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# Impact of Feeding Tube Status on Health Outcomes for Individuals with Oropharyngeal Cancer

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Health and Rehabilitation Sciences

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## **Abstract**

This study investigated differences in outcomes related to health, swallowing, and quality of life (QoL) for individuals with oropharyngeal squamous cell carcinoma (OPSCC) receiving either radiotherapy (RT) alone, or concomitant chemoradiotherapy (CRT). Differences were assessed based on whether patients received a feeding tube (FT group) or not (NFT group). Measures including the Functional Oral Intake Scale (FOIS), Performance Status Scale for Head and Neck Cancer (PSS-HN), M.D. Anderson Dysphagia Inventory (MDADI), and weight were collected for 126 individuals at baseline, and at 3, 6, and 12 months post-treatment. Data were analyzed to identify potential prognostic differences between the groups, and to assess pre-treatment differences which may have led to the need for and dependence on enteral feeding. Within-group analyses were also performed to determine the trajectory of recovery for both groups. In general, the most notable differences were found at 3 months, with the NFT group performing significantly better in outcomes related to functional oral intake and swallowing-related QoL. However, patients in the NFT group were more likely to have clinically significant decreases in weight, even at 12 months, showing difficulty with recovering back to baseline status. Although the results of this retrospective chart review are preliminary, the findings have the potential to contribute to improved decision-making and communication in a clinical setting, and may ultimately lead to better outcomes for those with OPSCC.

*Keywords:* oropharyngeal cancer, radiotherapy, chemoradiotherapy, enteral feeding, swallowing, dysphagia, oral intake, quality of life

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## Chapter 1: Introduction and Review of Literature

### Overview

To achieve favourable post-treatment outcomes, individuals diagnosed with head and neck cancer (HNC) are often prescribed aggressive forms of treatment, including surgery, radiotherapy (RT) and/or chemotherapy – alone or in combination (Guru, Manoor, & Supe, 2012). Despite being effective at treating HNC, and often successful in preserving organ structure, issues related to organ function are commonly experienced by patients/survivors (Shaw et al., 2015). Treatment-induced complications such as dysphagia (difficulty or discomfort in swallowing), oral mucositis (erythematous and ulcerative lesions of the oral mucosa), fatigue, xerostomia (subjective complaint of dry mouth), dermatitis (inflammation of the skin) and pain significantly impact the quality of life (QoL) and well-being of survivors (Manoor et al., 2012). Moreover, due to the unique anatomic location of the tumour itself (in the head and neck region) and the resultant impairments, difficulty and pain with oral intake is often experienced. As a result, the patient's ability to obtain the nutrition necessary to meet energy requirements and effectively undergo treatment is compromised, subsequently increasing the risk of weight loss (Shaw et al., 2015).

Current literature suggests that one marker of successful patient-centred treatment of HNC is the prevention of weight loss (Languis et al., 2016; Shaw et al., 2015; Bhayani et al., 2013), emphasizing the importance of nutritional management for this clinical oncology population. Consequently, physicians routinely utilize enteral feeding for nutritional support when oral intake is insufficient or inadequate (Lees, 1997; Magne et al., 2001). Enteral feeding tubes, such as a percutaneous endoscopic gastrostomy (PEG) tube, provide an alternative

method for patients to obtain adequate nutrition. Eating by mouth might be restricted due to treatment-related issues, such as pain, but also general fatigue. Patients often eat less because of pain, changes in taste, and altered energy levels. Severe treatment-related dysphagia can encompass a variety of issues such as poor mobility of the swallowing mechanism, altered sensation, increased risk of choking, and chronic aspiration, which also can lead to an overall reduced ability to sustain an oral diet (Nguyen et al., 2006).

Instead of relying on oral consumption of food/liquids, which may become more difficult and painful over the course of treatment, feeding tubes allow for more direct access to the gastrointestinal tract, such as into the stomach (enteral route), in cases where the tube has been inserted through the wall of the abdomen (Paleri & Patterson, 2010). Because this method allows patients to bypass the mouth and upper aerodigestive tract while meeting nutritional needs, pain associated with treatment-related toxicities is avoided, in turn allowing patients to receive adequate nutrition despite impaired swallowing function (Paleri & Patterson, 2010). As a result, it is believed that the risk of weight loss and malnutrition often experienced during treatment can be minimized or avoided altogether (Brown et al., 2015).

Despite the abundant literature demonstrating the impact of differing methods of enteral feeding, such as prophylactic versus reactive placement approaches (to be addressed in full later on in the paper) on weight loss and other swallowing-related health outcomes, little attention has been placed on determining the impact of feeding tube status on specific outcome measures. This includes variables such as the Functional Oral Intake Scale (FOIS), the M.D. Anderson Dysphagia Inventory (MDADI), the Performance Status Scale for Head and Neck Cancer (PSS-HN), weight, and feeding tube duration. At present the use of enteral feeding tubes

differs across institutions, and even across health care professionals within institutions. Paired with the fact that patients are encouraged to consume food by mouth even if they receive a feeding tube (Bhayani et al., 2013; Hutcheson et al., 2013), discrepancies in usage may be present despite the same method being utilized. As such, documenting feeding tube status and investigating the impact it has on these specific health outcomes may provide valuable information regarding the impact of feeding tube use on swallowing function and QoL of patients.

Due to the complex nature of treatment and the variety of ways in which treatment may be prescribed, it is important to not only investigate the differences between groups of patients who have received a tube or not, but to also consider how each group changes over time during the course of treatment with respect to the outcome variables of interest. In addition, examining how patients respond to treatment depending on their feeding tube status, rather than simply focusing on method of administration (prophylactic vs. reactive), will provide insight into the potential advantages and disadvantages of administering a feeding tube. Furthermore, determining the impact of feeding tube status on factors such as oral intake and QoL and investigating how they change during/after treatment offers a strategic advantage. By doing so, physicians may be able to better communicate with patients and set goals based on what amount of oral intake would be ideal depending on whether or not they have a feeding tube in place. It also establishes a sort of benchmark, indicating at what level/measure a patient should be at a specific point in time depending on whether or not they have a feeding tube in place.

## Head and Neck Cancer

Head and neck cancer (HNC) is a broad disease term encompassing epithelial malignancies arising in the oral cavity, paranasal sinuses, nasal cavity, pharynx and larynx (Canadian Cancer Statistics, 2015). HNC is currently the 13<sup>th</sup> most common type of cancer in Canada, affecting roughly 36,000 new Canadians each year (Forte, Niu, Lockwood, & Bryant, 2012). Worldwide, HNC is the fifth most common type of cancer with the seventh highest cancer mortality (Guru, Manoor, & Supe, 2012). This translates into greater than 500,000 new cases per year worldwide, adding to a global prevalence of 900,000 diagnosed individuals (Shaw et al., 2015). Most of the epithelial malignancies falling under the umbrella term HNC are squamous cell carcinoma of the head and neck (SCCHN; Argiris, Karamouzis, Raben, & Ferris, 2008). Squamous cells are found in mucous membranes (moist tissue lining cavities like the blood vessels, lungs, intestines and airways), allowing for necessary bodily processes to be carried out efficiently (Argiris et al., 2008). About 66% of patients diagnosed with SCCHN have advanced stage disease, often involving local lymph nodes. Nevertheless, distant metastasis upon initial presentation is uncommon, occurring in only 10% of patients (Ries et al, 2007).

The complexity of this disease is emphasized by its heterogeneous nature, with variation (with regards to risk factors, diagnosis and treatment) being present across different anatomic sub-sites. The oral cavity, representing the uppermost part of the digestive tract, starts at the lips and ends at the anterior surface of the faucial arch (Omura, 2014). Necessary for functions such as mastication, swallowing, and speech, the mucosal aspect of the oral cavity can be divided in to five main sites: the tongue, the floor of the mouth, maxillary/mandibular gingiva, buccal mucosa, and hard plate (Omura, 2014). Currently, oral cancer is the sixth most common

cancer worldwide, and is primarily treated according to the disease stage. Still, the main treatment modality for this disease remains to be surgery, offering the distinct advantage of adequate tumour tissue clearance and in turn decreasing the risk of local/regional recurrence, and increasing long-term survival rates (Omura, 2014).

The oropharynx is often described as the region of the pharynx immediately posterior to the oral cavity, including the palatine tonsils, base of tongue, lateral walls of the pharynx, and posterior pharyngeal wall (Sasegbon & Hamdy, 2016; National Cancer Institute, 2002). While there are various types (e.g., salivary gland carcinomas and lymphomas of Waldeyer's ring), oropharyngeal squamous cell carcinoma (OPSCC) makes up over 95% of oropharyngeal cancers (van Monsjou, Balm, van den Brekel, & Wreesmann, 2010). For most OPSCCs, the standard of care is RT, with or without chemotherapy (Bhayani et al., 2013)

The larynx, positioned between the base of the tongue and trachea, contains the vocal cords and is responsible for producing phonation. In addition, the larynx is also functions to protect the airway, and to regulate intra-thoracic and intra-abdominal pressure (Sasaki & Isaacson, 1988). Early stage laryngeal cancer is often treated using radiation therapy or transoral laser excision, while treatment of locally advanced laryngeal cancer favours a surgical approach, often requiring a total laryngectomy (Licitra et al., 2003; Tomeh & Holsinger, 2014). However, since performing laryngectomy is associated with poor health outcomes for patients (Daly et al., 2010), non-surgical, organ preserving treatments have been thoroughly investigated. Literature suggests that combining chemotherapy and RT for advanced carcinoma of the larynx provides similar results when compared to surgical treatment options (Wolf et al., 1991; Forastiere et al., 2003; Featherstone et al., 2004).

Risk factors associated with the development of HNC cancer are well-established, with the most significant being tobacco and alcohol abuse, as well as poor oral hygiene (Vineis et al., 2004). In fact, combined abuse of tobacco and alcohol has been demonstrated to lead to a three to six-fold increase in risk for the development of a malignant tumour of the tongue or oral mucosa (Wermker et al., 2011). Furthermore, the two risky behaviours are implicated in about 75% of all HNC, and when used in combination have an amplified effect (Vineis et al., 2004; Blot et al., 1988; Tuyns et al., 1988). In addition to placing individuals at a higher risk for HNC, these risk factors are often associated with poor nutrition and a reduced body mass index (BMI). This further contributes to difficulty with nutrition and weight management, which are recognized as important variables associated with successful treatment and recovery (Vineis et al., 2004). Not only does treatment vary based on the sub-site, but data also suggest that risk based on alcohol and tobacco use also differs according to the carcinoma location (Bhayani et al., 2013). Laryngeal cancer has a strong correlation with the use of tobacco, whereas alcohol use has been shown to have a strong correlation with an increased risk for oral and oropharyngeal cancer (Hashibe et al., 2009; Lubin et al., 2009; Purdue et al., 2008). Despite a decrease in risky behaviours such as smoking, oropharyngeal cancer incidence has been on the rise (Bhayani, 2013).

Conventionally, OPSCC is categorized as SCCHN, and grouped together with squamous cell carcinomas of all other sub-sites. While this may be useful based on the commonality shared between cancers of squamous cells, OPSCC is unique due to its etiological, biological and epidemiological characteristics (van Monsjou et al., 2010). The rise in incidence of OPSCC has been attributed to human oncogenic papillomavirus virus (HPV), as it has been found in 77% of

all patients with oropharyngeal cancer (De Stefani et al., 2013). Although the increased incidence of oropharyngeal cancer is concerning, improved survival outcomes are often seen with these patients compared to those with HNC not caused by HPV (Gillison et al., 2000; Ang et al., 2010; Chung & Gillison, 2009; Jemal et al., 2004). As a result, an HPV positive diagnosis is favourable for prognosis in patients with SCCHN. Tumours positive for HPV have been shown to respond better to chemoradiotherapy (CRT) treatment, and may be more prone to immune surveillance of tumour-specific antigens when compared to HPV-negative tumours (Argiris et al., 2008). Therefore, the HPV status of a HNC patient may serve as an important predictive biomarker, and is now taken into consideration during treatment. Because of the unique etiologic association between HPV and OPSCC, treating patients with OPSCC will differ based on whether or not the virus is present, as well as what structures of the oropharynx are involved.

### **Cancer of the Oropharynx**

Cancer of the oropharynx, as well as the treatment used to eradicate the disease has the potential to impede several vital functions. The oropharynx, which includes the soft palate, base of the tongue, side and back of the throat, and tonsils (National Cancer Institute, 2002), is one component of the pharynx, a hollow tube-like structure through which food and air pass on their way to the esophagus or trachea, respectively (National Cancer Institute, 2002). Therefore, it is clear that cancers arising in this region would negatively impact an individual's ability to eat and drink, considering the anatomical location of the involved structures. Out of the involved structures, the tonsils are most commonly the site of oropharyngeal cancer, followed by base of tongue cancer (Licitra et al., 2002).



OPSCC makes up the vast majority of oropharyngeal cancers and in general has survival rates comparable to that of SCCHN. When diagnosed with OPSCC, it has been suggested that individuals have a 5-year survival rate of approximately 66% (Howlader et al., 2014).

Oropharyngeal tumours, especially those that arise at the base of the tongue, are often more advanced when diagnosed, and are also more likely to have spread locally to adjacent lymph nodes. Tumours are often larger (i.e., more advanced), with evidence of local spread of disease by early detection made difficult since small tumours cause little discomfort and/or pain, ultimately going unnoticed (Ramqvist & Dalianis, 2010). Moreover, even when oropharyngeal tumours are at a similar stage, have comparable histologic features, and standardized treatment (often involving CRT) is used, predicting functional outcomes is difficult. A late diagnosis may also relate to the fact that initial symptoms of oropharyngeal cancer are often attributed to the presence of chronic inflammatory disease of the pharynx mucosa (Licitra et al., 2002). For this reason, establishing predictive/prognostic indicators would be clinically valuable in terms of prevention and treatment for OPSCC (Ramqvist & Dalianis, 2010).

### **Treatment of OPSCC**

**Surgical options.** With a demographic shift to a much younger population (related to the increase in HPV-associated OPSCC) that is usually high functioning and absent of comorbid illnesses, in combination with higher overall and disease-free survival rates, approaches concerned with the preservation of organs and functioning and have become even more relevant (Nasman et al., 2009). As such, open surgery has fallen out of favour, but transoral surgical approaches are now associated with promising results. The use of transoral robotic surgery (TORS) has demonstrated the ability to positively improve post-treatment functioning

and QoL for individuals diagnosed with OPSCC (Dowthwaite et al., 2012) and for some patients, this may be the treatment of choice.

**Radiation therapy treatment.** Radiation therapy is routinely used in the treatment of HNC. For many early stage cancers, RT may be the only treatment necessary (Guru, Manoor, & Super, 2012). Organ-sparing treatments (i.e., treatments that do not involve removal of complete structures), such as RT and chemotherapy, are often successful at treating HNC and are able to preserve tissue structure without compromising patient survival outcomes (Shaw et al., 2015). Previously, 3D-conformal RT was used to achieve such results (Marta et al., 2013). Technological advancements in radiation therapy techniques have also yielded improvements in the capacity of treatment to deliver radiation effectively to the tumour while minimizing irradiation of normal tissues surrounding the target (Sheets et al., 2014). Since many tissues in close proximity to the area being treated with radiation therapy are at risk, contouring around and avoiding these areas has been vital in maintaining function post-treatment (Sun et al., 2013).

The emergence of new techniques has led to the development of intensity-modulated radiotherapy (IMRT), an advanced form of 3D-conformal RT which uses non-uniform radiation intensities to achieve a higher dose-delivery to the tumour, while simultaneously limiting the radiation dose directed to surrounding tissues (Sheets et al., 2014; Marta et al., 2013). Sparing adjacent tissues (e.g., salivary tissues) from the toxic effects of radiation will allow for improved rehabilitation while minimizing associated adverse effects from treatment. IMRT offers several advantages over conventional RT treatment including a reduction in side effects (especially xerostomia), as well as reduced damage to the parotid gland, preserved salivary flow, and

improved quality of life for patients (Sheets et al., 2014; Marta et al., 2013). Since maintaining nutritional status is crucial for successful treatment (i.e., ridding the body of the tumour while minimizing toxicities and maintaining a high QoL post-treatment), reducing the severity of side effects such as dysphagia and xerostomia may allow patients to eat/drink more comfortably, resulting in improved weight control, nutritional status, and overall allow for patients to be less effected by treatment in a negative manner. Accordingly, IMRT has been adopted as the primary treatment modality in clinical settings (Marta et al., 2013).

**Concomitant/concurrent chemoradiotherapy.** Treatment of HNC is often further intensified by the addition of a chemotherapy regimen. As a result of the unacceptably low survival rate of this patient population (Lasrado et al., 2014), the feasibility and impact of concomitant/concurrent CRT (instead of RT alone, or one followed by the other) has been extensively researched. Concomitant CRT is an alternative, combined modality treatment option for HNC patients, involving the use of chemotherapy drugs in addition to RT (Bernier & Cooper, 2004). Different classes of agents, including platinum compounds, antimetabolites, and taxanes have demonstrated effectiveness in treating SCCHN (Covelas, 2006). Cisplatin, a chemotherapeutic platinum-based compound, is currently regarded as a standard agent used in combination with radiation therapy.

Another common platinum-based compound used in chemotherapy regimens is carboplatin, which is typically well tolerated but less active (thus may take more treatments to administer) than cisplatin (De Andres et al., 1995; Forastierre et al., 1992) despite their similar radiosensitizing (the ability to make tumour cells more sensitive to RT) capabilities (Jeremic et al., 1997). Additionally, agents involved in the suppression of epidermal growth factor receptor

(EGFR) such as cetuximab are becoming more widely used for CRT (Karamouzis, Grandis, & Argiris, 2007). The ability of such agents to suppress this receptor, which is responsible for many critical cellular functions in epithelial malignancies and whose expression is detected in more than 90% of SCCHN patients, allows for improved locoregional control. Magrini et al. (2016) found that hematologic, renal, and GI toxicities were more frequently observed in patients treated with concomitant cisplatin compared to those treated with concomitant cetuximab. On the contrary, cutaneous toxicity and the need for nutritional support were discovered to be significantly more frequent in the group receiving concomitant cetuximab treatment. Factors such as patterns of failure, locoregional control, and survival were similar between the two groups of patients (Magrini et al., 2016). All of the listed compounds are commonly used in CRT treatment, and are likely to form part of the treatment received by participants in this research investigation.

In spite of the advantages and apparent superiority of CRT as a treatment modality as demonstrated in a number of large randomized controlled trials (Adelstein et al., 2003; Brizel et al., 1998; Budach et al., 2005), the use of CRT has also been associated with increased treatment-related toxicities (Adelstein et al., 2003; Brizel et al., 1998; Aquilar-Ponce et al., 2013; Vokes et al., 2000; Moroney et al., 2017). In fact, patients receiving IMRT alone experience a lower incidence of adverse events and symptoms compared to those receiving CRT, with CRT patients having at least twice the risk of experiencing most symptoms (Moroney et al., 2017). The increase in adverse events such as dysphagia, mucositis (oral and pharyngeal), xerostomia, nausea, and radiodermatitis can lead to even more difficulty in nutritional management for HNC patients because of their negative impact on the structure and

functioning of the head and neck (Moroney et al., 2017). These issues make eating and drinking even more painful and difficult than when RT is used alone, emphasizing the importance of proper nutrition throughout treatment, which is especially important for this patient population. However, because of high locoregional control (Al-Sarraf et al., 1997; Vokes et al., 2000; Bernier & Cooper, 2004), increased survival rates with organ preservation (Bonner et al., 2004; Vokes et al., 2000, Bernier & Cooper, 2004) and the capability to reverse a historical pattern of failure with more traditional, monotherapeutic treatments (Vokes et al., 2000), CRT is commonly used in modern clinical practice and thus will be the main treatment modality utilized by physicians in this research study.

OPSCC is cured at a relatively high rate, especially in cases of HPV-positive tumours (Ang et al., 2010). Not only do patients have relatively normal functioning and performance at baseline, but they are also living longer after completing treatment (Jang et al., 2013). Accordingly, treatment-related toxicities should play a key role in determining treatment strategy. Due to the prolonged life expectancy, coupled with the common need for enteral feeding, emphasis should be placed on minimizing the toxic effects of treatment (such as dysphagia and mucositis) as well as lowering the risk of becoming dependent on enteral feeding. These concerns raise numerous questions specific to how treatment-related side effects influence outcomes, particularly in association with feeding and nutritional status during and following treatment.

Critical to the improved survival outcomes are the treatments used for oropharyngeal cancer patients. New treatment advances are centred on de-escalation as a way to improve function post treatment, and in turn lead to improved health outcomes and QoL despite the

rise in incidence of oropharyngeal cancer. Research has shown that RT in combination with chemotherapy is ideal in improving locoregional control, organ preservation, and improved survival for these patients. For many centres, the standard of care for OPSCC for the last couple of decades has been CRT; in light of TORS, treatment paradigms may shift in the future.

### **Swallowing and Treatment-Related Side Effects**

Even though treatment has become more effective and less toxic for patients, CRT still has the unfortunate consequence of damaging healthy cells, and in turn, causing severe side effects. More specifically, CRT has broad ranging effects on muscle and connective tissue, mucosa, and salivary glands, and changes to any these structures may result in functional consequences/impairments, negatively affecting patients' health and QoL. These areas, along with the physiology and role of swallowing, will be presented briefly in the sections to follow.

**Physiology of swallowing.** Swallowing is a vital process necessary for survival and the enablement of life. Requiring the use of more than 30 muscles and nerves, and including the use of both volitional and reflexive behaviours, eating and swallowing are complex actions that allow for food and fluids to be ingested in a safe and efficient manner (Matsuo & Palmer, 2009). By doing so, the regular physiological and biochemical processes are maintained (Sasegbon & Hamdy, 2016). The physiology behind this multifaceted process is often described using the Four Stage Model, which includes the oral preparatory, oral propulsive, pharyngeal, and esophageal stages of swallowing (Matsuo & Palmer, 2009). In order to compensate for the inability of the Four Stage Model to describe the movement of the bolus and the process of eating solid food, the Process Model of Feeding was established (Palmer, Rudin, Lara, & Crompton, 1992; Dua, Ren, Bardan, Xie, & Shaker, 1997; Hiiemae & Palmer, 1999). This model

takes into account the formation of a bolus in the oropharynx several seconds preceding the pharyngeal stage and the passage and accumulation of portions of food in the oropharynx while food remains in the oral cavity during chewing. Together, these models encompass the whole swallowing mechanism and the passage of food from the mouth to the stomach. Issues are experienced at any point along the swallowing pathway may lead to dysphagia (Sasegbon & Hamdy, 2016).

For food and/or liquid to be safely consumed and subsequently digested as a means of obtaining nutrition, the swallowing process must go through stages according to the models described above. Consequences resulting due to difficulty with swallowing (dysphagia) can present themselves in various ways. One unfortunate consequence is aspiration, described as coughing or choking as a result of food entering into the trachea/windpipe through the larynx. Aspiration, if it occurs during the treatment of HNC in combination with neutropenia (deficiency in neutrophils predisposing patients to bacterial infection; Boxer & Dale, 2002), may lead to aspiration pneumonia, sepsis, and respiratory failure (Lakshmaiah et al., 2013). Avoiding aspiration is essential for the bolus to safely pass into the pharynx. Fortunately, built into the swallowing process are several mechanisms designed to protect against aspiration of materials into the trachea (Matsuo & Palmer, 2009). One way in which the trachea is protected during swallowing is by the closure of the larynx at various levels (Lundy et al., 1999). Closure of the vocal folds occurs to seal the glottis, with the arytenoids tilting anteriorly, contracting the base of the epiglottis prior to the opening of the upper esophageal sphincter (Matsuo & Palmer, 2009). Additionally, the epiglottis tilts back to cover the laryngeal opening, and the larynx and hyoid are pulled anteriorly and superiorly by the contraction of the suprahyoid and thyrohyoid

muscles, effectively removing the larynx from the path of the bolus (Lundy et al., 1999; Matsuo & Palmer, 2008). In essence, the larynx is displaced and tucked under the base of the tongue, preventing food and liquid from entering and moving further into the trachea. Improper coordination/timing of events which occur either prior to, during, or after the pharyngeal stage of swallowing, can also lead to aspiration despite the above-mentioned laryngeal mechanisms still being intact (Lundy et al., 1999).

In addition to protecting the airway to avoid an unsafe swallow and the potential consequences (i.e., aspiration and pneumonia), swallowing also facilitates efficient bolus flow to support nutrition and hydration (Sasegbon & Hamdy, 2016). When the bolus is transported from the oral cavity to the oropharynx, the pharyngeal response is initiated as well. A series of motor actions are subsequently activated, including the elevation of the soft palate, retraction of the tongue base, closure of the larynx and contraction of the pharynx. All of the actions listed above are required for efficient transport of the bolus into the esophagus (Lundy et al., 1999). This explains why damage to the aforementioned structures (via CRT or surgical resection) will exhibit the greatest impact on swallowing (Mittal et al., 2003; Braggren et al., 2007). By ensuring sufficient food and liquid pass through the system to be absorbed, swallowing plays a major supportive role in obtaining required nutrients.

Many HNC patients receive a tube to keep them nourished, rather than to avoid unsafe swallowing (although this may be the case for some patients who may develop difficulty with closing off the airway). The supportive role of swallowing, often impaired due to treatment-related toxicities, is then taken on by the feeding tube. In summary, humans must swallow in order to protect the airway (preventing aspiration and possible pneumonia) and to get



sufficient food and liquid through the system, in turn supporting nutrition and hydration. Difficulty with swallowing (dysphagia) can affect this process and make it far more difficult to obtain nutrition and to maintain weight, which is especially concerning during CRT treatment. As well as being important for eating and allowing adequate nutrition and hydration to be obtained, swallowing has a part in the enjoyment of eating, which plays an important role in one's perception of their QoL (Sasegbon & Hamdy, 2016). Since eating and drinking can be enjoyable and positively affect one's QoL (Ney et al., 2010; Eslick & Talley, 2008), any impairment affecting the swallowing process has the potential to negatively impact QoL.

**Musculature and connective tissue.** A common yet serious and potentially dangerous complication resulting from HNC treatment and its damaging effects on human musculature and connective tissue is dysphagia (Nguyen et al., 2006). Dysphagia can be described as difficulty or discomfort in swallowing, often leading to malnutrition, dehydration, significant morbidity, increased mortality and decreased QoL (Langendijk et al., 2008; Nguyen et al., 2005). There are various diseases that have the potential to disrupt regular swallowing, thereby resulting in dysphagia (Sasegbon & Hamdy, 2016). In this case however, it is not the disease itself (although a tumour in the head and neck may be disruptive to the swallowing process if obstructive enough) causing dysphagia. It is the unwanted side-effects from treating the cancer affecting the musculature and connective tissues in the head and neck affecting the individual's ability to swallow. These harmful changes impact the patient's ability to eat by mouth, with potential to cause malnutrition, dehydration and aspiration pneumonia, leading to significant mortality and morbidity (Jaradeh, 1994).

The toxic effects experienced by patients receiving CRT are especially influential on the structure and function of the pharyngeal constrictor muscles. In spite of the numerous ways to measure dysphagia in HNC patients, including duration of feeding tube use, stricture, aspiration, videofluoroscopy, and physician/patient reported toxicity, the majority of research on the topic indicates that treatment-induced damage to the pharyngeal constrictor muscles is a main contributor to persistent and late dysphagia (Vlachic et al., 2013; Duprez, Madani, De Potter, Boterberg, & De Neve, 2013). Vlachic et al. also reported that only dose to the inferior pharyngeal constrictor muscle was associated with length of feeding tube dependency, further emphasizing the link between structure and function related to oral nutrition. The link between damage to pharyngeal constrictor muscles and treatment-induced complications (e.g. dysphagia, mucositis, etc.) is evident, indicating that healthy constrictor muscles are necessary to ensure proper swallowing function. Functioning of the constrictor muscles as a swallowing-related health outcome is valuable because of its association with feeding tube dependence and severe dysphagia (Shaw et al., 2015). In addition, functioning of the constrictor muscles is an objective measure of dysphagia, which is in turn significantly associated with patient morbidity (Shaw et al., 2015).

One of the most common and often debilitating consequences of cancer and its treatment is pain, especially with swallowing. Pain associated with swallowing is referred to as odynophagia, and along with dysphagia is quite common in HNC patients. Despite substantial improvements in the treatment of OPSCC, pain is still frequently experienced by patients (McMenamin & Grant, 2015). The tumour itself may be responsible for causing pain, potentially compressing blood vessels and/or nerves. Moreover, because CRT treatment is not yet able to

specifically target cancer cells, normal cells in close proximity to the cancerous ones are often damaged, causing many side-effects and pain (Epstein et al., 2010).

Increased pain may lead to subsequent issues including the use of opioid medication, feeding tubes, and potentially increase the risk of hospitalization (Murphy et al., 2009). Equally important is that odynophagia may result in a noticeable decrease in QoL, health-related QoL, and disease-free survival (McMenamin & Grant, 2015; Raber-Durlacher et al., 2011).

Odynophagia may cause the process of eating and drinking to become challenging or nearly impossible (thus the necessity of a feeding tube). Additionally, eating and drinking may not be pleasurable, and may take up a significant amount of time, impacting the patients' desire/motivation to eat and drink (Raber-Durlacher et al., 2011). The potential for pain to negatively impact oropharyngeal cancer patients is evident, and the fact that patients with higher levels of pain tend to have feeding tubes inserted means their ability to take in the required nutrition is compromised. Just like dysphagia, which may lead to a state of compromised nutrition due to difficulty with swallowing, odynophagia makes getting adequate levels of nutrition difficult simply because it hurts to do so. Enteral feeding can ensure nutritional needs are met in both the case of painful swallowing resulting from toxicities (i.e., odynophagia), and also in the case of impaired swallowing function (i.e., dysphagia).

**Mucosal damage.** In addition to dysphagia, toxic chemotherapeutic agents and radiation to the oral mucosa often damage the mucous membrane of the (aero)digestive tract, leading to mucositis and more specifically, oral mucositis if the affected mucous lines the oropharyngeal or oral region (Rastogi, Dwivedi, & Kazi, 2011). The subsequent inflammation of the mucous membrane can lead to oral pain and discomfort, an increased predisposition to

bacterial and fungal infections, and potentially severe ulcers that may last for five to seven weeks post-treatment (Rodriguez-Caballero et al., 2012; Lockhart & Sonis, 1981; Stokman et al., 2003). Pain associated with oral mucositis is exacerbated by movement of oral structures, thus impacting one's desire/ability to consume food orally. The risk for mucositis is increased by the use of concurrent CRT (Rastogi et al., 2011).

**Salivary glands.** Another common side-effect affecting HNC patients is xerostomia - a subjective complaint of dry mouth (Dirix, Nuyts, & Van den Bogaert, 2006). CRT is a common cause of xerostomia (Pinna, Campus, Cumbo, Mura, & Milia, 2015), with damage to the salivary glands resulting in reduced salivary output, and consequently leading to issues such as a sore throat, oral discomfort/pain, dental decay, modified taste, and impaired ability to chew and swallow (Pinna et al., 2015; de Graeff et al., 1999). Moreover, another complication of reduced salivary output is compromised immunity, a consequence resulting from the role of saliva in host defense of the oral cavity (Pinna et al., 2015).

More often than not, expressing the influence of subjective elements of health (e.g., the subjective sensation of dry mouth) as measurable quantitative outcomes is challenging. For xerostomia, however, this may not be the case. An investigation conducted by Kakoei et al. (2012) found that instead of salivary flow being the main predictor of QoL (up to 6 months post-treatment), patients' perception of xerostomia was more strongly correlated with changes in QoL. QoL was noted to significantly worsen over time, while the severity of xerostomia increased as well (Kakoei et al., 2012). The results indicate that a decrease in saliva and increase in xerostomia resulting from therapy play an important role affecting QoL, seemingly making it worse. In a recent study, Memtsa et al. (2017) corroborated the previous findings, in that the

subjective perception of xerostomia may strongly correlate with salivary flow, with QoL (as measured by several functional scales) deteriorating at 6 months post-treatment as salivary flow rate and xerostomia worsened as well (Memsta et al., 2017). Still, HNC patients may expect some relief from xerostomia and its effect on QoL, since the findings from Memsta et al. (2017) suggest a significant improvement in salivary flow in addition to the functional scales used to represent QoL over time, approximating near-baseline levels by 12 months post-treatment.

With complications from CRT affecting the functioning of structures in the head and neck, eating and drinking often become difficult and painful tasks (Guru et al., 2013). Consequently, reductions in eating and drinking may lead to significant weight loss for patients during treatment, and if the side effects experienced are severe enough, they may require hospitalization (Piquet et al., 2002). In addition, weight loss percentage has also been shown to be correlated with interruption of oncological treatment (Capuano et al., 2007). Interruptions or delays in CRT treatment can be harmful or even fatal, potentially allowing for the repopulation of cancer cells, negatively affecting the patient's ability to effectively complete treatment, in turn reducing the QoL and well-being of survivors (Guru et al., 2013; Shaw et al., 2015).

### **Adequate Nutrition and Weight Management**

Individuals being treated for HNC face many unique challenges, one of which is the limited ability to ensure adequate nutritional intake before, during and after treatment. Patients with advanced stage HNC are frequently affected by malnutrition, which is recognized as a complication of HNC and its treatment (Bhayani et al., 2013). Weight loss can be a

significant issue even prior to diagnosis, with the possibility of symptoms worsening as a result of treatment and treatment-induced consequences. Evidence supports this claim, with research showing that by the end of treatment, anywhere from 33-88% of HNC patients suffer from malnutrition or weight loss (Languis et al., 2010). The maintenance of adequate nutrition during treatment for HNC is crucial as it has the ability to improve bodily healing, reduce treatment-related toxicity, morbidity, and mortality (Shaw et al., 2015). As a result of this dynamic relationship, many radiation therapy centres have acknowledged importance of preventing weight loss and have included nutritional support as an integral part of the treatment they provide (Languis et al., 2010).

What separates HNC from other types of cancer is the critical location of the structural and functional impairments that may emerge; namely, those related to eating, drinking, swallowing, and voice and speech. As a consequence of having cancer in the upper aerodigestive tract, the tongue, or floor of the mouth, patients will often experience difficulty and pain while carrying out these complex, yet “taken-for-granted” everyday tasks (Gee, Kiraly, McCarthy, & Martindale, 2012). Furthermore, these functional impairments are unique as they present a challenge in terms of recovery. Maintaining adequate nutrition and preventing weight loss are critical for improving prognosis as well as minimizing the suffering and damage caused by the cancer and treatment. This maintenance is important as it can improve patients’ ability to heal. Specifically with regard to HNC, the relationship between weight loss and survival has been well documented and demonstrated in various studies (Languis et al., 2013; Shaw et al., 2015).

Consequently limiting their ability to recover effectively, weight loss has also been associated with depression and depressive symptoms (Van Liew et al., 2016). Van Liew et al. (2016) discovered that changes in depressive symptoms over time for HNC patients were associated with same-month changes in weight loss. Not only is this an issue with regard to the effect of depression on the mental health of HNC patients, but this evidence suggests that depression is correlated with weight loss, directly and negatively the impacting treatment, recovery and the quality of life of HNC patients (Van Liew et al., 2016).

The impact of poor nutrition and weight loss has also recently been shown to have a significant prognostic effect on reducing survival outcomes for patients with HNC who are receiving CRT (Languis et al., 2013). Poor nutrition and weight management is also an accepted risk factor for intolerance of radiation therapy treatment (Gee et al., 2012). Furthermore, more than a 10% reduction in weight from baseline, during or soon after treatment, has been associated with a significant deterioration of factors such as social contact, social eating, and QoL (Languis et al., 2013). Simply put, individuals undergoing CRT for HNC are at a greater risk at baseline for malnutrition and dehydration. Not ensuring adequate nutrition and proper weight management during treatment can exacerbate negative consequences, including a reduction in muscle mass and functional capacity (Norman et al., 2005), increased risk of cardiac arrest/failure, diminished quality of life (Shaw et al., 2015) and increased rates of mortality (Correia, 2003). Accordingly, these changes may result in a cascade of negative sequelae including interruptions in treatment, increased time of recovery, increases in depressive symptoms, and even reduced survival (Gee et al., 2012; Shaw et al., 2015; Languis et

al., 2013). As a result, the patients' ability to follow through with CRT, receive effective treatment, and live a pain-free, quality enriched life is drastically altered.

### **Enteral Feeding**

Supporting HNC patients nutritionally is essential for managing symptoms of their cancer as well as allowing for treatment to be administered without delays and/or interruptions. This is often accomplished through the use of enteral feeding: the placement of nutrients directly into the stomach or digestive system (DeLegge, 2007). In essence, the role of enteral feeding is to supply individuals with their daily requirement of nutrients, including macronutrients (proteins, carbohydrates and fats) in addition to vitamins and minerals. Because the physical and functional issues associated with CRT mainly affect the head and neck area causing difficulties with oral intake for oropharyngeal cancer patients, and because the stomach and lower gastrointestinal tract are usually still intact and functional, providing feeding directly into the stomach is considered effective and safe practice, and is thus commonly used during treatment (Raykher et al., 2007).

Other than being utilized to maintain nutrition by avoiding oral intake (whether partially or completely) due to insufficient swallowing capabilities or pain associated with swallowing, enteral nutrition – when supplemented with different agents such as dietary fibre and arginine – has demonstrated the ability to improve local wound complications and contribute to a stronger immune system (de Luis, Aller, Izaola, Cuellar, & Terroba, 2002). Seeing as malnutrition and immunosuppression are two characteristics associated with HNC patients (Riboli, Kaaks, & Esteve, 1996), this may be considered a significant advantage of using enteral nutrition.



Physicians confronted with this issue will commonly recommend a nasogastric (NG), gastrostomy (G-tube) or a gastro-jejunostomy (G-J) feeding tube to assist with food intake (Shaw et al., 2015). The latter two can be placed surgically or via a percutaneous approach. Although they are similar in the role they play in providing nutritional support, these different types of feeding tubes are not identical. NG feeding tubes offer more of a short-term solution, when the impairments and issues with oral intake are not as severe (Nugent, Parker, & McIntyre, 2010). Literature on this topic indicates that patients who are administered a NG enteral feeding tube have a higher chance of having them removed earlier than patients who are G-tube fed (Nugent et al., 2010). For more severe impairments, however, G-tubes tubes provide a longer-term, and potentially more reliable and simple non-oral feeding solution. Therefore, G-tube use is most often the choice when it comes to HNC patients receiving CRT (Wermeker et al., 2012). Currently, a gastrostomy feeding tube may be preferred rather than a NG tube for patients with radiation-induced oral and esophageal mucositis, offering several advantages including enhanced mobility, a reduced length of hospital stay, and increased patient satisfaction (Nugent et al., 2010). Developed by surgeons in the 1970's, PEG is a procedure commonly used to maintain the nutritional status of patients who are unable to orally ingest food as a result of impaired swallowing or discomfort (Silander et al., 2012; Bannister, 2016). The feeding tube, inserted through the wall of the abdomen and directly into the stomach, allows patients who are unable to swallow to avoid regular feeding through the upper aerodigestive tract while still acquiring adequate nutrition. Although initially developed for children with chronic neurological disorders (Bannister, 2016), PEG feeding tubes are commonly used as an adjunct to HNC treatment (Bossola, 2015). Since the obstructive tumour

or treatment-related toxicities (e.g. mucositis and dysphagia) interfere with a patient's ability to swallow, tube feeding may be considered as a means of providing enteral nutrition to avoid deterioration of their nutritional status and the associated risks.

In addition to nasogastric and G-tubes, HNC patients may be administered a G-J feeding tube instead. G-J feeding tubes differ in that they include direct access not only to the stomach, but the tube is placed further down into the jejunum - the middle section of the small intestine - as well (Kwon et al., 2010). Just like with a G-tube, this method allows patients who are unable to ingest a sufficient quantity of food to receive adequate nutrition while bypassing the regular swallowing mechanism. Since this method involves the intake of nutrients directly into the stomach/jejunum, it requires the stomach to function properly and the intestine to have unimpaired absorptive capabilities (Blumenstein, Shastri, & Stein, 2014). Patients with issues such as severe gastroesophageal reflux, gastric outlet obstruction, recurrent vomiting, and feeding tube-related aspiration may be better off having a G-J tube to aid in nutrition and weight management (Blumenstein et al., 2014). Although commonly used in some institutions, literature relating to the use of G-J tubes in the HNC population is scarce, with the bulk of the research almost exclusively tied to paediatric care. The various types of feeding tubes make the decision of prescribing enteral feeding complicated and physicians must determine, based on patient characteristics and treatment goals, which type is required for their patient. Further complicating matters is the added factor of timing (i.e., should the tube be placed prior to treatment, or during when issues present themselves), and what effect this has on treatment and QoL.

**Prophylactic vs. reactive approach.** Despite the well-documented advantages of feeding tube placement in appropriately selected HNC patients, the timing of administration continues to be a highly debated and controversial topic. Physicians and/or institutions (often a program- or institution-level policy) will at times advocate for prophylactic insertion (i.e., prior to the commencement of treatment) if the cancer is at an advanced stage or if patients are at a high risk for malnutrition and other adverse events (e.g. dysphagia, oral mucositis, xerostomia). Multiple studies show a significant benefit in weight management between a prophylactic approach versus a reactive approach (i.e., insertion when physician deems it necessary based on patient's reaction to treatment), in favour of the prophylactic approach (Brown et al., 2016; Wiggendaad et al., 2007; Lewis, Brody, Touger-Decker, & Epstein, 2014; Silander et al., 2012). Furthermore, evidence also demonstrates a reduction in unplanned hospital admission for up to one month post-treatment in patients who received prophylactic gastrostomy tubes versus reactive tubes (Brown et al., 2016).

Using the prophylactic approach has been associated with fewer hospital admissions, lower rates of dehydration, fewer treatment breaks due to radiation-related toxicities, and lower medical costs (Shaw et al., 2015). In some instances, deciding to treat a patient in a reactive/therapeutic manner when the patient can no longer sustain adequate oral nutrition can also be associated with risk and uncertainty. The possibility of uncertainty is due to long wait times for tube insertion, especially at facilities where resources are limited or there is a high volume of patients (Shaw et al., 2015). As a consequence, these facilities may choose to routinely place feeding tubes prophylactically for HNC patients undergoing CRT treatment (Cady, 2007; Moor, Patterson, Kelly, & Paleri, 2010).

Although the primary purpose of enteral feeding tube use is to improve nutrition and weight management, the prophylactic approach may be doing patients a disservice in the long run by altering their ability to regain independent eating. As previously mentioned, prophylactic feeding tube placement has been shown to increase long-term dependence on enteral feeding, negatively impacting long-term swallowing function (Langmore, Krisciunas, Miloro, Evans, & Cheng, 2012), and further contributing to difficulty in weight management (Shaw et al., 2015). Evidence also demonstrates that prophylactic feeding tube use may reduce a patient's incentive to continue oral intake, since they become dependent and overly comfortable with using the feeding tube instead of orally ingesting their food (Shaw et al., 2015). Despite current research claiming that prophylactic feeding tube placement is associated with an increased risk for dysphagia (Chen et al., 2010), other studies have suggested that in fact, this relationship may not exist (Silander, Jacobsson, Berteus-Forslund, & Hamerlid, 2013; Silander et al., 2012).

As a result of many contradictory studies on the advantages and disadvantages of each approach, it remains undecided whether or not prophylactic feeding tube placement provides an advantage to patients with regard to survival and health-related outcomes compared to the reactive approach (when patients are supported with an enteral feeding tube once it becomes difficult to maintain their nutritional status and weight). It may be concluded that neither approach can be generalized as being ideal for every patient. Instead, a more tailored and specific approach may be necessary to determine optimal timing of insertion, as well as whether or not enteral feeding is necessary at all. Despite the lack of consensus and ongoing debate, it is agreed upon that many HNC patients will require a feeding tube for nutritional support (Bhayani et al., 2013). Therefore it is extremely important to understand the short and

long-term impact of feeding tube status on health, swallowing-related outcomes and overall QoL. Specific inquiry into outcome variables related to health, swallowing and QoL may be the most effective way to determine the impact of feeding tube use on health and swallowing-related outcomes, rather than simply addressing prophylactic versus reactive methods.

**Feeding tube status.** Much of the available literature investigating differences between enteral methods of feeding compare prophylactic PEG tubes, reactive PEG tubes and nasogastric feeding tubes to one another. Very few studies directly compare a group of patients with a feeding tube to those without. For example, a meta-analysis performed by Zhang, Zhu, Zhang, & Wan (2015) comparing the effects of various methods of enteral feeding did not include a 'no feeding tube' group in their final write up of results, despite finding some studies using this group in their search. There was an emphasis on comparing prophylactic and reactive methods with nasogastric feeding tubes, with the conclusion that prophylactically placed PEG tubes may be a superior choice in the management of malnutrition (Zhang et al., 2015). Other studies do in fact include a control group consisting of patients who have not been administered a feeding tube. However, these investigations often compare a prophylactic approach to a heterogeneous control group. In other words, the control group consists of patients who have not received a feeding tube prophylactically, but also includes patients administered a tube under the reactive approach if required during treatment.

A retrospective review by Chang et al. (2009) included a control group of patients who did not receive a prophylactic feeding tube, however within the control group, nasogastric feeding tubes were used when the physician decided the patient was unable to maintain enough nutrition orally or had lost too much weight (usually around 5% or more of their

baseline weight). This type of grouping consequently lead to a control group with a mix of patients: those who did not receive a feeding tube, in addition to patients who received reactive nasogastric feeding tubes (Chang et al., 2009). Despite the apparent issues, many other studies share this type of methodology (Brown et al., 2018; Silander et al., 2011; Langmore et al., 2012; Lee et al., 1998). Due to the mixing of patients in control groups for the studies cited above, the results are not applicable in the context of this investigation, and may be difficult to extend to real-world settings. A clear need for direct comparison between patients based on their absolute feeding tube status is evident.

Rather than include patients prescribed the reactive method and no feeding tube at all in the same group, Quon et al. (2015) included three groups when comparing patient pre-treatment characteristics and functional outcomes of HNC patients: a reactive group, a prophylactic group, and a group of patients who did not receive any feeding tube during treatment. This type of grouping allows for more accurate and externally valid comparisons between very specific groups of patients. A significant finding in this study was that when comparing all three groups, patients who did not require a feeding tube had a lower tumour and overall stage, fewer sessions of concurrent chemotherapy treatment, as well as less pre-treatment dysphagia and weight loss. In addition, significant baseline differences were found between the reactive and no feeding tube groups, as well as between the prophylactic and no feeding tube groups (Quon et al., 2015). These findings suggest that all three of these groups were inherently different, and that they cannot be grouped into the same category if meaningful results are to be obtained. Although this investigation seems to effectively group participants based on feeding tube status, many received RT in 2004-2007, meaning that 3D-

conformal radiation therapy was the primary treatment modality. The remainder (from years 2008 and 2009) were treated with IMRT (Quon et al., 2015), again contributing to a lack of homogeneity within the groups.

While the majority of studies have assessed individuals who did not use a feeding tube as a control group to test for differences, Lewis et al. (2014) used a 'no feeding tube' group as a primary group for comparison. Results indicate that patients without a feeding tube had a significantly higher body mass index (BMI) and significantly less chemotherapy cycles when compared to patients with prophylactic feeding tube insertion. In contrast, patients without a feeding tube also lost significantly more weight than those in both other groups (Lewis et al., 2014). While this study does separate the reactive and no feeding tube groups, the use of many different types of HNC (oropharyngeal, laryngeal, etc.) takes away from producing results that can be applied to a specific population outside the context of the investigation (Lewis et al., 2014). To gain a better understanding of the role that feeding tube status plays in short- and long-term treatment outcomes, inquiry should be done examining a specific, homogeneous group of patients.

### **Transition to Oral Feeding**

An important factor to consider when deciding to administer a feeding tube is the possibility of dependence on enteral feeding. Ideally, feeding tubes are administered to patients when they need them, and removed once the patient is able to consume food orally without pain or issues. As previously described, multiple studies support the prophylactic placement of PEG feeding tubes to prevent outcomes such as weight loss and dehydration, which in turn help the patient complete treatment without interruption. However, there is

evidence to support the claim that this approach may lead to long-term dependence on enteral feeding, in turn contributing to the development of esophageal toxicity and dysphagia (Bhayani et al., 2013). Many patients who have feeding tubes go through lengthy periods without oral intake, which has also been demonstrated to be predictive of long-term dependence (Bhayani et al., 2013).

Prophylactically-placed feeding tubes also have a higher rate of unnecessary placement (almost 50% as per the definitions provided by Madhoun et al.), with one study finding an increased likelihood of prolonged dependence, especially with advanced T-stage and pre-existing dysphagia (Verma et al., 2015). For these reasons, the evident risks to functional outcomes associated with prophylactic PEG tube insertion cannot be ignored; consequently emphasis should be placed on customization of treatment plans according to patients and their feeding tube use in order to ensure the potential benefits outweigh these risks. Identifying the effect that maintained oral intake has on PEG dependence is especially important for limiting these damaging consequences.

With growing evidence supporting the idea that the prophylactic approach may indeed place HNC patients at an increased risk for dependence and dependence-related outcomes, priority should be placed on maximizing the amount of oral intake during treatment, even if the patient has a feeding tube. In order to so, the ideal amount of oral intake during treatment should be decided and treatment goals planned accordingly. While many studies do assess the impact on health outcomes in order to determine whether or not a method of enteral feeding is effective, examining the effect of tube status on oral intake and on swallowing outcomes during treatment can offer more information on how dependence affects the patient. Further



investigating how oral intake and dependence may change over time, depending on whether or not a patient has a feeding tube inserted, will supplement this understanding of dependence and the ways in which it can be avoided.

### **Maintained Oral Intake**

Patients who report adherence to swallowing exercises are significantly less likely to have any form of feeding tube administered to them compared to those who do not report adherence (Bhayani et al., 2013; Hutcheson et al., 2013). Research has also shown that patients actively exercising the swallowing muscles during treatment are better able to maintain swallowing function (Carnaby-Mann, Crary, Schmalfuss, & Amdur, 2012). One form of exercise is continued oral intake during treatment, which may be influenced by the use of and dependence on feeding tubes. Continued oral intake may not be restricted when a feeding tube is inserted, however, patients may feel satiated by the tube alone. Also, with significant pain in the upper aerodigestive tract, patients may no longer wish to eat by mouth (Starmer et al., 2015).

Pain caused by acute toxicities such as mucositis and the associated dependence on tube feeding in turn decrease the regular resistive load placed on the swallowing mechanism, leading to disuse atrophy, or a decrease in the size of the muscle (e.g. pharyngeal constrictor muscle atrophy; Kasper, Talbot, & Gaines, 2002; Clark, 2009) . In addition, negative swallowing outcomes resulting from a reduction in swallowing activity during feeding tube use can be attributed to the effects of pharyngeal fibrosis of tissues (Corry et al., 2008; Gillespie et al., 2006; Crombie et al., 2013). In this case, neglecting to use the muscles necessary for the swallowing mechanism by reducing oral intake encourages adverse remodelling of these

muscles, or atrophy, leading to a worsening of symptoms (Kasper et al., 2002; Clark, 2009).

Over time, atrophy resulting from disuse of muscles necessary for the swallowing mechanism leads to a reduction in muscle strength, irregular motor control, and increased muscle fatigue (Hutcheson et al., 2013). Therefore, the effect of muscle wasting and the remodelling of musculature has led to the adoption of a “use it or lose it” approach to treatment, emphasizing the importance of continuing oral intake even when a feeding tube has been inserted (Hutcheson et al., 2013).

Research has found proactive swallowing exercises to lead to better swallowing-related QoL (Kulbersh et al., 2006; Shinn et al., 2013), lower rates of feeding tube placement (Bhayani et al., 2013), superior tongue and base and epiglottic movement (Caroll et al., 2008), and shorter duration of PEG dependence (Bhayani et al., 2013). Randomized controlled trials by Carnaby-Mann et al. (2012) and Kotz et al. (2012) investigated the use of swallowing exercises/interventions on swallowing-related outcomes, both reaching a similar conclusion: patients who performed swallowing exercises had better swallowing-related health outcomes than those who did not. While there was no inquiry into how maintaining oral intake would affect swallowing-related outcomes, the conclusion that using musculature responsible for the swallowing mechanism during CRT treatment through the implementation of swallowing exercises (e.g. tongue press, hard swallow, Therabite, Effortful Swallow, and tongue base retraction) aids in the improvement of swallowing functionality is extremely valuable.

Maintaining oral intake during treatment would serve a similar purpose. That is, exercising the muscles by putting them through the regular swallowing mechanism would in turn reduce muscle atrophy and adverse remodelling, leading to improved swallowing for

patients despite the administration of a feeding tube. Supporting this claim is an investigation conducted by Ames et al. (2011), which compared the effects of continued oral intake during tube placement on nutritional outcomes in HNC patients. The results were somewhat predictable, finding that patients with absolutely no oral intake (39% of 91) were more likely to have advanced disease as well as significantly worse observed survival (Ames et al., 2011). Patients who maintained oral intake while having a feeding tube in place, then subsequently had their tube removed had a higher likelihood of maintaining their weight and were more likely to report eating scores in a high-functioning category (Ames et al., 2011). Thus, by encouraging maintained oral intake, the same benefits could potentially be had, without the need to implement additional exercises or therapy for patients.

### **Statement of Problem**

While research has demonstrated that feeding tubes can be beneficial to patients undergoing CRT for HNC, there is a lack of consensus on ideal timing of insertion based on patient characteristics. Both prophylactically (i.e., before treatment) or reactively (i.e., during or following treatment when oral intake is insufficient) inserted feeding tubes have proven to be useful in minimizing the risks associated with treatment side-effects (Wiggenraad et al., 2007; Lewis et al., 2014; Silander et al., 2012; Shaw et al., 2015). Nonetheless, a superior method has yet to be identified. A systematic review by Shaw et al. (2015) examined which approach was superior in limiting weight loss during treatment, only to identify that out of 15 studies, only 6 found statistically significant differences between the two methods of administration. The remainder of studies concluded that differences were non-significant, with two of the studies reporting no significant differences between these two approaches (Shaw et

al., 2015). Determining whether patients are at risk for adverse events related to malnutrition and weight loss is critical in deciding whether or not a feeding tube will be a necessary part of patient care. Having the ability to predict the impact of enteral feeding on health outcomes based on feeding tube status has the potential to address risk factors associated with both the prophylactic and reactive approach, with the added benefit of figuring out how patients with feeding tubes compare to those without.

While attempts have been made to develop a standardized protocol to guide the decision making process, there is currently no consensus on the optimal timing of feeding tube insertion for HNC patients undergoing CRT treatment (Kramer, Newcomb, Hessler, & Siddiqui, 2014). The development and validation of guidelines for feeding tube administration for high-risk HNC patients by Brown et al. (2013) has proven to be useful in decreasing the amount of unplanned hospital admissions, reducing interruptions in treatment (Hughes et al., 2013) and contributing to improved nutritional outcomes (Brown et al., 2013). However, this approach is dependent on the assumption that patients will be treated with a proactive approach, hence limiting its ability to contribute to decisions regarding timing of insertion for the general HNC population. Still, further research is necessary in order to decide on a standardized protocol, “with consideration of patients’ disease characteristics and baseline feeding capacity” (Kramer et al., 2014).

All currently available evidence suggests that a standardized protocol specific to the timing of tube insertion in HNC patients is unavailable. However, if evidence can be generated to guide standardization, the ability to maximize positive health outcomes after insertion may be possible. To address this shortcoming in the field of enteral nutrition, attention should also

be placed on improving the physician's ability to communicate and set goals for patients based on their feeding tube status and their ability to maintain oral intake, regardless of the timing of insertion. Because no standardized protocol exists to aid physicians in the decision making process for when, or even if to administer a feeding tube (Kramer et al., 2014), this raises considerable clinical concerns. Given the discrepancy in findings comparing prophylactic and reactive tube feeding, questions regarding which type of approach is ideal remain unanswered, and there remains "a critical void in the current literature" (Shaw et al., 2015).

One particular factor that may contribute to the varied results across studies is the general lack of attention that is given to the actual use of the feeding tubes. Administration of a feeding tube does not ensure consistent usage between patients, since how much it is actually used may vary widely depending on the patients' needs. If two patients have been administered a feeding tube prophylactically, existing studies have grouped these two patient cohorts together. Although some patients may share the same method of administration, how much they rely on enteral feeding will most likely vary, as some are able to eat a higher percentage of their diet orally compared to others. Moreover, this commonly used methodology fails to take into account patients without a feeding tube, thus ignoring a large portion of HNC patients and their needs/treatment outcomes. Examining the amount of maintained oral intake with whichever approach is used (prophylactic vs. reactive) may provide information of greater value. In turn, this may allow researchers to group the patients into more homogeneous groups based on how much they use the tube, regardless of which method was prescribed. By comparing outcomes such as oral intake and swallowing function based on feeding tube status, then further investigating how these outcomes change for each group over

time, this study will attempt to limit the shortcomings of previous research investigations listed above.

Information comparing differences based on a more objective measure of oral intake has the potential to greatly improve communication between physician and patient. The ability to disclose long-term expectations on swallowing-related outcomes based on feeding tube status could greatly enhance the clarity of the situation in terms of prognosis and recovery, ultimately allowing for timely and precise patient education, and improved communication in a clinical setting. This would offer more comfort to patients, who are experiencing ongoing psychological and emotional challenges in addition to the physical pain of having the cancer and receiving treatment. It has been reported that patients desire as much detailed information as possible regarding their prognosis, even if the news is negative (Fujimori & Uchitomi, 2009). Therefore, by identifying the impact of feeding tube status on oral intake, swallowing-related QoL, weight, and feeding tube dependence, and further investigating how these variables change over time, side-effects secondary to radiation treatment and weight management can be better managed and improved.

## **Objectives**

Based on collective information provided in the preceding review and the fact that little is known about feeding tube status on individual health, swallowing and QoL in a reactive model, many questions emerge. Consequently, the prior review provides information that warrants investigation into differences between patients with a reactively placed feeding tube, and a control group (patients without a feeding tube). Therefore, the purpose of the proposed research investigation seeks to address the impact of feeding tube status on health outcomes

of patients undergoing chemoradiation therapy treatment for HNC. More specifically, this investigation seeks to:

- 1) Determine if baseline characteristics predict feeding tube use and dependence for individuals diagnosed with oropharyngeal cancer which was treated with IMRT.
- 2) Investigate the impact of feeding tube status on long-term swallowing-related outcomes, weight loss and QoL.
- 3) Describe differences in the trajectory of recovery for outcome measures based on feeding tube use.

## Chapter 2: Method

### Participants

A retrospective chart review was conducted for patients with oropharyngeal squamous cell carcinoma that was treated with definitive RT or CRT London Health Sciences Centre – Victoria Hospital between January 2013 and December 2015. After preliminary review of the medical records of 1197 consecutive patients, 126 eligible patients were selected based on the criteria above. Patients were excluded from the study based on the following criteria: (1) primary surgical treatment or surgery within 12 months post-radiation therapy, (2) patient's decline of curative treatment (i.e., pursued palliative means of care), and/or (3) distant tumour metastasis leading to a change in treatment strategy (e.g., more centred on palliative care, with less involvement of allied health professionals).

Additionally, retrospective data was collected on demographic and treatment characteristics from electronic medical records. This included information on age, sex, tumour staging (T and N classification), type of treatment (RT or CRT), p16 status (as a surrogate marker of HPV status), radiation dose, the type of drugs used for chemotherapy and comorbidities. Data was also collected on variables to be used as primary outcome measures, including the FOIS, MDADI, PSS-HN, and weight. Outcome variable data was collected at baseline (immediately prior to treatment), and at 3, 6, and 12 months post-treatment.

For patients who received a feeding tube at some point during RT/CRT treatment, information was collected about the type of tube, timing of placement, and duration of placement (calculated based on date of insertion and data of removal). The first patient group consisted of oropharyngeal cancer patients who have had a feeding tube inserted during their



RT/CRT treatment (FT group). The second group used in this investigation consisted of oropharyngeal cancer patients who had not had a FT inserted over the course of their RT/CRT treatment (NFT group). The exclusion criteria for the second patient group were identical to the first (FT) patient group.

### **Baseline Patient and Treatment Characteristics**

One hundred twenty-six patients with oropharyngeal cancer who met the inclusion criteria were included in this investigation. In this sample, 40 patients (32%) were administered a FT, whereas 86 patients (68%) completed treatment without requiring enteral nutrition. The median age of all included patients was 60.5 years (range, 31-89). For the FT group, the median age was 63 years (range, 44-77), and for the NFT group it was 60 years (range, 31-89). Overall, 107 (85%) of patients were male, with 32 (80%) males in the FT group and 75 (86%) males in the NFT group.

For the 40 patients who were administered a FT, 38 (95%) received a G-J tube, while only 2 (5%) received a G- tube. The most common tumour staging for both groups combined was T2 (51 patients; 41%) and T3 (28 patients; 22%), followed by T1 (25 patients; 20%) and T4 (21 patients; 17%). Within the FT group, the most common tumour staging was T2 (13 patients; 33%), followed by T4 (11 patients; 28%) and T3 (9 patients; 23%). As for the NFT experimental group, T2 tumour staging was most prevalent (38 patients; 44%), followed by T1 and T3, which were both identical (19 patients; 22.1%). Based on eligibility criteria, only patients undergoing primary CRT or RT treatment were included in the study.

Overall, the majority of patients received CRT (114 patients; 91%), with the remainder receiving RT alone (12 patients; 10%). When divided into groups based on FT placement, those

with a FT largely received CRT (38 patients; 95%). Patients without a feeding tube also mainly received CRT (76 patients; 88%). All patients received IMRT as the type of RT. Bivariate associations (with respect to FT status) using chi-square tests yielded no significant results for sex, tumour and lymph node staging, and treatment type at baseline. Additional information on patient-related characteristics is summarized below in Table 1.

Table 1

*Demographics for Oropharyngeal Cancer Patients from 2013 to 2015*

Characteristics	Overall	FT	NFT	<i>p</i> value
Number of participants	126	40	86	
Age in years at enrollment				
Mean, median (range)	60.14, 60.5 (31-89)	61.75, 63 (44-77)	59.40, 60 (31-89)	
Sex: male, N(%)	107(84.9%)	32(80.0%)	75(87.2%)	0.292
Tumour staging, N(%)				0.096
X	1(0.8%)	1(2.5%)	0(0.0%)	
0	0(0.0%)	0(0.0%)	0(0.0%)	
1	25(19.8%)	6(15.0%)	19(22.1%)	
2	51(40.5%)	13(32.5%)	38(44.2%)	
3	28(22.2%)	9(22.5%)	19(22.1%)	
4	21(16.7%)	11(27.5%)	10(11.6%)	
Nodes, N(%)				0.238
N0	14(11.1%)	3(7.5%)	11(12.8%)	
N1	10(7.9%)	3(7.5%)	7(8.1%)	
N2a, N2b, N2c	94(74.6%)	29(72.5%)	65(75.6%)	
N3, N3b	8(6.3%)	5(12.5%)	3(3.5%)	
Treatment Regimen N(%)				0.238
Radiotherapy alone	12(9.5%)	2(5.0%)	10(11.6%)	
Radiotherapy plus chemotherapy	114(90.5%)	38(95.0%)	76(88.4%)	

Alpha = 0.05 (2-tailed)

\* denotes significant *p* value*p* values were obtained using the Chi-Square test for categorical variables

## Outcome Measures

**Functional Oral Intake Scale (FOIS).** The Functional Oral Intake Scale (FOIS), which is a tool created to document the functional level of oral intake of food/liquids for patients experiencing dysphagia (Crary, Carnaby Mann, & Groher, 2005), was recorded for each patient and was used as a surrogate marker for maintained oral intake during treatment. This validated, seven-point ordinal scale reflects changes in oral intake of food/liquids over time, and is a suitable tool for the clinical documentation of change in functional oral intake and oral dietary tolerance (Crary et al., 2005). The scale was chosen to give insight into how much of the patient's diet is consumed orally in relation to enteral intake, ranging from complete dependence on tube feeding (1 point) to tolerance of an oral diet with no restrictions (7 points; Crary et al., 2005; Kotz et al., 2012). Since this investigation placed emphasis on investigating the effects of maintained oral intake over the course of treatment on swallowing-related outcomes, the FOIS was used as a marker of maintained oral intake.

**Performance Status Scale (PSS-HN).** The PSS-HN offers a quantifiable rating of various eating habits based on reports from patients and has been validated as a speech and swallowing outcome measure (List, Ritter-Sterr, & Lansky, 1990). Consisting of three differing subscales, Normalcy of Diet, Understandability of Speech, and Eating in Public, patients report on each subscale with a score ranging from zero to 100, with a higher score being indicative of better functioning (List et al., 1990). The Normalcy of Diet subscale was thought to be most relevant to this investigation, as it is used to assess the degree to which a patient is able to tolerate a normal diet (List et al., 1990). Foods easier to eat (e.g., pureed foods) are situated at the low end of the scale, generating a lower score, while foods that are more difficult to eat

(e.g., peanuts) occur at the high end of the scale, and will generate a higher score (List et al., 1990). By using the PSS-HN (Normalcy of Diet) variable in addition to the FOIS, this research study sought to provide a comprehensive description of how maintained oral intake affects the QoL of patients inside and outside of clinical settings.

**M.D. Anderson Dysphagia Inventory.** The M. D. Anderson Dysphagia Inventory (MDADI) is a validated dysphagia-specific QoL questionnaire (Chen et al., 2001) which allowed for specific inquiry into the impact of treatment on this study's population. The patient-reported questionnaire includes 20 items, with each item being rated on a 5-point scale. The overall score is summarized, ranging from 20 (e.g., 1 point for every item) to 100 (e.g., 5 points for every item). A superior outcome is represented by higher score on the MDADI, and a fluctuation of 10 points or more indicates a clinically significant difference (Goff et al., 2017). After its introduction into medical literature in 2001, the MDADI has become a widely-used and popular patient-reported outcome (PRO) measure of swallowing-related QoL.

A review of the literature indicated that MDADI measures are reported in greater than 40 research publications, with validation of the PRO measure being presented in five different languages (Schindler et al., 2008; Speyer et al., 2011; Carlsson et al., 2012; Guedes, Angelis, Chen, Kowalski, & Vartanian, 2013; Kwon, Kim, Park, Byung-Mo, & Han, 2013). Given the extensive adoption of the MDADI in medical literature and its use world-wide, the MDADI is arguably the main PRO measure of dysphagia in HNC research. In addition to being the most commonly used patient-reported outcome metric (Geopfert et al., 2016), the MDADI has a multi-factorial approach to evaluating swallowing based on questions related to the functional, physical and emotional impact of their perceived function (Chen et al., 2001; Gillespie, Brodsky,

Day, Lee, & Martin-Harris, 2004; Yang et al., 2015; Geopfert et al., 2016). By doing so, the MDADI allows researchers/physicians to determine how patients view their swallowing capability during and after treatment, and how this in turn affects their QoL and overall health (Chen et al., 2001).

Therefore, by evaluating the effect of dysphagia on the QoL of patients using the MDADI, a connection can be established between how maintained oral intake (measured using the FOIS) influences swallowing-related outcomes and whether this relationship changes over the course of treatment. The functional subscale was utilized to assess the impact of dysphagia on patients' daily activities in an attempt to understand how treatment- and/or cancer-related difficulties impact QoL (Chen et al., 2001). Additionally, the composite MDADI score, which provides a summary of the MDADI as a weighted average of three other subscales (functional, emotional and physical), was also used as a primary outcome measure. The decision to use the composite scale was primarily based on the fact that it summarizes overall performance on 19-items present in the MDADI. Furthermore, the composite score has been demonstrated to be less variable (low standard deviation) and have high consistency when compared to clinical anchors of swallowing function. In addition, the composite score of the MDADI has been shown to have real-world carry over, with a change of 10 points being associated with clinically meaningful differences in swallowing function (Hutcheson et al., 2016).

### **Data Analysis**

Following data collection, descriptive statistics were used to obtain measures of central tendency for all outcome variables. Bivariate associations for categorical outcomes (FT status) were analyzed using the chi-square test (Daniel & Cross, 2013). For continuous outcome

variables such as the duration of G-tube tube placement, between-group differences (FT vs. NFT) were examined using Student's t-test (Daniel & Cross, 2013). Statistical analyses to test for within-group differences for normally distributed variables (using Linear Mixed Effects analysis) and the non-normally distributed FOIS variable (using the Skilling's Mack test) were performed using R statistical software (R Core Team, 2018). The following statistical packages were utilized: lme4 (Bates, Maechler, Bolker, & Walker, 2015), lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017), lsmeans (Lenth, 2016), and Skillings.Mack (Srisuradetchai, 2015). All other analyses were completed using SPSS (version 25.0) statistical software. The alpha value for between and within group comparisons was set at 0.05, and at 0.0083 for post-hoc pairwise comparisons. The decision to utilize 0.0083 as the alpha value was based on the need to adjust for multiple comparisons across 6 post-hoc tests (Bonferroni correction). The primary focus of this investigation was direct comparisons between the two treatment groups. The variables collected (FOIS, MDADI, PSS-HN, weight, FT duration) were used as the primary outcome measures when comparing the two groups, with the intention of exploring the potential differences between the two in terms of their diet, health, swallowing, and overall QoL.

**Feeding tube dependency.** To determine if variables (or groups of variables) are able to predict dependence on tube feeding, a multiple linear regression analysis was performed. This was done with the intention of estimating and fitting a structural model to explain variation in the values of the dependent variable (duration of FT use) in relation to the independent variable(s) of interest. As a result, the variables (or combinations of variables) significantly affecting duration of FT use and estimates of the magnitude of their contribution were determined and expressed as a coefficient of multiple determination (or  $R^2$  value; Evans, 2014).

**Between-group comparison.** All outcome variables were analyzed to determine normality of distribution and to guide the selection of appropriate statistical tests. While most of the variables were normally distributed (weight, MDADI subscales, PSS-HN subscales, and duration of use), data from the FOIS presented a unique challenge. Initial inquiry showed a frequency histogram skewed to the left, which indicated that the spread of this variable was non-normal (also confirmed with Levene's test for normality). As a result, standard parametric tests like the independent sample t-test, paired t-test, and ANOVA were not used for statistical analysis (Evans, 2014). In order to test between group differences for the FOIS, the nonparametric Mann-Whitney U/ Wilcoxon Rank Sum test was used in place of the independent samples t-test (Evans, 2014; Daniel & Cross, 2013). Frequency histograms and Levene's test for normality indicated that the other outcome measures (MDADI, PSS-HN, weight, FT duration) were normally distributed, thus independent samples t-tests were used for between group comparisons (Evans, 2014). An alpha value of 0.05 was applied to all statistical tests mentioned above.

**Within-group comparison.** Within group analyses was also performed in order to determine how each group changed over time, specifically at baseline, 3, 6, and 12 months. Typically, to investigate differences within groups, a one-way repeated measures ANOVA would be the statistical test of choice (Daniel & Cross, 2013). However, as a result of the non-normal distribution of the FOIS, and the presence of missing-at-random values, the Skillings-Mack test was selected as the nonparametric alternative to be used (Evans, 2014). Important to note is the requirement of this statistical test to remove any block/participant with only one observation (Chatfield & Mander, 2009). Despite the removal of participants with only one



measurement, the sample sizes used were still sufficient enough to produce meaningful and statistically sound results.

If statistical significance was observed for either group with respect to the FOIS ( $p < 0.05$ ), post-hoc analysis was conducted to determine where that difference is. The non-parametric Wilcoxon Signed-Rank Test (alternative to dependent samples t-test) was used for post-hoc analysis since the main purpose of this test is to investigate differences for the same individual between two points in time (Daniel & Cross, 2013; Evans, 2014). Additionally, since the sample sizes are reasonably large ( $\geq 20$  participants), the sampling distribution approached normality, thus allowing for the z-statistic to be used for significance testing (Daniel & Cross, 2013). Resulting from the use of four time points (baseline, 3 months, 6 months, and 12 months), there was a total of six post-hoc tests performed, thus lowering the alpha value of each post-hoc analysis to 0.0083 ( $0.05 / 6$ ). By using this approach, known as the Bonferroni correction, the chance of obtaining a false-positive result/type 1 error was reduced (Daniel & Cross, 2013).

The variability in sample size within each group was cause for adjustment even for the normally distributed variables, such as the MDADI, PSS-HN, weight, and FT duration. Rather than using the parametric repeated measures ANOVA for these variables, a Linear Mixed Effects (LME) analysis was used to test if there is a difference across time for each group (Bates, Machler, Bolker, & Walker, 2014). By using LME, participants with data missing at random can still be included in the analysis, despite the resulting variations in sample size (Bates, Machler, Bolker, & Walker, 2014). However, as with the Skillings-Mack test, participants with only one measurement were excluded from analysis. Data from participants with no baseline

measurement were excluded as well. Dependent samples t-tests were utilized in post-hoc analysis to compare all time points to one another (Evans, 2014), with the alpha value once again set at 0.0083 based on the Bonferroni correction. As a result of the different sample variances and varying sample sizes at each point in time, the Satterthwaite approximation was used to calculate the degrees of freedom for each t-test (DiSantostefano & Muller, 1995).

## Chapter 3: Results

### Baseline Characteristics

Analyses were performed at baseline to determine which factors distinguish those who received a FT from those who did not. For the FOIS, no significant difference was observed at baseline ( $p = .096$ ). Between group comparisons for differences in weight revealed baseline weight to be significantly lower for the FT group compared to the NFT group ( $p = .003$ ). The MDADI subscales used in this investigation (functional and composite) were found not to be significantly different at baseline when comparing the two patient groups. Similarly, baseline PSS-HN (Normalcy of Diet) scores were not significantly different between the FT and NFT groups.

### Feeding Tube Dependency

A multiple linear regression analysis was performed to explain the relationship between duration of FT use and the various outcome variables of interest (e.g., FOIS, PSS-HN, MDADI, and weight) at baseline and 3 months post-treatment. The findings suggest that these variables are far more effective at predicting duration of FT use when data were used from the 3 month time point (Table 3), compared to using baseline data (Table 2).

Table 2

*Multiple Linear Regression on FT Duration at Baseline*

<b>Independent Variable(s)</b>	<b>Sample Size (n)</b>	<b>R<sup>2</sup> Value</b>
Weight	29	0.133
FOIS + PSS(Diet) + MDADI(C) + MDADI(F) + Weight	23	0.050
FOIS + PSS(Diet)	33	0.026
PSS (Diet)	33	0.035
FOIS + MDADI(C) + MDADI(F)	30	0.033
PSS(Diet) + MDADI(C) + MDADI(F)	30	0.031
MDADI(C) + MDADI(F)	30	0.031
FOIS	33	0.029
MDADI (C)	30	0.023
PSS(Diet) + MDADI(F)	30	0.015
MDADI (F)	30	0.012

Table 3

*Multiple Linear Regression on FT Duration at 3 Months Post-Treatment*

Independent Variable(s)	Sample Size ( <i>n</i> )	R <sup>2</sup> Value
FOIS + PSS(Diet) + MDADI(C) + MDADI(F) + Weight	9	0.740
FOIS + PSS (Diet) + MDADI(C) + MDADI(F)	19	0.463
FOIS + MDADI (C) + MDADI (F)	19	0.452
PSS (Diet) + MDADI (C) + MDADI (F)	19	0.374
MDADI (C) + MDADI (F)	19	0.363
PSS (Diet) + MDADI (F)	20	0.288
MDADI (F)	20	0.286
FOIS + PSS (Diet)	31	0.237
FOIS	31	0.236
PSS (Diet)	31	0.162
MDADI(C)	19	0.156
Weight Loss	19	0.021

## Feeding Tube Status

**Maintained oral intake.** The FOIS variable was used as a marker of maintained oral intake, and was collected at baseline, as well as 3, 6, and 12 months post-treatment. When comparing the two experimental groups on this metric, a significant difference was observed only at 3 months ( $p = .003$ ) and at 6 months ( $p = .005$ ), indicating that FOIS scores at both points in time were significantly lower for the FT group (Figure 1). No significant difference was observed at 12 months post-treatment ( $p = .965$ ). Analyses performed to test within group differences over time found a significant relationship between FT status and FOIS score from baseline to 12 months post-treatment for each group. For the FT group, post-hoc analysis revealed baseline FOIS scores to be significantly higher than FOIS scores at 3 months ( $p = <.001$ ) as well as 6 months ( $p = .007$ ). As for the NFT group, post-hoc analysis showed a significant difference between baseline and 3 months ( $p = <.001$ ), baseline and 6 months ( $p = .007$ ), and baseline and 1 year ( $p = .001$ ), indicating that baseline scores were significantly higher for this group at these specific points in time post-treatment.

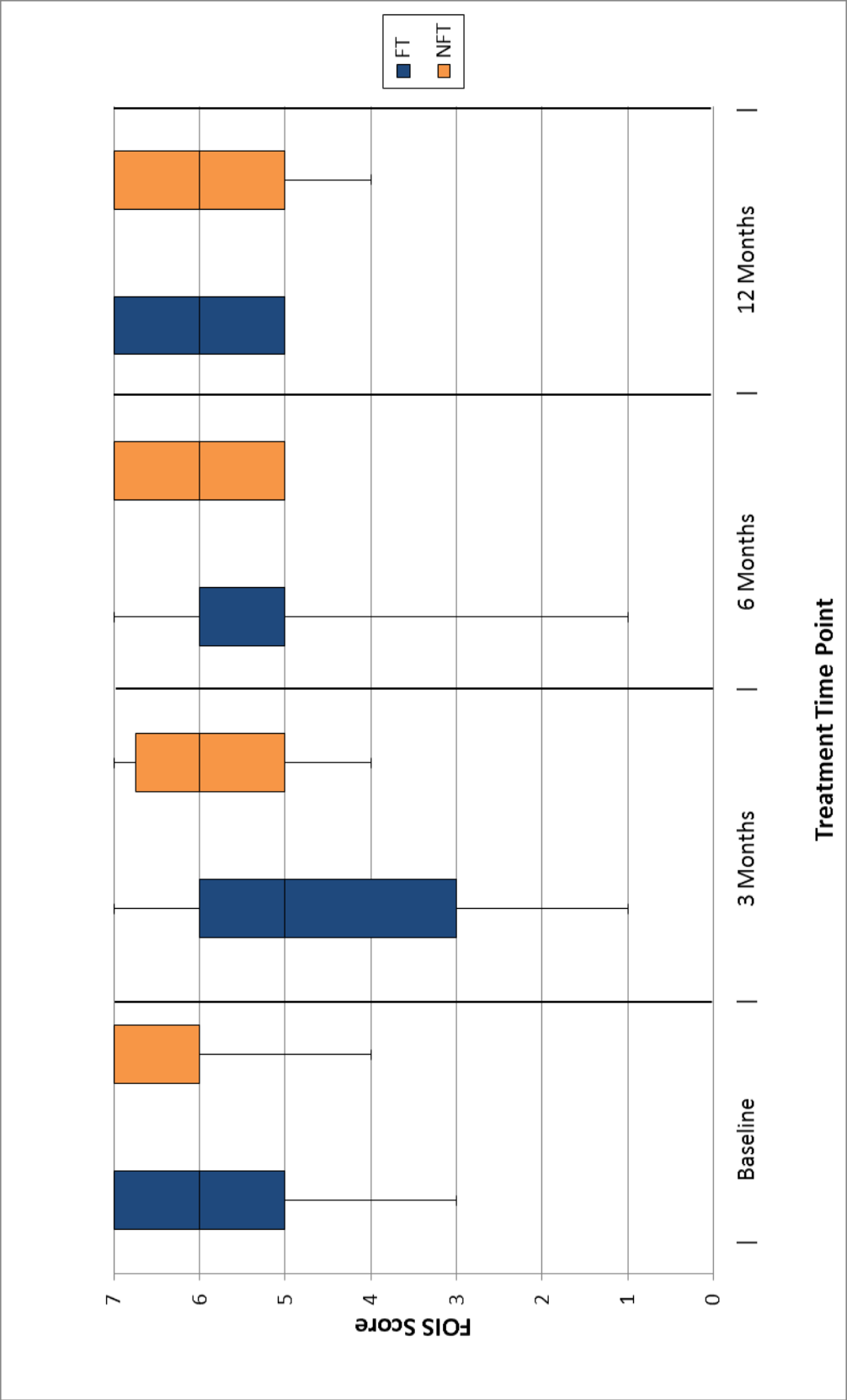


Figure 1. Distribution of FOIS Scores According to Feeding Tube Status.

**Normalcy of diet.** Between group comparisons using the PSS-HN (Normalcy of Diet) scale yielded no significant differences. Repeated measures analyses performed on both patient groups also revealed no significant differences over time.

**Dysphagia and QoL.** Two MDADI subscales were used in order to compare the two patient groups. For the functional MDADI subscale, there were no significant differences found between the two groups when comparing their scores at the four time points. Similar results were obtained for the composite subscale, except that at 3 months post-treatment, patients in the FT group had a significantly lower mean MDADI-composite score ( $p = .046$ ).

Repeated measures analysis using linear mixed effects found a significant change in MDADI-functional scores over time for patients in the NFT group ( $p = .020$ ). Post-hoc analysis using the independent samples t-test (with the Satterthwaite method for calculating degrees of freedom) found mean baseline MDADI-functional scores to be significantly higher when compared to 3 months ( $p < .001$ ) and 6 months as well ( $p < .001$ ). Similarly, MDADI-composite scores were found to be significantly different over time (Figure 2) in the NFT group ( $p < .001$ ). Further analysis revealed baseline MDADI-composite scores to be significantly higher than scores at 3 months ( $p < .001$ ) and at 6 months ( $p < .001$ ). There was no significant change over time in MDADI-functional ( $p = .548$ ) and MDADI-composite scores for  $p = .179$  the FT group.

Clinically significant changes in the MDADI-composite subscale were investigated as well (Figures 3 and 4). For this subscale, a change in either direction of 10 points or more is considered to be significant in a real-world, clinical setting (Hutcheson et al., 2015). Investigating these changes at 3 months, it was observed that 53% of patients with a FT experienced a decrease of 10 points or more, while 45% of those without a FT experienced this



same change. At 6 months post-treatment, 43% of FT patients had a decrease of at least 10 points, while this change was observed for 44% of patients in the NFT group. Finally, after 12 months, 29% of patients who received a FT during treatment had a clinically significant decrease in MDADI-composite scores, compared to the 33% of patients without a FT who were found to have this same decrease. Additionally, 12% of patients with a FT reported a clinically significant increase in MDADI-composite score at 3 months, while only 2% of patients with a FT were found to have increased their score by 10 or more points. When examining this change at 6 months, 19% of patients in the FT group experienced a 10 point increase, with only 7% experiencing this change in the NFT group. At 12 months post-treatment, 18% of patients with a FT were able to increase their composite MDADI score by 10 or more points, with 8% of patients without a FT were recorded as having this increase.

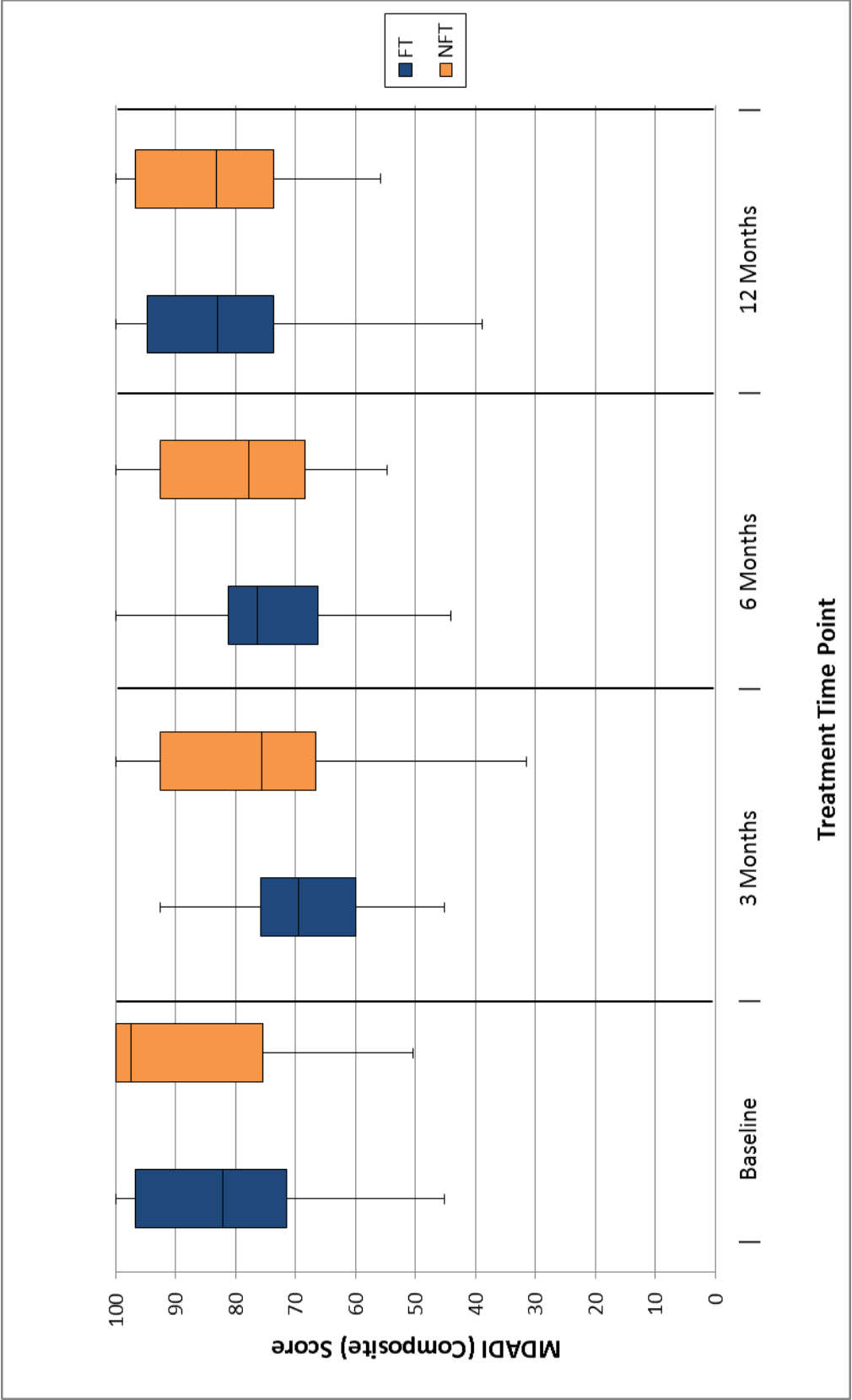
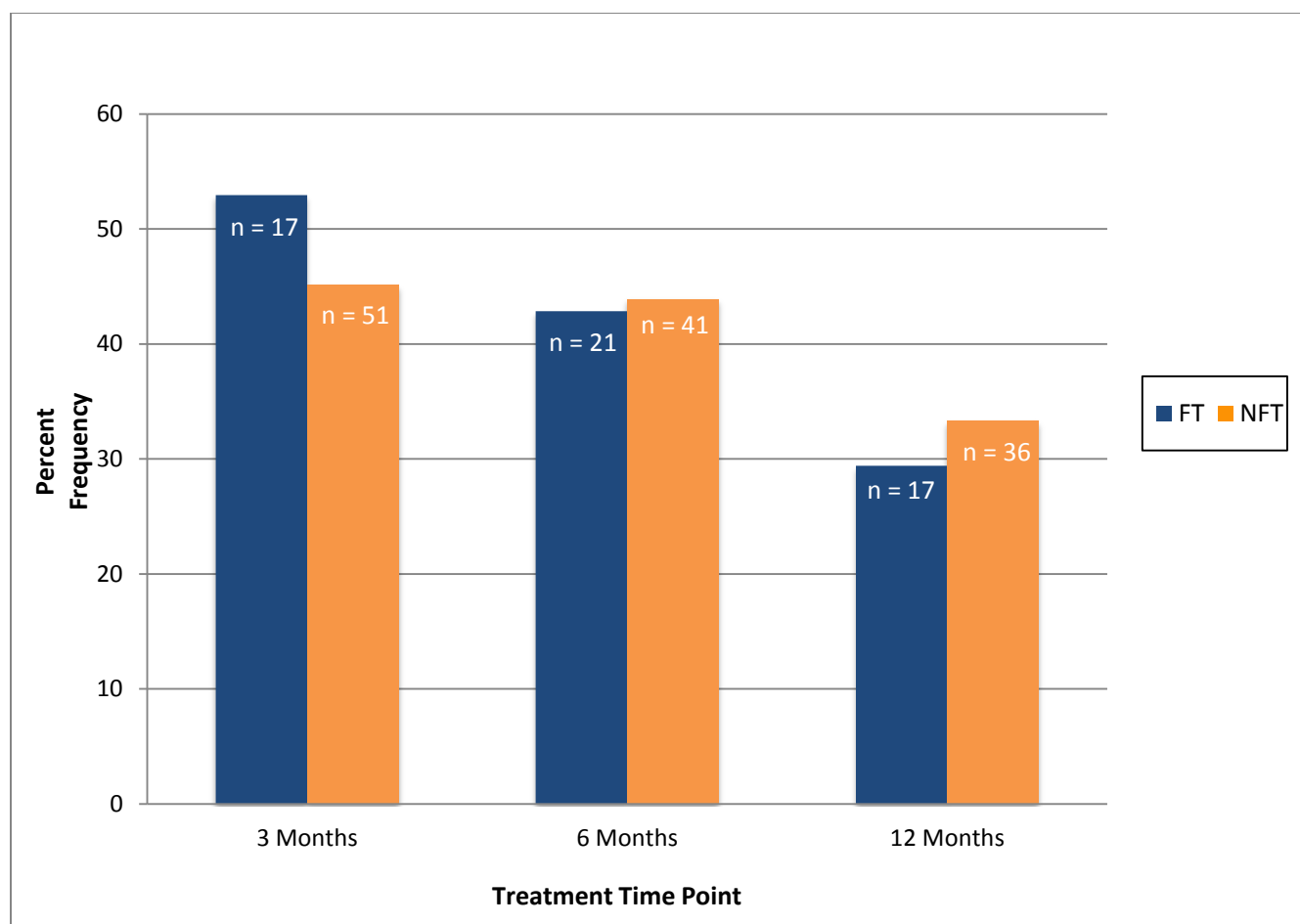
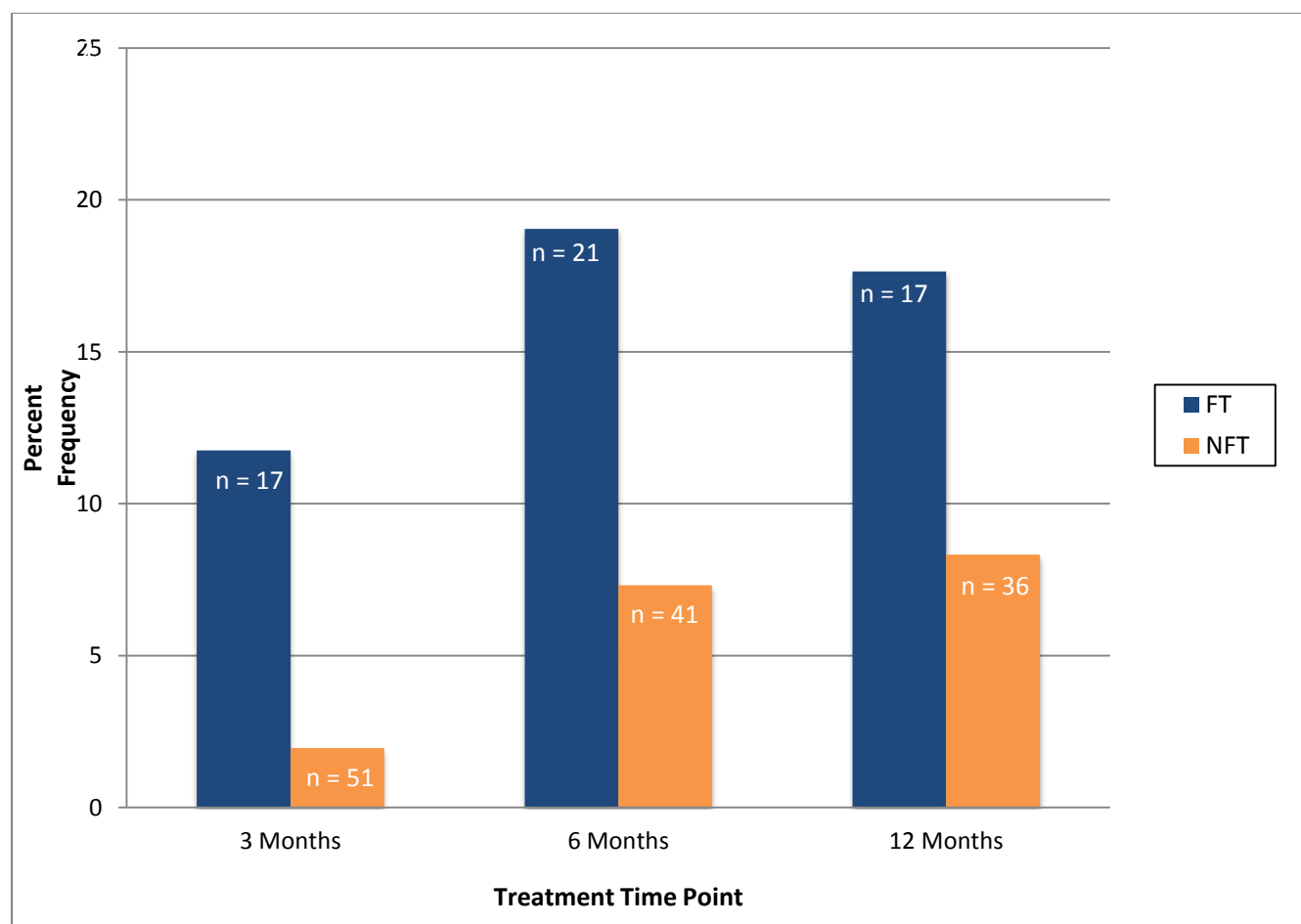


Figure 2. Distribution of MDADI-Composite Scores According to Feeding Tube Status.



*Figure 3. Percentage Frequency Distribution for Clinically Significant MDAD-Composite Score Decrease ( $\geq 10$  points) from Baseline for Oropharyngeal Cancer Patients.*



*Figure 4.* Percentage Frequency Distribution for Clinically Significant MDADI-Composite Score Increase ( $\geq 10$  points) from Baseline for Oropharyngeal Cancer Patients.

**Weight.** There was no significant difference observed between the two groups with respect to weight at any time point other than baseline (see 'Baseline Patient and Treatment Characteristics'). When analyzing within group differences, both the FT group ( $p = <.001$ ) and the NFT group ( $p = <.001$ ) produced significant results. Further post-hoc testing revealed baseline weight to be significantly higher than weight at 3 months ( $p = .001$ ) and at 6 months ( $p = <.001$ ) for patients in the FT group. As for the NFT group, baseline weight was found to be significantly higher compared to weight at 3 months ( $p < .001$ ), 6 months ( $p < .001$ ), and 1 year ( $p < .001$ ) post-treatment (Figure 5).

Clinically significant decreases in weight ( $\geq 10\%$ ) from baseline were also observed for both groups (Figures 6 and 7). Overall, the percentage of patients who had a clinically significant decrease in weight from baseline was higher for the NFT group at every point in time. At 3 months, the FT group had 30% of patients lose more than 10% body weight, whereas the NFT group had 50% of patients lose this clinically significant amount of weight. At 6 months post-treatment (compared to baseline), 23% of patients with a FT had lost more than 10% of their body weight, compared to 44% of patients without a FT. Finally, at 12 months post-treatment (also compared to baseline), only 13% of patients with FTs were still at a 10% deficit in relation to baseline weight, compared to 40% of patients in the NFT group (Figure 6). In terms of patients gaining a clinically significant amount of weight, only patients in the FT group were documented to have gained more than 10% of their baseline weight at 3 (5%), 6 (5%), and 12 months (7%) after the completion of treatment. The NFT group showed no clinically significant increases in weight at any time point of interest (Figure 6). Between-group and within-group results are summarized below (Tables 4-6).

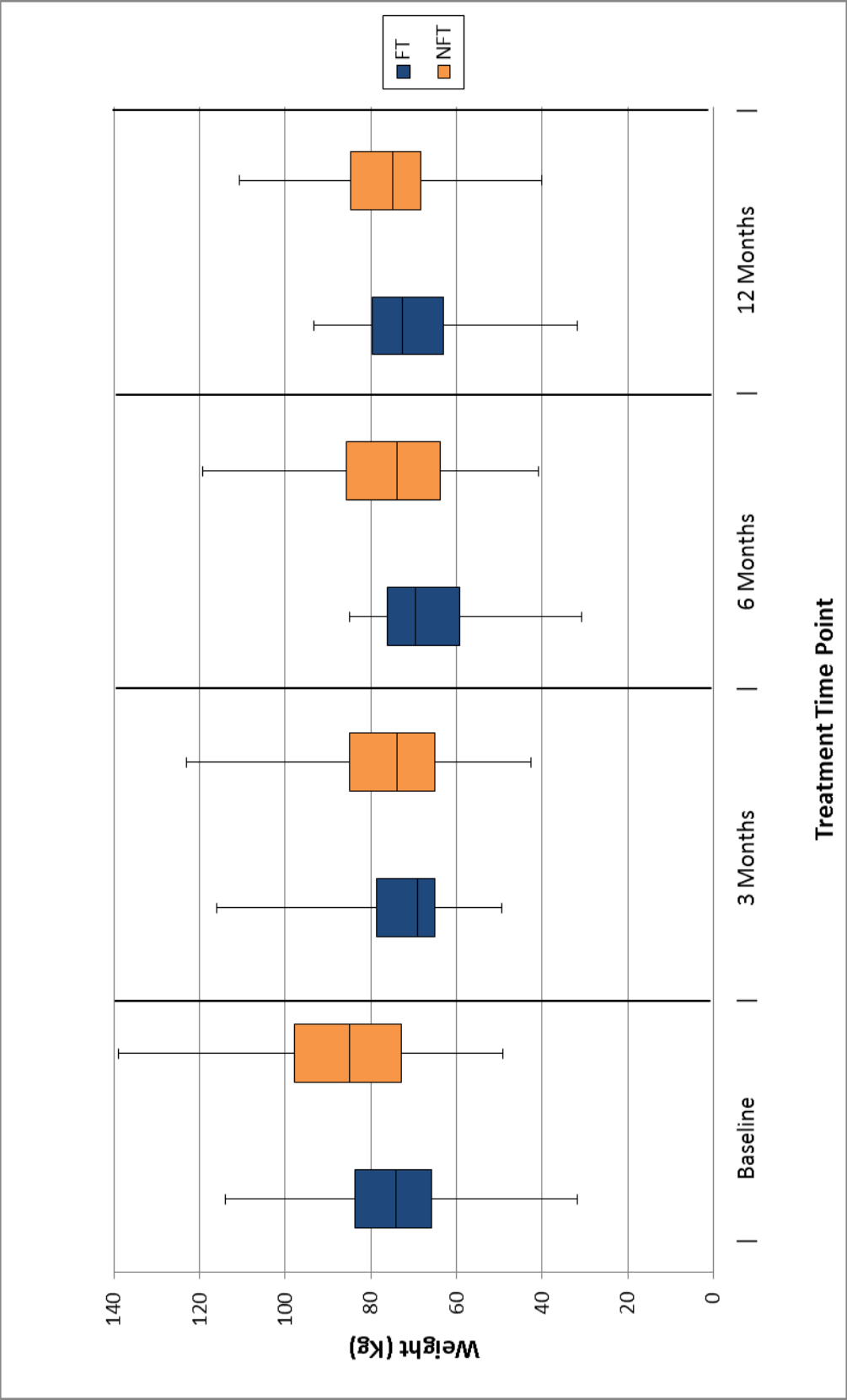
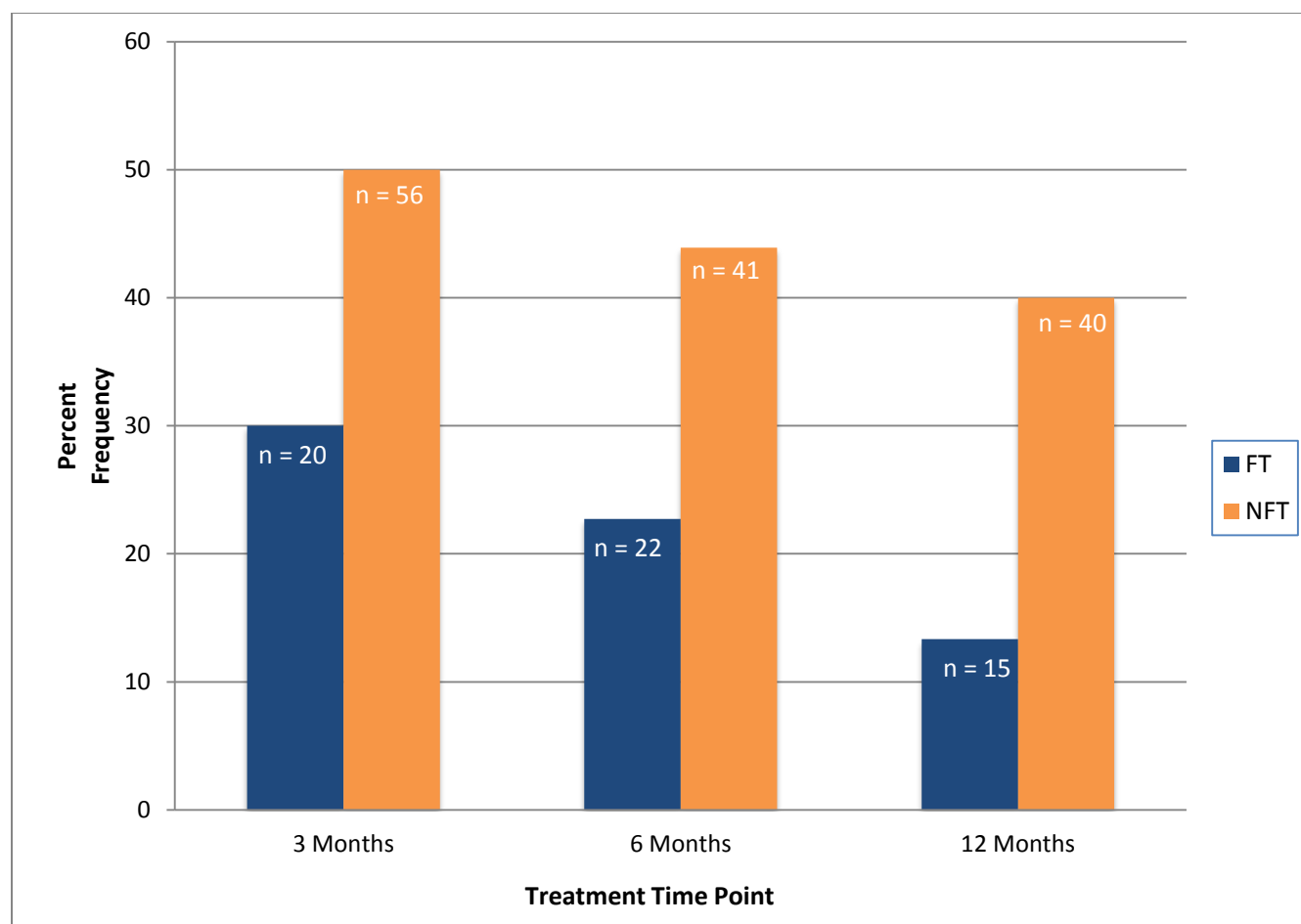
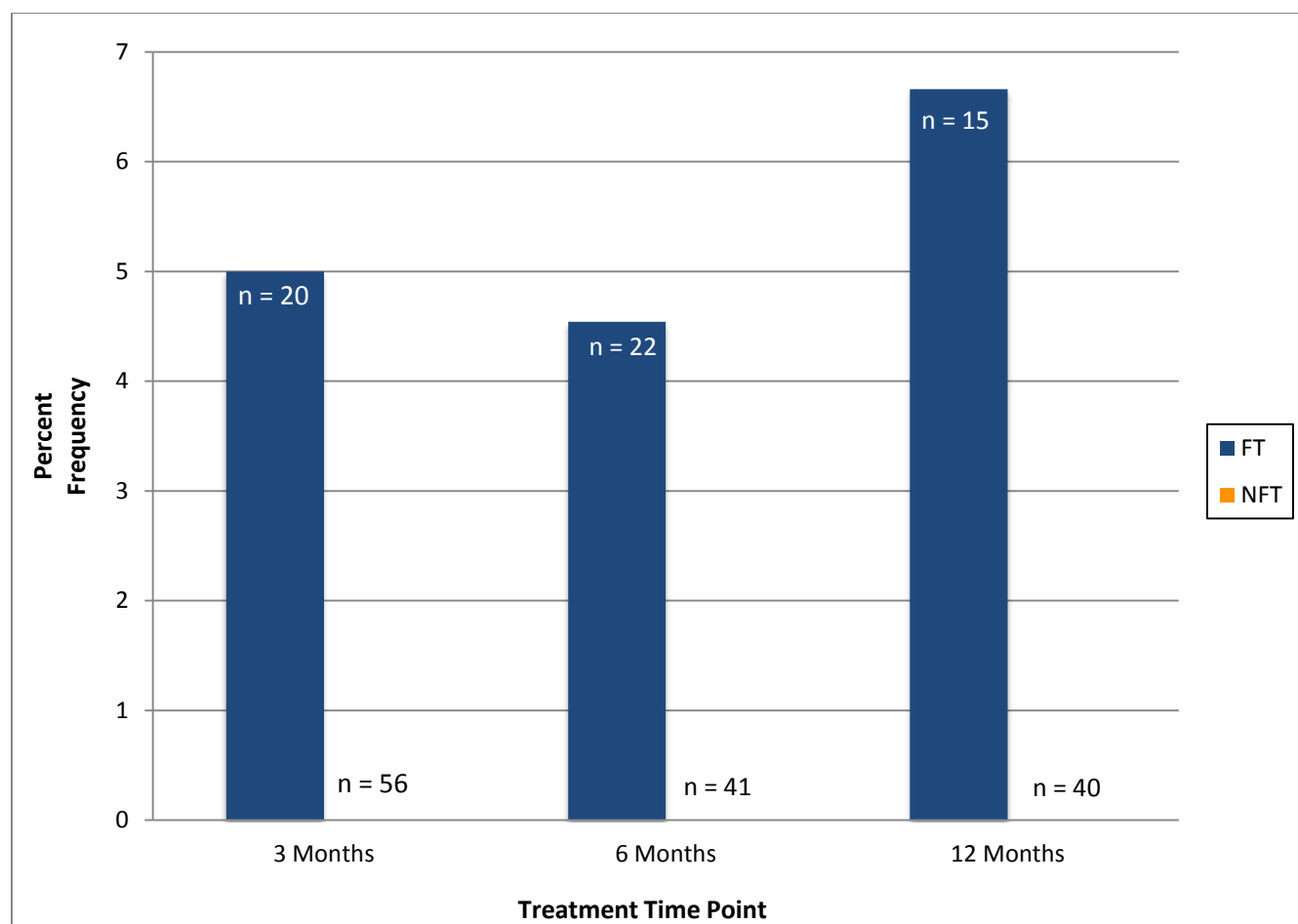


Figure 5. Distribution of Weight According to Feeding Tube Status.



*Figure 6.* Percentage Frequency Distribution for Clinically Significant Weight Decrease ( $\geq 10\%$ ) from Baseline for Oropharyngeal Cancer Patients.



*Figure 7. Percentage Frequency Distribution for Clinically Significant Weight Increase ( $\geq 10\%$ ) from Baseline for Oropharyngeal Cancer Patients.*



Table 4

*Between-Group Comparison at Four Time Points (FT vs. No FT)*

Outcome Measure	Baseline	3 Months	6 Months	12 Months
FOIS				
FT	6.06	4.70	5.14	6.00
NFT	6.41	5.76*	6.00*	5.98
PSS-HN (Diet)				
FT	78.9	57.0	62.5	78.6
NFT	82.0	66.5	70.9	76.3
MDADI (Functional)				
FT	87.1	70.5	80.0	86.0
NFT	90.0	78.6	81.3	88.1
MDADI (Composite)				
FT	83.2	67.8	73.3	79.5
NFT	88.1	75.8*	79.6	83.0
Weight (Kg)				
FT	74.3	71.4	66.7	71.0
NFT	85.7*	74.8	74.9	76.0

Alpha = 0.05 (2-tailed)

\* denotes significant *p* value

FOIS analysis utilized MWU/Wilcoxon Rank Sum; all other analyses utilized independent samples t-test

Table 5

*Repeated Measures Analysis Summary*

Outcome Measure	Baseline	3 Months	6 Months	12 Months	<i>p</i> value
FOIS					
FT	6.06	4.70	5.14	6.00	.012*
NFT	6.41	5.76	6.00	5.98	.005*
PSS-HN (Diet)					
FT	78.9	57.0	62.5	78.6	.169
NFT	82.0	66.5	70.9	76.3	.061
MDADI (Functional)					
FT	87.1	70.5	80.0	86.0	.548
NFT	90.0	78.6	81.3	88.1	.020*
MDADI (Composite)					
FT	83.2	67.8	73.3	79.5	.179
NFT	88.1	75.8	79.6	83.0	<.001*
Weight (Kg)					
FT	74.3	71.4	66.7	71.0	<.001*
NFT	85.7	74.8	74.9	76.0	<.001*

Alpha = 0.05 (2-tailed)

\* denotes significant *p* value

FOIS analysis utilized the Skillings-Mack Test; all other analyses utilized Linear Mixed Effects

Table 6

*Post-Hoc Analysis Summary for Significant ANOVA's*

Variable	Patient Group	Time Points Compared	Significance ( <i>p</i> value)
FOIS (Wilcoxon Signed Rank Test)	FT	Baseline v. 3 Months	<.001*
		Baseline v. 6 Months	.007*
		Baseline v. 12 Months	.245
		3 Months v. 6 Months	.489
		3 Months v. 12 Months	.039
		6 Months v. 12 Months	.111
	No FT	Baseline v. 3 Months	<.001*
		Baseline v. 6 Months	.007*
		Baseline v. 12 Months	.001*
		3 Months v. 6 Months	.096
		3 Months v. 12 Months	.127
		6 Months v. 12 Months	.986
Weight (Satterthwaite)	FT	Baseline v. 3 Months	.001*
		Baseline v. 6 Months	<.001*
		Baseline v. 12 Months	.035
		3 Months v. 6 Months	.993
		3 Months v. 12 Months	.914
		6 Months v. 12 Months	.901
	No FT	Baseline v. 3 Months	<.001*
		Baseline v. 6 Months	<.001*
		Baseline v. 12 Months	<.001*
		3 Months v. 6 Months	.969
		3 Months v. 12 Months	.528
		6 Months v. 12 Months	.336
MDADI (Functional) (Satterthwaite)	No FT	Baseline v. 3 Months	<.001*
		Baseline v. 6 Months	<.001*
		Baseline v. 12 Months	.226
		3 Months v. 6 Months	.791
		3 Months v. 12 Months	.010
		6 Months v. 12 Months	.144
MDADI (Composite) (Satterthwaite)	No FT	Baseline v. 3 Months	<.001*
		Baseline v. 6 Months	<.001*
		Baseline v. 12 Months	.009
		3 Months v. 6 Months	.631
		3 Months v. 12 Months	.043
		6 Months v. 12 Months	.484

Alpha = 0.0083 (Bonferroni Correction)

\* denotes significant *p* value

## Chapter 4: Discussion

Individuals diagnosed with OPSCC are likely to experience treatment-induced complications which may ultimately affect their ability to meet nutritional demands. Thus, the ability to promptly decide whether enteral feeding will be necessary is important to prevent deterioration of nutrition and health. The capacity of physicians to communicate prognostic expectations based on FT status has the potential to considerably improve treatment for nutritionally compromised OPSCC patients. While it is well understood that many individuals with HNC would benefit from nutritional support during their treatment, the optimal timing of FT insertion may be extremely difficult to determine. Moreover, a widely-adopted, standardized protocol to guide decision making regarding the timing of FT insertion is currently lacking. Recalling Kramer et al. (2014), “considering patients’ disease characteristics and baseline feeding capacity is an essential component for future research attempting to contribute to the development of a protocol”. Therefore, comparing outcome measures related to oral intake, dysphagia, and QoL has the potential to highlight key differences between those who are given a FT and those who are not. This may in turn contribute to the establishment of an evidence-based protocol, guiding tube placement and improving health outcomes for HNC patients.

This study investigated differences in outcomes related to oral intake between individuals diagnosed with oropharyngeal cancer who received an enteral FT during treatment versus those who did not. Attention was focused on comparing specific outcome variables at four treatment time points: at baseline (pre-treatment), and then at 3, 6, and 12 months post-treatment. Given these time points, inquiry was made into how the FOIS, PSS-HN (Normalcy of

Diet subscale), MDADI-Composite and Functional scales), and weight changed over time for each group in order to describe differences in trajectory of recovery. By exploring how the outcome variables differed between the two groups – FT (FT) and no FT (NFT) at baseline, this study also sought to determine pre-treatment differences that may in part have been responsible for the placement of a FT. From these data, a secondary objective of this investigation was directed toward determining potential predictive factors associated with dependence on use of enteral FTs. Outcome variables were collected and then used to address the following objectives:

- 1) To determine if baseline characteristics predict FT use and dependence for individuals diagnosed with oropharyngeal cancer which was treated with IMRT;
- 2) Investigate the impact of FT status on long-term swallowing-related outcomes, weight loss and QoL; and
- 3) Describe differences in the trajectory of recovery for outcome measures based on FT use.

The discussion to follow will first address which baseline characteristics were likely to predict FT use and dependence for this population. FT dependence will then be discussed in terms of which outcome variable(s) was/were most useful in predicting duration of FT use, as well as the magnitude of their effect. Next, key differences in outcomes at three post-treatment time points will be addressed. This will include between-group comparisons of the FOIS, PSS-HN (Normalcy of Diet), MDADI (functional and composite scales), and weight/weight change at 3, 6, and 12 months post-treatment. This will be followed by of how each of the aforementioned variables changed over time for each group, specifically addressing recovery and if their status

returned to baseline levels. Finally, the clinical implications of the present data will be presented, along with limitations and directions for future research.

### **Feeding Tube Placement**

**Patient characteristics.** Based on patient/disease characteristics at baseline, no differences between the two groups were found to exist (Table 1), with the exception of weight. Other studies have shown a significantly increased risk of FT placement in patients who had a higher T and N stage (T3/T4 and  $N \geq 2$ ) disease (Bhayani et al., 2012; Mays et al., 2014; Yang et al., 2016). Additionally, factors such as sex have also been shown to be predictive of enteral feeding, with males having a higher incidence of FT placement compared to females (Wermker et al., 2012), making the present findings somewhat unexpected. The lack of a difference could have been due to the highly selective approach taken to ensure a homogeneous sample of participants. Many confounding factors that may have contributed to FT use were removed through the inclusion criteria (e.g., disease site, IMRT vs. 3D conformal RT, no surgery, etc.), leaving only outcome measures to potentially influence FT placement.

The findings from this study indicate that the FOIS, PSS-HN (Normalcy of Diet), and both the functional and composite MDADI scores did not differ significantly between the FT and NFT patient groups at baseline (see Table 2). Since individuals in the NFT group are able to tolerate an oral diet without the need for enteral feeding, it would be expected that they would perform significantly better at baseline, however, this was not the case. While baseline scores may not fully represent a patient's health considering they have yet to be exposed to the toxic effects of treatment, the literature indicates that baseline measures of swallowing may be useful for predicting who receives a FT and who does not (Bhayani et al., 2014; Yang 2016). While the NFT

patient group did outperform the FT group over time in terms of the above-noted outcome measures (Table 4), the lack of significant differences between groups indicates that those who receive a FT during treatment are not much different than those who do not. These data suggest that the ability to predict FT use and the decision to administer a FT may not be made simply based on pre-treatment differences in FOIS, PSS-HN, and MDADI scores.

**Pre-treatment oral function.** While using the FOIS as a marker of oral intake presents unique challenges, the measure does provide insight into the ability of patients to sustain oral consumption of foods. Considering that no difference was found at baseline between the two groups, a patient's oral intake seems to be more affected by treatment rather than pre-treatment issues. However, these findings conflict to some extent with established literature; for example, Quon et al. (2015) found that those who did not require a FT had less pre-treatment dysphagia and weight loss. Although these issues do not objectively represent oral intake, they may be indicative of difficulty with eating/drinking even before treatment began.

A possible explanation for the lack of pre-treatment differences in oral intake could lie in the weakness of the FOIS as an outcome measure. This cohort of patients did not undergo prophylactic FT placement, and thus, all scored at the upper end of the FOIS (i.e., scores ranging from 4 to 7) at baseline, since scores at the lower end of the FOIS (i.e., 1 to 3) inherently imply the presence of a FT. However, once treatment began and many patients required a FT, those who were provided enteral feeding then received FOIS scores that are distinctive from those in the NFT group. Therefore, it seems that oral intake as measured by the FOIS may be used to as a prognostic marker after the commencement of treatment, rather than as a predictive variable at baseline to decide whether or not a patient will require a FT.

**Pre-treatment weight.** The overwhelming consensus in the field of HNC rehabilitation is that limiting weight loss is crucial for progressing through treatment with minimal interruptions (Bhayani et al., 2013; Shaw et al., 2015; Laguis et al., 2016). While decreases in weight ( $\geq 10\%$ ) have been demonstrated to have clinically meaningful implications, associations between weight at baseline and tube status have yet to be thoroughly investigated. The current findings may be used to distinguish between patients who will need a tube and those who will be able to orally consume their nutrition before treatment begins.

In the direct comparison of FT and NFT patients at baseline, weight was the only variable that emerged as being significantly different (Table 4). This finding is consistent with current literature on tube status and weight loss; Quon et al. (2015) also showed that patients who did not require a FT had less pre-treatment weight loss. Because the NFT group had a significantly higher mean baseline weight, meaningful conclusions can be suggested. First, despite the absence of other significant between-group differences at baseline (e.g., disease characteristics, FOIS score, etc.), the findings appear to indicate that there may be a common variable among patients in the FT group that affects maintenance of one's pre-treatment weight compared to their NFT counterparts. Furthermore, baseline differences in weight suggest the need for specific weight loss screening alongside the use of other function-related outcome measures used. Perhaps the most valuable finding is that while weight has been confirmed to be an important pre-treatment indicator of FT use/placement, none of the variables assessed in this study have the ability to represent the lower average weight at baseline for patients with a FT. Additionally, they cannot be used to predict post-treatment FT placement.



## Feeding Tube Duration

Because there is evidence to suggest that FT use can lead to an increased likelihood of long-term dependence, especially for those with pre-existing dysphagia and weight loss (Bhayani et al., 2013; Jang et al., 2013; Verma et al., 2015), this study sought to examine variables that may have predicted duration of FT use in this patient population. The strongest predictor of FT duration was the combination of the FOIS, PSS-HN (Normalcy of Diet), the two MDADI scales (functional and composite), and weight. Although the  $R^2$  value was quite high for this combination of variables (Table 2), the true significance of this analysis is unknown given the small number of data points available ( $n = 9$ ). Further, these variables were far better at predicting FT duration when values at 3 months were used compared to baseline scores. The largest  $R^2$  value for baseline prediction was less than almost every value at 3 months, indicating that the 3 month time point should be used to determine whether or not patients will require a FT.

The decision to leave a FT in place is complex and multidimensional, relying on many factors outside of objective patient characteristics. Other factors (e.g., the absence of family/friends to help with feeding, variations in lifestyle, the presence of unrelated comorbidities, etc.) are not represented in the outcomes used and may contribute to extended FT use. The presence of confounding variables may help to explain variance not captured by statistical analysis. Therefore, this finding should not be interpreted to suggest that the measures included in this study alone are the only variables that may be useful in predicting FT duration/dependence, especially at 3 months post-treatment.

## Feeding Tube Status

**Functional oral intake.** The current body of literature on the use of the FOIS as a marker of oral intake and/or oral dietary tolerance is extensive (Kotz et al., 2012; Carnaby-Mann et al., 2012; Messing et al., 2017; Ringash et al., 2017). The FOIS enabled objective characterization of oral dietary intake on a scale of one through seven, allowing for direct comparisons between the groups. While numerous measurement tools that allow for documentation of oral intake of food and liquids are available, many also measure additional aspects of impairment, and are commonly disease-specific (List, Ritter-Sterr, & Lansky, 1990; Hillel et al., 1989). The FOIS was chosen as a primary outcome measure in the present study because of its singular focus on documenting mode of nutritional intake.

Of equal importance in selecting a primary outcome measure is consideration of the psychometric of the measure. Inter-rater reliability for the FOIS was initially established by 6 experienced Speech-Language Pathologists (S-LPs; Crary et al., 2005). Despite the fact that no training was provided to raters (other than a simple description of the scale), agreement between paired judges ranged from 85%-95% (Crary et al., 2005). This finding demonstrates the robust nature of the FOIS and supports use without additional training by clinicians specializing in the treatment of dysphagia.

Moreover, the FOIS also showed high consensual validity, with the raters often agreeing (81%-98%) with the scale ratings as predefined by the authors (Crary et al., 2005). This finding reflects exceptional agreement with the progression of items across the seven FOIS levels, supporting the present use of this scale to monitor changes in oral intake. Finally, because the FOIS provides information regarding the special preparations or limitations patients make in

their diet, as well as the necessity for supplementation with a FT, it is ideal to use when assessing how much of one's diet is consumed orally, especially with a FT.

However, despite the frequent use and application of the FOIS, little is known regarding how scores differ between those with a FT and those without, and how this affects the trajectory of recovery for each unique group. Research emphasizes the importance of maintaining oral intake – regardless of tube status – to prevent muscle wasting and remodelling of musculature (Kasper et al., 2002; Clark, 2009; Hutcheson et al., 2013). Investigating such differences is critical to establish and communicate realistic treatment goals, as well as to the development of a standardized protocol based on patient characteristics and FT status.

In the current study, patients in the FT group had significantly lower FOIS scores at 3 and 6 months post-treatment when compared to the NFT group, despite no statistical difference being found at baseline and 12 months (Table 4). As expected, those without a FT are generally able to tolerate a fully oral diet, thus, their oral intake as represented by the FOIS should indeed be higher. It is noteworthy to understand that patients in the FT group did not approximate baseline oral intake until 12 months post-treatment. The findings of this study provide information on the oral intake of patients with and without FTs as they progress through treatment.

Within-group analyses revealed that both the FT and NFT groups demonstrated altered oral intake at 3 and 6 months compared to baseline (see Table 6). This indicates that both patient groups may be at risk for negative health outcomes associated with a nutritionally compromised status during this time frame. Interestingly, the trajectory of altered oral intake

differed between the groups. Specific inquiry into where these differences emerged yielded interesting results.

For individuals in the FT group, a significant difference was found when comparing FOIS scores at baseline and 3 months, as well as between baseline and 6 months. Similarly, individuals in the NFT group also exhibited a significant difference between scores at baseline and 3 months, and baseline and 6 months. While these results indicate a drop in functional oral intake, independent of tube status, a key difference in the trend of recovery was evident. For NFT patients, there was also a significant difference between baseline and 12 months (Table 6). Because FOIS scores for NFT individuals were higher at baseline compared to 12 months, and because the difference was statistically significant, it is fair to conclude that the functional oral intake of this group did not return to baseline levels even after 12 months. This trend is inherently different from the return to baseline levels noted at 12 months post-treatment for the FT group. Interpreting this difference between the groups is challenging in the context of a retrospective study. In future investigations, it would be interesting to examine if significant change in FOIS scores at 3 months, or even at an intervening time point after the start of treatment, might prove to be a useful indicator of need for nutritional support.

**Normalcy of diet.** To complement the FOIS, and to provide an idea of the patients' ability to tolerate a range of foods by mouth, between-group comparisons were also conducted using the PSS-HN (Normalcy of Diet) subscale. The present finding of no significant differences between groups relative to Normalcy of Diet ratings was surprising. Considering the variation in FOIS scores over time for both groups, and the fact that a large proportion (32%) of patients received FTs (Table 1), the degree to which patients were able to tolerate a range of foods by

mouth was expected to diminish after treatment. Although current literature using the PSS-HN as an outcome measure reports no relation between the scale and gastrostomy tube placement (Morton, Crowder, Mawdsley, Ong, & Izzard, 2008), differences were nonetheless expected considering that individuals with a FT are expected to have an abnormal/altered diet.

Based on findings by Quon et al. (2015), the lack of significant change in PSS-HN Normalcy of Diet scores across time is also unexpected. Quon et al (2015) found that all three groups of patients (prophylactic, reactive, and no FT) showed a similar trend in post-treatment scores, demonstrating a decline in the number of patients without dietary restrictions, as well as an increase in patients limited to foods of softer consistency. In contrast, the present study found no such change over time. One possible explanation for the contrasting results is that Quon et al. (2015) included patients from 2004-2007, when 3D-conformal radiation therapy was still commonly being used to treat HNC. Thus, differences in the sample populations and treatment modality could have contributed to the contradictory findings.

**Dysphagia and QoL.** Established literature makes it clear that dysphagia is a common and serious issue in those treated for OPSCC (Langendijk et al., 2008; Nguyen et al., 2005; Nguyen et al., 2006), leading to significant alterations in QoL (Manoor et al., 2012). To better understand the impact of OPSCC treatment on swallow function and swallowing-related QOL, scores from the functional and composite subscales of the MDADI were collected. To fully understand the impact of altered oral intake on one's health, it is of great value to investigate swallowing-related QoL. Consisting of four subscales addressing the global, emotional, functional and physical impact of dysphagia on QoL, the MDADI allows for a comprehensive analysis of how patients are affected by treatment.

The MDADI must have psychometrical rigour, and strong reliability and validity in order to be utilized as an outcome measure. Each MDADI subscale has demonstrated acceptable internal consistency and test-retest reliability (Chen et al., 2001). The criterion validity of the MDADI was determined in comparison to the Performance Status Scale-Head and Neck (PSS-HN), an instrument considered as a gold standard measurement tool with respect to oral intake and swallowing function. Within the global, emotional, and physical subscales of the MDADI, criterion validity ranges from moderate to moderately-high (Chen et al., 2001).

MDADI data were used to supplement information obtained from the PSS and FOIS. Because it allows for inquiry into how dysphagia affects a patient's psychosocial and emotional well-being, the scale provides a more complete analysis of the effects of HNC treatment. Finally, the assumption can be made that the longer the interval between the end of treatment and MDADI assessment, the higher the scores should be. In theory, if a patient has been post-treatment for a long period, they have had more time to adapt to the deficits caused by the tumour and/or or treatment itself. Taking this into account, Chen et al. (2001) found that the longer the time interval between the end of treatment and MDADI assessment, the higher the global MDADI score, reflecting higher QoL scores and a higher level of swallowing functionality.

Together, the composite and functional MDADI scales assess QoL in relation to difficulty with swallowing. In this study, data from the functional subscale failed to reveal significant differences between the FT and NFT groups. However, individuals without a FT still experienced higher/better overall scores at each point in time (Table 4). This may be a trend that simply requires a larger sample size to become statistically significant. Although a patient-reported measure, the functional subscale has been shown to be reflective of swallowing function in the

absence of objective, direct examination (Hutcheson et al., 2017). Based on the present findings, it is reasonable to suggest that these groups did not differ relative to swallowing function. This might indicate that patients in the FT group did not receive enteral feeding because of swallowing function, but other variables (e.g., odynophagia).

The composite subscale, a score summarizing overall performance as a weighted average of the physical, emotional, and functional subscale scores, provides a more holistic view of the impact of swallowing impairment on QoL (Hutcheson et al., 2017). With respect to the composite MDADI subscale, a statistically significant difference was identified between groups at 3 months post-treatment. This finding suggests that a FT is associated with lower perceived swallowing-related QoL at 3 months post-treatment. The benefit that comes from knowing about changes in QoL over time, and in particular, the significant difference between the groups at 3 months, is that the information can help health care professionals provide more accurate counselling and education to patients. This will allow the professionals to be attuned to this anticipated change in QoL.

Neither the functional or composite MDADI scores changed significantly over time for individuals who received a FT. One study that investigated factors predicting two-year composite MDADI outcomes for oropharyngeal cancer patients reported a significant reduction in scores at 6 months post-treatment when compared to baseline (Goepfert et al., 2017). Even though participants in the Goepfert et al. (2017) study were not grouped according to FT status, the finding suggests that a decline in MDADI scores should still be expected within this population. In contrast, statistically significant changes were observed over time for both the functional and composite MDADI scores in the NFT group. These findings suggest that the NFT

group had a more difficult time, relative to their baseline standing, at 3 and 6 months after their treatment concluded.

The utility of administering the composite MDADI scale has been enhanced by the identification that fluctuation of  $\geq 10$  points is indicative of clinically significant differences (Hutcheson et al., 2016; Goff et al., 2017) Upon examining the percentage of patients with this clinically relevant decrease in composite MDADI scores, a higher proportion of patients in the FT group were found to have this decline at 3 months post-treatment (Figure 6). However, over time, the percentage of FT patients demonstrating a clinically significant decline in their scores decreased, and by 12 months, a much smaller percentage of those in the FT group exhibited this decrease compared to the NFT group (Figure 6). Perhaps the most interesting discovery in regard to composite MDADI scores is that a far higher percentage of patients in the FT group had a  $\geq 10$  point increase in their score at every assessment time. The FT group outperformed the NFT group, with the NFT group demonstrating a more protracted course of improvements in swallowing-related QoL. These findings indicate that the two groups differ in their baseline QoL, and their trajectory of recovery, a finding which may be useful information to provide to patients ahead of treatment. FTs are indicated to improve nutritional outcomes, but they may have unintended consequences for QoL – patients who know this prior to treatment may be less apt to have large declines in QoL.

A potential explanation as to why dysphagia may not have a significant effect on the daily activities of FT individuals (i.e., functional MDADI scores) is that they may attribute these difficulties to the FT itself. Patients with a FT are more likely to eat alone (Quon et al., 2015), thus, may be restricted and may not participate in many of their regular daily activities.



Additionally, because the MDADI is reported by the patient themselves, objective changes in swallowing function may not necessarily be represented. How the patient perceives their swallowing function may be different than compared to objective, quantifiable changes. Nonetheless, the fact that these individuals required enteral feeding suggests that they could have had some clinically relevant drop in swallowing function, which functional MDADI scores were unable to detect.

**Weight.** The prevention of weight loss is an established marker of successful HNC treatment, leading to less treatment-related toxicity and complications (Languis et al., 2016; Shaw et al., 2015; Bhayani et al., 2013). The efficacy of reactive FT placement for the prevention of weight loss is highlighted by the lack of statistically significant differences between the two groups at all post-treatment time points. Despite those in the NFT group having a higher mean weight at every point of assessment (Table 4), a significant difference was only found at baseline between the two groups. The findings corroborate the current stance on weight loss prior to treatment, in that patients without a FT are more likely to have less pre-treatment weight loss (Quon et al., 2015). Thus, it may be inferred that significant differences in mean weight after treatment are not solely dependent on FT status. One explanation is that raw weight may not be the most appropriate metric to compare long-term outcomes, since many factors outside of FT status can influence one's weight.

Although there was no statistical difference in mean weight post-treatment, the percentage of individuals losing  $\geq 10\%$  of their baseline weight was higher in the NFT group, especially at 12 months (Figure 6). It was expected that by 12 months, patients not requiring enteral feeding – and in turn were able to consume their nutrition orally – would not have such

a high proportion of individuals (16/40, 40%) with a clinically significant decline in weight. Further, when investigating the percentage of patients with a clinically significant increase in weight, no patients in the NFT group showed any such improvement (Figure 7). In contrast, a notable number of FT patients did increase their weight by 10% at each time point. This finding leads to two possible conclusions: (1) reactive FT placement served the intended purpose of maintaining weight in patients otherwise at risk, and (2) those who did not receive a FT went on to experience significant decreases in weight with greater frequency than those with tube feeding. Weight loss negatively affects prognosis and leads to reduce survival outcomes in HNC (Languis et al., 2013). Therefore, not only should weight or weight change at baseline be a consideration for nutrition management, but ongoing monitoring may identify patients who experience clinically significant weight loss later in treatment, who may also benefit from nutritional monitoring and support (Lynch, 2017).

Despite the mean weight of NFT patients being consistently higher, it is interesting to note that their mean weight did not return to pre-treatment levels at 12 months (Table 5). Results indicated that for those without a FT, weight at 12 months was significantly lower than at baseline. On the contrary, the patients with a FT exhibited no significant difference, indicating recovery back to their baseline weight. Since their initial weight was lower, a return to baseline may have been easier for the FT group. Still, this finding indicates that although baseline weight may be utilized to predict tube placement, it does not predict long-term (12 month) prognosis. Furthermore, a significant difference was observed for both groups between baseline and 3 months, and baseline and 6 months, indicating that mean weight decreased significantly from baseline at these two points in time. The trajectory of recovery for both

groups, with respect to all outcome variables of interest used in this investigation, seems to follow this trend.

### **Clinical Implications**

Based on the three primary objectives, this study highlights important differences in outcomes related to health, swallowing, and QoL for those with OPSCC grouped according to FT status. Several components of the results obtained may be of value from a clinical decision-making perspective. When using outcome variable data to determine if differences exist based on FT status, it is important to first determine the time point at which this difference exists and whether individuals recover back to baseline status. If differences are commonly identified at a specific time, and if these differences seem to affect recovery in the long term, then the variables in question can be used to provide more specific treatment recommendations based on treatment and patient characteristics.

Patients utilizing enteral feeding during treatment differ in relation to health outcomes and recovery when compared to those who are able to consume a fully oral diet. These differences most often manifest at 3 months post-treatment, with outcomes representing maintained oral intake and difficulty with swallowing being significantly better for those without a FT. As a result, consideration at this point in time (or even prior to 3 months) by clinicians should be undertaken to determine whether or not treatment will necessitate the use of enteral feeding.

Within this setting and for this population, the absence of statistically significant differences between the two groups at 12 months could indicate that current clinical practice is meeting patient needs. No outcome variables were found to significantly differ at this time,

implying that reactive FTs were appropriately selected for those at-risk. There was, however, a concerning inability for patients without a FT to return to their baseline weight and oral intake level. This finding suggests that some patients without a FT may have benefited from enteral feeding. A more detailed investigation into the characteristics of specific patients without a FT which may have led to a decline in long-term outcomes would offer valuable information for guiding standard clinical practice. After this type of information is collected, factors responsible for long-term deficits could emerge and be utilized in the decision-making process for gastrostomy tube insertion.

This investigation also addressed how specific outcome variables correlate with the length of tube insertion in order to determine which have the greatest impact on prolonging tube use. Since dependence on enteral feeding has been associated with issues such as the development of esophageal toxicity and dysphagia (Bhayani et al., 2013), identifying those variables which have the strongest correlation with duration of tube insertion may provide valuable information. Health care professionals will be able to focus on and allocate resources towards improving the variables they know will have the greatest positive impact.

The benefits of maintaining oral intake throughout treatment have been described, with Hutcheson et al. (2013) conducting an investigation to assess the effects of maintained oral intake and adherence to swallowing exercises on long-term outcomes. The present investigation built onto the knowledge generated from studies such as the Hutcheson paper, with variations in the methodology used. Hutcheson et al. (2013) investigated maintained oral intake using only three categories: (1) nothing by mouth (fully gastrostomy tube dependent) (2)

partial oral intake (tube feeding supplemented by consistent daily oral intake) and (3) full oral intake (100% diet consumed orally).

By using the FOIS and PSS-Diet scales to determine the level of maintained oral intake throughout treatment, this present research has provided more specific information regarding the amount of oral intake that accompanies FT use in this patient population. Hutcheson et al. (2013) used two main swallowing-related outcome measures to test the effect of maintained oral intake, diet level and length of FT dependence. However, little emphasis has been placed on determining what level of maintained oral intake is directly associated with actual swallowing functionality, and how this relates to other variables such as weight loss during treatment. Future investigations investigate questions relating to the maintenance of oral intake in terms of the ratio of oral to enteral feeding, providing more specific numbers unable to currently be obtained by using any validated scale. Furthermore, the diversity of patient characteristics and treatment variables seen in the Hutcheson et al. (2013) investigation were controlled for in this study, since all patients had oropharyngeal cancer and were treated with either concurrent CRT or RT alone, using IMRT as the only RT technique.

By knowing how health-related outcomes impact FT dependence and which have the greatest effect, physicians can direct their focus and attention to improving issues they know will make the greatest impact on their patient's health and well-being. The present study found that data from all outcome measures at 3 months correlated more strongly with length of tube duration than did data from baseline. Since patients with OPSCC are living longer post-treatment, minimizing the associated toxicities of treatment and decreasing the risk of FT dependency is essential. The increased survival of this population would be less meaningful if

treatment and reliance on enteral feeding led to a long-term decrease in QoL. Therefore, clinicians may wish to identify patients at a high risk for FT dependence using assessment at 3 months post-treatment.

### **Limitations and Directions for Future Research**

**Documenting oral intake.** Shaw et al. (2015, p. 170) noted that, “...ideally, future studies would measure the proportion of oral vs. enteral intake to determine the impact of continued swallowing during RT on long-term swallowing-related outcomes”. The retrospective nature of the present investigation is limiting in that this information was unavailable. While the FOIS does possess several distinct advantages, a key limitation must be addressed in future work if it is to be used as an outcome measure comparing patients based on FT status. That is, because the scale is ultimately divided into two categories, it may depict biased results in attempting to measure oral intake in patients without a FT.

Levels one to three of the FOIS imply that a FT is in place and oral intake is judged accordingly. This presents a significant concern with attempting to compare groups of patients based on whether or not they have a FT inserted. For example, if there is no FT, the patient must receive a score of 4 or greater. On the other hand, if a patient does have a FT, they are likely to be given a score between 1 and 3. Thus, only individuals with a FT are able to score in the lower end of the scale (1 to 3), making their average FOIS score seem lower even if a similar level of oral intake is observed compared to NFT individuals. To reduce this limitation, future prospective research should aim to objectively capture the full functional oral intake of participants by calculating the percent/ratio of oral intake to enteral intake, and using the calculated percentage instead of the FOIS in statistical analyses comparing levels of oral intake.

**Missing data.** As is commonly the case with retrospective chart reviews, outcome measure data was missing at several points in time. Although data was available for some patients at all four time points, the remainder of the sample provided data at one, two or three points in time. This led to an unequal distribution of sample size ( $n$ ) at every time point, complicating the repeated measures analysis for objective three (trajectory of recovery). Within a data set, “missingness” may be grouped according to whether the data are “missing completely at random”, “missing at random”, and “missing not at random” (Sterne et al., 2009). The missing data within this investigation can be described as “missing completely at random”, since the missing observations are a random subset of all observations (Bhaskaran & Smeeth, 2014). It is likely that the observed values and the missing values will have similar distributions due in part to the multiple variable reasons why data were missing in the first place. Often, if patients became extremely ill, instrument-driven data collection ceased and became more descriptive as focus was directed increasingly towards palliative care and symptom management. Also, inherent logistical challenges in scheduling a multitude of patient follow-up appointments at each time point may have impacted the completeness of the dataset. As a result, there may have been no systematic difference the missing and observed outcome measures, allowing the data to be used an unbiased and statistically valid manner. To effectively handle the missing-at-random data, the appropriate selection of statistical analyses was required. Several tests capable of incorporating large data sets with missing variables were used, allowing for the production of statistically sound results.

It is unfair to suggest that a specific methodology could be utilized in future research to ensure that all variables are collected at every point in time. Work with oncology populations

does carry real risk relative to data collection, seeing as a wide variety of issues could arise, ultimately limiting complete collection of data (e.g., patients foregoing curative treatment and instead pursuing palliative care, asymptomatic patients not requiring consistent care/assessment, high case load demands for health care professionals, etc.). Researchers interested in conducting a more data-rich investigation should ensure that variables of interest are prospectively collected. Additionally, health care professionals responsible for collecting research data should be supported in prioritizing patient assessment and the recording of assessment results when appropriate to ensure a complete data set is obtained.

**Methodology.** As a consequence of retrospective data collection, the option of randomizing patients to groups based on FT status was not possible. To some extent, this may have resulted in differences in baseline/pre-treatment characteristics between the two groups. As a result, it is likely that patients with more baseline weight loss, and/or worse overall health-status were chosen to undergo reactive FT placement. Moreover, although FT status was the independent variable for almost every comparison, the exact timing of placement was not as an indicator of tube status.

Randomizing patients into groups, and taking into account timing of insertion would ensure that individuals in the FT group actually have a tube inserted at the time of comparison. In addition, collecting outcome variable data immediately after the completion of RT/CRT would be worthwhile. The 3-month time point appears to most often be associated with significant differences based on FT status. Therefore, it would be valuable to collect data at some point between the end of treatment and 3 months. Identifying an earlier point in time where the groups differ significantly may contribute to the development of a decision-guiding



protocol which is able to identify nutritionally compromised patients much sooner, leading to timely and effective gastrostomy tube placement.

Finally, the clinical literature has found proactive swallowing exercises to lead to better swallowing-related QoL (Kulbersh et al., 2006; Shinn et al., 2013), lower rates of FT placement (Bhayani et al., 2013), superior tongue and base and epiglottic movement (Caroll et al., 2008), and shorter duration of PEG dependence (Bhayani et al., 2013). However, the present study was unable to account for the amount of exercise that was prescribed to patients and this factor may limit the external validity of these findings. Accordingly, future studies should control or account for the prescription of swallowing exercise to investigate the impact of oral intake in a more systematic manner.

## **Conclusions**

Within the literature, there exists a need for a standardized protocol to guide optimal timing of FT insertion for the HNC population. The present study investigated how health- and QoL-related outcome variables are impacted by FT status, and if these variables are able to predict FT placement. The findings indicated that such differences are most apparent at 3 months post-treatment, as patients without enteral feeding showed significantly better results in outcomes related to oral intake and dysphagia. Clinically significant decreases in weight stood out as the primary concern/difference amongst individuals without enteral feeding and indicated difficulty with returning to baseline weight.

Differences in patient characteristics based on FT status may contribute to the development of standardized protocol to determine optimal timing of FT placement. These findings also have the potential to contribute to improved decision-making and communication

in a clinical setting. Future research should focus on using prospectively collected outcome measures to ensure they better represent the issues at hand (i.e., using the ratio of oral to enteral feeding to represent continued oral intake). Given the key differences between FT and NFT patients, and the potential differences which could emerge as a result of utilizing a much larger sample size, the value of continuing such research is evident. Data of this type hold substantial potential to improve communication with those who are undergoing treatment for OPSCC and may ultimately lead to better outcomes.

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## Appendices

### Appendix A: List of Abbreviations

BMI	Body mass index
CRT	Concurrent chemoradiotherapy
FOIS	Functional Oral Intake Scale
FT	Feeding tube
G-J	Gastro-jejunostomy
G-tube	Gastrostomy tube
HNC	Head and neck cancer
HPV	Human papillomavirus
IMRT	Intensity modulated radiotherapy
MDADI	M.D. Anderson Dysphagia Inventory
NG	Nasogastric
NFT	No feeding tube
OPSCC	Oropharyngeal squamous cell carcinoma
PEG	Percutaneous endoscopic gastrostomy
PSS-HN	Performance Status Scale for Head and Neck Cancer
QoL	Quality of life
RT	Radiotherapy
SCCHN	Squamous cell carcinoma of the head and neck
TORS	Transoral robotic surgery

**Appendix B: Functional Oral Intake Scale (FOIS)****Functional Oral Intake Scale<sup>1</sup>****TUBE DEPENDENT (levels 1-3)**

- 1 No oral intake
- 2 Tube dependent with minimal/inconsistent oral intake
- 3 Tube supplements with consistent oral intake

**TOTAL ORAL INTAKE (levels 4-7)**

- 4 Total oral intake of a single consistency
- 5 Total oral intake of multiple consistencies requiring special preparation
- 6 Total oral intake with no special preparation, but must avoid specific foods or liquid items
- 7 Total oral intake with no restrictions

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<sup>1</sup> Czary MA, Carnaby-Mann GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. *Arch Phys Med Rehabil*. 2005;86:1516-1520.

## Appendix C: Performance Status Scale for Head and Neck Cancer (PSS-HN)

### PERFORMANCE STATUS SCALE FOR HEAD & NECK CANCER PATIENTS - PSS-HN

#### **Suggestions for Administration**

These performance scales may be rated by health professionals (e.g., physicians, nurses, nutritionists) or other personnel (e.g., clerks, data managers). Ratings are determined through use of an unstructured interview format.

#### **Normalcy of Diet**

Begin by asking the patient what kinds of foods (s)he has been eating. Ask what foods are difficult to eat. Based on the patient's response, choose an item at the low end of the scale. Move up the scale giving examples of foods in each category and asking the patient if (s)he is eating those food items. Even if the patient says that (s)he eats everything, inquire about specific items beginning with 50, soft chewable foods and moving upwards. Stop at the item at, and above which the patient cannot eat. The patient then receives the score **below** that. If the patient indicates that (s)he is eating a full diet, also inquire whether (s)he needs to drink more liquids than usual with meals; eating a full diet with intake of extra fluids is scored 90. If the patient can take foods orally, but is also using a feeding tube, score based on solid food.

#### **Public Eating**

Score the Public Eating scale by asking the patient where (s)he eats (in a restaurant, at home, at friends/relatives' homes, etc.) and with whom (s)he eats (always alone, with family/friends, etc). Ask patient if (s)he chooses different foods (softer, less messy, etc.) when eating with others. When was the last time the patient ate in a restaurant, cafeteria, MacDonald's, picnic, family reunion? Choose the score beside the description that best fits the patient. A patient on a restricted diet, (e.g., tube feeding, pureed foods) who does not eat in public but will join others in a public eating setting should be rated 75. Score 999 for inpatients.

#### **Understandability of Speech**

This scale is scored based on the interviewer's ability to understand the patient during conversation (in this case, based on conversation about patient's diet and social activities). Choose the score beside the description that best fits the patient. See if you can understand the patient if you are looking away while (s)he is talking.

**Special Considerations for Inpatients:** Administration of the PSS-HN varies somewhat for inpatients. Score the Normalcy of Diet and Understandability of Speech Scale as indicated. The Eating in Public Scale is not applicable as inpatients generally have little opportunity to eat with others or leave their hospital rooms. Inpatients receive a score of 999 on the Eating in Public Scale.

Patient Name _____	ID# / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____	Date / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____ / ____
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<b>NORMALCY OF DIET / ____ / ____ / ____ /</b>  100 Full diet (no restrictions)  90 Full diet (liquid assist)  80 All meat  70 Raw carrots, celery  60 Dry bread and crackers  50 Soft chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)  40 Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)  30 Pureed foods (in blender)  20 Warm liquids  10 Cold liquids  0 Non-oral feeding (tube fed)	<b>PUBLIC EATING / ____ / ____ / ____ /</b>  100 No restriction of place, food or companion (eats out at any opportunity)  75 No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods (e.g., liquids))  50 Eats only in presence of selected persons in selected places  25 Eats only at home in presence of selected persons  0 Always eats alone  999 Inpatient
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<b>UNDERSTANDABILITY OF SPEECH / ____ / ____ / ____ /</b>  100 Always understandable  75 Understandable most of the time; occasional repetition necessary  50 Usually understandable; face-to-face contact necessary  25 Difficult to understand  0 Never understandable; may use written communication	
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## Appendix D: M.D. Anderson Dysphagia Inventory (MDADI)

The M. D. Anderson Dysphagia Inventory					
<p><i>This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.</i></p> <p><i>The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.</i></p> <p><i>Please read each statement and circle the response which best reflects your experience in the past week.</i></p>					
My swallowing ability limits my day-to-day activities.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
E2. I am embarrassed by my eating habits.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
F1. People have difficulty cooking for me.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P2. Swallowing is more difficult at the end of the day.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
E7. I do not feel self-conscious when I eat.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
E4. I am upset by my swallowing problem.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P6. Swallowing takes great effort.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
E5. I do not go out because of my swallowing problem.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
F5. My swallowing difficulty has caused me to lose income.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P7. It takes me longer to eat because of my swallowing problem.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P3. People ask me, "Why can't you eat that?"					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
E3. Other people are irritated by my eating problem.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P8. I cough when I try to drink liquids.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
F3. My swallowing problems limit my social and personal life.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
F2. I feel free to go out to eat with my friends, neighbors, and relatives.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P5. I limit my food intake because of my swallowing difficulty.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P1. I cannot maintain my weight because of my swallowing problem.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
E6. I have low self-esteem because of my swallowing problem.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
P4. I feel that I am swallowing a huge amount of food.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
F4. I feel excluded because of my eating habits.					
Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	
Thank you for completing this questionnaire!					

## Appendix E: Ethics Approval



**Western  
Research**

Research Ethics

**Western University Health Science Research Ethics Board  
HSREB Delegated Initial Approval Notice**

**Principal Investigator:** Prof. Julie Theurer

**Department & Institution:** Health Sciences\Communication Sciences & Disorders, Western University

**HSREB File Number:** 105936

**Study Title:** Exploring functional and quality of life outcomes in patients with oropharyngeal squamous cell carcinoma

**Sponsor:**

**HSREB Initial Approval Date:** November 04, 2014

**HSREB Expiry Date:** December 31, 2015

**Documents Approved and/or Received for Information:**

Document Name	Comments	Version Date
Other	Master log	2014/10/16
Data Collection Form/Case Report Form	Data Collection Form	2014/10/16
Western University Protocol		2014/10/21

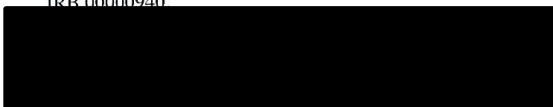
The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB 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.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.



Ethics Officer to Contact for Further Information

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*This is an official document. Please retain the original in your files.*

## Curriculum Vitae

**Nedeljko Jovanovic**

M.Sc. Candidate

### Education

**Western University**

Masters of Science in Health and Rehabilitation Sciences

2016 - Present

**University of Waterloo**

Honours Health Studies, Specialization in Human Nutrition

2011 - 2016

### Employment

**Graduate Research Assistant**

Graduate and Postdoctoral Programs

2016 - Present

### Awards and Achievements

Western Graduate Research Scholarship (\$10,000)

2017 - 2018

Western Graduate Research Scholarship (\$10,000)

2016 - 2017

Dean's Honours List

2016

Dean's Honours List

2013

Dean's Honours List

2012

University of Waterloo Merit Scholarship

2012

University of Waterloo Merit Scholarship

2011

### Scholarly and Professional Activities

**Research Associate**

- Voice Production and Perception Laboratory &

The Laboratory for Well-Being and Quality of Life in Oncology

2016 - Present

**Student Member**

- Rehabilitation Sciences Journal Club, Western University

2016 – Present

**Operations Manager**

- St. George Banquet Hall, Waterloo, ON

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**Assistant Physiotherapist**

- SOS Physiotherapy Clinic, Kitchener, ON

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### Extra-Curricular Activities

KW Men's Basketball League Captain and Team Manager	2014 - 2017
Grand River Soccer League Team Manager	2014
Physiotherapy Clinic Volunteer	2013
Senior Martial Arts Instructor	2007 - 2012

### Research Projects

**Jovanovic, N.**, Theurer J., & Doyle, P.C. (2018). Impact of feeding tube status on health outcomes for individuals with oropharyngeal cancer.

Davis, E., Doyle, P.C., Lynch, M., MacDonald, C. & **Jovanovic, N.** (2017, November). Relationship of postlaryngectomy voice disability with age and time post-treatment. Paper presented at the annual convention of the American Speech-Language-Hearing Association, Los Angeles, CA.