Compliance, Pain Experience, and Outcomes from Dysphagia Exercises in Individuals with Oropharyngeal Cancer with Latent Dysphagia

By

Stephanie Marcia Knollhoff

M.A., Speech-Language Pathology, University of Kansas
B.S., Communication Science and Disorders, Saint Louis University

Submitted to the graduate degree program in Speech-Language-Hearing and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

_____

Chairperson: Jeff Searl, Ph.D., CCC-SLP

_____

Debra Daniels, Ph.D., CCC-SLP

_____

Susan Jackson, Ph.D., CCC-SLP

_____

Christopher Lominska, MD

_____

Murad Moqbel, Ph.D., MBA

Date Defended: January 17, 2017

The Dissertation Committee for Stephanie Marcia Knollhoff

certifies that this is the approved version of the following dissertation:

Compliance, Pain Experience, and Outcomes from Dysphagia Exercises in Individuals with Oropharyngeal Cancer with Latent Dysphagia

_____

Chairperson: Jeff Searl, Ph.D., CCC-SLP

Date approved: January 17, 2017

Abstract

Background: Several studies in the past ten years support the use of dysphagia exercises before and during RT as a means of reducing swallowing difficulty in people with head and neck cancer (HNC) prompting widespread change in the standard of clinical care that now emphasizes such intervention. However, latent dysphagia (i.e., dysphagia that occurs three months or more after completion of oncologic treatment) is still common. Three studies have focused on exercises to treat latent dysphagia, each with mixed results but sharing two common problems: poor compliance and heterogeneous participant groups. The purpose of this study was to address both of these issues while describing the outcomes and individual experience of completing a four-week exercise program targeted at improving latent dysphagia.

Methods: Twelve individuals who received radiation therapy (RT) for base of tongue (BOT) tumors and who were experiencing latent dysphagia completed an exercise protocol, consisting of four oral and swallowing exercises completed five times per day, seven days per week, for four weeks. Lingual strength, lingual endurance, swallowing related quality of life (QOL) via the MD Anderson Dysphagia Inventory (MDADI), oral pain, and sense of effort pre- and post-exercise completion were analyzed. Compliance to the exercise protocol was also described and quantified.

Results: Participants completed 78.9% of prescribed exercise sessions, on average, with moderate-strong compliance reported by 75% of participants. Lingual strength and lingual endurance were not statistically significantly different from pre- to post-exercise completion, but lingual endurance did have a medium effect size. A statistically significant change and a large effect size were demonstrated between pre- and post- MDADI emotional subscale scores. Three of the remaining MDADI scores (composite, global subscale, physical subscale) did not have a

statistically significant change but the composite score had a large effect size and the global and physical scores had medium effect sizes. The functional subscale of the MDADI did not have statistically significant change and had a small effect size. Participants reported essentially no pain or change in sense of effort associated with completing the exercises at any of the data collection intervals before, during or after the exercise protocol.

Conclusions: Four weeks of oral and swallowing exercises by adults with BOT cancer who had latent dysphagia after RT did not significantly improve tongue strength or endurance but did improve dysphagia related QOL in the emotional domain. Medium to large effect sizes despite non-statistically significant differences for three of the other dysphagia QOL scores and lingual endurance suggest that further investigation of the exercise regimen is prudent.

Acknowledgements

Dr. Jeff Searl, there will never be enough words to thank you for the contributions you have made to my professional career. Without you this would have never been possible. You provided me with invaluable wisdom and guidance. Thank you once again for being such an influential factor in an unforgettable experience.

Drs. Chris Lominska, Debby Daniels, and Susan Jackson, thank you for your participation throughout this project. Your wealth of knowledge and commitment helped me surpass standards and achieve a level of excellence I never thought imaginable.

To the participants and their families, this project would not have been possible without you. Your overwhelming support and dedication to further research was truly inspiring.

Lastly, but most certainly not the least, an endless thank you to my family. To my parents for understanding that this was the journey I was destined to travel and showing me nothing but absolute love and support. To my husband, Anthony, and my children, Allie and Ryan, you deserve all the credit. Your unconditional love and never-ending support made this all possible.

Table of Contents

List of Tables

List of Figures

Chapter I: Introduction

Dysphagia is the most disabling unintended effect of radiation therapy (RT), with or without chemotherapy (CT), in individuals with head and neck cancer (HNC). Restrictions in oral intake and marked decline in a person's quality of life (QOL) are common (Hutcheson & Lewin, 2012; van der Molen, van Rossum, Rasch, Smeele, & Hilgers, 2014), with dysphagia occurring in at least 39% (Caudell et al., 2009) and up to 64% (Francis, Weymuller, Parvathaneni, Merati, & Yueh, 2010) of individuals with HNC treated with definitive RT. Dysphagia can occur months or years after oncologic treatment. This is referred to as latent dysphagia and can result in significant impairments. Fibrosis and neuropathy from RT can begin and then continue well past the end of RT or these changes may start months or years post-RT, resulting in restricted range of motion of structures critical for swallowing (Eisbruch et al., 2004; Kotz, Costello, Li, & Posner, 2004). When range of motion is restricted, preparation of the bolus and transport through the mouth and pharynx is compromised. Protection of the airway can also be greatly affected such that aspiration of food, liquid, and saliva occurs. Additionally, RT can significantly alter saliva production, causing or exacerbating chewing and swallowing difficulties, and further diminishing QOL (Ferlito, Rogers, Shaha, Bradley, & Rinaldo, 2009; Forastiere et al., 2005; Mallick & Waldron, 2009). These side effects can continue to evolve for several years post oncologic treatment.

Recent studies have assessed the benefits of completing oral exercises and swallowing maneuvers prior to and during RT in order to prevent or minimize dysphagia (Carnaby-Mann, Crary, Schmalfuss, & Amdur, 2012; Kotz et al., 2012; Virani, Kunduk, Fink, & McWhorter, 2014). The emerging literature has resulted in clinical practice changes such that oral exercise completion during RT is now considered by many to be standard of care for individuals with

HNC (Hutcheson et al., 2013). However, there are a variety of reasons why people may not be completing such exercises thereby increasing the likelihood of dysphagia either during RT or in the weeks, months, and years that follow. First, compliance with exercise completion during RT is poor (Hutcheson et al., 2013; Langmore et al., 2016; Lazarus, Husaini, et al., 2014). The most common reasons for not completing dysphagia exercises were: 1) failure to understand the importance; 2) RT side effects, particularly pain, fatigue, and nausea; and 3) forgetting. Second, some facilities have had slow adoption of the use of a dysphagia exercise protocol. Third, limited resources in terms of available personnel to train and complete dysphagia therapy are anecdotally reported as an issue that causes some individuals to not receive the therapy during RT. Therefore, while swallowing exercises completed prior to and during RT appear helpful in limiting long-term swallowing problems in this population there are many people who do not adhere fully to the prescribed regimen, or who are never instructed in the exercises. This limits the total number of people who benefit from this worthwhile intervention.

Lack of completion of oral exercises during RT, whether because of compliance issues such as pain and fatigue or because a person was never trained or instructed to do such exercises, is likely one contributing factor to the growing population of individuals with HNC who report latent dysphagia. However, even completing an exercise regimen during RT does not guarantee that latent dysphagia will be avoided. It may simply be the case that regardless of completing a dysphagia exercise program during RT, some individuals are at risk for developing latent dysphagia.

Clinically, physicians and speech-language pathologists (SLPs) are now recognizing the need to be vigilant for dysphagia symptoms in individuals with HNC that may emerge even several years after RT is completed. Understanding that latent dysphagia is not uncommon in

people with HNC has prompted empirical study of the phenomenon. In particular, the impact that dysphagia exercises might have in such individuals has been reported in a few studies with somewhat discouraging results (Langmore et al., 2016; Lazarus, Husaini, et al., 2014). However, there are issues with these studies that need to be addressed in order to more accurately understand whether the exercises are beneficial for the latent dysphagia in individuals with HNC. One significant problem is that compliance rates with the exercises in these trials has been poor, just as it has been when trying to implement exercise regimens during RT (Langmore et al., 2016; Lazarus, Husaini, et al., 2014). The authors' descriptions led to the conclusion that a sizeable proportion of the study subjects did not complete the exercise program as prescribed. As such, it is problematic to conclude that the exercise program is or is not effective. Second, the HNC participant pool in these studies was heterogeneous. For example, in Langmore et al. (2016), the participants included those treated for oral, oral-pharyngeal, nasopharyngeal, hypopharyngeal, laryngeal, and 'other' cancer. The data were analyzed as one group. Some of the cancer sites were represented by only a few participants. Assessing the effectiveness across many cancer subsites may have been intentional on the part of the investigators to allow the possibility of drawing broader conclusions about the effectiveness of a dysphagia exercise program for individuals with HNC in general. However, it creates the risk of masking potential benefits for select subgroups of people with HNC. That is, a particular cancer site group may actually benefit from the exercises but because proportionally that cancer site is underrepresented in the study, that benefit cannot emerge in the analysis.

The current study described the individual experience and evaluated the impact of a dysphagia exercise program in individuals with HNC who have latent dysphagia after completing RT many years prior. The study was designed to address the two major concerns

about trials completed to date that have focused on this issue, namely participant compliance and heterogeneity of the study population. Heavy investment was given to increased compliance with a swallowing program and to document the level of compliance. Careful attention to training, daily reminders and encouragement, and tracking of the amount of daily exercise were intended to increase compliance substantially. Vigilant tracking of compliance (rather than general comments or ratings by investigators) allowed for detailed understanding of daily compliance with the exercise program. Second, the study focused solely on individuals with oropharyngeal cancer (OPC). This is the largest group of people with HNC receiving RT. Having a more homogenous participant group than has been investigated previously should allow for more definitive conclusions about dysphagia exercise impact within this subset of individuals.

Chapter II: Literature Review

Cancer

The World Health Organization (WHO) defines cancer as a large group of diseases that can affect any part of the body. The formation of cancer cells begins when damage occurs during cell proliferation, the process of cell division and growth, resulting in abnormal cells. There are two types of cell damage that result in cancer-genetic and epigenetic (Saunders, Coman, & Guminski, 2014). DNA is directly damaged when genetic lesions are present in the form of mutations, deletions, or amplifications. Epigenetic lesions are alterations to the cells that do not directly affect the DNA sequence, as occurs, for example, with the human papillomavirus (HPV). In either instance, the cells continue to divide and grow. The result is numerous undesirable, useless cells continuing to replicate and cause damage to body tissues and functions (Stephens & Aigner, 2009). One hallmark of cancer is unregulated cell growth and division (Saunders et al., 2014).

Cancer cells differ from normal cells in numerous ways. Normal cells that have damaged DNA will either undergo repair or die (i.e., apoptosis). In contrast, cancer cells continuously create new cells that the body does not need. These cells invade body tissues and organs potentially causing dysfunction in that organ or body part. Cancer cells not only differ functionally from normal cells but also structurally. Normal cells have clear, defined margins and shapes. Cancer cells have peculiar and uncharacteristic shapes and sizes. A general rule of thumb for cancer cells is: the more outrageous the features, the more aggressive the behavior (Hanahan & Weiberg, 2011; Serewko et al., 2002).

Recent evidence suggests that all cancers are caused by damage to the genetic make-up of cells. More specifically, cancer occurs when there are 6-12 genetic mutations by a single cell in vital tumor suppressors and proto-oncogenes (Stephens & Aigner, 2009). Tumor suppressors are genes that reduce the rate of cell division or cause apoptosis when needed. Proto-oncogenes are genes that control when cells grow and divide into DNA.

Although an individual may acquire cancer from inheriting damaged DNA, the two most widely accepted causes of cancer are age and environment. The more often cells divide, the greater chance there is for mistakes to occur and therefore cancer to develop. Human development, maturation, and aging involve ongoing cell division and, therefore, an ever increasing opportunity for cell damage. Many environmental factors such as smoking, alcohol, gases, and chemicals can cause damage to cells. Repeated exposure to such toxins requires increased need for cell repair which, like age, increases the chance that mistakes occur during cell proliferation (Saunders et al., 2014; Stephens & Aigner, 2009; Sturgis, Wie, & Spitz, 2004).

Once a group of cancer cells bond together a tumor is formed. Tumors can be benign, pre-cancerous, or cancerous. The most common type of tumor is benign. Benign tumors are not

cancer. This type of tumor does not invade other tissues and does not spread to other areas of the body. The typical course of treatment for a benign tumor is surgical removal. Pre-cancerous tumors are ones that have the possibility of later developing into cancer. Surgical treatment is the usual first course of action. For pre-cancerous tumors, the surgery is likely to include removal of a margin of heathy, normal cells that surround the tumor to better ensure that all pre-cancerous cells are removed. Cancerous tumors, also called malignant tumors, are what the lay public generally refers to as cancer. These tumors can invade other tissues and spread into other areas of the body. Spreading of cancer cells from a primary tumor location to other parts of the body is referred to as metastasis (Stephens & Aigner, 2009). As stated by Saunders et al. (2014), for a cell to become cancerous and exhibit metastatic behavior, a number of critical cellular functions must be disrupted. When metastasis occurs, the tumor becomes more dangerous because it signals that the cancer cells have entered an individual's lymph vessels and/or bloodstream. Once in the lymph system or the blood stream, multiple body components can be affected. Treatment of malignant tumors can take a variety of approaches. Surgery, CT, and RT are all treatment options that can be implemented independently, in sequence, or simultaneously.

Head and Neck Cancer Overview

Epidemiology

The worldwide annual incidence of HNC is more than 500,000 (Kantarjian, Wolff, & Koller, 2011). Head and neck cancer is the eighth most common cancer in Western countries (Saunders et al., 2014). In 2016, an estimated 48,330 new cases of cancer located in the oral cavity and pharynx were diagnosed in the United States and 9,570 people died from cancer in these regions (American Cancer Society, 2016). Men are twice as likely as women to receive a

diagnosis of cancer in the head and neck region. Incidence of this type of cancer does not differ between Caucasians and African Americans.

Some of the first signs of OPC are the detection of leukoplakia or erythroplakia, which are considered as possible pre-cancerous cells (Tan, Stoker, & Smeele, 2014). Leukoplakia are patches of gray or white tissue. Erythroplakia are red areas that easily bleed. Both are abnormal tissues that can appear within the mouth and throat. Smoking and chewing tobacco are the most frequent causes of leuko- and erythroplakia. Some research suggests individuals also can develop these abnormal tissue types due to poorly fitted dentures (Manoharan, Nagaraja, & Eslick, 2014); however, this remains controversial. Leukoplakia is more common than erythroplakia, yet erythroplakia typically is more serious and develops into cancer more often.

Squamous cell carcinomas are the most commonly occurring tumor in the oral cavity and pharynx (Tan et al., 2014). More than 9 out of 10 OPCs are squamous cell carcinomas. Squamous cells are flat cells that form the lining of the oral cavity and oropharynx (Hamilton, Khan, O'Hara, & Paleri, 2015). Carcinomas, in general, are malignant tumors of epithelial origin. Therefore, squamous cell carcinoma is a cancer that begins in the lining of the oral cavity and/or oropharynx. If this cancer metastasizes, it is often to lymph nodes, initially close by and later more distant (Stephens & Aigner, 2009).

Risk Factors

Risk factors are parameters that influence an individual's chance of having cancer. Some risk factors for OPC are controllable such as smoking, sun exposure, and nutrition, whereas others simply define who a person is such as age, gender, and complexion. Squamous cell carcinoma is strongly correlated with smoking, alcohol consumption, and HPV (Kreimer, Clifford, Boyle, & Franceschi, 2005; Merletti, Boffetta, Ciccone, Mashberg, & Terracini, 1989;

Saunders et al., 2014; Sturgis et al., 2004). Two of the strongest risk factors associated with HNC are tobacco and alcohol (Kantarjian et al., 2011; Merletti et al., 1989). Alcohol and smoking have a synergistic relationship such that the combined use has a greater increase in risk than the summation of the separate risks from each factor. The amount, type, and length of smoking and alcohol use have an influence on the level of the cancer risk. Substantial alcohol consumption, or 'heavy drinking,' also has been identified as a contributor for delayed presentation of individuals with HNC to medical professionals, resulting in more advanced tumors at the time of initial diagnosis (Brouha, Tromp, Hordijk, Winnubst, & De Leeuw, 2005). Lower socioeconomic status has been linked to HNC, most likely through the correlation between increased social deprivation and increased tobacco use and alcohol consumption (Thorne, Etherington, & Birchall, 1997). Smoking cannabis has been associated with HNC, particularly in individuals under the age of 55 years (Hashibe, Ford, & Zhang, 2002).

Human papillomavirus is another risk factor for the development of OPC (Huber & Tantiwongkosi, 2014). This disease is changing the current demographic of individuals with HNC in that HPV–associated cancer is commonly diagnosed in younger individuals with little or no history of other risk factors. Cancer from HPV does not directly result from DNA damage but instead is epigenetic. Tumors resulting from HPV respond more favorably to non-surgical treatments such as RT and therefore these individuals have a better prognosis (Gillison et al., 2012). Healthcare providers now generally consider people with HPV-related OPCs to be distinct from those with non-HPV cancers. Ang et al. (2010) reported results from a retrospective investigation of HPV status and survival. Participants included individuals with stage III or IV OPC; 63.8% of participants had HPV-positive tumors. Three-year overall survival rates were higher in individuals with HPV-positive tumors (82.4%) compared to individuals with HPV-

negative tumors (57.1%). Individuals with HPV-positive tumors also were noted to have a 58% reduction in risk of death and 51% reduction in the risk of relapse when adjustments were made for age, race, tumor stage, treatment, and tobacco exposure. This study also provided important demographic and prognostic information. Individuals with HPV-positive tumors were described as younger, more often Caucasian, having smaller primary tumors, and no history of smoking or a lower number of cumulative packs per year. A study by Fakhry et al. (2008) reported similar results. Data from 96 participants with stage III or IV oropharyngeal or laryngeal cancer were analyzed, specifically investigating survival differences between HPV-positive and HPV-negative tumors. Individuals with HPV-positive tumors demonstrated significantly higher response rates after induction CT (82% vs. 55%) and after RT+CT (84% vs. 57%) compared to those with HPV-negative tumors. Overall survival rates two years post-oncologic treatment were significantly higher in individuals with HPV-positive tumors (95% vs. 62%). After adjusting for contributing factors such as age and tumor stage, individuals with HPV-positive tumors demonstrated lower risks of disease progression and death.

Two risk factors for oral cancer that individuals have some control over are exposure to sun and nutrition. Increased exposure to ultraviolet light, typically seen in those who have outdoor occupations but more recently discovered in individuals who use tanning beds, predisposes the individual to oral cancer (Wehner et al., 2014). Identifying exact nutritional contributors to cancer development is difficult due to interactions with all other risk factors. Galeone et al. (2005) reported a moderate risk increase for OPC in individuals who consume large amounts of fried foods. Research also points to a diet that is low in fruits and vegetables as a risk factor for cancer. Fruits and vegetables tend to be high in carotene, vitamin C, and vitamin E which may have a cancer protection effect, particularly when combined (Chainani-Wu, 2002).

Aging is inevitable and it is a risk factor for cancer (Stephens & Aigner, 2009). As a person ages, there is an increased need for cellular repair, thereby providing more chance for the genes that regulate cell proliferation to become damaged and result in cancer. While research varies, most persons diagnosed with HNC are older than 55 years of age (American Cancer Society, 2014; Kantarjian et al., 2011). A host of other factors outside of an individual's control may contribute to cancer development including a weakened immune system, genetic syndrome, and graft-versus-host disease.

Treatments

Surgery and RT are the proven curative methods for HNC because organ preservation is typically the main aim when determining a treatment method (Kelly, 2014; Wang, Hu, & Eisbruch, 2011). Current practice results in fewer surgeries and greater use of RT as the initial treatment for tumors that are not in advanced stage (Saunders et al., 2014). Chemotherapy is not a standalone curative treatment. Rather it is sometimes utilized prior to surgery or RT, or in conjunction with RT, to reduce tumor size and reduce the chance of metastases (Kelly, 2014).

Surgical intervention can result in dysphagia as the anatomical structures that are necessary for feeding and swallowing are altered and/or completely removed. The degree of impact on swallowing can largely be attributed to the location and extent of the tumor resection. Quality of reconstructive surgery, if necessary, also plays a role in long-term swallowing outcomes.

Oropharyngeal Cancer

The oropharynx is composed of the posterior two-thirds of the tongue, soft palate, tonsils, and valleculae. A diagnosis of OPC means that the cancer started in one of these locations. Included within this region are various salivary glands that are vital to keep the oral cavity moist

and to aid food digestion. The structures of the oropharynx assist in essential life activities such as breathing, eating, chewing, swallowing, and talking. Oropharyngeal cancers have distinctive features of epidemiology, anatomy, and pathology (Kantarjian et al., 2011). Fortunately, metastasis of cancer in the oropharyngeal region occurs in only a relatively small number of individuals (Huber & Tantiwongkosi, 2014). If metastasis does occur, it is possible for the primary oropharyngeal tumor to be cured but the cancer to be detected elsewhere later.

Epidemiology

Global epidemiology of OPC is complicated by the fact that some countries group all cancers within the oral cavity and the pharynx rather than reporting subsites of cancer such as lips, tongue, and oropharynx. With that caveat, oral and pharyngeal cancers have been reported as the sixth most common site of cancer world-wide (Vigneswaran & Williams, 2014). The Global Cancer Observatory reports statistics on cancer around the world (see http://gco.iarc.fr/today/home). Information from this organization indicates that the incidence of oral and oropharyngeal cancers does vary by country with highest rates in countries in Southeast Asia, portions of Latin America and the Caribbean, and select locations within Europe and the Pacific Rim. Oropharyngeal cancer occurs in approximately 2.5 out of every 100,000 males and 1 out of every 100,000 females worldwide per year (Tan et al., 2014). Cancers of the oropharynx will account for roughly 20% of the 2016 estimated oral and pharyngeal cancer incidence in the United States, making it the most common pharyngeal cancer (Howlader et al., 2015). The average age of the individual with OPC is 62 years with slightly more than one-fourth of the people with OPC being younger than 55 years of age. Recently the number of new cases has been stagnant in men and dwindling in women. However, there is a rising incidence of OPCs in younger individuals related to the HPV (American Cancer Society, 2014). Human

papillomavirus infection in the United States of America is common with approximately 7% of the population having such infection (Gillison et al., 2012). Not all HPV infections lead to OPC; however, subtypes HPV16 and HPV18 have emerged as indicators of HNC in recent decades. Kreimer et al. (2005) conducted a meta-analysis concluding the strongest link resides between HPV16 and OPC. Human papillomavirus 16-infection is present in more than 85% of HPV related OPCs (Huber & Tantiwongkosi, 2014). The prevalence of HPV-positive tumors is approximately 25% of all HNC squamous cell carcinomas (Tan et al., 2014).

Treatments

For relatively small tumors of the oropharynx the primary treatment option is RT (Kelly, 2014). As tumor size increases, treatment options shift to a multimodal approach. The multimodal approach usually involves RT prior to surgery with the possibility of RT or CT after surgery. Multimodal approaches have proved successful for tumor control, disease remission, organ preservation, and individual survival (Tan et al., 2014). This treatment approach is necessary for individuals with more advanced OPC and/or those who have cancer protruding deeper in the oropharynx (Goldsmith & Jacobson, 2015; Kantarjian et al., 2011).

Resection of a tumor can result in obvious causes of dysphagia because tissues are removed, muscles and nerves may be transected, and scarring can occur. The resections produce varying degrees of decreased sensation and motor abilities that can alter swallowing function (Murphy & Gilbert, 2009). The degree of dysphagia does correlate to the site and size of the tumor and to the extent of surgical resection and reconstruction (Denk, Schima, & Eibenberger, 1997; Logemann & Bytell, 1979; Martini, Lucente, & Slavit, 1997). One of the most debilitating surgical interventions a person with OPC can receive is total glossectomy (Knott & Lewin, 2013). This procedure involves complete removal of the oral and base of tongue. The oral phase

of the swallow, including mastication, bolus manipulation, and oral transportation, as well as the pharyngeal swallow are greatly affected because of absence of a key anatomical structure. Aspiration risk is increased in such cases. When resection of the tongue occurs, reconstructive surgery likely follows. This reconstruction often involves a free flap taken from the abdomen, thigh, or forearm. There is no sensory or motor nerve innervation in the flap, although some spontaneous recovery may occur (Knott & Lewin, 2013). Surgeons attempt to ensure that the flap is large enough to cover the entire area, therefore initially these flaps can be rather bulky. Some of the bulk will diminish as recovery occurs; however, if the flap is too bulky initially this can have lasting impacts on the feeding and swallowing process.

A summary and analysis of 51 published studies compromising 6400 persons with oropharyngeal tumors was compiled by Parsons et al. (2002). They concluded that there was no significant difference in survival rate and local control of the disease when comparing RT with or without neck dissection (i.e., removal of groups of lymph nodes) to surgery with or without RT. Individuals who underwent surgery did have significantly more severe (32% vs. 3.8%) and fatal (3.5% vs. 0.4%) complications compared to those who received RT. Denis et al. (2004) completed a phase III randomized control trial with 226 persons with stage III or IV OPC. Results indicated a significantly increased overall survival rate (22% vs. 16%) and locoregional control (48% vs. 25%) for individuals who received a multimodal treatment approach compared to persons who received only RT. Outcomes from 424 persons with stage III or IV squamous-cell carcinoma of the oropharynx, hypopharynx, or larynx from 73 different institutions were reviewed by Bonner et al. (2006). They concluded that individuals who received multimodal oncologic treatment had more favorable outcomes. Specifically, overall survival rates at two years (62% vs. 55%) and three years (55% vs. 45%) post-treatment were higher for persons who

received multimodal treatment compared to individuals who received RT only. Additionally, the use of a multimodal treatment approach resulted in a 26% lower risk of death and a significantly decreased risk of disease progression. Finally, rates of locoregional disease control were significantly higher in persons treated with multimodal treatment compared to RT only at one (63% vs 55%), two (50% vs. 41%), and three years (47% vs. 34%) post treatment.

Specific physiologic changes to the swallow were assessed by Pauloski et al. (1998) in individuals with various HNC tumor sites. They compared swallow changes for people who received surgery plus RT and those receiving surgery alone. In the analysis, persons in the surgery alone and the surgery plus RT groups were matched for tumor site. Those who received surgery plus RT demonstrated larger amounts of pharyngeal residue, decreased swallow efficiency, and difficulties with cricopharyngeal sphincter opening compared to individuals matched for tumor site but who received only surgical intervention. This suggested that RT increases the swallowing changes beyond what is occurring with surgery alone.

Dysphagia

The act of swallowing is a complex process that requires synchronization of swallowing and breathing, and coordination of numerous muscles in the oral cavity, pharynx, larynx, and esophagus. There are both voluntary and involuntary components of the neural control of swallowing, which require interactions among both cortical hemispheres, the brainstem, specific cranial nerves, and pharyngeal receptors (T. Murray & Carrau, 2012). Disruption to any one of these components likely results in dysphagia (i.e., swallowing difficulties). Aspiration is one of the most harmful results of dysphagia. Aspiration occurs when foreign material passes below the true vocal folds, entering the airway before, during, or after the swallow (Murray & Carrau, 2012). Silent aspiration (i.e., aspiration not detected by the individual, typically not

accompanied by cough) is a common occurrence in individuals with HNC (Eisbruch et al., 2002) perhaps because the cough reflex is absent or ineffective in approximately half of such persons (Nguyen et al., 2007). Dysphagia associated with HNC is often delineated as being acute or latent. Acute dysphagia is swallowing impairment occurring prior to, during, or immediately after the primary medical treatment for the cancer. In contrast, latent dysphagia is the onset or possibly the worsening of dysphagia symptoms well after the cancer treatment has been completed.

Wall, Ward, Cartmill, and Hill (2013) conducted a systematic review of 19 publications investigating the frequency and prevalence of physiological swallowing deficits observed after oncologic treatment in individuals with HNC. Pharyngeal phase swallowing deficits were found to be the most apparent, particularly reduced laryngeal elevation which was the most frequently reported (79% of articles). Other noteworthy pharyngeal phase deficits cited included limited contact between BOT and pharyngeal wall (74%; most articles citing BOT impairment is over 75% of patients), reduced epiglottic inversion (53%), and laryngeal vestibule closure impairment (37%).

Acute Dysphagia

Acute dysphagia is common in individuals with HNC who are treated with RT alone or as part of a multimodal approach (Wilson, Carding, & Patterson, 2011). The cancer itself can pose limitations to the individual's feeding and swallowing as evidenced by Logemann et al. (2008). They reported a majority of individuals with HNC with some degree of swallowing dysfunction prior to any surgical or oncologic treatment, implicating the tumor as the cause of the dysphagia. Nonetheless, the literature suggests that the oncologic and surgical treatments pose the greater threat to swallowing dysfunction (Huber & Tantiwongkosi, 2014; Lazarus, Wall,

Ward, & Yiu, 2014). The head and neck region is particularly susceptible to the negative impacts of RT (Sullivan & Guilford, 1999). Radiation therapy damages the mucosa and soft tissue resulting in inflammation (Murphy, 2007; Sonis & Keefe, 2004). Frowen and Perry (2006) provided description of swallowing impairments commonly seen after RT is complete. Poor pharyngeal motility, epiglottic immobility, reduced laryngeal excursion, residue, decreased closure of the laryngeal vestibule, and aspiration were all identified. Silent aspiration was found to be a common occurrence with incidence ranging from 50-100%.

Other acute side effects of RT include mucositis, xerostomia, fibrosis, and neuropathy (Chambers, Rosenthal, & Weber, 2007; Delanian, Lefaix, & Pradat, 2012; Kelly, 2014; Lazarus, Wall, et al., 2014; Murphy, 2007; D. Rosenthal & Trotti, 2009). These side effects commonly result in oral pain, which can restrict the range of motion of structures critical for swallowing. Mucositis is inflammation of the mucosal membrane lining the oral cavity. It typically manifests as erythema (i.e., ulcerations) and is often associated with pain. As an acute effect of RT, mucositis typically arises about 14 days into RT and lasts for a few weeks after completion of RT (Kelly, 2014; Murphy, 2007). Radiation-induced mucositis resulting in lesions throughout the oral and pharyngeal cavity results in pain throughout these regions, swallowing difficulty, aspiration, fatigue, nausea, altered taste, and weight loss (Rosenthal & Trotti, 2009). As RT progresses, mucositis becomes more severe due to the fact that the body is unable to adequately replace the dying cells. This results in more ulcerations, pain, and edema which negatively affects an individual's desire to eat, preparation of the bolus, movement of food and liquid throughout the oral and pharyngeal cavities, and weight loss (Lazarus, Wall, et al., 2014). Concomitant CT tends to worsen mucositis (Kelly, 2014; Trotti et al., 2003). The WHO has developed an oral mucositis grading scale ranging from 0 (none) to IV (life threatening). The

degree of mucositis affects eating, drinking, and swallowing abilities such that the higher the grade of oral mucositis, the more restrictive these functions become. Trotti et al. (2003) conducted a systematic review that included 33 studies reported in the literature. They noted that mucositis was reported most often by patients with OPC compared to patients with other tumor sites in the head and neck. The mean incidence of mucositis in the literature that they reviewed was 80%; however, the frequency of mucositis varied depending on the type of RT received with the highest frequency for those receiving altered fraction RT (100%).

Xerostomia also can be an acute result of RT that causes dysphagia symptoms (Chambers et al., 2007; Kelly, 2014; Lazarus, Wall, et al., 2014). Xerostomia, more commonly referred to as dry mouth, is the result of reduced or absent saliva flow. Because the saliva glands are often located within the field of radiation required to treat head and neck tumors, the salivary glands can be affected during RT (Chambers et al., 2007). The degree of xerostomia is often attributed to the damage of salivary glands, which is dependent on the radiation dose and field. Saliva plays a key role in the mastication and propulsion of the bolus during eating and swallowing (Perkins, Hancock, & Ward, 2014). Decreased or absent saliva negatively affects swallowing function and digestion because there is not adequate lubrication to properly break down food, form the bolus, and move the bolus through the mouth, throat, and esophagus (Hamlet et al., 1997; Kendall, Leonard, McKenzie, & Jones, 2000). If materials are not properly transported through the oral and pharyngeal cavity they can remain in the valleculae or other spaces and can potentially enter the laryngeal vestibule causing aspiration. Xerostomia also can result in tooth decay and gum disorders, decreased oral and pharyngeal sensation, and pain throughout the oral and pharyngeal cavities (Chambers et al., 2007). These side effects can cause a person to become more reluctant to eat, reducing the enjoyment that previously accompanied eating. They also may develop

adverse reactions and unconscious compensatory strategies during swallowing. It can take months, even years, for salivary glands to restart saliva production and even then most individuals report long-term altered saliva production and dry mouth difficulties (Hamlet et al., 1997; Logemann et al., 2001; NIH, 2011; Vissink et al., 2010). Xerostomia-related dysphagia is a predominant acute and late complication of RT that results in decreased QOL (Wang et al., 2011).

Latent Dysphagia

The most commonly cited long-term complication of intensive chemoradiotherapy in the head and neck region is dysphagia (Feng et al., 2010; Frowen, Drosdowsky, Perry, & Corry, 2016; Hanna et al., 2004; Hutcheson et al., 2012; Logemann et al., 2006; Nguyen et al., 2007). If clinically acute side effects from oncologic treatment are going to resolve, they typically do so by three months post RT treatment (Murphy & Gilbert, 2009). Therefore, when latent dysphagia is discussed, it is often referring to the time frame extending beyond three months after cancer treatment has stopped. However, longer intervals post cancer treatment termination also have been associated with the term 'latent' dysphagia. For example, Hutcheson et al. (2012) defined latent dysphagia from RT as swallowing impairment that is new or progressive dysphagia five years or more after treatment completion.

The onset and progression of latent dysphagia symptoms has received increased attention in the past 10-15 years as the phenomenon has become more clinically apparent. Bonner et al. (2006) reported severe late effects related to RT in 40% of individuals with HNC. Frowen et al. (2016) conducted a prospective study evaluating long-term swallowing outcomes and risk factors five years after completion of RT (+/- CT). Participants were 39 individuals with tumors of varying stages located in the oropharynx (72%), hypopharynx (3%), and larynx (25%). There

was a significant increase in pharyngeal residue over time indicating a decline in swallowing function. Feeding tubes were present in 5% of participants at five years post-treatment. Based on participant report of swallowing function, poorer swallowing outcomes were significantly correlated with decreased swallowing function at baseline, more advanced disease, higher mean radiation dose to the pharyngeal constrictor muscles, and living in rural areas. Based on swallowing dysfunction as identified by modified barium swallow study, poorer swallowing outcomes were significantly correlated with decreased swallowing function at baseline, larger tumor, higher mean radiation dose to the pharyngeal constrictor muscles, older age, and living in rural areas. Hutcheson et al. (2014) followed patients enrolled in an institutional phase II trial prior to treatment and up to two years after. Although this study included a heterogeneous sample, it is worth noting that 87.2% of participants had oropharyngeal tumors. Swallowing function was noted to be slightly worse two years after treatment compared to baseline with the only significant change on modified barium swallow studies observed with pudding consistency. These authors identified pharyngeal residue as a primary issue. The MDADI also was utilized with similar scores at baseline and two years post-treatment with the exception of the 'physical' subcategory, which resulted in significantly lower total MDADI scores at two years after treatment than baseline. Feng et al. (2010) reported on 44 individuals with OPC, noting no change in swallow function between three months and two years post-treatment with presence of aspiration being unchanged one year after treatment. This study documents that significant changes to swallow function resulting in dysphagia can persist past the end of RT even if they do not worsen.

Individuals with well-established dysphagia that begins or worsens beyond three months post-oncologic treatment are at significant risk of long-term impairment and potential worsening

of dysfunction over time (Perkins et al., 2014). Hutcheson et al. (2012) reported on 29 individuals who presented with dysphagia a median of nine years (range=5-19 years) after completion of definitive radiation with or without CT. Twenty-one percent of these participants were dependent on a feeding tube to meet their daily nutritional needs. Additionally, 7% required oxygen from alternate sources. Findings from modified barium swallow studies revealed all persons demonstrated pharyngeal residue and aspiration; specifically noted were impaired laryngeal elevation, decreased or absent epiglottic inversion, limited tongue base retraction, and impaired pharyngeal contraction. Strictures were confirmed in 24% of individuals. During the follow-up period of this study, which varied by participant, 86% developed pneumonia with 62% experiencing recurrent pneumonias. Pneumonia required 52% of patients to be hospitalized and ultimately 14% to undergo tracheotomy. Kraaijenga et al. (2015) followed up on 22 participants ten or more years after oncologic treatment who had previously participated in a randomized clinical trial. Participants had varying tumors sites; however, it is worth noting that 82% had a primary tumor located in the oropharynx. Completion of a videoflouroscopy swallow study demonstrated abnormal amounts of residue in all participants with 32% demonstrating safe oral intake, 68% demonstrating penetration and/or aspiration, and 45% exhibiting silent aspiration. Fifty-four percent of participants had restrictions on their oral intake with approximately 14% of all participants being feeding tube dependent. Fifty-nine percent of participants self-reported swallowing difficulties, with 18% citing pain during swallowing. Szczesniak, Maclean, Zhang, Graham, and Cook (2014) conducted a single institution retrospective study with the primary aim of determining the prevalence and severity of persistent dysphagia in HNC after treatment. Participants included 83 individuals with various tumor locations who completed treatment six months to eight years (median 33 months) prior to study initiation. Participant self-report

revealed dysphagia in 59%, with 37% scoring in the severe dysphagia category. Primary symptoms that were reported included difficulty swallowing dry foods and hard foods, feeling of food getting stuck in the throat, and coughing/choking while swallowing solid foods. One area of investigation was cause of mortality. Aspiration pneumonia was responsible for 8% of overall mortality and 19% of the non-cancer related deaths. Taberna et al. (2015) investigated 152 individuals who were treated for HNC 24-214 months prior (median 60 months) to study enrollment; participants with various tumor locations were included. All participants demonstrated at least one late toxicity effect. Noteworthy were permanent tracheostomy (8.6%), permanent feeding tube (3.9%), dysphagia (43.4%), dry mouth (45.4%), and sticky saliva (82.2%). One of the most significant dosimetric predictors of latent dysphagia is the mean dose to the pharyngeal constrictor muscles (Caudell et al., 2010; Duprez, Madani, DePotter, Boterberg, & DeNeve, 2013). Perkins et al. (2014) developed a table of patient-reported symptoms of latent dysphagia that included: limited texture and consistency of foods that could be swallowed, increased concentration to achieve swallow, limited ability to comply with suggested changes due to pain, increased time for meal completion, dry mouth, altered saliva, altered taste, pain during swallowing, reduced motivation, and weight loss.

The causes of latent dysphagia after RT are most often attributed to fibrosis, lymphedema, neuropathy, stricture, and atrophy of the muscles in the oral, pharyngeal, and laryngeal cavities (Hutcheson et al., 2012). During RT, connective tissue is damaged resulting in an abnormal production of the tissue protein fibrin. When fibrin accumulates in the radiated tissues, thickening and scarring of the tissue occurs. This altered tissue is called fibrosis (Wynn, 2008). Tissues are continuously becoming fibrotic and rigid as they heal from the radiation. Lack of oxygen reaching the tissue may continue to cause damage for an extended period of time after

RT has been completed (Rosenthal, Lewin, & Eisbruch, 2006; Wynn, 2008). Excessive fibrosis is one cause of restriction to movement of swallowing muscles that leads to aspiration and other feeding difficulties (Smith, Kotz, Beitler, & Wadler, 2000). Fibrosis affects the swallowing mechanism by causing decreased range of motion in the BOT, pharyngeal constrictors, and larynx; reduced airway closure; and reduced cricopharyngeal relaxation (Hutcheson et al., 2012). Radiation-induced fibrosis is capable of spreading to nearby structures and does not spontaneously diminish, making prevention and management a hardship (Perkins et al., 2014). Because the process of fibrosis development can extend over many months or years, onset of dysphagia also can extend over months and years after oncologic treatment.

Lymphedema is swelling as the result of an impaired lymphatic system that cannot transport fluid away from a region of the body (Purcell & Turner, 2014). Lymphedema is a common occurrence in individuals with HNC who have had surgery and/or RT (Smith & Lewin, 2010) with more than 50% of patients developing some degree of lymphedema (Buntzel, Glatzel, Mucke, Micke, & Bruns, 2007; Deng et al., 2012). Lymphedema is classified as a secondary condition when the condition arises after treatment for HNC, meaning it manifested from acquired damage to the lymphatic system (Thoma, 2012) as opposed to a primary condition that is the result of a congenital malformation (Withey, Pracy, Wood, & Rhys-Evans, 2001). Head and neck cancer, along with its treatment, is the most common cause of head and neck lymphedema (Withey et al., 2001). Lymphedema associated with HNC is caused by obstruction and/or damage to the lymphatic system, scarring, inflammation, and/or reduced movement of muscles (Lewin, Hutcheson, Barringer, & Smith, 2010; Withey et al., 2001). Increased incidence and severity of head and neck lymphedema is associated with treatment from surgery combined with RT (Lewin et al., 2010). Head and neck lymphedema typically develops after completion of

oncologic treatment (Murphy, Gilbert, Cmelak, & Ridner, 2007) and can result in significant functional deficits, including dysphagia (Murphy & Gilbert, 2009; Smith & Lewin, 2010). Structures pertinent to swallowing that have the potential to be affected by lymphedema include the neck, face, tongue, larynx, and pharynx (Deng, Ridner, & Murphy, 2011). Dysfunction in any one of these areas can cause decreased motor and sensory innervation limiting bolus manipulation, transportation, proper clearing of the oral and pharyngeal vestibule, and protection of the laryngeal vestibule.

Peripheral nerve damage can occur latently with RT (Murphy & Gilbert, 2009). This nerve damage, called neuropathy, can present clinically in different ways. A sensation of pain or numbness and weakness are relatively common presentations of neuropathy that can affect swallowing. Notable cranial nerves that are damaged include the facial, hypoglossal, glossopharyngeal, and vagus leading to facial weakness, lingual atrophy, lingual fasciculation, lingual deviation, nasopharyngeal regurgitation, and aspiration (Perkins et al., 2014). These side effects are often irreversible and typically present years after RT (Delanian et al., 2012; Epstein, Wilkie, Fischer, Kim, & Villines, 2009). Incidence is rising with the advancement of medical treatment and increased long-term survivorship (Delanian et al., 2012). To detail the impacts of neuropathy in HNC, Hutcheson, Yuk, Holsinger, Gunn, and Lewin (2015) reported on two case studies of long-term OPC survivors. Participant 1 presented with neuropathy four and a half years after treatment as evident by facial asymmetry, lingual atrophy and deviation, and moderate dysphagia. One year later, this participant presented with bilateral hypoglossal cranial nerve palsy and increased dysphagia. At the final follow-up, the participant presented with complete bilateral hypoglossal nerve, unilateral left vagus nerve, and unilateral right facial nerve palsies resulting in facial asymmetry, lingual atrophy, immobility of the bilateral tongue, and left

unilateral vocal fold paralysis. Throughout the course of follow-up, the participant experienced a 25% weight loss, 36% increase in oral impairment, and 11% increase in pharyngeal impairment; the participant ended the study on an altered oral diet averaging one and a half hours to consume. Participant 2 presented 19 years after treatment with bilateral hypoglossal nerve palsy and severe dysphagia. Over four years of follow up, the patient reported maintaining an oral diet and was noted to maintain weight.

Strictures are a narrowing (i.e., stenosis) (Ward, Kerle, Hancock, & Perkins, 2014) seen in individuals with HNC in the pharynx and/or esophagus. Strictures can develop in people with HNC after surgery and/or RT (Perkins et al., 2014; Ward et al., 2014). Late stricture formation as a long-term complication of oncologic treatment can be common (Sloan, Blackwell, Harris, Genden, & Urken, 2003; Ward et al., 2014). Exact cause of strictures is unclear; however, it has been proposed that treatment-induced mucositis may result in ulceration and subsequent scarring that creates a stricture (Hanna et al., 2004; Sullivan et al., 2004). Dependency on a feeding tube resulting in pharyngeal and esophageal inactivity are risk factors for stricture (Lee et al., 2006). Lee et al. (2006) conducted a retrospective study involving individuals with tumors of the oropharynx (approximately 50% of participants), hypopharynx, larynx, and oral cavity treated with chemoradiation. Of the participants who underwent a swallow evaluation (41%), 50% were found to have strictures. Of this 50%, 58% had an oropharynx tumor. Ward et al. (2016) conducted a retrospective study with the purposes of describing the incidence and timing of severe late dysphagia. Eighty-three percent of participants underwent initial treatment for stricture within five years of oncologic treatment, and 66.6% required multiple medical interventions for strictures. This study noted stricture dilation within the first year after RT to be the most common severe late dysphagia event. Strictures reduce the surface area of the pharynx

and/or esophagus, limiting the movement of solid foods and, in severe cases, liquids. Common complaints from individuals experiencing strictures include increased effort to eat, considerably longer meal times, limited oral intake, oral and nasal regurgitation, sensation of food getting stuck in throat, and weight loss (Perkins et al., 2014; Ward et al., 2014).

Although fibrosis, lymphedema, neuropathy, and stricture are the causes most often described in the literature, there may be others to consider that have been less thoroughly described. For example, Denis et al. (2004) reported that 75% of the 44 participants with OPC (stage III and IV) who followed up at a median of 5.5 years post treatment had xerostomia and mucositis. Additional issues in this patient sample were alterations to taste (57% of the sample) and poor dentition (36%).

Feeding tube placement has been reported as a possible outcome from dysphagia due to RT. Murphy and Gilbert (2009) list permanent or long-term feeding tube dependency as a common complication of latent dysphagia. Additionally, feeding tubes are used to support health during treatment by maintaining patient weight and nutrition (Beer, Krause, Zuercher, & Stanga, 2005; Kiss & Isenring, 2014; Tyldesley et al., 1996). Nguyen et al. (2004) reported 15% of participants with HNC developing aspiration pneumonia, which was the cause of death in 62.5% of this group. In contrast to the descriptions of feeding tubes as supporting the life and recovery of individuals with HNC, some investigators have described tube placement as a potential contributor to the development of long-term dysphagia in people with HNC. Mekhail et al. (2001) conducted a retrospective study investigating nasogastric feeding tubes versus gastrostomy feeding tubes. Results indicated that placement of a nasogastric feeding tube led to decreased feeding tube dependency, need for medical dilation, and long-term dysphagia. The authors speculated that placement of gastrostomy feeding tubes led to longer use of the

alternative support leading to overall weakness of the pharyngeal musculature that in turn might have caused long-term dysphagia and strictures. Similarly, Rosenthal et al. (2006) reported that nutritional support via a feeding tube may decrease local control and survival.

Treatment for Latent Dysphagia

Research into prevention and treatment of RT-related dysphagia has increased over the past decade, with most of the focus on treatment prophylactically and/or during RT. Multiple studies in the past ten years support the use of dysphagia exercises before and during RT as a means of reducing swallowing difficulty in people with HNC (Carnaby-Mann et al., 2012; Carroll et al., 2008; Hutcheson et al., 2013; Kotz et al., 2012; Kulbersh et al., 2006; Virani et al., 2014). This set of studies has prompted widespread change in the standard of clinical care that now emphasizes such intervention. Unfortunately, the mounting evidence that latent dysphagia is not uncommon after RT in individuals with HNC has highlighted gaps in the knowledge base that must be addressed. For example, it is not clear whether latent dysphagia is still likely to occur several months or years after RT even if dysphagia exercises were done before and/or during RT. What is increasingly clear is that approaches to minimize or eliminate latent dysphagia are needed.

Three studies have evaluated the impact of dysphagia exercises completed after RT is done. Langmore et al. (2016) studied 170 people with HNC with varying tumor sites who completed RT at least three months prior to enrollment in the study. The methodology of this was rated by the author of the current study (SK) as a nine on the PEDro-P rating scale (E. Murray et al., 2013) indicating a high level of methodological quality (PEDro-P rating was not available on http://www.speechbite.com). Participants were randomized into an active neuromuscular electrical stimulation (NMES) group or a sham NMES group. The active NMES

group utilized neuromuscular electrical stimulation done while completing swallowing exercises. The sham NMES group had the NMES electrodes placed on the neck in a manner identical to participants in the treatment arm, but the current-carrying wire was disabled so that no electrical stimulation was applied. The sham NMES participants also received the same audio tones and visual feedback that was provided in the active NMES group. Both groups completed a set of identical swallowing exercises. In essence, the sham NMES arm simply had the subjects completing dysphagia exercises without NMES being applied. Three swallow maneuvers were conducted by both groups (during NMES and during sham NMES): the Mendelsohn (Lazarus, Logemann, & Gibbons, 1993), the super-supraglottic swallow (Lazarus et al., 1993), and the effortful swallow (Bulow, Olsson, & Ekberg, 2001). Participants were to complete swallowing exercises twice daily, six days a week for 12 weeks. Participants enrolled in the study were, on average, 53.7 months post-RT (median: 24.5 months; range: 3-267 months). Several outcome measures were tracked. At the end of the study, the active NMES treatment group had a Penetration-Aspiration Scale (PAS) (Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996) that was unchanged from baseline; the sham NMES group had a significant improvement in the PAS. No other outcome measures (oropharyngeal swallowing efficiency score, physiological observations from modified barium swallow study, head and neck cancer inventory-eating score) differed significantly between the NMES and the sham NMES groups; however, all participants described better QOL and reported significantly better diet. The findings from the study presented a conflicting picture regarding the benefit of the interventions that were attempted. The authors interpreted the findings as an indication that active NMES was not effective. They further concluded that swallow exercises alone (sham NMES) did not significantly improve swallow function (presumably as reflected in the observations from modified barium swallow

study because the PAS score did significantly improve). Complicating the interpretation of the outcomes was the less than ideal exercise compliance of the participants. In the active NMES group, 57% of participants were judged as compliant from a treatment log; 48% of the sham NMES were judged to be compliant. This clearly indicates that approximately 40%-50% of participants were not compliant with the exercise program that they were assigned to complete, making it difficult to conclude that either intervention was ineffective.

The second study assessing the effectiveness of dysphagia exercises implemented post-RT was Lazarus, Husaini, et al. (2014). The speechBITE website provided a rating of five on the PEDro-P scale. This suggested fair methodological quality of the study. Twenty-three individuals with HNC were enrolled with varying tumor location sites (tonsil, BOT, lateral pharyngeal wall, soft palate). Participants were randomized to one of two groups: traditional therapy and strengthening exercises. Traditional therapy exercises focused on tongue and larynx exercises to increase range of motion (the authors referred to this as the control group). The strengthening group (experimental group) completed the same traditional exercises but added in isometric tongue strengthening maneuvers against resistance during protrusion, lateralization, and elevation. The exercises were completed five days a week for six weeks (five practice sessions per day, wherein each exercise was repeated 10 times). The participants began the exercises one month after completion of RT. As such, although dysphagia exercises were initiated after oncologic treatment was finished, the study did not enroll participants who fell within the more commonly-described latent dysphagia time frame of >3 months post-RT completion. However, it is one of only three studies available that initiated treatment after RT completion and so it is reviewed here. Tongue strength as measured by the Iowa Oral Performance Instrument (IOPI; IOPI Medical LLC) (Robin, Goel, Smoodi, & Luschei, 1992) did

not differ significantly between treatment groups or when comparing pre- to post-exercise for either group. There also was no significant improvement after exercise for either group on the oropharyngeal swallow efficiency, salivary flow, or head neck cancer inventory scores. The authors specifically focused a portion of the discussion on participant compliance issues, noting that poor compliance particularly in the treatment group may have adversely affected outcome measures.

Hutcheson et al. (2012) enrolled 29 survivors of HNC with various tumor sites (oropharynx 86%, hypopharynx 4%, supraglottic larynx 10%) who had complaints of latent dysphagia (median nine years after oncologic treatment) into a pre-post treatment study. The methodology of this case series was evaluated utilizing the PEDro-P scale. Since no formal rating was provided on the speechBITE website, the investigator of the current study (SK) completed the rating process and determined a score of three, suggesting relatively weak methodological quality. They provided minimal details regarding the actual therapeutic intervention they deployed, simply stating that it was individualized to the patient. Data collected during the last follow-up session (median 10 months) indicated that no patient achieved strong improvement. Despite the fact that movement of the bolus through the pharynx and/or airway protection was improved in 69% of participants, 66% were ultimately feeding tube-dependent.

Statement of the Problem

Oropharyngeal cancer is most often treated with RT in order to preserve the organs of the mouth and pharynx; however, it is now well-established that RT can cause significant dysphagia even when care is taken to limit this likelihood by completing dysphagia exercises before and during RT. Radiation therapy frequently causes symptoms such as mucositis and xerostomia that result in acute dysphagia symptoms. Although these swallowing problems can and often do

improve in the weeks and months after RT is completed, a sizeable proportion of individuals have an exacerbation of the dysphagia symptoms, or onset of dysphagia symptoms, that occurs months or years post RT. These individuals are described as having latent dysphagia symptoms from RT that are most likely due to the development of fibrosis and neuropathy.

Recent studies have attempted to determine whether completion of swallowing exercises after RT is completed can remediate or improve the swallowing problems. The approach in these studies was derived from the growing literature that has indicated completion of oral and swallowing exercises during RT may help limit the extent of dysphagia. Unfortunately, both Langmore et al. (2016) and Lazarus, Husaini, et al. (2014) had disappointing outcomes when implementing exercises post-RT, leading the authors to question the usefulness of the exercises. However, these studies have two notable deficits: poor compliance and heterogeneous groups. Although Hutcheson et al. (2012) did not comment directly on compliance, they did report on a heterogeneous group and state less than desirable results. Although positive outcomes have not yet been reported, it is premature to conclude that latent dysphagia cannot be minimized or eliminated in individuals with OPC because the participants in the three studies have had limited compliance with the experimental intervention and/or the studies collapsed participants with a range of tumor locations into a single group for analysis, thereby potentially masking benefits that might be present for specific tumor sites.

Purpose and Specific Aims

The long-term objective of this line of research is to enhance understanding of the effectiveness of swallowing exercises for individuals with HNC who have latent dysphagia from RT. The long-term goal is to design targeted exercise protocols that minimize pain and maximize compliance in order to achieve the best swallowing outcomes. As a first approach to achieving

the long-term objective, the purpose of this study was to describe the pain and exercise-related effort experience, and to evaluate the impact of dysphagia exercises on swallowing ability in individuals with OPC who have completed oncologic treatment. The study design and execution were intended to address non-compliance of participants, which has been a limiting factor in prior studies. Pain and exercise-related effort were tracked daily so this reported barrier could be more thoroughly described and understood.

Three specific aims were addressed in the current research.

Specific Aim (SA) 1: Evaluate the impact of dysphagia exercises on swallowing function in individuals with OPC who have completed RT and now are experiencing latent dysphagia. Swallowing function was evaluated in two ways, creating sub-aims 1a and 1b.

SA 1a evaluated changes in lingual strength and endurance as measured during non-swallow movements.

Hypothesis 1a: Isometric lingual strength and endurance will improve after completing the exercise regimen.

SA 1b evaluated swallow-related QOL using the MDADI.

Hypothesis 1b: Swallowing-related QOL will improve after completing the exercise regimen.

Specific Aim 2: Assess changes in pain associated with dysphagia exercises that are completed by individuals who had an OPC and who have completed RT. This was done by comparing the magnitude of pain rating a participant offered after completing the set of four exercises at baseline, weekly for four weeks, and one week after completing the daily exercise protocol. This sub aim addressed the issue of whether pain perceived after completing a set of dysphagia exercises changed as a function of more time spent doing the exercises on a daily basis.

Hypothesis 2: The perception of pain associated with completing the block of four dysphagia exercises will increase from baseline to Weeks 1 and 2, then decrease in Weeks 3, 4 and post-termination of the exercise protocol.

Specific Aim 3: Assess changes in sense of effort associated with dysphagia exercises that are completed by individuals who had an OPC and who have completed RT. This aim paralleled Aim 2 and was accomplished by comparing the sense of effort rating a participant offered after completing the set of four exercises at baseline, weekly for four weeks, and within one week of terminating daily exercises. This sub aim addressed the issue of whether sense of effort after completing a set of dysphagia exercises changed as a function of more time spent doing the exercises on a daily basis. Sense of effort was included in addition to pain because preliminary questioning of individuals with HNC who were post-RT revealed that some described heightened effort with oral movements, but did not necessarily describe pain.

Hypothesis 3: The perception of sense of effort associated with completing the block of four dysphagia exercises will increase from baseline to Weeks 1 and 2, then decrease in Weeks 3, 4 and post-termination of the exercise protocol.

An Exploratory Aim (EA1) to describe the extent of participant compliance with the daily exercise program was also included. Two of the three prior studies that assessed outcomes of dysphagia exercises started after RT was completed (Langmore et al., 2016; Lazarus, Husaini, et al., 2014) noted poor compliance but did not track compliance in detail. Using daily logs completed by the participant, various indices of compliance were computed including average

number of exercise sessions completed daily and number of days with completion or 0, 1, 2, 3, 4, or 5 exercise sessions. Field notes from study personnel who contacted the participants during the four-week exercise program also were qualitatively assessed for insight regarding compliance issues. This was not a hypothesis driven aim but rather a descriptive aim to learn more details about the extent of compliance and barriers to compliance with dysphagia exercise in individuals with OPC with latent dysphagia.

Chapter III: Methods

Participants

The inclusion criteria for participants were: 1) confirmed diagnosis of squamous cell carcinoma of the BOT (review of medical records and participant report), 2) 18 years of age or older (self-report and verified by medical record), 3) recipient of definitive or post-operative RT that was completed at least 3 months and no more than 20 years ago, and 4) experiencing latent dysphagia symptoms at time of consent into the study (self-report and baseline MDADI score less than 100). Exclusion criteria were: 1) surgery to the oral cavity or pharynx unrelated to management of the OPC excluding routine dental work, 2) neurological conditions such as stroke, head injury, or progressive conditions known to potentially affect swallowing, and 3) treatment for another type of cancer or cancer reoccurrence currently taking place. Cognitive status was not used as an inclusion or exclusion criteria for the study although each participant was required to demonstrate to research personnel that they understood and could execute all exercises in the protocol. Given this, and also given the emphasis on compliance with the protocol, cognitive screening was completed using the Montreal Cognitive Assessment (MoCA)

(Nasreddine et al., 2005) so that the information could later be considered when evaluating study results.

Participants were recruited from various sources including the clinical caseload at the KU Medical Center, the local support group for people with HNC, and the surrounding community. Eighteen individuals were consented into the study. Of these 18, six ultimately were not part of the analysis. Two of the individuals halted their participation in the first 24 hours after consent, citing emotional and psychological stress from having to think about a difficult time in their life related to swallowing. A third stopped after two days of doing the exercises and indicated that his busy schedule would not allow participation. The fourth person stopped after five days indicating that the exercises were boring. The fifth became ill during the latter part of the protocol and stopped participation. The sixth person had cognitive concerns raised during the baseline data collection but he was able to demonstrate the exercises and understanding of study procedures at that time. Confusion became more apparent during daily interactions once the exercise protocol commenced. At the conclusion of the protocol when the home journal was reviewed it was unclear what, if any, of the protocol was completed. These concerns about his cognition were validated by the participant's low score on the MoCA. He was, therefore, excluded from the analysis because it could not be determined whether he had followed the protocol.

Tables 1 andTable 2 include demographics and medical history information for the 12 participants who were retained for analysis. Demographics and medical history information of the six individuals who were not included in the analysis are in Tables 3 and Table 4. Potential differences between those retained and those dropped from analysis were explored statistically

(see Results). The six who were dropped either declined to come back for post-testing or simply did not respond to investigator communications asking them to return for post-testing.

The 12 participants retained consisted of 11 men and one woman ranging in age from 49-74 years (mean: 65.1 years, sd: 7.9 years). Tumor staging varied (see Table 2). Two of twelve had HPV-related tumors. On average, the participants were 7.6 years post-completion of their RT (sd: 2.4 years; range: 4-12 years). Based on the MoCA scores 83% were considered not to show evidence of cognitive decline using a cutoff score of ≥26 and 17% were identified as having abnormal MoCA scores indicating mild cognitive impairment (Nasreddine et al., 2005). Participants were asked to provide a list of their current medications, which was also verified by looking at medical records. In addition, participants were asked to list any pain related medication they had consumed prior to completing the exercise protocol. The intention was to identify medications specifically taken to manage pain (one of the variables participants were asked to rate in the study) or that might have side effects that could impact swallowing function. The medication Gabapentin, commonly prescribed for nerve pain, was the only pain medication reported within the group (participants 1, 3, 4, 7). This medication was prescribed on a 'take as needed basis' (i.e. prn) for all participants and was only reported as being taken prior to data collection by participant one at baseline. Two others (#4, 5) were taking Lorazepam for anxiety; this can cause dry mouth. Two others (#3, 9) were taking reflux medication (i.e. Pepcid, Prilosec) which also can cause dryness. A number of other medications were reported but review of the type of medication and side effects did not raise concern that swallowing function was likely to be impacted.

Power analysis completed prior to subject recruitment indicated that inclusion of 10 or more participants should be sufficient to detect a clinically meaningful change in one of the

primary outcome measures for this study, namely, the MDADI. The developers of the MDADI have published information indicating a 10-point change on that scale is associated with a clinically significant change in swallowing (Hutcheson et al., 2015). Hutcheson et al. (2015) reported that the difference in MDADI scores was normally distributed with a standard deviation of 9.5 in their sample of 1,136 individuals with HNC. Using that published information, sample size analysis was carried out using PS – Power and Sample Size Program v3.0 (January 2009). If one assumes that the current study has 10 pairs of data (10 subjects with pre- and post-exercise data) and if the true difference in the MDADI response of a subject's matched pairs is 10 points, the null hypothesis that this response difference is zero can be rejected with power of .843 if the associated type I error probability of .05 is used. There were not clearly applicable data for the tongue strength measures in the published literature to complete a power and sample size analysis for this study.

Table 1: Demographic information for participants included in data analysis

Participant	Age	Gender	Occupation	Education Level	MoCA Score
1	70	M	Retired	Trade School	21
2	65	M	Retired	Bachelor Degree	26
3	72	M	Retired	Some College	27
4	70	M	Retired	Graduate Degree or More	25
5	60	M	Retired	High School/GED	28
6	73	F	Retired	Graduate Degree or More	28
7	68	M	Company Owner	Some College	26
8	74	M	Recruiter	Graduate Degree or More	28
9	66	M	Retired	Bachelor Degree	26
10	61	M	Firefighter	Some College	27
11	49	M	Executive Manager	Graduate Degree or More	28
12	53	M	Railroad Worker	Some College	27

M=Male; F=Female

Table 2: Medical information for participants included in data analysis

Participant	Tumor Staging	HPV Status	Surgery	Neck Dissection	Years since treatment
1	$T_2N_3M_0$	Negative	No	Yes	8
2	$T_1N_1M_0$	Negative	No	Yes	9
3	$T_2N_{2b}M_0$	Negative	No	No	8
4	$T_3N_{2c}M_0$	Positive	No	No	4
5	$T_3N_{2c}M_0$	Positive	No	No	4
6	$T_3N_{2b}M_0$	Negative	No	No	8
7	$T_1N_2M_0$	Negative	No	No	6
8	$T_2N_{2c}M_0$	Negative	No	No	10
9	$T_3N_0M_0$	Negative	No	Yes	12
10	$T_0N_2M_0$	Negative	No	Yes	5
11	$T_1N_{2b}M_0$	Negative	Yes	Yes	8
12	$T_4N_{2b}M_0$	Negative	No	No	9

HPV=Human papillomavirus

Table 3: Demographic information for participants excluded from data analysis

Participant	Age	Gender	Occupation	Education Level	MoCA Score
1	68	M	Retired	Some College	28
2	73	M	Retired	Graduate Degree or More	15
3	66	F	Credit Union Manager	Associate's Degree	26
4	63	M	Disability	Some College	23
5	70	M	Retired	Some College	26
6	62	M	Electrician	Some College	27

M=Male; F=Female

Table 4: Medical information for participants excluded from data analysis

Participant	Tumor Staging	HPV Status	Surgery	Neck Dissection	Years since treatment
1	$T_2N_{2b}M_0$	Positive	No	No	3
2	$T_3N_0M_0$	Positive	No	No	6
3	$T_2N_2M_0$	Positive	No	No	6
4	$T_3N_0M_0$	Negative	No	No	12
5	$T_2N_1M_0$	Positive	No	Yes	5
6	$T_3N_2M_0$	Positive	No	No	5

HPV=Human papillomavirus

Instrumentation and Measurement Tools

Study-specific forms were completed to gather demographic and medical information at baseline and document any changes at post-exercise completion (Appendix A and Appendix B). Tongue strength was measured using the IOPI. The IOPI was specifically designed to quantify lingual pressures during isometric pressing tasks (Robin et al., 1992). The IOPI has been used in previous HNC research studies (e.g., Lazarus et al. 2000; Lazarus, Husaini, et al. 2014; White, Cotton, Hind, Robbins, & Perry 2009). The equipment consists of a small air-filled bulb attached by tubing to the IOPI device. The IOPI has a built-in pressure transducer that senses the amount of pressure applied to the bulb. Using peak-hold functions of the IOPI, the maximum pressure generated during a brief isometric tongue elevation maneuver is detected. Utilizing additional functions of the IOPI device, it is possible to set a 50% of maximum threshold with visual feedback. When set in the 50% of threshold function, a small series of LED lights are turned on as pressure is applied to the bulb. When the applied pressure reaches the 50% of maximum value, a green light turns on. As described in the procedures, this function can be used to assess endurance of tongue strength (recorded in seconds) by asking the participant to keep the green light turned on for as long as s/he can.

The MDADI was used to obtain an index of the impact of dysphagia on the participant's QOL. The survey has been validated for this purpose in individuals with HNC (Chen et al., 2001). The survey has 20 items, each of which is scored on a 5-point scale that includes the following scale points: strongly disagree, disagree, no opinion, agree, strongly agree. One of the questions is reported as a "global" score and it is a single rating in response to the statement: "My swallowing ability limits my day-to-day activities." From the remaining 19 questions scores

from specific questions are extracted to generate subscale scores for physical (ex. “Swallowing takes great effort.”), functional (ex. “People have difficulty cooking for me.”), and emotional (ex. “I do not go out because of my swallowing problem.”) domains. The scores for each domain are calculated by summing up the scale points within a domain and then scores are normalized to range from 20 (low functioning) to 100 (high functioning) for each subscale. Finally, a composite score (normalized to range from 20-100) is calculated to reflect scores on 19 items (the global question is excluded) using weighted scores from the physical, functional, and emotional subscale scores.

Study Personnel

Five study personnel participated in executing the procedures and obtaining measures of interest. In the Measurement section and Procedure section below the involvement of specific study personnel for specific tasks is designated. The primary researcher, Stephanie Knollhoff, was identified as SK. The remaining four study personnel were all graduate students in speech-language pathology who were trained to their tasks by SK. The graduate students’ roles are designated as GS 1, 2, 3, and 4. GS 1 and 2 were involved only in scoring of tests (e.g., MoCA, MDADI) and extracting ratings marked on the pain scale and the effort scale. The primary investigator trained them to these tasks but was not involved in completing the tasks during the study. GS 1 and GS 2 consulted with the primary investigator if they had questions but the intention was to exclude the primary investigator from involvement in scoring of the measures of interest for the study. Because of the technical nature of obtaining the lingual strength and endurance measures those were completed by the primary investigator, SK. GS 3 and GS 4 were involved in the daily contact with participants as described in more detail below. After all data collection was completed and GS 1 and GS 2 had completed their tasks, SK did check the

scoring of all MoCA and MDADI scores as well as the pain and effort ratings to ensure accuracy.

Measures

The following measures were tracked in this study:

1. Maximum pressure from the IOPI during an isometric pressing task of the tongue against the hard palate. This pressure was recorded in kPa to the nearest tenth. Three trials at a given data collection point were completed with the maximum being used in the statistical analysis.
2. Tongue endurance at 50% of maximum pressing was recorded in seconds from the IOPI. Two trials at a given data collection point were completed with the maximum used in the statistical analysis.
3. Sub-scores from the MDADI were used to calculate composite scores per the survey instructions. This scoring was done by GS 1 and GS 2. The composite score and sub-category scores were each analyzed in the statistical analysis.
4. The pain rating from the Wong-Baker Pain Rating Scale (Herr & Garand, 2001). This is a 10-point scale that includes a graphic depiction of a face that accompanies the numerical values. The faces reflect degrees of smiling (no pain) to frowning (more pain). This scale is routinely used within medical settings, including radiation oncology clinics, to track a person's perception of pain (included in Appendix C). These scores were extracted by GS 1 and GS 2.
5. The rating of sense of effort as indicated on a visual analog scale (VAS; see Appendix C). The VAS is a 100mm vertical line on which the participant placed a mark to indicate the degree of effort that s/he felt from doing the swallowing exercises. The line was

anchored on the bottom by the label “no effort” and on the top by “maximum effort.” The index of effort was the distance as measured from the bottom end of the line to the mark placed by the participant (recorded in mm to the nearest hundredth; done by GS 1 and GS 2).

Dysphagia Exercise Program

Four oral and swallowing exercises, each completed 10 times (40 total) constituted one block of exercises (see Figure 1). The protocol required a participant to complete a block of exercises five times a day, seven days a week, for four consecutive weeks. During a given day, the blocks were separated by 90-120 minutes. In total, 200 exercise movements were to be completed each day.

Four exercises were selected to address impairments that frequently occur in individuals with OPC who have latent dysphagia. Written instructions provided to participants are included in Appendix D. The exercises were the Mendelsohn maneuver, Masako maneuver, effortful swallow, and lingual tip press. The effortful swallow and Mendelsohn maneuver place specific aspects of the swallowing function under volitional control. Motor exercises, such as the Masako maneuver and lingual tip press, increase strength, mobility, and endurance of the swallowing mechanism (Murphy & Gilbert, 2009).

Instructions for completing the Mendelsohn maneuver were as follows: 1) start to swallow your saliva; 2) stop and hold the swallow by trying to keep the Adam's apple elevated, 3) hold this position for 3 seconds, 4) release the muscles and complete the swallow. After a brief break, the sequence was repeated until a total of 10 repetitions were completed. Small sips of water between trials were allowed if that was needed to moisten the mouth so that a saliva swallow could be completed during the maneuver.

To complete the Masako maneuver, the participant was instructed to hold the tongue between the front teeth or gums. With the tongue held firmly, a saliva swallow was completed while maintaining a firm hold of the tongue between teeth/gums. After a brief pause, the maneuver was completed again until 10 trials were recorded.

For the effortful swallow, a participant was asked to swallow his/her saliva while squeezing the muscles as tightly as possible during the swallow. They were encouraged to bear down and swallow "as hard as possible" during the task, which was repeated 10 times in a row.

Finally, instructions for the lingual tip press were: 1) with an open mouth, place the tip of your tongue on the roof of your mouth (specifically the 'bumpy spot,' aka the alveolar ridge), 2) press as hard as you can for five seconds. Ten repetitions were completed with a short pause between trials.

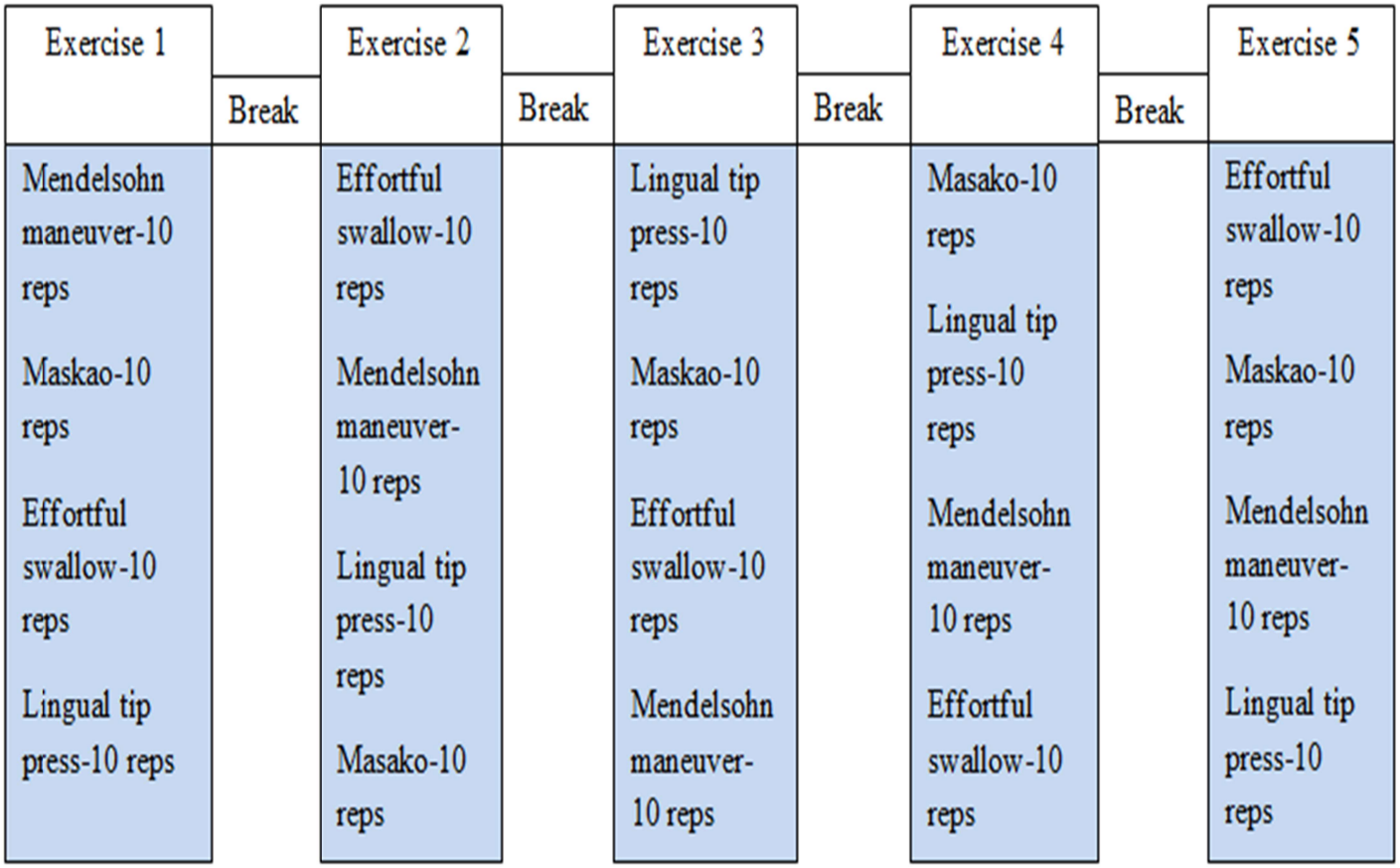


Figure 1: Example of exercise protocol block to be completed five times per day

Procedures

Figure 2 provides an overview of the procedures and time frame for a participant who completed the study. Baseline data collection occurred face-to-face and included the following:

1. Written informed consent was obtained (SK; see Appendix E).
2. Tongue strength and endurance were measured (SK) with the IOPI following the manufacturer's recommendations. The bulb was positioned in midline on the alveolar ridge. The individual was instructed to push the tongue against the bulb as forcefully as possible for three seconds. Three trials of the maximum press task were completed with a 30-second rest enforced between trials. The task then shifted to obtaining the endurance measure. For this task, the investigator first took the average maximum press value for the participant and divided that value by two to determine the 50% maximum pressure value to be targeted during the endurance trial. The IOPI settings were then adjusted so that the LED feedback light turned on when the applied pressure reached the value that was 50% of the participant's maximum pressure value. The participant was instructed to push just hard enough to turn the LED light on and keep it on. The IOPI provides a digital stop watch to allow the researcher to record the total number of seconds that they were able to keep the LED light turned on. Two trials of the endurance task were completed with a two-minute rest enforced between trials.
3. A history and demographics form was completed under the observation of SK (later data extraction by GS 1 or GS 2; Appendix A).
4. The MDADI was filled out under the observation of SK (later scored by GS 1 or GS 2).
5. The MoCA was administered under the observation of SK (later scored by GS 1 or GS 2).

6. Pre-exercise oral pain was rated using the Wong-Baker Pain Rating Scale under the observation of SK (later scored by GS 1 or GS 2; Appendix C).
7. Participants were instructed how to complete the swallow exercises (SK). The investigator instructed the participant verbally on how to complete each exercise and provided a written set of instructions that were taken home (Appendix D). The participant was required to demonstrate accurate completion of each exercise before s/he left this first visit.
8. The participant completed the Dysphagia Exercise Program described above in the presence of the investigator (SK). E-Prime software was utilized to present the four exercises in random order on a computer screen. The E-Prime software prompted the participant to provide an oral pain rating, using the Wong-Baker Pain Rating Scale, after 10 repetitions of each of the four exercises was completed. The software also prompted the participant to offer a rating of sense of effort, using a VAS. After completing the full set of exercises, the participant sat quietly for five minutes during which time s/he was instructed to avoid talking and swallowing as much as possible. After five minutes, the participant gave a post-exercise oral pain rating and sense of effort rating.
9. The participant was instructed to initiate the exercises on a daily basis starting the next morning (SK).

The full set of activities for Contact 1 took approximately 60-90 minutes for each participant. At the conclusion, the participant was given a packet of information and forms to take home. The packet included a Dysphagia Exercise Program Journal containing written instructions for each exercise, oral pain rating scales, sense of effort scales, and a way to log completion of the daily exercises (i.e., number of times per day, number of repetitions per time,

number of days per week; Appendix C and Appendix D). The primary researcher (SK) instructed the participant to initiate the swallowing exercise protocol on the next day and continue daily for four weeks. The packet was reviewed to ensure the participant was familiar with the contents and the procedures included in those materials (SK). Before ending Contact 1, the best means for study personnel to contact the participant on a daily basis was determined through a discussion in which the options of phone, email, or text messaging were presented. The participant chose their preferred method of being contacted. Each participant was assigned to be contacted daily by either GS 3 or GS 4; the pairing between a participant and GS 3 or GS 4 was held constant throughout the four weeks of the protocol. The intent of the daily contact was to provide prompts to the participant, reminding him/her to complete the exercises (see Appendix F).

The following steps were taken to maximize compliance over the four weeks of at-home exercise completion:

1. Participants were contacted daily throughout the course of the study (via phone, email, text per individual preference). This contact provided a daily remainder to complete the swallowing exercise protocol. Field notes from these contacts were maintained for later review (GS 3 or GS 4 depending on the participant).
2. Participants received a phone call once a week, regardless of contact preference listed above (GS 3 or GS 4 depending on the participant). Phone calls took place on days 6, 13, 20, and 27 as these were the days prior to the participants filling out full rating forms. Study personnel inquired about completion of the exercise protocol, offering encouragement and reinstruction as needed. Field notes from these contacts were maintained for later review.

Weekly data collection for pain and sense of effort ratings were extracted by GS 1 and GS 2 once the participant turned in their log at the post exercise data collection visit. Included within these logs were randomized exercise protocols for each block that the participant completed, along with written instructions on how to complete each exercise. Participants logged the number of exercise blocks completed each day, duration spent on each block, and made note of any barriers they experienced. Days 1, 7, 14, 21, and 28, included randomized exercise blocks with full pain and sense of effort ratings, similar to baseline and post-intervention data collection, and the MDADI.

Post-intervention data were obtained in person one to three days after completing the four-week dysphagia exercise protocol. Seven participants, 58%, participated in post-intervention data collection the day immediately following the last data of the exercise protocol (participants 2,3,4,5,7,11). Three participants (1,8,12) participated in post-intervention data collection two days following completion of the exercise protocol. Two participants (6 and 9) participated in post-intervention data collection three days after completing the exercise protocol. Post-intervention data included: tongue strength and endurance measurements, MDADI, pre-exercise pain rating, ratings of pain and sense of effort for each of the four exercises done 10 times, and post-exercise ratings.

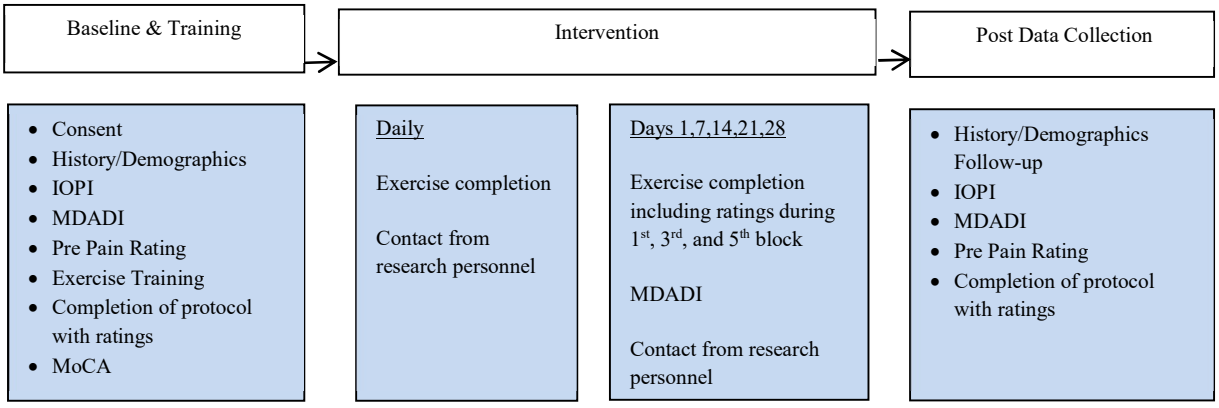


Figure 2: Procedures

Analysis

Descriptive statistics regarding the participant pool were calculated, including group means, standard deviations, and ranges for interval and ratio data such as age at time of study, age at diagnosis, months post-RT, etc. For other data that were nominal in nature (e.g., sex, co-morbid conditions, etc.), counts and frequencies were tabulated. Preliminary analysis was completed addressing comparison of participants retained and excluded from data analysis and compliance. The primary analysis to address each aim and sub-aim are detailed below. Non-parametric procedures were selected because some measures violated the parametric assumption regarding normal distribution and the population under study was not randomly selected from the population of individuals with BOT cancer who had latent dysphagia.

Specific Aim 1a. The maximum peak pressure obtained during baseline data collection was compared to the maximum peak pressure obtained during final data collection using the Wilcoxon Signed Ranked Test. Likewise, the endurance measure (at 50% of maximum) obtained during baseline data collection was compared to the maximum duration obtained at the post data collection visit using the Wilcoxon Signed Ranked Test (*W*). Effect size analysis was also conducted for both measures by deriving Cohen's *d* following guidelines from Fritz, Morris, and Richler (2012). A straightforward calculation of Cohen's *d* (Cohen, 1988) is not advisable when using nonparametric statistics wherein the assumption of normal distribution is not met (Fritz et al., 2012). Therefore, following procedures from Fritz et al. (2012), the *z* score that is part of the SPSS output for the Wilcoxon procedure was converted to a point biserial correlation *r* using the formula: $r = \frac{z}{\sqrt{N}}$. Cohen (1988) offers guidelines for this *r* value (large effect=.5; medium effect=.3; small effect=.1), however, convention within the speech-language research field is

typically to utilize the *d* rather than the *r* value. The formula from Fritz et al. (2012) for calculating *d* from the point biserial correlation *r* was used for this purpose: $d = 2r/\sqrt{(1 - r^2)}$. Magnitude of the effect sizes was judged relative to the guidelines suggested originally by Cohen (1988) for the *d* value: no effect=0-.19, small effect=.2-.49, medium effect=.5-.79, large effect≥.8. More stringent cutoffs (i.e., larger values of *d*) for within subject designs were apparently suggested by Barcikowski and Robey (1985) as cited in Robey (1998). However, the Barcikowski and Robey (1985) reference was for a presentation at a conference; a primary source within the peer-reviewed literature could not be found to assess how those elevated values were determined. Searching of the peer reviewed literature did not reveal any other sources suggesting use of elevated values when discussing cut-offs for effect sizes when using non-parametric procedures such as were used in the current study, including those using within subject measures. When reference was made to effect size cut-offs in relation to non-parametric procedures the typical cut points from Cohen (1988) were used (e.g., Fritz et al., 2012).

Specific Aim 1b. The MDADI composite score obtained at baseline was compared to the score obtained at the post-exercise visit using the Wilcoxon Signed Ranked Test. The four subscale scores of the MDADI (Emotional, Functional, Physical, Global) were analyzed in the same way. Effect size analysis was also conducted as described above.

Specific Aim 2. The pain rating at the end of completing all four exercises at baseline, weeks 1-4, and within 1 week of terminating the exercise was compared using the Friedman test. The Wilcoxon Signed Ranked Test was also used to compare pain ratings at baseline and post-exercise. Effect size was calculated for this pre- compared to post- measure as above.

Specific Aim 3. Sense of effort ratings was analyzed in the same manner as the pain data using the Friedman test. The Wilcoxon Signed Ranked Test was also used to compare sense of effort

ratings at baseline and post-exercise Effect size was calculated for this pre- compared to post-measure as detailed above.

Exploratory Aim. A frequency distribution of the number of participants completing all daily exercise sessions or lessor numbers of exercise sessions (4, 3, 2, 1, 0 sessions) was constructed for qualitative review. Field notes from the two graduate student research assistants who contacted participants throughout the 4-week exercise program were reviewed for recurrent themes or other insights related to compliance. Pearson product moment correlation coefficients were computed to evaluate the strength of the relationships between metrics of compliance and the change in MDADI composite scores, IOPI, pain ratings, and effort ratings from baseline to post-exercise protocol completion.

Chapter IV: Results

Preliminary Analysis

Two types of preliminary analyses were completed prior to running the primary analysis that was planned to address the specific aims. The first was a comparison of the participant pool that was retained for analysis and those who dropped out or were excluded from the analysis. This comparison was of importance in order to better understand if there were certain demographic or medical history variables that predisposed a participant to complete or not complete the protocol. The other preliminary analysis that was completed addressed the extent of compliance that the participants demonstrated with the four-week exercise protocol. A primary focus of the study design and the specific aims was to see if a pre-post change occurred in swallowing outcome measures after completing exercises so it was important to first describe the extent to which the exercise protocol was followed.

Comparison of Participants who were Included vs. Excluded from Analysis

Descriptive and frequency statistics along with chi-square analysis were run on the demographic and treatment information as a means of comparing the participants who were retained vs. dropped from the primary analysis. Non-parametric statistics (i.e. Mann-Whitney) were run on all baseline outcome measures and age. All 18 participants, regardless of group, were Caucasian and received RT and CT as part of their oncologic treatment. Mean age for those excluded from the analysis (67.0 years; range 62-73 years) was approximately two years older than that of those who were included (65.1 years; range 49-74 years). Chi-square analysis was completed to compare the distributions between the retained and dropped participants for gender, education level, surgical status, neck dissection status, and HPV status. Effect sizes for these chi squared values were calculated using the formula from R. Rosenthal and DiMatteo (2001) but can only be done for 2x2 contingency tables. Therefore, it was not possible to calculate effect size for "education level." As indicated in Table 5, the groups had comparable distributions for all variables with the exception of HPV status. HPV status was positive for 83% of those in the dropped group compared to 16% in the retained group; the effect size for this difference was large. It is also noted that although 'neck dissection' distributions did not differ significantly between groups, there was a medium effect size with 42% in the retained group having had a neck dissection compared to 17% in the excluded group.

Table 6 highlights that there was a statistically significant difference, and large effect sizes, between participants retained and excluded from the analysis on the MDADI composite, global, and physical scores. These scores were higher for the people excluded from the analysis indicating that they felt less impact on their quality of life from their dysphagia condition compared to those who remained in the analysis (raw data for the excluded participants are in

Appendix G). Note that the effect size for the functional subscale was also large, and the emotional subscale was nearly at the cut point between medium and large despite a lack of statistical difference on these two subscales. Overall, these results indicated that the people who were not retained for various reasons were experiencing less reduction in their QOL related to dysphagia compared to those who were retained. Additionally, though lingual strength did not differ significantly, the effect size was large. Baseline pain and effort ratings did not differ significantly between the retained and excluded participants. Overall, the MDADI results and the size of the effect for lingual strength suggest that the people retained for the analysis may have had more involved swallowing issues than those who were excluded from the analysis.

Table 5: Chi-Square outcomes of participants retained for analysis vs. participants excluded from analysis.

	Chi Square Value	***p* value**	***d***
Gender	0.281	.596	.252
Education Level	3.150	.533	--
Surgery	0.529	.467	.348
Neck Dissection	1.125	.289	.516
HPV Status	7.481	.006	1.687

HPV=Human Papillomavirus

Table 6: Means (and sd) on age and outcome variables, Mann-Whitney results, and associated Cohen's *d* values when comparing participants retained for analysis vs. participants excluded from analysis

	Participants Retained (n=12)	**Participants Excluded (n=6)**	**Test Statistic (*U*)**	***p* value**	***d***
Age	65.1 (7.9)	67.0 (4.2)	33.5	.814	.111
MDADI Composite	71.3 (11.3)	85.5 (7.5)	10.0	.015	1.402
MDADI Emotional	74.3 (14.1)	83.3 (10.9)	20.0	.132	.755
MDADI Functional	79.2 (15.5)	90.6 (8.5)	18.5	.096	.838
MDADI Global	75.0 (22.8)	96.7 (8.2)	13.5	.022	1.145
MDADI Physical	63.3 (11.3)	84.2 (15.0)	11.0	.019	1.324
Lingual Strength	44.7 (12.7)	56.7 (8)	16.5	.067	.954
Lingual Endurance	47.5 (45.1)	47.8 (9.2)	26.5	.373	.429
Pain	.2 (.39)	0 (0)	30.0	.616	.267
Sense of Effort	51.6 (23.5)	32.4 (31.8)	25.0	.335	.501
MoCA	26.4 (1.9)	24.2 (4.8)	24.5	.269	.525

MDADI=M.D. Anderson Dysphagia Inventory; MoCA=Montreal Cognitive Assessment

Program Compliance

Compliance was analyzed in two ways. The first was a simple tabulation of the total number of exercise sessions that were completed over the four-week protocol. Recall that exercises were to be completed five times per day for 28 consecutive days for a grand total of 140 exercise sessions. Figure 3 displays the number of sessions that each participant completed as reported in their daily journal. Across individuals, the total number of sessions completed ranged from a low of 50 sessions (35.7% of the sessions in the protocol) to a high of 140 sessions (100%). As a group, the average number of completed sessions was 110.4 (sd: 35.1 sessions), or 78.9% of the 140 prescribed exercise sessions. Six participants completed at least 90% of the sessions; two completed 80%-89% of the sessions; one completed 70%-79% of sessions; and the remaining three completed less than 50% of the sessions. Evaluating compliance in terms of the total number of sessions completed, nine of twelve participants (75%) completed at least 70% of the exercise sessions.

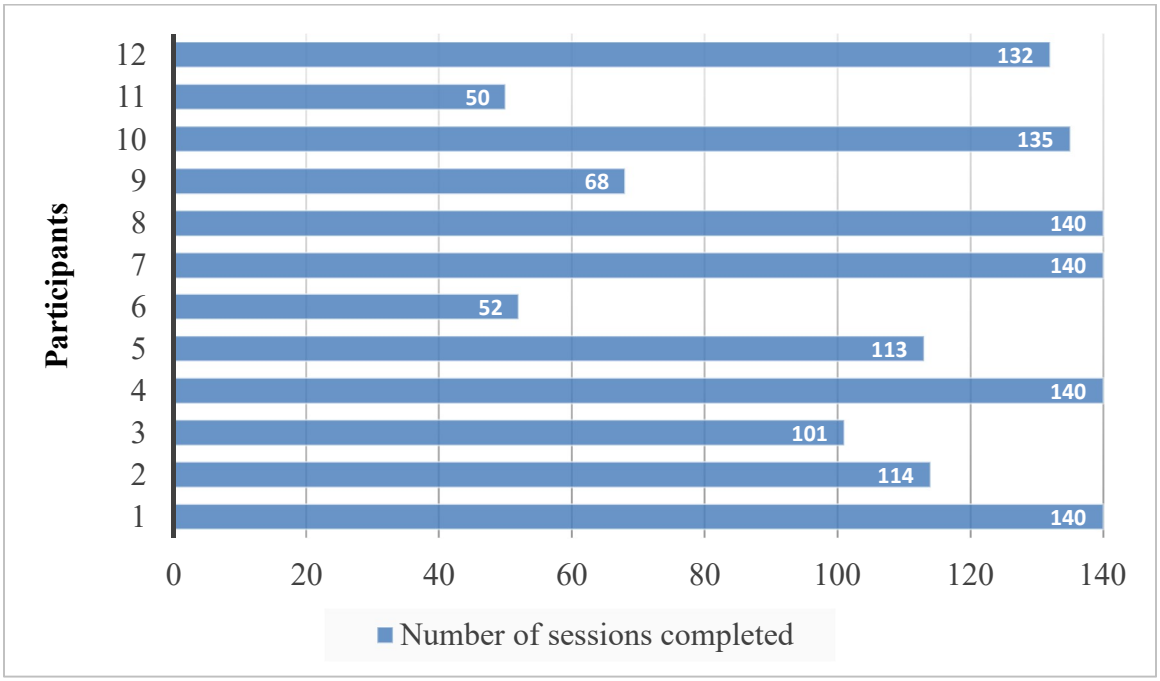


Figure 3: Total number of exercise sessions completed out of 140 that were prescribed in the protocol

A second approach to understanding the extent of compliance with the exercise protocol was to count how many days out of 28 that a participant had 'strong,' 'moderate,' or 'poor' compliance. Strong compliance was defined as completion of 4-5 sessions in a day; moderate compliance was defined as completing 2-3 sessions in a day; and poor compliance was defined as completing 0-1 session in a day. Figure 4 is a stacked bar chart showing the percentage of the 28 days with strong, moderate, and poor compliance for each individual. Four participants (6, 9, 10, 11) had at least one day in which compliance was poor. Participants #11 and 6 stand out as having a very large percentage of days with poor compliance. Participant 10, on the other hand, did have a few days with poor compliance, but the vast majority of days he had strong compliance. Conceptualizing compliance in this manner, it appeared that moderate-to-strong

compliance was present for nine participants (1, 2, 3, 4, 5, 7, 8, 10, 12), and moderate-to-poor compliance for the remaining three participants (6, 9, 11).

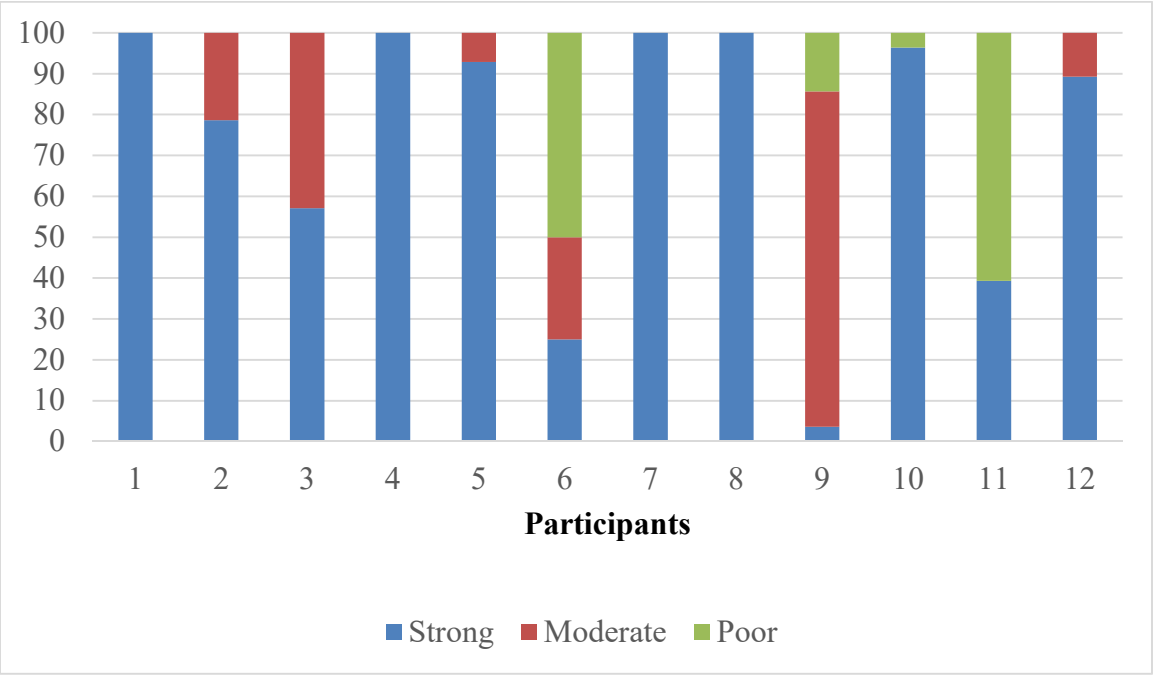


Figure 4: Individual participant compliance reported as a percentage of days with strong (4-5 sessions), moderate (2-3 sessions), and poor (0-1 session) compliance

Primary Analysis

Lingual Strength and Endurance

The baseline and post-protocol lingual strength values for individual participants and for the group are presented in Table 7. Change scores for maximum lingual strength ranged from -12.0 to 15.0 with a mean of 1.8. On average, the strength value increased by 7.8% relative to the baseline value. However, the percentage change varied markedly across participants from a 75% increase to a 19% decrease in maximum strength. The Wilcoxon Signed Rank Test

comparing the maximum lingual strength (kPa) from pre- to post-exercise resulted in a *W* value of 44.5 which was not statistically significant (*p*=.30), with a small effect size (*d*=.43).

Table 7: Lingual strength data

Participant	Baseline Lingual Strength (kPa)	Post Lingual Strength (kPa)	Change Score	Percentage Change from Baseline
1	42.0	42.0	0.0	0.0
2	63.0	73.0	10.0	23.8
3	50.0	38.0	-12.0	-19.0
4	36.0	43.0	7.0	14.0
5	20.0	15.0	-5.0	-13.9
6	46.0	61.0	15.0	75.0
7	35.0	37.0	2.0	4.3
8	31.0	32.0	1.0	2.9
9	46.0	47.0	1.0	3.2
10	58.0	56.0	-2.0	-4.3
11	49.0	52.0	3.0	5.2
12	60.0	61.0	1.0	2.0
Group Mean	**44.7**	**46.4**	**1.8**	**7.8**
Group SD	**12.7**	**15.5**	**6.9**	**23.9**

Table 8 includes pre- and post- lingual endurance values for each participant and the mean for the group. Endurance change scores ranged from -66.0 to 250.0 seconds with a mean of 47.5. The percentage of change in endurance values varied substantially across participants. Most of the participants demonstrated some degree of increase in endurance with 75% of them showing a positive change that ranged from 20% to more than 1500% increase relative to the baseline endurance. However, three participants had a reduction in endurance at the post testing ranging from a 5% to a 62% decrease. The Wilcoxon Signed Rank Test comparing the maximum lingual endurance (seconds) from pre- to post-exercise resulted in a value of *W*=60 which was not statistically significant (*p*=.09), with a medium effect size (*d*=.71). The median lingual

endurance measurement increased from baseline (median=34.0 seconds) to post-intervention (median=60.5 seconds) by 26.5 seconds. The minimum time of lingual endurance increased by 14 seconds from baseline to post-intervention; likewise, the maximum time of lingual endurance increased by 109 seconds (baseline=171.0, post=280.0).

Table 8: Lingual endurance data

Participant	Baseline Lingual Endurance (seconds)	Post Lingual Endurance (seconds)	Change Score	Percentage Change from Baseline
1	18.0	26.0	8.0	44.4
2	57.0	54.0	-3.0	-5.3
3	171.0	105.0	-66.0	-38.6
4	59.0	76.0	17.0	28.8
5	12.0	102.0	90.0	750.0
6	25.0	65.0	40.0	160.0
7	14.0	250.0	236.0	1685.7
8	88.0	33.0	-55.0	-62.5
9	30.0	280.0	250.0	833.3
10	15.0	41.0	26.0	173.3
11	43.0	52.0	9.0	20.9
12	38.0	56.0	18.0	47.4
Group Mean	**47.5**	**95.0**	**47.5**	**303.1**
Group SD	**45.1**	**83.2**	**99.8**	**527.6**

MDADI

Table 9-13 summarize the MDADI composite and subscale scores for pre- and post-treatment values per participant; change scores and percentage change from baseline are also included. As a group, the MDADI composite scores increased by 7.2%, but as with the other outcome measures, the direction and magnitude of change from pre to post varied markedly across participants. MDADI composite change scores ranged from -6.4 to 21.0 with a mean of 4.6. A clinically significant improvement (i.e., $\geq$10 points) was noted in 25% of the participants

(this included rounding the score of participant #6 from 9.6 to 10). The Wilcoxon Signed Rank Test comparing composite scores from pre- to post-exercise resulted in a value of W=62.5 which was not statistically significant (p=.06) but there was a large effect size (d=.82).

As a group the MDADI physical scores increased by 7.9% (i.e., improved dysphagia related quality of life), but as with the other measures, the direction and magnitude of change from pre to post varied markedly across participants. Three (25%) had a clinically significant improvement on this subscale and one (8%) had a clinically significant decline while the rest had change scores of less than 10 points in a given direction. MDADI physical change scores ranged from -15.2 to 42.9. Results from the Wilcoxon Signed Rank Test analysis indicated no statistical difference (W=33.5, p=.19) and there was a medium effect size (d=.56).

MDADI functional subscale scores varied markedly with change scores ranging from -19.9 to 23.3. Three participants (25%) demonstrated an improvement of at least 10 points on this subscale score and two participants (17%) reported a clinically significant decline. Results from the Wilcoxon Signed Rank Test analysis indicated no statistical difference (W=28.5, p=.48) and a small effect size (d=.3).

Five participants (42%) were noted to have a clinically significant improvement on the emotional subscale. As a group emotional scores increased on average by 13.6%. It is also worth noting that none of the participants demonstrated a decrease in the MDADI emotional scores from baseline to post-intervention. A Wilcoxon Signed Rank Test was statistically significantly different when comparing emotional subscale scores from pre- to post-exercise (W=28, p=.02) and the effect size was large (d=1.12).

The group average for the global subscale score increased by 15% when comparing pre-to-post exercise. Four of 12 (33%) improved on the global score, six (50%) were unchanged, and

two (17%) demonstrated worsening. Recall that the global score is a response to a single item. This response is then normalized to range from 20 to 100 to parallel the normalized scores for the other subscales. As such, a shift of 1 scale point represents a 20-point change in the normalized score. The Wilcoxon Signed Rank Test comparing global scores from pre- to post-exercise resulted in a value of W=16 which was not statistically significant (p=.23) and the effect size was medium (d=.49).

Table 9: MDADI composite scores

Participant	**Baseline MDADI Composite**	**Post MDADI Composite**	**Change Score**	**Percentage Change from Baseline**
1	70.4	75.7	5.3	7.6
2	92.7	86.3	-6.4	-6.8
3	55.8	52.6	-3.2	-5.6
4	74.8	70.5	-4.3	-5.7
5	72.7	79.0	6.3	8.6
6	57.8	67.4	9.6	16.5
7	65.3	71.6	6.3	9.6
8	88.5	94.8	6.3	7.1
9	65.3	75.8	10.5	16.0
10	75.9	76.8	0.9	1.2
11	61.2	82.2	21.0	34.4
12	74.8	77.9	3.1	4.2
Group Mean	**71.3**	**75.9**	**4.6**	**7.2**
Group SD	**11.3**	**10.4**	**7.5**	**11.6**

MDADI=M.D. Anderson Dysphagia Inventory

Table 10: MDADI physical scores

Participant	Baseline MDADI Physical	Post MDADI Physical	Change Score	Percentage Change from Baseline
1	67.5	65.0	-2.5	-3.7
2	82.5	70.0	-12.5	-15.2
3	55.0	47.5	-7.5	-13.6
4	57.5	62.5	5.0	8.7
5	75.0	75.0	0.0	0.0
6	50.0	50.0	0.0	0.0
7	55.0	60.0	5.0	9.1
8	75.0	90.0	15.0	20.0
9	52.5	75.0	22.5	42.9
10	72.5	72.5	0.0	0.0
11	50.0	67.5	17.5	35.0
12	67.5	75.0	7.5	11.1
Group Mean	**63.3**	**67.5**	**4.2**	**7.9**
Group SD	**11.3**	**11.7**	**10.2**	**17.7**

MDADI=M.D. Anderson Dysphagia Inventory

Table 11: MDADI functional scores

Participant	Baseline MDADI Functional	Post MDADI Functional	Change Score	Percentage Change from Baseline
1	63.3	76.7	13.4	21.1
2	100.0	96.7	-3.3	-3.3
3	53.3	53.3	0.0	0.0
4	93.3	73.4	-19.9	-21.4
5	80.0	86.7	6.7	8.3
6	56.7	80.0	23.3	41.2
7	73.3	76.7	3.4	4.6
8	100.0	100.0	0.0	0.0
9	80.0	73.3	-6.7	-8.3
10	90.0	76.7	-13.3	-14.8
11	80.0	100.0	20.0	25.0
12	80.0	80.0	0.0	0.0
Group Mean	**79.2**	**81.1**	**1.9**	**4.4**
Group SD	**15.5**	**13.3**	**12.7**	**17.5**

MDADI=M.D. Anderson Dysphagia Inventory

Table 12: MDADI emotional scores

Participant	Baseline MDADI Emotional	Post MDADI Emotional	Change Score	Percentage Change from Baseline
1	84.0	92.0	8.0	9.5
2	100.0	100.0	0.0	0.0
3	60.0	60.0	0.0	0.0
4	80.0	80.0	0.0	0.0
5	60.0	76.0	16.0	26.7
6	72.0	80.0	8.0	11.1
7	72.0	84.0	12.0	16.7
8	96.0	96.0	0.0	0.0
9	68.0	80.0	12.0	17.6
10	64.0	84.0	20.0	31.3
11	56.0	84.0	28.0	50.0
12	80.0	80.0	0.0	0.0
Group Mean	**74.3**	**83.0**	**8.7**	**13.6**
Group SD	**14.1**	**10.3**	**9.3**	**15.9**

MDADI=M.D. Anderson Dysphagia Inventory

Table 13: MDADI global scores

Participant	Baseline MDADI Global	Post MDADI Global	Change Score	Percentage Change from Baseline
1	40.0	80.0	40.0	100.0
2	80.0	100.0	20.0	25.0
3	40.0	20.0	-20.0	-50.0
4	100.0	80.0	-20.0	-20.0
5	80.0	80.0	0.0	0.0
6	40.0	80.0	40.0	100.0
7	100.0	100.0	0.0	0.0
8	100.0	100.0	0.0	0.0
9	80.0	80.0	0.0	0.0
10	80.0	80.0	0.0	0.0
11	80.0	100.0	20.0	25.0
12	80.0	80.0	0.0	0.0
Group Mean	**75.0**	**81.7**	**6.7**	**15.0**
Group SD	**22.8**	**21.7**	**19.7**	**44.2**

MDADI=M.D. Anderson Dysphagia Inventory

Table 14 depicts the patterns of change in the composite and subscale scores per participant. In this table only changes of 10 points or more are indicated to reflect what is expected to be a clinically significant change in dysphagia-related QOL. Of note is participant 11 who improved in all subscale scores and the composite score. Similarly, participants six and nine improved in the composite score and at least one of the subscale scores (functional for #6; emotional and physical for #9). Four others (#1, 5, 7, 8) improved on one subscale score but not the composite score; only one of these four also had a global rating that improved (#1) while the others had global scores that remained unchanged. Two participants (#2, 4) had a significant decrease on one subscale score. Participant four also gave a post-exercise global rating that was a significant decrease. Paradoxically, participant two's global rating improved despite the negative change in their physical subscale and no changes in the other subscales. Participant 10 had a positive change in the emotional subscale and a negative change in the functional with no change in the global or composite ratings. Finally, participant 12 had no clinically significant change in any subscale, composite, or global score.

Table 14: Clinically significant change scores (≥10 points) in positive (+) or negative (-) directions per participant for the MDADI composite and subscale scores

Participant	Composite	Emotional	Functional	Physical	Global
1			+		+
2				-	+
3					-
4			-		-
5		+			
6	+		+		+
7		+			
8				+	
9	+	+		+	
10		+	-		
11	+	+	+	+	+
12					

Self-Reported Pain After Completing Dysphagia Exercises

The oral pain rating that each subject reported after completing the exercise protocol at baseline, on days 1, 7, 14, 21 and 28, and at the post-protocol data collection session were compared within subjects. Due to missing data points from Participants 6, 7, and 11, the sample size for this analysis was reduced to nine participants. A non-parametric Friedman test of differences among repeated measures resulted in a Chi-square value of 6.00 with *df*=6 and an associated *p*-value of .42. This result indicated that self-rated pain did not differ significantly across the seven ratings that were completed. Inspection of the raw data for pain ratings revealed that no participant rated pain higher than a two on the 10-point scale at any of the rating intervals. Furthermore, the group mean pain rating at each reporting interval was less than one (Figure 5). These findings indicated that participants reported feeling little to no pain associated with completion of the dysphagia exercises at any point within the study.

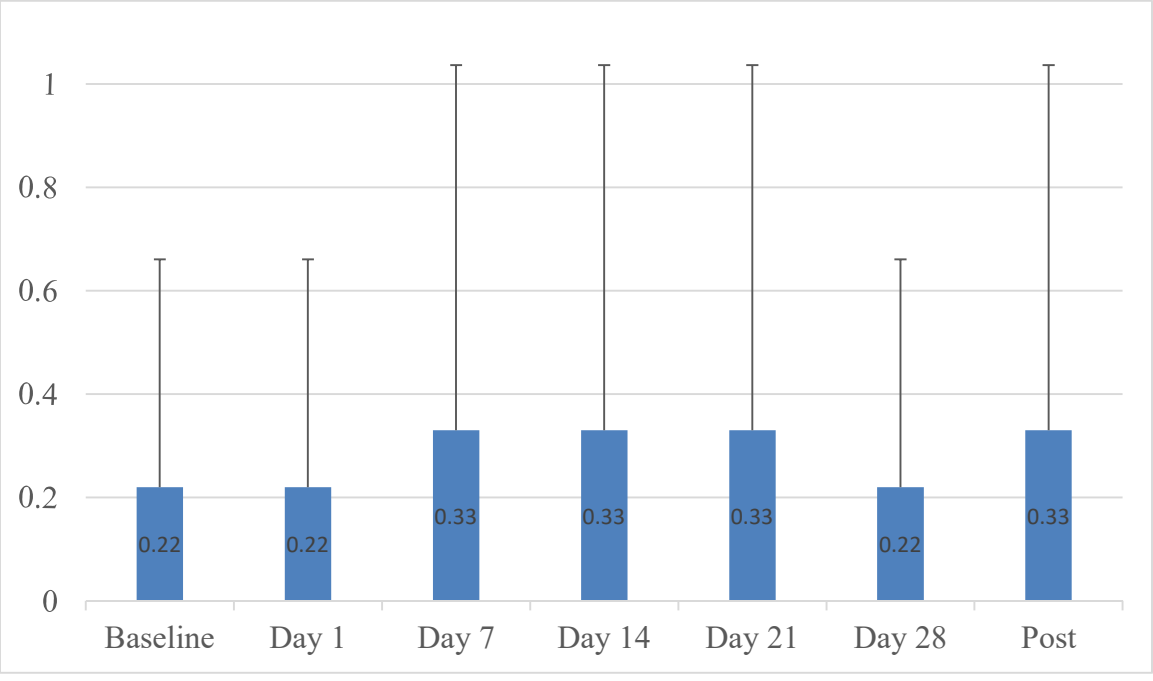


Figure 5: Group mean oral pain rating for each time point

A more specific planned comparison of the oral pain rating at baseline compared to the pain rating at the post protocol data collection was conducted. A Wilcoxon Signed Rank Test indicated that the post-intervention pain ratings were not statistically significantly different than the baseline pain ratings (W=1, p=.31); the effect size was small (d=.42). The median score for oral pain rating did not change from baseline to post-intervention (median=.00). The lack of statistical difference from baseline to post-treatment indicated no change in pain rating from the start of the study protocol to the end.

Sense of Effort after Completing Dysphagia Exercises

Similar to oral pain ratings, sense of effort ratings reported upon completion of the exercise at specified times (baseline, days 1, 7, 14, 21, and 28, and post treatment) were compared within subjects. Due to missing data points from Participants 6, 7, 9, 11, and 12, the sample size for this analysis was reduced to seven. A non-parametric Friedman test of differences among repeated measures resulted in a Chi-square value of 3.55 with df=6 and an associated p-value of .73. This result indicated that the sense of effort rating did not change significantly within participants across the seven rating intervals. Figure 6 displays the large variability in sense of effort rating across each time point.

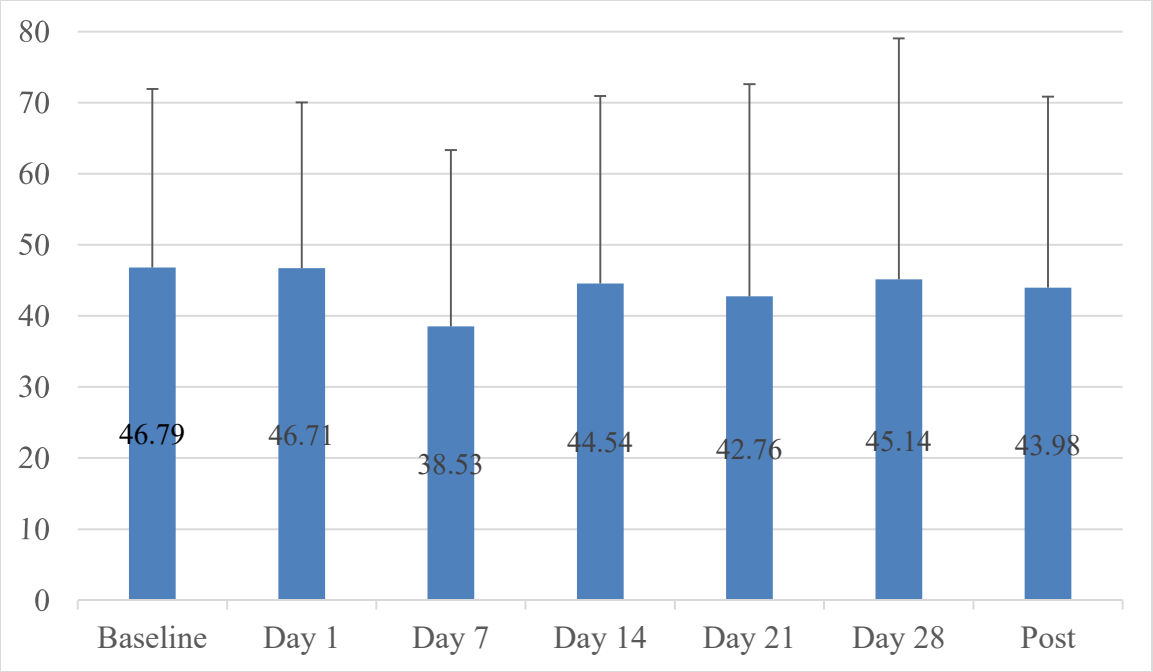


Figure 6: Group mean sense of effort ratings at each time point

A more specific planned comparison of the sense of effort rating at baseline compared to the sense of effort rating at the post-treatment data collection was conducted. A Wilcoxon Signed Rank Test indicated that the post-intervention ratings were not statistically significantly different than the baseline ratings (W=18, p=.09; medium effect size of d=.71). The median sense of effort rating decreased from baseline (median=46.25) to post-intervention (median=32.22) by 14.03mm. The minimum amount of effort reported to complete the exercise protocol decreased by 5.58mm from baseline to post-intervention. Likewise, the maximum amount of effort reported decreased by 7.12mm (baseline=91.60, post=84.48).

Pattern of Change in Outcome Measures Within Participants

Table 15 details each participant's percentage change from baseline on the two lingual measures (strength and endurance) and the MDADI composite score. The intention here was to see if there were patterns of change within a participant across the three main outcome measures.

Three participants demonstrated clinically significant change on the MDADI composite of 10-points or greater. These were participants 6, 9, and 11. Of note is that these three had the lowest levels of compliance with the exercise protocol (see Figure 3 and Figure 4). Participant 6 was the only female participant. She demonstrated sizeable percentage improvements in lingual strength (75%), lingual endurance (160%), and MDADI (16.5%). At the post-exercise data collection session, she reported to the study personnel that she noted improvement in her swallowing ability that she attributed to the exercise program. She indicated that she planned to continue the exercise protocol but at a lesser regimen even though the study participation was completed. Specifically, she stated, "Three times a day is doable. I am going to aim for doing that three times a week. The exercises became easier and I just feel there is more strength." Participant 11 had the greatest MDADI improvement (34.4%) and the fourth greatest percentage change in lingual strength (5.2%); lingual endurance did improve by 20.9% although this was just the 9th largest increase out of the group. He was the youngest participant and like Participant 6, he reported to the study personnel that he felt his swallow had improved during his time in the study. Specifically, he stated that prior to participation he was unable to drink from a water bottle while biking without coughing and choking. However, by the end of the study participation he found himself drinking during his bike rides without incident. Participant 9 had the second greatest increase in lingual endurance and the third largest increase in the MDADI; lingual strength increase was the 6th largest in the group.

Participant 3 regressed on all three outcome measures. Lingual strength decreased by 19%, endurance decreased by 39.6%, and the MDADI composite decreased by 5.6%. Of note also is that this person's single item MDADI global rating also decreased from "agree" to "strongly agree" on the statement: My swallowing ability limits my day-to-day activities. In

terms of compliance, he reported completing 72% of the total number of sessions; about 55% of the days he had high compliance and the remaining 45% of days he had poor compliance with the exercise program.

The pattern of change for the remaining participants was variable. Three participants (4, 5, and 8) had one of three outcome measures that worsened by at least 5% while at least one other measure improved by 5% or more. Participants 1, 7, 10, and 12 increased lingual endurance by at least 40%, but had relatively modest improvement, no change, or a modest decrease in lingual strength and MDADI. Finally, Participant 2 increased lingual strength by nearly 24% but had modest decreases on lingual endurance and the MDADI score.

Table 15: Participant percentage changes across each outcome measure

Participant	**Lingual Strength Percentage Change**	**Lingual Endurance Percentage Change**	**MDADI Percentage Change**
1	0.0	44.4	7.6
2	23.8	-5.3	-6.8
3	-19.0	-38.6	-5.6
4	14.0	28.8	-5.7
5	-13.9	750.0	8.6
6	75.0	160.0	16.5
7	4.3	1685.7	9.6
8	2.9	-62.5	7.1
9	3.2	833.3	16.0
10	-4.3	173.3	1.2
11	5.2	20.9	34.4
12	2.0	47.4	4.2
Group Mean	**7.8**	**303.1**	**7.2**
Group SD	**23.9**	**527.6**	**11.6**

MDADI=M.D. Anderson Dysphagia Inventory

Correlation between Compliance and Outcome Measures

Spearman correlation coefficients were calculated to assess the relation between total number of sessions completed and each of the outcome measures (Table 16). Table 17 provides a summary of individual change scores on the lingual strength, lingual endurance, and MDADI composite measures and total number of sessions completed. None of the correlations were statistically significant. Participants routinely tracked whether or not they completed the prescribed amount of daily exercises, and if not, how many blocks were completed. Total number of minutes to complete exercises, oral pain ratings, sense of effort ratings, and MDADI ratings were logged inconsistently by some participants. Refer to Appendix H for information about missing data.

Table 16: Spearman correlation coefficients (and associated probabilities) between the total number of exercise sessions completed and each of the outcome measures

	Total Sessions Completed	***p* value**
Lingual strength change	-.115	.723
Lingual endurance change	-.153	.635
MDADI composite score change	-.463	.130
MDADI physical score change	-.101	.756
MDADI functional score change	-.355	.258
MDADI emotional score change	-.348	.267
MDADI global score change	-.252	.429

MDADI=M.D. Anderson Dysphagia Inventory

Table 17: Participant change score on each outcome measure and compliance

Participant	Lingual Strength Change Score	Lingual Endurance Change Score	MDADI Composite Change Score	Total Number of Sessions Completed (out of 140)
1	0	8	5.32	140
2	10	-3	-6.34	114
3	-12	-66	-3.15	101
4	7	17	-4.3	140
5	-5	90	6.27	113
6	15	40	9.57	52
7	2	236	6.24	140
8	1	-55	6.3	140
9	1	250	10.46	68
10	-2	26	0.91	135
11	3	9	21.03	50
12	1	18	3.15	132

MDADI=M.D. Anderson Dysphagia Inventory

Chapter V: Discussion

Dysphagia is known to occur months or years after RT in people with HNC and there currently is no known means of effective behavioral treatment. Dysphagia exercises prior to and during RT are known to result in better swallowing outcomes in the immediate time period after RT is complete. Similar exercises attempted in people with latent dysphagia have not had promising results but the available studies had shortcomings in terms of the heterogeneity of the study populations and the actual extent to which the exercises were completed by participants. The purposes of the current study were to evaluate the impact of a dysphagia exercise program on the swallowing outcomes in adults with BOT cancer who have completed RT and to describe the exercise-related oral pain and effort. Specific attention was given to the two major limitations in the current literature, namely, participant compliance and heterogeneity of the study population. Specific aims addressed were evaluation of the impact of dysphagia exercises on

swallowing as assessed by lingual strength and endurance measures as well as swallow-related QOL (MDADI); assessment of pain associated with dysphagia exercises; and assessment of sense of effort associated with dysphagia exercises. Additionally, an exploratory aim was to describe participant compliance and relate this to the swallowing outcome measures.

The primary findings of this study were: 1) lingual function (strength and endurance) did not change a statistically significant amount from pre- to post-exercise completion and effect sizes were small for strength and medium for endurance; 2) some aspects of swallowing related QOL did appear to improve from pre-to-post exercise; and 3) pain and effort associated with exercise completion were minimal and did not change from pre- to post-exercise completion. Compliance rates were good for most participants but compliance metrics did not strongly correlate to any of the change scores in the measures that were assessed. The anecdotal reports of participants, and the individual participant outcomes for a subset of participants, suggested that some people did have positive changes in swallowing function; however, there was marked variability in the group. These findings are presented in more detail below relative to what is reported in the literature. The discussion concludes with consideration of preliminary clinical implications, study limitations, and future directions.

Primary Outcomes of the Dysphagia Exercise Program

Lingual Strength and Endurance Outcomes

The group mean tongue strength in the current study was approximately 10-15 kPa lower than the group mean values reported for non-dysphagic older adults reported in the literature. Table 18 includes group means and standard deviations of maximum lingual strength measured in individuals over the age of 60 years. The studies in Table 18 utilized IOPI equipment and similar instructions as were used in the current study. It is tempting to interpret the 10-15 kPa

difference in group means from the current study versus the normative values as an indication that individuals with BOT cancer have weaker tongues. However, the standard deviations are relatively large in all of these studies. As such, the current group mean strength value lies within two standard deviations of the means from the normative studies. More prudently one might conclude that as a group the BOT participants fall toward the lower half of the range of values reported in the normative studies.

The post-exercise maximum tongue strength in this group of participants with BOT cancer exhibited a mean increase of 1.8 kPa (7.8% increase) but this was not a statistically significant increase. Furthermore, the effect size for lingual strength was small. Together these findings indicate that tongue strength did not increase from pre-to-post exercise.

Table 18: Recent published normative values of lingual strength

Study	**Mean Lingual Strength (kPa) in Individuals >60 years**	**Standard Deviation in Individuals >60 years**
Youmans and Stierwalt (2006)	54.5	11.3
Stierwalt and Youmans (2007)	55.01	14.32
Youmans, Youmans, and Stierwalt (2009)	60.12	14.14
Clark and Solomon (2012)	51.00	15.00

Of the three prior studies assessing outcomes of exercise to treat latent dysphagia only Lazarus, Husaini, et al. (2014) included a measure of tongue strength. Although there are a number of differences between that study and the current one, the maximum lingual strength

group means (and standard deviations) are remarkably comparable for the two sets of OPC participants. Table 19 places the group means for controls and OPC participants from Lazarus, Husaini, et al. (2014) in contrast with those from the current study. Pre-exercise baseline mean strength for the individuals with OPC in both studies differed by only .07 kPa. Likewise, post-exercise strength values were nearly the same, differing by .10 kPa. Lazarus, Husaini, et al. (2014) did include non-dysphagic controls and their data suggested that an approximate 10% reduction in lingual strength might be anticipated in individuals with OPC although further studies that substantially expand the group enrollment are needed to establish confidence in this estimation. Without inclusion of non-dysphagic controls, the current study is not able to directly address this question of whether tongue strength is reduced in participants with BOT cancer who received RT. Of note, when comparing the current study with Lazarus, Husaini, et al. (2014), is the similarity in strength values (both baseline and post) despite some rather marked differences in the studies. Participants in Lazarus, Husaini, et al. (2014) were enrolled one month after completing RT compared to the current study wherein the average interval from RT completion to study enrollment was 7.6 years. This suggests there may be a shifting downward of group tongue strength toward the lower end of the normal range that can happen immediately after RT. Also of note is that Lazarus, Husaini, et al. (2014) included people with a variety of tumor location sites within the oral cavity and pharynx. It may be that RT, somewhat regardless of the specific tumor target, creates tongue weakness. This might be possible given the construction of the tongue as a muscular hydrostat wherein there are limited attachments to boney structures and many soft connections of muscular bundles to other muscular bundles. The nature of this construction allows for remarkable ability to move, shape and deform the tongue in various ways. However, it also opens the possibility that damage to one portion of the tongue could

conceivably alter movement and function of the whole tongue. Radiation damage to the oral tongue might logically be assumed to damage strength and movement of the anterior tongue; however, given the unique construction of the tongue it also is conceivable that RT damage to the BOT might alter how the bulk of the tongue, including the anterior tip, is able to move.

Table 19: Comparison of lingual strength in current study and Lazarus, Husaini, et al. (2014)

Study	**Baseline Mean Lingual Strength (kPa)**	**Baseline Standard Deviation**	**Post Mean Lingual Strength (kPa)**	**Post Standard Deviation**
Control Group (Lazarus, Husaini, et al., 2014)	49.30	10.53	52.40	10.78
Experimental Group (Lazarus, Husaini, et al., 2014)	44.63	13.39	46.50	16.50
Current Study	44.70	12.70	46.40	15.50

The manufacturer of the IOPI device (IOPI Medical LLC) states that endurance measurements of less than 10 seconds could be an indication of suspected low endurance. However, the source of this 10-second cut-off is unclear because specific normative data are not reported. The measure was included here given anecdotal reports of fatigue as a potential outcome of RT. No participants within the current study demonstrated lingual endurance

measurements of less than 10 seconds at baseline or at post-protocol data collection (Table 8). It may be the case that lingual endurance is not affected by RT in people with BOT cancer even though maximum isometric strength is decreased. Recall that endurance is assessed as the number of seconds that a person could generate 50% of maximum tongue pressure. The 50% maximum approach is somewhat commonly used in studies assessing muscular endurance in the limbs. It is possible that a more sensitive endurance measure for the tongue and other oral-facial muscles might require empirical assessment of the measure taken at various levels of the maximum, (e.g., perhaps endurance as assessed at 70% of maximum (or some other value) would provide a sensitive metric of lingual endurance). The value of 50% of maximum was suggested by the manufacturer and is often used in other types of muscle endurance studies (e.g., limbs), but it may not be the most appropriate for the tongue. Although there was substantial individual variability in the endurance values within the current group of participants, of the three main outcome measures tracked (strength, endurance, swallow-related quality of life), positive changes from pre- to post-exercise occurred for endurance for the largest proportion of the group. The change in lingual endurance also had a medium effect size despite the lack of statistical difference from the Wilcoxon Signed Rank Test. As a preliminary result from a small set of participants it may be worthwhile to further assess lingual endurance in future studies that perhaps have more power or that can specifically search for an optimal "percentage of maximum" that can sensitively assess endurance of the tongue.

Overall, lingual strength and endurance did not change a statistically significant amount within the participants in the current study. One of the four exercises, lingual tip press, specifically focused on anterior tongue movement and strength. The effortful swallow focuses on not just maximal tongue squeezing during swallowing, but more generally on effort throughout

the oral pharyngeal swallow. The Masako maneuver is targeted to pharyngeal wall as well as BOT squeezing, whereas the Mendelsohn is perhaps the least related to oral tongue movement given its focus on laryngeal elevation. Overall then, one exercise directly targeted the anterior tongue movement, whereas two others targeted, in part, BOT function. It may be that this set of exercises was simply insufficiently focused on oral tongue movements and function to cause a change in either maximum strength or endurance. It is known that similar exercises completed in adults post-stroke and in older adults without stroke can and do increase lingual strength (Robbins et al., 2005; Robbins et al., 2007). However, the mechanism of action that causes "weakness" in stroke and in RT is different, potentially requiring different types or intensities of exercises. It also might be that the damage from RT cannot be reversed by exercise. The participants in the current study underwent treatment an average of 7.6 years prior to study participation. Therefore, fibrosis, neuropathy, and atrophy of muscles may have been substantial and irreversibly altered. Studies that quantify the extent of fibrosis, neuropathy, and atrophy using those measures to stratify participants into groups for comparison, or tracking changes in these measures as a function of exercise might be useful although quantification of these parameters is complex. The fact that participants in Lazarus, Husaini, et al. (2014), who were enrolled very shortly after RT completion, dampens enthusiasm for the possibility that intervening sooner (i.e., before fibrosis and neuropathy have substantially progressed) will have a positive effect. Some optimism remains, however, from the studies of oral-swallow exercises in individuals done prior to and during RT that have shown positive short-term swallowing outcomes. It may be that such exercises must be initiated early and consistently during RT and then maintained as a regularly scheduled activity in the weeks, months and years after RT to help limit latent development of fibrosis, neuropathy, and atrophy that can arise.

Dysphagia Related Quality of Life (MDADI) Outcomes

The MDADI composite and subscale score results provide some tentative support that dysphagia related QOL may be improved in some domains from a four-week exercise program. The MDADI composite score for the group did not improve by a statistically significant amount, however, the effect size was large and 25% of the group did have a 10 point or greater improvement. That is, one in four had a clinically significant improvement in the MDADI composite score. While the goal clinically would be to improve swallowing for a much larger percentage of participants, this is not a trivial finding for a condition that may be particularly difficult to remediate. On its own, this set of findings for the MDADI composite score encourages further investigation of exercise as a means of helping at least a portion of this population particularly if future work can better identify a priori the candidates most likely to benefit from such exercise.

The results for the Emotional subscale are particularly encouraging. A 10 point or greater change in this subscale was noted in 42% of the group and the mean improvement of 13.6% was statistically significant with a large effect size. Examples of questions from the Emotional subscale are: “I am embarrassed by my eating habits; I am upset by my swallowing problem; I do not go out because of my swallowing problem; Other people are irritated by my eating problem.” Improving a person’s internal perceptions about how the swallowing problem effects them emotionally could be very powerful in improving that person’s life. The other subscale scores, Physical, Functional, and Global, had somewhat less encouraging outcomes in this group of participants. None were statistically significantly improved. However, two, Physical and Global, had medium effect sizes and both Physical and Functional had 25% of the participant group that demonstrated at least a 10-point improvement. As with the composite score where

25% of the group had clinically significant improvements, the ability to positively alter the physical and functional swallowing abilities of 1 out 4 participants should not be discarded when the RT effects are expected to be very difficult to modify through any means.

Although it is tempting to look somewhat positively on the MDADI results suggesting that a non-trivial percentage of participants with latent dysphagia improved after four weeks of exercise, the question can still be asked: why did "only" 25% to 40% (depending on the MDADI score of interest) of the participants show such change? There are a number of variables to consider. It might be that the severity of the dysphagia at the time of initiation of the exercise program is critical to the improvement that can happen. Of note is that participants #6, 9, and 11 were the three who demonstrated approximately a 10-point improvement or more on the composite score. If the participant group is ordered based on the magnitude of the MDADI composite severity at baseline, these three had the 2nd, 3rd, and 5th lowest scores at the start of the study. While not definitive, it is intriguing to consider that perhaps those with more involved (i.e., "worse") dysphagia at the onset of this type of study are the ones with the greatest probability of showing improvement. Paradoxically, these three also complied the least with the actual exercise regimen in terms of number of sessions completed. That issue is considered further in the section below titled *Pattern of Change in Outcome Measures Within Participant*.

In addition to the need to consider dysphagia severity at the time of exercise initiation in participants with latent dysphagia, other variables might help determine whether exercise invokes positive change. Some of these were identified in the lingual strength and endurance section. Again, it might be that the exercise program focus is not optimized to address the specific problems in people who are years post RT. The exercises selected have been routinely used clinically and in research studies to improve swallowing in individuals with HNC but

perhaps the very latent RT population will require unique behavioral exercises if one assumes the problems are because of progressive fibrosis, neuropathy, and/or atrophy beyond what occurs during and immediately after RT. At the moment it is not apparent what those unique interventions might be. The intensity of the exercise program also was not manipulated in this study but might be a critical parameter worthy of future investigation to identify the necessary level, if there is one, to induce change in the swallow. Again, there might also be a critical window during which behavioral exercises must be introduced in order to obtain positive changes in swallowing outcomes. The current participants had not had direct intervention for their swallowing that entailed oral-swallowing exercises. Early and sustained use might be necessary. Finally, it is possible that the RT changes are permanent and not amenable to improvement from any behavioral intervention.

In summary, results from the MDADI emotional subscale and the large effect size for the composite score can be viewed as encouraging for the need to delve further into behavioral exercise to treat latent dysphagia. Certainly larger scale studies are needed before suggesting definitive changes in clinical care. These preliminary results also suggest that less than a majority of individuals might benefit from the exercises. Again, however, latent dysphagia appears to be a recalcitrant problem. If the costs of completing an exercise program are relatively limited, and expectations for the likelihood of change are tempered and understood by the person, behavioral exercise might remain as a possible intervention, particularly if future work can better define for whom the exercises are of most benefit or more effective exercises and treatment schedules are devised.

Pain and Sense of Effort Experience

Pain as it relates to dysphagia exercises was investigated as part of the current study due to prior studies that identified pain as a compliance barrier to dysphagia exercise completion. The pain issue is most readily apparent during RT when issues such as oral mucositis are present. It was not known whether commonly used oral and swallowing exercises would induce pain in adults who have completed RT and had time for the acute effects of RT to resolve. Pain remained a reasonable target for investigation given that more long-term RT changes could cause movement-related pain. In particular, neuropathy can induce pain. Additionally, development of fibrosis can cause marked restriction in movements; if a person is attempting to maximally move a structure, they might put strain on tissues that is perceived as pain. Pain, however, did not appear to be present at baseline or at any other data collection point in the study. As such, the hypothesis that pain would increase in the first two weeks from baseline, but then decrease in the final two weeks as participants accommodated to the movements was not supported by the data. There simply was little to no pain at any point. Overall, the highest pain rating provided from any participant throughout the study was two on a ten-point scale. The conclusion then is that pain associated with completing oral and dysphagia exercises is not expected to be a barrier to completing the exercises in people who are several years post-RT completion. This pain experience (or lack thereof) is in stark contrast to what is reported for individuals who are in active RT when completing similar exercises. Although pain did not arise within the current study, the enrollment was small. Given that, and given that it is possible that the longer-term side effects from RT, such as neuropathy, lymphedema, fibrosis, and xerostomia, are known to cause pain in select individuals, the pain experience should not be dismissed as a possibility for individuals. There may be specific persons who are many months or years post-RT who

experience pain (with or without exercise) even though the group data in the current study did not identify pain in these 12 participants.

Sense of effort related to dysphagia exercises within the population had not yet been explored to the investigator's knowledge. Inclusion of sense of effort arose from discussions about dysphagia exercises that took place between the investigator and individuals who had undergone oncologic treatment and were reporting latent dysphagia. Throughout these interactions a number of individuals reported experiencing the need to be more careful, diligent and cognitively mindful of how they moved head and neck structures after RT. Sense of effort is a person's perception of the amount of work that is involved in a task and can include both perceived physical as well as cognitive effort. As with pain, the hypothesis that effort would increase for the first two weeks of the program and then decrease for the final two weeks was not supported by the data. The conclusion drawn is that the swallowing exercises did not induce a sense of effort for this group of participants.

Overall, the pain and effort results indicate that neither one was present as a potential barrier to completion of the oral and swallowing exercises. This is useful to know that elevated pain and effort should not get in the way of such work, but only to the extent that the exercises are worthy of completing in the first place.

Compliance with the Exercise Program

Compliance with oral and dysphagia exercise protocols in individuals with HNC who undergo RT has been described as a problem in studies done with people during active RT (Hutcheson et al., 2013; Kotz et al., 2012; Virani et al., 2014) as well as in studies after RT is done (Langmore et al., 2016; Lazarus, Husaini, et al., 2014). The current study invested substantial time in the planning and execution of the study to maximize compliance in order to

better assess whether the exercises, if completed as prescribed, demonstrated promise for improving swallowing. It is difficult to compare compliance in this study to compliance reported in the extant literature because prior studies did not report metrics of compliance but rather provided general ratings or commentary about compliance as a problem. This study measured compliance in two different ways. First, the total number of prescribed sessions completed was determined. Participants, as a group, completed nearly 80% of the total prescribed sessions (overall compliance with prescribed sessions); individual participant compliance measured in this manner ranged from 36% to 100%, with 75% of the participants above 70% compliance. Secondly, participation on a daily basis was described as strong, moderate, or poor based on how many sessions the person completed that day (i.e., daily compliance). Describing daily compliance in this manner came the closest to what others have reported in the literature (e.g., Langmore et al. 2016). On daily compliance, 75% of participants demonstrated moderate to strong compliance. Only four participants demonstrated one or more days with poor compliance (0-1 session completed).

The level of compliance in the current study appears to be better than that of any previously reported studies although direct comparisons are not possible because of differences in how compliance was tracked or because only informal comments were offered. Langmore et al. (2016) completed one of the three published studies of latent dysphagia. They judged 57% of participants in their active NMES group and 48% of participants in the sham NMES group to be compliant. Compliance was defined as completing 10 or more sessions per week (prescribed to be done two times per day for six days each week = 12 sessions/week) for 12 consecutive weeks. Lazarus, Husaini, et al. (2014) reported compliance based on how many sessions were completed per day and per week to classify individuals as having poor, fair, or moderate compliance. They

did not report specifically the percentages of participants who had particular compliance rates but did write that "relatively poor compliance, particularly within the treatment arm, may have had an effect on the outcomes" (p. 528). Hutcheson et al. (2012) did not report on participant compliance.

The current study included procedures directly intended to increase daily compliance. This included daily contact with each study participant by phone, email, or text messaging. This approach appeared to result in better compliance than what other investigators have reported. The familiarity and availability of electronic media options among the group of participants made it relatively easy to execute this regular daily contact. Although not executed in the current study, automated electronic contacts could easily be constructed to make this process less time-consuming.

While there was a degree of success in obtaining relatively high compliance, there was not a strong association between compliance and changes in the outcome measures of interest, namely the MDADI, lingual strength, and lingual endurance. Additionally, inspection of data from individual participants revealed that the three participants (6, 9, 11) who demonstrated the most change on outcome measures had the lowest compliance among participants in the current study. Conversely, some of the best compliers demonstrated negative change scores. These results regarding degree of compliance and positive change in swallowing outcome measures are counterintuitive to the notion that individuals must do extensive exercises to induce change. It might be that the intensity of the exercise program has to be reduced. This is speculative at this point given the small sample that is under consideration. However, the three with the lowest compliance rates demonstrating the greatest positive change, along with negative outcomes for some with the highest compliance begs the question about whether too much exercise could be

detrimental to swallowing function in this population. This possibility must be seriously considered in future work.

Preliminary Clinical Implications

Only a few studies have addressed the issue of trying to remediate latent dysphagia in individuals with HNC treated with RT. As such, it is too early to draw strong conclusions about how clinical activities could or should be structured to promote the best swallowing outcomes in those with latent dysphagia. While the MDADI composite and emotional subscale results offer encouragement that behavioral exercises can have some impact on latent dysphagia for some people, the totality of the results of the non-parametric testing and effect size estimates is not yet strong enough to forcefully argue for altering clinical practice. This is particularly the case when also considering the current results along with the small set of previously published studies wherein outcomes of behavioral intervention for latent dysphagia were deemed generally ineffective (Hutcheson et al., 2012; Langmore et al., 2016; Lazarus, Husaini, et al., 2014).

While the current results are insufficient to alter clinical practice, the results do provide encouragement to continue this line of investigation. As a preliminary study, there were enough positive outcomes in terms of statistical differences and effect sizes to suggest some meaningful changes occurred. Further investigation could help identify critical individual related or treatment related factors that influence the direction and magnitude of change in dysphagia.

Given that stronger positive results from behavioral intervention to improve latent dysphagia have not yet been reported, it is judicious to place current clinical emphasis on preventing dysphagia in those undergoing RT. The outcomes from trials in which exercises are started prior to and maintained during RT to the extent possible (Carnaby-Mann et al., 2012; Carroll et al., 2008; Hutcheson et al., 2013; Kotz et al., 2012; Kulbersh et al., 2006; Virani et al.,

2014) are supportive of the notion that swallowing is better preserved in those who do the exercises during RT. That should be the primary clinical focus at the moment while additional research is conducted on better ways to deal with latent dysphagia. Understanding that remediating latent dysphagia is challenging, and that perhaps only some (25% to 42% in the current study) can be helped, serves as strong motivation for trying to prevent RT-related swallowing decline in the first place. Related to this issue of completing exercises prior to and during RT is the need to track individuals for an extended period of time, (i.e., many years after RT). Some studies have looked at individuals longitudinally for up to 24 months post-RT (Goepfert, Lewin, Barrow, Gunn, Fuller, Beadle, Garden, Rosenthal, Kies, Papadimitrakopoulou, Lai, Gross, et al., 2016; Goepfert, Lewin, Barrow, Gunn, Fuller, Beadle, Garden, Rosenthal, Kies, Papadimitrakopoulou, Lai, Schwartz, et al., 2016). However, to date there has not been a report of the long-term dysphagia outcome beyond this time frame specifically for individuals who did complete the preventative exercise regimen. That is, it is not known whether those who complete the exercises during RT still might have an expectation of developing latent dysphagia several years later. The possibility that oral and swallowing exercises need to be done preventatively and then also in maintenance fashion after RT must also be considered.

Finally, because dysphagia can occur latently, and because it is not known who might develop latent dysphagia, it is imperative that SLPs actively follow individuals with HNC treated with RT for many years for periodic reassessment of the person's swallowing status. Although more research on behavioral interventions is needed, there may be ways to compensate for dysphagia symptoms that arise. This could be through modification of diet, training in compensatory swallowing postures or strategies, and consideration of alternatives or additions to oral intake of nutrition.

A few comments about the current group of participants are offered here related to these issues of the need for implementation of dysphagia exercises prior to and during RT and the need for more active SLP follow up after RT is complete. Only two individuals in the current study received any type of prophylactic swallowing exercise regimen. Contact with a SLP post RT varied. Thirty-three percent of participants received no SLP contact throughout the course of their cancer treatment or post-cancer follow-up. Six participants received dysphagia evaluation and/or treatment of some type. Of these six, one individual was in contact with a SLP within one year of his cancer diagnosis, one individual had contact two years post-diagnosis, three individuals had contact three years after their cancer diagnosis, and one individual had contact with a SLP six years post-cancer diagnosis. Overall, the group could be considered to have had limited to no intervention designed to prevent or treat dysphagia prior to their enrollment in this study. From a research perspective, this lack of prior intervention allowed for limiting the impact of at least one variable that could potentially have complicated interpretation of results should a positive change have occurred. These individuals were, on average, seven years post RT and so many of them had undergone their RT at a time prior to the change in the standard of care that focuses now on prophylactic use of swallowing exercises during RT. Long-term follow up of such persons who did not have prophylactic exercise will be required over many years to determine the extent to which RT side effects extend into the future.

Limitations

This study was principally designed as a preliminary investigation of a possible treatment effect from a set of commonly-used swallowing exercises in individuals with HNC treated with RT who have latent dysphagia. The focus was on getting participants to actually complete the exercise program as prescribed (a problem in the published literature) in order to allow

assessment of an effect from intervening. It was not a randomized controlled trial. There are limitations inherent to the design of the study including issues such as the lack of a control group or alternative treatment which would preclude determining that the exercises themselves were the cause of swallowing changes should such changes have occurred. Exercise may be ineffective at treating latent dysphagia in individuals with HNC treated with RT, but it is also possible that a differently constructed set of exercises than what was used in the current study has value; that possibility simply cannot be determined here because alternative programs were not included. Likewise, it is possible that a different schedule or intensity of treatment is of value. As alluded to previously, the fact that the three participants with the lowest compliance had the largest, positive change in outcome measures is intriguing in this regard. Perhaps a different duration to the overall treatment program is a critical feature. Finally, there may be a critical time interval relative to RT itself during which the exercises can have some effect. The current study and the few others published on latent dysphagia have all differed somewhat in the construction of the exercise program (the exercises, number of repetitions per session, day, and week, total duration of the program, etc.). A more systematic manipulation of these parameters is needed to fully understand what might be helpful in treating latent dysphagia.

The current study was limited in terms of the participant sample size. With some missing data the analyses for a few variables included fewer than 10 participants-the target sample size that was set prior to study execution. As such, statistical power was reduced in some instances. Related to small sample size is the recognition that a number of other variables that might be of potential influence and interest in future studies could not be considered within the statistical analyses. Examples of such variables of possible interest are participant sex, tumor staging, HPV status, and type/intensity of RT.

Structuring the study to maximize compliance with exercises was a major focus in planning this study. Poor compliance in prior studies called into question whether the lack of positive change in swallowing from exercises was because the exercises were ineffective or, alternatively, no positive change occurred because the exercises were not done as prescribed. Compliance was judged to be good overall for this group of 12 participants. However, the compliance estimates were based on participant self-report and not direct observation (or other confirmatory evidence of exercise completion). There is no obvious reason to distrust the self-report, but of greater concern is the possibility that exercises were not completed accurately, with the same intensity, or with sufficient number of trials when done at home. Participants demonstrated accurate completion of exercises in the investigator's presence before starting the four-week program and daily contact was made by text or email to address questions. However, no direct confirmation of exercise completion or accuracy of exercise completion was obtained.

The swallowing measures included here did not provide a direct assessment of the physiological swallowing function. The MDADI is commonly used as a valid and useful outcome measure for swallowing function in individuals with HNC but it is possible for the self-reported measures to not be directly correlated to underlying physiological function of the swallowing mechanism, particularly if a person has compensated (consciously or unconsciously). As such there could have been changes in swallowing physiology that were not reflected in responses on the MDADI. The lingual strength and endurance measures also have been used to provide a quantitative measure of one aspect of function, but this measure is not obtained during the act of swallowing. A different assessment, such as observations of physiology and function from modified barium swallow study or flexible endoscopic examination of swallowing, could be utilized in future work.

As alluded to previously, however, the changing trend in the treatment of persons with HNC who undergo RT is to begin swallowing exercises very early in the RT process. It remains to be seen if the prophylactic exercises actually limit or prevent dysphagia latently. If they do not, future studies will be needed to assess whether various combinations and structures of swallowing therapy can manage or remediate latent dysphagia.

Conclusions and Future Directions

The purpose of this study was to evaluate whether completion of a four-week swallowing exercise program changed lingual strength and endurance, and swallowing-related QOL, in individuals with HNC treated with RT who had latent dysphagia. A primary focus in the design and execution of the study was to limit the tumor location site, in this case to BOT tumors, and to increase participant compliance with the exercise program, an acknowledged problem in previously published studies. Compliance metrics in this study suggested that overall the group was generally compliant. However, no statistically significant changes in lingual measures occurred. The emotional subscale of the MDADI did improve significantly. This subscale as well as the composite MDADI score both had large effect sizes (but not a statistical difference for the composite score). Additionally, when considering each of the MDADI scores (composite, global, and the three other subscales), anywhere from 25% to 40% of participants did demonstrate clinically meaningful improvements. While this may be fewer participants improving than what is desired in clinical practice, it may be the case that latent dysphagia is simply challenging to remediate and having 25-40% of participants showing improvement may be what is attainable with approaches that are currently available. Individually, a few participants appeared to demonstrate positive gains on several of the swallowing outcome measures. This small group of three participants also were the ones who reported the lowest compliance with the exercise

program, raising into question whether an alternative intensity of exercise completion might be more effective.

The study of latent dysphagia from RT and how to treat it is in its infancy. Initial investigations, including the current study, have focused on whether behavioral intervention utilizing already available swallowing exercises completed on a daily basis over several weeks can induce positive changes. While the evidence so far has not emphatically supported the use of such a program of intervention, future work is needed to more systematically evaluate the exercise program effectiveness as well as identification of individual-related factors that might be of importance. As alluded to in the limitations section, exercise program parameters that require further investigation include: timing of the start of the intervention relative to RT, intensity of exercise completion, duration of the exercise program, and comparison of alternative or new exercises. To date, individual-related factors have largely been ignored regarding the possible interaction and influence on the outcomes from exercise intervention. Multicenter studies will be required to examine subgroups of individuals with HNC so that enough participants can be enrolled to look more finely at parameters that include: age, sex, HPV tumor status, tumor staging, RT intensity and dosage, among other variables. Of particular importance moving forward will be determining whether the new standard of care involving prophylactic usage of exercises to prevent or minimize dysphagia from RT has a lasting impact beyond the first several months or first few years after RT. It is now well recognized that fibrosis and neuropathy from RT can have onset many years post-RT completion. Whether prophylactic swallow exercises limit the very long-term onset of these symptoms that can cause swallowing problems is unknown. Future work must consider whether swallow exercises need to be completed not only during RT but on some as yet unknown schedule for many years after RT.

References

American Cancer Society. (2014). *Oral cavity and oropharyngeal cancers detailed guide*. American Cancer Society. Atlanta, GA.

American Cancer Society. (2016). *Cancer Facts & Figures 2016*. American Cancer Society. Atlanta, GA.

Ang, K., Harria, J., Wheeler, R., Weber, R., Rosenthal, D., Nguyen-Tan, P., . . . Gillison, M. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. *New England Journal of Medicine, 363*(1), 24-35.

Barcikowski, R. & Robey, R. (1985). *Sample size selection in the single group repeated measures analysis*. Presented before the annual convention of the American Educational Research Association, Chicago, IL.

Beer, K., Krause, K., Zuercher, T., & Stanga, Z. (2005). Early percutaneous endoscopic gastrostomy insertion maintains nutritional state in patients with aerodigestive tract cancer. *Nutrition and Cancer, 52*(1), 29-35.

Bonner, J. A., Harai, P., Giralt, J., Azarnia, N., Shin, D., Cohen, R., . . . Ang, K. (2006). Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *New England Journal of Medicine, 354*(6), 567-578.

Brouha, X., Tromp, D., Hordijk, G. J., Winnubst, J., & De Leeuw, R. (2005). Role of alcohol and smoking in diagnostic delay of head and neck cancer patients. *Acta Otolaryngol, 125*(5), 552-556.

Bulow, M., Olsson, R., & Ekberg, O. (2001). Videomanometric analysis of supraglottic swallow, effortful swallow, and chin tuck in patients with pharyngeal dysfunction. *Dysphagia, 16*, 190-195.

Buntzel, J., Glatzel, M., Mucke, R., Micke, O., & Bruns, F. (2007). Influence of amifostine on late radiation-toxicity in head and neck cancer--a follow-up study. *Anticancer Research, 27*(4A), 1953-1956.

Carnaby-Mann, G., Crary, M., Schmalfuss, I., & Amdur, R. (2012). "Pharyngocise": Randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *International Journal of Radiation Oncology, Biology, Physics, 83*(1), 210-219.

Carroll, W., Locher, J., Canon, C., Bohannon, I., McColloch, N., & Magnuson, J. (2008). Pretreatment swallowing exercises improve swallow function after chemoradiation. *Laryngoscope, 118*(1), 39-43.

Caudell, J. J., Schaner, P. E., Desmond, R. A., Meredith, R. F., Spencer, S. A., & Bonner, J. A. (2010). Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. *International Journal of Radiation Oncology, Biology, Physics, 76*(2), 403-409.

Caudell, J. J., Schaner, P. E., Meredith, R. F., Locher, J. L., Nabell, L. M., Carroll, W. R., . . . Bonner, J. A. (2009). Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics, 73*(2), 410-415.

Chainani-Wu, N. (2002). Diet and oral, pharyngeal, and esophageal cancer. *Nutrition and Cancer, 44*, 104-126.

Chambers, M. S., Rosenthal, D. I., & Weber, R. S. (2007). Radiation-induced xerostomia. *Head & Neck, 29*(1), 58-63.

Chen, A., Frankowski, R., Bishop-Leone, J., Hebert, T., Leyk, S., Lewin, J., & Goepfert, H. (2001). The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: The M.D. Anderson dysphagia inventory. *Archives of Otolaryngology-Head and Neck Surgery, 127*, 870-876.

Clark, H., & Solomon, N. (2012). Age and sex differences in orofacial strength. *Dysphagia, 27*, 2-9.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillside, NJ: Lawrence Earlbaum Associates.

Delanian, S., Lefaix, J. L., & Pradat, P. F. (2012). Radiation-induced neuropathy in cancer survivors. *Radiotherapy and Oncology, 105*(3), 273-282.

Deng, J., Ridner, S., & Murphy, B. A. (2011). Lymphedema in patients with head and neck cancer. *Oncology Nursing Forum, 38*(1), E1-E10.

Deng, J., Ridner, S. H., Dietrich, M. S., Wells, N., Wallston, K. A., Sinard, R. J., . . . Murphy, B. A. (2012). Prevalence of secondary lymphedema in patients with head and neck cancer. *Journal of Pain and Symptom Management, 43*(2), 244-252.

Denis, F., Garaud, P., Bardet, E., Alfonsi, M., Sire, C., Germain, T., . . . Calais, G. (2004). Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *Journal of Clinical Oncology, 22*(1), 69-76.

Denk, D., Schima, W., & Eibenberger, K. (1997). Prognostic factors for swallowing rehabilitation following head and neck cancer surgery. *Acta Otolaryngol, 117*, 769-774.

Duprez, F., Madani, I., DePotter, B., Boterberg, T., & DeNeve, W. (2013). Systematic review of the dose-volume correlates for structures related to late swallowing disturbances after radiotherapy for head and neck cancer. *Dysphagia, 28*(3), 337-349.

Eisbruch, A., Lyden, T., Bradford, C., Dawson, L., Haxer, M., Miller, A., . . . Wolf, G. (2002). Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics, 53*(1), 23-28.

Eisbruch, A., Schwartz, M., Rasch, C., Vineberg, K., Damen, E., Van As, C. J., . . . Balm, A. J. (2004). Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: Which anatomic structures are affected and can they be spared by IMRT? *International Journal of Radiation Oncology, Biology, Physics, 60*(5), 1425-1439.

Epstein, J. B., Wilkie, D. J., Fischer, D. J., Kim, Y. O., & Villines, D. (2009). Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy. *Head & Neck Oncology, 1(26)*.

Fakhry, C., Westra, W. H., Li, S., Cmelak, A., Ridge, J. A., Pinto, H., . . . Gillison, M. L. (2008). Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *Journal of the National Cancer Institute, 100*(4), 261-269.

Feng, F. Y., Kim, H. M., Lyden, T. H., Haxer, M. J., Worden, F. P., Feng, M., . . . Eisbruch, A. (2010). Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: Clinical and functional results. *Journal of Clinical Oncology, 28*(16), 2732-2738.

Ferlito, A., Rogers, S. N., Shaha, A. R., Bradley, P. J., & Rinaldo, A. (2009). Quality of life in head and neck cancer. *Acta Oto-Laryngologica, 123*(1), 5-7.

Forastiere, A., Ang, K., Brizel, D., Brockstein, B., Dunphy, F., Eisele, D., . . . Shah, J. (2005). Head and neck cancers: Clinical practice guidelines. *Journal of the National Comprehensive Cancer Network, 3*(3), 316-392.

Francis, D., Weymuller, E., Parvathaneni, U., Merati, A., & Yueh, B. (2010). Dysphagia, stricture, and pneumonia in head and neck cancer patients: Does treatment modality matter? *Annals of Otology, Rhinology & Laryngology, 119*(6), 391-397.

Fritz, C., Morris, P., & Richler, J. (2012). Effect size estimates: Current use, calculations, and interpretation. *Journal of Experimental Psychology: General, 141*(1), 2-18.

Frowen, J., Drosdowsky, A., Perry, A., & Corry, J. (2016). Long-term swallowing after chemoradiotherapy: Prospective study of functional and patient-reported changes over time. *Head & Neck, 38 Suppl 1*, E307-315.

Frowen, J. J., & Perry, A. R. (2006). Swallowing outcomes after radiotherapy for head and neck cancer: A systematic review. *Head & Neck, 28*(10), 932-944.

Galeone, C., Pelucchi, C., Talamini, R., Levi, F., Bosetti, C., Negri, C., . . . La Vecchia, C. (2005). Role of fried foods and oral/pharyngeal and oesophageal cancers. *British Journal of Cancer, 92*, 2065-2069.

Gillison, M., Alemany, L., Snijders, P., Chaturvedi, A., Steinberg, B., Schwartz, S., & Castellsague, X. (2012). Human papillomavirus and diseases of the upper airway: Head and neck cancer and respiratory papillomatosis. *Vaccine, 30S*, F34-F54.

Goepfert, R., Lewin, J., Barrow, M., Gunn, B., Fuller, C., Beadle, B., . . . Hutcheson, K. (2016). Long-term patient-reported dysphagia in low-risk oropharyngeal carcinoma after

intensity modulated radiation therapy. *International Journal of Radiation Oncology, Biology, Physics, 94*(4), 963-964.

Goepfert, R., Lewin, J., Barrow, M., Gunn, G. B., Fuller, C., Beadle, B., . . . Hutcheson, K. (2016). Prospective MD Anderson Dysphaiga Inventory outcomes after nonsurgical treatment of locoregionally advanced oropharyngeal carcinoma. *International Journal of Radiation Oncology, Biology, Physics, 94*(4), 962-963.

Goldsmith, T., & Jacobson, M. (2015). Revisiting swallowing function following contemporary surgical interventions for oral/oropharyngeal cancer: Key underlying issues. *Dysphagia, 24*, 89-98.

Hamilton, D., Khan, M., O'Hara, J., & Paleri, V. (2015). Re-emergence of surgery in the management of head and neck cancer. *Dysphagia, 24*, 79-88.

Hamlet, S., Faull, J., Klein, B., Aref, A., Fontanesi, J., Stachler, R., . . . Simpson, M. (1997). Mastication and swallowing in patients with postirradiation xerostomia. *International Journal of Radiation Oncology, Biology, Physics, 37*(4), 789-796.

Hanahan, D., & Weiberg, R. (2011). Hallmarks of cancer: The next generation. *Cell, 144*, 646-674.

Hanna, E., Alexiou, M., Morgan, J., Badley, J., Maddox, A., Penagaricano, J., . . . Suen, J. (2004). Intensive chemoradiotherapy as a primary treatment for organ preservation in patients with advanced cancer of the head and neck: Efficacy, toxic effects and limitations. *Archives of Otolaryngology–Head & Neck Surgery, 130*, 861-867.

Hashibe, M., Ford, D., & Zhang, A. (2002). Marijuana smoking and head and neck cancer. *Journal of Clinical Pharmacology, 42*, 103S-107S.

Herr, K., & Garand, L. (2001). Assessment and measurement of pain in older adults. *Clinics in Geriatric Medicine, 17*(3), 457-475.

Howlader, N., Noone, A., Krapcho, M., Garshell, J., Miller, D., Altekruse, S., . . . Cronin, K. (2015). SEER Cancer Statistics Review, 1975-2012. Bethesda, MD, National Cancer Institute.

Huber, M. A., & Tantiwongkosi, B. (2014). Oral and oropharyngeal cancer. *Medical Clinics of North America, 98*(6), 1299-1321.

Hutcheson, K., Bhayani, M., Beadle, B., Gold, K., Shinn, E., Lai, S., & Lewin, J. (2013). Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: Use it or lose it. *Otolaryngology–Head & Neck Surgery, 139*(11), 1127-1134.

Hutcheson, K. A., & Lewin, J. S. (2012). Functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. *Current Oncology Reports, 14*(2), 158-165.

Hutcheson, K. A., Lewin, J. S., Barringer, D. A., Lisec, A., Gunn, G. B., Moore, M. W., & Holsinger, F. C. (2012). Late dysphagia after radiotherapy-based treatment of head and neck cancer. *Cancer, 118*(23), 5793-5799.

Hutcheson, K. A., Lewin, J. S., Holsinger, F. C., Steinhaus, G., Lisec, A., Barringer, D. A., . . . Kies, M. S. (2014). Long-term functional and survival outcomes after induction chemotherapy and risk-based definitive therapy for locally advanced squamous cell carcinoma of the head and neck. *Head & Neck, 36*(4), 474-480.

Hutcheson, K. A., Yuk, M. M., Holsinger, F. C., Gunn, G. B., & Lewin, J. S. (2015). Late radiation-associated dysphagia with lower cranial neuropathy in long-term oropharyngeal cancer survivors: Video case reports. *Head & Neck, 37*(4), E56-62.

Kantarjian, H., Wolff, R., & Koller, C. (2011). *MD Anderson manual of medical oncology* (2nd ed.). China: The McGraw-Hill Companies, Inc.

Kelly, L. (2014). Radiation and chemotherapy. In E. C. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 63-101). San Diego, CA: Plural Publishing, Inc.

Kendall, A., Leonard, R., McKenzie, S., & Jones, C. (2000). Timing of swallowing events after single modality treatment of head and neck carcinomas with radiotherapy. *Annals of Oncology, Rhinology & Laryngology, 109*, 767-775.

Kiss, N., & Isenring, E. (2014). Nutrition intervention in head and neck cancer. In E. C. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 493-506). San Diego, CA: Plural Publishing, Inc.

Knott, J., & Lewin, J. (2013). Dysphagia rehabilitation following total glossectomy. *Dysphagia, 22*, 73-80.

Kotz, T., Costello, R., Li, Y., & Posner, M. R. (2004). Swallowing dysfunction after chemoradiation for advanced squamous cell carcinoma of the head and neck. *Head & Neck, 26*(4), 365-372.

Kotz, T., Federman, A. D., Kao, J., Milman, L., Packer, S., Lopez-Prieto, C., . . . Genden, E. M. (2012). Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: A randomized trial. *Archives of Otolaryngology–Head & Neck Surgery, 138*(4), 376-382.

Kraaijenga, S. A., Oskam, I. M., van der Molen, L., Hamming-Vrieze, O., Hilgers, F. J., & van den Brekel, M. W. (2015). Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. *Oral Oncology, 51*(8), 787-794.

Kreimer, A., Clifford, G., Boyle, P., & Franceschi, S. (2005). Human papillomavirus types in head and neck squamous cell carcimonas worldwide: A systemic review. *Cancer Epidemiology, Biomarkers & Prevention, 14*, 467-475.

Kulbersh, B. D., Rosenthal, E. L., McGrew, B. M., Duncan, R. D., McColloch, N. L., Carroll, W. R., & Magnuson, J. S. (2006). Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. *Laryngoscope, 116*(6), 883-886.

Langmore, S. E., McCulloch, T. M., Krisciunas, G. P., Lazarus, C. L., Van Daele, D. J., Pauloski, B. R., . . . Doros, G. (2016). Efficacy of electrical stimulation and exercise for dysphagia in patients with head and neck cancer: A randomized clinical trial. *Head & Neck, 38 Suppl 1*, E1221-1231.

Lazarus, C., Logemann, J. A., & Gibbons, P. (1993). Effects of maneuvers on swallowing function in a dysphagic oral cancer patient. *Head & Neck, 15*(5), 419-424.

Lazarus, C. L., Husaini, H., Falciglia, D., DeLacure, M., Branski, R. C., Kraus, D., . . . Sanfilippo, N. (2014). Effects of exercise on swallowing and tongue strength in patients with oral and oropharyngeal cancer treated with primary radiotherapy with or without chemotherapy. *International Journal of Oral and Maxillofacial Surgery, 43*(5), 523-530.

Lazarus, C. L., Logemann, J. A., Pauloski, B. R., Rademaker, A. W., Larson, C., Mittal, B., & Pierce, M. (2000). Swallowing and tongue function following treatment for oral and orophayrngeal cancer. *Journal of Speech, Language, and Hearing Research, 43*, 1011-1023.

Lazarus, C. L., Wall, L., Ward, E. C., & Yiu, E. (2014). Speech and swallowing following oral, oropharyngeal, and nasopharyngeal cancers. In E. C. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 63-101). San Diego, CA: Plural Publishing, Inc.

Lee, W. T., Akst, L. M., Adelstein, D. J., Saxton, J. P., Wood, B. G., Strome, M., . . . Esclamado, R. M. (2006). Risk factors for hypopharyngeal/upper esophageal stricture formation after concurrent chemoradiation. *Head & Neck, 28*(9), 808-812.

Lewin, J., Hutcheson, K., Barringer, D., & Smith, B. (2010). Preliminary experience with head and neck lymphedema and swallowing function in patients treated for head and neck cancer. *Dysphagia, 19*(2), 45-52.

Logemann, J., Rademaker, A., Pauloski, B., Lazarus, C. L., Mittal, B., Brockstein, B., . . . Liu, D. (2006). Site of disease and treatment protocol as correlates of swallowing function in patients with head and neck cancer treated with chemoradiation. *Head & Neck, 28*(1), 64-73.

Logemann, J. A., & Bytell, D. (1979). Swallowing disorders in three types of head and neck surgical patients. *Cancer, 44*, 1095-1105.

Logemann, J. A., Pauloski, B. R., Rademaker, A. W., Lazarus, C. L., Gaziano, J., Stachowiak, L., . . . Mittal, B. (2008). Swallowing disorders in the first year after radiation and chemoradiation. *Head & Neck, 30*(2), 148-158.

Logemann, J. A., Smith, C., Pauloski, B. R., Rademaker, A. W., Lazarus, C. L., Colangelo, L., . . . Newman, L. (2001). Effects of xerostomia on perception and perfomance of swallow function. *Head & Neck, 23*, 317-321.

Mallick, I., & Waldron, J. N. (2009). Radiation therapy for head and neck cancers. *Seminars in Oncology Nursing, 25*(3), 193-202.

Manoharan, S., Nagaraja, V., & Eslick, G. D. (2014). Ill-fitting dentures and oral cancer: A meta-analysis. *Oral Oncology, 50*(11), 1058-1061.

Martini, D., Lucente, F., & Slavit, D. (1997). Swallow and pharyngeal function in post-operative cancer patients. *Ear Nose Throat Journal, 76*, 450-456.

Mekhail, T. M., Adelstein, D. J., Rybicki, L. A., Larto, M. A., Saxton, J. P., & Lavertu, P. (2001). Enteral nutrition during the treatment of head and neck carcinoma: Is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? *Cancer, 91*(9), 1785-1790.

Merletti, F., Boffetta, P., Ciccone, G., Mashberg, A., & Terracini, B. (1989). Role of tobacco and alcoholic beverages in the etiology of cancer of the oral cavity/oropharynx in Torino, Italy. *Cancer Research, 49*, 4919-4924.

Murphy, B., Gilbert, J., Cmelak, A., & Ridner, S. (2007). Symptom control issues and supportive care of patients with head and neck cancers. *Clinical Advances in Hematology and Oncology, 5*(10), 807-822.

Murphy, B. A. (2007). Clinical and economic consequences of mucositis induced by chemotherapy and/or radiation therapy. *Journal of Community and Supportive Oncology, 5*, 13-21.

Murphy, B. A., & Gilbert, J. (2009). Dysphagia in head and neck cancer patients treated with radiation: Assessment, sequelae, and rehabilitation. *Seminars in Radiation Oncology, 19*, 35-42.

Murray, E., Power, E., Togher, L., McCabe, P., Munro, N., & Smith, K. (2013). The reliability of methodological ratings for speechBITE using the PEDro-P scale. *International Journal of Language & Communication Disorders, 48*(3), 297-306.

Murray, T., & Carrau, R. (2012). *Clinical management of swallowing disorders*. San Diego, CA: Plural Publishing, Inc.

Nasreddine, Z., Phillips, N., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*, 695-699.

Nguyen, N., Moltz, C., Frank, C., Vos, P., Smith, H., Karlsson, U., . . . Sallah, S. (2004). Dysphagia following chemoradiation for locally advanced head and neck cancer. *Annals of Oncology, 15*, 383-388.

Nguyen, N., Smith, H., Dutta, S., Alfieri, A., North, D., Nguyen, P., . . . Sallah, S. (2007). Aspriation occurence during chemoradiation for head and neck cancer. *Anticancer Research, 27*, 4.

NIH. (2011). *Dry Mouth*. NIH Publication no. 11-3174. Retrieved from https://www.nidcr.nih.gov/OralHealth/Topics/DryMouth

Parsons, J., Mendenhall, W., Stringer, S., Amdur, R., Hinerman, R., Villaret, D., . . . Million, R. (2002). Squamous cell carcinoma of the oropharynx. *Cancer, 94*, 2967-2980.

Pauloski, B., Logemann, J., Colangelo, L., Rademaker, A., McConnel, F., Heiser, M., . . . Esclamado, R. (1998). Surgical variables affecting speech in treated patients with oral and oropharyngeal cancer. *Laryngoscope, 108*(6), 908-916.

Perkins, K., Hancock, K., & Ward, E. (2014). Speech and swallowing following laryngeal and hypolaryngeal cancer. In E. C. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 63-101). San Diego, CA: Plural Publishing, Inc.

Purcell, A., & Turner, J. (2014). Associated morbidities affecting quality of life in patients treated with head and neck cancer. In E. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 507-524). San Diego, CA: Plural Publishing, Inc.

Robbins, J., Gangnon, R., Theis, S., Kays, S., Hewitt, A., & Hind, J. (2005). The effects of lingual exercise on swallowing in older adults. *Journal of the American Geriatrics Society, 53*, 1483-1489.

Robbins, J., Kays, S., Gangnon, R., Hind, J., Hewitt, A., Gentry, L., & Taylor, A. (2007). The effects of lingual exercise in stroke patients with dysphagia. *Archives of Physical Medicine and Rehabilitation, 88*, 150-158.

Robey, R. (1998). A meta-analysis of clinical outcomes in the treatment of aphasia. *Journal of Speech, Language, and Hearing Research, 41*, 172-187.

Robin, D., Goel, L., Smoodi, L., & Luschei, E. (1992). Tongue strength and endurance: Relation to highly skilled movements. *Journal of Speech and Hearing Research, 35*, 1239-1245.

Rosenbek, J. C., Robbins, J. A., Roecker, E. B., Coyle, J. L., & Wood, J. L. (1996). A penetration-aspiration scale. *Dysphagia, 11*(2), 93-98.

Rosenthal, D., Lewin, J., & Eisbruch, A. (2006). Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. *Journal of Clinical Oncology, 24*, 2636-2643.

Rosenthal, D., & Trotti, A. (2009). Strategies for managing radiation-induced mucositis in head and neck cancer. *Seminars in Radiation Oncology, 19*, 29-34.

Rosenthal, R., & DiMatteo, M. (2001). Meta-analysis: Recent developments in quantitative methods for literature reviews. *Annual Review of Psychology, 52*, 59-82.

Saunders, N., Coman, W., & Guminski, A. (2014). Cancer of the head and neck. In E. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 1-27). San Diego, CA: Plural Publishing, Inc.

Serewko, M., Popa, C., Dahler, A., Smith, L., Strutton, G., Coman, W., . . . Saunders, N. (2002). Alterations in gene expression and activity during squamous cell carcinoma development. *Cancer Research, 62*, 3759-3765.

Sloan, S., Blackwell, K., Harris, J., Genden, W., & Urken, M. (2003). Reconstruction of major defects in the head and neck following cancer surgery. In E. Myers, J. Suen, J. Meyers, & E. Hanna (Eds.), *Cancer of the head and neck* (4th ed., pp. 631-670). Philadelphia, PA: Sounders.

Smith, B., & Lewin, J. (2010). Lymphedema management in head and neck cancer. *Current Opinion in Otolaryngology & Head and Neck Surgery, 18*, 153-158.

Smith, R., Kotz, T., Beitler, J., & Wadler, S. (2000). Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: Initial results. *Archives of Otolaryngology–Head & Neck Surgery, 126*(3), 384-389.

Sonis, S., & Keefe, D. (2004). Perspectives on cancer therapy-induced mucosal injury pathogenesis, measurement, epidemiology, and consequences for patients. *Supportive Care in Cancer, 100*, 1995-2025.

Stephens, F., & Aigner, K. (2009). *Basics of oncology*. Verlag Berlin Heidelberg: Springer.

Stierwalt, J., & Youmans, S. (2007). Tongue measures in individuals with normal and impaired swallowing. *American Journal of Speech Language Pathology, 16*, 148-156.

Sturgis, E., Wie, Q., & Spitz, M. (2004). Descriptive epidemiology and risk factors for head and neck cancer. *Seminars in Oncology, 31*(6), 726-733.

Sullivan, C., Jaklitsch, M., Haddad, R., Goguen, L., Gagne, A., Wirth, L., . . . Norris, C. (2004). Endoscipic management of hypopharyngeal stenosis after organ sparing therapy for head and neck cancer. *Laryngoscope, 114*(11), 1924-1931.

Sullivan, P. A., & Guilford, A. M. (1999). *Swallowing intervention in oncology*. San Diego, CA: Singular Publishing Group, Inc.

Szczesniak, M., Maclean, J., Zhang, T., Graham, P., & Cook, I. (2014). Persistent dysphagia after head and neck radiotherapy: A common and under-reported complication with significant effect on non-cancer-related mortality. *Clinical Oncology, 26*, 697-703.

Taberna, M., Rullan, A., Hierro, C., Navarro, V., Vazquez, S., Lozano, A., . . . Mesia, R. (2015). Late toxicity after radical treatment for locally advanced head and neck cancer. *Oral Oncology, 51*, 795-799.

Tan, I., Stoker, S., & Smeele, L. E. (2014). Oral, oropharyngeal, and nasopharyngeal cancer: Intervention approaches. In E. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 103-120). San Diego, CA: Plural Publishing, Inc.

Thoma, H. (2012). Treatment of lymphedema of the head. In M. Foldi & W. Foldi (Eds.), *Foldi's textbook of lymphology for physicians and lymphedema therapists* (pp. 604-608). Germany: Elsevier.

Thorne, P., Etherington, D., & Birchall, M. (1997). Head and neck cancer in the southwest of England-influence of socio-economic status on incidence and second primary tumors. *European Journal of Surgical Oncology, 23*, 503-508.

Trotti, A., Bellm, L., Epstein, J., Frame, D., Fuchs, H., Gwede, C., . . . Zilberberg, M. (2003). Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: A systematic literature review. *Radiotherapy and Oncology, 66*(253-262).

Tyldesley, S., Sheehan, F., Munk, P., Tsang, V., Skarsgard, D., Bowman, C., & Hobenshield, S. (1996). The use of radiologically placed gastrostomy tubes in head and neck cancer

patients receiving radiotherapy. *International Journal of Radiation Oncology, Biology, Physics, 36*(5), 1205-1209.

van der Molen, L., van Rossum, M., Rasch, C., Smeele, L., & Hilgers, F. (2014). Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. *European Archives of Oto-Rhino-Laryngology, 271*, 1257-1270.

Vigneswaran, N., & Williams, M. D. (2014). Epidemiologic trends in head and neck cancer and aids in diagnosis. *Oral & Maxillofacial Surgery Clinics of North America, 26*(2), 123-141.

Virani, A., Kunduk, M., Fink, D., & McWhorter, A. (2014). Effects of 2 different swallowing exercise regimens during organ-preservation therapies for head and neck cancers on swallowing function. *Head & Neck, 37*, 162-170.

Vissink, A., Mitchell, J., Baum, B., Limesand, K., Jensen, S., Fox, P., . . . Reyland, M. (2010). Clinical management of salivary gland hypofunction and xerostomia in head-and-neck cancer patients: Successes and barriers. *International Journal of Radiation Oncology, Biology, Physics, 78*(4), 983-991.

Wall, L., Ward, E., Cartmill, B., & Hill, A. (2013). Physiological changes to the swallowing mechanism following (chemo)radiotherapy for head and neck cancer: A systematic review. *Dysphagia, 28*, 481-493.

Wang, X., Hu, C., & Eisbruch, A. (2011). Organ-sparing radiation therapy for head and neck cancer. *Nature Reviews Clinical Oncology, 8*(11), 639-648.

Ward, E., Kerle, S., Hancock, K., & Perkins, K. (2014). Swallowing rehabilitation following total laryngectomy. In E. Ward & C. J. van As-Brooks (Eds.), *Head and neck cancer* (pp. 343-373). San Diego, CA: Plural Publishing, Inc.

Ward, M., Adelstein, D., Bhateja, P., Nwizu, T., Scharpf, J., Houston, N., . . . Koyfman, S. (2016). Severe late dysphagia and cause of death after concurrent chemoradiation for larynx cancer in patients eligible for RTOG 91-11. *Oral Oncology, 57*, 21-26.

Wehner, M., Chren, M., Nameth, D., Choudhry, A., Gaskins, M., Nead, K., . . . Linos, E. (2014). International prevalence of indoor tanning: A systematic review and meta-analysis. *Dermatology, 150*(4), 390-400.

White, R., Cotton, S. M., Hind, J., Robbins, J., & Perry, A. (2009). A comparison of the reliability and stability of oro-lingual swallowing pressures in patients with head and neck cancer and healthy adults. *Dysphagia, 24*(2), 137-144.

Wilson, J., Carding, P., & Patterson, J. (2011). Dysphagia after nonsurgical head and neck cancer treatment patients' perspectives. *Otolaryngology-Head Neck Surgery, 145*(5), 767-771.

Withey, S., Pracy, P., Wood, S., & Rhys-Evans, P. (2001). The use of a lymphatic bridge in the management of head and neck lymphedema. *British Journal of Plastic Surgery, 54*(8), 716-719.

Wynn, T. A. (2008). Cellular and molecular mechanisms of fibrosis. *Journal of Pathology, 214*(2), 199-210.

Youmans, S., & Stierwalt, J. (2006). Measures of tongue function related to swallowing. *Dysphagia, 21*, 102-111.

Youmans, S., Youmans, G., & Stierwalt, J. (2009). Differences in tongue strength across age and gender: Is there a dimished strength reserve? *Dysphagia, 24*, 57-65.

Appendices

Appendix A: Demographics & Medical History Form

Demographics and Medical History

Name:_____ Subject ID:_____
Date : _____ Gender: M F Date of Birth:_____
Address:_____
Phone number:_____ Home Cell Work
Email Address:_____
Occupation / Job:_____
Highest level of education completed:_____
Cancer Diagnosis and Date:_____
Where did you receive your cancer treatment?_____

Did you receive radiation as part of your head and neck cancer treatment? Yes No

Did you receive chemotherapy as part of your head and neck cancer treatment? Yes No

Did you receive surgery as part of your head and neck cancer treatment? Yes No

Did you receive a swallow study before you began your cancer treatment?

Yes No I don't recall

Did you receive a swallow study after your cancer treatment was complete?

Yes No I don't recall

Did you receive a feeding tube or have an alternative way to get nutrition during your cancer treatment?

Yes No

Were you able to eat and drink whatever you wanted during your cancer treatment?

Yes No

What, if any, feeding/swallowing difficulties did you experience during your cancer treatment?_____

Did you receive a set of exercises to complete that focused on your mouth and throat before you began your cancer treatment, or any time during?

Yes No I don't recall

If you answered yes, please respond to the following questions.

a. Did you understand why you were given these exercises?
   Yes No

b. How often did you complete the exercises?

   Never 1-3 times per week 4-6 times per week

   Once per day 2-3 times per day

c. Please describe any barriers, reasons that made it difficult to complete the exercises

_____

_____

Are you currently experiencing any feeding or swallowing problems? Yes No

If you answered yes, please describe._____

How are nutritional needs being met? _____

Are you receiving any type of therapy or support for your feeding and swallowing?
Yes No

If you answered yes, please describe._____

Smoking History:_____

Medications:

Name	Dosage	Dosage Schedule	Purpose of Medication

List/describe any other medical diagnoses/problems:

Diagnosis/problem	Date of onset

Describe any surgeries:

Description/purpose of surgery	Date of surgery

Appendix B: Demographic & Medical Follow-up Form

Demographics and Medical History: Follow-Up

Date: _____ Subject ID: _____

1. Please list any changes to your medications since your last visit:

Name	Dosage	Dosage Schedule	Purpose of Medication

2. Please list/describe any medical information that has changed since your last visit (diagnosis, surgery, complication, etc):

New Condition/Complication	Date of onset	Influence on feeding/swallowing?

3. Please list/describe any changes to your communication, hearing, and/or eating since your last visit:

Description	Date of onset

Appendix C: Oral Pain & Sense of Effort Home Journal Rating Form: Example

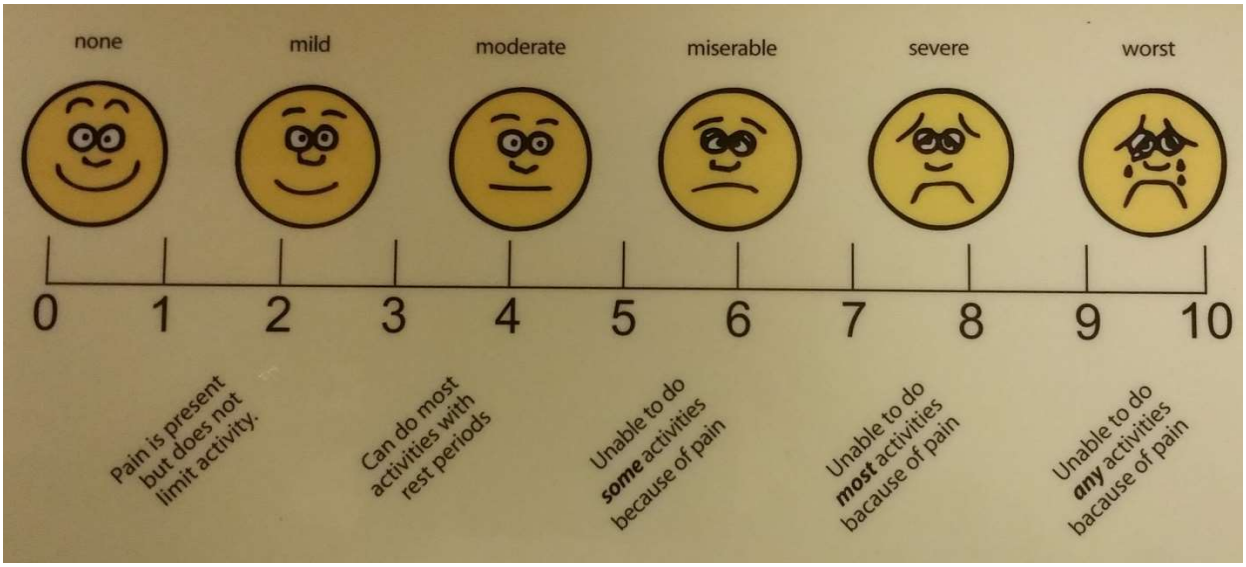
Oral Pain & Sense of Effort Rating

Name:_____ Date:_____ Start Time:_____

Please list the pain medications taken today including the dosage and time:_____

_____

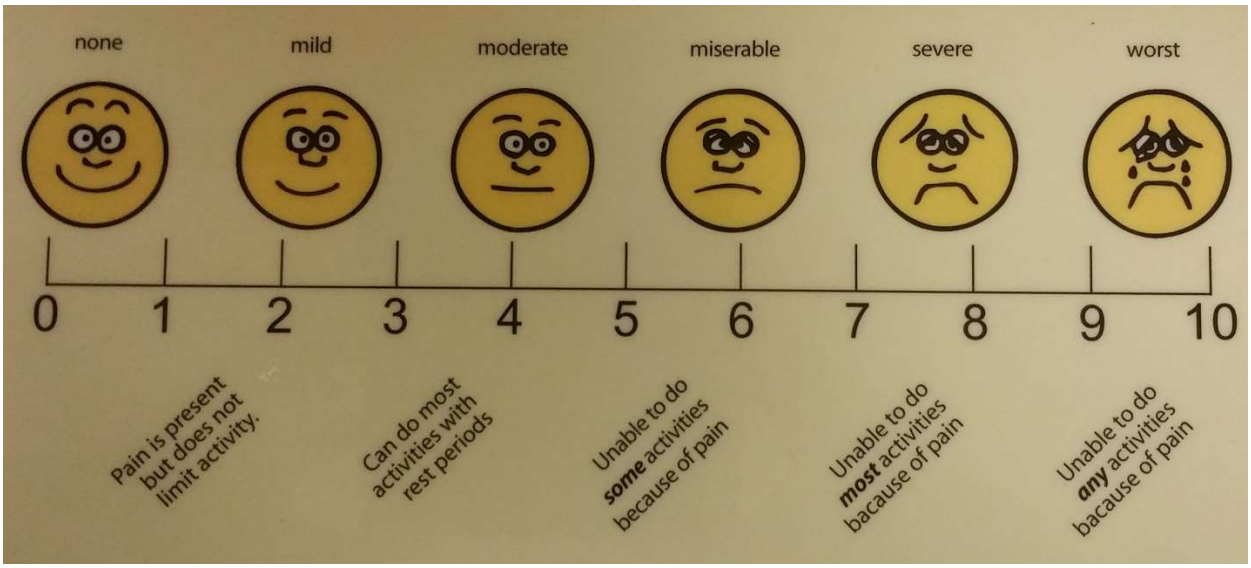
- Pre-exercise rating: Rate the amount of pain, if any, you are currently feeling in your mouth. This is pain that would impact your eating, drinking, and swallowing.



- 1st Exercise: _____.

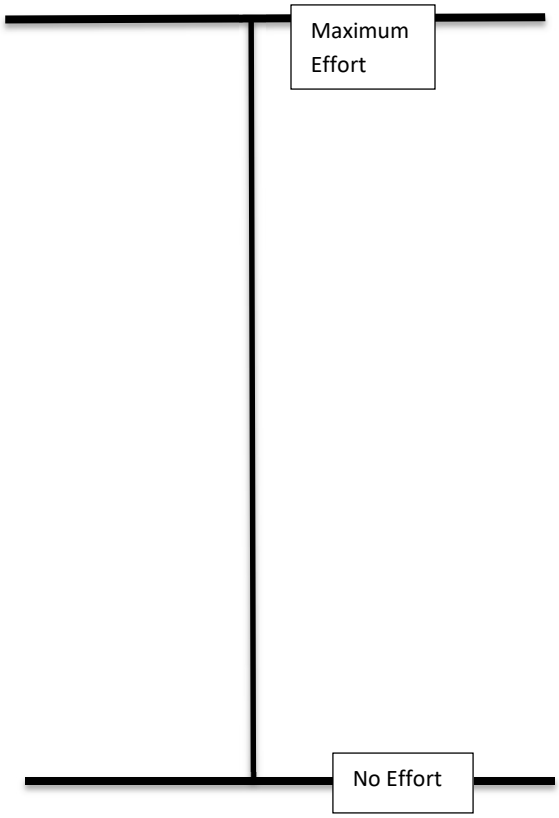
Please complete this exercise per the instructions.

- After 1st exercise: Rate the amount of pain, if any, you are currently feeling in your mouth. This is pain that would impact your eating, drinking, and swallowing.

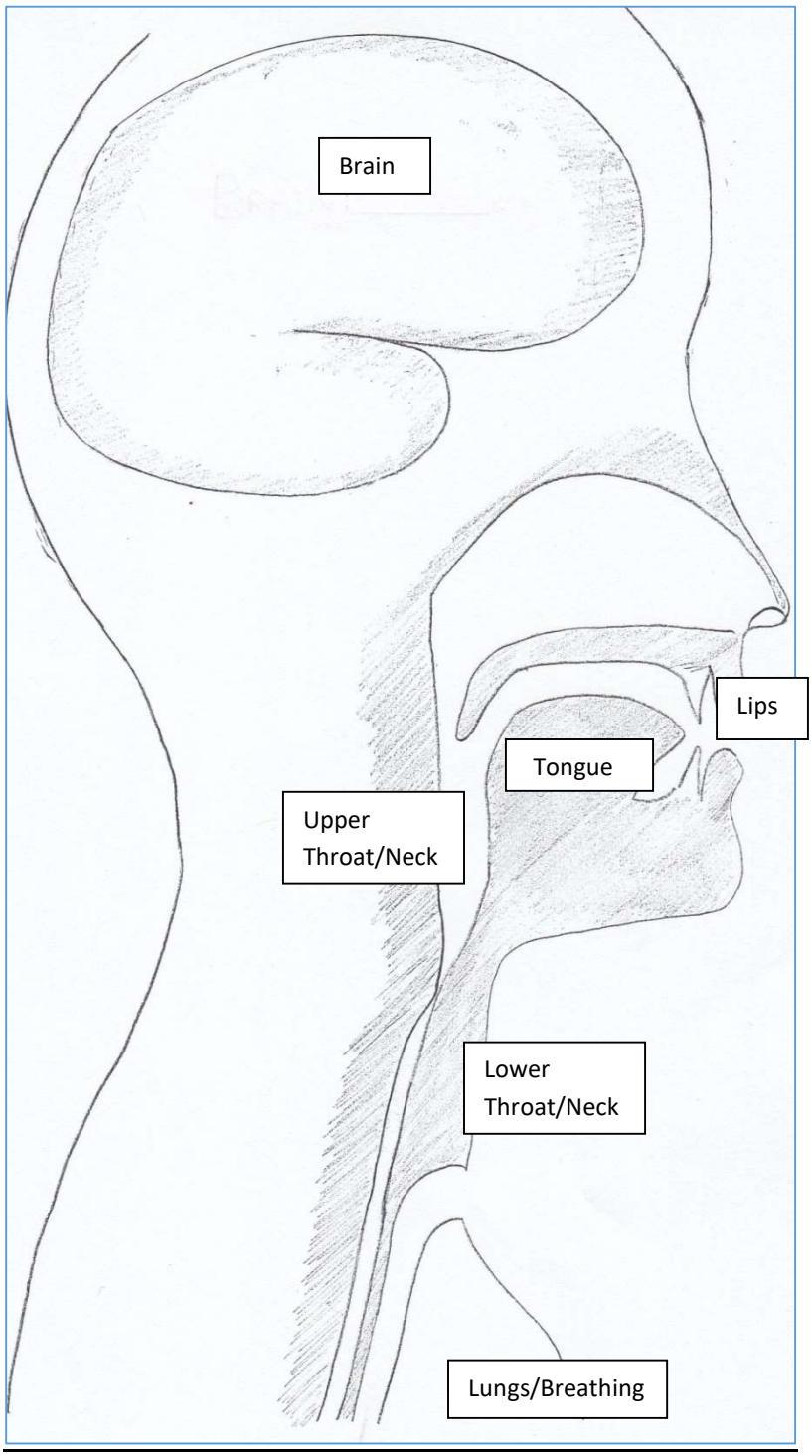


- After 1st exercise: Rate the sense of effort and location of effort you felt it took to complete the previous exercise

Mark the sense of effort you felt after completing the previous exercise



Mark the location of effort you felt after completing the previous exercise. If you felt effort in more than one place, number the locations with 1 being the location of greatest effort, 2 being the location you felt the second most effort, and so on.



Other Location.

Please list.

Appendix D: Written Instructions for Exercises

Swallowing Exercises

A. Effortful Swallow
   1. While swallowing your saliva:

      a. Bear down and swallow as hard as possible, squeezing your muscles as tight as you can

*Repeat this exercise 10 times

B. Masako Maneuver
   1. Place your tongue between your teeth/gums.

   2. Firmly hold your tongue in place and swallow. The goal is to keep your tongue between your teeth/gums and not let it move back behind them.

   3. Once you have fully swallowed, release your tongue and close your mouth in a resting position.

*Repeat this exercise 10 times.

C. Mendelsohn Maneuver
   1. While swallowing your saliva:

      a. Stop and hold your muscles trying to keep your Adam's apple up.

      b. Hold this position for 3 seconds. The goal is to not let your Adam's apple fall back down right away.

   2. Release your muscles and complete the swallow.

*Repeat this exercise 10 times.

D. Lingual Tip Press
   1. Open your mouth

   2. Place the tip of your tongue on the roof of your mouth (the bumpy spot)

   3. Press as hard as you can for 5 seconds, try to not let your jaw move

   4. Relax your tongue and close your mouth

*Repeat this exercise 10 times

Appendix E: Consent Form

Swallowing Exercise Pain in Head and Neck Cancer Patients Treated With Radiotherapy

Protocol #

Consent Form For:
Individuals Who COMPLETED Radiation Treatment For Oral or Oral-Pharyngeal Cancer

You are being asked to join a research study. You are being asked to take part in this study because you had a diagnosis of cancer in the head and neck region for which you completed radiation therapy within the last three years. You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas Medical Center (KUMC) with Jeffrey P. Searl, PhD and Christopher Lominska, MD as the researchers. About 40 people will be in the study at KUMC.

BACKGROUND

Many patients undergoing radiation treatment for cancer in the head and neck region will experience some degree of swallowing difficulty (dysphagia). Radiation therapy has become a common way to treat cancers in the mouth, throat, and larynx. Sometimes radiation therapy is done along with surgery and sometimes it is not. In either case, the side effects of radiation therapy can make movements of the swallowing muscles more difficult during, and sometimes weeks, months, or years after treatment. Recent studies have shown that a person who exercises the mouth and throat during radiation therapy is more likely to experience fewer problems swallowing once radiation therapy is complete. However, a lot of people have difficulty completing the exercises fully during radiation therapy because of the pain that they experience. One portion of our study is looking at how completing oral exercises during radiation therapy causes pain. The portion of the study that you are being asked to join focuses on whether people who have already completed their radiation therapy experience pain from these exercises and if the exercises can provide benefit to swallowing even when conducted after radiation therapy has been stopped.

PURPOSE

The purposes of this study are: 1) determine whether the swallow exercises increase the pain that occurs during radiation therapy; 2) evaluate how the pain changes each week during radiation therapy; 3) assess whether there are specific exercises that cause more pain than others; 4) determine if swallow exercises are beneficial if completed after medical treatment; and 5) assess whether pain is an influential factor in completing swallowing exercises after medical treatment.

PROCEDURES

If you are eligible and decide to participate in this study, your participation will last approximately 3 months. Your participation will include data collection days as follows: 1) initial visit, 2) two weeks after the initial visit 3) one month after the initial visit, and 4) two months after the initial visit.

For the initial visit and the visits that happen at one and two months after the initial visit you will be asked to do the following (estimated to take 1-1.5 hours each time):

1. The MD Anderson Dysphagia Inventory (MDADI) will be given to you. This is a survey that asks you questions about your swallowing ability.
2. You will be asked questions by the researchers so they can determine the diet level that you are taking, the type and amount of pain medication you take, and any problems you are having with your talking (if any).
3. You will be asked to rate the amount of pain, if any, that you feel in your mouth and throat.
4. You will be provided instruction on each of the exercises you will be asked to complete during your radiation therapy or after all your radiation therapy is done. These exercises are ones that are routinely given to patients in your situation. If your doctor or other care providers do not want you to do specific exercises we will remove those exercises from the list you do for this study. In order for us to know what exercises your care providers do not want you to complete during radiation therapy we need to look at your medical record.
5. You will be weighed on a scale.
6. Flexible endoscopic evaluation of swallow (FEES). A scope will be placed in your nose and you will be asked to eat and drink some things so your swallow may be assessed.
7. You will be asked to press your tongue to the top of your mouth, pushing on a device that measures the strength of your tongue.

For the visit two weeks after the initial visit you will do the following (estimated to take

30 minutes):

1. Rate your pain before doing the swallow exercises for that day. To rate your pain, you will read instructions about pain rating on a computer screen

and then click on a number on a pain scale number that shows up on the computer screen.

2. Complete each exercise and rate pain after each one. The same computer program will be used to have you rate your pain by clicking on a number on a pain scale.
3. Be weighed.
4. Complete the MDADI
5. Answer questions so that the researchers can determine the diet level you are taking and to describe how much pain medication you are taking and when you are taking it.

On each day after the initial visit you will be asked to complete a set of oral exercises that take approximately 10-15 minutes to complete. The researchers will teach you how to do these exercises on your initial visit and you will be given handouts that help explain what you are to do each day.

As part of your participation in this research you are giving permission for the researchers to look at your electronic medical record.

The reason that we want to look at your medical record is to get information about other medical issues that you might have, your full list of medications, and information about any surgeries that you might have had for the cancer.

RISKS

Possible risks to you are the following:

- Pain and fatigue may occur for you by doing oral exercises. We try to minimize this risk by asking you to work with your doctor who can talk with you about how to manage the pain after radiation therapy. You also can tell the study personnel if any particular exercise or study activity is creating significant pain or fatigue. You can chose to not complete those specific exercises or activities at any point during the study.

- Pain or fatigue could occur when we measure your tongue strength as you push the tongue forcefully against the roof of your mouth. We try to minimize this risk by having you only complete the task for a brief period of time (5 second press repeated three times with a break in between each press).

- Discomfort from having a flexible scope in the nose and throat to evaluate your swallowing may occur. We try to minimize this risk by applying a medicine to open up your nasal passageway (vasoconstrictor) and by applying a topical anesthetic. The topical anesthetic creates numbness that usually lasts for about

  15 minutes. You should not eat or drink for 30 minutes after the anesthetic is applied to give time for the numbness to go away. If during the exam you experience discomfort

causing you to want to stop the procedure you can tell the research personnel and it will be stopped.

- Embarrassment or distress may happen when we ask you questions about what you are eating and if you were able to complete the exercises each day. We try to minimize your embarrassment by doing this questioning in a clinic space with a closed door so no one but study personnel can hear your answers. We will also remind you regularly that you are free not to answer any questions asked of you. Finally, if you tell study personnel that you are embarrassed or distressed, Jeff Searl (the Principal Investigator) will talk with you about whether you want to continue in the study. He is a licensed speech-language pathologist with experience talking to people who have cancer and swallowing issues and he can try to answer your questions and minimize your embarrassment and distress about the study.

- Embarrassment or distress may happen when we weigh you during the study. We try to minimize possible embarrassment or distress by getting your weight in a private room with the door closed so no one but study personnel can see. If you indicate to study personnel that weighing you is embarrassing or distressing we will ask your permission to tell your radiation oncologist so they can talk with you about what is happening with your weight. You also can refuse to have the weight taken for the research study at any visit if you wish without impacting the clinical care that you receive at KU Medical Center.

There may be other risks of the study that are not yet known.

NEW FINDINGS STATEMENT

You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

You may or may not benefit from this study. If the swallowing exercises are effective at limiting the long-term swallowing problems after radiation therapy as found in other studies, you may be able to swallow better and you may have an increased ability to eat by mouth by completing the exercises in this study.

Researchers hope that the information from this research study may be useful in the swallowing treatment of patients with head and neck cancer. By gathering this information, the researchers can begin to tailor protocols to decrease pain for patients and therefore increase compliance. The goal is that better exercise programs can increase the person's ability to eat by mouth and improve their quality of life.

ALTERNATIVES

Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive at the University of Kansas Medical Center.

COSTS

There is no cost for being in the study.

PAYMENT TO SUBJECTS

There is no payment for this study.

IN THE EVENT OF INJURY

If you have problems during this study or if you feel that doing the study has caused an injury, you should immediately contact Jeffrey P. Searl, PhD at (913)588-5937. If it is after 5:00 p.m., a holiday or a weekend, you should call (913)945-7915 which is Dr. Searl's office number that he checks for messages regularly after hours and on weekends. A member of the research team will decide what type of treatment, if any, is best for you at that time.

INSTITUTIONAL DISCLAIMER STATEMENT

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities and from your medical record. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KU Medical Center by Dr. Searl, Dr. Lominska, members of the research team, the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. Study records might be reviewed by government officials who oversee research, if a regulatory review takes place.

All study information that is sent outside KU Medical Center will have your name and other identifying characteristics removed, so that your identity will not be known. Because identifiers will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Your permission to use and share your health information will not expire unless you cancel it.

QUESTIONS

Before you sign this form, Dr. Searl or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Searl. The mailing address is Jeffrey P. Searl, PhD, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

CONSENT

Dr. Searl or the research team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered. ***You will be given a signed copy of the consent form to keep for your records.***

_____

Print Participant's Name

_____	_____	_____
Signature of Participant	Time	Date

_____

Print Name of Person Obtaining Consent

_____	_____
Signature of Person Obtaining Consent	Date

Appendix F: Daily and Weekly Participant Contact Information

Table F-1: Participant contact preference for daily correspondence

Participant	Preferred Contact Method
1	Text
2	Email
3	Text
4	Text
5	Email
6	Text
7	Text
8	Email
9	Email
10	Text
11	Email
12	Text

Day 1 Email or Text

Good morning!

My name is ____ and I am a graduate student on the research project. I will be the one contacting you for the duration of the study.

This email/text is a reminder for you to complete your swallowing exercises today. They can be found in the binder that was given to you yesterday behind the label Day 1.

I will be emailing/texting you a short message every day to remind you to complete your exercises. If you have any questions at all about the exercises or other concerns, please call Jeff Searl or Stephanie Knollhoff at 913-588-5937 or just respond to this email/text.

Please respond to this initial email/text so we know you are receiving them (you won't need to respond to the daily reminders moving forward).

Thank you!

Email or Text Reminder Options for Daily Contact

Good morning/afternoon!

1. Don't forget to do your exercises today. Have a good one!

2. Today's a great day for doing your swallowing exercises! Have a good (insert day).

3. Guess what today is? Swallowing exercise day! Be sure to complete your exercises for today. Have a good one!

4. Just a quick reminder to do your swallowing exercises today. Enjoy your day!

5. Don't forget to complete your swallowing exercises today. I hope you have a great day!

6. Today is a wonderful day to do your swallowing exercises! Enjoy your day!

7. Gosh, swallowing exercises sound like a fun activity to do today! Don't forget to do all your exercises!

8. Completed swallowing exercises today? Check. Having a great day? Check. Take care!

Day 7, 14, 21, and 28 Reminder Text or Email

1 of the above + also don't forget to complete your full rating today.

Day 6, 13, 20, 27 Weekly Phone Call and Reminder to Complete Full Ratings

Hi, this is _____ from the University of Kansas Medical Center. May I please speak with _____ (participant or main contact)? This call is to remind you (or participant) that tomorrow is a full rating day meaning you must complete the rating scales and fill out the questionnaire about your swallowing. Additionally, I would like to remind you (him/her) to complete your (his/her) swallowing exercises for today. Have you (he/she) had any issues completing your exercises every day, 5 times a day? (Open dialogue about any difficulties they are having). Is there anything that I can do to help you to complete these exercises (contact you at a different time, contact you more, etc.)? If you have any questions, feel free to call Stephanie Knollhoff at 913-588-5937 or you can email me whenever you need to. Thanks and have a great day!

Appendix G: Raw data at baseline on outcome measures from participants excluded from analysis

Table G-1: Baseline data on lingual strength, lingual endurance, oral pain rating, and sense of effort rating for participants excluded from data analysis

Participant	Lingual Strength (kPa)	Lingual Endurance (seconds)	Oral Pain Rating	Sense of Effort Rating
1	46.0	30.0	0.0	49.4
2	42.0	51.0	0.0	54.3
3	61.0	47.0	0.0	9.2
4	68.0	55.0	0.0	0.0
5	53.0	50.0	0.0	4.9
6	58.0	54.0	0.0	76.8

Table G-2: Baseline data on MDADI scores for participants excluded from data analysis

Participant	MDADI Composite	MDADI Emotional	MDADI Functional	MDADI Global	MDADI Physical
1	80.1	88.0	93.3	80.0	65.0
2	91.6	84.0	86.7	100.0	100.0
3	92.7	84.0	100.0	100.0	100.0
4	74.8	76.0	80.0	100.0	70.0
5	82.2	68.0	83.3	100.0	90.0
6	91.6	100.0	100.0	100.0	80.0

Appendix H: Missing Data

An ‘x’ represents the data for that particular item is missing.

Table H-1: Day 1 missing data

Participants	Day 1 Exercise Log	Day 1 MDADI	Day 1 Oral Pain 1	Day 1 Oral Pain 2	Day 1 Oral Pain 3	Day 1 Sense of Effort 1	Day 1 Sense of Effort 2	Day 1 Sense of Effort 3
1								
2								
3								
4								
5					x			x
6								
7				x	x		x	x
8								
9				x	x		x	x
10								
11	x				x			x
12					x			x

Table H-2: Day 7 missing data

Participants	Day 7 Exercise Log	Day 7 MDADI	Day 7 Oral Pain 1	Day 7 Oral Pain 2	Day 7 Oral Pain 3	Day 7 Sense of Effort 1	Day 7 Sense of Effort 2	Day 7 Sense of Effort 3
1								
2								
3					x			x
4								
5								
6	x				x			x
7				x	x		x	x
8								
9								
10								
11					x			x
12								

Table H-3: Day 14 missing data

Participants	Day 14 Exercise Log	Day 14 MDADI	Day 14 Oral Pain 1	Day 14 Oral Pain 2	Day 14 Oral Pain 3	Day 14 Sense of Effort 1	Day 14 Sense of Effort 2	Day 14 Sense of Effort 3
1								
2								
3				x	x		x	x
4								
5								
6	x	x	x	x	x	x	x	x
7								
8								
9								
10								
11					x			x
12								

Table H-4: Day 21 missing data

Participants	Day 21 Exercise Log	Day 21 MDADI	Day 21 Oral Pain 1	Day 21 Oral Pain 2	Day 21 Oral Pain 3	Day 21 Sense of Effort 1	Day 21 Sense of Effort 2	Day 21 Sense of Effort 3
1								
2								
3					x			x
4								
5								
6	x		x	x	x	x	x	x
7								
8								
9								
10								
11	x	x	x	x	x	x	x	x
12								

Table H-5: Day 28 missing data

Participants	Day 28 Exercise Log	Day 28 MDADI	Day 28 Oral Pain 1	Day 28 Oral Pain 2	Day 28 Oral Pain 3	Day 28 Sense of Effort 1	Day 28 Sense of Effort 2	Day 28 Sense of Effort 3
1								
2								
3					x			x
4								
5								
6	x	x	x	x	x	x	x	x
7				x	x		x	x
8								
9						x	x	x
10								
11								
12								