Sarcopenia in Head and Neck Cancer: A Prognostic Analysis

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ABSTRACT

Introduction: In head and neck cancer (HNC), loss of skeletal muscle mass (SMM), or sarcopenia, is a strong prognostic factor for outcomes. However, inconsistencies in its assessment limit our understanding of the relationship between sarcopenia and nutrition-related outcomes. This project evaluated the significance of sarcopenia as described in the literature and as demonstrated in a cohort of HNC patients.

Methods: A scoping review was first conducted followed by a retrospective cohort study with data collected from 194 oropharyngeal carcinoma patients treated with definitive radiation/chemoradiation. Sarcopenia was assessed from computed tomography (CT) imaging at the third cervical vertebra (C3) and the fourth thoracic vertebra (T4). To determine the predictive nature of pre-treatment sarcopenia and its association with feeding tube (FT) outcomes, logistic and linear regression were performed.

Results: Seventy-six studies on sarcopenia in HNC published from 2016 to 2021 were included in the scoping review. Approximately two-thirds of studies used CT imaging to assess sarcopenia. Skeletal muscle index (SMI) at the third lumbar vertebra (L3) was the most prevalent metric used to identify sarcopenia, followed by SMI at the level of C3. Of the 194 eligible patients included in the retrospective cohort study, 30.9% received a FT at some point during treatment. Sarcopenia was identified at baseline in 72.7% of patients based on C3 measurements and in 41.7% based on measures at the level of T4. Those with sarcopenia were significantly more likely to receive a FT and had significantly worse freedom from FT placement compared to patients without sarcopenia. Sarcopenia assessed at T4 was a significant predictor of FT placement and age was the only significant predictor of duration of FT placement.
Conclusions: The most effective strategy to assess sarcopenia in HNC depends on access to resources, patient and treatment characteristics, and the prognostic significance of outcomes used to represent sarcopenia. SMI measured at T4 may represent a practical and valid biomarker for sarcopenia detection that is associated with the need for FT placement. These findings suggest that detection of baseline sarcopenia could guide decision-making related to the progression of treatment and the need for nutritional support.

Keywords: Sarcopenia, head and neck cancer, skeletal muscle mass, computed tomography, feeding tube
Individuals who are diagnosed with head and neck cancer (HNC) are likely to experience substantial issues related to swallowing and oral intake resulting from their cancer treatment. These challenges will often lead to weight loss, reductions in quality of life (QoL), and poor survival. Sarcopenia, or the loss of muscle mass, has the potential to be used as a pre-treatment marker to identify which patients are at a high risk of developing significant impairments. However, because the assessment of sarcopenia is inconsistent, and because little is known about the relationship between muscle mass and nutrition-related outcomes, it is difficult to understand the true impact of this condition. This study gathered information on the definition, measurement, and identification of sarcopenia for individuals undergoing treatment for HNC, investigated the relationship between sarcopenia and nutrition-related outcomes, and identified factors associated with muscle loss after treatment.

The information gathered indicated that best strategy to measure muscle mass and identify individuals with sarcopenia may depend on access to resources, the characteristics of each patient and their treatment, and the predictive value of the outcome used to represent sarcopenia. Muscle mass assessed on computed tomography scans at fourth thoracic vertebra (T4) is relatively simple to measure, convenient, non-invasive, and predictive of feeding tube (FT) placement. Therefore, this information may provide care providers with essential information about the risk for FT placement and in turn guide decision-making in HNC.
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<tbody>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BCAA</td>
<td>Branched-chain amino acids</td>
</tr>
<tr>
<td>C3</td>
<td>Third cervical vertebra</td>
</tr>
<tr>
<td>CRT</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>EWGSOP</td>
<td>European Working Group on Sarcopenia in Older People</td>
</tr>
<tr>
<td>FT</td>
<td>Feeding tube</td>
</tr>
<tr>
<td>HNC</td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield units</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>L3</td>
<td>Third lumbar vertebra</td>
</tr>
<tr>
<td>MDADI</td>
<td>M.D. Anderson Dysphagia Inventory</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MDT</td>
<td>Multidisciplinary team</td>
</tr>
<tr>
<td>NFT</td>
<td>No feeding tube</td>
</tr>
<tr>
<td>OPSCC</td>
<td>Oropharyngeal squamous cell carcinoma</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PSS-HN</td>
<td>Performance Status Scale for Head and Neck Cancer</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operator Characteristic</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<tr>
<td>SARC-F</td>
<td>‘Strength, assistance with walking, rising from a chair, climbing stairs, and falls’ questionnaire</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SMI</td>
<td>Skeletal muscle index</td>
</tr>
<tr>
<td>SMM</td>
<td>Skeletal muscle mass</td>
</tr>
<tr>
<td>T4</td>
<td>Fourth thoracic vertebra</td>
</tr>
<tr>
<td>TNM</td>
<td>‘Tumor-node-metastasis’ stage</td>
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CHAPTER 1

Introduction and Review of Literature

Overview

Considered one of the most dynamic and plastic tissues in the human body, skeletal muscle is essential for human functioning and survival. Mechanically speaking, the primary function of skeletal muscle is to generate force and power and to produce movement through the conversion of chemical energy into mechanical energy (Frontera & Ochala, 2015). In addition to the pivotal role that muscle plays in physical movement, posture, and essential functions such as chewing, swallowing, and breathing (Chromiak & Antonio, 2008; Shiozu et al., 2015), skeletal muscle also functions as a regulator for energy and protein metabolism. Containing approximately 50-70% of all proteins in the human body, skeletal muscle can act as a reservoir of amino acids (i.e., the constituents of proteins) to support protein synthesis and energy production throughout the body when depletion occurs (Wolfe, 2006). Because of its critical role in functioning and energy production, muscle wasting - or muscle atrophy – is associated with myriad adverse outcomes including mobility disorders (Morley et al., 2011), cognitive impairment (Chang et al., 2016), and cardiac and respiratory disease (Bahat & Ilhan, 2016; Bone et al., 2017). One condition associated with this loss of skeletal muscle is termed sarcopenia.

The European Working Group on Sarcopenia in Older People (EWGSOP) define sarcopenia as “… a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality.” (Cruz-Jentoft et al., 2019, p.18). This age-related condition, characterized and confirmed by the presence of low skeletal muscle mass (SMM), is especially prevalent in older
cancer patients due to the weight loss, malnutrition, immobilization, and inflammation commonly associated with both old age and malignancy (Chargi et al., 2019; Morishita, 2016). In head and neck cancer (HNC), the impact of the disease and the consequences of its treatment can result in significant anatomical and functional changes that have the potential to negatively affect one’s quality of life (QoL) (List & Bilir, 2004). Thus, individuals diagnosed with HNC are no exception.

Research indicates that the prevalence of sarcopenia in HNC ranges from 35.5% to 54.5%, with approximately 35%-60% of all HNC patients experiencing malnutrition and significant weight loss over the course of their treatment (Alshadwi et al., 2013). In addition, treatments used in the management of HNC, namely radiotherapy (RT) or chemoradiotherapy (CRT), may further impair one’s ability to maintain adequate levels of nutrition. These treatments can often lead to significant toxicities such as xerostomia, dysphagia, and oral mucositis, all of which are associated with poor oral intake and alimentation (Givens et al., 2009). Consequently, weight loss and malnutrition are especially common in the context of HNC treatment, with patients demonstrating an increased risk for muscle loss and sarcopenia (Marta et al., 2014). Given that sarcopenia is independently associated with frailty, physical disability, morbidity, and mortality (Offord & Witham, 2017), as well as the resultant negative influence on perceived QoL, efforts to develop an improved understanding of sarcopenia in HNC are critical. More specifically, the relationship of sarcopenia with clinical and functional outcomes, and factors contributing to its exacerbation may have important implications for guiding clinical practice and facilitating improved outcomes for those with HNC. The discussion to follow will describe the role of skeletal muscle in health and disease, outline the multifactorial causes of sarcopenia, and explore the impact of this muscle-wasting condition on one’s health and well-
being. Further, methods related to the measurement of muscle mass and assessment of sarcopenia will be discussed followed by a description of management strategies to mitigate its potential negative.

**Sarcopenia and Skeletal Muscle Mass**

Human aging is a complex and multifactorial process associated with significant anatomical and physiological changes which often result in a decline in functional status and an increased risk for adverse outcomes (Anjanappa et al., 2020). One such change is a gradual decrease in overall muscular strength and functioning triggered by a progressive decline in SMM (Cruz-Jentoft et al., 2010). The term ‘sarcopenia’ (meaning “loss of flesh” in the Greek language) was first proposed by Irwin Rosenberg in 1989 to describe this age-related condition (Rosenberg, 1997) and it was later defined as the loss of SMM and strength that occurs with advanced age (Morley et al., 2001). Nonetheless, a universally accepted definition of sarcopenia was required before the concept could be applied in research and clinical practice.

With the intention of fostering advances in identifying and caring for individuals with sarcopenia, the EWGSOP published an operational definition in 2010. At that time, sarcopenia was defined as, “a syndrome characterized by progressive and generalized loss of SMM and strength with a risk of adverse outcomes such as physical disability, QoL, and death” (Cruz-Jentoft et al., 2010, p.413). The EWGSOP met again in 2018 to determine whether an update to the definition was necessary to reflect the advancements in scientific evidence that had accumulated in the 10 years since the initial meeting. Accordingly, an update was generated which allowed for the consideration and assessment of the severity of the condition. Sarcopenia is considered severe when low muscle strength, low muscle quantity or quality, and low physical performance are all detected (Cruz-Jentoft et al., 2019). Currently, sarcopenia is most accurately described as a
geriatric syndrome associated with muscle failure; that is, decreased SMM accompanied by reduced muscle function and performance in advancing age (Anjanappa et al., 2020).

While sarcopenia is largely attributed to aging, researchers have found that other factors can have an influence on its development as well. As a result, sarcopenia may be classified as either ‘primary’ or ‘secondary’. ‘Primary’ sarcopenia refers to the classic, age-related loss of muscle mass and strength when no additional factors have influenced the process of development. For individuals with primary sarcopenia, muscle loss is exacerbated by components of the aging process including physical inactivity, poor nutrition, and a natural reduction in anabolic hormones (Anjanappa et al., 2020). When other factors are likely to have contributed to muscle loss in addition to aging such as those associated with an active malignancy or organ failure, the condition is referred to as ‘secondary’ sarcopenia (Cruz-Jentoft et al., 2010). Moreover, factors such as physical inactivity (i.e., sedentary lifestyle or disease-related immobility or disability) and inadequate intake of energy or protein can also contribute to the development of sarcopenia (Mijnarends et al., 2016). Cytokine-mediated inflammation – in which protein degradation exceeds protein synthesis - is thought to be a significant contributing factor for ‘secondary’ sarcopenia and ultimately results in a net loss of SMM (Roubenoff et al., 2003; Sandri, 2010).

To facilitate early intervention, the EWGSOP also recommends classifying sarcopenia as either an acute or chronic condition. Acute sarcopenia is typically associated with an acute illness or injury and has lasted for less than six months. On the other hand, chronic sarcopenia is related to chronic and progressive conditions, is associated with an increased risk of mortality, and has typically lasted for more than six months (Cruz-Jentoft et al., 2019). Another distinct subcategory of sarcopenia is “sarcopenic obesity” – a condition where excess adiposity and reduced lean body mass are both present simultaneously (Prado et al., 2012). Providing support or intervention for
those with sarcopenic obesity is challenging because the condition can be difficult to detect and is often overlooked, as these individuals often have a body mass index (BMI) greater than 30kg/m² in addition to low muscle mass (Prado et al., 2008). Lifestyle factors that are typically observed in individuals with cancer – such as physical inactivity and malnutrition – put them at an increased risk for muscle mass loss and adipose tissue gain, consequently leading to the development of sarcopenic obesity (Dhillon & Hasni, 2017). Because obesity can exacerbate sarcopenia and increase the rate at which fat is deposited into muscle, sarcopenic obesity is often associated with poor physical function and an increased risk of mortality (Kalinkovich & Livshits, 2017; Tian & Xu, 2016). Irrespective of its classification, it is evident that sarcopenia can have a profound negative impact on those who experience this condition.

**The role of skeletal muscle in health and disease.** Across one’s lifespan, muscle mass and muscle strength substantially vary. In general, both variables increase with growth during youth and early adulthood, are maintained during midlife, and then decrease in older age. Maximum levels of muscle mass and strength are typically achieved in young adulthood (i.e., up to 40 years of age) and are on average higher in males than females (Dodds et al., 2014). A loss of 1-2% per year in leg muscle mass and a decrease of 1.5-5% per year of strength have been reported after the age of 50 years (Keller & Engelhardt, 2013). Making up approximately 40% of one’s total body weight and containing 50-70% of all body proteins, skeletal muscle is considered one of the most dynamic and plastic tissues in the human body (Frontera & Ochala, 2015). Skeletal muscle is mostly comprised of water and protein and, in general, the quantity and quality of muscle mass is dependent on the balance between two processes, protein synthesis and protein degradation. From a biomechanical perspective, the primary function of skeletal muscle is to
generate force and power and produce movement through the conversion of chemical energy into mechanical energy (Frontera & Ochala, 2015).

Skeletal muscle plays a pivotal role in physical movement, maintenance of posture, and essential survival functions such as breathing, and eating (Chromiak & Antonio, 2008; Shiozu et al., 2015). Skeletal muscles found throughout the body are muscles that attach to bones and, through voluntary control, are responsible for body movements and locomotion. Some examples include the biceps, triceps, quadriceps, and hamstrings (McCuller et al., 2022). In addition, the role of skeletal musculature in the process of deglutition is critical. Deglutition, or swallowing, is an intrinsic process that is essential for human functioning and survival. Swallowing is a complex and multifaceted sensorimotor process that is comprised of four phases: (1) the oral preparatory phase, (2) the oral phase, (3) the pharyngeal phase, and (4) the esophageal phase (Dodds et al., 1990). The oral phase is described as voluntary, while the pharyngeal and esophageal phases are considered reflexive patterned motor responses under brainstem control. Thus, the process of deglutition involves the use of both volitional and reflexive behaviours which allow for the safe and efficient ingestion of food or fluids (Matsuo & Palmer, 2009) and support the maintenance of regular physiological and biochemical processes within the human body (Sasegbon & Hamdy, 2017). Consequently, issues experienced at any point in time along the swallowing pathway may lead to difficulties with swallowing, or dysphagia.

Over 30 muscles are required to enable the safe and efficient ingestion of food and liquids. For example, muscles of the tongue such as the hyoglossus, genioglossus, styloglossus, palatoglossus, and mylohyoid are voluntary skeletal muscles and are responsible for pushing the bolus towards the back of the mouth (Panara et al., 2022). Once the oral phase is complete and the bolus is transported from the oral cavity to the oropharynx, the pharyngeal response is initiated.
This phase of deglutition is involuntary, with sensations travelling through cranial nerves to activate a series of motor actions, including the elevation of the soft palate to close the nasopharynx, retraction of the tongue base, elevation and closure of the larynx, and contraction of the pharynx (Manikantan et al., 2009). This physiological act is highly regulated and coordinated involving the action of numerous muscles to facilitate safe and efficient swallowing. For example, the pharyngeal phase is characterized by rapid muscle contraction to propel the bolus through the upper esophageal sphincter and into the esophagus. This stage of swallowing utilizes the most muscles, relying on coordination from multiple nerves. First, the tensor veli palatini muscle is activated, which produces tension in the soft palate and assists another muscle known as the levator veli palatini with the subsequent elevation of the soft palate – an important step in occluding and preventing entry of ingested food particles into the nasopharynx (Malone & Arya, 2022). The tensing of the soft palate is also essential for providing a steady base, allowing for the pharynx to elevate during swallowing. In addition, the superior, middle, and inferior pharyngeal constrictor muscles form the posterior and lateral walls of the pharynx and function to facilitate the propagation of food towards the esophagus by constricting the walls of the pharynx during deglutition.

Given that the function of swallowing musculature is integral for efficient and safe transport of the bolus into the esophagus, damage to the aforementioned muscles and/or their nerve supply can have a negative effect on swallowing (Mittal et al., 2003). For example, radiation-induced neuropathies associated with HNC treatment can result in muscle or nerve dysfunction, limiting the physiological function of swallowing musculature (Lin et al., 2002). Such changes can result in fibrosis – a condition characterized by the loss of vascularity that may result in the thickening and scarring of connective tissue. The excessive collagen deposits associated with
fibrosis can ultimately entrap nerves and alter vascular networks, leading to neurologic deficits such as myopathy which is a general term used to describe diseases that affect skeletal muscles (Gillette et al., 1995).

Research indicates that even small doses of radiation can result in skeletal muscle atrophy, wherein muscle fibres are continually replaced with fibrotic tissue. Consequently, muscles in the irradiated area exhibit reduced activation, causing them to become weakened and atrophied (Delanian & Lefaix, 2004). Damage to structures in the upper aerodigestive tract can result in dysphagia, often due to poor coordination of swallowing musculature (Logemann et al., 2006). The superior pharyngeal constrictor muscle appears to be most at-risk for radiation-induced dysphagia given the strong association between radiation dose to this area and poor swallowing outcomes (Schwartz et al., 2010). Swallowing dysfunction resulting from muscular atrophy and fibrosis tends to present in a delayed manner, with symptoms occurring years after RT. Thus, both early and late-effects of radiation may occur (Cavanagh & Kearney, 2018). Considering the irreversible nature of delayed injuries such as those associated with functional changes in swallowing musculature, HNC patients often suffer from chronic dysphagia (King et al., 2016). Although the local atrophy of swallowing musculature that results from radiation-related disuse is detrimental to eating and swallowing, it is not representative of the systemic or generalized muscle loss associated with sarcopenia.

Beyond its role in supporting movement and locomotion, skeletal muscle acts as a regulator for energy and protein metabolism, produces heat to support core temperature maintenance, and consumes the majority of oxygen used during exercise and physical activity (Frontera & Ochala, 2015). Further, skeletal muscle may act as a reservoir of amino acids to support protein synthesis and energy production throughout the body when depletion occurs in other areas (Wolfe, 2006).
Through the process of proteolysis (i.e., the breakdown of proteins or peptides into amino acids through the action of enzymes), amino acids stored in muscle can be broken down and utilized for energy production (Argiles et al., 2016). Typically, this breakdown occurs when energy demands are high (e.g., with stress-induced hypermetabolism) or when supplies are reduced (e.g., with severe starvation or long-term malnutrition resulting in protein deficiency). As such, skeletal muscle can contribute to the maintenance of blood glucose levels (Meyer et al., 2002).

States of high energy demand and low energy supply that result in the breakdown of proteins within the muscle are commonly associated with disease-related metabolism dysregulation or can even occur due to the loss of appetite associated with general illness (Argiles et al., 2016). Because of its role in supporting the metabolic requirements of other bodily organs and its ability to function as a reserve of proteins for energy production, skeletal muscle is especially important during this state of disease or illness. For example, the muscle breakdown and atrophy that typically transpires with aging can result in reduced muscle mass. Consequently, these changes will result in a diminished reservoir of amino acid and protective molecules that support the body’s ability to successfully combat illness, infection, and wasting (Curtis et al., 2015; Fischer et al., 2015). Thus, the loss of muscle mass, or muscle atrophy, is associated with numerous and significant adverse health effects, especially for older individuals (Cerri et al., 2015; Clark & Manini, 2010; Hirani et al., 2015; Rizzoli et al., 2013).

**Multifactorial Causes of Sarcopenia**

Although sarcopenia is recognized as an age-related condition, its development can be described as multifactorial. Interestingly, researchers have found a positive association between weight at birth and reduced muscle mass and strength in adult life (Dodds et al., 2012), suggesting that individuals may be predisposed to sarcopenia according to early environmental influences.
Moreover, environmental factors are thought to contribute to the development of sarcopenia as older adults usually experience a decline in physical activity and nutritional intake. In part due to the increased burden associated with chronic disease that can lead to pain and fatigue, older individuals report being less active (Marquez et al., 2011) and experience a decline in calorie and protein intake – two main lifestyle factors associated with the development of sarcopenia (Robinson et al., 2012). In combination with age-related changes in physiology, these environmental influences contribute to the multifactorial mechanisms that can result in a decline in SMM and consequently increase the risk of developing sarcopenia.

**Pathophysiology.** With advanced aging, several physiological and morphological changes occur in skeletal muscle tissue. These changes can be described according to three distinct mechanisms: (1) a decrease in skeletal muscle stem cells and the associated reduction in type-2 muscle fibers, (2) a decline in hormones that contribute to muscle mass maintenance, and (3) inflammatory pathway activation. First, an overall decline in the size and number of type-2 (i.e., fast-twitch) skeletal muscle fibers is commonly observed in individuals with sarcopenia. Lexell and colleagues (1988) found a 26% reduction in the cross-sectional area of type-2 muscle fibers between 20 and 80-year-old individuals. This decrease in type-2 muscle fibers, a process associated with a decline in the number of neuromuscular junctions, has a substantial role in age-related muscle decline (Verdijk et al., 2012). Although the exact mechanisms responsible for this gradual loss in fast-twitch muscle fibers is unknown, some speculate that the important age-related changes that occur with satellite cells, or muscle stem cells (i.e., precursors to skeletal muscle cells), have a significant impact on this process. Collins-Hooper and colleagues (2012) found that the migration of satellite cells – an important process facilitating skeletal muscle regeneration – is much slower and thus compromised with advanced age. Because of their role in skeletal muscle
maintenance, repair and regeneration (Snijders et al., 2009), a decrease in the number of satellite cells is likely to lead to diminished skeletal muscle structure and function (Shefer et al., 2006). Accordingly, a reduction in the number of satellite cells in type-2 skeletal muscle fibers is associated with the development of sarcopenia (Verdijk et al., 2007).

The second potential cause is the inevitable decline in anabolic hormones that play a role in the maintenance of muscle mass. Vermeulen and Kaufman (1995) showed that a decrease of 35% in total and 50% in free testosterone occurred between the age of 20 and 80 years. In addition, researchers have found that circulating levels of another potent anabolic hormone released by the pituitary gland, known as human growth hormone, demonstrate a reduction of around 50% during the aging process in both men and women (Rudman, 1985; Welle, 1998). Finally, the activation of inflammatory pathways (e.g., with chronic disease and rheumatological conditions) has also been identified as an important contributing factor for sarcopenia (Jo et al., 2012). Ferrucci et al. (2002) reported an association between the inflammatory cytokine interleukin-6 and a decline in muscle mass and strength in part due to its influence on satellite cells in muscle fibers. It is valuable to understand that, given the role of skeletal muscle as a primary regulator of metabolic and inflammatory pathways, the development of sarcopenia may precipitate a lack of metabolic and inflammatory regulation. Consequently, the concomitant progression of sarcopenia and chronic disease results in a dangerous cycle that promotes a generalized inflammatory state (Dhillon & Hasni, 2017). Ultimately, this may result in the accelerated progression of existing health conditions, including cancer.

**Recent biological and molecular findings contributing to sarcopenia.** In addition to the multifactorial causes noted previously, a number of biological changes can also result in an increased risk for the development of sarcopenia. The mitochondrion is an organelle considered to
be a major source of chemical energy (Lanza & Nair, 2010). In older adults, Joseph et al. (2012) found that mitochondrial biogenesis and functioning are impaired and that this change may contribute to a decline in SMM and function. Another biological process that has been suggested to play a role in the development of sarcopenia is apoptosis. Proteins associated with apoptosis, or programmed cell death, are upregulated in older adults and may contribute to the loss of SMM (Armand et al., 2011). Moreover, current research suggests that skeletal muscle loss is associated with age-related changes in gene expression that occur in those with sarcopenia. In investigating the impact of mRNA turnover and translation on age-related muscle loss, Ma et al. (2012) suggested that transcriptional regulation of mRNA may have a negative impact on the ability of skeletal muscle satellite cells, or skeletal muscle precursors, to contribute to the regeneration and repair of skeletal muscle during aging. The processes described above comprise the multifactorial, physiological, biological, and age-related changes that contribute to the development of sarcopenia in older adults.

The Impact of Sarcopenia

Providing optimal care for individuals with sarcopenia is essential due to the high personal, social, and economic burdens associated with the condition (Mijnarends et al., 2016). Given that muscle mass accounts for up to 60% of one’s total body mass, it is unsurprising that pathological alterations to this important and metabolically active tissue can have a detrimental impact on the health and well-being of older adults (Walston et al., 2012). Research suggests that sarcopenia increases the risk of falls and fractures (Schaap et al., 2018), may lead to mobility disorders (Morley et al., 2011), and can result in an impaired ability to perform activities of daily living (Malmstrom et al., 2016). Moreover, sarcopenia is associated with cognitive impairment (Chang et al., 2016), cardiac and respiratory disease (Bahat & Ilhan, 2016; Bone et al., 2017), and
rheumatoid arthritis (Giles et al., 2008). Researchers have also found sarcopenia to be significantly associated with worse QoL (Beaudart et al., 2017). The collective consequences of this muscle wasting condition often results in the loss of independence and a need for placement in long-term care (Akune et al., 2014; Dos Santos et al., 2017). The financial impact of sarcopenia is also well-documented. Antunes and colleagues (2017) reported a 5-fold increase in hospitalization costs amongst those older adults with sarcopenia compared to those without, with additional studies supporting these findings (Sousa et al., 2016; Steffl et al., 2017).

Within the general oncology literature, there is a growing body of evidence to suggest that sarcopenia may be a poor prognostic indicator for those undergoing cancer treatments. Researchers have found that sarcopenic cancer patients have an increased risk for developing postoperative complications and treatment-related toxicity, have a significantly shorter overall survival (OS) compared to non-sarcopenic patients, and may experience prolonged hospital stays after their treatment (Simonsen et al., 2018; Gruber et al., 2019). Moreover, cancer patients with sarcopenia also experience poor CRT tolerance stemming from an increased prevalence of side-effects and interruptions to treatment (Prado et al., 2011).

In attempting to understand the impact of sarcopenia on treatment tolerance and outcomes in those undergoing HNC treatment, Ganju and colleagues (2019) found that sarcopenia was associated with higher rates of chemotherapy toxicity and prolonged RT interruptions. Moreover, a prospective study revealed that HNC patients with dysphagia had a high prevalence of sarcopenia during their initial oncologic evaluation (Silva et al., 2021). Researchers have also reported an association between sarcopenia and physician-rated dysphagia and xerostomia in HNC patients receiving definitive RT/CRT (van Rijn-Dekker et al., 2020). In HNC, diminished SMM may also contribute to the risk of prolonged feeding tube (FT) dependency and hospital stays, poor
locoregional disease control, and increased rates of postoperative complications (Bril et al., 2019; Grossberg et al., 2016; Karsten et al., 2019). Given that HNC patients with sarcopenia exhibit greater systemic inflammation – a state suggested to be indicative of cancer aggressiveness and poor prognosis (Cho et al., 2018) – the association of sarcopenia with poor outcomes in oncology and HNC is not unexpected.

In addition, the relationship between sarcopenia and survival outcomes are well-documented in the HNC literature. Evidence suggests that sarcopenia is a strong and negative prognostic factor for recurrence-free, disease-free, progression-free survival, and OS (Chargi et al., 2019; Ganju et al., 2019; Hua et al., 2020; van Rijn-Dekker et al., 2020). Grossberg et al. (2016) reported that sarcopenia identified both before and after treatment was associated with worse OS for HNC patients treated with CRT. Stone and colleagues (2019) also found that patients with sarcopenia had significantly inferior 2- and 5-year OS. Moreover, both a systematic review (Hua et al., 2019) and meta-analysis (Wong et al., 2021) concluded that the presence of sarcopenia is associated with a significant decrease in OS. Jung et al. (2019) reported a 3-fold increase in risk of overall recurrence, and even death, in HNC patients with sarcopenia, further emphasizing the importance of sarcopenia as a prognostic factor in HNC. Despite this, the challenges associated with the identification and evaluation of this condition has led researchers to call for a more consistent approach in measurement of sarcopenia (Cruz-Jentoft et al., 2019).

Methods of Measurement

Multiple tests, tools, and strategies are currently available to characterize and evaluate sarcopenia in both clinical practice and research (Mijnarends et al., 2013). While a wide variety of instruments exist, selecting the most appropriate tool can be challenging. Those interested in objectively evaluating sarcopenia must consider the resources at their disposal, the characteristics
of their patients and/or participants, and the purpose of said testing (Cruz-Jentoft et al., 2019). The first and perhaps most important factor in determining whether a person has sarcopenia is symptomology. A patient may report experiencing signs or symptoms of sarcopenia such as fatigue, falling, difficulty standing from a seated position, weight loss, and/or muscle wasting, prompting the need for further testing to confirm the presence of the muscle wasting condition (Morley et al., 2011). To elicit self-reported information from patients in order to identify these potential symptoms, the EWGSOP recommends a 5-item questionnaire known as the strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) (Malmstrom & Morley, 2013). Proven to be a valid, consistent, and effective tool, the SARC-F questionnaire is recommended as an inexpensive and convenient method to identify individuals at risk for sarcopenia (Cruz-Jentoft et al., 2019). However, because responses to the SARC-F are based on one’s perception of their experience with personally relevant adverse outcomes, some may value a more objective, formal instrument for use in research and clinical settings where sarcopenia is prevalent.

Muscle quantity is a parameter used to confirm the presence of sarcopenia (Cruz-Jentoft et al., 2019). Commonly reported as total body SMM, estimations for muscle quantity can be made through a variety of techniques that adjust for one’s BMI or height to achieve a more accurate and relevant measurement (Cooper et al., 2013). Currently, ‘radiologically-defined sarcopenia’ is a term used to describe a more objective technique to identify sarcopenia through use of computed tomography (CT) and magnetic resonance imaging (MRI) (MacDonald et al., 2011; Rubbieri et al., 2014). The advantages of these two methods are well-known and they are considered to serve as the “gold standard” for non-invasive evaluation of muscle quantity (i.e., SMM) (Beaudart et al., 2016). However, these methods require access to radiologic imaging.
Martin et al. (2013) were the first group of researchers to use CT imaging to evaluate sarcopenia in obese patients diagnosed with gastrointestinal and lung cancer. Sarcopenia was found to be predictive of poor outcomes independent of BMI, leading researchers to suggest that radiologically assessed sarcopenia has utility as a strong negative prognostic factor (Martin et al., 2013). Moreover, the findings from Lee and colleagues (2015) indicated that sarcopenia may be a more accurate marker for malnutrition compared to more conventional assessments such as BMI, serum albumin, and serum prealbumin levels in disease-free individuals. Nevertheless, because these tools are associated with high costs, lack portability, and require highly trained individuals to use the equipment (Beaudart et al., 2016), their use in research and clinical care may be limited.

For individuals diagnosed with cancer, CT scans are commonly used to image tumors and monitor their response to treatment. Such imaging may also provide a convenient and precise medium for the measurement of body composition (Mourtzakis et al., 2008). Due to the accuracy and strong correlation of SMM measurements at the third lumbar vertebra (L3) and whole-body muscle mass, SMM has traditionally been measured using abdominal CT imaging (Mourtzakis et al., 2008). However, a high percentage of individuals with HNC lack abdominal CT scans (Grossberg et al., 2016), limiting the applicability of L3 measurements in the HNC population. Fortunately, recently developed methods permit the assessment of SMM in HNC using neck imaging at the level of the third cervical vertebra (C3). Delineation of the paravertebral muscles (PVM), right sternocleidomastoid (SCM) muscle, and left SCM muscle in the axial/transverse plane at C3 allows for the calculation of cross-sectional area (CSA). The CSA of skeletal muscle is further adjusted for the height of each individual resulting in a measure known as skeletal muscle index (SMI) (Swartz et al., 2016). Since head and neck CT imaging is routinely available for
individuals with HNC, the assessment of SMM and sarcopenia can occur without the need for additional imaging.

While SMI does provide an objective, numeric value for SMM, the quantitative definition of sarcopenia is inconsistent and there is no consensus in the literature for specific cut-off values to identify sarcopenic patients. Wendrich et al. (2017) utilized a non-gender specific cut-off value of $<43.2 \text{ cm}^2/\text{m}^2$, a value which is determined by the likelihood of developing chemotherapy dose-limiting toxicity in those undergoing HNC treatment. An important consideration and concern for this approach is that it may identify a substantial number of individuals as sarcopenic. For example, Zwart and colleagues (2019) found that upon using $<43.2 \text{ cm}^2/\text{m}^2$ as a cut-off value, 97% of female patients were sarcopenic. This may be considered a limitation of using this non-gender specific threshold. Van Rijn-Dekker et al. (2020) used a gender-specific SMI threshold of $<42.4 \text{ cm}^2/\text{m}^2$ in men and $<30.6 \text{ cm}^2/\text{m}^2$ in women, which corresponded with the lowest gender-specific quartile. Prado et al. (2008) used a statistical analysis known as optimum stratification to determine their gender specific SMI cut-off values for sarcopenia. An SMI $<52.4 \text{ cm}^2/\text{m}^2$ for men and $<38.5 \text{ cm}^2/\text{m}^2$ for women was used to classify patients as sarcopenic. Evidently, these discrepancies may contribute to difficulties in the assessment of sarcopenia.

Management of Sarcopenia

Inadequate protein intake and physical activity are suggested to be two of the most important factors contributing to the decline in muscle mass that occurs with aging (Daly et al., 2014; Montero-Fernandez & Serra-Rexach, 2013). Thus, the treatment of sarcopenia should focus on strategies that improve muscle mass and physical function in order to attenuate this loss (Kim et al., 2013). Providing treatment for those at risk can help prevent or delay the onset of muscle atrophy, or even facilitate the rebuilding of muscle when muscle loss has already taken place.
Nutritional intervention. In those with cancer, the ability to stimulate protein synthesis may be reduced. Thus, there is some evidence to suggest that sarcopenia can be managed through nutritional intervention. The primary goal of any nutritional intervention in the management of sarcopenia should be to ensure adequate energy intake so that muscle proteins and their amino acid constituents are spared as a source of energy. Furthermore, nutritional strategies should ensure high levels of protein intake as this is critical for the treatment of muscle atrophy in addition to preventing or delaying its onset (Argiles et al., 2016). Because the amount of protein required to prevent muscle loss can vary greatly from person to person, the utilization of high-protein oral nutritional supplements (i.e., supplements with greater than 20% of total calories coming from protein) may be beneficial for older individuals at risk for malnutrition (Milne et al., 2009). In addition, the combination of nutritional counselling and enteral feeding via nasogastric or gastrostomy FTs has proven to be beneficial at reducing the prevalence and impact of sarcopenia in those undergoing treatment for HNC. Proactive and early nutritional intervention is associated with reduced weight loss during treatment, increased muscle mass and may lead to an improvement in treatment tolerance (Paccagnella et al., 2010).

Although their role in protein nutritional status is well-understood, essential amino acids are not synthesized within the human body and, therefore, must be introduced through diet. Branched-chain amino acids (BCAAs) are a subcategory of essential amino acids and are particularly relevant to this discussion because of their role in promoting protein synthesis in muscle (Ko et al., 2020). The value of BCAAs is evident, as one of their functions, in part, is to signal for a reduction in protein breakdown and an increase in protein synthesis in response to a
meal (i.e., the post-prandial response). However, in aged muscle and in muscle exposed to hypercatabolic conditions like cancer, the post-prandial response is not as effective and may result in the unnecessary breakdown of protein. Supplementation with high doses of leucine, an essential and BCAA, may have value in addressing some of these challenges. Clinical trials investigating the impact of leucine supplements suggest that it may be able to increase the secretion of anabolic hormones (e.g., insulin), in turn stimulating protein synthesis and reducing protein breakdown (Ham et al., 2014). Moreover, supplementation with amino acids such as glutamine, L-arginine, and b-hydroxy b-methyl butyrate has been shown to lead to an increase in lean body weight for individuals with cancer (May et al., 2002). On the contrary, nutritional supplements such as omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid, in addition to Vitamin D and Vitamin C have shown varying results with respect to limiting the loss of lean body mass (Dev et al., 2017). Due to the inherent difficulties with conducting clinical nutrition research including differences in baseline nutritional status of study participants, influence of confounding variables, and the ethics surrounding randomized controlled trials (Weaver & Miller, 2017), researchers have called for more data to be generated from randomized, double-blinded controlled trials before these practices are recommended for use in the clinical setting.

**Exercise.** While nutrition does play an important role in offsetting the potentially harmful metabolic changes associated with stress and inflammation, providing adequate levels of energy and protein alone cannot eliminate or reverse the age-related deterioration of muscle mass. As such, strategies used to manage sarcopenia typically include some form of exercise. When muscle fibers contract (i.e., during exercise) protein synthesis takes place (Miller et al., 2005), with physical activity having the potential to induce various anabolic signaling pathways (Pasini et al., 2012) and in turn reduce the degradation of muscle protein (Bowen et al., 2015). Conversely, a
lack of physical activity may lead to increased resistance of muscle to anabolic processes, limiting the production of proteins from amino acids (Dideriksen et al., 2013).

Two of the most effective and common interventions used in the treatment of sarcopenia are progressive resistance training and aerobic exercise (Beaudart et al., 2017; Montero-Fernandez & Serra-Rexach, 2013). Progressive resistance training is utilized to strengthen large muscle groups and increase muscle mass using free weights, machines, or elastic bands. The resistance is progressively increased according to the strength gained in muscle groups, allowing for a slow and progressive gain in muscle mass (Beaudart et al., 2017). Even in some of the oldest and most frail individuals, researchers have demonstrated the potential for significant functional improvement using a combination of nutrition and resistance exercise interventions (Fiatarone et al., 1994). In addition, aerobic exercise improves oxidative capacity and is associated with greater muscle strength throughout one’s life (Crane et al., 2013).

**Symptom management.** Interventions aimed at controlling and managing symptoms of cancer treatment such as nausea, vomiting, pain, and decreased appetite also may have value in reducing the burden and impact of sarcopenia. Supplementing individuals at risk for sarcopenia with exogenous hormones including corticosteroids, progesterone, and testosterone has demonstrated a positive, but somewhat small, effect on weight gain and appetite (Garcia et al., 2013; Willox et al., 1984). Non-steroidal anti-inflammatory drugs have also been found to suppress systemic inflammation and result in less weight loss and cachexia (Reid et al., 2013). Additionally, and specific to those with HNC, the use of gabapentin for pain management during CRT treatment has been found to facilitate patients in maintaining swallow function, result in favorable swallowing outcomes, and have a positive impact on oral intake (Starmer et al., 2014). Because pharmacotherapy research for sarcopenia is still evolving, the decision to use such interventions
should be considered in the context of their potential risks and side-effect profiles. Nevertheless, to proactively prescribe any of the aforementioned interventions, there needs to be a concentrated effort directed towards establishing a consistent description of sarcopenia and determining the most reliable and effective method of measurement to accurately detect the presence of this condition.

**Statement of Problem**

At the time of cancer diagnosis, sarcopenia has been recognized as an important prognostic factor for multiple adverse outcomes including treatment-related toxicity, postoperative complications, prolonged FT dependency, mortality, and survival (Karsten et al., 2019; Kazemi-Bajestani et al., 2016; Shachar et al., 2016; Stone et al., 2019; Van Rijn-Dekker et al., 2020). Thus, sarcopenia represents a clinically important variable that could be used to identify patients at risk for complications. Despite this evidence, the definition of sarcopenia in the literature is inconsistent and currently there is no consensus on specific cut-off values to accurately diagnose and document sarcopenia (Cruz-Jentoft et al., 2019).

Further, due to the challenges associated with determining which methods and/or measurement instruments to use, what variables to measure, which cut-off values are most appropriate to guide diagnosis and treatment, and the most effective methods to evaluate the impact of therapeutic interventions (Han et al., 2018), sarcopenia has been somewhat overlooked and undertreated in clinical practice (Keller, 2018). Failure to identify and provide early intervention for sarcopenic individuals may place them at risk for inferior treatment outcomes and cognitive impairment, impair their ability to perform activities of daily living, and contribute to financial burden, loss of independence, poor QoL, and death (Antunes et al., 2016; Beaudart et al., 2017;
De Buyser et al., 2016; Chang et al., 2016; Dos Santos et al., 2017; Malmstrom et al., 2015). It is, therefore, important to understand the factors related to sarcopenia and their impact on SMM.

**Objectives**

Based on the collective information provided in the preceding review of literature, it is apparent that the inconsistencies related to the definition, measurement, and evaluation of sarcopenia has contributed to a limited understanding of this muscle-wasting condition in those undergoing treatment for HNC. Moreover, little is known regarding the relationship between sarcopenia and FT-related outcomes in the context of HNC. Consequently, the prior review provides information that warrants investigation into the assessment of sarcopenia in HNC and the prognostic utility of SMM measurements with respect to FT placement and duration of use. Thus, the two research investigations presented in subsequent chapters represent a novel and systematic program of research that explores the issue of sarcopenia in HNC.

The first study, a scoping review, is planned in an effort to clarify working definitions and identify the methods used to objectively evaluate sarcopenia within the HNC literature. Second, a retrospective cohort study will be performed to determine the extent to which sarcopenia is associated with nutrition-related outcomes in HNC patients treated with definitive RT/CRT. This study will also seek to evaluate the direct relationship of pre-treatment patient- and treatment-related variables with SMM loss. The collective findings of these two projects are anticipated to provide an improved understanding of the description and measurement of sarcopenia in HNC, its relationship with functional outcomes related to eating and swallowing, and factors contributing to its exacerbation.
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CHAPTER 2

Scoping Review on Sarcopenia in HNC1

Introduction

Individuals undergoing treatment for HNC are likely to experience significant weight loss (Jackson et al., 2014) and substantial declines in physical activity, SMM, muscle strength, and overall physical performance (Lonbro et al., 2013; Silver et al., 2007). One condition characterized by these complications is termed sarcopenia. Sarcopenia is typically defined as an age-related muscle wasting condition that is associated with an increased likelihood of adverse outcomes such as falls, fractures, physical disability, and mortality (Cruz-Jentoft et al., 2019). Among older individuals between 60-70 years of age, the prevalence of sarcopenia is estimated to range between 5-13%, with a prevalence of up to 50% for individuals over the age of 80 years (von Haehling et al., 2010). In HNC, the prevalence of sarcopenia has been reported to be between 35.5-54.5% (Zwart et al., 2019). Considering that approximately 35%-60% of all HNC patients may present with malnutrition and weight loss of greater than 10% (Alshadwi et al., 2013), these numbers are not surprising. Moreover, organ sparing treatments such as RT or CRT have the potential to exacerbate issues related to nutrition and weight management. For example, treatment-related toxicities including xerostomia, dysphagia, and oral mucositis, which are associated with reduced oral intake (Givens et al., 2009; Marta et al., 2014), place the patient at an increased risk for malnutrition, weight loss, and consequently, sarcopenia.

1 This work has been published in peer-reviewed literature: Jovanovic, N., Chinnery, T., Mattonen, S. A., Palma, D. A., Doyle, P. C., & Theurer, J. A. (2022). Sarcopenia in head and neck cancer: A scoping review. Plos one, 17(11), e0278135. https://doi.org/10.1371/journal.pone.0278135
In those undergoing HNC treatment, sarcopenia is associated with higher rates of chemotherapy toxicity and prolonged RT interruptions (Ganju et al., 2019). Researchers have also reported an association between pre-treatment sarcopenia and a modified diet, objective speech problems, xerostomia, swallowing-related QoL, and physician-rated dysphagia in those receiving definitive CRT (Karsten et al., 2022; van Rijn-Dekker et al., 2020). Diminished SMM measured by CT imaging may also be associated with risk of prolonged FT dependency and hospitalization, poor locoregional disease control, and increased rates of postoperative complications in HNC (Bril et al., 2019; Grossberg et al., 2016; Karsten et al., 2019). Given that HNC patients with sarcopenia exhibit greater degrees of systemic inflammation – a state suggested to be indicative of cancer aggressiveness and poor prognosis (Cho et al., 2018) – its association with poor outcomes in oncology and HNC is somewhat expected. In addition, sarcopenia appears to be a significant negative predictor for relapse-free survival, disease-free survival, progression-free survival, and OS in patients with HNC (Chargi et al., 2019; Grossberg et al., 2016; Hua et al., 2020; Jung et al., 2019; Stone et al., 2019; Wong et al., 2021).

The variability in prevalence data for sarcopenia obfuscates the actual prognostic significance of this condition. This variability may be attributed to the fact that sarcopenia is inconsistently defined across studies and consensus on the use of cut-off values to guide diagnosis and treatment is lacking (Morley et al., 2008). Due to the challenges related to methods of measurement, including selection of variables to be measured and the most effective approach to evaluate the impact of therapeutic interventions (Han et al., 2018), sarcopenia has been somewhat overlooked and undertreated in clinical practice (Keller, 2018). As emphasized by the EWGSOP, “practitioners have ever-increasing possibilities for preventing, delaying, treating, and sometimes even reversing sarcopenia by way of early and effective interventions” (Cruz-
Jentoft et al., 2019, p.17). Failure to identify and provide early intervention for individuals with sarcopenia may place them at risk for inferior treatment outcomes and cognitive impairment, impair their ability to perform activities of daily living, and contribute to financial burden, loss of independence, poor quality of QoL, and death (Antunes et al., 2017; Beaudart et al., 2017; De Buyser et al., 2016; Chang et al., 2016; Dos Santos et al., 2017; Malmstrom et al., 2016).

The objective of this scoping review was to examine the extent, range and nature of the current research in the study of sarcopenia in HNC. This includes how sarcopenia was defined, the various methods of measurement for SMM, and how the classification of sarcopenia was decided. Knowledge gaps in the existing literature were also identified. A clearer understanding of how sarcopenia is currently assessed in HNC research is an important first step toward achieving consensus on its assessment in practice and research. Such consensus may serve to identify patients at risk for adverse outcomes in order to provide early, targeted interventions. Such efforts may allow for the indexing of sarcopenia as an accessible biomarker to identify patients who may benefit from proactive intervention, guiding clinical practice and facilitating improved outcomes. This information may also guide future research in this field.
Methods

Design and Research Questions

The methodology for this scoping review followed guidelines originally developed by Arksey and O’Malley (2005) including the following five phases: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting the results. The review was also guided by the Joanna Briggs Institute Manual for Evidence Synthesis (Peters et al., 2020). In accordance with these frameworks, a quality assessment was not performed. The protocol for this scoping review can be accessed on The Open Science Framework (http://dx.doi.org/10.17605/OSF.IO/FD7WJ). The specific research questions used to guide the review were: (1) How is sarcopenia assessed in HNC patients? (2) What methods have been used to assess sarcopenia in HNC? (3) How is the term sarcopenia defined and what cut-off values are used to classify sarcopenia in those undergoing HNC treatment? (4) What are the knowledge gaps and/or directions for future research within publications based on the primary review question?

Information Sources and Search Strategy

To identify potentially relevant studies, searches were carried out using MEDLINE, Embase, Scopus, Cochrane Library, and CINAHL databases from the earliest available time until July 22, 2021. The search strategy was developed for MEDLINE and then adapted for other databases in consultation with an experienced Health Sciences Librarian. Team discussion regarding uncertainties or challenges related to methodology, inclusion and exclusion criteria, participant selection, and source characteristics further refined the search strategy to ensure an appropriate and thorough literature search. Backward citation searching (i.e., inspection of
references cited within the sources of evidence recovered from the search) and forward citation searching (i.e., identification of articles that cite a source study using a citation index) were performed to identify additional articles (Briscoe et al., 2020) referring to sarcopenia in HNC. Reference lists of previous systematic reviews, meta-analyses, and scoping reviews were also manually searched to identify relevant studies. The MEDLINE search strategy is presented in Appendix B. The final search results were exported into Covidence (Veritas Health Innovation, Melbourne, Australia) – a web-based software supported through our institution’s library used to assist researchers in screening references and extracting data.

**Study Selection**

Peer-reviewed journal papers were considered for further review if they included adult HNC patients over the age of 18 years undergoing RT/CRT and/or surgery and listed sarcopenia as an outcome. To capture a broad range of published evidence on the assessment of sarcopenia in HNC patients, full-text, empirical literature written in English that was performed with a quantitative research design was included. Sole consideration of studies with a quantitative methodology allowed for the inclusion of evidence that focused on radiologically defined sarcopenia as assessed with CT imaging.

As a first step, two reviewers independently screened each article title and abstract for eligibility based on the pre-specified inclusion and exclusion criteria using Covidence. During this initial review, articles for which inclusion eligibility was uncertain were maintained for further review (i.e., maintained in a pool of potentially eligible articles for full read). Next, backward and forward citation searching was performed to identify other relevant sources. Reviewers met at the beginning, middle, and final stage of the review process to address potential ambiguity and to ensure that selected abstracts were appropriate for full review. Finally,
the resulting full-text version of all selected studies was retrieved and similarly screened. Disagreement between the reviewers was resolved through discussion or, if necessary, by a third reviewer. This review period took place over the course of four weeks.

**Data Extraction**

A data extraction form was developed by the research team to delineate which variables were to be extracted from included full-text articles (Appendix C). The following data were extracted and classified: general information (e.g., author[s], year of publication, and country of origin), article details and characteristics (e.g., aims/purpose, participant details, treatment type, methodology, and summary findings), and details/results from the source of evidence in relation to the concept of the scoping review (e.g., sarcopenia definition, sarcopenia cut-off value(s), measurement technique, timing of assessment, and knowledge gaps). Both reviewers independently charted the data. The results were discussed collaboratively, and the data-charting form was continuously updated in an iterative process. In accordance with the JBI scoping review protocol, the two researchers independently extracted data from the first five articles and then met to determine whether the approach to data extraction was consistent with the research question and purpose of the scoping review and that all relevant information was extracted (Peters et al., 2020). Any changes to the form resulting from the pilot process were recorded.
Results

The current review was performed to examine the definition, measurement, and classification of sarcopenia in HNC. A total of 1552 peer-reviewed articles were retrieved from all databases after duplicates were removed. Upon initial screening based on titles and abstracts, 144 studies met the inclusion criteria. The full-text version of these articles were evaluated for eligibility and 68 were excluded for the following reasons: no full-text article available (n=41), the article included patients with other cancer sites (n=19), a quantitative design was not utilized (n=3), the article was not written in English (n=2), the outcomes were unrelated to sarcopenia (n=2), and patients were treated with immune checkpoint inhibitors instead of RT/CRT therapy and/or surgery (n=1). Thus, 76 studies were included in this review. The study selection process is detailed using a PRISMA flow chart in Figure 1.
Figure 1.

PRISMA flow chart for the scoping review process.
Study Details and Characteristics

The 76 articles included in this scoping review represent international research published from 2016 to 2021. A total of 14 countries were represented including Netherlands (18), United States of America (14), Japan (11), China (7), Taiwan (7), Republic of Korea (5), Canada (3), Turkey (3), France (2), Italy (2), Australia (1), Brazil (1), Finland (1), and India (1). The sample size for included studies ranged from 19 to 1767 participants with the average age ranging from 45 years to 81.73 years. The majority of participants represented were male (Figure 2) and the most common tumor subsite was the oropharynx followed by the oral cavity (Figure 3). Four articles (5%) used the term “aerodigestive” to specify subsite, which included a combination of the oral cavity, oropharynx, hypopharynx, and/or larynx. Most tumors were primary (n=67; 88%) and stage IV (n=39; 51%). CRT and surgery were the most common treatment modalities across the studies included in this scoping review (Figure 4).
Figure 2.

Participant details (sex).
Figure 3.

Participant details (tumor subsites).
Figure 4.

Participant details (treatment type).
The majority of included articles utilized a retrospective study design (n=56; 74%). Eighteen studies were prospective in nature (24%), including one randomized controlled trial. Sixty-two studies (82%) were aimed at determining the prognostic impact of sarcopenia as the primary objective, eight (11%) investigated the association between specific outcomes/interventions and sarcopenia, five (7%) were designed to compare body composition measurements before and after treatment, and four (5%) were designed to determine the prevalence of sarcopenia. The remaining studies explored different measurement techniques for assessing sarcopenia in HNC patients.

Among the included studies, survival was the most prevalent primary outcome measure and was investigated as the dependent variable in association with sarcopenia in 68 publications. Complications and treatment-related toxicities were the second most common primary outcomes (n=29), followed by body composition (n=13), frailty (n=4), interruptions to treatment (n=3), and nutrition-related measurements (n=3). Sarcopenia was found to be a significant predictor of outcomes in 62 studies (82%). Across studies, the prevalence of sarcopenia ranged from 3.8% to 78.7%; 19 articles (25%) did not provide prevalence estimates. In addition, prevalence was not determined in 14 studies (18%) that interpreted SMM as a continuous variable. Characteristics and details of articles included are summarized in Appendix D.

Definition and Operational Outcomes

In 28 studies (37%), sarcopenia was defined as low SMM. Sarcopenia also was defined as low SMM and low function in four separate articles, and as low SMM, low strength/function and affected physical performance in 10 articles. The definition included a specific reference to “progressive and generalized” loss in 10 studies, and “age-related” in four articles. Muscle quantity was the primary variable used to assess sarcopenia and was measured in every study.
included in this scoping review. While the majority of articles (n=67; 88%) normalized measurements for patient height and used SMI as the primary outcome, 10 studies (13%) used the cross-sectional area (CSA) of musculature alone to quantify SMM. The most prevalent outcome used as a marker of SMM quantity was L3 SMI, which was used in 53 studies (70%). C3 SMI was the second most common operational outcome (n=4; 5%). Appendicular SMI and paravertebral muscle (PVM) CSA were used as the primary outcome in three studies (4%), and L3 CSA was measured in two articles (3%) included in this review (Figure 5). Twenty-one of 29 articles (72.4%) that used CT imaging of the neck to determine SMM were found to have applied the algorithm developed by Swartz and colleagues (2016) to convert measurements at C3 to L3 SMI. In seven studies that measured muscle strength, a handheld dynamometer was consistently used to measure handgrip strength. Physical performance was measured using a stopwatch to measure the Timed Up and Go (TUG) test (n=2), and gait speed (n=3) in five articles. Only one study used the self-reported SARC-F questionnaire to assess sarcopenia.
Figure 5.

Prevalence of outcomes used to represent sarcopenia.

*L3 SMI* skeletal muscle index at the third lumbar vertebra, *C3 SMI* skeletal muscle index at the third cervical vertebra, *ASMI* appendicular skeletal muscle index, *PVM CSA* paravertebral muscle cross-sectional area.
Measurement Technique

Nearly two-thirds of studies (64%) utilized CT imaging to measure SMM (n=49), with positron emission tomography (PET)-CT identified as the primary instrument in 25 studies (33%). Other less common measurement instruments included MRI, dual-energy x-ray absorptiometry (DEXA), bio-electrical impedance analysis (BIA), and b-mode ultrasonography. The most common location of SMM measurement was at L3 (n=37; 49%). Of the studies that conducted SMM measures at L3, 17 delineated abdominal wall musculature (i.e., transversus abdominus, external and internal obliques, rectus abdominus, psoas, erector spinae, and the quadratus lumborum), eight described delineating all muscles at L3 (i.e., the entire L3 vertebral arch and transverse process), and one study quantified the right and left psoas muscles to determine SMM quantity. C3 was the second most common location for SMM measurement (n=29; 38%). Twenty-four of the articles using the C3 location delineated both the PVM and sternocleidomastoid (SCM) muscles to obtain a measure for SMM quantity; the PVM and SCM were delineated separately in three articles. Full body (n=5; 7%) and appendicular (n=3;4%) SMM were also used to assess sarcopenia.

To delineate muscles and provide an estimate for SMM quantity, SliceOmatic (TomoVision, Montreal, Canada) (n=20; 26%) and ImageJ (National Institutes of Health and the Laboratory for Optical and Computational Instrumentation, University of Wisconsin, Wisconsin, USA) (n=7; 9%) software were commonly used. Other computer software used for this purpose included Volumetool (University Medical Center Utrecht, The Netherlands) (n=3; 4%), Pinnacle (Philips Radiation Oncology Systems, Andover, Massachusetts, USA) (n=3; 4%), Aquarius Workstation (TeraRecon, California, USA) (n=3; 4%), InBody (Biospace, Seoul, Korea) (n=3; 4%), and Monaco TPS (Elekta, United Kingdom) (n=3; 4%). Measurements were most often
obtained manually by a radiation oncologist (n=15; 20%). Twenty studies (26%) noted that either a researcher, observer, or examiner were involved in the measurement of SMM. One study utilized a deep learning segmentation algorithm to delineate muscles automatically. In 38 articles (50%), detailed information regarding the assessor was not provided. Assessors were blinded to patient outcomes in nine studies (12%) and only seven studies (9%) included reliability analysis with respect to the assessment of sarcopenia.

**Cut-Off Values**

The present scoping review revealed that 33 different cut-off (i.e., threshold) values have been used to diagnose sarcopenia in HNC patients. Thirty-five studies (46%) applied gender-specific cut-offs, with four articles (5%) using different threshold values based on the individual’s BMI (i.e., different threshold applied to those who are underweight vs. overweight). Fourteen articles (18%) measured and analysed SMM as a continuous variable and, therefore, did not apply cut-off values in their assessments. Recognizing the variation in sarcopenia assessment, most authors provided an explanation for their selection of specific threshold values. Thirty-six studies (47%) applied a cut-off based on previously published values, with 11 and 10 of these articles citing work by Prado et al. (2008) and Wendrich et al. (2017), respectively. Thirteen studies (17%) used receiver operating characteristic (ROC) curve analysis to determine a cut-off value that was specific to their sample and outcomes of interest. Other threshold values were based on the lowest log-likelihood values (n=3), the lowest gender-specific quartile (n=2), the EWGSOP definition (n=1), and optimal stratification techniques (n=1).
Timing of Assessment

Within the body of literature included, sarcopenia was most often investigated as a predictor of outcomes. This is reflected in the large proportion of studies that measured SMM prior to treatment (n= 75, 99%). Despite the frequent assessment of sarcopenia pre-treatment, the time elapsed between assessment and start of treatment greatly varied. Assessment occurred from time of diagnosis, during tumor staging, and the moment of admission, all the way up to the outset/beginning of treatment. Thirty-two of these studies failed to provide detailed information regarding timing of assessment, stating only that sarcopenia was assessed “prior to treatment”. Sarcopenia was assessed throughout the course of treatment in four studies (5%). Post-treatment sarcopenia assessment was reported in 21 studies (28%), ranging from immediately at the end of treatment to within one year after treatment. Four of these studies lacked temporal specificity, describing sarcopenia assessment as only occurring “after treatment”.
Discussion

Study Details and Characteristics

The current scoping review reports findings from 76 studies identified through a systematic literature search and published over a 6-year period (2016-2021) on the study of sarcopenia in HNC. Despite the growing body of literature in this field of research, discrepancies related to the definition, measurement, and assessment of this muscle-wasting condition present challenges in the interpretation of results and their application to patient care. Such discrepancies are reflected in the large range of reported prevalence of sarcopenia among included studies. The significant variability in prevalence may be attributed to inconsistency in applied cut-off values, which muscles are measured and at which position, and the specific outcome(s) used in the operational definition of sarcopenia. This may be considered as a substantial limitation within the literature and may contribute to difficulties in studying and in turn rectifying the issue of SMM loss in the HNC population.

Despite the inconsistencies related to its definition and assessment, sarcopenia is consistently reported to be a significant predictor of adverse outcomes in HNC. Sixty-two studies (82%) found sarcopenia to be a significant prognostic variable (Appendix D), providing a degree of confidence that the SMM quantity on its own may have clinical value. Consistent with these findings, two recent systematic reviews and meta-analyses demonstrated that based on SMM alone, sarcopenia had a significant and negative impact on survival outcomes in HNC (Hua et al., 2019; Wong et al., 2021). However, due to the variability in the definition and assessment of sarcopenia, the conclusions made within these sources of evidence are difficult to interpret. Further, despite the abundance of evidence demonstrating the prognostic implications of sarcopenia and low SMM, the scarcity of research on its impact on functional, psychosocial,
and QoL outcomes can be considered a significant gap in this area of research. To determine the full extent to which sarcopenia may impact individuals with HNC, a more comprehensive analysis is needed with regard to its impact on multiple outcomes.

Linguistic and Operational Definition of Sarcopenia

Our review highlighted substantial heterogeneity with respect to the linguistic and operational definitions of sarcopenia. In its most recent definition, the EWGSOP noted that low muscle strength – identified as the most reliable measure of muscle function – should be used as the primary variable for sarcopenia assessment (Cruz-Jentoft et al., 2019). Sarcopenia is probable when low muscle strength is detected, confirmed by the presence of low SMM, and considered severe when low physical performance is detected as well (Cruz-Jentoft et al., 2019). Providing a well-rounded and accurate description of sarcopenia, therefore, requires that all three parameters be included in the assessment of this muscle-wasting condition. However, in the majority of articles included in this scoping review, the primary parameter used to define and assess sarcopenia was low SMM quantity. Muscle strength has seldom been addressed, with severity (i.e., through the detection of low physical performance) rarely considered as well. This may be explained by the abundance of retrospective studies on sarcopenia in HNC. Because CT imaging of the head and neck is routinely performed in the context of HNC treatment, SMM measurements will often be available even with retrospective analyses. On the other hand, muscle function or muscle strength is often not assessed routinely, limiting its application in retrospective work and offering an explanation for the heterogeneity in the operational definition of sarcopenia in the present review. The fact that SMM measurements alone were primarily used to assess sarcopenia may overestimate its true prevalence and, moreover, the impact of this condition. Thus, assessment based on all three components of sarcopenia (i.e., muscle strength,
muscle mass, and physical performance) is warranted in order to improve consistency and accuracy within sarcopenia research and to facilitate its use as a prognostic factor in clinical practice.

An important consideration with respect to these findings is the potential advantage of using a multifactorial definition. Because the comprehensive definition of sarcopenia is narrow, assessing all three parameters outlined in the EWGSOP definition may help to identify an even more homogeneous, at-risk group of patients that would especially benefit from early intervention. For example, although Ganju and colleagues (2019) found that sarcopenia was not a significant prognostic factor in p16-positive HNC patients, they only used reduced SMM as the criteria for assessing sarcopenia. In examining the association between sarcopenia and frailty, Meerkerk et al. (2021) used reduced handgrip strength in addition to the loss of SMM to assess sarcopenia. The prevalence of sarcopenia was approximately 14%, even though 61% of patients were reported to have low SMM. The prevalence of sarcopenia in a study that included all three measures was found to be even lower at 3.8% (Kagifuku et al., 2020). It is apparent that a well-rounded assessment of sarcopenia using all three parameters (i.e., muscle quantity, muscle strength, and physical performance) would provide a more accurate risk profile and allow for a greater understanding of the true impact of this condition.

On the other hand, one unintended consequence associated with the application of this comprehensive definition may be that patients who are at risk but do not meet the full criteria for sarcopenia diagnosis (i.e., they only experience one of the three parameters) may be missed. Moreover, using more metrics in the assessment of sarcopenia may increase the difficulty of obtaining measurements; measuring SMM using CT imaging alone is simple and does not subject the patient to additional testing and the associated burden. Considering that sarcopenia
based solely on the loss of SMM is present in 35.5-54.5% of patients with HNC and is related to adverse health outcomes (Grossberg et al., 2016; Nishikawa et al., 2018), SMM alone appears to hold clinical and prognostic value. In future studies, researchers should aim to use all three measures, both in combination and independently, to investigate potential differences in prevalence and to determine which parameters lead to more significant changes in patient outcomes.

The need for a more consistent approach in the assessment of sarcopenia is also evident given the inconsistencies between linguistic and operational definitions. For example, in some articles, a full and comprehensive definition of sarcopenia outlining all three parameters described by the EWGSOP is presented in the introduction. However, only SMM quantity is used to determine the prevalence and impact of sarcopenia. Although muscle quantity was measured in every article, muscle strength and physical performance were only measured in seven and five studies, respectively. Given that a comprehensive linguistic definition incorporating all three parameters was provided in 13 articles, it is evident that even when sarcopenia is accurately defined, comprehensive assessment does not consistently occur. Thus, it appears as though the primary driver for the assessment of sarcopenia in HNC lies in the operational definition, rather than the linguistic.

Method of Measurement

Given the heterogeneity in methods used to measure and characterize sarcopenia in HNC, selecting the most appropriate approach may be challenging. The findings of this scoping review suggest that the “ideal” choice may be contextual and dependent on several elements, namely resources, patient and treatment characteristics, and the accuracy of selected outcomes. The first and perhaps most important factor in determining whether a person has sarcopenia is
symptomology. A patient may report experiencing signs or symptoms of sarcopenia such as fatigue, falling, difficulty standing from a seated position, weight loss, and/or muscle wasting, prompting the need for further testing to confirm its presence (Morley et al., 2011). To elicit self-reported information from patients in order to identify these potential symptoms, the EWGSOP recommends a 5-item questionnaire known as the SARC-F. Proven to be a valid, consistent, and effective tool, the SARC-F questionnaire is recommended as an inexpensive and convenient method to identify individuals at risk for sarcopenia (Cruz-Jentoft et al., 2019). Although the SARC-F is a valuable tool for identifying risk based on one’s perception of their experience with personally relevant adverse outcomes (i.e., limitations in walking ability, standing out of a seated position, strength, climbing stairs, and experiences with falling) (Malmstrom et al., 2016), it is limited by its self-reported nature, subjectivity, and low sensitivity (Kera et al., 2020). In this scoping review, only one article used the SARC-F questionnaire to assess sarcopenia. Thus, a more objective, formal instrument may be needed to accurately diagnose sarcopenia in both research and clinical settings. Given that symptomology is an important factor in sarcopenia assessment, use of the SARC-F in combination with other objective measures may facilitate a more comprehensive and accurate method of assessment.

Currently, radiologically-defined sarcopenia is a term used to describe a technique that identifies sarcopenia through use of CT and/or MRI (Rubbieri et al., 2014); our review revealed that the majority of articles assessed sarcopenia using one of these two methods. The advantages of using CT and MRI for body composition analysis are well-known, as they are considered to be the “gold standard” for non-invasive measurement of muscle quantity (Beaudart et al., 2016). For individuals diagnosed with cancer, CT scans are commonly used to acquire images for tumor staging and to monitor response to treatment. Accordingly, such imaging provides a convenient
and precise method for assessing sarcopenia in HNC. Historically, SMM has been measured on abdominal CT scans at the level of L3 due to the accuracy and strong correlation of the measurement with total body SMM (Mitsiopoulos et al., 1998; Mourtzakis et al., 2008). Although CT scans at L3 are routinely available in some oncology populations (e.g., abdominal oncology patients) (Shachar et al., 2016), performing abdominal imaging is not standard practice in diagnostic work-up in HNC. Accordingly, Grossberg and colleagues (2016) reported that 93% of individuals receiving HNC treatment lack abdominal imaging with CT. However, recent methods supporting the measurement of SMM in HNC using neck imaging at C3 have been described. Swartz et al. (2016) reported a strong correlation between the CSA of skeletal muscle at L3 and C3 and subsequently developed an algorithm for conversion. Because CT scans at C3 are routinely available in the diagnostic work-up for those undergoing HNC treatment (Swartz et al., 2016), SMM can be measured without requiring additional imaging and patient burden. This trend is reflected in the findings of our scoping review, as 21 of 29 articles (72.4%) which used CT imaging of the neck to determine SMM were found to have applied the algorithm developed by Swartz et al. (2016). Moreover, all studies selected for inclusion were published after 2016 – the same year Swartz and colleagues developed the algorithm allowing for SMM measurement using CT scans of the head and neck at C3. This development explains the time frame of included studies (i.e., from 2016 to present), highlighting the utility and applicability of the algorithm and subsequent ease of SMM measurement in HNC.

**Lumbar.** Commonly reported as total body SMM, estimations for muscle quantity can be made through a variety of techniques that adjust for one’s BMI or height to achieve a more accurate and relevant measurement (Cooper et al., 2013). Considering the variation in SMM between individuals with similar skeletal muscle area but differences in height, it may be
considered problematic to assess sarcopenia using only the CSA of skeletal musculature at any given location. Thus, to accurately diagnose sarcopenia, the use of a normalized measure of CSA incorporating the height of each individual is recommended. One such measure is SMI. Normalizing the CSA of muscles obtained on axial CT imaging for patient height to determine SMI is considered the international gold standard for body composition analysis in the quantification of SMM (Cruz-Jentoft et al., 2010). This is reflected in our scoping review by the tendency of researchers to favour SMI measurements in their assessment of SMM and sarcopenia and, in fact, the majority of articles did use SMI as the primary outcome.

SMI at the level of the L3 was most commonly used to represent sarcopenia. This is not unexpected given its strong correlation with whole-body SMM (Cooper et al., 2013). However, one potential concern regarding the use of L3 SMI as an indicator of sarcopenia is the process required to obtain lumbar imaging. In the present scoping review, nearly one third of included studies used PET-CT to determine L3 SMI. Because whole-body imaging (i.e., PET-CT) is primarily performed in HNC patients deemed to be of high risk for distant metastases or in those with advanced-stage disease (Fattouh et al., 2019), this method may introduce a substantial risk of selection bias, thus weakening the internal validity of findings and limiting their external applicability. Further, delineation of muscles at L3 may result in the overestimation of SMM measurement due to the complexity of L3 musculature and the potential need for third-party programs to provide accurate measurements (Swartz et al., 2016); applying this algorithm to convert C3 SMI to L3 SMI (without the need for PET-CT) can be a reliable alternative to using full-body imaging. However, the practice of deriving lumbar SMI estimations from C3 measurements is not without limitations as these estimations may be susceptible to calculation bias and differ from true L3 measurements (Chang et al., 2021).
**Head and neck.** The use of head and neck CT scans to measure muscle area at C3 was the second most common strategy for sarcopenia assessment within the present studies. This finding was expected given that CT imaging at the level of C3 is a part of the routine imaging protocol for those undergoing HNC treatment (Bril et al., 2019). CT imaging of the head and neck may also limit radiation exposure compared to the full-body imaging required for lumbar measurements, thereby resulting in less patient burden (Almada-Correia et al., 2019). SMM measured at C3 may be indicative of physical activity and nutritional status, emphasising the importance of early detection to implement corrective strategies. In addition, Ufuk et al. (2019) found that muscle mass quantity measured directly at C3 (i.e., C3 SMI) was best able to discriminate sarcopenia in male HNC patients. Skeletal muscle measured at the level of C3 also shows excellent inter- and intra-observer agreement, suggesting that C3 SMI is both reliable and reproducible (Zwart et al., 2019).

In addition to being a robust indicator of sarcopenia and having prognostic value for predicting duration of FT use (Karsten et al., 2019) and survival among patients with HNC (Chang et al., 2021), C3 SMI also has the advantage of being measured directly from conventional head and neck CT images. While CT-measured markers of sarcopenia are relatively straightforward to obtain, most other objective measurements require 5-10 minutes per patient which may be difficult to accommodate in real-time clinical practice (Meerkerk et al., 2021). Given that C3 SMI is easily identifiable on CT imaging, shows a strong and significant correlation with L3 SMI, and has proven prognostic value (Jung et al., 2019; Ufuk et al., 2019), the conversion of these measurements to L3 may be unnecessary. C3 SMI could be used in order to limit the time commitment required to measure SMM and the potential for calculation bias when converting C3 measurements to L3 SMI. Doing so may facilitate accurate, real-time SMM
measurement and allow for early therapeutic intervention to reduce the severity of sarcopenia and its complications. Still, SMM measurement at C3 is a relatively new concept with few studies available. More evidence is needed before C3 SMI can be used as a reliable method for body composition analysis and sarcopenia assessment in HNC.

While SMM measurements at C3 offer a cost-effective, feasible, and accurate alternative to L3 measurement in HNC patients, muscle delineation may be hindered due to metastatic cervical lymphadenopathy or previous neck dissection in locally advanced or recurrent HNC (Swartz et al., 2016). In evaluating the robustness of varying CSA measurements at C3, Bril et al. (2019) concluded that inter-observer agreement for the CSA of PVM muscles is most uniform; the highest level of variation was observed in SCM CSA measurements. One potential explanation for this observation is that the identification of muscles on head and neck CT imaging may be impaired by the presence of lymph node metastases (Swartz et al., 2016). Because lymph node stations are positioned closely around these muscles (Robbins et al., 2008), the SCMs in particular are at high risk for lymph node invasion that can interfere with assessment. Swartz et al. (2016) reported that lymph node metastases was responsible for the impaired measurement of SCM muscles in 11% of individuals with HNC, while PVM muscle measurement was possible in almost every patient. Moreover, Ufuk et al. (2019) found that SCM measurement was impaired due to lymphadenopathies in 6.9% of HNC patients. In the context of real-world clinical care, approximately 57% of those undergoing HNC treatment present with lymph node metastasis (Lindberg, 1972). Consequently, researchers should exercise caution when utilizing SCM measurements to assess sarcopenia if their study sample includes a high percentage of lymph node positive patients. To address the potential for impaired measurement related to lymph node metastases, it has been suggested that doubling the CSA of the SCM
muscle that can be measured without interference is a reliable, equally predictive alternative. This limitation can also be minimized by excluding the SCM altogether from CSA calculations, given that the CSA of PVM alone correlates well with CSA at L3 (Swartz et al., 2016).

**Appendicular.** Appendicular SMI (ASMI), or the sum of muscle mass of the upper and lower extremities adjusted for height, was also used as a marker of muscle quantity in three articles. Yeh et al. (2021) found that the impact of CRT, with respect to lean mass, was greater in the peripheral extremities, indicating that sarcopenia assessed using ASMI measurements is associated with a lower tolerance to treatment. In addition, when compared to body weight, BMI, total lean mass and total fat mass, pre-treatment ASMI was reported to be the only prognostic factor capable of predicting 2-year recurrence-free survival (Yeh et al., 2021). These findings are supported in the literature with researchers suggesting that patients with low ASMI have low physical functioning (Brown et al., 2015) and are more likely to experience complications such as pneumonia or infection (Nishigori et al., 2016). Consequently, it may become more difficult for patients to tolerate treatment. Researchers postulate that the strength of ASMI as a prognostic variable may be due to its potential association with full-body energy reservoir status. For example, in patients with a high ASMI, loss of muscle mass was observed throughout the entire body, while those with a low ASMI only had significant loss of lean mass within the appendicular skeletal muscle that was not observed in other regions of the body (Yeh et al., 2021).

Moreover, a high ASMI is associated with a well-functioning mitochondrial ATP synthesis cycle, thereby allowing the entire body to exchange lean mass for much-needed energy during times of muscle wasting, such as during CRT. Because skeletal muscle functions as a metabolic organ and has the ability to produce energy through mitochondrial ATP synthesis
(Romanello et al., 2019), and given that HNC patients commonly experience significant energy deficits related to impaired dietary intake and metabolic derangement, the use of ASMI as a marker of sarcopenia may be appropriate in studies that investigate patients receiving CRT; it may be especially applicable in situations where oral intake is impaired and significant weight loss occurs. Nevertheless, the measurement of appendicular muscle mass requires access to modalities such as DEXA which can involve radiation exposure and are not practical or routinely performed in HNC care.

Masticatory. Sarcopenia assessment is often centered around the degree to which measurements can accurately characterize whole body SMM. Because the term ‘generalized’ is considered a primary component of sarcopenia-associated SMM loss, the importance placed on whole-body SMM is warranted. Nevertheless, in HNC, it is the swallowing musculature that is often negatively impacted by treatment. Changes in the masticatory muscles can act as a reflection of swallowing function and nutritional status (Saitoh et al., 2016), with research also suggesting that these measurements are valid markers of sarcopenia in patients with trauma (Hu et al., 2018). Masticatory function is not only vital for mechanical breakdown of foods, but associations with handgrip strength, walking speed, and physical fitness - some of the primary characteristics of sarcopenia according to the EWGSOP – have also been documented (Gaszynska et al., 2014; Yamaguchi et al., 2019). Accordingly, these measurements have the potential to be used as an alternative to L3 imaging in sarcopenia assessment.

Research also has shown that the size of the primary masticatory muscles has a significant association with systemic nutritional biomarkers, even more so than the paraspinal muscles which are frequently used as measures of sarcopenia when lumbar CT imaging is used for assessment (Hwang et al., 2020). Although only one study used masticatory SMI
(MSMI) to assess sarcopenia in the current scoping review (Chang et al., 2021), the findings have significant implications for the application of this measurement in HNC. In their assessment of sarcopenia using MSMI, Chang et al. (2021) reported a significant relationship between sarcopenia and male sex. Moreover, they also noted that a potential advantage to using MSMI is that there is minimal opportunity for interference in this anatomical area for most cancers of the head and neck. Chang and colleagues (2021) noted that masticatory muscles could be clearly identified in CT scans of the head and neck and that neither primary tumor nor lymph node invasion was observed. Moreover, MSMI measurements obtained through manual delineation and threshold selection are consistent and may be less influenced by different measures (Chang et al., 2021). Thus, MSMI measurement may be feasible in most, if not all, HNC patients. Nonetheless, the application of the masseter muscle in the assessment of sarcopenia presents an inherent limitation, as its measurement may be dependent on external factors such as dental status and craniofacial structure (van Heusden et al., 2022).

**Psoas.** Only one study used the psoas, a paraspinal muscle positioned in the lower lumbar region of the spine that extends through the pelvis to the femur, as the outcome measure for sarcopenia assessment. Yoshimura and colleagues (2020) found that a low psoas muscle index (PMI) was associated with reduced disease-specific survival. While the optimal method to determine full-body SMM remains controversial, measurement of the psoas muscle has been suggested to be a simple and predictive measure of various morbidities (Yoshimura et al., 2020; Waki et al., 2019). In addition, a recent study comparing the accuracy of widely used measurements for sarcopenia found that PMI was more strongly associated with 1-year survival when compared to L3 SMI (Golse et al., 2017). Others suggest psoas muscle measurements are
faster and simpler if the alternative is peripheral abdominal SMM measurement given the likelihood of ascites and abdominal wall edema that may reduce the accuracy of the latter (Nam et al., 2019). Nevertheless, some researchers suggest that psoas muscle measurement may not be representative of overall, total body SMM considering that it is a minor muscle (Ebadi et al., 2018; Rutten et al., 2017). Furthermore, because delineation of the psoas muscle requires CT imaging of the lumbar region, its application in HNC is limited.

Cut-Off Values

Although CT imaging is considered to be the gold standard for non-invasive measurement of SMM and has been shown to provide practical and precise measures of body composition, the EWGSOP has stated that “… cut-off points for low muscle mass are not yet well defined for these measurements” (Cruz-Jentoft et al., 2019, p.20). Consequently, low muscle quantity measured in this manner is primarily used in research rather than in clinical practice (Cruz-Jentoft et al., 2019). This concern is highlighted in the current scoping review, as we revealed substantial heterogeneity in the selection of cut-off values used to diagnose sarcopenia in HNC. While some methods for determining cut-offs are more prevalent than others (e.g., ROC analysis, use of previously published values), the variability in assessment thresholds for sarcopenia is concerning. Wendrich et al. (2017) utilized a non-gender specific cut-off value of <43.2 cm²/m², a value which was determined by the likelihood of developing chemotherapy dose-limiting toxicity in those undergoing HNC treatment. An important consideration and concern for this approach is that it may identify a substantial number of individuals as sarcopenic. For example, Zwart and colleagues (2019) found that upon using <43.2 cm²/m² as a cut-off value, 97% of female patients were defined as sarcopenic. This may be considered a limitation of using this non-gender specific threshold. Van Rijn-Dekker et al. (2020) used a
gender-specific SMI threshold of <42.4 cm\(^2\)/m\(^2\) in men and <30.6 cm\(^2\)/m\(^2\) in women, which corresponded with the lowest gender-specific quartile. Prado et al. (2008) used a statistical analysis known as optimum stratification to determine their gender specific SMI cut-off values for sarcopenia, with an SMI of <52.4 cm\(^2\)/m\(^2\) for men and <38.5 cm\(^2\)/m\(^2\) for women used to classify patients as sarcopenic.

The current state of inconsistency in the application of cut-off values to identify sarcopenia in HNC presents challenges in terms of understanding the true impact of this condition and making comparisons between studies. These concerns are evident in the most recent meta-analysis on sarcopenia in HNC, in which Findlay and colleagues (2021) noted that a lack of consistency in SMI threshold values limited their ability to compare results from a large number of articles (e.g., only 7 were included for analysis) and called for a consensus on sarcopenia definition and assessment. The application of consistent threshold values to identify sarcopenia in HNC may also be limited by the unique characteristics of each patient group. For example, Yoshimiri et al. (2020) proposed that using identical cut-off values in both Western and Asian populations may be inappropriate considering variations in body size, lifestyle, and ethnicity. Cut-off values will also differ based on what instrument is used to assess sarcopenia and are dependent on the site (i.e., vertebral level) at which skeletal muscle is measured, making it difficult to determine which is most appropriate and clinically relevant in HNC.

The use of ROC curve analysis to determine optimal cut-off values may be preferred given the effectiveness and accuracy of this method and its ability to discriminate between patients (Hajian-Tilaki et al., 2013). Using this approach also ensures that low SMM is measured according to the individuals being investigated and in relation to the outcome of interest. Another option would be to simply avoid using cut-offs and to perform analyses with SMM as a
continuous variable. While this approach may circumvent the inherent limitations and inconsistencies associated with using cut-off values, it also may prevent the calculation of prevalence estimates, interfere with comparisons across different studies and populations, and subsequently limit the general applicability of results in a clinical context. Accordingly, it may be difficult to form a consensus and develop guidelines for research and clinical practice. More evidence is required before a consistent threshold can be applied to identify sarcopenia in HNC, and such evidence should be personalized to the characteristics of the population of interest.

Timing of Assessment

The point in time at which sarcopenia is assessed provides a clear impression of its utility in clinical care. With the majority of studies only having assessed sarcopenia prior to treatment, it is clear that current research is aimed at exploring the prognostic value of SMM loss and determining its ability to predict adverse outcomes in HNC. The assessment of sarcopenia both during and after treatment, however, could be beneficial in terms of establishing a clear pattern of loss and determining when patients would most benefit from proactive intervention. Only 4 (5%) and 21 (28%) studies assessed sarcopenia during and after treatment, respectively, highlighting a significant gap in the literature.

An important consideration with respect to the timing of measurement is the interval between assessment and beginning of treatment. Although most studies included in this review performed sarcopenia assessments prior to treatment, the timing fluctuated greatly ranging from one day to one year before treatment. Sarcopenia represents a modifiable risk factor that could potentially be targeted to improve patient outcomes. However, it remains to be seen whether there is enough time to target sarcopenia in the short period of time between assessment and the commencement of treatment. For example, in HNC, the time period between diagnosis and
surgery can be up to four weeks; for CRT, this period is even shorter and should be no longer than two weeks (Gilbert et al., 2009). The pre-treatment period in which muscle mass can be increased may be even more limited for some patients, such as those requiring immediate resection for oral cancer (Yamaguchi et al., 2017). Nevertheless, a randomized trial in patients with lung cancer reported less severe postoperative complications and a significant decrease in hospital stay post-treatment in those who had undergone one week of endurance and resistance training prior to surgery (Huang et al., 2017), suggesting that even when performed over a short period of time, physical activity may reduce the negative impact of sarcopenia.

In HNC, studies investigating exercise and nutritional support interventions have demonstrated that they are feasible and report high patient satisfaction (Brown et al., 2017; Sandmael et al., 2017). Yamaguchi and colleagues (2021) recently incorporated a preoperative exercise and nutritional intervention program for oral cancer patients with reduced daily activity. Although they found that a program consisting of warming up, walking, and resistance training performed 3-5 days per week for 4-6 weeks until admission for surgery was feasible, prospective follow-up is currently underway to determine the impact on postoperative complications and survival (Yamaguchi et al., 2021). With respect to patient outcomes, approximately 8 weeks of moderate physical activity was reported to be adequate to improve muscle mass and health-related QoL in patients with liver cirrhosis (Zenith et al., 2014). In addition, Yamamoto and colleagues (2017) explored the utility of pre-treatment exercise and nutritional support for older patients with gastric cancer diagnosed with sarcopenia and reported that a 1–4-week intervention significantly improved skeletal muscle strength and volume. Collectively, these results suggest that pre-treatment exercise and nutritional support is feasible and may facilitate an increase in SMM even when implemented over a short period of time. More high-quality research with
larger samples is needed to explore the benefit of such intervention in reducing SMM loss and improving HNC outcomes. In addition, if sarcopenia is to be assessed during and after treatment, more clarity and consistency must be applied in terms of the relationship between its linguistic and operational definition.

Sarcopenia is often described as an age-related and progressive disorder (Cruz-Jentoft et al., 2019), implying that its development takes time and occurs naturally. If SMM is being measured during and/or after treatment, consideration must be given to the fact that this treatment will likely have a negative impact on one’s ability to engage in physical activity, consume adequate oral intake, and, consequently, maintain muscle mass. This distinction is important because if treatment is inducing SMM loss and either causing or accelerating its development, then the “age-related” and “progressive” elements of sarcopenia may not apply. It may be more accurate to refer to such measurement as SMM loss rather than sarcopenia. Further, given that HNC is often diagnosed when tumor progression is advanced, even pre-treatment assessment of sarcopenia may not necessarily be age-related. ‘Secondary’ sarcopenia occurs in addition to aging when other variables are likely to contribute to the muscle wasting process (Cruz-Jentoft et al., 2010). For example, sarcopenia can occur secondary to a systemic disease that invokes an inflammatory response (e.g., organ failure and malignancy), neurological disorders, and conditions such as osteoarthritis (Mijnarends et al., 2016). Thus, it may be more accurate to describe sarcopenia as occurring secondary to HNC and its treatment. Based on these findings, future research should aim to determine the potential of early intervention to mitigate the impact of sarcopenia in HNC and whether it is possible for patients to continuously engage in physical activity during treatment.
Limitations

While important findings have emerged from this scoping review, several limitations should be noted. First, because this was a scoping review, the quality of included studies and extracted data were not appraised prior to inclusion. The heterogeneity in methodologies, objectives, and assessment methods of the included studies can also be considered a limitation, especially considering that not all studies included a detailed description of how sarcopenia was measured and assessed. Additionally, there was significant overlap between some of the collected data (e.g., studies evaluated the impact of sarcopenia with respect to multiple different outcomes); as such, it was difficult to summarize and interpret the results. Finally, our review collected information pertaining to the assessment of other concepts that were measured in a similar manner to sarcopenia (i.e., cachexia). More information regarding the differences between these concepts and their assessment would be useful for future study designs.

Compared to those with other cancers, individuals with HNC are at a higher risk of malnutrition and muscle atrophy (Pressoir et al., 2010). Thus, sarcopenia represents a critical index for those undergoing HNC treatment. Given the well-documented prognostic impact of sarcopenia (Hua et al., 2019; Wong et al., 2021) and the fact that diminished muscle mass can be a correctable factor (Cruz-Jentoft et al., 2010), the importance of accurate and clinically meaningful pre-treatment assessment is evident. If early assessment is performed and those at risk are identified, management strategies including nutritional counselling (e.g., the implementation of a diet regimen high in protein and consisting of high-quality amino acids) and physical activity intervention (e.g., both aerobic and resistance exercise) may be carried out in an attempt to avoid the potentially devastating complications associated with sarcopenia. Such
endeavors may result in an improvement to the patient’s response to cancer treatment and overall QoL (Denison et al., 2015).

**Conclusions**

The body of research on sarcopenia in HNC has grown substantially since 2016. However, given the heterogeneity in the definition of sarcopenia, the techniques and instruments used in its measurement, and the cut-off values applied to detect its presence, the optimal approach to assessment remains undetermined. At present, the most effective strategy in assessing sarcopenia may be dependent upon numerous factors, including access to resources, characteristics of the patient population and their treatment, and the potential accuracy of outcomes used to assess sarcopenia. For those with HNC, SMM measured at the level of C3 on head and neck CT imaging may represent a feasible, cost-effective, accurate, meaningful, and quick biomarker for the detection of sarcopenia. Further combining these SMM measurements with quick and reliable measures of muscle strength (i.e., handgrip strength) and/or physical performance may serve to increase the accuracy of sarcopenia assessments in those with HNC. More high-quality evidence is needed to determine the significance of SMM measured at C3 in relation to functional outcomes and QoL prior to its use in clinical settings.
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CHAPTER 3

Prognostic Role of Sarcopenia in Oropharyngeal Squamous Cell Carcinoma

Introduction

Individuals diagnosed with HNC often experience significant anatomical and functional changes that are associated with the disease and its treatment; when considered collectively, these changes may result in a substantial decline in QoL and well-being (List & Bilir, 2004). In the context of HNC, the presence of locally advanced disease is common at the time of diagnosis and, due to pain or the physical obstruction of swallowing musculature related to the physical presence of the tumor, normal swallowing physiology may be disrupted. Consequently, HNC is strongly associated with impaired swallowing function (Stenson et al., 2000). This is evident in the fact that individuals with HNC commonly experience significant weight loss (i.e., involuntary weight loss greater than 5% in one month or 10% over six months) even prior to the commencement of treatment (Jager-Wittenaar et al., 2007). Moreover, HNC treatments such as RT and CRT are associated with numerous treatment-related toxicities such as dysphagia, odynophagia, mucositis, and xerostomia that may contribute to difficulty with sustaining adequate levels of oral intake and nutrition (Givens et al., 2009; Marta et al., 2014).

Research suggests that up to 90% of HNC patients experience a range of symptoms that contribute to reduced nutritional intake (Crowder et al., 2018), and consequently, increase their risk for developing malnutrition – a condition that can reduce one’s physical strength, post-treatment recovery, and contribute to an overall reduction in QoL (Santarpia et al., 2011). Individuals with HNC are reported to have the second highest prevalence of malnutrition among cancer populations (Marshall et al., 2019). Moreover, poor nutritional status is also associated
with a decline in muscle mass and function, further contributing to swallowing dysfunction (Wopken et al., 2018). Difficulty sustaining adequate levels of dietary intake may exacerbate the functional impairment associated with HNC and its treatment. For example, difficulty consuming food may impair one’s response to treatment due to a reduced ability to absorb and utilize medication (Santarpia et al., 2011). Malnutrition is also associated with impaired recovery following RT/CRT treatment, reducing one’s QoL and ability to achieve a cure (Kubrak et al., 2020; Santarpia et al., 2011).

Those diagnosed with oropharyngeal squamous cell carcinoma (OPSCC), a subset of the HNC population, are especially at risk for short- and long-term swallowing dysfunction. Despite substantial improvements in the treatment of OPSCC, patients frequently experience pain associated with swallowing, or odynophagia (McMenamin & Grant, 2015). Those with OPSCC may experience odynophagia prior to treatment as the tumor itself may cause pain due to the compression of blood vessels and/or nerves in the affected area (Epstein et al., 2009). In addition, individuals with OPSCC have been reported to experience higher rates of post-treatment dysphagia and reduced oral intake compared to other head and neck subsites, with research suggesting that these individuals generally have impaired swallowing function prior to treatment as well (Pauloski et al., 2000). Consequently, OPSCC is also associated with significant weight loss during treatment (Jager-Wittenaar et al., 2007; Ottosson et al., 2013). Because malnutrition and significant weight loss both before and during treatment are well-established prognostic indicators for OS in those undergoing treatment for HNC (Bruixola et al., 2018; Langius et al., 2013), efforts which seek to limit such nutritional changes are of great importance to individual outcomes.
To address these concerns, patients often receive nutritional intervention from their care team in the form of enteral feeding to optimize caloric intake with the goal of preventing weight loss (Lees, 1997). Research suggests that FT placement may occur in 33% to 62% of individuals undergoing treatment for OPSCC (Bhayani et al., 2013; Jovanovic et al., 2021). Moreover, largely due to the pain and swallowing dysfunction experienced by those undergoing HNC treatment, a considerable proportion of these patients become dependent on FTs to sustain adequate levels of dietary intake and limit weight loss both during and after treatment (Karsten et al., 2019). Although nutritional support via enteral FTs can reduce the need for hospitalization related to nutritional deficits, weight loss, and may subsequently improve health-related QoL in appropriately selected HNC patients (Paleri & Patterson, 2010; Romesser et al., 2012), no universally accepted protocol currently exists to guide clinicians in the decision-making process for recommending a FT (Kramer et al., 2013; Shaw et al., 2015).

Despite the lack of consensus on guidelines for FT placement, baseline parameters that are easily accessible and have predictive value can be utilized to facilitate informed decision-making. For example, a risk model known as the total dysphagia risk score (TDRS) incorporates pre-treatment prognostic factors such as T3-T4 tumors, bilateral neck irradiation, weight loss prior to RT, oropharyngeal and nasopharyngeal tumors, and treatment modality (accelerated RT and CRT) to predict swallowing dysfunction at six months post-treatment (Nevens et al., 2016). Recently, measures of body composition have emerged as potential prognostic factors for adverse outcomes and survival in HNC (Jung et al., 2019). One variable that has demonstrated prognostic utility is termed sarcopenia. Sarcopenia is defined as “… a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality.” (Cruz-Jentoft et al., 2019,
Given the association between older age and malignancy with malnutrition, immobilization, and inflammation, sarcopenia is particularly prevalent in individuals with cancer (Chargi et al., 2019; Morishita, 2016).

In those with HNC, the prevalence of sarcopenia is reported to range from 35.5% to 54.5% (Zwart et al., 2019). Due to the substantial proportion of HNC patients affected by sarcopenia, and because this condition is independently associated with reduced SMM, muscle function, and poor swallowing function, those with sarcopenia are at an increased risk for functional impairment (Wakabayashi et al., 2015; Wakabayashi et al., 2019). Those affected by sarcopenia are especially susceptible to swallowing-related impairments associated with HNC treatment. These individuals are likely to experience swallowing muscle atrophy due to an inevitable decline in the activity of swallowing musculature – a state further associated with the loss of muscle mass and function (Hutcheson et al., 2013). Sarcopenia also may intensify these adverse outcomes, as those affected by this condition will often already present with limited SMM reserves and decreased muscle function. Consequently, in those with sarcopenia, non-use atrophy of the swallowing musculature may result in prolonged functional impairment with consequential reductions in perceived QoL (Wakabayashi et al., 2019; Wakabayashi et al., 2015). Further, the impact of treatment and the potential toxicities may further exacerbate deficits in swallowing function.

Ganju and colleagues (2019) found that sarcopenia was associated with higher rates of chemotherapy toxicity and prolonged RT interruptions. Interestingly, Silva and colleagues (2021) recently reported a high prevalence of sarcopenia in HNC patients with dysphagia at the time of their initial oncologic evaluation. An association between sarcopenia and physician-rated dysphagia and xerostomia in HNC patients receiving definitive RT/CRT has also been reported.
(van Rijn-Dekker et al., 2020). Based on several recent studies, data have demonstrated that diminished SMM assessed by CT imaging (i.e., radiographic assessment) also may contribute to an increased risk of prolonged FT dependency and hospital stay, poor locoregional disease control, and increased rates of postoperative complications (Bril et al., 2019; Grossberg et al., 2016; Karsten et al., 2019). In addition, the association between sarcopenia and survival is well-established within the HNC literature as patients with sarcopenia are reported to have significantly poorer survival outcomes (Chargi et al., 2019; Grossberg et al., 2016; Hua et al., 2019; Wong et al., 2020). In those with OPSCC, research suggests that sarcopenia is a significant prognostic factor for disease-free survival and OS (Chargi et al., 2020; Tamaki et al., 2019), further emphasizing the importance of investigating sarcopenia as a prognostic factor in this population.

**Statement of Problem**

Despite the apparent prognostic value of sarcopenia and its strong documented relationship with nutritional outcomes, little or no research has emerged investigating the prognostic significance of sarcopenia with respect to FT placement. To date, only one study has investigated the association between sarcopenia and FT outcomes. In this single study, Karsten et al. (2019) reported finding that a lower SMI, a biomarker of sarcopenia, led to an increased risk for prolonged FT dependency in multivariable analysis. However, the investigation by Karsten and colleagues included a heterogeneous cohort of those diagnosed with HNC. Currently, however, there is a limited understanding of the prognostic significance of sarcopenia specific to patients with OPSCC, especially with respect to FT use and functional outcomes. It is, therefore, of interest and relevance to study sarcopenia in the population of those with HNC; this is further
justified given that the oropharynx site is a predictor of treatment-associated weight loss (Jager-Wittenaar et al., 2007; Ottosson et al., 2012).

Equally concerning is the fact that despite the abundant evidence demonstrating the effectiveness of nutritional and exercise interventions and their association with positive outcomes for older individuals, evidence-based guidelines have yet to be established for the prevention and management of sarcopenia (Naseeb & Volpe, 2017). The value of assessing and understanding the pathophysiology of sarcopenia in older oncology populations is evident given the potentially modifiable nature of this muscle-wasting condition. Muscle loss associated with sarcopenia may be lessened through the implementation of pre-treatment interventions to optimize one’s nutritional status (Cruz-Jentoft et al., 2019); adequate nutrition and protein intake in addition to physical activity are essential for this to occur (Daly et al., 2014). Consequently, an improved understanding of the association between sarcopenia and functional outcomes, including FT placement and use, may facilitate improved risk stratification of HNC patients prior to treatment supporting the clinical team’s ability to identify those who would benefit from the previously identified interventions. By aiding our understanding of risk, the ability to minimize the harmful effects associated with muscle loss may be enhanced.

The EWGSOP stresses that, “practitioners have ever-increasing possibilities for preventing, delaying, treating, and sometimes even reversing sarcopenia by way of early and effective interventions” (Cruz-Jentoft et al., 2019, p.17). A better understanding of the potential relationship between pre-treatment sarcopenia and FT placement may be necessary to identify patients at-risk for adverse outcomes in a proactive manner to provide early, targeted interventions. In addition, the present scoping review identified a lack of research on sarcopenia at time points other than pre-treatment (Jovanovic et al., 2022). The identification of factors
associated with post-treatment sarcopenia or SMM loss may allow for the indexing of sarcopenia as an accessible biomarker to identify patients who may need support, guiding clinical practice and facilitating improved outcomes for individuals with OPSCC. As a first step toward defining the relationship between sarcopenia and FT placement and use in OPSCC patients treated with definitive RT/CRT, a comprehensive retrospective analysis was performed. The objective of the current study was to: (1) determine the prognostic significance of sarcopenia with respect to FT-placement and use, (2) evaluate the relationship between pre-treatment factors and post-treatment sarcopenia, and (3) explore the utility of different measurement methods for the assessment of sarcopenia.
Methods

Participants

A retrospective chart review was conducted to identify patients diagnosed with OPSCC and who were treated with definitive RT or CRT at a local tertiary care centre between January 2013 and October 2017 (i.e., 58 months). Patients were excluded based on the following conditions: (1) primary surgical treatment or surgery within 12 months after RT/CRT, (2) non-curative treatment intent (i.e., patient pursued palliative care), (3) distant tumor metastasis leading to a change in treatment strategy (e.g., transition from curative to non-curative intent), (4) placement of FT prior to multidisciplinary team (MDT) meeting, and/or (5) absence of CT imaging at the vertebral level of interest. The current study protocol was conducted in accordance with and approved by the Western University Health Sciences Research Ethics Board (#105936).

Data Collection

Data were collected on patient demographic and treatment characteristics from the electronic medical records of a consecutive cohort of patients treated for OPSCC. This included the following information: age, sex, height, weight, tumor-node-metastasis (TNM) stage, type of treatment (RT or CRT), OPSCC subsite, p16 status (as a surrogate biomarker of human papilloma virus [HPV] status), radiation dose, chemotherapeutic agents/regimen, comorbidities, date of death or last follow-up, and cause of death (if known). Outcome data were collected for variables to be used as primary outcome measures, including FT placement (yes vs. no), duration of FT placement (calculated in days from date of insertion to date of removal), Performance Status Scale for Head and Neck Cancer (PSS-HN) normalcy of diet scores (Appendix E), and
M.D. Anderson Dysphagia Inventory (MDADI) composite scores (Appendix F). Data on CT-assessed SMM (i.e., SMI) were prospectively collected and analyzed at both baseline and three months post-treatment. To investigate between-group differences at baseline with respect to demographic, treatment, and outcome variables, patients were classified based on FT Placement: (1) OPSCC patients who received a FT associated with their treatment and/or condition (FT group) and (2) OPSCC patients who did not receive a FT (NFT group). Patients were also stratified based on sarcopenia status (yes vs. no) as determined by the study team.

For those who received a FT over the course of treatment, information was collected about the type of enteral FT, timing of placement (i.e., time from the first MDT meeting to FT placement), and duration of use. The head and neck oncology team at our institution champions both proactive and reactive FT placement, by which proactive FTs are recommended at treatment outset for patients deemed “at risk”, while patients without specific risk indicators are recommended to take nutrition by mouth and as tolerated. A prophylactic approach to FT placement is not standard practice at our institution as this approach may prolong one’s return to full oral intake and increase the risk for FT dependence (Gutt et al., 2015). Additionally, routine prophylactic placement of FTs is associated with high costs (Callahan et al., 2001) and many tubes may go unused (Madhoun et al., 2011). Thus, proactive FT placement was recommended to patients who met one or more of the following criteria: (1) significant weight loss (> 5% in 1 month or > 10% over 6 months), (2) low BMI (18 or less) at baseline, (3) concurrent CRT, and (4) any symptoms that interfere with the ability to eat such as dysphagia, anorexia, dehydration, and/or pain (Gilbert et al., 2009). Based on these criteria, the oncology team recommended reactive FTs for patients demonstrating continued and excessive weight loss and declining oral intake throughout treatment.
Variables of Interest

**Age.** Aging is associated with several elements which may contribute to general muscle loss and place the individual at an increased risk for sarcopenia. These include inadequate nutritional intake, physical inactivity, and/or a natural reduction in anabolic natural hormones considered essential for muscle mass maintenance (Anjanappa et al., 2020). Moreover, Sachdev and colleagues (2015) found that age was the most significant predictor of enteral FT placement in HNC patients undergoing RT/CRT even when controlling for other clinical features such as BMI. Hence, in our investigation, we considered age as a covariate in regression analyses.

**Sex.** Another notable factor associated with sarcopenia is one’s biological sex. Although males are reported to have higher levels of muscle mass and strength compared to females (Dodds et al., 2014), research suggests that male cancer patients generally experience greater proportional weight loss or muscle wasting compared with patients of the opposite sex (Zhong & Zimmers, 2020). These differences may be attributed to the inherent anatomical and physiological differences between males and females, including muscle fiber type, the composition and function of muscle mitochondria, and global gene expression patterns for muscle (Zhong & Zimmers, 2020). For example, in a study of 287 HNC patients Cao and colleagues (2021) found that being male had a significant impact on muscle loss. Moreover, de Bree et al. (2022) observed that including sex within their prediction model improved the correlation between estimated and measured SMM. Therefore, given the relationship between one’s biological sex and body composition and muscle loss, we considered sex as a covariate for regression analyses in the current study.

**Treatment.** Advanced OPSCC often requires a multimodal approach to treatment with concurrent CRT considered standard of care (Cohan et al., 2009). Multiple clinical trials and a
large meta-analysis have demonstrated that concurrent CRT can improve disease-free survival and ultimately improve the likelihood of achieving a cure (Pignon et al., 2009). Nevertheless, several studies have shown that CRT is associated with significant toxicities including dysphagia, odynophagia, mucositis, and nausea – all of which may contribute to difficulty with eating and sustaining hydration by mouth (Adelstein et al., 2003; Machtay et al., 2008; Vangelov et al., 2017). Consequently, those undergoing CRT are reported to lose more than 5% of their total muscle mass in less than six months, a rate equivalent to the amount of muscle loss experienced by an inactive adult over the course of a decade (Baxi et al., 2016; Forbes & Reina, 1970). For those with OPSCC, the impact of treatment toxicity and a decline in muscle mass associated with concurrent CRT can be debilitating, permanent, and lead to an increased risk for and dependence on enteral feeding (Cheng et al., 2006; Chera et al., 2019; Setton et al., 2015). Therefore, we considered the modality of treatment (i.e., RT vs. CRT) in regression analysis when investigating the relationship between sarcopenia and FT placement.

**BMI.** The sequelae associated with concurrent CRT also may lead to a significant reduction in body weight with a significant number of patients experiencing clinically meaningful weight loss (i.e., >5% of pre-treatment body weight) during and after treatment. In the context of OPSCC, weight loss is associated with significant reductions in QoL and OS (Bruixola et al., 2018; Pingili et al., 2021). Hamer and O'Donovan (2017) also found that the risk of “all-cause” mortality was significantly higher in OPSCC patients who experienced weight loss combined with sarcopenia. Moreover, weight loss is also established as a primary criterion for the placement of enteral FTs (Gilbert et al., 2009) and is considered an additional risk factor for sarcopenia (Kokkinidis et al., 2019). HNC patients with a low BMI (i.e., one’s weight in kilograms divided by the square of height in meters) are more likely to present with advanced
tumor staging and have a FT placed, with a high BMI being associated with longer time to recurrence, locoregional control, and survival (Hicks et al., 2018). Accordingly, BMI measurements were used as a covariate in the present study to account for its association with sarcopenia and FT placement.

**Performance Status Scale for Head and Neck Cancer.** To investigate the relationship between sarcopenia and swallowing- and nutrition-related outcomes, data from the Performance Status Scale for Head and Neck Cancer (PSS-HN) and the M.D. Anderson Dysphagia Inventory (MDADI) also were collected and analyzed. The PSS-HN is a validated and clinician-rated outcome measure used in the assessment of functional performance related to speech and swallowing. Patient responses provide an overall score between zero and 100, with a higher score associated with increasingly superior function (List et al., 1990). Although this instrument consists of three subscales (i.e., normalcy of diet, understandability of speech, and eating in public), only data from the normalcy of diet subscale were used as a covariate in order to capture information pertaining to one’s level of oral intake (List et al., 1990).

**M.D. Anderson Dysphagia Inventory.** The MDADI is a validated questionnaire that provides information pertaining to the impact of disease and treatment on dysphagia-specific QoL. The MDADI is comprised of 20 items, each rated on a 5-point scale and then combined to provide an overall score between 20 and 100 (Chen et al., 2001). A higher score is reflective of a superior QoL in the context of dysphagia with a clinically meaningful difference represented by a change of 10 points or more (Hutcheson et al., 2016). The composite MDADI score provides a weighted average of the three different MDADI subscales (i.e., functional, emotional, and physical) and was utilized as a covariate in this investigation.
Measurement of Skeletal Muscle Mass

For this investigation, the third cervical (C3) and fourth thoracic (T4) vertebral levels served as points of reference on head and neck CT scans for the quantification of SMM and assessment of sarcopenia. These two landmarks were selected due to their strong correlation with full-body SMM (van Heusden et al., 2017; Swartz et al., 2016) and documented prognostic value in HNC (Sealy et al., 2020; Wong et al., 2021). To determine a consistent anatomic location for measurement of SMM across patients at the level of C3, one investigator (NJ) reviewed axial CT scan slices in a caudal to cephalad direction through the C3 vertebra (as per methods described by Swartz et al., 2016). The first caudal CT slice displaying the entire vertebral arc in addition to the transverse and spinous processes was selected for muscle contouring.

Measurement of SMM at this location first required delineation of the right sternocleidomastoid (SCM) muscle, left SCM muscle, and paravertebral muscles (PVM) which was manually performed (Figure 6). Other densities such as bone structures, fat infiltration, and large veins were excluded to limit the overestimation of SMM. Second, the cross-sectional area (CSA) of the delineated musculature at C3 was automatically retrieved as the total sum of pixels of the three muscles within the standard HU ranges from -29 to +150, corresponding with skeletal muscle density (Mitsiopoulos et al., 1998). Finally, CSA measurements at C3 were mathematically adjusted for the height of each patient (m²), resulting in a measure known as SMI (cm²/m²). The procedure described above (i.e., image selection, muscle contouring/delineation, and CSA calculation) was performed using delineation software MIM (MIM Software Incorporated, version 7.0.5, Beachwood, OH, USA).
Figure 6.

Axial CT-slice at the level of C3. (1) standard CT-slice at the C3 level, (2) delineated/contoured CT-slice at the C3 level (red: PVM; blue: right SCM muscle; green: left SCM muscle).
The process for measuring SMM on an axial CT slice at the T4 vertebral level was similar to the procedure for C3 slice selection, with the primary difference being the muscles that were contoured. Instead of contouring the PVM and the left and right SCM muscles, the group of muscles delineated at T4 were: (1) the left pectoralis minor and major muscles, (2) the right pectoralis minor and major muscles, and (3) the ‘back muscles’ (i.e., the combined bilateral muscles of the erector spinae, levator scapulae, rhomboideus minor and major, and transversospinalis groups) (Figure 7). The main observer (NJ) performed skeletal muscle analysis in all patients. To evaluate inter- and intra-observer reliability, 20 patients were randomly selected and both C3 SMI and T4 SMI were measured again by the main observer (approximately three months between initial and subsequent assessment) and another observer (SM) using explicit predefined procedural guidelines.

Figure 7.

Axial CT-slice at the level of T4. (1) standard CT-slice at the T4 level, (2) delineated/contoured CT-slice at the T4 level (red: back muscles; blue: right pectoralis muscle; green: left pectoralis muscle).
**Statistical Analysis**

Statistical analyses were performed using two-tailed statistical testing at the a priori probability level of 0.05 to reflect a 95% confidence interval (CI). Following data collection, descriptive statistics were generated to provide measures of central tendency for all outcome variables. Bivariate associations were compared using the Pearson’s chi-square test, Fisher’s exact test, independent two-sample t-test, or Wilcoxon rank sum test, as appropriate. All statistical analyses were completed using SAS Analytics Software (SAS Institute, Version 9.4, Cary, NC, USA).

All outcome variables were analyzed to determine normality of distribution and to guide the selection of appropriate statistical tests. Although most variables were normally distributed, initial inquiry into data from the PSS-HN normalcy of diet and MDADI composite scores revealed a frequency histogram skewed to the left, suggesting that the distribution of these variables was non-normal. This was confirmed with the Shapiro-Wilk test for normality (Evans, 2014). Thus, in order to appropriately investigate between-group differences at baseline for the PSS-HN normalcy of diet and MDADI composite scales, the non-parametric alternative to the independent two-sample t-test – the Mann-Whitney U/Wilcoxon rank sum test – was used for further statistical analysis. For continuous outcome variables that were found to be normally distributed (i.e., SMI, BMI, age), between-group differences at baseline were examined using the independent two-sample t-test (Daniel & Cross, 2013). For the reliability analyses, agreement between measurements was analyzed by calculating intraclass correlation coefficients (ICCs) using a two-way mixed single measures model with absolute agreement. ICC estimates were rated as poor (< 0.5), moderate (0.5 – 0.75), good (0.75 – 0.9) and excellent (>0.9) (Koo & Li, 2016).
A logistic regression analysis was performed separately for both C3 SMI and T4 SMI (i.e., biomarkers for sarcopenia) to determine if sarcopenia could predict FT placement in OPSCC patients undergoing RT/CRT. Univariable logistic regression analyses were performed with FT placement as the dependent variable and age, sex, treatment, BMI, and C3 as independent/predictor variables for both analyses. Baseline predictor variables were selected based on clinical relevance and our interpretation of evidence-based literature. Variables that yielded statistically significant results in the univariable regression (p < 0.25) were included in the multivariable regression model (Hosmer et al., 2013). A linear regression analysis also was performed separately using both C3 SMI and T4 SMI as the primary independent variable to determine the potential prognostic value of sarcopenia in relation to the duration of FT placement using the same covariates listed for the logistic regression. Assumptions of regression modelling including multicollinearity, homoscedasticity, and distribution of residuals were confirmed prior to conducting analyses.

Freedom from FT placement which was defined as the time from the first MDT meeting to FT placement or last follow-up was assessed using Kaplan-Meier\(^2\) estimates and compared by sarcopenia status (yes vs. no) using the log-rank test. To identify patients with sarcopenia, an optimal SMI cut-off value based on FT placement was determined for both C3 SMI and T4 SMI using a Receiver Operator Characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, and specificity of the cut-off value were provided and an AUC of ≥ 0.70 was considered adequate for assessing the diagnostic capability of SMI (Mandrekar, 2010). Finally,

\(^2\) The Kaplan-Meier statistical method is typically used to determine the probability of post-treatment survival for a given length of time. However, this type of methodology can be applied in any ‘time-to-event’ analysis. In the current study, Kaplan-Meier estimates were used to assess the time between one’s first MDT meeting and FT placement (i.e., freedom from FT placement).
the Youden index, also referred to as Youden’s J statistic for dichotomous data, was used to determine the optimal C3 and T4 SMI cut-off value (Fluss et al., 2005).

**Sample size.** Calculations were made to determine the appropriate sample size for regression analyses to ensure that the current study was adequately powered. Because of the dichotomous nature of the primary outcome measure (i.e., FT placement), we required a minimum of 10 events (i.e., FT placements) per factor or prediction variable. Given that the total number of factors in this investigation was five, a total of 50 events was considered necessary. To determine an appropriate sample size, the incidence rate of FT placement in this population, which was equivalent to 31.1% (Jovanovic et al., 2021), was multiplied by the number of required events and a sample size of 160 was determined to be sufficient.
Results

Baseline Patient and Treatment Characteristics

After preliminary review of the medical records of 1729 consecutive patients who presented to the Head and Neck MDT between January 2013 and October 2017, 194 patients met the inclusion and exclusion criteria. The median age at presentation was 61.0 years (interquartile range [IQR]: 55 - 67) and the majority of patients were male (n = 161; 83.0%). Among all patients and within the NFT group, T2 tumor staging was the most prevalent (n = 84; 43.3%). Within the FT group, most patients had T4 tumor staging. The most common nodal stage was N2 (n = 133; 68.6%), both overall and within each group as well. All patients received intensity modulated radiation therapy (IMRT) with 170 (87.6%) undergoing concurrent CRT treatment. Within this cohort of 194 patients, 60 (30.9%) received either a proactive or a reactive gastrojejunostomy (n = 48), gastrostomy (n = 9), or nasogastric (n = 3) enteral FT. The median duration of FT use (days from date of insertion to removal) was 143 days (IQR: 91-265) with the median timing of placement occurring at 47 days (IQR: 27-63) from the date of the first MDT meeting. Patients with a FT had significantly lower C3 SMI (mean ± standard deviation [SD]: 13.3 ± 2.3 vs. 15.0 ± 3.3, p < 0.001), BMI (mean ± SD: 25.0 ± 4.9 vs. 27.9 ± 5.2, p < 0.001), PSS-HN normalcy of diet (mean ± SD: 71.8 ± 27.8 vs. 82.0 ± 23.8, p = 0.030), and MDADI composite scores (mean ± SD: 82.5 ± 16.3 vs. 87.9 ± 15.2, p = 0.025). Additional information on demographics, tumor characteristics, and treatment type is summarized in Table 1.
Table 1.

Pre-treatment patient demographics and disease characteristics classified by FT status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>FT Group</th>
<th>NFT Group</th>
<th>( p ) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>194</td>
<td>60</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Age in years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR range)</td>
<td>61 (55-67)</td>
<td>63 (55-67)</td>
<td>60 (53-67)</td>
<td>0.284(^e)</td>
</tr>
<tr>
<td>Sex: male, n (%)</td>
<td>161 (83.0)</td>
<td>47 (78.3)</td>
<td>114 (85.1)</td>
<td>0.248(^b)</td>
</tr>
<tr>
<td>T classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 (^b)</td>
</tr>
<tr>
<td>T1</td>
<td>33 (17.0)</td>
<td>8 (13.3)</td>
<td>25 (18.7)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>84 (43.3)</td>
<td>19 (31.7)</td>
<td>65 (48.5)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>40 (20.6)</td>
<td>10 (16.7)</td>
<td>30 (22.4)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>37 (19.1)</td>
<td>23 (38.3)</td>
<td>14 (10.4)</td>
<td></td>
</tr>
<tr>
<td>N classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.861 (^b)</td>
</tr>
<tr>
<td>N0</td>
<td>22 (11.3)</td>
<td>6 (10.0)</td>
<td>16 (11.9)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>24 (12.4)</td>
<td>7 (11.7)</td>
<td>17 (12.7)</td>
<td></td>
</tr>
<tr>
<td>N2a, N2b, N2c</td>
<td>133 (68.6)</td>
<td>41 (68.3)</td>
<td>92 (68.7)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>15 (7.7)</td>
<td>6 (10.0)</td>
<td>9 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.106 (^b)</td>
</tr>
<tr>
<td>RT</td>
<td>24 (12.4)</td>
<td>4 (6.7)</td>
<td>20 (14.9)</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>170 (87.6%)</td>
<td>56 (93.3)</td>
<td>114 (85.1)</td>
<td></td>
</tr>
<tr>
<td>Tumor subsite, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.008(^c)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>98 (50.5)</td>
<td>22 (36.7)</td>
<td>76 (56.7)</td>
<td></td>
</tr>
<tr>
<td>BOT</td>
<td>78 (40.2)</td>
<td>29 (48.3)</td>
<td>49 (36.6)</td>
<td></td>
</tr>
<tr>
<td>Soft palate</td>
<td>3 (1.5)</td>
<td>0 (0.0)</td>
<td>3 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal wall</td>
<td>1 (0.5)</td>
<td>1 (1.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (7.2)</td>
<td>8 (13.3)</td>
<td>6 (4.5)</td>
<td></td>
</tr>
<tr>
<td>HPV status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.718 (^b)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>137 (70.6)</td>
<td>40 (66.7)</td>
<td>97 (72.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 (14.9)</td>
<td>10 (16.7)</td>
<td>19 (14.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 (14.4)</td>
<td>10 (16.7)</td>
<td>18 (13.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline variable, mean ± SD (n)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline value</th>
<th>Baseline value</th>
<th>Baseline value</th>
<th>Statistical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 SMI (cm²/m²)</td>
<td>14.5 ± 3.1 (194)</td>
<td>13.3 ± 2.3 (60)</td>
<td>15.0 ± 3.3 (134)</td>
<td>&lt;0.001&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>T4 SMI (cm²/m²)</td>
<td>51.1 ± 13.4 (187)</td>
<td>45.1 ± 11.5 (58)</td>
<td>53.8 ± 13.3 (129)</td>
<td>&lt;0.001&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 5.3 (194)</td>
<td>25.0 ± 4.9 (60)</td>
<td>27.9 ± 5.2 (134)</td>
<td>&lt;0.001&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>PSS-HN normalcy of diet</td>
<td>79.01 ± 25.4 (172)</td>
<td>71.8 ± 27.8 (50)</td>
<td>82.0 ± 23.8 (122)</td>
<td>0.030&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDADI composite</td>
<td>86.4 ± 15.6 (151)</td>
<td>82.5 ± 16.3 (43)</td>
<td>87.9 ± 15.2 (108)</td>
<td>0.025&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>IQR</sup> interquartile range, <sup>BOT</sup> base of tongue, <sup>HPV</sup> human papillomavirus, <sup>C3 SMI</sup> skeletal muscle index at the third cervical vertebra, <sup>PSS-HN</sup> Performance Status Scale for Head and Neck Cancer, <sup>MDADI</sup> M.D. Anderson Dysphagia Inventory.

<sup>a</sup>Probability (p) value reported from: <sup>b</sup>Pearson’s chi-square test, <sup>c</sup>Fisher’s exact test, <sup>d</sup>Mann-Whitney U/Wilcoxon Rank Sum test, and <sup>e</sup>Independent two-sample t-test.
Reliability Analysis

For inter-observer reliability, ICCs for both C3 SMI (ICC: 0.987, 95% CI: 0.950 – 0.997, p < 0.001) and T4 SMI (ICC: 0.983, 95% CI: 0.935 – 0.996, p < 0.001) measurements were determined to be excellent. ICCs based on intra-observer reliability also were determined to be excellent for C3 SMI (ICC: 0.989, 95% CI: 0.967 – 0.995, p < 0.001) and T4 SMI (ICC: 0.980, 95% CI: 0.955 – 0.997, p < 0.001). Based on this reliability analysis and the high levels of consistency identified for both intra- and inter-rater agreement, these data suggest that the measurement method used is highly replicable.

Predicting FT Placement

As outlined, a logistic regression analysis was performed to ascertain the relationship between radiographically assessed SMM and FT placement. For sarcopenia assessed at the level of C3, significant predictors of FT placement based on univariable analysis were C3 SMI (p = 0.001), CRT Vs. RT (p = 0.060), and BMI (p < 0.001). In the multivariable analysis, only BMI (OR per 1 unit increase: 0.660, 95% CI: 0.437 – 0.998, p = 0.049) remained significant. The multivariable logistic regression model was statistically significant (likelihood ratio test: $x^2[3] = 20.271$, p < 0.001). Based on this assessment, the model explained 14.0% (Nagelkerke $R^2$) of the variance in FT placement and correctly classified 70.1% of cases (concordance = 0.701). Table 2 presents the results for both univariable and multivariable logistic regression analyses for the association between C3 SMI and FT placement.
Table 2.

Logistic regression analysis of predictive factors for FT placement based on C3 SMI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FT Placement (Yes vs. No)</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.016</td>
<td>0.984 – 1.050</td>
<td>0.336</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>0.634</td>
<td>0.292 – 1.379</td>
<td>0.251</td>
</tr>
<tr>
<td>Treatment: CRT vs. RT</td>
<td>3.333</td>
<td>0.951 – 11.686</td>
<td>0.060*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.887</td>
<td>0.829 – 0.949</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>C3 SMI (cm²/m²)</td>
<td>0.828</td>
<td>0.740 – 0.927</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

* Denotes significant p value
For measurements obtained at the level of T4, significant predictors of FT placement based on univariable analysis were T4 SMI (p < 0.001), treatment (p = 0.073), and BMI (p < 0.001). T4 SMI (OR per 1 unit increase: 0.948, 95% CI: 0.912 – 0.984, p = 0.006) and CRT vs. RT (OR per 1 unit increase: 4.591, 95% CI: 1.202 – 17.529, p = 0.026) were the only factors to remain statistically significant in the multivariable analysis. Overall, the multivariable logistic regression model was statistically significant (likelihood ratio test: $\chi^2[3] = 26.360$, p < 0.001), explained 18.5% (Nagelkerke $R^2$) of the variance in FT placement, and correctly classified 71.1% of cases correctly (concordance = 0.701). The results associated with the logistic regression analysis based on the association between T4 SMI and FT placement are presented in Table 3.

**Table 3.**

*Logistic regression analysis of predictive factors for FT placement based on T4 SMI.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>FT Placement (Yes vs. No)</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.018</td>
<td>0.985 – 1.052</td>
</tr>
<tr>
<td>Sex: Male</td>
<td></td>
<td>0.635</td>
<td>0.291 – 1.385</td>
</tr>
<tr>
<td>Treatment: CRT vs. RT</td>
<td></td>
<td>3.167</td>
<td>0.898 – 11.163</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>0.882</td>
<td>0.823 – 0.946</td>
</tr>
<tr>
<td>T4 SMI (cm²/m²)</td>
<td></td>
<td>0.945</td>
<td>0.918 – 0.972</td>
</tr>
</tbody>
</table>

* Denotes significant p value
Predicting Duration of FT Placement

A linear regression analysis was conducted to determine the relationship between SMM and the duration of FT placement for HNC patients undergoing RT/CRT. For SMM measured at the level of C4, age (p = 0.012), BMI (p = 0.040), and C3 SMI (p = 0.033) were identified as significant predictors in univariable analysis. In the multivariable linear regression model, age was identified as the only statistically significant predictor (standardized β = 0.354, standard error = 3.058, p = 0.006). The overall regression also was found to be statistically significant (R² = 0.244, F(3,53) = 5.374, p = 0.003). The results associated with the regression analysis for associations with duration of FT placement are presented in Table 4.

Table 4.
Linear regression analysis of predictive factors for duration of FT placement based on C3 SMI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Duration of FT Placement</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Regression Coefficient</td>
<td>Standard Error</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.341</td>
<td>3.238</td>
</tr>
<tr>
<td>Sex: Male</td>
<td></td>
<td>-0.124</td>
<td>61.776</td>
</tr>
<tr>
<td>Treatment: CRT vs RT</td>
<td></td>
<td>0.098</td>
<td>136.382</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>-0.280</td>
<td>5.294</td>
</tr>
<tr>
<td>C3 SMI (cm²/m²)</td>
<td></td>
<td>-0.291</td>
<td>11.495</td>
</tr>
</tbody>
</table>

* Denotes significant p value
Based on the assessment of sarcopenia at the vertebral level T4, age (p = 0.011), BMI (p = 0.031), and T4 SMI (p = 0.37) were determined to be statistically significant predictors of FT placement duration based on univariable analysis. However, age was the only significant predictor in the multivariable linear regression model (standardized $\beta = 0.374$, standard error = 3.278, p = 0.006). Overall, the multivariable model was statistically significant ($R^2 = 0.241$, $F(3, 51) = 5.076$, p = 0.004). Table 5 presents the results of both univariable and multivariable linear regression analyses with respect to the association between T4 SMI and the duration of FT placement.

Table 5.

* Denotes significant $p$ value
Optimal Sarcopenia Cut-Off Value for C3 SMI

An optimal C3 SMI threshold value was calculated to identify patients with sarcopenia (i.e., low SMM) based on the outcome of FT placement. Results from the ROC analysis of sensitivity, specificity, and AUC associated with the optimal cut-off value are presented in Table 6. The AUC was 0.634 but remained significantly better than chance (AUC = 0.5) (p < 0.001). A ROC curve displaying the diagnostic accuracy for C3 SMI and the occurrence of FT placement is shown in Figure 8.

Table 6.

*ROC curve analysis for C3 SMI cut-off value based on FT placement.*

<table>
<thead>
<tr>
<th>C3 SMI Cut-Off (cm²/m²)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.424</td>
<td>0.933</td>
<td>0.358</td>
<td>0.634</td>
<td>0.556 – 0.712</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Figure 8.

*ROC curve for C3 SMI based on FT placement.*
Based on C3 SMI data, sarcopenia was identified using pre-treatment CT imaging in 141 (72.7%) patients. Among all patients and within both groups (i.e., sarcopenia and nonsarcopenia), T2 tumor staging (n = 84; 43.3%) and N2 nodal staging (n = 133; 68.6%) were most prevalent. Patients with sarcopenia were significantly less likely to be male (77.3% vs. 98.1%, p < 0.001) and significantly more likely to receive a FT (39% vs. 9.4%, p < 0.001) and have lower BMI (mean ± SD: 25.5 ± 4.6 vs. 31.1 ± 4.8, p < 0.001). Additional information on patients stratified based on their sarcopenia status at the C3 vertebral level is reported in Table 7.
Table 7.

Pre-treatment patient demographics and disease characteristics classified by sarcopenia status assessed at the level of C3.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>Sarcopenia</th>
<th>Nonsarcopenia</th>
<th>p value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>194</td>
<td>141</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Age in years: Median (IQR)</td>
<td>61 (55-67)</td>
<td>61 (55-67)</td>
<td>59 (53-66)</td>
<td>0.098$^e$</td>
</tr>
<tr>
<td>Sex: male, n (%)</td>
<td>161 (83.0)</td>
<td>109 (77.3)</td>
<td>52 (98.1)</td>
<td>&lt; 0.001$^b$</td>
</tr>
<tr>
<td>T classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.057$^b$</td>
</tr>
<tr>
<td>T1</td>
<td>33 (17.0)</td>
<td>19 (13.5)</td>
<td>14 (26.4)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>84 (43.3)</td>
<td>60 (42.6)</td>
<td>24 (45.3)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>40 (20.6)</td>
<td>30 (21.3)</td>
<td>10 (18.9)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>37 (19.1)</td>
<td>32 (22.7)</td>
<td>5 (9.4)</td>
<td></td>
</tr>
<tr>
<td>N classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.593$^b$</td>
</tr>
<tr>
<td>N0</td>
<td>22 (11.3)</td>
<td>15 (10.6)</td>
<td>7 (13.2)</td>
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</tr>
<tr>
<td>N1</td>
<td>24 (12.4)</td>
<td>17 (12.1)</td>
<td>7 (13.2)</td>
<td></td>
</tr>
<tr>
<td>N2a, N2b, N2c</td>
<td>133 (68.6)</td>
<td>100 (70.9)</td>
<td>33 (62.3)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>15 (7.7)</td>
<td>9 (6.4)</td>
<td>6 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.392$^b$</td>
</tr>
<tr>
<td>RT</td>
<td>23 (11.9)</td>
<td>15 (10.6)</td>
<td>8 (15.1)</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>171 (88.1)</td>
<td>126 (89.4)</td>
<td>45 (84.9)</td>
<td></td>
</tr>
<tr>
<td>Tumor subsite, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.689$^c$</td>
</tr>
<tr>
<td>Tonsil</td>
<td>98 (50.5)</td>
<td>67 (47.5)</td>
<td>31 (58.5)</td>
<td></td>
</tr>
<tr>
<td>BOT</td>
<td>78 (40.2)</td>
<td>59 (41.8)</td>
<td>19 (35.9)</td>
<td></td>
</tr>
<tr>
<td>Soft palate</td>
<td>3 (1.5)</td>
<td>3 (2.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal wall</td>
<td>1 (0.5)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (7.2)</td>
<td>11 (7.8)</td>
<td>3 (5.7)</td>
<td></td>
</tr>
<tr>
<td>HPV status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.206$^b$</td>
</tr>
<tr>
<td>Positive</td>
<td>137 (70.6)</td>
<td>96 (68.1)</td>
<td>41 (77.4)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>29 (14.9)</td>
<td>25 (17.7)</td>
<td>4 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>28 (14.4)</td>
<td>20 (14.2)</td>
<td>8 (15.1)</td>
<td></td>
</tr>
<tr>
<td>FT placement, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001$^b$</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 (30.9)</td>
<td>134 (69.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>14.5 ± 3.1 (194)</td>
<td>13.0 ± 2.0 (118)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-HN normalcy of diet</td>
<td>81.8 ± 18.4 (194)</td>
<td>77.4 ± 17.2 (118)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDADI composite</td>
<td>79.0 ± 25.4 (172)</td>
<td>76.7 ± 26.3 (102)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55 (39.0)</td>
<td>86 (61.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (9.4)</td>
<td>48 (90.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baseline variable, mean ± SD (n)

BMI (kg/m²): 14.5 ± 3.1 (194) vs. 13.0 ± 2.0 (118), p < 0.001

PSS-HN normalcy of diet: 81.8 ± 18.4 (194) vs. 77.4 ± 17.2 (118), p < 0.001

MDADI composite: 79.0 ± 25.4 (172) vs. 76.7 ± 26.3 (102), p = 0.065

Probability (p) value reported from: aPearson’s chi-square test, bFisher’s exact test, cMann-Whitney U/Wilcoxon Rank Sum test, and dIndependent two-sample t-test
Optimal Sarcopenia Cut-Off Value for T4 SMI

Patients with sarcopenia were also identified using a threshold value based on T4 SMI measurements. The results associated with the ROC curve analysis for T4 SMI are presented in Table 8. An optimal cut-off value of 48.385 cm²/m² was identified with an AUC of 0.638 (p < 0.001). The ROC curve representing the diagnostic accuracy of T4 SMI and the occurrence of FT placement is displayed in Figure 9.

Table 8.

ROC curve analysis for T4 SMI cut-off value based on FT placement.

<table>
<thead>
<tr>
<th>T4 SMI Cut-Off (cm²/m²)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>48.385</td>
<td>0.638</td>
<td>0.682</td>
<td>0.693</td>
<td>0.615 – 0.722</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Figure 9.

ROC curve for T4 SMI based on FT placement.
Based on the ROC curve analysis-derived T4 SMI cut-off value, 78 (41.7%) of patients were identified as having sarcopenia at baseline. Patients determined to have sarcopenia were significantly less likely to be male (66.7% vs. 93.6%, p < 0.001) and HPV-positive (53.8% vs. 84.4%, p <0.001). Individuals classified as sarcopenic were also significantly more likely to be of older age (median: 63 years vs. 59 years, p < 0.001), receive a FT (47.4% vs. 19.3%, p < 0.001), have lower BMI (mean ± SD: 23.6 ± 4.1 vs. 29.2 ± 4.5, p < 0.001), have lower PSS-HN normalcy of diet scores (mean ± SD: 74.0 ± 27.1 vs. 82.9 ± 23.8, p = 0.022), and have lower MDADI composite scores (mean ± SD: 81.3 ± 16.8 vs. 89. ± 4.5, p < 0.001). Table 9 presents additional information on patients classified based on sarcopenia status at the level of T4.
Table 9.
Pre-treatment patient demographics and disease characteristics classified by sarcopenia status assessed at the level of T4.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>Sarcopenia</th>
<th>Nonsarcopenia</th>
<th><em>p</em> value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>187</td>
<td>78</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Age in years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>61 (55-67)</td>
<td>63 (58-70)</td>
<td>59 (53-64)</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex: male, n (%)</td>
<td>154 (82.4)</td>
<td>52 (66.7)</td>
<td>102 (93.6)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>T classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.046&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>T1</td>
<td>33 (17.6)</td>
<td>12 (15.4)</td>
<td>21 (19.3)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>82 (43.9)</td>
<td>28 (35.9)</td>
<td>54 (49.5)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>36 (19.3)</td>
<td>16 (20.5)</td>
<td>20 (18.3)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>36 (19.3)</td>
<td>22 (28.2)</td>
<td>14 (12.8)</td>
<td></td>
</tr>
<tr>
<td>N classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.571&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>N0</td>
<td>21 (11.2)</td>
<td>11 (14.1)</td>
<td>10 (9.2)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>23 (12.3)</td>
<td>11 (14.1)</td>
<td>12 (11.0)</td>
<td></td>
</tr>
<tr>
<td>N2a, N2b, N2c</td>
<td>130 (69.5)</td>
<td>50 (64.1)</td>
<td>80 (73.4)</td>
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</tr>
<tr>
<td>N3</td>
<td>13 (7.0)</td>
<td>6 (7.7)</td>
<td>7 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.401&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>RT</td>
<td>22 (11.8)</td>
<td>11 (14.1)</td>
<td>11 (10.1)</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>165 (88.2)</td>
<td>67 (85.9)</td>
<td>98 (89.9)</td>
<td></td>
</tr>
<tr>
<td>Tumor subsite, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.052&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tonsil</td>
<td>94 (50.3)</td>
<td>37 (47.4)</td>
<td>57 (52.3)</td>
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</tr>
<tr>
<td>BOT</td>
<td>77 (41.2)</td>
<td>29 (37.2)</td>
<td>48 (44.0)</td>
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</tr>
<tr>
<td>Soft palate</td>
<td>3 (1.6)</td>
<td>3 (3.8)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal wall</td>
<td>1 (0.5)</td>
<td>1 (1.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (6.4)</td>
<td>8 (10.3)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>HPV status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Positive</td>
<td>134 (71.7)</td>
<td>42 (53.8)</td>
<td>92 (84.4)</td>
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</tr>
<tr>
<td>Negative</td>
<td>29 (15.5)</td>
<td>22 (28.2)</td>
<td>7 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>24 (12.8)</td>
<td>14 (17.9)</td>
<td>10 (9.2)</td>
<td></td>
</tr>
<tr>
<td>FT placement, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>-----------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>58 (31.0)</td>
<td>37 (47.4)</td>
<td>21 (19.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>129 (69.0)</td>
<td>41 (52.6)</td>
<td>88 (80.7)</td>
<td></td>
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</table>

Baseline variable, mean ± SD (n)

<table>
<thead>
<tr>
<th>Variable</th>
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<th></th>
<th>No</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 ± 5.2 (187)</td>
<td>23.6 ± 4.1 (78)</td>
<td>29.2 ± 4.5 (109)</td>
<td>&lt;0.001e</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-HN normalcy of diet</td>
<td>79.2 ± 25.4 (166)</td>
<td>74.0 ± 27.1 (68)</td>
<td>82.9 ± 23.8 (98)</td>
<td>0.022d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDADI composite</td>
<td>86.5 ± 15.8 (146)</td>
<td>81.3 ± 16.8 (55)</td>
<td>89.6 ± 14.4 (91)</td>
<td>0.002d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aProbability (p) value reported from: bPearson’s chi-square test, cFisher’s exact test, dMann-Whitney U/Wilcoxon Rank Sum test, and eIndependent two-sample t-test*
Freedom from FT Placement

Kaplan-Meier analysis of freedom from FT placement was performed for patients with and without sarcopenia based on the ROC analysis-derived cut-off values for both C3 SMI and T4 SMI. For sarcopenia assessed at the level of C3 (Figure 10), this translated into a significantly worse freedom from FT placement for patients with vs. without sarcopenia (1-year 61.9% vs. 90.6%, log-rank p < 0.001). The median number of days between the first MDT meeting and FT placement was 41.0 (IQR: 34-41) for those identified as having sarcopenia and receiving a FT (54/141) and 48.0 (IQR: 27-64) for individuals without sarcopenia and receiving a FT (5/53), however, this was not significantly different (p = 0.549).

Figure 10.

*Kaplan-Meier survival analysis based on freedom from FT placement in patients with and without sarcopenia assessed at the level of C3.*
For sarcopenia assessed at the level of T4 (Figure 11), patients with sarcopenia had significantly worse freedom from FT placement compared to patients without sarcopenia (1-year 53.9% vs. 80.7%, log-rank p < 0.001). For patients who received a FT, the median number of days between the first MDT meeting and FT placement was 42.0 (IQR: 18-60) for those with sarcopenia vs. 59.0 (IQR: 42-68) for individuals without sarcopenia. The time to FT placement based on sarcopenia status at T4 was significantly different (p = 0.031).

Figure 11.

*Kaplan-Meier survival analysis based on freedom from FT placement in patients with and without sarcopenia assessed at the level of T4.*
Factors Predicting Post-Treatment Sarcopenia

A linear regression analysis to determine the relationship baseline variables and SMM assessed using C3 SMI at three months post-treatment indicated the following. Significant predictors which were identified based on univariable analysis were: sex (p = 0.002), BMI (p = 0.011), and PSS-HN normalcy of diet (p = 0.208). In the multivariable linear regression, only male sex (standardized β = 0.359, standard error = 0.760, p < 0.001) and BMI (standardized β = 0.059, standard error = 0.304, p = 0.004) remained statistically significant. The multivariable linear regression was statistically significant ($R^2 = 0.222$, $F(3,75) = 5.374$, $p < 0.001$). The results associated with the linear regression analysis for predictors of SMM loss at three months are presented in Table 10.

Table 10.

*Linear regression analysis of predictive factors for C3 SMI at three months post-treatment.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>C3 SMI</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Regression Coefficient</td>
<td>Standard Error</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.001</td>
<td>0.038</td>
</tr>
<tr>
<td>Sex: Male</td>
<td></td>
<td>0.342</td>
<td>0.793</td>
</tr>
<tr>
<td>Treatment: CRT vs RT</td>
<td></td>
<td>0.004</td>
<td>1.042</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td></td>
<td>0.285</td>
<td>0.063</td>
</tr>
<tr>
<td>PSS-HN (normalcy of diet)</td>
<td></td>
<td>0.143</td>
<td>0.013</td>
</tr>
<tr>
<td>MDADI (composite)</td>
<td></td>
<td>0.112</td>
<td>0.020</td>
</tr>
</tbody>
</table>

* Denotes significant $p$ value
Discussion

This study was designed to identify the potential relationship between sarcopenia and FT outcomes in the context of HNC and its treatment. Based on our comprehensive review of the literature, the current study is the first to investigate the predictive capabilities of sarcopenia with respect to FT placement in OPSCC patients undergoing RT/CRT treatment. Our results indicate that SMI measured at the level of T4 as a biomarker of sarcopenia was significantly associated with an increased risk for FT placement. Consequently, muscle mass quantity may modify a patient’s risk for FT placement, as a one-unit increase in T4 SMI translates into a 5.2% decrease in the odds of having a FT placed. Moreover, T4 SMI remained significant in multivariable modelling when adjusting for potential covariates, indicating this relationship was not confounded. On the other hand, muscle mass measurements evaluated from routine, pre-treatment CT imaging at the level of C3 were not significantly associated with an increased risk for FT placement based on multivariable logistic regression modelling. This section provides a comprehensive discussion of these data on the basis of sarcopenia and its relationship with FT-related outcomes. As such, the prognostic and clinical significance of both C3 SMI and T4 SMI with respect to FT placement and duration of use will be discussed, followed by the importance of establishing clinically relevant cut-off values for the identification of sarcopenia. The discussion will also focus on the significance of sarcopenia specifically in those undergoing treatment for OPSCC, as well as factors associated with post-treatment SMM loss.

Relationship Between Sarcopenia, BMI, And FT Placement

In some populations, enteral nutrition has proven to be effective in terms of increasing SMM, soft lean mass, and fat-free mass, an outcome that may be attributed to the increased caloric and protein intake facilitated by the use of FTs (Gao et al., 2021; Saka et al., 2022).
Gresham and colleagues (2021) also found that tube feeding improved the capacity of cancer patients with cachexia to maintain weight, lean body mass, and appendicular lean mass. Although enteral FTs can be beneficial in appropriately selected patients, there are considerable risks associated with their placement. For example, Jovanovic and colleagues (2020) found that patients treated for OPSCC who received a FT over the course of treatment had significantly worse swallowing-related QoL at 6 months post-treatment and a reduced ability to maintain a normal diet at 3 months post-treatment.

Although C3 SMI is associated with numerous adverse outcomes and survival in those undergoing treatment for HNC (Bril et al., 2019; Karsten et al., 2019; Wong et al., 2021), its relationship was not significantly associated with FT placement when controlling for BMI. While these findings contradict the current and well-documented prognostic utility of sarcopenia in HNC (Jovanovic et al., 2022), research which does consider the potential confounding effect of BMI also has indicated that BMI may be a better prognostic indicator than sarcopenia for outcomes such as survival and locoregional control (Grossberg et al., 2016).

Because C3 SMI was significant in univariable analysis but not in the multivariable model, it is likely only predictive due to its association with other predictors (Wang et al., 2017). Adjusting for BMI resulted in substantial changes in the estimate of the odds ratio and associated significance, suggesting that the relationship between sarcopenia and FT placement was confounded. Moreover, these results are expected when considering the risk-guided approach to FT placement at our institution. The decision to place a FT is influenced by numerous factors, two of which are low BMI (18 or less) and significant weight loss (more than 5% in one month or more than 10% in six months). These factors in combination with a diagnosis of OPSCC predicate FT placement (Gilbert et al., 2009). In addition, a low BMI is most likely to be highly
correlated with significant weight loss. Consequently, sarcopenia assessed at C3 may have more prognostic utility in a non-OPSCC patient cohort, or in centers that employ a reactive FT placement philosophy.

Although BMI is cheap, relatively easy to calculate and apply, and has well-documented clinical value (Daniels, 2009), it is limited due to its inability to capture information pertaining to muscle mass. Because BMI does not consider one’s muscle mass, individuals with higher amounts of muscle may be considered obese when it would be more accurate to categorize them as normal. On the contrary, an individual’s body composition may be considered ‘normal’ based on their categorization of BMI even if they have low levels of muscle mass. Consequently, the challenges and potential risks these individuals are subject to may be underrecognized in a clinical environment. In addition, BMI also fails to capture information related to body fat percentage and the distribution of fat around different areas of the body. As a result, researchers have suggested that other variables such as waist circumference may be a more useful alternative to BMI (Nuttall, 2015).

The assessment of sarcopenia using imaging at the level of T4 may address the limitations associated with BMI and its inability capture information pertaining to muscle mass. T4 SMI represents a quantifiable, routinely accessible, relatively quick and simple measure that prioritizes muscle mass quantity yet still standardizes measurements for height in a similar manner to BMI. T4 SMI measurements are also relatively closer anatomically to the lumbar region in comparison to C3 SMI and, thus, may be more strongly associated with measures in this region that have a proven and strong association with full body SMM (Swartz et al., 2016). For these reasons, T4 SMI may be less confounded by measures such as BMI and thus may be a more clinically relevant prognostic factor in patients with OPSCC when compared to C3 SMI.
When classified based on FT status (yes vs. no), patients who received a FT had significantly lower C3 and T4 SMI measurements compared to patients without a FT. In addition, patients who were identified as having sarcopenia based on the ROC-analysis derived cut-off values were significantly more likely to receive a FT compared to patients without sarcopenia. We also found that patients with sarcopenia assessed at T4 were significantly more likely to receive a FT earlier and had significantly greater freedom from FT placement at 1-year compared to patients without sarcopenia. In addition, T4 SMI and C3 SMI measurements displayed excellent inter- and intra-rater reliability, indicating conformity between the measurements of different observers and suggesting that these data are reproducible and internally valid. Taken together, these findings highlight the unique pre-treatment status of patients with sarcopenia and suggest that those with excessive SMM loss at baseline may respond differently to treatment compared to patients without sarcopenia. Individuals with OPSCC who present with sarcopenia and have a low BMI may benefit from proactive FT placement.

**Relationship Between Sarcopenia and Duration of FT Placement**

The provision of tube feeding may be necessary in patients at a high-risk for nutritional deficits and weight loss during treatment (Paleri & Patterson, 2010). However, some individuals may become dependent on their FT to sustain caloric intake, leading to disuse atrophy of the swallowing musculature and ultimately increasing the risk for swallowing dysfunction (Hutcheson et al., 2013; Karsten et al., 2019). Moreover, in a retrospective analysis of 62 patients with locally advanced HNC, Friedes et al. (2020) reported a strong association between FT dependency and poor OS. Thus, the ability to discriminate which patients will benefit most from tube feeding may be extremely beneficial in terms of preventing the unnecessary placement of a FT (Madhoun et al., 2011), dependence on tube feeding, and the associated risks.
Results from the current retrospective analysis suggest that age is the only factor associated with the duration of FT placement in this patient population. To our knowledge, there are few studies investigating the prognostic impact of sarcopenia with respect to duration of FT use. Karsten and colleagues (2019) found that sarcopenia assessed at the level of C3 was associated with prolonged FT dependency greater than 90 days based on multivariable regression analysis. However, their regression only accounted for BMI, socioeconomic status, and functional oral intake but did not adjust for potential confounders such as age. Moreover, Karsten et al. (2019) investigated the prognostic impact of sarcopenia in a heterogeneous cohort of HNC patients. Because the treatment and rehabilitation of patients with HNC varies depending on the subsite affected (Stepnick & Gilpin, 2010), the prognostic impact of sarcopenia should be investigated in more homogeneous HNC populations to reflect the specific needs and challenges associated with each HNC subsite. Thus, more high-quality, prospective data pertaining to the association between diminished SMM and duration of FT use in those with OPSCC is needed to determine the true relationship between sarcopenia and FT dependency.

**Sarcopenia Prevalence and Optimal Cut-Off Values**

To facilitate pre-treatment intervention with the intention of minimizing SMM loss over treatment and improving outcomes, there needs to be an accurate, consistent, and replicable process for determining the threshold to identify patients with sarcopenia. However, there is substantial variability in the assessment of sarcopenia and the associated prevalence estimates in those with HNC. Zwart and colleagues (2019) have suggested that approximately one-third to one-half (35.5-54.5%) of HNC patients are affected by sarcopenia, while more recent findings a comprehensive scoping review (Jovanovic et al., 2022) indicate that the prevalence of sarcopenia in HNC is variable with data ranging anywhere from 3.8-78.7%. The variability in sarcopenia
prevalence may be attributed to the variation in inclusion criteria, tumor location, and disease stage of the included studies.

Moreover, inconsistencies related to the cut-off values used to identify patients with sarcopenia may play a large role in the wide-ranging prevalence estimates. Although the majority of available research reporting the prevalence of sarcopenia utilized SMM measurements from abdominal CT scans in the lumbar region (Jovanovic et al., 2022), the variability in cut-off values and associated prevalence estimates is also evident in studies evaluating SMM directly from conventional head and neck imaging using SMI at the level of C3. In a retrospective study of 125 oral squamous cell carcinoma (OSCC) patients, Chang and colleagues (2021) found that 38.4% of their cohort had low SMM when a threshold value of 20.71cm²/m² was used to identify sarcopenia. Ufuk et al. (2019) concluded that SMM measured at C3 exhibited excellent discrimination for sarcopenia and reported a prevalence of 50.3% based on a cut-off value of 9.3cm²/m² in male and 6.3cm²/m² in female HNC patients. Karsten et al. (2019) determined that the prevalence of sarcopenia in HNC patients was 57% based on the C3 SMI cut-off value of 12.7cm²/m². Lastly, although Bozkurt and colleagues (2018) used head and neck imaging at C3 to obtain SMM measurements, no cut-off values were reported and thus no prevalence estimates were obtained. Based on a review of the literature, the studies noted above are currently the only reports to assess the prognostic role of sarcopenia based on C3 SMI measurements obtained on routine head and neck CT imaging. In the current investigation, we found a much higher sarcopenia prevalence of 72.7% based on our ROC curve analysis-derived optimal cut-off value of 16.424cm²/m² for C3 SMI.

Given the relative novelty of SMM measurement at the level of T4 in HNC, studies reporting prevalence estimates, cut-off values and the methodology used to obtain them are
limited. For example, van Heusden et al. (2021) and Sealy et al. (2020) both measured SMM with CT at T4 but used T4 SMI as a continuous variable and thus did not report prevalence estimates or cut-off values. In addition, most of the literature on the measurement of SMM at T4 has been conducted in non-HNC populations (Gronberg et al., 2019; Moon et al., 2016; Van der Kroft et al., 2020) or with automatic muscle segmentation methods such as deep-neural network-based algorithms (Popuri et al., 2016; Dabiri et al., 2019). Evidently, the assessment of sarcopenia is highly dependent on what cut-off values are used to identify patients with this muscle wasting condition. Despite the fact that the majority of studies applied ROC curve analysis to determine cut-off values at C3, the prevalence estimates are uniquely different. This may be attributed to the difference between outcomes used in ROC analyses to determine the diagnostic capability of measurements at C3. For example, Karsten et al. (2019) determined their optimal cut-off value based on the ability of SMI at C3 to predict FT dependency (i.e., FT placement lasting for longer than 90 days). The variability in prevalence may also be attributed to differences in patient cohorts, as some studies investigated sarcopenia in multiple HNC subsites (Ufuk et al., 2019), while some investigated a more homogeneous group of patients, such as those with OSCC (Chang et al., 2021).

We reported a much lower sarcopenia prevalence (41.7%) when applying a T4 SMI cut-off value of based on ROC curve analysis. Our prevalence estimates are based on the discriminative capacity of SMI with respect to FT placement and given the similarities in outcomes applied for ROC curve analysis (i.e., FT outcomes) between the Karsten et al. (2019) paper and ours, the similarity in prevalence (57% vs. 72.7% and 41.7%) was expected. Compared to C3 SMI, T4 SMI had better diagnostic accuracy for determining FT placement and identified sarcopenia in a smaller percentage of patients (41.7% vs. 72.2%). In addition, unlike
C3 SMI, T4 SMI remained significantly associated with FT placement in multivariable analysis. Therefore, it may be accurate to state that T4 SMI is better able to discriminate between patients with and without sarcopenia. Future prospective research should focus on identifying a consistent cut-off value to diagnose sarcopenia at the level of T4. Consensus needs to be achieved on the application of a consistent and clinically meaningful outcome in ROC-curve analysis to determine optimal cut-off values for sarcopenia assessment.

Factors Associated with Post-Treatment Sarcopenia

Our scoping review revealed that 99% of studies (75/76) investigating sarcopenia in HNC measured SMM prior to treatment. Although baseline measures of SMM have utility for determining the prognostic significance of sarcopenia and its association with important clinical outcomes, there should be a concentrated effort to assess post-treatment sarcopenia as well to understand which factors may contribute to SMM loss after treatment. Based on multivariable linear regression modelling, the findings from the current study suggest that BMI and sex are excellent predictors of C3 SMI at three months post-treatment. Despite the value of assessing factors influencing changes in muscle composition, relatively few studies have investigated prognostic factors for post-treatment sarcopenia.

Out of the 28 studies identified in the scoping review that assessed sarcopenia loss after treatment, only 3 investigated potential predictors of muscle loss. Nejatinamini et al. (2018) found that poor vitamin intake status and sex were both significant predictors of post-treatment SMM loss for patients with HNC. In addition, patients with a higher BMI at baseline lost a significant amount of SMM during treatment (Nejatinamini et al., 2018). Kagifuku and colleagues (2020) investigated factors affecting post-treatment reductions in muscle mass using a multivariable regression analysis and found that male sex and higher pre-treatment BMI were
statistically significant predictors of SMM loss. Although McCurdy et al. (2019) measured SMM post-treatment and found that higher energy intakes were correlated with attenuated muscle loss, the analysis was not controlled for measures such as BMI or sex. Thus, there appears to be a clear need for the assessment of sarcopenia at time points other than baseline with an emphasis on determining predictors of post-treatment muscle loss.

Contrary to the findings noted above, the present study determined that higher BMI values were associated with improved muscle mass retention at three months post-treatment. The positive association between BMI and post-treatment SMM retention could be explained by the high proportion of HPV-positive individuals included in our study. When classified based on their T4 SMI sarcopenia status, a significantly higher proportion of HPV-positive patients were identified in the nonsarcopenia group. These individuals are also more likely to present as well-nourished at baseline (Tamaki et al., 2019). Consequently, patients with HPV-positive OPSCC may be less susceptible to experiencing significant muscle loss. Moreover, evidence suggests that increased pre-treatment BMI is associated with improved survival outcomes independent of clinical and pathological indicators. In a retrospective analysis of 441 patients with HNC, Fattouh and colleagues (2018) reported that patients with a high BMI (i.e., those that are overweight or obese) had significantly better OS compared to patients with a ‘normal’ BMI. Similarly, Albergotti et al. (2016) found that patients with a BMI less than 25kg/m² (i.e., individuals considered to be in the ‘normal’ weight range) had significantly shorter overall and disease-specific survival compared to their overweight counterparts. Consequently, it appears as though being overweight (according to BMI) can be a positive factor for those with OPSCC.

Research indicates that the prevalence of sarcopenia is significantly higher among normal-weight adults compared to obese adults (Delmonico et al., 2007). This inverse
relationship is also evident in numerous cancer populations (Martin et al., 2013; Prado et al., 2008). These associations reveal a unique and interesting relationship between BMI and sarcopenia, as a higher pre-treatment BMI appears to be protective against muscle loss. Although obesity is implicated in the development and progression of numerous chronic diseases, these data indicate that obesity may have a positive impact on survival in patients with cancer (Gonzalez et al., 2014). Proponents of this theory suggest that the excess adiposity associated with a high BMI and obesity may convey muscle-sparing effects in individuals undergoing cancer treatment (Gonzalez et al., 2014). In addition, excess fat stores may be beneficial in terms of counteracting the impact of catabolic stress (Flegal et al., 2013), suggesting that individuals with limited or reduced muscle mass may benefit from the energy reserves and muscle-sparing effect of excess adiposity and a higher BMI.

Accordingly, in our homogeneous cohort of OPSCC patients, a higher BMI at baseline may be advantageous in terms of limiting post-treatment muscle loss. This relationship further highlights the benefit of assessing sarcopenia, as special attention should be given to obese patients who also have sarcopenia (i.e., sarcopenic obesity) and thus may have similar survival outcomes compared to 'normal weight' patients with sarcopenia (Fattouh et al., 2019). However, sarcopenia is associated with adverse outcomes in HNC and for that reason BMI alone cannot accurately identify sarcopenia since fluctuations in muscle mass may not result in changes to BMI (Kyle et al., 2005). Therefore, both BMI and SMM loss are critical factors that should be accounted for when considering the unique physiological state of patients and attempting to determine which patients may benefit from pre-treatment intervention or FT placement.

The identification of pre-treatment factors associated with reduced SMM post-treatment also may be a valuable tool for treatment planning. For instance, high-dose IMRT regimens are
intended to target tumor volumes while sparing surrounding organs and tissues. This approach is undertaken in an attempt to reduce the risk for treatment-related toxicities, functional decline, and improve the QoL of patients undergoing treatment (Anderson et al., 2019). However, there is less margin for error when implementing these high-precision modalities. Any deviations from the original treatment plan may result in inaccurate “dosing” of target volumes to tissues at risk, increasing the risk for treatment-related toxicity (Gabani et al., 2019) and reducing the effectiveness of such treatment (Mali, 2016). Anatomical and physiological changes including muscle and/or weight loss could result in such deviations. The identification of prognostic factors for post-treatment SMM loss may lead to the preservation of specific body compositions that are present at baseline during treatment planning. A comprehensive understanding of factors that may result in SMM loss over the course of treatment for those with OPSCC may facilitate pre-treatment intervention to correct for such factors and limit changes in body composition. Thus, doing so may facilitate safe and effective treatment planning by ensuring optimal treatment tolerance and successful administration of de-escalated precision RT. Based on the evidence generated in the current study, female patients with a low BMI should be carefully monitored throughout treatment to limit changes in muscle mass and body composition that may necessitate treatment re-planning.

Limitations

The current investigation has several important limitations that should be noted. First, inherent to the retrospective nature of this investigation, outcome measure data were missing for several patients. Notably, 11.3% (n = 22) of PSS-HN normalcy of diet scores and 21.1% (n = 41) of MDADI composite scores were not available at baseline. The mechanism of “missingness” was assessed using Little’s Missing Completely at Random test, a statistical procedure which
tests the null hypothesis that data are missing completely at random (Li, 2013). This test revealed that data for these outcomes were in fact missing completely at random. Nevertheless, there is still the potential for the missing data to introduce bias into the results.

Second, because this study was conducted at a single tertiary care institution and for a homogeneous group of HNC patients (i.e., those with OPSCC), these results may not be generalizable to all patients with HNC. In our institution, risk-stratification for FT placement may also have biased the data considering that one of the covariates, BMI, was one of the criteria used to determine the need for a FT for individuals undergoing treatment for OPSCC. In addition, while it was found that sarcopenia was not associated with FT dependence, the application of ‘duration of FT placement’ as an outcome may be considered a limitation. That is, the decision to remove a FT may be influenced by variables other than one’s level of oral intake such as a patient’s inability to tolerate tube feeding and/or the potential for complications such as leakage and fistulae (Blumenstein et al., 2014). Thus, the duration of FT placement may not be an ideal indicator of the inability to eat by mouth.

Several additional limitations exist with respect to the measurement of SMM and assessment of sarcopenia. For example, there was a notable difference in quality between planning CT scans collected at baseline and imaging collected post-treatment. Moreover, it was difficult to select a consistent axial slice at C3 across different time points as the images were not consistent in terms of positioning and appearance (i.e., some were relatively thicker vs. thinner axials while others simply looked different for the same patient across time). For some, it was challenging to select an axial image that would satisfy both criteria in the image selection process (i.e., that the entire vertebral arc and the transverse and spinous processes were displayed). Nevertheless, because we found that both C3 SMI and T4 SMI displayed excellent
levels of reliability, these data appear to be consistent. Thus, the limitations associated with SMM measurement on CT imaging may have been mitigated to some degree.

One notable limitation for the assessment of sarcopenia based on thoracic measurements (i.e., T4 SMI) is that no consensus on the procedure for selecting an axial slice for muscle contouring exists. For example, one study described scrolling through axial slices in the caudad to cephalad direction and selecting the first slice that displays the head of both ribs connecting to the vertebral body of the T4 vertebra (Van Heusden et al., 2021). Another study described selecting the middle of the fourth thoracic vertebra as the landmark slice for delineation of musculature (Moon et al., 2019), while others selected the first image in the caudal direction where both vertebral transverse processes were visible (Gronberg et al., 2019). We employed the method used by Van Heusden and colleagues (2021) given that we believed it to be the most transparent, replicable, and accurate strategy for image selection. Moreover, one’s arm positioning during imaging may have an effect on how the pectoralis major and minor muscles are depicted on CT imaging (Van Hesusden et al., 2021), leading to potential inconsistencies in the measurement of SMM at the level of T4. In our retrospective database, arm positioning was not described and therefore a correction could not be applied.

Conclusions

Based on the evidence provided in the current retrospective study, SMM measured on CT imaging at the level of C3 does not appear to be a strong prognostic factor for FT outcomes such as placement and duration of use. Instead, the risk for FT placement may be more accurately determined according to SMM measurements obtained at the T4 level. Due to the significant association between sarcopenia status and FT placement, the fact that patients with sarcopenia are more likely to have a FT placed at one-year post-treatment, and the non-invasive and time-
efficient nature of measures obtained from head and neck CT scans, the routine assessment of both C3 SMI and T4 SMI may be valuable in the context of OPSCC and its treatment.

The detection of sarcopenia at its earliest appearance (i.e., baseline) in addition to other markers of malnutrition (Findlay et al., 2021) could guide decision-making and allow for the communication of vital information regarding the progression of treatment and the necessity for FT placement (Jovanovic et al., 2022). Moreover, post-treatment muscle loss is affected by multiple variables at baseline in patients with OPSCC undergoing RT/CRT. Based on our data, female patients with OPSCC who have a low BMI at baseline are susceptible to reductions in SMM and may benefit from early referral to interventions such as resistance training and cardiovascular exercise. Given its potentially modifiable nature, identifying patients with sarcopenia may indicate the need for pre-treatment interventions to mitigate muscle loss and optimize functional outcomes during treatment. The evidence generated in this investigation highlights the need for evidence-based guidelines to identify and treat sarcopenia, especially in homogeneous cohorts such as those with OPSCC. More evidence is warranted to assess the feasibility and effectiveness of such interventions.
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CHAPTER 4

Discussion

The current program of research is composed of two individual studies that were designed to explore the issue of sarcopenia in HNC. More specifically, the objectives of this research were to: (1) provide an improved understanding of the challenges related to the assessment of this muscle-wasting condition, (2) determine its association with clinical outcomes, and (3) investigate factors associated with post-treatment SMM loss. The first study, a comprehensive scoping review, focused on examining how sarcopenia is defined, which methods of measurement are applied in its evaluation, and how patients are identified with this muscle-wasting condition. For the second investigation, a retrospective cohort study, we sought to investigate the relationship between SMM loss and nutrition-related outcomes for those undergoing RT/CRT for OPSCC. In addition, the purpose of the second study centred on determining the direct relationship of pre-treatment factors with SMM loss after treatment. This chapter offers a comprehensive discussion of the findings based on the collective data gathered from these two investigations. Accordingly, the feasibility and clinical relevance of assessing sarcopenia will be discussed, followed by issues related to FT dependency. The discussion will also include a detailed description of sarcopenia specific to patients with OPSCC. Lastly, clinical implications of the findings and directions for future research will be presented.

Feasibility and Clinical Value of Sarcopenia Assessment

In the literature, inconsistencies related to the definition, measurement, and identification (i.e., cut-off value estimation) of sarcopenia (Cruz-Jentoft et al., 2019) have made it challenging to assess and subsequently mitigate some of the harmful effects of SMM loss (Keller, 2018).
These findings are reflected in the results of our scoping review which highlighted significant heterogeneity in the assessment of sarcopenia in patients undergoing treatment for HNC. Accordingly, the optimal strategy to measure SMM and identify patients with sarcopenia may be contextually driven and dependent on factors such as resource accessibility, patient- and treatment-related characteristics, and the clinical value of biomarkers to represent sarcopenia. In the context of HNC, the most feasible option to detect the presence of sarcopenia may be to measure SMM at the level of C3 on head and neck CT imaging. Measurements obtained C3 are cost-effective, meaningful, and have a proven relationship with adverse outcomes and survival in individuals with HNC (Jung et al., 2019; Ufuk et al., 2019). In addition, a major advantage of using SMM at the C3 vertebral level as an indicator for sarcopenia evolves from the fact these measurements can be obtained directly from head and neck CT imaging.

In the current study (see chapter 3), the relationship between sarcopenia assessed at C3 and clinical outcomes was investigated. First, the feasibility and accessibility of C3 SMI was evident, as measurements were available for 100% of the 194 patients included in our investigation. C3 SMI was also identified as the second most prevalent sarcopenia biomarker identified in studies included in our scoping review (Jovanovic et al., 2022), reflecting a pattern of growth and transition from the traditional lumbar-derived measurements (i.e., L3 SMI). Perhaps more importantly, when classified based on FT status (yes vs. no), patients who received a FT had significantly lower C3 SMI measurements at baseline compared to patients without a FT. In addition, patients who were identified as having sarcopenia based on the C3 SMI ROC analysis-derived cut-off value were significantly more likely to receive a FT compared to patients without sarcopenia. Individuals with sarcopenia assessed at C3 also had significantly worse freedom from FT placement at one-year post-treatment. Finally, the findings from our
univariable logistic regression analysis also suggest that muscle mass quantity measured at the level of C3 may modify a patient’s risk for FT placement, as a one unit increase in C3 SMI was associated with a 17.2% decrease in the odds of receiving a FT.

The accessibility and clinical significance of measurements obtained at the level of C3 as described in the current retrospective cohort study are consistent with findings of previous research (Chang et al., 2021; Jung et al., 2019; Karsten et al., 2019; Swartz et al., 2016; Ufuk et al., 2019). For example, Leger and colleagues (2018) reported that the head and neck CT scans required to measure C3 SMI are routinely available as they are necessary for RT treatment planning and, therefore, are commonly available for the majority of HNC patients. Chang et al. (2021) reported that low C3 SMI was an independent risk factor for both poor disease-free survival and OS in HNC patients undergoing treatment for cancers of the oral cavity. In the current study, we found that the reliability of SMM measurements at the level of C3 was exceptional. When past findings are paired with the results of the current program of research, it may be suggested that C3 SMI is reliable, as well as having a clinically meaningful impact on outcomes relevant to individuals with HNC.

Regardless of the previously stated advantages of SMM assessed at the level of C3 and the fact that that C3 SMI has proven to be an excellent prognostic indicator for FT-related outcomes (Karsten et al., 2019), the findings from the present investigation indicate that the relationship between pre-treatment C3 SMI and nutrition-related outcomes may be confounded. Therefore, these measures may not be ideal for predicting FT placement in OPSCC patients undergoing RT/CRT. Instead, SMM measured at the T4 vertebral level may be more suitable for determining the need for FT placement given its significant association in multivariable logistic regression modelling. However, only two studies reported in the literature were found to have
measured SMM using thoracic imaging (Jovanovic et al., 2022). These findings are not surprising given the relative novelty of sarcopenia assessment in HNC, especially at vertebral levels other than L3 (Swartz et al., 2016). Consequently, more research is needed to establish the clinical and prognostic significance of thoracic imaging at the T4 with an emphasis on comparing these associations with the more anatomically relevant C3 vertebral level.

**Dependence on Tube Feeding**

Despite our data indicating a significant association between sarcopenia and FT placement, we also found that age was the only pre-treatment variable associated with the duration of FT placement in our patient cohort (n = 60). Considering that FT-related outcomes have only been explored in one research investigation (Karsten et al., 2019), important conclusions can be drawn from comparisons between this prior research report and ours. In direct opposition to our findings, Karsten and colleagues (2019) found SMM measured at the C3 level was a significant prognostic factor for prolonged FT dependence based on multivariable regression model. Although Karsten et al. (2019) did not control for patient-related factors such as age and sex in their prediction model, they did include BMI as a covariate. As such, the discrepancy in findings may have two potential explanations: (1) the dichotomization of a FT dependency and (2) the inclusion of a heterogeneous group of HNC patients.

First, because Karsten et al. (2019) defined prolonged FT dependency as a tube in situ for greater than 90 days after FT placement, FT dependency was transformed from a continuous variable into one that is dichotomous. While converting FT dependency into a dichotomous outcome may simplify statistical analysis and lead to results that are relatively simple to interpret (Altman & Royston, 2006), there are important limitations to consider. The dichotomization of a variable typically results in the loss of information, meaning that the statistical power to detect a
relationship between said variable and an outcome of interest is reduced (MacCallum et al., 2002). Consequently, converting the duration of FT placement to a dichotomous variable (i.e., either less than or greater than 90 days) may increase the risk of a type I error and lead to false positive results (Austin & Brunner, 2004). Because Karsten and colleagues (2019) already had a sample size of 128 patients, their significant results may be explained by this phenomenon. Consequently, their approach may have resulted in the underestimation of the extent of variation in outcomes between the two groups of interest, such as the risk of an event occurring. In this case the event is FT dependence. In essence, individuals who are close to the cut-off of 90 days but on opposite sides are characterized as being different but may in fact be more similar statistically (MacCallum et al., 2002). In our study, FT dependency was assessed as a continuous variable, offering a potential explanation for the insignificant relationship between both C3 SMI and T4 SMI and the duration of FT placement.

Although the statistical limitations stated above provide a methodologically-based explanation for the differences in results between our study and the one conducted by Karsten and colleagues (2019), another explanation may be related to the characteristics of the population of interest. Despite the fact that oropharyngeal cancer was the most frequently represented HNC subsite according to results from the scoping review, very few studies have investigated this population without including a heterogeneous group of patients including multiple subsites. The paper by Karsten et al. (2019) is no exception, as patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx were included in their investigation. Consequently, their findings may not be applicable to a homogeneous sample of OPSCC patients. For this reason, the investigation of sarcopenia specifically in OPPSC using data from routinely obtained head and neck CT imaging, both at the level of C3 and T4, is warranted.
**Sarcopenia in OPSCC**

Few studies have investigated the impact of sarcopenia measured at C3 and T4, with even fewer using a homogeneous cohort of individuals with OPSCC (Jovanovic et al., 2022). Karsten and colleagues (2022) investigated the role of pre-treatment sarcopenia in OPSCC patients in relation to swallowing function, mouth opening, and speech and found that 45% (n = 49) of their patient cohort exhibited sarcopenia. Although patients with sarcopenia were more often female, had a lower BMI and a modified diet at baseline, and were identified as exhibiting poorer swallowing-related QoL compared to patients without pre-treatment sarcopenia, no multivariable regression analysis was performed to control for factors such as BMI. Moreover, out of the 248 patients included in their study, sarcopenia-related associations were only performed with 99 patients, as many were excluded from analysis due to the “missingness” of data. Although Karsten and colleagues (2022) utilized head and neck imaging at C3 to measure SMM, these measurements were converted to lumbar estimates using the previously mentioned algorithm developed by Swartz et al. (2016). Olson et al. (2020) also investigated sarcopenia in OPSCC and found that SMM measured at L3 had a negative association with OS in patients treated with either surgical resection or definitive RT. One noteworthy observation from that work is the fact that patients were required to have undergone whole-body PET-CT imaging or abdominal scans to be considered for inclusion. Given that whole-body imaging (i.e., PET-CT) is mainly performed in HNC patients thought to be at high risk for distant metastasis or in those identified as having advanced-stage disease (Fattouh et al., 2019), these individuals were likely to have relatively poor survival outcomes. Thus, this method of measurement may have resulted in selection bias. Tamaki et al. (2019) also found that in patients with advanced oropharyngeal cancer, sarcopenia was a significant prognostic factor for OS. Once again, PET-CT imaging at
the level of L3 was used to obtain SMM measurements, leading to the potential for selection bias and weakening the internal validity of results. In our study, patients with sarcopenia were significantly less likely to be male and were more likely to have a lower BMI at baseline compared to those without sarcopenia. Given the differences in treatment between patients with difference HNC subsites (Stepnick & Gilpin, 2010), more evidence pertaining to the relationship between sarcopenia and clinical outcomes is necessary to determine the true impact of sarcopenia in patients with OPSCC.

Clinical Implications and Directions for Future Research

**Potential for intervention and pre-treatment optimization of outcomes.** It is well-established that patients undergoing treatment for HNC often experience difficulties with swallowing and a subsequent reduction in oral intake (Jovanovic et al., 2021). Factors including pain associated with treatment-related toxicities (e.g., mucositis) and/or dependence on tube feeding lead to a reduction in the regular restrictive load and often result in a decrease in muscle fibre size, or muscle atrophy (Kasper et al., 2002). Progressively, atrophy arising as a consequence of swallowing muscle disuse leads to irregular motor control, increased muscular fatigue, and a reduction in muscle strength (Hutcheson et al., 2013). Thus, it is likely that disuse atrophy plays a significant role in the development of swallowing muscle impairment (Pauloski et al., 2011). Data also indicate that the maintenance of oral intake and swallowing exercise adherence can improve long-term swallowing function. Consequently, clinicians have adopted a “use it or lose it” approach to treatment and rehabilitation, emphasizing the importance of maintaining oral intake and strengthening the muscles necessary for the swallowing mechanism (Hutcheson et al., 2013).
Despite the potential benefits of utilizing swallowing exercises to prevent disuse atrophy of the swallowing musculature, this intervention does not address the impairments associated with sarcopenia. Sarcopenia is a systemic process that affects all muscles in the body, including those involved in swallowing (Cruz-Jentoft et al., 2019). Thus, while localized hypertrophy of swallowing musculature may improve swallowing function, sarcopenia can lead to swallowing difficulties and an increased risk for adverse outcomes such as aspiration pneumonia (Endo et al., 2021). Therefore, it is important to address both localized muscle hypertrophy and sarcopenia in the management of HNC. Considering that the physiological and functional changes associated with sarcopenia, namely a decline in SMM and muscle strength, are potentially modifiable, the present findings have direct therapeutic/intervention implications. Based on a review of the literature, current research findings suggest that in individuals with cancer, pre-treatment optimization of functional status may assist in improving functional outcomes (Bade et al., 2015; Payne et al., 2013). It is clear that there is an abundance of evidence to suggest that both resistance training and aerobic exercise can have a positive impact on muscle mass and strength, physical functioning, and lead to a reduction in cancer-related fatigue, anxiety, and weight loss (Fong et al., 2012; Speck et al., 2010). Additionally, the composite benefits of these types of changes will most likely also serve to positively impact QoL and well-being. Lonbro et al. (2013) evaluated the impact of progressive resistance training in those undergoing HNC treatment and found that interventions of this type resulted in a significant increase in muscle strength and improved lean body mass by 4.2%.

Thus, although the development of sarcopenia is primarily influenced by genetic and lifestyle factors which can accelerate muscle weakening and progression towards functional impairment and disability, nutrition and exercise training interventions have the potential to
slow, or in some instances even reverse these outcomes (Bloom et al., 2018). Therefore, in addition to exercise regimens prescribed to prevent disuse atrophy in the swallowing musculature and maintain swallow function (Greco et al., 2018; Kraaijenga et al., 2017), whole-body exercise interventions should be considered for this patient population. In fact, it is conceivable that in OPSCC, a disease which portends significant risks for weight/muscle loss and swallowing impairment, a two-pronged approach using exercise to limit both whole-body SMM loss and swallowing muscle atrophy may lead to improved swallowing and nutritional outcomes.

**The importance of timing in the assessment of sarcopenia.** Despite the potential for nutritional and exercise-based interventions to limit muscle loss and facilitate pre-treatment optimization of functional status, the present explorations found that the majority of studies investigating sarcopenia in HNC are of a prognostic research design and primarily focused on exploring the predictive value of changes in SMM (Jovanovic et al., 2022). That is, sarcopenia is commonly only measured at baseline to investigate its prognostic significance with respect to clinical outcomes. Moreover, results from the scoping review (Chapter 2) indicate that data on the timing of sarcopenia assessment is limited. One significant limitation with the study of sarcopenia in HNC is that SMM measurements during and after treatment are often unavailable. Therefore, one strategy to improve upon sarcopenia research in this population would be to place more of an emphasis on investigating changes in SMM over the course of treatment.

To address these limitations, the assessment of sarcopenia should occur at multiple time points before, during, and after treatment. In the present investigation, sarcopenia was assessed post-treatment and predictors of SMM loss were investigated. However, CT imaging data at time points during treatment were unavailable in our database. To understand the true impact of treatment on muscle loss and to subsequently provide support, changes in muscle quantity over
the course of treatment should be investigated. For example, Leger and colleagues (2019) found that data from CT scans gathered during the second week of treatment improved risk modelling for locoregional tumor control. Assessing sarcopenia over the course of treatment at multiple points in time may support researchers in determining the optimal point in time where they may need support and can also help in determining the feasibility and impact of interventions over the course of treatment. Considering that the current retrospective cohort study reported a significant association between BMI and post-treatment muscle loss, our data support the notion that pre-treatment optimization of outcomes is possible.

Conducting the assessment of sarcopenia both before and after treatment may offer valuable insight into the impact of treatment on muscle loss. Moreover, undiagnosed post-treatment sarcopenia could contribute to the severity or significance of late effects of treatment. However, one potential limitation of using C3 SMI as an outcome of interest is that post-radiotherapeutic treatment effects may influence these measurements considering the anatomical location of musculature being delineated (i.e., in the head and neck). Radiation is known to have a negative impact on the activation, proliferation, and differentiation of muscle cells (Jurdana et al., 2013). Thus, changes in muscle composition observed post-RT may be due to the effect of radiation and may not accurately correspond to systemic muscle loss. Measurements obtained at the level of T4 could serve as a useful alternative as they are not directly impacted by radiation or surgery in HNC patients. However, due to the retrospective design of the current investigation, SMM measurements at the level of T4 could not be conducted at post-treatment time points. Thus, we could not identify potential predictors of muscle mass measured using T4 SMI. Ideally, future prospective research should aim to assess sarcopenia using PET-CT imaging in all patients to allow for the comparison of SMM at multiple vertebral levels (e.g., C3 vs. T4
vs. L3) and to effectively investigate how one’s muscle mass changes over the course of treatment. However, given the myriad challenges in acquiring (serial) PET-CT imaging, it is possible that thoracic CT imaging (as used in standard practice to monitor disease response and metastatic progression) may be more feasible.

Based on the findings of the current program of research, if a patient has a low BMI and has been assessed to have low T4 SMI, pre-treatment optimization of one’s physical condition (i.e., improvements in muscle strength and function) could be considered to limit or delay the need for FT placement. Even if intervention does not fully mitigate skeletal muscle loss, postponing FT placement may still result in a reduction in the chance of FT dependency (Karsten et al., 2019). Because of this concern, the current information suggests that this dilemma is deserving of future investigation. Large-scale, prospective, randomized trials should be conducted to investigate the potential feasibility and utility of implementing regular nutritional and exercise interventions for the prevention and/or mitigation of sarcopenia. Special attention always should be given to the timeframe needed to achieve satisfactory results in order to determine whether or not such interventions are feasible and of benefit prior to and during treatment. Another important consideration is the capability of patients to continue exercise-based regimens during treatment, and what factors may influence their ability to do so. However, one must also be flexible in the structural approach to such interventions as to be adaptable to individual needs and limitations relative to participation in such activities.

**Decision making in OPSCC.** For individuals with early-stage OPSCC, selecting the most appropriate treatment can be challenging. Current guidelines recommend an array of treatment options, including primary surgery with potential adjuvant therapy, definitive RT, concurrent CRT, or induction chemotherapy and RT (Olson et al., 2020). The treatment of
OPSCC is further complicated by the fact that the landscape of surgical management for OPSCC is in a state of transition to identify better approaches that address unique profiles of each patient. Modalities such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) have been gaining significant interest in being used as the up-front treatments for early stage OPSCC (Nichols, Fung, et al., 2013). Researchers have found that these relatively new surgical techniques may lead to similar oncologic and survival outcomes for patients with OPSCC when compared to organ sparing treatments such as (C)RT, while ongoing trials are attempting to determine whether any differences exist with respect to functional outcomes (Monnier & Simon, 2015; Nichols et al., 2013; Yeh et al., 2015).

Given the changing nature of treatment for OPSCC and the extensive range of potential treatment options, the process of deciding which treatment will be optimal for each individual patient is difficult. Accordingly, the detection of clinically meaningful prognostic factors may facilitate risk-stratification and the identification of patients at-risk for poor outcomes, allowing researchers and clinicians to differentiate between which patients would benefit from these varied treatment modalities. The end result of such an approach may lead to a situation where both the patient and their multidisciplinary team are equipped with essential information about disease progression and prognosis, allowing for more informed shared decision-making and personalized healthcare (Jovanovic et al., 2022).

Conclusions

Patients undergoing treatment for HNC commonly experience tumor- and treatment-related difficulties which may lead to malnutrition and diminished SMM during and after treatment (Jovanovic et al., 2022). Thus, the prognostic significance of sarcopenia always should be evaluated to guide decision-making and to allow for the communication of vital information
regarding the progression of treatment in order to establish expectations. However, determining
the true impact of sarcopenia in HNC is challenging given the lack of methodological consensus
related to the definition, measurement, and cut-off values used to classify patients with this
muscle-wasting condition. Research identifying the most appropriate measurement techniques
and cut-off values specific to patients with OPCC based on a consistent method and relevant
outcomes is warranted. The present work has provided an important and insightful approach to
the assessment of sarcopenia in HNC and the potential impact this may have on individuals with
OPSCC.

Based on our review of the literature, the current study demonstrated for the first time
that pre-treatment sarcopenia assessed using T4 SMI directly from head and neck imaging may
accurately predict the placement of an enteral FT in patients receiving RT/CRT for OPSCC.
Compared to measures at the level of C3, the evidence provided herein support the
interpretations that T4 SMM measurements displayed better diagnostic accuracy for determining
the need for FT placement and were more strongly associated with time to FT placement. The
results of this study suggest that we should closely monitor OPSCC patients with low SMM
assessed at T4 on CT imaging to ensure optimization of nutritional status and to assess the need
for proactive nutritional and/or exercise intervention. Ultimately, the findings of the present
study provide insights into how an enhanced understanding of sarcopenia can facilitate the
inclusion of accessible information and promote improved patient care. This information may
also allow those who provide care to carefully monitor factors that may have a direct benefit on
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imaging during treatment improves radiomic models for patients with locally advanced
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https://doi.org/10.1007/s11864-015-0362-4


https://doi.org/10.1186/1471-2407-13-133


APPENDICES

Appendix A: Search Strategy for MEDLINE

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<td>1    Sarcopenia.tw. or Sarcopenia/ or Muscular Atrophy/ or Muscle, Skeletal/</td>
</tr>
<tr>
<td>2    Muscular Atrophy.tw.</td>
</tr>
<tr>
<td>3    skeletal muscle.tw.</td>
</tr>
<tr>
<td>4    muscle mass.tw.</td>
</tr>
<tr>
<td>5    skeletal muscle index.tw.</td>
</tr>
<tr>
<td>6    1 or 2 or 3 or 4 or 5</td>
</tr>
<tr>
<td><strong>Head and Neck Cancer</strong></td>
</tr>
<tr>
<td>7    &quot;head and neck neoplasms&quot;.mp. or exp &quot;Head and Neck Neoplasms&quot;/</td>
</tr>
<tr>
<td>8    &quot;head and neck squamous cell carcinoma&quot;.tw.</td>
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<td>9    7 or 8</td>
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<td>10   6 and 9</td>
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## Appendix B: Data extraction form

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<tr>
<td>Title</td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td></td>
</tr>
<tr>
<td>Year of publication</td>
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<tr>
<td>Country of origin</td>
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<tr>
<td>Aims/purpose</td>
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</tr>
<tr>
<td>Outcome measures</td>
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<tr>
<td>Sample size</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex (% of sample)</td>
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<td>Cancer subsite</td>
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<td>Cancer type (e.g., primary, recurrent, or metastatic.)</td>
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<tr>
<td>Clinical or pathological staging (% of sample)</td>
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</tr>
<tr>
<td>Treatment type</td>
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</tr>
<tr>
<td>Patients with sarcopenia (% of sample)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant Details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
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</tbody>
</table>

| Summary findings |  |

## Concept Details Extracted from Source of Evidence

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<tr>
<td>Sarcopenia cut-off value(s) and reasoning</td>
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</tr>
<tr>
<td>Measurement technique</td>
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</tr>
<tr>
<td>Measurement instrument</td>
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</tr>
<tr>
<td>Location of measurement</td>
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</tr>
<tr>
<td>Muscles examined</td>
<td></td>
</tr>
<tr>
<td>Software and individual measuring</td>
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</tr>
<tr>
<td>Reliability analysis (yes/no)</td>
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</tr>
<tr>
<td>Outcome (i.e., mathematical definition)</td>
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<tr>
<td>Timing of measurement</td>
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### Appendix C: Summary of included articles

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<th><strong>Country of origin</strong></th>
<th><strong>Aims/purpose</strong></th>
<th><strong>Outcome measures</strong></th>
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</thead>
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<tr>
<td><strong>Year of publication</strong></td>
<td>2016 (4), 2017 (4), 2018 (6), 2019 (19), 2020 (21), 2021 (22)</td>
<td>Netherlands (18), USA (14), Japan (11), Taiwan (7), China (7), South Korea – Republic of Korea (5), Canada (3), Turkey (3), France (2), Italy (2), Finland (1), Australia (1), India (1), Brazil (1)</td>
<td>To determine incidence/prevalence of sarcopenia (4) To investigate optimal level of variables to diagnose sarcopenia (1) To determine the prognostic/risk impact of sarcopenia/SMM (62) To determine association between outcomes/intervention (e.g., treatment type) and sarcopenia/SMM (8) To compare body composition before and after treatment (5) To compare lean body mass loss in different body regions (1) To assess the robustness of C3-assessed sarcopenia in terms of interobserver agreement (1) To determine whether sarcopenia/SMM can be assessed on neck MRI (1) To correlate SMM assessed on neck CT with abdominal imaging (1) To correlate masticatory SMI with L3 SMI (1) To assess the relationship between cervical PVM values and L3 SMI (1) To compare precision error in DEXA body composition scans before and after treatment (1) To determine if one of more height-weight formula(e) can be used clinically as a surrogate for CT-based imaging assessment of body composition before and after treatment (1) To detail techniques for collecting, processing of CT, validating data, and data de-identification and transfer (1)</td>
<td><strong>Independent:</strong> Sarcopenia/SMM (61) Lean body mass (1) Sarcopenic obesity (1) Obesity (1) Fat mass (2) Fat-free mass (1) Cachexia (2)</td>
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</table>
Weight loss (1)
Hypoluminaemia (1)
HPV/p16 status (1)
TNM stage (1)
Plasma EBV-DNA (1)
Myosteatosis (1)
Tumor site (1)
Comorbidities (2)
Strength training intervention (1)
Preventative rehabilitation program (1)
Nutritional program (1)
Intramuscular adipose tissue content (2)
Subcutaneous adipose tissue (2)
Visceral adipose tissue (1)
Three common lean body mass (LBM) formulae (1)
Nutritional status (5)
Dietary intake (1)
Systemic inflammation (3)
Monocyte to lymphocyte ratio -MLR (1)
Dysphagia (1)
Treatment type (2)

**Dependent:**

**Body composition (13)**

**QoL (1)**

**Nutrition-related (3)**

Intervention feasibility (1)
Locoregional control (1)
Biochemical markers (1)
Inflammation (2)
Postoperative delirium (1)

**Complications and treatment-related toxicity (29)**

**Interruptions to treatment (3)**

Length of hospital stay (1)
Unplanned hospital admissions (1)
Healthcare costs (1)
Blood transfusions (1)
Frailty (4)
Discharge disposition (1)
Inter-observer agreement of C3-assessed sarcopenia (1)
Precision error in DEXA composition scans (1)
Correlation between C3 and L3 SMM (1)
Correlation between masticatory SMI and L3 SMI (1)
Correlation between PVM and SCM areas at C2, C3, and C4 (1)

**Survival (68)**

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<td>Sex (male, %)</td>
<td>45 (18-84), 45 (18-84), 45.7 (23-69), 46 (18-79), 51 (45-58), 51.4 (11.39), 52 (9), 52.67 (14.13), 53.4 (8.3), 54.5 (9.4), 55 (12), 55.4 (1.5), 55.9 (8.8), 56.5 (0.2), 56.8 (7.3), 57.21 (9.78), 57.8 (10.8), 57.9 (10.3), 58.5 (12.8), 58.6 (8), 59 (7), 59 (18-94), 59.37 (8.4), 59.4 (13), 59.6 (13.9), 59.66 (9.12), 60, 60 (10), 60 (12), 60, 19-88, 60.3 (10.8), 60.3 (11.2), 60.3 (11.2), 60.4 (11.7), 60.4 (13.7), 61, 61 (11.6), 61 (61-64), 61.1 (11), 61.13 (9.04), 61.7 (10.9), 61.9 (10.5), 62.17 (7.22), 62.2 (12.1), 62.3 (7.8), 62.3 (10), 63 (9), 63 (39-81), 63.6 (9.6), 64 (33-70), 64 (56-73), 64.2 (8.3), 64.2 (10.2), 63.2, 63.5 (12.91), 64 (10), 64 (56-73), 64.7 (9.1), 65, 65 (43-85), 65 (58-74), 66.5 (45-81), 66.51 (12.5), 66.8 (11.6), 68 (59-77), 68 (60-76), 70.3 (7.26), 71.9 (5.1), 72 (41-92), 72.4 (7.1), 73.2, 81.5 (6.5), 81.73 (6.24) N/A (2)</td>
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<td>Cancer subsite Majority?</td>
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<td>Cancer type (e.g., primary, recurrent, or metastatic.)</td>
<td>Primary (67) Primary and recurrent (5) Primary, recurrent, and second primary (2) Primary and persistence/relapse (1) Relapse (1) Second primary (1)</td>
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<td>Clinical or pathological staging Majority?</td>
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<tr>
<td>Treatment type Majority?</td>
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<tr>
<td>--------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Patients with sarcopenia (% of sample)</td>
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<tr>
<td>Study design</td>
<td><strong>Observational</strong> Retrospective review (56), Prospective, cohort (10), Prospective, longitudinal (6), Prospective, cross-sectional (1), Prospective, survey (1) <strong>Interventional</strong> Randomized controlled trial (1)</td>
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<tr>
<td>Summary findings (significant association vs. no association)</td>
<td>Significant association/predictor (62) Non-significant association/predictor (3) Excellent interobserver agreement (1) Significant – correlation between masticatory SMI and L3 SMI (1) Significant – C2 SMI, C3 SMI, C4 SMI, and SCM SMI values can be used as alternatives for the diagnosis of sarcopenia Significant – SMM at C3 appears to be a good alternative to L3 Significant – high prevalence/incidence (3) Significant – CSA measurements on CT and 1.5-T and 3-T MRI neck scans at the C3 level can be used interchangeably (1) Non-significant – height-weight formulae with respect to CT-based measurements (1) Non-significant – DEXA precision error did not change (1) Body composition was significantly reduced from pre- to post-treatment (3)</td>
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**Concept Details Extracted from Source of Evidence**

<table>
<thead>
<tr>
<th>SMM depletion with or without fat loss (1)</th>
<th>Low SMM relative to healthy individuals (1)</th>
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<tbody>
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<td>Presence of low muscle quality or quantity (1)</td>
<td>Muscle-wasting condition (2)</td>
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<td>Geriatric syndrome characterized by the age-related loss of muscle mass and/or muscle function or decreased physical status (1)</td>
<td>Age-related loss of SMM (1)</td>
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<tr>
<td>Body composition metric associated with poor oncological outcomes</td>
<td>Age-related loss of SMM and strength (1)</td>
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<tr>
<td>N/A (12)</td>
<td>Age-related loss of SMM, strength, and physical performance (1)</td>
</tr>
<tr>
<td></td>
<td>Age-related, generalized, and progressive loss of SMM, muscle strength, and physical performance (1)</td>
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**Sarcopenia cut-off value(s)**

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<tr>
<th>Value</th>
<th>Population</th>
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</thead>
<tbody>
<tr>
<td>SMM</td>
<td>&lt; 55 cm²/m² for males and &lt; 39 cm²/m² for females (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 52.4 cm²/m² for men; &lt; 38.5 cm²/m² for women (13)</td>
</tr>
<tr>
<td></td>
<td>&lt; 51.74 cm²/m² for males and &lt; 34.30 cm²/m² for females (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 49 cm³/m² in men and &lt; 31 cm³/m² in women (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 42.4 cm²/m² (men) and &lt; 30.6 cm²/m² (women) (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 42.4 cm²/m² for men and &lt; 36.2 cm²/m² for women (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 41.6 cm²/m² for males and &lt; 32.0 cm²/m² for females (2)</td>
</tr>
<tr>
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<td>&lt; 40.8 cm²/m² for males and &lt; 34.9 cm²/m² for females (2)</td>
</tr>
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<td>&lt; 36.16 cm²/m² for males and &lt; 21.02 cm²/m² in females (1)</td>
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<tr>
<td></td>
<td>&lt; 36.02 cm²/m² for males, &lt; 31.76 cm²/m² in females (2)</td>
</tr>
<tr>
<td></td>
<td>&lt; 22.00 cm²/m² for men and &lt; 18.61 cm²/m² for women (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 21.99 cm²/m² in men and &lt; 18.60 cm²/m² in women (1)</td>
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<tr>
<td></td>
<td>&lt; 7.26 kg/m² for men and &lt; 5.45 kg/m² in women – using DEXA (1)</td>
</tr>
<tr>
<td></td>
<td>7.0 kg/m²(2) for men and 5.7 kg/m²(2) for women – using BIA (1)</td>
</tr>
<tr>
<td></td>
<td>Less than 605.77 cm³ and 445.42 cm³ for males and females (1)</td>
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<tr>
<td></td>
<td>&lt; 47.5 cm²/m² (1)</td>
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<tr>
<td></td>
<td>≤ 46.6 cm³/m² (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 45.2 cm²/m² (1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 43.2 cm²/m² (11)</td>
</tr>
</tbody>
</table>
< 39.7 cm²/m² (1)
<36.02 cm²/m² (1)
< 20.71 cm²/m² (1)
<18.82 cm²/m² (1)
<12.7 cm²/m² – neck SMI (1)
<12.3 cm²/m² (1)
≤ 0.97 cm² – rectus femoris (1)
<43 cm²/m² for underweight and normal weight males, <41 cm²/m² for overweight males and
<41 cm²/m² for females in all BMI categories (1)
<52 cm²/m² for men and <38 cm²/m² for women
for patients with BMI <30 kg/m², <54 cm²/m² or
men and < 47 cm²/m² in women for patients with
BMI >30 kg/m² (1)
<43 cm²/m² for males with BMI <25, and
<53 cm²/m² for males with BMI <25,
<41 cm²/m² for females regardless of BMI (2)
≥8.87 kg/m² for adults and ≥10.76 kg/m² for the
elderly - BIA (1)
<6.05 for males and <5.097 for females – AUC
using PET-CT (1)
<6.1 kg/m² – AUC using DEXA (1)
< 10th percentile (1)
N/A – used as continuous variable (14)
N/A – investigated interobserver agreement (1)
N/A – investigated correlation between C3 and
L3 (1)
N/A – used DEXA-derived lean body mass to
determine precision error (1)

**Muscle Strength/Function**

*Handgrip strength*

28 kg/m² (1)

< 30 kg for men and < 20 kg for women (2)

<27 kg for men, and < 16 kg for women (2)

<26 kg for men and <18 kg for women (1)

NA – used as continuous variable (1)

**Physical performance**

*Timed up and go test (TUG)*

Values over 10 seconds (up to 60 years), 8.1
seconds (60–69 years), 9.2 seconds (70–79 years)
and 11.3 seconds (80–99 years) characterised
impaired mobility (1)

*Gait speed*

<1 m/s (1)

<0.8 m/s (2)

N/A – used as continuous variable (1)

**Sarcopenia**

SARC-F scores ≥4 (1)

Sarcopenia cut-off value(s) REASONING

**SMM**

*Based on previously published cut-off values*

Prado et al. 2008 (11)
Go et al. 2016 – Korean patients using DEXA (1)
Van der Werf et al. 2018 (2)
Wendrich et al. 2017 (10)
Baracos et al. 2010 (1)
Makiguchi et al. 2019 (2)
Shen et al. 2004 (1)
Martin et al. 2013 (3)
Fearon et al. 2011 (1)
Zhuang et al. 2016 (2)
Mourtzakis et al. 2008 (1)
Jansen et al. 1985 (1)
Based on which values performed the best discriminatory ability (1)
Based on lowest gender-specific quartile (2)
Based on the EWGSOP and Foundation for the National Institute of Health criterion (1)
Based on AWGS algorithm (1)
Based on presence of chemotherapy dose-limiting toxicity – lowest log-likelihood value (2)
Based on median values (1)
Based on values below the 10th percentile (1)
Optimal stratification (1)
ROC curve analysis (13)
Lowest log-likelihood (1)

**Muscle Strength/Function**
Based on the EWGSOP and Foundation for the National Institute of Health criterion (2)
Based on AWGS algorithm (1)
Cruz-Jentoft et al. 2010 (1)
Cruz-Jentoft et al. 2019 (2)

**Physical Performance**
Based on the EWGSOP and Foundation for the National Institute of Health criterion (2)
Based on AWGS algorithm (1)
Cruz-Jentoft et al. 2010 (1)

**Sarcopenia (SARC-F)**
Malstrom et al. 2016 (1)

<table>
<thead>
<tr>
<th>Measurement technique</th>
<th>Measurement instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMM</strong></td>
<td></td>
</tr>
<tr>
<td>CT (49), PET-CT (25), MRI (10), BIA (4), DEXA (4), B-mode ultrasonography (2), Harpenden skinfold caliper (2), non-stretchable tape measure (1) OMRON Karada Scan Hbf 375 Body Composition Monitor (1), N/A (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle Strength/Function</strong></td>
<td></td>
</tr>
<tr>
<td>Jamar hydraulic handheld dynamometer (5), Saehan® dynamometer (1), Digital dynamometer (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Physical performance</strong></td>
<td></td>
</tr>
<tr>
<td>Stopwatch (5)</td>
<td></td>
</tr>
<tr>
<td>Location of SMM measurement</td>
<td>L3 (37), C3 (29), Full body (5), Appendicular (4 limbs)/ upper and lower extremities (3), Mid-arm circumference (2), C1 (1), C2 (1), C4 (1), T2 (1), T4 (1), Full body for DEXA (1), Quadriiceps (1), Triceps skinfold (1), Rectus femoris (1)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Muscle quantity**         | Abdominal wall musculature – transversus abdominis, external and internal obliques, rectus abdominus, psoas, erector spinae, and quadratus lumborum (17)  
All muscles at L3/ entire L3 vertebral arch and transverse processes (8)  
PVM and SCM (24)  
PVM and SCM separately (1)  
PVM only (1)  
SCM only (1)  
Right and left psoas muscles (1)  
BIA - Lean body mass; includes muscle mass, as well as bones, bodily fluid, skin, and organs; is equal to total weight minus fat mass (2)  
DEXA - Total body and regional (arm, leg, trunk, android, and gynoid) lean mass (1)  
Appendicular/upper and lower extremities (arms and legs) (3)  
Whole body (1)  
CT - Relative muscle area (1)  
Mid-arm circumference (2)  
Triceps skinfold (1)  
Vastus lateralis and rectus femoris (1)  
Rectus femoris (1)  
N/A (13)  
N/A – no image contouring (1)  
**Muscle quality**  
Multifidus muscles (1) |
| **Muscles examined**         | Abdominal wall musculature – transversus abdominis, external and internal obliques, rectus abdominus, psoas, erector spinae, and quadratus lumborum (17)  
All muscles at L3/ entire L3 vertebral arch and transverse processes (8)  
PVM and SCM (24)  
PVM and SCM separately (1)  
PVM only (1)  
SCM only (1)  
Right and left psoas muscles (1)  
BIA - Lean body mass; includes muscle mass, as well as bones, bodily fluid, skin, and organs; is equal to total weight minus fat mass (2)  
DEXA - Total body and regional (arm, leg, trunk, android, and gynoid) lean mass (1)  
Appendicular/upper and lower extremities (arms and legs) (3)  
Whole body (1)  
CT - Relative muscle area (1)  
Mid-arm circumference (2)  
Triceps skinfold (1)  
Vastus lateralis and rectus femoris (1)  
Rectus femoris (1)  
N/A (13)  
N/A – no image contouring (1)  
**Muscle quality**  
Multifidus muscles (1) |
| **Software**                | OsiriX software (3)  
SmartPACS (1)  
MiM Vista (1)  
Maltron Bio-Scan 916-917 – BIA (1)  
SECA analytics 115 – BIA (1)  
SliceOmatic (20)  
PACS (2)  
Xelis 3D (1)  
Volumetool (3)  
Pinnacle (3)  
enCORE (2)  
ImageJ (7)  
Aquarius workstation (3)  
AquariusNET Viewer (1)  
Lookin’Body 120 analyser – Inbody (3)  
Mirada DBx (1)  
DEXA (1) |
| Individual measuring | EclipseTM (1)  
| GE Medical Systems LOGIQ E9 (1)  
| Worldmatch (1)  
| PetaVision (1)  
| Monaco TPS (3)  
| 3D Slicer (1)  
| EV Insite Net (1)  
| Centricity Radiology RA1000 (1)  
| B-mode ultrasonography (2)  
| OMRON Karada Scan Hbf 375 Body Composition Monitor (1)  
| N/A – no software used; tape measurer and calipers (2)  
| N/A (8)  

| Physician | Trained HNC surgeon with verification by a radiologist with 15 years of training in body radiology (1)  
Single physician (1)  

| Radiation Oncologist | Single radiation oncologist (7)  
Radiation oncologist who was blinded to treatment outcomes (1)  
Single trained radiologist in two different sessions to avoid recall (1)  
Single radiation oncologist - muscles delineated automatically by deep learning segmentation algorithm (1)  
Single radiation oncologist and reviewed by another radiation oncologist (3)  
Two independent radiologists (1)  
Two independent radiologists blinded to patient outcomes (1)  

| Researcher | Single researcher (6)  
Single researcher blinded for patient outcomes (6)  
Single researcher supervised by an experienced head and neck radiation oncologist (1)  

| Observer | Trained observer (1)  
Single observer (1)  
Single observer trained in CT analysis and blinded to patient outcomes (1)  
Main observer and another observer (1)  
3 observers (medical student, doctoral student, and radiologist (1)  
Independently by 6 observers: one experienced head and neck radiologist, one experienced head and neck radiation oncologist, and four medically trained researchers from the departments of Head
| Reliability analysis (yes/no) | No (67), Yes (5), Yes – interobserver agreement study (1)
|------------------------------|------------------------------------------------------------------|
| Outcome (i.e., mathematical definition) | **Muscle quantity**
|                              | L3 SMI (53)
|                              | C2 SMI (1)
|                              | C3 SMI (4)
|                              | C4 SMI (1)
|                              | T2 SMI (1)
|                              | T4 and L3 SMI difference (1)
|                              | SCM SMI (1)
|                              | L3 Psoas Muscle Index (1)
|                              | Appendicular SMI (3)
|                              | PVM CSA (3)
|                              | Left SCM CSA (1)
|                              | Right SCM CSA (1)
|                              | Total CSA of PVM and SCM (1)
|                              | L3 CSA (2)
|                              | CSA of vastus lateralis and rectus femoris (1)
|                              | CSA of rectus femoris (1)
|                              | SCM muscle volume in cm³ (1)
|                              | SMI using BIA (1)
|                              | Total body and regional (arm, leg, trunk, android, and gynoid) lean mass – using DEXA (1)
|                              | SMM – reported in kg using DEXA (1)
|                              | SMM – reported in kg using BIA (2)
|                              | SMM – reported in kg using OMRON body composition monitor (1)
|                              | Cervical SMM volume (1)
|                              | Mid-arm muscle area (2)
|                              | Triceps skinfold thickness (1)
|                              | **Muscle quality**
|                              | Intramuscular adipose tissue content (1)
|                              | **Muscle Strength/Function**
|                              | Handgrip strength measured in kg (7)
|                              | **Physical Performance**
|                              | Timed up and go test measured in seconds (2)
|                              | Gait speed measured in m/s (1)
|                              | Gait speed (6-minute walk test) measured in m/s (1)
|                              | Gait speed (4-minute walk test) measured in m/s (1)
|                              | **Sarcopenia (SARC-F)**
|                              | 5-question self-report score (1)
| Timing of measurement | **Prior to treatment**
|                              | Eve of surgery (1)
<table>
<thead>
<tr>
<th>Timeframes</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>7 days (4)</td>
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<tr>
<td>7-14 days (1)</td>
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</tr>
<tr>
<td>14 days (3)</td>
<td></td>
</tr>
<tr>
<td>21 days (1)</td>
<td></td>
</tr>
<tr>
<td>30 days (4)</td>
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<tr>
<td>45 days (1)</td>
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<td>55 days (1)</td>
<td></td>
</tr>
<tr>
<td>60 days (2)</td>
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<tr>
<td>90 days (1)</td>
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<tr>
<td>Less than 4 weeks before treatment (1)</td>
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<tr>
<td>Less than 6 weeks before treatment (1)</td>
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<tr>
<td>Less than one month prior to treatment (4)</td>
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<tr>
<td>Less than 2 months prior to treatment (1)</td>
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<tr>
<td>Less than 3 months prior to treatment (4)</td>
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<tr>
<td>Within 6 months prior to treatment (1)</td>
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<tr>
<td>Within 1 year of treatment (1)</td>
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<tr>
<td>Moment of admission at institution (2)</td>
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<tr>
<td>Outset (beginning) of treatment (2)</td>
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<tr>
<td>Time of diagnosis (3)</td>
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<tr>
<td>Within a week of diagnosis (1)</td>
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<tr>
<td>During tumor staging (1)</td>
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<tr>
<td>During external beam radiation therapy simulation (1)</td>
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</tr>
<tr>
<td>60 seconds after contrast injection (1)</td>
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<tr>
<td>N/A – only written as prior to treatment (32)</td>
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</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Mid-treatment – day 15 ±2 (1)</td>
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</tr>
<tr>
<td>1(^{st}), 8(^{th}), 15(^{th}), and 22(^{nd}) RT-fraction (1)</td>
<td></td>
</tr>
<tr>
<td>3(^{rd}) and 7(^{th}) week of CRT (1)</td>
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</tr>
<tr>
<td>Weekly clinic visits during treatment (1)</td>
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</tr>
<tr>
<td><strong>Post-treatment</strong></td>
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<tr>
<td>End of treatment/at discharge (3)</td>
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</tr>
<tr>
<td>7 days after treatment (1)</td>
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<tr>
<td>8-12 weeks after treatment (1)</td>
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<td>12 weeks after treatment (1)</td>
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<td>1 month after treatment (3)</td>
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<td>2 months after treatment (1)</td>
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</tr>
<tr>
<td>2.77 months after treatment (1)</td>
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</tr>
<tr>
<td>3 months after treatment (2)</td>
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</tr>
<tr>
<td>3-6 months after treatment (1)</td>
<td></td>
</tr>
<tr>
<td>Within 1 year after treatment (1)</td>
<td></td>
</tr>
<tr>
<td>N/A – only written as after treatment (4)</td>
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</tr>
<tr>
<td>Pre-intervention – 57 ± 30 days after the final RT dose (1)</td>
<td></td>
</tr>
<tr>
<td>Post-intervention (1)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix D: Performance Status Scale for Head and Neck Cancer (PSS-HN)

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

### Normalcy of Diet / __ / __ / __ |

- 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)

### Public Eating / __ / __ / __ |

- 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

### Understandability of Speech / __ / __ / __ |

- 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

Appendix E: M.D. Anderson Dysphagia Inventory (MDADI)

The M. D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.
The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.
Please read each statement and circle the response which best reflects your experience in the past week.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My swallowing ability limits my day-to-day activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2. I am embarrassed by my eating habits.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>F1. People have difficulty cooking for me.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P2. Swallowing is more difficult at the end of the day.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E7. I do not feel self-conscious when I eat.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E4. I am upset by my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P6. Swallowing takes great effort.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E5. I do not go out because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>F5. My swallowing difficulty has caused me to lose income.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P7. It takes me longer to eat because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P3. People ask me, “Why can’t you eat that?”</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E3. Other people are irritated by my eating problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P6. I cough when I try to drink liquids.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>F3. My swallowing problems limit my social and personal life.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>F2. I feel free to go out to eat with my friends, neighbors, and relatives.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P5. I limit my food intake because of my swallowing difficulty.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P1. I cannot maintain my weight because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>E6. I have low self-esteem because of my swallowing problem.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td>P4. I feel that I am swallowing a huge amount of food.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
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<td>F4. I feel excluded because of my eating habits.</td>
<td>Strongly Agree</td>
<td>Agree</td>
<td>No Opinion</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
</tr>
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</table>

Thank you for completing this questionnaire!
Appendix F: Ethics approval

Western Research

Date: 28 April 2022
To: Dr. Julia Therwar
Project ID: 105936

Study Title: Exploring functional and quality of life outcomes in patients with oropharyngeal squamous cell carcinoma
Study Sponsor: Western University
Application Type: HSREB Amendment Form
Reviewer Type: Delegated
Full Board Reporting Date: 10 May 2022
Date Approval Issued: 28 Apr 2022 08:08
REB Approval Expiry Date: 04 Nov 2022

Dear Dr. Julia Therwar,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Document: Approved:

<table>
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<th>Document Name</th>
<th>Document Type</th>
<th>Document Date</th>
<th>Document Version</th>
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<td>105936_REDCap Instrument v1 2022-Apr27</td>
<td>Other Data Collection Instruments</td>
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<td>Other Materials</td>
<td>27-Apr-2022</td>
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Documents Acknowledged:

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<td>105936 Protocol v1 6 2022-Apr27 - tracked</td>
<td>Summary of Changes</td>
<td>27-Apr-2022</td>
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REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with and is committed in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP), Part C, Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IB-00000946.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Ms. Nicole Georgelou-Moynihan, Ethics Officer on behalf of Dr. Philip Jones, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
CURRICULUM VITAE

NEDELJKO JOVANOVIC, PH.D. (candidate)

EDUCATION

April 2023 (expected)  Doctor of Philosophy (PhD candidate), Faculty of Health Sciences
Western University, London, Ontario, Canada

August 2018  Master of Science (MSc), Faculty of Health Sciences
Western University, London, Ontario, Canada

August 2016  Bachelor of Science (BSc), Honours Health Studies - Minor in Human Nutrition
University of Waterloo, Waterloo, Ontario, Canada

RESEARCH EXPERIENCE

2016 – Present  Research Associate, Voice Production and Perception Laboratory & The Laboratory for Well-Being and Quality of Life in Oncology, Western University, London, ON, Canada

2016 – 2019  Graduate Research Assistant, Faculty of Health Science, Western University, London, ON, Canada

ACADEMIC AND PROFESSIONAL EXPERIENCE

2020 - 2022  Graduate Teaching Assistant, Introduction to Ethics and Health (HS2610G), Western University, London, ON, Canada

2019 – 2022  Vice-President and PhD Student Representative, Western’s Health and Rehabilitation Sciences (HRS) Graduate Student Society, London, ON, Canada

2021  Graduate Teaching Assistant, Critical Appraisal of Health Literature and Research Methods (APPLHSCI 9013 and AHCP 9600), Western University, London, Ontario, Canada

2013 – 2014  Volunteer Assistant Physiotherapist, SOS Physiotherapy, Kitchener, ON, Canada

PUBLICATIONS


**PRESENTATIONS (PEER-REVIEWED)**


