence from the Danish head and neck cancer group (DAHANCA) that shortening the overall treatment time by increasing the weekly fraction is beneficial. [70] There was no overall survival but disease-specific survival improved and now in Denmark, RT for SCC of the Head and Neck is delivered in six-fractions per week.

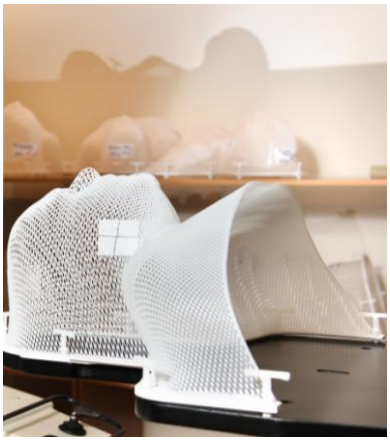
The reasons for fractionation are to allow normal cells time to recover between treatments and for RT to act on tumour cells in different stages of their cell cycle. The Royal College of Radiologists' Faculty Board of Clinical Oncology states that there is no single regimen of treatment delivery that will be appropriate for all tumours in all patients.[71] The dose of radiation used in photon radiation therapy is measured in Gray (Gy). The generally accepted fractionated regime has developed over many years and is typically 1.8-2Gy, total dose of 60-70 Gy, over 6.5-7 weeks. There is evidence, Le et al. [72], that a daily fraction rate of 1.8Gy for T1a glottis carcinomas gives a local control of 79% compared to a control rate of 94% with a dose >2.25Gy per day. However it is possible to treat with 1.8Gy by treating for more than 5 days per week.[73] The UK Head and Neck Cancer multidisciplinary management guidelines recommend hypofractionated RT schedules, using a fraction size greater than 2Gy, which results in equivalent outcomes to longer schedules, without increased toxicity.[36]

The recommendations from the Royal College of Radiologists is that patients with Stage I or II laryngeal cancer can be treated with either short or conventional regimens [71,74]:

- 64-70Gy in daily 2 Gy fractions over 6.5-7 weeks
- 54-55 Gy in 20 daily fractions over 4 weeks
- 50-52.5 Gy in 16 daily fractions over 3 weeks (small volume only)

Patients are treated in the supine position in an immobilisation fixation device such as a perspex or thermoplastic shell (figure 18). The spine is kept straight and the shoulders are fixed in the thermoplastic shell.[75] To allow lateral radiation beams, the shoulders are fixed as inferiorly as possible.

**Figure 18: Thermoplastic shell**

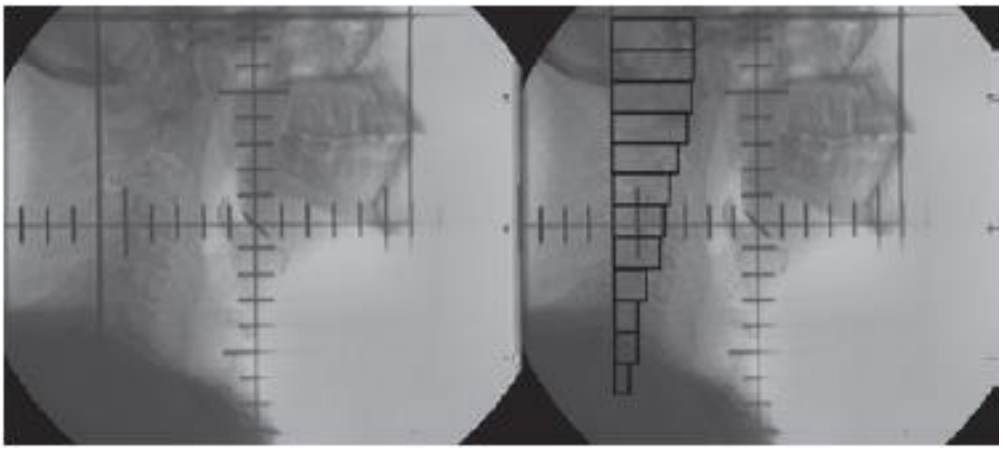


*Source: Adobe stock images*[1]

A simulator is used to plan the RT dosage to maximise tumour treatment and minimise toxicity of adjacent normal tissues. At the time of conducting this study, the method of RT was that opposing lateral beams were set with superior boundary being the mid body of the hyoid, inferiorly the inferior border of cricoid cartilage, anterior to skin and posterior anterior vertebral

column (see figure 19). In recent years IMRT has gained popularity in head and neck cancer by reducing unnecessary radiation to neighbouring healthy tissue. Recent studies have shown that IMRT to be comparable with conventional RT in local control and survival.[76]

**Figure 19: Simulator film showing lateral portals in relation to bony landmarks before and after spinal cord shielding**



*Source: Murthy et al., Postoperative Radiotherapy in Head and Neck Cancer. Otorhinolaryngology clinics, open access (2010).* [77]

The benefit of radiation is that it avoids risks associated with surgical intervention, such as bleeding and infection, and historically has been considered to result in better voice outcomes.[68] It is generally well tolerated with few severe adverse effects.[74] In a series of T1-T2 glottic carcinomas treated with RT there were no reported severe adverse effects or acute complications.[78] Severe complications were defined if a treatment break resulted.

Voice change is expected and will depend on the position of the tumour.

Most patients towards the end of treatment will develop some skin changes. This can vary from the neck feeling tight and uncomfortable, itchy, erythematous to skin breakdown. Other side effects include mucositis (inflammation of the lining of the throat), odynophagia, hair loss from the neck and laryngeal swelling (oedema). Dry mouth (xerostomia) is common risk of RT to the head and neck but is prevented by using the protective shell to shield the salivary glands. Most of these effects resolve 4–6 weeks after completion of treatment. More unusual complications would include oesophageal stricture, laryngeal fibrosis, chondronecrosis and hypothyroidism although these are extremely rare following RT for a glottic carcinoma. Should tumour recurrence occur then surgery would be necessary. The salvage options would include TLM, partial laryngeal surgery or total laryngectomy.

### 1.4.3 Comparison of laser and radiotherapy

There are a limited number of randomised controlled trials comparing the treatment options of early laryngeal SCC. The UK EaStER (Early Stage Glottic Cancer Endoscopic Excision versus Radiotherapy) trial outlines the difficulty in conducting a randomised controlled trial in this area.[79] The EaStER feasibility trial was approved for funding in 2004. The aim of the study was to evaluate the outcome of patients treated with either endoscopic excision or standard RT. The trial included Tis, T1 and T2 laryngeal carcinomas and compared the treatments of TLM and RT. The primary outcome was local regional recurrence and secondary measures included voice quality, quality of life, morbidity, mortality and cost effectiveness.[80]

Patients were randomised 1:1 to receive either TLM or RT. The RT doses were 50Gy for Tis and (non bulky) T1 tumours. A dose of 55 Gy was given for bulky T1 and T2 tumours. However due to recruitment failure to enlist adequate numbers, the trial was closed down in 2009. An investigation into the reasons for poor recruitment was undertaken and found many issues.[79] These issues included surgeons and recruiters did not all accept the primary outcome as the rationale for the trial. The equal success of the treatments meant that surgery was often preferred because of its convenience and in some centres there were logistical issues preventing recruitment.

*1.4.3.1 Oncology results*

The Cochrane collaboration review comparing RT and endolaryngeal surgery (with and without laser) was performed in 2002 and updated in 2004, 2007, 2010 and 2014. The most recent review includes research up to September 2014.[81] Four randomised control trials [82-85] comparing surgery and RT were identified although they excluded all but one of these due to inadequate numbers, lack of specification of randomization or staging data. There were limitations of the one trial included by Ogoltsova 1990[82] and was rated as having a high risk of bias due to missing data and selection bias. The Cochrane authors concluded that “for patients with early laryngeal cancer there remains uncertainty as to the comparative benefits and societal costs of different treatment modalities.” The limited number of studies that were identified by the Cochrane review illustrates the limitation of high quality comparative studies.

The randomised controlled trial by Ogoltsova 1990[82], indicated an improved result with surgery regarding mortality and control of local disease. This trial included both T1N0M0 (n=111) and T2N0M0 (n=158) patients. The five year survival was 91.7% following RT and 100% following surgery. The five-year loco-regional recurrence was 71.1% following RT and 100% following surgery. However the number of patients in comparator arms was unbalanced with 76 patients having surgery compared to 126 having RT.

Cochrane only include randomised controlled trials in their reviews. Therefore there are likely to be a significant number of other relevant studies that have been excluded. Higgins et al. performed a systematic review and meta-analysis in 2009 including all published studies comparing the oncological outcomes of TLM and RT for early glottic carcinoma.[86] They identified 26 studies of which six were direct comparisons of the two treatments. There was no statistically significant difference in local control between the treatment types, OR 0.81, 95% CI 0.51, 1.3 (p=0.38).

Laryngeal preservation refers to maintaining a functioning larynx and avoiding a total laryngectomy. This can include performing partial laryngectomies (either endoscopic or open)[87] but avoiding the more radical total laryngectomy. A total laryngectomy is reserved for salvage surgery following failed treatment although is more relevant for larger laryngeal tumours. Laryngeal preservation, following TLM treatment for early glottic carcinoma is over 90%.[88,89] Steiner [90] reported a laryngeal preservation rate of 97% following TLM with only 8 patients out of 158 (5%) requiring a total laryngectomy. Johansen [91] reported a 89% laryngeal preservation following RT for T1a laryngeal cancer and Schrijvers [88] reported 77% laryngeal

preservation after RT. A reason for this higher rate of preservation in the TLM patients is that if recurrence occurs after endolaryngeal surgery, there is the option of further TLM or RT.

Local control of disease and other treatment outcomes will also depend on the location and size of the tumour. Tumours involving the anterior commissure have a higher risk of recurrence.[92] This may be due to a number of different reasons; as access to this area for TLM can be more challenging and there is a concern about excising excess tissue which may affect voice outcome due to webbing or scarring.

*1.4.3.2 Comparison of voice outcomes between the two modalities*

Although both TLM and RT are likely to affect voice quality, historically RT has been thought to have better voice outcomes than laser resection.[39] However more recent studies have shown similar voice outcomes when comparing laser and RT.[93-95]

The studies published have used different methods of comparing voice outcomes. The most common methods include self-evaluation of voice (self reporting questionnaires), voice quality perceptual ratings, aerodynamics, acoustic analysis and videolaryngostroboscopy. The European Laryngological Society (ELS) has produced a protocol in attempt to standardise functional voice outcomes and to allow comparison of the literature.[96] However the majority of these tools are subjective with no actual or objective method available.

*1.4.3.2.1 Self-evaluation of voice*

There are number of different self reporting questionnaires used to evaluate voice. These include the VHI (Voice Handicap Index)[97], VoiSS (Voice Symptom Scale) questionnaire [98], Vocal Performance Questionnaire (VPQ)[99] and VRQOL (voice related quality of life).[100] In terms of voice questionnaires the VHI is the most commonly used (Appendix 2). Two versions exist - a 10 or 30 item self reported scale. A meta-analysis by Cohen [93] in 2006 assessed six studies comparing TLM against RT and the results demonstrated no statistically significant difference in the VHI between the two treatments. The six studies compared 202 T1a laryngeal carcinoma patients treated with TLM and 91 patients treated with RT. The VHI was chosen as it is the most common self reporting instrument used. The post VHI scores showed no statistically significant difference between the two treatment groups. Only one study, Peretti et al., included pre-treatment VHI scores.[101] This study found the average VHI pre-treatment to be 22.9 (range 0-80) and the post treatment mean scores were 6.23 (type II cordectomy), 16.5 (type III cordectomy), 15.8 (type IV cordectomy), 15.7 (type V cordectomy). The authors found that the mean VHI score doubled comparing type II cordectomy compared with more extensive resections. The VRQOL was assessed in a comparative prospective study by Oridate et al. [95], comparing 34 RT with 23 TLM for treatment of T1 glottic cancer. This study failed to find a statistically significant difference between the treatment modalities. The average social/emotional scores were 93.9 (RT) vs. 96.3 (laser), p=0.66; and physical scores were 91.6 (RT) vs. 90.0 (laser), p=0.82.

*1.4.3.2.2 Perceptual rating of voice*

Voice recordings can be analysed via a number of methods. Hirano's[102] GRBAS (grade, roughness, breathiness, asthenicity, strain) scale is one of the most popular scales used in both the literature and in routine clinical care.[103] Each domain is rated 0 to 3 in which 0 is normal, 1 represents a slight voice problem, 2 moderate and 3 is severe. This has been shown to be a reliable test but depends on an expert rater to make it reliable and reproducible.[104] Sjogren et al. [94] compared voice quality in 16 patients who had RT to 18 who had TLM for treatment of T1a glottic carcinoma. The GRBAS system was used to perform perceptual analysis following treatment. Although a small group, all the TLM patients had type I or II cordectomy. The results revealed the voices of 50% of both groups to be rated as dysfunctional. The RT group showed mixed pattern of roughness and breathiness whilst the post-TLM voices had higher breathiness scores. Over all there was no statistically significant difference between the very small groups. Rydell [105] et al. compared 36 patients (18 TLM and 18 RT) and found voice outcomes statistically significantly better in the post RT group compared to the TLM group. The results revealed decreased breathiness, asthenia and strain scores in the irradiated group. However Loughran et al. [106] also assessed voice outcomes in 18 patients on each treatment arm. The GRBAS assessment showed no difference between groups in any of the subscales.

Peretti et al. [107] and Vilaseca et al. [108] not surprisingly, found worsening GRBAS with more extensive laser cordectomy. In the Peretti study the TLM patients underwent types I-V cordectomy. The GRBAS scores were higher as the extent of cordectomy increased. Types I and II cordectomy patients had

the lowest score, of less than 1, for all subscales. Vilaseca et al. performed voice outcomes on 42 males following TLM including 35 patients with T1a glottis carcinoma. The patients had different types of cordectomy and the GRBAS score was higher with the more extensive cordectomy. Sixty-six percent of type I cordectomy patients had a normal perceptual voice analysis (the GRBAS score of the TLM patients were compared to a control group). Only a quarter of patients with more extensive resections involving muscle or anterior commissure had normal voice outcomes.

1.4.3.2.3 Aerodynamic analysis

The most common type of aerodynamic analysis is Maximum Phonation Time (MPT). This involves producing a prolonged sound (/a/) for as long as possible after maximum inspiration and at a comfortable volume and pitch. The result used is the best time in seconds over three attempts.[109] It is susceptible to bias due to the differing size of lungs as well as a fatigue effect. Tamura et al. [110] comparing 10 TLM patients with 5 RT patients found similar MPT in both groups. Sjogren et al. [94] in a cohort study found no statistically significant difference in MPT in 18 patients after laser cordectomy compared to 15 post RT patients. Mendelsohn et al. [111] collected data at different time periods on 11 patients undergoing TLM for T1 and T2 glottic carcinoma patients. The voice outcomes pre-operatively were compared to post-operative period of 4 months and more than 6 months. MPT showed substantial decrease in the initial postoperative period. The MPT did improve post-operative (as the soft tissue recovers) but did not return to pre-operative levels. However in this

group of patients there was a more extensive cordectomy (type III, IV and V) and also seven patients with T2 glottic carcinoma were included.

*1.4.3.2.4 Acoustic analysis*

Acoustic analysis of the voice signal is another method of assessment that provides an evaluation of sound and physical properties of voice. Acoustic analysis measures different characteristics of the sound waveform. The most common parameters collected are fundamental frequency, shimmer, jitter and noise-to-harmonic ratio (HNR) and will be discussed in more detail in section 1.5.5. Many studies using acoustic analysis have focused only on sustained isolated vowels (such as /a/); asking the patient to hold the pitch and loudness as constant as possible. A major downside of this technique is that it involves production of prolonged vowels which are not representative of connected speech.[112] Sjogren[94], McGuirt [113] and Tamura [110] found no significant statistical difference in the acoustic analysis between the two groups treated with RT or TLM. Sjogren et al. [94] analysed the voice outomes of 16 RT patients and 18 TLM patients using the mid section of a prolonged vowel recording. The Jitter %, fundamental frequency and shimmer % in the RT group were marginally higher than the TLM group but not found to be statistically significant. McGuirt et al. [113] compared 13 patient treated with RT compared to 11 treated with TLM for T1a glottic carcinoma. There was no statistically significant difference in either acoustic parameter between the two groups.

Tamura et al. [110] comparing 22 patients having laser surgery with eight patients treated with RT assessed fundamental frequency, Jitter, Shimmer

and HNR post treatment. The scores of all these parameters were similar in both groups.

Wedman et al. [114] measured the Jitter, Shimmer, fundamental frequency in nine RT patients and 15 TLM patients treated for T1a glottic carcinoma. There was no statistically significant difference in the groups.

Van Gogh et al. [115] assessed voice outcomes before and up to 2 years after treatment in 67 TLM patients and 39 RT patients. Using prolonged vowels, average fundamental frequency, jitter, shimmer and normalized noise energy (NNE) were analysed. In the TLM group there was an improvement in the NNE, jitter, shimmer and fundamental frequency at 3 months compared to pre-treatment. The jitter and shimmer scores were better in the TLM group at 3 months post-operatively compared to the RT. The RT patients took longer for the jitter, shimmer and NNE to become normal. The fundamental frequency was higher in the TLM group compared to the RT patients. This was the only long term difference between the two groups. This increase in fundamental frequency is thought to be due to increased stiffness of the vocal cords due to scar tissue formed following TLM. In addition, it was noted that there was an increase in the fundamental frequency in both groups pre-operatively compared to a normal cohort. This is thought to be due to the tumour causing increased vocal fold stiffness. Agarwal et al. [116] when analysing patients undergoing RT for early glottic carcinoma also noted the elevated fundamental frequency before treatment. The tumour can also cause a decrease in HNR due to an incomplete closure of the glottis and escape of air through the glottic gap.

*1.4.3.2.5 Videolaryngostroboscopy*

Peretti [107] assessed voice a year after laser cordectomy with a videolaryngostroboscopic examination. This was performed in clinic using a $70^0$ rigid endoscope and the movement of the vocal folds were evaluated by a panel of otolaryngologists and speech therapists using the rating system by Sittel.[117] There was no mention of whether the raters were blinded to the different treatment arms. They found the 89% (16 out of 18 patients) of patients with type I and II cordectomy to have complete glottic closure.

The amount of tissue excised with the laser and/or the extent of the cordectomy is related to the voice outcome. Hirano [102] emphasised the importance of preserving the vocal fold's lamina propria to reduce scarring.

Wedman [114] demonstrated no difference in mucosal waveform in 24 patients who had either RT or TLM for T1a laryngeal cancer. The stroboscopy showed excellent movement in both groups with only minor irregularities visible. There was no difference in symmetry or glottis closure between the groups. Roh et al. [118] from South Korea assessed 85 patients with T1 glottic carcinomas treated with TLM. Different cordectomies were performed depending on the position and extent of the tumour. The patients were divided into three groups depending on the extent of the surgery: type I and II cordectomy (group A), type III or IV cordectomy (group B) and extended type V cordectomy (group C). Video strobolaryngoscopic recordings were evaluated pre and (median of 20 months) post-operatively. Videostroboscopic examination revealed larger glottis gaps, scarring and decreased mucosal wave in groups B and C. Certainly, as might be predicted, the larger the tumour and the greater the surgical cordectomy the worse off the voice will be.[108]

Peretti et al. [107] concluded that, if oncologically possible, preservation of the anterior commissure and most of the vocalis muscle will help preserve the voice comparable to controls. It follows that the taking of as narrow as possible margins around the carcinoma during laser cordectomy [56] will help to preserve normal tissue and help preserve vocal function. Therefore type I and II cordectomies which are subligamentous and preserve muscle will have better voice outcomes.

*1.4.3.3 Health-Related Quality of Life (HRQoL)*

The comparison of health related quality of life following treatment with either RT or TLM has been performed for early glottic carcinomas. Smith [119] and Stoeckli [120] compared the HRQoL between RT and endoscopic laser surgery for early glottic cancer and found no statistically significant difference between the treatment modalities. Stoeckli assessed quality of life (QoL) using two validated questionnaires the European organization for research and treatment of cancer, quality of life questionnaire core 30 (EORTC QLQ-C30) and the head and neck specific EORTC QLQ-H&N35. He found a negative impact of RT on the ability of swallowing solid food and xerostomia. Whilst Smith [119] assessed quality of life using a revised version of the University of Washington Quality of Life Questionnaire version 4 (UW-QoLv4) and the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN). Peeters [121] also did not find any difference between functional health status using the COOP/WONCA charts between RT and TLM. These functional assessment charts COOP/WONCA (Care Co- operative/World Organization

of Colleges, Academics and Academic Associations of General Practicioners/Family Physicians) are also validated in the assessment of quality of life.[122]

*1.4.3.4 Cost*

In the current climate within the National Health Service in the United Kingdom, cost implications are more important than ever before and with two different treatments showing similar good local control then health care trusts may be justified in considering the cost implications. Goor [123] and Brandenburg[124] demonstrated that there is a vast difference between the two treatments with RT being much more expensive (table 4). Smith[119] also outlines societal costs including patient travel, days of work missed, and impact on quality of life. Goor et al. averaged costs over three stages: the diagnostic, treatment and follow up in TLM and RT patients. RT had higher costs of €8322 during the treatment stage due to an average of 23.4 sessions compared to TLM costs of €4434.

Brandenburg et al. [124] averaged three patient bills per procedure for carcinoma in situ and T1 glottic carcinoma treated with TLM or RT. RT was found to be $27460 more expensive than TLM. Myers et al. [125] calculated an average of 10 patient bills per procedure for T1 glottic carcinoma. They found that in 1992 TLM cost $12,956 compared to $32,588 for RT. Foote et al. [126] based in the Mayo Clinic estimated costs from surgery and RT by totalling billing fees (from 1995) with the appropriate procedure. Also outpatient and inpatient costs were included. Due to separate fee schedules in different

areas and some patients having medical insurance a proportional value was calculated. This found that TLM to be 100 healthcare charge while RT would be 137. Adding extra cost including inpatient stay and outpatient appointments the median charge for TLM was a health care charge value 174 and RT and RT 409.

Part of this additional cost is due to the number of appointments required for RT. RT patients require an average of 35 treatments, with three times as much time off work.[119]

**Table 4: Publications summarising costs of RT and TLM for early laryngeal carcinoma**

| Author | Year of Publication | Number of patients RT | Number of patients TLM | Average Costs RT | Average Costs TLM |
|---|---|---|---|---|---|
| Myers [125] | 1994 | 25 | 25 | $32588 | $12956 |
| Foote [126] | 1997 | 57 | 106 | 409 (proportion no unit) | 174 (proportion no unit) |
| Brandenburg [124] | 2001 | 41 | 30 | $ 29353 | $ 1893 |
| Goor [123] | 2007 | 35 | 54 | € 8322 | € 4434 |

Although these cost related studies have been performed in different countries and different health care systems the overall conclusion is that TLM is a cheaper treatment modality compared to RT. However the cost is only a relevant aspect if local control, morbidity, laryngeal preservation, voice quality and health related quality of life are comparable.

## 1.5 Measurements of voice quality

When comparing the impact of different treatment modalities on laryngeal function, voice outcomes are important and there are many methods to measure voice quality. There have been attempts to standardize voice outcomes to enable comparison of the literature.[96] This would enable comparison of different phonosurgical techniques. Guidelines from the European Laryngological Society (ELS) have recommended a set of assessments to be considered.[127] There are three main areas in which voice quality is measured:

1. Subjective self evaluation of voice
2. Perceptual rating of voice
3. Objective/instrumental measures

Perceptual ratings of voice and self-assessment (subjective) questionnaires are the most common tools used in the clinical and research setting. There are recommended methods in how to acquire a voice sample for analysis and electroglottography is another method of acquiring vocal fold activity. The objective measures include acoustic analysis, aerodynamics and videostrobscopy. They are often referred to as instrumental methods as there are such variations in the measurements. However, in addition to the above, there are other methods of assessment of voice that are not commonly used and will not be covered further. These include digital high-speed pictures where multiple images of the larynx are recorded and played back at a slower rate. Another imaging technique for assessing vocal fold movement is high-

speed single-line scanning (video-kymography).[128] In this method a video recording of the larynx focuses on a single line and monitors it at high speed.

### 1.5.1 Self-evaluation of voice

Well-designed and validated patient reported questionnaires are important as they inform us of how the voice affects the patient in everyday life. It is the patient that has to live with their voice and the effect that it has on them and therefore it can be argued, that the patient is the most important assessor of voice quality. It is important to appreciate however, that social and cultural differences are likely to be relevant when considering voice quality. The main aim of any voice assessment is to assess the variation of voice quality, the severity of disability and effect on quality of life. There are a number of different questionnaires which have been developed in an attempt to do this. These include: Voice Handicap Index (VHI), Voice Symptom Scale (VoiSS) and Voice Performance Questionnaire (VPQ). These questionnaires were all developed in different ways but have been validated and assessed for reliability and reproducibility (test-retest reliability).

#### *1.5.1.1 Voice handicap index (VHI)*

Jacobsen et al. developed the Voice Handicap Index (VHI) in 1997.[97] A handicap as described by the World Health Organization is a social, economic or environmental disadvantage resulting from an impairment or disability.[129] Thus it cannot be assessed only using an objective voice assessment as by definition the impact will vary depending on the patient's lifestyle and

aspiration. The original VHI self-assessment tool comprised 30 questions divided into three categories: functional, physical and emotional aspects of voice disorder.

The VHI has been assessed for reliability and validity. The VHI was derived retrospectively by review and analysis of the subject's symptoms and thus physician-centred in its development.[130] Due to this it has been questioned whether this may cause selection bias as the developers of the tool define what voice related problems are.[131]

A shortened version of the VHI was subsequently developed known as the VHI-10 (Appendix 2). The shortened version comprising 10 questions takes less time to complete and results in no loss of validity.[132] It also assesses and evaluates the overall state of voice handicap. Despite the criticisms in its development the VHI-10 provides a concise tool for initial and follow-up assessment of all types of patients with a voice disorder.[132] It has been adapted to different languages and is used worldwide both in the clinical setting and for research purposes.[133-135]

*1.5.1.2 Voice performance questionnaire (VPQ)*

The Voice Performance Questionnaire (VPQ) is a 12 item questionnaire. It assesses the physical symptoms and socio-economic impact of voice disorder.[136] For each of the 12-items the patient chooses the best answer for each question. The questionnaire was designed by Carding et al. [100,136] for a study into the treatment of 45 patients with nonorganic dysphonia. The development was not as rigorous as that of the VoiSS (see section 1.5.1.3).

Deary et al.[137] compare the VHI-10 and VPQ in 330 adults and found them to be highly correlated. The VPQ and VHI-10 are both short questionnaires which makes them useful in the busy clinical setting.

*1.5.1.3 Voice symptom scale (VoiSS)*

The VoiSS questionnaire developed by Dreary et al. in 2003[98] is a patient-designed self-assessment questionnaire (Appendix 3). It was developed by collecting an inventory of voice symptoms in adult dysphonia clinics.[131] An open ended questionnaire was used and this yielded 467 difficulties and problems related to their voice. This is unlike other questionnaires such as the VHI where the voice problems and questions were compiled by physicians. The VoiSS questionnaire was developed in several stages: firstly an open-ended problem sheet was compiled by the patients prior to a prototype which summarized the common problems[131]. A modified scale was created and then finally psychometric analysis to create the 30 item VoiSS. The process involved responses from over 800 subjects. The psychology team reviewed the difficulties perceived by the subjects and three distinct factors emerged: impairment, emotional and physical symptoms. There was no distinct testing of the subscales in the creation of the VHI questionnaire.[132] Thus the VHI assesses the overall state of voice handicap rather than individual subscales. The VoiSS questionnaire has had a robust development and compared to VHI and VPQ is the more extensively validated self-report voice measure.[98]

*1.5.1.4 Voice related quality of life*

Voice Related Quality of Life (V-RQOL) this is a 10 item self-administered validated voice outcome measure.[138] Developed by Hogikyan et al. [138] from Michigan in the United States and published in 1999, scores are reported in two domains (social-economic and physical functioning) and as a total score, each ranging from 0 to 100. A higher score indicates a better voice-related QOL. It has been validated and the developers proposed use of the instrument was for assessment of dysphonic patients and particularly for monitoring treatment outcomes.[138]

### 1.5.2 Acquisition of a voice sample for analysis

A high quality audio recording is required for voice assessment. The recordings can be stored and analysed at a later date. It also enables blinded evaluation by more than one rater. Digital recordings have made the data easier to use, store and analyse.

In 1994, at a workshop on voice, Titze et al. [139] made recommendations on voice recordings in an attempt to standardize them. These recommendations included recordings to be produced in a sound-proofed room, although a quiet room with ambient noise of less than 50dB is acceptable. The mouth to microphone distance needs to be at a constant distance of 10cm. A head-mounted microphone enables this distance to be measured and kept constant. Off-axis positioning (45-90$^{o}$ from the mouth axis) reduces aerodynamic noise from the mouth during speech production.[139]

There are a number of readily available passages which are phonetically balanced and which have been developed for use in the assessment of voice. Phonetically balanced sentences were developed for speech research, where standardized and repeatable sequences of speech are required. The Harvard Sentences are phonetically balanced English language sentences which were developed during World War II to test military communication systems.[140] Phonetically balanced passages include a broad range of English-language sounds, or phonemes, distributed in proportions similar to ordinary conversation. The passages should be easy to read and examples of commonly used passages in order to obtain samples of voice analysis include 'My Grandfather' (Appendix 1) [141], 'The Rainbow Passage'[142] and 'Arthur the Rat'.[143] The texts are approximately two minutes in length. This length of passage ensures it is not too tiring to read whilst being long enough to provide a range of intonation patterns and sufficient information for statistically reliable measures of fundamental frequency.[144] A comparison of these reading passages was performed by Powell et al..[145] Powell compared the characteristics of 15 different reading passages including 'My Grandfather', 'Rainbow Passage' and 'Arthur the Rat'. The phonetic characteristics were analysed including the number of syllables, consonant distribution, length of the passage and structural complexity (determined by the cluster of vowels and consonants). The majority of the passages provided a representative sample of the consonants and vowels. 'My Grandfather' and the 'Rainbow Passage' provide a varied sample that would be an appropriate sample for adults in normative studies.[145] A criticism of 'Arthur the Rat' passage is that is

contains sections of direct speech which may encourage the reader to change their normal range which has the potential to affect the analysis.[144]

Although considered to be an unnatural voice sample, sustained vowel recordings can be used for objective voice evaluation. This will be covered in the section 1.5.5. The sustained vowel production (such as /a/) provides voice material that is from the vocal folds and not affected by articulation from the rest of the vocal tract.[146] The mouth is more open using the vowel /a/ compared to other vowels and this helps to minimize vocal tract vibration.[147] Although Orlikoff [148] demonstrated that there was no change in the acoustic analysis when assessing different vowels. One protocol by Speyer et al. [149] included /a/ at a comfortable pitch/loudness, recorded three times to evaluate variability of quality. During the sustained vowels it is important the mouth-to-microphone distance is constant to maintain a high signal-to-noise ratio.[139]

### 1.5.3 Perceptual rating of voice

Perceptual rating of voice quality ideally requires an expert to listen and evaluate the voice. The assessor is referred to as a rater and is often a Speech and Language Therapist trained in using the assessment. The rater has to judge the extent to which the voice deviates from normality.

The GRBAS scale is the most commonly used voice rating scale in the literature when comparing voice outcomes following an intervention. This scale provides a structure for the evaluator to assess the voice in a systematic way whilst a phonetically balanced passage is read out. The development of GRBAS scale was undertaken by the Committee of Phonatory Function Tests

of the Japan Society of Logopedics and Phoniatrics and first published by Hirano in 1981.[150]

The scale comprises five different parameters; **G** = grade, **R** = roughness, **B** = breathiness, **A**= asthenia, **S** = strain. Grade is the overall degree of abnormality of voice. Roughness is the rattling sound which is mainly found when there are irregularities of vocal fold vibrations. Breathiness relates to the extent of air leakage through the glottis. This is a whispery voice which is heard when there is insufficient glottic closure such as that which occurs with vocal fold palsy. Asthenia means weakness or lack of strength in the voice. Finally, Strain relates to the hyperfunctional state of phonation of the voice. This is found in patients with spasmodic vocal conditions. Each domain is rated 0 to 3 where 0 is normal, 1 represents a slight voice problem, 2 moderate and 3, a severe dysphonia. The auditory-perceptual evaluation of dysphonia has been criticised on the basis of its reliability.[151] An expert rater is required to provide consistent, reliable and reproducible assessments and therefore raises the issue of general applicability.[104] The European Laryngological Society (ELS) guidelines on phonosurgery recommend GRBAS scale due to its reliability (inter and intraobserver reproducibility).[96]

De brodt et al.[104] assessed the test-retest reliability of the GRBAS scale by asking the same raters to rate two successive voice recordings more than two weeks apart. In the study, 23 raters assessed 12 different voices. The judges included professional Speech and Language Therapists and Otorhinolaryngologists with different levels of experience. There was no statistical inter or intra-rater differences between the raters despite their experience or profession.

There are aspects of the GRBAS that have been shown to be not as reliable. This includes Strain and Asthenia which have only been shown to have a low to fair intra- and inter-judge reliability.[151] This in some centres a simplified GRBAS version is used omitting Strain and Asthenia, known as GRB.[152]

A number of other scales have been described as an alternative to the GRBAS scale. These include the CAPE-V, Buffalo Voice Profile and Vocal Profile Analysis. The CAPE-V is the Consensus Auditory-Perceptual Evaluation of Voice and was developed by the American Speech Language Hearing Association. However, a study comparing three perceptual evaluation scales [153], GRBAS, Vocal Profile Analysis and Buffalo Vocal Profile, found that GRBAS was the most reliable with respect to the inter-rater, intra-rater and test-retest reliability.

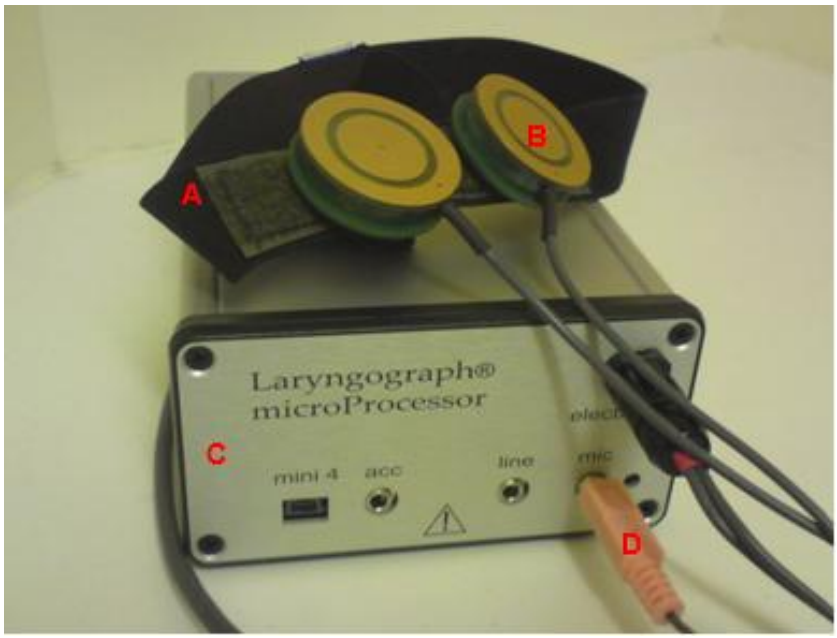
The advantages of perceptual evaluation scales are their ease of use. Although potentially time consuming, they are non-invasive and provide a workable basis for the speech therapist and clinician to reliable compare voice quality over time as well as the impact of treatment intervention.[154,155]

### 1.5.4 Electroglottography

Electroglottography (EGG) was first used in voice research by Fabre in 1957.[156] EGG is a simple electrical method of non-invasive examination of vocal fold phonatory vibration (figure 20).[157] Electrically isolated ring electrodes are placed on the neck skin overlying either side of the thyroid cartilage (figure 21). A small electrical current is passed from one electrode to the other and resistance to current flow (impedance), which varies with the

extent of vocal cord and mucosal wave contact, can be measured. Therefore, impedance measurements can then be used to calculate relative vocal fold contact area throughout the vocal cycle. The admittance is a measure of how easily an electrical circuit will allow current to flow and is the inverse of impedance. The small electric current is not perceptible to the subject as it is high frequency (0.3-5MHz).[158]

**Figure 20: Electrolaryngograph (A: neck strap, B: ring electrodes, C: microprocessor, D: cable to microphone)**

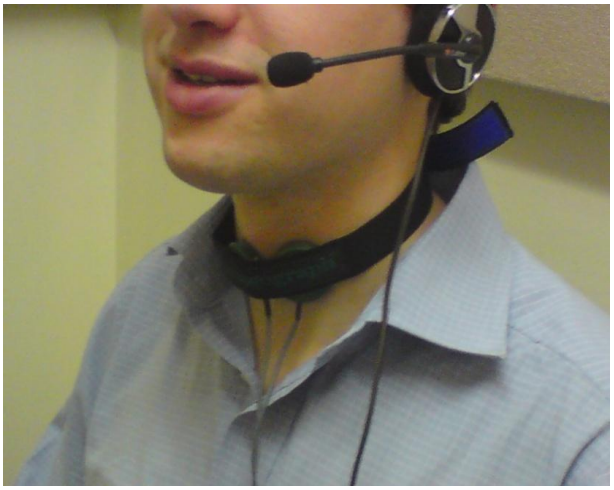



*Source: Image taken by author*

The EGG is able to monitor vocal fold contact, the rate and regularity of sound vibration during voice. However, the electric current from the EGG cannot be focused directly onto the vocal folds due to the surrounding tissues of the larynx. Thus it has been suggested, by Fourcin [159], that the term

‘electrolaryngograph’ be used as it represents the entire larynx. However EGG is still more widely accepted terminology in the literature. Fourcin also described the laryngograph waveform (Lx) created from the change in impedance.[159] This waveform corresponds to the different stages of vocal fold cycle and is referred to as Lx, as illustrated in figure 22.

**Figure 21: Electrodes are placed on either side of thyroid cartilage**



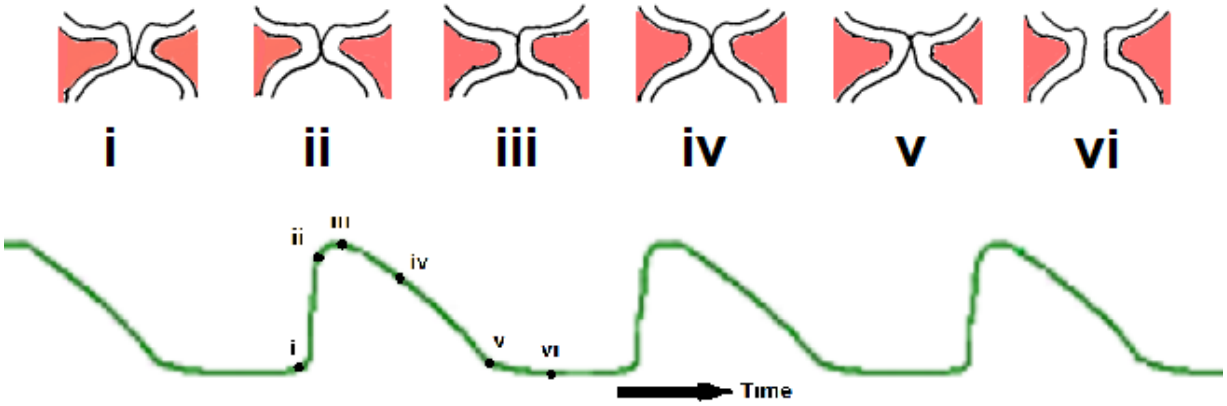
*Source: Image taken by author*

When vocal folds are closed, the impedance to current flow across the neck is reduced relative to when the vocal folds are apart. This causes a detectable signal change at the receiving electrode which can be converted into a waveform representing variations in impedance. The major advantage of this approach is the ability to analyze vocal fold activity without having to visualize them.

The impedance of the tissues does vary and this can affect the electrical signal. Adipose tissue has high impedance whilst muscle and blood have low impedance.[158] Other factors that may affect the electrical signal include

movement such as swallowing, breathing or articulation. However the EGG, such as Laryngograph®, has both a filter and gain control that can control the electrical signal. Thus, making it possible to filter out unwanted signals and focus on the impedance variation from the vibratory movement of the vocal folds. However if there is poor contact of the electrodes on the skin or thick soft tissues to the neck the electrical signal may not be detected.[22]

**Figure 22: Lx waveform and corresponding vocal fold cycle and contact**




*Source: Figure created by author with Lx waveform from SpeechStudio™ software*

In a normal Lx the closing and opening sequences should be regular. This is because normal vocal folds have similar mass, shape and stiffness. The steep rise in (i - ii on the curve in Figure 22) is due to the folds closing faster than they open (due to the 'Bernoulli Effect' as discussed previously in section 1.2). This is followed by the more gradual 'opening phase' (III-IV on the laryngograph curve).

Following the work of Fabre[156] the laryngograph was further developed by Fourcin [159] and much research was performed on the practical importance of vocal fold contact. Fourcin in 1971 [159] described the laryngograph (Lx)

waveform and further experiments were performed on cadavers assessing the waveform and its relation to physical factors[160]. Hampala et al. [161] created vocal fold vibration by blowing warm and humidified air trough the cadaver larynx. Thus it was possible to assess the relationship between the vocal fold contact area and the EGG signal. The peak of the Lx waveform in a normal voice is the main acoustic excitation of the vocal tract and this coincides with vocal fold closure. This is when there is maximum conductance and minimum impedance. The shape of Lx curve depends on the contact area of the vocal folds. Due to the complex nature of the vocal folds during the phonatory cycle, especially when the mucosal waveform is taken in to account, and the contact area not being fully understood there is still ongoing debate regarding the interpretation of Lx.[162] The use of the laryngograph and stroboscopy synchronously [163] was developed as a technique to improve accuracy. It also allows improved assessment of the pathological voice which can be irregular and difficult to analyse.

The EGG can be used to calculate different measurements of the vocal fold cycle collectively referred to as acoustic analysis and this will be covered in more detail in the section 1.5.5. The EGG has been shown to improve accuracy for some of these acoustic measurements.[148]

### 1.5.5 Acoustic analysis

Acoustic data provides non-invasive objective assessments of vocal function by measuring specific properties of the sound produced by the patient during voice or speech production. Acoustic analysis has been used to differentiate

normal from abnormal voice, help in diagnose voice pathology and evaluate the effectiveness of different treatments. Acoustic studies are typically performed using recorded or live voice.

The most commonly used and simplest method of analysis is using voice samples recorded using a microphone. Such recordings are accurate representations of what a voice sounds and contain the acoustic characteristics of the vocal tract and not just sound generated by the larynx. Following recording, the analogue signals are converted to a digital file in a process called digitization. The conversion of the frequency into a digital format is known as sampling and the digital conversion of the signal amplitude is known as quantization. The sampling rate or frequency rate is measured in Hertz (Hz) or cycles per second.

Once the acoustic signal is converted into a digital format it can then be analysed using computer software. As explained previously, acoustic analysis is most commonly performed using recordings of sustained vowels. This makes the analysis easier as the sustained vowels are produced by the vibrating vocal folds whilst maintaining a relatively fixed position.

One of the methods used to try and remove the effects of the vocal tract is inverse filtering approach. This can include a pneumotachograph mask to filter the sounds or by processing the speech pressure waveform from a microphone. The aim of this approach is to calculate the waveform produced by the glottis by cancelling out the other sounds from the vocal tract. The Linear Predictive Coding (LPC) is another speech analysis technique. This method again requires a vocal tract filter but also uses previous voice signals

to predict future values. LPC is used in most acoustic software to calculate frequencies.[162]

The commonest acoustic parameter used is fundamental frequency.[164] The fundamental frequency corresponds to the frequency of vibration of the vocal folds. Other measures include changes in frequency or amplitude. These changes are compared from vocal fold cycle-to-cycle and are known as perturbation measures.

### *1.5.5.1 Acoustic analysis parameters*

Titze et al. defined perturbation as a minor disturbance or a temporary change from an expected behaviour.[139] These perturbations are often small and go unnoticed without altering the qualitative appearance. Much research has been undertaken into the perturbation analysis of voice to help diagnose and assess voice disorders. Thus perturbation analysis is based on the idea that small changes in frequency and amplitude of the voice signal reflect an underlying cause. This premise forms the basis of acoustic analysis.

There are many different factors that can influence acoustic measurement. These include sex, age and dialect but also the equipment and software programmes used. Certain measures like jitter and shimmer using one software programme cannot always be directly compared to another software programme. This is because of the different methods and algorithms used to calculate these measures. For example there may be differences in how one programme determines the period and amplitude of a voice signal compared to another.

One software programme frequently used is the Multi-Dimensional Voice Program (MDVP) which was developed by Kay PENTAX 2008.[165] Praat is an open-source programme for the analysis of speech, developed at the University of Amsterdam.[166] Maryn et al. [167] compared two software programmes, MDVP and Praat software. There was a statistically significant difference between the different programmes when assessing the frequency and amplitude perturbations. They concluded that it is important that acoustic analysis normative data is system-specific. Thus for these reasons it is difficult to have a normal range of data for the different acoustic parameters.

*1.5.5.2 Sustained vowel analysis*

The most common acoustic analysis measures used are fundamental frequency (Fx), jitter and shimmer. Other measures are the noise ratios which include Harmonics to Noise Ratio (HNR), Normalized Noise Energy *(*NNE) and Signal-to-Noise Ratio (SNR). These measurements are performed on sustained vowels using computer software such as MDVP and Praat.

For perturbation analysis (Jitter and Shimmer) a voice sample of sustained vowels is required.[139] The voice recording (for example /a/) should be at a comfortable frequency and intensity. A stable portion of the voice should be included and any voice breaks excluded to calculate these data. The central portion of the sustained vowels is the most stable part avoiding the very start and end of vowel phonation.

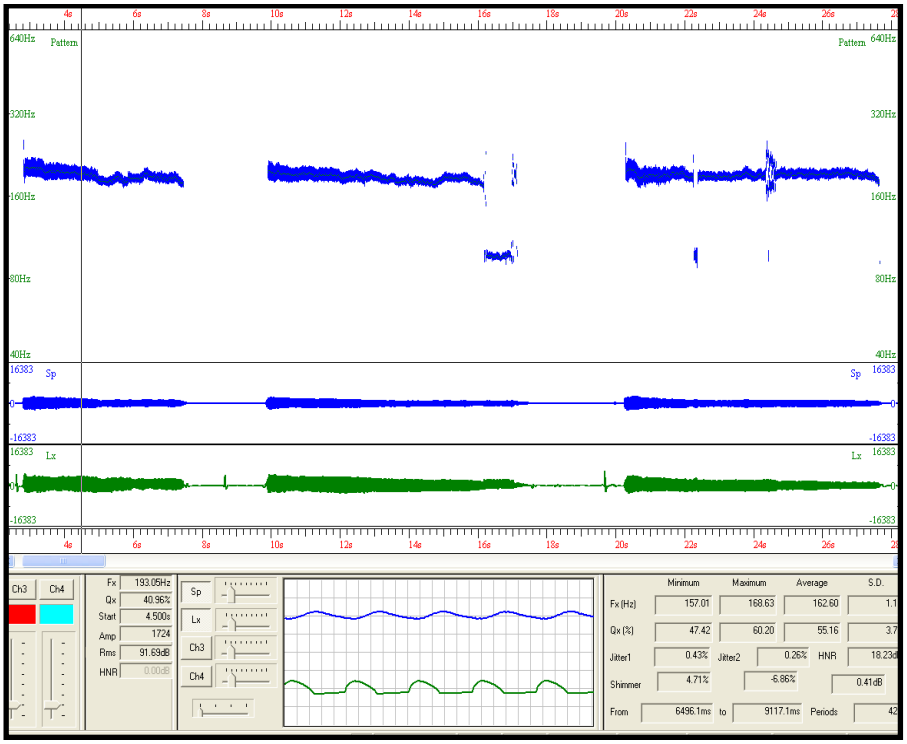
Sustained vowel recordings are used as the vocal folds are oscillating with less contamination from vibration of the rest of the vocal tract. The consonants in connected speech cause more vibration of the vocal tract and would affect

the results.[168] Although there are concerns that analysis of a stable portion of a sustained vowel may not reflect the quality of overall speech. In a review of 'Measuring Voice Outcomes' by Carding et al. [130] the limitations of the clinical application of these techniques were discussed. The published concerns are that the tests are only moderately reliable when tested on steady state vowel production rather than connected speech. The sustained vowels are usually /i/ (as in beet) or /a/ (as in card) and are produced at a comfortable volume and pitch [22] and therefore bear little relevance to the greater variability seen with connected speech. In addition, there are no fixed normal measures for many of these acoustic measures such as jitter and shimmer.

The acoustic analysis can also be performed using the EGG. An advantage of analysis using the Lx waveform (from the EGG) is that it can more accurately assess the sustained vowels as it can directly monitor the vocal fold cycles. The Speechstudio$^{TM}$ software used the Lx waveform to calculate Fx, Jitter and Contact Quotient (Qx) and the acoustic signal is used to measure the Shimmer, Relative Average Perturbation (RAP), Harmonics to Noise Ratio (HNR), Cepstral Peak Prominence (CPP) and Mean Speech Pressure Level (SPL).

An example of sustained vowel analysis using Speechstudio$^{TM}$ software is demonstrated in Figure 23. The blue waveform is the Sp (acoustic) signal and the green is the Lx (laryngograph) waveform. The stable mid-portion is used to improve accuracy.

**Figure 23: Screenshot illustrating section of sustained vowels on SpeechStudio™**




*Source: Image created by author using SpeechStudio™ software*

### *1.5.5.2.1 Fundamental frequency*

The frequency of a sound wave is the number of regular fluctuations which occur in a given time period. It is measured in Hz which is the number of cycles per second.

The fundamental frequency (Fx) can be defined as the lowest frequency of a periodic waveform. Previous studies have used both acoustic and EGG measurements to examine the Fx. A more reliable method of calculating Fx is by using the EGG to derive it directly from the Lx waveform.[148]

The Fundamental Frequency (Fx) can be calculated by measuring the interval between successive vocal fold closures on the Lx waveform.

*Fundamental frequency = 1/time to complete one vibratory cycle*

The fundamental frequency varies with age and gender (see table 5). The frequency depends on: vibratory mass and tension of the vocal folds; as well as changes in the aperture of the glottal opening and the subglottic pressure. For example, Fx is found to be lower than average in conditions such as Reinke's oedema – a collection of fluid in the superficial lamina propria normally due to smoking - as a result of increased mass of the vocal fold [169]. As a consequence, the sublgottic pressures have to be higher to overcome this increase mass of the vocal folds in order to generate sound. A higher than average Fx is found in scarring of the vocal folds and in glottic carcinoma.[170,171]

Gonzalez et al. [165] assessed the reliability of acoustic parameters in 148 healthy adults. The fundamental frequency was found to have high intra-subject stability.

**Table 5: Average Fundamental Frequencies with age**

| | Mean Fx (Hz) | |
|---|---|---|
| **Age** | **Females** | **Males** |
| **20-29** | **227** | **120** |
| **30-39** | **214** | **112** |
| **40-49** | **214** | **107** |
| **50-59** | **214** | **118** |
| **60-69** | **209** | **112** |
| **79-80** | **206** | **132** |
| **81-89** | **197** | **146** |

*Source: Aronson et al., Clinical Voice Disorders, fourth edition (2008)*[21]

The MDVP software includes the following outcomes regarding fundamental frequency: minimum Fx, maximum Fx, average Fx and Standard Deviation

(S.D) Fx. These measurements are performed directly from the Lx waveform. The MDVP takes the mean from four cycles as well as the minimum and maximum Fx.

*1.5.5.2.2 Jitter*

Perturbation of the waveform frequency is known as jitter. Jitter is calculated as a percentage. The equation of jitter percentage is the cycle to cycle frequency perturbation:

$$\text{Jitter \%} = \frac{\text{Average temporal perturbation}}{\text{Average vocal fold cycle duration}} \times 100$$

Higher values of jitter indicate an increase in perturbation and this has been found in abnormal voice samples.[171] However there are limitations to its use as an objective measure, for example Carding et al. [172] found the test-retest reliability of jitter to be only moderate.

Some studies have found a difference in Jitter in males compared to females.[173] Titze [174] theorised that males have larger vocalis muscle contraction compared to females which causes a medial bulge along the vocal fold surface. Thus a lower jitter reported in females was thought to be due to the shorter length of the vocal folds and the smaller muscle mass.[175] jitter is also referred to as a measurement of vocal stability. An elevated jitter corresponds to a hoarse, harsh or rough voice quality. In a 'normal' voice the jitter is usually less than 1% frequency variability. The jitter factor is the mean difference between two consecutive vocal frequencies divided by the overall mean frequency of phonation. This proportion is then multiplied by 100.

The relative average perturbation (RAP) compares an average jitter over a three cycle period. The RAP is calculated as the average absolute difference between a period and the average of its two neighbouring cycles, divided by the average period. Once multiplied by 100 then it is then called RAP%. The RAP measure attempts to reduce the effects of long term Fx changes, such as slowly rising or falling pitch.

*1.5.5.2.3 Shimmer*

In contrast to jitter, shimmer is the waveform cycle-to-cycle amplitude perturbation. It is normally expressed in decibels (dB). It is measured on the peak amplitude of the acoustic wave with each cycle. Raised values of shimmer correspond with a higher degrees of perturbation and this has been shown to be linked with abnormal voice samples.[171] Amplitude perturbation or vocal shimmer serves as an index of vocal stability and an excessive shimmer is associated with an increased perception of hoarseness.

Shimmer is different to the average amplitude which is the basis for the sound pressure level (SPL). SPL is the local pressure deviation from the average atmospheric pressure caused by a sound wave and is in decibels.

*1.5.5.2.4 Cepstral Peak Prominence (CPP)*

The CPP is a measure of periodicity and has been shown to measure dysphonia and is calculated from the frequency of each component wave making up the signal.[176] CPP is a measure of the degree of harmony within a voice and the more periodic the voice signal, the greater the harmony and thus the value of CPP.[177] Shrivastav found that CPP was more consistent in

predicting breathiness than jitter or shimmer[178]. In a study by Heman-Ackah et al.[179], 872 voice samples were analysed this included 92 dysphonic patients and 780 healthy volunteers. The mean CPP value was 4.77 (SD 0.97) compared to a CPP of 2.57 (SD 1.05) in 92 dysphonic voices. The difference between the normal and dysphonic voices was found to be statistically significant ($P<0.05$).

*1.5.5.2.5 Contact Quotient (Qx)*

The MDVP software also includes a measurement of when the vocal folds are in contact during the vocal fold cycle. The Qx is calculated as a percentage from the Lx on the EGG.

$$Qx\ (\%) = \frac{\text{Lx closure width 70\% down from positive peak}}{\text{Time to complete one vibratory cycle}}$$

There is a close relationship between the closed quotient value and the voice quality. When there is less vocal fold contact during a vocal fold cycle the voice is more breathy. Qx is expressed as a percentage and a Qx of 50% would indicate that the vocal folds are in contact for half the time period of the cycle. The MDVP with the Speechstudio™ software produces the following data set for Qx: minimum Qx, maximum Qx, average Qx and S.D Qx. The programme includes contact during the cycle if it is at the upper 70% or more of the peak amplitude. This would cover all those stages of the cycle where there is some vocal fold contact. In patients with vocal cord paralysis, Choi et al. demonstrated that by performing thyroplasty the Fx and Qx were improved. This corresponded with a perceptual decrease in breathiness in the voice quality.[180]

*1.5.5.2.6 Measurement of Noise Ratios*

Voice can be considered to have two main components. Firstly a well defined periodic signal of the vocal folds vibrating and secondly the random noise of vibration from the remaining vocal tract and turbulent air flow. The most common noise ratios include harmonics to noise ratio (HNR) and normalized noise energy *(*NNE).

*Harmonics to noise ratio (HNR)*

Yumoto et al. [181] , in 1982 proposed HNR, as an objective measure of the degree of hoarseness. HNR compares the level of desired signal to the level of background noise and is also termed the signal-to-noise ratio (SNR). HNR is calculated using a sustained vowel and assesses the relationship between the harmonics and the noise. The harmonics is the frequency of the vibrating vocal folds and is also known as the periodic part and the noise is the aperiodic part. The vowel /a/ provides the clearest sound from the vocal folds[22]. Voice, similar to speech, can be divided into two components: a well defined signal (harmonic) and random noise. The harmonic is from the vocal folds and/or vocal tract whilst the random noise can be turbulent airflow. An increased noise is due to turbulent airflow produced around the glottal opening during phonation and this may suggest a voice abnormality. In terms of the EGG the harmonics is the energy of the average Lx. It is measured in decibels (dB). The HNR has been found to be related to the perceptual variation in rough voices. Martin et al. [182] found that in 80 samples analysed, the severity of rough voice was predicted successfully by HNR. The severity

of dysphonia has also been correlated with the HNR.[183] The published evidence regarding the reliability of HNR is mixed. Leong [176] found the HNR measure to be the most variable in a group of 18 normal voices. However Wolfe et al. [184] assessed severity of dysphonia with different voice types, finding that HNR was the best prediction of severity. HNR correlated tightly with the basic perceptual elements of voice quality: grade, roughness and breathiness.[184]

Normalized noise energy (NNE) was described by Kasuya and Ogawa [185] in 1985. NNE measures primarily the turbulent noise caused by insufficient glottic closure during phonation. It does this by assessing the relative level of vocal noise to that of harmonics but only uses a small number of vocal periods. This can be altered by any pathology which impedes glottic closure, for example, vocal fold paralysis, vocal nodules or glottic carcinomas. In a study by Jotic et al.[186] 69 patients underwent treatment for Tis and T1a glottic carcinomas with either surgery or RT. Acoustic analysis was performed post operative and the NNE improved statistically significantly in patients at 6 months and 12 months following treatment. In terms of voice outcomes there was no difference between the treatment arms at 12 months.[186]

*1.5.5.3 Connective speech acoustic analysis*

The analysis of connective speech has the advantages of being representative of normal conversations. The Speech Studio software [187] can assess both sustained vowels and connective speech. When assessing the connective speech it uses both the EGG waveform (Lx) and the acoustic or

speech signal (Sp) from the microphone. In analysis of connective speech it correlates the Sp with the vocal fold cycle.

The availability of the Lx from the EGG reflects the vocal fold cycle. It can thus separate the cycle into closing, connecting and opening of the vocal folds.

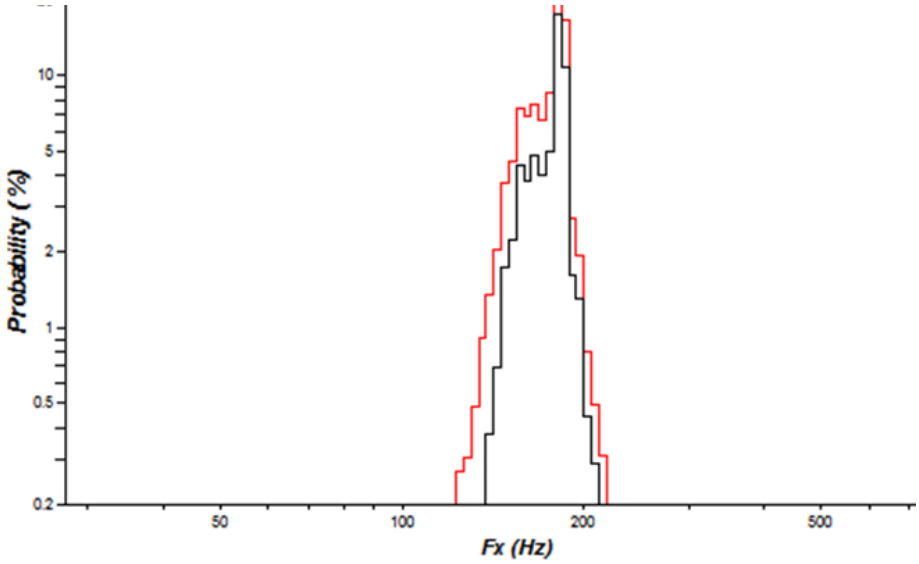
The connective speech analysis in the Speech Studio software with the Laryngograph$^{TM187}$ is known as quantitative analysis (QA). It provides a wide range of different analysis of connective speech including: frequency (Fx), amplitude (Ax), contact quotient (Qx) and different combinations of these. The Lx is used to calculate the frequency (Fx) measures and the contact measures (Qx). The acoustic signal (Sp) is used to measure the sound pressure level (dB).

*1.5.5.3.1 Frequency (Fx)*

The frequency of the vocal folds in connected speech can be illustrated in a histogram. The analysis is not standard as it is based on the period by period measurement of vocal fold frequencies with no smoothing. This distribution is called DFx.[188] DFx1 is the probability distribution for the frequency of each vocal fold cycle during voiced speech. It is performed by splitting the frequency range into consecutive intervals and dividing the total number of vocal fold cycles falling in each interval by the total number of vocal fold cycles in the whole data sample.[168] The frequency intervals are divided into 3% frequency steps so that there are practical measurements that can be used clinically. DFx2 is the second order distribution. This is based on successive pairs of vocal fold cycles in a 3% frequency bin. When these are plotted together the closer the two traces, the better the pitch control.

Therefore DFx2 represents regular, periodic vocal fold cycles over at least two cycles. Figure 24 illustrates a histogram of DFx 1 and 2.

**Figure 24: DFx 1&2 (DFx1 in red)**

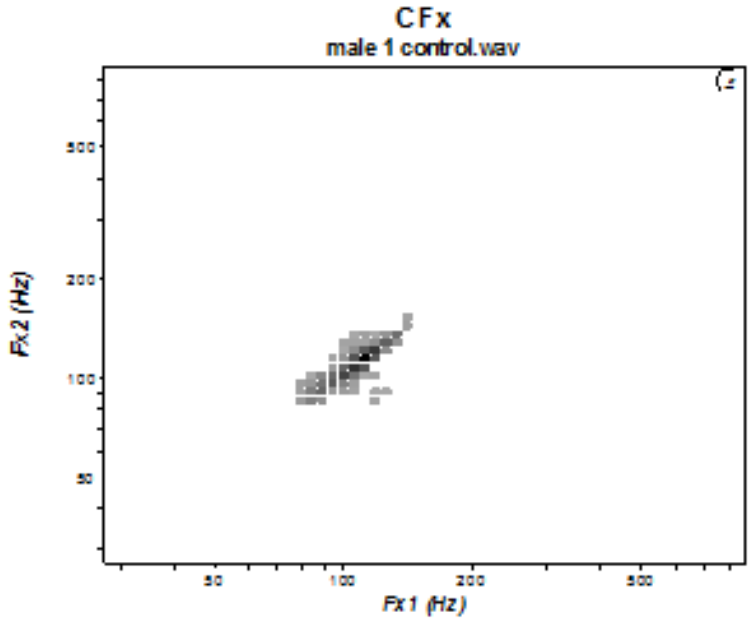



*Source: Image created by author using SpeechStudio™ software*

The CFx is an indicator of pitch irregularity which provides a numerical value for the degree of irregularity. The frequency of each vocal fold cycle is plotted against the frequency of the next cycle. When considering a `normal` voice most data points are within the core of the diagonal plot. When the irregularity from cycle to cycle increases so does the amount of scatter which is reflected in the numerical readout. Figure 25 illustrates an example of a scatter plot of CFx.

The SpeechStudio™ programme using the Lx waveform allows the following measures to be recorded from connective speech regarding Fx: mean (DFx1 & DFx2), mode (DFx1 & DFx2), median (DFx1 & DFx2), SD of Fx, coherence %, 80% and 90% Range Hz/Octaves, irregularity Score (CFx)%.

**Figure 25: CFx scatter plot**




*Source: Image created by author using SpeechStudio™ software*

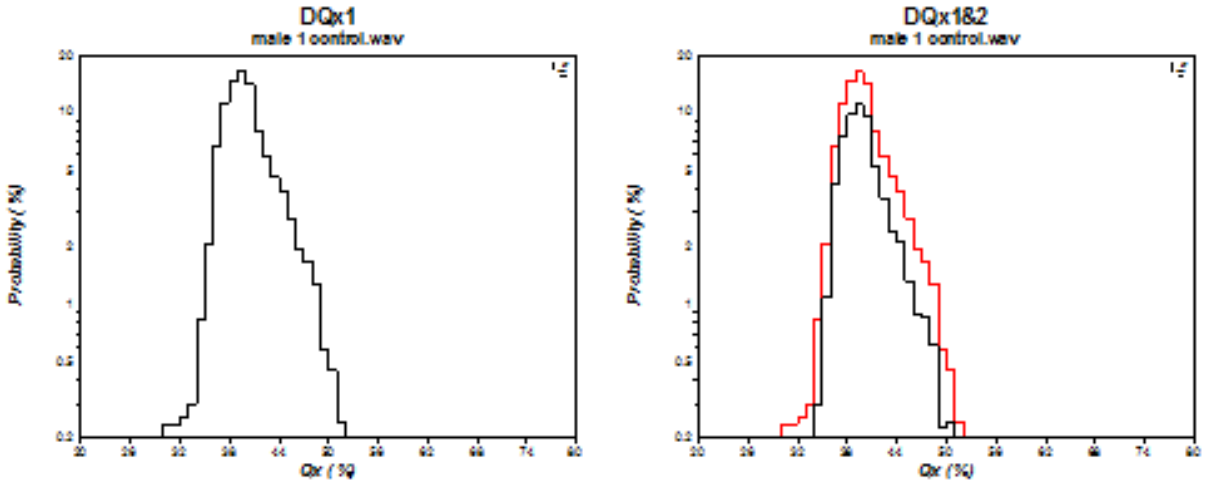
*1.5.5.3.1.2 Contact quotient (Qx)*

The Lx is also used to measure the contact quotient (Qx). The degree of contact between vocal folds during the vocal fold cycle can be measured from the EGG waveform. The closed quotient has been used as an indicator of voice quality.[168] The SpeechStudio™ uses the Lx to measure different aspects of Qx. These measurements include: mean, mode and median DQx1 & DQx2, S.D (DQx1 & DQx2), coherence %, 80% and 90% Range % and irregularity score (CQx)%.

A breathy voice leads to a decrease in the Qx value whereas a pressed voice causes the Qx values above normal. DQx1 is the probability distribution for the closed phase of each vocal fold cycle. The peak of the plot shows the most commonly occurring value (modal value). The DQx2 is the second distribution of the closed phase and is an indicator of its regularity. DQx2

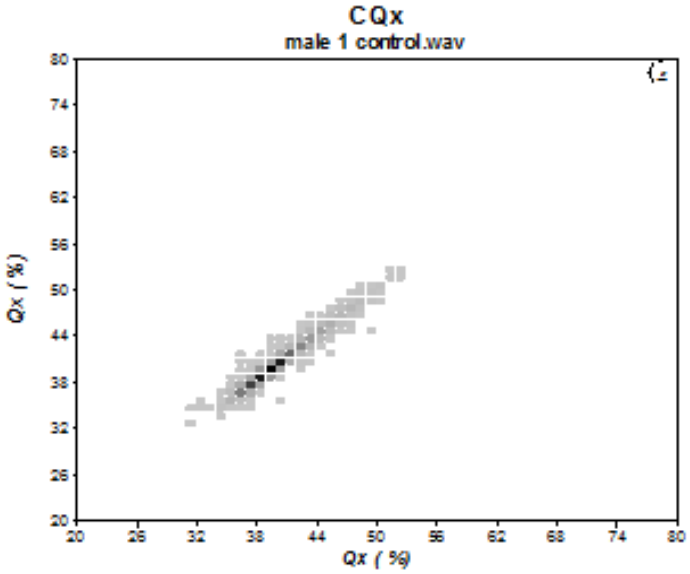
includes the adjacent vocal cycles. The better the closed phase of the vocal fold cycle the more similar DQx2 will be to DQx1. DQx1 is in red to allow comparison. Figure 26 illustrates a histogram of DQx 1 and 2.

**Figure 26: DQx1 and DQx1&2**




*Source: Image created by author using SpeechStudio™ software*

**Figure 27: CQx scatter plot**




*Source: Image created by author using SpeechStudio™ software*

CQx is a graphical indicator of the irregularity of the Qx within the vocal fold cycle. In the scatter plot as irregularity increases so do the amount of scatter and the associated irregularity score (CQx). Figure 27 illustrates an example of a scatter plot of CQx.

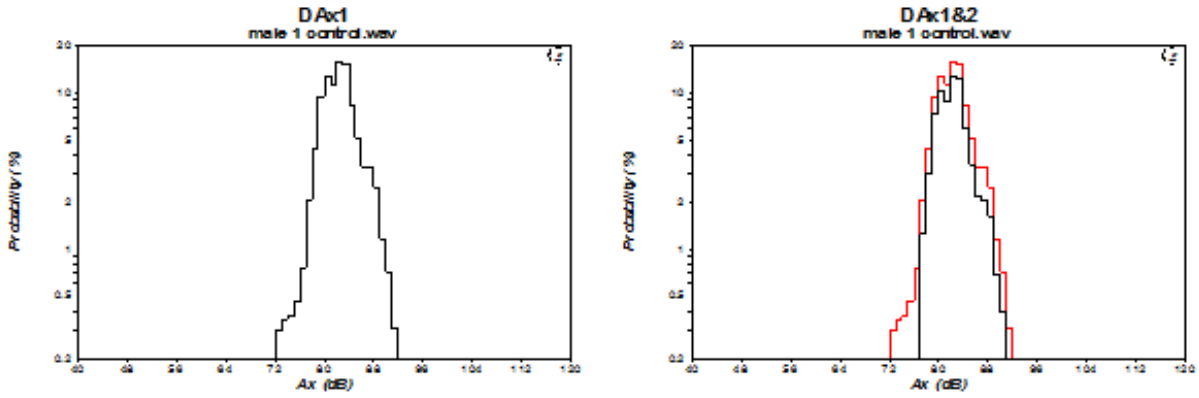
*1.5.5.3.1.3 Amplitude (Ax)*

The Ax measurements are calculated from the acoustic signal from the microphone. The DAx1 is the probability distribution for the peak amplitude of the acoustic signal during each vocal fold cycle. The peak of the plot shows the most commonly occurring value (modal value).[168] DAx2 is calculated similarly to DFx2 as explained in section 1.5.5.3.1. DAx2 is measured by assessing only regular periods and this is performed over at least two cycles. It therefore can be used as an indication of loudness regularity. The better the amplitude control the more similar DAx2 will be to DAx1. Using the SpeechStudio$^{TM}$ software the DAx1 is shown in red to allow comparison (Figure 28).

CAx is another graphical indicator of loudness irregularity and provides numerical value for the irregularity. The peak amplitude during each vocal fold cycle is plotted against the peak amplitude during the next cycle (Figure 29). In a normal voice most data points are within the core of the diagonal plot. With increased irregularity so does the amount of scatter and hence the irregularity score.

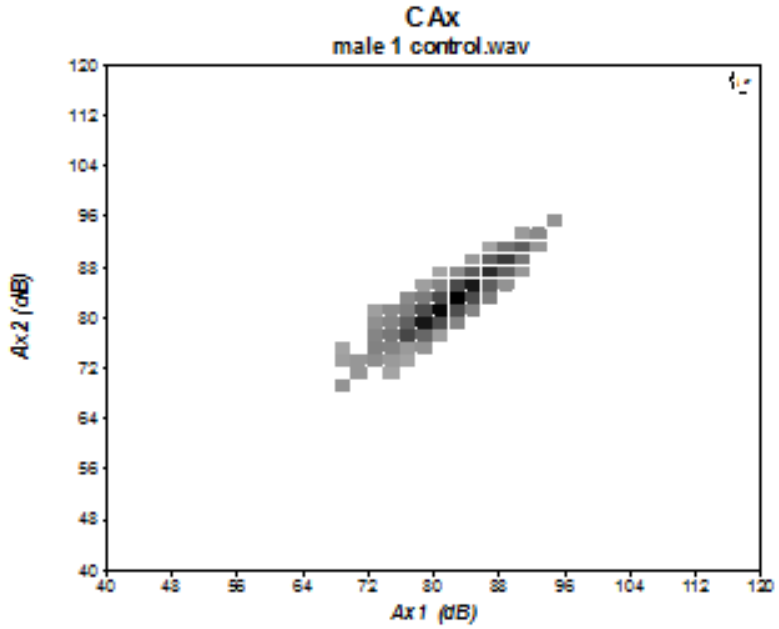
The SpeechStudio$^{TM}$ calculates from Ax the mean, mode and median of DAx1 & DAx2 dB, the SD DAx1 & DAx2 dB, coherence %, 80% and 90% range dB and irregularity Score (CAx) %.

**Figure 28: DAx1 and DAx1&2**




*Source: Image created by author using SpeechStudio™ software*

**Figure 29: Amplitude Scatter graph (CAx)**




*Source: Image created by author using SpeechStudio™ software*

*1.5.5.3.1.4 Combined parameters*

The different parameters of Fx, Ax and Qx can be combined and analysed. The amplitude (Ax) can be plotted against the Fx, known as Ax1Fx1. Ax1Fx1 is the first order relation between Ax and Fx. Every value of Fx is plotted against the corresponding value of Ax. It shows the range of the speaker's voice with respect to Fx and Ax. A normal voice should use a suitable range of loudness values across its pitch range.

Qx1Fx1 is the first order relation between Qx and Fx i.e every value of Fx is plotted against the corresponding value of Qx. It shows the range of the speaker's voice with respect to Fx and Qx. A normal voice should use a suitable range of closed phase values across its pitch range.

### 1.5.6 Videolaryngostroboscopy

Stroboscopy or videolaryngostroboscopy is useful in clinical settings to aid with the diagnosis of voice disorders. Stroboscopy can be used to assess the quality of vocal fold vibration by allowing the vocal folds to appear as if they are moving slowly using a strobe light at the end of an endoscope. There is a misconception that the slowing down of the image is due to the phenomenon of Talbot's law, that there is a persistence of an image on the human retina for 0.2 seconds after exposure.[189] In fact laryngeal stroboscopy creates an apparent slow-motion by sampling successive phases of the vocal fold cycle. It is ultimately subjective, relying on observer interpretation; however, it is often helpful when used in conjunction with other methods of voice assessment.

This technique has been used to assess the depth of the laryngeal tumour and help guide the extent of surgical resection. Manola et al. assessed patients with early glottic tumours with videolaryngostroboscopy using a $30^0$,$70^0$ and $120^0$ rigid optical endoscope.[190] If the lesion showed no evidence of infiltration (normal wave form of the vocal fold on stroboscopy) then a sub-epithelial partial cordectomy was performed. Thus preserving as much normal tissue as possible and having good voice quality post-operatively.

There are other parameters that can be assessed using stroboscopy such as glottal closure, regularity of the vocal fold cycle, mucosal wave form and symmetry. The rate of glottis closure on stroboscopy has been found to be a reliable tool in assessing vocal fold movement.[138] Unfortunately, this equipment is currently not used routinely in the otolaryngology department where this research was performed.

### 1.5.7 Aerodynamics

The vocal tract is an aerodynamic sound generator and resonator. Therefore variations in the flow of air through it can change both consonant and vowel articulations.[162]

Maximum Phonation Time (MPT) is one of the more basic methods of measuring aerodynamics and is used frequently to assess phonatory mechanisms.[191] It consists of sounding a prolonged vowel (/a/) for as long as possible after maximal inspiration, at a comfortable volume and pitch. There is variation with age and children (with smaller lung volume) will have shorter MPTs than adults.[192] There is also a difference between younger and older

adults, with the latter having a lower MPT. This is thought to be due to a change in physiological function of the lungs and muscles as well as an increased frequency of existing co-morbidities. MPT varies with respect to the pitch and intensity of phonation.

The Phonation Quotient (PQ) can help reduce these variables by including the vital capacity (VC) in the below equation.

*Average phonation airflow (PQ) = VC (ml)/MPT (s)*

The PQ therefore takes into account the speakers moveable air supply and reduces possible bias. The VC can be measured reliably using a spirometer. The PQ is therefore useful when assessing different ages because it takes into account the natural variation in VC.[96] The average airflow can also be measured using pneumotachography. This equipment measures the airflow as one produces a voice over a prolonged period through a tube or a fine wire-mesh.[162] During production of a sustained vowel most airway resistance is at the level of the glottis. Therefore airflow being a reflection of resistance, it can provide information regarding glottic function. However there are considerable variations of averaged phonation airflow among normal subjects and this limits its diagnostic value.

## 1.6 Health related quality of life

In the past, the outcome of different treatments has concentrated on local control as a definition of successful treatment. However the health-related quality of life (HRQOL) is now a well-recognised method of assessing outcomes after any treatment. The British Association of Head and Neck

Oncologists (BAHNO) recommend that HRQOL should be documented and provides an important insight into the patient's perspective.[36] Over the past two decades, in the field of head and neck cancer, there has been an increase in the number of publications on HRQOL.[95,118-120,123,193] The impact of head and neck cancer and its treatment can have such a profound detrimental effect on function and well-being that it is essential that the patient's perspective is taken into account.

Questionnaires are the commonest method of assessing HRQOL and there are many different questionnaires that are validated at assessing quality of life in head and neck patients.[194] Ringash reviewed eight different disease specific, multi-dimensional quality of life instruments for patients with head and neck cancer. The questionnaires varied in their methodology, strengths and weaknesses with no adequate prospective comparison between the assessments.[194] The commonest assessments used in head and neck oncology are the European Organization for Research and Treatment of Cancer (EORTC), Functional Assessment of Cancer Therapy – Head and Neck (FACT- H&N) and University of Washington Quality of Life (UW-QoL).

The European Organization for Research and Treatment of Cancer (EORTC) developed an integrated system for assessment of the health related QoL of cancer patients.[195] It was developed for head and neck cancer patients known as QoL Questionnaire – Head & Neck 35 (QLQ- H&N35).[196] It is a 35 item questionnaire which includes relevant questions regarding the effects of RT, chemotherapy and surgery. It has been shown to be reliable and distinguish between different stages of head and neck cancer treatment.[196]

The Functional Assessment of Cancer Therapy – Head and Neck (FACT-H&N) was developed by Cella et al. [197] and consists of 27 questions in 4 domains: physical, social/family, emotional and functional. It was specifically designed for head and neck cancer patients and has been translated into 37 languages. This tool has been directly compared with the EORTC QLQ-H&N35 [198] in 102 Head and Neck cancer patients. Both questionnaires demonstrated good internal consistency. The internal consistency is a measure of reliability and specifically is a measure of how well the items in a multi-item scale interrelate. However it was found that there were some differences in the QoL aspects it assessed. The FACT- H&N was found to have a more multidimensional view with a broader perspective, covering a variety of different areas compared to the EORTC QLQ- H&N35 which was more focused on physical and symptom aspects.

The University of Washington Head and Neck cancer Questionnaire (UW-QoL) has gone through several revisions since it was first published. Version 4 (UW-QoLV4) is the latest of these updates with the addition of mood and anxiety to the domains.[199]

A systematic review by Ojo et al. in 2012 [200] assessed the head and neck cancer quality of life tools. They found that UW-QoL and EORTC QLQ-H&N35 have been researched most since their development. Although this is partly due to the fact they have been used more widely for a longer period. The EORTC QLQ-H&N35 and UW-QoL were found to have criterion validity and internal consistency. Criterion validity refers to how well the scores of the test are compared to other similar instruments. The internal consistency relates to the reliability of the test and how consistent and reproducible it is.

The continual modifications of the questionnaire and the substantial number of published studies using UW-QoL are the reasons that many centres, like Aintree University Hospital NHS Foundation Trust, use this tool. There is also a local connection with the UW-QoL as Professor Simon Rogers (based at AUH) [199] lead in the development of version 4.

The UW-QoLv4 version four includes 12 domains and the higher the score, the better the quality of life. The domains are: pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. The UW-QoLv4 version four also creates two composite scores: 'Physical Function' and 'Social Function'. [199] The Physical Function score is the average of the following six domain scores: chewing, swallowing, speech, taste, saliva and appearance. The Social Function is the average of the scores for anxiety, mood, pain, activity, recreation and shoulder function.

There are also three global questions asked in the UW-QoLv4. The first question is how the patients feel relative to before they developed their cancer, the second about their health-related QoL and finally one about their overall QoL.

## 2. Aims and Objectives

This research has three main aims:

I. To describe acoustic parameters of ‘normal’ voice;

II. To compare voice outcomes in patients treated with TLM with those treated with radiotherapy for T1a SCC of the glottis;

III. To investigate longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of the glottis;

# 3. Methods

An application to study and record voices of patients with Head & Neck cancer at AUH was approved by the Liverpool Central North West Research Ethics Committee on 3rd August 2007. A substantial amendment was accepted by the ethics committee on 8th September 2008 (Reference 07/Q1505/46). This amendment included the use of three different questionnaires and also the recording and use of electrolaryngography.

The three aims outlined above were addressed in three individual studies.

## 3.1 Describing acoustic parameters of 'normal' voice

### 3.1.1 Study design

This study is a cross-sectional cohort study of the acoustic parameters of 'normal' voice.

### 3.1.2 Study population

Adult subjects with no known voice disorders were recruited from NHS staff at the AUH between January 2009 and January 2010. Subjects were purposefully chosen to provide a range of ages and gender balance. Subjects were approached by the researcher within the Head & Neck department at AUH and invited to participate in the study. Participants were provided an explanation of the study and details of how the measurements will be

collected. Verbal consent was taken to complete a voice questionnaire (VHI-10) and have their voices recorded.

Inclusion criteria:

- current non-smokers (or not smoked in the past five years);
- no known voice disorders or difficulties;
- score zero on the VHI-10 questionnaire;

Exclusion criteria:

- smokers (within the last five years)
- previous neck or phono surgery
- health issues that may affect the voice such as thyroid disease

### 3.1.3 Materials and methods

The same methodology was adopted for voice recording in all three studies. The voice recordings and associated electrolaryngography was undertaken in a designated sound proof booth in the Department of Otolaryngology – Head and Neck Surgery (ORL-HNS) at AUH. Audio readings were recorded by a headset SHURE® (Shure Distribution UK, Unit 2, The IO Centre, Lea Road, Waltham Abbey, Essex, EN9 1AS) microphone placed 10cm from the corner of the mouth. Concurrent with the sound recording, EGG readings were recorded using two gold-plated electrodes placed on the skin overlying each ala of the thyroid cartilage. The laryngograph® and microprocessor (Laryngograph Ltd, 78 Manor road, Wallington, Greater London, SM6 0AB)

equipment was used for the EGG recordings, connected to a Microsoft Windows® based desktop computer.

Subjects were required to produce three separate prolonged vowel sounds (/a/) and then repeated for the vowel /i/ at a comfortable pitch and volume and for as long as felt comfortable. Following this, subjects read out a phonetically balanced passage, 'The Grandfather Passage' (Appendix 1). All audio readings were recorded as a digital file (waveform audio file format for Microsoft Windows®), assigned a study number (and therefore anonymised) and stored on a password-protected hospital network computer. The voice recordings were copied onto a CD format as waveform audio files suitable for playback using Microsoft Windows Media Player®. The recordings were rated by experienced raters in the Speech and Language Department in AUH, Liverpool and in the Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle. There were a total of three experienced raters (one in AUH and two in the Freeman Hospital) and the recordings were scored according to the GRBAS voice scale. The raters were blinded and were not aware of the patient or participant details or which treatment they may have had.

Acoustic analysis of the recordings was performed using Speech Studio™ (Laryngograph® Ltd , 78 Manor Road, Wallington, Greater London, SM6 0AB, UK). The Speech Studio™ software enabled analysis of the sustained vowels using the multi-dimensional voice program (MDVP) and Quantative Analysis (QA) for the connected speech passage. The MDVP was undertaken using the stable mid portion of the sustained vowel recording. The QA was

undertaken on connected speech from the complete ‘Grandfather Passage’. The data capture was the same for all the three studies.

### 3.1.4 Outcome measures

1. Perceptual rating of voice with GRBAS scores
2. Acoustic analysis
    a. for sustained vowels:
    - The Fundamental Frequency, Fx (Hz)
    - Jitter (%)
    - Shimmer (dB)
    - Closed Quotient, Qx (%)
    - Relative Average Perturbation, RAP (%)
    - Cepstral Peak Prominence, CPP
    - Normalized noise energy, NNE (dB)
    - Harmonics to Noise Ratio, HNR (dB)
    - Speech Pressure Level, SPL (dB)
    b. for connected speech:
    - Frequency, Fx (Hz)
    - Amplitude, Ax (dB)
    - Closed Quotient, Qx (%)
    - Combined parameters of amplitude and frequency, AxFx (%)

### 3.1.5 Data collection and analysis

The resulting data were collated using Microsoft Office Excel® 2007. Baseline characteristics have been compared for males and females, using the Mann Whitney U test for age and the Fisher Exact test for smoking status. All data is presented with mean, standard deviation (SD), median and interquartile range (IQR), as the sample size is small and normal distribution cannot be assumed. Analysis of differences between men and women has been undertaken using the Mann Whitney U test. P values have also been adjusted for age using a proportional odds ordinal logistic model. Due to the small sample size, it was only possible to adjust for age and not other variables.

## 3.2 Voice outcomes in patients treated with TLM with those treated with RT for T1a SCC of the glottis

### 3.2.1 Study design

A comparative cross-sectional cohort study was undertaken to investigate differences in voice quality of patients treated for early laryngeal cancer (T1a) with TLM or RT.

### 3.2.2 Study population

Patients were identified using the AUH Head & Neck database. All patients coded as having treatment for laryngeal carcinoma from January 2000 to

January 2013 were initially screened. Clinic letters and case notes were then reviewed (on the hospital computer system) to identify patients treated for T1aN0M0 laryngeal carcinoma. Letters were sent to the patients informing them about the research and inviting them to participate. This was followed up with a telephone call. The researcher and the consultant surgeons also approached patients in the Head & Neck clinic to participate in the study.

Inclusion criteria:

- A diagnosis of T1aN0M0 laryngeal squamous cell carcinoma
- Completion of treatment in excess of twelve months previously
- TLM group only
    - TLM surgery performed at AUH
- RT group only
    - Completed RT in Clatterbridge Cancer Centre NHS Foundation Trust
    - RT regimes varied depending on the bulk of the tumour. The typical schedule was either 50-52 Gy in 16 fractions or 53-55Gy in 20 fractions over three to four weeks

Exclusion criteria:

- Previous other voice altering surgery or existing condition
- Signs of loco regional recurrence at last outpatient review

Patients meeting the inclusion criteria were contacted with a letter inviting them to participate in the research. This letter outlined the proposed study and

informed the participant that they would be contacted by telephone to discuss whether they wanted to be involved (Appendix 5). The patient was then telephoned and a date arranged for them to attend AUH for the voice recording and data collection.

### 3.2.3 Materials and methods

Clinicopathological demographic data of the included participants were retrieved from case notes and participant interview prior the voice recordings. Data collected included: age, sex, smoking history (non-smoker/active/ex-smoker), type of intervention, extent of surgical resection and any post-treatment speech therapy. Measurements of voice and speech parameters were undertaken through simultaneous audio and electrolaryngograph readings as described in section 3.1.3. Following the recording the participants completed two self-reported questionnaires for voice (VHI-10 and VoiSS) and one to assess quality of life (UW-QoLv4).

### 3.2.4 Outcome measures

1. Self-reported voice questionnaires:
    - VHI-10(Appendix 2)
    - VoiSS (Appendix 3)
2. Self-reported QoL questionnaire:
    - UW-QoLv4 (Appendix 4)
3. Perceptual rating of voice with GRBAS scores

4. Acoustic analysis for sustained vowel and connective speech as described in the section 3.1.4.

### 3.2.5 Data collection and analysis

The resulting data were collated using Microsoft Office Excel® 2007. Baseline characteristics have been compared for RT and TLM patients, using: Mann Whitney U test for age; Fisher Exact test for sex and co-morbidities; and Chi-squared test for smoking status and alcohol intake. All data is presented with mean, standard deviation (SD), median and interquartile range (IQR), as the sample size is small and normal distribution cannot be assumed. Analysis of differences between RT and TLM patients has been undertaken using the Mann Whitney U test. P values have also been adjusted for age using a proportional odds ordinal logistic model. Due to the small sample size, it was only possible to adjust for age and not other variables.

## 3.3 Longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of the glottis

### 3.3.1 Study design

A prospective longitudinal study design was used to investigate changes in voice quality and quality of life in patients treated with TLM for T1a glottis SCC.

### 3.3.2 Study population

All patients undergoing TLM for T1a laryngeal squamous cell carcinoma were invited to join the study. Patients due to attend for TLM for T1aN0M0 laryngeal carcinoma were identified at the weekly multi-disciplinary team (MDT) meeting at AUH between August 2008 and August 2010. Patients were approached in clinic by the researcher or the operating surgeon to participate in the study prior their surgery.

Inclusion criteria:

- Diagnosis of T1aN0M0 laryngeal squamous cell carcinoma
- MDT treatment decision for TLM at AUH

Exclusion criteria:

- Previous other voice altering surgery or existing condition
- Previous RT

Patients attending for their pre-operative assessments were approached and asked whether they would like to enrol in the study. If they expressed an initial interest they were given a patient information sheet (Appendix 5). Following a period of consideration, willing patients were then formally consented to enrol on the study (Appendix 5).

### 3.3.3 Material and methods

Patients undertook pre-operative voice recordings and then repeat voice recordings at least twelve months post-operatively. The same outcome measures were collected at each visit and the procedure for data collection

was standardised for all patients for each visit. Clinicopathological demographic data of the included participants were retrieved from case notes and participant interview prior the voice recordings. Data collected included: age, sex, smoking history (non-smoker/active/ex-smoker), type of intervention, extent of surgical resection and any post-treatment speech therapy.

Measurements of voice and speech parameters were undertaken through simultaneous audio and electrolaryngograph readings as described in section 3.1.3. Following the recording the participants completed two self-reported questionnaires for voice (VHI-10 and VoiSS) and one to assess quality of life (UW-QoLv4).

### 3.3.4 Outcome measures

1. Self-reported voice questionnaires:
    - VHI-10(Appendix 2)
    - VoiSS (Appendix 3)
2. Self-reported QoL questionnaire:
    - UW-QoLv4 (Appendix 4)
3. Perceptual rating of voice with GRBAS scores
4. Acoustic analysis for sustained vowel and connective speech as described in the section 3.1.4.

### 3.3.5 Data collection and analysis

The resulting data were collated using Microsoft Office Excel® 2007. The analyses only included patients where pre- and post TLM results were

available. Baseline characteristics have been compared for all pre-TLM patients compared with those where post-TLM data were available. Baseline characteristics were compared using: Mann Whitney U test for age; Fisher Exact test for sex and co-morbidities; and Chi-squared test for smoking status and alcohol intake. In addition, a comparison of quality of life and voice outcome has been included for patients included and excluded from pre- and post- TLM using a Mann Whitney U test.

All data is presented with mean, standard deviation (SD), median and interquartile range (IQR), as the sample size is small and normal distribution cannot be assumed. Analysis of differences between pre and post TLM results has been undertaken using the Wilcoxon test. P values have also been adjusted for age using a proportional odds ordinal logistic model. Due to the small sample size, it was only possible to adjust for age and not other variables.

# 4. Results

## 4.1 Describing acoustic parameters of 'normal' voice

Twenty adults with subjectively normal voices were recruited. All subjects invited to take part in the research consented to have their voice recorded and analysed. There were 10 males and 10 females. The age range varied from 24 to 59 years, with average age of 40 years. There were all NHS members of staff in AUH. They were all non-smokers and did not have any reported voice problems or had not undergone previous head and neck surgery or potentially voice altering surgery. All subjects were pre-screened and scored zero on the VHI-10 questionnaire. Summary of characteristics are presented in table 6.

**Table 6: Summary of characteristics for 'normal' voice**

| **Characteristic** | **Gender** | | **p-value** |
|---|---|---|---|
| | **Male (n = 10)** | **Female (n = 10)** | |
| **Age** | | | |
| *Mean (SD)* | 34 (9) | 44 (12) | 0.072 [a] |
| *Median (IQR)* | 34 (28–37) | 47 (34-51) | |
| **Smoking Status** | | | |
| *Never* | 10 (100%) | 10 (100%) | 1.000 [b] |
| *Smoker* | - | - | |
| *Ex-smoker* | - | - | |
| a. Mann-Whitney U test | | | |
| b. Fisher's exact test | | | |

### 4.1.1 Perceptual rating

All 20 adults scored zero for each GRBAS domain as judged by a single blinded expert rater.

### 4.1.2 Acoustic analysis

*4.1.2.1 Acoustic analysis on sustained vowels*

The full data set from the MDVP (Multi-Dimensional Voice Program) can be found in Appendix 6. The mean results have been calculated and are shown in Table 7. The mean results are expressed separately for males and females. Where there is a statistically significant difference between males and females, $p<0.05$, the p-value has been highlighted in bold font. There is a statistically significant difference in the minimum, maximum and average Fx ($p=<0.05$) between males and female, including when adjusting for age.

**Table 7: Mean and range of acoustic analysis of sustained vowels for 'normal' voice**

| | Males /a/ | | | | Males /i/ | | | | Females /a/ | | | | Females /i/ | | | | p value [a] | | adjusted p value [b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | IQR | Mean | SD | Median | IQR | Mean | SD | Median | IQR | Mean | SD | Median | IQR | /a/ | /i/ | /a/ | /i/ |
| **Minimum Fx (Hz)** | 132.9 | 35.0 | 118.5 | 113.4,148.6 | 124.0 | 38.6 | 124.3 | 104.4,139.0 | 211.7 | 20.9 | 118.5 | 200.0, 229.0 | 210.8 | 30.7 | 218.0 | 195.4,228.5 | **<0.001** | **<0.001** | **0.002** | **0.001** |
| **Maximum Fx (Hz)** | 195.7 | 165.8 | 130.7 | 125.9,197.6 | 163.6 | 55.0 | 140.7 | 131.3,185.5 | 227.2 | 19.4 | 130.7 | 216.7, 242.2 | 252.5 | 42.5 | 243.8 | 228.6,259.7 | **0.004** | **0.002** | **0.005** | **0.009** |
| **Average Fx (Hz)** | 138.5 | 35.7 | 122.0 | 119.9,154.7 | 148.5 | 41.8 | 130.5 | 125.6,163.8 | 218.7 | 20.9 | 122.0 | 205.7, 235.8 | 233.9 | 28.3 | 232.1 | 214.8,246.5 | **<0.001** | **0.001** | **0.001** | **0.005** |
| **S.D. Fx (%)** | 2.8 | 4.9 | 1.3 | 1.0,1.7 | 1.7 | 1.8 | 1.1 | 0.9,1.4 | 1.2 | 0.6 | 1.3 | 0.9, 1.2 | 1.9 | 2.4 | 1.0 | 0.8,1.6 | 0.159 | 0.698 | 0.143 | 0.350 |
| **Minimum Qx (%)** | 38.9 | 6.9 | 36.4 | 34.8,41.2 | 36.9 | 11.7 | 40.2 | 34.5,42.8 | 53.1 | 51.3 | 36.4 | 32.6, 46.5 | 39.6 | 12.0 | 39.5 | 29.1,48.5 | 0.944 | 0.725 | 0.998 | 0.859 |
| **Maximum Qx (%)** | 51.8 | 11.4 | 48.1 | 43.4,56.6 | 50.7 | 6.4 | 48.3 | 45.6,54.7 | 65.3 | 50.4 | 48.1 | 45.7, 56.4 | 56.4 | 13.6 | 56.1 | 47.4,60.4 | 0.597 | 0.324 | 0.522 | 0.880 |
| **Average Qx (%)** | 44.4 | 6.5 | 44.6 | 39.2,48.4 | 46.2 | 7.2 | 44.8 | 42.8,51.0 | 42.3 | 8.6 | 44.6 | 34.1, 49.0 | 49.1 | 13.0 | 45.7 | 42.0,56.1 | 0.573 | 0.725 | 0.154 | 0.449 |
| **S.D. Qx (%)** | 1.8 | 0.5 | 1.7 | 1.5,2.1 | 1.5 | 0.5 | 1.5 | 1.2,1.9 | 2.4 | 1.0 | 1.7 | 1.7, 2.7 | 3.5 | 3.4 | 1.7 | 1.3,4.8 | 0.105 | 0.291 | 0.143 | 0.591 |
| **Jitter First (%)** | 0.7 | 0.5 | 0.5 | 0.4,0.8 | 0.7 | 0.9 | 0.4 | 0.3,0.7 | 0.8 | 0.7 | 0.5 | 0.4, 0.8 | 0.9 | 0.5 | 0.7 | 0.6,1.1 | 0.418 | **0.048** | 0.531 | 0.105 |
| **Jitter Second (%)** | 0.4 | 0.4 | 0.3 | 0.2,0.5 | 0.4 | 0.6 | 0.2 | 0.1,0.4 | 0.5 | 0.4 | 0.3 | 0.2, 0.5 | 0.5 | 0.3 | 0.4 | 0.3,0.7 | 0.672 | **0.045** | 0.611 | 0.098 |
| **Shimmer + (%)** | 4.7 | 1.9 | 4.4 | 3.3,6.0 | 3.6 | 2.0 | 2.7 | 2.6,4.1 | 3.2 | 1.3 | 4.4 | 2.3, 3.7 | 3.9 | 3.5 | 3.0 | 2.3,3.7 | 0.067 | 0.833 | 0.074 | 0.883 |
| **Shimmer – (%)** | -4.2 | 1.7 | -4.4 | -5.2,-3.1 | -3.3 | 1.4 | -2.9 | -3.6,-2.4 | -3.0 | 1.4 | -4.4 | -3.5, -1.9 | -4.0 | 1.5 | -3.8 | -3.9,-3.2 | 0.078 | 0.139 | 0.102 | **0.031** |
| **Jitter Factor (%)** | 0.8 | 0.7 | 0.5 | 0.4,0.8 | 0.7 | 0.9 | 0.4 | 0.3,0.6 | 0.8 | 0.7 | 0.5 | 0.4, 0.8 | 0.9 | 0.5 | 0.7 | 0.6,1.1 | 0.647 | **0.032** | 0.576 | 0.063 |
| **RAP (%)** | 0.4 | 0.3 | 0.3 | 0.2,0.5 | 0.4 | 0.6 | 0.2 | 0.1,0.4 | 0.5 | 0.4 | 0.3 | 0.2, 0.5 | 0.6 | 0.3 | 0.4 | 0.3,0.7 | 0.597 | 0.057 | 0.550 | 0.127 |
| **Shimmer dB (dB)** | 0.4 | 0.2 | 0.4 | 0.3,0.5 | 0.3 | 0.2 | 0.2 | 0.2,0.4 | 0.3 | 0.1 | 0.4 | 0.2, 0.3 | 0.3 | 0.3 | 0.3 | 0.2,0.3 | **0.037** | 0.751 | 0.051 | 0.855 |
| **NNE (dB)** | -18.9 | 5.4 | -19.6 | -22.8,-15.2 | -22.3 | 5.5 | -22.9 | -25.7,-20.8 | -23.7 | 3.6 | -19.6 | -26.0, -20.8 | -20.6 | 4.3 | -21.6 | -22.6,-18.2 | **0.049** | 0.291 | 0.079 | 0.368 |
| **CPP** | 4.3 | 1.4 | 4.3 | 3.4,5.2 | 3.6 | 1.0 | 3.6 | 2.9,4.3 | 5.7 | 1.4 | 4.3 | 5.1, 6.7 | 4.4 | 1.1 | 4.2 | 3.6,4.9 | **0.041** | 0.149 | 0.069 | 0.391 |
| **HNR (dB)** | 16.6 | 3.4 | 16.8 | 15.5,18.9 | 19.5 | 3.5 | 20.5 | 18.1,21.3 | 19.3 | 2.5 | 16.8 | 17.1, 21.2 | 19.0 | 3.1 | 19.8 | 17.6,21.1 | 0.078 | 0.5732 | 0.137 | 0.851 |
| **Mean SPL (dB)** | 87.5 | 4.2 | 86.4 | 84.6,89.8 | 85.0 | 3.8 | 84.8 | 81.9,87.9 | 91.1 | 6.9 | 86.4 | 86.9, 97.4 | 87.4 | 5.7 | 86.6 | 84.4,89.8 | 0.175 | 0.4179 | 0.551 | 0.845 |

*a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation*

*4.1.2.2 Acoustic analysis on connected speech*

4.1.2.2.1 Frequency (Fx)

The results for the DFx1 and 2 using the connected speech passage are shown in Table 8. Data are presented separately for the groups of males and females and for the whole cohort.

**Table 8: Summary table of DFx1&2 connective speech for 'normal' subjects**

| | Mean DFx1 (Hz) | Mean DFx2 (Hz) | Coherence (%) | | | | CFx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **Males** | 134.7 | 136.5 | 72.3 | 8.9 | 73.5 | 68.0, 79.9 | 3.6 | 2.1 | 3.1 | 1.9, 4.6 |
| **Females** | 218.3 | 210.5 | 52.4 | 16.3 | 54.3 | 43.3, 60.2 | 12.2 | 10.0 | 11.4 | 3.7, 17.7 |
| **Total** | 174.5 | 171.7 | 62.8 | 16.3 | 66.2 | 54.7, 74.4 | 7.7 | 8.2 | 3.4 | 2.4, 8.2 |

*IQR = interquartile range; SD=standard deviation; DFx=frequency; CFx=frequency irregularity*

Of note the mean DFx is statistically significantly higher in the females compared with the males (p=<0.001). The coherence is statistically significantly lower in the females than in the males (54.3 and 73.5 respectively, p=0.004) and this is still statistically significant when adjusting for age (adjusted p=0.036). There is a statistically significantly higher pitch irregularity within the females (11.4 and 3.1 respectively, p=0.038), although this difference is non-statistically significant when adjusting for age (adjusted p=0.094).

4.1.2.2.2 Amplitude (Ax)

The results for the DAx1 and 2 using the connected speech passage are shown in Table 9. Data are presented separately for the groups of males and females and for the whole cohort.

**Table 9: Summary table of DAx1&2 connective speech for 'normal' subjects**

| | Mean DAx1 (dB) | Mean DAx2 (dB) | Coherence (%) | | | | CAx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ***Mean*** | **SD** | ***Median*** | ***IQR*** | ***Mean*** | **SD** | ***Median*** | ***IQR*** |
| **Males** | 85.2 | 85.7 | 71.9 | 5.8 | 72.9 | 68.8, 77.2 | 2.5 | 0.9 | 2.1 | 1.8, 2.9 |
| **Females** | 87.0 | 88.2 | 64.9 | 17.6 | 60.3 | 57.1, 74.0 | 6.7 | 6.2 | 4.9 | 1.4 10.1 |
| **Total** | 86.1 | 86.9 | 68.5 | 13.0 | 72.6 | 59.4, 77.0 | 4.5 | 4.7 | 2.3 | 1.7, 4.6 |

*IQR = interquartile range; SD=standard deviation; DAx=amplitude; CAx = amplitude irregularity*

No statistically significant difference between mean DAx (p=0.149), coherence (p=0.193) or loudness irregularity (p=0.290) is demonstrated between the groups of males and females. There is no statistically significant difference when adjusting for age in mean DAx (adjusted p=0.308), coherence (adjusted p=0.402) or loudness irregularity (adjusted p=0.867).

4.1.2.2.3 Contact quotient (Qx)

The results for the DQx1 and 2 using the connected speech passage are shown in Table 10. Data are presented separately for the groups of males and females and for the whole cohort.

**Table 10: Summary table of DQx1&2 connective speech for 'normal' subjects**

| | Mean DQx1 (%) | Mean DQx2 (%) | Coherence (%) | | | | CQx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **Males** | 44.8 | 45.3 | 48.2 | 6.3 | 47.9 | 43.3, 54.4 | 12.9 | 9.0 | 13.3 | 7.8, 15.4 |
| **Females** | 43.4 | 43.3 | 23.4 | 13.7 | 22.8 | 17.1, 28.4 | 42.6 | 15.1 | 45.0 | 32.7, 52.4 |
| **Total** | 44.2 | 44.3 | 36.4 | 18.3 | 36.1 | 25.3, 47.9 | 27.0 | 15.6 | 21.9 | 13.3, 41.4 |
| *IQR = interquartile range; SD=standard deviation; DQx=contact quotient; CQX=pitch irregularity* | | | | | | | | | | |

There is no statistically significant difference in contact quotient (DQx) for males and females (p=0.438), and there is no difference when adjusting for age (adjusted p=0.06). Coherence is statistically significantly higher in males (47.9 and 22.8 respectively, p=<0.001), and this statistically significant remains when adjusting for age (adjusted p=<0.001). Contact irregularity is statistically significantly lower in males (13.3 and 45.0 respectively, p=<0.001), and this significance remains when adjusting for age (adjusted p=<0.001).

4.1.2.2.4 Combined acoustic parameters

The results for the AxFx1 and 2 using the connected speech passage are shown in Table 11.

**Table 11: Summary table of AxFx1&2 connective speech for 'normal' subjects**

| | Mean | SD | Median | IQR |
|---|---|---|---|---|
| **Males** | 82.5 | 9.0 | 86.0 | 80.5, 87.9 |
| **Females** | 62.7 | 15.1 | 62.5 | 54.6, 71.0 |
| **Total** | 73.1 | 15.6 | 77.4 | 60.0, 86.0 |
| *IQR = interquartile range; SD=standard deviation* | | | | |

AxFx is statistically significantly higher in males compared with female (86.0 and 62.5, p=0.002), and this significance remains when adjusting for age (adjusted p=0.010).

## 4.2 Voice outcomes in patients treated with TLM with those treated with RT for T1a SCC of the glottis

### 4.2.1 Patient demographics

There were 122 patients identified as having treatment for T1 glottic carcinoma on the Head & Neck database. Following review of the electronic case notes and clinic letters sixty patients were invited to take part in the study.Forty patients were recruited to this study, 20 who had completed RT and 20 who had completed TLM for T1aN0M0 glottic carcinoma more than 12 months prior to inclusion in the study. One patient from the RT group was excluded from the study following recruitment as they had laryngeal surgery prior to undergoing RT for recurrent disease. There were four females and 35 males, reflecting the relative sex bias seen with larynx cancer. There is a statistically significant difference in sex between the two groups, with a higher proportion of men in the TLM group (100% vs. 73.7%, p=0.020). The mean age is 72 years in the RT group compared with 62 years in the TLM group, although date of birth was unavailable for one patient in the TLM group and seven in the RT group. There is a statistically significant difference in age between the groups (p=0.049). The majority (30/39) of patients were previous smokers. There is a statistically significantly higher proportion of ex-smokers

in the TLM group compared with the RT group (85.0% vs. 47.4%, p=0.013). There is a statistically significantly higher proportion of patients with asthma or with COPD in the RT group compared with the TLM group (31.6% vs. 5.0%, p=0.044). There is no statistically significant difference in alcohol history or other comorbidities between the groups (Table 12). TLM and RT patients were routinely offered speech and language therapy following treatment. However none of the patients were undergoing speech and language therapy at the time of their voice recording.

**Table 12: Baseline demographics for RT and TLM patients**

| **Characteristic** | **Treatment** | | **p-value** |
|---|---|---|---|
| | **RT (n=19)** | **TLM (n=20)** | |
| **Age** | | | |
| *Mean (SD)* | 72 (7) | 62 (12) | 0.049[b] |
| *Median (IQR)* | 71 (65,78) | 66 (59,68) | |
| **Sex** | | | |
| Male | 14 (73.7%) | 20 (100%) | **0.020** [c] |
| Female | 5 (26.3%) | 0 (0%) | |
| **Smoking Status** | | | |
| *Never* | 2 (10.5%) | 1 (5.0%) | **0.013**[d] |
| *Smoker* | 2 (10.5%) | 0 (0%) | |
| *Ex-smoker* | 9 (47.4%) | 17 (85.0%) | |
| *Unknown* | 6 (31.6%) | 2 (10.0%) | |
| **Alcohol history** | | | |
| *No alcohol* | 4 (21.1%) | 1 (5.0%) | 0.770 [d] |
| *Within recommended limits (<14 units)* | 4 (21.1%) | 8 (40.0%) | |
| *Above recommended limits (14 units or above)* | 4 (21.1%) | 5 (25.0%) | |
| *Unknown* | 7 (36.8%) | 6 (30.0%) | |
| **Comorbidities** | | | |
| *Reflux disease* | 4 (21.1%) | 6 (30.0%) | 0.716 [c] |
| *Has asthma/COPD* | 6 (31.6%) | 1 (5.0%) | **0.044** [c] |
| *Ischaemic heart disease* | 3 (15.8%) | 5 (25.0%) | 0.695 [c] |
| a. Mann-Whitney U test adjusted for baseline characteristics | | | |
| b. Mann-Whitney U test | | | |
| c. Fisher's exact test | | | |
| d. Chi squared test | | | |

### 4.2.2 Subjective voice questionnaires

The complete data set for subjective voice questionnaires for the RT and TLM patient groups can be found in Appendix 7.

#### *4.2.2.1 Voice Handicap Index – 10*

The VHI-10 results for TLM and RT are presented in Table 13. The total median score for the RT group is 4 (IQR 1,7) compared with 6 in the TLM group (IQR 0,7). There is no statistical difference between the two groups with regards to Voice Handicap Index.

**Table 13: Voice handicap index–10 for RT and TLM patients**

| Domain (range) | RT (N=19) | | | | TLM (N=20) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **Functional (0 - 20)** | 2.0 | 2.1 | 1 | 0,3 | 2.4 | 2.3 | 2 | 0,4 | 0.666 | 0.925 |
| **Physical (0 - 12)** | 2.4 | 2.1 | 2 | 1,4 | 2.0 | 2.0 | 2 | 0,3 | 0.574 | 0.328 |
| **Emotional (0 - 8)** | 0.6 | 1.0 | 0 | 0,1 | 0.5 | 0.8 | 0 | 0,1 | 0.567 | 0.350 |
| **Total (0 - 40)** | 4.9 | 4.4 | 4 | 1,7 | 4.9 | 4.3 | 6 | 0,7 | 0.809 | 0.614 |
| *a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

#### *4.2.2.2 VoiSS*

The VoiSS questionnaire results for TLM and RT are shown in Table 14. The highest scores are recorded for the impairment domain whilst the emotional domain questions resulted in the lowest scores. The total median score for the RT group is 17 (IQR 8, 32) compared with 18 in the TLM group (IQR 9,28). There is no statistical difference between the two groups with regards to VoiSS scores.

**Table 14: VoiSS questionnaire for RT and TLM patients**

| Domain (range) | RT (N=19) | | | | TLM (N=20) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **Impairment (0-60)** | 14.2 | 10.9 | 13 | 5,23 | 11.4 | 8.8 | 11 | 4,18 | 0.396 | 0.187 |
| **Emotional (0-32)** | 1.1 | 1.8 | 0 | 0,2 | 1.7 | 2.2 | 1 | 0,2 | 0.431 | 0.903 |
| **Physical (0-28)** | 5.9 | 4.7 | 5 | 2,9 | 5.0 | 2.4 | 5 | 4,6 | 0.906 | 0.247 |
| **Total (0-120)** | 21.2 | 15.6 | 17 | 8,32 | 18.0 | 10.8 | 18 | 9,28 | 0.715 | 0.255 |
| *a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

*IQR – interquartile range

### 4.2.3 QoL questionnaire: UW-QoLv4

The health related QoL results are shown in Table 15. The full data set can be found in Appendix 8. There is a statistically significantly higher score in the TLM compared with the RT group for appearance (p=0.003), recreation (p=0.048), chewing (p=0.015) and saliva (p=0.016), however these are not statistically significant when adjusted for age. The lowest mean scores are recorded for the RT group in the activity (76.3) and recreation (77.6) domains. Whilst for the TLM group the lowest mean scores are reported for the anxiety (85.8) and mood (88.8) domains.

**Table 15: Summary table for UW-QoLv4 domain scores for RT and TLM patients**

| | RT (N=19) | | | | TLM (n=20) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **Pain** | 92.1 | 20.5 | 100.0 | 100.0,100.0 | 97.5 | 7.7 | 100.0 | 100.0,100.0 | 0.529 | 0.178 |
| **Appearance** | 90.8 | 12.4 | 100.0 | 75.0,100.0 | 100 | 0.0 | 100.0 | 100.0,100.0 | **0.003** | 0.996 |
| **Activity** | 76.3 | 30.6 | 100.0 | 50.0,100.0 | 92.5 | 16.4 | 100.0 | 100.0,100.0 | 0.055 | 0.075 |
| **Recreation** | 77.6 | 26.2 | 75.0 | 62.5,100.0 | 91.3 | 18.6 | 100.0 | 100.0,100.0 | **0.048** | 0.137 |
| **Swallowing** | 95.3 | 11.2 | 100.0 | 100.0,100.0 | 100 | 0.0 | 100.0 | 100.0,100.0 | 0.068 | 0.996 |
| **Chewing** | 84.2 | 29.1 | 100.0 | 75.0,100.0 | 100 | 0.0 | 100.0 | 100.0,100.0 | **0.015** | 0.996 |
| **Speech** | 88.4 | 19.5 | 100.0 | 70.0,100.0 | 95.3 | 11.2 | 100.0 | 100.0,100.0 | 0.236 | 0.341 |
| **Shoulder** | 91.6 | 18.6 | 100.0 | 100.0,100.0 | 95.0 | 16.7 | 100.0 | 100.0,100.0 | 0.370 | 0.291 |
| **Taste** | 94.7 | 22.9 | 100.0 | 100.0,100.0 | 98.5 | 6.7 | 100.0 | 100.0,100.0 | 0.941 | 0.760 |
| **Saliva** | 84.2 | 30.6 | 100.0 | 85.0,100.0 | 100 | 0.0 | 100.0 | 100.0,100.0 | **0.016** | 0.997 |
| **Mood** | 92.1 | 14.6 | 100.0 | 87.5,100.0 | 88.8 | 20.6 | 100.0 | 75.0,100.0 | 0.735 | 0.609 |
| **Anxiety** | 86.3 | 23.4 | 100.0 | 70.0,100.0 | 85.8 | 20.3 | 100.0 | 70.0,100.0 | 0.690 | 0.813 |
| *a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

The two composite scores, calculated from the UW-QoLv4, 'Physical Function' and 'Social Function' are shown in Table 16. The RT group have a statistically significantly lower median score compared to TLM in physical function (p=0.004) and this remains statistically significant when adjusted for age (adjusted p=0.036). There is no statistically significant difference for social function (adjusted p=0.114)

**Table 16: UW-QoLv4 composite quality of life scores of physical and social function for RT and TLM patients**

| | RT (N=19) | | | | TLM (N=20) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Median*** | ***IQR*** | ***Mean*** | ***SD*** | ***Median*** | ***IQR*** | | |
| **Physical function** | 89.6 | 12.9 | 95.0 | 83,100 | 99.0 | 2.1 | 100 | 100,100 | **0.004** | **0.036** |
| **Social function** | 86.0 | 14.7 | 89.1 | 70.6,100 | 91.8 | 9.6 | 93.3 | 89.8,100 | 0.297 | 0.114 |
| *a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

The composite scores are illustrated in box-plots for physical function and social function in Figure 30 and 31. The box plot graphs demonstrate the worse score and the increased range in the physical and social function of the RT group.

**Figure 30: Box plot of physical function for RT and TLM patients**

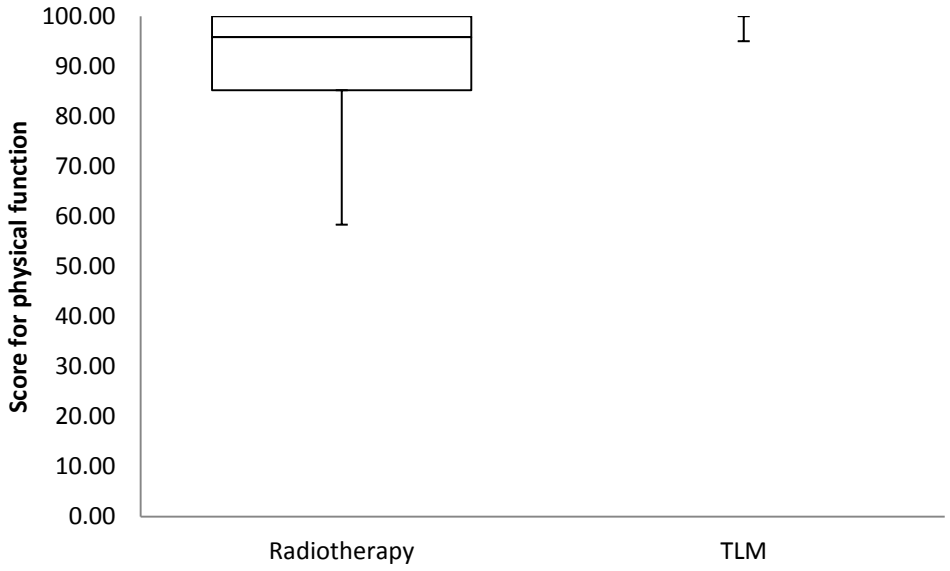
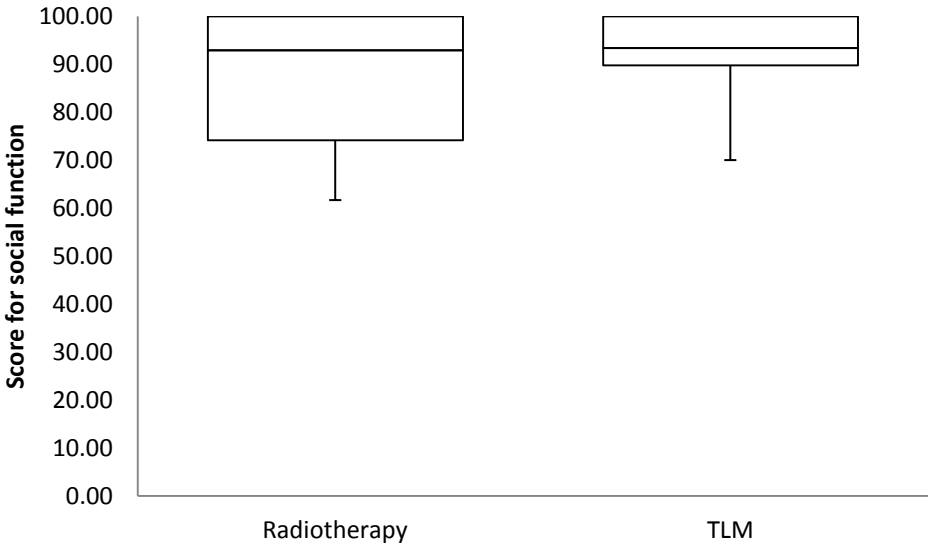



**Figure 31: Box-plot of social function for RT and TLM patients**




The global questions of the UW-QoLv4 were completed for only eight out of 20 patients from the TLM group due to an administrative error in the printing of the questionnaires, which was not possible to resolve at a later stage. The results for global questions are presented in Table 17. No statistically

significant difference in the global questions is demonstrated between the two groups.

**Table 17: Summary table for UW-QoLv4 global questions for RT and TLM patients**

| | RT (N=19) | | | | TLM (N=20) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **A. Health-related QOL compared to month before had cancer** | 56.9 | 22.4 | 50.0 | 50.0, 50.0 | 68.8 | 25.9 | 50.0 | 50.0, 100.0 | 0.248 | 0.453 |
| **B. Health-related QOL during the past 7 days** | 72.2 | 21.8 | 80.0 | 60.0, 80.0 | 70.0 | 18.5 | 70.0 | 60.0, 80.0 | 0.705 | 0.931 |
| **C. Overall QOL during the past 7 days** | 75.6 | 22.3 | 80.0 | 60.0, 95.0 | 77.5 | 12.8 | 80.0 | 75.0, 80.0 | 0.953 | 0.538 |
| *a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

In the final part of the UW-QoLv4 it asks participants to report which are the three most important domain issues over the past seven days. The most commonly selected domain issues across both groups are: speech (9/39); activity (8/39); recreation (6/39) and anxiety (6/39).

### 4.2.4 Perceptual rating

The full data set is presented in Appendix 9. Voice was rated by three expert raters for 14 of the 20 TLM patients and for 7 out of 19 RT patients. The remaining six TLM and 12 RT patients were rated by one expert rater.

The mean for each GRBAS indicator is similar for the RT and TLM groups except for roughness where the mean GRBAS score is statistically significantly higher for RT compared with TLM group (1.46 vs. 0.85, adjusted p=0.001). There is no statistically significant difference between the combined

mean for the RT and TLM groups, 5.49 [95% CI 3.95, 7.04] vs. 5.12 [95% CI 3.79, 6.44], adjusted p=0.254 (Table 18).

**Table 18: Combined mean GRBAS scores for RT and TLM patients**

| | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) | Total (0-15) |
|---|---|---|---|---|---|---|
| **RT (n=19)** | 1.72 | 1.46 | 0.98 | 0.49 | 0.86 | 5.49 |
| **TLM (n=20)** | 1.50 | 0.85 | 1.13 | 0.65 | 1.02 | 5.12 |
| **p value [a]** | 0.424 | **0.004** | 0.909 | 0.383 | 0.461 | 0.682 |
| **Adjusted p value [b]** | 0.172 | **0.001** | 0.803 | 0.414 | 0.836 | 0.254 |
| *a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test* | | | | | | |

### 4.2.5 Acoustic analysis

#### *4.2.5.1 Acoustic analysis on sustained vowels*

Analysis was undertaken on sustained /i/ and /a/ vowel sounds. A full data set is available in Appendix 10. It was not possible, for technical reasons, despite repeated attempts, to gain a waveform for /i/ and /a/ vowel sounds for two RT patients. Similarly waveforms for /i/ and /a/ vowel sounds were not achievable for three patients in the TLM group. In two of the RT patients the neck tissue rigidity (due to fibrosis following RT) prevented the measurement of a constant Lx waveform signal. In addition a further two patients found the neck strap too tight and uncomfortable and therefore could not tolerate an optimal EGG. Thus the waveform measured in these two patients was inconsistent as the neck straps were too loose during the EGG recording. Finally, a further patient with a larger neck size due to excess adipose tissue made it difficult to gain an adequate EGG recording.

Table 19 presents mean values, 95% confidence intervals and p values for acoustic groups. The majority of acoustic parameters do not show any statistical difference between RT and TLM groups for either /i/ or /a/ vowel sounds. Without adjusting for age, only SD Fx for /a/ and HNR for /a/ show any statistically significant difference between groups. The only age-adjusted statistically significant differences are for average Fx for /a/, S.D. Fx /i/, and HNR for /a/.

**Table 19: Acoustic analysis of both sustained vowels for RT and TLM patients**

| | RT /a/ | | | | RT /i/ | | | | TLM /a/ | | | | TLM /i/ | | | | P value [a] | | Adjusted p value [b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | IQR | Mean | SD | Median | IQR | Mean | SD | Median | IQR | Mean | SD | Median | IQR | /a/ | /i/ | /a/ | /i/ |
| **Minimum Fx (Hz)** | 119.2 | 49.3 | 118.4 | 55.2, 205.0 | 125.3 | 40.4 | 130.7 | 87.9, 151.4 | 146.2 | 35.4 | 149.2 | 134.7,172.3 | 146.4 | 50.0 | 151.9 | 119.8, 179.0 | 0.052 | 0.186 | 0.057 | 0.133 |
| **Maximum Fx (Hz)** | 430.1 | 433.4 | 217.9 | 112.3, 1335.1 | 265.4 | 236.2 | 169.8 | 139.6, 255.1 | 243.0 | 251.6 | 167.3 | 157.1,196.8 | 267.0 | 279.5 | 197.7 | 166.1, 223.1 | 0.517 | 0.985 | 0.281 | 0.132 |
| **Average Fx (Hz)** | 171.6 | 51.3 | 169.2 | 104.7, 305.9 | 164.2 | 43.7 | 158.1 | 137.4, 184.7 | 165.8 | 33.6 | 156.9 | 150.4,185.8 | 186.0 | 38.1 | 182.5 | 162.3, 207.9 | 0.052 | 0.131 | **0.048** | 0.238 |
| **S.D. Fx (%)** | 18.9 | 29.4 | 4.1 | 0.8, 85.4 | 12.8 | 23.4 | 2.5 | 1.2, 6.5 | 6.3 | 18.7 | 1.5 | 1.0,2.1 | 8.0 | 19.5 | 1.1 | 0.8, 2.0 | **0.032** | 0.519 | 0.112 | **0.024** |
| **Minimum Qx (%)** | 25.9 | 19.9 | 34.7 | 0.0, 46.4 | 28.8 | 18.6 | 34.3 | 14.9, 43.5 | 34.3 | 14.8 | 36.4 | 30.8,41.7 | 34.8 | 18.2 | 35.9 | 25.5, 42.7 | 0.971 | 0.346 | 0.936 | 0.120 |
| **Maximum Qx (%)** | 59.4 | 13.2 | 55.2 | 43.6, 88.2 | 54.8 | 10.0 | 53.5 | 50, 61.4 | 50.6 | 7.4 | 51.0 | 43.8,54.9 | 55.3 | 14.2 | 51.8 | 46.7, 62.4 | 0.564 | 0.905 | 0.973 | 0.897 |
| **Average Qx (%)** | 44.0 | 8.0 | 46.4 | 23.2, 55.1 | 45.0 | 9.4 | 46.8 | 40.6, 49.1 | 44.5 | 8.0 | 41.5 | 38.5,48.4 | 45.3 | 9.8 | 43.3 | 39.0, 48.9 | 0.517 | 0.922 | 0.964 | 0.357 |
| **S.D. Qx (%)** | 6.1 | 6.9 | 2.9 | 0.7, 23.9 | 5.4 | 5.8 | 2.9 | 1.9, 6.23 | 3.8 | 4.1 | 2.2 | 1.3,5.2 | 3.8 | 5.2 | 1.7 | 1.1, 3.2 | 0.149 | 0.412 | 0.122 | 0.456 |
| **Jitter First (%)** | 8.9 | 18.0 | 2.0 | 0.5, 67.7 | 8.0 | 14.0 | 1.4 | 0.6, 5.2 | 3.3 | 10.3 | 0.8 | 0.4,1.3 | 5.3 | 11.5 | 0.7 | 0.4, 1.3 | 0.027 | 0.552 | 0.162 | 0.123 |
| **Jitter Second (%)** | 7.1 | 14.1 | 1.2 | 0.3, 49.5 | 6.3 | 11.4 | 0.8 | 0.3, 3.1 | 3.1 | 11.0 | 0.5 | 0.2,0.8 | 3.5 | 8.1 | 0.4 | 0.2, 0.8 | 0.041 | 0.418 | 0.164 | 0.671 |
| **Shimmer + (%)** | 11.3 | 11.6 | 7.4 | 3.6, 46.4 | 6.1 | 6.5 | 4.3 | 2.34, 7.0 | 8.2 | 6.0 | 6.8 | 3.9,10.7 | 5.7 | 5.9 | 4.2 | 3.0, 5.3 | 0.126 | 0.852 | 0.055 | 0.580 |
| **Shimmer – (%)** | -9.9 | 10.2 | -4.9 | -34.1, -3.4 | -8.2 | 8.8 | -5.0 | -7.4, -3.41 | -6.7 | 5.7 | -5.4 | -8.0,-3.6 | -5.4 | 3.1 | -4.7 | -7.5, -3.2 | 0.313 | 0.231 | 0.124 | 0.981 |
| **Jitter Factor (%)** | 11.6 | 23.0 | 2.0 | 0.5, 80.6 | 10.1 | 18.2 | 1.4 | 0.6, 5.1 | 4.8 | 16.8 | 0.8 | 0.4,1.3 | 5.7 | 13.2 | 0.7 | 0.4, 1.3 | 0.028 | 0.424 | 0.169 | 0.690 |
| **RAP (%)** | 5.5 | 12.0 | 1.2 | 0.3, 46.4 | 4.2 | 7.6 | 0.9 | 0.3, 3.2 | 1.5 | 4.4 | 0.5 | 0.2,0.8 | 4.1 | 9.6 | 0.4 | 0.2, 0.9 | 0.035 | 0.960 | 0.145 | 0.600 |
| **Shimmer dB (dB)** | 1.1 | 1.2 | 0.6 | 0.3, 4.2 | 0.6 | 0.6 | 0.4 | 0.2, 0.9 | 0.7 | 0.6 | 0.6 | 0.4,1.0 | 0.4 | 0.3 | 0.4 | 0.3, 0.5 | 0.120 | 0.298 | 0.051 | 0.660 |
| **NNE (dB)** | -12.8 | 6.8 | -14.9 | -21.1, 0.8 | -15.7 | 8.1 | -17.3 | -20.6, -15.3 | -18.2 | 7.0 | -18.2 | -22.8,-16.0 | -17.0 | 8.0 | -18.1 | -21.9, -16.2 | 0.117 | 0.657 | 0.213 | 0.369 |
| **CPP** | 3.4 | 1.0 | 3.6 | 1.1, 4.7 | 3.1 | 1.0 | 3.4 | 2.66, 3.6 | 4.4 | 1.4 | 4.3 | 3.7,5.1 | 3.4 | 1.3 | 3.3 | 2.2, 3.7 | 0.517 | 0.399 | 0.591 | 0.955 |
| **HNR (dB)** | 14.5 | 3.2 | 14.3 | 13.3, 16.2 | 16.2 | 5.5 | 17.7 | 14.9, 18.4 | 16.4 | 3.6 | 16.1 | 15.2,18.7 | 18.2 | 2.5 | 18.1 | 16.4, 19.2 | **0.041** | 0.172 | **0.043** | 0.414 |
| **Mean SPL (dB)** | 89.0 | 10.4 | 90.2 | 64.3, 107.7 | 88.2 | 6.9 | 88.2 | 84.9, 93.0 | 90.5 | 9.5 | 90.4 | 82.8,96.1 | 88.5 | 9.3 | 90.7 | 82.5, 93.9 | 0.773 | 0.909 | 0.824 | 0.996 |

*a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation*

*4.2.5.2 Acoustic analysis of connected speech*

The acoustic analysis could only be performed on 17 RT patients and 17 TLM patients. The reasons for not obtaining an adequate EGG recording in all of the patients have been explained in section 4.2.5.1.

4.2.5.2.1 Frequency (Fx)

The mean Fx analysis on connective speech is statistically significantly higher in the TLM group, 161.2Hz and 164.4Hz compared to 131.1Hz and 137Hz (p=0.044, p=0.009) in the RT group (Table 20). This difference remains statistically significant when adjusted for age (adjusted p=0.001). Coherence is statistically significantly higher in the TLM group (48.6% vs. 36.0%, p=0.028, adjusted p=0.027). Pitch irregularity is statistically significantly higher in the RT group (26.7% vs. 14.9%, p=0.004, adjusted p=0.013).

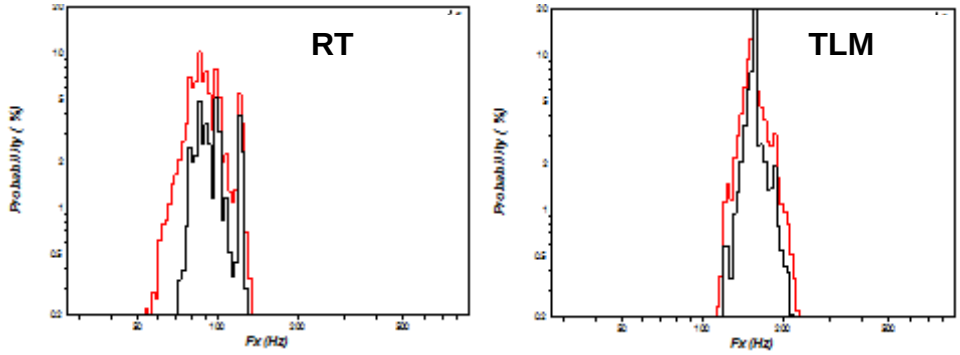
**Table 20: Summary table of DFx1&2 connective speech for RT and TLM patients**

| | Mean DFx1 (Hz) | Mean DFx2 (Hz) | Coherence (%) | | | | CFx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **RT (n=17)** | 131.1 | 137.0 | 36.0 | 18.2 | 36.5 | 24.3, 46.4 | 26.7 | 14.3 | 25.8 | 15.9, 29.2 |
| **TLM (n=17)** | 161.2 | 164.4 | 48.6 | 19.4 | 50.9 | 41.2, 60.3 | 14.9 | 19.0 | 7.7 | 4.0, 17.8 |
| **p value[a]** | **0.044** | **0.009** | **0.028** | | | | **0.004** | | | |
| **Adjusted p value[b]** | **0.001** | **0.001** | **0.027** | | | | **0.013** | | | |

*a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation; DFx=frequency; CFx=frequency irregularity*

An example of DFx1&2 on connected speech in a RT and a TLM patient is presented in figure 32.

**Figure 32: Example of DFx1&2 on connected speech in a RT and a TLM patient**




4.2.5.2.2 Amplitude (Ax)

There is no statistically significant difference in mean amplitude between the two groups. Coherence is statistically significantly higher in the TLM group compared with the RT group when adjusted for age (p=0.076, adjusted p=0.006). CAx is statistically significantly higher in the RT group, (12.4% vs. 6.3%, p=0.005, adjusted p=0.005, Table 21).

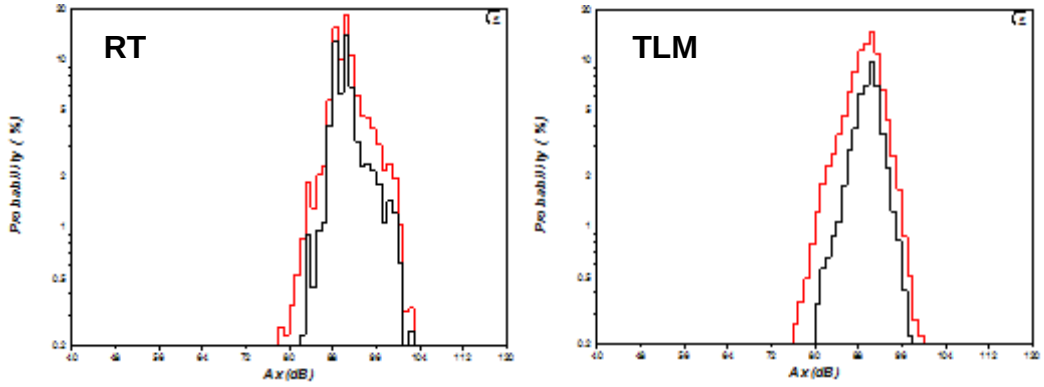
**Table 21 : Summary table of DAx1&2 connective speech for RT and TLM**

| | Mean DAx1 (dB) | Mean DAx2 (dB) | Coherence (%) | | | | CAx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **RT (n=17)** | 83.9 | 85.1 | 41.6 | 16.0 | 43.2 | 30.8, 51.0 | 12.4 | 7.0 | 10.0 | 7.7, 16.1 |
| **TLM (n=17)** | 84.8 | 85.8 | 50.2 | 10.8 | 52.5 | 42.8, 56.6 | 6.3 | 3.7 | 6.3 | 3.0, 8.1 |
| **p value[a]** | 0.380 | 0.547 | 0.076 | | | | **0.005** | | | |
| **Adjusted p value[b]** | 0.162 | 0.128 | **0.006** | | | | **0.004** | | | |

*a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation; DAx=amplitude; CAx=amplitude irregularity*

An example of DAx1&2 on connected speech in a RT and a TLM patient is presented in figure 33.

**Figure 33: Example of DAx1&2 on connected speech in a RT and a TLM patient**




4.2.5.2.3 Contact quotient (Qx)

There is no statistically significant difference in mean contact quotient (p=0.368), coherence (p=0.236) or irregularity (p=0.125) between the two groups (Table 22).

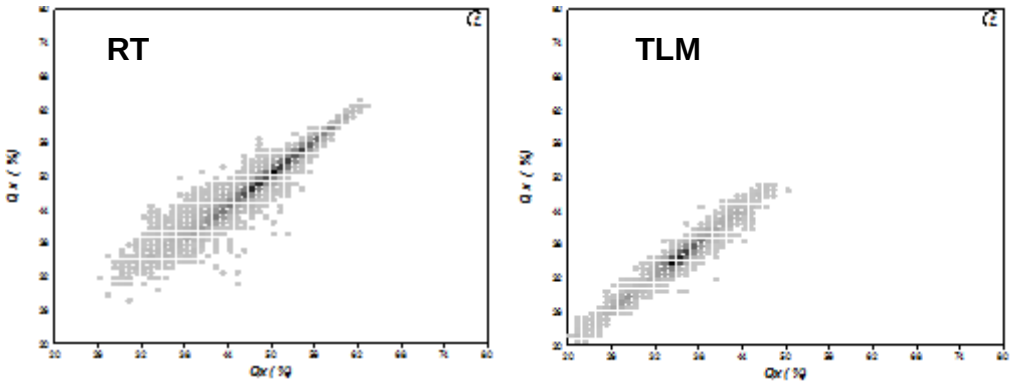
**Table 22: Summary table of DQx1&2 connective speech for RT and TLM**

| | Mean DQx1 (%) | Mean DQx2 (%) | Coherence (%) | | | | CQx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **RT (n=17)** | 45.7 | 47.4 | 24.0 | 11.0 | 21.7 | 17.1, 30.8 | 43.7 | 17.4 | 42.4 | 32.7, 38.1 |
| **TLM (n=17)** | 43.8 | 44.4 | 30.1 | 12.5 | 33.4 | 25.2, 36.1 | 34.5 | 21.0 | 26.7 | 21.3, 38.1 |
| **p value[a]** | 0.286 | 0.134 | 0.130 | | | | 0.085 | | | |
| **Adjusted p value[b]** | 0.368 | 0.104 | 0.236 | | | | 0.125 | | | |

*a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation; DQx=contact quotient; CQx=contact quotient irregularity*

An example of CQx on connected speech in a RT and a TLM patient is presented in figure 34.

**Figure 34: Example of CQx on connected speech in a RT and a TLM patient**




4.2.5.2.4 Combined acoustic parameters

The combined parameters, including amplitude and frequency, are statistically significantly higher in the TLM group compared with the RT group (61.2% vs. 47.2%, p=0.013, adjusted p=0.013, Table 23).

**Table 23: Summary table of AxFx1&2 connective speech for RT and TLM**

| | AxFx1&2 | | | |
|---|---|---|---|---|
| | ***Mean*** | **SD** | ***Median*** | ***IQR*** |
| **RT (n=17)** | 47.2 | 18.6 | 47.2 | 39.0, 57.1 |
| **TLM (n=17)** | 61.2 | 20.1 | 67.0 | 54.2, 72.9 |
| **p value[a]** | **0.013** | | | |
| **Adjusted p value[b]** | **0.015** | | | |
| *a. Mann Whitney U test; b. Age-adjusted Mann Whitney U test; IQR = interquartile range; SD=standard deviation; DFx=frequency; CFx=frequency irregularity* | | | | |

## 4.3 Longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of glottis

### 4.3.1 Patient demographics

Thirty-three patients were enrolled into this study and consented to voice recording and completion of voice (VHI-10, VoiSS) and QoL (UW-QoLv4) questionnaires prior to and twelve months after surgery. All patients approached agreed to take part in the study. All patients recruited underwent surgery between December 2008 and August 2010. Four patients were subsequently excluded from the study: two patients had tumours which were upstaged from T1a to T2 at time of the resection; one patient initially scheduled for TLM opted instead for RT; following resection one patient was diagnosed with a spindle cell carcinoma and post-operative RT was advised following MDT discussion. Consequently 29 patients met the inclusion criteria: 26 males and three females. Patient demographic information is included in Table 24. Patients were routinely offered speech and language therapy as part of the MDT. There were no patients undergoing speech and language therapy at their follow up voice recording.

Follow up data collection was performed between 12 and 24 months post TLM. Patients with a complete pre and post TLM dataset were included in the analysis. In total only 17 (58.6%) patients attended for follow up study assessments (Figure 35). There were different reasons for the patients not attending for follow up data collection. Two patients developed a primary lung carcinoma one as a synchronous primary and one as metastases and were

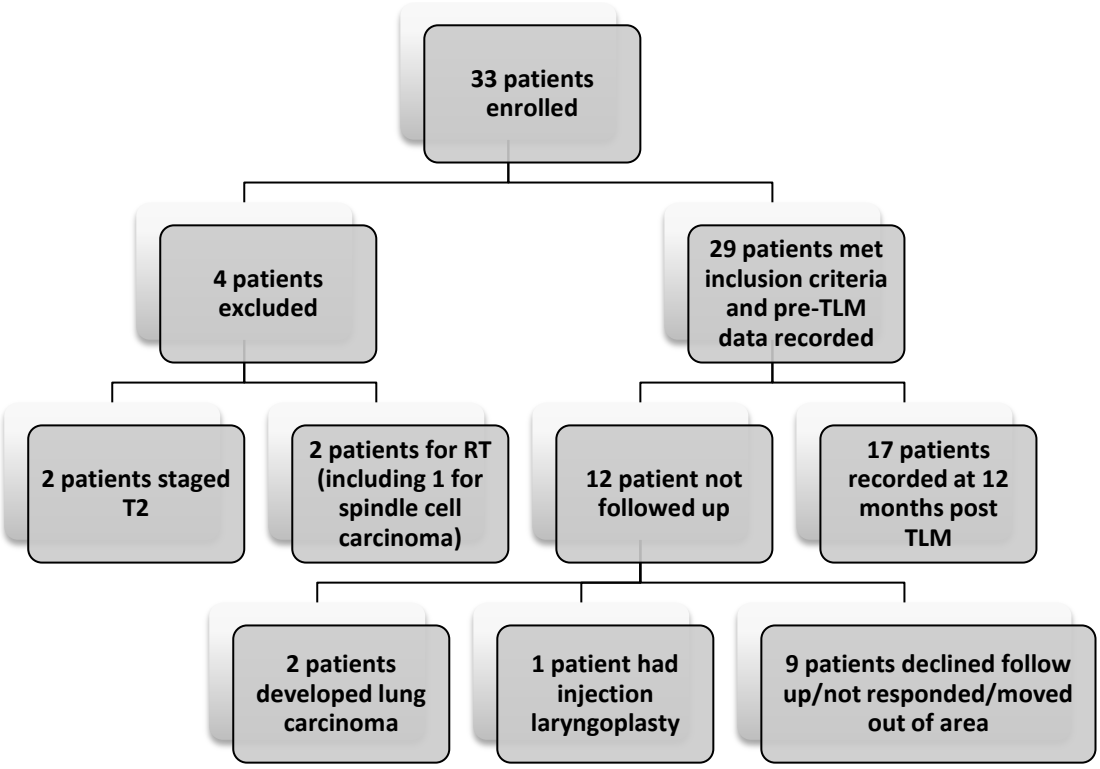
unable to return for a follow-up recording due to ill health. One patient underwent vocal cord medialisation surgery rendering them ineligible. One patient lived in the Midlands and opted for local oncological follow-up. In addition, eight patients either declined to attend or did not respond to invitations for a post TLM data recordings.

**Table 24: Baseline demographics for prospective TLM patients**

| Characteristic | Treatment | | p-value |
|---|---|---|---|
| | Pre- TLM (n=29) | Post-TLM (N=17) | |
| **Age** | | | |
| *Mean (SD)* | 61.7 (9.3) | 60 (7.0) | 0.766[b] |
| *Median (IQR)* | 60.4 (56.2, 67.8) | 59.2 (57.3, 62.0) | |
| **Sex** | | | |
| Male | 26 (89.7%) | 16 (94.1%) | 1.000[c] |
| Female | 3 (10.3%) | 1 (5.9%) | |
| **Smoking Status** | | | |
| *Never* | 4 (13.8%) | 3 (17.6%) | 0.074[d] |
| *Smoker* | 5 (17.2%) | 7 (41.2%) | |
| *Ex-smoker* | 20 (69.0%) | 7 (41.2%) | |
| **Alcohol history** | | | |
| *No alcohol* | 0 (0%) | 0 (0%) | 0.694[d] |
| *Within recommended limits (<14 units)* | 14 (48.3%) | 8 (47%) | |
| *Above recommended limits (14 units or above)* | 7 (24.1%) | 5 (29.4%) | |
| *Unknown* | 8 (27.6%) | 4 (23.5%) | |
| **Comorbidities** | | | |
| *Reflux disease* | 17 (58.6%) | 10 (58.8%) | 0.989[d] |
| *Has asthma/COPD* | 2 (6.9%) | 0 (0%) | 0.524[c] |
| *Ischaemic heart disease* | 3 (10.3%) | 1 (5.9%) | 1.000[c] |
| a. Mann Whitney U test adjusted for baseline characteristics | | | |
| b. Mann Whitney U test | | | |
| c. Fisher's exact test | | | |
| d. Chi squared test | | | |

A full dataset for all 29 patients has been included in Appendices 11 to 14.There was no statistically significant difference in quality of life or voice outcomes between the 17 included patients and the 12 excluded patients (Appendix 15).

**Figure 35: Study flow chart: outline of patient follow up**




### 4.3.2 Subjective voice questionnaires

The complete data set for subjective voice questionnaires for pre- and post-TLM patients can be found in Appendix 11.

#### *4.3.2.1 VHI-10*

There is no statistically significant difference in median scores for functional, physical and emotional outcomes pre and post TLM (Table 25).

**Table 25: Voice handicap index–10 pre and post TLM**

| Domain (range) | Pre-TLM (N=17) | | | | Post-TLM (N=17) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **Functional (0 - 20)** | 6.4 | 4.2 | 5 | 3,9 | 6.8 | 5.1 | 6 | 2,11 | 0.708 | 0.687 |
| **Physical (0 - 12)** | 6.1 | 2.6 | 6 | 4,7 | 4.6 | 3.5 | 5 | 2,7 | 0.480 | 0.413 |
| **Emotional (0 - 8)** | 2.1 | 2.2 | 2 | 1, 2 | 2.0 | 2.3 | 1 | 0,3 | 0.497 | 0.498 |
| **Total (0 - 40)** | 14.5 | 8.0 | 13 | 11, 18 | 13.4 | 10.5 | 12 | 5,20 | 0.842 | 0.843 |
| *a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

*4.3.2.2 VoiSS*

There is no statistically significant difference in median scores for impairment, emotional and physical in the pre- and post- TLM groups (Table 26).

**Table 26: VoiSS questionnaire for pre-TLM and TLM patients**

| Domain (range) | Pre-TLM (N=17) | | | | Post-TLM (N=17) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **Impairment (0-60)** | 29.2 | 10.5 | 31.0 | 21.0,32.0 | 25.1 | 14.0 | 25.0 | 13.5,40.0 | 0.897 | 0.942 |
| **Emotional (0-32)** | 4.9 | 5.0 | 4.0 | 3.0,5.0 | 5.7 | 6.3 | 2.5 | 0,11.3 | 0.594 | 0.770 |
| **Physical (0-28)** | 7.2 | 3.2 | 7.0 | 6.0, 9.0 | 7.3 | 3.8 | 6.0 | 5.0,9.3 | 0.786 | 0.757 |
| **Total (0-120)** | 41.3 | 15.5 | 43.0 | 29.0 ,49.0 | 38.1 | 21.7 | 32.5 | 19.5, 58.5 | 0.892 | 0.987 |
| *a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

### 4.3.3 QoL questionnaire: UW-QoLv4

Table 27 depicts the UW-QoLv4 results of the pre- and post-TLM patients. The full data set can be found in Appendix 12. The lowest mean scores in the pre-TLM group are anxiety (66.5), followed by speech (75.3) and mood (79.4). The post-TLM the mean anxiety, speech and mood scores have improved

(80.0, 85.9 and 83.8 respectively). There is no statistically significant difference in the UW-QOLv4 domain scores in patients pre- and post- TLM.

**Table 27: Summary table UW-QoLv4 domain scores for pre- and post-TLM patients**

| | Pre-TLM (N=17) | | | | Post-TLM (N=17) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **Pain** | 83.8 | 17.5 | 75 | 75, 100 | 95.6 | 13.2 | 100 | 75, 100 | 0.13 | 0.142 |
| **Appearance** | 97.1 | 8.3 | 100 | 100, 100 | 97.1 | 12.1 | 100 | 100, 100 | 0.900 | 0.879 |
| **Activity** | 95.6 | 13.2 | 100 | 100, 100 | 80.9 | 22.6 | 100 | 100, 100 | 0.238 | 0.163 |
| **Recreation** | 89.7 | 15.5 | 100 | 75, 100 | 86.8 | 17.9 | 100 | 75, 100 | 0.893 | 0.721 |
| **Swallowing** | 98.2 | 7.3 | 100 | 100, 100 | 94.7 | 11.8 | 100 | 100, 100 | 0.301 | 0.259 |
| **Chewing** | 100.0 | 0.0 | 100 | 100, 100 | 97.1 | 12.1 | 100 | 100, 100 | 0.997 | 0.996 |
| **Speech** | 75.3 | 25.8 | 70 | 70, 100 | 85.9 | 15.4 | 100 | 70, 100 | 0.078 | 0.042 |
| **Shoulder** | 90.0 | 23.7 | 100 | 100, 100 | 82.4 | 31.9 | 100 | 100, 100 | 0.360 | 0.314 |
| **Taste** | 98.2 | 7.3 | 100 | 100, 100 | 92.9 | 13.1 | 100 | 100, 100 | 0.805 | 0.365 |
| **Saliva** | 95.9 | 17.0 | 100 | 100, 100 | 92.4 | 18.9 | 100 | 100, 100 | 0.507 | 0.30 |
| **Mood** | 79.4 | 20.2 | 75 | 75, 100 | 83.8 | 24.9 | 100 | 75, 100 | 0.371 | 0.393 |
| **Anxiety** | 66.5 | 20.0 | 70 | 70, 70 | 80.0 | 19.7 | 70 | 70, 100 | 0.146 | 0.237 |
| *a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

The composite scores show that there is no statistically significant difference in physical (p=0.424) or social (p=0.755) function pre and post TLM (Table 28).

**Table 28: UW-QoLv4 composite scores of physical and social function for pre- and post-TLM patients**

| | Pre-TLM (N=17) | | | | Post-TLM (N=17) | | | | p value [a] | Adjusted p value [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Median* | *IQR* | *Mean* | *SD* | *Median* | *IQR* | | |
| **Physical function** | 94.1 | 5.3 | 95.0 | 90,100 | 93.3 | 9.3 | 95.0 | 90.0,100 | 0.365 | 0.424 |
| **Social function** | 84.2 | 11.3 | 86.7 | 82.5,90.8 | 84.9 | 15.3 | 90.8 | 82.5,91.7 | 0.535 | 0.755 |
| *a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation* | | | | | | | | | | |

The composite scores are illustrated in box-plots for physical function and social function in Figure 36 and 37.

**Figure 36: Box plot of physical function for pre- and post-TLM patients**

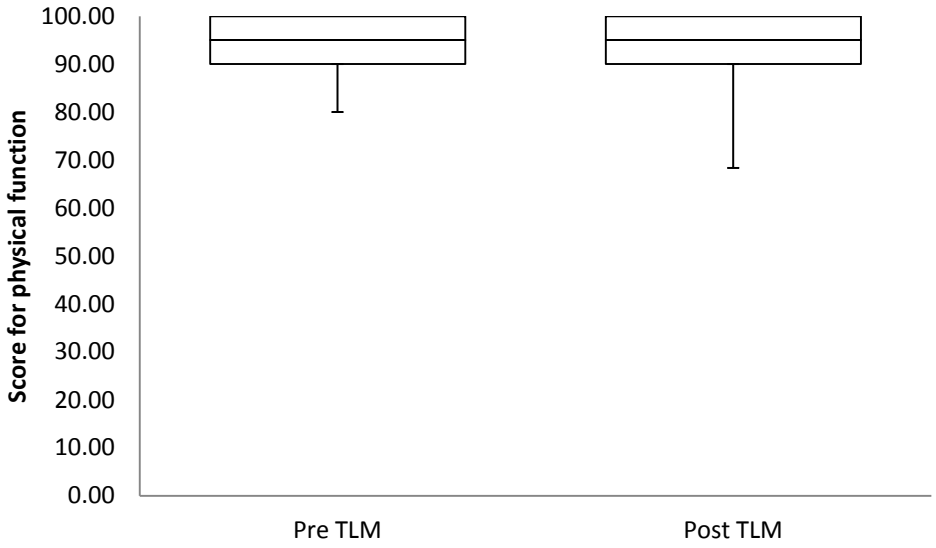
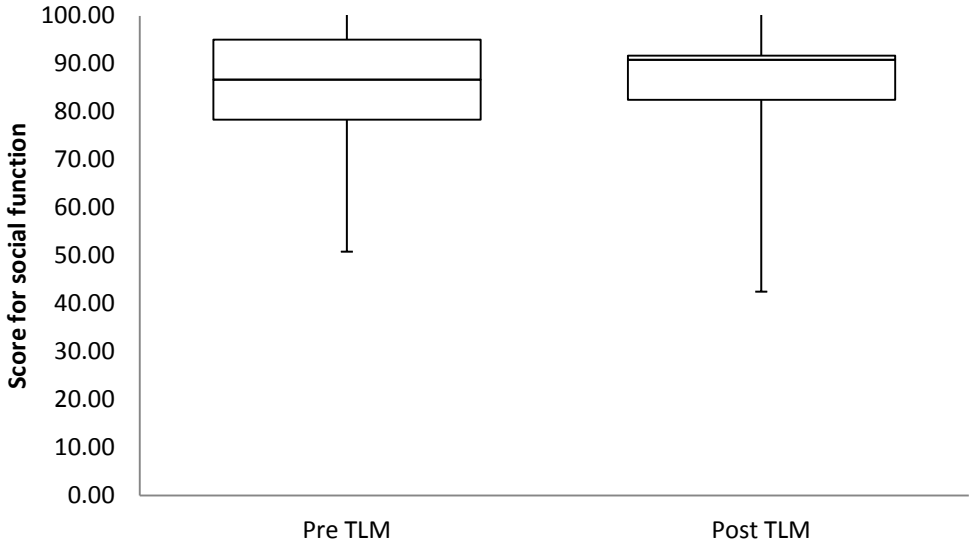



**Figure 37: Box plot of social function for pre- and post-TLM patients**




The global questions of the UW-QoLv4 were only completed by a small number of patients in the pre-operative group. The sample size is too small to allow a direct comparison of pre- and post-TLM responses.

### 4.3.4 Perceptual rating

The full data set is presented in Appendix 13. Voice was rated by one expert rater for all patients. The expert was unable to rate one pre-operative voice due to poor quality recording. This patient has been excluded from the GRBAS analysis.

There is no statistically significant difference in mean score for 'G','R','B' and 'S' indicators between pre and post TLM patients. Asthenia was statistically significantly lower in post-TLM patients (0.97 vs. 0.94, p=0.018, adjusted p=0.015, Table 29).

**Table 29: Combined mean GRBAS scores for pre- and post-TLM patients**

| | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) | Total (0-15) |
|---|---|---|---|---|---|---|
| **Pre TLM (n=16)** | 1.82 | 1.41 | 1.28 | 0.97 | 1.17 | 6.66 |
| **Post TLM (n=16)** | 1.81 | 1.38 | 1.31 | 0.94 | 1.00 | 6.44 |
| **p value [a]** | 0.648 | 0.416 | 0.058 | **0.018** | 0.345 | 0.572 |
| **Adjusted p value [b]** | 0.759 | 0.439 | 0.112 | **0.015** | 0.295 | 0.606 |
| *a. Wilcoxon test; b. Age-adjusted Wilcoxon test* | | | | | | |

### 4.3.5 Acoustic analysis

#### *4.3.5.1 Acoustic analysis on sustained vowels*

Analysis was undertaken on sustained /i/ and /a/ vowel sounds. The full data set is available in Appendix 14. Table 30 presents mean values, 95% confidence intervals and p values for acoustic analysis of sustained vowels (/a/ and /i/) for pre- and post- TLM patients. There is no statistically significant difference in the mean values for pre and post TLM in any of the indicators. This included either of the sustained vowels (/i/ or /a/).

There was acoustic data missing on five of the follow-up patients despite repeated attempts. In one patient it was not possible to gain an Lx waveform on pre or post TLM. This was due to the neck size and excess adipose tissue preventing good conduction between the electrodes. In the four patients with no acoustic data post TLM this was due to a technical error with the Laryngograph. It was not noted until after the recordings had been performed that the acoustic data had not been captured.

**Table 30: Acoustic analysis of both sustained vowels for pre- and post-TLM patients**

| | Pre-TLM /a/ (n=12) | | | | Pre-TLM /i/ (n=12) | | | | Post-TLM /a/ (n=12) | | | | Post-TLM /i/ (n=12) | | | | P value [a] | | Adjusted p value [b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | IQR | Mean | SD | Median | IQR | Mean | SD | Median | IQR | Mean | SD | Median | IQR | /a/ | /i/ | /a/ | /i/ |
| Minimum Fx (Hz) | 134.4 | 41.9 | 143.4 | 127.0, 156.7 | 140.7 | 43.8 | 149.6 | 131.9, 169.7 | 125.5 | 50.8 | 142.0 | 72.8, 159.4 | 146.0 | 59.9 | 151.9 | 113.7, 175.7 | 0.921 | 0.791 | 0.751 | 0.836 |
| Maximum Fx (Hz) | 244.1 | 221.6 | 168.7 | 155.7, 182.5 | 209.4 | 134.5 | 175.9 | 162.7, 192.0 | 314.2 | 340.9 | 188.0 | 172.6, 241.6 | 274.1 | 274.5 | 199.9 | 172.4, 227.6 | 0.042 | 0.617 | 0.054 | 0.602 |
| Average Fx (Hz) | 166.0 | 41.3 | 160.2 | 148.1, 168.4 | 167.7 | 26.8 | 167.1 | 150.5, 188.6 | 181.0 | 50.7 | 169.5 | 155.5, 185.9 | 195.5 | 65.2 | 174.9 | 161.8, 202.1 | 0.072 | 0.375 | 0.062 | 0.445 |
| S.D. Fx (%) | 11.4 | 25.7 | 1.3 | 1.1, 2.5 | 6.2 | 12.3 | 1.4 | 1.1, 1.8 | 18.5 | 34.1 | 2.0 | 1.7, 11.4 | 12.4 | 25.1 | 1.7 | 1.2, 5.0 | 0.159 | 0.661 | 0.131 | 0.733 |
| Minimum Qx (%) | 25.1 | 13.5 | 30.8 | 20.8, 34.7 | 33.1 | 14.9 | 36.5 | 30.1, 40.7 | 20.5 | 14.6 | 23.7 | 10.7, 27.7 | 26.4 | 18.4 | 31.7 | 13.7, 35.5 | 0.170 | 0.276 | 0.269 | 0.348 |
| Maximum Qx (%) | 44.4 | 13.9 | 42.7 | 39.6, 45.0 | 50.6 | 11.8 | 46.6 | 42.9, 56.2 | 49.5 | 20.5 | 43.7 | 34.6, 57.5 | 50.7 | 17.8 | 45.4 | 37.2, 65.2 | 0.903 | 0.419 | 0.869 | 0.598 |
| Average Qx (%) | 34.8 | 6.3 | 36.7 | 32.6, 37.9 | 41.5 | 6.3 | 39.7 | 36.8, 44.2 | 34.8 | 8.0 | 35.8 | 31.4, 40.1 | 37.6 | 9.3 | 36.4 | 32.5, 41.5 | 0.334 | 0.121 | 0.500 | 0.213 |
| S.D. Qx (%) | 3.7 | 4.6 | 1.9 | 1.4, 3.4 | 3.4 | 4.2 | 1.4 | 0.9, 3.7 | 7.2 | 9.7 | 2.6 | 1.5, 7.8 | 6.9 | 11.5 | 1.4 | 1.0, 4.4 | 0.508 | 0.280 | 0.520 | 0.754 |
| Jitter First (%) | 7.9 | 18.7 | 0.8 | 0.5, 2.8 | 5.5 | 11.6 | 0.8 | 0.5, 1.6 | 13.3 | 25.6 | 1.8 | 0.7, 9.4 | 14.7 | 29.9 | 1.9 | 0.9, 5.0 | 0.257 | 0.288 | 0.264 | 0.331 |
| Jitter Second (%) | 6.4 | 14.1 | 0.5 | 0.3, 1.7 | 3.5 | 7.7 | 0.4 | 0.3, 1.0 | 9.9 | 19.6 | 1.2 | 0.4, 5.1 | 8.7 | 17.6 | 1.2 | 0.5, 2.9 | 0.304 | 0.304 | 0.307 | 0.341 |
| Shimmer + (%) | 13.8 | 21.0 | 7.3 | 5.9, 11.9 | 7.2 | 6.7 | 4.2 | 3.3, 7.1 | 12.5 | 10.7 | 10.0 | 6.8, 12.5 | 7.9 | 8.7 | 6.1 | 3.0, 8.8 | 0.686 | 0.966 | 0.695 | 0.979 |
| Shimmer – (%) | -13.3 | 17.5 | -8.3 | -12.9, -6.2 | -8.4 | 7.5 | -5.4 | -9.8, -4.0 | -12.7 | 10.5 | -9.3 | -13.8, -6.8 | -7.6 | 8.0 | -5.2 | -7.4, -3.7 | 0.745 | 0.746 | 0.690 | 0.901 |
| Jitter Factor (%) | 9.9 | 21.8 | 0.8 | 0.5, 2.8 | 5.6 | 12.0 | 0.7 | 0.5, 1.6 | 16.2 | 32.3 | 1.8 | 0.7, 8.7 | 14.4 | 29.9 | 1.9 | 0.9, 4.5 | 0.328 | 0.288 | 0.336 | 0.322 |
| RAP (%) | 4.8 | 11.8 | 0.5 | 0.3, 1.7 | 3.6 | 7.7 | 0.4 | 0.3, 1.0 | 7.5 | 13.4 | 1.2 | 0.4, 6.5 | 9.6 | 18.6 | 1.2 | 0.5, 3.9 | 0.297 | 0.251 | 0.308 | 0.299 |
| Shimmer dB (dB) | 1.3 | 2.3 | 0.7 | 0.5, 1.2 | 0.7 | 0.7 | 0.4 | 0.3, 0.7 | 1.2 | 1.1 | 0.9 | 0.6, 1.1 | 0.7 | 0.8 | 0.5 | 0.3, 0.8 | 0.745 | 0.837 | 0.762 | 0.826 |
| NNE (dB) | -14.0 | 6.9 | -16.2 | -17.5, -12.4 | -16.0 | 8.4 | -19.0 | -21.0, -10.6 | -13.1 | 9.1 | -16.7 | -18.8, -5.5 | -16.7 | 10.4 | -19.9 | -22.1, -11.9 | 0.973 | 0.744 | 0.849 | 0.804 |
| CPP | 3.1 | 1.0 | 3.3 | 2.4, 3.7 | 2.8 | 1.5 | 2.5 | 2.1, 3.0 | 3.0 | 1.6 | 3.0 | 1.8, 3.7 | 2.7 | 1.6 | 2.4 | 1.8, 3.9 | 0.670 | 0.725 | 0.605 | 0.687 |
| HNR (dB) | 12.7 | 10.1 | 15.2 | 13.6, 16.7 | 17.4 | 4.6 | 18.4 | 15.2, 20.9 | 12.5 | 6.7 | 14.3 | 9.5, 16.9 | 16.9 | 9.1 | 19.6 | 16.3, 21.8 | 0.408 | 0.674 | 0.320 | 0.707 |
| Mean SPL (dB) | 89.4 | 7.1 | 89.6 | 84.7, 95.6 | 87.1 | 4.4 | 87.7 | 83.9, 89.7 | 84.5 | 9.1 | 84.8 | 78.8, 91.7 | 82.6 | 10.5 | 82.4 | 77.6, 89.9 | 0.037 | 0.148 | 0.071 | 0.238 |

*a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation*

*4.3.5.2 Acoustic analysis of connected speech*

4.3.5.2.1 Frequency (Fx)

The mean DFx is statistically significantly higher in the post TLM group (p=0.001, adjusted 0.001, Table 31). There is no statistically significant difference in the coherence (p=0.098, adjusted p=0.140) or irregularity (p=0.320, adjusted p=0.370) when comparing pre and post TLM.

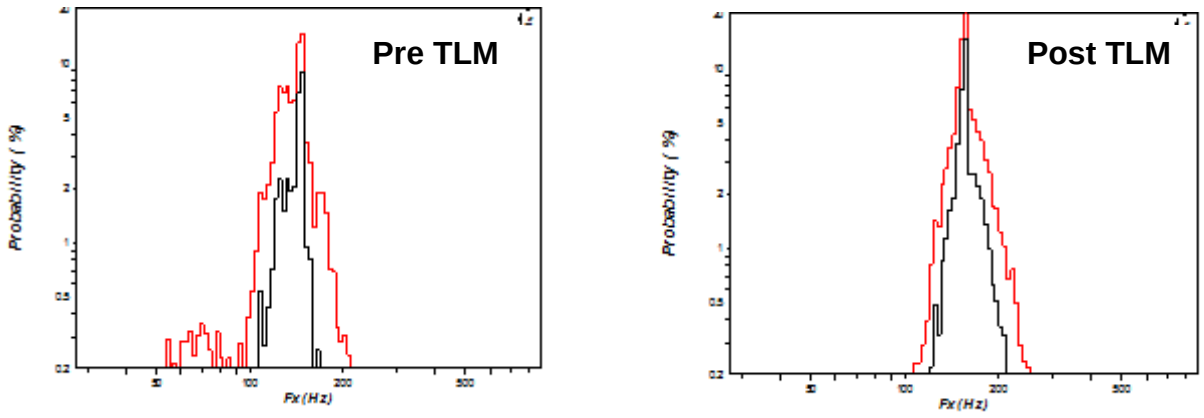
**Table 31: Summary table of DFx1&2 connective speech for pre- and post-TLM patients**

| | Mean DFx1 (Hz) | Mean DFx2 (Hz) | Coherence (%) | | | | CFx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **Pre-TLM (n=12)** | 154.4 | 150.3 | 41.0 | 14.9 | 42.6 | 32.6, 50.8 | 20.4 | 19.0 | 12.1 | 7.4, 23.5 |
| **Post-TLM (n=12)** | 197.3 | 185.1 | 28.8 | 24.5 | 22.1 | 11.3, 46.7 | 35.9 | 30.5 | 32.8 | 12.8, 49.6 |
| **p value**[a] | **0.001** | **0.002** | 0.098 | | | | 0.320 | | | |
| **Adjusted p value**[b] | **0.001** | **0.004** | 0.140 | | | | 0.370 | | | |

*a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation; DFx=frequency; CFx=frequency irregularity*

An example of DFx1&2 on connected speech on a patient pre and post TLM is presented in figure 38.

**Figure 38: Example of DFx1&2 on connected speech in a pre and post TLM patient**



4.3.4.2.2 Amplitude (Ax)

There is no statistically significant difference in the mean DAx (p=0.121), coherence (p=0.472) or irregularity of amplitude (p=0.184) when comparing pre and post TLM (Table 32).

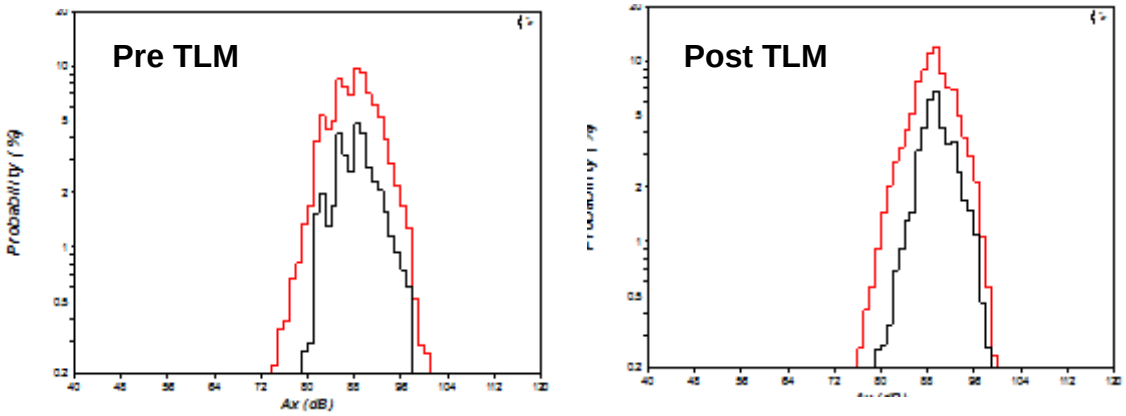
**Table 32: Summary table of DAx1&2 connective speech for pre- and post-TLM patients**

| | Mean DAx1 (dB) | Mean DAx2 (dB) | Coherence (%) | | | | CAx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **Pre-TLM (n=12)** | 84.9 | 86.1 | 48.7 | 15.8 | 47.9 | 39.5, 54.6 | 8.0 | 6.5 | 6.5 | 4.1, 9.6 |
| **Post-TLM (n=12)** | 79.8 | 80.7 | 42.5 | 22.8 | 45.0 | 24.8, 56.3 | 12.6 | 14.1 | 7.1 | 2.5, 14.8 |
| **p value[a]** | 0.113 | 0.088 | 0.481 | | | | 0.805 | | | |
| **Adjusted p value[b]** | 0.195 | 0.165 | 0.479 | | | | 0.905 | | | |

*a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation; DAx=amplitude; CAx=amplitude irregularity*

An example of DAx1&2 on connected speech on a patient pre and post TLM is presented in figure 39.

**Figure 39: Example of DAx1&2 on connected speech in a pre and post TLM patient**



4.3.5.2.3 Contact quotient (Qx)

There is no statistically significant difference in the mean DQx (p=0.654, adjusted p=0.904), coherence (p=0.231, adjusted p=0.293) or irregularity of the contact quotient (p=0.312, adjusted p=0.400) when comparing pre and post TLM (Table 33).

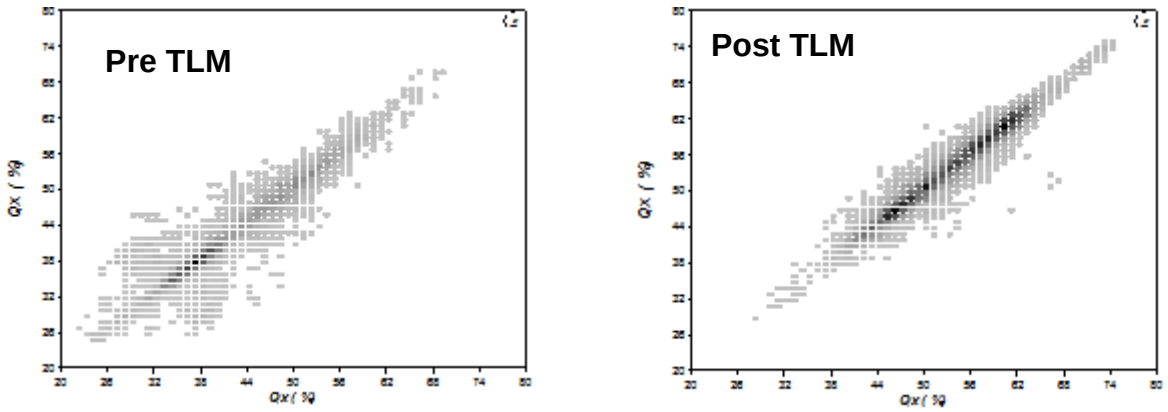
**Table 33: Summary table of DQx1&2 connective speech for pre- and post-TLM patients**

| | Mean DQx1 (%) | Mean DQx2 (%) | Coherence (%) | | | | CQx (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Mean* | SD | *Median* | *IQR* | *Mean* | SD | *Median* | *IQR* |
| **Pre-TLM (n=12)** | 38.3 | 38.5 | 25.3 | 8.6 | 28.7 | 20.1, 31.1 | 39.5 | 15.4 | 33.0 | 28.1, 46.0 |
| **Post-TLM (n=12)** | 39.9 | 38.5 | 19.9 | 14.9 | 17.1 | 10.5, 28.7 | 50.7 | 28.0 | 50.4 | 32.3, 64.4 |
| **p value[a]** | 0.908 | 0.654 | 0.231 | | | | 0.312 | | | |
| **Adjusted p value[b]** | 0.678 | 0.904 | 0.293 | | | | 0.400 | | | |

*a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation; DQx=contact quotient; CQx=contact quotient irregularity*

An example of CQx on connected speech on a patient pre and post TLM is presented in figure 40.

**Figure 40: Example of CQx on connected speech in a pre and post TLM patient**



4.3.4.2.4 Combined acoustic parameters

The combined parameters demonstrate amplitude (Ax) and frequency (Fx) distribution. There is no statistically significant difference in the combined parameters pre and post TLM (p=0.098, adjusted p=0.134, Table 34).

**Table 34: Summary table of AxFx1&2 connective speech for pre- and post-TLM patients**

| | AxFx1&2 | | | |
|---|---|---|---|---|
| | ***Mean*** | **SD** | ***Median*** | ***IQR*** |
| **Pre-TLM (n=12)** | 54.2 | 16.8 | 60.5 | 45.5, 65.3 |
| **Post-TLM (n=12)** | 39.2 | 26.8 | 37.9 | 20.0, 60.5 |
| **p value[a]** | 0.098 | | | |
| **Adjusted p value[b]** | 0.134 | | | |

*a. Wilcoxon test; b. Age-adjusted Wilcoxon test; IQR = interquartile range; SD=standard deviation; DFx=frequency; CFx=frequency irregularity*

# 5. Discussion

There were three parts to this research: to describe acoustic parameters of 'normal' voice; to compare voice outcomes in patients treated with TLM with those treated with radiotherapy for T1a SCC of the glottis; and to investigate longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of the glottis.

## 5.1 Acoustic parameters of a 'normal' voice

The aim of the study of 'normal' voice was to develop a range of acoustic parameters for the 'normal' voice. Defining the acoustic parameters of 'normal' voice in a healthy group of subjects is an important initial part of this research. To date, there are no standardised values for the acoustic parameters of 'normal' voice. This is due to the number of different potential variables (including age, sex, social history and environment) which influence voice characteristics. These variables and possible combinations make it difficult to define normal acoustic parameters. It also means that research groups have to be standardised to allow comparison. In addition to these variables, different software packages use slightly different methodology to calculate acoustic parameters and so published data cannot always be directly compared.

In order to define the acoustic parameters of 'normal' voice, only subjects who scored zero on the standardised patient reported voice outcome

questionnaire, VHI-10, and on assessment of their voice recording using the GRBAS score were included.

### 5.1.1 Acoustic analysis of sustained vowels in 'normal' subjects

The electroglottographic (EGG) analysis of sustained vowels demonstrated the inherent variability of the subjectively 'normal' adult voice in males and females. The data confirms the variability between male and female voices as well as the influence of the different recorded vowel sounds used for the analysis. In terms of the fundamental frequency (Fx), the female subjects have a statistically significantly higher mean value for both vowel sounds recorded. Mean Fx is 218.7Hz for /a/ and 233.9Hz for /i/ in females and average Fx in males is 138.5Hz for /a/ and 148.5Hz for /i/.The difference in Fx between males and females is statistically significant, (adjusted p=0.001 for /a/, adjusted p=0.005 for /i/). This is consistent with the published literature on the subject, described in section 1.2.2, and is primarily due to the anatomical differences of the vocal cords between the sexes. The male vocal folds are thicker and larger compared to females. Izadi et al. [201] assessed 200 healthy adult voices (100 males and 100 females). The Fx was greater in females (170-240 Hz) compared to males (107-140Hz) and the difference was statistically significant ($p<0.05$). Studies of Fx of voice in 'normal' subjects comparing the sustained vowels /i/ and /a/ found that Fx of /i/ was higher than Fx of /a/, in line with the findings of this research.[201-203] Robb et al. in a study of 30 adults (15 females and 15 males) found average Fx in females 220 Hz /a/ and 236 Hz /i/ compared to 124 Hz /a/ and 136Hz /i/ in males.[203] This

higher mean Fx of /i/ is explained by the intrinsic higher pitch of vowel sound /i/ compared with the vowel /a/, which in turn is dictated by sex differences in laryngeal anatomy.

Contact quotient (Qx) is a measurement of the vocal fold contact during the vocal fold cycle. The mean Qx in males is 44.4% /a/ and 46.2% /i/ compared to females 42.3% /a/ and 49.1% /i/. These values show that around 45% of the time the vocal folds are in contact for the period of the vocal fold cycle. No statistically significant difference in mean Qx between males and females is identified (p=0.573 /a/, p=0.725 /i/). The literature on the difference in contact quotient between males and females is mixed, with some studies suggesting that males have a higher contact quotient and others stating there is no difference. Awan et al. [204] assessed difference in contact quotient between 25 males and 25 females with 'normal' voice. The authors found a statistically significantly higher mean Qx using EGG in males than females (0.44% vs 0.37%), although p values were not presented, i.e. males have a longer vocal fold contact time. Faria et al. [205] assessed contact quotient in 20 male and 20 female Portuguese-speakers without voice-related complaints. The authors found no statistically significant difference in Qx, or contact time, between males and females (0.447vs. 0.443, p=0.835).

Jitter is a measurement of variation of the frequency from one vocal fold cycle to another. The mean jitter factor is 0.8% and 0.7% for males for /a/ and /i/ respectively, and 0.8% and 0.9% for females for /a/ and /i/ respectively. There is no statistically significant difference in jitter factor for /a/ between males and females, however there is a statistically significant difference in /i/ (p=0.032), although this difference is no longer statistically significant once adjusted for

age (p=0.063). The literature on the difference in jitter between males and females is mixed, with some studies suggesting that males have a higher jitter and others stating there is no difference. Felippe et al. in a study of 40 'normal' voices (20 males and 20 females) reported no statistically significant difference in average jitter for /a/ between females and males (0.6% vs. 0.5% respectively), although no p values were presented.[206] Faria et al. assessed jitter in 20 male and 20 female Portuguese-speakers without voice-related complaints.[205] The authors also found no statistically significant difference in jitter factor between males and females (1.34% vs. 1.60%, p=0.285). Orlikoff [173] compared 10 'normal' males and 10 females. The mean jitter was calculated as an average of eight different sustained vowels. Mean EGG jitter was statistically significantly higher in males compared with females (0.046ms vs. 0.037ms, p=<0.0001).

The RAP (relative average perturbation) provides an average of the jitter across three vocal fold cycles. RAP is 0.4% and 0.4% for males for /a/ and /i/ respectively, and 0.5% and 0.6% for females for /a/ and /i/ respectively. There is no statistically significant difference in RAP for /a/ or /i/ between males and females (adjusted p=0.550 for /a/, adjusted p=0.127 for /i/). There is limited evidence base surrounding differences in RAP between sexes. Faria et al. assessed RAP in 20 male and 20 female Portuguese-speakers without voice-related complaints.[205] The authors found no statistically significant difference in RAP between males and females (0.1 vs. 0.1, p=0.05).

Shimmer is the variation in amplitude from one vocal fold cycle to another. Mean shimmer dB is 0.4dB and 0.3dB for males for /a/ and /i/ respectively, and 0.4dB and 0.3dB for females for /a/ and /i/ respectively. There is no

statistically significant difference in mean shimmer dB for /i/ between males and females, however there is a statistically significant difference in /a/ (p=0.037), although this difference is no longer statistically significant once adjusted for age (p=0.051). The mean shimmer dB is less than 0.5 in both sexes and vowels, which is similar to other published studies report the mean shimmer of 'normal' voice. Felippe et al. reported an average shimmer of 0.23dB for /a/ in males and 0.22dB females. [206] There was no statistically significant difference between the males and females, although no p values were presented. Orlikoff compared 10 'normal' males and 10 females. [173] The mean shimmer was calculated as an average of eight different sustained vowels. There was no statistically significant difference in mean shimmer using EGG recordings between males and females (0.34dB vs. 0.27dB respectively, p=0.47).

NNE, normalized noise energy, measures turbulent noise caused by insufficient glottic closure during phonation. NNE is -18.9dB and -22.3dB for males for /a/ and /i/ respectively, and -23.7dB and -20.6dB for females for /a/ and /i/ respectively. There is no statistically significant difference in NNE for /i/ between males and females, however there is a statistically significant difference in /a/ (p=0.041), although this difference is no longer statistically significant once adjusted for age (p=0.069). I was unable to find any English language papers but two studies, one in Spanish and one in Chinese, found statistically significant differences in NNE across the sexes[207,208].

CPP, cepstral peak prominence, is a measure of the degree of harmony within a voice and predicts breathiness of voice. CPP is 4.3 and 3.6 for males for /a/ and /i/ respectively, and 5.7 and 4.4 for females for /a/ and /i/ respectively.

There is no statistically significant difference in CPP for /i/ between males and females, however there is a statistically significant difference in /a/ (p=0.041), although this difference is no longer statistically significant once adjusted for age (p=0.069). These values are similar to values presented in study of 780 'normal' voice samples conducted by Shrivastav, where mean CPP was found to be 4.8.[178] This study did not differentiate CPP by sex.

HNR, harmonics to noise ratio, is an objective measure of hoarseness. HNR is 16.6dB and 19.5dB for males for /a/ and /i/ respectively, and 19.3dB and 19.0dB for females for /a/ and /i/ respectively. There is no statistically significant difference in HNR for /a/ or /i/ between males and females (adjusted p=0.137 for /a/, adjusted p=0.851 for /i/). There is limited evidence base surrounding differences in HNR between sexes. In a study of Turkish speakers (44 women and 39 men) there was no gender effect in HNR, p=0.097 for /i/ and p=0.280 for /a/ .[209]

SPL, sound pressure level, is the local pressure deviation from the average atmospheric pressure caused by a sound wave. Mean SPL is 87.5dB and 85.0dB for males for /a/ and /i/ respectively, and 91.1dB and 87.4dB for females for /a/ and /i/ respectively. There is no statistically significant difference in SPL for /a/ or /i/ between males and females (adjusted p=0.551 for /a/, adjusted p=0.845 for /i/). There is limited evidence base surrounding differences in SPL between sexes. Wang et al. assessed voice in 45 Taiwanese females and 45 Taiwanese males. [210] There is no statistically significant difference in mean SPL between males and females (77.5dB vs.77.8dB), although no p value was provided.

In summary, frequency was statistically significantly different between males and females, resulting in females having a subjectively higher pitched voices. All other parameters were not statistically significantly different, when adjusted for age. There is variation in the literature relating to these other parameters. Our data adds to the current evidence base.

### 5.1.2 Acoustic analysis of connected speech in 'normal' subjects

The analysis of connected speech in the 'normal' subjects also demonstrated an increase in Fx in females. Mean Fx is statistically significantly higher in females than males (218.3Hz and 210.5Hz in females vs. 134.7Hz and 136.5Hz in men, p=<0.001). As described above, females are known to have higher voice frequency than males, primarily due to the anatomical differences of the vocal cords between the sexes. The distribution of frequency was also calculated, known as DFx1 and a second order distribution, DFx2, was based on successive pairs of vocal fold cycles. Irregularity is calculated by measuring the difference between DFx1 and DFx2. In contrast, coherence is calculated by measuring the similarity between DFx1 and DFx2.

Coherence of frequency is statistically significantly lower in females than in males (54.3% and 73.5% respectively, p=0.004) and this is still statistically significant when adjusting for age (p=0.036). There is a statistically significantly higher pitch irregularity in females compared with males (11.4% and 3.1% respectively, p=0.038), although this difference is not statistically significant when adjusting for age (p=0.094). These values are similar to those presented in the published literature from other patients with 'normal' voices.

Kazi et al. used a control group of 31 ‘normal’ subjects when comparing speech outcomes from laryngectomy patients.[211] In the ‘normal’ group the CFx irregularity was 11.5% in males and 7.7% in females, although no p values were presented. In contrast to data presented in this thesis, Moon et al. performed acoustic analysis on 202 healthy volunteers, 87 males and 115 females.[212] The subjects were native Korean speakers aged 20 to 69 years of age. The mean CFx was 29.32% (+/- SD 16.39) in males and 23.83 (+/- SD 17.64) in females and this difference was statistically significant ($p<0.05$).

Amplitude (Ax) is an indication of loudness of voice. There is no statistically significant difference between mean amplitude ($p=0.149$), coherence ($p=0.193$) or loudness irregularity ($p=0.290$) between males and females. There was no statistically significant difference when adjusting for age in mean amplitude ($p=0.308$), coherence ($p=0.402$) or loudness irregularity ($p=0.867$). In contrast to my results, Moon et al. assessed voice in 202 healthy Korean speakers. The authors found the mean CAx to be higher in men and this was statistically significant ($p<0.05$).[212] In patients aged 30 to 49, the CAx was 10.5% in males and 9.1% females, and for those aged 50 to 69, the CAx was 10.9% in males and 6.5% for females. This study illustrates the differences in CAx by age, and hence why it is was important to adjust for it in the analysis.

Contact quotient (Qx) is the degree of contact between vocal folds during the vocal fold cycle. A breathy voice leads to a decrease in the Qx value whereas a pressed voice causes the Qx values above ‘normal’. There is no statistically significant difference in mean Qx for males and females (adjusted $p=0.060$). Coherence is statistically significantly higher in males (47.9% and 22.8%

respectively, p=<0.001), and this statistically significant remains when adjusting for age (p=<0.001). Contact irregularity is statistically significantly lower in males (13.3% and 45.0% respectively, p=<0.001), and this statistically significant remains when adjusting for age (p=<0.001). As described above in the section on sustained vowels there have been reported gender differences in the Qx. Awan et al. [204] found a greater mean contact quotient in men compared to women in 50 'normal' subjects. The authors found a statistically significantly higher mean Qx in males than females (0.44% vs 0.37%), although p values were not presented. I could not find any published evidence to support a gender difference in irregularity or coherence. In summary, fundamental frequency is statistically significantly different between males and females, with females having a perceived higher pitch of voice. This corresponded with the published data. Amplitude and CQx were not statistically significantly different, when adjusted for age. There is variation in the literature on these other parameters and this data adds to the current evidence base. There is limited published data on coherence and irregularity of the laryngograph waveform (Lx) on 'normal' voice.

### 5.1.3 Study limitations

An inevitable criticism of the 'normal' voice dataset is the size of the cohort. There are only 20 subjects and therefore, taking into account the high number of variables discussed above, such a small cohort will not be fully representative of the adult population, as a whole. Despite these limitations the acoustic analysis data on 'normal' subjects does provide a large number

of parameters for each subject for both sustained vowels and connective speech.

#### *5.1.3.1 Differences between groups*

Although it is possible to compare this ‘normal’ cohort of participants with patients with T1a carcinoma of the larynx included in the other two studies, there are differences in these populations which make the comparison less robust. The age, gender, smoking history and comorbidities are substantially different between these groups of individuals. Ideally, in order to compare with the T1a patients, the ‘normal’ cohort would be matched by these factors. Another possibility would be to account for these variables in the statistical analyses. However, given the small number of patients and the large number of variables, it was only possible to adjust for age.

As the data were assumed to be non-parametric, the adjustment required was a proportional odds ordinal logistic model. Due to the small sample size, it was not possible to adjust for any other variable. In particular, there were only five females in this study, and so it was not possible to adjust for sex.

#### *5.1.3.2 Statistical concerns*

As this study is exploratory in nature, no primary outcome was identified and no sample size calculation was undertaken. A large number of statistical tests have been performed on the data, and this leads to a risk of statistical error, in

particular a type II error or having a false negative result. Therefore it is important to read the results of the statistical analysis with some caution.

## 5.2 Voice outcomes in patients treated with TLM with those treated with RT for T1a SCC of the glottis

The voice of 20 patients who had TLM were compared to 19 patients who had RT for T1a of the larynx. All patients recruited were at least one year post treatment. When comparing demographic data of the TLM group compared with the RT group, the TLM group are statistically significantly younger (mean age 62yrs vs. 71yrs, p=0.049 in the TLM and RT groups respectively); there is a higher proportion of males in the TLM group (100% vs 73.7%, p=0.020); and there is a statistically significantly higher proportion of smokers and ex-smokers in the TLM group (57.9% vs. 85.0%, p=0.013). There is a statistically significantly higher proportion of patients with asthma and COPD in the RT group compared with the TLM group (15.8% vs. 5.0%, p=0.044). There is no statistically significant difference in the number of patients with reflux disease or ischaemic heart disease.

### 5.2.1 Self-reported questionnaire TLM and RT

There is no statistically significant difference between median scores in VHI-10 for RT or TLM groups (4 vs. 6 respectively p=0.809, adjusted p=0.614). The maximum score for the VHI-10 questionnaire is 40, with the highest score for patients with perceived poor voice. As the median scores are only 4 and 6

for the two groups, both groups of patients report good outcomes in the questionnaire.

Several studies have been published which used both the full VHI and the VHI-10 to assess voice outcomes in early glottic carcinoma treated with different modalities. There is no consistency in outcome between the studies with most finding no statistically significant difference in VHI between patients undergoing TLM and RT, although there are studies which found a statistically significantly worse outcome for patients undergoing both TLM and RT. Cohen et al. performed a systematic review and meta-analysis in 2006 to compare VHI scores in patients with T1a carcinomas undergoing TLM and RT.[93] Six studies were included, which involved 208 TLM and 91 RT patients. There was no statistically significant difference in VHI score for TLM or RT patients (12.9 95% CI 10.4, 15.4 vs. 18.5 95% CI 15.1 to 22.0 respectively, p=0.2). One study included in the meta-analysis provided data on the post-operative scores post TLM depending on the type of cordectomy. There was no statistically significant difference between VHI scores in patients who had a type I or II cordectomy compared patients who had a type III cordectomy (6.2 vs. 16.5, p=0.15). A more recent meta-analysis by Du et al, assessed VHI scores for TLM and RT for T1a carcinoma in five studies (n=125 RT, n=160 TLM).[213] Only two of the papers included in Du's meta-analysis were also included in the study by Cohen. The included studies were homogenous ($I^2$=0%, p=0.41). Du found no statistically significant difference in VHI between TLM and RT (mean difference -2.19, 95% CI -5.75 to 1.37, p=0.23). Kerr et al. assessed voice outcomes in 83 patients post TLM and 49 patients post RT treated for early glottic carcinomas in three centres in Canada using the VHI-

10 questionnaire, and was not included in either meta-analysis.[214] The range of median VHI-10 scores at three time intervals over a 12 month post treatment period were 9.5-12.0 in the TLM patients and 3.5-8.0 in the RT patients. The scores were worse in the TLM group, although these values were only statistically significant at some time intervals (p=0.01-0.08). However this study also included T1b and T2 glottic tumours which are likely to have worse voice outcomes.

Greulich et al performed a meta-analysis on voice outcomes comparing RT and TLM for T1 glottic carcinoma in 2015.[215] In total eight retrospective cohort studies were included and described the outcomes of 362 patients. Six studies showed no difference in the VHI between treatment arms and two studies that favoured RT over surgery. However the meta-analysis revealed no significant difference in post treatment VHI between RT and TLM (mean difference, -5.52; 95% confidence interval, -11.40, 0.36; heterogeneity I (2) = 61%, P = .01).[215]

The total median VoiSS score for the RT group is 17 compared with 18 in the TLM group. There is no statistical difference between the two groups with regards to VoiSS scores (adjusted p=0.255). The maximum score for the VoiSS questionnaire is 120, with the highest score for patients with perceived poor voice. As the median scores are only 17 and 18 for the two groups, both groups of patients report good outcomes in the questionnaire. Two studies have been published which used both the VoiSS questionnaire to assess voice outcomes in early glottic carcinoma treated with different modalities. Robertson et al. assesses voice outcomes in 43 patients post TLM and 26 patients post RT treated for T1 carcinoma of the larynx using VoiSS

questionnaire[216] . They did not identify a difference in median VoiSS scores between TLM and RT groups (20.5, range 2-62 vs. 15.0, range 0-93 respectively, p=0.331). This study includes both T1a and T1b tumours and has not provided analysis by sub-type. Therefore VoiSS outcomes may be worse than results produced by this research. Loughran et al. assessed voice outcomes in 23 patients post TLM and 30 patients post RT treated for T1a carcinoma of the larynx using VoiSS questionnaire [106]. The authors found no statistically significant difference in mean VoiSS score between the TLM and the RT groups (27.5 vs. 20.4 respectively, p=0.35).

The quality of life questionnaire (UW-QoL version 4) demonstrated a statistically significantly higher score in the TLM compared with the RT group for appearance (p=0.003), recreation (p=0.048), chewing (p=0.015) and saliva (p=0.016), however these are not statistically significant when adjusted for age. The radiotherapy group have a statistically significantly lower median score compared to TLM in physical function (p=0.004) and this remains statistically significant when adjusted for age (p=0.036). There is no statistically significant difference for social function (p=0.441)

This may correspond with a greater number of co-morbidities in RT cohort, although it is not possible to say what the cause for the poorer quality of life rating in the RT compared with the TLM group. There is likely to be selection bias when deciding which treatment a patient should have, as patients with more co-morbidities may not be suitable for general anaesthetic and therefore require RT rather than TLM. As described previously, this was part of the difficulty with the EaStER trial in randomisation patients into treatment groups, as only fitter patients received TLM. One study was identified which assesses

quality of life in patients treated with TLM or RT for early glottic cancer. Robertson et al. assesses quality of life in 43 TLM patients and 26 RT patients treated for T1 carcinoma of the larynx using UW-QoL v4 questionnaire .The UW-QoL median score was 100 for both TLM and RT groups, p=0.586.[216]. These results are similar to those seen in this study.

In summary, I found no statistically significant difference in VHI-10, VoiSS or UW-QoLv4 scores when comparing TLM and RT. There is variation in the published data, and this study adds to the evidence base.

### 5.2.2 Perceptual rating of voice comparing TLM and radiotherapy

Perceptual rating of voice was undertaken using GRBAS voice ratings. The mean for each GRBAS indicator is similar for the RT and TLM groups except for roughness where the mean GRBAS score is statistically significantly higher for RT compared with TLM group (1.46 vs. 0.85, p=0.004, adjusted p=0.001). There is no statistically significant difference between the combined mean for the RT and TLM groups, 5.49 [95% CI 3.95, 7.04] vs. 5.12 [95% CI 3.79, 6.44], p=0.254, adjusted p=0.254. These results are similar to previous studies. Loughran et al. assessed voice outcomes using GRBAS in 18 patients in both TLM and RT treatment groups. This study demonstrated higher GRBAS scores in the TLM group compared to the RT group although this was not statistically significant (p=0.287) [106]. Vilaseca et al. has shown that with a more extensive resection of the tumour with TLM the voice outcomes are worse[108]. In this study, 42 patients were treated for T1 glottic carcinoma with TLM. The extent of the TLM resection varied from type I to V

cordectomy. In the 16 patients with extended cordectomy (types IV and V) there was a statistically significantly higher score in all GRBAS domains compared with type I-III cordectomy, with breathiness having the highest mean score across the domains. Mendelsohn et al. assessed GRBAS scores in 11 patients with T1 or T2 glottic carcinoma treated with TLM.[111] The authors demonstrated a more breathy voice in the period immediately following TLM (up to four months post-operatively) compared with pre-operatively (mean 'B' 2.50 vs. 0.75 respectively, p=0.003). However, the delayed post-operative rating of voice, after six month, improved and was statistically significantly higher than the result from up to four months post-operative (mean 'B' 1.17 vs. 2.50, p=0.005) The reason for the improvement in breathiness with time post-TLM is due to the healing of the resected tissue with fibrosis which fills in the defect and improves vocal fold contact. Kono et al. [217] compared voice outcomes of 27 RT patients with 37 TLM patients at 12 months post treatment. There GRBAS scores of roughness, asthenia and strain were similar in both groups. However the grade (0.9 for RT vs 1.28 for TLM p=0.049) and breathiness (0.61 for RT vs 0.7 for TLM, p=0.31) were worse in the TLM group.

In summary, this study showed no statistically significant difference in the perceptual rating of voice between TLM and RT, except for roughness where the mean score is statistically significantly higher for RT compared with TLM group. Published data shows a more breathy voice with an extended cordectomy. This study is generally limited to type I to III cordectomy, which may account for better voice outcomes. Published data also often includes

T1b and T2 tumours, which this study excludes, and may further account for the better voice outcomes demonstrated by the presented data.

### 5.2.3 Acoustic analysis comparing TLM and radiotherapy

#### *5.2.3.1 Acoustic analysis of sustained vowels in TLM and RT*

Average Fx is 171.6Hz and 164.2Hz for RT for /a/ and /i/ respectively, and 165.8Hz and 186.0Hz for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /i/ between RT and TLM, however there is a statistically significant difference in /a/ when adjusted for age (p=0.052, adjusted p=0.048). There is a significant difference in the baseline characteristics of the two groups with respect to gender (RT 26% females and TLM 0% females, p=0.020). This may account for the difference in the Fx between the groups. Compared to the control males the average Fx is higher in both of these groups. This is particularly relevant in the TLM group where all patients are men (average Fx 171.6Hz and 164.2Hz for /a/ and /i/ respectively for TLM and average Fx 138.5Hz and 148.5Hz for /a/ and /i/ respectively for 'normal' males). This increase in Fx for patients post treatment for TLM and RT is in line with current literature on the subject. The theories on the increase in Fx in patients post TLM is the scarring (fibrosis) following the TLM which raises the tension of the vocal folds. Du et al. undertook a meta-analysis assessing Fx in sustained vowels for TLM and RT for T1a carcinoma in four studies (n=69 RT, n=114 TLM).[213] The included studies were homogenous ($I^2$=0%, p=0.85). Du et al. found that frequency was statistically significantly higher in post TLM patients, compared with RT (mean difference -11.00, 95% CI -12.60 to -9.40, p<0.0001). Two other studies were not

included in the meta-analysis. Vilaseca et al. analysed 42 patients post TLM including 35 T1a carcinomas [108]. Compared to a control group the post TLM patients had an increase in Fx. The Fx for TLM in type I-III cordectomies were statistically significantly higher than the control group, 168.2+/-35.7Hz for /a/ and 165.5+/-43.5Hz for /i/ in the TLM group, compared to 119.7+/-19.8Hz for /a/ and 127.4+/-36.7Hz for /i/ in the control group (p=<0.001). Rovirosa et al. assessed voice outcomes in 18 patients that underwent RT for the treatment of T1 carcinoma of the larynx compared with 31 'normal' subjects.[218] In contrast to the other published papers, this study identified an increase in mean Fx in the RT group (149.7Hz in control group vs. 182.4Hz in RT group, p=0.034).

Contact quotient (Qx) is a measurement of the vocal fold contact during the vocal fold cycle. Average Qx is 44.0% and 45.0% for RT for /a/ and /i/ respectively, and 44.5% and 45.3% for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /a/ or /i/ between RT and TLM. I was unable to find any published studies including contact quotient in patients post TLM or RT on sustained vowels.

Jitter is a measurement of variation of the frequency from one vocal fold cycle to another. Jitter factor is 11.6% and 10.1% for RT for /a/ and /i/ respectively, and 4.8% and 5.7% for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /a/ or /i/ between RT and TLM groups. Both figures are substantially higher than jitter factor in 'normal' males (0.8% and 0.7% for /a/ and /i/). Other published studies have found a higher jitter post RT and TLM.

Rovirosa et al. [218] assessed the voice of 18 patients post-RT for T1 laryngeal carcinoma to 31 'normal' subjects. In sustained vowel analysis they found the

jitter was statistically significantly higher in those patients that were post RT (RT 3.5% vs. 'normal' 1.5%, p=0.0001). Du et al. undertook a meta-analysis assessing jitter in sustained vowels for TLM and RT for T1a carcinoma in three studies (n=54 RT, n=60 TLM).[213] The included studies were homogenous ($I^2$=0%, p=0.80). Du found that there was no statistically significant difference in jitter post-TLM compared with post RT (mean difference -0.03, 95% CI -0.30 to 0.23, p=0.8). One additional study, not included in the meta-analysis assessed voice in 15 patients post RT and 18 patients post TLM for mid-cord glottic T1a carcinomas[94]. The authors found no statistically significant difference in jitter between RT and TLM groups (1.00% vs. 0.45%, p=0.06).

The RAP (relative average perturbation) provides an average of the jitter across three vocal fold cycles. RAP is 5.5% and 4.2% for RT for /a/ and /i/ respectively, and 1.5% and 4.1% for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /a/ or /i/ between RT and TLM. The RAP is substantially higher for both RT and TLM compared with values for 'normal' voice. I was unable to find any published studies including RAP in patients post TLM or RT. Niedzielska et al. assessed voice outcomes in 45 men with T1 (n=24) and T2 (n=21) glottic carcinomas post RT.[219] Mean RAP was statistically significantly lower after treatment (5.33% before vs. 1.47% after, p<0.001). RAP was statistically significantly higher post treatment compared with the control (1.47% before vs. 0.61% after, p<0.05).

Shimmer is variation in amplitude from one vocal fold cycle to another. Mean shimmer dB is 1.1dB and 0.6dB for RT for /a/ and /i/ respectively, and 0.7dB and 0.4dB for TLM for /a/ and /i/ respectively. There is no statistically

significant difference in /a/ or /i/ between RT and TLM. These values are similar to those presented for 'normal' voice. The literature on shimmer post RT or TLM is mixed. Rovirosa et al. [218] assessed the voice of 18 patients post-RT for T1 laryngeal carcinoma to 31 'normal' subjects. In sustained vowel analysis they found a statistically significantly higher shimmer in those patients that were post RT compared with the 'normal' subjects (RT 2.26% vs. 'normal' 1.24%, p= 0.024). Du et al. undertook a meta-analysis assessing shimmer in sustained vowels for TLM and RT for T1a carcinoma in three studies (n=54 RT, n=48 TLM).[213] The included studies were homogenous ($I^2$=16%, p=0.30). Du found that there was no statistically significant difference in shimmer post-TLM compared with post RT (mean difference 0.19, 95% CI -0.04 to 0.43, p=1).

NNE, normalized noise energy, measures turbulent noise caused by insufficient glottic closure during phonation. Mean NNE is -12.8dB and -15.7dB for RT for /a/ and /i/ respectively, and -18.2dB and -18.1dB for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /a/ or /i/ between RT and TLM. Kazi et al. assessed voice outcomes on 17 T1 and seven T2 patients, post RT compared with 25 'normal' subjects.[220] There was no statistically significant difference in NNE post RT compared with 'normal' subjects (-14.9dB vs. -19.7dB respectively, p=0.09).

CPP, cepstral peak prominence, is a measure of the degree of harmony within a voice and predicts breathiness of voice. Mean CPP is 3.4 and 3.1 for RT for /a/ and /i/ respectively, and 4.4 and 3.4 for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /a/ or /i/ between RT and TLM. The mean CPP in the 'normal' subjects is 4.3 for /a/ and 3.6 for /i/ in the

males. The CPP appears to be similar for ‘normal’ subjects compared with post treatment patients. Stone et al. assessed voice outcomes in 14 patients treated with TLM for early glottic carcinoma.[221] The voice recordings were taken post TLM and mean time following surgery was 3.7 years. The mean CPP for sustained vowel /a/ was 5.9 (SD 2.8). There were no studies that compared CPP post TLM and RT.

HNR, harmonics to noise ratio, is an objective measure of hoarseness. Mean HNR is 14.5dB and 16.2dB for RT for /a/ and /i/ respectively, and 16.6dB and 18.2dB for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /i/ between RT and TLM. There is a statistically significant difference between /a/ (p=0.041). Rovirosa et al. [218] assessed the voice of 18 patients post-RT for T1 laryngeal carcinoma to 31 ‘normal’ subjects. In sustained vowel analysis they found no statistically significant difference in HNR in those patients that were post RT compared with the ‘normal’ subjects (RT 4.21 vs. ‘normal’ 3.63, p=0.520). Tamura et al. assessed voice in 22 patients post TLM and eight patients post RT. There was no statistically significant difference in HNR between TLM and RT groups (15.8% vs. 15.2%, p=0.58). [110]

SPL, sound pressure level, is the local pressure deviation from the average atmospheric pressure caused by a sound wave. Mean SPL is 89.0dB and 88.2dB for RT for /a/ and /i/ respectively, and 90.5dB and 88.5dB for TLM for /a/ and /i/ respectively. There is no statistically significant difference in /a/ or /i/ between RT and TLM. Jotic et al. assessed voice outcomes in 69 patients treated for Tis and T1 glottic carcinoma with TLM (n=19), RT (n=15) and

laryngofissure (n=35). Analysis was conducted using phonetogram, different to EGG used in this study. The SPL at six to 12 months following treatment was 30.1dB for TLM and 29.4dB for RT ($p<0.05$).

In summary the acoustic analysis on sustained vowels demonstrated a statistically significant difference in average Fx for /a/ when adjusted for age. The average Fx for RT and TLM is higher compared to the Fx in the control group. The literature does suggest that an increase in Fx post TLM and RT is expected. The HNR is statistically significantly higher in TLM compared with RT for /a/. Published literature found no statistically significant difference in HNR between the groups and so this result adds to the limited evidence base. The other values from in MDVP (Multi-Dimensional Voice Programme) show no statistically significant difference between RT and TLM. This demonstrates that there are similar objective voice outcomes from either treatment.

*5.2.3.2 Acoustic analysis of connected speech in TLM and RT*

In the acoustic analysis on the connective speech, the mean Fx is also higher in the TLM group compared to RT, 161.2Hz and 164.4Hz compared to 131.1Hz and 137Hz ($p=0.044$, $p=0.009$) in the RT group. This difference remains statistically significant when adjusted for age ($p=0.001$). This concurs with the discussion on the Fx in the sustained vowels and the expected elevation of Fx post treatment due to scarring of the vocal folds. Coherence of frequency is statistically significantly higher in the TLM group compared with the RT group (48.6% vs. 36.0%, $p=0.028$, adjusted $p=0.027$). Pitch irregularity is statistically significantly higher in the RT group than the TLM

group (26.7% vs. 14.9%, p=0.004, adjusted p=0.013). Therefore the RT voice is deeper and more irregular than the post TLM voice.

There are very few studies in the literature that have used EGG and connected speech analysis to assess this group of patients. Kazi et al. compared the voice of 25 T1 and T2 glottic carcinoma patients who had RT compared to a 'normal' cohort (n=25).[220] The CFx was statistically significantly worse (11.3% vs 36.7%, p=0.001) in the RT group at 12 months post treatment compared to the control. The study did not conduct any analysis to account for difference in tumour size, and did not present results for T1 compared with T2 tumours.

There is no statistically significant difference in mean amplitude between the two groups. Coherence is statistically significantly higher in the TLM group compared with the RT group when adjusted for age (p=0.076, adjusted p=0.006). CAx is statistically significantly higher in the RT group, (12.4% vs. 6.3%, p=0.005, adjusted p=0.005). I was unable to find any published literature considering amplitude in connected speech comparing TLM and RT.

There is no statistically significant difference in mean contact quotient (p=0.368), coherence (p=0.236) or irregularity (p=0.125) between the TLM and RT. The mean CQx is 43.7% and 34.5% for RT and TLM respectively and this is higher than the mean CQx in 'normal' males (12.9%). This increase in CQx has previously been described by Fourcin, who suggests that dysphonic patients with a breathy voice have a higher irregularity of contact quotient.[188]

In summary there is a higher Fx in connected speech in TLM and RT compared to the control. The TLM Fx is also statistically significantly higher than the RT Fx. This corresponds with the published literature on increase in Fx in post treatment patients. TLM can potentially cause more scarring and thus a greater post treatment Fx. In terms of the DQx analysis it might be hypothesised that TLM would create a gap in the glottis affecting this measurement. However the mean DQx are similar in TLM, RT and 'normal' subjects.

### 5.2.4 Study limitations

#### *5.2.4.1 Differences between groups*

There were statistically significant differences in age, sex, smoking status and co-morbidities between TLM and RT groups. This partly due to a selection bias, as patients with multiple co-morbidities may not be suitable for surgery. The EaStER (Early Stage Glottic Cancer Endoscopic Excision versus RT) trial, discussed in the introduction, outlines the difficulty in conducting a randomised controlled trial in this area. The aim of the EaStER study was to evaluate the outcome of patients treated with TLM or standard RT. An investigation into the reasons for the difficulties in recruitment found many issues[79]. One of the issues identified was surrounding the selection bias, where patients were not suitable for surgery.

Despite the differences in baseline characteristics, it was only possible to adjust for age. As the data was assumed to be non-parametric, the adjustment required was a proportional odds ordinal logistic model. Due to the

small sample size, it was not possible to adjust for any other variable. In particular, there were only five females in this study, and so it was not possible to adjust for sex.

*5.2.4.2 Statistical concerns*

As this study is exploratory in nature, no primary outcome was identified and no sample size calculation was undertaken. A large number of statistical tests have been performed on the data, and this leads to a risk of statistical error, in particular a type II error or having a false negative result. Therefore it is important to interpret the results of the statistical analysis with some caution.

*5.2.4.3 Missing data*

Although the UW-QoLv4 was completed by all patients the global questions were not completed by everyone. This was an administration error in the printing of the questionnaires and some patients did not receive the question to be completed. This was not identified until a later stage. It was decided to collect data at a single time point in order that the data could be compared directly for each patient and therefore patients were not asked to re-attend for a complete data recollection.

The perceptual rating was performed by three blinded expert raters. These were speech and language therapist in two separate departments. At the outset, two raters were identified to conduct the GRBAS scores on the 39 voice recordings. However, the lead contact for these raters moved out of the UK during the study and therefore another local expert rater was used to

complete the dataset. Inter-rater reliability was not completed due to there being only one rater who completed all the GRBAS scores. Ideally another rater should have been used to repeat the GRBAS scores and allow for inter-rater reliability to be assessed. The reasons another rater was not found was due to time limitations and the focus of this research being on different aspects of data analysis. The subjective outcomes and acoustic analysis were prioritised in this research.

Another study limitation was the failure to gain a complete data set of the acoustic analysis. There is missing data for two of the RT patients and three of the TLM patients. The reasons for the two RT patients were due to the rigidity of neck tissue and in the TLM patients due to the size of the neck and the discomfort of wearing the neck straps for the EGG. Multiple attempts were made to gain EGG readings but it was found not to be possible.

The extent of the surgical resection was not documented by the operating surgeons and therefore has not been included in the analysis. Locally the surgeons would select TLM over RT for smaller and mid vocal cord tumours. The typical cordectomy chosen would be a type I-III. A tumour requiring a larger resection would normally be recommended RT due to the impact on perceived voice outcomes. However, as this has not been documented, it is not possible to confirm the cordectomy type. Similarly different RT regimes have been used in the past, depending on the clinical oncologists' treatment plan. As RT is performed in an oncology centre in a different NHS Trust, it has not been possible to identify the RT regime for each patient.

## 5.3 Longitudinal changes in voice quality in patients undergoing TLM for T1a SCC of glottis

### 5.3.1 Self-reported questionnaires pre and post TLM

The VHI-10 demonstrated no statistically significant change comparing the pre and post-TLM. The mean total pre-TLM is 14.5 and 13.4 post TLM (adjusted p=0.843). In a longitudinal study by Mendelsohn et al. [111] a small number of cases  TLM (n=11) were followed up post TLM. The full VHI survey was used to record pre-operative and two post-operative TLM scores, (less than four months and more than six months from surgery). The mean VHI score was 40.9 pre-op and initially worsened to 43.8 (p=0.003) before improving in the delayed VHI to 23.7 (p=0.037). The higher score found in this study is due to the authors using the full VHI survey, rather than the shortened VHI-10 survey. The healing process and the closure of any phonatory gap were the reasons given for the initially worsening of voice and then improvement.

The VoiSS questionnaire also does not show any statistically significant difference between the pre and post TLM scores for the different domains. The total mean pre-TLM is 41.3 and post TLM 38.1 (adjusted p=0.987). I was unable to find any published evidence including VoiSS to compare voice outcomes pre and post TLM. Loughran et al. and Robertson et al. both include VoiSS data post TLM and this is included in the discussion of RT compared with TLM.[106,216]

There is no statistically significant difference between the UW-QoL4 scores for any of the domains when comparing QoL pre and post TLM. There were high

scores, throughout the domains, indicating a good pre and post TLM QoL. The composite scores show that there is no statistically significant difference in physical (p=0.424) or social (p=0.755) function pre and post TLM. This is consistent with the published literature regarding early glottic carcinomas. Stoeckli et al. assessed QoL in 91 patients treated with TLM and RT for T1 and T2 carcinoma of the larynx.[120] The study uses different QoL questionnaires (EORTC, QLQ-H&N35) however it demonstrates a good level of QoL for these patients. This study does not provide longitudinal data pre and post treatment.

### 5.3.2 Perceptual rating of voice pre and post TLM

There is no statistically significant difference in mean perceptual rating by an expert rater (6.66 pre vs. 6.44 post, adjusted p=0.606). There is no statistically significant difference in mean scores across any of the domains, except asthenia, which is statistically significantly worse pre TLM compared with post (0.97 pre vs. 0.94 post, adjusted 0.015). Vilaseca et al. reviewed the voice of 42 patients post TLM and compared with 21 control subjects [108]. No pre TLM data was available. The authors found worse GRBAS scores for all domains in post TLM compared with the control ($p<0.05$). However, this study compared patient post TLM with those with 'normal' voice, and therefore this level of dysphonia would be expected in this cohort. In a longitudinal study by Mendelsohn et al. [111] a small number of TLM cases (n=11) were followed up post TLM for T1 and T2 glottic carcinoma. The GRBAS was measured pre-operatively, initial post TLM (up to four months) and more than six months.

The mean breathiness showed a statistically significant worsening score in the initial post operatively rating (mean breathiness 0.75 to 2.50, p=0.003). However the voice recovered in the delayed post-operative rating of breathiness (1.17, p=0.005). This demonstrates the recovery of voice post TLM after six months. In my study, all patients were followed up for post TLM recordings at least 12 months post treatment. Therefore it is expected that patients' voice would have had time to recover by this point.

### 5.3.3 Acoustic analysis comparing pre and post TLM

#### *5.3.3.1 Acoustic analysis of sustained vowels on pre and post TLM*

There is no statistically significant difference in any of the acoustic parameters for pre and post TLM voice recordings. This is consistent with the findings from the perceptual ratings of voice, as described above. I was unable to find any published literature considering the acoustic parameters pre and post TLM. Therefore this shows the value of this study as it is an under-researched area. The reasons for the lack of studies including pre and post TLM data is likely to be due to the difficulty in identifying and following up patients for a considerable time period.

#### *5.3.3.2 Acoustic analysis of connected speech on pre and post TLM*

The mean DFx is statistically significantly higher in the post TLM group (p=0.001, adjusted 0.001). This is in contrast of the results of the Fx on sustained vowels. The connected speech analysis is performed on a longer

and more varied passage. Therefore analysis of connective speech is more likely to identify a statistically significant difference in Fx compared to sustained vowel analysis. There is no statistically significant difference in the coherence of frequency (p=0.098, adjusted p=0.140) or pitch irregularity (p=0.320, adjusted p=0.370) when comparing pre and post TLM.

There is no statistically significant difference in the mean DAx (p=0.121), coherence (p=0.472) or irregularity of amplitude (p=0.184) when comparing pre and post TLM.

There is no statistically significant difference in the mean DQx (p=0.654, adjusted p=0.904), coherence (p=0.231, adjusted p=0.293) or irregularity of the contact quotient (p=0.312, adjusted p=0.400) when comparing pre and post TLM. I was unable to find any published literature considering the acoustic analysis on connective speech pre and post TLM.

### 5.3.4 Study limitations

#### *5.3.4.1 Lost to follow up*

There were 29 patients included in the initial pre-operative data collection but 12 patients were not followed up. The reasons for loss to follow up are described in section 4.3.1. There is no statistically significant difference in quality of life or voice outcomes between the 17 included patients and the 12 excluded patients (Appendix 15).

Despite the differences in baseline characteristics, it was only possible to adjust for age. As the data was assumed to be non-parametric, the adjustment required was a proportional odds ordinal logistic model. Due to the small sample size, it was not possible to adjust for any other variable. In particular, there were only five females in this study, and so it was not possible to adjust for sex.

*5.3.4.2 Statistical concerns*

As this study is exploratory in nature, no primary outcome was identified and no sample size calculation was undertaken. A large number of statistical tests have been performed on the data, and this leads to a risk of statistical error, in particular a type II error or having a false negative result. Therefore it is important to interpret the results of the statistical analysis with some caution.

*5.3.4.3 Missing data*

Although there were 29 patients enrolled into this study only 17 were able to be recorded post TLM. The explanation for the 12 patients not being followed up has been described in section 4.3. It was not possible to undertake any analysis using all 29 patients enrolled, accounting for the missing data. This is as there are too many baseline characteristics and outcome variables to account for.

Although the UW-QoLv4 was completed by all patients the global questions were not completed by everyone. This was an administration error as previously discussed. Due to the limited completed global questions of the

UW-QoLv4 and the small sample size, there were insufficient data to allow a direct comparison of pre- and post-TLM responses.

Voice was rated by one expert rater for all patients. The expert was unable to rate one pre-operative voice due to poor quality recording. This patient has been excluded from the GRBAS analysis. Only one rater performed the GRBAS scores. Ideally another rater should have been used to repeat the GRBAS scores and allow for inter-rater reliability to be assessed. The reasons another rater was not found was due to time limitations and the focus of this research being on different aspects of data analysis. The subjective outcomes and acoustic analysis were prioritised in this research.

Another study limitation was the failure to gain a complete data set of the acoustic analysis. Out of the 17 patients with follow up data included in the study there was missing acoustic analysis reading in five of these cases. This was despite multiple attempts made to gain EGG readings but it was found not to be possible. In one patient it was not possible to gain an Lx waveform on pre or post TLM. This was due to the neck size and excess adipose tissue preventing good conduction between the electrodes. In the four patients with no acoustic data post TLM this was due to a technical error with the Laryngograph. It was not noted until after the recordings had been performed that the acoustic data had not been captured.

The extent of the surgical resection was not documented by the operating surgeons and therefore has not been included in the analysis. Locally the surgeons would select TLM over RT for smaller and mid vocal cord tumours. The typical cordectomy chosen would be a type I-III. A tumour requiring a

larger resection would normally be recommended RT due to the impact on perceived voice outcomes. However, as this has not been documented, it is not possible to confirm the cordectomy type.

## 5.4 Clinical implications

Only minor differences in subjective and objective voice outcomes between the groups were identified in the study comparing TLM and RT. This is useful information that clinicians can share with their patients as it may guide both a clinician's and patient's decision regarding which treatment to opt for. Due to the subjective voice questionnaire results, it may also reassure patients that they are unlikely to notice a great change in their voice post treatment. Although there are larger studies in the published literature, this is the first from the local area and therefore is the most applicable to the local patient population. In addition, the number of published studies and patients included is limited and so this adds additional data to a limited evidence base. There is a cost benefit to the National Health Service in TLM as described in the introduction and this series helps to back up the clinical case for TLM.

In the longitudinal study there are minimal differences in subjective and objective voice outcomes pre and post TLM. Again, this is reassuring for the patient and clinician and important information to help them chose their treatment option. This is the first study of voice outcomes pre and post TLM for early glottic tumours undertaken at AUH. This is important information locally to guide the local Head and Neck MDT in its decision making process.

Voice outcome measures are important when undertaking any voice altering surgery. This, unfortunately, is not always routine practice in the UK. As discussed in the introduction there are a plethora of voice outcome measures. Some measures are more suited to research as opposed to clinical settings due to time constraints and the need for specific equipment. In practice, I would suggest that the VHI-10 is routinely used. The VHI-10 provides a quick subjective assessment that is both reliable and validated. It is commonly used in published studies and therefore comparisons can easily be made. Documentation of the perceptual rating of voice by an expert rater using the GRBAS scale is another valuable measure that can be used in clinical practice. To an expert rater, GRBAS is also validated and reliable. However this is more resource and time intensive and is used more commonly by speech and language therapists than by physicians in medical settings.

## 5.5 Future areas of research

To improve research into voice outcomes a standardised measurement of voice should be introduced to improve the ability to compare outcomes of studies. Currently researchers use a variety of questionnaires, acoustic parameters and computer programs to measure voice outcomes. An important aspect of future research would be to identify the optimal tools to be used. In terms of the objective measures of voice there is a gap in the knowledge base describing the parameters of ‘normal’ voice. This would require evaluating a large cohort of participants with ‘normal’ voice of varying age, gender, co-morbidities and social history.

Advances in technology are likely to change the way we manage patients with laryngeal carcinoma. For example the improvement in endoscopy, NBI and transoral robotic surgery to identify the extent of the tumour and aid excision may influence the treatment plan. It is important with any new techniques that as well as local control, voice outcomes are reported and can be compared to the current techniques.

# 6. Conclusion

The treatment of T1a laryngeal carcinoma with either TLM or RT has been shown to have comparable good local control. There are advantages and disadvantages of both treatments, however TLM is often preferred by patient and clinician as it is a day case procedure, can provide histological clearance and leaves the option to use RT or further surgery in the future. However the voice outcomes of both procedures have been debated and results in the published literature are mixed. It is challenging to conduct a study to directly compare voice outcomes of TLM and RT as there are a number of other factors that impact voice, including: patient factors such as age, sex, co-morbidities such as reflux disease, smoking history; tumour factors such as size and position; and treatment factors such as type of cordectomy performed and RT regime. The EaStER trial outlines the difficulty in conducting an RCT in this area.[79] These variables mean that comparison of published data in this area is difficult, as underlying factors may influence the results.

In this comparison of voice quality following RT or TLM of T1a laryngeal carcinomas, I found little difference between the treatment groups. This was consistent throughout the different methods of assessing voice quality, both subjective and objective. In addition, QoL was found to be very good in both treatment groups. These data show that with either treatment option, there are good voice and QoL outcomes at a year post treatment.

In the comparison of voice quality pre and post TLM of T1a laryngeal carcinomas, I found little difference pre and one year post-treatment. This was

consistent throughout the different methods of assessing voice quality, both subjective and objective. In addition, QoL was found to be very good pre and post treatment. These data show that patients can be reassured that voice and QoL is not likely to be statistically significantly different a year following TLM treatment for T1a laryngeal carcinomas.

# 7. References


1. Adobe Systems Incorporated. Adobe Stock Images,. 2016; https://stock.adobe.com/uk/.
2. Moore KL, Persaud TVN. *The Developing Human: Clinically Orientated Embryology*. Elsevier/Saunders; 2013.
3. Belin P. Voice processing in human and non-human primates. *Philos Trans R Soc Lond B Biol Sci.* 2006;361(1476):2091-2107.
4. Lieberman PH, Klatt DH, Wilson WH. Vocal tract limitations on the vowel repertoires of rhesus monkey and other nonhuman primates. *Science.* 1969;164(3884):1185-1187.
5. Claassen H, Kirsch T, Simons G. Cartilage canals in human thyroid cartilage characterized by immunolocalization of collagen types I, II, pro-III, IV and X. *Anat Embryol (Berl).* 1996;194(2):147-153.
6. Wikipedia. The larynx,. 2016; https://en.wikipedia.org/wiki/Larynx.
7. Gray H, Lewis WH. *Anatomy of the human body.* 20th ed. Philadelphia: Lea & Febiger; 1918.
8. Meiteles LZ, Lin PT, Wenk EJ. An anatomic study of the external laryngeal framework with surgical implications. *Otolaryngol Head Neck Surg.* 1992;106(3):235-240.
9. Titze IR, Liang H. Comparison of Fo extraction methods for high-precision voice perturbation measurements. *J Speech Hear Res.* 1993;36(6):1120-1133.
10. Titze IR. *Principles of voice production.* Englewood Cliffs, N.J. ; London: Prentice Hall; 1994.
11. Sprinzl GM, Eckel HE, Sittel C, Pototschnig C, Koebke J. Morphometric measurements of the cartilaginous larynx: An anatomic correlate of laryngeal surgery. *Head Neck.* 1999;21(8):743-750.
12. Ballenger J, Snow J. Ballenger's Otorhinolaryngolgoy and Head and Neck Surgery. In: 16th, ed.
13. Rucci L, Gammarota L, Borghi Cirri MB. Carcinoma of the anterior commissure of the larynx: I. Embryological and anatomic considerations. *Ann Otol Rhinol Laryngol.* 1996;105(4):303-308.
14. Maue WM, Dickson DR. Cartilages and ligaments of the adult human larynx. *Arch Otolaryngol.* 1971;94(5):432-439.
15. National Cancer Institute. Cancer of the Larynx. In: U.S. Department of Health and Human Services, ed2010.
16. Hammer GP, Windisch G, Prodinger PM, Anderhuber F, Friedrich G. The cricothyroid joint--functional aspects with regard to different types of its structure. *J Voice.* 2010;24(2):140-145.
17. Gómez-Puerta JA, Cisternas A, Hernández MV, Ruiz-Esquide V, Vilaseca I, Sanmartí R. Laryngeal assessment by videolaryngostroboscopy in patients with rheumatoid arthritis. *Reumatol Clin.* 2014;10(1):32-36.
18. Standring S. *Gray's Anatomy.* 40th ed2009.
19. Kersing W. Comparative histochemical aspects of mammalian thyroarytenoid musculature. *Logoped Phoniatr Vocol.* 2005;30(3-4):125-128.
20. Malmgren LT, Fisher PJ, Bookman LM, Uno T. Age-related changes in muscle fiber types in the human thyroarytenoid muscle: an

immunohistochemical and stereological study using confocal laser scanning microscopy. *Otolaryngol Head Neck Surg.* 1999;121(4):441-451.
21. Aronson AE, Bless DM. *Clinical voice disorders.* 4th ed. ed. New York: Thieme; 2009.
22. Gleeson M, Clarke RC. *Scott-Brown's Otorhinolaryngology: Head and neck surgery.* seventh edition ed2008.
23. Office for National Statistics. Cancer research UK, Office for National Statistics. 2013.
24. UK Cancer Information Services. Laryngeal Cancer European age-standardised incidence rates by UK Cancer Networks. January 2014.
25. Coleman MP, Cancer. IAfRo, Cancer. IUa, International Association of Cancer Registries. *Trends in cancer incidence and mortality.* Lyon: International Agency for Research on Cancer; 1993.
26. Parkin DM. Tobacco-attributable cancer burden in the UK in 2010. *Br J Cancer.* 2011;105 Suppl 2:S6-S13.
27. Department of Health. Improving outcomes: a strategy for cancer. 2011.
28. La Vecchia C, Zhang ZF, Altieri A. Alcohol and laryngeal cancer: an update. *Eur J Cancer Prev.* 2008;17(2):116-124.
29. Torrente MC, Rodrigo JP, Haigentz M, et al. Human papillomavirus infections in laryngeal cancer. *Head Neck.* 2011;33(4):581-586.
30. Langevin SM, Michaud DS, Marsit CJ, et al. Gastric reflux is an independent risk factor for laryngopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev.* 2013;22(6):1061-1068.
31. Isayeva T, Li Y, Maswahu D, Brandwein-Gensler M. Human papillomavirus in non-oropharyngeal head and neck cancers: a systematic literature review. *Head Neck Pathol.* 2012;6 Suppl 1:S104-120.
32. Upile NS, Shaw RJ, Jones TM, et al. Squamous cell carcinoma of the head and neck outside the oropharynx is rarely human papillomavirus related. *Laryngoscope.* 2014;124(12):2739-2744.
33. Boing AF, Antunes JL, de Carvalho MB, et al. How much do smoking and alcohol consumption explain socioeconomic inequalities in head and neck cancer risk? *J Epidemiol Community Health.* 2011;65(8):709-714.
34. Groome PA, O'Sullivan B, Irish JC, et al. Glottic cancer in Ontario, Canada and the SEER areas of the United States. Do different management philosophies produce different outcome profiles? *J Clin Epidemiol.* 2001;54(3):301-315.
35. Edge SB, American Joint Committee on Cancer, American Cancer Society. *AJCC cancer staging handbook : from the AJCC cancer staging manual.* 7th ed. New York: Springer; 2010.
36. Roland NJ, Paleri V. Head and Neck Cancer: Multidisciplinary Management GuidelinesSeptember 2011.
37. O'Sullivan B, Mackillop W, Gilbert R, et al. Controversies in the management of laryngeal cancer: results of an international survey of patterns of care. *Radiother Oncol.* 1994;31(1):23-32.
38. Shah JP, Karnell LH, Hoffman HT, et al. Patterns of care for cancer of the larynx in the United States. *Arch Otolaryngol Head Neck Surg.* 1997;123(5):475-483.

39. Pellitteri PK, Kennedy TL, Vrabec DP, Beiler D, Hellstrom M. Radiotherapy. The mainstay in the treatment of early glottic carcinoma. *Arch Otolaryngol Head Neck Surg.* 1991;117(3):297-301.
40. Kleinsasser O. [Microlaryngoscopy and endolaryngeal microsurgery. II: A review of 2500 cases (author's transl)]. *HNO.* 1974;22(3):69-83.
41. Maiman TH. Stimulated Optical Radiation in Ruby. *Nature.* 1960;187:493-494.
42. Patel CKN. Continuous-Wave Laser Action on Vibrational-Rotational Transitions of C02. *Physics Rev.* 1964;136(A1187).
43. Strong MS, Jako GJ. Laser surgery in the larynx. Early clinical experience with continuous CO 2 laser. *Ann Otol Rhinol Laryngol.* 1972;81(6):791-798.
44. Huettenbrink KB. *Lasers in Otorhinolaryngology.* Thieme; 2003.
45. Yan Y, Olszewski AE, Hoffman MR, et al. Use of lasers in laryngeal surgery. *J Voice.* 2010;24(1):102-109.
46. Lumenis™. AcuBladeTM Brochure. http://www.sigmacon.co.uk/PDFs/AcuBlade%20bro.pdf2015.
47. Dilkes MG. *Invited Review Lasers in Otolaryngology.* Lasers in Medical Science1994.
48. Fagan J, Steiner W. Transoral Laser Microsurgery (TLM) of Cancers & Other Pathology of the Upper Aerodigestive Tract. 2000.
49. Steiner W, Ambrosch P. *Endoscopic Laser Surgery of the Upper Aerodigestive Tract.* New York2000.
50. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope.* 2006;116(9 Pt 2 Suppl 111):1-13.
51. Steiner W. Results of curative laser microsurgery of laryngeal carcinomas. *Am J Otolaryngol.* 1993;14(2):116-121.
52. Csanády M, Czigner J, Sávay L. Endolaryngeal CO2 laser microsurgery of early vocal cord cancer. A retrospective study. *Adv Otorhinolaryngol.* 1995;49:219-221.
53. Eckel HE. Local recurrences following transoral laser surgery for early glottic carcinoma: frequency, management, and outcome. *Ann Otol Rhinol Laryngol.* 2001;110(1):7-15.
54. Wilkie MD, Lightbody KA, Lythgoe D, Tandon S, Lancaster J, Jones TM. Transoral laser microsurgery for early and moderately advanced laryngeal cancers: outcomes from a single centralised United Kingdom centre. *Eur Arch Otorhinolaryngol.* 2015;272(3):695-704.
55. Pham TA, De Freitas R, Sigston E, Vallance N. Factors leading to the use of alternate treatment modalities following transoral laser excision of T1 and T2 glottic squamous cell carcinoma. *ANZ J Surg.* 2012;82(10):720-723.
56. Delsupehe KG, Zink I, Lejaegere M, Bastian RW. Voice quality after narrow-margin laser cordectomy compared with laryngeal irradiation. *Otolaryngol Head Neck Surg.* 1999;121(5):528-533.
57. Remacle M, Eckel HE, Antonelli A, et al. Endoscopic cordectomy. A proposal for a classification by the Working Committee, European Laryngological Society. *Eur Arch Otorhinolaryngol.* 2000;257(4):227-231.
58. Bocciolini C, Presutti L, Laudadio P. Oncological outcome after CO2 laser cordectomy for early-stage glottic carcinoma. *Acta Otorhinolaryngol Ital.* 2005;25(2):86-93.

59. Murray CE, Cooper L, Handa KK, MacLeod T, MacKenzie K. A technique for the orientation of endoscopically resected laryngeal lesions. *Clin Otolaryngol.* 2007;32(3):201-203.
60. Sigston E, de Mones E, Babin E, et al. Early-stage glottic cancer: oncological results and margins in laser cordectomy. *Arch Otolaryngol Head Neck Surg.* 2006;132(2):147-152.
61. Bradley PJ, Mackenzie K, Wight R, Pracy P, Paleri V, Group E-UHN. Consensus statement on management in the UK: transoral laser assisted microsurgical resection of early glottic cancer. *Clin Otolaryngol.* 2009;34(4):367-373.
62. Peretti G, Cappiello J, Nicolai P, Smussi C, Antonelli AR. Endoscopic laser excisional biopsy for selected glottic carcinomas. *Laryngoscope.* 1994;104(10):1276-1279.
63. Garofolo S, Piazza C, Del Bon F, et al. Intraoperative narrow band imaging better delineates superficial resection margins during transoral laser microsurgery for early glottic cancer. *Ann Otol Rhinol Laryngol.* 2015;124(4):294-298.
64. Zabrodsky M, Lukes P, Lukesova E, Boucek J, Plzak J. The role of narrow band imaging in the detection of recurrent laryngeal and hypopharyngeal cancer after curative radiotherapy. *Biomed Res Int.* 2014;2014:175398.
65. Grammaticos PC. Pioneers of nuclear medicine, Madame Curie. *Hell J Nucl Med.* 2004;7(1):30-31.
66. Coutard H. The Results and Methods of Treatment of Cancer by Radiation. *Ann Surg.* 1937;106(4):584-598.
67. Vermund H. Role of radiotherapy in cancer of the larynx as related to the TNM system of staging. A review. *Cancer.* 1970;25(3):485-504.
68. Marks RD, Fitz-Hugh GS, Constable WC. Fourteen years' experience with cobalt-60 radiation therapy in the treatment of early cancer of the true vocal cords. *Cancer.* 1971;28(3):571-576.
69. Morrison R. *Radiation therapy in diseases of the larynx.* The British Journal of Radiology1971.
70. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet.* 2003;362(9388):933-940.
71. The Royal College of Radiologists. Radiotherapy Dose-Fractionation. *The Royal College of Radiologists,.* 2006.
72. Le QT, Fu KK, Kroll S, et al. Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. *Int J Radiat Oncol Biol Phys.* 1997;39(1):115-126.
73. Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 glottic carcinomas. *Cancer.* 2004;100(9):1786-1792.
74. Gowda RV, Henk JM, Mais KL, Sykes AJ, Swindell R, Slevin NJ. Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital Experience. *Radiother Oncol.* 2003;68(2):105-111.
75. Barrett A, Dobbs J, Roques T. *Practical Radiotherapy Planning.* Fourth Edition ed2009.

76. Berwouts D, Swimberghe M, Duprez F, et al. Intensity-modulated radiotherapy for early-stage glottic cancer. *Head Neck.* 2016;38 Suppl 1:E179-184.
77. Murthy V, Kundu S, Shahid T, et al. Postoperative Radiotherapy in Head and Neck Cancer. *Otorhinolaryngology Clinics.* 2010;1.
78. Mendenhall WM, Amdur RJ, Morris CG, Hinerman RW. T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. *J Clin Oncol.* 2001;19(20):4029-4036.
79. Hamilton DW, de Salis I, Donovan JL, Birchall M. The recruitment of patients to trials in head and neck cancer: a qualitative study of the EaStER trial of treatments for early laryngeal cancer. *Eur Arch Otorhinolaryngol.* 2013;270(8):2333-2337.
80. Dey P, Arnold D, Wight R, MacKenzie K, Kelly C, Wilson J. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. *Cochrane Database Syst Rev.* 2002(2):CD002027.
81. Warner L, Chudasama J, Kelly CG, et al. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. *Cochrane Database Syst Rev.* 2014(12):CD002027.
82. Ogol'tsova ES, Paches AI, Matiakin EG, et al. [Comparative evaluation of the effectiveness of radiotherapy, surgery and combined treatment of stage I-II laryngeal cancer (T1-2NoMo) based on the data of a cooperative randomized study]. *Vestn Otorinolaringol.* 1990(3):3-7.
83. Hintz B, Charyulu K, Chandler JR, Sudarsanam A, Garciga C. Randomized study of local control and survival following radical surgery or radiation therapy in oral and laryngeal carcinomas. *J Surg Oncol.* 1979;12(1):61-74.
84. Li GZ. [A comparison of the therapeutic effect between preoperative radiotherapy plus operation and operation alone for laryngocarcinoma. A prospective study of 260 cases]. *Zhonghua Er Bi Yan Hou Ke Za Zhi.* 1993;28(3):170-173, 188.
85. Yin ZP. Surgery plus postoperative radiation vs operation alone for glottic carcnioma. Vol 14. 2000 International and 6th National Head and Neck Cancer Conference. : Journal of Henan Oncology; 2001:184-185.
86. Higgins KM, Shah MD, Ogaick MJ, Enepekides D. Treatment of early-stage glottic cancer: meta-analysis comparison of laser excision versus radiotherapy. *J Otolaryngol Head Neck Surg.* 2009;38(6):603-612.
87. Lefebvre JL. Larynx preservation. *Curr Opin Oncol.* 2012;24(3):218-222.
88. Schrijvers ML, van Riel EL, Langendijk JA, et al. Higher laryngeal preservation rate after CO2 laser surgery compared with radiotherapy in T1a glottic laryngeal carcinoma. *Head Neck.* 2009;31(6):759-764.
89. Moreau PR. Treatment of laryngeal carcinomas by laser endoscopic microsurgery. *Laryngoscope.* 2000;110(6):1000-1006.
90. Steiner W, Ambrosch P, Rödel RM, Kron M. Impact of anterior commissure involvement on local control of early glottic carcinoma treated by laser microresection. *Laryngoscope.* 2004;114(8):1485-1491.
91. Johansen LV, Grau C, Overgaard J. Glottic carcinoma--patterns of failure and salvage treatment after curative radiotherapy in 861 consecutive patients. *Radiother Oncol.* 2002;63(3):257-267.

92. Chone CT, Yonehara E, Martins JE, Altemani A, Crespo AN. Importance of anterior commissure in recurrence of early glottic cancer after laser endoscopic resection. *Arch Otolaryngol Head Neck Surg.* 2007;133(9):882-887.
93. Cohen SM, Garrett CG, Dupont WD, Ossoff RH, Courey MS. Voice-related quality of life in T1 glottic cancer: irradiation versus endoscopic excision. *Ann Otol Rhinol Laryngol.* 2006;115(8):581-586.
94. Sjögren EV, van Rossum MA, Langeveld TP, et al. Voice outcome in T1a midcord glottic carcinoma: laser surgery vs radiotherapy. *Arch Otolaryngol Head Neck Surg.* 2008;134(9):965-972.
95. Oridate N, Homma A, Suzuki S, et al. Voice-related quality of life after treatment of laryngeal cancer. *Arch Otolaryngol Head Neck Surg.* 2009;135(4):363-368.
96. Dejonckere PH, Bradley P, Clemente P, et al. A basic protocol for functional assessment of voice pathology, especially for investigating the efficacy of (phonosurgical) treatments and evaluating new assessment techniques. Guideline elaborated by the Committee on Phoniatrics of the European Laryngological Society (ELS). *Eur Arch Otorhinolaryngol.* 2001;258(2):77-82.
97. Jacobsen BH, Johnson A, Grywalsky C. The Voice Handicap Index (VHI): development and validation. *American Journal of Speech Language Pathology.* 1997;6:66-70.
98. Deary IJ, Wilson JA, Carding PN, MacKenzie K. VoiSS: a patient-derived Voice Symptom Scale. *J Psychosom Res.* 2003;54(5):483-489.
99. Webb AL, Carding PN, Deary IJ, MacKenzie K, Steen IN, Wilson JA. Optimising outcome assessment of voice interventions, I: Reliability and validity of three self-reported scales. *J Laryngol Otol.* 2007;121(8):763-767.
100. Carding PN, Horsley IA. An evaluation study of voice therapy in non-organic dysphonia. *Eur J Disord Commun.* 1992;27(2):137-158.
101. Peretti G, Piazza C, Balzanelli C, Mensi MC, Rossini M, Antonelli AR. Preoperative and postoperative voice in Tis-T1 glottic cancer treated by endoscopic cordectomy: an additional issue for patient counseling. *Ann Otol Rhinol Laryngol.* 2003;112(9 Pt 1):759-763.
102. Hirano M, Hirade Y, Kawasaki H. Vocal function following carbon dioxide laser surgery for glottic carcinoma. *Ann Otol Rhinol Laryngol.* 1985;94(3):232-235.
103. Omori K. Diagnosis of Voice Disorders. *JMAJ.* 2011;54((4)):248-253.
104. De Bodt MS, Wuyts FL, Van de Heyning PH, Croux C. Test-retest study of the GRBAS scale: influence of experience and professional background on perceptual rating of voice quality. *J Voice.* 1997;11(1):74-80.
105. Rydell R, Schalén L, Fex S, Elner A. Voice evaluation before and after laser excision vs. radiotherapy of T1A glottic carcinoma. *Acta Otolaryngol.* 1995;115(4):560-565.
106. Loughran S, Calder N, MacGregor FB, Carding P, MacKenzie K. Quality of life and voice following endoscopic resection or radiotherapy for early glottic cancer. *Clin Otolaryngol.* 2005;30(1):42-47.
107. Peretti G, Piazza C, Balzanelli C, Cantarella G, Nicolai P. Vocal outcome after endoscopic cordectomies for Tis and T1 glottic carcinomas. *Ann Otol Rhinol Laryngol.* 2003;112(2):174-179.

108. Vilaseca I, Huerta P, Blanch JL, Fernández-Planas AM, Jiménez C, Bernal-Sprekelsen M. Voice quality after CO2 laser cordectomy--what can we really expect? *Head Neck.* 2008;30(1):43-49.
109. Neiman GS, Edeson B. Procedural aspects of eliciting maximum phonation time. *Folia Phoniatr (Basel).* 1981;33(5):285-293.
110. Tamura E, Kitahara S, Ogura M, Kohno N. Voice quality after laser surgery or radiotherapy for T1a glottic carcinoma. *Laryngoscope.* 2003;113(5):910-914.
111. Mendelsohn AH, Matar N, Bachy V, Lawson G, Remacle M. Longitudinal Voice Outcomes Following Advanced CO2 Laser Cordectomy for Glottic Cancer. *J Voice.* 2015.
112. Kania RE, Hartl DM, Hans S, Maeda S, Vaissiere J, Brasnu DF. Fundamental frequency histograms measured by electroglottography during speech: a pilot study for standardization. *J Voice.* 2006;20(1):18-24.
113. McGuirt WF, Blalock D, Koufman JA, et al. Comparative voice results after laser resection or irradiation of T1 vocal cord carcinoma. *Arch Otolaryngol Head Neck Surg.* 1994;120(9):951-955.
114. Wedman J, Heimdal JH, Elstad I, Olofsson J. Voice results in patients with T1a glottic cancer treated by radiotherapy or endoscopic measures. *Eur Arch Otorhinolaryngol.* 2002;259(10):547-550.
115. van Gogh CD, Verdonck-de Leeuw IM, Wedler-Peeters J, Langendijk JA, Mahieu HF. Prospective evaluation of voice outcome during the first two years in male patients treated by radiotherapy or laser surgery for T1a glottic carcinoma. *Eur Arch Otorhinolaryngol.* 2012;269(6):1647-1652.
116. Agarwal JP, Baccher GK, Waghmare CM, et al. Factors affecting the quality of voice in the early glottic cancer treated with radiotherapy. *Radiother Oncol.* 2009;90(2):177-182.
117. Sittel C, Eckel HE, Eschenburg C. Phonatory results after laser surgery for glottic carcinoma. *Otolaryngol Head Neck Surg.* 1998;119(4):418-424.
118. Roh JL, Kim DH, Kim SY, Park CI. Quality of life and voice in patients after laser cordectomy for Tis and T1 glottic carcinomas. *Head Neck.* 2007;29(11):1010-1016.
119. Smith JC, Johnson JT, Cognetti DM, et al. Quality of life, functional outcome, and costs of early glottic cancer. *Laryngoscope.* 2003;113(1):68-76.
120. Stoeckli SJ, Guidicelli M, Schneider A, Huber A, Schmid S. Quality of life after treatment for early laryngeal carcinoma. *Eur Arch Otorhinolaryngol.* 2001;258(2):96-99.
121. Peeters AJ, van Gogh CD, Goor KM, Verdonck-de Leeuw IM, Langendijk JA, Mahieu HF. Health status and voice outcome after treatment for T1a glottic carcinoma. *Eur Arch Otorhinolaryngol.* 2004;261(10):534-540.
122. Van Weel C. Functional status in primary care: COOP/WONCA charts. *Disabil Rehabil.* 1993;15(2):96-101.
123. Goor KM, Peeters AJ, Mahieu HF, et al. Cordectomy by CO2 laser or radiotherapy for small T1a glottic carcinomas: costs, local control, survival, quality of life, and voice quality. *Head Neck.* 2007;29(2):128-136.
124. Brandenburg JH. Laser cordotomy versus radiotherapy: an objective cost analysis. *Ann Otol Rhinol Laryngol.* 2001;110(4):312-318.
125. Myers EN, Wagner RL, Johnson JT. Microlaryngoscopic surgery for T1 glottic lesions: a cost-effective option. *Ann Otol Rhinol Laryngol.* 1994;103(1):28-30.

126. Foote RL, Buskirk SJ, Grado GL, Bonner JA. Has radiotherapy become too expensive to be considered a treatment option for early glottic cancer? *Head Neck.* 1997;19(8):692-700.
127. Friedrich G, Dejonckere PH. [The voice evaluation protocol of the European Laryngological Society (ELS) -- first results of a multicenter study]. *Laryngorhinootologie.* 2005;84(10):744-752.
128. Remacle M, Eckel HE. *Surgery of Larynx and Trachea.* Springer; 2010.
129. World Health Organization. *International Classification of Impairments, Disabilities and Handicaps: A manual of Classification Relating to the Consequences of Disease.* 1980.
130. Carding PN, Wilson JA, MacKenzie K, Deary IJ. Measuring voice outcomes: state of the science review. *J Laryngol Otol.* 2009;123(8):823-829.
131. Wilson JA, Webb A, Carding PN, Steen IN, MacKenzie K, Deary IJ. The Voice Symptom Scale (VoiSS) and the Vocal Handicap Index (VHI): a comparison of structure and content. *Clin Otolaryngol Allied Sci.* 2004;29(2):169-174.
132. Rosen CA, Lee AS, Osborne J, Zullo T, Murry T. Development and validation of the voice handicap index-10. *Laryngoscope.* 2004;114(9):1549-1556.
133. Lam PK, Chan KM, Ho WK, Kwong E, Yiu EM, Wei WI. Cross-cultural adaptation and validation of the Chinese Voice Handicap Index-10. *Laryngoscope.* 2006;116(7):1192-1198.
134. Seifpanahi S, Jalaie S, Nikoo MR, Sobhani-Rad D. Translated Versions of Voice Handicap Index (VHI)-30 across Languages: A Systematic Review. *Iran J Public Health.* 2015;44(4):458-469.
135. Forti S, Amico M, Zambarbieri A, et al. Validation of the Italian Voice Handicap Index-10. *J Voice.* 2014;28(2):263.e217-263.e222.
136. Carding PN, Horsley IA, Docherty GJ. A study of the effectiveness of voice therapy in the treatment of 45 patients with nonorganic dysphonia. *J Voice.* 1999;13(1):72-104.
137. Deary IJ, Webb A, Mackenzie K, Wilson JA, Carding PN. Short, self-report voice symptom scales: psychometric characteristics of the voice handicap index-10 and the vocal performance questionnaire. *Otolaryngol Head Neck Surg.* 2004;131(3):232-235.
138. Hogikyan ND, Sethuraman G. Validation of an instrument to measure voice-related quality of life (V-RQOL). *J Voice.* 1999;13(4):557-569.
139. Titze I. *Workshop on acoustic voice analysis: summary statement.* . National Center for Voice and Speech,The University of Iowa,Iowa City;1995.
140. Institute of Electrical and Electronics Engineers. *IEEE transactions on audio and electroacoustics.* New York: Institute of Electrical and Electronics Engineers; 1966.
141. Darley FL, Aronson AE, Brown JR. *Motor speech disorders.* Philadelphia ; London: Saunders; 1975.
142. Fairbanks G. *Voice and Articulation Drillbook. Second edition.* New York: Harper & Bros.; 1960.
143. MacMahon MKC. The woman behind Arthur. *J Int Phon Association.* 1991;21(i):29-31.
144. Abberton E. Phonetic considerations in the design of voice assessment material. *Logoped Phoniatr Vocol.* 2005;30(3-4):175-180.

145. Powell TW. A comparison of English reading passages for elicitation of speech samples from clinical populations. *Clin Linguist Phon.* 2006;20(2-3):91-97.
146. Revis J, Giovanni A, Wuyts F, Triglia J. Comparison of different voice samples for perceptual analysis. *Folia Phoniatr Logop.* 1999;51(3):108-116.
147. Tsanas A, Zañartu M, Little MA, Fox C, Ramig LO, Clifford GD. Robust fundamental frequency estimation in sustained vowels: detailed algorithmic comparisons and information fusion with adaptive Kalman filtering. *J Acoust Soc Am.* 2014;135(5):2885-2901.
148. Orlikoff RF. Vocal stability and vocal tract configuration: an acoustic and electroglottographic investigation. *J Voice.* 1995;9(2):173-181.
149. Speyer R, Wieneke GH, van Wijck-Warnaar I, Dejonckere PH. Effects of voice therapy on the voice range profiles of dysphonic patients. *J Voice.* 2003;17(4):544-556.
150. Hirano M. *Clinical examination of voice.* 1981.
151. Oates J. Auditory-perceptual evaluation of disordered voice quality: pros, cons and future directions. *Folia Phoniatr Logop.* 2009;61(1):49-56.
152. Nawka T, Hosemann W. Surgical procedures for voice restoration. *GMS Curr Top Otorhinolaryngol Head Neck Surg.* 2005;4:Doc14.
153. Webb AL, Carding PN, Deary IJ, MacKenzie K, Steen N, Wilson JA. The reliability of three perceptual evaluation scales for dysphonia. *Eur Arch Otorhinolaryngol.* 2004;261(8):429-434.
154. De Bodt MS, Van de Heyning PH, Wuyts FL, Lambrechts L. The perceptual evaluation of voice disorders. *Acta Otorhinolaryngol Belg.* 1996;50(4):283-291.
155. Carding P, Carlson E, Epstein R, Mathieson L, Shewell C. Formal perceptual evaluation of voice quality in the United Kingdom. *Logoped Phoniatr Vocol.* 2000;25(3):133-138.
156. Fabre P. Un procédé électrique percutané d'inscription de l'accolement glottique au cours de la phonation.1957, Bull. Nat. Med., 141,66-99.
157. Kent RD, Balls MJ. *Voice Quality Measurement.* San Diego: Singular Publishing Group; 2000.
158. Ferlito A. *Diseases of the larynx.* London: Arnold; 2000.
159. Fourcin AJ, Abberton E. First applications of a new laryngograph. *Med Biol Illus.* 1971;21(3):172-182.
160. Laukkanen AM, Vilkman. *Tremor in the Light of Sound Production with Excised Human Larynges.* Vibrato: Singular Publishing; 1995.
161. Hampala V, Garcia M, Švec JG, Scherer RC, Herbst CT. Relationship Between the Electroglottographic Signal and Vocal Fold Contact Area. *J Voice.* 2016;30(2):161-171.
162. Baken RJ. *Clinical Measurement of Speech and Voice.* San DiegoLondon Singular Publisher Group; 1996.
163. Anastaplo S, Karnell MP. Synchronized videostroboscopic and electroglottographic examination of glottal opening. *J Acoust Soc Am.* 1988;83(5):1883-1890.
164. Hillenbrand J. Acoustic Analysis of Voice: A Tutorial. Vol 21. Perspectives on Speech Science and Orofacial Disorders 2011:31-43.

165. González J, Cervera T, Miralles JL. [Acoustic voice analysis: reliability of a set of multi-dimensional parameters]. *Acta Otorrinolaringol Esp.* 2002;53(4):256-268.
166. *Praat: doing phonetics by computer* [computer program]. Version 5.3.51. http://www.praat.org/2013.
167. Maryn Y, Corthals P, De Bodt M, Van Cauwenberge P, Deliyski D. Perturbation measures of voice: a comparative study between Multi-Dimensional Voice Program and Praat. *Folia Phoniatr Logop.* 2009;61(4):217-226.
168. Fourcin A, Abberton E. Hearing and phonetic criteria in voice measurement: clinical applications. *Logoped Phoniatr Vocol.* 2008;33(1):35-48.
169. Zeitels SM, Hillman RE, Bunting GW, Vaughn T. Reinke's edema: phonatory mechanisms and management strategies. *Ann Otol Rhinol Laryngol.* 1997;106(7 Pt 1):533-543.
170. Berry DA, Reininger H, Alipour F, Bless DM, Ford CN. Influence of vocal fold scarring on phonation: predictions from a finite element model. *Ann Otol Rhinol Laryngol.* 2005;114(11):847-852.
171. Rovirosa A, Martínez-Celdrán E, Ortega A, et al. Acoustic analysis after radiotherapy in T1 vocal cord carcinoma: a new approach to the analysis of voice quality. *Int J Radiat Oncol Biol Phys.* 2000;47(1):73-79.
172. Carding PN, Steen IN, Webb A, MacKenzie K, Deary IJ, Wilson JA. The reliability and sensitivity to change of acoustic measures of voice quality. *Clin Otolaryngol Allied Sci.* 2004;29(5):538-544.
173. Orlikoff RF, Baken RJ. Consideration of the relationship between the fundamental frequency of phonation and vocal jitter. *Folia Phoniatr (Basel).* 1990;42(1):31-40.
174. Titze IR. Physiologic and acoustic differences between male and female voices. *J Acoust Soc Am.* 1989;85(4):1699-1707.
175. Sussman JE, Sapienza C. Articulatory, developmental, and gender effects on measures of fundamental frequency and jitter. *J Voice.* 1994;8(2):145-156.
176. Leong K, Hawkshaw MJ, Dentchev D, Gupta R, Lurie D, Sataloff RT. Reliability of objective voice measures of normal speaking voices. *J Voice.* 2013;27(2):170-176.
177. Heman-Ackah YD, Heuer RJ, Michael DD, et al. Cepstral peak prominence: a more reliable measure of dysphonia. *Ann Otol Rhinol Laryngol.* 2003;112(4):324-333.
178. Shrivastav R, Sapienza CM. Objective measures of breathy voice quality obtained using an auditory model. *J Acoust Soc Am.* 2003;114(4 Pt 1):2217-2224.
179. Heman-Ackah YD, Sataloff RT, Laureyns G, et al. Quantifying the cepstral peak prominence, a measure of dysphonia. *J Voice.* 2014;28(6):783-788.
180. Choi HS, Chung SM, Lim JY, Kim HS. Increasing the closed quotient improves voice quality after type I thyroplasty in patients with unilateral vocal cord paralysis: analysis using SPEAD program. *J Voice.* 2008;22(6):751-755.
181. Yumoto E, Gould WJ, Baer T. Harmonics-to-noise ratio as an index of the degree of hoarseness. *J Acoust Soc Am.* 1982;71(6):1544-1549.
182. Martin D, Fitch J, Wolfe V. Pathologic voice type and the acoustic prediction of severity. *J Speech Hear Res.* 1995;38(4):765-771.

183. Núñez Batalla F, Corte Santos P, Sequeiros Santiago G, Señaris González B, Suárez Nieto C. [Perceptual evaluation of dysphonia: correlation with acoustic parameters and reliability]. *Acta Otorrinolaringol Esp.* 2004;55(6):282-287.
184. Wolfe V, Fitch J, Martin D. Acoustic measures of dysphonic severity across and within voice types. *Folia Phoniatr Logop.* 1997;49(6):292-299.
185. Kasuya H, Ogawa S, Mashima K, Ebihara S. Normalized noise energy as an acoustic measure to evaluate pathologic voice. *J Acoust Soc Am.* 1986;80(5):1329-1334.
186. Jotic A, Stankovic P, Jesic S, Milovanovic J, Stojanovic M, Djukic V. Voice quality after treatment of early glottic carcinoma. *J Voice.* 2012;26(3):381-389.
187. Laryngograph**TM**. Speech Studio Users Guide. London2006.
188. Fourcin A, McGlashan J, Blowes R. Measuring voice in clinic - Laryngograph Speech Studio Analyses2000.
189. Mehta DD, Deliyski DD, Hillman RE. Commentary on why laryngeal stroboscopy really works: clarifying misconceptions surrounding Talbot's law and the persistence of vision. *J Speech Lang Hear Res.* 2010;53(5):1263-1267.
190. Manola M, Moscillo L, Costa G, et al. Conservative laser microsurgery for T1 glottic carcinoma. *Auris Nasus Larynx.* 2008;35(1):141-147.
191. Maslan J, Leng X, Rees C, Blalock D, Butler SG. Maximum phonation time in healthy older adults. *J Voice.* 2011;25(6):709-713.
192. Mendes Tavares EL, Brasolotto AG, Rodrigues SA, Benito Pessin AB, Garcia Martins RH. Maximum phonation time and s/z ratio in a large child cohort. *J Voice.* 2012;26(5):675.e671-674.
193. Arias F, Arraras JI, Asin G, et al. Quality of life and voice assessment in patients with early-stage glottic cancer. *Head Neck.* 2015;37(3):340-346.
194. Ringash J, Bezjak A. A structured review of quality of life instruments for head and neck cancer patients. *Head Neck.* 2001;23(3):201-213.
195. Bjordal K, Ahlner-Elmqvist M, Tollesson E, et al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. *Acta Oncol.* 1994;33(8):879-885.
196. Sherman AC, Simonton S, Adams DC, Vural E, Owens B, Hanna E. Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Head and Neck module (QLQ-H&N35). *Arch Otolaryngol Head Neck Surg.* 2000;126(4):459-467.
197. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993;11(3):570-579.
198. Silveira AP, Gonçalves J, Sequeira T, et al. Patient reported outcomes in head and neck cancer: selecting instruments for quality of life integration in clinical protocols. *Head Neck Oncol.* 2010;2:32.
199. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA. The addition of mood and anxiety domains to the University of Washington quality of life scale. *Head Neck.* 2002;24(6):521-529.

200. Ojo B, Genden EM, Teng MS, Milbury K, Misiukiewicz KJ, Badr H. A systematic review of head and neck cancer quality of life assessment instruments. *Oral Oncol.* 2012;48(10):923-937.
201. Izadi F, Mohseni R, Daneshi A, Sandughdar N. Determination of fundamental frequency and voice intensity in Iranian men and women aged between 18 and 45 years. *J Voice.* 2012;26(3):336-340.
202. Chu Chu YH, Hsiung MW, Lin CS, Lee MH, Wang HW, Su WY. Voice analysis in normal young men and women. *Journal Taiwan Otolaryngology Head and Neck Surgery.* 2002;37:159-162.
203. Robb MP, Chen Y, Gilbert HR, Lerman JW. Acoustic comparison of vowel articulation in normal and reverse phonation. *J Speech Lang Hear Res.* 2001;44(1):118-127.
204. Awan SN, Awan JA. The effect of gender on measures of electroglottographic contact quotient. *J Voice.* 2013;27(4):433-440.
205. Faria BS, Oliveira KV, Silva JP, Reis C, Ghio A, Gama AC. Electroglottography of speakers of Brazilian Portuguese through Objective Multiparameter Vocal Assessment (EVA). *Braz J Otorhinolaryngol.* 2012;78(4):29-34.
206. Naufel de Felippe AC, Grillo MH, Grechi TH. Standardization of acoustic measures for normal voice patterns. *Braz J Otorhinolaryngol.* 2006;72(5):659-664.
207. Hou L, Han D, Xu W, Zhang L. [Study on voice characteristics of people with different sexes and ages]. *Lin Chuang Er Bi Yan Hou Ke Za Zhi.* 2002;16(12):667-669.
208. Fernández Liesa R, Damborenea Tajada D, Rueda Gormedino P, et al. [Acoustic analysis of the normal voice in nonsmoking adults]. *Acta Otorrinolaringol Esp.* 1999;50(2):134-141.
209. Demirhan E, Unsal EM, Yilmaz C, Ertan E. Acoustic Voice Analysis of Young Turkish Speakers. *J Voice.* 2016;30(3):378.e321-375.
210. Wang CC, Huang HT. Voice acoustic analysis of normal Taiwanese adults. *J Chin Med Assoc.* 2004;67(4):179-184.
211. Kazi R, Kanagalingam J, Venkitaraman R, et al. Electroglottographic and perceptual evaluation of tracheoesophageal speech. *J Voice.* 2009;23(2):247-254.
212. Moon KR, Chung SM, Park HS, Kim HS. Materials of acoustic analysis: sustained vowel versus sentence. *J Voice.* 2012;26(5):563-565.
213. Du G, Liu C, Yu W, et al. Voice outcomes after laser surgery vs. radiotherapy of early glottic carcinoma: a meta-analysis. *Int J Clin Exp Med.* 2015;8(10):17206-17213.
214. Kerr P, Mark Taylor S, Rigby M, et al. Oncologic and voice outcomes after treatment of early glottic cancer: transoral laser microsurgery versus radiotherapy. *J Otolaryngol Head Neck Surg.* 2012;41(6):381-388.
215. Greulich MT, Parker NP, Lee P, Merati AL, Misono S. Voice outcomes following radiation versus laser microsurgery for T1 glottic carcinoma: systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2015;152(5):811-819.
216. Robertson SM, Yeo JC, Sabey L, Young D, MacKenzie K. Effects of tumor staging and treatment modality on functional outcome and quality of life after treatment for laryngeal cancer. *Head Neck.* 2013;35(12):1759-1763.

217. Kono T, Saito K, Yabe H, Uno K, Ogawa K. Comparative multidimensional assessment of laryngeal function and quality of life after radiotherapy and laser surgery for early glottic cancer. *Head Neck.* 2016;38(7):1085-1090.
218. Rovirosa A, Ascaso C, Abellana R, et al. Acoustic voice analysis in different phonetic contexts after larynx radiotherapy for T1 vocal cord carcinoma. *Clin Transl Oncol.* 2008;10(3):168-174.
219. Niedzielska G, Niedzielski A, Toman D. Voice after radiotherapy of the larynx carcinoma. *Radiother Oncol.* 2010;97(2):276-280.
220. Kazi R, Venkitaraman R, Johnson C, et al. Prospective, longitudinal electroglottographic study of voice recovery following accelerated hypofractionated radiotherapy for T1/T2 larynx cancer. *Radiother Oncol.* 2008;87(2):230-236.
221. Stone D, McCabe P, Palme CE, et al. Voice outcomes after transoral laser microsurgery for early glottic cancer-considering signal type and smoothed cepstral peak prominence. *J Voice.* 2015;29(3):370-381.

# 8. Appendices

## Appendix 1: The ‘Grandfather passage’

(A phonetically balanced passage)

My Grandfather

You wished to know all about my grandfather.

Well, he is nearly ninety-three years old; he dresses himself in an ancient black frock coat, usually minus several buttons; yet he still thinks as swiftly as ever.

A long, flowing beard clings to his chin, giving those who observe him a pronounced feeling of utmost respect. When he speaks, his voice is just a bit cracked and quivers a trifle.

Twice each day he plays skilfully and with zest upon our small organ. Except in the winter when the ooze or snow or ice prevents, he slowly takes a short walk in the open air each day. We have often urged him to walk more and smoke less, but he always answers “Banana oil!”

Grandfather likes to be modern in his language.

## Appendix 2: VHI-10 questionnaire

Aintree University Hospitals NHS
NHS Foundation Trust

UNIVERSITY OF LIVERPOOL

# The Voice Handicap Index (VHI - 10)

Unit number ☐☐☐☐☐☐☐☐ Age ☐☐

Date ☐☐ ☐☐ ☐☐☐☐

These are statements that many people have used to describe their voices and the effects of their voices on their lives.

Please circle one answer for each item
**Please do not leave any blank items**

| | | | | | | |
|---|---|---|---|---|---|---|
| F1 | My voice makes it difficult for people to hear me. | Never | Occasionally | Some of the time | Most of the time | Always |
| F3 | People have difficulty understanding me in a noisy room. | Never | Occasionally | Some of the time | Most of the time | Always |
| P10 | People ask, "What's wrong with your voice?" | Never | Occasionally | Some of the time | Most of the time | Always |
| P14 | I feel as though I have to strain to produce voice. | Never | Occasionally | Some of the time | Most of the time | Always |
| F16 | My voice difficulties restrict my personal and social life. | Never | Occasionally | Some of the time | Most of the time | Always |
| P17 | The clarity of my voice is unpredictable. | Never | Occasionally | Some of the time | Most of the time | Always |
| F19 | I feel left out of conversation because of my voice. | Never | Occasionally | Some of the time | Most of the time | Always |
| F22 | My voice problem causes me to lose income. | Never | Occasionally | Some of the time | Most of the time | Always |
| E23 | My voice problem upsets me. | Never | Occasionally | Some of the time | Most of the time | Always |
| E25 | My voice makes me feel handicapped. | Never | Occasionally | Some of the time | Most of the time | Always |

**Thank you for completing this questionnaire**
**Have you remembered to circle one response for each item?**

**For Office use:**

Functional: .....
Physical: .....
Emotional: .....
Total VHI = .....

## Appendix 3: VoiSS questionnaire

Aintree University Hospitals NHS
NHS Foundation Trust

UNIVERSITY OF LIVERPOOL

# The VoiSS- Voice Symptoms Scale

Unit number ☐☐☐☐☐☐☐☐ Age ☐☐

Date ☐☐ ☐☐ ☐☐☐☐

Please circle one answer for each item
**Please do not leave any blank items**

| | | | | | | |
|---|---|---|---|---|---|---|
| 1. | Do you have difficulty attracting attention? | Never | Occasionally | Some of the time | Most of the time | Always |
| 2. | Do you have problems singing? | Never | Occasionally | Some of the time | Most of the time | Always |
| 3. | Is your throat sore? | Never | Occasionally | Some of the time | Most of the time | Always |
| 4. | Is your voice hoarse? | Never | Occasionally | Some of the time | Most of the time | Always |
| 5. | When talking in company do people fail to hear you? | Never | Occasionally | Some of the time | Most of the time | Always |
| 6. | Do you lose your voice? | Never | Occasionally | Some of the time | Most of the time | Always |
| 7. | Do you cough or clear your throat? | Never | Occasionally | Some of the time | Most of the time | Always |
| 8. | Do you have a weak voice? | Never | Occasionally | Some of the time | Most of the time | Always |
| 9. | Do you have problems talking on the telephone? | Never | Occasionally | Some of the time | Most of the time | Always |
| 10. | Do you feel miserable or depressed because of your voice problem? | Never | Occasionally | Some of the time | Most of the time | Always |
| 11. | Does it feel as if there is something stuck in your throat? | Never | Occasionally | Some of the time | Most of the time | Always |
| 12. | Do you have swollen glands? | Never | Occasionally | Some of the time | Most of the time | Always |
| 13. | Are you embarrassed by your voice problem? | Never | Occasionally | Some of the time | Most of the time | Always |
| 14. | Do you find the effort of speaking tiring? | Never | Occasionally | Some of the time | Most of the time | Always |
| 15. | Does your voice problem make you feel stressed and nervous? | Never | Occasionally | Some of the time | Most of the time | Always |
| 16. | Do you have difficulty competing against background noise? | Never | Occasionally | Some of the time | Most of the time | Always |

**Please Turn Over ⇒**

1

# VoiSS (continued)

Please circle the correct answer for each item
**Please do not leave any blank items**

| | | | | | | |
|---|---|---|---|---|---|---|
| 17. | Are you unable to shout or raise your voice? | Never | Occasionally | Some of the time | Most of the time | Always |
| 18. | Does your voice problem put a strain on your family and friends? | Never | Occasionally | Some of the time | Most of the time | Always |
| 19. | Do you have a lot of phlegm in your throat? | Never | Occasionally | Some of the time | Most of the time | Always |
| 20. | Does the sound of your voice vary throughout the day? | Never | Occasionally | Some of the time | Most of the time | Always |
| 21. | Do people seem irritated by your voice? | Never | Occasionally | Some of the time | Most of the time | Always |
| 22. | Do you have a blocked nose? | Never | Occasionally | Some of the time | Most of the time | Always |
| 23. | Do people ask what is wrong with your voice? | Never | Occasionally | Some of the time | Most of the time | Always |
| 24. | Does your voice sound creaky and dry? | Never | Occasionally | Some of the time | Most of the time | Always |
| 25. | Do you feel you have to strain to produce voice? | Never | Occasionally | Some of the time | Most of the time | Always |
| 26. | How often do you get throat infections? | Never | Occasionally | Some of the time | Most of the time | Always |
| 27. | Does your voice 'give out' in the middle of speaking? | Never | Occasionally | Some of the time | Most of the time | Always |
| 28. | Does your voice make you feel incompetent? | Never | Occasionally | Some of the time | Most of the time | Always |
| 29. | Are you ashamed of your voice problem? | Never | Occasionally | Some of the time | Most of the time | Always |
| 30. | Do you feel lonely because of your voice problem? | Never | Occasionally | Some of the time | Most of the time | Always |

**Thank you for completing this questionnaire**
**Have you remembered to circle one response for each item?**

**For Office use:**

Total VoiSS= .....

Impairment: 1, 2, 4, 5, 6, 8, 9, 14, 16, 17, 20, 23, 24, 25, 27 (max 60) = .....
Emotional: 10, 13, 15, 18, 21, 28, 29, 30 (max 32) =.....
Physical: 3, 7, 11, 12, 19, 22, 26 (max 28) =.....

# Appendix 4: UW-QoLv4 Questionnaire

## (University of Washington Quality of Life version 4 Questionnaire)

This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by ticking one box for each question.

1. **Pain**. (Tick one box: ☑ )

    □ I have no pain.

    □ There is mild pain not needing medication.

    □ I have moderate pain - requires regular medication (e.g. paracetamol).

    □ I have severe pain controlled only by prescription medicine (e.g. morphine).

    □ I have severe pain, not controlled by medication.

2. **Appearance**. (Tick one box: ☑ )

    □ There is no change in my appearance.

    □ The change in my appearance is minor.

    □ My appearance bothers me but I remain active.

    □ I feel significantly disfigured and limit my activities due to my appearance.

    □ I cannot be with people due to my appearance.

3. **Activity**. (Tick one box: ☑ )

□ I am as active as I have ever been.

□ There are times when I can't keep up my old pace, but not often.

□ I am often tired and have slowed down my activities although I still get out.

□ I don't go out because I don't have the strength.

□ I am usually in bed or chair and don't leave home.

4. **Recreation**. (Tick one box: ☑ )

□ There are no limitations to recreation at home or away from home.

□ There are a few things I can't do but I still get out and enjoy life.

□ There are many times when I wish I could get out more, but I'm not up to it.

□ There are severe limitations to what I can do, mostly I stay at home and watch TV.

□ I can't do anything enjoyable.

5. **Swallowing**. (Tick one box: ☑ )

□ I can swallow as well as ever.

□ I cannot swallow certain solid foods.

□ I can only swallow liquid food.

□ I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing**. (Tick one box: ☑ )

□ I can chew as well as ever.

□ I can eat soft solids but cannot chew some foods.

□ I cannot even chew soft solids.

7. **Speech**. (Tick one box: ☑ )

□ My speech is the same as always.

□ I have difficulty saying some words but I can be understood over the phone.

□ Only my family and friends can understand me.

□ I cannot be understood.

8. **Shoulder**. (Tick one box: ☑ )

□ I have no problem with my shoulder.

□ My shoulder is stiff but it has not affected my activity or strength.

□ Pain or weakness in my shoulder has caused me to change my work / hobbies.

□ I cannot work or do my hobbies due to problems with my shoulder.

9. **Taste**. (Tick one box: ☑ )

- ☐ I can taste food normally.
- ☐ I can taste most foods normally.
- ☐ I can taste some foods.
- ☐ I cannot taste any foods.

10. **Saliva**. (Tick one box: ☑ )
    - ☐ My saliva is of normal consistency.
    - ☐ I have less saliva than normal, but it is enough.
    - ☐ I have too little saliva.
    - ☐ I have no saliva.

11. **Mood**. (Tick one box: ☑ )
    - ☐ My mood is excellent and unaffected by my cancer.
    - ☐ My mood is generally good and only occasionally affected by my cancer.
    - ☐ I am neither in a good mood nor depressed about my cancer.
    - ☐ I am somewhat depressed about my cancer.
    - ☐ I am extremely depressed about my cancer.

12. **Anxiety**. (Tick one box: ☑ )
    - ☐ I am not anxious about my cancer.
    - ☐ I am a little anxious about my cancer.
    - ☐ I am anxious about my cancer.

□ I am very anxious about my cancer.

---

Which issues have been the most important to you <u>during the past 7 days?</u>

Tick ☑ **up to 3 boxes.**

□ Pain
□ Swallowing
□ Taste
□ Appearance
□ Chewing
□ Saliva
□ Activity
□ Speech
□ Mood
□ Recreation
□ Shoulder
□ Anxiety

---

## GENERAL QUESTIONS

**Compared to the month before you developed cancer**, how would you rate your health-related quality of life? (Tick one box: ☑ )

- ☐ Much better
- ☐ Somewhat better
- ☐ About the same
- ☐ Somewhat worse
- ☐ Much worse

In general, would you say your **health-related quality of life** during the past 7 days has been: (Tick one box: ☑ )

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends,

spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (Tick one box: ☑ )

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

---

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

## Appendix 5: Consent form and information sheet

Professor Terry Jones
Department of Head and Neck
Surgery
University Hospital Aintree
Lower Lane
Liverpool L9 7AL
Tel 0151-525-5980
Fax 0151-529-5263

# Analysis of voice characteristics of ENT patients

**We are inviting you to take part in a research study. Before you decide, it is important to understand why the research is being done and what it will involve. This information sheet provides you with an outline of the study so that you can think about whether you want to take part, and discuss it with others if you wish.**

**You may be currently experiencing a change in your voice. The investigation or treatment you will be undergoing may also affect your voice. The degree of voice change varies according to what condition you have and the type of treatment or investigation you will be having, however we do not know this in as much detail as we would like to.**

### WHAT IS THE PURPOSE OF THIS STUDY?

We aim to analyse voice recordings from ENT patients to assess the degree of voice change that the condition itself and treatment may cause

## WHY HAVE I BEEN CHOSEN?

You have been chosen because you have a condition which has caused voice change or you will be undergoing an investigation or treatment which can cause a change in your voice.

## DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw or not to take part will not affect the standard of care you receive.

## WHAT WILL HAPPEN TO ME IF I TAKE PART?

You will not notice any difference in your treatment. We will record your voice speaking a phrase and three prolonged “aah” sounds. This will be done prior to your procedure and then1 week, 3 weeks and 6 weeks after your procedure. It will take only 10 minutes of your time and will be done at University Hospital Aintree in the ENT department. You will not undergo any procedures other than those normally applied.

## WHAT ARE THE SIDE EFFECTS OF ANY TREATMENT RECEIVED WHEN TAKING PART?

As no extra procedures will be performed, there will be no side-effects.

## WHAT HAPPENS IF I WANT TO STOP BEING INVOLVED IN THIS STUDY?

If you do not want to continue being in this study, you may simply contact any of the members of the research team and you will be removed from the study. You may do this at any time.

## WHAT ARE THE POSSIBLE DISADVANTAGES OR RISKS OF TAKING PART?

There are no major disadvantages from taking part over and above those from routine normal care.

## WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

The only benefit is the knowledge that you are helping to improve information given to patients in the future.

## WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Information collected about you during the course of the research will be kept strictly confidential. The data we have recorded will be kept securely and safely on a computer with in the hospital

## WHAT HAPPENS WHEN THE RESEARCH STOPS?

The data will be kept on the computer for analysis with access to the recordings limited to the research team only.

## WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

Once it has all been completed we will present the results at an international meeting attended by doctors from around the world interested in voice. After this, we will publish the results in an appropriate scientific journal. If you wish, we will make sure you receive your own copy of the results and paper as soon as we have them.

## WHO IS ORGANISING AND FUNDING THE RESEARCH?

The study is being organised and funded by the Department of ENT and Head and Neck surgery at University Hospital Aintree.

## WHO HAS REVIEWED THE STUDY?

This study has been reviewed by the Local Research Ethics Committee covering the hospital in which you are treated.

## WHAT IF I HAVE OTHER CONCERNS?

If you have any concerns or questions, you may contact the doctor listed below for advice at their University Hospital Aintree number 0151-525-5980 or on the number shown at the top of the page:

Professor Terry Jones

If you have any complaints about the way the investigator has carried out the study, you may contact: local complaints procedure officer at Aintree Hospitals NHS Trust.

You may also wish to contact Cancer BACUP, an independent advisory group.
3 Bath place, Rivington Street, London EC2A 3DR. Freephone: 0800 800 1234
www.cancerbacup.org

Centre Number:
Study Number:
Patient Identification Number for this trial:

# CONSENT FORM

## Analysis of voice characteristics of ENT patients

Name of Researcher: Mr Terry Jones *Please initial box*

1. I confirm that I have read and understand the information sheet dated 27/03/05 (version 3) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from [company name] or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study.

_____ _____ _____
Name of Patient Date Signature

_____ _____ _____
Name of Person taking consent (if different from researcher) Date Signature

_____ _____ _____
Researcher Date Signature

*Copies:1 for patient; 1 for researcher; 1 to be kept with hospital notes*

# Appendix 6: Complete data set: for sustained vowels for ‘normal’ voice

**Table 35: ‘Normal’ males sustained vowel /i/ (complete data set)**

| Control | age | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| male1 | 27 | 10905.5 | 124.25 | 135.17 | 130.51 | 1.09 | 40.16 | 45.9 | 43.2 | 1.12 | 0.27 | 0.14 | 1.66 | -1.69 | 0.27 | 0.14 | 0.14 | -30.98 | 3.64 | 24.03 | 84.75 |
| male 2 | 34 | 5141.4 | 200.28 | 209.9 | 204.77 | 0.86 | 43.58 | 53.84 | 48.76 | 1.79 | 0.4 | 0.2 | 1.7 | -2.32 | 0.4 | 0.2 | 0.15 | -26.05 | 4.59 | 20.48 | 86.01 |
| male 3 | 37 | 11802.3 | 165.34 | 183.48 | 174.76 | 1.42 | 41.93 | 53.26 | 48.52 | 2.12 | 1.41 | 0.88 | 6.78 | -6.16 | 1.41 | 0.88 | 0.59 | -14.52 | 2.06 | 12.8 | 81.69 |
| male 4 | 35 | 17337.1 | 125.42 | 133.65 | 129.42 | 1.16 | 50 | 55.64 | 53.21 | 0.81 | 0.19 | 0.1 | 2.57 | -3.07 | 0.19 | 0.1 | 0.22 | -22.42 | 4.69 | 18.41 | 89.78 |
| male 5 | 28 | 4852 | 97.46 | 103.95 | 100.18 | 1.02 | 40.64 | 48.12 | 44.81 | 1.46 | 0.33 | 0.16 | 3.82 | -3.24 | 0.33 | 0.16 | 0.33 | -23.98 | 3.07 | 21.5 | 80.04 |
| male 6 | 37 | 26915.7 | 146.75 | 159.18 | 152.84 | 1.4 | 50.46 | 59.61 | 56.28 | 1.4 | 0.42 | 0.25 | 2.63 | -2.23 | 0.42 | 0.25 | 0.23 | -21.25 | 5.16 | 18.62 | 90.82 |
| male 7 | 30 | 13729.1 | 111.38 | 119.17 | 114.99 | 0.87 | 34.26 | 42.96 | 38.92 | 1.3 | 0.27 | 0.14 | 2.67 | -2.64 | 0.27 | 0.14 | 0.24 | -25.41 | 3.86 | 21.11 | 80.8 |
| male 8 | 24 | 13806.8 | 64.28 | 187.61 | 125.82 | 6.96 | 16.5 | 42.97 | 33.24 | 2.03 | 3.13 | 1.97 | 7.92 | -5.34 | 3.15 | 1.96 | 0.75 | -11.46 | 2.75 | 14.75 | 82.11 |
| male 9 | 50 | 8343.6 | 75.18 | 298.32 | 239.19 | 2.05 | 15.02 | 61.29 | 55.93 | 1.91 | 0.7 | 0.41 | 4.42 | -2.47 | 0.66 | 0.53 | 0.38 | -20.38 | 4.01 | 21.19 | 85.58 |
| male 10 | 24 | 12530.4 | 122.57 | 128.89 | 125.4 | 0.72 | 39.06 | 45.38 | 42.31 | 0.76 | 0.23 | 0.11 | 2.53 | -3.9 | 0.23 | 0.11 | 0.23 | -26.35 | 2.65 | 23.65 | 83.67 |

**Table 36: 'Normal' male sustained vowel /a/ (complete data set)**

| Control | age | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| male1 | 27 | 5998.1 | 119.8 | 130.66 | 124.24 | 1.6 | 34.1 | 41.4 | 38.46 | 1.54 | 0.46 | 0.27 | 3.69 | -2.54 | 0.46 | 0.27 | 0.36 | -23.31 | 4.29 | 19.8 | 85.29 |
| male 2 | 34 | 323.7.2 | 200 | 209.95 | 205.16 | 0.82 | 36.36 | 45.56 | 40.55 | 1.7 | 0.4 | 0.24 | 3.05 | -1.41 | 0.4 | 0.24 | 0.27 | -27.32 | 6.54 | 21.23 | 93.16 |
| male 3 | 37 | 16980.9 | 179.34 | 199.72 | 188.23 | 0.99 | 49.39 | 59.03 | 52.69 | 1.83 | 0.39 | 0.23 | 4.37 | -4.71 | 0.39 | 0.23 | 0.38 | -15.66 | 3.75 | 16.24 | 86.37 |
| male 4 | 35 | 7892.3 | 119.28 | 131.44 | 122.02 | 1.03 | 42.63 | 54.26 | 50.09 | 1.85 | 0.29 | 0.16 | 2.34 | -2.28 | 0.29 | 0.16 | 0.22 | -23.38 | 6.33 | 18.41 | 95.69 |
| male 5 | 28 | 5562 | 94.43 | 105.95 | 101.42 | 1.73 | 39.49 | 48.07 | 44.55 | 1.28 | 1.85 | 1.12 | 5.56 | -5.59 | 1.84 | 1.12 | 0.5 | -8.69 | 2.42 | 9.38 | 83.85 |
| male 6 | 37 | 23494.2 | 112.1 | 123.67 | 119.14 | 1.29 | 52.55 | 59.85 | 56.3 | 1.51 | 0.28 | 0.13 | 3.52 | -3.86 | 0.28 | 0.13 | 0.31 | -19.6 | 4.91 | 16.82 | 90.12 |
| male 7 | 30 | 9448 | 110.18 | 116.13 | 113 | 0.81 | 35.41 | 43.57 | 38.96 | 1.63 | 0.34 | 0.19 | 2.76 | -3.71 | 0.34 | 0.19 | 0.24 | -22.35 | 5.44 | 17.72 | 82.76 |
| male 8 | 24 | 6925.9 | 115.72 | 128.33 | 120.61 | 1.24 | 35.82 | 43.18 | 39.4 | 1.3 | 0.68 | 0.39 | 8.22 | -6.32 | 0.68 | 0.39 | 0.75 | -12.88 | 3.21 | 12.53 | 83.19 |
| male 9 | 50 | 2937.9 | 177.3 | 195.54 | 184.55 | 1.81 | 29.88 | 42.52 | 35.99 | 2.67 | 0.89 | 0.52 | 6.97 | -4.41 | 0.89 | 0.52 | 0.6 | -20.21 | 2.74 | 19.38 | 87.21 |
| male 10 | 24 | 10160 | 118.49 | 683.06 | 124.85 | 17.55 | 33 | 80 | 45.09 | 2.38 | 1.28 | 1.39 | 6.46 | -6.83 | 2.22 | 0.64 | 0.58 | -14.83 | 3.66 | 14.71 | 85.82 |

**Table 37: 'Normal' female sustained vowel /i/ (complete data set)**

| Control | age | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **female 1** | 24 | 6302.9 | 205.25 | 214.36 | 209.59 | 0.65 | 38.15 | 44.73 | 41.67 | 1 | 0.42 | 0.24 | 2.51 | -3.93 | 0.42 | 0.24 | 0.22 | -23.82 | 4.27 | 21.65 | 84.63 |
| **female 2** | 51 | 8595.6 | 229.3 | 285.06 | 236.63 | 1.05 | 39.28 | 51.47 | 47.66 | 1.29 | 1.1 | 0.67 | 13.71 | -7.72 | 1.1 | 0.67 | 1.14 | -17.17 | 3.42 | 13.73 | 79.65 |
| **female 3** | 41 | 8440.6 | 213.4 | 224.11 | 218.96 | 0.82 | 49.29 | 58.66 | 55.17 | 1.67 | 0.44 | 0.27 | 2.26 | -3.06 | 0.44 | 0.27 | 0.2 | -21.65 | 4.19 | 20.37 | 85.78 |
| **female 4** | 32 | 1469.9 | 187.19 | 244.2 | 213.44 | 2.62 | 26.02 | 58.66 | 39.99 | 11.59 | 1.62 | 0.95 | 3.99 | -4.68 | 1.62 | 0.95 | 0.35 | -12.05 | 4.09 | 14.71 | 89.3 |
| **female 5** | 32 | 10391.9 | 225.93 | 242.07 | 233.07 | 1.16 | 24.28 | 35.82 | 28.95 | 1.75 | 1 | 0.65 | 3.77 | -3.81 | 1 | 0.65 | 0.32 | -21.61 | 3 | 19.67 | 84.31 |
| **female 6** | 50 | 1892.5 | 222.61 | 243.48 | 231.19 | 1.75 | 46.26 | 70 | 58.89 | 5.26 | 0.67 | 0.38 | 3.42 | -3.78 | 0.67 | 0.38 | 0.3 | -22.86 | 4.22 | 21.32 | 87.45 |
| **female 7** | 59 | 2149.8 | 143.12 | 352.6 | 296.54 | 8.5 | 23.71 | 53.57 | 43.67 | 3.58 | 2 | 1.09 | 2.13 | -2.82 | 1.91 | 1.28 | 0.18 | -19.78 | 5.16 | 17.48 | 100.01 |
| **female 8** | 49 | 888.3 | 192.08 | 201.97 | 196.43 | 0.88 | 57.31 | 83.95 | 75.79 | 6.46 | 0.56 | 0.32 | 2.69 | -3.47 | 0.56 | 0.32 | 0.23 | -21.93 | 3.41 | 17.76 | 81.69 |
| **female 9** | 59 | 3074.8 | 246.42 | 260.82 | 252.91 | 0.8 | 39.68 | 46.03 | 43.17 | 1.2 | 0.7 | 0.41 | 1.53 | -2.53 | 0.7 | 0.41 | 0.13 | -27.97 | 6.28 | 23.57 | 89.92 |
| female 10 | 45 | 8149.1 | 242.42 | 256.34 | 249.78 | 0.93 | 52.38 | 60.93 | 56.47 | 1.43 | 0.69 | 0.44 | 3.4 | -3.73 | 0.69 | 0.44 | 0.3 | -17.65 | 5.97 | 19.99 | 91.1 |

**Table 38: 'Normal' female sustained vowels /a/ (complete data set)**

| Control | age | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **female 1** | 24 | 3445.6 | 196.73 | 207.51 | 202.54 | 0.85 | 196.73 | 207.51 | 33.18 | 2.62 | 0.54 | 0.31 | 3.61 | -3.55 | 0.54 | 0.31 | 0.33 | -24.64 | 5.65 | 19.55 | 86.83 |
| **female 2** | 51 | 4248.4 | 229.99 | 242.54 | 235.45 | 0.81 | 36.76 | 45.58 | 40.59 | 1.55 | 0.82 | 0.51 | 6.29 | -6.24 | 0.82 | 0.51 | 0.54 | -21.69 | 4.04 | 16.42 | 82.25 |
| **female 3** | 41 | 6414.8 | 212.58 | 223.06 | 218 | 0.81 | 43.83 | 54.66 | 48.98 | 1.93 | 0.41 | 0.23 | 3.77 | -3.19 | 0.41 | 0.23 | 0.33 | -18.63 | 5.53 | 15.84 | 89.17 |
| **female 4** | 32 | 612.4 | 172.95 | 215.14 | 188.25 | 2.9 | 32.18 | 46.06 | 37 | 2.59 | 2.46 | 1.54 | 2.15 | -1.79 | 2.49 | 1.51 | 0.19 | -25.25 | 7.01 | 19.69 | 101.35 |
| **female 5** | 32 | 2543.5 | 225.88 | 241.37 | 235.9 | 0.88 | 26.08 | 38.23 | 32.85 | 2.89 | 0.39 | 0.22 | 2.46 | -2.91 | 0.39 | 0.23 | 0.22 | -26.52 | 3.54 | 22.99 | 84.4 |
| **female 6** | 50 | 1992.8 | 209.73 | 221.43 | 215.16 | 1.09 | 20.54 | 43.42 | 33.02 | 4.92 | 0.65 | 0.41 | 3.87 | -3.89 | 0.65 | 0.41 | 0.33 | -18.47 | 5.6 | 16.99 | 88.87 |
| **female 7** | 59 | 2927.1 | 230.94 | 243.42 | 238.5 | 0.9 | 44.77 | 52.23 | 48.88 | 1.24 | 0.6 | 0.22 | 2.78 | -1.89 | 0.36 | 0.22 | 0.24 | -26.06 | 7.45 | 21.73 | 100.44 |
| **female 8** | 49 | 271.3 | 186.74 | 191.35 | 186.74 | 1.22 | 47.12 | 56.97 | 51.23 | 2.35 | 0.5 | 0.27 | 3.54 | -3.45 | 0.5 | 0.27 | 0.31 | -20.46 | 5.09 | 17.4 | 87.22 |
| **female 9** | 59 | 75588.9 | 214.08 | 230.04 | 220.6 | 1.42 | 33.8 | 48.61 | 40.8 | 2.71 | 1.56 | 0.96 | 2.28 | -1.92 | 1.56 | 0.96 | 0.2 | -29.17 | 5.15 | 20.45 | 91.26 |
| female 10 | 45 | 9677.1 | 237.19 | 255.68 | 245.77 | 1.18 | 49.23 | 60 | 56.57 | 1.68 | 0.37 | 0.21 | 1.55 | -1.66 | 0.37 | 0.21 | 0.14 | -25.83 | 7.71 | 21.48 | 99.51 |

# Appendix 7: Complete data set: voice questionnaires for RT and TLM patients

**Table 39: VHI-10 for RT patients (complete data set)**

| Patients | Functional (VHI-10 F) (max=20) | Physical (VHI-10 P) (max=12) | Emotional (VHI-10 E) (max=8) | Total (max=40) |
|---|---|---|---|---|
| 1 | 1 | 0 | 0 | 1 |
| 2 | 2 | 4 | 0 | 6 |
| 3 | 3 | 5 | 1 | 9 |
| 4 | 4 | 3 | 0 | 7 |
| 5 | 4 | 3 | 2 | 9 |
| 6 | 7 | 6 | 2 | 15 |
| 7 | 2 | 2 | 1 | 5 |
| 8 | 0 | 1 | 0 | 1 |
| 9 | 1 | 4 | 2 | 7 |
| 10 | 6 | 1 | 0 | 7 |
| 11 | 3 | 1 | 0 | 4 |
| 12 | 0 | 4 | 0 | 4 |
| 13 | 0 | 1 | 0 | 1 |
| 14 | 0 | 2 | 0 | 2 |
| 15 | 1 | 0 | 1 | 2 |
| 16 | 0 | 1 | 0 | 1 |
| 17 | 0 | 0 | 0 | 0 |
| 18 | 1 | 0 | 0 | 0 |
| 19 | 3 | 7 | 3 | 13 |

**Table 40: VHI-10 for TLM patients (complete data set)**

| Patients | Functional (VHI-10 F) (max=20) | Physical (VHI-10 P) (max=12) | Emotional (VHI-10 E) (max=8) | Total (max=40) |
|---|---|---|---|---|
| 1 | 1 | 0 | 0 | 1 |
| 2 | 2 | 4 | 0 | 6 |
| 3 | 3 | 5 | 1 | 9 |
| 4 | 4 | 3 | 0 | 7 |
| 5 | 4 | 3 | 2 | 9 |
| 6 | 7 | 6 | 2 | 15 |
| 7 | 2 | 2 | 1 | 5 |
| 8 | 0 | 1 | 0 | 1 |
| 9 | 1 | 4 | 2 | 7 |
| 10 | 6 | 1 | 0 | 7 |
| 11 | 3 | 1 | 0 | 4 |
| 12 | 0 | 4 | 0 | 4 |
| 13 | 1 | 4 | 2 | 7 |
| 14 | 0 | 1 | 0 | 1 |
| 15 | 0 | 2 | 0 | 2 |
| 16 | 1 | 0 | 1 | 2 |
| 17 | 0 | 1 | 0 | 1 |
| 18 | 1 | 0 | 0 | 1 |
| 19 | 2 | 4 | 0 | 6 |
| 20 | 3 | 5 | 1 | 9 |

**Table 41: VoiSS for RT patients (complete data set)**

| Patients | Impairment (max=60) | Emotional (max=32) | Physical (max=28) | Total (max=120) |
|---|---|---|---|---|
| 1 | 12 | 1 | 3 | 16 |
| 2 | 16 | 0 | 11 | 27 |
| 3 | 26 | 2 | 7 | 35 |
| 4 | 18 | 0 | 5 | 23 |
| 5 | 26 | 5 | 14 | 45 |
| 6 | 40 | 3 | 16 | 59 |
| 7 | 13 | 0 | 1 | 14 |
| 8 | 5 | 0 | 1 | 6 |
| 9 | 24 | 6 | 9 | 39 |
| 10 | 6 | 0 | 11 | 17 |
| 11 | 3 | 0 | 1 | 4 |
| 12 | 14 | 0 | 6 | 20 |
| 13 | 2 | 0 | 4 | 6 |
| 14 | 7 | 0 | 4 | 11 |
| 15 | 3 | 1 | 0 | 4 |
| 16 | 8 | 0 | 8 | 16 |
| 17 | - | - | - | - |
| 18 | 4 | 0 | 3 | 7 |
| 19 | 29 | 2 | 2 | 33 |

**Table 42: VoiSS for TLM patients (complete data set)**

| Patients | Impairment (max=60) | Emotional (max=32) | Physical (max=28) | Total (max=120) |
|---|---|---|---|---|
| 1 | 0 | 2 | 2 | 4 |
| 2 | 25 | 2 | 6 | 33 |
| 3 | 15 | 3 | 6 | 24 |
| 4 | 21 | 1 | 10 | 32 |
| 5 | 2 | 0 | 7 | 9 |
| 6 | 6 | 0 | 4 | 10 |
| 7 | 1 | 7 | 4 | 12 |
| 8 | 0 | 0 | 0 | 0 |
| 9 | 13 | 4 | 10 | 27 |
| 10 | 17 | 2 | 4 | 23 |
| 11 | 24 | 6 | 4 | 34 |
| 12 | 4 | 0 | 3 | 7 |
| 13 | 19 | 5 | 5 | 29 |
| 14 | 18 | 0 | 4 | 22 |
| 15 | 10 | 0 | 7 | 17 |
| 16 | 12 | 1 | 5 | 18 |
| 17 | 10 | 0 | 6 | 16 |
| 18 | 25 | 0 | 5 | 30 |
| 19 | 5 | 0 | 4 | 9 |
| 20 | 0 | 0 | 3 | 3 |

# Appendix 8: Complete data set: UW-QoLv4 questionnaire for RT and TLM patients

**Table 43: UW-QoLv4 for RT patients (complete data set)**

| QOL - Questionnaire (UW-QOL v4) | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety | Total (1200) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 2 | 25 | 100 | 75 | 75 | 100 | 100 | 100 | 30 | 100 | 100 | 100 | 100 | 1005 |
| 3 | 100 | 100 | 50 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1125 |
| 4 | 100 | 75 | 100 | 75 | 70 | 50 | 70 | 100 | 100 | 70 | 100 | 100 | 1010 |
| 5 | 75 | 100 | 50 | 50 | 70 | 100 | 100 | 70 | 100 | 30 | 100 | 100 | 945 |
| 6 | 100 | 100 | 25 | 25 | 70 | 50 | 30 | 70 | 0 | 100 | 50 | 100 | 720 |
| 7 | 100 | 75 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 100 | 100 | 1145 |
| 8 | 100 | 100 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 1120 |
| 9 | 50 | 75 | 50 | 75 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 30 | 925 |
| 10 | 100 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 1145 |
| 11 | 100 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1175 |
| 12 | 100 | 75 | 0 | 50 | 100 | 50 | 100 | 70 | 100 | 30 | 75 | 100 | 850 |
| 13 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 14 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 70 | 1115 |
| 15 | 100 | 100 | 50 | 25 | 100 | 0 | 100 | 100 | 100 | 0 | 100 | 70 | 845 |
| 16 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 17 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 18 | 100 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1175 |
| 19 | 100 | 100 | 75 | 50 | 100 | 50 | 70 | 100 | 100 | 70 | 75 | 30 | 920 |

**Table 44: UW-QoLv4 for TLM patients (complete data set)**

| QOL - Questionnaire (UW-QOL v4) | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety | Total (1200) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 100 | 100 | 50 | 50 | 100 | 100 | 100 | 100 | 100 | 100 | 50 | 70 | 1020 |
| 2 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 100 | 100 | 1170 |
| 3 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 1145 |
| 4 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 5 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 6 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 7 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 25 | 25 | 1050 |
| 8 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 9 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 30 | 100 | 100 | 100 | 70 | 1100 |
| 10 | 100 | 100 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1175 |
| 11 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 70 | 1115 |
| 12 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 100 | 1170 |
| 13 | 100 | 100 | 100 | 50 | 100 | 100 | 70 | 100 | 100 | 100 | 100 | 100 | 1120 |
| 14 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 15 | 100 | 100 | 50 | 50 | 100 | 100 | 100 | 100 | 70 | 100 | 75 | 70 | 1015 |
| 16 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 70 | 1120 |
| 17 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 18 | 100 | 100 | 100 | 100 | 100 | 100 |  | 100 | 100 | 100 | 75 | 70 | 1045 |
| 19 | 100 | 100 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1150 |
| 20 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |

**Table 45: UW-QoLv4 domain scores for RT patients (complete data set)**

| | N | 0 | 25 | 30 | 50 | 70 | 75 | 100 | Mean | SE | % Best Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pain | 19 | 0 | 1 | | 1 | | 1 | 16 | 92.1 | 4.7 | 78.9 |
| Appearance | 19 | 0 | 0 | | 0 | | 7 | 12 | 90.8 | 12.4 | 63.2 |
| Activity | 19 | 1 | 1 | | 4 | | 3 | 10 | 76.3 | 7.0 | 52.6 |
| Recreation | 19 | 0 | 2 | | 3 | | 5 | 9 | 77.6 | 6.0 | 47.4 |
| Swallowing | 19 | 0 | | 0 | | 3 | | 16 | 95.3 | 2.6 | 84.2 |
| Chewing | 19 | 1 | | 0 | 5 | 0 | | 14 | 84.2 | 6.7 | 73.7 |
| Speech | 19 | 0 | | 1 | | 5 | | 13 | 88.4 | 4.5 | 68.4 |
| Shoulder | 19 | 0 | | 1 | | 3 | | 15 | 91.6 | 4.3 | 78.9 |
| Taste | 19 | 1 | | 0 | | 0 | | 18 | 94.7 | 5.3 | 94.7 |
| Saliva | 19 | 1 | | 2 | | 2 | | 16 | 84.2 | 7.0 | 73.7 |
| Mood | 19 | 0 | 0 | | 1 | | 4 | 14 | 92.1 | 3.3 | 73.7 |
| Anxiety | 19 | 0 | | 2 | | 4 | | 13 | 86.3 | 5.4 | 68.4 |

**Table 46: UW-QoLv4 domain scores for TLM patients (complete data set)**

| | N | 0 | 25 | 30 | 50 | 70 | 75 | 100 | Mean | SE | % Best Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pain | 20 | 0 | 0 | | 0 | | 2 | 18 | 97.5 | 1.7 | 95.0 |
| Appearance | 20 | 0 | 0 | | 0 | | 0 | 20 | 100 | 0 | 100 |
| Activity | 20 | 0 | 0 | | 2 | | 2 | 16 | 92.5 | 3.7 | 80.0 |
| Recreation | 20 | 0 | 0 | | 3 | | 1 | 16 | 91.3 | 4.2 | 80.0 |
| Swallowing | 20 | 0 | | 0 | | 0 | | 100 | 100 | 0 | 100 |
| Chewing | 20 | 0 | | 0 | 0 | 0 | | 100 | 100 | 0 | 100 |
| Speech | 20 | 0 | | 0 | | 2 | | 13 | 95.3 | 2.5 | 80.0 |
| Shoulder | 20 | 0 | | 1 | | 1 | | 18 | 95.0 | 3.7 | 90.0 |
| Taste | 20 | 0 | | 0 | | 1 | | 19 | 98.5 | 1.5 | 95.0 |
| Saliva | 20 | 0 | | 0 | | 0 | | 20 | 100 | 0 | 100 |
| Mood | 20 | 0 | 1 | | 1 | | 4 | 14 | 88.8 | 4.6 | 70.0 |
| Anxiety | 20 | 0 | | 1 | | 7 | | 12 | 85.8 | 4.5 | 60.0 |

**Table 47: UW-QoLv4 rank within past 7 days for RT patients (complete data set)**

| | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 6 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 7 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 13 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| 15 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 19 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Total | 1 | 3 | 3 | 2 | 2 | 2 | 2 | 0 | 2 | 3 | 3 | 3 |

**Table 48: UW-QoLv4 rank within past 7 days for TLM patients (complete data set)**

| | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 3 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| 4 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 11 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 13 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 14 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 15 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 19 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 3 | 2 | 5 | 4 | 0 | 0 | 7 | 0 | 0 | 1 | 1 | 3 |

**Table 49: UW-QoLv4 global question scores for RT patients (complete data set)**

| | How would you rate your health-related QOL? | Your Health-related QOL is? | Overall QOL? |
|---|---|---|---|
| 1 | 50 | 80 | 80 |
| 2 | 25 | 60 | 60 |
| 3 | 75 | 60 | 40 |
| 4 | 100 | 80 | 100 |
| 5 | 25 | 80 | 80 |
| 6 | 50 | 20 | 20 |
| 7 | 50 | 80 | 100 |
| 8 | 50 | 80 | 80 |
| 9 | 50 | 60 | 80 |
| 10 | 50 | 100 | 100 |
| 11 | 50 | 60 | 60 |
| 12 | 50 | 60 | 60 |
| 13 | 50 | 40 | 60 |
| 14 | 50 | 60 | 80 |
| 15 | 50 | 100 | 80 |
| 16 | 50 | 80 | 80 |
| 17 | 100 | 100 | 100 |
| 18 | 100 | 100 | 100 |
| 19 | - | - | - |

**Table 50: UW-QoLv4 global question scores for TLM patients (complete data set)**

| | How would you rate your health-related QOL? | Your Health-related QOL is? | Overall QOL? |
|---|---|---|---|
| 1 | - | - | - |
| 2 | - | - | - |
| 3 | - | - | - |
| 4 | - | - | - |
| 5 | - | - | - |
| 6 | - | - | - |
| 7 | - | - | - |
| 8 | - | - | - |
| 9 | - | - | - |
| 10 | - | - | - |
| 11 | - | - | - |
| 12 | 100 | 80 | 80 |
| 13 | 50 | 40 | 80 |
| 14 | - | - | - |
| 15 | 100 | 80 | 80 |
| 16 | 50 | 60 | 60 |
| 17 | 50 | 80 | 80 |
| 18 | 50 | 60 | 60 |
| 19 | 50 | 60 | 80 |
| 20 | 100 | 100 | 100 |

**Table 51: UW-QoLv4 global questions for RT patients (complete data set)**

| | N | 0 | 20 | 25 | 40 | 50 | 60 | 75 | 80 | 100 | Mean | SE | % Best Scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Health-related QOL compared to month before had cancer | 19 | 0 | | 2 | | 13 | | 1 | | 3 | 56.9 | 5.1 | 15.8 |
| B. Health-related QOL during the past 7 days | 19 | 0 | 1 | | 1 | | 7 | | 6 | 4 | 72.2 | 5.0 | 21.1 |
| C. Overall QOL during the past 7 days | 19 | 0 | 1 | | 1 | | 4 | | 8 | 5 | 75.6 | 5.1 | 26.3 |

**Table 52: UW-QoLv4 global questions for TLM patients (complete data set)**

| | N | 0 | 20 | 25 | 40 | 50 | 60 | 75 | 80 | 100 | Mean | SE | % Best Scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Health-related QOL compared to month before had cancer | 8 | 0 | | 0 | | 5 | | 0 | | 3 | 68.8 | 9.1 | 37.5 |
| B. Health-related QOL during the past 7 days | 8 | 0 | 0 | | 1 | | 3 | | 3 | 1 | 70.0 | 6.5 | 12.5 |
| C. Overall QOL during the past 7 days | 8 | 0 | 0 | | 0 | | 2 | | 5 | 1 | 77.5 | 4.5 | 12.5 |

**Table 53: UW-QoLv4 domain issue seen as most important in past seven days for RT and TLM patients (complete data set)**

| | N | Number of RT patients choosing domain | Number of TLM patients choosing domain | Total number of patients choosing domain | Rank order |
|---|---|---|---|---|---|
| Pain | 39 | 1 | 3 | 4 | =6 |
| Appearance | 39 | 3 | 2 | 5 | 5 |
| Activity | 39 | 3 | 5 | 8 | 2 |
| Recreation | 39 | 2 | 4 | 6 | =3 |
| Swallowing | 39 | 2 | 0 | 2 | =9 |
| Chewing | 39 | 2 | 0 | 2 | =9 |
| Speech | 39 | 2 | 7 | 9 | 1 |
| Shoulder | 39 | 0 | 0 | 0 | 12 |
| Taste | 39 | 2 | 0 | 2 | =9 |
| Saliva | 39 | 3 | 1 | 4 | =6 |
| Mood | 39 | 3 | 1 | 4 | =6 |
| Anxiety | 39 | 3 | 3 | 6 | =3 |

# Appendix 9: Complete data set: perception rating for RT and TLM patients

**Table 54: GRBAS scores for RT patients (complete data set)**

| | Rater 1 scores | | | | | Rater 2 scores | | | | | Rater 3 scores | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) |
| 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 2 | 3 | 3 | 2 | 0 | 2 | 3 | 3 | 2 | 0 | 2 | 2 | 2 | 1 | 0 | 0 |
| 3 | 3 | 3 | 1 | 1 | 3 | 3 | 3 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 |
| 4 | 3 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 2 |
| 5 | 3 | 1 | 2 | 1 | 2 | 3 | 2 | 2 | 1 | 2 | 1 | 1 | 0 | 0 | 0 |
| 6 | 3 | 2 | 3 | 2 | 3 | 3 | 2 | 3 | 2 | 3 | 3 | 2 | 2 | 2 | 3 |
| 7 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 1 |
| 8 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 1 | 0 | 0 |
| 9 | - | - | - | - | - | - | - | - | - | - | 2 | 2 | 1 | 0 | 1 |
| 10 | - | - | - | - | - | - | - | - | - | - | 2 | 2 | 1 | 1 | 1 |
| 11 | - | - | - | - | - | - | - | - | - | - | 2 | 1 | 2 | 1 | 1 |
| 12 | - | - | - | - | - | - | - | - | - | - | 2 | 2 | 1 | 0 | 0 |
| 13 | - | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 0 | 0 |
| 14 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 0 | 0 | 0 |
| 15 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 0 | 0 | 0 |
| 16 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 0 | 0 | 0 |
| 17 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 1 | 0 | 0 |
| 18 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 1 | 0 | 0 |
| 19 | - | - | - | - | - | - | - | - | - | - | 2 | 1 | 1 | 1 | 2 |

**Table 55: GRBAS scores for TLM patients (complete data set)**

| | Rater 1 scores | | | | | Rater 2 scores | | | | | Rater 3 scores | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) |
| 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 2 | 2 | 2 | 0 | 2 |
| 2 | 2 | 1 | 2 | 2 | 1 | 2 | 0 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 |
| 3 | 2 | 0 | 0 | 1 | 2 | 2 | 0 | 0 | 2 | 2 | 2 | 1 | 2 | 1 | 2 |
| 4 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 2 | 1 | 2 | 1 | 2 |
| 5 | 2 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 0 | 2 | 0 | 1 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 2 | 0 | 1 |
| 7 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 |
| 8 | 2 | 1 | 0 | 0 | 2 | 2 | 1 | 0 | 0 | 2 | 2 | 2 | 1 | 0 | 1 |
| 9 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 2 | 2 | 2 | 0 | 1 |
| 10 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 2 | 0 | 2 | 0 | 0 |
| 11 | 2 | 0 | 2 | 1 | 2 | 2 | 0 | 2 | 1 | 2 | 2 | 1 | 2 | 1 | 2 |
| 12 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| 13 | 3 | 0 | 3 | 2 | 3 | 3 | 0 | 2 | 2 | 3 | 3 | 3 | 3 | 2 | 3 |
| 14 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| 15 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 1 | 1 | 1 |
| 16 | - | - | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 0 | 0 |
| 17 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 1 | 1 | 0 |
| 18 | - | - | - | - | - | - | - | - | - | - | 3 | 2 | 3 | 2 | 2 |
| 19 | - | - | - | - | - | - | - | - | - | - | 2 | 1 | 2 | 1 | 1 |
| 20 | - | - | - | - | - | - | - | - | - | - | 1 | 1 | 1 | 0 | 0 |

# Appendix 10: Complete data set: sustained vowels for RT and TLM patients

**Table 56: Sustained vowel /i/ for RT patients (complete data set)**

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1612.0 | 116.5 | 129.5 | 123.7 | 2.0 | 50.0 | 58.5 | 55.1 | 1.8 | 0.5 | 0.3 | 3.0 | -3.3 | 0.5 | 0.3 | 0.3 | -22.9 | 4.0 | 18.4 | 94.8 |
| 2 | 248.0 | 87.6 | 91.2 | 89.8 | 1.0 | 38.2 | 62.1 | 46.8 | 6.2 | 0.9 | 0.5 | 2.3 | -3.4 | 0.9 | 0.5 | 0.2 | -24.6 | 2.7 | 21.5 | 85.7 |
| 3 | 4364.0 | 51.8 | 1024.6 | 144.0 | 82.0 | 0.0 | 74.4 | 39.8 | 14.7 | 31.0 | 32.1 | 28.5 | -32.6 | 51.1 | 14.8 | 2.7 | -1.0 | 0.9 | 2.4 | 93.0 |
| 4 | 596.0 | 127.1 | 255.1 | 229.2 | 4.6 | 0.0 | 50.0 | 40.6 | 4.2 | 2.6 | 1.5 | 2.3 | -3.8 | 2.5 | 1.8 | 0.2 | -20.6 | 2.9 | 24.5 | 87.8 |
| 5 | 240.0 | 149.7 | 205.4 | 176.1 | 7.0 | 14.9 | 33.3 | 25.0 | 5.2 | 9.3 | 5.8 | 2.5 | -3.8 | 9.4 | 5.7 | 0.2 | -18.0 | 3.6 | 19.8 | 89.4 |
| 6 | 136.0 | 206.2 | 259.4 | 232.8 | 6.5 | 43.5 | 52.2 | 48.4 | 2.9 | 2.5 | 1.5 | 4.3 | -6.0 | 2.5 | 1.5 | 0.4 | -15.5 | 3.6 | 18.2 | 94.5 |
| 7 | 1012.0 | 148.8 | 169.2 | 158.1 | 2.4 | 45.0 | 53.5 | 49.1 | 1.9 | 2.2 | 1.3 | 1.0 | -10.0 | 2.2 | 1.3 | 0.9 | -11.5 | 1.9 | 14.0 | 89.7 |
| 8 | 1488.0 | 81.7 | 503.8 | 240.0 | 42.1 | 0.0 | 59.8 | 27.7 | 10.2 | 48.0 | 31.2 | 9.7 | -12.7 | 50.9 | 28.7 | 0.9 | 1.1 | 1.9 | 5.1 | 102.6 |
| 9 | 8261.0 | 104.2 | 112.6 | 107.7 | 1.2 | 46.2 | 65.1 | 59.2 | 3.6 | 0.5 | 0.3 | 7.0 | -3.3 | 0.5 | 0.3 | 0.6 | -17.8 | 2.8 | 17.7 | 80.9 |
| 10 | 11112.0 | 172.4 | 206.4 | 184.7 | 2.5 | 34.9 | 47.8 | 43.4 | 1.9 | 0.7 | 0.4 | 4.8 | -4.4 | 0.7 | 0.4 | 0.4 | -17.8 | 3.6 | 17.7 | 76.3 |
| 11 | 2655.0 | 87.9 | 207.5 | 168.2 | 5.8 | 29.6 | 66.0 | 55.8 | 6.6 | 5.2 | 3.1 | 5.3 | -5.6 | 5.1 | 3.2 | 0.5 | -15.8 | 1.8 | 17.7 | 76.4 |
| 12 | 502.6 | 151.4 | 169.8 | 162.9 | 2.3 | 34.3 | 50.5 | 47.0 | 2.6 | 1.4 | 0.8 | 9.2 | -5.9 | 1.4 | 0.8 | 0.9 | -17.3 | 2.8 | 17.1 | 82.3 |
| 13 | 2058.0 | 156.3 | 585.8 | 209.8 | 53.8 | 0.0 | 61.4 | 46.1 | 22.8 | 28.4 | 26.1 | 11.7 | -28.0 | 41.5 | 11.4 | 1.2 | -2.9 | 3.4 | 12.9 | 84.9 |
| 14 | 2412.6 | 152.5 | 160.3 | 156.1 | 0.9 | 29.8 | 39.8 | 33.5 | 2.1 | 0.6 | 0.3 | 4.5 | -7.4 | 0.6 | 0.3 | 0.4 | -15.3 | 3.9 | 14.9 | 85.6 |
| 15 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 16 | 3847.0 | 69.6 | 157.0 | 138.7 | 2.9 | 30.0 | 53.4 | 49.1 | 2.4 | 1.3 | 0.8 | 4.0 | -5.0 | 1.3 | 0.9 | 0.4 | -16.4 | 3.5 | 14.9 | 88.2 |
| 17 | 7023.0 | 130.7 | 134.1 | 132.4 | 0.5 | 50.0 | 56.2 | 52.7 | 1.0 | 0.2 | 0.1 | 1.7 | -1.8 | 0.2 | 0.1 | 0.2 | -27.0 | 4.5 | 17.5 | 93.0 |
| 18 | 400.0 | 135.6 | 139.6 | 137.4 | 0.6 | 42.6 | 47.0 | 45.5 | 0.9 | 0.4 | 0.2 | 2.0 | -2.9 | 0.4 | 0.2 | 0.2 | -23.9 | 4.2 | 20.3 | 93.9 |
| 19 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

**Table 57: Sustained vowel /i/ for TLM patients (complete data set)**

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1733.6 | 157.8 | 166.1 | 162.3 | 1.1 | 57.1 | 59.8 | 58.4 | 0.5 | 1.3 | 0.8 | 8.2 | -7.5 | 1.3 | 0.9 | 0.7 | -16.5 | 3.3 | 16.4 | 103.5 |
| 2 | 1021.0 | 104.8 | 253.4 | 216.2 | 11.4 | 24.8 | 53.4 | 45.2 | 4.6 | 9.5 | 5.4 | 6.9 | -13.9 | 8.6 | 7.2 | 0.6 | -8.2 | 2.2 | 14.5 | 87.0 |
| 3 | 3738.7 | 205.2 | 223.1 | 212.6 | 1.2 | 33.8 | 46.7 | 39.9 | 2.4 | 1.2 | 0.7 | 3.7 | -8.5 | 1.2 | 0.7 | 0.3 | -16.2 | 2.1 | 17.0 | 91.8 |
| 4 | 4984.0 | 151.9 | 162.2 | 156.7 | 0.9 | 25.5 | 43.7 | 30.6 | 3.2 | 0.6 | 0.4 | 4.6 | -8.0 | 0.6 | 0.4 | 0.4 | -16.6 | 1.9 | 16.8 | 90.9 |
| 5 | 1499.0 | 179.0 | 186.7 | 182.5 | 0.8 | 42.0 | 56.2 | 48.9 | 3.2 | 0.4 | 0.3 | 3.0 | -2.8 | 0.4 | 0.3 | 0.3 | -21.9 | 3.7 | 18.9 | 93.9 |
| 6 | 5553.0 | 204.0 | 211.5 | 207.9 | 0.5 | 39.0 | 47.4 | 44.2 | 1.9 | 0.3 | 0.2 | 2.1 | -3.4 | 0.3 | 0.2 | 0.2 | -21.3 | 3.3 | 19.6 | 90.7 |
| 7 | 2013.3 | 164.1 | 170.1 | 167.1 | 0.7 | 57.7 | 62.5 | 60.1 | 0.8 | 0.1 | 0.1 | 1.7 | -2.0 | 0.1 | 0.1 | 0.2 | -26.5 | 5.7 | 19.0 | 100.9 |
| 8 | 1861.6 | 210.7 | 229.1 | 219.0 | 1.2 | 62.2 | 67.1 | 64.7 | 1.1 | 1.0 | 0.6 | 3.4 | -5.9 | 1.0 | 0.6 | 0.3 | -11.6 | 5.8 | 15.5 | 97.1 |
| 9 | 1207.6 | 173.1 | 197.7 | 183.2 | 2.0 | 42.7 | 51.8 | 45.4 | 1.7 | 0.6 | 0.3 | 2.8 | -3.2 | 0.6 | 0.3 | 0.2 | -19.2 | 3.4 | 18.1 | 90.0 |
| 10 | 2507.0 | 147.0 | 181.3 | 177.8 | 0.8 | 37.5 | 43.3 | 40.3 | 1.0 | 0.7 | 0.4 | 3.0 | -3.5 | 0.7 | 0.4 | 0.3 | -24.7 | 3.6 | 17.7 | 92.4 |
| 11 | 7496.0 | 201.6 | 214.9 | 207.9 | 0.8 | 35.9 | 41.0 | 38.3 | 0.8 | 0.7 | 0.4 | 4.8 | -8.3 | 0.7 | 0.4 | 0.4 | -16.6 | 2.8 | 18.9 | 98.3 |
| 12 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 13 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 14 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 15 | 4112.0 | 78.2 | 199.6 | 165.9 | 5.1 | 16.2 | 48.4 | 39.0 | 4.2 | 2.8 | 1.6 | 5.3 | -2.8 | 2.6 | 2.0 | 0.5 | -18.1 | 2.0 | 22.6 | 76.2 |
| 16 | 15241.0 | 146.5 | 158.3 | 151.8 | 0.9 | 33.0 | 49.1 | 43.3 | 1.6 | 0.2 | 0.1 | 4.9 | -4.7 | 0.2 | 0.1 | 0.4 | -20.6 | 4.9 | 19.2 | 79.1 |
| 17 | 5507.0 | 119.8 | 126.7 | 123.7 | 1.1 | 54.2 | 62.4 | 59.0 | 1.6 | 0.3 | 0.2 | 4.2 | -2.5 | 0.3 | 0.2 | 0.4 | -26.2 | 2.6 | 23.5 | 73.6 |
| 18 | 569.0 | 50.2 | 387.6 | 285.0 | 27.7 | 0.0 | 76.8 | 36.8 | 17.9 | 34.9 | 16.1 | 7.1 | -6.8 | 26.7 | 36.5 | 0.7 | 0.7 | 2.2 | 15.2 | 72.7 |
| 19 | 4982.0 | 61.0 | 1328.0 | 203.3 | 78.8 | 0.0 | 93.3 | 42.4 | 16.6 | 35.7 | 31.1 | 27.6 | -4.9 | 50.5 | 19.2 | 1.4 | -1.0 | 3.2 | 16.0 | 83.9 |
| 20 | 4970.0 | 133.9 | 143.2 | 139.5 | 1.1 | 29.9 | 36.8 | 33.8 | 1.4 | 0.5 | 0.2 | 3.7 | -3.8 | 0.5 | 0.2 | 0.3 | -23.7 | 4.9 | 20.7 | 82.5 |

**Table 58: Sustained vowel /a/ for RT patients (complete data set)**

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2804.0 | 96.2 | 104.5 | 100.2 | 1.2 | 43.5 | 55.2 | 48.5 | 2.1 | 0.4 | 0.2 | 3.4 | -3.8 | 0.4 | 0.2 | 0.4 | -23.0 | 4.8 | 18.1 | 95.8 |
| 2 | 252.0 | 176.1 | 207.2 | 190.3 | 3.3 | 0.0 | 47.7 | 39.0 | 13.5 | 2.7 | 1.4 | 13.5 | -3.8 | 2.7 | 1.4 | 1.4 | -25.2 | 4.3 | 20.6 | 87.9 |
| 3 | 4308.0 | 55.8 | 688.2 | 112.4 | 81.5 | 0.0 | 73.5 | 42.0 | 15.1 | 29.5 | 30.4 | 46.4 | -34.1 | 49.9 | 12.9 | 4.0 | 0.1 | 1.1 | - | 96.3 |
| 4 | 112.0 | 118.4 | 207.5 | 196.3 | 2.4 | 43.2 | 48.1 | 45.5 | 1.3 | 2.0 | 1.1 | 9.5 | -4.1 | 2.0 | 1.0 | 0.8 | -16.1 | 4.5 | 16.5 | 90.2 |
| 5 | 2456.0 | 138.4 | 158.7 | 148.5 | 2.3 | 30.7 | 46.8 | 36.9 | 4.4 | 0.9 | 0.5 | 5.7 | -3.8 | 0.9 | 0.5 | 0.5 | -17.8 | 4.4 | 15.9 | 88.3 |
| 6 | 240.0 | 180.2 | 230.2 | 211.0 | 6.1 | 34.7 | 46.8 | 40.8 | 2.7 | 3.0 | 2.0 | 11.1 | -17.7 | 3.0 | 2.0 | 0.9 | -12.1 | 3.0 | 12.9 | 93.1 |
| 7 | 3624.0 | 148.2 | 163.8 | 156.2 | 1.7 | 26.2 | 53.9 | 40.4 | 6.1 | 1.8 | 1.1 | 25.5 | -26.2 | 1.8 | 1.1 | 2.4 | -4.8 | 2.2 | 8.2 | 93.9 |
| 8 | 1774.0 | 84.9 | 1200.0 | 253.1 | 80.8 | 0.0 | 58.6 | 42.0 | 14.3 | 44.5 | 47.1 | 16.4 | -7.1 | 72.2 | 19.2 | 1.4 | -0.6 | 5.1 | 9.4 | 101.3 |
| 9 | 2498.0 | 88.7 | 112.3 | 104.7 | 4.1 | 39.6 | 58.0 | 46.4 | 3.6 | 1.2 | 0.6 | 6.6 | -4.8 | 1.2 | 0.7 | 0.6 | -12.8 | 3.5 | 11.9 | 86.9 |
| 10 | 8069.0 | 71.3 | 485.2 | 150.8 | 9.5 | 28.3 | 52.5 | 38.8 | 5.7 | 1.2 | 0.7 | 9.6 | -8.0 | 1.2 | 0.7 | 1.0 | -16.0 | 2.7 | 13.6 | 81.1 |
| 11 | 2336.0 | 170.3 | 188.0 | 180.1 | 1.9 | 39.8 | 62.2 | 48.3 | 5.5 | 1.6 | 0.9 | 6.3 | -10.9 | 1.6 | 0.9 | 0.5 | -16.0 | 3.0 | 15.7 | 74.8 |
| 12 | 448.4 | 141.7 | 156.1 | 150.2 | 2.2 | 41.3 | 50.9 | 47.0 | 2.3 | 0.9 | 0.5 | 11.8 | -9.1 | 0.9 | 0.5 | 1.0 | -15.2 | 3.7 | 14.7 | 79.3 |
| 13 | 3242.0 | 144.3 | 157.0 | 149.2 | 1.5 | 45.3 | 53.7 | 49.5 | 1.6 | 1.8 | 1.2 | 4.3 | -3.4 | 1.8 | 1.2 | 0.4 | -16.8 | 3.7 | 14.3 | 89.1 |
| 14 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 15 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 16 | 2568.0 | 117.2 | 149.4 | 141.0 | 1.3 | 46.4 | 52.3 | 49.3 | 1.0 | 0.9 | 0.5 | 7.4 | -4.9 | 0.9 | 0.5 | 0.6 | -16.6 | 4.7 | 14.3 | 87.2 |
| 17 | 13520.0 | 124.2 | 134.4 | 129.3 | 1.1 | 45.9 | 50.8 | 48.3 | 0.7 | 0.5 | 0.3 | 3.6 | -4.3 | 0.5 | 0.3 | 0.3 | -21.1 | 4.3 | 18.0 | 92.7 |
| 18 | 1961.0 | 58.9 | 288.0 | 121.9 | 10.7 | 0.0 | 57.7 | 51.1 | 9.9 | 3.5 | 2.0 | 6.0 | -4.8 | 3.7 | 2.3 | 0.5 | -9.8 | 3.8 | 13.9 | 97.3 |
| 19 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

**Table 59: Sustained vowel /a/ for TLM patients (complete data set)**

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2977.0 | 163.6 | 186.0 | 169.2 | 2.5 | 44.1 | 62.5 | 55.1 | 5.2 | 0.8 | 0.5 | 10.0 | -10.3 | 0.8 | 0.5 | 0.9 | -14.9 | 3.6 | 12.5 | 107.7 |
| 2 | 4987.0 | 205.0 | 217.9 | 210.4 | 0.9 | 35.1 | 48.1 | 42.9 | 2.2 | 0.5 | 0.3 | 5.8 | -5.4 | 0.5 | 0.3 | 0.5 | -17.3 | 2.9 | 18.9 | 89.9 |
| 3 | 2047.0 | 99.2 | 261.1 | 208.7 | 5.5 | 28.4 | 43.6 | 35.8 | 2.7 | 2.4 | 1.5 | 6.1 | -3.8 | 2.4 | 1.5 | 0.5 | -20.7 | 4.0 | 16.8 | 96.2 |
| 4 | 4737.0 | 152.9 | 161.1 | 157.5 | 0.9 | 32.4 | 43.6 | 38.4 | 2.9 | 0.5 | 0.3 | 8.7 | -10.1 | 0.5 | 0.3 | 0.8 | -13.5 | 2.5 | 15.0 | 90.3 |
| 5 | 1563.0 | 173.0 | 187.3 | 181.1 | 1.2 | 43.0 | 51.1 | 48.4 | 1.3 | 0.4 | 0.2 | 3.8 | -2.9 | 0.4 | 0.2 | 0.3 | -25.1 | 6.6 | 19.3 | 99.3 |
| 6 | 2274.0 | 184.5 | 190.5 | 187.4 | 0.6 | 39.3 | 43.5 | 41.5 | 0.7 | 0.5 | 0.3 | 4.8 | -2.4 | 0.5 | 0.3 | 0.4 | -21.8 | 4.3 | 18.9 | 90.4 |
| 7 | 1318.0 | 163.8 | 170.7 | 167.7 | 0.8 | 55.9 | 60.4 | 58.4 | 0.7 | 0.2 | 0.1 | 1.4 | -1.6 | 0.2 | 0.1 | 0.1 | -27.4 | 7.1 | 22.2 | 105.7 |
| 8 | 1192.0 | 194.3 | 207.0 | 199.0 | 1.6 | 55.6 | 63.0 | 60.5 | 1.4 | 0.3 | 0.1 | 2.1 | -2.0 | 0.3 | 0.1 | 0.2 | -26.3 | 6.9 | 21.0 | 107.5 |
| 9 | 1009.0 | 150.2 | 160.2 | 153.7 | 1.3 | 37.5 | 44.2 | 41.5 | 1.6 | 0.3 | 0.1 | 8.3 | -7.9 | 0.3 | 0.1 | 0.7 | -17.7 | 4.0 | 15.7 | 90.4 |
| 10 | 6833.0 | 167.0 | 181.4 | 175.3 | 0.8 | 25.3 | 55.2 | 34.2 | 2.9 | 0.6 | 0.4 | 5.0 | -3.8 | 0.6 | 0.4 | 0.4 | -18.8 | 4.1 | 18.0 | 90.8 |
| 11 | 4997.0 | 189.7 | 198.9 | 194.6 | 0.7 | 34.9 | 40.2 | 37.5 | 0.8 | 0.7 | 0.4 | 11.1 | -7.4 | 0.7 | 0.4 | 1.0 | -16.6 | 3.8 | 16.2 | 96.2 |
| 12 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 13 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 14 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 15 | 6739.0 | 55.2 | 1335.1 | 176.0 | 47.9 | 0.0 | 77.7 | 48.6 | 15.8 | 15.1 | 11.8 | 9.5 | -6.2 | 19.0 | 11.1 | 0.7 | -6.5 | 2.9 | 16.9 | 73.3 |
| 16 | 10072.0 | 147.8 | 156.5 | 151.5 | 0.8 | 31.1 | 43.5 | 36.6 | 2.8 | 0.3 | 0.2 | 4.2 | -4.0 | 0.3 | 0.2 | 0.4 | -22.4 | 5.4 | 17.3 | 80.5 |
| 17 | 11521.9 | 115.8 | 134.7 | 124.3 | 1.6 | 41.8 | 53.1 | 59.4 | 2.0 | 1.3 | 0.8 | 3.0 | -3.5 | 1.3 | 0.8 | 0.3 | -18.6 | 3.9 | 16.9 | 77.4 |
| 18 | 664.0 | 57.2 | 1319.3 | 305.9 | 85.4 | 0.0 | 74.1 | 23.2 | 23.9 | 67.7 | 49.5 | 30.6 | -32.4 | 80.6 | 46.4 | 4.2 | 0.8 | 2.0 | 6.6 | 64.3 |
| 19 | 3409.0 | 152.6 | 984.3 | 163.1 | 32.0 | 0.0 | 88.2 | 46.6 | 3.6 | 3.6 | 4.3 | 7.4 | -8.3 | 6.7 | 1.8 | 0.7 | -9.3 | 3.3 | 14.2 | 79.4 |
| 20 | 2349.0 | 133.4 | 144.2 | 137.3 | 1.1 | 35.3 | 39.7 | 37.5 | 0.6 | 0.8 | 0.5 | 7.2 | -6.8 | 0.8 | 0.5 | 0.6 | -19.5 | 4.9 | 16.0 | 88.1 |

# Appendix 11: Complete data set: voice questionnaires for pre- and post- TLM patients

**Table 60: VHI-10 for pre-TLM patients (complete data set)**

| | Functional (VHI-10 F) (max=20) | Physical (VHI-10 P) (max=12) | Emotional (VHI-10 E) (max=8) | Total (max=40) |
|---|---|---|---|---|
| 1 | 7 | 8 | 6 | 21 |
| 2 | 12 | 11 | 2 | 25 |
| 3 | 13 | 8 | 4 | 25 |
| 4 | 6 | 5 | 2 | 13 |
| 5 | 6 | 7 | 1 | 14 |
| 6 | 9 | 7 | 2 | 18 |
| 7 | 2 | 3 | 1 | 6 |
| 8 | 6 | 6 | 0 | 12 |
| 9 | 3 | 6 | 4 | 13 |
| 10 | 9 | 3 | 1 | 13 |
| 11 | 3 | 3 | 0 | 6 |
| 12 | 0 | 0 | 2 | 2 |
| 13 | 6 | 4 | 3 | 13 |
| 14 | 3 | 4 | 2 | 9 |
| 15 | 3 | 1 | 1 | 5 |
| 16 | 18 | 12 | 8 | 38 |
| 17 | 5 | 4 | 4 | 13 |
| 18 | 2 | 4 | 0 | 6 |
| 19 | 5 | 6 | 1 | 12 |
| 20 | 4 | 5 | 2 | 11 |
| 21 | 11 | 10 | 7 | 28 |
| 22 | 7 | 6 | 2 | 15 |
| 23 | 4 | 5 | 2 | 11 |
| 24 | 8 | 5 | 6 | 19 |
| 25 | 10 | 7 | 2 | 19 |
| 26 | 0 | 0 | 0 | 0 |
| 27 | 4 | 5 | 0 | 9 |
| 28 | 3 | 6 | 2 | 11 |
| 29 | 0 | 0 | 0 | 0 |

**Table 61: VHI-10 for post-TLM patients (complete data set)**

| | Functional (VHI-10 F) (max=20) | Physical (VHI-10 P) (max=12) | Emotional (VHI-10 E) (max=8) | Total (max=40) |
|---|---|---|---|---|
| 1 | 7 | 6 | 1 | 14 |
| 2 | 2 | 2 | 1 | 5 |
| 3 | 6 | 5 | 1 | 12 |
| 4 | 12 | 10 | 4 | 26 |
| 5 | 11 | 9 | 4 | 24 |
| 6 | 7 | 5 | 2 | 14 |
| 7 | 16 | 10 | 6 | 32 |
| 8 | 2 | 0 | 0 | 2 |
| 9 | 12 | 5 | 3 | 20 |
| 10 | 10 | 7 | 2 | 19 |
| 11 | 0 | 0 | 0 | 0 |
| 12 | 3 | 0 | 0 | 3 |
| 13 | 6 | 3 | 0 | 9 |
| 14 | 1 | 1 | 2 | 4 |
| 15 | 2 | 3 | 0 | 5 |
| 16 | 15 | 9 | 8 | 32 |
| 17 | 3 | 3 | 0 | 6 |

**Table 62: VoiSS for pre-TLM patients (complete data set)**

| | Impairment (max=60) | Emotional (max=32) | Physical (max=28) | Total (max=120) |
|---|---|---|---|---|
| 1 | 38 | 5 | 11 | 54 |
| 2 | 40 | 6 | 8 | 54 |
| 3 | 38 | 12 | 9 | 59 |
| 4 | 30 | 2 | 8 | 40 |
| 5 | 21 | 3 | 4 | 28 |
| 6 | 32 | 7 | 6 | 45 |
| 7 | 20 | 3 | 2 | 25 |
| 8 | 39 | 0 | 11 | 50 |
| 9 | 30 | 3 | 12 | 45 |
| 10 | 23 | 4 | 6 | 33 |
| 11 | 9 | 1 | 7 | 17 |
| 12 | 8 | 0 | 9 | 17 |
| 13 | 31 | 10 | 1 | 42 |
| 14 | 25 | 14 | 5 | 44 |
| 15 | 20 | 7 | 8 | 35 |
| 16 | 54 | 22 | 7 | 83 |
| 17 | 32 | 4 | 7 | 43 |
| 18 | 21 | 0 | 2 | 23 |
| 19 | 27 | 9 | 6 | 42 |
| 20 | 20 | 6 | 7 | 33 |
| 21 | 47 | 16 | 8 | 71 |
| 22 | 31 | 11 | 7 | 49 |
| 23 | 32 | 4 | 13 | 49 |
| 24 | 29 | 12 | 8 | 49 |
| 25 | 31 | 5 | 7 | 43 |
| 26 | 0 | 0 | 2 | 2 |
| 27 | 16 | 4 | 9 | 29 |
| 28 | 31 | 4 | 4 | 39 |
| 29 | 0 | 0 | 13 | 13 |

**Table 63: VoiSS for post-TLM patients (complete data set)**

| | Impairment (max=60) | Emotional (max=32) | Physical (max=28) | Total (max=120) |
|---|---|---|---|---|
| 1 | 27 | 12 | 12 | 51 |
| 2 | 23 | 0 | 8 | 31 |
| 3 | 25 | 0 | 3 | 28 |
| 4 | 43 | 15 | 6 | 64 |
| 5 | 43 | 9 | 8 | 60 |
| 6 | - | - | - | - |
| 7 | 34 | 14 | 6 | 54 |
| 8 | 8 | 0 | 0 | 8 |
| 9 | 40 | 11 | 11 | 62 |
| 10 | 40 | 9 | 9 | 58 |
| 11 | 1 | 0 | 10 | 11 |
| 12 | 6 | 0 | 5 | 11 |
| 13 | 25 | 4 | 5 | 34 |
| 14 | 14 | 1 | 5 | 20 |
| 15 | 21 | 0 | 6 | 27 |
| 16 | 40 | 16 | 16 | 72 |
| 17 | 12 | 0 | 6 | 18 |

# Appendix 12: Complete data set: UW-QoLv4 questionnaire for pre- and post-TLM patients

**Table 64: UW-QoLv4 for pre-TLM patients (complete data set)**

| | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety | Total (1200) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50 | 75 | 100 | 100 | 100 | 100 | 30 | 100 | 100 | 100 | 75 | 70 | 1000 |
| 2 | 50 | 100 | 50 | 50 | 100 | 100 | 70 | 30 | 100 | 100 | 75 | 70 | 895 |
| 3 | 75 | 75 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 70 | 1065 |
| 4 | 75 | 100 | 75 | 75 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 70 | 1040 |
| 5 | 75 | 100 | 100 | 75 | 100 | 100 | 70 | 100 | 100 | 100 | 25 | 30 | 975 |
| 6 | 75 | 100 | 100 | 100 | 70 | 100 | 70 | 30 | 100 | 100 | 100 | 100 | 1045 |
| 7 | 75 | 100 | 100 | 100 | 100 | 100 | 30 | 100 | 100 | 100 | 75 | 70 | 1050 |
| 8 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 70 | 1120 |
| 9 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 1145 |
| 10 | 100 | 100 | 100 | 75 | 100 | 100 | 30 | 100 | 100 | 100 | 75 | 70 | 1050 |
| 11 | 100 | 100 | 100 | 75 | 100 | 100 | 100 | 70 | 100 | 30 | 50 | 30 | 955 |
| 12 | 100 | 100 | 100 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 1145 |
| 13 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 30 | 1075 |
| 14 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 70 | 100 | 100 | 100 | 1140 |
| 15 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 70 | 1145 |
| 16 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 1170 |
| 17 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 1170 |
| 18 | 50 | 100 | 50 | 50 | 100 | 100 | 100 | 100 | 70 | 70 | 100 | 70 | 960 |
| 19 | 50 | 100 | 75 | 75 | 70 | 100 | 70 | 70 | 70 | 70 | 100 | 100 | 950 |
| 20 | 100 | 100 | 50 | 50 | 100 | 100 | 70 | 0 | 100 | 100 | 75 | 30 | 875 |
| 21 | 100 | 100 | 50 | 50 | 100 | 100 | 70 | 100 | 70 | 100 | 75 | 30 | 945 |
| 22 | 100 | 100 | 50 | 100 | 100 | 100 | 70 | 100 | 70 | 100 | 75 | 70 | 1035 |
| 23 | 100 | 100 | 75 | 75 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 30 | 1025 |
| 24 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 100 | 1145 |
| 25 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 100 | 1145 |
| 26 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 100 | 70 | 1140 |
| 27 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 70 | 100 | 100 | 100 | 1140 |
| 28 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 70 | 1145 |
| 29 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |

**Table 65: UW-QoLv4 for post-TLM patients (complete data set)**

| | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety | Total (1200) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 100 | 50 | 50 | 50 | 70 | 50 | 70 | 0 | 70 | 100 | 25 | 30 | 665 |
| 2 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 70 | 1140 |
| 3 | 100 | 100 | 100 | 75 | 100 | 100 | 70 | 100 | 100 | 100 | 100 | 70 | 1115 |
| 4 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 70 | 1115 |
| 5 | 100 | 100 | 50 | 50 | 100 | 100 | 100 | 30 | 70 | 100 | 75 | 70 | 945 |
| 6 | 100 | 100 | 75 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 75 | 70 | 1090 |
| 7 | 100 | 100 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 70 | 1095 |
| 8 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 9 | 100 | 100 | 50 | 100 | 70 | 100 | 70 | 100 | 100 | 100 | 25 | 70 | 985 |
| 10 | 50 | 100 | 50 | 75 | 100 | 100 | 70 | 30 | 100 | 70 | 100 | 100 | 945 |
| 11 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 100 | 100 | 100 | 100 | 1145 |
| 12 | 100 | 100 | 50 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1125 |
| 13 | 100 | 100 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1150 |
| 14 | 100 | 100 | 100 | 100 | 70 | 100 | 70 | 100 | 70 | 30 | 75 | 70 | 985 |
| 15 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |
| 16 | 100 | 100 | 100 | 100 | 100 | 100 | 70 | 70 | 70 | 100 | 100 | 70 | 1080 |
| 17 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 1200 |

**Table 66: UW-QoLv4 domain scores for all pre-TLM patients (complete data set)**

| | N | 0 | 25 | 30 | 50 | 70 | 75 | 100 | Mean | % Best Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Pain | 29 | 0 | 0 | | 4 | | 7 | 18 | 87.1 | 62.1 |
| Appearance | 29 | 0 | 0 | | 0 | | 2 | 27 | 98.3 | 93.1 |
| Activity | 29 | 0 | 0 | | 4 | | 3 | 21 | 88.8 | 72.4 |
| Recreation | 29 | 0 | 0 | | 4 | | 7 | 18 | 86.9 | 62.1 |
| Swallowing | 29 | 0 | | 0 | | 2 | | 27 | 97.9 | 93.1 |
| Chewing | 29 | 0 | | 0 | | 0 | | 29 | 100.0 | 100 |
| Speech | 29 | 0 | | 3 | | 16 | | 10 | 76.2 | 34.5 |
| Shoulder | 29 | 1 | | 2 | | 2 | | 24 | 89.7 | 82.8 |
| Taste | 29 | 0 | | 0 | | 6 | | 23 | 93.8 | 79.3 |
| Saliva | 29 | 0 | | 1 | | 2 | | 26 | 95.5 | 89.7 |
| Mood | 29 | 0 | 1 | | 1 | | 16 | 11 | 81.9 | 37.9 |
| Anxiety | 29 | 0 | | 6 | | 16 | | 7 | 69.0 | 24.1 |

**Table 67: UW-QoLv4 domain scores for included pre-TLM patients (complete data set)**

| | N | 0 | 25 | 30 | 50 | 70 | 75 | 100 | Mean | % Best Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Pain | 17 | 0 | 0 | | 2 | | 7 | 8 | 83.8 | 47.1 |
| Appearance | 17 | 0 | 0 | | 0 | | 2 | 15 | 97.1 | 88.2 |
| Activity | 17 | 0 | 0 | | 1 | | 1 | 15 | 95.6 | 88.2 |
| Recreation | 17 | 0 | 0 | | 1 | | 5 | 11 | 89.7 | 64.7 |
| Swallowing | 17 | 0 | | 0 | | 1 | | 16 | 98.2 | 94.1 |
| Chewing | 17 | 0 | | 0 | | 0 | | 17 | 100.0 | 100 |
| Speech | 17 | 0 | | 3 | | 7 | | 7 | 75.3 | 41.2 |
| Shoulder | 17 | 0 | | 1 | | 2 | | 14 | 90.0 | 82.4 |
| Taste | 17 | 0 | | 0 | | 0 | | 17 | 98.2 | 100 |
| Saliva | 17 | 0 | | 1 | | 0 | | 16 | 95.9 | 94.1 |
| Mood | 17 | 0 | 1 | | 1 | | 9 | 6 | 79.4 | 35.3 |
| Anxiety | 17 | 0 | | 3 | | 12 | | 2 | 66.5 | 11.8 |

**Table 68: UW-QoLv4 domain scores for post-TLM patients (complete data set)**

| | N | 0 | 25 | 30 | 50 | 70 | 75 | 100 | Mean | % Best Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Pain | 17 | 0 | 0 | | 1 | | 1 | 15 | 95.6 | 88.2 |
| Appearance | 17 | 0 | 0 | | 1 | | 0 | 16 | 97.1 | 94.1 |
| Activity | 17 | 0 | 0 | | 5 | | 3 | 9 | 80.9 | 52.9 |
| Recreation | 17 | 0 | 0 | | 2 | | 5 | 10 | 86.8 | 58.8 |
| Swallowing | 17 | 0 | | 0 | | 3 | | 14 | 94.7 | 82.4 |
| Chewing | 17 | 0 | | 0 | 1 | 0 | | 16 | 97.1 | 94.1 |
| Speech | 17 | 0 | | 0 | | 8 | | 9 | 85.9 | 52.9 |
| Shoulder | 17 | 1 | | 2 | | 2 | | 12 | 82.4 | 70.6 |
| Taste | 17 | 0 | | 0 | | 4 | | 13 | 92.9 | 76.5 |
| Saliva | 17 | 0 | | 1 | | 2 | | 14 | 92.4 | 82.4 |
| Mood | 17 | 0 | 2 | | 0 | | 5 | 10 | 83.8 | 58.8 |
| Anxiety | 17 | 0 | | 1 | | 9 | | 7 | 80.0 | 41.2 |

**Table 69: UW-QoLv4 rank within past 7 days for pre-TLM patients (complete data set)**

| | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| 3 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| 5 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 6 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| 11 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 13 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 14 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 16 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| 19 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 20 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 21 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| 22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 23 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| 24 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 26 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| 27 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 28 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 5 | 2 | 5 | 0 | 2 | 1 | 13 | 2 | 1 | 1 | 4 | 17 |

**Table 70: UW-QoLv4 rank within past 7 days for post-TLM patients (complete data set)**

| | Pain | Appearance | Activity | Recreation | Swallowing | Chewing | Speech | Shoulder | Taste | Saliva | Mood | Anxiety |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 |
| 5 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| 7 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 13 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| 15 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 16 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| 17 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Total | 0 | 3 | 0 | 0 | 2 | 4 | 7 | 1 | 3 | 3 | 5 | 3 |

**Table 71: UW-QoLv4 domain issue seen as most important in past seven days for pre- and post- TLM patients (complete data set)**

| | N | Number of pre-TLM patients choosing domain | Number of post-TLM patients choosing domain | Total number of patients choosing domain | Rank order |
|---|---|---|---|---|---|
| Pain | 46 | 5 | 0 | 5 | =4 |
| Appearance | 46 | 2 | 3 | 5 | =4 |
| Activity | 46 | 5 | 0 | 5 | =4 |
| Recreation | 46 | 0 | 0 | 0 | 12 |
| Swallowing | 46 | 2 | 2 | 4 | =8 |
| Chewing | 46 | 1 | 4 | 5 | =4 |
| Speech | 46 | 13 | 7 | 20 | =1 |
| Shoulder | 46 | 2 | 1 | 3 | 11 |
| Taste | 46 | 1 | 3 | 4 | =8 |
| Saliva | 46 | 1 | 3 | 4 | =8 |
| Mood | 46 | 4 | 5 | 9 | 3 |
| Anxiety | 46 | 17 | 3 | 20 | =1 |

**Table 72: UW-QoLv4 global question scores for pre-TLM patients (complete data set)**

| | How would you rate your health-related QOL? (n=14) | Your Health-related QOL is? (n=15) | Overall QOL? (n=15) |
|---|---|---|---|
| 1 | 50 | 60 | 60 |
| 2 | - | - | - |
| 3 | - | - | - |
| 4 | - | - | - |
| 5 | 50 | 60 | 60 |
| 6 | - | - | - |
| 7 | 50 | 60 | 60 |
| 8 | - | - | - |
| 9 | 50 | 80 | 80 |
| 10 | - | - | - |
| 11 | - | - | - |
| 12 | - | - | - |
| 13 | - | - | - |
| 14 | 50 | 80 | 80 |
| 15 | - | - | - |
| 16 | - | - | - |
| 17 | 50 | 80 | 80 |
| 18 | 50 | 60 | 80 |
| 19 | 50 | 60 | 60 |
| 20 | - | - | - |
| 21 | 25 | 40 | 40 |
| 22 | 50 | 60 | 60 |
| 23 | - | - | - |
| 24 | 50 | 60 | 60 |
| 25 | 50 | 80 | 80 |
| 26 | 50 | 80 | 80 |
| 27 | - | - | - |
| 28 | 50 | 80 | 80 |
| 29 | - | 100 | 100 |

**Table 73: UW-QoLv4 global question scores for post-TLM patients (complete data set)**

| | How would you rate your health-related QOL? | Your Health-related QOL is? | Overall QOL? |
|---|---|---|---|
| 1 | - | - | - |
| 2 | - | - | - |
| 3 | 50 | 60 | 60 |
| 4 | 50 | 60 | 60 |
| 5 | | | |
| 6 | 50 | 60 | 60 |
| 7 | 50 | 20 | 20 |
| 8 | 50 | 80 | 80 |
| 9 | - | - | - |
| 10 | 25 | 60 | 40 |
| 11 | 100 | 100 | 100 |
| 12 | 100 | 75 | 75 |
| 13 | 75 | 60 | 80 |
| 14 | 50 | 60 | 60 |
| 15 | 50 | 60 | 60 |
| 16 | 50 | 80 | 80 |
| 17 | 100 | 80 | 80 |

**Table 74: UW-QoLv4 global questions for all pre-TLM patients (complete data set)**

| | N | 0 | 20 | 25 | 40 | 50 | 60 | 75 | 80 | 100 | Mean | % Best Scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Health-related QOL compared to month before had cancer | 14 | 0 | | 1 | | 13 | | 0 | | 0 | 48.2 | 0 |
| B. Health-related QOL during the past 7 days | 15 | 0 | 0 | | 1 | | 7 | | 6 | 1 | 69.3 | 6.7 |
| C. Overall QOL during the past 7 days | 15 | 0 | 0 | | 1 | | 6 | | 7 | 1 | 70.7 | 6.7 |

**Table 75: UW-QoLv4 global questions for included pre-TLM patients (complete data set)**

| | N | 0 | 20 | 25 | 40 | 50 | 60 | 75 | 80 | 100 | Mean | % Best Scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Health-related QOL compared to month before had cancer | 6 | 0 | | 0 | | 6 | | 0 | | 0 | 50 | 0 |
| B. Health-related QOL during the past 7 days | 6 | 0 | 0 | | 0 | | 4 | | 2 | 0 | 70 | 0 |
| C. Overall QOL during the past 7 days | 6 | 0 | 0 | | 0 | | 3 | | 3 | 0 | 70 | 0 |

**Table 76: UW-QoLv4 global questions for post-TLM patients (complete data set)**

| | N | 0 | 20 | 25 | 40 | 50 | 60 | 75 | 80 | 100 | Mean | SE | % Best Scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Health-related QOL compared to month before had cancer | 14 | 0 | | 1 | | 8 | | 1 | | 3 | 61.5 | 5.9 | 21.4 |
| B. Health-related QOL during the past 7 days | 14 | 0 | 1 | | 0 | | 7 | | 3 | 1 | 65.8 | 4.5 | 7.1 |
| C. Overall QOL during the past 7 days | 14 | 0 | 1 | | 1 | | 7 | | 4 | 1 | 65.8 | 4.9 | 7.1 |

# Appendix 13: Complete data set: perception rating for pre- and post- TLM patients

**Table 77: GRBAS scores for pre and post-TLM patients (complete data set)**

| | Pre-TLM | | | | | Post-TLM | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) | Grade (0-3) | Roughness (0-3) | Breathiness (0-3) | Asthenia (0-3) | Strain (0-3) |
| 1 | 2 | 2 | 1 | 1 | 0 | 2 | 0 | 1 | 1 | 2 |
| 2 | 3 | 3 | 2 | 2 | 2 | 1 | 0 | 1 | 1 | 1 |
| 3 | 1 | 1 | 1 | 0 | 0 | - | - | - | - | - |
| 4 | 2 | 1 | 1 | 1 | 2 | - | - | - | - | - |
| 5 | 3 | 2 | 2 | 2 | 2 | 3 | 2 | 3 | 2 | 3 |
| 6 | 1 | 1 | 1 | 1 | 1 | - | - | - | - | - |
| 7 | 2 | 1 | 2 | 1 | 1 | 3 | 2 | 2 | 2 | 2 |
| 8 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 |
| 9 | 2 | 1 | 2 | 1 | 1 | 2 | 1 | 2 | 2 | 2 |
| 10 | 1 | 1 | 1 | 0 | 0 | 2 | 1 | 2 | 2 | 2 |
| 11 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 2 | 2 | 2 |
| 12 | 1 | 0 | 1 | 1 | 1 | - | - | - | - | - |
| 13 | 2 | 1 | 2 | 1 | 1 | - | - | - | - | - |
| 14 | 3 | 3 | 0 | 0 | 3 | - | - | - | - | - |
| 15 | 2 | 2 | 2 | 2 | 1 | - | - | - | - | - |
| 16 | 3 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 0 |
| 17 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 |
| 18 | 3 | 3 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 |
| 19 | 3 | 3 | 2 | 2 | 3 | 2 | 1 | 2 | 2 | 1 |
| 20 | 2 | 1 | 1 | 2 | 0 | - | - | - | - | - |
| 21 | 3 | 2 | 3 | 1 | 3 | - | - | - | - | - |
| 22 | 1 | 1 | 0 | 1 | 0 | - | - | - | - | - |
| 23 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 0 | 0 | 1 |
| 24 | 2 | 1 | 1 | 1 | 2 | - | - | - | - | - |
| 25 | 2 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 2 | 2 |
| 26 | 2 | 2 | 1 | 0 | 0 | - | - | - | - | - |
| 27 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 2 | 1 | 1 |
| 28 | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 2 | 1 | 0 |
| 29 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | - |

# Appendix 14: Complete data set: sustained vowels for pre- and post-TLM patients

### Table 78: Sustained vowel /i/ for pre-TLM patients (complete data set)

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1506.0 | 142.3 | 149.9 | 146.3 | 1.1 | 34.3 | 38.0 | 36.2 | 0.8 | 0.5 | 0.3 | 2.5 | -2.7 | 0.5 | 0.3 | 0.2 | -27.0 | 3.2 | 23.1 | 88.3 |
| 2 | 527.0 | 74.9 | 177.5 | 124.6 | 32.9 | 23.4 | 47.2 | 35.1 | 9.0 | 36.8 | 23.4 | 18.2 | -14.5 | 36.3 | 24.8 | 1.6 | 1.5 | 1.1 | 6.1 | 83.9 |
| 3 | 1561.0 | 166.8 | 185.3 | 175.3 | 1.5 | 40.2 | 56.7 | 49.2 | 3.6 | 1.0 | 0.6 | 4.6 | -9.4 | 1.0 | 0.6 | 0.4 | -17.2 | 3.0 | 17.3 | 83.9 |
| 4 | 2507.0 | 159.2 | 172.0 | 165.5 | 1.3 | 34.3 | 43.0 | 37.2 | 1.4 | 0.8 | 0.4 | 5.2 | -6.0 | 0.8 | 0.4 | 0.5 | -19.1 | 1.9 | 17.5 | 87.2 |
| 5 | 789.6 | 55.3 | 254.6 | 220.3 | 9.0 | 0.0 | 61.7 | 38.3 | 10.1 | 7.7 | 4.4 | 5.0 | -9.4 | 7.0 | 6.3 | 0.4 | -5.7 | 2.1 | 18.1 | 88.6 |
| 6 | 2921.0 | 144.4 | 163.4 | 153.7 | 2.4 | 35.8 | 56.0 | 42.5 | 4.0 | 2.7 | 1.8 | 18.2 | -10.9 | 2.7 | 1.8 | 1.8 | -8.9 | 1.5 | 11.8 | 87.9 |
| 7 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 8 | 1389.0 | 134.5 | 145.3 | 139.2 | 1.3 | 42.5 | 49.6 | 45.2 | 1.3 | 0.5 | 0.2 | 3.2 | -4.7 | 0.5 | 0.2 | 0.3 | -20.7 | 2.1 | 20.6 | 83.9 |
| 9 | 2786.0 | 163.8 | 174.2 | 168.7 | 1.1 | 48.4 | 54.7 | 51.1 | 0.9 | 0.2 | 0.1 | 3.4 | -3.9 | 0.2 | 0.1 | 0.3 | -20.3 | 2.7 | 21.0 | 84.8 |
| 10 | 1286.0 | 185.0 | 192.4 | 188.6 | 0.7 | 55.3 | 57.6 | 56.5 | 0.5 | 0.2 | 0.1 | 2.4 | -3.2 | 0.2 | 0.1 | 0.2 | -18.9 | 6.8 | 20.8 | 94.9 |
| 11 | 10730.0 | 184.9 | 191.9 | 188.7 | 0.6 | 38.8 | 45.9 | 42.6 | 1.1 | 0.3 | 0.2 | 3.6 | -4.0 | 0.3 | 0.2 | 0.3 | -18.5 | 5.9 | 15.8 | 92.0 |
| 12 | 542.0 | 185.4 | 201.6 | 194.8 | 1.5 | 38.1 | 41.5 | 39.6 | 0.8 | 0.7 | 0.3 | 3.7 | -6.2 | 0.6 | 0.3 | 0.3 | -19.2 | 2.3 | 18.6 | 91.7 |
| 13 | 180.0 | 152.7 | 163.7 | 159.8 | 1.6 | 42.0 | 45.7 | 43.9 | 0.9 | 1.0 | 0.6 | 11.4 | -15.4 | 1.0 | 0.6 | 1.1 | -11.2 | 3.1 | 13.5 | 87.5 |
| 14 | 1269.0 | 52.8 | 702.7 | 197.4 | 41.4 | 0.0 | 85.8 | 37.0 | 15.0 | 32.8 | 22.5 | 23.1 | -32.3 | 35.9 | 21.2 | 2.6 | -1.5 | 2.4 | 11.9 | 91.3 |
| 15 | 972.0 | 178.3 | 184.5 | 181.5 | 0.7 | 37.1 | 42.7 | 39.7 | 1.2 | 0.7 | 0.4 | 2.4 | -4.3 | 0.6 | 0.4 | 0.2 | -23.6 | 2.6 | 21.2 | 89.1 |
| 16 | 8631.0 | 123.9 | 130.6 | 127.6 | 1.0 | 28.8 | 38.9 | 34.9 | 1.4 | 0.4 | 0.3 | 3.3 | -3.8 | 0.4 | 0.3 | 0.3 | -24.3 | 1.8 | 21.5 | 78.1 |
| 17 | 2396.0 | 146.5 | 160.6 | 152.0 | 1.4 | 30.5 | 44.7 | 35.5 | 3.1 | 1.2 | 0.7 | 5.6 | -4.4 | 1.2 | 0.7 | 0.5 | -21.9 | 2.8 | 19.9 | 80.9 |
| 18 | 437.0 | 65.0 | 623.0 | 187.8 | 39.2 | 0.0 | 41.4 | 26.6 | 8.9 | 37.5 | 22.9 | 18.3 | -18.7 | 37.6 | 26.6 | 2.3 | 1.0 | 1.1 | 2.5 | 87.7 |
| 19 | 1239.0 | 52.5 | 905.8 | 231.3 | 57.1 | 0.0 | 78.6 | 36.8 | 23.5 | 60.1 | 41.7 | 18.8 | -23.9 | 67.0 | 36.0 | 1.9 | -0.4 | 1.6 | 4.9 | 92.7 |
| 20 | 1383.0 | 149.1 | 156.6 | 152.2 | 1.0 | 39.6 | 43.4 | 41.8 | 0.7 | 0.5 | 0.3 | 2.3 | -3.3 | 0.5 | 0.3 | 0.2 | -25.3 | 2.9 | 22.4 | 92.9 |
| 21 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 22 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 23 | 1592.8 | 218.4 | 233.3 | 225.1 | 1.3 | 33.3 | 48.6 | 39.5 | 3.3 | 0.5 | 0.3 | 7.7 | -7.5 | 0.5 | 0.3 | 0.7 | -15.0 | 3.2 | 15.8 | 92.9 |
| 24 | 9962.0 | 202.9 | 222.2 | 210.4 | 0.8 | 32.9 | 40.0 | 36.6 | 1.0 | 0.6 | 0.3 | 1.6 | -1.6 | 0.6 | 0.3 | 0.1 | -32.0 | 4.1 | 25.6 | 88.1 |
| 25 | 932.0 | 147.0 | 952.4 | 156.3 | 43.1 | 15.7 | 76.5 | 27.9 | 4.5 | 2.5 | 5.0 | 9.6 | -4.6 | 7.7 | 0.9 | 0.7 | -18.5 | 1.9 | 19.4 | 87.6 |
| 26 | 4340.0 | 136.8 | 148.0 | 142.7 | 1.4 | 61.1 | 69.4 | 66.2 | 0.8 | 1.1 | 0.7 | 5.6 | -6.4 | 1.1 | 0.7 | 0.5 | -13.1 | 2.7 | 13.4 | 87.1 |
| 27 | 4068.0 | 169.0 | 181.5 | 175.5 | 1.3 | 35.9 | 40.4 | 38.1 | 0.7 | 0.3 | 0.1 | 1.4 | -2.5 | 0.3 | 0.1 | 0.1 | -27.0 | 3.6 | 22.0 | 88.8 |
| 28 | 752.0 | 204.3 | 228.5 | 216.2 | 2.1 | 0.0 | 46.6 | 41.6 | 4.0 | 2.6 | 1.6 | 6.3 | -8.5 | 2.6 | 1.6 | 0.6 | -15.7 | 2.1 | 16.6 | 92.3 |
| 29 | 4507.0 | 138.0 | 143.1 | 140.5 | 0.7 | 47.8 | 54.9 | 51.3 | 1.0 | 0.2 | 0.1 | 2.8 | -2.7 | 0.2 | 0.1 | 0.2 | -24.1 | 4.3 | 18.5 | 88.5 |

**Table 79: Sustained vowel /i/ for post-TLM patients (complete data set)**

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1425.0 | 153.9 | 159.8 | 156.9 | 0.7 | 58.8 | 64.4 | 61.0 | 1.0 | 0.4 | 0.2 | 3.1 | -6.5 | 0.4 | 0.2 | 0.3 | -21.6 | 4.2 | 20.8 | 89.3 |
| 2 | 273.0 | 138.7 | 142.0 | 140.6 | 0.5 | 34.8 | 37.2 | 35.9 | 0.6 | 0.3 | 0.1 | 2.0 | -4.0 | 0.3 | 0.1 | 0.2 | -27.2 | 2.7 | 24.8 | 89.5 |
| 3 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 4 | 670.0 | 55.6 | 1136.4 | 368.3 | 84.3 | 0.0 | 84.6 | 29.1 | 29.6 | 94.8 | 54.3 | 33.5 | -31.9 | 96.2 | 55.6 | 3.0 | -0.3 | 0.6 | 0.3 | 62.7 |
| 5 | 1546.0 | 64.4 | 242.4 | 190.5 | 13.5 | 0.0 | 67.6 | 41.6 | 9.5 | 12.6 | 6.6 | 9.0 | -9.9 | 10.7 | 10.9 | 0.8 | -4.8 | 1.6 | 11.8 | 84.4 |
| 6 | 1541.0 | 258.5 | 273.0 | 266.7 | 1.0 | 37.7 | 45.0 | 41.5 | 1.4 | 1.0 | 0.6 | 3.1 | -3.8 | 1.0 | 0.6 | 0.3 | -23.5 | 3.8 | 26.5 | 100.5 |
| 7 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 8 | 1893.0 | 126.3 | 136.8 | 131.1 | 1.3 | 34.7 | 39.7 | 36.9 | 0.9 | 1.0 | 0.6 | 7.2 | -7.2 | 1.0 | 0.6 | 0.6 | -19.9 | 1.8 | 17.8 | 70.9 |
| 9 | 1351.0 | 149.9 | 179.1 | 166.5 | 2.2 | 32.6 | 46.4 | 41.2 | 1.8 | 2.4 | 1.5 | 7.2 | -4.5 | 2.4 | 1.5 | 0.6 | -19.8 | 1.8 | 19.2 | 72.9 |
| 10 | 22.6 | 76.0 | 222.7 | 163.4 | 38.6 | 0.0 | 76.2 | 32.3 | 32.2 | 56.7 | 36.3 | 11.2 | -7.9 | 54.5 | 41.1 | 1.0 | 2.2 | 0.5 | -1.5 | 90.9 |
| 11 | 4883.0 | 189.9 | 207.6 | 198.4 | 1.6 | 39.5 | 45.7 | 42.3 | 1.1 | 2.4 | 1.6 | 2.8 | -3.5 | 2.4 | 1.6 | 0.2 | -19.6 | 5.6 | 20.0 | 79.1 |
| 12 | 721.0 | 207.9 | 221.0 | 213.3 | 1.3 | 30.7 | 34.2 | 32.5 | 0.8 | 0.5 | 0.3 | 1.6 | -2.2 | 0.5 | 0.3 | 0.1 | -30.3 | 4.8 | 25.1 | 91.0 |
| 13 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 14 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 15 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 16 | 2543.0 | 171.0 | 192.1 | 179.4 | 1.9 | 29.5 | 37.0 | 32.9 | 1.4 | 1.9 | 1.2 | 8.7 | -5.9 | 1.9 | 1.2 | 0.8 | -14.2 | 2.1 | 18.1 | 79.2 |
| 17 | 1229.0 | 160.3 | 176.6 | 170.3 | 1.8 | 18.3 | 30.9 | 23.9 | 2.7 | 1.8 | 1.1 | 5.0 | -3.3 | 1.8 | 1.1 | 0.4 | -21.5 | 2.8 | 20.4 | 80.4 |

**Table 80: Sustained vowel /a/ for pre-TLM patients (complete data set)**

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2061.0 | 139.5 | 159.4 | 148.6 | 2.4 | 34.3 | 41.4 | 38.0 | 1.3 | 2.9 | 1.8 | 12.4 | -12.0 | 2.9 | 1.8 | 1.1 | -13.1 | 2.1 | 13.8 | 83.3 |
| 2 | 77.0 | 155.7 | 168.9 | 162.8 | 2.3 | 29.9 | 40.8 | 32.7 | 3.3 | 2.8 | 1.6 | 20.3 | -14.6 | 2.7 | 1.6 | 1.8 | -10.3 | 1.5 | 7.6 | 95.9 |
| 3 | 168.0 | 170.5 | 175.3 | 172.3 | 0.7 | 25.8 | 32.3 | 30.6 | 1.4 | 0.8 | 0.5 | 5.4 | -8.9 | 0.8 | 0.5 | 0.5 | -16.5 | 3.8 | 15.0 | 96.8 |
| 4 | 1939.0 | 159.8 | 170.0 | 163.7 | 1.1 | 33.7 | 43.9 | 37.4 | 1.8 | 0.5 | 0.3 | 11.1 | -7.9 | 0.5 | 0.3 | 1.0 | -15.9 | 2.9 | 14.9 | 89.6 |
| 5 | 297.0 | 24.5 | 218.1 | 166.2 | 18.7 | 21.1 | 44.1 | 36.0 | 5.4 | 20.6 | 12.5 | 15.0 | -13.0 | 19.5 | 14.8 | 1.3 | -0.8 | 1.9 | 9.3 | 95.5 |
| 6 | 2464.0 | 148.3 | 157.8 | 152.4 | 0.9 | 37.5 | 45.7 | 41.6 | 1.9 | 0.4 | 0.2 | 7.7 | -5.0 | 0.4 | 0.2 | 0.7 | -14.6 | 3.6 | 15.3 | 87.0 |
| 7 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 8 | 1273.0 | 115.7 | 125.2 | 119.9 | 1.4 | 0.0 | 44.7 | 41.3 | 3.5 | 0.8 | 0.4 | 4.4 | -5.4 | 0.8 | 0.4 | 0.4 | -21.0 | 3.3 | 18.5 | 83.1 |
| 9 | 1975.0 | 135.8 | 147.5 | 141.0 | 1.7 | 20.0 | 25.4 | 22.5 | 1.2 | 0.5 | 0.2 | 6.7 | -7.2 | 0.5 | 0.2 | 0.6 | -15.8 | 3.2 | 15.0 | 85.1 |
| 10 | 1183.0 | 143.6 | 149.4 | 146.4 | 0.8 | 36.1 | 39.6 | 37.3 | 0.6 | 0.4 | 0.3 | 3.4 | -6.5 | 0.4 | 0.3 | 0.3 | -19.1 | 4.1 | 16.8 | 99.1 |
| 11 | 3105.0 | 149.7 | 159.4 | 153.6 | 1.1 | 32.0 | 39.6 | 35.8 | 1.4 | 0.4 | 0.2 | 4.7 | -4.7 | 0.4 | 0.2 | 0.4 | -20.3 | 5.2 | 16.6 | 97.9 |
| 12 | 358.0 | 195.3 | 203.9 | 198.8 | 1.1 | 36.3 | 45.7 | 41.7 | 2.3 | 0.7 | 0.4 | 7.4 | -3.9 | 0.7 | 0.4 | 0.7 | -22.4 | 3.3 | 20.7 | 89.3 |
| 13 | 56.0 | 129.2 | 131.3 | 130.6 | 0.5 | 35.8 | 40.2 | 37.7 | 1.5 | 0.5 | 0.4 | 6.0 | -12.9 | 0.5 | 0.4 | 0.5 | -16.4 | 3.4 | 17.3 | 89.5 |
| 14 | 519.0 | 56.4 | 679.8 | 305.2 | 49.9 | 0.0 | 58.2 | 19.6 | 18.4 | 73.9 | 50.0 | 90.6 | -77.5 | 77.6 | 46.7 | 9.7 | -0.3 | 2.2 | -23.2 | 92.0 |
| 15 | 737.0 | 163.5 | 174.7 | 169.4 | 1.2 | 26.6 | 35.4 | 32.2 | 1.8 | 0.1 | 0.7 | 6.2 | -8.3 | 1.1 | 0.7 | 0.5 | -16.9 | 4.0 | 16.3 | 93.3 |
| 16 | 9979.0 | 120.3 | 915.8 | 168.0 | 95.2 | 0.0 | 89.5 | 34.7 | 10.5 | 18.0 | 31.2 | 11.7 | -16.7 | 47.6 | 6.7 | 1.3 | -3.0 | 2.7 | 12.9 | 77.4 |
| 17 | 2053.9 | 143.2 | 168.5 | 157.5 | 2.6 | 31.7 | 44.0 | 37.9 | 2.5 | 2.4 | 1.4 | 7.2 | -8.3 | 2.4 | 1.4 | 0.6 | -16.8 | 2.4 | 16.7 | 75.3 |
| 18 | 75.9 | 51.6 | 117.7 | 71.1 | 38.3 | 44.9 | 62.1 | 55.0 | 6.7 | 52.2 | 39.1 | 130.1 | -99.9 | 61.6 | 24.3 | 9.1 | - | 0.0 | - | 88.5 |
| 19 | 393.0 | 60.6 | 121.0 | 104.2 | 9.7 | 36.7 | 62.9 | 53.9 | 6.3 | 10.9 | 6.3 | 26.2 | -28.8 | 10.5 | 7.2 | 2.5 | 0.3 | 1.0 | 1.8 | 93.2 |
| 20 | 1482.0 | 142.9 | 149.2 | 145.7 | 0.7 | 36.4 | 39.4 | 37.8 | 0.6 | 0.4 | 0.2 | 9.1 | -8.9 | 0.4 | 0.2 | 0.8 | -14.2 | 3.0 | 14.5 | 91.6 |
| 21 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 22 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 23 | 2415.0 | 210.7 | 225.9 | 216.7 | 0.9 | 45.3 | 54.1 | 50.2 | 1.5 | 0.6 | 0.4 | 11.8 | -6.5 | 0.6 | 0.4 | 1.0 | -14.4 | 5.1 | 13.9 | 94.6 |
| 24 | 1237.0 | 205.7 | 221.3 | 213.4 | 1.2 | 26.0 | 32.5 | 29.2 | 1.1 | 1.2 | 0.7 | 3.7 | -3.2 | 1.2 | 0.7 | 0.3 | -24.3 | 4.9 | 20.8 | 87.5 |
| 25 | 725.0 | 150.3 | 158.2 | 154.1 | 1.2 | 25.5 | 41.2 | 29.3 | 3.0 | 0.4 | 0.2 | 7.4 | -7.9 | 0.4 | 0.2 | 0.6 | -16.6 | 2.7 | 16.8 | 87.6 |
| 26 | 3891.0 | 91.1 | 189.1 | 124.3 | 7.2 | 0.0 | 80.7 | 71.0 | 4.1 | 5.3 | 3.2 | 14.3 | -13.1 | 5.2 | 3.3 | 1.3 | -3.1 | 3.0 | 9.4 | 97.2 |
| 27 | 3865.0 | 164.8 | 174.2 | 168.9 | 1.2 | 35.5 | 43.3 | 40.4 | 1.7 | 0.2 | 0.1 | 1.7 | -1.7 | 0.2 | 0.1 | 0.2 | -30.3 | 5.1 | 25.2 | 90.0 |
| 28 | 547.0 | 115.7 | 261.2 | 228.8 | 7.4 | 0.0 | 47.0 | 37.2 | 12.9 | 7.3 | 4.4 | 18.5 | -14.7 | 6.9 | 5.3 | 1.6 | -6.9 | 2.6 | 11.9 | 91.3 |
| 29 | 5580.0 | 135.4 | 142.5 | 138.8 | 0.9 | 44.0 | 48.7 | 46.9 | 0.8 | 0.3 | 0.1 | 2.6 | -1.9 | 0.3 | 0.1 | 0.2 | -26.6 | 5.3 | 21.2 | 91.0 |

**Table 81: Sustained vowel /a/ for post-TLM patients (complete data set)**

| | Duration (ms) | Minimum Fx (Hz) | Maximum Fx (Hz) | Average Fx (Hz) | S.D. Fx (%) | Minimum Qx (%) | Maximum Qx (%) | Average Qx (%) | S.D. Qx (%) | Jitter First (%) | Jitter Second (%) | Shimmer + (%) | Shimmer – (%) | Jitter Factor (%) | RAP (%) | Shimmer dB (dB) | NNE (dB) | CPP | HNR (dB) | Mean SPL (dB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1196.0 | 139.6 | 180.4 | 155.4 | 1.8 | 44.6 | 51.8 | 46.7 | 1.1 | 1.5 | 1.0 | 6.1 | -6.6 | 1.5 | 1.0 | 0.5 | -16.5 | 3.7 | 13.6 | 86.7 |
| 2 | 120.0 | 174.9 | 184.8 | 180.2 | 1.7 | 30.0 | 35.6 | 32.2 | 1.5 | 0.5 | 0.3 | 9.7 | -9.5 | 0.5 | 0.3 | 0.9 | -18.8 | 3.8 | 14.9 | 99.6 |
| 3 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 4 | 1021.0 | 50.1 | 1342.3 | 326.4 | 106.4 | 0.0 | 85.7 | 36.5 | 29.3 | 86.3 | 64.2 | 41.9 | -37.1 | 107.2 | 44.5 | 4.4 | -0.4 | 0.7 | 0.3 | 72.4 |
| 5 | 1903.5 | 60.9 | 236.1 | 192.0 | 6.2 | 0.0 | 50.0 | 40.3 | 7.1 | 4.5 | 2.5 | 11.9 | -12.2 | 4.2 | 3.3 | 1.0 | -7.1 | 1.9 | 10.9 | 82.8 |
| 6 | 759.0 | 75.3 | 258.0 | 183.9 | 27.0 | 20.6 | 82.1 | 43.4 | 10.0 | 24.2 | 12.9 | 23.5 | -18.7 | 22.1 | 15.9 | 2.1 | -0.5 | 1.6 | 5.1 | 91.8 |
| 7 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 8 | 1301.0 | 116.0 | 128.8 | 122.1 | 2.0 | 26.8 | 44.7 | 35.1 | 3.5 | 1.4 | 0.8 | 8.1 | -6.9 | 1.4 | 0.8 | 0.7 | -18.8 | 2.7 | 16.6 | 70.3 |
| 9 | 1126.0 | 144.4 | 159.1 | 151.6 | 2.0 | 26.7 | 37.7 | 32.1 | 2.2 | 0.8 | 0.4 | 10.3 | -9.0 | 0.8 | 0.4 | 0.9 | -16.9 | 3.2 | 15.1 | 74.7 |
| 10 | 130.5 | 65.2 | 540.2 | 155.5 | 68.8 | 0.0 | 74.6 | 38.8 | 24.8 | 35.6 | 33.4 | 13.8 | -28.4 | 50.7 | 20.1 | 1.3 | 0.0 | 1.2 | 2.1 | 91.6 |
| 11 | 1534.0 | 156.7 | 164.2 | 160.6 | 1.1 | 36.7 | 42.6 | 40.0 | 1.4 | 0.4 | 0.2 | 3.3 | -2.6 | 0.4 | 0.2 | 0.3 | -23.8 | 5.7 | 17.9 | 87.9 |
| 12 | 1297.0 | 200.8 | 209.6 | 205.2 | 0.9 | 26.9 | 31.6 | 29.1 | 1.1 | 0.4 | 0.3 | 2.9 | -2.9 | 0.4 | 0.3 | 0.3 | -24.6 | 5.7 | 21.4 | 94.1 |
| 13 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 14 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 15 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 16 | 1338.0 | 167.3 | 191.1 | 174.3 | 1.6 | 19.8 | 31.3 | 23.1 | 1.5 | 2.0 | 1.3 | 12.0 | -11.7 | 2.1 | 1.3 | 1.0 | -10.9 | 2.6 | 13.4 | 81.9 |
| 17 | 921.0 | 155.3 | 175.4 | 164.6 | 2.0 | 14.3 | 26.3 | 19.7 | 2.9 | 2.5 | 1.5 | 7.0 | -7.1 | 2.5 | 1.5 | 0.6 | -18.7 | 3.2 | 18.3 | 80.2 |

# Appendix 15: Comparison of quality of life and voice outcome in patients included and excluded from pre- and post- TLM comparison

**Table 82: Comparison of quality of life and voice outcome in patients included and excluded from pre- and post- TLM comparison**

| **VH1-10** | | | |
|---|---|---|---|
| Median score (IQR) | Included | Excluded | p value |
| Functional (VHI-10 F) | 5 (3,9) | 5 (2.3,6.3) | 0.535 |
| Physical (VHI-10 P) | 6 (4,7) | 4.5 (0.8, 5) | 0.101 |
| Emotional (VHI-10 E) | 2 (1,2) | 2 (1.8, 2.3) | 0.412 |
| Total | 13 (11,18) | 12 (4.3, 13.5) | 0.453 |
| **VoiSS** | | | |
| Median score (IQR) | Included | Excluded | p value |
| Impairment | 31 (21,32) | 27 (17,30.3) | 0.208 |
| Emotional | 4 (3,5) | 8.5 (1.5,11.3) | 0.222 |
| Physical | 7 (6,9) | 8 (6.5,8) | 0.726 |
| Total | 43 (29,49) | 41 (29,45.25) | 0.726 |
| **UW-QOL v4** | | | |
| Mean | Included | Excluded | p value |
| Pain | 83.8 | 91.7 | 0.278 |
| Appearance | 97.1 | 100.0 | 0.163 |
| Activity | 95.6 | 79.2 | 0.043 |
| Recreation | 89.7 | 83.3 | 0.402 |
| Swallowing | 98.2 | 97.5 | 0.812 |
| Chewing | 100.0 | 100.0 | 1.000 |
| Speech | 75.3 | 77.5 | 0.767 |
| Shoulder | 90.0 | 89.2 | 0.936 |
| Taste | 98.2 | 87.5 | **0.041** |
| Saliva | 95.9 | 95.0 | 0.870 |
| Mood | 79.4 | 85.4 | 0.338 |
| Anxiety | 66.5 | 72.5 | 0.540 |
| **Perceptual rating** | | | |
| Mean | Included | Excluded | p value |
| G | 1.8 | 1.8 | 0.956 |
| R | 1.4 | 1.5 | 0.734 |
| B | 1.3 | 1.3 | 0.857 |
| A | 0.9 | 1.0 | 0.821 |
| S | 1.0 | 1.3 | 0.437 |
| TOTAL | 6.4 | 6.9 | 0.752 |
| **Acoustic analysis on /i/** | | | |
| Mean | Included | Excluded | p value |
| Minimum Fx (Hz) | 141.7 | 148.3 | 0.759 |
| Maximum Fx (Hz) | 176.2 | 379.4 | 0.077 |
| Average Fx (Hz) | 164.2 | 183.8 | 0.177 |
| S.D. Fx (%) | 4.5 | 14.8 | 0.199 |

| | | | |
|---|---|---|---|
| Minimum Qx (%) | 34.2 | 26.6 | 0.356 |
| Maximum Qx (%) | 48.2 | 54.0 | 0.299 |
| Average Qx (%) | 41.2 | 40.6 | 0.889 |
| S.D. Qx (%) | 2.9 | 4.8 | 0.431 |
| Jitter First (%) | 4.3 | 10.6 | 0.404 |
| Jitter Second (%) | 2.7 | 7.3 | 0.356 |
| Shimmer + (%) | 6.2 | 7.4 | 0.640 |
| Shimmer – (%) | -6.1 | -8.0 | 0.492 |
| Jitter Factor (%) | 4.2 | 11.8 | 0.345 |
| RAP (%) | 3.0 | 6.7 | 0.435 |
| Shimmer dB (dB) | 0.6 | 0.7 | 0.560 |
| NNE (dB) | -16.9 | -17.0 | 0.982 |
| CPP | 2.9 | 2.8 | 0.871 |
| HNR (dB) | 17.9 | 16.1 | 0.522 |
| Mean SPL (dB) | 86.9 | 89.9 | 0.077 |
| **Acoustic analysis on /a/** | | | |
| Mean | Included | Excluded | p value |
| Minimum Fx (Hz) | 136.0 | 132.9 | 0.884 |
| Maximum Fx (Hz) | 228.7 | 176.0 | 0.431 |
| Average Fx (Hz) | 156.6 | 156.6 | 0.999 |
| S.D. Fx (%) | 10.8 | 6.9 | 0.657 |
| Minimum Qx (%) | 26.1 | 29.4 | 0.616 |
| Maximum Qx (%) | 45.4 | 51.2 | 0.361 |
| Average Qx (%) | 36.4 | 45.1 | 0.071 |
| S.D. Qx (%) | 3.0 | 3.9 | 0.546 |
| Jitter First (%) | 4.2 | 7.9 | 0.514 |
| Jitter Second (%) | 4.2 | 5.5 | 0.789 |
| Shimmer + (%) | 9.3 | 22.5 | 0.309 |
| Shimmer – (%) | -8.8 | -18.7 | 0.322 |
| Jitter Factor (%) | 6.6 | 8.7 | 0.768 |
| RAP (%) | 2.4 | 4.2 | 0.508 |
| Shimmer dB (dB) | 0.9 | 1.8 | 0.315 |
| NNE (dB) | -14.4 | -15.1 | 0.866 |
| CPP | 3.0 | 3.3 | 0.703 |
| HNR (dB) | 14.8 | 15.1 | 0.935 |
| Mean SPL (dB) | 88.2 | 91.3 | 0.236 |
| **Acoustic analysis of connected speech** | | | |
| Mean | Included | Excluded | p value |
| Mean DFx1 (Hz) | 158.0 | 156.0 | 0.894 |
| Mean DFx2 (Hz) | 144.2 | 153.8 | 0.427 |
| Fx Coherence (%) | 41.3 | 43.2 | 0.835 |
| CFx (%) | 20.4 | 21.6 | 0.895 |
| Mean DAx1 (Hz) | 85.2 | 86.9 | 0.336 |
| Mean DAx2 (Hz) | 85.4 | 87.8 | 0.182 |
| Ax Coherence (%) | 50.0 | 47.2 | 0.714 |
| CAx (%) | 7.5 | 8.2 | 0.784 |
| Mean DQx1 (Hz) | 38.0 | 42.1 | 0.194 |
| Mean DQx2 (Hz) | 38.2 | 42.8 | 0.206 |
| Qx Coherence (%) | 25.5 | 27.5 | 0.706 |
| CQx (%) | 39.5 | 39.2 | 0.974 |
| AxFx1 &2 (%) | 54.2 | 54.8 | 0.949 |