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INVESTIGATING THE EFFICACY OF VOCAL FUNCTION EXERCISES IN IMPROVING VOCAL FUNCTION IN ADULTS IRRADIATED FOR LARYNGEAL CANCERS: A THREE PART DISSERTATION

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INVESTIGATING THE EFFICACY OF VOCAL FUNCTION EXERCISES IN IMPROVING VOCAL FUNCTION IN ADULTS IRRADIATED FOR LARYNGEAL CANCERS: A THREE PART DISSERTATION

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Health Sciences at the University of Kentucky

By

Vrushali Angadi

Lexington, Kentucky

Lexington, Kentucky

ABSTRACT OF DISSERTATION

INVESTIGATING THE EFFICACY OF VOCAL FUNCTION EXERCISES (VFE) IN IMPROVING VOCAL FUNCTION IN ADULTS IRRADIATED FOR LARYNGEAL CANCERS: A THREE PART DISSERTATION

Deterioration in voice quality following radiation therapy for the treatment of laryngeal cancers (LC) is well documented in literature. The majority of studies show that these voice problems are long term and in some cases permanent. Deterioration in voice quality, especially over a period of time could lead to significant communication difficulties in daily life or in some cases could even result in loss of profession. Despite the negative effects of radiation therapy on voice quality being well documented, few studies have focused on the efficacy of voice therapy in the irradiated LC population.

The purpose of this study was to investigate the efficacy of a well researched, evidence based voice therapy approach, known as Vocal Function Exercises (VFEs) in improving vocal function in patients who have been irradiated for LCs. The present study conducted in three systematic stages with distinct and related study aims. The first involved characterizing the head and neck cancer treatment seeking population at the University of Kentucky (UK). Stage 2 involved characterizing vocal function following irradiation for LC using a multidimensional assessment approach. Stage 3 was a phase 2 clinical trial aimed at treating these deficits in vocal function identified through stage 2 using a systematic evidence based voice therapy approach, Vocal Function Exercises. For the phase 2 clinical trial, the comparison group received vocal hygiene (VH) counseling.

Observations from stage 1 showed that majority of patients from the treatment seeking population at UK between a 3 year time period from 2008 to 2010 were diagnosed with laryngeal cancers and were treated with chemoradiation therapy. Stage 2 demonstrated a multidimensional deterioration in vocal function following radiation therapy for laryngeal cancers. Stage 3 demonstrated a significant improvement in vocal function across the primary outcome measure (Voice Handicap Index) as a result of VFE+VH. Improvements were also seen in select parameters across the five domains of voice assessment in the VFE group. No significant improvements were observed in the vocal hygiene group in any parameters in each domain of voice assessment.

Our study demonstrated adults irradiated for laryngeal cancers demonstrated a multi-dimensional deterioration of vocal function. These changes were long term since study participants were 2- 7 years post radiation therapy. Implementation of VFE+VH demonstrated a significant improvement in voice related quality of life and select parameters across the five domains of voice assessment. The present study demonstrated promising preliminary evidence for the use of VFE+VH to improve vocal function in patients irradiated for laryngeal cancers.

Key words: Laryngeal cancer, Radiation therapy, Vocal Function Exercises, vocal hygiene, Appalachian Kentucky

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Student signature

7/29/2016

Date

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CHAPTER 1: INTRODUCTION

The curative role of radiation therapy (XRT) in the treatment of laryngeal cancers is well documented. Early laryngeal cancers can be treated with XRT alone, while advanced laryngeal cancers are often treated with a combination of chemotherapy and radiation therapy.[1-3] Radiation therapy, however, was not always the primary mode of choice for treatment of laryngeal cancers. A shift in the treatment trends of laryngeal cancers occurred in the early 1990s following completion of a clinical trial conducted by the Department of Veteran's Affairs (VA) Laryngeal Cancer Study Group. The clinical trial completed by the VA showed comparable survival rates between primary chemoradiation therapy and total laryngectomy for the treatment of laryngeal cancers.[4] Prior to 1990, advanced laryngeal cancers were primarily treated with surgical resection which involved complete removal of the larynx, also known as total laryngectomy. If the extent of the cancer warranted further intervention, patients were treated with radiation therapy after surgery. A total laryngectomy is associated with significant morbidity since it results in the alteration of a patient's anatomy such that breathing subsequently takes place through a permanent tracheostoma. Undergoing total laryngectomy also means losing one's natural source of voicing, the larynx itself. Consequently, following results from the VA study and a 10-year follow-up study which supported the initial findings,[5] an increasing number of patients with laryngeal cancers have been treated primarily with radiation therapy, with or without chemotherapy, with the intent of preserving laryngeal structure and function.

Preservation of structure through radiation therapy, with or without chemotherapy for treatment of laryngeal cancers has not necessarily led to preservation of function. A number of studies have documented long-term voice and swallowing problems post-radiation, consequent to radiation-related toxicity. These prolonged, and in some cases permanent, post-radiation voice and swallowing problems are indicators that preserving laryngeal structure does not translate to preserving laryngeal function. In fact, collateral damage to the laryngeal, oral, and oropharyngeal structures caused by radiation toxicity absent chemotherapy is a well-documented clinical entity.[6-

[9] Radiation damage to the larynx results in edematous and dehydrated tissues, leading to excessive compensatory compression of laryngeal structures during phonation, thus affecting vocal fold vibratory characteristics and impacting perceptual vocal quality.[8,10-12]

Another characteristic feature of radiation toxicity is delayed injury. Consequently, in addition to acute changes to the laryngeal mechanism, ongoing damage occurs as a result of radiation toxicity. Acute and long-term deterioration of voice quality post-radiation may lead to significant communication deficits in daily life or in some cases may result in loss of livelihood. Therefore, post-radiation therapy voice rehabilitation is important. Unfortunately, there is a dearth of knowledge with respect to voice rehabilitation in the irradiated population. Only four studies have investigated the efficacy of voice therapy in post-radiation laryngeal cancer patients, with no recommended standardized treatment.[13-16] In these existing studies, vocal hygiene (VH) counseling is an approach that is commonly recommended.[13-17] However, results of outcomes research related to VH demonstrate that this therapy approach may be more effective when coupled with a more exercise-intensive physiologic voice therapy approach.[18-20] The Vocal Function Exercise (VFE) program is one such evidence-based physiologic approach to voice therapy.[19,21]

VFEs include a series of isometric and endurance-based exercises aimed at strengthening laryngeal musculature, improving vocal fold vibratory characteristics, and balancing the three sub-systems of voice production, respiration, phonation and resonance.[22] Although VFEs have been employed successfully in treating a variety of voice disorders, the efficacy of this approach for improving vocal function in patients who have undergone XRT for laryngeal cancer has not been established.[18,19,22,23] The overall objective of this study was to investigate the efficacy of VFEs to improve vocal function in adults irradiated for laryngeal cancers. This investigation was performed in three systematic stages, which are described briefly in the next section.

Dissertation Stages

Stage I primary objective

This stage involved characterizing the trends in head and neck cancers among a treatment-seeking population at the University of Kentucky Otolaryngology clinic.

Stage I rationale: Rehabilitation following laryngeal cancers is especially relevant to the study population in the present dissertation since all participants of the study were residents of Kentucky. Laryngeal cancers are a subgroup of head and neck cancers. At 13.5%,[24,25] Kentucky has the highest incidence rate for head and neck cancers in the United States (U.S.).[25,26] The association between smoking and head and neck cancer risk is strongest for the laryngeal cancer subgroup.[27] Furthermore, while the overall incidence of head and neck cancers (HNC) continues to decrease throughout the U.S., Kentucky has alarmingly shown a rise of 1.6% in the incidence of HNCs since 2007.[24] The high incidence of HNCs in Kentucky can be linked to the increased prevalence of tobacco use in the state, since 90% of HNCs occur after prolonged exposure to tobacco and/or ethanol.[27,28] Unfortunately, within the U.S., Kentucky leads in smoking prevalence rates.[29] Within Kentucky, smoking rates are higher for Appalachian Kentucky (rural Eastern Kentucky) as compared to the urban regions within Kentucky.[29] Within the subgroups of all HNCs, laryngeal cancers show the highest incidence rates (5.7 per 100,000) in Kentucky.[24] As a result, large numbers of individuals within the state receive treatment for laryngeal cancers. This initial stage of research helped in identifying my target population, specifically patients who have been treated with radiation therapy for laryngeal cancers. Individuals identified through stage I were subsequently recruited for stage II. The following section briefly describes the primary objective and rationale for stage II.

Stage II primary objective

The primary objective of stage II was to establish the effects of radiation therapy on vocal function in adults irradiated for laryngeal cancers, as assessed by the five domains of voice assessment.

Stage II rationale: A number of studies have documented the undesirable effects of radiation on vocal function.[1,9,30-32] However, these studies used limited outcome measures to assess voice production following radiation therapy. Normal vocal function or voice production is dependent on an interaction of physiological and psychosocial factors. Consequently, vocal function is best assessed with measures that account for both physiological as well as psychosocial measures using a multidimensional voice assessment battery, which utilizes the five domains of voice assessment.[33] These measures include stroboscopic (laryngeal visualization), acoustic, aerodynamic, patient self-report and auditory-perceptual parameters.[33] To this end, assessment of vocal function in my study population was assessed using this multidimensional assessment battery in patients following XRT for laryngeal cancers. Vocal function of irradiated individuals was also compared to a control group of individuals who were matched in terms of age, sex and smoking habits. This stage was meant to identify the nature of voice problems faced by patients irradiated for laryngeal cancers and also establish a patient's perspective on the impact of these voice problems on the individual. Results from stage II highlighted the deleterious effects of radiation therapy on vocal function, thus creating a lens through which to investigate optimal rehabilitation techniques.

Stage III primary objective

The primary objective of stage III was to investigate the efficacy of Vocal Function Exercises (VFE) in improving voice production in adults radiated for laryngeal cancers, as compared to vocal hygiene therapy. This stage was designed as a pilot study to collect preliminary data on the efficacy of VFEs in the irradiated population to support a possible future multi-center trial.

Rationale for Stage III: Despite post-radiation voice problems being well-documented in literature, only four studies have investigated the efficacy of voice therapy in the laryngeal cancer population.[13-17] The voice therapy interventions across all four studies, however, were varied and not specified. Central to treatment approaches across all studies was vocal hygiene counseling. The outcomes research on vocal hygiene as a sole method of treatment, however, is not favorable.[19,20,34] In fact, previous studies have shown vocal hygiene works best when coupled with a more exercise-intensive physiologic voice therapy approach.[19,20,34] The Vocal Function Exercise (VFE) program is one such prescriptive evidence based physiologic voice therapy approach and has been successful in treating various voice pathologies in schoolteachers, singers and the aging voice.[18,23,35,36] Given the efficacy of VFEs in treating various voice disorders, this therapy approach was chosen as the experimental treatment modality for adults who experienced voice problems as a result of radiation therapy for the treatment of their laryngeal cancer.

This chapter was intended to provide the reader with an overview of the significance and rationale for the three stages of this dissertation. The next chapter provides a more detailed review of literature pertinent to the main study objective; investigating the efficacy of VFEs in improving voice quality in adults irradiated for laryngeal cancers.

CHAPTER 2: REVIEW OF LITERATURE

This chapter reviews pertinent literature in the domains of radiation therapy for treatment of laryngeal cancers. First, laryngeal cancer trends in the United States are discussed. The second section will review literature pertinent to voice problems following radiation therapy. The third section will briefly discuss the available evidence on voice rehabilitation following radiation therapy for laryngeal cancers. The fourth section will discuss the rationale for choosing Vocal Function Exercises (VFE) as the treatment for voice problems following radiation therapy for laryngeal cancers.

LARYNGEAL CANCER

Laryngeal cancers are a sub-group of head and neck cancers that originate in one or more sub-sites of the larynx. The number of estimated new cases and deaths from laryngeal cancer in the United States in 2014 were 12,630 and 3,610 respectively.[37] For the purposes of clinical staging, the larynx is divided into three sub-sites; glottis, supraglottis and subglottis.[38] The glottis consists of the superior and inferior aspects of the true vocal folds, as well the anterior and posterior commissures.[38] The supraglottis is comprised of the false vocal folds, arytenoids, aryepiglottic folds and epiglottis.[38] The subglottis is comprised of the area from the lower boundary of the glottis to the lower margin of the cricoid cartilage.[38] The most common histological type of laryngeal cancer is squamous cell carcinoma, which is associated with more than 90% of all laryngeal cancers.[27,28]

Depending on the tumor stage and sub-site, laryngeal cancers can be treated with surgery alone, radiation therapy (XRT) alone, a combination of chemotherapy and radiation therapy or a combination of all of the above modalities. For the purpose of this dissertation, I focus on the role of XRT in the treatment of laryngeal cancers and its effects on laryngeal tissues and vocal function following completion of treatment.

Radiation therapy modalities used in the treatment of laryngeal cancers

Radiation therapy for patients with laryngeal cancers is traditionally delivered via two modalities; wide field radiation therapy and narrow field radiation therapy. As the names suggest, wide field radiation therapy is delivered over a wide field of tissues, which in the case of a larynx cancer patient may include the primary site and neck.[3] Narrow field radiation therapy, also known as intensity modulated radiation therapy (IMRT) delivers the required radiation dose in a concentrated area.[1,39] Wide field radiation therapy is commonly used in the treatment of advanced laryngeal cancers since these tumors are often large and include cervical lymph nodes.[39] IMRT is commonly used to treat early glottic cancers as it is successful in concentrating the radiation beam on smaller areas.[39] Wide field radiation therapy causes greater collateral damage of surrounding tissues as compared to narrow field radiation therapy.[39,40] Radiation dosage typically ranges from 60-70 Gy and is administered for 5-7 weeks.[41,42]

Effects of radiation therapy on voice quality

Since the 1990s, an increasing number of patients are being treated with XRT with the intent of preservation of laryngeal structure and function.[3] However, with increasing outcomes research in the area of voice and swallowing rehabilitation, it is apparent that preservation of structure after radiation therapy does not necessarily translate into preservation of function.[9,12,15,30,43-45] The following section describes the effects of radiation toxicity on vocal function.

Voice problems following radiation therapy

There are a number of studies that have documented the effects of radiation on voice quality. Since a majority of these studies were retrospective chart reviews, it was interesting to note that these studies frequently reported disordered voice status and findings years after radiation therapy was completed. These findings are a strong indicator of the prolonged detrimental effects of XRT on vocal function. Normal vocal function is an interaction of physiological and psychosocial factors.[46] Physiologically, normal voice production is dependent on a balanced interaction of respiration, phonation and resonance.[21] The psychosocial aspect of voice production is dependent on the individual's voice use in his or her environment with regards to activities of daily living and professional demands.[47] Due to its multifactorial nature, voice production is best evaluated using a multidimensional voice assessment battery, which encompasses physiological and psychosocial factors of voice production. To this end, research on voice outcomes suggests that voice production or vocal function is best assessed through the five domains of voice assessment which includes visual perceptual parameters (laryngeal imaging), auditory-perceptual parameters (clinician's perception of voice quality), patient perception (voice-related quality of life), acoustic analysis and aerodynamic analysis.[33] Studies that have investigated voice outcomes following radiation therapy have used one or more, but not all recommended parameters from the five domains of voice assessment. The following section provides the reader with a brief description of procedures contained within the five domains of voice assessment. The section has a special focus on select parameters in each domain that were chosen as assessment parameters for stage 2 and stage 3 of the present dissertation.

Domain 1: Auditory Perceptual Measures

Ray Kent said "the ear is an essential tool of the speech-language pathologist".[48] Auditory perceptual assessment of voice quality essentially involves a clinician rating a patient's voice disorder or dysphonia using various descriptive parameters. These parameters can be general, for example, "patient presents with moderate dysphonia" or can be more specific to features heard in patient's voice, for example, "patient presents with a moderate degree of roughness, and mild breathiness and strain". An auditory-perceptual evaluation is one of the most traditional and widely used methods of voice assessment. However, as is evident from these variable descriptions above, speech-language pathologists (SLPs) are recommended to use standardized assessments for auditory perceptual evaluation of voice to ensure consistency amongst clinicians and in turn strengthening external validity. There are various scales that are utilized in the auditory perceptual evaluation of voice but few that have been standardized. Two of the most widely used scales for voice assessment are the GRBAS [49] and Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V).[50] The GRBAS scale is easy to administer and was developed to rate vocal quality within five perceptual categories: overall grade (G), roughness (R), breathiness (B), asthenia (A), and strain (S). However, its sensitivity in detecting vocal alterations has been demonstrated to be lower than that observed with CAPE-V, possibly because GRBAS is an ordinal scale with only three alternatives (mild, moderate, and severe). The GRBAS has also been shown to be less sensitive than CAPE-V to evaluate subtle differences in voice quality.[51] The use of the CAPE-V has been highly recommended and SLPs are being increasingly being encouraged to use the CAPE-V. Since its inception, the CAPE-V was devised to promote the standardization of evaluating and documenting auditory-perceptual judgements of voice quality. [52,53] The CAPE-V assesses perceptual vocal parameters which are (a) Overall Severity; (b) Roughness; (c) Breathiness; (d) Strain; (e) Pitch; and (f) Loudness. The CAPE-V displays each parameter accompanied by a 100- millimeter line forming a visual analog scale (VAS). Please see Appendix 1 for CAPE-V form. Judgments are marked on each scale on the CAPE-V: “MI” refers to "mildly deviant," “MO” refers to “moderately deviant,” and “SE” refers to "severely deviant." Its greater sensitivity in detecting small differences in the voice, as compared with GRBAS, has been attributed to the use of its visual analog scale. [50,54,55] A slightly improved rater reliability using the CAPE-V to make perceptual judgments of voice quality, in comparison with the GRBAS scale, has also been reported.[51] The present dissertation study utilized CAPE-V scores as the outcome measure for the auditory-perceptual domain given its standardization, high reliability and its high recommendation to being the auditory perceptual scale of choice. The following section gives us a brief description of the reliability and validity measures for the CAPE-V.

CAPE-V: The CAPE-V has demonstrated criterion validity and both intra- and interrater reliability. Intrarater reliability using Pearson's r ranged from .35 to .82 depending on the voice quality measured.[54] Strain had the lowest reliability and breathiness had the highest reliability. Interrater reliability was measured with Shout-Fleiss intraclass correlation coefficients (ICC) and ranged from .28 to .76 with pitch having the lowest reliability and overall severity having the highest reliability. Zraick et al., reported the intra and interrater reliability of this instrument.[53] Pearson's r for intrarater reliability revealed the following: Overall severity .57, Roughness .77, Breathiness .82, Strain .35, Loudness .78, Pitch .64. Interrater reliability using Shout-Fleiss intraclass correlation coefficients revealed: Overall severity .76, Roughness .62, Breathiness .60, Strain .56, Loudness .54, Pitch .28.[53]

Domain 2: Patient self assessment

Voice disorders can have a significant effect on quality of life.[56] Patient self assessment scales for voice disorders evaluate the impact of a voice disorder on a person's quality of life. There are several scales available for patient self assessment in the voice disordered population.[56] However, a previous review article rated the Voice Handicap Index (VHI) and the Voice-Related Quality of Life (V-RQOL) as the psychometrically strongest of the existing measures.[57] The Voice Handicap Index (VHI), developed by Jacobson et al.,[47] is a 30-item questionnaire designed to assess the patient's perceived impact of a voice disorder in three domains: physical, emotional, and social. The Voice related Quality of Life (V-RQOL) [46] is a 10 item questionnaire which also probes patient perceived difficulty with their voice in physical and socio-emotional domains. Internal consistency of the V-RQOL has been demonstrated to be high at Cronbach's alpha of 0.89.[46] VHI and VRQOL scores have been demonstrated to be highly correlated.[58] For the purpose of this dissertation, the VHI was chosen as the outcome measure of choice since it has been used in other studies investigating the efficacy of voice therapy in the irradiated population.[15,16] Below is a brief description of reliability and validity measures directly related to VHI scores.

Voice Handicap Index (VHI): Criterion validity was established by comparing the VHI scores with patient-perceived severity of their voice. Test re-test reliability for the three domains was Functional (r = 0.86), Physical (r = 0.86), Emotional (r = 0.92), and Total (r = 0.92). The minimum detectable change in the total score of 18 points was determined to indicate a clinically significant change in pre- and post-therapy measures.[47]

Domain 3: Acoustic analysis

An acoustic analysis of voice production offers the clinician an instrumental objective analysis of a patient's voice. There are a number of acoustic measures available. However, for the purpose of this section we will review three common measures used across studies and which were used as outcome measures for stages 2 and 3 of the present dissertation study. It should be noted that frequency and intensity based-measures do have inherent limitations. However they continue to be used as outcome measures in studies because they can provide change scores demonstrating post-therapeutic voice changes.

These limitations are related to their reliance on the accurate tracking of fundamental frequency during voice production. These limitations can be overcome by methods that rely on cepstral analysis of voice which is in turn is not dependent on fundamental frequency.[59] As a result, commonly used perturbation and noise measures (jitter, shimmer, noise-to-harmonic ratio) are used in the analysis of sustained vowels,[60] and cepstral measures are used in the analysis of connected speech and highly disordered voices.[60] Below is a brief description reliability and validity of acoustic measures used in the present dissertation study.

Perturbation measures: Jitter is the short-term cycle-to-cycle variation in frequency in a voice sample, whereas shimmer is the short-term cycle-to-cycle variation in amplitude. Both of these measures failed to demonstrate strong reliability because of differences in extraction methods across systems and because highly dysphonic voice signals decrease reliability. [61] These measures are reliable for sustained vowels, but not for connected speech and highly dysphonic voices.[60] To overcome this barrier, the present study also included the Cepstral Speech Index of Dysphonia which accounts for aperiodicity and connected speech.[60]

Noise measures: Harmonics-to-Noise Ratio (HNR) is based on the premise that normal vocal production consists of a strong harmonic component with a smaller degree of aperiodic noise .[62] Voices which carry a stronger harmonic component compared to the noise component should yield better perceptual voice quality. HNR validity has been examined by comparing HNR results to auditory-perceptual ratings of voice. Yumoto et al. [63] found a significant correlation (r = 0.81) between HNR results and perceptual ratings. The reliability of HNR for repeated measures of subjects' voices was examined by Bough et al.[64] The study examined the intra- and inter-day reliability for measures of HNR. Intraclass Correlation Coefficients for HNR measures taken within a single day ranged from 0.93 to 0.98. Coefficients for measures taken across a series of days ranged from 0.761 to 0.86. [64] The present study used the Noise to Harmonics ratio which is an inverse ratio of the HNR and has been found to be highly reliable as well.[65,66]

Cepstral Speech Index of Dysphonia (CSID): The cepstrum has been described by Noll [67] as a Fourier transform of the logarithm power spectrum. [65] The principal advantage of spectral analysis methods is that estimates of aperiodicity and/or additive noise may be achieved without the identification of cycle boundaries.[60] A study by Awan, et.al. demonstrated that acoustic estimates of dysphonia severity can be achieved in both continuous speech and vowel contexts using a model incorporating spectral/cepstral measures. The study also demonstrated a strong relationship between perceptual (CAPE-V measures) and acoustic estimates of dysphonia using cepstral analysis (R=0.96, R=0.81).[60]

Domain 4: Aerodynamic Measures

Aerodynamic measurement of voice production concerns measurements of air pressures and air flows that are meaningful in clinical diagnosis and treatment. These measures may help interpret the valving activity of the larynx. The vocal tract is an aerodynamic sound generator and resonator system. Variations in the flow of air through it reflect changes in the "manner" of consonant & vowel articulations. Evaluation of airflow can provide insight into speech or voice system dysfunction and efficiency.[65] The aerodynamic measures used for stages 2 and 3 of the present dissertation are described below with their reliability and validity measures.

Subglottic pressure (PSub)*:* Psub is a measure of air pressure beneath the vocal folds necessary to overcome the resistance of the approximated folds to initiate and maintain phonation.[65] Estimated subglottic pressure is taken from a pressure sensing tube placed in the mouth during production of a pressure consonant, typically /p/. Because the pressure in the lungs rapidly is transmitted to the lips a useful estimate of the subglottic pressure can be obtained. [65] Subglottic pressure has established criterion validity when compared to tracheal puncture. Direct measures of subglottic pressure and indirect estimated subglottic pressure at the lips have been demonstrated to have comparable results.[65]

Mean airflow rate*:* The mean airflow rate of a speech sample refers to the average rate of airflow during a given production.[65] The mean airflow rate of a speech sample refers to the average rate of airflow during a given production.[65] This measure is commonly taken using an anesthesia-type mask placed over the nose and mouth so that oral airflow during vowel production is passed through a pneumotachometer which senses pressure changes and mathematically converts these into airflow rates.

Laryngeal Airway Resistance: To calculate mean estimated subglottic pressure and mean airflow rate, syllable trains of a pressure consonant and a vowel may be used, usually /pa/. Pressure is sensed during the consonant and airflow is transduced during the vowel. These measures may be interpreted individually or as a ratio of pressure to flow, termed laryngeal airway resistance. Smitheran and Hixon [68] calculated the reliability with intraclass correlation cofficients of laryngeal airway resistance across three sessions using normal participants to be 0.96.

Domain 5: Laryngeal imaging or Visual Perceptual Measures

Laryngeal stroboscopy is a commonly used clinical method to assess vocal fold vibration. Another visualization method that is gaining popularity is high speed laryngeal imaging since it helps overcome the instrumental limitations of laryngeal stroboscopy.[69] Although high speed laryngeal imaging is gaining popularity as a method of assessing vocal fold vibration, it is not readily available in a number of clinical settings. As a result, its clinical utility continues to be under investigation. Stroboscopy and high speed laryngeal imaging permit direct visualization of the vibrating vocal folds, allowing detailed assessment of laryngeal structure and function.[70] Because of the large number of vocal fold vibration parameters and somewhat subjective nature of interpreting visual examinations, these measures do hold reliability concerns. Some of these concerns include examiner bias, clinician training, and lack of standardization in rating parameters. Quantification of imaging parameters has not gained universal acceptance clinically because of its cumbersome nature.[71,72] There are, however, many rating scales that may be used to guide interpretation of imaging parameters.[70,73-75] There is some reliability data in interpretation of imaging parameters which supports its use. Intrajudge reliability for overall ratings has been demonstrated to range from 0.31 to 0.97,[73] and interjudge reliability ranged from 0.75 to 0.98.[76]

Since the previous section has informed the reader on select parameters and their role in the assessment of voice disorders, the next section provides the reader with a brief description of study findings across the five domains of post-radiation voice assessment for patients treated for laryngeal cancers.

***Stroboscopic findings*:** In a detailed study performed by Lehman et al (1988),[77] significant abnormalities were seen on stroboscopic analysis in patients irradiated for stage I glottic cancers.

Around 60% of patients showed irregular vocal fold closure, 65% showed increased supraglottic activity, 85% showed irregular vibratory margins, 80% showed shorter phase closure, and 85% showed irregular phase symmetry. The stroboscopic finding which was consistent across the group was decreased vibratory amplitude not only on the treated vocal fold but also on the non-diseased fold. These findings were consistent with those in a study by McGuirt et al. (1994)[12] and Wedman et.al[78] that reported decreased mucosal wave on both the affected and non-diseased fold. In addition, subjects showed signs of muscle tension dysphonia, ventricular phonation, and partial antero-posterior compression.

Aerodynamic measures: McGuirt et al. (1994)[12] revealed mean laryngeal airway resistance (LAR) values 4.5 times greater than normal values (mean=177cmH2O/L/s) in patients who had been irradiated for T1a glottic cancer. These LAR values were comparable to those in a study by Dworkin (1997)[30] who found that none of 12 irradiated patients attained normal aerodynamic measures. Increased airflow rates in patients who had undergone radiotherapy (n=6) were also observed in a study by Tamura (2003)[79] in which mean airflow rates of 165 cc/s were measured. Increased aerodynamic resistance values reflect the signs of supraglottic hyperfunction seen stroboscopically and are also indicative of issues with glottal valving during phonation.

Acoustic measures: A majority of studies showed that radiation therapy had a negative impact on voice production demonstrated by increased perturbation and noise measures. Voice production was gradually found to improve over 3-6 months post radiotherapy. However, none of the post-treatment values were within the normal range. [78-80]

Auditory-Perceptual findings: Auditory-perceptual findings from previous studies report varied vocal symptoms. Perceptually patients often present with hoarseness, decreased volume, increased strain and persistent voice changes.[8,13,81]

Voice-related quality of life: A recent study by Karlsson, et al. (2016) [17] that investigated voice-related quality of life in patients with early and advanced laryngeal cancers revealed no significant differences between pre-radiation and post-radiation scores one year after completion of treatment.

These results indicate that the deterioration in voice quality perceived by the patient as a result of laryngeal cancer did not improve after completion of treatment to eliminate laryngeal cancer.[17] A study that investigated voice problems as a result of radiation for early glottic cancers demonstrated that 87.8% of the patients sampled reported their voice as being abnormal, ranging from slight to moderate dysfunction.[82] From the above clinical findings, it is established that patients irradiated for laryngeal cancers experience long-term voice problems that affect quality of life. The next section provides a brief description of voice intervention studies in the irradiated laryngeal cancer population.

Voice rehabilitation following radiation therapy for laryngeal cancers

Only four studies document the application of voice therapy for individuals irradiated for laryngeal cancers.[13-16] Two studies by Van Gogh et. al[15,16] focused on voice rehabilitation in patients following irradiation for early glottic cancers, and studies by Tuomi et.al[14] and Bergstorm et. al[13] included patients who had received XRT for early and advanced laryngeal cancers across all laryngeal sub-sites.

Van Gogh et.al, reported improvements in Voice Handicap Index (VHI) scores for patients irradiated for early glottic cancers following voice therapy interventions.[16] The second study by Van Gogh et.al[15] followed patients who had received voice therapy following irradiation for early glottic cancer for one year post-treatment to investigate if the effects of voice therapy were maintained. Their study demonstrated that beneficial short-term effect on the mean VHI, percent jitter, and shimmer were maintained after more than one year of follow-up. Voice rehabilitation in both studies included vocal hygiene with non-specified voice and breathing exercises. The control group in both studies did not receive any voice treatment.

Results from the study by Tuomi et.al[14] showed that patients who received vocal rehabilitation experienced improved self-rated vocal function after rehabilitation. Patients with supraglottic tumors who received voice rehabilitation had statistically significant improvements in voice quality and self-rated vocal function, whereas the control group did not. In a randomized controlled trial, Bergstorm et.al,[13] reported that subjects receiving voice rehabilitation showed no functional decline in vocal roughness 6-12 months post radiation therapy and perceived their voices to improve to a greater extent as a result of voice rehabilitation than the control group. In both studies, the control group received voice education and vocal hygiene as an intervention. The study by Bergstorm et.al described their voice rehabilitation intervention as a "structured hierarchy consisting of both direct and indirect voice interventions, including tasks such as breathing, relaxation, posture and specific physiology-targeted phonation exercises."[13] Tuomi et.al[14] listed their voice therapy activities hierarchically; however specific production tasks under each activity were not specified.

From the four study results reported above, it appears as though voice therapy or voice rehabilitation was beneficial in patients irradiated for both early as well as advanced laryngeal cancers. However, none of the studies specified a systematic or consistent voice therapy approach across all patients.

The present dissertation study was aimed at using an evidence- based prescriptive voice therapy approach in individuals irradiated for laryngeal cancers. The next section focuses on the rationale behind choosing Vocal Function Exercises as the experimental intervention method.

Rationale for choosing Vocal Function Exercises as choice of experimental intervention

There are a number of voice therapy methods or voice therapy orientations that have been used over the years for the treatment of voice disorders.[34,83] Based on a review article by Thomas and Stemple,[20] three primary orientations to the treatment of functional voice disorders have emerged in literature; hygienic voice therapy, symptomatic voice therapy and physiologic voice therapy. The following section provides the reader with a brief description of each of these voice therapy orientations.

Hygienic voice therapy: Hygienic voice therapy is based on the belief that many functional voice disorders are caused and maintained by behaviors that can damage laryngeal structure and function, and subsequently, eliminating these behaviors will result in improved vocal performance.[20] Often, hygienic voice therapy is a precursor in managing voice disorders and is most effective when used in combination with other techniques.[19,20,84,85] When compared to no treatment at all, vocal hygiene has been proven to be effective in the management of voice disorders;[85,86] however in studies that compared vocal hygiene to other voice therapy interventions such as Vocal Function Exercises and Resonant Voice Therapy,[19,87-89] the consistent finding across all of these studies was an improvement in voice quality when a more physiologic approach was employed. Some authors describe vocal hygiene as an indirect method of voice rehabilitation since it targets behaviors around voice use and not vocal physiology directly.[86,88] It is clear from these studies that while vocal hygiene is an important part of voice therapy, it is not effective as a stand-alone mode of treatment and often more effective when coupled with a more direct therapy approach.[20] More specifically, when vocal hygiene education was compared to voice therapy exercises in subjects irradiated for early glottic cancers, it was the voice therapy exercise group that showed long term significant improvement in voice quality.[15,16]

Symptomatic voice therapy: Organized by Daniel Boone (1971), symptomatic voice therapy operates on the basis that voice disorders are caused by functional misuse or abuse of vocal components including respiration, pitch and loudness. Symptomatic voice therapy aims at modifying these deviant vocal symptoms that are expressed as breathiness, low pitch, glottal fry phonation, use of hard glottal attacks or using an inappropriate pitch in general.[90,91] Various facilitation techniques employed in symptomatic voice therapy are geared towards reducing or eliminating these inappropriate components and promoting better voice production. Some studies have described symptomatic voice therapy as a direct therapy method when compared to vocal hygiene.[92,93]

Physiologic voice therapy: [20,91] As the name suggests, this approach includes techniques that directly involve altering and modifying the physiology of the voice-producing mechanisms. Normal voice production is dependent upon a balance among the respiratory, phonatory and resonance systems. This requires a relative balance among the airflow from the lungs, strength and coordination of the intrinsic laryngeal muscles, and the structural and functional integrity of the vocal tract and participating resonating cavities. In addition, the emphasis of physiologic voice therapy is on maintaining the health of the vocal fold cover.[91]

Some of the most commonly used physiologic voice therapy approaches are implementation of Vocal Function Exercises, Resonant Voice therapy and the Accent method of voice therapy. The rationale behind these methods is described below in detail:

I) Vocal Function Exercises:[21] Vocal Function Exercises, first described by Barnes and then further developed by Stemple[20] are aimed at strengthening and rebalancing the three sub-systems of voice production, namely respiration, phonation and resonance. It is based on the principles of basic exercise physiology that state the role of resistance and endurance exercises in improving muscle function and strength.[94,95] The exercise program itself is comprised of a series of four exercises which include a warm up exercise, stretching, contraction and increased resistance exercises. The typical exercise program lasts for about 6-8 weeks depending upon patient progress. The exercise program like any other program of the same nature involves repetitive strengthening tasks, endurance tasks and relies heavily on patient compliance. Patient progress and technique therefore need to be tracked carefully through the exercise program. A number of studies have employed Vocal Function Exercises successfully in the management of voice disorders, both organic and non-organic.[19,20,22,23] A number of outcomes studies have been reported that used VFEs across different high-risk populations such as singers and school teachers.

II) Resonant Voice Therapy (RVT): RVT was first described in literature by Arthur Lessac and was developed further by Katherine Verdolini. Resonant voice is defined as voice production involving oral vibratory sensations, usually on the anterior alveolar ridge or higher in the face in the context of easy phonation.[21] RVT is aimed at maximizing voice production by achieving a strong and clean voice quality in the presence of minimal vocal effort. This therapy method operates on the rationale that minimizing vocal fold impact during voice production would minimize the likelihood of vocal fold injury. Like VFEs, RVT too has been the subject of outcomes studies, either as a stand-alone method, or in conjunction with other voice therapy methods.[19,89,96,97]

III) Accent Method (AM) of voice therapy: The AM targets holistically the improvement of the respiratory, phonatory, articulatory, and gesticulatory aspects of verbal communication in an integrated manner. The AM may be considered holistic also from the vocal point of view as it collectively and simultaneously targets the various parameters of voice such as pitch, loudness and timbre. The AM rests technically on three major principles: (1) optimal abdomino-diaphragmatic breath support; (2) rhythmic play of accentuated relaxed vowels with progressive carryover to connected speech, and (3) dynamic rhythmic body and arm movements. The therapeutic procedure consists of: (1) respiratory exercises; (2) phonatory exercises, and (3) articulatory exercises, by which the beneficial new vocal habits are transferred to connected speech. In the past, the accent method has been used successfully in treating both organic and non-organic voice disorders.[98-100]

Of all of the voice therapy methods described above, the most researched voice therapy intervention has been Vocal Function Exercises. To date, there are 23 peer-reviewed studies that have demonstrated that VFEs are efficacious in enhancing vocal function in individuals with disordered voices, individuals over the age of 60 years diagnosed with presbylaryngeus and professional voice users.[18,19,22,35,36,69,87,88,91,101-114] In individuals with normal voices and elite voice users such as singers, VFEs were effective in enhancing vocal function. Based on the disturbances noted in voice production as a result of radiation-induced disruption in vocal fold vibratory parameters, VFEs may prove efficacious in improving vocal function post-XRT.

In addition to a strong clinical evidence base, there are other factors that justify the use of VFEs following XRT for laryngeal cancers. These factors have to do with the unique muscle properties of intrinsic laryngeal muscles and the benefits of an exercise intensive program for improving voice quality following radiation damage to the larynx. In the next few sections, the reader will be informed on unique properties of laryngeal muscles, the effect of exercise on skeletal muscles, motor control theory and the effect of radiation therapy on intrinsic laryngeal muscles. These findings contribute to a strong case for using a physiologic approach to voice therapy following XRT, which focuses on strength and balance training of the laryngeal musculature, specifically through Vocal Function Exercises (VFEs).

Intrinsic Laryngeal Muscles (ILM), what sets them apart?

Since ILMs are skeletal muscles, they have been thought to resemble limb skeletal muscles in terms of structure and function. However, unlike limb skeletal muscles, ILMs are constantly active during respiration and are protective in function as they serve to protect the airway. As a result it is important that these muscles remain more fatigue-resistant as compared to limb skeletal muscles.[115-117] Therefore with the unique demand placed on these muscles, it has become apparent that they differ from limb skeletal muscles in certain key aspects. These differences are discussed further in the present section.

Muscle fiber**:** Laryngeal muscle fibers are relatively smaller when compared to limb skeletal muscles[118] but are comparable to extraocular muscle (25-50 µm).[119] The mean fiber diameter for Thyroarytenoid (TA), Lateral cricoarytenoid (LCA), Posterior cricoarytenoid (PCA) and

Cricothyroid (CT) is around 20-35 µm[118] which is smaller compared to limb muscles, which range from 35-75 µm.[120]

Contractile properties: The speed of contraction and sustainability of contraction of muscles are determined primarily by the muscle's myosin heavy chain (MyHC-I) isoform. In human skeletal muscles MyHC-I yield slow contractions while IIa, IIx produce rapid contractions.[121] In the rat model, laryngeal muscles show Type I, IIA and IIB myosins.[117] Studies in rats and non-human primates suggest that the TA is nearly homogeneous in its myosin heavy chain expression, being composed entirely of fast, type II myosin. [122,123] Unlike reports in the rat and non-human primate model, human ILMs display a combination of fast and slow isoforms within a single muscle. Muscles responsible for glottic closure and airway protection demonstrate faster MyHC isoforms than abductors.[115-117] Research on human laryngeal muscles has suggested that some laryngeal fibers are capable of contractile speeds that far exceed those of limb muscles.[124]

Mitochondrial density**:** Mitochondrial volume density is the portion of cellular volume occupied by the mitochondria (mitochondrial volume percent)[125] or the percentage of the volume fiber occupied by the mitochondria. TA, PCA and CT muscles show higher densities of mitochondria when compared with limb skeletal muscles. [122,126] The constant activation of the muscle during life sustaining functions such as respiration require these muscles to be far more fatigue-resistant as compared to the typical demand of limb skeletal muscles.

Since we have now established that ILMs are different from limb skeletal muscles in terms of size, role, and composition, the next section will describe the changes seen in laryngeal tissues and musculature following radiation therapy.

Effect of radiation therapy on vocal fold tissue

The elements most at risk of radiation injury in the larynx are the epithelia- both squamous and columnar- and the blood vessels. Cartilages of the larynx also appear to be an important site of delayed injury.[127] The response of the larynx to radical doses of radiotherapy varies from mild erythema to severe inflammation with edema and induration caused by obliterative vasculitis and local ischemia.[128] In a retrospective study of 348 patients receiving radiotherapy as the primary treatment for laryngeal carcinoma, Mintz et al reported that chondritis developed after curative-dose radiotherapy in 15% of their patients.[9] There are very few studies that have studied the effects of vocal fold muscle after radiation specifically. A study done by Tedla et al.[129] investigated the changes in muscle structure of irradiated intrinsic laryngeal musculature. Comparisons were made between two groups of samples; those obtained from patients who had the total laryngectomy as their primary treatment modality and those who had salvage laryngectomy. Salvage laryngectomy is the term used for a total laryngectomy following failure of primary radiation therapy. For the salvage laryngectomy group, the time post radiation ranged from 7-15 months. The histological differences between the vocalis muscle, vocal process of the arytenoid, cricoarytenoid joint and superior and recurrent laryngeal nerves were compared. They found significant differences in the muscle structure as a result of radiation injury characterized by decreased number of muscle fibers, widening of spaces between muscle fibers and reorganization of muscle fibrils. These changes are indicative of increased atrophic changes in the irradiated laryngeal muscle as compared to non-irradiated muscle. They also found a change in the thickness of the perineurium of the recurrent laryngeal nerve and superior laryngeal nerve. The thickness was lesser in the irradiated group as compared to the non-radiation group. This could possibly influence the motor and sensory characteristics of the laryngeal vestibule. Although this examination focuses on the role of the larynx in voice production, it is relevant to note that this mechanism of injury may be a reason why swallowing problems characterized by silent aspiration are prevalent in patients who have been irradiated. [43,130]

A study by Johns et.al [31] demonstrated that human irradiated vocal folds demonstrated increased collagen transcription, with increased deposition and disorganization of collagen in both the thyroarytenoid muscle and the superficial lamina propria. An increase in fibronectin levels was noted in the superficial lamina propria. Laminin decreased in the thyroarytenoid muscle. All of these findings would explain the decrease in vocal fold pliability following completion of radiation therapy. Whole genome microarray analysis demonstrated increased transcription of markers for fibrosis, oxidative stress, inflammation, glycosaminoglycan production, and apoptosis. Post radiation changes therefore extend to the level of gene transcription which can hinder treatment approaches that only target post- radiation structural damage. Interestingly, the study also demonstrated an increase in collagen content as greater time had passed since the completion of radiation therapy. This finding further highlights the late effects of radiation toxicity.

Motor control theory and neuroplastic influences

From the studies that investigated voice quality after radiation therapy, it is apparent that a number of changes in vocal quality are a result of faulty voice use. From the previous section it is also apparent that a number of sensory and motor alterations take place as a result of radiation therapy. Studies that performed laryngeal examinations after radiation therapy demonstrated that this group of patients often exhibit compensatory behaviors such as laryngeal hyperfunction which are not conducive to normal voice production.[12,79] It is possible that as patients undergo changes during and after XRT, they tend to develop adaptive and compensatory strategies as a result of the various pathophysiological changes occurring during treatment. Theories of motor control may help us understand this phenomenon better regarding not just physical changes but also the various environmental changes that result from the experience of radiation therapy. The field of motor control is directed at studying the nature of movement, and how movement is controlled. Motor control is defined as the ability to regulate or direct mechanisms essential to movement.[131] Though application of motor control theories have been studied in greater detail in the Physical Therapy and Occupational Therapy literature, researchers have more recently tried to explain speech motor control based on these theories as well.[132] Though these theories have not been applied to explain voice production, there are a number of overlapping concepts which could better explain the compensation and adaptability of the vocal fold mechanism.

One such concept is the interaction between the feedback and feedforward system of physiological motor control.[133] This interaction between the two mechanisms could shed light on the compensatory vocal behaviors developed as a result of radiation therapy. Feedforward control involves all techniques for controlling a motor apparatus (the effector organs, for example, muscle) without reference to one or more controlled variables (possibly muscle length or joint angles) describing the current state of the motor system. In contrast, feedback control uses some knowledge of the controlled variables to determine the outgoing motor commands. For example, the controller could assess the difference between the sensed state of the motor apparatus and a reference value for that variable. The controller could then seek to adjust the difference using negative feedback.[134] Considering the alterations to sensorimotor components described in the previous section, the possibility of a shift in the feedforward and feedback mechanism is inevitable. The shift that is possibly occurring in the feedforward and feedback mechanism as a result of laryngeal injury secondary to radiation is probably why individuals compensate through hyperfunction, which in turn produces a strained voice quality. This shift which results in faulty compensatory voice production strategies also makes a case for why voice therapy needs to be more task-specific and focus on changing movement based on striking a balance between respiration, phonation and resonance. Another issue that further adds complexity to ongoing structural changes is that sensory deprivation caused as a result of radiation damage to the larynx is late onset. Studies investigating neuroplasticity have demonstrated that neuroplastic changes are more striking early in life during the critical period of development.[135] Therefore retraining a highly specialized mechanism like the larynx , which is now mechanically injured, genetically altered and which now suffers from late sensory deprivation, can prove challenging. As involved as the peripheral motor and sensory systems are, the role of the cortex cannot be ignored. As is evident from studies, individuals continued to show compensatory and deviant voice production years after radiation was completed. With ongoing alterations in sensory and motor mechanisms consequently affecting the feedforward and feedback mechanisms, it is possible that cortical representations are being altered as well. Areas for laryngeal control in the cortex have been identified [136-138] and while the effects of radiation to the larynx on cortical mapping have not been studied, it can be expected that the various sensory and motor changes taking place would influence cortical reorganization as well. We shall describe the basis for our theory of cortical reorganization in the next section.

Neuroplastic influences of voice problems on cortical representation: Cortical reorganization following deafferentation and amputation has been studied extensively in the animal model. [139-144] Reorganization following amputation is similar in the pattern which it follows considering the taking over of the now deprived field by neighboring areas. The formation of 'new' representations is also indicative of the fact that there are certain latent anatomical regions that come into play when certain regions are completely deprived of sensory input, as seen in cases of nerve resection or amputation. Deafferentation studies in adult macaque monkeys showed that it was not just the receptive fields of the surrounding digits that took over the deprived area; but it was also neighboring areas that represented the facial receptive field area that expanded over the deafferented region.[143] These findings were supported by further exploration of cortical reorganization in adult primates.[141] Similarly as changes in the perineurium of the recurrent laryngeal nerve take place as a result of radiation therapy, it is possible that cortical representations become weaker as a lack of sensory and motor input. Is this why patients in some cases display severe dysphagia and voice issues over a long period of time after the completion of radiation? As mentioned before, this has not been studied, and it is possible that laryngeal cortical representations reorganize differently. But until investigated further, this can be considered as a strong factor in recovery.

In studies of cortical reorganization and recovery, one of the major influences in recovery was activity-dependent neuroplasticity. The role of repetitive practice and increasing task complexity has been linked to a better quality of neuroplastic change. Considering repetitive nature of tasks, the role of exercise in neuroplastic changes has been the subject of investigation. The next section focuses on the effects of exercise on neuromuscular changes and gene expression.

Exercise and neuroplasticity in influencing gene expression: Plasticity is the interface between physical and neural activity.[145] Studies have repeatedly shown that, depending on intensity, endurance exercise increases neurotrophins and thereby induces neuroplasticity.[146-151] An increase of Brain Derived Nerve Factor (BDNF) has been interpreted as an important factor raising adult Central Nervous System (CNS) plasticity. In addition, aerobic exercise up-regulated expression of insulin-like growth factor-I (IGF-1) and raised uptake of peripheral circulating IGF-I into the brain.[148,149,152] Studies have shown that IGF-I increases neurogenesis and also angiogenesis.[146] Basal and exercise-induced angiogenesis are regulated in part by vascular endothelial growth factor (VEGF). VEGF is produced by skeletal muscle cells during exercise and can be released into the circulation, which also seems to be necessary for the effects of aerobic exercise on neurogenesis.[146] Considering findings on diminished vascular supply to tissues after radiation therapy, this is a possible indicator that exercising laryngeal muscles may improve vascular supply to the irradiated muscle. A study by Gomez-Pinnilla (2002)[151] investigated the effect of voluntary exercise on neuroplasticity. Voluntary exercise increased the expression of several molecules associated with the action of BDNF on synaptic function and neurite outgrowth in the lumbar region of the spinal cord and the soleus muscle. While we acknowledge that the study focused on limb skeletal muscles, there were a number of interesting findings related to activity-dependent plasticity. Their study demonstrated that voluntary physical activity can lead adult sensory neurons to enhanced axonal regeneration after subsequent axotomy. [151] This again has been linked to the increase in neurotrophins following exercise. This study also emphasized the effect that voluntary exercise has on synaptic plasticity subsequently improving neuromuscular functions.[151]

Exercises and peripheral neuroplasticity: Exercise has been shown to be beneficial in not only improving muscle strength in normal muscle, but also in aging and inflamed muscles.[153] Using high-intensity, low-repetitive, strength-type exercise, human skeletal muscle tissue exhibits marked gains in strength that are due both to neuronal adaptations and to an increase in muscle cross-sectional area. [154] A study by Luthi et al studied the effects of resistance training on muscle structure in human subjects.[154] They found an increase in muscle cross sectional area and muscle size. Structural and functional properties of skeletal muscle generally correlate to the level of demand placed on individual muscles.[154] As demand increases, skeletal muscle can adapt via an increase in myofiber size and an alteration in the composition of the metabolic and contractile proteins expressed.[95] Training programs that have employed relatively pure shortening, lengthening, or isometric loading have demonstrated that each of these three modes of loading can stimulate muscle adaptations, including hypertrophy and strength gains.[94,154] It is well established that a prolonged program of resistance training brings about fiber type conversions within the trained muscle.[94,154] These findings are also influenced by repetitive exercise patterns. Most changes were observed after the first 4 weeks of exercise. One of the methods of documenting if these changes are more permanent would be to document changes in gene expression as a result of exercise. These changes would be indicative of a more long-lasting change in muscle structure. Would resistance exercises during the radiation period slow down or nullify delayed injury? If yes, voice therapy could have important implications on not just voice but swallowing rehabilitation as well. A study by Booth and Neufer (2005)[155-157] describes the mechanism of gene expression following exercise. If work demand on a muscle increases even for relatively short periods, the muscle adaptively remodels its protein composition to allow energy to be used more efficiently when the muscle contracts. For skeletal muscles to exhibit plasticity, specific genes in the muscle sense the change in muscle usage and respond by altering the quantities of proteins they produce. Neufer[155] measured gene changes by measuring mRNA concentration, or how quickly a specific gene was transcribed. He investigated whether exercise activated a specific target gene and whether this took place within a specific time period. Three categories of genes were expressed as a result of exercise, mainly endurance training, based on the duration of their activities. These included 1) stress response genes (mainly consisting of heat shock proteins) which were activated during the later phases of endurance training, 2) metabolic priority genes: proteins which are required as a consequence of particular metabolic stress, for example when blood glucose or blood oxygenation levels drop, and 3) mitochondrial enzyme: which is directly responsible for the energy production in a cell.

Though these changes were documented in limb skeletal studies, the concept can be applied to endurance training with intrinsic laryngeal muscles. Changes in muscle composition based on the effect of fictive exercise in normal rat intrinsic laryngeal muscle have been established.[158] It would be of interest to see the changes in gene expression and muscle composition following radiation therapy.

The effect of exercise on vocal fold muscles

From the previous sections it is clear that while ILMs are skeletal muscles, they are highly specialized as compared to limb skeletal muscles. As is apparent from previous studies there is ample evidence to conclude that endurance and resistance exercises improve muscle strength in the limb skeletal muscle. However, in the previous section we also highlighted the differences between limb skeletal and intrinsic laryngeal muscles. It is apparent that intrinsic laryngeal muscles resemble extraocular muscles and are more fatigue-resistant than fast contracting skeletal muscle fibers. However, basic substrates that drive muscle strength such as mitochondrial content, oxidative metabolic capacity and quantity of neuromuscular junctions remain common between both limb skeletal and intrinsic laryngeal musculature. The effects of chronic electrical stimulation on the rat TA muscle were investigated by McMullen et al (2011).[158] The thyroarytenoid muscle was stimulated via nerve cuffs on the recurrent laryngeal nerve for a period of one week for one group and two weeks in the other group. Differences in muscle structure were compared at one-week intervals and two-week intervals. The authors found a decrease in mean thyroarytenoid fiber area, evidence of higher mitochondrial content in the muscle after chronic stimulation, and increase in the number of neuromuscular junctions in muscles that had been stimulated. These findings are similar to those changes seen in other skeletal muscles after endurance training. [159,160] The stimulated thyroarytenoid muscles displayed increased oxidative metabolic capacity which is a sign of adaptive progression in fast-twitch limb skeletal muscle undergoing endurance training. [161] The increase in neuromuscular junctions in stimulated group was also a significant finding. Previous studies have reported an increase in neuromuscular junctions (NMJ) as a sign of activity dependent plasticity.[162] Increased neuromuscular activity can influence NMJ structure, with NMJ remodeling being a common finding after endurance and resistance exercise. An increase in NMJ quantity or density would lead to an increase of the area in contact with the muscle fiber, which would result in more release sites and greater levels of transmitter release. [163] The only finding that did not match findings from other studies was a decrease in fiber size instead of an increase. The authors speculate the reduction in fiber size was possibly due to lack of load applied to the muscle. [164]

From the previous sections it is clear that exercise seems to be important in facilitating activity-dependent plasticity. More importantly, changes after exercise appear to be more long-lasting since they influence gene expression.

Summary

It is clear from outcomes studies after radiation therapy that XRT adversely affects voice production.[12,30,81,165] There are a number of studies which have documented changes in vocal fold structure, objective voice data and also microscopic changes that influence laryngeal tissues.[12,30,81,165] The changes occurring at tissue level appear to be inflammatory, causing muscle weakness and stiffness.[62,129] In addition, changes to the nerve and blood supply have also been documented.[31,129] More concerning, ongoing changes are noted at the level of gene transcription even after completion of radiation therapy.[31] The paucity of research on the treatment of these long-standing voice problems is concerning as well. The present review attempted to decide whether there is a rehabilitation method that would best treat voice disorders in this population. From reviewing rehabilitation research across other disciplines like physical and occupational therapy, exercise emerges as a common theme for neuromuscular rehabilitation. Though the effect of exercise has been studied in limb skeletal muscle more extensively, the basic mechanism of inflammation and exercise-based changes are similar to those seen in vocal folds after exposure to radiation. Considering the changes seen in the muscular and vascular damage in intrinsic laryngeal muscles as a part of radiation injury, exercising seems to be the choice of treatment to regain structural integrity. Studies state that exercise not only reduces inflammation but also promotes angiogenesis.[146,150,152,161] These changes seem to occur in the presence of resistance and endurance training.[146,150,152,161] When exercise was simulated in the rat intrinsic laryngeal muscles, changes seen were similar to those reported in limb skeletal muscles after endurance exercise, which is indicative of common strengthening patterns seen in ILMs after exercise.[163] These changes were reflected in an increase in mitochondrial content as well as an increase in neuromuscular junctions.[163] The increase in neuromuscular junctions is an indicator of activity-dependent plasticity as a result of exercise. Though these changes have never been studied in the larynx areas in the cortex, based on limb exercise research and amputation and deafferentation studies, cortical changes secondary to laryngeal muscle exercise is a feasible possibility. This could also be indicative of permanent changes occurring as a result of gene expression due to exercise. [156,157,163]

While evidence on exercise and neuroplastic changes is still speculative and needs to be investigated further, the need for more concrete, exercise-based voice rehabilitation is apparent from voice therapy outcomes studies. The Vocal Function Exercise program is a prescriptive exercise program and is presently the most researched therapy program compared to other voice therapy interventions. However, we fully acknowledge that the choice of therapy methods across these studies is subjective, and we need more extensive and well-planned studies for voice therapy outcomes. The decision for a therapy plan for the irradiated laryngeal cancer population can only be made once the effects of various voice therapy methods are studied in greater detail. Until now, there have four studies that reported the positive effects of voice therapy in this population, but the intervention methods have not been specified.[13-16]

The gap in research between disorder and treatment in this population is glaring. Based on the findings of this review, it appears as though a starting point for voice rehabilitation in this population is exercise that aims to strengthen the sub-systems of voice production. The VFE program is the only program presently that aims to strengthen and rebalance the laryngeal musculature through a series of resistance and endurance exercises. The first step to voice rehabilitation would logically be to set a strong neuromuscular foundation and in addition retrain the irradiated laryngeal system by implementing VFEs to gain strength and balance of the laryngeal mechanism.

The next chapter includes a detailed description of the first stage of the investigation targeted towards the completion of this dissertation study. This stage focused on characterizing the head and neck cancer population at a single center, the University of Kentucky Medical Center. Rehabilitation following laryngeal cancers is especially relevant to the population in Kentucky largely because of the high incidence rates of laryngeal cancers, and HNCs in general in the state. This study stage helped identify individuals who were irradiated for laryngeal cancers for later stages of the dissertation.

CHAPTER 3: STUDY I

Study title: Addressing the head and neck cancer burden in Appalachian Kentucky: A single center experience

Chapter 3 describes stage I of the dissertation study in detail. This stage of the study helped in identifying patients irradiated for laryngeal cancers at the University of Kentucky. However, in addition to laryngeal cancers, an increased incidence of head and neck cancers (HNC) has been reported in the state of Kentucky since 2007. In fact, at 13.5% Kentucky has the highest incidence of head and neck cancers in the United States. [24,37] As described in previous sections, laryngeal cancers are a sub-group of head and neck cancers (HNCs). Therefore, instead of limiting our investigation to laryngeal cancers only, we characterized the distribution trends of all HNCs seen at the University of Kentucky to highlight the HNC burden in Appalachian Kentucky. The present section includes the background, specific aims, methodology, results and discussion directly related to study 1.

Background

Appalachian regions across the United States include 420 counties in 13 states [166] and are known to be regions associated with significant health disparities. [166,167] Health disparities between Appalachian and non- Appalachian counties have chiefly been attributed to the geographic isolation of most Appalachian counties, low socioeconomic status, low levels of education and literacy, and limited access to healthcare.[166] These health disparities result in higher rates of heart disease, stroke,[168] chronic conditions and cancer in Appalachian vs. non-Appalachian regions. [166,169,170] The growing incidence of cancer in Appalachia has been of great concern with cancer incidence and mortality rates being much higher as compared to non-Appalachian regions.[170] Increased incidence and mortality of cancer holds true for the

Appalachian counties within the state of Kentucky as well,[24] in fact, to an even much graver degree .[167]

Studies have shown that the 54 Appalachian counties of Kentucky have socioeconomic status factors which are the poorest among all Appalachian regions of the United States .[171] Limited finances and limited access to medical facilities has resulted in the medical needs of this population remaining largely underserved .[166,167,172,173] With limited access to healthcare, it is not surprising that Appalachian regions of Kentucky show a higher incidence of lung, colorectal, cervical and head and neck cancers as compared to non- Appalachian regions.[169] Associations such as Appalachia Community Cancer Network (ACCN) and Appalachian Regional Health (ARH) are attempting to address this growing incidence of cancers in Appalachian Kentucky through education and early detection programs.[174] The Appalachia Community Cancer Network (ACCN) comprises a multidisciplinary team of collaborators from academic institutions and communities in Kentucky, West Virginia, Ohio, Pennsylvania, New York, Maryland, and Virginia. The ACCN, located at the University of Kentucky's Markey Cancer Center, addresses cancer health disparities in the Appalachian areas within these seven states, which are home to some of the most medically underserved and economically disadvantaged people in the United States.[174]

While the ACCN has made significant efforts in Eastern Kentucky to address the cancer burden related to colorectal, lung, breast and cervical cancers ;[167,175,176] the head and neck cancers have not been addressed. The incidence rates for head and neck cancer statistics for Kentucky in general have not been favorable.[177] According to recent data reported by the Kentucky Cancer Registry (2007-2011), at 13.5 percent, Kentucky has one of the highest reported incidence of head and neck cancers (HNC) in the United States. [24,177] This is a matter of great concern since Kentucky is one of the few states where incidence rates of HNC have increased in the past few years. [25] The rising incidence in HNC can be attributed to a high prevalence of smoking in the state at 28%, which is also the highest smoking prevalence rate in the country. [29]

When detected early, HNC are highly treatable and have significantly better five-year survival rates and low rates of treatment related morbidity.[178,179] Improved treatment morbidity is due to the single modality treatment that is required to combat early cancers.[175] Treatment for advanced stages of HNC results in significant morbidity including severe detrimental effects on speech and swallowing. [39] Multiple interventions including surgery, radiation therapy, chemotherapy, other surgeries and subsequent rehabilitation as a result of these treatments contribute to severe detrimental effects on quality of life and consequently increases treatment costs.[175] These costs are related to the required multimodality treatments and multiple professionals involved in direct patient care. For patients who are financially compromised in regions such as Appalachian Kentucky, treatment costs only add to the disease burden.

When assessed in totality, the multiple referenced hurdles to medical care (high prevalence of smoking, geographical isolation, low socioeconomic status, low literacy, lack of awareness of health risks related to lifestyle) contribute to challenges in addressing and managing the HNC burden in Appalachian Kentucky. Therefore an effort needs to be made to identify and address the medical needs for HNCs in Kentucky, especially Appalachian Kentucky in order to plan educational, screening and prevention programs. To effectively plan such programs, it is important to first characterize the HNC population in the targeted region. The present study characterizes the HNC population at the University of Kentucky (UK) otolaryngology clinic and HNC clinic at the Markey Cancer Center. The University of Kentucky otolaryngology clinic and HNC clinic are considered tertiary care centers for cancer management. The HNC clinic is located in the Markey Cancer Center (MCC). The Markey Cancer Center is also Kentucky's only National Cancer Institute (NCI) designated center. The Markey Cancer Center at the University of Kentucky is located in central Kentucky and serves a large number of patients around

Kentucky (both central and eastern) as well as some surrounding states .[176] We believe that the sample collected through the present study is a close representation of trends seen across the state.

The objective of the present study was to characterize the head and neck cancer population at the University of Kentucky over a 3-year period. Factors under study included trends in basic demographics, site of lesion, staging information, treatment types and tobacco use. Through this study we aimed to highlight the differences in trends between the Appalachian and non-Appalachian regions of Kentucky. Characterizing the HNC cancer population and highlighting differing trends between the two regions within Kentucky helps healthcare professionals identify high risk regions. Once identified, these high risk regions can be targeted for outreach, screening, education and health programs that promote increased awareness, early identification, and prevention of head and neck cancers.

Specific aims

Specific aim1: To characterize the distribution of head and neck cancers in the treatment seeking population at a University of Kentucky Markey Cancer Center in terms of site, stage, treatment trends, tobacco use and basic demographics in patients who sought treatment from January 2008 to December 2010.

Specific aim 2: To compare the distribution of head and neck cancers across Appalachian and non-Appalachian counties. *Given the higher rate of tobacco use in Appalachian in comparison to non-Appalachian counties,[169] we hypothesize that a larger number of patients identified at UK will belong to Appalachian counties.*

Specific aim 3: To compare stage of cancer at the time of detection across Appalachian and non-Appalachian counties. *Considering the limited access to medical facilities faced by the Appalachian population ,[167,171,180] we hypothesize that the Appalachian population will have more advanced stage cancers at the time of their first visit.*

Methods

Following approval from the Institutional Review Board (IRB) at the University of Kentucky, data for the present study were obtained from the Kentucky Cancer Registry (KCR). KCR is part of the Surveillance, Epidemiology, and End Results (SEER) program, which is considered to be among the most accurate and complete population-based cancer registry programs in the world.[179] Using the SEER site ICD-O-3 definitions, [181] cancers included in the final analysis included cancers of the lip (C00.0-C00.9), tongue (C01.9-C02.9), salivary glands (C07.9-C08.9) , floor of mouth (C04.0-C04.9), gum and other mouth (C03.0-C03.9, C05.0-C05.9, C06.0-C06.9), nasopharynx (C11.0-C11.9), tonsil (C090-C099), oropharynx (C100-C109), other oral cavity and pharynx (C14.0, C14.2-C14.8), larynx (C32.0-C32.9) and esophagus (C15.0-C15.9). Since this was a single site study, only data from patients seen at UK were included. Data were collected for patients diagnosed from January 1, 2008 to December 31, 2010. The following data were included in the final analysis; age at time of diagnosis, sex, county at diagnosis, site of lesion, AJCC stage at the time of diagnosis (American Joint Committee on Cancer -Sixth edition),[182] type of treatment administered and tobacco use. Since the entire treatment seeking population in the three year period was included, there were no exclusions made based on age or number of primaries. One of the main objectives of this study was to investigate the differences in the above mentioned data between non-Appalachian and Appalachian counties for all included counties. Appalachian and non- Appalachian counties were determined according to the Appalachian Regional Commission classification.

Statistical analysis

Statistical analyses were completed using SPSS Ver.21. Main analyses included frequencies of the factors under study (i.e. age, sex, county, site of lesion, county- wise distribution, stage at the time of diagnosis, type of treatment administered and tobacco use). Using a Fisher's exact test, comparisons were made between non- Appalachian and Appalachian counties for the following factors: stage at the time of diagnosis, type of treatment administered and tobacco use. All tests are two sided with a 0.05 significance level.

Results

Basic demographics: A total of 476 patients were diagnosed with head and neck cancers at the University of Kentucky between January 1, 2008 and December 31, 2010. HNC were more prevalent in males as compared to females (3:1). The mean age of diagnosis was 58.61 years (SD=10.9) for males and 59.1 years (SD=13.1) for females. The most common type of HNC was squamous cell carcinoma which is similar to trends nationally and worldwide. The most common site of lesion was laryngeal cancers which made up 28% of the total sample (Table 3.1). In terms of tobacco use, 72% of the total sample was tobacco users (Table 3.2). Tobacco use included cigarette smoking and smokeless tobacco. When comparing treatments, a majority of patients (27%) received primary chemoradiation therapy (Table 3.3).

Appalachian versus non-Appalachian comparisons: Comparisons were made with respect to total number of people diagnosed, stage at the time of diagnosis, treatment type and tobacco use between the Appalachian and non-Appalachian population. A total of 45 Appalachian counties and 22 non- Appalachian counties were included in the final analyses. Appalachian and non-Appalachian counties were determined based on the Appalachian Regional Commission (ARC) classification.[183]

The number of people diagnosed between January 1st 2008 and December 31st 2010 was higher in Appalachian counties (n=278) as compared to non- Appalachian counties (n=198). There were a higher number of patients diagnosed with advanced stage disease (Stage III-IV) in Appalachian counties (n=160) as compared to non- Appalachian counties (n=135). However, when compared to the total population under study, the percentage of patients diagnosed with advanced disease was higher in non-Appalachian regions as compared to Appalachian regions. A

Fisher's exact test was performed to analyze if there was a difference in the number of people diagnosed with late stage HNC in Appalachia as compared to non- Appalachian regions. Results showed that there was a significant difference between the Appalachian and non- Appalachian population (Table 3.5). The number of people who received multi-modality treatments was larger in Appalachian Kentucky as compared to non- Appalachian Kentucky; however these numbers were not statistically significant (Table 3.6). Tobacco use was comparable in Appalachian and non- Appalachian counties (72%) (Table 3.2).

Discussion

The present study was a single center hospital based study with the objective of characterizing the head and neck cancer population at the University of Kentucky over a 3-year period. Data from the present study serves as preliminary data to investigate differences seen in Appalachian and non- Appalachian Kentucky, at a single tertiary care center in urban Kentucky. We propose to perform a larger study which includes state-wide data to further highlight the HNC burden in Appalachian Kentucky.

According to the recent population census, non- Appalachian Kentucky is roughly three times more populated then Appalachian Kentucky [184] Despite this difference in population, the present study showed a higher number of patients with HNC in Appalachian Kentucky compared to non- Appalachian Kentucky. An important risk factor for HNC, smoking rates were comparable between Appalachian and non- Appalachian counties. However, an important factor that was not assessed was alcohol consumption in combination with smoking. Alcohol consumption in addition to smoking increases the risk for HNC by tenfold .[27,28] This is a limitation which needs to be addressed for future studies. In terms of total numbers, Appalachian Kentucky also showed a higher number of patients diagnosed with advanced stage disease as compared to non- Appalachian Kentucky. However, when compared to the total population under study, for Appalachian and non- Appalachian regions included in the present study, non-

Appalachian regions showed a higher percentage of patients diagnosed with advanced stage disease. This is possibly because majority of patients diagnosed with HNC belong to Fayette county; an urban county, which is also where UK is located. This is a limitation since data from the entire state of Kentucky were not included. Despite this limitation, higher numbers of patients from Appalachia were seen at an urban tertiary care center in Kentucky (University of Kentucky) as compared to patients from non- Appalachian regions. These numbers continue to highlight the elevated HNC burden in Appalachia. The elevated number of patients diagnosed with HNC and the advanced disease stage add to the cost burden of the disease in an already financially compromised population.

The unique health issues faced by the Appalachian population in Kentucky have long been a topic of discussion. Appalachian Kentucky's 'All Cancer Rate' is 17% higher than that of the national rate. [185] The National Cancer Institute (NCI) has recognized Appalachians as a population with severe cancer disparities.[180] Some of the issues that have been identified to contribute to these health disparities include lower levels of literacy and low socioeconomic status. [186] A study by Elnicki et al. listed lack of knowledge about prevention (51%) and cost (36%) as the top two patient perceived barriers to seeking healthcare in Appalachia .[172] The geographic isolation of Appalachia further compounds the issue of ease of access to standard healthcare. The problem of access to health care services is magnified in rural areas that are remote and exist well outside urban boundaries where transportation is limited .[172,186]

To complicate matters further, problems related to health disparities in Appalachia are not limited to socioeconomic, geographic or environmental factors. Unfortunately problems related to health disparities in Appalachia are deeply rooted in the Appalachian culture and the attitudes towards seeking healthcare in general. Perceptions of the Appalachian population towards cancer have been the topic of various studies as well. [166,171,186] People in Appalachia believe that contracting cancer is inevitable, thus ignoring the role of prevention. [187] Most Appalachians have a fear of doctors and do not seek medical help when require. [187] Since most

Appalachians are economically challenged, missing work to seek medical help is not an option. [187]

For the past few years, several screening programs have been implemented for colorectal, cervical, breast, ovarian and prostate cancers. One example of a successful screening program for Kentucky is the colorectal cancer screening program. Ten years ago, Kentucky had the second lowest screening rate in the country and had one of the highest incidences of CRC in the country. [188] However, with joined efforts from Colon Cancer Prevention Project, American Cancer Society, the Kentucky Department for Public Health, the Kentucky Cancer Program, the Kentucky Cancer Registry and a few other organizations within the Kentucky cancer consortium, the incidence rate for colorectal cancer has reduced by 25 percent and the death rate has reduced by 28 percent .[188] From barriers listed above which include economic, environmental, geographical barriers and a negative attitude towards seeking healthcare; it is apparent that outreach is the need of the hour. Consequently, outreach programs need to focus on education and prevention, early identification and screening. Screening programs also must be affordable. HNC screening, protocols and instrumentation are relatively affordable especially when compared to those required for colorectal, prostate, breast, cervical or ovarian cancers .[179] Ideally, screening, educational and prevention programs can be propagated by healthcare professionals known to the community, such as primary healthcare providers (PCP). To this end, PCPs need to be educated and trained on HNC screening procedures, knowledge on prevention of HNC and the importance of early detection and intervention. Subsequently, educational programs for HNC screening, prevention and early detection and intervention can be expanded to community health workers such as nurses, dental hygienists and community aid workers. The idea is to provide easy access to patients closer to their homes where they do not need to arrange finances for transportation. Reaching out to patients through means within the community would certainly help in overcoming barriers of geographical isolation. A low cost screening program also reduces the financial burden of a physician's visit. We recognize that issues related to increasing HNC incidence in Appalachian Kentucky extend beyond the low socioeconomic status of Appalachian Kentucky and the lack of access to healthcare. A general change in attitude towards seeking healthcare in the Appalachian population is just as vital. Implementation of screening, educational and prevention programs would only be the first of many steps towards tackling a serious problem faced by the people of Appalachian Kentucky, one that should no longer be ignored.

The next chapter will provide the reader with a detailed description of stage 2 of the present dissertation study. Individuals irradiated for laryngeal cancers identified from stage 1 were recruited for stage 2 of the study. Stage 2 involved characterizing vocal function in individuals irradiated for laryngeal cancers.

CHAPTER 4: STUDY 2

Study title: A study of vocal function using a multi-dimensional assessment battery in adults irradiated for laryngeal cancer

Chapter 4 describes Stage II of the dissertation study in detail. As described in previous chapters, vocal function is best assessed using a multidimensional assessment battery which encompasses physiological and psychosocial factors of voice production. The objective of the present study was to characterize vocal function in adults irradiated for laryngeal cancers using the five domains of voice assessment. The present irradiated study population was also matched in age, sex and pack years of smoking to a control group of adults without history of irradiation for head and neck cancers. The next few sections inform the reader on background, study methodology and results of the present study. This chapter also includes a detailed discussion of the study findings.

Background

Primary radiation therapy (XRT), with or without chemotherapy, has proven to be an effective curative modality in the treatment of both early and advanced laryngeal cancers. Early laryngeal cancers are often treated with radiation therapy alone,[1,189] while advanced laryngeal cancers are treated with a combination of radiation therapy and chemotherapy.[32] Since the 1990s, an increasing number of patients are being treated with primary radiation therapy, with or without chemotherapy.[31] The intent of treating laryngeal cancers in this manner is to preserve laryngeal structure and function while eliminating disease.[31] However, a number of post-treatment studies have demonstrated poor voice and swallowing outcomes as a result of radiation toxicity. Voice and swallowing dysfunction following radiation are indicators that preservation of laryngeal structure is not necessarily translating into preservation of laryngeal function for these patients.

These voice and swallowing changes are known to persist over long periods of time and in some cases are permanent.

A number of studies have documented the effects of radiation on vocal function.[1,9,30,32] However, these studies have often used limited outcome measures which do not capture the multidimensional nature of vocal function. Normal voice production is dependent upon the physiological and psychosocial aspects of voice use. Physiologically, normal voice production requires an interaction among the three subsystems of voice production: respiration, phonation and resonance. Psychosocial factors reflect the individual's voice use with respect to activities of daily living. To incorporate these physiological and psychosocial domains to provide a holistic description of an individual's vocal function, voice production should ideally be assessed using a multidimensional assessment battery.[33] Hirano[190] stated, "Voice is multidimensional in nature, so we need a set of tests to evaluate function in its entirety." This sentiment was reiterated by Titze et.al.,who stated, "Diagnostic hypotheses should not be made on basis of one test or measure because one cannot look at an isolated phenomenon without running the risk of misinterpreting the results". [191,192] Multidimensional assessment of voice helps overcome the limitations of any one assessment type. [191]

Select assessment parameters within these domains have been recommended by researchers in the field of voice disorders based on their reliability and validity measures. The measures recommended through research were used in the present study. The five domains of voice assessment include stroboscopic (laryngeal visualization), acoustic, aerodynamic, patient self-report and auditory-perceptual parameters.[33] Study parameters within the five domains of voice assessment are presented in Table 4.1. The next section informs the reader on clinical findings in select parameters of voice assessment following XRT. The findings are divided according to the parameters within each of the five domains of voice assessment.

Auditory-Perceptual findings: Auditory perceptual findings from previous studies report varied vocal symptoms. These studies used an informal scale for perceptual assessment and not a standardized scale such as the GRBAS or CAPE-V.[51,53] Perceptually patients often present with hoarseness, decreased volume, increased strain and persistent voice changes.[8,13,81]

Voice related quality of life: A recent study by Karlsson, et al. (2016) [17] that investigated voice-related quality of life measures in patients with early and advanced laryngeal cancers revealed no significant differences between pre-radiation and post-radiation scores one year after completion of treatment. These results indicate that the deterioration in voice quality perceived by the patient as a result of laryngeal cancer did not improve after completion of treatment to eliminate laryngeal cancer.[17] A study that investigated voice problems as a result of radiation for early glottic cancers demonstrated that 87.8% of the patient sample reported their voice as being abnormal, ranging from slight to moderate dysfunction.[82]

Acoustic measures: The majority of studies showed that radiation therapy had a negative impact on voice quality, as revealed by increased perturbation and noise measures. Voice quality was gradually found to improve over 3-6 months post-radiotherapy. However, none of the post-treatment perturbation values fell within the normal range. [78-80]

Aerodynamic measures: McGuirt et al. (1994)[12] revealed mean laryngeal airway resistance (LAR) values 4.5 times greater than normal values (mean=177cmH2O/L/s) in patients who had been irradiated for T1a glottic cancer. These LAR values are comparable to those in a study by Aref (1997)[30] who found that none of 12 patients attained normal aerodynamic measures. Increased airflow rates in patients who had undergone radiotherapy (n=6) were also observed in a study by Tamura (2003)[79] in which mean airflow rates of 165 cc/s were measured. Increased aerodynamic resistance values reflect the signs of supraglottic hyperfunction seen stroboscopically and are also indicative of issues with reduced glottal valving.

Laryngeal imaging (Stroboscopic findings)**:** In a detailed study performed by Lehman et al (1988),[77] significant abnormalities were seen on stroboscopic analysis in patients irradiated for stage I glottic cancers. Around 60% of patients showed irregular vocal fold closure, 65% increased supraglottic activity, 85% irregular vibratory margins, 80% shorter closure phase and 85% irregular phase symmetry. The stroboscopic finding consistent across the group was decreased vibratory amplitude not only on the treated vocal fold but also on the non-diseased fold. These findings were consistent with those in a study by McGuirt et al. (1994)[12] that reported decreased mucosal wave on both the treated and non-diseased fold. In addition, subjects showed signs of muscle tension dysphonia, ventricular phonation, and partial antero-posterior compression.

From the study findings described in the previous section, it is clear that multiple domains of vocal function are affected as a result of radiation toxicity to the laryngeal mechanism. To this end, in the present study we characterized vocal function after radiation therapy for laryngeal cancers as assessed holistically by all five domains of voice assessment.

The next section describes aims specific to stage II of the dissertation.

Specific aims

Specific aim 1**:** To characterize vocal function in subjects who have been treated with radiation therapy for laryngeal cancers as determined by stroboscopic imaging; high-speed digital laryngeal imaging; acoustic, aerodynamic, and perceptual analyses; and patient self-report measures. *Previous studies have reported post-radiation therapy deterioration of select parameters within the five domains of voice assessment. None have included all five domains in the same study. We hypothesize that the present study results will follow similar trends.*[1,12,30,77,193]

Specific aim 2**:** To compare vocal function in individuals who have been treated with radiation therapy with age, sex and pack-years matched controls as determined by stroboscopic imaging, high-speed laryngeal imaging, acoustic, aerodynamic, perceptual and patient self-report measures. *Previous studies have reported deterioration in vocal function after radiation therapy.*[1,12,30,77,193] *However, additional factors such as tobacco smoking and age-related changes have been known to affect vocal function adversely as well.*[194,195] *To account for these factors, we matched subjects in the control group based on age, sex and tobacco use. We hypothesize that the present study will show clinically worse values of vocal function in the irradiated group as compared to the control group.*

Methods

Participants for Stage II were recruited from the multidisciplinary head and neck cancer clinic at the Markey Cancer Center (University of Kentucky) following approval from the Institutional Review Board (IRB) at the University of Kentucky (UK). A sample size of 20, with 10 participants in each group was required to achieve 80% power to detect a difference of 12 points in VHI between healthy and irradiated individuals at a significance level of 0.05.[16,196] Stage II was designed as a cohort study.

Participants

After completion of informed consent, 18 participants were included in the study based on inclusion and exclusion criteria. Participants in the radiation therapy group met the following inclusion criteria: adults over 18 years of age, previously irradiated for laryngeal cancer (with or without chemotherapy), hearing levels appropriate to follow directions, and deemed cancer-free at the time of study recruitment. Participants had to have completed XRT at least 6 months prior to study participation. Presence of vocal fold paralysis or surface vocal fold pathology at the time of study recruitment constituted exclusion from the study. Participants in the control group met the following inclusion criteria: adults over 18 years of age, former/current/non-smokers, hearing levels appropriate to follow directions and no history of head and neck cancer. Presence of surface vocal fold pathology, vocal fold paralysis or neurological disorder constituted exclusion from the study. Participants in the control group were recruited based on age, sex and pack years of smoking parameters as compared to the radiation group.

Assessment battery

Participants in both groups underwent the same multidimensional vocal assessment battery. The battery included assessment protocols belonging to the five domains of voice assessment. A checklist for the assessment battery is available in Appendix I. The five common domains of voice assessment are: auditory-perceptual measures, patient self assessment, acoustic analyses, aerodynamic analyses, and laryngeal imaging or visual perceptual assessments. Outcome measures and their normative values are available in Table 4.1. Outcome measures are listed below with reference to each domain of voice assessment.

1) *Auditory- Perceptual assessment*: Consensus Auditory Perceptual Evaluation of Voice (CAPE-V- Appendix II) was utilized. Blinding: Audio samples of patient's voices reading the rainbow passage (Appendix III) were presented to a licensed and certified speech-language pathologist with over 40 years of clinical experience in the field of voice disorders. The assessor was blinded to group assignments.
2) *Patient self-assessment*: Voice Handicap Index (Appendix IV) was utilized. Total scores and domain specific scores (Physical, Functional, Emotional) were included for final analysis.
3) *Acoustic analyses*: The Multidimensional Voice Profile (MDVP) and Analysis of Dysphonia in Speech and Voice (ADSV) were utilized. Specific measures included jitter, shimmer, noise to harmonics ratio (NHR), maximum phonation time (MPT) and pitch range for MDVP; and Cepstral Spectral Index of Dysphonia (CSID) for ADSV stimuli.[197] CSID included sustained

vowel and sentence stimuli. Sentences included easy onset, voiceless plosive, all voiced and hard glottal attacks.

4) *Laryngeal imaging/visual perceptual assessment*: Measures included were laryngeal stroboscopy and high speed laryngeal imaging. Stroboscopic and high speed features were rated on a scale (Appendix V). Stroboscopic and high speed parameters include glottic closure, mucosal wave, amplitude of vibration and phase symmetry. Ratings were performed by a licensed and certified speech-language pathologist with over 40 years of clinical experience in the field of voice disorders. The speech-language pathologist was blinded to group assignments.

Instrumentation

1) Laryngeal stroboscopy: Laryngeal stroboscopy was performed using the Kay Elemetrics Rhino-Laryngeal Stroboscope – (Model RLS 9100 B, Halogen lamp: 150 watts, Xenon lamp: 120 watts, frequency range: 60 Hz – 1000 Hz, laryngeal microphone), a Kay Elemetrics 70 degree 22 rigid scope (Model 9106, total length: 252 mm), Kay distal endoscope, and a C-mount camera (Panasonic 3CCHD).

2) High speed digital imaging: For the HSDI recordings, a KayPentax high-speed system model 9710 was used. Images were recorded at 4000 frames/s for a maximum duration of 4 seconds with a spatial resolution of 5123256 pixels. A 300W Xenon light source was used

3) Acoustic analysis: For acoustic assessment, the Computerized Speech Lab Model 4500 by KayPentax was used with a hand-held microphone (mouth-to-microphone distance = 3 inches) [System Requirements: Analog Inputs: 4 channels: two XLR and two phono-type, 5mV to 10.5V peak-to-peak, adjustable gain range >38dB, 24-bit A/D, Sampling Rates: 8,000-200,000Hz, THD+N: <-90dB F.S. Frequency Response (AC coupled): 20-22kHz +.05dB at 44.1kHz. Digital Interface: AES/EBU or S/P DIF format, transformer-coupled. Software Interface: ASIO and MME. Computer Interface: PCI (version 2.2-compliant), PCI card; 5.0" H x 7.4" W x 0.75" D (half-sized PCI card). Analog Output: 4 channels, line and speaker, headphone output, channels 1

& 2 provide line & speaker outputs. Physical: 4" W x 8.25" H x 12.5" D, 4 lbs. 12 oz., 45 watts, speaker, and microphone (Shure SM-48 or equivalent, XLR-type)].

4) Aerodynamic analysis: The Phonatory Aerodynamic System Model 6600 by KayPentax was used for the aerodynamic measurements (300 ml pneumotachograph - System requirements same as CSL model 4500). Airflow measures were taken using an airflow mask and a pneumotachograph, which uses the principle of differential pressure across a known resistance to estimate airflow rate.

Statistical analysis

Statistical analyses were performed using SPSS ver.22. Statistical analyses included descriptive statistics, frequencies and comparisons between the radiation therapy (RT) and control groups. Comparisons for continuous variables between the two groups were performed using independent sample t-tests and Mann-Whitney U-tests depending on normality of distribution. Continuous variables included CAPE-V measures, VHI scores, acoustic measures (jitter, shimmer, Noise to Harmonic Ratio, Maximum Phonation Time, pitch range and CSID measures). Comparisons for non-continuous variables between the two groups were performed using a Fisher's exact test. Non- continuous variables included stroboscopic and high speed parameters. Significance levels were set at 0.05.

Results

Descriptive statistics: A total of 18 participants were recruited for the study (RT=10, control=8). The RT group consisted of seven males and three females, and the control group consisted of six males and two females. The mean age of participants in the RT group was 66.1 years (standard deviation:12.96) and the mean age of participants in the control group was 55.5 years (standard deviation: 13.8). In terms of smoking status, the RT group consisted of six former smokers, two current smokers, and two non-smokers. Nine participants in the RT group had a history T1 glottic cancer and one participant had a history of T2 supraglottic cancer. The control group consisted of three former smokers, four current smokers and one non-smoker. In terms of smoking habits, the mean pack years in the RT group was 37.9 years (standard deviation: 38.91) and control group was 41.38 years (standard deviation= 26.62). For the RT group, time from completion of radiation therapy ranged from 24 – 84 months. Descriptive statistics for participant demographics are available in Table 4.2.

Prior to comparisons of vocal function parameters, the two groups under study were compared for age, sex and pack years of smoking. The two groups were closely matched in sex distribution. Results from independent sample t-tests showed no significant differences between the two groups in terms of age (p= 0.118) or pack years of smoking (p= 0.825).

Results from continuous variables: The two groups differed significantly for; CAPE- V parameters of overall severity (p=0.11) (Table 4.4), loudness (p=0.012) (Table 4.5), breathiness (p=0.001) (Table 4.4), roughness (0.008) (Table 4.4) and strain (p=0.007) (Table 4.5), Voice Handicap Index-Physical domain (p= 0.036) (Table 4.7), pitch range (p= 0.045) (Table 4.10) and mean peak air pressure/PSub (p= 0.01) (Table 4.13) .

Overall abnormal clinical values were seen in the RT group as observed in their mean scores for CAPE-V overall severity (29.4) (Table 4.3), CAPE-V loudness (29.9, SD: 13.74) (Table 4.3), CAPE-V breathiness (32, SD: 12.4) (Table 4.3), CAPE-V roughness (31.7, SD:15.48) (Table 4.3) and CAPE-V strain (36.1, SD: 12.7) (Table 4.3); overall VHI scores (22.6, SD: 13.5) (Table 4.6); jitter percentage (2.14) (Table 4.9), shimmer dB (0.68) (Table 4.9), noise to harmonics ratio (0.209) (Table 4.9), CSID /a/ (23.79) (Table 4.9), CSID for easy onset stimulus (18.62) (Table 4.9), CSID for voiceless plosive stimulus (19.43) (Table 4.9), CSID for hard glottal attack stimulus (19.59) (Table 4.9); Psub (9.08, SD: 2.41) (Table 4.12), laryngeal airway resistance (74.69, SD: 84.6) (Table 4.12) and phonation threshold pressure (5.9, SD:3.25) (Table

4.12). Means and standard deviations for all continuous variables under study are available in Tables 4.3 to 4.12.

Results from non-continuous variables: Clinically abnormal findings were seen across majority of stroboscopic and high speed parameters under study for both groups. High speed laryngeal imaging could not be performed on two participants from the RT group and one participant from the control group due to participant difficulty tolerating the presence of a rigid endoscope. However, the RT group showed a higher percentage of participants with abnormal stroboscopic and high-speed parameters. Percentage of participants who demonstrated abnormal stroboscopic and high-speed parameters is displayed in tables 4.15 and 4.17 respectively. The control group showed a higher percentage of abnormal findings only for the parameters of phase symmetry (Table 4.15). However, the two groups under study only showed a statistical significant difference for amplitude of vibration for stroboscopic examination (p=0.009) (Table 4.16). No significant differences were observed between the two groups for any of the high speed parameters (Table 4.18).

Discussion

Previous studies have demonstrated that radiation therapy negatively affects voice quality;[9,30,77,81] however these studies have examined limited voice outcome measures. As a result it is difficult to characterize vocal function issues following radiation therapy in a comprehensive manner. The present study confirmed findings from previous studies since it demonstrated that patients exhibited abnormal vocal function across various voice parameters following radiation therapy. Interestingly, participants in the radiation group were 24-84 months post-completion of radiation therapy and continued to exhibit clinically abnormal values in voice parameters, further highlighting the long-term and in some cases permanent deleterious effects of radiation toxicity on voice quality. However, the aim of the present study was to characterize vocal function beyond simply one parameter by examining the five domains of voice assessment. Participants in the RT group were also compared to participants who were matched in terms of sex, age and smoking habits to account for changes to the vocal mechanism that take place as a result of these factors. The results from the present study are discussed in detail in the next section with reference to each of the domains of voice assessment.

Domain I- Auditory perceptual measures (Tables: 4.3,4.4,4.5)

The present study compared CAPE-V scores between the two groups under study. The assessor for CAPE-V is a licensed and certified speech-language pathologist with over 40 years of experience in the field of voice disorders. The assessor was blinded to group assignments. CAPE-V scores in the radiation therapy group were consistently worse as compared to the control across all CAPE-V parameters except for pitch (overall severity, loudness, breathiness, roughness and strain). For parameters of overall severity, roughness and strain, CAPE-V scores were in the clinically abnormal range for both groups, but were higher in the RT group, which is indicative of a greater degree of dysphonia. The control group showed mild dysphonia across overall severity, roughness and strain, and the RT group showed moderate dysphonia across the same parameters. Similar findings were reported in studies by Bergstorm, et.al, Hocevar, et.al and Sjoren, et.al.[8,13,81] Scores for loudness and breathiness were within normal limits for the control group, whereas the RT group showed scores that demonstrated moderate levels of dysphonia. Statistically, the groups differed across all parameters except for pitch. These findings demonstrate that the voice quality of participants who had been irradiated sounded distinctly abnormal and moderately dysphonic to an experienced listener as compared to a control group of participants who were matched in age, sex and pack years of smoking.

Domain II- Patient self assessment (Tables: 4.6,4.7,4.8)

The present study compared Voice Handicap Index scores between the two groups under study. Participants in the RT group had higher total scores (mean: 22.6, SD: 13.5) as compared to the control group (mean:11.63, SD: 12.68) indicative of a greater level of voice handicap. However, in the RT group, these scores were in the clinically abnormal range only for the physical domain of voice handicap (mean: 13.3, SD: 9.4).[47] Each of the domain scores for participants in the control group was within clinically normal limits. The physical domain of the voice handicap index represents self-perceptions of laryngeal discomfort and voice output characteristics.[47] Findings of reduced scores on voice-related quality of life were consistent with findings on studies by Karlsson, et.al and Cohen, et.al.[17,193] These results indicate that individuals continue to experience challenges related to voice use following radiation therapy. Participants in the RT group consistently rated high levels of impairment on the following statements:

1) I feel as though as I have to strain to produce voice

2) I use a great deal of effort to speak

3) My voice sounds creaky and dry

4) The sound of my voice varies throughout the day

5) The clarity of my voice is unpredictable

6) My voice gets worse in the evening

These findings are reflected in the CAPE-V scores, as voices of participants in the RT group were described as having increased roughness, increased breathiness and increased strain.

Domain III- Acoustic analysis (Table 4.9,4.10,4.11)

Comparisons were made between two groups for measures of jitter, shimmer, noise to harmonics ratio, pitch range, maximum phonation time and CSID measures. The RT group demonstrated clinically abnormal values on sustained vowel /a/ for measures of jitter (mean: 2.14, SD: 2.61), shimmer (mean: 0.68, SD: 87) and Noise to Harmonic Ratio (Mean: 0.209, SD: 0.21). These values were within clinically normal limits for the control group. For connected speech and sustained phonation when analyzed using the Analysis of Dysphonia for Speech and Voice (ADSV), CSID (Cepstral Speech Index of Dysphonia) values were higher in the RT group across all sentence types (easy onset- EOS, all voiced- AVS, voiceless plosives- VPS and hard glottal attacks-HGAS) as compared to the control group. These values were also in the clinically abnormal range for all parameters with the exception of VPS in the RT group. These parameters were within normal limits in the control group. Pitch range in the RT group was also lower as compared to the control group. Average maximum phonation times between the two groups only differed by three seconds. Values of increased perturbation measures are consistent with findings of studies by Tamura et.al and Wedman, et.al.[78,79] However, even though these values fell within the clinically abnormal range for the RT group, the only measure that demonstrated statistically significant differences between the two groups was pitch range ($p= 0.045$). Elevated perturbation, noise measures and CSID values further describe the dysphonia perceived in the auditory-perceptual analysis. Increased perturbation, noise and CSID measures can be associated with increased roughness and breathiness heard on the auditory-perceptual analysis. An increase in these measures is also reflected in the patients' perception of their voices on the VHI when they describe their voices as sounding "creaky or dry."

Domain 4: Aerodynamic measures (Tables 4.12,4.13,4.14)

Aerodynamic measures of mean peak air pressure, laryngeal airway resistance, mean airflow during voicing and phonation threshold pressure were compared between the two groups. Clinically abnormal values were seen in the RT group for measures of mean peak air pressure (mean: 9.08, SD: 2.41), laryngeal airway resistance (mean: 74.69, SD: 84.7) and phonation threshold pressure (mean: 5.93, SD: 3.25). Findings of elevated peak pressure and airway resistance values are consistent with findings of studies by McGuirt, et.al and Tamura, et.al.[12,79] These values were within normal limits in the control group. The control group showed clinically abnormal values for airflow rate (mean: 0.205, SD: 0.29); average airflow rate was within normal limits for the RT group. Although these values were in the clinically abnormal range, the only parameter that demonstrated statistically significant difference between the two groups was Psub (p=0.01). Increased resistance, Psub and phonation threshold pressure values are suggestive of the presence of increased effort and hyperfunctional voice use in the RT group .[198] The increase in Psub and LAR values is also indicative of increased stiffness offered by edematous vocal folds.[65],[198] These elevated clinical values are reflected in the strain scores of the CAPE-V, as well as in the responses of participants on select VHI items ("I feel as though I have to strain my voice," "I use a great deal of effort to speak").

Domain 5: Visual perceptual measures or laryngeal imaging (Tables 4.15,4.16,4.17,4.18)

Laryngeal imaging was performed using laryngeal stroboscopy and high speed laryngeal imaging. Visual perceptual ratings were performed by a licensed and certified speech- language pathologist with over 40 years experience in voice disorders. The assessor was blinded to the groups under study. Comparisons on both methods of visualization were made on parameters of glottic closure, mucosal wave, amplitude of vibration, phase asymmetry and presence or absence of hyperfunction. Qualitative assessments were made on the overall appearance of the laryngeal mechanism (dehydrated appearance, edema) and true vocal folds (erythema, edema, hypervascularity or combination of erythema, edema and hypervascularity) considering the structural damage to the laryngeal tissues following RT, as well as exposure to tobacco and age related changes. Between the two groups, the RT group demonstrated a higher percentage of participants with clinically abnormal findings for mucosal wave (90%), amplitude of vibration (100%) and phase symmetry (70%). Both groups showed a high percentage of participants with presence of hyperfunction (100% in both groups). The overall appearance of the larynx was judged as being abnormal (dehydrated and erythematous) in 70% percent of participants in the RT group as compared to 37.5% percent (erythema only) in the control group. Similar findings were noted for appearance of the true vocal folds, where eighty percent of the participants in the RT group were judged as having some abnormality of the true vocal folds and these abnormal findings were noted on the primary cancer site as well as on the vocal fold unaffected by cancer. The abnormal findings of overall laryngeal appearance and changes on the unaffected vocal fold as a result of XRT further highlight the collateral damage caused due to radiation toxicity. These findings are consistent with studies by Wedman et. al,[78] Tamura, et.al[79] and Mintz, et.al.[9]

High speed laryngeal imaging was found to be a more effective tool for judging vocal fold vibratory parameters. There was a decrease in abnormal findings when judging vocal fold pliability (mucosal wave and amplitude) in both groups on high speed imaging. There was increase in abnormal findings in RT group for glottic closure judgement using high speed imaging. The overall level of dysphonia was higher in the RT group, making stroboscopic parameters less reliable due to tracking errors.[199] This is consistent with findings in previous studies which have favored the use of high speed laryngeal imaging in judging vocal fold vibratory parameters in patients with highly dysphonic voices.[199]

As demonstrated by the results above, one or more parameters in each domain of voice assessment was found to be clinically abnormal in the RT group. The control group demonstrated abnormal findings for the domains of laryngeal imaging (100% showed hyperfunction) and one parameter of the aerodynamic domain (airflow rate). The present study demonstrates the effect of radiation toxicity on vocal function holistically. The present study shows that physiological and psychosocial domains of vocal function are affected following XRT and continue to be affected for several years after completion of XRT. Considering that XRT has a significant negative impact on vocal function, voice rehabilitation following XRT is important, which is the focus of the next chapter.

Limitations

For our present study, we were not successful in accruing the target sample size. However, our groups were well matched in age, sex and pack years of smoking. Our study had certain limitations that need to be addressed. Since we were addressing issues of vocal function as a result of XRT, we did not perform pre-XRT voice assessments. However, pre-XRT assessments would be helpful in identifying the deterioration in vocal function as a result of laryngeal cancer itself and then comparing these deficits with those seen as a result of XRT to gain a more holistic picture of the individual's experience. Another limitation was the variation in the RT group itself between early and late stage cancers. A majority of the group was early stage glottic cancers and our participant with advanced cancer had a history of supraglottic cancer. For future studies, equally distributed groups in terms of stage and site are suggested within groups. Stratification of site and stage is also suggested since individuals with advanced laryngeal cancers also receive chemotherapy. Future studies may seek to identify changes in vocal function as a result of chemotherapy compared to XRT alone.

The next chapter focuses on stage 3 of this dissertation, which consisted of investigating the efficacy of an evidence based voice rehabilitation method (Vocal Function Exercises) in adults who had undergone XRT.

CHAPTER 5: STUDY 3

Study title: Investigating the efficacy of Vocal Function Exercises in improving voice production in adults irradiated for laryngeal cancers

Chapter 5 describes Stage III of the dissertation study in detail. As described in previous chapters, vocal function is negatively affected following radiation therapy for laryngeal cancers. As observed in previous studies, and as demonstrated in Stage II of this dissertation, multiple dimensions of vocal function are affected as a result of radiation therapy. These changes are chronic in most cases and can cause significant voice-related quality of life issues. Though post-radiation voice problems are a well-established clinical entity, there is an observable dearth of evidence into investigating the rehabilitation of these voice disorders. At present, there is no standardized approach to voice rehabilitation in patients irradiated for laryngeal cancers. The objective of the present study was to investigate the efficacy of a systematic evidence-based approach to improving vocal function following radiation therapy for laryngeal cancers. The next few sections inform the reader on background, study methodology, and results of the present study. This chapter also includes a detailed discussion of the study findings.

Background

The curative role of radiation therapy (XRT) in the treatment of laryngeal cancers is well documented. Since the 1990s, increasing numbers of patients with laryngeal cancers have been treated primarily with radiation therapy, with or without chemotherapy, with the intent of preserving laryngeal structure and function. Early laryngeal cancers can be treated with XRT alone, while advanced laryngeal cancers are treated with a combination of chemotherapy and radiation therapy. [2,3] However, collateral damage to the laryngeal and oral structures caused by radiation toxicity absent chemotherapy is a well-documented clinical entity.[6-9] These prolonged, and in some cases, permanent voice and swallowing problems post-radiation are indicators that preserving laryngeal structure is not translating into preserving laryngeal function.

Radiation damage to the larynx results in edematous and dehydrated tissues, leading to excessive compensatory compression of laryngeal structures during phonation, thus affecting vocal fold vibratory characteristics.[8,10-12] Another characteristic feature of radiation toxicity is delayed onset of injury.[10] Consequently, following these acute changes to the laryngeal mechanism, ongoing negative changes occur as a result of radiation toxicity. Acute and long-term deterioration in voice quality post-radiation may lead to significant communication deficits in daily life or in some cases may result in loss of livelihood. Therefore, voice rehabilitation post-radiation therapy is relevant consideration and warrants attention. Unfortunately, there is a paucity of research with respect to voice rehabilitation in the irradiated population. Only four studies have investigated the efficacy of voice therapy in post-radiated laryngeal cancer patients with no recommended standardized treatment.[13-16] The two studies conducted in patients irradiated for early glottic cancers did not describe the type of voice therapy used; however the study did demonstrate that voice therapy was successful in improving perceptual voice quality and voice-related quality of life.[15,16] Two other studies investigated the efficacy of voice therapy when utilized post-radiation for not only early but also advanced laryngeal cancers.[13,14] In both studies, patients showed a greater improvement in voice quality as measured by auditory-perceptual measures and voice-related quality of life as compared to a control group. The voice therapy interventions across these four studies, however, were varied and not specified. According to these publications, the authors used direct and indirect voice interventions, ranging from tasks such as breathing, relaxation, and posture adjustment to specific physiology-targeted phonation exercises. However, the studies do not assert whether or not one of these methods was more efficacious than the others. In addition, only two dimensions of vocal function – perceptual quality and voice-related quality of life self-assessment - were used to measure improvement in both studies, instead of a more comprehensive voice assessment method.

Central to treatment approaches in the above studies was vocal hygiene (VH) counseling.[13-16] However, results of outcomes research related to VH demonstrate that this form of therapy may be more effective when coupled with a more exercise-intensive physiologic voice therapy approach.[20] The Vocal Function Exercise (VFE) program is one such evidence-based physiologic approach to voice therapy. VFEs include a series of isometric and endurance-based exercises aimed at strengthening laryngeal musculature, improving vocal fold vibratory characteristics, and balancing the three sub-systems of voice production: respiration, phonation and resonance.[22] Although VFEs have been employed successfully in treating a variety of voice disorders, the efficacy of this approach for improving voice quality in adults following laryngeal radiation has not been investigated.[18,19,22,23] The success of VFEs with various voice disorders has led to the principal question of the present dissertation:

Research question: Is the Vocal Function Exercise program efficacious in improving voice production in adults radiated for laryngeal cancers?

The following specific aims were addressed in Stage III of the dissertation:

Specific aims

Specific aim 1: To investigate the efficacy of Vocal Function Exercises (VFE) for improving voice production in adults irradiated for larynx cancers as demonstrated by change in pre- and post-intervention Voice Handicap Index scores. The present stage was designed as a Phase 2 clinical trial with Voice Handicap Index being the primary outcome measure. Secondary outcome measures include laryngeal stroboscopy, high-speed laryngeal imaging, acoustic analysis, aerodynamic analysis and auditory-perceptual measures. Participants were randomly assigned to one of two groups: VFE and vocal hygiene (VFE+VH), and vocal hygiene (VH) alone. VH was used as the comparison treatment group since previous studies have utilized vocal hygiene as a treatment approach for patients irradiated for laryngeal cancers. *We hypothesize that the VFE + VH group will demonstrate significantly greater improvement in pre- and post-treatment Voice Handicap measures as compared to the VH only group.*

Specific aim 2*:* To investigate the efficacy of Vocal Function Exercises (VFE) for improving voice production in adults irradiated for larynx cancers as demonstrated by improvement in select parameters from the five domains of voice assessment. Outcome measures from the five domains of voice assessment include patient self- assessment, auditory-perceptual measures, acoustic analysis, aerodynamic analysis, laryngeal stroboscopy and high-speed laryngeal imaging. *We hypothesize that the VFE + VH group will demonstrate a larger proportion of participants with an improvement across all five domains as compared to the VH only group.*

The next section describes our study methodology in detail which addresses the specific aims stated above.

Methods

Participants for Stage III were recruited from the multidisciplinary head and neck cancer clinic at the Markey Cancer Center (University of Kentucky) following approval from the Institutional Review Board (IRB) at the University of Kentucky (UK). Sample sizes of 8 in each group achieve 80% power to detect a difference in VHI (pre and post intervention) of 14.3 in the voice therapy group and 0.5 change in vocal hygiene group.[16] An n of 16, with 8 participants in each group was determined considering VHI change and a common standard deviation equal to 11.6, a significance level (alpha) of 0.1, and a two-sided z-test.[16] These results assume that 2 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries. Stage III was designed as Phase 2 clinical trial. Participants were randomly assigned to one of two groups: VFE+VH (Vocal Function Exercise + Vocal Hygiene) or VH (Vocal Hygiene).

Participants

After completion of informed consent, 12 participants were recruited for the study. Participants in both groups met the following inclusion criteria; adults over 18 years of age, previously irradiated for laryngeal cancer (with or without chemotherapy), hearing levels appropriate to follow directions, and deemed cancer-free by the treating physician at the time of study recruitment. Participants had to have completed XRT at least 6 months prior to study participation. Presence of vocal fold paralysis or surface vocal fold pathology at the time of study recruitment constituted exclusion from the study.

Assessment battery

Participants in both groups underwent the same multidimensional vocal assessment battery. The battery included assessment protocols belonging to the five domains of voice assessment and was the same assessment battery used for Stage II of the dissertation. A checklist for the assessment battery is available in Appendix I. The five common domains of voice assessment are: auditory-perceptual measures, patient self-assessment, acoustic analyses, aerodynamic analyses, and laryngeal imaging or visual-perceptual assessments. Outcome measures and their normative values are available in Table 4.1. Outcome measures are listed below with reference to each domain of voice assessment.

5) *Auditory- perceptual assessment*: The Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V- Appendix II) was utilized. Blinding: Audio samples of patients' voices reading the rainbow passage (Appendix III) were presented to a licensed and certified speech-language pathologist with over 40 years of clinical experience in the field of voice disorders. The assessor was blinded to group assignments.
6) *Patient self-assessment*: Voice Handicap Index (Appendix IV) was utilized. Total scores and domain specific scores (Physical, Functional, Emotional) were included for final analysis.
7) *Acoustic analyses*: The Multidimensional Voice Profile (MDVP) and Analysis of Dysphonia in Speech and Voice (ADSV) were utilized. Specific measures included jitter, shimmer, noise to harmonics ratio (NHR), maximum phonation time (MPT) and pitch range for MDVP; and Cepstral Spectral Index of Dysphonia (CSID) was used for ADSV stimuli.[197] CSID included

sustained vowel and sentence stimuli. Sentences included easy onset, voiceless plosive, all voiced and hard glottal attacks.

8) *Laryngeal imaging/visual perceptual assessment*: Measures included were laryngeal stroboscopy and high-speed laryngeal imaging. Stroboscopic and high-speed features were rated on a scale (Appendix V). Stroboscopic and high-speed parameters include glottic closure, mucosal wave, amplitude of vibration and phase symmetry. Ratings were performed by a licensed and certified speech-language pathologist with over 40 years of clinical experience in the field of voice disorders. The speech-language pathologist was blinded to group assignment.

Instrumentation

1) Laryngeal stroboscopy: Laryngeal stroboscopy was performed using the Kay Elemetrics Rhino-Laryngeal Stroboscope – (Model RLS 9100 B, Halogen lamp: 150 watts, Xenon lamp: 120 watts, frequency range: 60 Hz – 1000 Hz, laryngeal microphone), a Kay Elemetrics 70 degree 22 rigid scope (Model 9106, total length: 252 mm), Kay distal endoscope, and a C-mount camera (Panasonic 3CCHD).

2) High-speed digital imaging: For the HSDI recordings, a KayPentax high-speed system model 9710 was used. Images were recorded at 4000 frames/s for a maximum duration of 4 seconds with a spatial resolution of 5123256 pixels. A 300W Xenon light source was used.

3) Acoustic analysis: For acoustic assessment, the Computerized Speech Lab Model 4500 by KayPentax was used with a hand-held microphone (mouth-to-microphone distance = 3 inches) [System Requirements: Analog Inputs: 4 channels: two XLR and two phono-type, 5mV to 10.5V peak-to-peak, adjustable gain range >38dB, 24-bit A/D, Sampling Rates: 8,000-200,000Hz, THD+N: <-90dB F.S. Frequency Response (AC coupled): 20-22kHz +.05dB at 44.1kHz. Digital Interface: AES/EBU or S/P DIF format, transformer-coupled. Software Interface: ASIO and MME. Computer Interface: PCI (version 2.2-compliant), PCI card; 5.0" H x 7.4" W x 0.75" D (half-sized PCI card). Analog Output: 4 channels, line and speaker, headphone output, channels 1

& 2 provide line & speaker outputs. Physical: 4" W x 8.25" H x 12.5" D, 4 lbs. 12 oz., 45 watts, speaker, and microphone (Shure SM-48 or equivalent, XLR-type)].

4) Aerodynamic analysis: The Phonatory Aerodynamic System Model 6600 by KayPentax was used for the aerodynamic measurements (300 ml pneumotachograph - System requirements same as CSL model 4500). Airflow measures were taken using an airflow mask and a pneumotachograph, which uses the principle of differential pressure across a known resistance to estimate airflow rate.

Study Interventions

Participants were randomized to one of two intervention groups based on a pre-determined randomization protocol. Participants were randomized to the VH group or VFE + VH. Each intervention lasted for 6 weeks. The two intervention methods are described in detail below:

I) *Vocal hygiene counseling*: Vocal hygiene counseling involved educating and informing patients regarding factors that influence voice use and voice care. Sessions generally revolved around strategies that enhance and maintain vocal health. These include tips on healthy voice use, hydration and dietary modifications required to maintain a healthy vocal system. Post-radiation vocal hygiene counseling stressed hydration and dietary considerations since significant changes in salivary status and tissues are noted during this period.

II) *Vocal Function Exercises*: Vocal Function Exercises (VFEs) are a series of isometric and endurance-based exercises which aim at strengthening and balancing the three sub-systems of voice production, specifically respiration, phonation and resonance. VFEs also aim directly at strengthening vocal fold musculature thus improving their vibratory characteristics. The exercises program consists of a series of four exercises which include a warm-up, vocal fold stretching, vocal fold contraction and endurance exercise. The warm-up and endurance exercises are timed (in seconds) and performed on strategically determined musical notes. The VFE program for the proposed study lasted 6 weeks where the patient was required to perform the exercises twice a day, every day. As a result, these exercises relied heavily on compliance.

Treatment plan: Specific treatment plans are described below in detail:

Vocal hygiene group: During the pre-intervention assessment, each study participant attended a session on voice care with a licensed and certified speech-language pathologist trained specifically in the care of patients with laryngeal cancer. Participants were also provided with handouts with tips about vocal hygiene. Participants followed up 6 weeks later to undergo post-intervention assessments. Participants in the VH group were seen a total of 2 times (pre-intervention and post-intervention). Appendix VI contains details regarding the Vocal Hygiene Handout.

VFE + VH group: During the pre-intervention assessment, each study participant attended a session on voice care with a licensed and certified speech-language pathologist trained specifically in the care of patients with laryngeal cancer. Participants were also provided with written handouts that included tips on vocal hygiene. Participants were then taught Vocal Function Exercises (VFEs) by the same speech-language pathologist trained in the administration of VFEs (Please refer to Appendix VII for description and log sheets for VFEs). Participants were given an audio CD with the VFEs as well as log sheets to track their maximum phonation times during twice-daily exercise. Patients were monitored through weekly in-person or distance sessions to monitor both technique and progress. They underwent the above described assessments at the beginning of therapy and after 6 weeks of exercises.

Statistical analysis

Statistical analyses were performed using SPSS ver.22. Statistical analyses included descriptive statistics, frequencies and comparisons between VFE+VH and VH only groups. Comparisons for continuous variables between the two groups were performed using paired t-tests. Continuous variables included CAPE-V measures, VHI scores, acoustic measures (jitter, shimmer, Noise to Harmonic Ratio, Maximum Phonation Time, pitch range and CSID measures). Comparisons for non-continuous variables between the two groups were performed using the McNemar's test. Non-continuous variables included stroboscopic and high-speed parameters. Significance levels were set at 0.1.

Results

Following completion of informed consent, 12 participants were recruited for the study. However, one participant from each group had to be excluded from the study. The participant from the VFE+VH group opted out of the study citing personal reasons. The participant from the VH group had concerning findings for recurrent disease during her routine follow-up visit. She underwent biopsies which were negative for recurrent disease. Data from 10 participants were included for the final analysis.

The mean age in the VH group (n=4) was 69 years (SD: 5.34) and the mean age in the VFE+VH group (n=6) was 57.5 years (SD: 14.2). All participants in the VH group had a history of early glottic cancer and had received narrow field radiation therapy as treatment. The VFE+VH group consisted of three participants with early glottic cancer and three participants with advanced stage glottic (n=1) and supraglottic cancer (n=2). Three participants with a history of early glottic cancers had received narrow field radiation therapy (XRT), while participants with a history of advanced laryngeal cancers had received wide field radiation therapy and adjuvant chemotherapy. Time since completion of XRT for the VH group ranged from 18 months to 48 months. Time since completion of XRT in the VFE+VH group ranged from 24 months to 84 months. The VH group consisted of two current smokers and two former smokers. Five participants in the VFE+VH group were non-smokers and one participant was a former smoker. The average pack years of smoking in the VH group was 70 pack years (SD: 43.97) and in the

VFE+VH group was 33.5 pack years (SD: 40.25). Patient demographics and characteristics are available in Table 5.1.

As stated above, participants in each group underwent the entire assessment battery at pre-intervention and at 6 weeks. Participants in the VFE+VH group underwent in-person or face to face (distance: Skype/Facetime) therapy weekly. Participants in the VH group were seen only at the pre-intervention and post-intervention session. The numbers of sessions attended by participants of the VFE+VH group are presented in table 5.2. The table also informs the reader on the adherence to the entire VFE protocol. Traditionally, VFE activities are to be performed two times each, twice a day (2x2). However, only three participants performed the entire VFE protocol (2x2). Three participants performed the VFE protocol only two times each, once per day (2x1). Three participants attended voice therapy with the principal investigator (in person) at UK. Three participants received voice therapy over Skype or Facetime (distance) with the principal investigator. In addition, participants in the VFE+VH group also received VFE exercises on an audio CD.

The next sections will discuss results related to pair wise comparisons for continuous variables by group.

Paired t-tests

Paired t-test results in the present section will be discussed according to the five domains of voice assessment. For ease of discussion, only statistically significant results are presented in this section. Means and standard deviations for all parameters under study for the two groups are available in tables 5.3 – 5.13.

Patient self-assessment: Overall a decrease in VHI scores was seen across all domains in both groups; however pre and post VHI scores were significant for the physical domain (p=0.03) in the VFE+VH group (Table 5.3). Pre and post VHI measures were not statistically significant for any of the VHI scores in the VH group (Table 5.4).

Auditory-perceptual measures: An overall decrease in CAPE-V scores was observed across all CAPE-V parameters in both groups (Table 5.5,5.6). However, pre and post CAPE-V parameters were statistically significantly different for the CAPE-V overall severity score only in the VFE+VH group (Table 5.5). CAPE-V parameters in the VH group did not approach statistical significance.

Acoustic analysis: An overall improvement in acoustic parameters was observed across both groups (Tables 5.7, 5.8). In the VFE+VH group, the average CSID for easy onset sentences (EOS) showed an increase in scores which indicates a worsening in this parameter. The VFE+VH group showed statistical significance for improvements in pitch range and maximum phonation time (Table 5.7). The VH group values did not approach statistical significance across any of the parameters (Table 5.8).

Aerodynamic analysis: Overall trends for aerodynamic measures were highly varied for both groups under study. The VFE+VH group demonstrated a statistically significant pre-post difference for subglottic pressure (PSub) (Table 5.9). The VH group did not show statistical differences across any aerodynamic parameters (Table 5.10).

Laryngeal imaging (Stroboscopic and high-speed parameters): Pre to post changes were seen for stroboscopic parameters of mucosal wave, amplitude and phase symmetry in the VFE+VH group (Tables 5.11). The VH group did not show any pre-post change on stroboscopic parameters (Table 5.12). On high speed imaging, changes were observed pre-post for amplitude of vibration in the VFE+VH group (Table 5.13). The VH group did not show any pre-post changes on high speed parameters (Table 5.14).

A challenge that we faced through the present data analysis was the high variability seen in the data, which was compounded by our low sample size. To make our data more comprehensive, Table 5.15 provides an analysis of improvement by participant. If an improvement was seen in one or more parameters of one domain, the domain column was marked with an '+'. Table 5.15 provides the number of improved domains for each participant at post-intervention assessment. Overall, none of the participants in the VH group showed an improvement across all five domains. Three participants in the VFE+VH group showed improvements across select parameters in all five domains of voice assessment. However, for our primary outcome measure of VHI, improvements were made in both groups across all but one participant in each group.

Discussion

Previous studies have demonstrated improvements in voice-related quality of life and auditory-perceptual measures of voice as a result of voice therapy interventions following radiation therapy for laryngeal cancers.[13-16] The present study supported these previous findings since greater improvement was noted in the VHI physical domain and the CAPE-V measures for overall severity in the VFE+VH group as compared to the VH only group. Statistically significant differences were also seen in the VFE+VH group for parameters of pitch range (acoustic analysis), MPT (acoustic analysis) and Psub (aerodynamic analysis). The VH group did not show statistically significant changes across any of the parameters, further strengthening previous study findings that VH alone is not highly effective in improving voice quality and but rather is most useful when paired with a physiologic voice therapy approach.[20] To account for the high variability of data seen in the present study, we also performed an analysis accounting for the improvement seen in each domain by each of the study participants. This analysis demonstrated that 50% of participants in the VFE+VH group showed improvement across all five domains of voice assessment, while 0% of participants in the VH group showed improvement across all five domains. However, for our primary study outcome, VHI, an improvement was seen across all but one participant in each group. Though none of the improvements in VHI in the control group were statistically significant, it is possible that participants were more aware of voice care strategies, and as a result, experienced an improved voice-related quality of life. The use of VH therefore cannot be discounted in the present study population. Not surprisingly, study participants who completed the full VFE protocol improved across all domains of voice assessment. This supports previous study findings by Nguyen et.al.[106] who demonstrated that individuals who completed the full VFE protocol showed the largest magnitude of improvement as compared to individuals who completed the partial VFE protocol. However, these results were demonstrated in individuals with no prior history of radiation therapy for HNC. Our findings showed pre to post intervention changes in the VFE+VH group for mucosal wave, amplitude and phase symmetry on stroboscopy. No changes were seen for laryngeal imaging studies (Stroboscopy and high speed) in the VH group. However, the judgement of laryngeal imaging parameters was challenging due to the generalized abnormality of laryngeal structures that occur as a result of XRT. Although certain stroboscopic and high speed parameters improved, the pre-post results did not shift from abnormal to normal. This is in agreement with the objective voice parameters obtained at the post intervention period for both groups. Although an improvement was observed in objective parameters such as CAPE-V, acoustics and aerodynamics, not all participants approached normative clinical values. Clinically, these findings are significant since it is quite possible normal voice production or normative clinical values may not be a realistic goal in this population. Ideally, the clinical goal should be targeted towards improvement and overall functionality of voice production. From our previous chapter, it is evident that high-speed laryngeal imaging was a better assessment tool for assessing vocal fold vibratory features, and we still advise clinicians to use it as an assessment tool for this population. Subglottic pressure measures appear to be affected the greatest in this population. All participants in the study demonstrated elevated Psub levels, which is reflective of the chronic edematous changes that occur in the irradiated larynx.[9,12,14] Elevated Psub levels persisted even after completion of both interventions.

In conclusion, VFEs in combination with vocal hygiene were found to be effective in improving vocal function across all five domains of voice assessment in 50% of our study participants. Vocal hygiene alone was not found to be effective in improving vocal function across all five domains in any of the study participants. Even though these findings are difficult to generalize due to our limited sample size, these study findings serve as promising pilot data in demonstrating the utility of VFEs in individuals irradiated for laryngeal cancers.

Limitations

We were unsuccessful in accruing our required sample size as dictated by the power analysis. One of the greatest challenges for our study participants in both groups was travel distances with distances ranging from 80 miles (Somerset, KY) to a 115 miles (Hazard, KY). When given the option for voice therapy over Facetime or Skype, we experienced issues with insufficient computer literacy and lack of smartphone/computer accessibility. For future studies, the option of organized telehealth for a cost-effective method of delivery of voice therapy should be explored. The issue of availability for voice therapy can also be resolved by changing the time of recruitment. In the present study, participants were recruited 6 months after the completion of XRT. At this time, patients only make visits to their treating physician at a 6-month intervals. For future studies, patients may be recruited during XRT intervention since they need to be present at the medical center every day for 6 weeks throughout the treatment. Another limitation of the study was the discrepancy in the degree of attention to treatment received by the participants in the VH only group versus the VFE+VH group. The VH group received only one in-person session on vocal hygiene counseling which is a typical clinical practice across most centers. Participants in the VFE+VH group were seen in person or via distance weekly and could address any questions that participants had pertaining to vocal hygiene. As a result, it is possible that participants in the VFE+VH group were more adherent to their vocal hygiene routine as well, secondary to increased contact with the treating professional (SLP). For future studies, the VH group ideally should receive weekly check-in sessions as well to monitor adherence.

The next chapter provides the reader with a synthesized discussion on the three stages of the dissertation study.

CHAPTER 6: SYNTHESIZED DISCUSSION

The principal focus of this dissertation was to investigate the efficacy of Vocal Function Exercises (VFEs) in adults irradiated for laryngeal cancers. This investigation was performed in three systematic stages that are listed below.

Stage 1: This stage involved identifying patients who had been irradiated for laryngeal cancers at the University of Kentucky (UK). However, considering the rising incidence of head and neck cancers in Kentucky, we extended the study to all head and neck cancers (HNC). In addition to helping identify our study population, this study stage was helpful in highlighting the head and neck cancer burden in Kentucky, with a special focus on Appalachian Kentucky.

Stage 2: Disorders of voice production as a result of radiation therapy are a well-documented clinical entity. However, few studies have performed a multidimensional analysis of voice production in the irradiated population. To paint a holistic picture of voice problems in the irradiated population, we performed a detailed voice assessment battery in adults irradiated for laryngeal cancers. This stage further helped highlight physiological and psychosocial issues as a result of disordered voice production in this population since multiple dimensions of voice production were affected as a result of radiation toxicity in our study population.

Stage 3: Stage 3 focused on the rehabilitation of physiological and psychosocial issues identified in Stage 2 by implementing a systematic prescriptive evidence-based voice therapy program (Vocal Function Exercises) in adults irradiated for laryngeal cancers. Presently there is a dearth of evidence in the field of voice rehabilitation following radiation therapy (XRT) for laryngeal cancers. This stage was designed as a Phase 2 clinical trial to investigate the efficacy of the VFE program in the current study population with the intent of collecting preliminary (pilot) data to justify a larger multicenter clinical trial. A VFE + vocal hygiene group was compared to vocal hygiene counseling in isolation, which has been the most commonly used intervention method for voice rehabilitation in this population. Based on our preliminary data, VFEs appear to be a promising voice therapy method for exploration in the treatment of voice problems following radiation therapy (XRT) when compared to vocal hygiene alone (VH).

The following section summarizes and discusses findings from all three study stages.

Stage 1 of the dissertation study highlighted the head and neck cancer burden in Kentucky, with a focus on trends in Appalachian Kentucky. A larger proportion of patients diagnosed and/or treated at UK belonged to Appalachian Kentucky as compared to urban Kentucky. Within urban and Appalachian Kentucky, a larger number of patients were diagnosed with advanced stage HNC during the specified study period (January 1, 2008 to December 31, 2010). Advanced HNCs are often treated with multiple modalities which can be a combination of surgery and/or radiation therapy and/or chemotherapy. Each of these modalities by themselves is associated with treatment-related morbidity. Consequently, a combination of multiple modalities further intensifies treatment-related morbidity. The need for multi-modality treatment also adds to the cost burden. High levels of treatment-related morbidity coupled with a significant cost burden can have negative effects on an individual's overall quality of life and can hamper overall recovery after treatment. The cost burden is especially significant for patients in Appalachian Kentucky since 54 Appalachian counties of Kentucky have socioeconomic status factors which are the poorest among all Appalachian regions of the United States. [167,171,180] In addition, patients treated for advanced HNCs often require long-term voice and swallowing rehabilitation.[45] The issue of requiring long-term voice and swallowing rehabilitation is further compounded by the limited access to medical facilities in these geographic regions [166,167,172,173] which can result in this population remaining largely underserved. To alleviate the issue of healthcare access and costs, outreach programs that focus on prevention through education, and early identification through screening for HNCs can be implemented. Early diagnosis and intervention of HNC reduces the need for multimodality treatment, improves treatment outcomes, and can consequently reduce treatment costs. To this end, we plan to implement outreach programs with a focus on education, screening and prevention of HNCs in the identified high-risk counties in Appalachian Kentucky. While steps are yet to be taken to address issues related to late diagnosis in Kentucky, there is a large population of patients that have been treated for HNCs who require subsequent long-term voice and swallowing rehabilitation. As a result, voice and swallowing rehabilitation following treatment for HNCs is an issue that requires special attention in Kentucky. For the present dissertation, our focus was on voice rehabilitation following XRT for laryngeal cancers. In the current sample the most commonly diagnosed HNC site was laryngeal cancer and a majority of these patients were treated with XRT. Therefore, we can expect to see a large proportion of patients with long-term voice problems as a result of post-radiation sequelae. The next section describes stage 2 of the study which was aimed at characterizing vocal function in adults previously irradiated for laryngeal cancers.

As established in previous chapters, voice production is negatively affected as a result of XRT. Stage 2 presented the reader with a holistic picture of physiological and psychosocial changes in voice production that occur as a result of XRT. This study stage also compared the RT (radiation therapy group) group's voice production characteristics to a control group of individuals who were matched in terms of age, sex and pack years of smoking. Data from 18 participants (RT=10, control=8) were included for final analysis. The RT group consisted of one patient that had a history of advanced laryngeal cancer and 9 patients with a history of early glottic cancer. The participant with advanced laryngeal cancer was the only participant who had received adjuvant chemotherapy as part of treatment. For the first time, the voice assessment battery consisted of a detailed assessment protocol which included all five domains of voice assessment. These domains encompass the physiological and psychosocial factors of voice production. The study demonstrated that voice production in the RT group was significantly more disordered across all five domains of voice assessment as compared to the control group. These findings in the RT group also reiterated the long term deficits in vocal function as a result of XRT [11,17,45] since the time of completion from treatment was 24-84 months. None of the participants in the RT group showed normal clinical values across all five domains of voice assessment. Our study findings were consistent with previous study findings which have investigated the effects of XRT on voice quality. These changes are not only seen in parameters of voice production, but also at the level of laryngeal tissues and intrinsic laryngeal muscles.[31,129] Studies by Tedla et.al and Johns, et.al both demonstrated long term changes in intrinsic laryngeal muscles which were characterized by reorganization of muscle fibrils and increased deposition of collagen. [31,129] The study by Johns et.al. also showed an increase in fibronectin levels in the superficial layer of the lamina propria. All of these findings would translate into reduced pliability of the vocal fold tissues. [31] These changes were reflected in the stroboscopic and high speed laryngeal parameters in the present RT group since a larger proportion of participants demonstrated abnormal vocal fold vibratory characteristics as compared to the control group. In addition, 80% of participants in the RT group were judged as having abnormal vocal fold findings such as erythema, edema and increased vascularity. Disruption in voice production was also reflected in the patient self assessment, auditory perceptual, acoustic and aerodynamic measures. Participants in the RT group demonstrated a higher score on the VHI which reflects a greater voice handicap. The scores in the physical domain of the VHI were affected the greatest. Individuals scored themselves high on items that were related to the voice sounding creaky, breathy, or dry. These changes perceived by participants were reflected in increased auditory-perceptual ratings of roughness, breathiness, and strain on the CAPE-V. These auditory-perceptual ratings were further reflected in the acoustic and aerodynamic findings in the RT group. Perturbation and noise measures were higher in the RT group, however these measures were not statistically significant. The aerodynamic measure that was significantly different between the two groups was Psub. The increase in PSub levels is indicative of the increased stiffness and decreased pliability observed in vocal fold tissues. These findings are consistent with laryngeal findings in the present study group since the majority of participants in the RT group showed vocal fold edema and decreased pliability of the vocal folds (100% showed a reduced amplitude of vibration and 90% showed a reduced mucosal wave). The entire sample in the RT group also demonstrated laryngeal hyperfunction which is an indicator of faulty compensatory patterns resulting from sensory and motor feedback changes in the laryngeal mechanism. This stage of the study further strengthened previous study findings of long term, and in some cases permanent deleterious voice changes as a result of XRT. Despite the fact that these changes in voice production are well established, currently, there is no standardized treatment to the rehabilitation for voice problems in this population.

The next stage, stage 3 of the study investigated the efficacy of a well-researched, prescriptive voice therapy approach in improving vocal function in adults irradiated for laryngeal cancers. This stage of the study was aimed at investigating a standardized treatment protocol for this population. The following section summarizes results from stage 3 of the dissertation.

The focus of Stage 3 was on investigating the efficacy of Vocal Function Exercises (VFE) in improving vocal function in adults irradiated for laryngeal cancers. VFEs are a set of laryngeal manipulations which are aimed at strengthening and rebalancing the three subsystems of voice production.[21] This exercise program is highly prescriptive and allows for easy plotting of progress through the course of voice therapy. To date, there are 23 peer-reviewed studies which have demonstrated the efficacy of VFEs in elite voice users, normal voices, pathological voice disorders and individuals over the age of 60 years. [18,19,22,35,36,69,87,88,91,101-114] However, the efficacy of VFEs utilized with patients irradiated for laryngeal cancers has never been studied. Previous studies that investigated voice rehabilitation subsequent to XRT have demonstrated an improvement in voice related quality of life and auditory-perceptual measures. However, none of these studies have specified their intervention methods. Central to treatment approaches across these studies has been vocal hygiene counseling. [13-16] To this end, the present study compared the efficacy of VFEs to vocal hygiene (VH) in improving vocal function in the current study population. Participants were randomized to either the VFE+VH group or the VH group. The intervention period was 6 weeks. The primary end point for our study was improvement in VHI scores and secondary end-points included improvements in auditory-perceptual, acoustic, aerodynamic, stroboscopic and high speed measures. These parameters were selected based on the five domains of voice assessment. Study findings demonstrated an overall statistically significant improvement in patient self-assessment and select auditory perceptual measures. These results were consistent with previous study findings from Van Gogh, et.al,[15,16] Tuomi et.al.,[14] and Bergstorm, et.al.[13] Select stroboscopic and high speed measures also improved in the VFE+VH group. Though select parameters in the VH group improved as well, none of the parameters were statistically significant at p=0.1.

We also performed a detailed analysis by participant in each group. We analyzed the number of participants who improved across all five domains in both groups. Fifty percent of participants in the VFE+VH group demonstrated an improvement across all five domains. Zero percent of participants in the VH group showed improvement across all five domains. Interestingly, the three participants in the VFE+VH groups who showed the best adherence to the full VFE protocol showed an improvement in all five domains of voice assessment. This is consistent with previous study findings by Nguyen, et.al[106] which demonstrated that participants who performed the full VFE protocol showed the greatest improvement in voice parameters when compared to those who completed a partial VFE protocol. However, the VH group also showed an improvement in some, if not all study parameters. Therefore the use of VH with the current population cannot be discounted. These improvements in the VFE+VH group support previous study findings which have demonstrated that VH is more effective when coupled with a more physiologic voice therapy approach such as VFE.[18-20] These study findings support the utility of preliminary use of VFEs in this population.

Each of the above study stages had discrete study aims and hypotheses which are described below. In addition, the next section informs the reader on the acceptance or rejection of study hypotheses with respect to each dissertation stage.

Specific aims and Hypotheses

Stage 1

Study title**:** Addressing the head and neck cancer burden in Appalachian Kentucky: A single center experience

Specific aim 1: To characterize the distribution of head and neck cancers in the treatment-seeking population at the University of Kentucky Markey Cancer Center in terms of site, stage, treatment trends, tobacco use and basic demographics in patients who sought treatment from January 2008 to December 2010.

Hypothesis: Specific aim 1 was purely observational and did not operate on a specific hypothesis

Specific aim 2: To compare the distribution of head and neck cancers across Appalachian and non-Appalachian counties. *Given the higher rate of tobacco use in Appalachian in comparison to non-Appalachian counties, we hypothesized that a larger number of patients identified at UK would belong to Appalachian counties.*

Hypothesis for specific aim 2 was accepted since a larger proportion of patients seen between 2008 and 2010 belonged to Appalachian counties (n=278) as compared to non- Appalachian counties (n=198).

Specific aim 3: To compare stage of cancer at the time of detection across Appalachian and non-Appalachian counties. *Considering the limited access to medical facilities faced by the*

Appalachian population,[167] *we hypothesized that the Appalachian population would have more advanced stage cancers at the their initial visit.*

Hypothesis for specific aim 3 was rejected because although a larger number of patients within Appalachian Kentucky were diagnosed with advanced stage HNC, proportionally non-Appalachian Kentucky showed a higher proportion of patients diagnosed with advanced stage HNC.

Stage 2

Study title: A study of vocal function using a multi-dimensional assessment battery in adults irradiated for laryngeal cancer

Specific aim 1**:** To characterize vocal function in subjects who have been treated with radiation therapy for laryngeal cancers as determined by stroboscopic imaging, high-speed digital laryngeal imaging, acoustic, aerodynamic, and perceptual analyses and, patient self-report measures. *Previous studies have reported deterioration of select parameters within all of the above domains of voice assessment after completion of radiation therapy. We hypothesized that the present study would follow similar trends.*[187,188]

Hypothesis for specific aim 1 was accepted since study participants in the RT group demonstrated clinically worse values on select parameters in all five domains of voice assessment as compared to the control group.

Specific aim 2**:** To compare vocal function in individuals who have been treated with radiation therapy with age, sex and pack-years matched controls as determined by stroboscopic imaging, high-speed laryngeal imaging, acoustic, aerodynamic, perceptual and patient self-report measures. *Previous studies have reported deterioration in vocal function after radiation therapy.*[1,12,77,193,200] *However, factors such as tobacco smoking and age-related changes have been* *known to affect vocal function adversely as well.*[194,195] *In an attempt to use matched controls, we matched subjects in the control group based on age, sex and tobacco use. We hypothesized that the present study would show clinically worse values of vocal function in the irradiated group as compared to the control group.*

Hypothesis for specific aim 2 was accepted because statistically significant differences were observed between select parameters of the five domains of domains of voice assessment between the RT and control groups with the RT group demonstrating worse clinical values of vocal function.

Stage 3

Study title: Investigating the efficacy of Vocal Function Exercises in improving vocal function in adults irradiated for laryngeal cancers

Specific aim 1: To investigate the efficacy of Vocal Function Exercises (VFE) for improving voice production in adults irradiated for larynx cancers as demonstrated by change in pre- and post-intervention Voice Handicap Index scores. The present stage was designed as a Phase 2 clinical trial with Voice Handicap Index being the primary outcome measure. Secondary outcome measures include laryngeal stroboscopy, high-speed laryngeal imaging, acoustic analysis, aerodynamic analysis and auditory-perceptual measures. *We hypothesized that the VFE + VH group will demonstrate significantly greater improvement in pre- and post-treatment Voice Handicap measures as compared to the VH only group.*

The hypothesis for specific aim 1 was accepted since a statistically significant change was seen in the VFE+VH group for the physical domain of the Voice Handicap Index for pre to post treatment measures at $p \leq 0.1$. The VH group did not show statistically significant changes for any domains of VHI for pre to post treatment measures.

Specific aim 2*:* To investigate the efficacy of Vocal Function Exercises (VFE) for improving voice production in adults irradiated for larynx cancers as demonstrated by improvement in select parameters from the five domains of voice assessment. Outcome measures from the five domains of voice assessment include patient self assessment, auditory-perceptual measures, acoustic analysis, aerodynamic analysis, laryngeal stroboscopy, and high-speed laryngeal imaging. *We hypothesized that the VFE + VH group would demonstrate a larger proportion of participants with an improvement across all five domains as compared to the VH only group.*

The hypothesis for specific aim 2 was accepted since 50% of participants in the VFE+VH group demonstrated an improvement across select parameters in five domains of voice assessment. None of the participants in the VH group showed an improvement across all five domains of voice assessment.

CONCLUSIONS AND FUTURE DIRECTIONS

From the three stages of the present dissertation, we have established the need for standardized voice rehabilitation programs for patients following XRT. Stage 2 further strengthened previous study findings that demonstrated the deleterious effects of radiation therapy on overall vocal function. To this end, stage 3 provides us with preliminary data on the efficacy of a prescriptive and well-researched voice therapy program, known as Vocal Function Exercises (VFE) in the current study population. Our preliminary results are promising for the utility of VFEs in the irradiated population considering the improvement seen in our primary outcome measure as well as multiple voice parameters. Stage 1 was effective in highlighting the need for voice rehabilitation in our sample of the Kentucky population, especially Appalachian Kentucky owing to an observed high proportion of laryngeal cancers and high proportion of patients being treated with XRT. Stage 1 also highlighted the need for education, prevention and, screening programs for underserved areas of Appalachian Kentucky to reduce HNC-related morbidity and mortality, consequently improving survival and quality of life.

However, these studies were not without limitations which have been described in chapters 3,4, and 5. Future directions for each of these stages are directly related to study limitations as well as additional information that needs to be gained from this study population. Future directions with reference to each stage are described in the following section:

Future directions for Stage 1**:** It is difficult to generalize the present study findings to the rest of Kentucky since we focused on a sample from a single center. For further analysis, data from the whole of Kentucky can be analyzed for the same study parameters. This would help us identify high risk regions that can be targeted for prevention and screening programs. One of the first steps to implementing such a program would ideally be collaborating with primary care physicians in the area. This is in keeping with the colorectal screening program in Kentucky, which as been so successful partially due to strong collaboration from PCPs in the community

Future directions for Stage 2: Our study was limited in terms of sample size since we were unsuccessful in accruing the target sample size. In addition, the RT group was not equal in terms of site and stage since a majority of our participants had a history of early glottic cancers and only one participant was a history of advanced supraglottic cancer. For future studies, stratification of RT group by site and stage is suggested. Also, the majority of studies that have investigated vocal function following XRT have focused on early glottic cancers. It would be interesting to compare vocal function following irradiation of early and late stage laryngeal cancers. In addition, a baseline evaluation prior to XRT would be interesting to analyze as well to account for changes as a result of cancer itself and immediate treatment effects.

Future directions for Stage 3: As previously stated, our study was limited in terms of sample size since we were unsuccessful in accruing the target sample size. This makes generalization of results to larger populations difficult. For future studies, accrual of a larger sample size is suggested with a larger multicenter clinical trial. Similar to stage 2, participants need to be stratified by site and stage which would be possible with a larger sample size.

Another drawback of this study was the discrepancy in the contact time with the treating SLP between each group. For future studies, an improved plan for assessing adherence to VH needs to be developed. In addition, the VH group should ideally receive the same contact time with the treating SLP as the VFE+VH group. The next step of this study needs to be extended to a larger population which should be followed up over a longer period of time. Fifty percent of the present study participants in the VFE+VH group demonstrated an improvement in all five domains of voice assessment, however whether these improvements can be maintained given the delayed nature of XRT is uncertain. Ideally participants need to be followed for up to 12 months to investigate whether these initial improvements in vocal function as a result of VFE+VH are maintained.

The present study investigated the efficacy of VFE in adults who had completed XRT at least 6 months prior to study recruitment. Prophylactic swallowing exercises have been demonstrated to be efficacious in the alleviation of swallowing problems secondary to XRT.[201,202] Similarly, it would be interesting to investigate if implementation of VFE during XRT alleviates the severity of voice problems that occur after XRT.

The effectiveness of exercise on the irradiated larynx also should also be assessed at the level of laryngeal tissues (intrinsic laryngeal muscles, vocal fold mucosa and laryngeal mucosa, laryngeal cartilage) to investigate if behavioral changes seen in voice parameters are in fact being engendered as changes at the structural level. This investigation can be accomplished by implementing an animal study where irradiated larynges are exposed to fictive exercise. Subsequently, these exercised tissues can be studied in detail to document structural or cellular improvements.

Summary

These studies demonstrate that Kentuckians suffer with a disproportionately high incidence of head and neck cancers. Radiation treatment for laryngeal cancer has significant and long-lasting physiological and psychosocial effects on voice production which significantly affect quality of life. Vocal Function Exercises may provide a promising intervention approach for improving disordered voice production caused by the toxic effects of XRT. These studies lay the groundwork for meaningful future studies aimed at prevention and treatment of this life altering disorder.

TABLES: CHAPTER 3

Table 3.1: Site of primary lesion (n=476). Appalachian versus non- Appalachian

Site of lesion	Appalachian	Non-Appalachian
Larynx	83	47
Tongue	46	41
Esophagus	37	30
Oropharynx	2	1
Gum and hard palate	21	19
Floor of mouth	19	10
Hypopharynx	15	9
Buccal mucosa	2	2
Nasopharynx	8	3
Lip	6	2
Salivary gland	10	7
Tonsil	29	27
Total	278	198

distribution

Table 3.2: Percentage of tobacco users (n=475, 1 missing), Appalachian versus non-Appalachian distribution

Type of tobacco use	Appalachian	Non-Appalachian
Cigarette smokers	190	129
Never smokers/non- smokers	33	32
Mixed use: Smoking+ smokeless tobacco	6	4
Smokeless tobacco	6	3
Cigar/ pipe	2	4
Not recorded	40	26
Total	277	198

Table 3.3. Primary treatments administered (n=476), Appalachian versus non- Appalachian distribution

Treatment modality	Appalachian	Non-Appalachian
Chemotherapy (CT) + Radiation therapy (RT)	69	60
Surgery	72	37
Surgery + Chemotherapy+ Radiation therapy	62	46
Surgery + Radiation therapy	34	24
Radiation therapy	15	20
No definitive treatment	20	9
Chemotherapy	4	2
Surgery + Chemotherapy	1	0
Radiation therapy + Chemotherapy + other treatment	1	0
Total	278	198

Table 3.4: Disease stage at the time of diagnosis (n=476), Appalachian versus non-Appalachian distribution

Stage	Appalachian	Non-Appalachian
Stage 0	8	1
Stage I	50	25
Stage II	42	24
Stage III	46	46
Stage IV	114	89
Unknown	18	13
Total	278	198

Table 3.5: Results from Fisher's exact test comparing early versus late stage cancers between Appalachian and non- Appalachian regions

Stage	Counties		Significance 2- sided ($p \leq 0.05$)
	Appalachian	Non- Appalachian	
Early (Stage 0, I , II)	100 (38.4%)	50 (27%)	0.014*
Late (Stage III- IV)	160 (61.5%)	135 (72.9%)	
Total	260	185	

(*Fisher's exact test p-value, indicates significance at $p<0.05$)

Table 3.6: Results from Fisher's exact test comparing single versus multimodality treatments in Appalachian and non- Appalachian regions

Treatment	Counties		Significance 2- sided ($p \leq 0.05$)
	Appalachian	Non- Appalachian	
Single modality	111 (39%)	68 (34%)	0.249
Multi-modality	167 (60%)	130 (65%)	
Total	278	198	

(*Fisher's exact test p-value)

TABLES: CHAPTER 4

Table 4.1: Five domains of voice assessment with select assessment parameters

Assessment Domain	Test tool	Measures	Normative values
Auditory perceptual	Consensus Auditory Perceptual Evaluation – Voice (CAPE-V)	Overall severity, roughness, breathiness rating (100 mm Visual Analog Scale) on the rainbow passage	<10 for each parameter and overall severity
Patient self-assessment	Voice Handicap Index (VHI)	Total score, physical domain, emotional domain and functional domain	<10 on each domain <30 for total score
Acoustic	KayPentax® Computerized Speech Laboratory	Jitter (%) Shimmer (dB) Noise-to-harmonics ratio (NHR) Pitch range Maximum phonation time (MPT) CSID /a/ CSID – easy onset sentence(EOS) CSID – all voiced sentence (AVS) CSID – hard glottal attack sentence (HGAS) CSID – voiceless plosive sentence	Jitter <1% Shimmer <0.35dB NHR< 0.194 Pitch range: variable MPT: variable (dependent on individual's lung capacity) CSID /a/ -4.5 to 14 CSID EOS -10.85 to 21.08 CSID AVS -12.4 to 14.4 CSID HGAS -8 to 19.6 CSID VPS -0.6 to 29.2
Aerodynamic	KayPentax® Phonatory Aerodynamics System	Mean airflow rate (L/s) Subglottal pressure (Psub) (cm H2O) Laryngeal airway resistance (LAR) (cm H2O/L/s) Phonation threshold pressure (PTP) (cm H2O)	Airflow rate : 0.08 to 0.2 Psub : 5-8 cmH20 LAR : 30 to 60 PTP: 3-5
Visual imaging	Laryngeal stroboscopy and high speed laryngeal imaging	Glottic closure (GC), mucosal wave (MW), amplitude of vibration (AMP), phase symmetry (PS), overall appearance and appearance of vocal folds	GC: 0- complete, 1-insufficiency noted, 2-incomplete MW and AMP: 0- normal, 1-reduced, 2-absent PS: 0 – symmetric, 1-asymmetric Overall appearance: 0-normal, 1-abnormal and qualitative description Appearance of vocal folds: Qualitative description

Table 4.2: Participant demographics (n=18) for study 2

Characteristics	Number of participants		Fisher's exact
	Radiation therapy (RT), n=10	Control, n=8	
Sex			
Male	7	6	0.618
Female	3	2	
Age			
Mean (age in years)	66.1	55.5	
Standard deviation	12.96	13.8	
Stage (TNM stage)			
T1N0M0	8	N/A	N/A
T2N0M0	1	N/A	
T2N2	1	N/A	
Smoking status			
Never	2	1	0.618
Former	6	3	
Current	2	4	
Pack years (mean and SD)	37.92 (38.9)	41.38 (23.62)	

Table 4.3: CAPE-V findings (means and standard deviations by group)

Parameter	Group		Mean	Std. Deviation
CAPE- V overall severity	Control	8	11.25	12.748
	RT	10	29.40	13.745
CAPE- V pitch	Control	8	1.25	3.536
	RT	10	3.00	4.830
CAPE- V loudness	Control	8	7.50	11.339
	RT	10	29.90	19.186
CAPE- V breathiness	Control	8	5.63	9.039
	RT	10	32.00	12.419
CAPE-V roughness	Control	8	11.25	12.748
	RT	10	31.70	15.485
CAPE- V strain	Control	8	11.88	14.377
	RT	10	36.10	12.714

Table 4.4: CAPE- V comparisons – Parametric tests (Independent sample t-tests)

Parameter	t	df	Significance
CAPE-V overall severity	-2.873	16	**.011***
CAPE-V breathiness	-5.024	16	**.000***
CAPE- V roughness	-3.004	16	**.008***

(* indicates significance at p=0.05)

Table 4.5: CAPE – V comparisons – non parametric tests (Mann-Whitney U test)

Parameter	**Group (n=18)**	**Median**	**Range**	**Std. error of mean**	**p-value**
CAPE-V pitch	Control (n=8)	0	0-10	1.25	0.388
	RT (n=10)	0	0-10	1.528	
CAPE-V loudness	Control (n=8)	0	0-25	4.01	**0.012***
	RT (n=10)	35	0-57	6.067	
CAPE- V strain	Control (n=8)	5	0-35	5.08	**0.007***
	RT (n=10)	35	20-57	4.021	

(* indicates significance at p=0.05)

Table 4.6: Voice Handicap Index (VHI) (means and standard deviations by group)

Parameter	Group	n	Mean	Std. Deviation
VHI total score	Control	8	11.63	12.682
	Radiation	10	22.60	13.501
VHI -Physical	Control	8	4.88	4.673
	Radiation	10	13.30	9.476
VHI-Functional	Control	8	4.38	5.290
	Radiation	10	6.60	4.926
VHI-Emotional	Control	8	2.38	3.777
	Radiation	10	2.60	3.596

Table 4.7: VHI comparisons – Parametric tests (Independent sample t-tests)

Parameter	t	df	Significance
VHI total	-1.760	16	0.098
VHI -Physical	-2.292	16	**0.036***

(* indicates significance at p=0.05)

Table 4.8: VHI comparisons – non-parametric tests (Mann-Whitney U tests)

Parameter	**Group**	**Median**	**Range**	**Std.error of mean**	**p- value**
VHI-Functional	Control (n=8)	3	0-13	1.87	0.302
	RT (n=10)	6.5	0-16	1.56	
VHI-Emotional	Control	1	0-11	1.33	0.812
	RT	1	0-11	1.13	

Table 4.9: Acoustic analyses (means and standard deviations by group)

Parameter	Group	n	Mean	Std. Deviation
Jitter	Control	8	1.095	.99
	RT	10	2.141	2.61
Shimmer	Control	8	0.353	.20
	RT	10	0.683	.87
NHR	Control	8	0.159	.051
	RT	10	0.209	.21
MPT	Control	8	18.82	4.40
	RT	10	15.03	8.9
Pitch range	Control	8	378.21	150.6
	RT	10	225.54	128.7
CSID /a/	Control	8	12.84	10.92
	RT	10	23.79	21.72
CSID EOS	Control	8	11	14.93
	RT	10	18.62	19.13
CSID AVS	Control	8	2.97	10.88
	RT	10	8.62	20.39
CSID VPS	Control	8	16.47	10.99
	RT	10	19.4358	14.10456
CSID HGAS	Control	8	8.8349	8.76605
	RT	10	19.5928	29.28840

Table 4.10: Acoustic analysis – Parametric tests (Independent sample t-tests)

Parameter	t	df	Significance
Shimmer	-.912	15	.376
Pitch range	2.118	13	**.045***
CSID a	-1.286	15	.218
CSID EOS	-.906	15	.379
CSID AVS	-.697	15	.496
CSID VPS	-.478	15	.639
CSID HGAS	-.997	15	.335

(* indicates significance at p=0.05)

Table 4.11: Acoustic analysis – Non-parametric tests (Mann-Whitney U test)

Parameter	**Group (n=18)**	**Median**	**Range**	**Std. error of mean**	**p-value**
Jitter	Control (n=8)	0.678	0.376-2.82	0.351	0.248
	RT (n=10)	1.342	0.52-8.76	0.781	
NHR	Control (n=8)	0.146	0.104-0.275	0.0183	0.563
	RT (n=10)	0.134	0.121-0.77	0.064	
MPT	Control (n=8)	17.29	14-8-28.7	1.55	0.286
	RT (n=10)	13.94	1.86-29.54	2.74	

Table 4.12: Aerodynamic analysis (means and standard deviations by group)

Parameter	Group	n	Mean	Standard deviation
Psub	Control	8	6.03	1.73
	RT	10	9.08	2.41
Mean airflow rate	Control	8	0.205	0.29
	RT	10	.196	0.12
LAR	Control	8	60.04	31.74
	RT	10	74.69	84.71
PTP	Control	8	3.56	1.59
	RT	10	5.93	3.25

Table 4.13: Aerodynamic analysis – Parametric tests (Independent sample t-tests)

Parameter	t	df	Significance
Psub	-2.952	15	**.010***
LAR	-.460	15	.652
PTP	-1.844	14	.086

(* indicates significance at p=0.05)

Table 4.14: Aerodynamic analysis – Non-parametric tests (Mann Whitney U test)

Parameter	**Group**	**Median**	**Range**	**Std. error of mean**	**p-value**
Airflow rate	Control (n=8)	0.115	0.04-0.17	0.015	0.214
	RT (n=10)	0.215	0.02-0.43	0.036	

Table 4.15: Stroboscopic parameters (percentage of patients with abnormal stroboscopic findings)

Parameter	Control (n=8)	RT (n=10)
Glottic closure	2 (25%)	4 (40%)
Mucosal wave	4 (50%)	9 (90%)
Amplitude	3 (37.5%)	10 (100%)
Hyperfunction	8 (100%)	10 (100%)
Overall appearance	3 (37.5%)	7 (70%)
Phase symmetry	2 (25%)	7 (70%)
VF appearance	3 (37.5%)	8 (80%)

Table 4.16: Stroboscopic parameters (Fisher's exact test)

Parameter	Significance
Glottic closure	0.437
Mucosal wave	0.239
Amplitude *	**0.009***
Hyperfunction	0.236
Phase symmetry	0.07
Overall appearance	0.268

(* indicates significance at p=0.05)

Table 4.17: High speed (percentage of patients with abnormal high speed findings)

Parameter	Control (n=7) Missing 1	RT (n=8) Missing 2
Glottic closure	2 (28.5%)	6 (75%)
Mucosal wave	3 (42.8%)	6 (75%)
Amplitude	2 (28.5%)	1 (12.5%)
Phase symmetry	3 (42.5%)	3 (30%)

Table 4.18: High speed laryngeal imaging parameters (Fisher's exact test)

Parameter	Significance
Glottic closure	0.073
Mucosal wave	0.348
Amplitude	0.194
Phase symmetry	0.622

TABLES: CHAPTER 5

Table 5.1: Participant demographics by group for study 3 (n=10)

Characteristics	Number of participants		Fisher's exact
	VH=4	VFE+VH, n=6	
Sex			
Male	4	3	0.164
Female	0	3	
Age			
Mean (age in years)	69	57.5	0.199
Standard deviation	5.34	14.2	
Stage (TNM stage)			
T1N0M0	3	3	0.167
T2N0M0	1	0	
T2N2	0	2	
T3N0M0	0	1	
Treatment type			
Narrow field XRT	4	3	0.167
Wide field XRT	0	3	
Chemotherapy+XRT	0	3	
Smoking status			
Never	0	5	0.335
Current	2	0	
Former	2	1	
Mean pack years (SD)	70 (43.97)	33.5 (40.25)	0.11

Table 5.2: Participant attendance and adherence to the VFE protocol

Participant	Session type	Percentage of sessions attended	Performed full VFE protocol twice a day (2x2)	Performed full VFE protocol once a day (2x1)
1	In person	100% (6/6)	X	
2	In person	100% (6/6)	X	
3	Distance	66.6% (4/6)		X
4	Distance	50% (3/6)		X
5	Distance	66.6% (4/6)		X
6	In person	66.6% (4/6)	X	

Table 5.3: Voice Handicap Index (VHI) Paired t-test: VFE+VH group

Parameter	Mean	Standard deviation	t	df	Significance
Pre VHI total	39.50	19.807	1.38	5	0.224
Post VHI total	32.50	23.020			
Pre VHI Physical	19.83	6.401	2.97	5	**0.031***
Post VHI Physical	15.67	8.524			
Pre VHI Functional	12.00	6.356	0.32	5	0.761
Post VHI Functional	11.33	10.172			

(*Indicates significance at p= 0.1)

Table 5.4: Voice Handicap Index (VHI) Paired t-test: VH group

Parameter	Mean	Standard deviation	t	df	Significance
Pre VHI total	26.00	18.779	.577	3	0.604
Post VHI total	19.75	16.879			
Pre VHI Physical	15.25	10.308	1.268	3	0.294
Post VHI Physical	11.00	8.287			
Pre VHI Functional	7.00	8.083	.241	3	0.825
Post VHI Functional	5.75	4.349			

Table 5.5: Voice Handicap Index (VHI) Wilcoxon sign test: VFE+VH group

Parameter	**Group (n=6)**	**Median**	**Range**	**Std. error of mean**	**p-value**
VHI-Emotional	Pre	2.5	0-31	4.84	0.892
	Post	4	0-14	2.419	

Table 5.6: Voice Handicap Index (VHI) Wilcoxon sign test: VH group

Parameter	**Group (n=4)**	**Median**	**Range**	**Std. error of mean**	**p-value**
VHI-Emotional	Pre	2.5	0-9	2.179	0.655
	Post	0.5	0-11	2.67	

Table 5.7: Auditory-perceptual measures (CAPE-V scores) for VFE+VH group (Paired t-tests)

Parameter	Mean	Standard deviation	t	df	Significance
Pre CAPE-V overall severity	34.83	30.499	2.025	5	**0.099***
Post CAPE-V overall severity	25.50	26.898			
Pre CAPE-V breathiness	10.17	11.462	1.663	5	0.157
Post CAPE-V breathiness	7.00	9.879			
Pre CAPE-V roughness	32.50	28.933	1.963	5	0.107
Post CAPE-V roughness	18.33	21.248			

(*Indicates significance at p= 0.1)

Table 5.8: Auditory-perceptual measures (CAPE-V scores) for VFE+VH group (Wilcoxon sign tests

Parameter	**Group (n=6)**	**Median**	**Range**	**Std. error of mean**	**p-value**
CAPE-V pitch	Pre	6.5	2-25	4.088	0.715
	Post	7.5	0-25	3.069	
CAPE-V loudness	Pre	1	0-10	1.585	0.317
	Post	0	0-10	1.633	
CAPE- V strain	Pre	40.85	2-45	8.68	0.116
	Post	8.5	0-42	6.87	

Table 5.9: Auditory-perceptual measures (CAPE-V scores) for VH group (Paired t-tests)

Parameter	Mean	Standard deviation	t	df	Significance
Pre CAPE-V overall severity	40.75	34.277	1.414	3	0.252
Post CAPE-V overall severity	25.75	14.431			
Pre CAPE-V pitch	18.00	22.405	.994	3	0.393
Post CAPE-V pitch	14.25	15.435			
Pre CAPE-V roughness	46.25	33.049	1.733	3	0.181
Post CAPE-V roughness	20.00	19.131			
Pre CAPE-V strain	33.75	27.789	2.089	3	0.128
Post CAPE-V strain	20.25	16.899			

(*Indicates significance at p=0.1)

Table 5.10: Auditory-perceptual measures (CAPE-V scores) for VH group (Wilcoxon sign tests)

Parameter	**Group (n=4)**	**Median**	**Range**	**Std.error of mean**	**p- value**
CAPE-V loudness	Pre	2	2-10	2	0.655
	Post	2.5	0-10	2.17	
CAPE-V breathiness	Pre	4	2-50	11.68	0.655
	Post	10	3-35	7.32	

Table 5.11: Acoustic measures for VFE+VH group (Paired t-tests)

Parameter	Mean	Standard deviation	t	df	Significance
Pre jitter	2.55	1.43	.506	5	0.634
Post jitter	2.24	1.58			
Pre MPT	15.03	5.76	-3.269	5	**0.022***
Post MPT	20.15	8.70			
Pre pitch range	290.05	260.79	-4.370	4	**0.012***
Post pitch range	565.47	126.21			
Pre CSID /a/	36.921	27.47	.728	4	0.507
Post CSID /a/	30.237	28.635			
Pre CSID EOS	25.66	25.56	-.813	5	0.453
Post CSID EOS	30.07	18.59			
Pre CSID AVS	20	30.83	.979	5	0.373
Post CSID AVS	16.07	27.73			
Pre CSID VPS	30.86	27.17	1.17	5	0.295
Post CSID VPS	24.71	17.58			
Pre CSID HGAS	31.81	36.69	1.270	5	0.260
Post CSID HGAS	27.51	29.96			

(*Indicates significance at p=0.1)

Table 5.12: Acoustic measures for VFE+VH (Wilcoxon sign tests)

Parameter	**Group (n=6)**	**Median**	**Range**	**Std.error of mean**	**p- value**
Shimmer	Pre	0.55	0.322-1.21	0.133	0.463
	Post	0.384	0.181-1.23	0.191	
NHR	Pre	0.139	0.108-0.401	0.447	0.6
	Post	0.14	0.113-0.276	0.307	

Table 5.13: Acoustic measures for VH group (Paired t-tests)

Parameter	Mean	Standard deviation	t	df	Significance
Pre jitter	3.77	3.61	.875	3	0.446
Post jitter	1.95	.93			
Pre shimmer	1.56	1.41	1.333	3	0.275
Post shimmer	0.67	0.43			
Pre NHR	0.38	0.31	1.288	3	0.288
Post NHR	0.17	0.050			
Pre MPT	10.08	9.38	-1.328	3	0.276
Post MPT	16.04	2.56			
Pre pitch range	222.15	197.56	-1.697	3	0.188
Post pitch range	283.9	263.96			
Pre CSID EOS	28.32	7.03	1.581	3	0.212
Post CSID EOS	19.11	10.28			
Pre CSID AVS	24.85	25.42	1.129	3	0.341
Post CSID AVS	11.68	8.62			
Pre CSID VPS	23.67	7.33	1.479	3	0.236
Post CSID VPS	8.67	17.18			
Pre CSID HGAS	34.58	22.46	1.340	3	0.273
Post CSID HGAS	8.67	17.18			

Table 5.14: Acoustic measures for VH group (Wilcoxon sign tests)

Parameter	**Group (n=4)**	**Median**	**Range**	**Std. error of mean**	**p-value**
CSID-AVS	Pre	21.73	-0.833-56.79	12.71	0.465
	Post	15.17	-1.14-17.53	4.31	

Table 5.15: Aerodynamic measures for VFE+VH group (Paired t-tests)

Parameter	Mean	Standard deviation	t	df	Significance
Pre Psub	11.59	3.66	-2.112	5	**.088***
Post Psub	14.07	1.63			
Pre phonation threshold pressure	8.18	2.67	.891	5	.414
Post phonation threshold pressure	6.71	2.22			

(*Indicates significance at p=0.1)

Table 5.16: Aerodynamic measures for VFE+VH group (Wilcoxon sign tests)

Parameter	**Group (n=6)**	**Median**	**Range**	**Std.error of mean**	**p- value**
Airflow rate	Pre	0.26	0.14-0.43	0.038	1.00
	Post	0.325	0.08-0.39	0.055	
Laryngeal airway resistance	Pre	40.27	28.71-61.86	5.103	0.463
	Post	41.18	33.09-196.59	26.15	

Table 5.17: Aerodynamic measures for VH group (Paired t-tests)

Parameter	Mean	Standard deviation	t	df	Significance
Pre Psub	8.22	2.79	0.456	3	0.679
Post Psub	7.66	3.21			
Pre airflow rate	0.18	.054	0.805	3	0.480
Post airflow rate	0.16	.038			
Pre Laryngeal airway resistance	43.18	11.43	-0.081	3	0.941
Post Laryngeal airway resistance	44.19	21.009			
Pre phonation threshold pressure	6.27	1.49	-0.486	2	0.675
Post phonation threshold pressure	7.63	5.48			

Table 5.18: Pre to post differences for stroboscopic parameters for VFE+VH group

Parameter (n= 4, Missing = 2)	Significance
Glottic closure	0.136
Mucosal wave	**0.062***
Amplitude	**0.017***
Phase symmetry	**0.05***
Hyperfunction	0.329

(Significant at p=0.1)

Table 5.19: Pre to post differences for stroboscopic parameters for VH group

Parameter (n=3, Missing=1)	Significance
Glottic closure	1.00
Mucosal wave	0.513
Amplitude	0.135
Phase symmetry	1.00
Hyperfunction	0.33

Table 5.20: Pre to post differences for high speed parameters for VFE+VH group

Parameter (n= 4, Missing = 2)	Significance
Glottic closure	0.157
Mucosal wave	0.238
Amplitude	**0.062***
Phase symmetry	0.174

(Significant at p=0.1)

Table 5.21: Pre to post differences for high speed parameters for VH group

Parameter (n= 2, Missing = 2)	Significance
Glottic closure	0.5
Mucosal wave	0.33
Amplitude	CNA
Phase symmetry	CNA

(CNA=could not assess due to low sample size)

Table 5.22: Improvement in domain demonstrated by each study participant

Participant by group (improved domains/total domains)	Patient self assessment	Auditory perceptual	Acoustic analysis	Aerodynamic analysis	Stroboscopic assessment	High-speed assessment
VH 1 (4/5)		+	+	+	+	
VH 2 (3/5)	+	+	+			
VH 3 (1/5)	+					CNA
VH 4 (3/5)	+	+	+			CNA
VFE+VH 1 (5/5)	+	+	+	+	+	+
VFE+ VH 2 (5/5)	+	+	+	+	+	+
VFE+VH 3 (2/5)	+		+			
VFE+VH 4 (3/5)	+	+	+			
VFE+VH 5 (3/4)		+	+	+	CNA	CNA
VFE+VH 6 (5/5)	+	+	+	+	+	CNA

(+ = improvement, CNA=could not assess)

APPENDIX I: STUDY CHECKLIST

Please circle 'yes; for each item that has been completed

Subject #:

Informed consent: Yes / No

VHI: Yes / No: **Score**: Physical: _____ , Functional: _____, Emotional: _____ , Total: _____

CAPE-V: Yes / No

Overall quality	
Pitch	
Loudness	
Breathiness	

Acoustics: Yes/No

F_o	
Jitter	
Shimmer	
NHR	
Maximum Phonation Time	
CSID for /a/	
CSID for easy onset sentences	
CSID for voiced plosive sentences	
CSID for hard glottal attack sentences	
CSID for All voiced sentences	

Aerodynamics: Yes/No

Vital capacity	
Mean airflow during voicing	
Mean peak air pressure	
Airway resistance	
Phonation threshold pressure	

Strobe: Yes/No, **Exam**: Flexible/Rigid
0= normal / 1= Abnormal

High Speed Laryngeal imaging : Yes/No, if 'no' please state reason:_____________________

APPENDIX II: CAPE-V

Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V)

Name:___________________________ **Date:**__________

The following parameters of voice quality will be rated upon completion of the following tasks:

1. Sustained vowels, /a/ and /i/ for 3-5 seconds duration each.
2. Sentence production:
   a. The blue spot is on the key again.
   b. How hard did he hit him?
   c. We were away a year ago.
   d. We eat eggs every Easter.
   e. My mama makes lemon muffins.
   f. Peter will keep at the peak.
3. Spontaneous speech in response to: "Tell me about your voice problem." or "Tell me how your voice is functioning."

Legend: C = Consistent I = Intermittent
MI = Mildly Deviant
MO =Moderately Deviant
SE = Severely Deviant

				SCORE
Overall Severity	________________ MI MO SE	C	I	____/100
Roughness	________________ MI MO SE	C	I	____/100
Breathiness	________________ MI MO SE	C	I	____/100
Strain	________________ MI MO SE	C	I	____/100
Pitch	(Indicate the nature of the abnormality): ____________ ________________ MI MO SE	C	I	____/100
Loudness	(Indicate the nature of the abnormality): ____________ ________________ MI MO SE	C	I	____/100
________	________________ MI MO SE	C	I	____/100
________	________________ MI MO SE	C	I	____/100

COMMENTS ABOUT RESONANCE: NORMAL OTHER (Provide description):_______________

____

ADDITIONAL FEATURES (for example, diplophonia, fry, falsetto, asthenia, aphonia, pitch instability, tremor, wet/gurgly, or other relevant terms):

Clinician:__________________

From: ASHA. *Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V)*

ASHA Special Interest Division 3, Voice and Voice Disorders. 2009

APPENDIX III: RAINBOW PASSAGE

The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch with it its path high above and its two ends apparently beyond the horizon.

APPENDIX IV: VOICE HANDICAP INDEX (VHI)

VOICE HANDICAP INDEX

Name: ______________________________ Date: ____________________

These are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience.

0-never 1-almost never 2-sometimes 3-almost always 4-always

Part I-F

My voice makes it difficult for people to hear me.	0	1	2	3	4
People have difficulty understanding me in a noisy room.	0	1	2	3	4
My family has difficulty hearing me when I call them throughout the house.	0	1	2	3	4
I use the phone less often than I would like to.	0	1	2	3	4
I tend to avoid groups of people because of my voice.	0	1	2	3	4
I speak with friends, neighbors, or relatives less often because of my voice.	0	1	2	3	4
People ask me to repeat myself when speaking face-to-face.	0	1	2	3	4
My voice difficulties restrict my personal and social life.	0	1	2	3	4
I feel left out of conversations because of my voice.	0	1	2	3	4
My voice problem causes me to lose income.	0	1	2	3	4

SUBTOTAL __________

Part II-P

I run out of air when I talk.	0	1	2	3	4
The sound of my voice varies throughout the day.	0	1	2	3	4
People ask, "What's wrong with your voice?"	0	1	2	3	4
My voice sounds creaky and dry.	0	1	2	3	4
I feel as though I have to strain to produce voice.	0	1	2	3	4
The clarity of my voice is unpredictable.	0	1	2	3	4
I try to change my voice to sound different.	0	1	2	3	4
I use a great deal of effort to speak.	0	1	2	3	4
My voice is worse in the evening.	0	1	2	3	4
My voice "gives out" on me in the middle of speaking.	0	1	2	3	4

SUBTOTAL __________

Part III-E

I am tense when talking to others because of my voice.	0	1	2	3	4
People seem irritated with my voice.	0	1	2	3	4
I find other people don't understand my voice problem.	0	1	2	3	4
My voice problem upsets me.	0	1	2	3	4
I am less outgoing because of my voice problem.	0	1	2	3	4
My voice makes me feels handicapped.	0	1	2	3	4
I feel annoyed when people ask me to repeat.	0	1	2	3	4
I feel embarrassed when people ask me to repeat.	0	1	2	3	4
My voice makes me feel incompetent.	0	1	2	3	4
I am ashamed of my voice problem.	0	1	2	3	4

SUBTOTAL __________

TOTAL __________

The Voice Handicap Index (VHI): Development and Validation
Barbara H. Jacobson, Alex Johnson, Cynthia Grywalski, Alice Silbergleit, Gary Jaconsen, Michael S. Benninger

From: The voice handicap index (VHI) development and validation. *American Journal of Speech Language Pathology*. 1997;6(3):66-70.

APPENDIX V: STROBE AND HIGH SPEED RATING FORMS

i) Strobe rating form: Blinded subject ID_____________________

Rater: _______________________

Glottic closure: __________________ (0= complete, 1= insufficient – please identify type of insufficiency, 2= spindle shaped or incomplete)

Phase symmetry: ___________________ (0= symmetric, 1= asymmetric)

Parameter	Right VF (0=normal, 1= reduced, 2= absent, 3= exaggerated)	Left vocal fold (0=normal, 1= reduced, 2= absent, 3= exaggerated)
Mucosal wave		
Amplitude		
Qualitative descriptors of TVFs (erythema, edema etc)		
Hyperfunction (0=no hyperfunction, 1=hyperfunction present)		
Overall laryngeal appearance (0=normal, 1=abnormal), description		

ii) HSV rating form: Blinded subject ID_____________________

Rater: _______________________

Glottic closure: __________________ (0= complete, 1= insufficient – please identify type of insufficiency, 2= spindle shaped or incomplete)

Phase symmetry: ___________________ (0= symmetric, 1= asymmetric)

Parameter	Right VF (0=normal, 1= reduced, 2= absent, 3= exaggerated)	Left vocal fold (0=normal, 1= reduced, 2= absent, 3= exaggerated)
Mucosal wave		
Amplitude		

APPENDIX VI: VOCAL HYGIENE INFORMATION SHEET

Voice Conservation & Vocal Hygiene: Tips for a Healthy Voice

Side effects of Radiation therapy: Radiation therapy is an extremely effective and curative method used in the management of throat cancers. However you may have noticed a number of side effects through treatment. Many of these side effects occur due to the damage caused to the salivary glands during the course of radiation. These include:

1) Dryness of the throat and mouth
2) Difficulty swallowing
3) Hoarseness
4) Weight loss and nausea

What is vocal hygiene? The following suggestions are meant to guide you in taking care of your voice and overcoming and preventing some voice problems. Vocal hygiene is positive change – suggestions that will make you feel better and make you sound better too!

Drink lots of water: As mentioned one the main issues with radiation therapy is throat and mouth dryness due to damage to the salivary glands. One of the first steps to minimize dryness therefore is adequate hydration. The entire voice producing mechanism (mouth, throat, vocal folds and lungs, too) needs moisture to work efficiently. If you do a lot of talking (on the telephone, group meetings, one-on-one discussion) or singing, always have water nearby and take frequent sips. Sometimes, when people are not in the habit of drinking water, they don't even realize that they are thirsty until after they begin drinking. And water is good for the health of your entire body.

Limit Caffeine and Alcohol use: Both Caffeine and alcohol have significant drying effects on tissues of the mouth and throat. A way to stay well hydrated is to limit use of products that dehydrate vocal fold and oral structures.

Don't smoke and completely eliminate tobacco use: Smoking cigarettes, pipes, cigars and other substances can seriously harm your overall health, and damage the entire respiratory system including the upper airway, throat, mouth and nose. The heat and inhaled chemicals cause inflammation, swelling, sometimes irreversible damage, and cancer. The only way to counter the effects of smoking is to stop.

Eliminate habitual and frequent throat clearing. We all must clear our throats on occasion, but recognize that when you clear your throat you are "slamming" the vocal folds together hard. This can damage the vocal folds by causing inflammation and localized irritation. It is common for people to get into the habit of clearing the throat after radiation therapy due to the dryness they experience.

Control and limit vocal loudness. Do not speak louder than the situation or environment demands. Don't "compete vocally". Avoid yelling, loud cheering, speaking over loud noises. Use non-vocal methods to get the attention of others (i.e., clap your hands, raise your arm, blow a whistle, ring a bell, turn lights on and off). Use amplification in large or noisy places. Don't try to "out talk" others by increasing loudness. Be aware of how you use your voice in talking over music, over the TV, communicating up and down stairs in the home, calling the dog, etc.

Balance extra vocal demands with voice rest. If you have to give a lecture or you know that you will be speaking for extended periods of time, try to reduce voice use before and after these episodes. If you must talk a lot at work, try to reduce the amount of talking outside of work. Listen more and talk less. If you know that you will be using your voice heavily in the evening (giving a lecture, talking in a noisy environment), then rest your voice more during the day and after the evening is over.'

Use caution with medications (over-the-counter and prescription).

Decongestants, allergy medicines and some other drugs tend to release fluid from body tissues, including the vocal folds. If your doctor has recommended that you take these medicines, you need to try to counteract their drying effect by increasing your water intake. Ask you doctor if there are any alternative medicines that don't have such a drying effect. Certain medications are also contraindicated after radiation therapy. Please consult your cancer care team before administering any new medication.

(Adapted from The Voice and Swallowing Institute, New York Eye and Ear infirmary)

APPENDIX VII: VOCAL FUNCTION EXERCISE LOG SHEET

Vocal Function Exercise Practice Record

Week 1			1st Day	2nd	3rd	4th	5th	6th	7th
		DATE							
AM	1	**"Eee"** *Sustain the vowel "ee" for as long as you can. Placement should be extremely forward, almost but not quite nasal. Do this as soft as possible, but not breathy. Engage the voice. This is a warm-up. Time this exercise. Record times for 2 attempts below.*							
			/	/	/	/	/	/	/
	2	**Glide from your lowest note to your highest on "knoll."** *You may also choose to use "woo" or "whoops". Check off 2 attempts at this exercise, but you do not need to time or measure the pitch. The goal is no voice breaks, with buzzing in the lips.*							
			☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
	3	**Glide from a comfortable high pitch to your lowest pitch on "knoll."** *You may also choose to use "woo" or "whoops". Check off 2 attempts at this exercise, but you do not need to time or measure the pitch. The goal is no voice breaks, with buzzing in the lips.*							
			☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
	4	**Sustain the following 5 ascending pitches** *for as long as possible on the sound "ooooo". This should also feel buzzy in the lips. If you place a finger in front of your mouth you feel a narrow stream of air for as long as you voice.*							
		Pitch 1	/	/	/	/	/	/	/
		Pitch 2	/	/	/	/	/	/	/
		Pitch 3	/	/	/	/	/	/	/
		Pitch 4	/	/	/	/	/	/	/
		Pitch 5	/	/	/	/	/	/	/
PM	1	"Eee"	/	/	/	/	/	/	/
	2	Up glide	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
	3	Low glide	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
	4	Pitch 1	/	/	/	/	/	/	/
		Pitch 2	/	/	/	/	/	/	/
		Pitch 3	/	/	/	/	/	/	/
		Pitch 4	/	/	/	/	/	/	/
		Pitch 5	/	/	/	/	/	/	/

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