Physiology of the Swallow and the Impact of Thickened Liquids in Post-Radiation Head and Neck Cancer Patients

by

Carly E A Barbon

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Rehabilitation Sciences Institute
University of Toronto

© Copyright by Carly E A Barbon, 2019
Physiology of the Swallow and the Impact of Thickened Liquids in Post-Radiation Head and Neck Cancer Patients

Carly Elena Antoniette Barbon

Doctor of Philosophy

Rehabilitation Sciences Institute
University of Toronto

2019

Abstract

There is an increasing prevalence of head and neck cancers (HNC) in Canada and the United States, with approximately 52,000 new cases every year, and approximately 9,500 deaths annually due to the disease in the United States alone. In Canada, there are approximately 220 new diagnoses of oropharyngeal cancer and an estimated 120 deaths resulting from this cancer type per annum. Patients with oropharynx cancers commonly are undergo radiation treatment for their disease, which has good results in terms of tumor control. While survival is improving, patients are left suffering from radiation-induced toxicities. Dysphagia (swallowing impairment) is one of the side effects that can become a long-term, pervasive issue. Individuals with dysphagia are at risk for aspiration (food/liquid entering into the airway). Aspiration is estimated to occur in 30-69% of HNC patients after radiation treatment (range of 1-12 months) and is often silent (i.e. with no overt symptoms). Thickened liquids are commonly used to reduce aspiration in the neurogenic dysphagia population but there is a gap in our knowledge with regards to the impact that viscosity and texture modification have on swallowing in the head and neck cancer population. The studies in this dissertation will examine the potential of thickened liquids to reduce aspiration in patients who present with unsafe swallowing on thin liquids after the completion of radiation treatment (post-3-6 months) for cancers focal to the oropharynx.
Dedications

For my mom and dad, who instilled in me the importance of kindness and hard work.
Acknowledgments

I am so incredibly grateful for all of the experiences that these past few years have brought me. They have been truly life-changing and I am thankful for both the challenges and rewards that have come my way. It is extremely difficult for me to put into words how blessed I feel to have had the love and support of my family, friends, mentors and patients throughout my doctoral tenure. There are a few individuals that I would like to thank specifically.

_Catriona,_ I’m not sure how to begin to thank you and express my gratitude. I want to first thank you for your guidance, your support, your opinion, your friendship and your time. You have had high expectations of me from the very beginning and this has pushed me to always put forth my best product. I have been so lucky to have you as a mentor. Your care for me not only as your student but as an individual is something I cannot thank you enough for and the steadfast support you have shown through the difficult and happy times has never wavered. Your focus on patient-care is admirable and it has been motivating to watch as your student. I will be forever grateful and look forward to life-long learning with you. It is truly an honour and a privilege to have been your student.

_To my committee members:_ Dr. Andrew Hope, thank you for your time and for helping me to understand an extremely small aspect of radiation oncology. Your part in this project has been invaluable and truly appreciated. Dr. Douglas Chepeha, I am so glad that you followed me back to Canada. You have been a true mentor and I cannot thank you enough for sharing your expertise, your clinic space and your surgical patients with me. Your trust in my ability has provided me with learning opportunities that I am so grateful for. Thank you for all of your input on this project and your strong mentorship from the very beginning.

_To my lab family:_ Thank you for all of your support and your help over the years. Thank you for listening to countless presentations, providing invaluable feedback and helping with data collection (and my computer issues)! To Ashley Waito, Melanie Peladeau-Pigeon, Cecilia Campolongo, Emily Barrett, Melanie Tapson, Sana Smaoui, Talia Wolkin (and past lab members Teresa Valenzano, Andrea Guran, Ashwini MacDonald, Brittany Guida, Natalie Muradian, Robbyn Draimin and Sonya Torreiter), thank you.

_Alysia,_ thank you for always being beside me. These years have been filled with ups and downs and you haven’t missed a beat. Thank you for always being there when I needed you most. I love you.
Laurie Coleman, you saved me. This would not have been possible if God had not put you in my life. Thank you to Dr. Sarah Warden & Shauna Corbin for truly caring and helping me to journey through this processes as gracefully as possible.

To my participants: thank you for allowing me to be a part of your journey and for trusting me at a vulnerable time. I will forever be grateful to you.

Zia, this is your fault. That one fateful day in Sudbury (and the drive) changed everything. Thank you for moving me to every city and always waiting to cry until I was out of your sight.

Justin, thank you for being my rock and my sounding board. You have been my constant cheerleader and I can’t thank you enough for your time, your love and your support. You have made this journey that more enjoyable. Olive juice.

To my sister, you are so incredibly wise beyond your years. You have helped me more than you could ever imagine. Thank you for always lending your ear and most of all, your opinion. I value your thoughts and your feedback that you’ve never hesitated to provide me with. You’ve always been so selfless with your time when it comes to me, I love you and am so thankful for you. “I’ll love you forever...”

Mom and Dad, thank you for teaching me the importance of staying grounded and having faith in my path (and for always leading by example). We have worked many, many years to get me to this point. I am me because of you.

Dad, you have always taught me of the importance of education. You have taught and shown me strength, unconditional love, grit and hope. Thank you for loving me and watching over me. I know you are always riding beside me and I promise to never forget to give anyone a card.

Mom, our lives have been filled with countless moves, cities and phone calls. Oh, the places we will go! Thank you for filling my soul with strength and faith. Your spirit is infectious and is what has gotten me through all of the good and the bad. You’ve always believed in me and that has provided me with what I needed to carry on. This is your accomplishment as much as it is mine. Thank you for your sacrifice, your unwavering love and your warmth. I love you in the morning.
# Table of Contents

Dedications .......................................................................................................................... iii

Acknowledgments ................................................................................................................ iv

Table of Contents ................................................................................................................. vi

List of Tables ......................................................................................................................... xii

List of Figures ......................................................................................................................... xiv

List of Abbreviations ............................................................................................................. xv

List of Appendices ................................................................................................................ xvii

Chapter 1 Introduction, Thesis Overview and Background ...................................................... 1
  1.1 Introduction ..................................................................................................................... 1
  1.2 Thesis Overview ............................................................................................................. 1
  1.3 Background ................................................................................................................... 3
    1.3.1 Head and Neck Cancer .......................................................................................... 3
    1.3.2 Dysphagia in Head and Neck Cancer ..................................................................... 4
    1.3.3 Interventions for Dysphagia ................................................................................. 7
    1.3.4 Thickened Liquids for Dysphagia Intervention .................................................... 7
  1.4 References ...................................................................................................................... 9

Chapter 2 ................................................................................................................................ 17
  2 Radiation Tutorial for the Speech-Language Pathologist ..................................................... 17
    2.1 Preface ....................................................................................................................... 17
    2.2 Abstract ..................................................................................................................... 18
    2.3 Introduction ............................................................................................................... 18
    2.4 What is Radiation? ................................................................................................. 19
3.5.1 Articles Accepted for Qualitative Synthesis .............................................. 42
3.5.2 Timing of VFSS Post-Treatment ................................................................. 46
3.5.3 Aspiration Status and Operational Definition .............................................. 46
3.5.4 Stimuli used in Videofluoroscopy ............................................................... 47
3.5.5 Other Interventions .................................................................................. 50
3.5.6 Risk of Bias ............................................................................................... 50
3.5.7 Rates of Aspiration .................................................................................. 52

3.6 Conclusion .................................................................................................... 53

3.7 References .................................................................................................... 54

Chapter 4 ............................................................................................................ 59

4 Characterizing the Flow of Thickened Barium and non-Barium Liquid Recipes Using the IDDSI Flow Test ..................................................................................... 59

4.1 Preface .......................................................................................................... 59

4.2 Abstract ......................................................................................................... 60

4.3 Introduction .................................................................................................. 61

4.4 Methods ....................................................................................................... 63

4.4.1 Stimulus Mixing ....................................................................................... 63

4.4.2 Flow Testing ............................................................................................. 64

4.4.3 Stability Testing ....................................................................................... 65

4.4.4 Temperature Testing ............................................................................... 65

4.5 Analyses ....................................................................................................... 65

4.6 Results ........................................................................................................ 66

4.7 Discussion ................................................................................................... 69

4.8 Limitations .................................................................................................. 71
SWALLOWING PHYSIOLOGY AND THICKENED LIQUIDS IN HNC

7.5 Discussion ........................................................................................................................................142
7.6 Limitations ........................................................................................................................................142
7.7 Conclusion .......................................................................................................................................143
7.8 References .....................................................................................................................................143

8 Final Discussion ..................................................................................................................................148

8.1 Summary of Unique Contributions .................................................................................................151
  8.1.1 The Introduction of Barium and non-Barium Flow-Matched Recipes .................................151
  8.1.2 Efficacy of Thickened Liquids in the HNC Population .......................................................151
  8.1.3 Analyses of Swallow Timing and Kinematics in the HNC Population ............................152
  8.1.4 Homogeneous Sample in the HNC Population .................................................................152

8.2 Limitations ......................................................................................................................................152

8.3 Future Directions .............................................................................................................................154

8.4 Conclusions ....................................................................................................................................155

8.5 References .......................................................................................................................................156
List of Tables

Table 3.1. Questions used in the quality rating ................................................................. 40

Table 3.2. Demographics of the study samples of the articles selected for detailed review .... 43

Table 3.3. Detailed list of radio-opaque stimuli used in the reviewed studies ....................... 48

Table 3.4. Summary of risk of bias assessments .................................................................. 51

Table 4.1. Final Recipes (g/100 ml) for all non-barium and barium liquids by IDDSI level ...... 69

Table 5.1. Exclusion criteria for all participants in the study ............................................... 81

Table 5.2. Study participant demographics ......................................................................... 82

Table 5.3. Frequency of at-risk swallows by consistency in study participants ..................... 89

Table 5.4. Descriptive statistics for worst residue by consistency ......................................... 90

Table 5.5. Presence of post-swallow residue by location ..................................................... 90

Table 5.6. Worst residue scores by participant for all IDDSI levels tested ............................ 92

Table 6.1. Participant study demographics ......................................................................... 109

Table 6.2. Inter-rater agreement statistics for PAS scores, frame selection, and pixel-based... 112

Table 6.3. Timing measures for HNC and healthy participants ............................................. 117

Table 6.4 Pixel-based measures for HNC and healthy participants ..................................... 117

Table 6.5. LVC timing and integrity for HNC and healthy participants ................................. 118

Table 6.6. Bolus-level frequency of safe and at-risk swallows in HNC patients .................... 119

Table 6.7. Crosstabulation of above-normal frequencies of post-swallow residue by binary classification of pharyngeal area at MPC ............................................................ 122
Table 7.1. Patient demographics for participants included in the palatability portion of the study
List of Figures

Figure 4.1. IDDSI Flow Test results at one hour for (a) non-barium starch; (b) non-barium xanthan-gum; (c) starch thickened barium and (d) xanthan-gum thickened barium at 1 hour post-mixing.................................................................67

Figure 4.2 Figures a) and b) illustrate differences in flow of thickened barium between room temperature and refrigerated samples across time. Although the refrigerated barium stimuli were thicker than the room temperature stimuli, this difference was not statistically significant. .................................................................68

Figure 5.1. Full VFSS protocol including stopping rules..................................................84

Figure 5.2. Image of pixel-based tracings of post-swallow residue ....................................87

Figure 6.1. Outline of the ASPEKT Method for videofluoroscopy rating ................................111

Figure 6.2. Image showing pixel-based tracings of post-swallow residue..........................115

Figure 6.3. LVC reaction time between groups.....................................................................120

Figure 6.4. Depiction of the correlation between pharyngeal area at maximum constriction and post-swallow residue...............................................................122

Figure 7.1. Hedonic scale, taken from Pelletier and colleagues.............................................139

Figure 7.2. Graph depicting saliva weight for all participants with corresponding hedonic scale scores. ..................................................................................................................140

Figure 7.3 Graph of the frequency of like vs. dislike hedonic scale scores by IDDSI level and thickener......................................................................................................................141

Figure 7.4. Graph of the frequency of like vs. dislike hedonic scale scores by IDDSI level with and without barium.......................................................................................142
List of Abbreviations

ANOVA  Analysis of Variance
ASPEKT Analysis of Swallowing Physiology: Events, Kinematics and Timing
BOT  Base of Tongue
C2-C4 Cervical Spines 2 to 4
CRT, XRT Chemoradiation
CT  Computerized Tomography
CTV  Clinical Target Volume
DARS  Dysphagia Aspiration Related Structures
FEES  Fiberoptic Endoscopic Evaluation of Swallowing
GTV  Gross Tumor Volume
Gy  Gray
HNC  Head and Neck Cancer
HPV  Humanpapilloma Virus
HYB  Hyoid Burst
IDDSI  International Dysphagia Diet Standardisation Initiative
IMRT  Intensity-Modulated Radiation Therapy
Late RAD Late Radiation Associated Dysphagia
LVC  Laryngeal Vestibule Closure
LVCdur  Duration of Laryngeal Vestibule Closure
LVCrt  Laryngeal Vestibule Closure Reaction Time
mGy  Milligray
mPa.s  Millipascal Seconds
### SWALLOWING PHYSIOLOGY AND THICKENED LIQUIDS IN HNC

**MPC**  Maximum Pharyngeal Constriction  
**NDD**  National Dysphagia Diet  
**OPC**  Oropharyngeal Cancer  
**PAS**  Penetration-Aspiration Scale/Score  
**PCR**  Pharyngeal Constriction Ratio  
**PhAMPC**  Pharyngeal Area at Maximum Constriction  
**PhAR**  Pharyngeal Area at Rest  
**PO**  Per Os  
**PRISMA**  Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
**QUANTEC**  Quantitative Analysis of Normal Tissue Effects in the Clinic  
**RT**  Radiation Therapy  
**RTOG**  Radiation Therapy Oncology Group  
**SEER**  Surveillance, Epidemiology and End Results  
**SLP**  Speech-Language Pathologist  
**Sv**  Sievert  
**TNM**  Tumor, Node, Metastasis  
**UES**  Upper Esophageal Sphincter  
**UESC**  Upper Esophageal Sphincter Closure  
**UESDiameter**  Upper Esophageal Sphincter Diameter  
**UESDur**  Duration of Upper Esophageal Opening  
**VFSS**  Videofluoroscopic Swallow Study
List of Appendices

Thickened Liquids for Dysphagia Management: A Current Review of the Measurement of Liquid Flow.................................................................................................................................158

ASPEKT Rating Steps and Definitions (Round 1).........................................................................167

ASPEKT Rating Steps and Definitions (Round 2).........................................................................174

Head and Neck Cancer Study Ethics Protocol.............................................................................181

Study Materials .............................................................................................................................193

Research Information Sheet ........................................................................................................199

Consent Form ...............................................................................................................................200

Poster: Viscosity of Barium Thickened Products ........................................................................209

Research Ethics Board Documentation, Head and Neck Cancer Study .....................................210

Research Ethics Board Documentation, Healthy Study .............................................................217
Chapter 1
Introduction, Thesis Overview and Background

1.1 Introduction

With increasing prevalence of head and neck cancer, a growing number of individuals are undergoing radiation treatment for their disease, which has good results in terms of tumor control (Chen et al., 2013). Successful treatment means that patients survive but may be left with side effects of radiation, including dysphagia. Dysphagia is a main side effect that can persist long after radiation therapy. Individuals with dysphagia are at increased risk both for aspiration, which is defined as the entry of food or liquids into the airway, and for impaired swallow efficiency, which is defined as material left in the pharynx that has not been cleared by the swallow. Aspiration can cause aspiration pneumonia, which is associated with a risk of death. Thickened liquids are commonly used to reduce aspiration but there are current gaps in our literature regarding the impact of texture modification in head and neck cancer patients. The overarching objective of this dissertation is to determine the impact of texture-modified liquids on swallowing kinematics and aspiration status in patients who have been radiated.

1.2 Thesis Overview

The development of this dissertation began with the amalgamation of two interests that have yet to be studied collectively: texture modification as an intervention for dysphagia and dysphagia in patients diagnosed with cancer of the head and neck. Head and neck cancers (HNC) are the sixth most common cancer in the world (Marur, D'Souza, Westra, & Forastiere, 2010). A common sequela of radiation therapy for HNC is dysphagia, with changes occurring in swallowing function both in the acute and chronic stages post treatment (Eisbruch et al., 2002; Machtay et al., 2008; Schwartz et al., 2010). Aspiration is a serious component of dysphagia in individuals who have had treatment for their cancer, and is linked to an increased risk of pneumonia and death. Recent studies have reported aspiration rates in the head and neck literature to be between 30-69% while a recent systematic review discovered mortality rates associated with aspiration pneumonia in other studies ranging from 20-65% (Caudell, Schaner, & Meredith, 2009; Denaro, Merlano, & Russi, 2013; Eisbruch et al., 2004; Langerman et al., 2007; Nguyen et al., 2006). Thickened liquids are a common intervention used to reduce the risk of aspiration in patients
with dysphagia of other etiologies (e.g., stroke, neurodegenerative disease, traumatic brain injury (Cichero et al., 2017; Newman, Vilardell, Clave, & Speyer, 2016; Robbins et al., 2008; Steele et al., 2015). Our understanding of the impact of thickened liquids on swallowing function in the HNC population is limited to previous explorations of swallowing with thin compared to extremely-thick liquids, which are excessively thick and are reported to be disliked by many patients (Graner et al., 2003; Pauloski, Rademaker, Logemann, & Colangelo, 1998; Pauloski et al., 2002). Recent developments in the use of thickened liquids for dysphagia management include the introduction of a new standardized nomenclature and definitions for 4 degrees of liquid thickening (i.e. slightly, mildly, moderately and extremely thick) by the International Dysphagia Diet Standardisation Initiative (IDDSI; Cichero et al., 2017) and the emergence of xanthan-gum thickened liquids on the market, which are reported to be more slippery than starch-thickened liquids and may leave less residue (Vilardell, Rofes, Arreola, Speyer, & Clave, 2016). Given these developments, we were interested to explore the impact of thickened liquids at the thinner end of the continuum (i.e. slightly and mildly thick) on swallowing in patients with head and neck cancer.

The dissertation begins with a general background on head and neck cancer and dysphagia and a description of how radiation impacts the swallow in these patients. In Chapter 3, a systematic review summarizes the literature with respect to the use of thickened liquids in the HNC population and regarding the efficacy of texture modification for reducing aspiration.

The lack of texture modified stimuli available for use in videofluoroscopy motivated the next study, to develop an array of both barium and non-barium thickened liquids across the continuum from thin to extremely thick liquids and to characterize their flow (Chapter 4). These recipes were created to introduce consistency between VFSS and what patients are then recommended to drink post-assessment. This work was based on the new IDDSI framework, which has had widespread uptake across the globe (Cichero et al., 2017). Using a subset of these thickened barium stimuli, representing 3 levels from the IDDSI framework, the final study in this dissertation (Chapter 5) was developed to measure the impact of thickened liquids on penetration-aspiration in individuals who demonstrate unsafe swallowing on thin barium following radiation treatment for oropharyngeal cancer. Chapter 6 delves into the timing kinematics and mechanisms related to the findings found in Chapter 5. Chapter 7 explores
preliminary trends in the palatability of thickened liquids. The final chapter of this dissertation will summarize the evidence gleaned from each study, discuss the importance of the findings and outline directions for future research.

1.3 Background

1.3.1 Head and Neck Cancer

Cancers of the head and neck have various tumor locations, each with their own clinical presentation and natural history. Historically, cancers of the head and neck region were largely precipitated by lifestyle, and predominantly included patients who smoked cigarettes and ingested alcohol on a regular basis (IARC, 2004). Typically, cancers associated with inhalation of carcinogens present as squamous cell carcinomas; these are on the decline (Maurer, Hipp, Schäfer, & Kölbl, 2011; Siegel, Miller, & Jemal, 2016). Conversely, reports suggest that the incidence of HPV (human papillomavirus)-associated oropharyngeal cancer is increasing (Chaturvedi et al., 2011). The Surveillance, Epidemiology, and End Results (SEER) program was used in a US study and determined that the incidence of base of tongue tumors rose by 1.3% every year between 1973 and 2004. The rise in these tumors is due specifically to HPV 16, which is the strain of HPV associated with cancer causation (Chaturvedi, Engels, Anderson, & Gillison, 2008; Maurer et al., 2011). Approximately 60% of oropharyngeal squamous cell carcinomas are positive for HPV 16 in the United States (Maurer et al., 2011). Tumors that are HPV positive are typically located in the oropharynx, with the tongue base being a common site, and are most commonly seen in men in their 50’s.

Advances in medicine have allowed for the standard detection of HPV at the time of initial diagnosis. Diagnostics in the past were not able to differentiate HPV positive from HPV negative tumors. HPV positive cancers have better prognosis for successful treatment and tumor eradication when compared to HPV negative cancers of the oropharynx (Chen et al., 2013; Maurer et al., 2011). Radiation treatment (RT), either with or without chemotherapy, has been shown to provide good locoregional control of HPV positive tumors and offers patients a good chance of survival (Spence, Bruce, Yip, & Liu, 2016). Unfortunately, however, radiation therapy can have both short-term and long-term negative side effects, including dysphagia (Caudell et al., 2009; Hutcheson et al., 2013).
1.3.2 Dysphagia in Head and Neck Cancer

Dysphagia involves two primary functional concerns: swallowing safety and swallowing efficiency (Clavé, 2008). Impaired swallowing safety involves aspiration or entry of material into the airway. Impaired swallowing efficiency involves difficulty propelling food or liquid completely through the mouth and pharynx to the esophagus. People with impaired swallowing efficiency typically experience an accumulation of residue in the pharynx after food/liquid swallowing attempts. In addition to these functional concerns, dysphagia has a significant impact on quality of life (Wilson, Carding, & Patterson, 2011). Each of these issues will be discussed in this section.

Dysphagia has been reported to be present pre-treatment in 28% of patients with oral cancer (Pauloski & Logemann, 2000). Among the factors that are thought to be relevant for predicting dysphagia in people with HNC are the primary tumor site, patient age, tumor size (T) and nodal involvement (N) as captured in the tumor-node-metastasis (TNM) staging hierarchy, treatment modality and lifestyle factors (Denaro et al., 2013). Individuals with a more advanced T stage are at a greater risk for dysphagia, due not only to the increased risk that a larger tumor will directly impact swallowing, but also to the likelihood that a more aggressive radiation treatment modality will be used to treat the disease. Patients who smoke and/or drink are also at greater risk.

The prevalence of dysphagia after treatment for HNC has been estimated at 30% to 69%, and has been shown to increase over time after RT (Awan et al., 2014; Caudell et al., 2009; Hutcheson et al., 2013; Hutcheson et al., 2012). One of the factors that is thought to be important in contributing to dysphagia following radiation treatment for HNC is the dose of radiation received by structures that are critical for swallowing. These DARS (dysphagia/aspiration related structures) are frequently in the radiation field for patients with oropharyngeal cancers (OPC). Eisbruch and colleagues have determined that the superior pharyngeal constrictor muscle is particularly susceptible to radiation exposure during RT and that the dose to this structure is an important predictor of subsequent dysphagia (Eisbruch et al., 2011). This finding has been corroborated by other research groups (Levendag et al., 2007; Schwartz et al., 2010).

Base of tongue cancers are typically treated with a combined radiation and chemotherapy regimen, which has been shown to have greater efficacy than surgery or RT alone (Raber-
Durlacher et al., 2012). Despite the goal of limiting the radiation exposure of healthy tissue, functional deficits are commonly seen. The extent of functional impairment is thought to be dependent on the radiation approach (i.e., IMRT, proton beam, etc.), dose, fractionation schedule, fractionation size, concurrent chemotherapy, and lifestyle factors such as smoking and/or alcohol among other variables (Pauloski, 2008).

One of the main consequences of dysphagia in this patient group is the aspiration of material into the trachea. Langerman and colleagues reported increased aspiration in oral cavity cancer patients after the completion of chemoradiotherapy (CRT) compared to pre-treatment (Langerman et al., 2007). An additional finding of concern is the fact that sensory deficits following CRT mean that many patients may have silent aspiration, i.e. aspiration that is not followed by an overt cough or throat clear response (Rosenthal, Lewin, & Eisbruch, 2006). The fact that aspiration is silent in many of these patients, means that swallowing impairment may go unnoticed by patients and medical professionals (Eisbruch et al., 2011).

In addition to dysphagia and aspiration being life-threatening consequences of RT, this avenue of treatment may also leave the patient with swallowing efficiency deficits. Inefficient bolus transport is a critical aspect of dysphagia, leaving the patient with post-swallow residue with the potential for aspiration after the swallow (Christianen et al., 2012; Lazarus et al., 1996; Rogus-Pulia, Pierce, Mittal, Zecker, & Logemann, 2014).

Radiation treatment has evolved in recent years to spare as much normal tissue as possible, however, there are still acute and chronic complications that occur. A decline in saliva production has been extensively investigated as a side effect of radiation treatment. Along with investigations into the dose-volume correlates of xerostomia after radiation, investigators have asked questions regarding how dose to the parotid glands specifically impacts the occurrence of xerostomia (Eisbruch et al., 2001; Greenspan, 1990, 1996; Jabbari et al., 2004; Mittal et al., 2003; Porter, 2010). Eisbruch and colleagues assessed both stimulated and unstimulated saliva flow rates from the parotid glands before RT, and at 1, 3, 6 and 12 months post treatment. They found that individuals who received a dose of 24-26 Gray (Gy) were able to preserve some functional saliva flow rates after RT, and increase their salivary flow over time. As such, patients with high doses of radiation to the parotid glands present with low saliva output, which is likely
to remain low over time (Eisbruch & Terrell, 2003). Those patients with dry oral mucosa may present with greater difficulty when swallowing thick, sticky substances. The decreased ability to form a cohesive bolus due to reduced amounts of serous-type saliva can increase the amount of effort expended to safely and efficiently swallow a bolus, and thicker liquids may present as noxious to these patients. Christianen and colleagues studied swallowing dysfunction after CRT, and concluded that problems swallowing liquids versus solids were due to different treatment types and various structures receiving a majority of the radiation dose. They found a correlation between food consistency causing difficulty and the anatomical structures involved, with solid food dysphagia attributed to damage of the superior pharyngeal constrictor muscle (Christianen et al., 2012). Additionally, Rogus-Pulia and colleagues have reported a trend towards higher rates of residue with pudding and cookie boluses (compared to thin and nectar-thick consistencies), and attributed the severity of residue to fibrosis of the critical musculature involved in the swallowing process, leading to a reduction in strength and poor pharyngeal constriction. They also found that patients’ awareness of swallow difficulty varied with bolus consistency, with a trend towards patients reporting more difficulty on pudding and cookie boluses (Rogus-Pulia et al., 2014).

The presence of dysphagia is not only detrimental to one’s health, but is also associated with poorer quality of life in individuals with head and neck cancer (Wilson et al., 2011). Quality of life is an important factor, specifically in terms of patient motivation. Although these patients are typically ambulatory after treatment, they seldom return to their previous level of functioning (List et al., 1996). The addition of chemotherapy to a patients’ radiotherapy schedule has been shown to decrease quality of life. Lazarus and colleagues studied 29 patients after CRT, and found that quality of life was poor over the first 6 months (Lazarus, Husaini, Hu, et al., 2014). Additionally, as patients’ acute toxicities improved, quality of life remained significantly impaired at 6 months post-treatment as it related to the patients’ saliva output (Lazarus, et al., 2014). Hunter and colleagues reported that reductions of quality of life are common even in patients presenting with mild swallowing impairment (Hunter et al., 2013).
1.3.3 Interventions for Dysphagia

There are a variety of avenues that a clinician may choose to manage a patient’s dysphagia and attempt to eliminate aspiration. These options include compensatory maneuvers, prophylactic or rehabilitative exercises, and diet texture modification. Compensatory strategies may include tucking the chin to reduce airway exposure to food and liquids, the super-supraglottic swallow, and the chin-down maneuver (Logemann, Pauloski, Rademaker, & Colangelo, 1997; van der Molen et al., 2011; 2013).

Rehabilitative exercises may include indirect exercise for different muscles involved in swallowing such as tongue strengthening exercises, or more direct strengthening techniques like effortful swallows (Lazarus, Husaini, Falciglia, et al., 2014). Van der Molen and colleagues investigated the efficacy of strengthening exercises versus rehabilitation based exercises in patients with stage III and IV squamous cell carcinoma diagnoses with heterogeneous sites in the head and neck, after a course of CRT (van der Molen et al., 2011). The strengthening protocol consisted of three exercises: the effortful swallow, the Masako maneuver and the super-supraglottic swallow; while the comparison protocol consisted of passive and slow opening of the mouth using the TheraBite device at 50% maximum opening, and swallowing with maximum tongue to palate contact. Minimal differences were found between the groups; the study concluded that rehabilitation after treatment may be helpful for reducing the extent and/or the severity of some of the functional short-term effects of CRT, acting as a type of early intervention. A particularly interesting finding was that the patients in the comparison group practiced less and had poorer adherence overall (van der Molen et al., 2011). Speech pathologists working with patients with HNC typically recommend a standard exercise regimen which targets hyolaryngeal excursion, airway protection, and tongue base retraction (Hutcheson et al., 2013). However, contrary to the findings reported by van der Molen and colleagues, a recent systematic review by Perry and colleagues suggests that these techniques have limited efficacy (Perry, Lee, Cotton, & Kennedy, 2016).

1.3.4 Thickened Liquids for Dysphagia Intervention

Diet texture modification involves the thickening of liquids, and is commonly used to limit aspiration in patients with neurogenic dysphagia (Robbins, Gensler, Hind, & et al., 2008). Two
recent systematic reviews concur that thickening liquids is an effective technique for reducing aspiration, but that the degree of thickening that is required to achieve this benefit remains unclear (Newman et al., 2016; Steele et al., 2015). Additionally, although research in adults with dementia suggests that very thick liquids (“honey” thick or “spoon thick” liquids) are more effective than lesser degrees of thickening (“nectar thick” liquids) for reducing aspiration, residue is more likely with these thicker consistencies (Robbins et al., 2008).

A recent international initiative, the International Dysphagia Diet Standardisation Initiative (www.iddsi.org), has identified a lack of common nomenclature, clear definitions and measurement specifications for thickened liquids as a source of variation in dysphagia practice (Cichero et al., 2013). The process of developing a new framework for labelling, describing and measuring thickened liquids and texture modified foods used in dysphagia management was a large undertaking for the IDDSI task force (Cichero et al., 2017). The task force conducted a systematic review of research literature describing the impact of liquid consistency and food texture on swallowing behaviour (Steele et al., 2015). Along with the additional review of existing terminology guidelines around the world and stakeholder surveys, they were able to develop the IDDSI framework.

Texture modification is seldom used in the HNC population, but studies suggest that aspiration occurs less frequently with pureed or pudding thick liquids compared to thin (Barbon & Steele, 2014). The literature regarding the use of texture modification in the HNC population will be discussed further in Chapter 3.

Historically, thickening products for people with dysphagia consisted primarily of modified corn starch. Recently, new thickening agents comprised of gums, with xanthan gum being the most common ingredient, are emerging. A recent paper by Vilardell et al suggests that gum-thickened liquids may slip more easily than starch thickened liquids and be less prone to leaving residue behind (Vilardell et al., 2016). Head and neck cancer patients commonly present with xerostomia and thick, sticky mucous. As such, the exploration of xanthan-gum’s slippery quality and the outcomes of use in this patient population is of particular interest.

The following chapters will address thickening in the head and neck cancer population, and whether thicker consistency levels (IDDSI levels 1-2) prove to be beneficial for this patient
group. Using the IDDSI Framework, we aim to determine the percentage of at-risk swallowing in a very homogeneous sample of oropharynx cancer patients and how texture modification can be used to improve safety in our patients.

1.4 References


affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. *Radiother Oncol*, 85, 64-73.


Chapter 2

2 Radiation Tutorial for the Speech-Language Pathologist

2.1 Preface

The development of swallowing disorders in the head and neck cancer population is multifaceted. Interactions between varying treatments and their sequelae can impact the swallowing mechanism in a variety of ways. Patients who undergo surgical treatment are often left with visible anatomical changes that directly impact the swallow, while other treatments damage mucosa and muscle tissue at the cellular level. The goal of this tutorial was to understand the complexity of radiation in terms of damage to cancer cells and healthy tissue both acutely and over time.

This chapter provides a basis for understanding the way cancer treatments impact important swallowing structures and continue to do so with increasing time post treatment. The information provided in this chapter also demonstrates the complexity of radiation and how the knowledge of dose, schedule and volume provide critical insights into the radiated swallow.

With permission from Perspectives, this chapter was excerpted in its entirety from the following journal article: Barbon, C. E. A., Hope, J., & Steele, C. M. (2017). Radiation 101: A Guide for Speech-Language Pathologists. Perspectives of the ASHA Special Interest Groups, 2(2), 63-72. doi: 10.1044/persp2.SIG13. References in this chapter are formatted according to the journal style.
2.2 Abstract

Dysphagia, or disordered swallowing is an unfortunate consequence for individuals with a head and neck cancer diagnosis. Swallowing is altered in many ways due to tumor location and presence, and afterwards due to the mechanisms of tumor eradication. As a common treatment, radiation therapy (RT) has been proven to halt tumor progression and kill quickly growing cancer cells. However, the side effects of such treatments are often prominent in this patient population. As swallowing professionals, it is important that speech-language pathologists (SLPs) understand the repercussions of RT for those patients undergoing such treatments. This paper aims to provide a basic overview of RT for clinicians working with head and neck cancer patients.

2.3 Introduction

Disordered swallowing, or dysphagia is a common side effect of head and neck cancer. The extent and location of the tumor may impact the swallow directly. In addition, dysphagia may also develop as a consequence of primary cancer treatment. Radiation therapy is an integral part of cancer treatment protocols and remains the standard of care for tumor eradication and patient survival. The prevalence of long-term dysphagia after radiation therapy (RT) has been documented to be approximately 40% and higher (Caudell, Schaner, & Meredith, 2009). While the goal of radiation therapy is to kill the tumor and prevent spread, maintaining the integrity of tissue that may have otherwise been damaged by surgical procedures is also imperative. It is therefore important to understand radiation and the impacts it may have on the patient’s oropharyngeal tissue and swallowing mechanism post-treatment.

Speech-language pathologists (SLP) who work with head and neck cancer patients need to be well versed in the effects of RT and its impact on speech/swallowing. Understanding the type, schedule, and effects of RT to both the tumor and normal tissues is critical for treatment planning. The purpose of this paper is to provide a basic understanding of radiation and the negative effects it poses in relation to swallowing. The paper will define the basics of radiation
therapy; the principles and benefits of treatment; negative sequelae and tissue toxicity; and will inform clinicians on how to interpret dose-effects of RT for head and neck cancer patients.

2.4 What is Radiation?

2.4.1 The Chemistry of Radiation

When radiation is administered, and the energy from that radiation is absorbed by tissue, excitation or ionization of the tissue may occur. Excitation refers to the situation where the energy of an electron in an atom or molecule increases without ejection of that electron. Ionization occurs when enough radiation-associated energy is absorbed to cause ejection of orbital electrons from an atom or molecule. Ionizing radiation involves the localized release of large amounts of energy (Hall & Giaccia, 2012).

Radiation comes in two main forms: electromagnetic or particulate. X-rays are a type of electromagnetic radiation and “can be viewed as waves of electrical and magnetic energy” (Hall & Giaccia, 2012). When an x-ray is absorbed into human tissue, energy is deposited in an uneven fashion, in the form of packets. When energy in a beam of x-rays is parsed into large, individual packets, chemical bonds can be broken and biological change is induced. Radiation via x-rays is delivered externally, but there are also internal means of radiation delivery (brachytherapy). The second type of radiation, particulate radiation, is sometimes used experimentally and includes neutrons, electrons, protons, neutrons and alpha particles. Some of these forms of radiation are in fact used in radiation therapy or have potential uses in diagnostic radiology (Hall & Giaccia, 2012). However, this paper will focus on externally delivered radiation therapy.

There are two main ways that SLPs may encounter radiation in their clinical work. Firstly, radiation is used as a diagnostic measure for clinicians who manage and rehabilitate swallowing disorders. Precautions are taken specifically to limit radiation exposure to both the patients and clinicians, but some amount of radiation exposure to both parties is ultimately inevitable. A Gray (Gy) is the unit typically used when discussing radiation, and is the amount of radiation that the patient is exposed to/absorbs (1 Gy = energy absorption of 1 J/Kg). Another unit of radiation is the Rad; 1Gy=100 rad (Moro & Cazzani, 2006). While a Gy measures absorbed dose of ionizing
radiation, Sieverts (Sv) measure the health effect of radiation on the human body namely the risk of developing cancerous cells. A dose of 1 Sv equates to a ~5.5% risk of developing cancer later in life within the irradiated area. An absorbed dose of 1 Gray is considered to involve an equivalent dose of 1 Sievert. During a standard videofluoroscopic swallow examination (VFSS) of 149 seconds duration, dose to the clinician is estimated to be <6 micrograys (1Gy= 1,000,000 μGy) while dose to the patient is estimated to be ~0.35 mSv (0.35 mGy; McLean, 2006; Moro & Cazzani, 2006). According to Moro and Cazzani, this patient dose is associated with a risk of 1 in 39,000 of developing a radiation induced cancer (Moro & Cazzani, 2006). Therefore, for evaluation purposes, VFSS involves minimal radiation exposure to both the patient and the clinician, and the dose is not likely to cause serious harm. Despite minimal risk, clinicians who are responsible for oversight of the VFSS should follow routine precautions to limit exposure, including wearing lead aprons and thyroid shields, and moving away from the source of exposure.

The second place where SLPs encounter radiation in their practice is with patients who have undergone radiation treatment (RT) to damage the DNA of cancerous cells. Unfortunately, radiation treatment also causes damage to healthy cells within the target field, and this may lead to toxicities along with the possibility of evoking the production of cancerous cells via mutations. It is for this reason that clinical discussion of radiation as a form of treatment should take place. Additionally, although the treatment does cause tumor damage and cell death, there is an extensive list of acute (early) and late secondary effects that may contribute to the development of dysphagia in the head and neck cancer patient.

2.5 What is the Goal of Radiation Therapy?

In order to understand radiation, one must conceptualize what occurs when x-rays are absorbed into human tissue. Electromagnetic rays (x-rays) are indirectly ionizing, meaning that they do not produce biologic and chemical damage directly, but they do so by being absorbed into the material through which they pass. When these rays are absorbed, a process of energy exchange occurs within cells in the area, and fast moving charged particles are the end result. These charged particles are able to produce biological and chemical damage. The process by which x-ray photons may be absorbed into biologic material during radiotherapy is called the Compton
process. Energy from x-ray wavelengths is passed along on its way through the material, and as a result of this exchange in energy one is left with a large number of fast moving electrons within the tissue. These fast-moving electrons then ionize other atoms, and break chemical bonds; this begins a chain of events that can induce biological damage to DNA in the target field (Hall & Giaccia, 2012). Damage to DNA occurs via breaks in the double helix that typically cannot be repaired, resulting in cell death of both oncologic and healthy cells (Hall & Giaccia, 2012).

2.5.1 DNA Strand Breaks

The main purpose of the RT process is to target biological tissue and cause apoptosis (cell death) by DNA damage, in which breaks in the double helix structure occur. This leads to mitotic death, in which the damaged chromosomes prohibit the cell from dividing, causing an inability of the cell to reproduce. Many single DNA strand breaks may occur when smaller doses of radiation are administered, leaving the DNA with repairable damage. Conversely, radiation may also cause more significant double strand breaks, which are unrepairable. In these cases, when single strand breaks on each side are close enough in proximity (i.e., the breaks are directly opposite each other or separated by only a few base pairs), the DNA chromatin snaps into two pieces. Destruction of the DNA double helix interferes with cell proliferation leading to cell death during mitosis. For a clear visual of this concept, see Hall and Giaccia, figure 2.2 (Hall & Giaccia, 2012).

When two double strand breaks occur in close proximity to one another, one of three consequences may arise:

1) Cell death may occur, which is beneficial when tumor cells are involved.

2) Carcinogenesis is also a potential consequence of double strand breaks whereby healthy cells form into cancer cells. This is a risk that comes with the use of radiation treatment, in much the same way that exposure to cigarette smoke is considered to be carcinogenic.

3) Mutations may occur as a result of critical DNA strand breaks, and when these occur in the cells of the human body, they may result in cancer or cell death.
Therefore, it is important for SLPs to keep in mind that tumor recurrence is a risk for patients after radiation treatment (Hall & Giaccia, 2012).

Radiation induced chromosome breaks occur when the ends of the unpaired bases (or broken unpaired ends) of the chromosome fail to join with a normal, unbroken chromosome to form a new pair (Hall & Giaccia, 2012). These abberations in mitosis may cause chromosome deletion or distortions when the broken ends re-join with other broken ends. Aberrations may happen when the cell is irradiated early in the mitotic phase, where the chromosomes are yet to be duplicated. Deletions that occur in the mitotic cycle may also be associated with carcinogenesis if the material that is deleted or lost contains a gene that is responsible for tumor suppression. It is important to understand that the occurrence of most radiation-induced aberrations is a function of the overall dose (Hall & Giaccia, 2012).

2.6 The Importance of Telomeres in Cell Death

Telomeres are defined as “long arrays of TTAGGG repeats [i.e., sequences of DNA at the end of each chromosome] that cap and protect the ends of chromosomes. Each time a normal somatic cell divides, the terminal end of the telomere is lost” (Hall & Giaccia, 2012). Telomeres decrease and become fewer with age and successive divisions until the cell at some point is unable to divide any further. Cancer cells reproduce and avoid aging by activating the enzyme telomerase. By continuing to activate telomerase, cancer cells avoid the eventual terminal end of telomere, thereby avoiding cell death. Essentially, telomerase activation makes the cell immortal (Hall & Giaccia, 2012).

2.7 Fractionation and Dose

Radiation doses for head and neck cancer treatment may range from 40-80 Gy. Higher doses (60-80Gy) are used for curative intent, while doses of 40-60 Gy are used as adjuvant treatment, and doses from 45-55 Gy are used for subclinical disease or palliation. The total radiation dose is typically divided, or fractioned into smaller doses delivered over a period of weeks or months. The standard fractionation schedule for head and neck cancers (oropharyngeal, laryngeal, tonsillar, or pharyngeal constrictors) is 70 Gy delivered in 35 fractions. Typically, the fractioned
dose is delivered once daily, every 5 days over 7 weeks, or on a less frequent basis over a few months.

Fractionation as a technique is more beneficial than providing one large single dose of radiation, because it allows healthy cells to repair damage prior to the next treatment, while allowing cancerous cells to be targeted with the intent of causing cell death. The goal is for healthy cells to be left with a minimal number of single strand DNA breaks (allowing rapid repair), in addition to causing little to no overall damage to new, dividing cells. In cancer treatment, the ability of the normal tissue surrounding a tumor to tolerate the radiation acts as a natural limit for the dose of the radiation that can be delivered to the tumor.

Since normal tissues have a better repair mechanism than do oncologic cells, fractionation causes a greater amount of damage to cancer cells. As a part of radiation treatment planning, the gross tumor volume (GTV) is defined as well as the clinical target volume (CTV), which contains margins of adjacent tissue, which are considered to be areas of potential tumor proliferation. The dose that may accumulate in normal tissue over the radiation schedule is hard to predict due to differences in patient anatomy that may occur during radiation (Jaffray, 2010). These changes may include extensive edema, or tumor shrinkage. If the GTV decreases quickly after delivery of only a few fractions, the radiation oncologist may need to re-plan and re-trace the radiation fields to avoid including normal tissue in the target area (Jaffray, 2010).

### 2.8 Fractionation Schedules

In addition to the typical fractionation schedule, hyperfractionated radiation or hypofractionated radiation may be used. With a hyperfractionated radiation schedule, the daily dose is divided into two radiation treatments each day. Conversely, hypofractionated radiation schedule doses are divided into larger doses, delivered in fewer than one treatment per day during the week (Network, 2006). Finally, an accelerated fractionation schedule option may be used, in which, the weekly dose exceeds the typical limit of 10Gy/week, thereby reducing the total amount of time over which the patient is receiving RT. The schedule will affect how quickly the patient will begin to experience side effects after radiation begins. With more rapid or accelerated schedules, SLPs must be aware that critical toxicities may happen more quickly than with a regular fractioned schedule. For example, when odynophagia (painful swallowing) arises as an early
onset toxicity, nutritional support will require special attention. It is important to note that no matter the schedule, a majority of head and neck cancer patients who complete a full course of radiation treatment will experience long-term effects. The risk and impact of these long-term effects is further influenced by factors including age, T-stage, primary cancer site, dosage and the use of chemotherapy agents used as radiosensitizers (Machtay et al., 2008). Consideration of the fractionation schedule will help clinicians plan treatment accordingly, and anticipate the emergence of potential toxicities.

In addition to radiation-only fractionation schedules, treatment for some patients may include chemotherapy. This treatment process has been shown to significantly improve survival in patients with late stage disease (Network, 2006). Chemotherapy can be combined with radiation (or surgery) in three different ways: it can be given in the weeks before RT (neoadjuvant), during RT (concurrent) or after RT (adjuvant). The most beneficial schedule, in terms of patient survival, is adjuvant chemoradiation (CRT). Although beneficial for survival, the combination of chemotherapy (e.g., cisplatin, gemcitabine, etc.) and radiation (CRT, sometimes seen as XRT) exacerbates post-radiation swallowing issues for the patient, and particularly involves mucosal toxicity due to increased radiosensitivity of the targeted tissue (Network, 2006; Nguyen & Sallah, 2000).

2.9 Radiation Volume Effects

After taking dose and fractionation into consideration, it is also important to understand radiation volume. Volume is typically reported as \( V_{\text{dose}=x\%} \), where \( V_{\text{dose}} \) is the amount of targeted radiation (or Gy) being absorbed by an organ and \( x\%\) is the percentage of the organ that is receiving the radiation dose. For example, if one sees dose-volume to a structure in the head and neck written in the format \( V_{70\text{Gy}=50\%} \), this means that 50% of the structure has received 70Gy of radiation. Dose-volume histograms (Bratengeier, Meyer, & Flentje, 2008) provide a quick and effective method for visualizing the dose delivered to the volume or area of the target.

2.10 Clinical Response of Normal Tissue

General toxicities are those that occur with all administered radiation therapy. The radiated area can become sensitive to touch, much like a bad sunburn that progresses throughout treatment. It
is important to note that the skin is one of the most easily observed organs to experience radiation effects. In particular, the mucosal epithelium inside the mouth and pharynx may be affected and become quite irritated. Mucositis is usually considered an acute toxicity because it occurs early but may last weeks after treatment in some patients depending on tumor location, dose and patient risk. Fatigue is also experienced by many patients who receive radiation, due to the body’s response and attempt to heal cells that are under attack. These side effects of radiation treatment are quite common; nausea may be added to this list given the addition of concurrent chemotherapy (Network, 2006).

One main concern regarding radiation is that it is quite difficult to attenuate. Normal tissue complications surrounding the larynx and the pharyngeal constrictors increase by 50% when radiation doses reach or exceed 50-60 Gy (Rancati et al., 2010). After exposure to the maximum dose, desquamation (the shedding of the outer layer of skin) of the oral cavity occurs by approximately day 12, with recovery within 2-3 weeks. This varies from patient to patient, and various risks must also be taken into account (e.g., tumor site, history of RT, smoking history). Merlotti and colleagues (2014) conducted a review of IMRT targets for the head and neck, which includes a list of dose-constraints to specific structures in that region. The Radiation Therapy Oncology Group (RTOG; a group focused on radiation-based research) also offers an on-line list of dose-constraints.

### 2.11 Mechanisms of Swallowing Impairment

In addition to the previously mentioned toxicities, radiation can alter the mechanics and the anatomy of critical structures involved in swallowing. There are general radiation dose thresholds at which the risk of developing dysphagia arises. When the pharyngeal constrictors receive more than 50 Gy, patients have increased chance of swallow-related complications. For the larynx, doses above 20 Gy have been associated with complications (Eisbruch et al., 2011).

Acute mucosal toxicity may take 3-6 months to resolve. Other swallowing-related concerns include xerostomia, dysgeusia (altered taste), dysphagia and odynophagia. Swallowing physiology after radiation is characterized by impaired safety (poor airway protection, with aspiration occurring both before and after the swallow) along with impaired efficiency (inadequate bolus propulsion, leading to increased amounts of residue; Lazarus et al., 1996).
These two deficits may lead to severe dysphagia secondary to radiation treatment of head and neck cancer.

Aspiration is one of the most serious aspects of dysphagia following radiation or chemoradiotherapy. The prevalence of aspiration has been reported to be anywhere from 24% to 62% and is generally thought to be underreported (Eisbruch et al., 2002; Goguen et al., 2006; Hutcheson & Lewin, 2012). A large number of head and neck cancer patients are “silent aspirators,” due to radiation-induced sensory deficits (Hunter et al., 2014). The silent nature of dysphagia in this patient population represents a primary reason for deficits in their swallowing going unnoticed. Fibrosis (tissue hardening) is an additional RT-related effect that has the potential to impact swallowing. Any type of mucosal or submucosal fibrosis in the base of the tongue or affecting the pharyngeal constrictors is likely to cause residue accumulation due to inefficiency in bolus propulsion. Fibrosis affecting the upper esophageal sphincter (UES) may lead to restricted size or duration of sphincter opening, thereby also contributing to residue accumulation and the secondary risk of aspiration after the swallow.

It is important to take into consideration the location of the primary tumor in addition to the dose/fractionation of the radiation when predicting clinical outcomes pertaining to dysphagia. Different primary tumor sites are associated with different rates of pre- and post-radiation abnormalities in swallowing (Logemann et al., 2006). For example, some patients with base of tongue primary tumors may have pre-existing swallowing deficits at baseline.

One study has reported on dysphagia end points after radiation therapy and found correlations between swallowing function and the dose delivered to the pharyngeal constrictors and glottis-supraglottic larynx. There are possible benefits associated with the reduction of dose to these areas (Feng et al., 2007). Feng and colleagues (2007) found that 62% (16/26) of patients who had received doses to the pharyngeal constrictors above 60 Gy aspirated. By contrast, in the 9 patients who received lower doses to the constrictors (< 60 Gy), aspiration was not seen. This evidence, showing that radiation dose to specific structures may precipitate the occurrence of aspiration has prompted some authors to propose that limiting radiation dose to these important swallowing structures may minimize impairment (Eisbruch et al., 2004; Feng et al., 2007; Hunter et al., 2014). Data coming out of the MD Anderson Cancer Center in Houston, Texas show that
there are specific muscles in the swallow complex that are at particular risk in terms of radiation damage and atrophy (Dale et al., 2016). These muscles are proposed to include those in the floor of mouth, namely the suprahyoid muscles and the mylohyoid. Eisbruch and colleagues (2004) aimed to identify those structures in the head and neck that were most vulnerable to radiation damage and most closely associated with dysphagia and aspiration. They reviewed CT scans pre-and post-therapy for evidence of damage and those anatomical structures demonstrating change were termed dysphagia/aspiration-related structures (DARS). The structures included in DARS are the pharyngeal constrictors along with the glottis and supraglottic larynx. It is important for clinicians to expect changes in swallowing during and after radiation and to plan for patient needs based on knowledge of tumor location, radiation field, fractionation and volume, and the involvement of structures that are critical to swallowing within the radiation field.

In addition to the early and late toxicities, late radiation associated dysphagia (late RAD) may emerge many months beyond the completion of radiation treatment (Dale et al., 2016). The human papillomavirus (HPV) has been identified as a factor in cancers of the oropharynx (Worden et al., 2008). This new rising phenomenon occurs most commonly in patients who are young (specifically, men aged 50-55). Fortunately, HPV locoregional control is reported to have good results. However, because these patients have longer post-treatment life expectancies, clinicians are beginning to encounter a greater number of individuals who return with dysphagia and other toxicities 10-15 years post-radiation. Late-radiation induced dysphagia toxicities are ill defined, and the phenomenon of late onset dysphagia involves denervation and multiple cranial neuropathies. A review by the RTOG summarized the different types of late toxicity seen across several clinical trials. Of a total of 230 patients who were studied, 99 had severe late toxicities, and were compared against 131 controls, who did not report late toxicities. Risk factors for the development of late-RAD include age, T-stage and larynx/hypopharynx primary sites, as well as neck dissection post-treatment (Machtay et al., 2008). One study has reported that individuals who have experienced late-RAD with the inclusion of cranial neuropathies had higher radiation doses to the superior pharyngeal constrictors (Awan et al., 2014). The constrictors may then be considered a structure at risk for late-RAD effects in those patients with a history of large doses to this area (Awan et al., 2014; Eisbruch et al., 2004).
Guidelines have been developed for quantifying the amount of radiation to normal tissue and are termed Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC). These guidelines evaluate dose/volume/outcome data for critical organs in order to make radiation therapy more efficient and safe for patients. A study conducted by Beetz and colleagues (2014), which followed QUANTEC guidelines for minimizing xerostomia determined that from week 4 of radiation up to 24 months post treatment, patients who were considered to be at lower risk (i.e., with at least one parotid gland receiving < 20 Gy and/or both parotids receiving < 25 Gy) reported better recovery. In the same study, the predictors for xerostomia at 6-24 months following radiation therapy included the QUANTEC criteria, older age and pre-irradiation xerostomia.

In addition to aspiration and xerostomia, patients are also likely to experience mucositis, thick mucosal secretions and pain. When patients reduce the frequency of their swallowing due to these symptoms, disuse atrophy may also occur. For this reason, proactive swallowing therapy is often prescribed and advised (Carnaby-Mann, Crary, Schmalfuss, & Amdur, 2012; Hutcheson et al., 2013). Some retrospective studies suggest that patients report better outcomes given prophylactic swallow therapy regimens (Carroll et al., 2008; Kulbersh et al., 2006). One randomized controlled trial showed superior diet tolerance in the short term amongst those patients who performed prophylactic swallowing exercises (Kotz et al., 2012). Overall, data suggest that PO status (per os, meaning nutrition/hydration by mouth) at the end of radiation treatment to the head and neck predicts PO status 10 years later (Gillespie, 2004; Langmore, 2012). Recent studies from the MD Anderson Cancer Center have shown that patients who are adherent to an exercise regime and who also maintain oral intake throughout RT/CRT are more likely to maintain some form of oral intake after the completion of treatment (Hutcheson et al., 2013).

Another common sequela of radiation treatment (especially when paired with chemotherapy) is the need for gastrostomy tube feeding to alleviate the burden of oral intake when dysphagia becomes severe (Hutcheson & Lewin, 2012). Some institutions prophylactically place feeding tubes, while others place them only when patients cannot rely on their swallowing for safe and adequate nutrition/hydration. The experience from the MD Anderson trials suggests that treatment should aim to avoid tube dependence, with the specific goal of maintaining oral intake
for these patients post-radiation treatment. Other studies have not demonstrated a difference in outcomes when patients rely on enteral means of feeding (Nguyen et al., 2006).

2.12 Advances in Radiation

Intensity-Modulated Radiation Therapy (IMRT) is a fairly recent advance in head and neck radiation oncology, designed to reduce toxicity to normal tissue. IMRT uses CT (computerized tomography) planning and specific identification of targets, along with careful allocation of radiation dose. Essentially, the region that is being targeted for a high dose of radiation takes on the silhouette image of the structure during planning, as seen on the CT scan. In comparison to conventional radiation therapies, this technique helps to limit dose to specific structures in the radiation field. IMRT utilizes multiple beams to target tumors from multiple angles. This allows for a more specific high dose target, while also creating low-dose radiation exposure to adjacent areas. IMRT, when compared to conventional radiation, does show reduced toxicity and equivalent outcomes in addition to better specific survival (Beadle et al., 2014; Nutting, 2011).

Generally, the doses involved in IMRT vary pending the area and volume of the tumor that is to be radiated. Dose prescriptions are defined by the tissue involved and may be low-risk (dose to neck areas for preventative measure, ~55Gy), intermediate-risk (areas contiguous but not involved by the tumor, ~63Gy), or high-risk regions (areas of tumor invasion including affected metastatic nodes, 70Gy; Chao, Low, Perez, & Purdy, 2000). It may be useful for clinicians to estimate areas that may be receiving higher doses related to tumor location. However, patients treated with intensity-modulated radiation therapy for oropharyngeal and nasopharyngeal cancers and those with lymph node metastasis are more likely to have their parotid glands irradiated. This is because of the overlap of the planned target volumes with sections of the parotid gland, and it is important for clinicians to realize that these patients are at an increased risk of xerostomia due to the tumor location. Those patients whose parotids can be spared with more ease include those with laryngeal carcinoma, unilateral radiation, early stage disease, and lymph node metastasis from unknown primary tumor sites (Beetz et al., 2014). It is not possible to include an exhaustive discussion of the issues related to xerostomia within this particular paper.
2.13 Conclusion

Radiation therapy continues to be one of the primary treatments for loco-regional tumor control and survival in the head and neck cancer patient. The primary objective of radiation therapy is tumor eradication. Given this goal, normal tissues may be irradiated, and dysphagia may develop as a toxicity after cancer has been cured. SLPs are an integral part of the multidisciplinary care team, and are intimately involved in the maintenance of oral nutrition and hydration for these patients during and after treatment. It is ultimately up to the SLP to plan appropriately for the emergence of expected swallowing toxicities and to support patients in maintaining swallowing throughout treatment to the best of their ability. Knowledge of radiation dose, schedule and volume may provide the head and neck clinician with the tools to predict swallowing outcomes. In order to develop and deliver optimal swallowing rehabilitation post-radiation, SLPs must have a clear understanding of RT.

2.14 References


Chapter 3

3 Efficacy of Thickened Liquids for Eliminating Aspiration in Head and Neck Cancer: A Systematic Review

3.1 Preface

Given the complexity of dysphagia in patients with head and neck cancer and the acute and chronic toxicities of radiation therapy, we were curious about how patients maintained safe oral intake during and after radiation. Thickened liquids are widely used as an intervention for dysphagia, and specifically for aspiration, in a variety of populations. We wished to review the current evidence regarding the impact of thickened liquids on the swallow, post head and neck cancer.

We chose to conduct a comprehensive multi-engine literature search, to identify the efficacy of thickening for eliminating aspiration in head and neck cancer patients. The review was conducted according to the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). This study enabled us to identify gaps in knowledge, on which this thesis is based.


This article can be found on the publisher’s website at:
http://oto.sagepub.com/content/early/2014/10/30/0194599814556239
3.2 Abstract

**Objective:** To appraise the current videofluoroscopic evidence on the reduction of aspiration using thickened liquids in the head and neck cancer population.

**Data Sources:** Search terms relating to deglutition or dysphagia or swallow and neoplasms and oncology or head and neck cancer and viscosity or texture and apira or residu* were combined with honey or nectar, xerostomia, respiratory aspiration using Boolean operators.

**Review Methods:** A multi-engine literature search identified 337 non-duplicate articles of which 6 were judged to be relevant. These underwent detailed review for study quality and qualitative synthesis.

**Results:** The articles reviewed in detail predominantly described heterogeneous study samples with small sample sizes, making for difficult interpretation and generalization of results. Rates of aspiration were typically not reported by bolus consistency, despite the fact that a variety of stimulus consistencies was used during VFSS. Studies confirmed that aspiration is a major concern in the head and neck cancer population and reported a trend towards more frequent aspiration post-(chemo)radiotherapy.

**Conclusion:** Overall, the literature on thickened liquids as an intervention to eliminate aspiration in the head and neck cancer population is limited. Because aspiration is known to be prevalent in the head and neck cancer population and thickened liquids are known to eliminate aspiration in other populations, it is important to determine the effectiveness of thickened liquids for reducing aspiration in the head and neck cancer population.
3.3 Introduction

Dysphagia (swallowing impairment) is a common and debilitating consequence for patients who undergo radiation therapy for the treatment of head and neck cancer (HNC). Often, individuals who undergo radiation therapy (RT) suffer from both acute and long-term swallowing complications (1). The long-term side effects that negatively impact swallowing not only affect the survivor physically, but may contribute to decreased quality of life and decreased participation in everyday life (2). A variety of reviews have been conducted regarding swallowing outcomes in those treated with radiation and/or chemotherapy (3-6). Although multiple reviews have been conducted, the literature still lacks specific information regarding the prevalence, severity and management of aspiration (i.e., entry of foreign material into the airway) following radiation therapy.

Aspiration is a primary concern when HNC patients present with dysphagia, as it involves material passing through the vocal folds and entering the trachea. Penetration is a related event, in which material enters the supraglottic space during videofluoroscopic assessment (VFSS), but is not observed to travel all the way below the vocal folds. Aspiration risk will be defined for the purposes of this review as a score of 3 or above on the Penetration-Aspiration Scale (7). This is a widely-used scale, which classifies the severity of penetration-aspiration based on the depth of airway invasion and whether or not material is successfully ejected. Scores of 1 and 2 are seen in healthy people and reflect either complete absence of material entering the laryngeal vestibule, or transient penetration of material into this area with subsequent ejection. Scores of 3 and higher are considered to reflect abnormal airway protection, and indicate the presence of material in the supraglottic space or below, without spontaneous clearing. Aspiration remains under-identified and under-reported in the head and neck cancer population, including those who have undergone RT (8, 9). One reason why aspiration may not be apparent to patients and clinicians during non-instrumental assessment is the fact that RT may lead to sensory impairments in the tracheal area (8). Aspiration that is not sensed by the patient, thereby leading to a lack of any overt physical response to the aspiration event (such as coughing or throat clearing) is known as “silent aspiration”. Aspiration is dangerous to individuals who have undergone physically rigorous treatments for cancer, and may lead to pneumonia and fatality (10). Although some may view
aspiration as an acute toxicity of dysphagia, research has also shown that chronic aspiration remains common up to one-year post-RT in head and neck patients (11).

Many different interventions may be used to decrease the risk of aspiration while aiming to make swallowing easier and safer. These strategies include the implementation of postural changes, modification of cancer treatment techniques, therapeutic exercises, tailored radiation to spare important structures involved in swallowing, and texture modification of liquids and foods (8). Thickened liquids are used to slow bolus flow in the hopes of preventing aspiration and are widely thought to be effective for neurogenic dysphagia (12). One randomized clinical trial has shown reduced aspiration with thickened liquids in individuals with dementia and/or Parkinson’s disease who are known to aspirate thin liquids (13). However, gaps remain in our understanding of the efficacy of thickened liquids for reducing aspiration in the head and neck cancer population. The purpose of this systematic review is to appraise and synthesize the current evidence regarding the reduction of aspiration using thickened liquids, as tested using videofluoroscopy in the HNC population.

3.4 Methods

3.4.1 Search Strategy

The intent of this review is to examine the use and effectiveness of thickened liquids for reducing aspiration in the HNC population with dysphagia. We conducted a comprehensive multi-engine literature search, according to the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [PRISMA] (14). Our search strategy is illustrated in Figure 1. The initial yield of 351 candidate records for review was obtained through two searches, which were later combined. In the first search, electronic databases Ovid Medline, Ovid Medline in Process, Embase, AMED and PsycInfo were searched for the MeSH terms ‘deglutition or deglutition disorders or dysphagia or swallow’, ‘neoplasms and oncology’ or ‘cancer and head and neck’, and ‘viscosity or texture or thick or liqui*’ and ‘aspira* or residu* or xerostomia’. The use of asterisks in search term specification allows for words sharing a common stem but different endings (e.g., “aspirate”, “aspiration”, “aspirating”) to be found based on the single search term. Dates of inclusion were specified as 1985 forward to current. In the second search, electronic databases Medline and Embase were searched for the MeSH terms
‘deglutition’, ‘deglutition disorders’, and ‘swallow* or deglutition or dysphagi*’, ‘head and neck neoplasms or neoplasms or head or neck’, ‘viscosity’, ‘honey’, ‘thin* or thick* or gum*’, ‘vise*’, ‘honey or nectar’, ‘respiratory aspiration’, ‘pneumonia aspiration’, ‘inhalation’, ‘aspirat*’, ‘xerostomia’. This search had no date limitation.

Duplicate articles were removed from the initial search yield of 351 articles, leaving 337 articles, for which the titles and abstracts were screened for relevance by the first author (CB). A total of 262 articles were excluded based on lack of relevance to the study questions, meaning that they did not describe swallowing function for different consistencies of food and liquid in the head and neck cancer population. The remaining 70 articles underwent a second level of screening via full-text review to confirm relevance; this led to the exclusion of an additional 44 articles. The remaining 26 articles underwent detailed full-text review and appraisal of study quality using the questions listed in Table 3.1. Five full-text articles (i.e. 19%) were reviewed in duplicate by an independent blinded rater (CMS), with 100% agreement between both raters regarding quality and inclusion decisions. In the event that discrepancies had occurred at this stage, a meeting would have been convened to establish consensus. The quality review led to a final set of 6 articles to be included in the qualitative synthesis. A risk of bias assessment was conducted for each of these 6 articles, according to the criteria set out by the Cochrane Bias Methods Group (15). Based on the small number of articles that qualified for final review, and heterogeneity in participant demographics across studies, it was decided that data pooling and meta-analysis could not be performed.
Table 3.1. Questions used in the quality rating

<table>
<thead>
<tr>
<th>Quality Rating Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the article in a peer reviewed journal?</td>
</tr>
<tr>
<td>2. Does the study involve individuals with new HNC treated with radiotherapy with or without chemotherapy?</td>
</tr>
<tr>
<td>3. Is the article in English?</td>
</tr>
<tr>
<td>4. Does the study use VFSS to examine the swallow?</td>
</tr>
<tr>
<td>5. Are at least two textures reported (one thin)</td>
</tr>
<tr>
<td>6. Are consistencies repeatable to make?</td>
</tr>
<tr>
<td>7. Is aspiration status reported?</td>
</tr>
<tr>
<td>8. Is sufficient data reported for at least one thickened consistency?</td>
</tr>
<tr>
<td>9. Have individuals had previous surgery or radiation?</td>
</tr>
<tr>
<td>10. Does the study include subjects with additional disorders that would cause dysphagia or have a history of dysphagia?</td>
</tr>
</tbody>
</table>

3.4.2 Inclusion Criteria

Studies were required to be in English and published in a peer-reviewed journal. Studies included were those that involved subjects with HNC treated with radiation with or without chemotherapy or surgery. It was required that articles assess swallowing function using VFSS, and that aspiration status be reported. It was our original intent to limit inclusion to articles in which swallowing function had been studied using more than one thickened liquid; however, this strategy led to a severely limited set of articles for consideration. Consequently, the requirement was relaxed to allow the inclusion of studies describing swallowing with thin liquid barium in addition to at least one other texture.

3.4.3 Exclusion Criteria

Abstracts and conference posters were excluded from the search. Studies describing cancers other than primary cancer in the oral cavity, nasopharynx, hypopharynx or larynx were excluded, as were studies in which participants were reported to have etiologies of dysphagia involving
disorders other than, or in addition to head and neck cancer. Studies involving cases that were not newly diagnosed were also examined (16). Studies involving patients who were unable to take food/liquid orally were excluded, as the review focused on efficacy of thickened liquids for reducing aspiration. A handful of studies examined a mixture of radiation with or without chemotherapy and was most frequent for treatment approaches, while surgery (with or without radiation therapy) was least occurring (17-26). Articles selected for detailed review were excluded on the basis that they either did not meet the criterion of evaluating the swallow via VFSS, studying swallowing with both a thin and at least one other consistency, or failed to report rates of aspiration in their study (17, 22, 27-31).

Instrumental swallowing assessments were used in each of the 26 papers considered for review. Videofluoroscopy was the primary means of assessment, while a few of the articles used endoscopy (FEES) to assess swallow function (24, 32, 33). Although FEES and VFSS are both used frequently for the assessment of swallow function, endoscopy involves a period of visual white-out during pharyngeal constriction, which hampers the ability to directly visualize aspiration and laryngeal closure. Since the aim of this review is to examine the occurrence of aspiration with thickened liquids, studies using FEES were excluded.

3.5 Results

The subset of articles selected for qualitative synthesis included largely heterogeneous samples of patients with varying tumor sites, stage, and treatment type. Detailed descriptions of participants were, however, provided in all 6 articles and are summarized in Table 3.2. Cancer sites included but were not limited to the oral cavity, nasopharynx, larynx, and hypopharynx. Tumor stages spanned I-IV and specific TNM staging was reported in three studies (34-36). Of the six articles reviewed, three articles disclosed the absence of related disorders and/or previous history of dysphagia (34, 37, 38). The remaining articles did not provide details regarding any known history of dysphagia or potential additional causes of dysphagia.

Patient participants in the identified studies had undergone a variety of different primary cancer treatments. Among these, radiation with or without chemotherapy was identified to be the most frequent primary cancer treatment approach, while surgery (with or without radiation therapy) was reported with the least frequency (17-24). While one article included patients who had
undergone surgery or neck dissection (35), all participants had also undergone various forms of radiation with or without chemotherapy (see Table 3.2). Summaries of each included study follow below.

3.5.1 Articles Accepted for Qualitative Synthesis

Agarwal and colleagues (34) conducted a study to assess factors affecting swallow function following curative intent definitive (chemo) radiotherapy for HNC patients. Swallow function was assessed in 47 patients who were all treated with CRT. VFSS was conducted at baseline as well as at 2, 6, and 12 months post-treatment. Agarwal and colleagues used the Penetration-Aspiration Scale (7) as an objective measure of aspiration severity. They found the prevalence of PAS scores of 3 and higher, indicating penetration, increased from 27% at baseline to 37% at the 6 month follow up. Similarly, aspiration (i.e., scores of 6-8) was observed in 19% of patients at baseline and increased to 29% at the 6 month post-CRT VFSS. Specific information regarding aspiration prevalence by bolus consistency was not reported.

Lazarus and colleagues (38) examined swallowing in nine patients undergoing CRT (external beam radiation and chemotherapy) compared with age-matched healthy controls. Analyses included observation of abnormal oropharyngeal motility, residue and aspiration, temporal analyses, and biomechanical analyses. It was found that oral and pharyngeal motility may become compromised when external-beam radiation is provided to laryngeal or tongue areas. Overall, three patients were reported to be able to handle liquids, three were able to handle liquids and paste/pudding consistency, and the remaining three were able to tolerate all bolus consistencies. A total of 8/9 patients aspirated on liquid during the VFSS. Maneuvers or postures were attempted in order to eliminate aspiration in five of these patients, and aspiration was successfully eliminated for at least one bolus volume in all five. Details regarding the reduction of aspiration with thicker consistencies in those who aspirated liquids were not reported.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Sample Size</th>
<th>Tumor Location</th>
<th>Patient Sample</th>
<th>Treatment Method</th>
<th>Neck Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al.</td>
<td>2011</td>
<td>Objective assessment of swallowing function after definitive concurrent (chemo)radiotherapy in patients with head and neck cancer</td>
<td>N=47</td>
<td>Oropharynx, hypopharynx or larynx</td>
<td>Non-metastatic, non-nasopharyngeal head and neck SCC (u=51 y/o)</td>
<td>Planned for definitive CRT</td>
<td>None</td>
</tr>
<tr>
<td>Eisbruch et al.</td>
<td>2002</td>
<td>Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer</td>
<td>N=29</td>
<td>Oropharynx, oral cavity, hypopharynx, nasopharynx, larynx, paranasal sinuses, external ear canal, thyroid gland</td>
<td>Non-resectable head and neck cancer without distant metastasis (mean age=62 y/o)</td>
<td>Radiation with intravenous gemcitabine</td>
<td>None</td>
</tr>
<tr>
<td>Graner et al.</td>
<td>2003</td>
<td>Swallow function in patients before and after intra-arterial chemoradiation</td>
<td>N=11</td>
<td>Oropharynx, hypopharynx, larynx</td>
<td>Resectable SCC of the head and neck (mean age=57 y/o)</td>
<td>Intra-arterial chemoradiation</td>
<td>Select, modified or radical</td>
</tr>
<tr>
<td>Lazarus et al.</td>
<td>1996</td>
<td>Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy</td>
<td>N=18 (9 HNC subjects with age matched)</td>
<td>Pyriform sinus, tongue base, pharyngeal wall, epiglottis, aryepiglottic folds, tongue base, vocal folds, soft palate, tonsil</td>
<td>Stage III-IV laryngeal/hypopharyngeal tumors (mean age=60 y/o)</td>
<td>External-beam irradiation with chemotherapy</td>
<td>None</td>
</tr>
<tr>
<td>Newman et al. 2002</td>
<td>Swallowing and speech ability after treatment for head and neck cancer with targeted intraarterial versus intravenous chemoradiation</td>
<td>N=30</td>
<td>Oral, pharynx, larynx</td>
<td>Cancer of the head and neck (mean age=61)</td>
<td>n=14 RADPLAT vs n=16 systemic CRT</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----</td>
<td>----------------------</td>
<td>------------------------------------------</td>
<td>----------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Pauloski et al. 2002</td>
<td>Swallow function and perception of dysphagia in patients with head and neck cancer</td>
<td>N=132</td>
<td>Oral cavity, pharynx, larynx, unknown</td>
<td>Stage I-IV (73% stage IV) of the oral cavity, pharynx, larynx (mean age=60 y/o)</td>
<td>Primary radiotherapy +/- chemotherapy</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Eisbruch and colleagues (37) examined swallow function via VFSS after intensive chemoradiation for HNC patients. Aspiration was observed in 14% of participants at baseline VFSS, but increased to 65% prevalence at 1-3 month follow up, and 62% at 6-12 month follow up. Eisbruch and colleagues concluded that changes in the swallow occur post-treatment that promote aspiration in head and neck cancer patients treated with CRT. Details regarding the relationship between bolus consistency and aspiration prevalence were not reported.

Graner and colleagues (35) aimed to assess swallow function before and after CRT with neck dissection. Upon review of VFSS, it was noted that 55% of patients had penetration on thin and thick liquid. Aspiration was seen in 64% of the patients involved in the study. Six patients aspirated thin liquid while six aspirated thick liquid. Overall, three subjects aspirated with puree consistency. The specific relationship between bolus consistency and aspiration within individuals was not reported.

Pauloski and colleagues (39) compared objective swallow function with patient complaints of dysphagia in subjects with HNC treated with radiotherapy with or without chemotherapy. Participants were evaluated via VFSS, from which objective timing measures were derived. In addition, participants were asked whether they felt they had a swallowing problem and to subjectively estimate the amounts of food/liquid taken orally, and to document the consistencies they were consuming. The data show that patients with complaints of dysphagia showed a higher frequency of swallows with aspiration on all bolus consistencies than the individuals without complaint. Within-participant comparisons of swallowing pre- versus post-treatment were not provided. Aspiration was reported to occur between 16-22% of the time for liquid swallows (at 1, 3, 5, and 10 ml), yet only 8% of the time with a paste consistency (3 cc). When aspiration was compared by tumor site and complaint versus no complaint of dysphagia, it was found that subjects with oral cavity tumors experience less aspiration overall. However, patients with tumors based in the pharynx or larynx who complained of dysphagia had a higher frequency of aspiration on most bolus types than those who did not complain of dysphagia.
Newman and colleagues (36) aimed to compare RADPLAT (concurrent selective supra-dose intraarterial Cisplatin and external-beam radiation) to systemic chemoradiation treatment and to document the effects they each have on swallowing and speech. Aspiration at one month post-treatment occurred at various volumes with both liquid and paste consistencies. Aspiration occurred more frequently with 5 mL liquid boluses in the RADPLAT group (27%), while aspiration occurred frequently with 1 mL (31%), 3 mL (40%) and 10 mL (22%) liquid boluses in the CRT group. Both groups aspirated on the 3 cc paste bolus with similar frequency (13% collectively). Overall, subjects who underwent RADPLAT experienced less aspiration on small volume liquid boluses.

3.5.2 Timing of VFSS Post-Treatment

The time-point at which VFSS was conducted for the six articles chosen for qualitative synthesis was inconsistent. Two of the studies evaluated swallow function approximately one year post-treatment, which allows the patient time to recover from acute symptoms (34, 37). Many of the studies also evaluated the swallow at earlier time points (e.g., at 3 months and 6 months), which provides a more complete picture of progression over time post-treatment (34-39). A quality limitation of one study was the lack of baseline measures of swallow function (38). It should be noted that baseline measures in the studies analyzed for this review reflect swallowing status in individuals with confirmed head and neck cancer, prior to the initiation of chemo- and/or radiotherapy for their cancer. As such, these baseline measures capture any abnormalities that may have been present in swallowing function as a result of the cancer itself and allow a better appreciation of the impact (either positive or negative) of intervention. In the absence of baseline measures, such comparisons are not possible.

3.5.3 Aspiration Status and Operational Definition

All 6 studies included for qualitative synthesis reported aspiration status based on videofluoroscopic evaluation. However, operational definitions of aspiration were only provided in 3 of the studies (34, 35, 37). A validated rating tool to measure aspiration (i.e., the Penetration-Aspiration Scale (7) was used in only one study (34).
3.5.4 Stimuli used in Videofluoroscopy

The food and liquid stimuli used in the studies selected for qualitative synthesis are detailed in Supplementary Table 3. Liquid barium was used in all VFSS procedures, however, only 1 of the 6 studies specified the liquid brand (34). Thick liquids were used in two studies (34, 35). One of these studies described swallowing for a thin liquid compared with a medium thick liquid and an even thicker liquid (34). Although three thickness levels of liquids were utilized, additional details were not provided characterizing the viscosity or flow properties of the stimuli. Other consistencies used in the studies reviewed include puree (with or without barium paste), pudding, paste (with or without pudding), soft solids, and solids (cookie coated with barium paste). It is evident that there are inconsistencies across protocols with regards to the stimuli given to patients (see Table 3.3). Furthermore, detailed information on how different stimuli were mixed with barium was lacking from all articles, such that reproduction of the stimuli would not be possible. In an ideal situation, both rheological values of viscosity and information regarding barium concentration are required in order to adequately describe the stimuli used in a given study. In addition, other information such as temperature and bolus volume is important, and if reported, would represent desirable methodological rigor and quality.
Table 3.3. Detailed list of radio-opaque stimuli used in the reviewed studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Consistencies Used</th>
<th>Specified Recipe/Barium?</th>
<th>Aspiration Reported by Consistency?</th>
<th>Maneuver Attempted?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al.</td>
<td>2011</td>
<td>Objective assessment of swallowing function after definitive concurrent (chemo)radiotherapy in patients with head and neck cancer</td>
<td>Thin barium (Microbar®) diluted with water, medium barium undiluted, and thick barium made with barium suspension and barium powder in 1:1 ratio</td>
<td>Yes</td>
<td>Overall—not by consistency</td>
<td>Yes</td>
</tr>
<tr>
<td>Eisbruch et al.</td>
<td>2002</td>
<td>Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer</td>
<td>Thin liquid barium (diluted with water), nondiluted barium, puree, soft food (fruit mixed with barium), and a solid (shortbread cookie) coated with barium</td>
<td>No</td>
<td>Overall—not by consistency</td>
<td>No</td>
</tr>
<tr>
<td>Graner et al.</td>
<td>2003</td>
<td>Swallow function in patients before and after intra-arterial</td>
<td>Liquid, thick liquid, apple sauce mixed</td>
<td>No</td>
<td>By consistency for (thin, thick, puree)</td>
<td>Yes</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Description</td>
<td>Consistency</td>
<td>Preferred Form</td>
<td>By Consistency</td>
<td>Result</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------------------</td>
<td>---------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Lazarus et al.</td>
<td>1996</td>
<td>Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy</td>
<td>No</td>
<td>Thin, pudding, solid</td>
<td>By consistency (liquid, paste, cookie)</td>
<td>Yes</td>
</tr>
<tr>
<td>Newman et al.</td>
<td>2002</td>
<td>Swallowing and speech ability after treatment for head and neck cancer with targeted intraarterial versus intravenous chemoradiation</td>
<td>No</td>
<td>Liquid (not specified) and paste</td>
<td>By consistency (liquid and paste)</td>
<td>No</td>
</tr>
<tr>
<td>Pauloski et al.</td>
<td>2002</td>
<td>Swallow function and perception of dysphagia in patients with head and neck cancer</td>
<td>No</td>
<td>Liquid barium and barium paste mixed with chocolate pudding</td>
<td>By consistency (liquid, paste)</td>
<td>No</td>
</tr>
</tbody>
</table>
3.5.5 Other Interventions

In addition to exploring swallowing with different liquid consistencies, 3 of the 6 articles explored postural changes or compensatory maneuvers as interventions to eliminate aspiration for some patients (34, 35, 38) (see Table 3.3). Postural change has been found to reduce the risk of aspiration in individuals with HNC post-surgery while airway protection maneuvers are reported to help those HNC patients with radiation history (40, 41). In the studies reviewed, Agarwal and colleagues (34) found postural change to be more effective with thick barium. Newman reported that the use of maneuvers aided in reduction of laryngeal penetration in two patients (36).

3.5.6 Risk of Bias

Evaluation of the risk of bias was performed for all 6 articles selected for qualitative synthesis, according to the guidelines set out by the Cochrane Bias Methods Group (15). As shown in Table 3.4, one of the most common risks of bias lay in videofluoroscopy protocols that were terminated early, resulting in incomplete data. This is not an unexpected finding given the typical clinical rules for terminating VFSS exams when repeated aspiration events are witnessed despite attempts to resolve the problem; nevertheless, this reality contributes to uneven numbers of observations across participants within a study. An additional common bias was the failure to report blinding of raters when assessing the VFSS evaluations. Many studies failed to disclose whether the raters were blinded to the time of assessment (pre-vs. post-treatment) or to the type of bolus consistency being evaluated. In addition, 50% of the articles did not clearly define the term “aspiration”, leading to potential differences in interpretation across studies.
Table 3.4. Summary of risk of bias assessments

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Title</th>
<th>Risk of Bias</th>
<th>Type of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al., 2011</td>
<td>Objective assessment of swallowing function after definitive concurrent (chemo)radiotherapy in patients with head and neck cancer</td>
<td>+</td>
<td>Rater blinding not disclosed; reliability of ratings not disclosed; sex not balanced in sample; more than 1 swallow/consistency not disclosed</td>
</tr>
<tr>
<td>Eisbruch et al., 2002</td>
<td>Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer</td>
<td>+</td>
<td>Protocol incomplete; rater blinding not disclosed; reliability of ratings not disclosed; information regarding sample age/gender not disclosed; missing data</td>
</tr>
<tr>
<td>Graner et al., 2003</td>
<td>Swallow function in patients before and after intra-arterial chemoradiation</td>
<td>+</td>
<td>Protocol incomplete; rater blinding not disclosed; small sample size; statistical bias</td>
</tr>
<tr>
<td>Lazarus et al., 1996</td>
<td>Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy</td>
<td>+</td>
<td>Protocol incomplete; rater blinding not disclosed; sex not balanced in sample; small sample size; statistical bias; absense of operational definition of aspiration</td>
</tr>
<tr>
<td>Newman et al., 2002</td>
<td>Swallowing and speech ability after treatment for head and neck cancer with targeted intraarterial versus intravenous chemoradiation</td>
<td>+</td>
<td>Protocol incomplete, rater blinding not disclosed; absense of operational definition of aspiration</td>
</tr>
<tr>
<td>Pauloski et al., 2002</td>
<td>Swallow function and perception of dysphagia in patients with head and neck cancer</td>
<td>+</td>
<td>Rater blinding not disclosed; reliability of ratings not disclosed; sex not balanced in sample;</td>
</tr>
</tbody>
</table>
3.5.7 Rates of Aspiration

Articles were assessed for the percentage of participants in the sample displaying aspiration post-treatment. Overall, three studies could be compared given a baseline aspiration status and post-evaluation at approximately 6 months. A fourth study provided aspiration in “number of swallows” rather than per participant. Within the three studies providing comparable data, 19% of participants aspirated pre-treatment, while 30% of subjects aspirated approximately 6 months post-treatment (34, 35, 37). The percentages of aspiration occurrence represent aspiration over the entire VFSS examination; sufficient detail to allow comparisons of rates of aspiration on particular consistencies could not be obtained from these articles. It would be extremely desirable to determine whether specific consistencies would have aided in the elimination of aspiration in these participants.

Four studies specifically reported aspiration status for each consistency provided (35, 36, 38, 39). Graner and colleagues (35) found that 6 individuals (n=11) aspirated on both thin and thick liquid post-treatment. A list of the stimuli utilized in this study can be found in Supplementary Table 3. There was no difference in aspiration rates between the two consistencies in this study, but the overall subject number is quite small. Newman and colleagues (36) report aspiration of various liquid volumes and a paste consistency. Chemoradiation patients’ aspiration prevalence with liquid was reported as 31%, 40%, and 22% for 1 ml, 3 ml, and 10 ml volumes, respectively, while RADPLAT aspiration prevalence with thin liquid was reported as 27% for 5 ml volumes. Aspiration rates for the thicker, puree consistency for RADPLAT and chemoradiation patients combined were reported to be substantially lower at 13% (36). Pauloski and colleagues (39) accounted for aspiration in each swallow for 1, 3, 5, and 10 mL liquid volumes plus one paste bolus. Swallows with aspiration were also separated by tumor site and by the subject’s view of their swallowing impairment. Aspiration frequency ranged from 0% on thin liquids in
individuals with oral cancer who did not complain of dysphagia to 30% of swallows on thin liquids in individuals with laryngeal tumors who complained of dysphagia. A trend towards less aspiration on pureed consistencies for patients with laryngeal and pharyngeal tumor sites was reported.

3.6 Conclusion

Based on the studies identified for detailed review and qualitative synthesis, it is clear that aspiration is a burden for HNC patients both before and after radiation treatment. It is also evident that there is a significant gap in the literature with regards to describing the effectiveness of thickened liquids for reducing aspiration in the head and neck cancer population as a whole. Although the 6 studies identified for synthesis report aggregate information regarding rates of aspiration, only 4 report any detail regarding aspiration by consistency (35, 36, 38, 39). Only one study reported data in a way that would permit comparison of aspiration status on a thin liquid to aspiration status on thicker liquids. The lack of detailed descriptions of the stimuli used represents a serious limitation with respect to understanding the impact of bolus consistency on aspiration in the HNC population.

Despite these limitations, the literature does contain some evidence to suggest that thicker consistencies may prevent aspiration in the HNC population. For example, aspiration occurred on 17% of 1 mL liquid boluses in individuals treated with (C)RT in one study, while aspiration occurred only 8% of the time on 3 cc of paste (39). Although these data are insufficient to support the conclusion that aspiration was effectively eliminated by 50% by use of a paste consistency, the data provide an important preliminary indication suggesting reduced aspiration risk with thicker consistencies.

One observation arising from the literature reviewed is the fact that most studies had a primary goal of detailing the impact of cancer treatment on swallowing function, and explored interventions other than texture modification to address aspiration and dysphagia in patients with HNC. Temporal and biomechanical analyses were sometimes used but these measures were not applied to understanding the impact of bolus consistency on swallowing function (35-39). As such, we conclude that a complete understanding of the impact of thickened liquids as a compensatory technique for addressing swallowing dysfunction in the HNC population is
currently lacking. Although compensatory maneuvers have been shown to eliminate some aspiration in this population, thickened liquids have yet to be employed as an evidence-based intervention for HNC patients. There is clearly a need for rigorous and controlled research to address this gap in our understanding.

3.7 References


Chapter 4

4 Characterizing the Flow of Thickened Barium and non-Barium Liquid Recipes Using the IDDSI Flow Test

4.1 Preface

The findings from the systematic review identify gaps in current knowledge regarding texture modification and its efficacy as a strategy for decreasing the incidence of penetration-aspiration in head and neck cancer patients. In order to properly evaluate the effects of thickened liquids on swallowing, radio-opaque liquid stimuli with controlled flow characteristics are needed for use in videofluoroscopy, and the similarity in flow properties between these assessment stimuli and liquids that may be consumed outside the clinical setting needs to be understood. The following study of liquid development was guided by the International Dysphagia Diet Standardisation Initiative (IDDSI). IDDSI is a framework for texture modified foods and liquids used for dysphagia management, with 8 levels of consistency. Five levels of liquid (thin, slightly thick, mildly thick, moderately thick and extremely thick) are defined based on a gravity flow test (the IDDSI Flow Test). All stimuli in this chapter were developed to target consistencies using the IDDSI Flow Test.

The stimuli developed in this chapter were used for the videofluoroscopy and palatability experiments described in subsequent chapters.

With permission from Springer publishing, this chapter was excerpted in its entirety from the following journal article: Barbon, C. E. A., & Steele, C. M. (2018). Characterizing the flow of thickened barium and non-barium liquid recipes using the IDDSI Flow Test. Dysphagia, 33(3). doi: 10.1007/s00455-018-9915-6. This article can be found on the publisher’s website at: https://link.springer.com/article/10.1007/s00455-018-9915-6
4.2 Abstract

The use of thickened liquids for dysphagia management has become wide-spread. Videofluoroscopy is commonly used to determine dysphagia severity and to evaluate effectiveness of interventions, including texture modification, but this requires the use of radio-opaque contrast media. In order for the results of a videofluoroscopy to have validity with respect to confirming swallowing safety and efficiency on different liquid consistencies, it is important to understand the flow characteristics of the contract media used and how the flow of these stimuli compares to the flow of liquids that are provided outside the assessment context. In this study, we explored the flow characteristics of 20% w/v barium and non-barium stimuli prepared using starch and gum thickeners to reach the slightly, mildly and moderately thick liquid categories defined by the International Dysphagia Diet Standardisation Initiative (IDDSI). Our goal was to identify recipes that would produce stimuli with stable flow properties over a 3h time frame post mixing. Thickener combination of barium and thickeners resulted in further thickening, particularly with starch-based thickening agents. A probe of the influence of refrigeration showed no difference in flow measures between chilled and room temperature stimuli over a 3h time frame. Overall, recipes with stable flow over three hours were identified for all barium and non-barium tested.
4.3 Introduction

Diet texture modification is widely recommended to promote and maintain patient safety when managing dysphagia [1]. Thickened liquids are used as an intervention based on evidence that boluses with higher viscosity travel more slowly through the oropharynx, and are less likely to be aspirated [2]. Despite the widespread use of thickened liquids, little is known regarding the specific flow characteristics that are needed to achieve therapeutic benefit [2]. Recent studies have also shown a risk of greater post-swallow residue with extremely thick liquids [2]. In light of this evidence of potential risk as well as benefit with the use of thickened liquids, the effectiveness and optimal consistency of thickened liquids should be evaluated on a case by case basis using instrumental swallowing examinations.

In order for a bolus to be visualized in videofluoroscopy, a radiographic contrast agent must be used. In North America, barium is the most common contrast agent used. In the United States, there is one line of available barium products that comes in an array of different consistencies, specifically intended for imaging of the oropharynx (Bracco Varibar®). However, this line of products is not currently approved for clinical use outside the United States. Consequently, the standard of care in Canada and many other countries is for clinicians to prepare barium stimuli in different consistencies using off-label recipes. However, the addition of a thickening agent to a barium solution (or vice versa, the addition of barium powder to a pre-thickened liquid) may result in further thickening [3]. When this happens, the validity of the assessment stimulus for predicting swallowing function outside the context of the exam becomes a concern [2, 4, 5].

In addition to the amount of thickener that is used in a recipe for a thickened liquid [6, 7], a number of other factors may influence the flow characteristics of the resulting stimulus. These factors have relevance for the preparation of thickened barium stimuli as well as non-barium stimuli. Since the first descriptions of thickened liquids used for managing aspiration risk [8, 9], an increasing variety of thickeners and pre-thickened liquids has emerged on the market. Variations in liquid flow occur across different thickener-types (e.g., modified corn starch versus xanthan gum) [10, 11]. Other factors that may be relevant include thickening technique (e.g., hand mixed versus machine mixed) [12], time-post mixing [10, 11, 13]; temperature [13]; and characteristics of the liquid being thickened (e.g., pH, fat content, protein content, volume of
liquid in the recipe) [14, 15]. Non-linear concentration curves may be observed with some thickening agents [16].

Historically, guidelines regarding thickened liquids used in dysphagia management have defined categories of progressively thicker liquids in terms of viscosity [17, 18]. The National Dysphagia Diet Task Force, (NDD) most commonly reported at a shear rate of 50/s [17]. However, neither the equipment nor the expertise required to measure viscosity at controlled shear rates is accessible to clinicians. Recently, the International Dysphagia Diet Standardization Initiative (www.iddsi.org) has released new guidelines for classifying liquid thickness according to gravity flow through a syringe [18, 19]. Three levels of thickened liquid (slightly thick, mildly thick, and moderately thick) are defined based on the height of the residual fluid column (in ml) after 10 seconds of flow through a standard 10 ml slip tip syringe (Becton Dickinson manufacturer code 301604). A fourth level of extremely thick liquids shows no flow through the syringe; supplementary spoon tilt and fork drip tests are recommended to confirm the characteristics of liquids at this level.

In this manuscript, we explore the flow characteristics of barium stimuli prepared according to recipes using two different commercial thickeners (modified corn starch and xanthan gum) in combination with water and barium sulfate powder, and compare the results of these tests to non-barium stimuli prepared using water and the same thickening agents. The method of flow measurement selected for this study is the gravity flow test recommended by the International Dysphagia Diet Standardisation Initiative (IDDSI) [18, 19]. The primary objective was to identify recipes for barium stimuli that would meet the IDDSI definitions of slightly, mildly and moderately thick liquids [18] at 1 hour post mixing and remain stable within these defined flow ranges up to 3 hours post mixing. The process involved testing of different concentrations of thickener to determine the need to adjust the amount of thickener in a barium recipe compared to the amounts used when preparing non-barium stimuli. As an additional objective, we wanted to conduct a preliminary probe of the impact of temperature (i.e., room temperature vs. chilled) on the flow characteristics of thickened barium stimuli.
4.4 Methods

4.4.1 Stimulus Mixing

Thickened non-barium liquids were prepared using Nestlé ThickenUp® (starch) and Nestlé ThickenUp® Clear® (xanthan-gum) powders and a commercially available lemon-flavoured water (Nestlé® Lemon Splash). The non-barium stimuli were developed for use in a related study of swallowing; lemon flavored water was chosen to make these stimuli more palatable than thickened water. The taste of the unthickened Lemon Splash product was rated by a blinded taste panel, who judged the intensity of the sourness to be similar to a solution of 0.02% lemon juice and sweetness to 0.02% sucrose in water. This degree of sourness falls well below the levels reported to impact swallowing behaviors [20]. For the barium stimuli, the same thickening agents were mixed with a 20% w/v concentration barium suspension, comprised of bottled water (Nestlé® Pure Life) and Bracco E-Z-Paque® 96% w/w barium powder. All stimulus mixing was performed by a single research team member using a commercially available Bosch stand mixer (Model MUM4405UC, 4 speed, 400 watt motor). Mixer speed was confirmed prior to the experiment by placing markers on the whisk, video recording the whisk in motion and determining the number of rotations per second. The standard operating procedure for mixing was as follows:

1) The desired amount of water was poured into the Bosch stand mixer mixing bowl, with the amount confirmed by weight on an OHAUS digital balance (model number PA1502 analytical scale: capacity: 1.5kg; readability 0.01g).

2) The mixing bowl was removed and a plastic non-static weigh boat (VWR® 20.5 cm³ capacity) was placed on the balance.

3) The balance was tared to account for the weigh boat, and the thickener was added until the target weight was achieved.

4) For the barium stimuli, the required amount of barium powder was similarly measured using a weigh boat.

5) The water was set in motion using the Bosch stand mixer at a low spin speed of 60 rpm.
6) The weighed barium powder was added to the water, while in motion.

7) The weighed thickening powder was added while the water was in motion. This process was completed slowly (over 10-20 seconds) in order to avoid clumping of the thickener.

8) Once the thickener was added, the speed was increased by one level for 10 seconds, and then lowered back to low speed.

9) The liquid was then left to mix for a period of one minute and 50 seconds (2 minutes mixing time overall) at a slow spin speed of 60 rpm.

10) The liquid stimulus was portioned into separate, disposable cups with lids to allow for testing at subsequent time points.

Trials of various amounts of thickener were tested at the one hour mark, beginning with the manufacturer instructed amount. If the liquid flow fell outside the targeted IDDSI range, iterative testing of small differences in thickener concentration was explored, as follows:

1) Non-barium thickened with starch in concentrations of 4.1, 4.15, 4.2, 4.75, 4.77, 4.8, 5.0, 5.5, 5.8, 6.0 and 7.8 g/100 ml;

2) Non-barium thickened with xanthan gum in concentrations of 0.65, 1.0, 1.1, 1.25, 1.3, 1.4, and 2.1 g/100 ml;

3) Barium thickened with starch in concentrations of 2.64, 2.85, 2.87, 3.0, 3.3, 3.75, 3.8, 3.9, 5.1, 6.7, 7.4 and 7.6 g/100 ml; and

4) Barium thickened with xanthan gum in concentrations of 0.35, 0.5, 0.9, 1.0, 1.02, 1.05, 2.0, 2.2, 4.2 and 4.5 g/100 ml.

4.4.2 Flow Testing

The IDDSI Flow Test was used to measure the flow properties of all liquid stimuli created for the study. Detailed instructions for this test can be found at: http://iddsi.org/framework/drink-testing-methods. All tests were conducted by a single research team member. Each stimulus was tested in triplicate at each measurement timepoint. Clean, fresh syringes were used for each
sample. Stability in flow was considered to have been achieved when results across successive timepoints remained within a 1 ml flow test result range. In the event that the observed range in flow test results across three repeated samples spanned more than 1 ml, a 4th sample was tested to correct for possible outlier results attributable to the possibility that small lumps or bubbles might have blocked the syringe nozzle. In these cases, the outlier result was discarded and the 3 closest test results were retained for analysis. Similarity in flow across the different stimuli (barium + thickener combinations) was considered to have been achieved when results at the same time point fell within a flow test result range of 1 ml across stimuli.

4.4.3 Stability Testing

To assess stability of the flow characteristics of the stimuli, we performed repeated testing over time (1, 2 and 3 hours post mixing), with a goal to identify recipes that produced liquids with IDDSI flow test results that remained stable within IDDSI level over a timeframe of 3 hours.

4.4.4 Temperature Testing

Exploration of the impact of temperature was conducted using barium thickened with 0.35, 0.5, 1.0, 2.0 and 4.2 g/100ml of xanthan gum and with 3, 3.3, 3.9, 5.1, and 6.7 g/100 ml of starch. The initial batch was divided into portions that were maintained either at room temperature or stored in a refrigerator (at approximately 4 degrees Celsius). Repeated flow tests were performed on both room-temperature and chilled samples at 1, 2 and 3 hours post mixing.

4.5 Analyses

Means and ranges for flow test results were calculated by thickener concentration (g/100ml) for each time point of measurement. Descriptive statistics and graphs will be used to illustrate the results of the flow testing.

For the demonstration of recipe stability, we conducted repeated measures ANOVAs of IDDSI Flow Test result within liquid type (barium/non-barium plus starch or gum) across time with a covariate of concentration. Similarly, for the exploration of temperature based variations, we conducted a repeated measures ANOVA of IDDSI Flow Test result within liquid type (starch;
gum) for matched chilled versus room-temperature barium recipes across time points with a covariate of concentration.

4.6 Results

Trends in the flow test results across thickener concentrations at the 1 hour timepoint post mixing can be seen in Figures 4.1a to 4.1d. A clear pattern of higher flow test residual volumes (i.e. thicker liquids) is seen with higher concentrations of thickener within each liquid type. The stability analysis showed this result to be statistically significant for all four liquids, with p-values ranging from < 0.001 to 0.002.

Across time, none of the recipes showed a shift across IDDSI level boundaries. However, statistically significant increases in thickness within IDDSI level were found in pairwise comparisons between the 1 hour and 2 hour (p = 0.009) and the 2 hour and 3 hour time points (p = 0.004) for the non-barium starch thickened stimuli. This effect was not found for the other liquids.
Figure 4.1. IDDSI Flow Test results at one hour for (a) non-barium starch; (b) non-barium xanthan-gum; (c) starch thickened barium and (d) xanthan-gum thickened barium at 1 hour post-mixing
Figure 4.2 Figures a) and b) illustrate differences in flow of thickened barium between room temperature and refrigerated samples across time. Although the refrigerated barium stimuli were thicker than the room temperature stimuli, this difference was not statistically significant.
4.7 Discussion

The creation of assessment stimuli that have similar flow properties to non-barium liquids that are available for dysphagia management is important for patient care and diagnosis. The IDDSI Flow Test provides clinicians with a means of confirming similarity in flow across liquids. This study was designed to identify recipes for slightly, mildly and moderately thick liquid barium stimuli that would remain stable at 1 hour after mixing and up to 3 hours afterwards. Final recipes of the barium and non-barium stimuli can be found in Table 4.1. The results underscore the importance of clinicians developing awareness of factors that can contribute to variations in the flow of liquids and of methods for measuring flow. This is of particular relevance when preparing barium stimuli for use in videofluoroscopy.

Table 4.1. Final Recipes (g/100 ml) for all non-barium and barium liquids by IDDSI level

<table>
<thead>
<tr>
<th>IDDSI level</th>
<th>Non-barium</th>
<th>Barium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xanthan gum</td>
<td>Starch</td>
</tr>
<tr>
<td>1</td>
<td>0.65</td>
<td>4.15</td>
</tr>
<tr>
<td>2</td>
<td>1.25</td>
<td>4.77</td>
</tr>
<tr>
<td>3</td>
<td>2.1</td>
<td>5.85</td>
</tr>
</tbody>
</table>

The study highlights the flow of four different types of liquid, depending on thickener, and whether or not barium has been added. Figure 4.1 a-d shows the decrease in flow that was seen as the amount of thickener was increased. It is important to highlight that the amount of thickener needed to reach any given level of thickness on the IDDSI continuum is much lower when using xanthan gum rather than starch based thickeners. For example, Figures 4.1a and 1b show non-barium liquids thickened with the starch and xanthan gum thickeners, respectively. In both graphs, the first data point shows a slightly thick liquid with an average of 1.4 ml left in the syringe after 10 seconds of flow. For the starch-thickened liquid (figure 4.1a) 4.1g/100ml of thickener were required to reach this level; the corresponding xanthan-gum thickened liquid (figure 4.1b) required only 0.65g/100ml of thickener to achieve the same flow. The common trend for thickener labels to specify the amount of thickener needed using a simplified 1-scoop, 2-scoop or 3-scoop methodology obscures this difference. Users may not be aware that the size of the scoop included in a package of thickener has been adjusted to compensate for the different concentrations required across thickener types.
Several of the recipes that were tested in this study yielded IDDSI flow test results of 10 ml (i.e., no drip). It is important to mention that this result represents saturation of the IDDSI flow test. Confirmation that a liquid falls in the IDDSI extremely-thick liquid category requires supplementary spoon tilt and fork drip tests as per IDDSI guidelines. It is acknowledged that these supplementary tests are subjective and do not permit precise matching of flow characteristics across liquids within this level.

In some cases, the recipes in this study produced flow test results that fell close to the boundaries of the IDDSI levels. For example, in figure 4.1b 1.0g/100ml of xanthan-gum thickener added to water produced a liquid with an average flow test result of 4.5 ml, just above the lower boundary of the IDDSI mildly thick range. In such cases, our data show that small changes in thickener concentration can shift the liquid closer to the center of the target IDDSI range. In the example cited, the addition of 0.3g of xanthan gum (1.3g/100ml) moved the flow test result to the middle of the mildly thick range at 6.1 ml. Until clearer evidence regarding the clinical significance of small differences in liquid flow is available we recommend that clinicians target flow test results closer to the middle of each IDDSI range.

The reconstitution of barium sulfate powders with water and thickening agents is a widespread but off-label practice that has arisen due to restricted access to pre-thickened barium products outside the United States. The variations in flow that were seen across small differences in thickener concentration in this study underscore the need to follow recipes when preparing barium for videofluoroscopy. Clinicians should not assume that addition of the same amount of thickener to a non-barium liquid and a barium suspension will result in liquids with similar flow. For example, in Figure 4.1b 1.0g/100ml of xanthan-gum thickener added to water resulted in an average flow test result of 4.4 ml at the one hour timepoint post mixing; by contrast, figure 4.1d shows that the same amount of xanthan-gum thickener (1.0g/100ml) in a 20% w/v barium suspension resulted in a thicker liquid with a flow test result of 5.7ml. Despite this difference, both of these results fall in the IDDSI mildly-thick range; it is not yet known whether a flow difference of this magnitude has clinical significance. However, more dramatic differences are seen with the starch based thickener. As seen in Figure 4.1a, 5g/100ml of starch-based thickener in water yields a mildly thick liquid with a flow test result of 4.9ml. However, a similar amount of the same thickener (figure 4.1c; 5.1g/100ml) added to a 20% w/v barium suspension resulted
in a moderately thick liquid with a flow test result of 9.3 ml. These examples are consistent with previous literature [21-23] showing that the combination of barium and thickening agents may alter multiple rheological parameters, and specifically may lead to further thickening. Additionally, it must be emphasized that the barium stimuli in this study were prepared in a low concentration (20% w/v); one might expect that the addition of thickener to higher concentrations of barium may lead to even greater thickening. The reader should be cautioned that the interactions illustrated in this study are likely to be specific to the particular brands of barium suspension and/or thickener studied, based on their composition, and the patterns seen cannot be generalized to other products.

When comparing room temperature liquids to liquids that were chilled, we found very few differences in flow. All of the barium-based recipes yielded stable IDDSI flow test results over time, up to 3 hours. The addition of refrigeration as a variable had very little impact. As seen in figure 4.2a), only one barium-thickened liquid recipe (3.3g/100ml starch) showed temperature-related thickening which crossed the boundary from slightly- to mildly-thick for the chilled product.

### 4.8 Limitations

This study is not without limitations. The thickeners tested are limited to two particular products, mixed with a single commercially available barium sulfate suspension. The results may not be generalizable to other products. Furthermore, these products were reconstituted with commercially available bottled waters. In clinical practice, off-label use of barium may involve reconstitution with other liquids, such as infant formula or breastmilk [24, 25]. Clinicians should be cautioned that the kinds of interactions seen between thickeners and barium in the current study may also occur when thickeners or barium are added to other liquids, based on the protein or macronutrient composition of the liquid [16]. In such cases, the IDDSI flow test provides a means of checking flow and confirming similarity between the barium and non-barium product.

### 4.9 Conclusions

A practical goal of this study was to determine recipes for matched non-barium and barium stimuli, which would fall clearly within the slightly to moderately-thick levels of the IDDSI
framework and remain in those levels over a 3 hour time frame post mixing at room temperature. This goal was achieved. As a rule, the combination of barium powder and thickener led to additional thickening compared to thickened liquids prepared without barium. Adjustments to the thickener amounts were required to correct for this interaction, particularly when using starch-based thickeners.

4.10 References


Chapter 5

5 Determining the Impact of Thickened Liquids on Swallowing Safety and Efficiency in Irradiated Oropharynx Cancer Patients

5.1 Preface

In previous chapters, we have identified gaps in knowledge regarding the efficacy of thickened liquids for managing dysphagia and aspiration in head and neck cancer patients after radiation. A major limitation of the existing literature is the fact that the thickened liquids used in previous studies involving HNC patients were exceedingly thick (i.e. pudding-thick liquids or paste barium). In order to properly understand the impact of thickened liquids on swallowing in patients with head and neck cancer, we created recipes for slightly thick, mildly thick and moderately thick liquids. As described in the previous chapter, we were able to develop arrays of both barium and non-barium stimuli with matched flow, demonstrated using the IDDSI Flow Test and with stability across time.

The study in this chapter begins by documenting the incidence of penetration-aspiration on thin liquids in a group of 12 oropharynx cancer patients and subsequently explores the role of slightly and mildly thick liquids to ameliorate impaired swallowing safety. Additionally, we explore the incidence of post-swallow residue with these stimuli in this population and explore the impact of pharyngeal constriction on swallow efficiency.

This work is part of a larger study in the Swallowing Rehabilitation Research Laboratory (Toronto Rehabilitation Institute—University Health Network, Toronto, ON) exploring differences in swallowing function and physiology across the range from thin to extremely thick liquids in different populations. Funding for this project is supported by the National Institute of Deafness & Other Communication Disorders (5R01DC011020), as well as doctoral funding from the University of Toronto and Toronto Rehabilitation Institute.
5.2 Abstract

Due to an increase in the prevalence of oropharyngeal cancers, a growing number of individuals are receiving radiation treatment to the head and neck region. Treatments for head and neck cancers (HNC) can be curative but patients are often left with impaired swallowing. Thickened liquids are a common intervention for patients with neurogenic dysphagia. However, we lack evidence to guide the modification of liquid textures for clinical benefit in the HNC population. The objective of this study was to assess the efficacy of thickened liquids for improving swallowing safety in patients with oropharyngeal cancers who display penetration-aspiration on thin liquid and to quantify the amount of post-swallow residue present with thickened liquids in this patient population. Twelve patients with oropharyngeal cancer underwent videofluoroscopic swallow examination 3-6 months after completion of radiotherapy. Participants swallowed 3 thin liquid barium boluses; for those who demonstrated penetration-aspiration, slightly and mildly thick liquids were tested. The results showed significantly fewer instances of penetration-aspiration with both the slightly and mildly thick liquids compared to thin. However, greater residue was seen with mildly-thick liquids suggesting that the optimal consistency for balancing swallowing safety and efficiency in these participants was the slightly thick level.
5.3 Introduction

Head and neck cancer (HNC) diagnoses are becoming more prevalent with 550,000 new cases annually worldwide, and approximately 380,000 deaths yearly (Fitzmaurice, 2017). The majority of head and neck cancers stem from alcohol and tobacco use or the Human Papillomavirus (HPV). Estimations of global incidence differ by cancer site. Lip and oral cavity cancers impact over 400,000 patients while cancers of the pharynx are diagnosed in approximately 160,000 people annually. Cancers of the larynx and nasopharynx are also prevalent, with anywhere from 100,000-200,000 new cases yearly (Global Burden of Disease Cancer, 2017). Traditional treatment approaches for cancers focal to the head and neck include surgery and/or radiation treatment (RT). Unfortunately, the tissue-altering effects of RT can lead to both acute and chronic toxicities. These include xerostomia, mucositis, odynophagia (painful swallowing) and edema (swelling), fibrosis of important musculature and neuropathy, all of which have deleterious effect on a person’s ability to eat by mouth and on their quality of life (Dische et al., 1997; Lazarus et al., 2014).

Both the acute and chronic sequelae of radiation contribute to functional impairments of swallowing safety (penetration-aspiration, i.e., food/liquid entering the airway) and efficiency (residue accumulation in the pharynx). Radiation to specific anatomical areas (i.e. so-called “dysphagia-aspiration related structures” or DARS) has been associated with a greater risk of dysphagia and aspiration (Eisbruch et al., 2004). The DARS structures include the pharyngeal constrictor muscles, base of tongue and the larynx. Despite advances in the ability to focus the radiation in order to limit collateral damage to adjacent healthy tissues and structures, the radiation field for cancers of the head and neck commonly includes the DARS structures. Radiation to the pharynx is thought to result both in early effects (i.e., within the first 3 months) of mucositis, edema, inflammation, and xerostomia due to involvement of mucosa and salivary glands and also late effects (i.e., after 6 months) including fibrosis of the muscles, changes to the neuromuscular unit and nerve damage (King, Dunlap, Tennant and Pitts, 2016). The degree to which reported changes in swallowing function arise from mechanisms of tissue stiffness or inflammation, motor (i.e. muscle) damage or sensory (i.e. nerve) damage remains unclear.
Maintenance of swallowing activity throughout the acute stage post-RT (i.e. 0-12 weeks post treatment; King et al., 2016) is thought to be critical to avoid a decline of swallow function. Patients are strongly encouraged to continue eating and drinking during this phase, despite the fact that little is known about the safety or efficiency of their swallowing. Aspiration of food or liquid into the airway can be a serious event and may occur without overt clinical signs (“silent aspiration”) in individuals with impairments focal to sensory nerve receptors. Silent aspiration is frequent in patients who have undergone chemoradiotherapy and is frequently under-recognized (Nguyen et al., 2004; Pauloski et al., 2002; Wu, Hsiao, Ko, & Hsu, 2000). Aspiration in the 3-6 month timeframe after RT has been reported in several studies (Eisbruch et al., 2004; Graner et al., 2003; Lazarus et al., 1996). In one study, aspiration was reported to occur in 59% of HNC patients who underwent concurrent chemotherapy and RT, with 9% of those patients dying and the cause of death attributed to aspiration pneumonia (Nguyen et al., 2006). In a second study, Nguyen and colleagues reported acute toxicities in 45/55 patients including the development of aspiration pneumonia in 3 patients, with two of those patients dying (Nguyen et al., 2004). A third investigation of 213 patients who underwent radiation concurrent with intra-arterial high-dose cisplatin found similar results, with three cases of death from pneumonia and two of those cases attributed to aspiration (Robbins et al., 2000). These studies show that impaired swallowing safety is both common and associated with a risk of death in HNC patients (Denaro, Merlano, & Russi, 2013; Eisbruch et al., 2002; Hunter et al., 2014; Madan et al., 2015; Mortensen, Jensen, Aks oglaede, Behrens, & Grau, 2013; Nguyen et al., 2004; Xu et al., 2015).

Aspiration risk is generally highest with thin liquids. When a patient presents with impaired swallowing safety, a common clinical intervention is to alter the consistency of the fluids they consume. Thicker liquids are intended to flow more slowly and reduce the risk of airway invasion. Two recent systematic reviews have concluded that thickening liquids reduces the risk of aspiration (Newman, Vilardell, Clave, & Speyer, 2016; Steele et al., 2015), however, the amount of thickening required to achieve therapeutic benefit remains unclear. Furthermore, despite widespread use of thickened liquids to remediate aspiration in patients with neurogenic etiologies of dysphagia, we lack evidence demonstrating the effect of texture modification as an intervention in the head and neck cancer population (Barbon & Steele, 2014).
Historically, degrees of thickening have been defined based on target ranges of apparent viscosity measured at a shear rate of 50 reciprocal seconds. There are a variety of methods available for flow measurement of the liquids used in dysphagia management (see Appendix p. 158-166). The National Dysphagia Diet (2002) defined three levels of thickened liquid: nectar-thick (50-150 mPa.s), honey-thick (151-350 mPa.s) and spoon-thick or pudding thick (351-1750 mPa.s). In 2017, a new framework of terminology and definitions for thickened liquids was published by the International Dysphagia Diet Standardisation Initiative (IDDSI; Cichero et al., 2017). The IDDSI framework defines four levels of thickening, based on height of the residual fluid column after 10 seconds of flow through a standard 10 ml slip tip syringe: slightly, mildly, moderately and extremely thick (Barbon & Steele, 2018a, 2018b; Cichero et al., 2017; Hanson, 2016). See Appendix p. 158-166 for a discussion related to viscosity and flow using a variety of testing methods. As discussed in Chapter 3, previous studies of the use of thickened liquids in the HNC population have focused on extremely thick paste or pureed stimuli. Despite effectiveness in reducing aspiration, increased post-swallow residue has been reported as a negative outcome with very thick liquids, both in healthy adults and in patients with dysphagia, including those with HNC (Feng et al., 2007; Gillespie, 2004; Hind, 2012; Lazarus et al., 1996; Meyer, Pisegna, Krischiunas, Pauloski, & Langmore, 2017; Pearson Jr, Davidoff, Smith, Adams, & Langmore, 2016; Vilar dell, Rofes, Arreola, Speyer, & Clave, 2016). Given these concerns with excessively thick liquids, we were interested to explore the therapeutic effectiveness of slightly and mildly thick liquids for ameliorating swallowing safety concerns without exacerbating impaired swallowing efficiency. In particular, the new slightly thick level of the IDDSI framework was of interest, given that readily available smoothies and yogurt drinks are likely to fall within this level without the need for added thickening agents.

The objective of the current study was to assess the efficacy of thickened liquids in the slightly and mildly thick range of the IDDSI framework for improving swallow safety and to determine how they impact the efficiency of the swallow. The study differs from others conducted with the HNC population because of the target population. Study populations in HNC research have traditionally been heterogeneous, with a mix of either tumor locations or treatment methods (surgical vs. chemoradiotherapy). We aimed to recruit a homogeneous sample of HNC patients
with oropharyngeal tumor locations and primary radiotherapy as their treatment. Our hypotheses were:

Hypothesis 1: Thickened liquids will be effective for reducing the frequency of penetration-aspiration in participants who present with penetration-aspiration on thin liquids, with increased effectiveness expected for mildly thick compared to slightly thick liquids.

Hypothesis 2: Thickened liquids will lead to greater post-swallow residue in the pharynx compared to thin liquids; mildly thick liquids are expected to cause more post-swallow residue than slightly thick.

5.4 Methods

The study was conducted in the radiation therapy clinic at a major academic cancer hospital. The target study population was defined as individuals with a primary diagnosis of oropharyngeal cancer (base of tongue, tonsils, or soft palate), with tumor staging not greater than T3, nodal staging not greater than N2c and either positive or negative HPV status. Eligible participants were required to have undergone bilateral radiation therapy (with or without chemotherapy) and to be within the 3-6 month timeframe post radiation therapy at the start of the study. Exclusion criteria are listed in Table 5.1. In total, 760 charts were screened for eligibility over a 12-month time frame. Twelve men (\(\bar{x} = 63.3\) years, range 49 – 78 years) consented to participate (see Table 5.2 for participant demographics). Approximately 50-75 patients were approached for study participation. Among the remaining individuals who were screened for eligibility, many patients self-excluded based on travel distance and scheduling constraints. Other individuals lacked interest and reported a lack of concern regarding their swallow function.
Table 5.1. Exclusion criteria for all participants in the study

1. Previous health conditions known to cause swallowing impairment;
2. Previous extensive radiation to the head/neck area (e.g., multiple CT scans prior to cancer diagnosis);
3. History of neck dissection;
4. Feeding tube and/or tracheostomy tube in situ;
5. Safe swallowing (≤ 2 PAS);
6. Patients with cognitive communication difficulties that contribute to understanding of the protocol or study instructions;
7. Individuals with known latex allergies, dental glue or barium were excluded, due to the risk of contact with these substances during data collection;
8. Participants who reported having Type 1 Diabetes were excluded from the study, because of the requirement to swallow stimuli carrying a significant carbohydrate load (starch-based thickeners);
9. Pregnant women and those under the age of 18.
Table 5.2. Study participant demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Stage</th>
<th>Total dose delivered to primary, cGy</th>
<th>Chemotherapy Drug</th>
<th>HPV status</th>
<th>Days Between RT and VFSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>Male</td>
<td>BOT</td>
<td>T2, N2b</td>
<td>5200</td>
<td>NA</td>
<td>+</td>
<td>105</td>
</tr>
<tr>
<td>67</td>
<td>Male</td>
<td>BOT</td>
<td>T3, N2b</td>
<td>7000</td>
<td>Cisplatin</td>
<td>-</td>
<td>111</td>
</tr>
<tr>
<td>66</td>
<td>Male</td>
<td>BOT</td>
<td>T2, N2b</td>
<td>7000</td>
<td>Cisplatin</td>
<td>+</td>
<td>113</td>
</tr>
<tr>
<td>61</td>
<td>Male</td>
<td>BOT</td>
<td>T3, N2b</td>
<td>7000</td>
<td>Cisplatin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
<td>113</td>
</tr>
<tr>
<td>58</td>
<td>Male</td>
<td>Oropharynx</td>
<td>T0, N2b</td>
<td>7000</td>
<td>Cisplatin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
<td>151</td>
</tr>
<tr>
<td>49</td>
<td>Male</td>
<td>Soft Palate</td>
<td>T3, N2b</td>
<td>7000</td>
<td>Cisplatin</td>
<td>-</td>
<td>140</td>
</tr>
<tr>
<td>77</td>
<td>Male</td>
<td>Soft Palate</td>
<td>T1, N0</td>
<td>6000</td>
<td>NA</td>
<td>-</td>
<td>134</td>
</tr>
<tr>
<td>61</td>
<td>Male</td>
<td>R Tonsil</td>
<td>T2, N1</td>
<td>7000</td>
<td>NA</td>
<td>+</td>
<td>92</td>
</tr>
<tr>
<td>75</td>
<td>Male</td>
<td>BOT</td>
<td>T1, N2b</td>
<td>7000</td>
<td>NA</td>
<td>+</td>
<td>89</td>
</tr>
<tr>
<td>58</td>
<td>Male</td>
<td>R Tonsil/BOT</td>
<td>T2, N2c</td>
<td>7000</td>
<td>Cetuximab&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
<td>111</td>
</tr>
<tr>
<td>60</td>
<td>Male</td>
<td>L Tonsil</td>
<td>T1, N2b</td>
<td>7000</td>
<td>Cisplatin (high dose)</td>
<td>+</td>
<td>135</td>
</tr>
<tr>
<td>51</td>
<td>Male</td>
<td>BOT</td>
<td>T3, N2b</td>
<td>7000</td>
<td>Cisplatin</td>
<td>+</td>
<td>203</td>
</tr>
</tbody>
</table>

<sup>a</sup>Full chemotherapy protocol not completed.

*Note. BOT = base of tongue.*
All participants underwent a videofluoroscopic swallowing study (VFSS) as part of data collection. Additionally, measures of saliva, maximum isometric tongue pressure and swallow pressures were collected but will not be discussed in this chapter.

5.4.1 Videofluoroscopy Protocol

The videofluoroscopy was performed at a temporal resolution of 30 pulses/second and captured on the KayPENTAX Digital Swallow Workstation at 30 frames/second. Participants were asked to swallow thin, slightly thick and mildly thick liquid barium stimuli (Bracco E-Z-Paque® barium with Nestlé PureLife bottled water, prepared in a 20% w/v concentration). Thickened liquids were prepared using two different thickeners: Nestlé ThickenUp® (starch) and Nestlé ThickenUp® Clear® (xanthan-gum). Recipes can be found in a previous manuscript (Barbon & Steele, 2018a). Each participant was provided with a tray containing cups of liquid barium, each filled with 40 ml of liquid. Participants were instructed to take a single, naturally-sized sip from each cup. Pre- and post-sip cup weights were taken using an OHAUS digital balance (model number PA1502 analytical scale: capacity: 1.5kg; readability 0.01g) to calculate sip size for each bolus. Participants were asked to swallow up to 3 boluses of each stimulus, for a total of 15 possible bolus trials (see Figure 5.1 for protocol and Chapter 4 for stimulus development). Additionally, participants who completed all 3 thin boluses without any apparent safety concerns were asked to complete a 4th consecutive cup drinking trial from a cup containing ~200 ml of thin liquid barium. If participants did not demonstrate penetration-aspiration on any of the thin liquid trials, the VFSS study was terminated. When the attending clinician noted penetration or aspiration (i.e. Penetration-Aspiration Scale Score, PAS, ≥ 3) on a given consistency, further trials of that consistency were discontinued and the protocol continued with the next level of liquid thickness. Additionally, for safety reasons, the protocol was terminated after the fourth observation of penetration-aspiration overall (PAS score of ≥3; see Figure 5.1).
Figure 5.1. Full VFSS protocol including stopping rules

- Consent
- Prepare stimuli for data collection
- With participant seated in the VFSS suite
- Saxon Test (of Saliva Weight)
- Collect thin barium sips
- Participant to take a comfortable sip and swallow
- Did this thin sip have a PAS of 3 or higher?
  - YES
    - END thin barium sips, proceed to thickened liquids
  - NO
    - Was this the third thin sip?
      - YES
        - Sequential sips thin
        - PAS of 3 or higher?
          - YES
            - END PROTOCOL
          - NO
      - NO

Collect slightly thick barium sip with thickener 1

Participant to take a comfortable sip and swallow

Did this sip have a PAS of 3 or higher? NO

Was this the 3rd slightly thick sip, thickener 1? NO

Collect slightly thick barium sip with thickener 2

Did this sip have a PAS of 3 or higher? NO

Continue with slightly thick barium sips

YES

YES

END slightly thick liquid barium sips
Collect mildly thick barium sip with thickener 1

Participant to take a comfortable sip and swallow

Did this sip have a PAS of 3 or higher?

YES

Collect mildly thick barium sip with thickener 2

NO

Was this the 3rd mildly thick sip, thickener 1?

YES

Continue with mildly thick barium sips

NO

Did this sip have a PAS of 3 or higher?

YES

END mildly thick liquid barium sips

END PROTOCOL
5.4.2 Videofluoroscopy Rating

The videofluoroscopy recordings were rated using ImageJ software (National Institutes of Health, Bethesda, MD) according to a standard operating procedure known as the ASPEKT Method (Analysis of Swallowing Physiology: Events, Kinematics and Timing; Steele et al., 2018; Waito, Steele, Peladeau-Pigeon, Genge, & Argov, 2018; see Appendix p. 167-180). Each recording was first spliced into shorter bolus-level clips, which were randomly assigned to two trained raters for independent duplicate rating. Measures of swallow safety were recorded based on the worst score achieved on the Penetration-Aspiration Scale (PAS; Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996) for each bolus. Pharyngeal area for measures of swallow efficiency was traced on the frames of maximum pharyngeal constriction and swallow rest relative to the squared length of each individual’s C2-C4 anatomical reference scalar (Molfenter & Steele, 2014). In addition, pixel-based tracings of residue in the vallecular, pyriform sinuses and elsewhere in the pharynx were performed on the frame of swallow rest. All pixel-based tracings of residue were calculated relative to the squared length of the individual’s C2-C4 anatomical scalar. An example of pixel-based tracings can be found in Figure 5.2. See Appendix p 174-180 for standard operating procedures and operational definitions of the ASPEKT method.

Figure 5.2. Image of pixel-based tracings of post-swallow residue

Note. Image a) yellow areas are residue tracings, while white tracings denote the housing of the valleculae and pyriform sinuses. b) depicts extra pharyngeal residue traced in yellow. The squared C2-C4 reference area is denoted by green hatched lines.
5.5 Analysis

For the determination of swallowing safety, the worst PAS score across all sub-swallows was tallied for each bolus and converted to a binary rating of safe vs. at-risk (i.e., PAS scores < vs ≥ 3; see Table 5.3). The frequency of boluses that were identified to be at-risk were then tallied for each participant by consistency. Initial inspection of the swallow safety ratings showed no differences in the frequency of at-risk swallows by thickener type (i.e. starch vs gum) for the slightly and mildly thick liquids. Given the small sample size and limited number of data points, the decision was made to pool swallow safety ratings across thickeners within consistency for each participant.

Similarly, initial data inspection suggested that there was no pattern with respect to residue presence or severity according to thickener type. Residue values were therefore pooled across thickener within each IDDSI level and the participant’s worst total residue score for each consistency was calculated for use in the efficiency analysis. One outlier was detected in the residue data, and was removed and replaced with the participants’ second-worst residue score. The data were normally distributed, as assessed by Shapiro-Wilk’s test (p > .05). The assumption of sphericity was also met, as assessed by Mauchly’s test of sphericity χ2 (2)=3.519, p = .172.

Statistical analyses were performed in SPSS version 24. A Friedman test was carried out to determine if there were differences in the frequency (i.e. percent occurrence) of ≥ 3 PAS events by IDDSI level (0 – thin, 1 – slightly thick, 2 – mildly thick) for participants with at-risk swallows on thin liquids who were subsequently provided with thickened liquids (n = 6) as per the study protocol. A one way repeated-measures ANOVA was conducted to determine whether there were any differences in residue severity according to bolus consistency.

5.6 Results

Table 5.3 displays data regarding the frequency of at-risk swallows. Of the 12 participants in the study, 6 (i.e. 50%) participants were identified to have at-risk swallows on thin liquids during the procedure and these individuals continued on to the thickened liquid portion of the protocol. Subsequent blinded rating identified a further 3 participants for whom the PAS scores for thin
liquid were ≥ 3; however, because these events were not detected during the videofluoroscopy, these participants were not recognized to have impaired swallowing safety and did not proceed to the thickened liquid trials.

The frequency of at-risk swallows was significantly different between IDDSI levels, $\chi^2(2) = 8.667$, $p < 0.005$. Post hoc analysis revealed significantly fewer at-risk swallows ($p < 0.05$) with slightly thick liquids (Mdn = 17%) compared to thin (Mdn= 100%) and for mildly thick liquids (Mdn=16.5%, $p < .05$) compared to thin (Mdn = 100%). There was no significant difference in the frequency of at-risk swallows between slightly thick and mildly thick liquids (see Table 5.3).

Table 5.3. Frequency of at-risk swallows by consistency in study participants

<table>
<thead>
<tr>
<th>Participant</th>
<th>Frequency of unsafe swallows: thin (%)</th>
<th>Frequency of unsafe swallows: slightly (%)</th>
<th>Frequency of unsafe swallows: mildly (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note.* Blanks = liquid consistency not tested.

Details of residue severity for each participant are summarized by IDDSI level as well as residue location in Tables 5.4 and 5.5. Statistically significant increases in residue were seen with thicker liquids compared to thin, $F(2, 10) = 8.929$, $p < .05$. Post hoc analysis of pairwise contrasts with a Bonferroni adjustment revealed a statistically significant difference in residue for thin vs. mildly thick liquids, with a mean difference of 2% of the C2-C4$^2$ reference scalar, squared (95% CI, 0.4% to 3.2%), $p < .025$, and a medium effect size, Cohen’s $d = .612$. 
Table 5.4. Descriptive statistics for worst residue by consistency

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement approach</th>
<th>IDDSI Level</th>
<th>Mean</th>
<th>SD</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total residue (all pharyngeal areas combined)</td>
<td>% of squared C2-C4 reference area</td>
<td>Thin</td>
<td>2.45</td>
<td>2.71</td>
<td>-0.40</td>
<td>5.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slightly</td>
<td>3.33</td>
<td>2.80</td>
<td>0.40</td>
<td>6.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mildly</td>
<td>4.22</td>
<td>3.05</td>
<td>1.01</td>
<td>7.42</td>
</tr>
</tbody>
</table>

Table 5.5. Presence of post-swallow residue by location

<table>
<thead>
<tr>
<th>Participant</th>
<th>IDDSI level</th>
<th>Total Residue (%C2-C4)</th>
<th>Vallecular Residue (%C2-C4)</th>
<th>Pyriform Residue (%C2-C4)</th>
<th>Extra Residue (%C2-C4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.60</td>
<td>0.58</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4.00</td>
<td>1.11</td>
<td>1.01</td>
<td>1.48</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>4.60</td>
<td>3.33</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.90</td>
<td>3.47</td>
<td>0.63</td>
<td>1.75</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>3.10</td>
<td>0.78</td>
<td>1.90</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1.40</td>
<td>0.57</td>
<td>0.00</td>
<td>0.86</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3.70</td>
<td>1.41</td>
<td>0.07</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.40</td>
<td>2.75</td>
<td>0.00</td>
<td>1.14</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>14.40</td>
<td>14.40</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.80</td>
<td>0.00</td>
<td>0.00</td>
<td>0.81</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0.20</td>
<td>0.19</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>7.30</td>
<td>2.79</td>
<td>4.48</td>
<td>2.82</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>8.00</td>
<td>3.46</td>
<td>0.00</td>
<td>4.47</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>9.00</td>
<td>3.49</td>
<td>0.00</td>
<td>5.47</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.90</td>
<td>0.87</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>2.40</td>
<td>2.42</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.20</td>
<td>2.54</td>
<td>0.00</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.30</td>
<td>0.00</td>
<td>0.26</td>
<td>0.00</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>1.10</td>
<td>0.47</td>
<td>0.67</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.80</td>
<td>2.61</td>
<td>0.15</td>
<td>0.00</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>2.40</td>
<td>1.03</td>
<td>0.66</td>
<td>0.00</td>
</tr>
</tbody>
</table>
5.7 Discussion

This study explored the efficacy of thickened liquids for improving swallowing safety in a homogeneous sample of HNC patients who presented with at-risk swallowing on thin liquids. Our investigations confirm that impaired swallow safety is a concern among patients in the subacute phase post-radiation, evidenced by the fact that the majority of participants demonstrated penetration-aspiration on thin liquids (9/12, 75%; see Table 5.3). The high prevalence of penetration-aspiration among the participants in this study is consistent with the findings reported in previous studies conducted in the subacute timeframe (Eisbruch et al., 2002; Graner et al., 2003; Lazarus et al., 1996). The subacute stage is a time when patients frequently use liquid nutritional supplements to maintain their nutritional status and also drink large amounts of water to manage mucositis and xerostomia. The fact that penetration-aspiration occurs frequently with thin liquids in this population raises concerns about the risks associated with the dietary habits seen in the subacute stage. The fact that sensory deficits may obscure clinical signs and patient symptoms of aspiration is an increased reason for concern (see table 5.2 for days elapsed between end of RT and VFSS; Murphy & Gilbert, 2009; Rosenthal, Lewin, & Eisbruch, 2006). Our findings show that penetration-aspiration can be reduced using slightly thick liquids in this patient group. Previous studies have explored aspiration reduction with extremely thick liquids, which are reported to be disliked by the majority of patients. The option to achieve safe swallowing with minimal thickening is exciting.

Regarding the presence and amount of residue (3.1%-5.9% of the C2-C4 scalar reference area), the data demonstrate increased residue with mildly thick liquids (see Table 5.4 and 5.6). Given that there was no significant increase in residue with slightly thick liquids compared to thin, our findings suggest that slightly thick may be the optimal consistency for improving swallowing safety without compromising efficiency in HNC patients. Previous studies provide limited data regarding the severity of residue in this patient population based on liquid consistency. Our method calculated total residue, summing scores from the valleculae, pyriform sinuses and other pharyngeal locations, each measured as a percentage of the C2-C4 scalar reference area. It is noteworthy that ten out of twelve participants (83%) had residue on thin liquids. Of the individuals who continued on to the thicker liquids portion of the protocol, half displayed residue on at least one thickened liquid consistency; see Table 5.5. Of course, it is unknown whether the
participants with residue on thin stimuli who did not continue onto the thicker stimuli would also have shown residue on thickened liquids. Participants who displayed post-swallow residue in other pharyngeal locations tended to present with larger volumes of post-swallow residue in the valleculae and pyriform sinuses. Residue measured in the extra pharyngeal space occurred for all liquid consistencies. Despite a lack of emerging patterns of residue location, it is important to note that thickener-types varied, as the participants’ worst residue scores were used for analysis. Thickener-type and IDDSI level may impact the presence of post-swallow residue due to the liquid characteristics when in contact with radiated mucosa. Larger patient cohorts are required in order to analyze thickener-type and consistency level as they relate to the presence of post-swallow residue.

Table 5.6. Worst residue scores by participant for all IDDSI levels tested

<table>
<thead>
<tr>
<th>Participant</th>
<th>Residue Thin (%)</th>
<th>Residue Slightly Thick (%)</th>
<th>Residue Mildly Thick (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>4.6</td>
<td>5.9</td>
</tr>
<tr>
<td>3</td>
<td>3.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.4</td>
<td>3.7</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>14.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>0.8</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>9</td>
<td>7.3</td>
<td>8.0</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>0.9</td>
<td>2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>11</td>
<td>0.3</td>
<td>1.1</td>
<td>2.8</td>
</tr>
<tr>
<td>12</td>
<td>2.4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note.* Residue amounts are measured as a percentage of the squared C2-C4² reference area. Blanks = liquid not tested.

It is important to determine the mechanisms behind at-risk swallows in this patient population to better understand the impairment and potential treatments. Delayed or incomplete LVC has been identified as a primary contributing factor to penetration and aspiration in a systematic review (Steele et al., 2015). Logemann and colleagues described delayed laryngeal vestibular closure (LVC) in HNC patients at the 3 month post-radiation time point (Logemann et al., 2008). Thickened liquids are likely to allow for additional time in which to achieve laryngeal vestibule
closure. Furthermore, recent data from our lab also suggest that the time interval between the onset of the hyoid burst and achieving LVC (so-called Laryngeal Vestibule Closure Reaction Time) may be accelerated with thicker liquids (Steele et al., 2018). Further investigation into the timing and completeness of laryngeal vestibular closure across different liquid consistencies in HNC patients is warranted and will be explored in Chapter 6 (with thin liquids).

In addition to determining the mechanisms of impaired safety in the HNC swallow, it is important to determine the mechanisms that contribute to residue. As demonstrated in Table 5.6, residue was present for all liquid types. Recent data from our lab have identified minimal residue in healthy patients after drinking thin liquids. Furthermore, the study identified a small increase in the frequency of residue in healthy adults (with an upper boundary of 1% of C2-C42) when swallowing slightly and mildly thickened liquids (Steele et al., 2018). Despite these findings, the overall presence of residue for healthy swallows has been described as <1% of the C2-C42 area. The data presented in this particular study demonstrate an overall presence of residue for head and neck cancer patients, regardless of liquid consistency. Our data have demonstrated a considerable presence of post-swallow residue on thin liquids alone that cross the threshold of <1% of residue as seen in healthy patients. This finding was unexpected and suggests that mechanisms contributing to residue with thin liquid need to be further explored. Along with the benefit of improved safety that is offered through the use of thickened liquids, it is also important to be cognizant of the accumulation of post-swallow residue that results with thicker liquids.

5.8 Limitations

This study is not without limitations. The sample size is limited due to the heterogeneity of the population from which we recruited. The requirement that impaired safety be identified during videofluoroscopy on thin liquids prior to continuing to thicker consistencies resulted in limited available data for thickened liquids. As reported above, several instances of at-risk thin liquid swallowing were missed by the clinicians present during the videofluoroscopy session and only detected during post-exam blinded review.
5.9 Conclusions

In our study, we have investigated the impact that thickened liquids have on patients with oropharynx cancers who experience penetration-aspiration on thin liquids. More specifically, the data illustrate that thickened liquids can be an effective intervention for some individuals who are experiencing dysphagia post-radiation. Individuals in our study who had at-risk swallows characterized by a PAS of ≥3 on thin liquids benefitted from the implementation of thickened liquids. Our data support the consideration of thickened liquids as a potential benefit during VFSS examinations for HNC patients. Specifically, the swallow at the 3-6 month timeframe post-RT has demonstrated a positive response to some degree of thickening. Slightly thick liquids are the first consistency to implement, as many naturally thick liquids may fall into this flow level. Mildly thick liquids may be an alternative consideration for patients who do not benefit from slightly thick liquids. However, it is important for clinicians be aware that increased residue may occur with the use of mildly thick liquids. Further research is recommended regarding the mechanisms behind impaired swallowing safety and efficiency in HNC patients.

5.10 References


Chapter 6

6 Preliminary Analysis of Timing and Kinematics Related to Dysphagia in Patients with Oropharyngeal Cancer

6.1 Preface

We have identified the benefit of slightly and mildly thick liquids in patients who penetrate-aspirate on thin liquids in our HNC cohort. Specifically, slightly thick liquids demonstrate a particular benefit for those who aspirate on thin liquids. In order to understand our results found in chapter 5, we determined that it was necessary to delve into the pathophysiology of the swallow.

The study in this chapter further explores the mechanisms behind impaired swallowing safety and efficiency, which we identified in the previous chapter. We investigate the potential mechanisms associated with swallow safety including laryngeal vestibule closure integrity in addition to a variety of swallow timing parameters. Moreover, we explore the incidence of post-swallow residue on thin liquids in this population and explore the impact of pharyngeal constriction, pharyngeal area at rest, and UES width/opening durations on swallow efficiency.

Again, this work is part of a larger study in the Swallowing Rehabilitation Research Laboratory (Toronto Rehabilitation Institute—University Health Network, Toronto, ON) exploring differences in swallowing function and physiology across the range from thin to extremely thick liquids in different populations. Funding for this project is supported by the National Institute of Deafness & Other Communication Disorders (5R01DC011020), as well as doctoral funding from the University of Toronto and Toronto Rehabilitation Institute.
6.2 Abstract

Dysphagia is one of the most debilitating chronic symptoms experienced by individuals with head and neck cancers after undergoing curative treatments. Despite the prevalence of dysphagia in patients undergoing treatment for head and neck cancer (HNC), we lack understanding of the distinct changes in swallowing physiology associated with various treatments, such as radiation, and how these changes impact swallowing safety. This study sought to describe the pathophysiology of dysphagia in a small sample of 12 post-radiation oropharynx cancer patients compared to data from 12 healthy controls. Participants swallowed up to 4 boluses each of 20% w/v thin liquid barium under videofluoroscopy (VFSS). The VFSS recordings were rated for safety, efficiency, timing parameters and pixel-based measures of structural area or movement. Analyses were conducted to identify differences in timing, pharyngeal areas, and residue between groups. We established relationships between penetration-aspiration and laryngeal vestibule closure integrity (complete vs. incomplete) and timing in the HNC participants. The HNC patients also had post-swallow residue above the healthy range (>1% of the C2-C4² space), and residue was found to be significantly correlated with reduced maximum constriction of the pharynx. These findings highlight primary mechanisms behind impaired safety and efficiency of the swallow in patients post-radiation for oropharyngeal cancer.
6.3 Introduction

6.3.1 Swallowing in Head and Neck Cancer

Radiation therapy (RT) has become a first line of treatment for individuals diagnosed with oropharyngeal carcinomas. Rather than have patients undergo surgery, radiation allows for preservation of the structure of muscles and tissues of the head and neck. Unfortunately, despite advances in radiation oncology, preservation of structure does not always equate to preservation of function. Recent studies have demonstrated an increased risk of dysphagia and aspiration when particular structures of the head and neck are exposed to large radiation doses. A seminal study by Eisbruch and colleagues highlighted several key anatomic structures that appear to be related to dysphagia and aspiration after intensive chemoradiotherapy, including the superior pharyngeal constrictor muscles and the glottic and supraglottic larynx (Eisbruch et al., 2004). Eisbruch named these structures the “dysphagia-aspiration related structures” (DARS) and argued for more targeted approaches for radiation therapy with the goal of sparing the DARS from damage (2004). Nevertheless, RT has become the preferred treatment approach for oropharyngeal cancer and radiation dose to structures that are critical for swallowing is unavoidable.

More recent investigations have explored the extent to which iatrogenic damage to specific structures appears to contribute to impaired swallowing function in patients with HNC. Surgical patients who have undergone resections involving the floor of mouth muscles (geniohyoid and mylohyoid, in particular) frequently experience aspiration (Starmer et al., 2014). Kumar and colleagues reported similar results in oropharynx cancer patients who had undergone chemoradiation (Kumar et al., 2014). Similarly, Feng and colleagues reported aspiration rates to be higher in patients with larger mean radiation doses to the pharyngeal constrictors and larynx (Feng et al., 2007). Starmer and colleagues concluded that the radiation dose to the floor of mouth and geniohyoid muscles caused damage that contributed to Penetration-Aspiration Scale (PAS; Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996) scores of 3 or higher in their patients, indicating entrance of material into the laryngeal vestibule or lower (Starmer et al., 2015). Eisbruch and colleagues described the following changes in swallowing post-RT: reduced contact between the base of tongue and the posterior pharyngeal wall, a reduction in laryngeal closure, and impairment in upper esophageal sphincter (UES) opening; they associated these
changes with high rates of aspiration and post-swallow residue in their patients (Eisbruch et al., 2002). This list of impairments is not exhaustive but highlights the need to measure swallowing physiology in patients who have undergone treatments for head and neck cancer. It is important to compare these measures to reference values from healthy adults in order to determine which pathophysiological mechanisms pose a threat to the safety and efficiency of the swallow.

The previous chapter’s findings detail the frequency of impaired swallowing safety and efficiency found in a small subset of head and neck cancer patients with oropharyngeal cancers. Specifically, at-risk swallowing involving PAS scores of 3 or higher was found in 75% of our participants on thin liquid barium. We also observed impaired swallowing efficiency on thin liquids in 50% of our participants, with residue filling > 1% of the C2-C4 reference area on thin liquids (see Chapter 5, Table 5.4). The purpose of the analysis in this chapter is to explore swallow timing and kinematics from videofluoroscopic analysis on thin liquid boluses in order to elucidate the mechanisms behind the impaired swallowing safety and efficiency displayed by our participants with oropharyngeal cancer.

6.3.2 Factors Related to Swallowing Safety

Airway protection during the swallow involves closure of the laryngeal vestibule (Logemann et al., 1992; Vose & Humbert, 2018), which provides a barrier to airway invasion. There are many variables that are involved in and impact laryngeal vestibule closure (LVC) including multiple kinematic events (i.e., elevation of the laryngeal complex, arytenoid adduction) and bolus characteristics, such as sip volume (Guedes et al., 2017; Logemann et al., 1992; Molfenter & Steele, 2011; Young, Macrae, Anderson, Taylor-Kamara, & Humbert, 2015). Kotz and colleagues observed impaired closure of the vestibule in HNC patients post-RT with 3 and 5 mL liquid boluses (Kotz, Costello, Li, & Posner, 2004). Although 70-75% of their participants were reported to display reductions in LVC, the manuscript was unclear whether this abnormality involved incomplete closure, late closure or closure of limited duration; detailed data describing penetration-aspiration and its relationship to LVC were not provided.

In addition to the structural integrity of LVC, studies also suggest that the timing of vestibule closure is related to the risk of penetration-aspiration (Rofes et al., 2010). The term laryngeal vestibule closure reaction time (LVCrt) has recently emerged in the literature as a parameter
capturing details of LVC timing, measured relative to earlier events such as glosso-palatal junction opening (Nativ-Zeltzer, Logemann, & Kahrilas, 2014; Rofes et al., 2010), bolus passing mandible (Humbert et al., 2018) or the onset of the hyoid burst movement (Guedes et al., 2017; Humbert et al., 2018; Steele, Peladeau-Pigeon, Barbon, Guida, Namasivayam-MacDonald, et al., 2018). A comparison study between three groups of male participants (Nativ-Zeltzer et al., 2014) found that patients who presented with penetration and aspiration had longer laryngeal vestibule closure reaction times than healthy controls. The authors queried a possible contribution of sensory impairment, which may be a consideration in HNC patients for whom silent aspiration is often present (Eisbruch et al., 2002). Although several studies concur that delays in laryngeal vestibule closure may be a factor contributing to penetration-aspiration in different patient groups, measures of swallow timing have been found to be highly variable across studies in healthy individuals (Molfenter & Steele, 2012). It is therefore important to investigate whether LVCrt differs in individuals with HNC (compared to healthy controls) and whether it is related to airway invasion.

Once laryngeal vestibule closure has been achieved, the duration of closure (LVCdur) is another parameter that may be related to aspiration risk In a review of swallowing timing measures, Molfenter and Steele reported a large range for LVCdur from 0.31-1.07 seconds for healthy individuals, reflecting considerable variability across studies (Molfenter & Steele, 2012). Part of the observed variation may be attributable to variation in bolus volumes tested across studies. In a subsequent study, Molfenter and Steele aimed to identify kinematic and temporal swallowing measures associated with penetration and aspiration (defined as PAS of ≥3 at the participant level) in a group of subacute patients with mixed etiologies of dysphagia (Molfenter & Steele, 2013). They defined LVCdur as the interval between the first frame of laryngeal closure and the first frame of laryngeal opening based on frame by frame VFSS ratings. Study findings demonstrated similar LVCdur values for individuals without penetration-aspiration (555 ms, 95% CI, 510-599) and those individuals presenting with penetration-aspiration (578 ms, 95% CI, 465-690). They noted that the convention of classifying data based on a participant’s worst performance with respect to penetration-aspiration might obscure pathophysiological mechanisms that exist at the bolus level, given that participants displayed variable penetration-aspiration scores across boluses. Other studies have also found non-significant differences
between LVCdur in healthy participants and patients post-stroke who aspirate on thin liquids (Oommen, Kim, & McCullough, 2011). Provided the evidence listed above, LVC integrity, LVCrt and LVCdur are three parameters that warrant further investigations.

6.3.3 Factors Related to Swallowing Efficiency

Post-swallow residue is a common indicator of swallowing inefficiency. Previous studies have implicated reduced pharyngeal constriction as a mechanism associated with post-swallow residue (Dejaeger, Pelemans, Ponette, & Joosten, 1997; Stokely, Peladeau-Pigeon, Leigh, Molfenter, & Steele, 2015; Ursino et al., 2016; Waito, Tabor-Gray, Steele, & Plowman, 2018). From a mechanistic perspective, both pharyngeal constriction and pharyngeal shortening have been posited to facilitate bolus clearance through the pharynx (Kahrilas, Logemann, Lin, & Ergun, 1992). Post-swallow pharyngeal residue is common in HNC patients post-RT (Langmore & Krisciunas, 2010), and it is notable that these patients commonly present with both atrophy and fibrosis of pharyngeal muscular tissue after radiation. Pearson and colleagues examined swallow timing and kinematics in a HNC patient cohort compared with age-matched controls (Pearson Jr, Davidoff, Smith, Adams, & Langmore, 2016). They computed pharyngeal constriction ratios (the unobliterated area at maximum constriction divided by the pharyngeal area at rest) in order to assess pharyngeal mechanics. They found larger PCR measures in the HNC patients, equating to less-complete constriction, as well as impaired pharyngeal shortening, implicating damage to the longitudinal muscles of the pharynx. Kendall and colleagues assessed swallowing in a group of radiated head and neck cancer patients compared to healthy controls (Kendall, McKenzie, Leonard, & Jones, 1998). Study findings determined that patients with tumors focal to the base of tongue presented with larger pharyngeal areas at maximum constriction compared to alternate tumor locations (i.e., pharynx, larynx). Kotz and colleagues also described poor pharyngeal motility and an abnormal pharyngeal stripping wave in two different cohorts of HNC patients post-radiation and associated these impairments with an increase in post-swallow residue, particularly along the posterior pharyngeal wall (Kotz, Abraham, Beitle, Wadler, & Smith, 1999; Kotz et al., 2004).

Stokely and colleagues examined measures of pharyngeal area at rest in relation to post-swallow residue and determined that pharyngeal area measures in individuals with above-normal residue
were generally larger (Stokely et al., 2015). In a recent study from our lab, we measured the area of the pharyngeal lumen at rest in young, healthy adults and reported mean values of 58% of the C2-C4 reference area (95% CI, 53% - 64%). Measures in older adults have been reported to be larger (Leonard, Kendall, & McKenzie, 2004b) suggesting atrophy of the pharyngeal musculature with aging, which has been posited as one mechanism that may lead to difficulties in achieving pharyngeal constriction, thereby contributing to residue accumulation (Kotz et al., 1999; Stokely et al., 2015).

In addition to pharyngeal muscle atrophy, HNC patients may also experience pharyngeal edema and swelling in the sub-acute phase after RT (Isitt, 2006; Murphy & Gilbert, 2009). These changes may well contribute to impaired swallowing efficiency. One recent study examined acute edema in a group of oral and oropharynx patients post-CRT by tracing the width of pharyngeal wall on the frame of swallow rest (Turcotte, Herzberg, Balou, & Molfenter, 2018). The study revealed differences in pharyngeal wall thickness for pre-and post-CRT groups but with no apparent correlation to swallow function.

In addition to pharyngeal constriction, both the diameter and duration of upper esophageal sphincter (UES) opening may have implications for bolus clearance. The literature suggests that the anterior-posterior diameter of UES opening in healthy individuals ranges from 0.9 to 1.5 cm and is related to the volume swallowed (Kahrilas, Dodds, & Hogan, 1988). Radiation-induced stenosis of the UES is reported in up to 23% of patients who undergo definitive treatment for head and neck cancer (Farwell et al., 2010), while presence of strictures in patients post-chemoradiation (CRT) is reported in up to 21% of patients (Lee, de Arruda, & Puri, 2006). Kotz and colleagues reported post-radiation reductions in UES opening in 17% of their participants for both 3 and 5ml volumes of liquid, with no volume effect (Kotz et al., 2004). Unfortunately, UES opening was not measured quantitatively in their study. Eisbruch and colleagues’ analysis of HNC patients pre and post-CRT found incomplete UES relaxation to result in post-swallow residue in both the pyriform sinuses and valleculae (Eisbruch et al., 2002). Patients in their study who presented with increased post-swallow residue were also found to have higher incidences of aspiration after the swallow.
Molfenter & Steele’s review of temporal measures in healthy swallowing found fairly stable measures of UES opening duration (UESDur) across 20 studies with a mean of 0.46 seconds, and a range from 0.21-0.67 seconds (Molfenter & Steele, 2012). Studies by Kern (1999), Logemann and colleagues (2002) and Leonard (2004a) report 95% confidence intervals for UES opening duration from 0.37 to 0.62 with bolus volumes ranging from 10-20 ml in healthy young adults and comparison measures of 0.39-0.69 seconds in older adults (Namasivayam-MacDonald, Barbon, & Steele, 2018). UES opening duration is reported to vary as a function of bolus volume, with larger volumes eliciting longer durations of opening (Farwell et al., 2010; Kahrilas, Logemann, Krugler, & Flanagan, 1991; Leonard, Kendall, McKenzie, Gonçalves, & Walker, 2000; Molfenter & Steele, 2012). A comparison of swallowing outcomes in a group of patients who had undergone surgical treatment for their cancer versus patients who had also undergone postoperative radiation (Pauloski, Rademaker, Logemann, & Colangelo, 1998) found that those who had undergone radiation presented with significantly shorter UES opening durations (350 ms vs 410 ms in the surgery-only cohort) in addition to an increase in post swallow residue. Given these findings, Pauloski and colleagues suspected a link between post-swallow residue and shorter UES opening durations (Pauloski et al., 1998). Further investigations are required in order to determine the connection between post-swallow residue and UES function.

Our specific questions regarding the physiological mechanisms behind impaired swallowing safety and efficiency post-radiation for oropharyngeal cancer were.

1a) What is the incidence of incomplete laryngeal vestibule closure on thin liquid swallows in our HNC cohort compared to healthy controls, and is it associated with penetration-aspiration?

1b) Do the timing or duration of laryngeal vestibule closure differ in these patients compared to healthy controls, and are these parameters associated with penetration-aspiration?

We expected participants with HNC to present with incomplete closure of the vestibule and long LVC reaction times when compared to healthy participants, and that these features would be associated with penetration-aspiration.
2a) Do measures of pharyngeal area at rest, at maximum constriction or the duration and diameter of UES opening differ between HNC participants and healthy controls?

2b) Are measures of pharyngeal area or UES opening related to the presence of post-swallow residue?

Compared to healthy controls, we expected HNC participants to display smaller pharyngeal area at rest; larger pharyngeal areas at maximum constriction; smaller diameters of UES opening; and shorter durations of UES opening. We expected that all of these differences would be associated with increased post-swallow residue in the HNC cohort.

6.4 Methods

6.4.1 HNC Cohort

As previously reported in Chapter 5, 12 men (x̅ = 63.3 years, range 49 – 78 years) with a primary diagnosis of oropharyngeal cancer were recruited from a clinic at a large cancer institution. Cancer locations included the base of tongue, tonsils, and soft palate and ranged in severity from T1 to T3, N0 to N2c with positive or negative HPV status. Additional details regarding the sample can be found in Table 5.1. All participants had undergone bilateral radiation therapy (with or without chemotherapy), and were within the 3-6 month post-treatment timeframe at the time of data collection. Each participant underwent a videofluoroscopic swallowing study beginning with a series of thin liquid barium swallows.

6.4.2 Healthy Sample Data

Videofluoroscopy data for thin liquid swallows by healthy control participants were extracted from the dataset for an ongoing, larger study exploring the physiology of healthy swallows across a range of liquid consistencies. The study was approved by the local institutional Research Ethics Board. Participants provided written consent prior to their participation (see Appendix p.181-192, 200-208 for study protocol and consent forms). Twelve males participants were chosen as case controls for the HNC participants, based on age, with an average HNC-control age difference of 11 years (see Table 6.1)
Table 6.1. Participant study demographics

<table>
<thead>
<tr>
<th>HNC Participant</th>
<th>Age (HNC)</th>
<th>Site</th>
<th>Stage</th>
<th>Radiation Dose (cGy)</th>
<th>Chemotherapy?</th>
<th>Healthy Participant</th>
<th>Age (Healthy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>BOT</td>
<td>T2, N2b</td>
<td>5200</td>
<td>no</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>BOT</td>
<td>T3, N2b</td>
<td>7000</td>
<td>yes</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>BOT</td>
<td>T2, N2b</td>
<td>7000</td>
<td>yes</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>BOT</td>
<td>T3, N2b</td>
<td>7000</td>
<td>d/c</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Oropharynx</td>
<td>T0, N2b</td>
<td>7000</td>
<td>d/c</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>Soft Palate</td>
<td>T3, N2b</td>
<td>7000</td>
<td>yes</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>Soft Palate</td>
<td>T1, N0</td>
<td>6000</td>
<td>no</td>
<td>7</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>R Tonsil</td>
<td>T2, N1</td>
<td>7000</td>
<td>no</td>
<td>8</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>BOT</td>
<td>T1, N2b</td>
<td>7000</td>
<td>no</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>R Tonsil/BOT</td>
<td>T2, N2c</td>
<td>7000</td>
<td>yes</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>BOT</td>
<td>T3, N2b</td>
<td>7000</td>
<td>yes</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>L Tonsil</td>
<td>T1, N2b</td>
<td>7000</td>
<td>yes</td>
<td>12</td>
<td>33</td>
</tr>
</tbody>
</table>

*Note:* BOT = base of tongue, d/c = discontinued

*a*participants who had 1-2 chemotherapy sessions, but discontinued due to adverse reactions
6.4.3 Videofluoroscopy Rating

The videofluoroscopy recordings were rated using ImageJ software (National Institutes of Health, Bethesda, MD) according to a standard operating procedure known as the ASPEKT Method (Analysis of Swallowing Physiology: Events, Kinematics and Timing; Steele, Peladeau-Pigeon, Barbon, Guida, Namasivayam-MacDonald, et al., 2018; Waito, Steele, Peladeau-Pigeon, Genge, & Argov, 2018; see Figure 6.1). See Appendix p.167-180 for standard operating procedures and operational definitions of the ASPEKT method. A priori thresholds for inter-rater agreement were set by parameter (see details in Appendix p.167-180). Any disagreements in rating which fell outside these pre-specified thresholds were resolved by consensus. Interclass correlation coefficients (ICC; two-way mixed, absolute agreement) were calculated to measure interrater reliability between the two raters for continuous measures; Kappa scores were calculated for binary categorical measures (see Table 6.2). Overall, interrater agreement varied between moderate to excellent, with the exception of UESDiameter. On inspection, 3 outliers were identified pre-consensus and associated with the same participant who was identified as having a cricopharyngeal bar. Following removal of these outliers, agreement increased from an ICC of 0.569 to an ICC of 0.890, see Table 6.2.
Figure 6.1. Outline of the ASPEKT Method for videofluoroscopy rating

1. VFSS Recording is spliced into separate video clips for each bolus

2. # of swallows for bolus documented

3. Penetration-Aspiration Scale rating for each swallow

4. Event detection for each swallow

4a) Bolus Past Mandible
4b) Bolus Past Valcular Pit
4c) Onset Laryngeal Elevation
4d) Onset Hyoid Burst
4e) Max. Laryngeal Vestibule Approximation (LVA)
4f) UES Opening
4g) Max. UES Distension
4h) Maximum Pharyngeal Constriction
4i) Offset Laryngeal Vestibule Closure
4j) UES Closure
4k) Epiglottic Return
4l) Swallow Rest

5a) Bolus Location at Swallow Onset
5b) Bolus Location at LVA

6a) Hyoid Tracking*
6b) Peak XY Hyoid Position*
6c) Hyoid Burst Duration, Velocity

7a) UES Width*
7b) Max. Pharyngeal Constriction Area*
7c) Maximum Pharyngeal Dilation*

8a) Ordinal Residue Ratings
8b) Normalized Residue Rating Scale*

* Pixel-based measures, normalized to the length of the C2-C4 spine
Table 6.2. Inter-rater agreement statistics for PAS scores, frame selection, and pixel-based

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Level of Data</th>
<th>Agreement Statistic</th>
<th>Value (95% CI)</th>
<th>Interpretation(^a)</th>
<th>% Requiring Consensus Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>Nominal</td>
<td>Kappa</td>
<td>.483 (71% in agreement)</td>
<td>Moderate</td>
<td>29%</td>
</tr>
<tr>
<td>LVC (+/-)</td>
<td>Binary</td>
<td>Kappa</td>
<td>.539 (88% in agreement)</td>
<td>Moderate</td>
<td>12%</td>
</tr>
<tr>
<td>Hyoid Burst Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.996 (.995-.997)</td>
<td>Excellent</td>
<td>2%</td>
</tr>
<tr>
<td>LVA Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.996 (.994-.997)</td>
<td>Excellent</td>
<td>6%</td>
</tr>
<tr>
<td>LVC Offset Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.997 (.996-.998)</td>
<td>Excellent</td>
<td>2%</td>
</tr>
<tr>
<td>Maximum Pharyngeal Constriction Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.998 (.997-.998)</td>
<td>Excellent</td>
<td>10%</td>
</tr>
<tr>
<td>UES Opening Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.998 (.997-.998)</td>
<td>Excellent</td>
<td>2%</td>
</tr>
<tr>
<td>Max. UES Distension Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.998 (.997-.998)</td>
<td>Excellent</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>UES Closure Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.957 (.889-.936)</td>
<td>Good-to-Excellent</td>
<td>14%</td>
</tr>
<tr>
<td>Swallow Rest Frame</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.925 (.898-.945)</td>
<td>Good-to-Excellent</td>
<td>21%</td>
</tr>
<tr>
<td>nUES</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.890 (.256-.736)</td>
<td>Poor-to-Moderate</td>
<td>4%</td>
</tr>
<tr>
<td>PhAR</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.808 (.708-.869)</td>
<td>Moderate-Good</td>
<td>3%</td>
</tr>
<tr>
<td>PhAMPC</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>.900 (.863-.926)</td>
<td>Good-Excellent</td>
<td>5%</td>
</tr>
<tr>
<td>Total Residue (%C2-C4(^2))</td>
<td>Continuous</td>
<td>ICC(^c)</td>
<td>0.890 (0.837-0.924)</td>
<td>Good-to-Excellent</td>
<td>2%</td>
</tr>
</tbody>
</table>

\(^a\) ICC model = two-way mixed, absolute agreement; \(^c\) Qualitative interpretation of agreement statistics from following references: Viera and Garrett (2005), Koo and Li (2016).
Each recording was first spliced into shorter bolus-level clips, which were assigned to two trained raters for independent duplicate rating. Measures of swallow safety were recorded based on the worst score achieved on the Penetration-Aspiration Scale (PAS) for each bolus, Figure 6.1, step 3. These were subsequently transformed into binary scores reflecting safe vs at-risk swallowing, i.e. PAS scores of 1 and 2 vs 3 and higher (Argolo, Sampaio, Pinho, Melo, & Nóbrega, 2015; Plowman et al., 2016; Starmer et al., 2015).

In order to support the calculation of timing measures and kinematics, raters identified the frame numbers at which the following events occurred: onset of the hyoid burst (HYB); laryngeal vestibule closure or maximum approximation of the arytenoids to the undersurface of the epiglottis (LVC); upper esophageal sphincter opening (UESO); maximum pharyngeal constriction (MPC); upper esophageal sphincter closure (UESC); laryngeal vestibule closure offset (LVCoff); and swallow rest. Definitions for each of these events can be found in Appendix (p.167-180).

6.4.4 Laryngeal Vestibule Closure

The degree of laryngeal vestibule closure (LVC) was recorded as complete or incomplete (Figure 6.1, 4e). Complete LVC was recorded when a seal was observed between the epiglottis and arytenoids leaving no visible airspace and creating a barrier to material entering the vestibule; a rating of incomplete closure was assigned when air space or contrast was visible in the laryngeal vestibule or when there was no contact between the arytenoids and the laryngeal surface of the epiglottis.

Timing measures were calculated for the initial swallow of each bolus as follows:

- *Laryngeal Vestibular Closure reaction time (LVCrt)* was calculated as the interval between HYB and LVC.

- *Laryngeal Vestibular Closure duration (LVCdur)* was calculated as the interval between LVC and LVCoff.

- *UES Opening Duration (UESOdur)* was calculated as the interval UESO and UESC.
6.4.5 PAS Timing

In cases where PAS scores ≥ 3 were observed, the frame of airway invasion was also recorded, and the timing of PAS relative to LVC was determined (before vs. simultaneous/after).

6.4.6 Pixel-Based Measures

Swallow efficiency was evaluated using pixel-based measures of residue in the valleculae, pharynx and elsewhere in the pharynx (e.g., base of tongue, pharyngeal wall; Figure 6.1, 8b). Residue amounts were traced on the frame of swallow rest and referenced against the squared area of the C2-C4² spine reference scalar, to derive a residue percentage, Figure 6.2, (Molfenter & Steele, 2014). In the event that multiple swallows were observed for a single bolus, the swallow rest frame exhibiting the greatest residue was selected. Total residue was subsequently transformed into a binary categorical variable, i.e. < vs ≥ 1% of the C2-C4² reference area, based on descriptive statistics reported for healthy adults (Steele, Peladeau-Pigeon, Barbon, Guida, Namasivayam, et al., 2018).

Pixel based measures of pharyngeal area at rest (PhAR) and on the frame of maximum pharyngeal constriction (PhAMPC) were made using the terminal swallow rest frame and initial swallow MPC frame for each bolus (6.1, a-c) were made, and normalized to the C2-C4² reference scalar (Pearson et al., 2012; Steele et al., 2018). Data from our lab have previously characterized healthy young participants to have a mean PhAR of 58% of the C2-C4² scalar reference area (95% CI, 53% - 64%). We used the lower confidence interval of these reference data (53%) as a threshold for transforming PhAR measures into a binary categorical variable of reduced versus normal (i.e., < vs ≥ 53% C2-C4²). For measures of PhAMPC a similar transformation was used to generate a binary parameter, based on reference data for healthy young adults, with a threshold < vs ≥ 1% C2-C4². UES opening diameter (i.e. anterior-posterior width as viewed on a lateral x-ray image) was measured on the frame of maximum UES distension for the initial swallow of each bolus (4g), by tracing a line perpendicular to the spine at the narrowest point between C4 and C6 (Leonard et al., 2004a) and expressed as a percent of the C2-C4 scalar.
Figure 6.2. Image showing pixel-based tracings of post-swallow residue

Note. a) The yellow tracings denote residue areas of the valleculae and pyriform sinuses, while the white tracings depict the housing area of these two structures. b) The yellow tracings depict traced area of extra residue. The squared C2-C4 reference area is shown by the green dashed lines.

6.5 Analysis

Descriptive statistics were calculated for all parameters at the participant-level unless otherwise noted. In order to summarize performance per participant, the following rules were applied.

1) For measures of penetration-aspiration, the worst score seen across all boluses for each participant was used.

2) For measures capturing LVC integrity or timing, the bolus with the worst PAS score was used. In the event that all boluses for a participant displayed safe PAS scores of 1 or 2, LVC data for the first bolus were used.

3) For measures of PhAR, the average was calculated across all available thin liquid boluses for each participant in both the HNC and healthy cohorts.
4) For measures of residue, PhAMPC and UES opening diameter/duration, the bolus displaying the worst residue was used. In the event that all boluses for a participant displayed residue < 1% of the C2-C4 area, data for the first bolus were used.

Prior to statistical analysis, continuous parameter data were inspected for extreme outliers (i.e., more than 2 standard deviations above the interquartile range), normality (assessed by Shapiro-Wilk tests) and homogeneity of variance (assessed using Levene’s tests). One outlier was identified in the LVCrt and LVCdur data; this case was removed and replaced with a missing value. UES diameter data were unavailable for one HNC and one healthy participant and were replaced with missing data points.

Fisher’s exact testing and odds ratios were used to investigate the relationship between binary classifications of LVC integrity (complete vs. incomplete) and swallowing safety (≤2 safe vs. ≥ 3 at-risk). One-way analyses of variance (ANOVAs) were conducted to determine whether measures of LVC timing (LVCrt; LVCdur), pharyngeal area (PhAMPC) and UES opening duration and diameter differed between the HNC participants and healthy controls. Due to non-normal distribution of residuals, Kruskal-Wallis H tests were performed to determine if there were differences in PhAR and post-swallow residue between HNC and healthy participants. Finally, in order to evaluate the relationship between residue and both PhAMPC and UESOdur, Spearman’s rank-order correlations were performed. Additional analyses were conducted to determine associations between binary classifications of PhAMPC (< vs ≥ 1% C2-C4) and residue (< vs ≥ 1% C2-C4) using Fishers exact testing and odds ratios.

6.6 Results

Descriptive statistics are summarized by group (HNC vs healthy controls) in Table 6.3 for parameters related to swallowing safety and Table 6.4 for parameters related to swallowing efficiency. Table 6.5 shows the timing of PAS for the 10 participants (9/12 HNC, 1 healthy control) who displayed at-risk swallows. With one exception, in the form of a PAS event that occurred on a second subswallow, all of the PAS events occurred prior to LVC on the initial swallow.
### Table 6.3. Timing measures for HNC and healthy participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>95% LCI</th>
<th>95% UCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVCrt (milliseconds)(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNC</td>
<td>295</td>
<td>131</td>
<td>211</td>
<td>378</td>
</tr>
<tr>
<td>HNC at-risk</td>
<td>326</td>
<td>121</td>
<td>233</td>
<td>419</td>
</tr>
<tr>
<td>HNC safe</td>
<td>200</td>
<td>133</td>
<td>-133</td>
<td>532</td>
</tr>
<tr>
<td>Healthy</td>
<td>91</td>
<td>78</td>
<td>39</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td>LVCdur (milliseconds)(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNC</td>
<td>509</td>
<td>186</td>
<td>391</td>
<td>627</td>
</tr>
<tr>
<td>HNC at-risk</td>
<td>467</td>
<td>185</td>
<td>325</td>
<td>609</td>
</tr>
<tr>
<td>HNC safe</td>
<td>634</td>
<td>145</td>
<td>273</td>
<td>995</td>
</tr>
<tr>
<td>Healthy</td>
<td>552</td>
<td>116</td>
<td>474</td>
<td>630</td>
</tr>
<tr>
<td></td>
<td>UESOdur (milliseconds)(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNC</td>
<td>556</td>
<td>97</td>
<td>494</td>
<td>618</td>
</tr>
<tr>
<td>HNC at-risk</td>
<td>571</td>
<td>109</td>
<td>487</td>
<td>654</td>
</tr>
<tr>
<td>HNC safe</td>
<td>512</td>
<td>19</td>
<td>464</td>
<td>559</td>
</tr>
<tr>
<td>Healthy</td>
<td>503</td>
<td>59</td>
<td>465</td>
<td>541</td>
</tr>
</tbody>
</table>

*Note.* LCI = lower confidence interval; UCI = upper confidence interval; LVCrt = laryngeal vestibule closure reaction time; LVCdur = laryngeal vestibule closure duration; UESOdur = duration of UES opening.  
\(^a\)The measures were calculated in frames and converted to milliseconds using a formula of 29.975 frames/second.

### Table 6.4 Pixel-based measures for HNC and healthy participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>95% LCI</th>
<th>95% UCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PhAMPC (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNC</td>
<td>3.9</td>
<td>5.1</td>
<td>0.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Healthy</td>
<td>1.4</td>
<td>1.3</td>
<td>0.5</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>PAaR (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNC</td>
<td>54.2</td>
<td>14.1</td>
<td>45.3</td>
<td>63.2</td>
</tr>
<tr>
<td>Healthy</td>
<td>62.7</td>
<td>11.2</td>
<td>55.6</td>
<td>69.8</td>
</tr>
<tr>
<td></td>
<td>UESDiameter (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNC</td>
<td>21</td>
<td>7.5</td>
<td>15.6</td>
<td>26.4</td>
</tr>
<tr>
<td>Healthy</td>
<td>21.3</td>
<td>4.6</td>
<td>18.3</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>Residue (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNC</td>
<td>2.9</td>
<td>4.2</td>
<td>0.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Healthy</td>
<td>2.4</td>
<td>2.7</td>
<td>0.6</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*Note.* LCI = lower confidence interval; UCI = upper confidence interval; PhAMPC = pharyngeal area at maximum constriction; PAaR = pharyngeal area at rest. All measures reported as a percentage of the participant C2-C4\(^2\) reference space.
### Table 6.5. LVC timing and integrity for HNC and healthy participants

<table>
<thead>
<tr>
<th>Participant</th>
<th>Worst PAS</th>
<th>LVC</th>
<th>Is PAS pre or post LVC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNC 1</td>
<td>3</td>
<td>✓</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 2</td>
<td>3</td>
<td>x</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 3</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HNC 4</td>
<td>5</td>
<td>x</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 5</td>
<td>2</td>
<td>✓</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 6</td>
<td>3</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HNC 7</td>
<td>5</td>
<td>✓</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 8</td>
<td>5</td>
<td>x</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 9</td>
<td>3</td>
<td>x</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 10</td>
<td>3</td>
<td>✓(^a)</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 11</td>
<td>3</td>
<td>x</td>
<td>pre</td>
</tr>
<tr>
<td>HNC 12</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 1</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 2</td>
<td>2</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 3</td>
<td>3</td>
<td>x</td>
<td>pre</td>
</tr>
<tr>
<td>HV 4</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 5</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 6</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 7</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 8</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 9</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 10</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 11</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>HV 12</td>
<td>1</td>
<td>✓</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)penetration-aspiration event on a second subswallow. A ✓ denotes complete LVC, while an x signifies incomplete LVC.

The cross-tabulated frequencies of safe/at-risk swallows by LVC integrity can be found in Table 6.6. We found a statistically significant association between safe/at-risk PAS scores and LVC integrity as assessed by Fisher’s exact test, \( p < .001 \). Of the at-risk swallows (\( n = 10 \)), 6 (60%) occurred in the context of incomplete vestibule closure; by contrast, LVC was documented as complete in 100% of safe swallows. The odds ratio showed that incomplete LVC was associated with a 5.7-fold increase in the risk of PAS scores ≥ 3 (95% CI, 2.0-15.8).
Table 6.6. Bolus-level frequency of safe and at-risk swallows in HNC patients

<table>
<thead>
<tr>
<th>PAS</th>
<th>Complete</th>
<th>Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>At-risk</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Laryngeal vestibule closure reaction time was significantly longer in the HNC patients compared to the healthy controls, $F(1, 21) = 20.074, p < .0001$. Post-hoc Sidak tests were conducted between three subgroups within the data: healthy participants, HNC participants with PAS scores of $< 3$ (n = 3), and HNC participants with PAS of $\geq 3$ (n = 9). LVCrt values for the HNC safe swallows did not differ significantly from the healthy control swallows ($p = .319$) or from the HNC at-risk swallows ($p = .227$). However, the pairwise difference in LVCrt between healthy participant swallows and the at-risk HNC swallows was statistically significant, ($p < .001$) and had a large effect size, Cohen’s $d = 2.16$. No significant differences in LVCdur were found between participant groups, see Figure 6.3.
Significant associations between LVCrt for HNC and healthy swallowing, using one-way ANOVA ($p < .001$).

Descriptive statistics for total residue ($\% \text{ C}2\text{-C}4^2$) can be found in Table 6.4 by group. A total of 6/12 of the HNC participants displayed post swallow residue on thin liquids above the 1% C2-C4² threshold considered to be an upper boundary in healthy young individuals (Steele, Peladeau-Pigeon, Barbon, Guida, Namasivayam-MacDonald, et al., 2018) with a mean total residue measurement of 2.9% C2-C4² (95% CI, .3% - 5.6%). Notably, however the healthy controls also had slightly higher residue measures than the reported norms for healthy young adults, with a mean total residue measurement of 2.4% C2-C4² (95% CI, .6% - 4.1%). The small increase in residue in the healthy participants compared to available reference values may reflect the fact that the control group had an average age over 60. The difference in post-swallow residue between groups was not statistically significant, $H (1) = .014, p = .907$.

As shown in Table 6.4, the range of PhAR in the HNC patients ($\bar{x} = 54\%, \ 95\% \ CI, 45\% - 63\%$) was smaller than that seen in healthy participants ($\bar{x}=63\%, \ 95\% \ CI, 56\% - 70\%$); however, this
difference was not statistically significant $H(1) = 1.76, p = .184$. Furthermore, the current data did not reveal any apparent relationship between unusually small PhAR measures (<53% C2-C4$^2$) and above-normal total residue (Fisher’s exact test, $p = .605$) however, the odds ratio did show that a PhAR <53% was associated with a 1.19 fold increase in the risk of >1% post-swallow residue.

The average pharyngeal area at MPC for HNC participants measured 3.9% of the C2-C4$^2$ space (95% CI, 0.6% - 7.1%), compared to mean values in the healthy controls of ($\bar{x} = 1.4\%$, 95% CI, 0.5% - 2.2%). The difference in PhAMPC between the two cohorts was not significant, $H(1) = .492, p = .483$. Of the 24 swallows in the dataset, 14 (50%) displayed poor pharyngeal constriction (>1% of C2-C4$^2$). On this subset of swallows with poor constriction, the mean measure of total post-swallow residue was 4.8% C2-C4$^2$ (95% CI 0.4% - 9.2%) for 7 HNC patients and 4% (95% CI, 1.6% - 6.3%) for 7 healthy participants. Overall, there was a strong, positive correlation between PhAMPC and the presence of residue, $r_s(24) = .859, p < .001$, see Figure 6.4. When binary classifications of above-normal PhAMPC were cross-tabulated with above-normal residue, with a near-perfect relationship was found, with 93% of the poor constriction cases displaying above-threshold residue (13/14) and 100% of the normal constriction cases displaying below-threshold residue (Fisher’s exact test, $p < .001$; see Table 6.7). No significant differences were found between groups for measures of UES opening diameter, $F(1, 20) = .010, p = .920$ or duration $F(1, 22) = 2.592, p = .122$ or and there were no correlations between UESODur and residue $r_s(24) = .369, p = .076$ or UES opening diameter and residue $r_s(24) = .155, p = .492$. 
Figure 6.4. Depiction of the correlation between pharyngeal area at maximum constriction and post-swallow residue

The Correlation Between Pharyngeal Constriction and Post-Swallow Residue

Table 6.7. Crosstabulation of above-normal frequencies of post-swallow residue by binary classification of pharyngeal area at MPC

<table>
<thead>
<tr>
<th>PhAMPC</th>
<th>&lt;1%</th>
<th>&gt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1%</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

Note. PhAMPC >/< 1% of the pharyngeal area at maximum constriction
6.7 Discussion

The purpose of this study was to characterize swallow physiology in a sample of oropharynx cancer patients who have undergone single-modality RT for their cancer. We explored the relationships between swallowing physiology and functional measures of swallowing safety and efficiency on thin liquids. Additionally, we compared swallow timing and kinematics in HNC patients to a group of healthy controls.

Penetration-aspiration events in our HNC patient cohort predominantly occurred prior to laryngeal vestibule closure, highlighting long LVCrt to be a primary contributor to penetration-aspiration in this sample. Additionally, incomplete vestibule closure appears to be a key issue, given that all safe swallows in our data set were characterized by complete closure. These findings of impaired LVC and LVCrt are consistent with those reported by Starmer and colleagues, who found absent of LVC or longer LVCrt to be associated with increased aspiration (Starmer et al., 2015). These findings highlight the importance of compensatory techniques intended to facilitate complete and timely LVC, such as the chin-down maneuver (Young et al., 2015) or the use of thickened liquids as illustrated in chapter 5. The detection of an almost 6-fold increase in the risk of ≥3 PAS with incomplete LVC confirms the importance of LVC for swallowing safety in HNC patients. Our explorations did not reveal any group differences in LVC duration. This finding differs from reports of shorter LVCdur in patients who presented with unsafe PAS scores (≥3; Starmer et al., 2015).

The mean duration of laryngeal vestibule closure in unsafe patients in the Starmer study was reported to be 117 ms, while our at-risk participant group had much longer durations of closure with a mean value of 467 ms. There are differences in protocol that warrant caution when comparing these two studies. Starmer’s analyses included both 3 ml and cup-sips of thin, while our study analyzed cup-sips only. The inclusion of a smaller bolus size may have contributed to differences in LVCdur (Starmer et al., 2015). Our findings related to LVCdur are similar to those from a study by Pauloski and colleagues, in which participants presented with similar LVCdur (460 ms) to that seen in our at-risk HNC cohort (467; 1998). However, the data from Pauloski’s study were pooled across thin and thick boluses. Power and colleagues determined that shorter LVCdur was associated with penetration-aspiration, which was seen on at least one thin liquid
bolus in 41% of their sample of stroke patients (Power et al., 2009). Differences in protocols and definitions of the boundary events for calculations of LVCdur make further comparisons across studies difficult.

Despite non-significant differences between groups regarding residue, our results highlight the relationship between impaired pharyngeal constriction and the presence of post-swallow residue. Our HNC participants displayed reductions in pharyngeal constriction compared both to the control group and to normative data for healthy young adults (Steele, Peladeau-Pigeon, Barbon, Guida, Namasivayam-MacDonald, et al., 2018). Impaired constriction was seen on approximately 50% of swallows in our patient cohort. Other studies have also reported impaired pharyngeal constriction in HNC patients (Starmer et al., 2014). In a study in head and neck cancer patients treated with radiation therapy alone, Kendall and colleagues found that patients exhibited larger pharyngeal area at maximum constriction when compared to normal controls (Kendall et al., 1998).

The association between reduced pharyngeal constriction and post-swallow residue appears not to be unique to HNC patients; this relationship has been observed in patients with Oculopharyngeal Muscular Dystrophy (Waito, Steele, et al., 2018) and neurogenic dysphagia (Stokely et al., 2015). We postulate that radiation damage to pharyngeal tissue in the form of either edema or fibrosis leads to inefficiency in HNC swallows. Pharyngeal edema may contribute to inefficient movement of musculature necessary for swallowing, especially soon after radiation (Pauloski et al., 1998; Popovtzer, Cao, Feng, & Eisbruch, 2009).

It has been suggested that post-RT edema may also impact other measures; however Turcotte and colleagues were unable to find a relationship between edema and swallow biomechanics in 40 HNC patients (Turcotte et al., 2018). In our study, the participants with HNC did not display marked restrictions in PhAR compared to age-matched controls and we did not find any relationship between PhAR and measures of post-swallow residue. It is important to consider age-related differences between healthy young and healthy older participants. Our healthy comparison cohort was heavily populated by older males, in whom large pharyngeal area at rest has been previously observed (Leonard et al., 2004b). Despite our non-significant findings regarding pharyngeal area at rest and residue, we did find that the odds of residue showed a 1.19-fold increase when the pharyngeal area at rest fell below 53% of the C2-C4² space. These
relationships will need to be further explored in future research using larger sample sizes. Similarly, our data did not demonstrate any relationships between measures of UES Diameter or opening duration and post-swallow residue. Eisbruch and colleagues reported observations of reductions in UES opening in their patients and associated these findings with an increased risk of aspiration during the swallow (Eisbruch et al., 2002). However, objective measures of UES diameter were not reported and the timing of penetration-aspiration events relative to laryngeal vestibule closure or UES opening was not described. Pauloski and colleagues found increased post-swallow residue and shorter UES opening durations in patients who had undergone RT; however our study failed to find similar results (Pauloski et al., 1998). Further research is required to confirm whether reductions in UES diameter or opening duration relate either to swallowing safety or to post-swallow residue, especially in HNC participants who are prone to cricopharyngeal bar and dysfunction (Queija Ddos, Portas, Dedivitis, Lehn, & Barros, 2009).

6.8 Limitations

It is important to acknowledge the limitations of this study. Our study was conducted with a small sample of HNC patients. Due to our goal of achieving homogeneity in our sample, accrual was a laborious process. The descriptions of swallowing mechanics were made on thin liquid swallows only, and did not incorporate variations in bolus size as a covariate. Additionally, all data were analyzed at the participant level, rendering it difficult to compare to previous studies with data reported at the bolus level.

6.9 Conclusions

In this study, we identified the mechanisms behind impaired swallowing safety and efficiency in a group of 12 HNC patients, compared to 12 healthy controls. Our data demonstrate the importance of the integrity and timing of laryngeal vestibule closure related to swallow safety. These mechanisms were significantly impaired in our patient cohort within the 3-6 month timeframe post-RT for oropharyngeal carcinoma. Dysphagia in our HNC cohort was also characterized by reduced pharyngeal constriction and associated post-swallow residue. While our analyses point to key pathophysiological components of swallowing following RT, larger longitudinal studies are warranted to investigate the progression of these mechanisms over time. Additional research exploring swallowing in larger groups of HNC participants across various
consistencies is recommended in order to expand the available knowledge regarding swallowing in this patient population.

6.10 References


Chapter 7

7 Palatability

7.1 Preface

Despite the potential benefits offered by thickened liquids, previous studies report that compliance with texture-modified diets is low in the HNC population. A common explanation for this poor compliance is the fact that thickened liquids are not palatable. Given that previous studies have only studied pudding-thick and paste stimuli at the extremely-thick end of the continuum, the possibility that liquids at the intervening levels on the IDDSI framework (i.e. slightly thick, mildly thick, moderately thick) might be both effective for reducing penetration-aspiration and acceptable to patients needs to be explored. Certainly, if a liquid is not palatable, the probability of use is low, regardless of the clinical effectiveness. The initial portion of this final chapter describes the palatability of the thickened liquid stimuli used in the experiments described in the previous chapter, as rated by half of the HNC participant cohort.
7.2 Introduction

The question of acceptance and whether it drives compliance is an important consideration when recommending thickened liquids for patient use. Several studies suggest that the taste and form of thickened liquids renders them unacceptable to many patients, leading to poor compliance (Low, Wyles, Wilkinson, & Sainsbury, 2001; Macqueen, Taubert, Cotter, Stevens, & Frost, 2003). It is important that clinicians understand concerns regarding the palatability of thickened liquids with specific patient groups before recommending them as an intervention.

In a study that examined speech-language pathologists (SLP) practice patterns regarding thickened liquids, SLPs were asked to answer various survey questions regarding preferred thickeners and patient perception (Garcia, Chambers IV, & Molander, 2005) SLPs reported that they believed thickened liquids were generally disliked by their patients (Garcia et al., 2005). Despite the anecdotal nature of the study, SLPs’ perceptions regarding the poor acceptance of thickened liquids by their patients is supported by other studies in which a particular dislike for thickened liquids is reported (Macqueen et al., 2003). Garcia and colleagues also detected a potential trend towards a greater dislike of thickened liquids as thickness of the liquid increases. Survey respondents reported a strong dislike of honey- and spoon-thick liquids (i.e. moderately and extremely thick liquids on the IDDSI framework) by an estimated 46-48% of their patients. Conversely, SLPs reported that an estimated 34% of their patients had neutral views regarding the likeability of nectar-thick (mildly thick) liquids. Respondents were also asked how their patient’s perceptions differed over time. A majority of the survey respondents described a decline in the acceptability of thickened liquids with continued use over time (33%). However, 75% of respondents also indicated that the acceptability of thickened liquids was situational and that one of the main factors that promoted a greater level of patient acceptance was when thickened liquids were the patients’ only means of oral intake. Thickened liquids are rarely the only means of intake for head and neck cancer patients who present with dysphagia. However, thickened liquids may be used clinically to transition patients’ to oral feeding post-RT or may be used for those with chronic dysphagia. The probability of requiring enteral feeding does increase with chronic dysphagia that is largely refractory to common therapies.
The construct of palatability or acceptability of a food or liquid stimulus is complex. Several different sensory properties are involved, including the visual appearance of the food or liquid, smell and taste (which combine to create the experience of flavour) and texture. Alterations to consistency by adding thickeners may impact flavour release (Delwiche, 2004; Overbosch, Afterof, & Haring, 1991), and this may, in turn impact ratings of palatability and subsequent compliance (Macqueen et al., 2003; Pelletier, 1997; Stahlman et al., 2001). In one study, Stahlman and colleagues studied acceptability of pureed peaches both with and without thickener added. Participants rated the regular, pureed peaches without thickener highest for overall likeability and taste (2001). The study authors acknowledge that their use of a starch-based thickener may have overridden or reduced the true peach flavor in the thickened version, which is consistent with results found by Pelletier, 1997. The use of flavouring agents has been recommended in order to enhance the taste of thickened liquids which tend to be altered with the use of commercial thickeners (Pelletier, 1997).

Two different types of thickeners are commonly available for thickening liquids. Modified maize starch is widely used as a thickener in dysphagia management, with familiar brand names including Nestlé Resource® ThickenUp®, Hormel Thick & Easy® and Kingsmill®, Quick Thick. Starch-based thickeners tend to thicken over time and are susceptible to thin when exposed to amylase in saliva (Barbon & Steele, 2015; Dewar & Joyce, 2006; Hanson, O'Leary, & Smith, 2012). By contrast, gum-based thickeners (which are typically available in the form of guar or xanthan-gums) are generally more stable over time, require smaller amounts to thicken when compared to starch-based thickeners, and are more slippery in texture. Familiar brands of gum-based thickeners for dysphagia management include Nestlé Resource® ThickenUp Clear®, Hormel Thick & Easy® Clear, Simply Thick® EasyMix™ and Nutricia’s Nutilis Clear.

It is unknown whether properties of thickeners used in neurogenic populations with dysphagia behave similarly in the oral cavity in those with HNC. Changes to the oral cavity are likely to occur in patients who have undergone radiation therapy. These potential changes are characterized by an inflammatory reaction of the mucosal tissue (mucositis, radiation dermatitis, stomatitis and edema of the soft tissues) that are likely to involve changes to taste (dysgeusia) and smell and contribute to painful food oral processing (Murphy & Gilbert, 2009). Additional alterations that occur post-RT include viscous mucous and a lack of saliva due to salivary gland
damage, both of which contribute to dysgeusia and patient reports of swallowing difficulties (Isitt, 2006; Pinna, Campus, Cumbo, Mura, & Milia, 2015). Given the decline in saliva that HNC patients experience, it is unknown whether starch-based thickeners may behave differently in the post-radiated oral cavity. Characteristics of liquids such as chemical composition and temperature may also have a tendency to cause pain or irritation in patients who present with dysphagia post-RT. Liquids that are exceptionally acidic or spicy have the potential to be aversive to participants with acute stomatitis (Miller & Kearney, 2001; Pinna et al., 2015). While xerostomia may impact the overall swallowing process in patients with head and neck cancer, studies have demonstrated a loss of taste sensitivity alongside the presence of xerostomia (Temmel, Quint, Schickinger-Fischer, & Hummel, 2005). Topical products for dry mouth containing a variety of ingredients (e.g., carboxymethylcellulose or mucin-based) have been tested in individuals with xerostomia, in the hopes of improving quality of life. Some studies have also demonstrated a change in taste with the use of some saliva substitutes (Ship, McCutcheon, Spivakovsky, & Kerr, 2007; Vadcharavivad & Boonroung, 2013). Dysgeusia and xerostomia are common in patients who present post-RT and both have the potential to impact acceptance of thickened liquids.

Given the findings in Chapters 5 and 6, demonstrating preliminary evidence of the efficacy of slightly and mildly thick liquids for improving swallowing safety on our HNC patients cohort, it is important also to understand how such patients rate the acceptability and palatability of liquids thickened to different IDDSI levels. Below, we will describe our preliminary findings regarding palatability of thickened liquids used in the assessment of dysphagia and those recommended for home use. This portion of the study was designed as part of the main study; however, due to the requirement that participants attend an additional appointment in order to complete the palatability rating experiment, we experienced patient attrition. Patients who completed this portion of the study ranged in age from 58-78 years old, T0-T3, N0-N2b. The demographics of these individuals can be found in Table 7.1 with a full list of participant demographics provided in Table 5.2.
Table 7.1. Patient demographics for participants included in the palatability portion of the study

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor Location</th>
<th>T Stage</th>
<th>N Stage</th>
<th>Total dose delivered to primary, cGy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>BOT</td>
<td>T2</td>
<td>N2b</td>
<td>5200</td>
<td>NA</td>
</tr>
<tr>
<td>67</td>
<td>BOT</td>
<td>T3</td>
<td>N2b</td>
<td>7000</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>66</td>
<td>BOT</td>
<td>T2</td>
<td>N2b</td>
<td>7000</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>61</td>
<td>BOT</td>
<td>T3</td>
<td>N2b</td>
<td>7000</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>58</td>
<td>Oropharynx</td>
<td>T0</td>
<td>N2b</td>
<td>7000</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>77</td>
<td>Soft Palate</td>
<td>T1</td>
<td>N0</td>
<td>6000</td>
<td>NA</td>
</tr>
<tr>
<td>61</td>
<td>R Tonsil</td>
<td>T2</td>
<td>N1</td>
<td>7000</td>
<td>NA</td>
</tr>
</tbody>
</table>

7.2.1 Palatability Data Collection

Stimulated saliva was collected using the Saxon Test, which required the participant to chew on folded sterile gauze for two minutes (Kohler & Winter, 1985). The gauze was weighed pre-and post-chewing to determine the amount of saliva production.

Participants (n=7) were asked to either swallow or taste and spit 6 non-barium stimuli (slightly to moderately thick) and 4 barium stimuli (slightly and mildly thick), thickened using starch-and xanthan-gum thickeners. Recipes for all stimuli used can be found in chapter 4 of this dissertation. Lemon flavored water (Nestlé Lemon Splash) was chosen as the base liquid for the non-barium stimuli, based on preliminary testing by a blinded taste panel comprising members of the lab team, who determined that this product was more palatable than plain thickened water. The intensity of the sourness of the un-thickened Lemon Splash product was rated by the panel to be similar to a solution of 0.02% lemon juice and the intensity of sweetness similar to 0.02% sucrose in water. This degree of sourness falls well below the levels reported to impact swallowing behaviors (Pelletier, 1997). Each cup was filled with approximately 40ml of stimuli. Participants were instructed to take one natural sip from each cup at their own pace, swish the liquid in their mouth and spit or swallow the stimulus when they felt ready.

After sampling each stimulus the participant rated palatability on a visual, hedonic scale (see Figure 7-2) and they were instructed to take a sip of water to cleanse their palate and prepare for the next sip.
Five participants completed the full protocol, and one participant withdrew part-way through the protocol due to reported mucosal irritation.

**Figure 7.1.** Hedonic scale, taken from Pelletier and colleagues

- LIKE EXTREMELY
- LIKE VERY MUCH
- LIKE MODERATELY
- LIKE SLIGHTLY
- NEITHER LIKE NOR DISLIKE
- DISLIKE SLIGHTLY
- DISLIKE MODERATELY
- DISLIKE VERY MUCH
- DISLIKE EXTREMELY

### 7.3 Analysis

First, saliva measures were graphed with the hedonic rating measures in order to identify any possible trends. No trends were found; therefore, the saliva measures will not be discussed further in relation to palatability. This result is consistent with findings by Rogus-Pulia and colleagues, who did not find saliva production to influence perception of liquids or physiological differences (Rogus-Pulia, 2013). Frequencies and histograms were created in order to assess the spread of the data.
Fifty-two percent of the data fell at or below the “like slightly” option and this rating was therefore used as a binary cut-off score. Therefore, scores of “neither like nor dislike” (5) or worse were rated as “dislike” and scores above 5 were rated as “less disliked”. For the purposes of our analysis and results, we will refer to the “less disliked” scores as “like” in order to avoid confusion. Once hedonic scores were turned into binary ratings, they were graphed to capture trends in the data.

7.4 Results

There was a general trend of greater dislike as the liquids increased in thickness. When the data were organized by IDDSI level, we observed an overall trend toward stronger preference for slightly thick liquids compared to mildly thick and moderately thick liquids (see Figure 7.3). Non-barium liquids were also preferred over their barium counterparts. When the data were further broken down by IDDSI level and thickener, participants showed a preference for slightly thick liquids (regardless of thickener type) and for starch-thickened mildly thick liquids (see Figure 7.4).

*Figure 7.2. Graph depicting saliva weight for all participants with corresponding hedonic scale scores.*
Figure 7.3 Graph of the frequency of like vs. dislike hedonic scale scores by IDDSI level and thickener
7.5 Discussion

Although we are unable to draw strong conclusions, the trend toward greater dislike of liquids as they grow thicker can be seen in these data. Barium is also known to affect the perception of palatability and the intensity of taste (Dietsch, Solomon, Steele, & Pelletier, 2014). Consistent with the literature, the liquids with barium contrast received more dislike scores overall. Whether the addition of barium resulted in taste suppression in our dataset is unknown.

7.6 Limitations

We must acknowledge several limitations of this preliminary probe of palatability. The small sample size means that comparisons cannot be drawn between our data and other studies in the current literature. The liquids tested were matched with a barium option for 2/3 consistencies tested, but not all three. Furthermore, we did not account for genetic taste status of the
participants, although these results may have been altered by radiation-induced changes to taste. With hindsight, we also realized that the use of lemon flavoured water might have caused irritation to the oral mucosa in some participants, potentially rendering the liquid unpalatable.

7.7 Conclusion

These data are preliminary and statistical analyses were not conducted due to the small sample size. We have highlighted the potential for slightly thick liquids to be accepted by patients with head and neck cancer given our preliminary findings. If accepted by patients, slightly thick liquids may have potential to ameliorate swallowing dysfunction for individuals post-radiation. Future studies including liquids across the full range of IDDSI levels are recommended in order to determine how palatability may impact compliance. Regardless of the benefit, compliance regarding the use of thickened liquids is an area that requires further exploration.

7.8 References


Chapter 8

8 Final Discussion

The goal of this dissertation was to understand the frequency with which patients with head and neck cancer aspirate on thin liquids and to determine whether the option of using thickened liquids increases swallow safety. These questions were inspired by my personal clinical experience working with the HNC population, which left me with many questions, one of which was regarding the limited implementation of texture modification as an intervention in this population. The literature clearly identifies a high incidence of aspiration in patients having undergone radiation (Eisbruch, 2002, 2004), yet few studies have explored the benefits of (often disliked) thickened liquids. As a clinician, prior to embarking on my doctoral work, I observed many HNC patients who underwent videofluoroscopic assessment using “thin” stimuli on which they appeared to present with safe swallows. The particular product used was most commonly “diluted” Liquid Polibar Plus®, which is a very concentrated 105% w/v barium – however, the degree of dilution was not standardized in the clinical setting where I practiced. Previous research has identified potential differences in swallowing as a function of barium concentration (Dantas, Dodds, Massey, & Kern, 1989; Fink & Ross, 2009; Stokely, Molfenter, & Steele, 2014). Furthermore, the literature suggests that the addition of barium powder to thickened liquids can result in further thickening. My own work in testing the viscosity of different liquids demonstrated a trend for higher concentrations of barium to increase the viscosity of a liquid, as documented in a conference poster included in the appendix (Appendix p.209, Barbon & Steele, 2015; Steele, Molfenter, Peladeau-Pigeon, & Stokely, 2013). The combination of these issues led me to question whether the apparent swallowing safety demonstrated by my previous patients when swallowing a high concentration barium liquid reflected a possible artifact, whereby the barium used was just thick enough to be therapeutically beneficial. Given that this patient population has traditionally demonstrated high rates of airway invasion with thin liquids (Eisbruch et al., 2002), I became interested in the possibility that minor thickening might be beneficial for increasing swallowing safety.

The early literature on dysphagia in the head and neck cancer population typically describes patient groups that are extremely heterogeneous. This makes it challenging to gain a clear
understanding of the pathophysiology of dysphagia in specific patient subgroups and makes it difficult to compare results across studies. Given the challenges associated with this heterogeneity, I set out to study a more homogeneous group of patients who had received radiation focal to the dysphagia-aspiration related structures (DARs). Participants with oropharynx cancers were chosen for inclusion based on the high probability that the pharyngeal constrictor muscles would have been captured within the targeted radiation field. I anticipated that there would be a large pool of patients to choose from, since approximately 80% of oropharynx patients will receive RT at least once during the course of their disease (Strojan et al., 2017). However, enrollment proved challenging given the narrowness of our stated inclusion criteria and also given other factors such as challenges with scheduling and the need for participants to travel to attend multiple appointments. Although the final sample was homogeneous with respect to tumor site, stage and treatment considerations, the presentation of dysphagia appeared to be more variable and less straight-forward than I had expected.

This dissertation involved a series of related studies. The initial radiation-focused review (Chapter 2) was conducted in order to better understand the mechanisms of damage to both cancerous and normal tissue that occur with radiation therapy. I then investigated the current literature in order to understand more about the use of texture modification in the head and neck cancer patient population. This systematic review (Chapter 3), found only a small number of research papers describing swallowing in HNC patients using consistencies other than thin liquid. Overall, thickened liquids were described to be efficacious for preventing airway invasion; however the liquid stimuli used in these previous studies were exceedingly thick in texture (puree, paste). It became clear that liquids of varying (thinner) textures had yet to be investigated for the improvement of swallow safety in head and neck cancer patients. The identification of this gap in knowledge inspired the experimental plans for Chapters 5 and 6, but required the development of recipes for flow-matched barium and non-barium stimuli in IDDSI-defined slightly, mildly, moderately and extremely thick consistencies described in Chapter 4. This experiment has resulted in the dissemination of barium recipes spanning the IDDSI framework that will allow for a better match between liquids used in assessment of the swallow and those recommended for post-assessment use by patients. The development of these recipes enabled us to proceed with the investigations in Chapter 5 and 6 in this dissertation. We recruited 12 patients with oropharynx cancer, who underwent VFSS, and in which those patients who
showed airway invasion on thin liquids continued on to swallow slightly and mildly thick liquids. We found a 75% occurrence of penetration-aspiration on thin liquids in our cohort. Slightly thick liquids were effective for reducing the frequency of penetration-aspiration, with mildly thick liquids having even greater efficacy. However, we also observed an increase in post-swallow residue as the liquids became thicker, indicating a potential drawback to the use of mildly thick liquids. Collectively, these findings point to slightly thick liquids being optimal for decreasing the frequency of airway invasion without increasing post-swallow residue (see Chapter 5, Table 5.4). In Chapter 6 of this dissertation, we conducted a further analysis of swallow timing and kinematics on thin liquids in our HNC patient cohort. We wished to explore the underlying pathophysiology of the swallowing impairments seen on thin liquids in Chapter 5 in comparison to data from 12 healthy, older control participants. We found significant differences in LVCrt between the HNC and healthy groups, $F(1, 21) = 20.074, p < .0001$, with incomplete LVC being associated with a 5.7-fold increase in the risk of PAS scores of 3 and higher, representing impaired swallowing safety (95% CI, 2.0-15.8). With regards to the presence and severity of post-swallow residue, the HNC and healthy cohorts did not differ. However, we confirmed hypotheses regarding a correlation between poor pharyngeal constriction and the presence of post-swallow residue, showing that the persistence of unobliterated pharyngeal space measuring > 1% of the C2-C4$^2$ reference area is associated with post-swallow residue. Other mechanisms with the potential to contribute to post-swallow residue such as unusually large or small measurements of pharyngeal area at rest and or differences in the diameter or duration of UES opening showed no association with the presence of post-swallow residue. Finally, the dissertation concluded with a preliminary exploration of the acceptability of thickened liquids by a subgroup of our HNC patient cohort. The data demonstrated a trend towards greater acceptability of slightly thick liquids over thicker textures.

The results of these studies point to overall benefit with the use of slightly thick liquids for managing aspiration risk in patients who have undergone radiation therapy for oropharynx cancer. Swallow timing measures indicate that laryngeal vestibule closure plays a key role in swallowing safety, with both the degree of closure (LVC integrity) and the timing of closure (LVC reaction time) being relevant. Swallow inefficiency was also observed in the HNC patient cohort with both thin and thickened liquids, revealing difficulty with bolus clearance regardless of consistency. Our data demonstrated better efficiency with slightly thick compared to thicker
liquids, further supporting consideration of these liquids as an effective treatment for reducing penetration-aspiration. Furthermore, the data suggest that patients may be more likely to comply with recommendations to use slightly thick liquids given the favourable palatability ratings compared to thicker stimuli.

8.1 Summary of Unique Contributions

Taken as a whole, this dissertation offers several unique insights related to dysphagia following radiation treatment for head and neck cancer. Each of these contributions is discussed below.

8.1.1 The Introduction of Barium and non-Barium Flow-Matched Recipes

Thickened liquids are widely recommended for dysphagia management, however, variability in thickening practice has become a barrier to patient safety (Cichero, Jackson, Halley, & Murdoch, 2000). Data demonstrate an increase in thickening with the addition of barium (Barbon & Steele, 2015; Steele et al., 2013) and results of the systematic review in this dissertation (Chapter 3) suggested that only excessively thick liquids had been considered for dysphagia management in HNC patients historically. Chapter 4 provides thickened liquid recipes for diagnostic purposes that have been matched with recipes for subsequent home use. These recipes have been shown to remain stable in their flow properties across thickener-type and time. This contribution to the dysphagia literature provides clinicians (and patients/caregivers) with the tools to use standard recipes in their practice. This contribution also provides a basis upon which the validity of findings seen in videofluoroscopy can be expected to translate to swallowing function with liquids having similar flow characteristics outside the clinic.

8.1.2 Efficacy of Thickened Liquids in the HNC Population

Another novel contribution in this dissertation is the finding that slightly and mildly thick liquids can be effective for reducing the frequency of penetration-aspiration in individuals who demonstrate impaired swallowing safety on thin liquids. This important finding opens up possibilities for these liquids to be used in treatment for a group of patients in whom aspiration is both common and represents a serious risk for negative outcomes. The novel finding that slightly and mildly thick liquids can be effective in ameliorating penetration-aspiration is exciting given the fact that compliance with thicker liquids is known to be poor in this clinical population due to poor palatability.
8.1.3 Analyses of Swallow Timing and Kinematics in the HNC Population

Third, this dissertation offers a unique contribution to the literature in the form of swallow timing and kinematic measures for patients who have undergone radiation treatment for oropharynx cancer, using a standardized and rigorous VFSS analysis protocol (Steele et al., 2018). This approach advanced our understanding of the pathophysiological mechanisms underlying penetration-aspiration and post-swallow residue in this population. In particular, the results emphasize the importance of complete and timely laryngeal vestibule closure for airway protection and the importance of complete pharyngeal constriction to facilitate complete bolus clearance. These findings are helpful in guiding clinicians to confirm the mechanisms behind impairment in their patients, and in pointing to specific pathophysiology that can be more precisely targeted with rehabilitative interventions. Whether individuals with oropharyngeal cancer who have undergone different primary treatment approaches would display mechanisms of impairment similar to those seen in this study is a question for future research.

8.1.4 Homogeneous Sample in the HNC Population

Finally, this dissertation provides information regarding swallowing physiology across the range of liquid consistencies in an etiologically homogeneous sample of head and neck cancer patients within the first 6 months following radiation treatment. Recruiting a homogeneous sample of participants turned out to be an incredibly laborious and challenging process. The majority of studies describing dysphagia in HNC involve patients who have heterogeneous tumor sites and T stages and have undergone a variety of treatment approaches; this makes comparisons across studies difficult. Therefore, our participant sample offers data specific to one tumor location and treatment type and timeframe, which is important due to the amount of variability discovered within this homogeneous group.

8.2 Limitations

As with all studies, there are limitations in this dissertation that warrant discussion. First, our efforts to recruit a homogeneous sample of patients led a small sample size. Further work in larger prospective studies is strongly recommended.

Another limitation of our study involves the binary classification of our HNC cohort into safe and at-risk groups. Participants were deemed to have at-risk swallowing if they presented with 1...
or more PAS scores of 3 or above on thin liquids, in both our protocol bail-out and data analysis criteria. These rules limited the number of boluses swallowed by patients who demonstrated penetration-aspiration early within the assessment, such that the true frequency of impaired airway protection across a fixed number of boluses could not be determined. This use of a participant’s worst PAS scores is a bias that also exists in many practice settings, and may penalize patients in whom penetration-aspiration is actually quite rare. On the other hand, our protocol also demonstrated the fact that penetration-aspiration can be missed during videofluoroscopy, as seen in the 3 individuals in whom problems with thin liquid were only detected during post-examination review. It is very important for clinicians to realize that penetration-aspiration may not be detected online during VFSS assessment, and that post-assessment review may identify events that were not seen online.

A further limitation of this dissertation is the fact that the analysis of timing and kinematics was performed using thin boluses only. This decision was made primarily because we did not obtain recordings of thickened liquid swallowing in the participants in whom penetration-aspiration was not noted on the thin liquid tasks in the videofluoroscopy. This decision led to a sample size that was too small to warrant analysis with the thicker stimuli. Future studies should compare swallow timing and kinematics across the full range of liquid consistencies in head and neck cancer patients. Notably, the healthy control participants selected for inclusion in the Chapter 6 analysis comprised a cohort of healthy middle-aged and older males; age-related changes in swallowing have been reported in this population, including larger pharyngeal areas at rest (Leonard, Kendall, & McKenzie, 2004) and prolonged LVC reaction times (Power et al., 2009). The literature suggests that these age-related changes emerge around 60-70 years of age (Feng et al., 2013; Robbins, Levine, Wood, Roecker, & Luschei, 1995). It is important to factor both sex and age considerations into studies characterizing swallowing physiology in specific patient groups such as those with HNC.

In Chapter 5, we identified problems with swallowing efficiency, in the form of post-swallow residue regardless of consistency in our HNC cohort. Residue is commonly considered to represent a risk for subsequent aspiration. In our study, we did not include surveillance for subsequent penetration-aspiration of residue. In fact, as a trend, the penetration-aspiration events observed in our participants were found to occur early in the swallowing sequence, prior to
closure of the laryngeal vestibule. Whether the residue seen in these patients also represented a risk for later airway invasion is unknown. Further studies are needed to elucidate this question.

Finally, our studies were limited to investigating slightly and mildly thick liquids. These two consistencies were chosen because they were hypothesized to be more palatable than the pureed and paste consistency stimuli described previously in the HNC literature. Although we were able to collect preliminary data regarding palatability, it is unknown whether our study participants would have been compliant with continued use of these thickened liquids at home. Further studies exploring palatability using larger datasets are warranted in order to determine the likelihood of patient compliance in consuming thickened liquids across all levels in the IDDSI framework.

8.3 Future Directions

Future directions arising from this dissertation research should involve expansion of the VFSS protocol used in Chapters 5 and 6 to include all liquid levels on the IDDSI framework for implementation in HNC patients, i.e. thin, slightly thick, mildly thick, moderately thick/liquidized and extremely thick/pureed. Throughout the data collection process, patients described that they commonly drank smoothies, and experienced particular difficulty with solids. Solid foods were described as frequently becoming “stuck” in the throat, being “difficult to swallow” and requiring “lots of water or gravy to wash foods down”. Further research is definitely needed to better understand the challenges experienced by these patients with foods and liquids of different consistencies. Studies with larger sample sizes but maintaining homogeneity within subgroups of patients according to tumor location, staging, treatment approach and time post onset would be ideal to fully document swallowing function and pathophysiology in the HNC population. The incorporation of palatability testing would also be beneficial to properly appreciate the barriers that may exist regarding acceptability and compliance with recommendations for food and liquid texture modification. Similarly, the incorporation of information regarding saliva output would be desirable to obtain an accurate picture of swallowing function across the continuum of liquid and food textures, as would research in which the impact of saliva substitutes is explored.

The field would also benefit from additional data collection to properly characterize swallow timing and kinematics across numerous tumor locations and treatment modalities (surgical, CRT,
RT), even with a single consistency such as thin liquid. Use of a standard low concentration barium stimulus and a standard data collection protocol across all participants would be important for such an endeavor as well as the use of a standard operating procedure for videofluoroscopy rating and analysis. Such data would provide the field with temporal and kinematic measure reference data for different patient subgroups, which would set the stage for more precise measurement of treatment effects with different intervention approaches. In particular, this dissertation points to a priority with respect to identifying treatment techniques that are effective for improving the integrity and timeliness of laryngeal vestibule closure in patients with penetration-aspiration and for improving pharyngeal constriction in those who experience difficulties with bolus clearance.

Finally, the field would benefit from the collection of standardized videofluoroscopy data across serial videofluoroscopy exams performed at baseline, 3-6, 18-24 and 60+ months following radiation for head and neck cancer to better document and understand the natural history and evolution of swallowing (dys)function with time post treatment. It is expected that the nature of pathophysiology would evolve over time, with LVC integrity and safety concerns being most prominent during the early post-RT phase (from 3-6 months). By contrast, concerns regarding pharyngeal constriction and impaired swallowing efficiency are considered likely to become more prominent at later time points due to the progression of radiation-induced myopathy and other late radiation effects. Gaining a better understanding of the typical progression of swallowing impairment over time in the head and neck cancer population will equip clinicians with information to guide better prognosis and treatment planning.

8.4 Conclusions

This dissertation was largely motivated by my passion and excitement both for working with head and neck cancer patients and by my interest in texture modification as an intervention. I wanted to explore knowledge gaps regarding dysphagia in HNC patients and I found my niche when I encountered the fact that texture modification is seldom used and rarely researched in this patient population. Given that radiation treatment for head and neck cancer inevitably includes critical swallowing structures in the field, I was motivated to explore avenues for improving swallowing function in these patients. I am encouraged that despite small sample sizes, this dissertation research was able to demonstrate benefit through the use of slightly thick liquids for
managing penetration-aspiration in HNC patients and that this consistency appears to be more acceptable to patients than thicker consistencies. Confirmation that mildly thick liquids are more likely than slightly thick to leave post-swallow residue in this population is also a finding of importance, pointing to an optimal consistency for dysphagia management. Overall, the process of completing the research studies in this dissertation has led me to have many more questions. I am inspired to continue pursuing research with the goal of improving our understanding of dysphagia, and finding effective techniques for improving swallowing outcomes in people with head and neck cancer.

8.5 References


Thickened Liquids for Dysphagia Management: a Current Review of the Measurement of Liquid Flow

Carly E. A. Barbon & Catriona M. Steele
Your article is protected by copyright and all rights are held exclusively by Springer Science+Business Media, LLC, part of Springer Nature. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer’s website. The link must be accompanied by the following text: "The final publication is available at link.springer.com".
Thickened Liquids for Dysphagia Management: a Current Review of the Measurement of Liquid Flow

Carly E. A. Barbon¹,² · Catriona M. Steele¹,²

Abstract
Purpose of Review The use of thickened liquids has become one of the most common management strategies for individuals with dysphagia. The purpose of this paper is to review methods that can be used to measure the flow characteristics of liquids used in dysphagia management. We describe the measurement of apparent viscosity, measures of extensional flow, slump tests (specifically the line-spread test and Bostwick consistometry), gravity flow tests, and subjective methods.

Recent Findings We discuss the relationship between different approaches to measuring flow, the 2002 American National Dysphagia Diet and the 2017 International Dysphagia Diet Standardisation Initiative (IDDSI) framework. A comparison of test results across four methods is provided.

Summary A consistent approach is needed for the measurement of flow for thickened liquids used in dysphagia management. This review highlights differences that can be expected across different flow testing methodologies. Adherence to a common method and measurement definitions will promote patient safety and facilitate future research regarding the effectiveness of texture modification as an intervention for dysphagia.

Keywords Deglutition · Deglutition disorders · Dysphagia · Viscosity · Thickened liquids · Texture modification

Introduction
Texture modification is a widely used intervention for dysphagia [1•, 2]. Thickened liquids flow more slowly than thin liquids, and this provides extra time for a person with dysphagia to achieve airway protection during swallowing. In 2008, a landmark study by Logemann and colleagues showed that individuals with dementia or Parkinson’s disease who aspirated thin barium were less likely to aspirate thicker liquids [3•]. However, to date, the literature has not identified the degree of thickening that is required to achieve therapeutic benefit [4•].

Despite the widespread use of thickened liquids in dysphagia management, without clear definitions for different degrees of thickening, there is a high likelihood of variability in practice. A 2013 review of terminology and guidelines around the world clearly illustrated the potential for confusion across countries [1•]. In North America, liquids used in dysphagia management have been known by the labels thin, nectar-like, honey-like, and spoon- or pudding-thick since the publication of the National Dysphagia Diet (NDD) in 2002 [5]. Viscosity measurements for these categories were proposed at a shear rate of 50 reciprocal seconds (s⁻¹) as follows: thin: 1–50 cP; nectar-like: 51–350 cP; honey-like: 351–1750 cP; and spoon-thick: > 1750 cP. However, neither the equipment nor the skills necessary to perform accurate viscosity measurements at controlled shear rates are accessible to clinicians, caregivers, or patients with dysphagia. This means that individuals who are involved in purchasing or preparing thickened liquids for people with dysphagia rely on the information on product labels or on subjective measures, such as the stirring and manipulation of a liquid, observation of the liquid while being poured from a cup or analysis of the liquid by mouthfeel, or oral appraisal [6]. This dependency on subjective impressions leads to poor quality control of liquid
consistency: Glassburn and Deem demonstrated that clinicians showed poor inter- and intra-individual reliability when using powdered thickeners to achieve targets of nectar- and honey-thick liquids based on subjective impression [7]. Similarly, Cicherio and colleagues found significant differences in the viscosities of thickened meal-time and videofluoroscopy liquids labeled with identical names across ten different hospitals [8]. They cautioned that such variability creates the potential for patients to receive inappropriate thicknesses of liquid in their diets when transferred across facilities. In 2017, a new international framework for classifying liquids and foods used in dysphagia management was published with the goal of establishing common terminology and measurement guidelines to promote safety in the delivery of texture modified foods and thickened liquids to people with dysphagia [9•]. Implementation of this International Dysphagia Diet Standardisation Initiative (IDDSI) Framework is underway around the world.

In this manuscript, we will review methods that are available to measure the flow properties of liquids used in dysphagia. Both low- and high-technology approaches will be described. We will then illustrate comparative measures across four of these methods for a set of liquids.

Measures of Apparent Viscosity

Viscosity, in lay terms, is the appearance or perception of the “thickness” of a liquid. Technically, viscosity is the resistance of a substance to flow under an applied force. Rheometers are instruments that measure viscosity through the application of force to a liquid, which causes deformation or shearing of the liquid. The rate at which this deformation occurs is called shear rate. Viscosity remains constant across the shear rate continuum for some liquids (i.e., Newtonian liquids) but varies across different shear rates for other liquids (i.e., non-Newtonian); shear-thinning behavior, in which lower viscosities are seen at higher shear rates, is a common characteristic of liquids used in dysphagia management [10•]. For this reason, accurate measurements of viscosity require control of shear rate on the rheometer; but not all models of rheometer come with this option [11]. When viscosity is reported at specific shear rates, we use the term apparent viscosity.

During swallowing, a liquid bolus is first squeezed through the mouth by the tongue and then propelled into and through the pharynx [12]; the shear rates that apply during this process are likely to vary at different locations in the oropharynx. In particular, shear rates are likely to differ between the horizontally and vertically oriented planes of the oral cavity and the pharynx, as well as between zones within a fluid, depending on proximity to the walls of the oropharynx [13–15]. Although the NDD recommended the classification of liquids using ranges of viscosity specified at a single shear rate of 50/s, research by Shama and Sherman suggested that shear rate in the oropharynx ranges from 10/s to over 1000/s [16].

Although the measurement of apparent viscosity has been an established way of reporting flow in the field of dysphagia, this method has its limitations and should not be used as the only measure of liquid behavior [10•]. Other liquid properties fall outside the scope of rheological measurement, including fattness, slipperiness, roughness, cohesiveness, elasticity, adhesiveness, and homogeneity (to name a few) [17]. Two recent studies illustrate that liquids with similar apparent viscosities, but prepared using different thickeners can have significantly different perceptual characteristics in the mouth [18, 19]. Stokes and colleagues suggest that further measures, including measures of extensional flow (see below), are required to fully reveal similarities and differences in liquid flow characteristics [17].

Tests of Extensional Flow

Extensional flow testing involves placing a liquid between two plates and slowly moving the plates apart, allowing the liquid to stretch, while maintaining constant volume. Upon stretching, a strand develops as the plates move in opposite directions. The area to volume ratio of the strand is much higher in extensional flow than it is in shear flow. During oral processing and pharyngeal swallowing, bolus deformation patterns include both shear and extensional flow [10, 20].

In a recent Swedish study [21], both shear-controlled and extensional viscosity testing were performed on liquids thickened with five commercial thickeners used for dysphagia management. Liquids thickened with xanthan gum had higher extensional viscosities (and were slightly more shear-thinning) than those thickened with starch [21]. This finding demonstrates the ability of extensional testing to detect additional properties of liquids that might not be measured by other available testing methods.

Slump Tests: Line-Spread Test and Bostwick Consistometer

Another method of liquid flow testing involves the observation of flow across a flat, level surface over time; these tests are called slump tests and include the line-spread test and Bostwick consistometry. Budke and colleagues [22] describe line-spread test methodology, as follows:

1) A cylinder standing 3.5-cm high and 5.0 cm in diameter is placed on a flat, level clear surface, which is marked with concentric circles with ½-cm spacing;
2) The test liquid is placed in the cylinder, which is then lifted, allowing the sample to flow;
3) The average distance flowed across four equal quadrants of the circle template is measured at 60 s;
4) High numbers represent greater spread (i.e., lower viscosity) while low numbers represent less spread (i.e., higher viscosity).

Variations across line-spread tests may include differences in cylinder height and capacity, in the spacing between the lines on the concentric circle grid, and in the number of points around the circle where measurements are taken. The line-spread test cannot be used to determine shear viscosity, but is useful for broad categorization of liquids into therapeutic groupings of similarly behaving liquids [23, 24]. Notably, this approach has been heavily used for classifying liquids for dysphagia management into different consistencies in Japan [25].

Bostwick consistometry is a second type of slump test. The Bostwick consistometer device allows a specified volume of liquid (i.e., 75 ml) to flow from a small holding chamber into a longer measurement chamber when a gate is released. The long chamber is marked with distance measurements in half centimeters, and distance flowed (at the leading edge) is measured at 30 s. Liquids that are higher in viscosity will have lower numbers on the Bostwick, while those that are lower in viscosity will flow further. Liquids with very low viscosity are likely to exhibit a floor effect while thin liquids will flow quickly to the end of the long chamber, demonstrating a ceiling effect. Such limitations are also seen with line-spread testing.

In the province of Québec (Canada), Bostwick flow distances are used to categorize thickened liquids for clinical purposes as follows: “clair”/thin: 16–24 cm; “nectar”: 13–15 cm; “miel”/honey: 7–9 cm; and “pudding”: 3–5 cm [26, 27]. While the Bostwick test provides results on a continuous scale, clinicians may experience difficulty when attempting to categorize liquids that fall in the gaps between these ranges.

### Gravity Flow Tests: Posthumus Funnel, Zahn Cups, and IDDSI Flow Test

Similar to slump tests, gravity flow tests involve observation of liquid flow, but oriented in a vertical direction. A variety of testing methods fall under the gravity flow test category. Historically, the posthumus funnel was used to measure the viscosity of yogurt [28]; a predetermined amount of liquid was allowed to flow through the funnel and the time to exit the funnel was measured as an index of apparent viscosity. Studies have found similarities between funnel flow time and oral examination of viscosity [29]. The Zahn cup is a similar method of liquid flow testing, based on time [30]. The stainless-steel Zahn cup comes in various sizes and has a small hole in the bottom. Generally, large cup sizes are used for liquids with low flow and small cup sizes are used when the liquid is fast-flowing (low viscosity). To determine the flow of the liquid, the cup is dipped into the liquid, filled and pulled out of the body of liquid [31]. Once the Zahn cup has surfaced and the fluid is allowed to flow out of the bottom, the time until the stream of liquid breaks is measured. This “breaking” of the liquid stream is known as efflux time [32]. Some gravity flow testing methods also provide a measure of kinematic viscosity, in centistokes (cSt). Kinematic viscosity can be derived from efflux time using equations provided by Zahn cup manufacturers.

Other gravity flow tests are based on residual volume in the testing device after flow has occurred for a set amount of time; this is analogous to slump test methodology. IDDSI has selected this type of gravity flow test as their primary recommended method of liquid flow characterization. The IDDSI Flow Test involves the observation of liquid flow through a standard 10-ml slip-tip syringe [10]. Instructions can be found at www.iddsi.org. After 10 s of flow, the height of the residual column of liquid is used to categorize the liquid, as follows: Level 0, Thin: no liquid left in the syringe; Level 1, Slightly Thick: 1–4 ml of liquid left in the syringe; Level 2, Mildly Thick: 4–8 ml of liquid left in the syringe; Level 3, Moderately Thick: 8–10 ml of liquid left in the syringe; Level 4, Extremely Thick: 10 ml liquid left, no drips observed.

### Drip Tests

As mentioned above, the IDDSI Flow Test reaches a point of saturation, such that extremely thick liquids do not display any flow through the syringe in the 10-s test period. At this point, the IDDSI testing guidelines recommend further testing using more subjective methods of observing the manner in which a bolus drops or drips from a utensil. Both forks and spoons are used in these tests.

Fork-drip tests aim to classify thick drinks and fluid foods based on whether they flow through the prongs of a fork. This type of testing is sensitive to differences in viscosity, both in a descriptive approach and with more objective measurements of time-to-first-drip of the liquid through the fork [33, 34]. Historically, the Australian guidelines for dysphagia diet classification included fork drip testing to describe distinct categories of liquid flow as follows: regular liquids will run through the prongs of a fork quickly, leaving no coating behind; mildly thick liquids still run fairly quickly through the prongs of a fork but leave a visible coating behind; moderately thick liquids coat the fork and drop slowly (in dollops) through the prongs; extremely thick liquids remain on the fork with no dripping and hold together well [35]. Similarly, the 2011 British guidelines incorporated fork testing to differentiate levels of thickness, based on whether or not an item could be eaten with a fork. Thin purees were described as not being possible to eat with a fork, because they drip (albeit slowly) through the prongs [36]. By contrast, thick purees can be eaten with a fork, because they do not drop through the prongs.
Spoon drop or tilt testing is used to measure the adhesive-
ness of a liquid, and the ability for the sample to remain co-
hesive. The behavior of the liquid is observed after being
loaded onto a spoon and then tipping or tilting the spoon.
IDDSI recommends use of the Spoon Tilt Test to distinguish
between levels 4 and 5 in the framework. At Level 4 (extremely
thick liquids), a sample should: be cohesive enough to hold
its shape while on the spoon (but may spread or slump once
on a plate); slide/drop-off of the spoon as a single bolus when
tilted, or with a slight shake or flick; leave very little residue
behind on the spoon. In particular, this test is useful for iden-
tifying items that are sticky and likely to be challenging for
individuals with dysphagia to move efficiently through the
mouth.

Illustration

In order to illustrate the differences that may be seen
across different methods of flow measurement, we will
share results of shear-controlled rheometry, line-spread
testing, Bostwick consistometry, and gravity flow testing
using the IDDSI Flow Test for two arrays of liquids span-
ning the thin to extremely thick continuum. One array was
prepared using a starch-based thickener (Nestlé®
Resource® ThickenUp®) in concentrations of 0, 4.15,
4.77, 5.85, and 7.8 g/100 ml of flavored water (Nestlé®
Lemon Splash); the second array was prepared using a
xanthan gum-based thickener (Nestlé® Resource®
ThickenUp® Clear) in concentrations of 0, 0.65, 1.25,
2.1, and 7.5 g/100 ml of the same flavored water.

Table 1 provides comparison results for the four types
of testing for both arrays. The values shown represent the
mean test result obtained across three repeated tests at
room temperature, 1 h after mixing. A few of the results
are worth highlighting. First, it is obvious that much
larger amounts of starch thickener were required (com-
pared to xanthan gum-based thickener) to achieve target
flow within each of the IDDSI liquid flow levels. Notice
also that the apparent viscosities of the starch thickened
liquids are substantially higher than those of the gum-
thickened liquids, despite the fact that these liquids dis-
play similar gravity flow. Notably, a large jump can be
seen in the amount of xanthan gum thickener required to
achieve an extremely thick (Level 4) IDDSI flow test
result, compared to Level 3. This reflects the fact that a
small number of drips from the syringe may be seen as
the IDDSI Flow Test reaches its saturation point. This fact
also illustrates the fact that switching to fork drip and
spoon tilt testing is appropriate and important to confirm
the characteristics of extremely thick liquids. Furthermore,
the results in Table 1 clearly illustrate both floor and ceiling effects for the line-spread and Bostwick
methods. In fact, the slightly thick liquids reached satura-
tion (i.e., 24 cm of flow) on the Bostwick test in approx-
imately 7 s, well in advance of the 30-s time frame speci-
ified for reading flow results.

Figure 1 expands upon the data in Table 1 by plotting
flow test, line-spread, and Bostwick test results, and clearly
illustrates the inverse relationship that can be expected
between the IDDSI Flow Test and slump test methods.
The different degrees of test saturation can also be appre-
ciated in a comparison of the three methods. For the
slightly thick and mildly thick liquids, both the line-
spread and Bostwick results display test saturation,
whereas differences between these levels and between
the starch and gum-thickened liquids within the mildly
thick level can be seen using the IDDSI Flow Test.
Conversely, the extremely thick liquids show saturation
on the IDDSI Flow Test. Slight differences between the
starch and gum-thickened stimuli can be appreciated in

<table>
<thead>
<tr>
<th>Thickener type</th>
<th>Thickener amount (g/100 ml)</th>
<th>Viscosity at 50/s (mPa.s)*</th>
<th>Line-spread test (mean flow at 60 s)</th>
<th>Bostwick consistometry (mean flow at 30 s)</th>
<th>IDDSI flow test: mean residual fluid at 10 s (ml)*</th>
<th>IDDSI level</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>1</td>
<td>8.0</td>
<td>24.0</td>
<td>0.0</td>
<td>0—Thin</td>
</tr>
<tr>
<td>Starch</td>
<td>4.15</td>
<td>75</td>
<td>6.1</td>
<td>24.0</td>
<td>1.9</td>
<td>1—Slightly thick</td>
</tr>
<tr>
<td></td>
<td>4.77</td>
<td>141</td>
<td>5.1</td>
<td>24.0</td>
<td>5.0</td>
<td>2—Mildly thick</td>
</tr>
<tr>
<td></td>
<td>5.85</td>
<td>338</td>
<td>3.4</td>
<td>15.0</td>
<td>9.4</td>
<td>3—Moderately thick</td>
</tr>
<tr>
<td></td>
<td>7.80</td>
<td>1400</td>
<td>1.6</td>
<td>3.0</td>
<td>10.0</td>
<td>4—Extremely thick</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>0.65</td>
<td>48</td>
<td>7.9</td>
<td>24.0</td>
<td>1.9</td>
<td>1—Slightly thick</td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>126</td>
<td>5.5</td>
<td>24.0</td>
<td>5.2</td>
<td>2—Mildly thick</td>
</tr>
<tr>
<td></td>
<td>2.10</td>
<td>287</td>
<td>4.9</td>
<td>13.5</td>
<td>9.1</td>
<td>3—Moderately thick</td>
</tr>
<tr>
<td></td>
<td>7.50</td>
<td>1050</td>
<td>2.8</td>
<td>4.0</td>
<td>10.0</td>
<td>4—Extremely thick</td>
</tr>
</tbody>
</table>

*Results represent the mean values obtained across three repeated tests per stimulus at 25 °C (19). †Results represent the mean value obtained across four quadrants of measurement on the line-spread grid at 25 °C
the Bostwick results, while the line-spread test was sensitive to differences between thickeners at all consistency levels. At this point, it remains unknown whether small differences either in slump test results or in gravity flow measures (i.e., those that fall within the boundaries of the IDDSI flow levels) have clinical significance, either with respect to eliciting differences in swallowing physiology or in the frequency of airway invasion.
Conclusion

The existence of multiple labelling conventions for thickened liquids, without an accessible and valid method of confirming flow properties is a patient safety risk [1•]. There are numerous examples in coronial literature of choking deaths due to the provision of inappropriate food textures to patients with dysphagia. For example, the Ontario Office of the Coroner has recently identified inconsistencies in diet texture labelling as a contributing factor in a death due to choking [37]. With respect to liquids, current evidence regarding the effectiveness of thickened liquids for reducing aspiration and preventing negative sequela is hampered by a lack of consistent use of clear terminology and measurement [3, 4]. One example of the confusion that can arise in this respect is seen in a randomized control trial which involved the observation of pneumonia and other outcomes in older adults with dementia or Parkinson’s disease over a 3-month time frame [38]. Two levels of thickened liquid were studied, along with consumption of thin liquids using a chin-down technique. The thickened liquids were labeled “nectar” and “honey”; however, the apparent viscosity of the honey-thick liquids was twice as thick as the NDD guideline for honey-thick liquids. Participants in that study showed unexpected negative outcomes with this honey-thick consistency, including higher rates of pneumonia, dehydration, and death. It would, however, be incorrect to generalize these results to liquids with a viscosity within the NDD category of honey-thick because the “honey” thick liquid used in the study actually belonged to the “pudding” thick consistency class.

The standard definitions and measurement methods recommended by the IDDSI provide a path out of the confusion that has dominated the clinical use of thickened liquids. The low-technology testing methods developed by IDDSI are accessible not only to hospitals, food service providers, and clinicians, but importantly also to caregivers. As such, they empower end users to check the consistency of liquids for people with dysphagia at the point of service, and facilitate risk reduction through improved adherence to diet texture recommendations.

Acknowledgments The authors would like to thank Steve Pong for his assistance with line-spread testing.

Compliance with Ethics Guidelines

Conflict of Interest Carly E. A. Barbon declares no conflicts of interest. Catriona M. Steele serves as a board member for the International Dysphagia Diet Standardisation Initiative and has received speaker fees/travel expense support from International Dysphagia Diet Standardisation Initiative.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance


4. Steele CM, Alsanei WA, Ayanikalath S, Barbon CE, Chen J, Cicero JA, et al. The influence of food texture and liquid consistency modification on swallowing physiology and function: a systematic review. Dysphagia. 2015;30(1):2–26. https://doi.org/10.1007/s00455-014-9578-x. http://bit.ly/1wvZydP. Systematic review of > 10,000 references from the medical and engineering scientific literature regarding the influence of liquid consistency and food texture on swallowing function and physiology. Findings include evidence that thicker liquids do help to decrease aspiration. However, evidence was also found that residue begins to accumulate when liquids are too thick.


techniques to classify texture modified foods and thickened liquids used in dysphagia management.


38. Robbins J, Gensler G, Hind J, et al. Comparison of 2 interventions for liquid aspiration on pneumonia incidence: a randomized trial. Ann Intern Med. 2008;148(7):509–18. Follow up to Logemann’s randomized trial of the effect of liquid consistency on in people with dysphagia, looking at 3 month health status outcomes including pneumonia. Extremely thick liquids resulted in poorer outcomes for adults with dementia or Parkinson’s disease who were confirmed to aspirate on thin liquids; these outcomes included a higher incidence of pneumonia as well as higher rates of dehydration and mortality.
Appendix: ASPEKT Rating Method – Standard Operating Procedures

Round 1 VFSS Rating Steps and Definitions (Lateral View)

Raters will be provided with a Round 1 rating macro, developed in Microsoft Excel by an SRRL Engineer, which will prompt them for specific information (described in sequence below). The macro automatically prompts with 4 pages where up to 3 swallows are rated in detail and any remaining swallows (4+) are grouped together on the final page.

1. Choose Swallow Type:
   a. *Single Bolus:* New bolus crosses the ramus of the mandible in just one swallow. This can be followed by a clean-up swallow (where no new material crosses the ramus); however, if new material crosses the ramus on a subsequent swallow, it is considered a piecemeal swallow.
   
   b. *Piecemeal (either first or subsequent):* If the bolus crosses the ramus of the mandible on multiple swallows, the first and subsequent swallows are all considered “piecemeal”. Note: the amount of material crossing the ramus of the mandible may be very small but still considered a piecemeal swallow.
   
   c. *Clean-up:* Material being swallowed comes from the pharynx, only – no new material crosses the ramus of the mandible.
   
   d. *Attempt(s):* Unsuccessful swallow(s) defined as pharyngeal constriction + hyolaryngeal elevation, or obvious volitional elevation of the larynx in effort to initiate a swallow. The UES does not open despite effort.

   i. If there is more than one attempt in a row, they are all grouped together on the same macro page.

   e. *Final event(s):* Selected automatically by the macro when there are more than 3 swallows to capture the remaining swallow events in a group.

   f. *No other events in the video clip:* Selected if there are fewer than 4 events in the swallow to inform the rating macro that there are no remaining swallows or attempts.
2. **Rate Penetration/Aspiration (PAS) using the following scale:**
   
a. 8-Point Penetration-Aspiration Scale

   1 = Material does not enter airway  

   2 = Material enters the airway, remains above the vocal folds, and is ejected from the airway  

   3 = Material enters the airway, remains above the vocal folds, and is not ejected from the airway  

   4 = Material enters the airway, contacts the vocal folds, and is ejected from the airway  

   5 = Material enters the airway, contacts the vocal folds, and is not ejected from the airway  

   6 = Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway  

   7 = Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort  

   8 = Material enters the airway, passes below the vocal folds, and no effort is made to eject  


   b. PAS should only be rated on new material entering the airway for each swallow. In the event that there is residue in the airway from a previous swallow, but no new material is penetrated or aspirated on the current swallow, PAS would be scored as 1.

3. **Choose the Penetration-Aspiration Score frame (PAS_frame):**
   
a. If PAS > 1, record the first frame showing penetration of the material into the laryngeal vestibule (i.e. first frame showing PAS of 2 or higher)

   b. If PAS = 1, PAS_frame is N/A

4. **Choose the Bolus at Mandible frame (BPM_frame):**
   
a. Record the first frame where the leading edge of the bolus touches or crosses the shadow of the ramus of the mandible.

   b. In cases of premature spill, the first entry of bolus material into the pharynx should be counted as the BPM frame.
c. If there is a double mandible shadow, use the lower edge of the more superior ramus as the landmark.

5. Choose the Bolus Passing Valleeular Pit frame (BPV_frame):

   a. Record the first frame where the leading edge of the bolus touches or crosses the vallecular pit (or a line at the level of the vallecular pit).

   b. Optional: It may be helpful to use the angle tool to draw a line at the level of the vallecular pit, for a reference:

      i. Select the Angle tool from the main ImageJ toolbar

      ii. Click on the inferior anterior corner of C4, then the inferior anterior corner of C2, then the posterior aspect of the tongue where the angle is approx. 90 degrees (shown in the ImageJ toolbar)

      iii. Use the arrow keys to move the 90 degree angle up or down, until the line that is perpendicular to the spine is positioned at the pit of the vallecula.

      iv. You may need to adjust the height of the line, with movement of the tongue

6. Choose the frame containing the first jump of the hyoid (1Hyoid_frame):

   a. Record the first anterior-superior ‘jump’ of the hyoid that is associated with a swallow (or swallow attempt).

   b. This is the moment where the hyoid appears to ‘take off’ or ‘burst’; small movements around the starting position that occur prior to this burst should not be counted.

   c. The 1Hyoid frame often has 2 hyoid images on it, because of the speed of the hyoid taking off.

   d. For Final Events or Attempts, 1Hyoid is marked on the first event in the sequence.

7. Choose the frame containing the first elevation of the larynx (LE_frame):

   a. Identify the frame containing the first elevation of the laryngeal air column (LAC; detected anteriorly at the thyroid cartilage) from its rest position, prior to laryngeal vestibule closure.

      i. Note: If the thyroid cartilage is not visible, use the superior tip of the arytenoid cartilage instead.

   b. Start monitoring from the peak laryngeal position associated with the swallow and move backwards frame-by-frame until the point where LAC reverses direction or remains stationary for 5 successive frames. Move forward again to identify the first frame of movement towards peak position.
c. Laryngeal movement associated with jaw opening/closing before the swallow should not be considered part of the LE movement.

8. **Choose the first frame of Maximal Laryngeal Approximation (LVA_frame):**
   
a. The first frame where there is maximum approximation of the arytenoids to the laryngeal surface of the epiglottis.

   Complete closure of the laryngeal vestibule (i.e. a seal between epiglottis and arytenoids leaving no visible airspace) may or may not be present.

9. **Indicate completeness of laryngeal vestibule closure (LVC):**
   
a. Mark whether the frame identified as LVA_frame has:
      
      i. Complete closure – no air or contrast in the laryngeal vestibule
      
      ii. Partial closure – narrow column of air or contrast in the laryngeal vestibule OR partial tissue contact between the arytenoids and laryngeal surface of epiglottis with small amount of contrast or airspace visible in part of the vestibule
      
      iii. Incomplete closure – wide column of air or contrast in the laryngeal vestibule


10. **Choose the first frame of UES opening (1UES_frame):**
    
a. The first frame where the leading edge of the bolus (or in rare cases, air) passes through the upper esophageal sphincter (UES).
    
b. The UES is a narrow segment or region that typically lies between C4-C6; the narrowest opening seen between C4-6 during a swallow is usually marked as the location of the sphincter (as per Kendall & Leonard). In the SRRL, our criteria recognize that the UES moves superiority during the swallow. Therefore, the narrowest portion may be located above C4. The laryngeal air column can be used as a guide to decide where the location of the UES is during pharyngeal shortening.

11. **Choose the frame of maximum UES distension (UESmax_frame)**
    
a. Identify the frame where the distension of the upper esophageal sphincter has the widest width (i.e., widest lumen width and/or bolus column)

12. **Choose the frame of maximum pharyngeal constriction (MPC_frame):**
    
a. Choose the earliest frame of maximum pharyngeal constriction (i.e., least amount of bolus flow and/or airspace in the pharynx)
b. Typically occurs between 1UES and LC_Offset

c. Must choose frame before upper pharynx begins to relax, and before the laryngeal air column begins to open/descend

13. Choose the first frame of UES closure (UESc_frame):

   a. Choose the first frame where the UES achieves closure behind the bolus tail. This does not require closure of the entire UES segment, simply closure at any point along the segment

14. Choose the first frame of laryngeal opening (LC_offset_frame)

   a. The first frame where there is a visible opening (white space) in the laryngeal vestibule.

   b. This requires some separation of the tissues or of the arytenoids from the under surface of the epiglottis. Complete opening is not required. The leaf of the epiglottis may still be in a downward position.

   c. If LVC was marked “incomplete”, this variable is N/A “not applicable”

15. Choose the frame of epiglottic return (EpiVert_frame)

   a. The first frame depicting the return of the epiglottis to a vertical position. This is usually accompanied by relaxation of the pharynx.

16. Choose swallow rest frame (SwalRest_frame):

   a. Select the first frame showing the pyriform sinuses at the lowest position, relative to the spine, within 30 frames (approx. 1 second) of UES closure.

   b. The selected frame must occur before any of the following:

      i. End of clip/fluoro

      ii. Hyoid burst of subsequent swallow/clearing swallow

      iii. Non-swallow events (e.g., coughing, talking, UES re-opening)

      iv. No more than 30 frames past UES closure

   c. Note: If UESc cannot be rated (e.g., UES did not open, such as in the case of swallow attempts) the first frame of pharyngeal relaxation will be used as the reference time point for determining swallow rest. To do so:

      i. Identify the first frame of pharyngeal relaxation;

      ii. Select the frame showing the pyriform sinuses at the lowest position, relative to the spine, within 30 frames of pharyngeal relaxation.
d. For Attempts or Final Events, swallow rest is marked on the last event of the sequence

e. Additional notes for Swallow Rest:

- If the pyriform sinus stays in the same lowest position for multiple frames, select the first of the frames where it reaches its lowest location.

- The base of the pyriform sinus will likely arrive at its lowest position after the hyoid has descended.

- If a structure obstructs the view of the pyriform sinus (e.g., it descends behind a raised shoulder), select the frame immediately before it becomes obstructed.

- The pharynx must reach a minimum of 75% dilation in order to be considered “rested”. If the pharynx does not reach 75% dilation, this parameter is considered unratable.

17. Rate post-swallow residue (Eisenhuber):

a. At swallow rest, rate residue in the vallecular and pyriform sinuses using the following scale:

0 = no residue

1 = ‘mild’ residue (the fluid level of contrast material fills < 25% of the available space of the structure)

2 = ‘moderate’ residue (the fluid level of contrast material fills > 25% and <50% of the available space of the structure)

3 = ‘severe’ residue (the fluid level of contrast material is > than 50% of the available space of the structure)


a. Additional notes for Eisenhuber:

- “Collapsed sinuses” – if the epiglottis collapses tightly to the base of the tongue, or if the pyriform sinuses collapse upon relaxation, Eisenhuber is still rated based on the amount of material in reference to the available space remaining. Therefore, a small amount of residue may be rated as a 2 or 3 if the sinus has reduced significantly in size.

- The following should NOT be measured as post-swallow residue:
i. Additional spill from the mouth after the swallow (i.e., oral residue from a prior bolus or new bolus material crossing the ramus of the mandible)

ii. Regurgitation of material through UES and back into pyriform sinuses

- However, post-swallow residue from the valleculae that is observed to spill further into the pyriform sinuses should be measured.

b. Certain adjustments may be made to the selection of the frame for residue measurement when needed:

- In the case of additional oral spillage or UES regurgitation (noted above), select the frame immediately prior to the additional oral spillage or regurgitation for residue measurement.

- If there is poor visibility of residue on swallow rest frame and the frames prior to swallow rest show incomplete pharyngeal relaxation, then the first frame after swallow rest with adequate visibility may be selected for residue measurement.

- IMPORTANT: Make note of the selected frame number for rating residue in the “Comments” box if it differs from the Swallow Rest frame.

18. Rate overall bolus-level PAS:

a. In some cases, a PAS event may evolve (worsen or resolve) over the course of the bolus clip. To account for this, the macro will prompt for a “Bolus-Level PAS” rating.

b. The macro will present the PAS ratings you initially assigned for each swallow, highlight the WORST score that occurred across all swallows, and prompt “Did this material recover or worsen?”

   i. If the worst identified PAS event did not change on subsequent swallows, choose “No”

   ii. If the PAS event resolved or worsened after the swallow, click “Yes” and identify the appropriate PAS score at the bolus-level, using the Penetration-Aspiration Scale.
Round 2 VFSS Rating Steps and Definitions (Lateral View)

Raters will be provided with a Round 2 rating macro, developed in Microsoft Excel by an SRRL Engineer, which will prompt them for specific information (described in sequence below). Frame numbers obtained in Round 1 ratings will be provided within the macro to inform the rater when to take measurements.

1. Rate bolus location at swallow onset (BL@SO):
   a. On the frame provided (1Hyoid; obtained in Round 1), determine the location of the bolus according to the following scale:

      0 = Bolus head in oral cavity or at posterior angle of ramus (first hyoid excursion)

      1 = Bolus head at vallecular pit

      2 = Bolus head at posterior laryngeal surface of epiglottis

      3 = Bolus head at the level of the pyriform sinuses (i.e., inferior to the arytenoids)

      4 = No appreciable initiation at any location


2. Bolus location at laryngeal closure (BL@LVA):
   a. On the frame provided (LVA_frame; obtained in Round 1), determine the location of the bolus according to the following scale:

      0 = Bolus head in oral cavity or at posterior angle of ramus (first hyoid excursion)

      1 = Bolus head at vallecular pit

      2 = Bolus head at posterior laryngeal surface of epiglottis

      3 = Bolus head at the level of the pyriform sinuses (i.e., inferior to the arytenoids)

      4 = Bolus head in UES

      5 = No appreciable initiation at any location

3. **Maximum UES opening (UESmax)**

   I. Find the frame of interest in ImageJ (UESmax_frame, obtained in Round 1)

   II. Measure C2-C4 length (scalar)
       a. Use the Line tool to measure C2-C4 length
       b. Press Ctrl+M to obtain the measurement – record the Length

   III. Measure the *narrowest point* UES Width at frame of maximum distension:
       a. Find the frame of interest in ImageJ (UESmax_frame, obtained in Round 1)
       b. Measure C2-C4 length (scalar)
       a. Use the Line tool to measure C2-C4 length
       b. Press Ctrl+M to obtain the measurement – record the Length
       c. Measure the *narrowest point* within UES at the frame of maximum distension:
          a. Select the Line tool.
          b. Hold the mouse button down and drag the line across the *narrowest point of the bolus/lumen visible on the image below the base of the pyriform sinuses, extending down not lower than the top of C6*, keeping the line perpendicular to the cervical spine.
            - Note: this position will typically appear as the apex of an hourglass shape in the upper esophagus. The height of the laryngeal air column may be used as a guide to identify the position of the UES during pharyngeal shortening.
          c. Press Ctrl+M
          d. Record the Length value from the Results box

4. **Measure maximum pharyngeal constriction (MPC):**
   
   I. Find the frame of interest in ImageJ (MPC_frame, obtained in Round 1)
   
   II. Open the ROI Manager
       a. Click on Analyze → Tools → ROI Manager
       b. Make sure the Show All option is checked
   
   III. Draw the X and Y axes by making a right angle.
       a. Select the Angle tool from the main ImageJ toolbar
       b. Click on the inferior anterior corner of C4, then the inferior anterior corner of C2, then the posterior aspect of the tongue where the angle is approx. 90 degrees (shown in the ImageJ toolbar)
       c. In the ROI Manager, click Add
       d. Use the arrow keys to move the right angle up until its vertex is at the superior anterior point of C2. **This is your upper margin.**
   
   IV. Trace bolus residue and/or any visible air space captured in the pharynx
       a. Select the Freehand tool.
       b. Click and hold to trace a contour line around the unconstructed space in the pharynx.
       c. Refer to the following boundaries to capture residue/space:
          - Superiorly: a line perpendicular to the spine connecting the top of C2 vertebra to the tongue base (the line drawn in step III)
          - Posteriorly: the posterior pharyngeal wall
          - Anteriorly: the base of tongue and pharyngeal surface of the epiglottis; connecting the base of the epiglottic petiole to the arytenoid cartilage
          - Inferiorly: Pit of the pyriform sinuses, superior to UES
       d. Press Ctrl+M to obtain the measurement – record the Area
   
   V. Measure C2-C4 length (scalar)
       a. Use the Line tool to measure C2-C4 length
       b. Press Ctrl+M to obtain the measurement – record the Length

---

1 Note: in the rare event that the velum is captured in the space defined by the upper margin line and the base of tongue, it should be INCLUDED in the pharyngeal space. The upper boundary does not change.
5. **Measure maximum pharyngeal dilation (MPD):**
   
   I. Find the frame of interest in ImageJ (Swallow Rest, obtained in Round 1)
   
   II. Open the ROI Manager
       a. Click on Analyze → Tools → ROI Manager
       b. Make sure the Show All option is checked
   
   III. Draw the X and Y axes by making a right angle.
       a. Select the *Angle* tool from the main ImageJ toolbar
       b. Click on the inferior anterior corner of C4, then the inferior anterior corner of C2, then the *posterior aspect of the tongue* where the angle is approx. 90 degrees (shown in the ImageJ toolbar)
       c. In the ROI Manager, click Add
       d. Use the arrow keys to move the right angle shape up until the superior corner (the vertex of the right angle) is at the superior anterior point of C2. **This is your upper margin.**
   
   IV. Trace bolus residue and/or any visible air space captured in the pharynx
       a. Select the *Freehand* tool.
       b. Click and hold to trace a contour line around the unconstricted space in the pharynx.
       c. Refer to the following boundaries to capture residue/space:
           - Superiorly: a line perpendicular to the spine connecting the top of C2 vertebra to the tongue base (the line drawn in step III)
           - Posteriorly: the posterior pharyngeal wall
           - Anteriorly: the base of tongue and pharyngeal surface of the epiglottis; connecting the base of the epiglottic petiole to the arytenoid cartilage
           - Inferiorly: Pit of the pyriform sinuses, superior to UES
       d. Press Ctrl+M to obtain the measurement – record the Area
   
   V. Measure C2-C4 length (scalar)
       a. Use the Line tool to measure C2-C4 length
       b. Press Ctrl+M to obtain the measurement – record the Length
6. **Calculate Normalized Residue Ratio Scale (NRRS):**

   I. Find the frame of interest in ImageJ (Swallow Rest, obtained in Round 1)

   II. Draw a scalar reference line from C2 to C4
       a. Select the Line tool.
       b. Click on the anterior-inferior edge of C2 vertebra.
       c. Hold the mouse button down and drag the line the anterior inferior edge of C4.
       d. Press Ctrl+M. Record the Length value from the Results box.

   III. Capture the vallecular residue (if any)
       a. Select the Freehand tool.
       b. Click and hold to trace a contour line around the vallecular residue.
       c. Press Ctrl+M. Record the Area value from the Results box (residue).
       d. Select the Oval/Brush Selection tool.
       e. Click and hold to nudge the contour line to include the vallecular housing.
       f. Press Ctrl+M. Record the Area value from the Results box (housing).

   IV. Capture the piriform sinus residue (if any)
       a. Select the Freehand tool.
       b. Click and hold to trace a contour line around the piriform sinus residue.
       c. Press Ctrl+M. Record the Area value from the Results box (residue).
       d. Select the Oval/Brush Selection tool.
       e. Click and hold to nudge the contour line to include the piriform sinus housing.
       f. Press Ctrl+M. Record the Area value from the Results box (housing).

**Additional Criteria:**

- The top of the piriform sinus is defined using a line extending from the tip of the arytenoid shadow to the posterior pharyngeal wall, perpendicular to the vertebral axis.
- If the c-spine vertebrae appear to have two inferior edges (e.g., due to a slightly oblique posture), mark the C2-C4 scalar from the lower lines.
- “Engulfing Sinuses” – if two bilateral sinuses are visible with residue (e.g., due to an oblique position or physical asymmetry), use the Oval/Brush Selection tool to engulf both visible cavities.
- If there are visible osteophytes (or similar) extending the anterior aspect of the cervical vertebrae, C2-C4 scalar measurement should be taken from the true vertebral body.

Following these rating measurements, an SRRL Engineer will process the data to calculate the NRRS values:

\[
NRRS = \left( \frac{\text{Residue Area}}{\text{Housing Area}} \right) \times 10 \times \left( \frac{\text{Residue Area}}{\text{CSpine Scalar}^2} \right)
\]
Agreement Thresholds & Final Reporting

Round 1 Measures:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discrepancy Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>Any differences</td>
</tr>
<tr>
<td>PAS_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>BPM</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>BPV</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>1hyoid</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>LE</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>LVA_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>LVC (complete or incomplete)?</td>
<td>Any differences</td>
</tr>
<tr>
<td>LC_offset</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>1UES</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>UESmax_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>MPC frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>UESc_frame</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>EpiVert</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>Swallow Rest</td>
<td>&gt;5 frames</td>
</tr>
<tr>
<td>VRes and PSRes (Eisenhuber)</td>
<td>Any differences</td>
</tr>
</tbody>
</table>

For video pairs where there is a less than 5 frame difference between raters, the following criteria are used for final frame selection and reporting:

- **Choose the earlier frame** for the following variables:
  - PAS_frame
  - BPM
  - BPV
  - 1hyoid
  - LE
  - LVA_frame

- **Choose the later frame** for the following variables:
  - LC_offset
  - Swallow Rest
  - MPC
  - UESc
  - 1UES
  - EpiVert
  - UESmax

---

1 Agreement definitions of “>5 frames” difference is based on videos captured at 30 frames per second
Round 2 Measures:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discrepancy Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL@SO</td>
<td>Any difference</td>
</tr>
<tr>
<td>BL@LVA</td>
<td>Any difference</td>
</tr>
<tr>
<td>nUES</td>
<td>Project specific</td>
</tr>
<tr>
<td>nMPC</td>
<td>Project specific</td>
</tr>
<tr>
<td>nMPD</td>
<td>Project specific</td>
</tr>
<tr>
<td>NRRSv</td>
<td>Project specific</td>
</tr>
<tr>
<td>NRRSp</td>
<td>Project specific</td>
</tr>
</tbody>
</table>

Final reporting:
For video pairs where the difference between the two raters is below the threshold, the following criteria are used for final number selection and reporting:

- Choose the *smallest value* for the following variables:
  - nMPD
  - NRRSv
  - NRRSp
  - nMPC

- Choose the *largest value* for the following variables:
  - nUES

Project specific thresholds:
For each project, an initial subset of the data is used as the basis for determining whether inter-rater agreement in normalized pixel based ratings (i.e., nUES, nMPC, nMPD, NRRSv, and NRRSp) is acceptable. Ratings for this initial subset are performed in duplicate, and difference scores between raters are calculated for the initial duplicate rating set. A 95% confidence interval for rater difference is established where the upper confidence interval boundary serves as a threshold to which difference scores for subsequent duplicate ratings are compared. Difference scores are defined as the absolute values of the difference between the measure of rater 1 and the measure of rater 2.
Ethics Protocol

Title: Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

Principal Investigator: Catriona M. Steele, Ph.D. (Toronto Rehabilitation Institute)

Douglas B. Chepeha, MD, MScPH, FACS, FRCS(C)

Andrew J. Hope, MD, FRCPC
### Table of Contents

1. Introduction ............................................................................................................................................. 3
2. Purpose and Specific Aims ......................................................................................................................... 3
3. Methods .................................................................................................................................................. 4
4. Risks and Benefits ................................................................................................................................. 9
5. Privacy and Confidentiality ..................................................................................................................... 10
6. Compensation ....................................................................................................................................... 10
7. Conflicts of Interest ............................................................................................................................... 11
8. Informed Consent Process ..................................................................................................................... 11
9. Scholarly Review .................................................................................................................................. 11
10. Additional Ethics Reviews .................................................................................................................... 11
11. Contracts ............................................................................................................................................. 12
12. Budget .................................................................................................................................................. 12
1. Introduction

This protocol covers a subproject of a larger project entitled Physiological Flow of Liquids Used in Dysphagia Management. The larger project (henceforth referred to as the parent grant) has been reviewed and funded by the National Institutes of Health as a 5-year R01 grant awarded to the PI (Catriona Steele, Ph.D).

The overall goal of the parent grant is to collect measurements of liquid flow through the oropharynx (i.e., mouth and throat) during swallowing. The factors that are expected to influence liquid flow include the liquid consistency (i.e., thin, slightly-thick, mildly-thick, moderately-thick, extremely-thick) and the forces applied during swallowing (i.e., tongue pressures and swallowing muscle contraction). The overarching objective is to determine how these factors interact to influence the flow of a liquid through the oropharynx. The goal of this subproject is to explore this question in adults with head and neck cancer.

Work on the parent grant to date has included the development, characterization and testing of liquid stimuli to be used in the current project, in which measures of liquid flow and swallowing behaviour will be collected in patients with head and neck cancer. Data collection will take place at the Swallowing Rehabilitation Research Lab of the Toronto Rehabilitation Institute. Videofluoroscopy x-rays will be conducted on a purchased service basis in the diagnostic imaging department at the Toronto General Hospital. We will also use patient questionnaires to evaluate the acceptability of thickened liquids by people with head and neck cancer.

2. Purpose and Specific Aims

Dysphagia (swallowing impairment) involves two primary concerns: 1) the ability to swallow safely, without material entering the airway; 2) the ability to swallow efficiently, without leaving residue behind in the pockets of the pharynx. Impaired swallowing safety is linked to pneumonia while impaired efficiency contributes to risk of malnutrition. Dysphagia is common in patients with head and neck cancer prior to, and as a result of treatment. Radiation treatment for the cancer can cause and exacerbate symptoms of dysphagia. Due to an increase in the prevalence of oropharyngeal cancers secondary to the Human Papilloma Virus (HPV), a growing number of individuals are receiving radiation treatment for their disease. However, because of the typically young age at diagnosis, these individuals can expect longer post-treatment lifespans during which there is a significant chance for negative sequelae to develop, including dysphagia. When a person presents with dysphagia, a common intervention is to alter the consistency of the foods and fluids they consume. However, we lack evidence to guide the modification of food and liquid textures for clinical benefit. In particular, we lack studies demonstrating the effect of texture modification as an intervention in the head and neck cancer population. In this study, we propose to measure the flow of thin, slightly thick and mildly thick liquids in patients who have completed radiation treatment for base of tongue cancer, to understand whether or not thickened liquids provide benefit.
We have three specific aims:

**Aim 1: To determine whether slightly-thick and mildly-thick liquids are palatable and acceptable to patients with base of tongue cancer.** We will collect palatability measures for starch- and gum-thickened liquids with slightly-thick and mildly-thick consistencies, as defined by the International Dysphagia Diet Standardisation Initiative syringe flow test. We will also collect baseline quality of life measures to understand the impact of swallowing impairment on the participant’s quality of life. Following a videofluoroscopy swallowing assessment (described under Aim 2), participants will be advised to use thickened liquids that are effective for improving their swallowing. A follow-up phone call will monitor compliance and acceptance of this recommendation. **Significance:** This will determine how likely participants are to adhere to a thickener recommended based on its efficacy to reduce aspiration.

**Aim 2: To determine how slightly-thick and mildly-thick liquids flow and whether they reduce aspiration compared to thin liquids in patients with base of tongue cancer.** We will collect concurrent videofluoroscopic x-rays of swallowing and physiological measures of tongue pressure in patients with head and neck cancer using thin, slightly- and mildly-thick liquid barium stimuli. This appointment will occur approximately 3-6 months after the completion of the participants’ radiation schedule. **Significance:** This will demonstrate the impact of consistency on bolus flow through the mouth and pharynx, controlling for the forces used to initiate flow and propel the bolus. Additionally, the data collected will aid in characterizing swallow physiology after completion of radiation therapy.

**Aim 3: To determine whether the use of starch vs. gum thickeners impact the results of aims 1 and 2**
The thickened liquids used for aims 1 and 2 will be prepared using both starch- and gum-based thickeners. Additionally, we will collect measures of salivary flow to control for possible interactions between thickener type and oral dryness on the results. **Significance:** Individuals may find one thickener more palatable or comfortable to swallow. Understanding this may impact compliance, swallowing safety and quality of life.

3. **Methods**

**Participants:**

The protocol will involve a single sample of adults, aged 18 or older with an initial cancer diagnosis of base of tongue cancer (T1-T3, N0-N2c, HPV + or -). The eligibility criteria will include completion of bilateral radiation therapy to the neck 3 months prior to enrollment, and removal of enteral feeding tube.

Participants will be asked to attend appointments and complete all data collection sessions described in this protocol. Participation involves two appointments, and two follow-up phone calls.
Exclusion Criteria:

- Participants will be accepted into the study provided they have no previous health condition known to cause swallowing impairment (e.g., stroke; brain injury; neurodegenerative disease).
- Individuals with a previous history of radiation to the head and/or neck area (prior to the current radiation treatment) will be excluded from this study given the possibility of long-term radiation effects to the swallowing apparatus.
- Individuals with a previous cancer diagnosis will be excluded from the study.
- Participants who do not show impaired swallowing safety on thin liquids in the videofluoroscopy (Penetration Aspiration Scale scores of 1 and 2) will be withdrawn from the study.
- Participants who have had, or have a planned neck dissection will be excluded.
- Individuals with tracheostomy in situ will be excluded from the study.
- Individuals with cognitive communication difficulties that preclude the understanding of the protocol or following study instructions will be excluded from the study.
- Due to the requirement to swallow stimuli containing starch based thickeners, which carry a significant carbohydrate load, individuals with Type 1 Diabetes will be excluded.
- Individuals with known allergies to latex, dental glue or barium will be excluded, due to the probability that these items will come into contact with the oral mucosa during data collection.
- Children and pregnant women will be excluded from the study due to the use of radiation.
- Occupational exposure to radiation exceeding half the limit specified for Ontario exposed workers within the past 12 months.

These exclusion criteria will be confirmed using a self-report questionnaire form at the time of intake into the study (see standard operating procedures [SOP], provided as an additional study document). Any questions will be clarified through discussion with the research assistant responsible for participant intake, and, where necessary with the principal investigator.

Recruitment:
This is a preliminary study that will demonstrate feasibility for a future planned extension. We propose to recruit 10-12 participants. Potential participants will be identified by study Co-PIs Dr. Andrew Hope and Dr. Douglas Chepeha through the current radiation therapy clinics and base of tongue cancer caseloads at Princess Margaret Cancer Centre.

Stimuli:
An array of barium and non-barium stimuli has been developed for this study. These stimuli include thin, slightly-thick and mildly-thick liquids, defined using the International Dysphagia Diet Standardisation Initiative (IDDSI) gravity flow measures. The barium stimuli used for videofluoroscopy will be prepared using E-Z-Paque® barium in 20% w/v barium concentration with starch and gum-based thickening agents (Nestlé Resource® ThickenUp® and ThickenUp Clear®). The non-barium stimuli will be prepared using Nestle’s Lemon Spash® lemon-flavoured water and the same starch and gum-based thickening agents.
(Nestlé Resource® ThickenUp® and ThickenUp Clear®). All stimuli will be prepared in the Swallowing Rehabilitation Research Laboratory not longer than 6 hours prior to scheduled use, according to a strict standard operating procedure (refer to additional reference documents). Following preparation, stimuli will be stored in the swallowing lab until needed. Barium stimuli will be transported to the radiology suite at Toronto General Hospital in a cooler, as per routine clinical procedures.

**Data to be collected from each participant:**

The following types of data will be collected from participants:

a) An intake questionnaire noting age, sex, ethnicity and race data and confirming eligibility based on the absence of reported exclusion criteria.

b) During the intake process, we will review a list of conditions that could alter the results of the research study and identify whether any of these conditions apply. This will include disclosing the use of any medications that the participant is currently taking, in order to allow us to control for the possible influence of medication on oral sensory and motor function. Medications do not qualify as the basis for exclusion. However, it is important for us to collect information regarding the use of benzodiazepines and neuroleptic medications that are known to have possible effects on swallowing, particularly with respect to causing xerostomia (dry mouth).

c) Palatability ratings for thickened liquids (with barium and without barium).

d) The MD Anderson Dysphagia Inventory (a quality of life scale related to dysphagia)

e) The Performance Status Scale – Head and Neck (a scale capturing dysphagia and diet status)

f) The University of Washington Quality of Life Revised Version 4 (UW-WOL-R4).

g) Tongue-pressure waveform data, collected at the anterior, middle and posterior palate using the 3-bulb tongue-pressure bulb array of the KayPENTAX Swallowing Signals Lab. If the participant is unable to tolerate the attachment of the sensors, we will measure tongue strength using the Iowa Oral Performance Instrument (IOPI). This approach does not include adhered attachments to the oral mucosa.

h) A measure of stimulated saliva (the Saxon Test), using a 2x2 inch of folded gauze that is chewed for 2 minutes, expectorated and then weighed prior to being discarded.

i) A videofluoroscopy recording of swallowing collected at a pulse rate of 30 pulses per second and video capture at 30 frames per second.

j) Responses to follow-up phone calls exploring acceptance of thickened liquids.

**Data Collection Procedures: Data Collection Session 1:** The participant will arrive at the lab and will be asked to complete two questionnaires: the MD Anderson Dysphagia Inventory (MDADI), the Performance Status Scale for Head and Neck Cancer (PSS-HN) and the University of Washington Quality of Life Revised Version 4 (UW-WOL-R4).

Prior to data collection, saliva flow will be collected using the Saxon Test, for which the participant will chew on folded sterile gauze for 2 minutes. The gauze will be weighed before and after chewing to determine amount of saliva production. The participant will then be asked to swallow 6 non-barium
stimuli, and 2 barium stimuli thickened using starch and xanthan-gum based thickeners. After the participant has sampled each stimulus, they will be asked to rate palatability on a visual, hedonic scale (see study instruments provided).

Data Collection Session 2: Prior to data collection, saliva flow will be collected using the Saxon Test, for which the participant will chew on folded sterile gauze for 2 minutes. The gauze will be weighed before and after chewing to determine amount of saliva production. The participant will then be seated in the videofluoroscopy suite for tongue pressure sensor attachment. A silicon strip housing three 8 mm diameter pressure bulbs will be attached in midline to the roof of the participant’s mouth, with the front sensor located immediately behind the participant’s upper incisor teeth. The sensor strip will be attached using a medical adhesive (Stomahesive®, Convatec, St-Laurent, Quebec, Canada).

Following sensor attachment, the video output line from the fluoroscopy unit and the tongue pressure sensors will then be connected to the KayPENTAX Digital Swallowing Workstation Swallowing Signals Lab equipment, which is located on a properly insulated cart with an uninterrupted power supply and isolation transformer (see Image 1). If the participant is unable to tolerate the attachment of the sensors due to mucositis or general discomfort, we will measure tongue strength using the Iowa Oral Performance Instrument (IOPI) and collect the videofluoroscopy measures without the use of the adhered sensors.

Participants will be asked to swallow a series of thin, slightly-thick and mildly-thick barium stimuli 1 (3 boluses each of 5 stimuli, for a total of 15 boluses) in videofluoroscopy, with concurrent measurement of tongue-palate pressure. Videofluoroscopy will be performed at optimal temporal resolution (30 pulses/second) and captured at 30 frames/second. The stimuli will be presented in a randomized design, blocked by stimulus type. Participants will be allowed to take natural sized sips of each stimulus from cups containing 40 ml. Sip volume and mass will be calculated, by weighing the cups prior to and after the videofluoroscopic assessment.

Data Processing:
The tongue-pressure waveform will be segmented using an automatic segmentation algorithm developed previously in the PI’s lab. Similarly, the videofluoroscopy recordings will be spliced into single bolus clips and the audio channel will be muted to remove cues that might bias rating. Blinded videofluoroscopy rating will then be performed in duplicate by trained raters in the Steele Lab following established procedures (see SOP provided as an additional study document). Discrepancies between raters will be flagged and resolved at consensus meetings, as required. These procedures will yield a
large number of parameters for each swallow. We will use established measures within our lab to collect
and analyze measures related to kinematics and residue.

**Follow-up phone calls:** If deemed appropriate, the participant may be offered the opportunity to
complete a follow-up component. For those willing to participate, this optional experiment will involve
two follow-up telephone calls (at 2 weeks and 3 months following the videofluoroscopy) to determine
compliance with use of thickened liquids recommended following the videofluoroscopy (see study
instruments provided for questionnaires).

**Data Analysis:**

For Aim 1, we will compare hedonic ratings for the different stimuli using a univariate ANOVA. It is
hypothesized that ratings will be significantly better for the thin and slightly thick stimuli compared to
the mildly-thick stimuli, and that a preference will be seen for the gum compared to the starch
thickened liquids.

For Aim 2, blinded videofluoroscopy rating will be performed in duplicate, and discrepancies between
raters will be flagged and resolved at a consensus meeting. The frequency of aspiration will be explored
with the thin stimuli and compared to the prevalence of aspiration when thickeners are introduced
using chi-square statistics.

We will model the impact of stimulus on two timing measures of pharyngeal bolus flow from the
videofluoroscopy (i.e., a) the interval from the bolus passing the mandibular ramus until laryngeal
vestibular closure; b) the interval from the bolus passing the mandibular ramus until entering the upper
esophageal sphincter) and on measures of post-swallow residue (Normalized Residue Ratio Scale). The
Saxon test results regarding oral dryness will be used as a covariate for all analyses, as illustrated in the
Figure below:

![Diagram of path analysis]

A path analysis approach will be used to first identify differences in tongue pressure across stimuli.
(Question 1). If confirmed, this potential modulator will be added to the Question 2 model as a covariate (Question 3). The planned analyses will involve linear mixed model repeated measures ANOVAs with a factor of stimulus.

For Aim 3, we will use qualitative methods to describe participant reports of adherence to the prescribed thickener. Information from the quality of life and performance status scales collected in session 1 will be used to inform our understanding of variations on patterns of thickener acceptance.

4. Risks and Benefits

Risks
The following risks will be disclosed to all participants prior to obtaining their consent to participate:

a) Participants may experience local mucosal irritation from the glue on the adhesive strip used to attach the tongue-pressure bulbs for data collection. The glue usually wears off within 90 minutes following the conclusion of data collection. In the incidence that participants are unable to tolerate the attachment of the sensors, we will use the IOPI tongue bulbs to collect tongue measurements, and collect videofluoroscopic data using the same protocol.

b) Participants may dislike the taste or texture of some of the thickened liquid stimuli in the study. Participants will be reminded that they are free to discontinue participation at any time.

c) Participants may experience some fatigue during the videofluoroscopy data collection session. Participants will be reminded that they should disclose any fatigue or discomfort to the research team, and that they are free to discontinue any particular session or to withdraw from the study at any time.

d) Participants will receive additional exposure to radiation during the videofluoroscopy, in addition to their recent radiation treatment protocol. Based on a previous videofluoroscopic study that we have conducted in healthy adults, the study is expected to involve 118+/18 seconds of radiation exposure (Molfenter & Steele, 2013), with an associated dose estimate of <0.35 milliSieverts. Moro and Cazzani showed that this dose (0.35mSv) corresponds to a risk of 1 in 39,000 of developing a radiation-induced stochastic effect from a videofluoroscopy. We will use a 2-minute warning bell to alert the data collection team to exposure time, and will terminate the protocol at the first opportunity following the bell.

e) Aspiration (entry of material into the airway) is a possible risk during the videofluoroscopic swallowing study that will be performed. This risk is always present for videofluoroscopic swallowing studies, which are intended to document the presence and severity of swallowing abnormalities, including (but not limited to aspiration). When aspiration is observed, standard procedures will be followed to encourage coughing and throat clearing to expel the aspirated material. The protocol will be terminated immediately. Any participant who experiences aspiration will be counseled regarding aspiration prevention strategies and aspiration-risk following the videofluoroscopy.

f) Choking is an extremely unlikely event. However, in the event of choking, routine emergency procedures will be followed. All study personnel carry current CPR certification.
g) In the unlikely event that an incidental finding is noted on the videofluoroscopy (such as a diverticulum or a mass) the attending SRRL licensed speech-language pathologist will consult the on-call radiologist and generate a clinical report documenting the observation. These findings will be communicated with the participant as per usual clinical practice and follow up with their physician will be recommended.

**Benefits**

Participants who aspirate during the videofluoroscopy and demonstrate safer swallows using the thickened stimuli that are tested will be provided with 2 cans of the thickener-type from which they benefitted and instructions for use. Ongoing use of this thickener, as instructed, may reduce their risk for subsequent aspiration and related sequelae.

5. **Privacy and Confidentiality**

Routine practices for ensuring the confidentiality and privacy of all participants will be followed in this study. All research personnel at the Toronto Rehabilitation Institute are required to sign a confidentiality agreement at the time of hire.

Participants will be assigned a non-identifying alphanumeric study code, and the master key for this code will be retained separately by the PI in a password-protected file on a secure, password-protected, encrypted research server. Daily back-up of this research server is performed centrally at the Toronto Rehabilitation Institute to protect against data loss. Hard copies of the participant consent forms will be maintained in a folder, kept in a locked filing cabinet in the Swallowing Rehabilitation Research Lab.

All waveform and videofluoroscopic data will be stored electronically on the secure, password protected, encrypted research server. Any hard copy data will be transcribed into an electronic file (stored on the server), and the hard copy records will be stored in a locked filing cabinet in the Swallowing Rehabilitation Research Lab. Only the participant’s alphanumeric study code number will appear on the data collection sheets and in the data collection files.

Access to participant information and experimental raw data will be restricted to the study personnel named in this application. All records will be destroyed after 10 years under the supervision of Dr. Steele.

In the event of inappropriate release of personal health information, further release of information will be stopped, any information that can be retrieved will be retrieved, the UHN Privacy Office and REB will be notified, and any recommended further actions will be taken.

6. **Compensation**
Data collection for each participant will involve 3 separate appointments and two post-study follow-up telephone call: a) intake; b) Session 1; c) Session 2 (videofluoroscopy); and d) follow-up phone calls at 2 weeks and 3 months following Session 2. Each face-to-face appointment is expected to last 1 hour. An honorarium of $50 will be provided per participant to cover expenses associated with participation in the study. This will be paid at the end of the videofluoroscopy session. Additionally, two cans of thickener will be provided to participants for whom thickening is shown to be effective for reducing aspiration.

7. **Conflicts of Interest**
Dr. Steele, the principal investigator, holds current and prior research contracts with Bracco Canada and Nestlé Health Science, who are manufacturers of the barium products and thickening agents that will be used in this study. She has also served in an advisory capacity on expert panels for Nestlé Health Science. These relationships will be disclosed to participants in the study information sheet. All products for use in the study will be purchased. Neither Bracco Canada nor Nestlé Health Science will have any role as sponsors of this study. Dr. Steele will not receive any financial payment, either personally or to the lab, related to the use of Nestlé or Bracco products in this study. Carly Barbon receives a stipend from the University of Toronto.

8. **Informed Consent Process**
All participants who show an interest in participating will be provided with detailed information about this study via the Participant Information Sheet and Consent Form two weeks prior to the scheduled intake appointment. Only after confirming they have understood all the information that is provided and after verifying they have no more questions, can they sign the consent form. A copy of the consent form will be provided to them. When the ability to comprehend the study is in question we will also request assent from the patient’s substitute decision maker prior to enrolling a patient in the study.

The consent form includes a specific section requesting consent to use of study-related images for future educational and teaching purposes.

9. **Scholarly Review**
This parent grant of which this project is a subproject has undergone scientific review by the MFSR Study Section of the National Institutes of Health (USA).

10. **Additional Ethics Reviews**
There are no additional ethics reviews planned.
11. Contracts
There are no contracts required for this project, which will be conducted exclusively at the Toronto Rehabilitation Institute.

12. Budget
All costs for this study will be covered by the grant received from the National Institutes of Health.
The M. D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My swallowing ability limits my day-to-day activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2. I am embarrassed by my eating habits.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>F1. People have difficulty cooking for me.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P2. Swallowing is more difficult at the end of the day.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E7. I do not feel self-conscious when I eat.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E4. I am upset by my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P6. Swallowing takes great effort.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E5. I do not go out because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>F5. My swallowing difficulty has caused me to lose income.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P7. It takes me longer to eat because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P3. People ask me, “Why can’t you eat that?”</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
</tbody>
</table>
E3. Other people are irritated by my eating problem.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

P8. I cough when I try to drink liquids.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

F3. My swallowing problems limit my social and personal life.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

F2. I feel free to go out to eat with my friends, neighbors, and relatives.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

P5. I limit my food intake because of my swallowing difficulty.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

P1. I cannot maintain my weight because of my swallowing problem.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

E6. I have low self-esteem because of my swallowing problem.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

P4. I feel that I am swallowing a huge amount of food.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

F4. I feel excluded because of my eating habits.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

*Thank you for completing this questionnaire!*
### PERFORMANCE STATUS SCALE FOR
HEAD AND NECK CANCER PATIENTS: PSS-HN

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>ID#</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>NORMALCY OF DIET / / / /</th>
<th>PUBLIC EATING / / / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 Full diet (no restrictions)</td>
<td>100 No restriction of place, food or companion (eats out at any opportunity)</td>
</tr>
<tr>
<td>90 Full diet (liquid assist)</td>
<td>75 No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less &quot;messy&quot; foods (e.g., liquids)</td>
</tr>
<tr>
<td>80 All meat</td>
<td>50 Eats only in presence of selected persons in selected places</td>
</tr>
<tr>
<td>70 Raw carrots, celery</td>
<td>25 Eats only at home in presence of selected persons</td>
</tr>
<tr>
<td>60 Dry bread and crackers</td>
<td>0 Always eats alone</td>
</tr>
<tr>
<td>50 Soft chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)</td>
<td>999 Inpatient</td>
</tr>
<tr>
<td>40 Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)</td>
<td></td>
</tr>
<tr>
<td>30 Pureed foods (in blender)</td>
<td></td>
</tr>
<tr>
<td>20 Warm liquids</td>
<td></td>
</tr>
<tr>
<td>10 Cold liquids</td>
<td></td>
</tr>
<tr>
<td>0 Non-oral feeding (tube fed)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UNDERSTANDABILITY OF SPEECH / / / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 Always understandable</td>
</tr>
<tr>
<td>75 Understandable most of the time; occasional repetition necessary</td>
</tr>
<tr>
<td>50 Usually understandable; face-to-face contact necessary</td>
</tr>
<tr>
<td>25 Difficult to understand</td>
</tr>
<tr>
<td>0 Never understandable; may use written communication</td>
</tr>
</tbody>
</table>

University of Washington Quality of Life Questionnaire (UW-QOL)

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

1. Pain. (Check one box: ☐)
   - I have no pain.
   - There is mild pain not needing medication.
   - I have moderate pain - requires regular medication (codeine or nonnarcotic).
   - I have severe pain controlled only by narcotics.
   - I have severe pain, not controlled by medication.

2. Appearance. (Check one box: ☐)
   - There is no change in my appearance.
   - The change in my appearance is minor.
   - My appearance bothers me but I remain active.
   - I feel significantly disfigured and limit my activities due to my appearance.
   - I cannot be with people due to my appearance.

3. Activity. (Check one box: ☐)
   - I am as active as I have ever been.
   - There are times when I can't keep up my old pace, but not often.
   - I am often tired and have slowed down my activities although I still get out.
   - I don't go out because I don't have the strength.
   - I am usually in bed or chair and don't leave home.

4. Recreation. (Check one box: ☐)
   - There are no limitations to recreation at home or away from home.
   - There are a few things I can't do but I still get out and enjoy life.
   - There are many times when I wish I could get out more, but I'm not up to it.
   - There are severe limitations to what I can do, mostly I stay at home and watch TV.
   - I can't do anything enjoyable.

5. Swallowing. (Check one box: ☐)
   - I can swallow as well as ever.
   - I cannot swallow certain solid foods.
   - I can only swallow liquid food.
   - I cannot swallow because it "goes down the wrong way" and chokes me.

6. Chewing. (Check one box: ☐)
   - I can chew as well as ever.
   - I can eat soft solids but cannot chew some foods.
   - I cannot even chew soft solids.
7. **Speech.** (Check one box: ☐)
   - My speech is the same as always.
   - I have difficulty saying some words but I can be understood over the phone.
   - Only my family and friends can understand me.
   - I cannot be understood.

8. **Shoulder.** (Check one box: ☐)
   - I have no problem with my shoulder.
   - My shoulder is stiff but it has not affected my activity or strength.
   - Pain or weakness in my shoulder has caused me to change my work.
   - I cannot work due to problems with my shoulder.

9. **Taste.** (Check one box: ☐)
   - I can taste food normally.
   - I can taste most foods normally.
   - I can taste some foods.
   - I cannot taste any foods.

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

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

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

Which issues have been the most important to you during the past 7 days?
Check ☒ up to 3 boxes.

- Pain  ☐  Swallowing  ☐  Taste  ☐
- Appearance  ☐  Chewing  ☐  Saliva  ☐
- Activity  ☐  Speech  ☐  Mood  ☐
- Recreation  ☐  Shoulder  ☐  Anxiety  ☐
GENERAL QUESTIONS

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

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

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

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

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (check one box: ☐)

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

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).
The aim of this study is to learn about thickened liquids, and whether or not they prevent thin, fast flowing liquids from “going down the wrong pipe” in individuals who have been treated for base of tongue cancer with radiation with or without chemotherapy.

Participating in the study involves two 1-hour sessions, and two optional follow-up phone calls, for which you would be compensated with a Shopper’s Drugmart giftcard. The study involves the following five tasks:

- **Questionnaires**: you fill out two questionnaires related to your swallowing;
- **Liquid “Acceptability” Testing**: you sample different thicknesses of lemon-flavoured water and rate the “likeability” on a visual scale provided;
- **Chew-and-spit task for Saliva Collection**: you chew on a sterile piece of gauze for 2 minutes, and then spit it out into a cup to be weighed;
- **Videofluoroscopy Swallow Assessment**: you will swallow thin and thickened liquids with barium under X-ray in order to see your swallow (this is typically done in patients who have trouble with their swallowing);
- **Tongue Pressure Measurements**: you squeeze an air bulb (pictured below, right) between your tongue and the roof of your mouth.

We would like to look at your swallow, and see if slightly thickened liquids help you to swallow safer. If we identify liquids that help and you would like to be provided with thickener, we will teach you how to thicken for home use.

If you have recently undergone (or are undergoing) radiation treatment for cancer located in the base of tongue, and you are interested in participating in this study, please let your medical oncologist know. You can also contact the study coordinator, Carly Barbon, at 416 597 3422 X 7839 or by email at carly.barbon@uhn.ca to discuss this study. If we do not hear from you in the next 2 weeks, Carly will contact you by phone to confirm whether or not you are interested in participating.
CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

Investigator: Catriona M. Steele, Ph.D.
Senior Scientist, Toronto Rehabilitation Institute
550 University Avenue, Room 12030,
Toronto, ON, M5G 2A2
Phone: 416-597-3422, extension 7603
Fax: 416-597-7131

Sponsor: National Institute on Deafness and Other Communication Disorders (USA)
Grant #: 2 R01 DC011020-04

Contact Information:
Clinical Research Coordinator: Carly Barbon
Phone: 416-597-3422 Ext. 7839
E-mail: tri-swallowinglab@uhn.ca

Please note that the security of e-mail messages is not guaranteed. Messages may be forged, forwarded, kept indefinitely, or seen by others using the internet. Do not use e-mail to discuss information you think is sensitive. Do not use e-mail in an emergency since e-mail may be delayed.
Introduction:
You are being asked to take part in a research study. Please read the information about the study presented on this form. This form includes details on the study’s risks and benefits that you should know before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the investigator or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

Background/Purpose
Swallowing is an activity that we perform many times per day, without giving it a second thought. However, a large number of individuals with head and neck cancer experience dysphagia, or disordered swallowing after their cancer treatment. Specifically, patients can experience food/liquids going down the wrong way when swallowing, which can be dangerous to one’s health.

People with swallowing impairment often have difficulty controlling the flow of very thin liquids like water. **The aim of this research study** is to learn more about swallowing and what can help to stop liquids from going the wrong way while swallowing (aspiration.)

We are interested in learning how liquids of different consistencies flow through the throat during swallowing in individuals who have had radiation treatment for head and neck cancer. We would like to know if these liquids can prevent aspiration. We would also like to know how acceptable these liquids are to individuals who are asked to swallow them, and whether or not different types of thickener impact the acceptability of these liquids.

You will be one of 12 participants in this study. For this experiment, we will enroll adults who have recently completed radiation treatment for tongue cancer.

Study Procedure
If you agree to take part in this study, you will need to attend two or three 1-hour appointments, and you will have two optional follow-up phone calls, scheduled on different days:

1) **Appointment #1:**
First, we will review the research study with you and answer your questions. If you wish to proceed, we will ask you to sign the consent form. We will then ask you some brief questions about your health to make sure that there are no situations like allergies that suggest that you should not participate.
2) **Appointment #2:**
The second session will be held in the Swallowing Rehabilitation Research Laboratory at the Toronto Rehabilitation Institute. You will be provided with three questionnaires, so that we can be aware of your current diet level and how your swallowing function impacts your quality of life. We will also ask you to sample 10 cups of thickened liquid and indicate how much you like or dislike these liquids on a rating scale. Appointments 1 and 2 may be combined in a single session if that is most convenient for you.

3) **Appointment #3: Swallowing X-ray**
An appointment will be scheduled at the x-ray department of the Toronto General Hospital. During this procedure, we will collect 3 different types of measures:

   a) **Collection of Saliva**
   We will measure your saliva to determine the amount you produce while chewing. You will be asked to chew on a piece of gauze for approximately two minutes. The gauze will then be removed from your mouth and weighed to determine the amount of saliva you produce.

   b) **Tongue Pressure Measurements**
   We will measure the amount of pressure your tongue generates during swallowing. To do this, we will attach a strip containing 3 air-filled pressure sensors to the roof of your mouth, as shown in the Image. Small tubes run from the sensor strip to a computer, which will register the pressure in each air-filled bulb. The sensor strip is attached using a medical adhesive strip, like a band-aid. This adhesive is easily removed at the end of the appointment.

   c) **X-ray Movie of your Swallowing**
   We will collect an x-ray movie of your swallowing called a videofluoroscopy. We will ask you to take a total of 15 sips of liquids containing barium and prepared to different consistencies (thin, slightly-thick and mildly-thick) Barium is a safe substance that is visible on an x-ray. The swallowing x-ray (videofluoroscopy) is a procedure that is used...
in clinical practice to document the presence and severity of swallowing abnormalities, including (but not limited to) aspiration.

If deemed appropriate, you may be offered to complete a follow-up component. For those who wish to participate, this optional component will involve being recommended a thickener based on your swallow study results. If you are recommended a thickener, you will be asked to participate in the follow-up phone call component. The thickeners that will be used include xanthan-gum based and starch-based thickeners. These are over-the-counter thickeners, typically used and prescribed to individuals with swallowing disorders. Those participants who do not complete the follow-up component will not receive any follow-up phone calls.

4) Follow-up Telephone Call (optional)
1. We will call you approximately two weeks after the final session. During this call, we will ask you approximately 8-10 questions regarding a prescribed thickener that have been provided to you at the end of your videofluoroscopy.

2. A second and final telephone call will be made approximately 3 months after the videofluoroscopy. This time, you will be asked a few questions about the thickener provided. If you do not receive a two week follow-up call, you will not receive a 3-month follow-up call.

Potential Risks
Taking part in this study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about, which have not been seen in humans to date. Please call the investigator or study staff if you experience any side effects, even if you do not think it has anything to do with this study.

The risks we know of are:

- You might experience irritation from the glue used to attach the tongue-pressure bulbs. The glue usually wears off within 90 minutes following the data collection. If you know that you are allergic to latex or dental glues, please tell us this. In the case that you experience an unexpected allergic reaction, standard emergency procedures will be followed.
- You may dislike the taste or texture of some of the liquids that we ask you to swallow in the study. You are free to discontinue participation at any time.
- Your tongue and swallowing muscles may become tired during data collection. Please let us know immediately if you experience any pain or discomfort. You are free to discontinue any particular session or to withdraw from the study at any time.
• You will receive an x-ray test called a videofluoroscopy. **Videofluoroscopy** involves low levels of radiation exposure, which carries a risk of radiation effects (such as cancer). Radiation dose is measured in millisieverts (mSv). Background radiation exposure is known to occur in everyday activities such as flying in a plane (0.005 mSv per hour) or between 2 and 4 mSv background radiation exposure each year. The videofluoroscopy in this study is expected to involve dose of <0.35 milliSieverts. This dose is about the same exposure as 40 hours of flying in an airplane. A dose of 0.35 mSv corresponds to a risk of 1 in 39,000 of developing a radiation-induced stochastic effect from a videofluoroscopy, which is considered very rare.

Having videofluoroscopy after completion of radiation therapy for treatment of cancer is not expected to contribute to additional toxicity, due to the low dose of exposure in comparison to a standard radiation treatment protocol for head and neck cancer.

• Aspiration (entry of material into the airway) is a possible risk when you swallow. This risk is always present during swallowing. If you experience aspiration during the swallowing x-ray, we will follow standard procedures to encourage coughing and throat clearing to expel the aspirated material from your airway and we will discontinue data collection immediately. If we identify that you experience aspiration, we will arrange a follow-up appointment to discuss the issue with you, and will provide you with a report to take to your family doctor identifying recommended next steps.

• Choking is an extremely unlikely event, but is always a risk during swallowing. In the event of choking during data collection, routine emergency procedures will be followed. All study personnel carry current CPR certification.

**Incidental Findings**

In the unlikely event that the videofluoroscopy reveals an unexpected medical finding, we will consult the on-call radiologist and generate a clinical report with the observation for you to take to your family doctor. We will arrange a separate appointment to discuss these findings with you and will suggest appropriate resources for any further investigations that might be needed.

**Benefits**

Proposed liquids presented during the videofluoroscopy study may prevent or limit signs of aspiration and/or aid for a more comfortable swallow. During the videofluoroscopy, you will be notified if any of the liquids may provide benefit to your swallowing, and it will be recommended that you continue to consume these liquids after your videofluoroscopy.
Confidentiality

If you agree to participate in this study, we will collect some of your personal health information. The specific personal health information that we will collect is your:

- Name and initials
- Year of birth
- Sex
- Race and ethnicity
- Contact information (for contact purposes only):
  - your mailing address including the postal code;
  - your telephone number;
  - your email address.
- Health information related to your participation in the study.

Any information learned about you during the study will be kept confidential. Your name and any other identifying information will not be made available to anyone other than the investigators. You will not be named in any reports, publications or presentations that may come from this study.

Representatives of the University Health Network including Research Ethics Board and the funding sponsor may also access the study records for auditing and review purposes.

Information we collect about you through this research project, including information about your health and the care you receive, will be stored on a computer system. Some information about you may also be stored in paper form, in research or clinical hospital charts. Paper records will be kept stored in a secure locked filing cabinet in the Dr. Steele’s office or the Swallowing Rehabilitation Research Laboratory at Toronto Rehabilitation Institute. Computer records will be kept in a secure, password-protected drive on the Toronto Rehab research server and a back-up hard drive. All research records will be destroyed after a period of 10 years.

Information in Clinical Records

Since the x-ray information collected in this study may be useful in supporting your current or future clinical care, this information will be included in your UHN electronic patient record. UHN also shares information with other health care organizations in order to provide patients with care. For this reason, the information related to your health or care collected for this research might also be shared with other hospitals or health care providers in Ontario who are providing you with health care or treatment. The kind of information that will be collected for this research study and could be shared includes the results of the swallowing x-ray. If you have any concerns about this, or have any questions, please contact the UHN Privacy Office at 416-340-4800, x6937 (or by email at privacy@uhn.ca)
Voluntary Participation
Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time.

We will give you new information that is learned during the study that might affect your decision to stay in the study.

Withdrawal from the Study
You can withdraw from this study at any time without further consequences or limitations. If you choose to leave the study, this will have no impact on any clinical services you require at the University Health Network.

If at any time during data collection the study staff become concerned that you are having difficulty tolerating the study procedures, they will discontinue data collection and withdraw you from the study.

Honorarium
Participants who complete at least one data collection session will receive a $50 honorarium as a token of appreciation for participating in the study. This will be paid at the end of your final data collection visit. If you end up discontinuing the study early (i.e., after the first session but before the videofluoroscopy), you will still receive the honorarium.

Conflicts of Interest
The National Institutes of Health in the USA have funded this study and will reimburse the hospital and researcher for the costs of doing this study. All of these people have an interest in completing this study. Their interests should not influence your decision to participate in this study.

In this study, we will be asking you to swallow liquids prepared with Bracco EZPaque Barium powder and with two thickening agents manufactured by Nestlé (ThickenUp™ and ThickenUp Clear™). These products have been chosen because they are readily available and approved for clinical use in Canada. Dr. Steele, the principal investigator for the study, has past and current research relationships with Bracco Canada and with Nestlé Health Science. She also serves in an advisory capacity to Nestlé Health Science on expert panels. Neither Bracco Canada nor Nestlé Health Science are involved as sponsors of this study and they will not have access to the study data. The products for this study will be purchased from the study budget. Dr. Steele will not receive any payments (either personally or to the lab) from Bracco Canada or Nestlé Health Science related to the use of these products in the study.
Participant’s Rights
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Future Use of Images
We would like your permission to use the images collected from this research study in future conference presentations and teaching. A separate form will be provided to you; however, you do not have to give your permission for this request.

Questions about the Study
If you have any questions, concerns or would like to speak to the study team for any reason, please call:

Research Coordinator Carly Barbon
Tel: 416-597-3422, extension 7839; e-mail: tri-swallowinglab@uhn.ca

or

Principal Investigator Catriona Steele
Tel: 416-597-3422, extension 7603; e-mail: steele.catriona@uhn.on.ca.

If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (UHN REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential.

You will be given a signed copy of this consent form.
Consent

This study has been explained to me and any questions I had have been answered.

I know that I may leave the study at any time. I agree to the use of my information as described in this form. I agree to take part in this study.

______________________________                  ______________________  __________________
Print Study Participant’s Name                      Signature                   Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

______________________________                  ______________________  __________________
Print Name of Person Obtaining Consent              Signature                   Date

______________________________                  ______________________  __________________
Print Name of Principal Investigator                Signature                   Date

Was the participant assisted during the consent process? ☐ YES ☐ NO

If YES, please check the relevant box and complete the signature space below:

☐ The person signing below acted as an interpreter for the participant during the consent process and attests that the study as set out in this form was accurately interpreted and has had any questions answered.

______________________________                  ______________________  __________________
Print Name of Interpreter                            Signature                   Date

Relationship to Participant                          Language

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

______________________________                  ______________________  __________________
Print Name of Witness                                Signature                   Date

Relationship to Participant
Introduction

- Stimuli for videofluoroscopy are intended to represent non-barium stimuli but the addition of barium is necessary for visualization.
- Studies suggest that barium may interact with thickening agents and contribute to further thickening.
- In this study, we explored the viscosities of starch and gum-thickened barium stimuli prepared in 20% and 40% weight-to-volume concentrations.

Viscosity Measurement

- Viscosity was measured on a TA 2000 Rheometer
- Measurements were performed at 25 degrees Celsius
- All liquids were tested with a unidirectional shear sweep from 0.1-1000/s.

Results

- A general trend of thickening was seen with the increase from 20% to 40% w/v barium:
  - Starch-thickened stimuli increased in viscosity by 30-212% (mean=95%);
  - Gum-thickened stimuli increased to a lesser degree, by 15-60% (mean=32%);
  - Starch-thickened liquids tended to thicken beyond their National Dysphagia Diet target range when prepared in 40% w/v barium concentration.

Conclusions

- Combining barium with thickened liquids will result in further thickening in a concentration dependent manner.
- The physiological impact of thickening that occurs as a function of barium concentration should be studied in order to allow for texture mapping between assessment stimuli and treatment recommendations.
- Addition of barium should be done in such a way that stimuli remain radiopaque for assessment purposes; however, caution should be taken when determining weight-to-volume proportions in order to avoid the thickening of stimuli.

Acknowledgments

- This project was funded by BRACCO Canada.
- We acknowledge Dr. David James and Peter Aldridge for assistance with the rheological testing required for this study.

For further information

Please contact swallowinglab@uhn.on.ca

Concentration-dependent increases in viscosity of barium thickened with gum and starch thickeners

Carly E. A. Barbon1,2, Catriona M. Steele1,2,3

1. Toronto Rehabilitation Institute – University Health Network, Toronto, Canada; 2. University of Toronto, Toronto, Canada; 3. Bloorview Research Institute, Toronto, Canada

<table>
<thead>
<tr>
<th>Barium Concentration</th>
<th>Water</th>
<th>Amount of EZPaque®</th>
<th>Thickener</th>
<th>Thicker Amount</th>
<th>Consistency</th>
<th>Final Sample Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% w/v</td>
<td>165 mL</td>
<td>37g</td>
<td>ThickenUpClear®</td>
<td>2.1 g</td>
<td>Nectar</td>
<td>175 mL</td>
</tr>
<tr>
<td></td>
<td>226 mL</td>
<td>51g</td>
<td>ThickenUp®</td>
<td>3.2 g</td>
<td>Honey</td>
<td>240 mL</td>
</tr>
<tr>
<td>40% w/v</td>
<td>155 mL</td>
<td>77g</td>
<td>ThickenUpClear®</td>
<td>1.2 g</td>
<td>Honey</td>
<td>175 mL</td>
</tr>
<tr>
<td></td>
<td>212 mL</td>
<td>100g</td>
<td>ThickenUp®</td>
<td>0.3 g</td>
<td>Spoon-thick</td>
<td>240 mL</td>
</tr>
</tbody>
</table>

Stimuli

- E-Z-Paque® powdered barium (BRACCO Diagnostics) was reconstituted with water in 20% w/v and 40% w/v concentrations, and mixed with thickeners to produce nectar-, honey- and spoon-thick barium.
- Thickening agents were:
  - a starch-based thickener (Nestlé Resource® ThickenUp®); and
  - a xanthan-gum based thickener (Nestlé Resource® ThickenUpClear®).
- Thickening agents were added according to manufacturer instructions and adjusted for the volume of the barium sample.
Notification of REB Initial Approval

Date: December 19th, 2016
To: Dr. Catriona Steele
Room 12-101, Toronto Rehabilitation Institute, 550 University Avenue
Toronto, Ontario, Canada, M5G 2A2

Re: 16-5190-CE
Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

REB Review Type: Expedited
REB Initial Approval Date: December 19th, 2016
REB Expiry Date: December 19th, 2017

Documents Approved:
- Protocol
- Consent Form- for Image Use
- Consent Form
- Recruitment Script
- Introduction
- Race and Ethnicity Inquiry
- Questionnaire
- MD Anderson Dysphagia Inventory-QOL
- Performance Status Scale-HN (Without inclusion of "Patient Name" information)
- 3 month Follow-up
- 2 Week Follow-up

Version date: August 23rd, 2016
Version date: November 30th, 2016
Version date: November 30th, 2016
Version date: November 2nd, 2016
Version date: November 30th, 2016
Version date: November 18th, 2016
Version date: November 18th, 2016
Received on: September 7th, 2016

Version date: 1990
Received on: September 7th, 2016
Received on: September 7th, 2016

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing.

Furthermore, members of the Research Ethics Board who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

Best wishes on the successful completion of your project.

Sincerely,

Jack Holland, MD FRCPC, Co-Chair, University Health Network Research Ethics Board
NOTIFICATION OF REB AMENDMENT APPROVAL

Date: March 1, 2017

To: Catriona Steele
Room 12-101; Room 12-101; Toronto Rehabilitation Institute; 550 University Avenue, M5G 2A2; Toronto, Ontario, Canada

Re: 16-5190
Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

REB Review Type: Delegated
REB Initial Approval Date: December 19, 2016
REB Amendment Approval Date: March 1, 2017
REB Expiry Date: December 19, 2017

Documents Approved:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Version Date</th>
<th>Version ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Form</td>
<td>February 14, 2017</td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>February 14, 2017</td>
<td></td>
</tr>
<tr>
<td>Questionnaire - UW-WOL-R4</td>
<td>December 31, 1999</td>
<td></td>
</tr>
</tbody>
</table>

The University Health Network Research Ethics Board has reviewed and approved the Amendment (16-5190.1) for the above mentioned study.

The Amendment is approved as described in the Amendment Description section. The Protocol is approved as modified by the changes within the Protocol.

Best wishes on the successful completion of your project.

Sincerely,
Larissa Potanina
Ethics Coordinator, University Health Network Research Ethics Board

For: Jack Holland
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.
NOTIFICATION OF REB AMENDMENT APPROVAL

Date: February 6, 2017

To: Catriona Steele
    Room 12-101; Room 12-101; Toronto Rehabilitation Institute; 550 University Avenue, M5G 2A2; Toronto, Ontario, Canada

Re: 16-5190
Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

REB Review Type: Delegated
REB Initial Approval Date: December 19, 2016
REB Amendment Approval Date: February 6, 2017
REB Expiry Date: December 19, 2017

Documents Approved:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Version Date</th>
<th>Version ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment</td>
<td>February 6, 2017</td>
<td></td>
</tr>
</tbody>
</table>

The University Health Network Research Ethics Board has reviewed and approved the Amendment (16-5190.0) for the above mentioned study.

Best wishes on the successful completion of your project.

Sincerely,

Larissa Potanina
Ethics Coordinator, University Health Network Research Ethics Board

For: Jack Holland
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.
NOTIFICATION OF REB AMENDMENT APPROVAL

Date: September 1, 2017

To: Catriona Steele
Room 12-101; Room 12-101, University Centre;
Toronto Rehabilitation Institute; 550 University
Avenue, M5G 2A2; Toronto, Ontario, Canada

Re: 16-5190
Physiological Flow of Liquids in Head and Neck
Cancer Patients: A Pilot Study

REB Review Type: Delegated
REB Initial Approval Date: December 19, 2016
REB Amendment Approval Date: September 1, 2017
REB Expiry Date: December 19, 2017

Documents Approved:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Version Date</th>
<th>Version ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Form</td>
<td>August 21, 2017</td>
<td></td>
</tr>
</tbody>
</table>

The University Health Network Research Ethics Board has reviewed and approved the Amendment (16-5190.3) for the above mentioned study.

The Amendment is approved as described under Amendment Description section.

Best wishes on the successful completion of your project.

Sincerely,

Larissa Potanina
Ethics Coordinator, University Health Network Research Ethics Board

For: Jack Holland
Co-Chair, University Health Network Research Ethics Board
NOTIFICATION OF REB RENEWAL APPROVAL

Date: December 8, 2017

To: Catriona Steele
   Toronto Rehabilitation Institute, University Centre, 550 University Avenue, Room 12-101, Toronto, Ontario, Canada, M5G 2A2

Re: 16-5190
    Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

REB Review Type: Delegated
REB Initial Approval Date: December 19, 2016
REB Renewal Approval Effective Date: December 19, 2017
Lapse In REB Approval: N/A
REB Expiry Date: December 19, 2018

The University Health Network Research Ethics Board has reviewed and approved the Renewal (16-5190.4) for the above mentioned study.

Best wishes on the successful completion of your project.

Sincerely,

Larissa Potanina
Ethics Coordinator, University Health Network Research Ethics Board

For: Jack Holland
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.
NOTIFICATION OF REB AMENDMENT APPROVAL

Date: January 16, 2018

To: Catriona Steele
Toronto Rehabilitation Institute, University Centre, 550 University Avenue, Room 12-101, Toronto, Ontario, Canada, M5G 2A2

Re: 16-5190
Physiological Flow of Liquids in Head and Neck Cancer Patients: A Pilot Study

REB Review Type: Delegated
REB Initial Approval Date: December 19, 2016
REB Amendment Approval Date: January 16, 2018
REB Expiry Date: December 19, 2018

Documents Approved:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Version Date</th>
<th>Version ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>consent form</td>
<td>November 20, 2017</td>
<td>16-5190.5</td>
</tr>
<tr>
<td>IntroPage</td>
<td>January 5, 2018</td>
<td>16-5190.5</td>
</tr>
<tr>
<td>protocol</td>
<td>November 20, 2017</td>
<td>16-5190.5</td>
</tr>
<tr>
<td>Amendment</td>
<td>November 20, 2017</td>
<td>16-5190.5</td>
</tr>
</tbody>
</table>

The University Health Network Research Ethics Board has reviewed and approved the Amendment (16-5190.5) for the above mentioned study.

The Amendment is approved as presented under Amendment Description section; the Protocol is approved as modified by the changes within the Protocol.
Best wishes on the successful completion of your project.

Sincerely,

Larissa Potanina  
Ethics Coordinator, University Health Network Research Ethics Board

For: Jack Holland  
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.
Notification of REB Initial Approval

Date: September 17th, 2015
To: Dr. Catriona Steele
Room 12-101, Toronto Rehabilitation Institute, 550 University Avenue, Toronto
Ontario, Canada, M5G 2A2

Re: 15-9431-D
Physiological Flow of Liquids in Healthy Swallowing

REB Review Type: Full Board
REB Meeting Date: August 26th, 2015
REB Initial Approval Date: September 17th, 2015
REB Expiry Date: September 17th, 2016

Documents Approved:
- Protocol
  Version date: September 16th, 2015
- Consent Form
  Version date: September 16th, 2015

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing.

Furthermore, members of the Research Ethics Board who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB. Specifically, Dr. Antony Burns, a UHN REB member, was not present during the discussion on the study due to a conflict of interest.

Best wishes on the successful completion of your project.

Sincerely,

Ann Heesters, BA MA BEd PhD (ABD)
Co-Chair, University Health Network Research Ethics Board