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The Effect of Radiation Therapy and a 12-week Novel Strength Training Intervention on Neuromuscular Function and Fatigability in People Diagnosed with Head & Neck Cancer

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The Effect of Radiation Therapy and a 12-week Novel Strength Training Intervention on Neuromuscular Function and Fatigability in People Diagnosed with Head & Neck Cancer

by

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Abstract

Treatment for head and neck cancer (HNC) is associated with multiple side-effects and deleterious consequences including reductions in body mass, physical function and health-related quality of life (HRQL). Little is understood about alterations in neuromuscular function and fatigability induced by radiation therapy (RTx). Early evidence suggests strength training is beneficial following treatment for HNC. We hypothesized that exercise prescription could be optimized to promote improvements in muscle strength and mass.

This work aimed to investigate the impact of RTx ± chemotherapy on muscle strength, muscle cross-sectional area (CSA) and patient-reported outcomes, and central and peripheral alterations during a whole-body exercise task. Also, we aimed to investigate the feasibility of a 12-week strength training program with the intention of optimizing muscle strength and muscle mass.

In the first study, volunteers (n = 10) attended the laboratory before (5 ± 5 days) and after (56 ± 30 days) the completion of anti-cancer treatment. Participants performed a neuromuscular assessment (involving maximal isometric voluntary contractions [MIVC] in the knee extensors and electrical stimulation of the femoral nerve) before and during intermittent cycling to volitional exhaustion. Anthropometrics, self-reported fatigue and HRQL were also assessed. From before to after treatment, MIVC, potentiated twitch, and muscle CSA decreased approximately 18%, 16%, and 20%, respectively. Time to volitional exhaustion was also reduced, and peripheral processes contributed to a reduction in maximal force due to cycling exercise.

In the second study, participants (n = 22) were randomized to either an experimental (EXP) strength training intervention involving eccentric overloading and neuromuscular electrical stimulation (n = 11) or a conventional (CON) strength training intervention (n = 11) similar in overall frequency and repetitions. Feasibility outcomes were quantified as rates of accrual, completion, adherence and compliance. Regardless of allocation, 86% of participants completed the intervention and adherence was 88%. From before to after the interventions, muscle strength and muscle CSA in the knee extensors increased ~22% and 18%, respectively. Patient-reported fatigue severity and HRAL also demonstrated clinically relevant improvements.

The results of this work suggest that muscle strength and muscle CSA are reduced following treatment for HNC but are regained to a similar extent after 12-weeks of strength training. Also, peripheral fatigue, rather than central fatigue is more pronounced in people affected

by HNC following a maximal effort cycling task. Fully supervised strength training programs in survivors of HNC are feasible. These findings offer greater flexibility for future training programs where conventional strength training may not be tolerable.

Preface

This project is an original, unpublished work by the author, Colin Lavigne. The research presented in this project, of which this thesis is a part, received ethics approval from the Health Research Ethics Board of Alberta – Cancer Committee (ID: HREBA.CC-16-0744), under the project name "The effects of an innovative resistance training intervention on muscle strength, muscle mass and fatigue in cancer survivors" on 14 September 2016.

The work contained in this thesis is spread over five chapters. Chapter one is a brief introduction of the contents contained in this work. Chapter two is comprised of a review of the current literature, of which provides a summary of the contributing theoretical and practical applications of key disciplines involved in the conceptualization of this work. Chapters three and four are based on scientific manuscripts detailed below. Lastly, chapter five contains an overall discussion and summary of the findings, future directions and implications, and concluding remarks.

Chapter Three

Lavigne C, Lau H, Francis G, Culos-Reed SN, Millet GY, Twomey R (2019). *Neuromuscular function and fatigability in people diagnosed with head and neck cancer before versus after treatment*. [Unpublished].

Chapter Four

Lavigne C, Twomey R, Lau H, Francis G, Culos-Reed SN, Millet GY (2019). *Feasibility and preliminary efficacy of eccentric overloading and neuromuscular electrical stimulation to improve muscle strength and muscle mass after treatment for head and neck cancer*. [Unpublished].

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List of Symbols, Abbreviations and Nomenclature

Acronym	Definition
BF	biceps femoris
BMI	body mass index
CSEP-CEP	Canadian Society for Exercise Physiology-Certified Exercise Physiologist
CNS	central nervous system
CON	conventional strength training intervention
CRF	cancer related fatigue
CSA	cross-sectional area
ECC	eccentric
EMG	electromyography
EORTC QLQ-C30	Treatment of Cancer Quality of Life Core Questionnaire, version 3.0
EXP	experimental strength training intervention
FACIT-F	Functional Assessment of Cancer Illness Treatment – Fatigue
FACT-H&N	Functional Assessment of Cancer Therapy – Head and Neck
FACT-G	Functional Assessment of Cancer Treatment – General
FNES	femoral nerve electrical stimulation
Gy	Grey
HNC	head and neck cancer
HRQL	health-related quality of life
HPV	human papillomavirus
IMRT	intensity modulated radiation therapy
ITT	interpolated twitch technique
MCID	minimal clinically important difference
MIVC	maximal isometric voluntary contraction
M wave	compound muscle action potential
η_{p2}	partial eta-squared
NMES	neuromuscular electrical stimulation
NMF	neuromuscular function
POT	potentiated twitch
QoL	quality of life
Q_{pot}	potentiated twitch amplitude
RF	rectus femoris
RMS	root means square
RMS-EMG	electromyography root means square
RPE	rating of perceived exertion
RTx	radiation therapy
SIT	superimposed twitch
VA	voluntary activation
VL	vastus lateralis

Chapter One: Introduction

Malignancies collectively known as head and neck cancers (HNC) are comprised of mutations that mainly originate in squamous cells that line the upper aerodigestive tract (Vigneswaran & Williams, 2014). In the past, these types of neoplasms were most commonly identified in older adults with a history of high tobacco and alcohol consumption. However, a minority of HNCs are caused by human papillomavirus (HPV) infection that appear typically in the oropharynx, which has a rapidly increasing incidence (Young et al., 2015). People diagnosed with HPV-positive HNCs have different demographic characteristics to what has been observed in HPV-negative patients, including higher incidences in men and a younger mean age at diagnosis (Cramer, Burtness, Le, & Ferris, 2019).

Radiation therapy (RTx) is a mainstay treatment for people with HNC and offered to approximately 75% of patients (Ratko, Douglas, de Souza, Belinson, & Aronson, 2014). Although modern developments in RTx techniques continue to improve survival, the majority of patients treated with RTx experience unintentional weight loss between 6–12% of pre-treatment body weight of which over 70% is lean body mass (Silver, Dietrich, & Murphy, 2007). Weight loss may be caused by the disease itself (i.e. tumor invasion), however, occurs primarily due to side effects from RTx and/or chemotherapy (Lønbro, Dalgas, Primdahl, Overgaard, & Overgaard, 2013). Side effects such as mucositis and dysphagia contribute to decreased nutritional intake causing involuntary weight loss, which may persist years following treatment (Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013). Physical challenges (muscle wasting, decreased muscle strength, impaired functional independence), emotional challenges (depression, anxiety), and social challenges (personal interactions, isolation from pre-cancer social networks) can all be resultant of treatment for HNC, consequently affecting overall health-related quality of life (HRQL).

Depending on the anatomical site of tumor growth and/or the type of cancer treatment, neoplasms can have a negative impact on the neuromuscular system (Grisold, Grisold, & Löscher, 2016). Recent research has found that RTx dose to discrete structures in the central nervous system (CNS) during treatment for HNC contributes to higher perceived fatigue scores (Ferris et al., 2017). Twomey et al. have recently discussed the potential causes of CRF in HNC (Twomey, Culos-Reed, Millet, & Lau, 2017) but the potential complications of the neuromuscular system are not explored due to the limited information available on the topic. It has been proposed that both peripheral (i.e. muscle wasting) (Madeddu, Mantovani, Gramignano, & MacCiò, 2015) and central

(i.e. RTx dose to CNS structures) (Ferris et al., 2017) mechanisms contribute to perceptions of fatigue in HNC, however objective measures of neuromuscular correlates have not been established. Investigating these changes may inform the discussion about the importance of exercise prescription in this population.

To mitigate the side-effects experienced by people who have received RTx for HNC, early research has shown some success in the use of dynamic strength training interventions (i.e. traditional resistance training). Indeed, muscle mass, muscle strength, and functional performance can effectively be enhanced when correct training principles are applied (i.e. progressive overload, specificity, variation, rest/recovery). However, these principles may be less effective in eliciting positive outcomes in people affected by HNC and its treatment due to the functional limitations they are faced with.

The subsequent chapter includes a review of the literature summarizing the current understanding of HNC and its treatment, disease side effects, a brief review of what is currently being done to combat the functional declines experienced in this population, and finally potential strength training alternatives that can safely be applied to counteract cancer-related muscle wasting and improve physical function, with the overall aim of improving HRQL in survivors of HNC.

Chapter Two: Review of Literature

2.1 Head and neck cancer

2.1.1 Overview of head and neck cancer

Malignancies that arise from different anatomical subsites in the head and neck region, and include nasopharyngeal, oropharyngeal, laryngeal, hypopharyngeal and oral cavity carcinoma, are collectively known as head and neck cancer (HNC) (Uta et al., 2018). More than 90% of HNCs are squamous cell carcinomas, that originate in the mucosal surfaces of the upper aerodigestive tract (Kozakiewicz & Grzybowska-Szatkowska, 2018; Vigneswaran & Williams, 2014). These types of neoplasms typically occur in older adults who have a history of tobacco and alcohol use (Young et al., 2015), and are more common in men compared with women (Hussein et al., 2017). However, the landscape of HNC has experienced a shift over the past three decades. The human papillomavirus (HPV) infection has become a well-established causative factor of oropharyngeal HNC (Windon et al., 2018), and has become an increasingly important factor in the etiology and prognosis of HNC (Uta et al., 2018).

2.1.2 Incidence, mortality and survival rate

Incidence: The incidence (the number of new cases occurring) of HNC varies widely by geographical location. Worldwide, HNC is the 6th most common cancer type, where the annual incidence of individuals diagnosed with this disease is > 830,000 (Bray et al., 2018). In Canada, it is estimated that 4,700 individuals are diagnosed with HNC each year, accounting for the 13th most common cancer type. Approximately 75% of HNCs are related to tobacco and alcohol use (Blot et al., 1988). While HNCs have been declining overall, HPV-positive HNCs have a rapidly increasing incidence. However, the incidence of HPV-positive tumors varies substantially by geographical location, with 60–70% of oropharyngeal HNCs in North America and Western Europe but < 10% in low-income and middle-income countries (Cramer et al., 2019). A possible explanation for these disparities is the declining use of cigarettes in developed countries (remains higher in developing countries), which coincide with the increased awareness of the health hazards of tobacco use and widespread tobacco control efforts (Siegel, Miller, & Jemal, 2017).

Mortality: The mortality rate (the number of deaths occurring in one year) for HNC in Canada was > 1,200 in the year 2018, while worldwide > 430,000 die from HNC each year. In

Canada, mortality rates have declined by 1.3% for females and 2% for males each year between 1992 and 2012 (Canadian Cancer Society, 2017).

Survival rate: Survival rate (the ratio of mortality to incidence) represents the approximate ratio of fatalities (Parkin, Bray, Ferlay, & Pisani, 2005). Five-year net survival rates are increasing in HNC with all-time highs of 63% in Canada (Canadian Cancer Society, 2017). HNC patients diagnosed with HPV-positive tumors have shown favorable survival rates (Cramer et al., 2019).Recent data has shown that 3-year survival rates are approximately 82% in HPV-positive HNCs compared to 57% in patients with HPV-negative tumors (Ang et al., 2010). However, regardless of specific diagnoses, HNC patients are faced with treatment regimens that may result in deleterious side-effects.

2.1.3 Treatment for head and neck cancer

Curative-intent treatment for HNC patients is complex because unfortunately, the majority of HNC patients (approximately 60%) are diagnosed when the malignancy has already developed into a locally advanced disease (Stage III/IV) (Adelstein et al., 2017; Bressan et al., 2016; Uta et al., 2018). As such, curative-intent treatment typically includes the use of multimodal therapies, including surgical treatment complemented with radiation therapy (RTx) with/without concurrent chemotherapy (Kozakiewicz & Grzybowska-Szatkowska, 2018). Patients identified in the early stages (Stage I/II) of the disease are usually treated with a single curative method (i.e. surgery or RTx), and typically remain cancer free after therapy has concluded (Vermorken & Specenier, 2010). With surgical treatments becoming less invasive, and continually developing systemic therapies/RTx, these combined modality techniques are recommended for approximately 60% of HNC patients (Adelstein et al., 2017). Despite improvements, more than half of patients presenting with advanced (stage III/IV) HNC will experience a relapse or distant metastases (Uta et al., 2018; Vermorken & Specenier, 2010). In these cases, oncologists rely on surgical treatment and/or RTx for patients identifying with locally recurrent or metastatic disease (Uta et al., 2018; Vermorken & Specenier, 2010). For recurrent systemic disease no longer susceptible to local therapies, platinum-based chemotherapy has become the standard of care; however, the median survival rate for a patient remains under a year (Uta et al., 2018).

Ongoing clinical studies continue to investigate future developments crucial to further improve the outcomes for HNC patients. For example, intensity modulated radiation therapy

(IMRT) is an advanced therapeutic modality used for the curative-intent of HNC that delivers three-dimensional conformal RTx. The purpose of IMRT is to maximize radiation doses to localized regions within the tumor while limiting exposure to surrounding tissues by using multiple levels of intensity across each radiation beam (Gulliford et al., 2012; Rathod et al., 2013). As such, IMRT has become the standard of care for curative-intent in HNC (Twomey, Culos-Reed, et al., 2017). Nevertheless, these aggressive treatments result in debilitating side-effects that can occur during curative treatment, and persist (or even develop) years after the completion of treatment (Bressan et al., 2016). These symptoms include treatment related side-effects such as dermatitis, and a series of oral cavity complications including dysphagia, oral mucositis and xerostomia, and relatively general symptoms including fatigue and pain (Xiao et al., 2018). These side effects can impair multiple domains of quality of life (QoL), a broad concept and difficult measurement that encompasses all areas of life (Calman, 1984), and health-related quality of life (HRQL), a more precise measurement of the effect of a disease or treatment on a patient's wellbeing and daily functioning (Licitra, Mesía, & Keilholz, 2016).

2.1.4 Treatment related side effects

2.1.4.1 Dermatitis

Acute dermatitis is the most common RTx-induced side effect during curative treatment for HNC. Approximately 95% of patients experience mild to moderate symptoms (Iacovelli et al., 2018), and 25% experience severe symptoms (Gutiérrez, Khosravi-Shahi, & Álvarez, 2012). Radiation dermatitis is a dose-dependent reaction that causes damage to the epithelium and underlying structures of the epidermis, and is characterized by mild to transient erythema, peeling of the skin, ulcerations, and rarely, life-threatening conditions such as localized necrosis (Ferreira et al., 2017; Iacovelli et al., 2018). In most cases, skin reactions resolve leaving little to no scaring (Gutiérrez et al., 2012). However, depending on the severity it can lead to late effects that negatively impact physical appearance (Bernier et al., 2008). Currently, there is no standard of care for the prevention and treatment of radiation dermatitis. A variety of remedies including topical agents, dressings, and advanced oral and intravenous medications have been reported to prevent or treat acute radiation dermatitis, however, its management is not standardized and no evidence-based consensus on preventative or therapeutic interventions exist (Franco et al., 2014; Iacovelli et al., 2018).

2.1.4.2 Dysphagia

Dysphagia, defined as difficulty in swallowing, has been reported in up to 50% of HNC patients undergoing RTx (Schindler et al., 2015). Dysphagia may be caused by the cancer disease itself, for example, tumor obstruction of critical structures essential in the swallowing process and/or predominately as a result of the destruction of neural and soft tissues due to RTx (Schindler et al., 2015). Swallowing impairments depend largely on site-specific locations of the tumor (i.e. proximal to anatomical structures that are crucial to swallowing), the extent of resection and total radiation dose. Dysphagia can significantly impact dietary intake and negatively impact HRQL and overall survival (Schindler et al., 2015). Recommendations for preventative and therapeutic swallowing exercises designed to increase the range of motion and strengthen the targeted muscles pertinent to swallowing have demonstrated the ability to improve and/or maintain swallowing function in HNC patients post-treatment (Carroll et al., 2008; Kulbersh et al., 2006), but seems to remain under-diagnosed and mistreated (Schindler et al., 2015).

2.1.4.3 Lymphedema

Lymphedema is swelling caused by impaired tissue drainage resulting from lymphatic dysfunction with an accumulation of fluid within epithelial-lined spaces and occurs when the lymphatic system is damaged caused by cancer therapy (Deng et al., 2016). Due to aggressive treatment regimens, up to 90% of people treated for HNC experience lymphedema as a late side effect (Ridner et al., 2016). Head and neck lymphedema is categorized into external lymphedema, which involves soft tissues of the head and neck region, and internal lymphedema, which involves the upper aerodigestive tract (Jackson et al., 2016). Individuals who experience lymphedema are likely to experience greater levels of distress from experiencing sensations of numbness, heaviness, localized pain, and increased difficulties swallowing and breathing (Pigott, Nixon, Fleming, & Porceddu, 2018). Also, lymphedema may increase the risk psychosocial concerns, particularly in relation to altered appearance (Pigott et al., 2018). Due to the distinctly different etiology of head and neck lymphedema when compared to other sites of the body, head and neck lymphedema requires a tailored approach to its assessment and treatment (Smith et al., 2015). As a result of a lack of effective assessment methods, there is limited information on the effectiveness of its treatment (Pigott et al., 2018).

2.1.4.4 Oral mucositis

Acute and late toxicities such as oral mucositis and xerostomia are associated with dysphagia (Bressan et al., 2016). Together these can contribute to reduced energy intake and weight loss. Mucositis is one of the most debilitating and painful toxicities associated with HNC patients (Mercadante et al., 2015). It is comprised of inflammation and ulceration of the mucous membranes lining aerodigestive tract and has a complex etiology. In some cases, oral mucositis can lead to hospitalization, morbidity and mortality (Mercadante et al., 2015).

2.1.4.5 Xerostomia

Xerostomia, or dry mouth, is a common and debilitating late toxicity of curative treatment for HNC that occurs due to high cumulative doses of radiation, which cause harmful and damaging effects to salivary glands (Bressan et al., 2016; Mercadante et al., 2015; Rathod et al., 2013). These adverse effects can cause significant oral pain, taste alterations and difficulty in speech and swallowing (Rathod et al., 2013). It has been previously observed from the phase III parotid sparing radiotherapy trial, PARSPORT, that comparing IMRT to conventional RTx significantly reduces xerostomia (Gulliford et al., 2012), however, substantial symptom burden remains, for example, greater deteriorations in HRQL (Rathod et al., 2013), and increased fatigue (Gulliford et al., 2012).

2.1.5 Symptom burden

The side effects described beforehand, i.e. dysphagia, mucositis and xerostomia can negatively impact normal swallowing function (Bressan et al., 2016), limiting a patients ability to consume the daily nutritional requirements needed to sustain an adequate energy balance (Ganzer, Rothpletz-Puglia, Byham-Gray, Murphy, & Touger-Decker, 2015). Consequently, this can lead to undesirable weight loss. During RTx ± concurrent chemotherapy, up to 88% of patients with HNC experience malnourishment (Langius, Zandbergen, et al., 2013). As a result, people in this population frequently require methods of nutritional support (i.e. individualized dietary counseling, percutaneous-endoscopic-gastrostomy and/or nasogastric feeding tubes) (Rabinovitch et al., 2006). Considering the use of feeding tubes, there is concern that the prolonged disuse of anatomical structures required for normal swallowing may develop into late effects such as dysphagia (Schindler et al., 2015) and atrophy (Russi et al., 2012). These symptoms can persist up

to 8 – 11 years after treatment (Mehanna & Morton, 2006; Oskam et al., 2013), negatively impacting HRQL long into survivorship. Advanced curative modalities such as IMRT have demonstrated superior outcomes in physical functioning, distortion of senses, and swallowing when compared to conventional RTx (Rathod et al., 2013). However, the symptom burden remains high with IMRT (Twomey, Culos-Reed et al., 2017), and there is limited data available on its impact on HRQL (Rathod et al., 2013). It is clear that many survivors of HNC continue to experience various disease and treatment-related impairments and nutritional complications long after treatment has concluded, which can result in inadequate dietary intake causing involuntary weight loss. Importantly, the need for collaboration to advance an interdisciplinary approach among health professionals in key positions (i.e. oncologists, dietitians, dentists, nurses, physiotherapists, etc.) to effectively and successfully improve therapeutic strategies to improve the overall health and well-being for HNC patients remains. Overall, in patients and survivors of HNC, symptoms such as involuntary weight loss, fatigue, and functional fitness are common (Silver et al., 2010), and result in impaired functional performance and HRQL.

2.1.6 Cancer cachexia

Cancer cachexia is a multifactorial metabolic syndrome characterized by decreased body weight and skeletal muscle wasting (i.e. sarcopenia; with or without adipose tissue loss) (Aversa, Costelli, & Muscaritoli, 2017). It is associated with symptoms such as fatigue and anorexia that negatively impacts a patients' prognosis, HRQL and survival (Roberts, Frye, Ahn, Ferreira, & Judge, 2013; Solheim et al., 2017). Cancer cachexia results from a negative energy balance caused by a reduction in caloric intake, coupled with altered metabolism involving inflammation, increased catabolism, and elevated energy expenditure (Duval, Jeanneret, Santoro, & Dormond, 2018). A reduction in protein synthesis has also been reported (Duval et al., 2018). Consequently, cancer cachexia is associated with decreased muscle strength as an element of sarcopenia (Morley, Anker, & von Haehling, 2014) and possibly other aspects of neuromuscular function critical to the development and maintenance of physical well-being (Madeddu et al., 2015). Furthermore, cancer cachexia is associated with reduced tolerance to cancer therapies and increased mortality rates (Bachmann et al., 2008; Duval et al., 2018; Fearon et al., 2011).

Cancer cachexia is recognized as the main cause of death in more than 20% of all cancer patients (Couch et al., 2007). People affected by HNC are among the tumor groups at a higher risk

of developing cachexia due to the unique challenges they are faced with. The incidence of cachexia in HNC is between 60–80%, however, varies depending on the proximity of the malignancy to structures crucial for nutritional intake (Kwon et al., 2017). Interestingly, approximately one third of HNC patients are already cachectic before the start of cancer treatment due to tumor obstruction (Couch et al., 2015). The 5-year survival rate in people with HNC presenting with cancer cachexia ranges from 40–80%, with superior outcomes in HPV-positive than HPV-negative patients (Orell-Kotikangas et al., 2017). Although the definition and diagnostic criteria for cancer cachexia has been debated (Evans et al., 2008), in 2011, a consensus panel developed a relatively simple definition and diagnostic criteria including: (1) weight loss > 5% over the previous 6 months; (2) weight loss >2% in individuals with a body mass index (BMI) below 20 kg/m$_2$; and (3) sarcopenia combined with weight loss > 2% (Fearon et al., 2011).

Single modality interventions have shown to improve nutritional and physical outcomes in patients with cancer cachexia (Solheim et al., 2017). A systematic literature review evaluating dietary counseling in cachectic individuals concluded that there were positive effects on energy intake, and decreased weight loss (Balstad, Solheim, Strasser, Kaasa, & Bye, 2014). Dietary nutritional supplementation, for example, protein (Cintineo, Arent, Antonio, & Arent, 2018), creatine (Fairman et al., 2019), and branched chain amino acids (Madeddu et al., 2015) have all shown positive effects on stimulating protein synthesis, therefore may be efficacious in attenuating muscle wasting. However, dietary nutritional supplementation alone cannot fully negate the loss of muscle mass and muscle strength, and with the multifactorial nature of cancer cachexia, it has been suggested that to optimize the effectiveness of treatment, multimodal approaches are necessary (Aversa et al., 2017; Couch et al., 2007; Solheim et al., 2017). As such, strength training to counteract atrophy may be an effective tool in the multimodal approach to mitigating the effects of cancer cachexia. This has recently been demonstrated in the work of Lønbro et al. (Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013), and found that combined protein and creatine supplementation possibly favored lean body mass, however, did not demonstrate a statistical advantage over strength training alone. Despite these promising results, there is a need for an increased understanding and awareness of cancer cachexia, and additional investigations are required to better understand and further advance therapeutic approaches. Therefore, new strategies are needed before or after treatment in HNC to help further negate the substantial loss of skeletal muscle mass.

2.1.7 Psychosocial side-effects associated with head and neck cancer

HNC has been identified as the most distressing and emotionally traumatic type of cancer (Budhrani-Shani, Chau, & Berry, 2018), and people with HNC have consistently been identified as having some of the highest suicidal rates among all cancer types (Kendal, 2007; Misono, Weiss, Fann, Redman, & Yueh, 2008). With the physical and emotional burdens of HNC and its treatment, HNC patients also rate among the highest of developing a major depressive disorder (Budhrani-Shani et al., 2018), with prevalence rates reaching 46% (Archer, Hutchison, & Korszun, 2008).

Treatment for HNC may negatively impact self-image (Budhrani-Shani et al., 2018) and can be linked to other psychosocial symptoms, particularly anxiety (Britton et al., 2012; Dropkin, 2001; Horney et al., 2011), which may lead to decreased psychological function (Mehanna & Morton, 2006). Difficulty swallowing and the lack of an ability to produce saliva may also lead to a decrease in relationships and social activities, which have been found to be predictive of feelings of anxiety (Carlson, Waller, Groff, Giese-Davis, & Bultz, 2013). It has been demonstrated that recovery from HNC treatment can include debilitating late and long-term effects on physical, emotional and behavioural functioning (Dropkin, 2001). Although some people affected by HNC may adjust to their situation, and resolve the possible psychosocial symptoms over time, others may carry feelings of depression and anxiety long into survivorship, including poor coping strategies and feelings such as “helplessness” and “hopelessness”, that may impact social functioning and work status (Horney et al., 2011). It remains crucial that people living beyond HNC treatment continue to receive supportive care services.

2.1.8 Health-related quality of life in head and neck cancer

Patients with HNC can experience significant deteriorations in HRQL during treatment, that only slowly recover to pre-treatment levels (Langius, Van Dijk, et al., 2013). While some issues directly relate to the cancer site, stage of the disease or severity of treatment (Rogers, Clifford, & Lowe, 2011), other effects are not as easily observed, are less predictable and more individualized, and can go unrecognized if patients fail to receive the multidisciplinary healthcare they require (Rogers et al., 2011). Traditionally, medical professionals specializing in HNC have focused on the diagnosis and treatment of physical symptoms and disorders (Williams, 2017), with endpoints of medical care for cancer treatment based primarily on survival and complication rates

(Wan Leung et al., 2011). These endpoints, which have typically been assessed from physician's points of view, fail to recognize patients' mental and emotional well-being (Wan Leung et al., 2011) despite the high frequency of clinically significant HRQL declines in HNC patients (Williams, 2017). This is of particular concern as distress is a common response to curative treatment and when left untreated, has been associated with significantly worse psychosocial and medical outcomes (Aarstad, Osthus, Olofsson, & Aarstad, 2014; Williams, 2017). However, as treatment for HNC has evolved, the field has progressed toward patient-centered care. As such, increased recognition of HRQL has become an inherently important aspect of medical outcomes in HNC patients (Williams, 2017; Zhang, Xie, Archibald, Jackson, & Gupta, 2018).

HRQL can generally be defined as "the patient's perception of the effects of the disease and the impact on the patient's daily functioning" (Wan Leung et al., 2011), and is constructed on two fundamental principles. First, HRQL is a multidimensional survey that includes the assessment of disease and treatment related symptoms including physical, emotional, social and functional domains (Ringash et al., 2008; Wan Leung et al., 2011). Second, it is subjective and must be self-reported (i.e. patient-reported outcomes) (Twomey, Bebb & Culos-Reed, 2018; Wan Leung et al., 2011). Although the effects of cancer diagnosis and curative-intent treatment on HRQL are now well recognized, determining and quantifying these subjective outcomes remains challenging (Zhang et al., 2018). Several clinical outcomes have been implemented to assess the effects of treatment for HNC with an increasing emphasis on patient-reported outcomes. There are a variety of well-validated HRQL constructs available for use in the field of oncology. They include generic measures of health status, e.g. the Short Form-36 (SF-36) (Ware & Gandek, 1998), cancer specific questionnaires, e.g. the Functional Assessment of Cancer Treatment (FACT-G) (D. Cella et al., 1993) and Treatment of Cancer Quality of Life Core Questionnaire, version 3.0 (EORTC QLQ-C30) (Aaronson et al., 1993), and cancer site-specific questionnaires, e.g. HNC sub-scales in EORTC (EORTC QLQ-HN35) (Bjordal et al., 1999) and FACT (FACT-H&N) (Ringash et al., 2008). The FACT-H&N is a commonly used, reliable and valid disease-specific QoL instrument that is short, and can be completed quickly (Ringash & Bezjak, 2001). With regard to quantification it is also easy to score, where each response across 4 domains [physical (7), social/family (7), emotional (6), and functional (7)], and an 11-item HNC specific sub-scale of the 38 item FACT-H&N instrument is rated from 0–4 on a Likert index, based on the past 7 days (Ringash & Bezjak, 2001), making it feasible for use in clinical trials. Scores from each domain

are calculated separately then added together, where the maximum score of 144 reflects the best possible HRQL (Ringash & Bezjak, 2001; Ringash, Bezjak, O'Sullivan, & Redelmeier, 2004). Ringash and colleagues determined through cross-sectional analysis that on average, clinically meaningful improvements in HRQL could be detected in raw scores of about 6/144 (4%), whereas a decline in a raw score of at least 12/144 (9%) would indicate clinically meaningful worsened HRQL (Ringash et al., 2004).

2.1.9 Societal impacts

Recovery from HNC and its treatment can continue for months or years. Individuals who are not able to resume their activities of daily living may become socially isolated from pre-cancer social networks (Rhoten, Murphy, Dietrich, & Ridner, 2018). For example, individuals may not be able to operate a vehicle safely due to limited neck mobility as a result of muscular atrophy or swelling from lymphedema, and others who experience difficulty eating may find it uncomfortable to socialize with family and friends over meals. Change in a survivor's voice may also make it difficult to communicate clearly. This disruption to everyday life may lead to a sense of social anxiety and isolation, making interactions with family, friends, and others difficult (Rhoten, Murphy, & Ridner, 2013).

The general decline in physical function due to treatment has significant implications on employment, as the likelihood that an individual will not return to work after anti-cancer treatment is far too high. Previous research has found that up to 57% of HNC survivors are unable to return to work after treatment (Verdonck-de Leeuw, van Bleek, René Leemans, & de Bree, 2010; Weis, Koch, & Geldsetzer, 1992). The cessation or reduction of work hours during and/or after treatment can lead to financial instability, which may also lead to feelings of social isolation. For someone affected by HNC, returning to work is a means of regaining a sense of normality and control (Giuliani et al., 2018), and can provide structure to everyday life, allowing an individual to regain personal identity (Isaksson, Wilms, Laurell, Fransson, & Ehrsson, 2016). More needs to be done beyond what the current standard of care is. This warrants the development of specific rehabilitation programmes to this patient group. For instance, involving exercise physiologists and/or occupational therapists to regain functional strength and prepare for a safe return to work beyond what is already being offered may be of importance.

2.1.10 Fatigue in head and neck cancer

Fatigue is one of the most prevalent symptoms reported by cancer patients, and is a common side-effect of treatment for malignant disease (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003). However, fatigue remains a poorly understood symptom. According to the National Comprehensive Cancer Network, cancer-related fatigue (CRF) is defined as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (Berger et al., 2015). By contrast, CRF differs from fatigue experienced by healthy individuals (e.g. resulting from intense or prolonged exercise) in that it cannot be completely relieved by rest, leaving the patient with a continually overwhelming sense of exhaustion (Ahlberg et al., 2003). There is no objective measure of CRF, thus its clinical relevance is assessed by patient-reported questionnaires. A multitude of scales have been developed to quantify CRF (Minton & Stone, 2009), notability the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997), a 13-item self-report unidimensional instrument that is widely recommended (Minton & Stone, 2009). The vast majority of cancer patients present with CRF during primary curative treatment (Jereczek-Fossa et al., 2007; Spratt et al., 2012; Twomey, Martin, Temesi, Culos-Reed, & Millet, 2018). Although CRF often returns to baseline after curative treatment, it can persist for months or even years (Prue, Rankin, Allen, Gracey, & Cramp, 2006). This can negatively impact an individual's adherence to medical treatment (Solberg Nes, Ehlers, Patten, & Gastineau, 2013), their functional status (Schmidt et al., 2012) and quality of life (Xiao et al., 2018).

Previous studies have indicated that patients with HNC have consistently ranked fatigue among their top three most severe side-effects (Xiao et al., 2016, 2018, 2013). In fact, fatigue has been reported to affect all patients undergoing RTx for HNC (Jereczek-Fossa et al., 2007; Spratt et al., 2012). In people undergoing RTx for HNC, fatigue will typically worsen throughout treatment, peak 1–2 weeks after treatment, and slowly decrease thereafter (Jereczek-Fossa et al., 2007; Spratt et al., 2012). After RTx, fatigue can remain an issue for HNC survivors, and at 2 years, 50% of patients continue to experience clinically significant levels of fatigue (Spratt et al., 2012). Patients undergoing RTx for HNC have particularly high rates of fatigue (Gulliford et al., 2012) due in part, to the degree of radiation to central nervous system structures that are in close proximity to malignancies of the head and neck region (Ferris et al., 2017; Twomey, Culos-Reed, et al., 2017). Ferris and colleagues recently found a link between maximum medulla and brainstem

RTx dose was significantly associated with patient-reported fatigue (Ferris et al., 2017). However, that alone does not fully explain the conundrum of high levels of fatigue in people living with, or beyond HNC, and the etiology of CRF remains under investigation. Additional research has postulated that individual variability regarding fatigue may be attributable to metabolic and inflammatory responses (Tariman & Dhorajiwala, 2016), suggesting changes in gene expression may play an important role in predicting fatigue, which has recently been examined in HNC patients (Eldridge et al., 2018). Other studies have reported that alterations associated with physiological determinants such as cancer cachexia (Aversa et al., 2017) and neuromuscular complications (Grisold et al., 2016) may also contribute to CRF, however its relationship remains unclear (Twomey, Aboodarda, et al., 2017). There have been several proposed neuromuscular complications associated with cancer and its treatment (Grisold et al., 2016), however there is a limited understanding of the relationship between the mechanisms of exercise-induced fatigue (acute) and CRF (chronic). Understanding why an individual becomes fatigued under certain circumstances, in particular how cancer influences fatigue from the aspect of perceptions of 'tiredness' relative to neuromuscular decline would be a valuable addition to current knowledge. Of importance, there is no research to-date on neuromuscular function in people affected by HNC.

2.2 Neuromuscular fatigue in head and neck cancer

2.2.1 Defining neuromuscular fatigue

Fatigue is a complex phenomenon with multiple definitions (Doyle-Baker, Temesi, Medysky, Holash, & Millet, 2018; Millet & Lepers, 2004). For example, in earlier sections CRF (i.e. chronic fatigue) was defined as a persistent, subjective sense of tiredness related to cancer or cancer treatment that cannot be relieved by rest, and only measured by self-report. Muscle fatigue (i.e. acute fatigue) on the other hand, encompasses a number of different mechanisms and physiological processes that result in the acute inability to perform a motor task (Enoka, 1995). One well-established definition of muscle fatigue is an exercise-induced reduction in the ability of a muscle or muscle group to produce force, regardless if the task can be sustained (Bigland-Ritchie & Woods, 1984; Enoka & Duchateau, 2008). The mechanisms that cause muscle fatigue are task dependent (i.e. intensity and duration of exercise) and can arise from multiple sites. There are two concepts that support this notion, and are categorized broadly as being central (proximal to the neuromuscular junction) or peripheral (at or distal to the neuromuscular junction) (Millet &

Lepers, 2004). In this context, fatigue induced acutely by a motor task, which can begin at the onset of exercise, progress as exercise continues, and is reversible by rest, can henceforth be referred to as neuromuscular fatigue.

2.2.2 Potential role of understanding neuromuscular alterations in HNC

Together with other critical organs, structures of the central nervous system lie adjacent or in close proximity to tumors categorized as HNC. Ferris and colleagues have shown that it is common for structures of the central nervous system to receive radiation doses during treatment which may consequently contribute to cancer-related fatigue in HNC patients, specifically when the medulla and brainstem are affected (Ferris et al., 2017). However, a limitation of this study was that the researchers only used patient-reported outcomes as a measure of fatigue. Patient-reported outcomes are important to measure fatigue, and HRQL, and should be included in current and future research. However, future research will benefit from the use of objective measures to determine if HNC is a more centrally or peripherally driven disease. Furthermore, cancer cachexia can result in significant reductions in muscle mass and intrinsic force, and is associated with fatigue and impairment of normal functioning (Madeddu et al., 2015). Therefore, it is likely that people who receive RTx for HNC may experience significantly reduced neuromuscular function. As central nervous system structures commonly receive moderate doses of radiation, it is conceivable that neural drive can be altered, consequently having a negative impact on VA. Additionally, decreases in skeletal muscle mass due to cachexia, and in part muscular strength, occur at the site of the peripheral nervous system. Consequently, this decrease can negatively impact the amplitude of potentiated contractile responses and M-wave properties, which may result in changes at the peripheral level. Maintaining muscle function is important to neuromuscular function and essential for the maintenance of functional well-being and independence. Therefore, evaluating properties of neuromuscular function can be considered crucial parameters to monitor in people affected by HNC. Greater insight into these parameters can provide some of the possible mechanisms of fatigue following treatment for HNC.

Despite exercise-induced fatigue being a known factor in human performance, little is understood about how exercise interventions influence the neuromuscular capacity to complete a task. It is important to understand these elements as disease conditions and exercise interventions induce responses (acute) and adaptations (chronic) of the neuromuscular system. The additional

element needed to understand disease and fatigue is the influence of conscious elements of performance (i.e. tiredness and motivation). By using stimulation paradigms non-volitional aspects of performance can be measured, and thus the element of the person performing the task can be separated from the neuromuscular changes. Also, central and peripheral aspects of neuromuscular function at rest, and neuromuscular fatigue subsequently following a specific exercise task, can be determined.

2.2.2.1 The central contribution to neuromuscular fatigue

Central factors of neuromuscular fatigue are physiological processes that result from alterations within the central nervous system, in which case a reduction in the optimal firing frequency of motoneuron recruitment or spatial de-recruitment occur (Taylor, Amann, Duchateau, Meeusen, & Rice, 2016). The origin can be at the spinal and/or supraspinal level, including the brain, spinal cord, motor output, sensory input and autonomic function, and can impair muscle force (Taylor et al., 2016). Central fatigue can be defined as an exercise-induced failure in the voluntary activation (VA) of a muscle or muscle group during exercise (Taylor & Gandevia, 2007). Although alone does not fully explain the potential mechanisms of central fatigue, VA, the level of voluntary drive during a voluntary muscle contraction, is conventionally measured using twitch interpolation. Here, a supramaximal stimulation is delivered to the motor nerve of the contracted muscle or muscle group during a voluntary effort (Gandevia, 2001; Merton, 1954). For example, the femoral nerve can be stimulated to evoke muscle contractions in the knee extensors. By comparison with the stimulus delivered to the motor nerve during voluntary contraction [i.e. superimposed twitch (SIT)], VA is considered incomplete if an increase in force is present above that being produced voluntarily. An increase in the size of the SIT indicates a greater reduction in motor unit recruitment and/or firing rates. VA is quantifiable by eliciting the same stimulus in the potentiated relaxed muscle after voluntary contraction, then normalizing the amplitude of the SIT to the potentiated response obtained from the potentiated relaxed muscle (Millet, Martin, Martin, & Vergès, 2011; Twomey, Aboodarda, et al., 2017). Although debated (Taylor, 2009), the interpolated twitch technique (ITT) remains the gold standard to assess VA of muscle (Bachasson et al., 2013). In exercise-induced fatigue, it is generally accepted that mechanisms of central contributions may predominately develop during prolonged exercise (Froyd, Beltrami, Millet, & Noakes, 2016). However, it's been found that immediately following a sustained isometric

maximal voluntary contraction of the knee extensors, voluntary activation is significantly reduced (i.e. indicating high central fatigue) (Goodall, Romer, & Ross, 2009). Contrary, peripheral contributions may predominate during short-term, metabolically demanding exercise, particularly if eccentric contractions are involved (Millet & Lepers, 2004).

2.2.2.2 The peripheral contribution to neuromuscular fatigue

Fatiguing processes may also be of peripheral origin. In this case, the contractile response of the muscle or muscle group are diminished in comparison to pre-exercise. The outcome of these processes is quantifiable using supramaximal electrical stimulation over the motor nerve of a muscle to evoke a response in its potentiated state (Twomey, Aboodarda, et al., 2017). Under these conditions, peripheral fatigue is relatively easy to detect, where a decrease in the amplitude of the evoked contractile response is considered to be an accurate measure of muscle fatigue (Macintosh & Rassier, 2002; Twomey, Aboodarda, et al., 2017). Alterations to the response in muscle compound action potentials (M-wave) to electrical stimuli may also provide insight into peripheral changes (Millet et al., 2011), although M-wave responses are susceptible to contamination such as change in temperature and sweat (Twomey, Aboodarda, et al., 2017). It has been proposed that the physiological mechanisms that likely occur due to peripheral fatigue can be characterized by any of the steps in the excitation-contraction coupling process (Macintosh & Rassier, 2002), and/or decrease in cytoplasmic Ca^{2+} availability (MacIntosh, 2003), that is known to modulate force development in skeletal muscle. Also, reduced Ca^{2+} sensitivity can modify cross-bridge cycling therefore resulting in less available force development (MacIntosh, 2003).

2.3 Therapeutic interventions for head and neck cancer survivors

A number of different therapeutic interventions have been investigated to combat the side effects of treatment for HNC. Several studies have investigated interventions that support swallowing rehabilitation exercises to restore dysphagia [reviewed in (Govender, Smith, Taylor, Barratt, & Gardner, 2017)]. Management for the prevention and rehabilitation for salivary gland hypofunction and dermatitis have also been well investigated, and are typically divided into non-pharmacological and pharmacological methods (see Ferreira et al. 2017 and Vissink et al. 2010). Also, therapeutic effects of nutritional supplementation in individuals with low muscle mass in cancer have regularly been investigated as a means to ameliorate treatment-related adverse effects

(see Langius et al., 2013 for a review). While beneficial effects of nutritional supplementation on lean body mass, strength, and physical function have been found (Fairman et al., 2019), these strategies alone have not been completely satisfactory in reversing cachexia. Therefore, there is a therapeutic potential for exercise interventions in individuals affected by cancer to mitigate the risk of muscle loss, alleviate fatigue, and increase HRQL.

The benefits of exercise are well-known, yet there have been a limited number of studies investigating the effects of training interventions in people affected by HNC. The benefits of exercise training interventions far outweigh the risks, and although the concept of 'exercise is medicine' (Pedersen & Saltin, 2015) is established it needs to be better understood in specific clinical populations including HNC.

2.4 Exercise interventions for head and neck cancer survivors

Current research supports the notion that 'exercise is medicine' for people affected by HNC (Capozzi, Nishimura, McNeely, Lau, & Culos-Reed, 2015), and first evidence has demonstrated that structured exercise programmes can positively impact HRQL for people affected by HNC (Eades et al., 2013; Lønbro, Dalgas, Primdahl, Johansen, et al., 2013). However, ongoing investigations are required to obtain a better understanding of exercise for HNC, and to determine its benefits on HRQL.

Strength training is unequivocally important in maintaining or improving muscle mass and muscle strength, essential for functional capacity. In individuals affected by HNC, strength training is a beneficial strategy to promote recovery and/or maintenance of muscle function by attenuating and (possibly) reversing both the impairment of protein synthesis and protein catabolism (Lira, Antunes, Seelaender, & Neto, 2015). Both during and following treatment of HNC, physical activity has been found to be feasible (Capozzi, Boldt, et al., 2015; Lønbro, Dalgas, Primdahl, Johansen, et al., 2013; Sandmæl et al., 2017), safe (Capozzi, Nishimura, et al., 2015; Lonkvist, Vinther, et al., 2017; Rogers et al., 2013), and effective (Capozzi, Nishimura, et al., 2015; Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013; Lonkvist, Vinther, et al., 2017). Because physical activity seems to be a viable treatment option for people affected by HNC, exercise interventions to reverse the loss of muscle strength, and improve physical function and overall HRQL are warranted. However, a relatively new field of research, data have only begun to accumulate since 2003 (Capozzi, Nishimura, et al., 2015), thus a limited number of studies exist.

A literature search was conducted using a single database (PubMed) from inception to June 2018, to systematically review (not related to a registered protocol) and summarise physical activity and exercise training interventions in people affected by HNC; where physical activity refers to "any bodily movement produced by skeletal muscle that requires energy expenditure for a sustained amount of time", and exercise training refers to "structured and intentional repetitive bodily movement performed to improve or maintain one or more components of physical fitness" (Caspersen, Powell, & Christenson, 1985). The search was conducted using the following medical subject heading search terms: "head and neck cancer" AND "exercise" AND "physical activity" NOT "swallowing" NOT "trismus" NOT "dysphagia". Twelve articles were identified from 2004 to 2018, four of which have been previously reviewed elsewhere (Capozzi, Nishimura, et al., 2015). A single reviewer identified and selected articles investigating full-body strength training of major muscle groups and localized rehabilitation needs (i.e. shoulder function) with or without additional exercise prescription (i.e., combination of cardiorespiratory, flexibility and/or balance training). The initial screening consisted of title and abstract review, and if the eligibility was difficult to detect the full text was reviewed. The inclusion criteria for studies were based on the following participant characteristics: 1) aged 18 years or older; 2) diagnosed with HNC of any stage; and 3) participants who were either on active HNC treatment (RTx ± concurrent chemotherapy), had completed HNC treatment, or who had only completed surgical treatment.

The objectives of Table 2.1 were to report on previous exercise prescription (i.e., the frequency, intensity, timing and type) and program design in HNC survivors. The main objectives of Table 2.2 were to report on: 1) associated outcomes observed with physical activity/exercise interventions; 2) recruitment and feasibility; 3) adherence rates; and 4) adverse events. The purpose of Table 2.3 was to identify the study design, participant characteristics and additional non-exercise details of the review studies.

Table 2.1: Description of exercise intervention training programs among current studies. Adapted from Capozzi et al., 2015.

Author/year	Intervention timing	Delivery mode	Exercise intervention	Frequency	Intensity	Time	Length	Training sessions	Progression
Capozzi *et al*, 2015	Mean time after treatment completion: 9.7 ± 10.0 months	Once weekly supervised; twice weekly unsupervised	Resistance training	3 days per week	"Moderate intensity" using the modified 0–10 Borg PRE scale	Not clearly stated	12 weeks	2 sets of 8–10 repetitions of 10 full body exercises	Progression offered at 4, 6, 9 weeks
Capozzi *et al*, 2016	ILI, initiation of cancer treatment; DLI, after treatment competition, 12 weeks post-randomization	Twice weekly supervised; twice weekly unsupervised	Physical activity focused on progressive resistance training	4 days per week	"Moderate-intensity" warm-up and 8–10 RM for exercises targeting major muscle groups	Not clearly stated	12 weeks	2 sets of 8–10 RM; working to 3 sets of 8 RM	Progression offered at 4, 6, 9 weeks, as appropriate
Lønbro *et al*, 2013	2 months post-treatment completion	Unsupervised, (supervised 2 or 3 sessions during initial 2 weeks, and average of 5 supervised sessions during the remaining 10 weeks)	Resistance training	30 training sessions total	12 RM	Not clearly stated	12 weeks	2 sets of 12 repetitions of 7 full body exercises	Worked up to 3 sets of 8 RM
Lønbro *et al*, 2013	3 months post-treatment completion	Unsupervised, (supervised 2 or 3 sessions during initial 2 weeks, and average of 5 supervised sessions during the remaining 10 weeks)	Resistance training	30 training sessions total	12 RM	Not clearly stated	12 weeks	3 sets of 12 repetitions of 7 full body exercises	Worked up to 3 sets of 8 RM
Lonkvist *et al*, 2017	During cancer treatment	Fully supervised	Resistance training using training machines (Technogym)	3 days per week (36 training sessions total)	15–8 RM	Not clearly stated	12 weeks	2–3 sets of 15–8 repetitions of 7 conventional exercises targeting large muscle groups (abdominal crunches, back extensions, chest press, low row, hamstring curls, knee extensions, leg press)	Began with low load/high repetitions and progressed to high load/less repetitions
McNeely et al, 2004	(1) "early": within 8 weeks of neck dissection; (2) "late": 8 or more weeks after neck dissection	Fully supervised by a physical therapist	Progressive resistance exercise training for shoulder function	3 days per week, excluding statutory holidays	RPE no greater than 13 on Borg Scale: "somewhat hard"	Not clearly stated	12 weeks	Up to 2 sets of 20 repetitions for 6 exercises targeting the following muscles: rhomboids, levator scapulae, biceps, triceps, infraspinatus, middle deltoid, supraspinatus, and subscapularis; total of approximately 45 mins	Progressed from 1 set of 25 repetitions to 2 sets of 20 with increased weight resistance

Continued

Table 2.1 Continued.

Author/year	Intervention timing	Delivery mode	Exercise intervention	Frequency	Intensity	Time	Length	Training sessions	Progression
McNeely *et al*, 2008	Post-surgical treatment (range, 2–180 months)	Fully supervised with option of 1 unsupervised session per week	PRET - progressive resistance exercise training TP - active and passive ROM/stretching exercises, postural exercises, and basic strengthening exercises	Minimum of 2 sessions per week with optional third session	No greater than RPE of 13 to 15 of 20 (described as "somewhat hard to hard") on the Borg scale	Not clearly stated	12 weeks	2 sets of 10 – 15 repetitions of 5 to 8 exercises, starting at 25 – 30% 1 RM progressing to 60 – 70% 1 RM by the end of the intervention	When the participant was able to complete 2 sets of 15 repetitions with proper form
Rogers *et al*, 2013	During cancer treatment	Supervised sessions during initial 6 weeks followed by unsupervised sessions during remaining 6 weeks	Resistance exercise	2 days per week	Light to heavy resistance bands	1 hour – 1 hour 15 mins	12 weeks	Up to 10 repetitions of 9 difference exercises	Gradually increased load bi-weekly if a participant could perform 12 repetitions easily
Samuel *et al*, 2013	During concurrent chemoradiotherapy	Supervised	Brisk walking programme; tailored active exercise programme (major muscle groups of upper and lower limbs)	5 days per week	RPE of 3–5 out of 10	15–20 mins walking + tailored active exercise	6 weeks	Brisk walking programme; active exercise programme (2 sets of 8 – 10 repetitions	Active to active resisted exercises for biceps, triceps, hamstrings, quadriceps
Sandmæl *et al*, 2017	EN-DUR, initiated during the first week of radiation therapy; EN-AF, initiated 2–4 weeks after the end of radiation therapy	Fully supervised	Resistance training	EN-DUR, 2 days per week; EN-AF, 3 days per week	Low to moderate intensity	EN-DUR, 30 mins; EN-AF, 45 mins	EN-DUR, 6 weeks; EN-AF, 3 weeks	EN-AF, 3–4 sets of 6–12 repetitions	Week to week progression in load
Wang *et al*, 2018	Within a month after cancer treatment (chemotherapy, radiation, or chemoradiation)	Supervised 1-hour, weekly home visits from an oncology nurse; 10-minute weekly calls for 3 weeks after the 6-week intervention period	PAfitME exergame platform (Wii Fit U; Nintendo)	3–5 days per week	Moderate intensity	First 3 weeks ~36 mins per week; second 3 weeks 40.1 mins (range 23–80 mins)	6 weeks, plus additional 3 weeks with minimal contact/supervision	cardiorespiratory fitness, muscular strength, flexibility, and balance	Participants were instructed to start with a short period, then progressively increase activity, stopping when they got tired or symptoms became worse

Continued

Table 2.1 Continued.

Author/year	Intervention timing	Delivery mode	Exercise intervention	Frequency	Intensity	Time	Length	Training sessions	Progression
Zhao *et al*, 2016	During concurrent chemoradiation therapy	Supervised sessions during initial 7 weeks, unsupervised during last 7 weeks	Functional resistance training and home walking programme	3 days per week	Moderate intensity (11 to 13 on the Borg Scale	Resistance training: N/A; walking: 30 mins	14 weeks	3 sets of 8 – 12 repetitions (chest press in squat, wall push up, military press, side arm raises, biceps curl, shoulder shrugs, calf raises)	Customized individually based on concurrent CRT side effects

CRT, chemotherapy; DLI, delayed lifestyle intervention; EN-AF, exercise and nutrition intervention after radiation therapy; EN-DUR, exercise and nutrition intervention during radiation therapy; ILI, immediate lifestyle intervention; PAfitME, physical activity intervention with fitness graded motion exergames; PRET, progressive resistance exercise training; RM, repetition maximum; ROM, range of motion; RPE, rate of perceived exertion; TP, standardized therapeutic exercise protocol; QoL, quality of life.

Table 2.2: Measurement outcomes and results of reviewed studies in people affected by head and neck cancer.

Author/year	Recruitment rate	Exercise adherence rate	Measurement outcomes	Primary findings	Secondary findings	Adverse events
Capozzi *et al*, 2015	71.9% (23 of 32) recruitment rate for assessment; 65.6% (21 of 32) recruitment rate for intervention	65.7% attended weekly group exercise sessions 52.4% completed the program	‣ Feasibility (recruitment rate, attendance rate, safety ‣ Symptom severity (ESAS) ‣ Anthropometrics (body weight, circumference measurements) ‣ Muscular strength (handgrip dynamometer) ‣ Functional performance (30 s sit-to-stand) ‣ Functional aerobic capacity (6MWT)	‣ See R*ecruitment rate, Exercise adherence rate*	‣ Of 9 symptoms in ESAS, significant decreases in tiredness (p=0.038) and drowsiness (p=0.035) were noted* ‣ No significant changes found in body weight, grip strength, waist circumference ‣ Participants performed an additional 5.4±4.9 stands in 30 s sit to stand (p=0.004) and 49.6±65.4 m in the 6MWT (p=0.059)	No adverse events were reported
Capozzi *et al*, 2016	55.6%	ILI, 45.2±38.5% DLI, 61.5±43%	‣ Body composition (BMI, LBM, % BF [DXA]) ‣ Physical activity minutes (Godin's Leisure Time Exercise Questionnaire) ‣ Muscular strength (handgrip dynamometer) ‣ Functional lower body strength (30 s sit-to-stand) ‣ Functional aerobic capacity (6MWT) ‣ Flexibility (sit-and-reach) ‣ QoL (FACT-An and FHNSI-22) ‣ Depression (CES-D) ‣ Nutrition (PG-SGA) ‣ Participant satisfaction	‣ No significant changes in BMI (p=0.698), LBM (p=0.756), or %BF (p=0.741) between groups across 24 weeks ‣ Cohen d effect sizes revealed a small effect in ILI group on LBM (d=0.130), BMI (d=0.183), and %BF (d=0.146)	‣ ILI group maintained physical activity through 6 weeks of treatment then declined; DLI increased physical activity throughout their intervention reaching a significant increase at 5 weeks (120.0±50.8 minutes; p=0.019) ‣ Fitness outcomes did not differ by group across 24-weeks for 30 s sit-to-stand (p=0.079); 6MWT (p=0.987); hand grip strength; (p=0.086) or; sit-and-reach (p=0.086) ‣ Significant declines in QoL were present by 12 weeks, and returned to baseline scores by 24 weeks ‣ Both groups reported increased depression over 12 weeks and returned to baseline scores by 24 weeks; no between-group differences were detected ‣ Between-group differences were not detected for nutritional status ‣ DLI group reported significantly higher satisfaction than ILI group (p=0.026)	No adverse events were reported

Continued

Table 2.2 Continued.

Author/year	Recruitment rate	Exercise adherence rate	Measurement outcomes	Primary findings	Secondary findings	Adverse events
Lønbro *et al*, 2013 (DAHANCA 25A)	28% (30 of 109)	97% (29 out of 30 sessions over a mean of 13 weeks)	‣ Feasibility of whole-body progressive resistance training ± protein and creatine supplementation (inclusion rate, adherence to exercise intervention, adherence to dietary supplementation, adverse events) ‣ LBM (DXA) ‣ Muscle strength (isokinetic dynamometry) ‣ Functional performance (10 m walk, 30 s sit-to-stand, stair climb, 30 s max arm curl)	‣ See *Recruitment rate, Exercise adherence rate, Adverse events* ‣ 69% of participants completed all dietary supplementation	‣ Significant increase in LBM by 5.0±3.8% (50.5±9.3 to 53.1±10.8 kg) in PROCR group (p<0.0001) and 2.8±2.5% (50.4±8.4 to 51.7±8.3 kg) in PLA group ‣ Significant increase in functional performance among groups pre- to post-exercise with no difference between groups	No adverse events were reported
Lønbro *et al*, 2013 (DAHANCA 25B)	22% (41 of 191)	95% for both groups	‣ LBM (DXA) ‣ Maximal muscle strength (isokinetic dynamometry) ‣ Functional performance (10 m walk, 30 s sit-to-stand, stair climb, 30 s max arm curl) ‣ QoL (EORTC QLQ-C30)	‣ After first 12 weeks, LBM increased 4.3% (2.3 kg; p<0.001) in EE; DE increased 1.5% in LBM, which was 1.5±0.5 kg larger (p=0.005) ‣ After last 12 weeks, LBM increased 4.2% (2.4 kg; p<0.001) in DE; EE increased 0.5%, which was 2.1±0.5 kg larger (p<0.001)	‣ Isometric KE strength increased by 20% (33Nm; p<0.001) in EE; DE increased by 21% (34Nm; p<0.001) after the first 12 weeks ‣ Isometric KE strength increased by 21% (34Nm; p<0.001) in DE; 32±10Nm greater (p=0.003) than EE after the last 12 weeks ‣ Significantly greater improvements in chair raise and arm curl in DE after the last 12 weeks ‣ Greater overall QoL and 'cognitive function' in EE; DE improved 'physical function' more than EE	No adverse events were reported

Continued

Table 2.2 Continued.

Author/year	Recruitment rate	Exercise adherence rate	Measurement outcomes	Primary findings	Secondary findings	Adverse events
Lonkvist *et al*, 2017	63% (12 of 19)	77±22% (range 36 – 100%) overall attendance during 12-week program 93% (range 67–100%) attendance rate during treatment 75% of patients completed at least 25 of 36 training sessions completion time was 12.7 weeks (range 11.7–13.7 weeks)	‣ Feasibility (measured by participation in training sessions ‣ Functional performance (maximal stair climbing, 30 s sit-to-stand, arm curl test) ‣ Muscle strength (1RM chest press and leg press) ‣ Body composition (LBM and fat mass measured by DXA) ‣ Self-reported physical activity (physical activity during leisure time was measured via questionnaires) ‣ QoL (EORTC QLQ-C30 and QLQ-H&N35)	‣ See *Exercise adherence rate*	‣ Functional performance during treatment remained unchanged; increased continuously after the treatment period; at 13-month follow up, arm curls and 30 s sit-to-stand increased significantly compared to baseline (p<0.01 and p<0.001) ‣ 1RM chest press decreased significantly (p<0.01) ‣ 1RM leg press increased continuously (144.4±41.6 kg – 182.0±63.2 kg) ‣ Loss of body mass during CCRT was 5.1±3.5 kg (p<0.001); at 12-week assessment, body mass loss was 3.6±2.4 kg (p<0.001); at 13-month follow-up, body mass loss was not significantly different from baseline. ‣ There was a positive correlation between self-reported physical activity when compared to functional performance and muscle strength (p<0.05 and p<0.05) ‣ QoL declined during the 12-week intervention and returned to baseline values at 5-month follow up	No adverse events were reported
McNeely et al, 2004	80% (20 of 25)	93% (31.2 of 33.6 total sessions; 95% CI, 29.4–33.6); 5 participants in the exercise group completed 100% of the prescribed exercise sessions	‣Feasibility (recruitment rate, competition rate, adherence rate) ‣ Shoulder function (goniometric measurements of shoulder flexion, abduction, external rotation, internal rotation, horizontal abduction ‣ Shoulder pain and disability index (SPADI) ‣ QoL (FACT-H&N)	‣ See *Recruitment rate, Exercise adherence rate* ‣ Overall competition rate of 85% (17/20)	‣ A significant difference occurred between groups for external rotation (p=0.001); PRET improved by 13.5% vs 3.8% in controls; all other ROM measurements were non-significant ‣ Significance was found in the SPADI pain scale between groups (p=0.038); PRET decreased 17% compared to a slight increase in controls (1.7%) ‣ Non-significance was found in the SPADI disability scale (p=0.111); PRET group decreased 10.1% vs 0.1% in the control group ‣ QoL decreased in both groups from baseline to post-intervention with no significance	One participant in the early exercise group complained of nausea and reported minimal nutritional intake. This incident was medically managed, and the participant had no further difficulties completing the PRET program

Continued

Table 2.2 Continued.

Author/year	Recruitment rate	Exercise adherence rate	Measurement outcomes	Primary findings	Secondary findings	Adverse events
McNeely *et al*, 2008	33% (15/45) accrual from mailed letter of invitation; 57% (37/65) accrual from otolaryngology/head and neck follow-up clinics	PRET, 95% TP, 87%	‣ Change in patient-rated pain and disability from baseline to post-intervention (SPADI) ‣ Muscular strength (seated row and chest press 1 RM) ‣ Muscular endurance (50% submaximal seated row test) ‣ Shoulder ROM (universal goniometer based on standardized procedures) ‣ QoL and fatigue (FACT-An) ‣ Treatment specific QoL (NDII)	‣ Overall SPADI score decreased by 14.1 in the PRET group compared with a decrease of 4.8 in the TP group (95% CI; p=0.001) ‣ Pain subscale score decreased by 16.4 in PRET group and by 2.2 in the TP group (95% CI; p=0.004) ‣ Disability subscale score decreased by 11.8 in the PRET group and by 7.4 in the TP group (95% CI; p=0.005)	‣ Muscular endurance improved significantly in the PRET group vs the TP group (95% CI; p=0.039) ‣ Shoulder ROM in external rotation and abduction reached significance (p<0.001 and p=0.029), respectively ‣ No difference detected in QoL and fatigue (FACT-An) ‣ NDII scores improved in both groups however not significantly different	One participant in the PRET group sustained a soft-tissue injury to the scapular region resulting in increased pain and elected to withdraw from the study
Samuel *et al*, 2013	Details not provided	Adherence rate was not a part of the study objective	‣ Functional capacity (6MWT) ‣ QoL (SF-36: MCS, PCS ‣ Adverse events ‣ Protocol deviations	‣ 6MWT improved in the exercise group (42m) while controls decreased 96m (p<0.001) from baseline within the groups ‣ PCS remained the same in the exercise group (p=0.478) vs 18% decrease (p=0.064) in the controls; MCS increased 12% in exercise group (p=0.014) vs 75% decrease in controls (p=0.004)	‣ See *Adverse events* ‣ No protocol deviations	No adverse events were reported

Continued

Table 2.2 Continued.

Author/year	Recruitment rate	Exercise adherence rate	Measurement outcomes	Primary findings	Secondary findings	Adverse events
Rogers *et al*, 2013	45% (15 of 33)	83% (70 of 84) first 6 weeks; 53% (32 of 60) second 6 weeks at home	‣ Feasibility (eligibility rates, recruitment rates, retention, adverse events, intervention process evaluation, exercise adherence) ‣ LBM (BIA) ‣ Muscle strength (back/leg and handgrip dynamometer) ‣ Physical functioning (8-foot walk time, 5 chair rise-to-sit) ‣ Fatigue (FACIT-F subscale) ‣ QoL (FACT-H&N, FACT-G)	‣ See *Recruitment rate, Exercise adherence rate, Adverse events* ‣ 45% (15/33) eligibility ‣ 100% (week 6 assessment); 87% (week 12 assessment)	‣ Small to medium effect size improvements (intervention vs control) in LBM at 6 weeks (d=0.35) ‣ Small to medium effect size increase in hand grip at 6 (d=0.22) and 12 weeks (d=0.34) ‣ Small effect size decrease in back/leg extensor strength at 6 (d=−0.21) and 12 weeks (d=−0.19) ‣ Small to medium effect size improvement in 5 chair raise time at 6 and 12 weeks (d=−0.63 and d=−0.60) ‣ Small to medium effect size for improvements in fatigue at 6 weeks (d=–0.64) ‣ Medium and small effect size improvements were noted for QoL at 6 and 12 weeks (d=0.52 and d=0.39)	All adverse events were unrelated to intervention: 1) control participant experienced left arm pain (non-serious) 2) control participant admitted to hospital for dehydration and constipation (serious) 3) Intervention participant admitted to hospital for diarrhea (serious)
Sandmæl *et al*, 2017	82%	EN-DUR, 74% ONS 52%; EN-AF, 49%, ONS 40%; Overall 81%	‣ Feasibility (recruitment rate, attendance, adherence, attrition) ‣ Skeletal muscle mass (cross-sectional area) ‣ Body weight	‣ See *Recruitment rate, Exercise adherence rate* ‣ Attendance: EN-AF, 52%; EN-DUR, 89% (16 patients) completed >50% (7 out of 12 sessions) ‣Attrition rate for intervention: EN-DUR, 90% (18 out of 20); EN-AF, 52% (11 out of 21)	‣ No difference in change in muscle mass between groups from baseline to week 14 (-0.3 cm_2/m_2; p=0.821) ‣ No difference in change in body weight between groups from baseline to week 14 (0.7 kg; p=0.818)	Data not collected

Continued

Table 2.2 Continued.

Author/year	Recruitment rate	Exercise adherence rate	Measurement outcomes	Primary findings	Secondary findings	Adverse events
Wang *et al*, 2018	47%	First 3 weeks (78.9% adherence to total minutes); second 3 weeks 100% adhered to their prescription; in the last 3 weeks (minimal supervision, i.e. 10 min phone calls), there was a mean adherence of 77.0% ± 55.7%	‣ Feasibility ‣ Acceptability ‣ Safety ‣ Cancer related fatigue (BFI) ‣ Activities of daily living (IADL) ‣ Cardiorespiratory fitness (6MWT) ‣ Balance (Berg Balance Scale) ‣ Muscle strength (handgrip dynamometer) ‣ Flexibility (shoulder ROM, abduction and forward flexion)	‣ Eligibility (73%) ‣ Attendance (99%) ‣ Completion (80%)	‣ Cancer related fatigue significantly reduced; BFI (mean Δ=–2.0, d=1.3)* ‣ Participants experienced reduced activities of daily living dependence; IADL (mean Δ=1.8, d=1.0) ‣ Improvement in cardiorespiratory fitness; 6MWT (mean Δ=51.3 d=1.0) ‣ Balance significantly improved; Berg balance scale (mean Δ=1.8, d=1.2) ‣ Muscular strength increased; combined grip strength sum (mean Δ=0.1, d=0.7) ‣ Left shoulder forward flexion improved (mean Δ=9.1, d=0.6)	No adverse events were reported
Zhao *et al*, 2016	Details not provided	72% (15.2 sessions of maximum 21)	‣ Muscle strength (knee extension; isokinetic dynamometer) ‣ Functional mobility (6MWT, timed up and go) ‣ Self-reported QoL (MOS SF-36 and MOS-Sleep 6) ‣ BMI and LBM (DXA) ‣ Self-reported physical activity (PASE questionnaire) ‣ Objectively assessed physical activity (Actigraphy GT3x+ accelerometer) ‣ Head and neck-specific QoL (20-question Head and Neck Quality of Life questionnaire) ‣ Barriers to exercise (34-item survey)	‣ Knee extension strength was maintained during all 14 weeks in MPACT vs a decline in controls (–4 N-m and –46 N-m; p<0.05) ‣ 6MWT showed less decline in MPACT (–71 feet) vs controls (–166 feet) at 7 weeks; MPACT improved (60 feet) compared to controls (–19 feet) at 14 weeks ‣ QoL declined less in MPACT vs controls at 7 weeks (–19 vs –24) and improved at 14 weeks (+4 vs –6)	‣ BMI declined 3 points at 7 weeks and 4–5 points at 14 weeks in both MPACT and control groups ‣ LBM improved at 7 weeks in MPACT (0.2%) and in controls (1%); substantial increases at 14 weeks (5% and 4%), respectively ‣ There was a decline in self-reported physical activity (PASE questionnaire) at 7 weeks; improvements occurred at 14 weeks compared to baseline in MPACT vs controls (7 weeks, –65 vs –96; 14 weeks, ≠42 vs –10 points) ‣ Significant difference between MPACT vs controls in lack of interest at 7 weeks (0 vs + 1.6; p<0.05) ‣ Exercise being classified as "boring" was significantly different at 7 weeks in controls vs MPACT group (+0.8 vs –0.6; p<0.05)	Data not collected

* indicates clinically relevant as reported by author; %BF, percent body fat; 6MWT, 6 min walk test; AUDIT, Alcohol Use Disorders Identification Test; BFI, Brief Fatigue Inventory; BIA, bio-electrical impedance analysis; BMI, body mass index; CES–D, Center for Epidemiological Studies–Depression; CRT, chemoradiotherapy; DE, delayed exercise; DLI, delayed lifestyle intervention; DXA, dual-energy x-ray absorptiometry; EE, early exercise; EN-AF, exercise and nutrition intervention after radiation therapy; EN–DUR, exercise and nutrition intervention during radiation therapy; EORTC QLQ C–30, Treatment of Cancer Quality of Life Core Questionnaire; ESAS, Edmonton Symptom Assessment Survey; FACT–An, Functional Assessment of Cancer Therapy–Anemia; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT–G, Functional Assessment of Cancer Therapy–General; FACT–H&N, The Functional Assessment of Cancer Therapy–Head and Neck; FHNSI, FACT–Head and Neck Symptom Index; IADL, Lawton Instrumental Activates of Daily Living Scale; ILI, immediate lifestyle intervention; KE, knee extensor; LBM, lean body mass; MCS, mental component score; MOS, medical outcomes study; MPACT, maintaining physical activity during cancer treatment; NDII, neck dissection impairment index; ONS, oral nutritional supplements; PAfitME, physical activity intervention with fitness graded motion exergames; PASE, Physical Activity Scale for the Elderly; PCS, physical component score; PG–SGA, Patient Generated–Subjective Global Assessment; PLA, placebo; PRET, progressive resistance exercise training group; PROCR, protein and creatine; QoL, quality of life; RM, repetitions maximum; ROM, range of motion; RPE, rate of perceived exertion; SF-36, medical outcomes survey short form-36; SPADI, shoulder pain and disability index; TP, standardized therapeutic exercise protocol.

Table 2.3: Study design, participants, and non-exercise details of reviewed studies.

Author/year	Study Design	Participants	Non-exercise details
Capozzi *et al*, 2015	Pre-test, post-test one group design	N=21 Mean age: 52.9 ± 9.4 years	N/A
Capozzi *et al*, 2016	Exploratory randomized controlled trial	N=60 (31 ILI; 29 DLI) Mean age: 56.1 ± 9.2 years	Physician referral and clinical support Health education Behavioural support Social support
Lønbro *et al*, 2013	Single center, randomized, stratified and parallel-grouped feasibility study	N=30 (16 PROCR; 14 PLA) Mean age: 56 years PROCR; 59 years (range: 40–68) PLA	Dietary supplementation (protein and creatine supplementation)
Lønbro *et al*, 2013	Multi-center, randomized, stratified and parallel-grouped study	N=41 (20 EE; 21 DE) Mean age: 55 ± 7 years EE; 58 ± 7 years DE	N/A
Lonkvist *et al*, 2017	Single-center, prospective study	N=12 Mean age: 56 years (range: 47–66)	N/A
McNeely et al, 2004	Prospective randomized controlled trial	N=17 (8 exercise group; 9 control group) Mean age: 61 ± 7.7 years (exercise group, 60 ± 7.4 years; control group, 61 ± 8.1 years)	N/A
McNeely *et al*, 2008	Prospective randomized controlled trial	N=52 (25 TP; 27 PRET) Mean age: 52 years); TP: 57 years; PRET 53 years	N/A
Rogers *et al*, 2013	Pilot, 2-arm, randomized controlled trial	N=15 (7 intervention, 8 control) Mean age: 61 ± 13 years (intervention, 55 ± 11 years; control 66 ± 13 years)	Participants received nutritional counseling with (intervention) and without (control) resistance exercise prescription
Samuel *et al*, 2013	Randomized controlled trial	N=48 (24 control; 24 exercise) Mean age: control, 53 ± 8 years; 52 ± 10 years	N/A
Sandmæl *et al*, 2017	Single-center, 2-arm, randomized controlled pilot trial	N=41 (20 EN-DUR, 21 EN-AF) Mean age: 62 ± 2 years (EN-DUR, 64 ± 2 years; EN-AF, 64 ± 2 years)	Nutritional supplementation
Wang *et al*, 2018	Pre-efficacy, single-group design	N=8 Mean age: 57 ± 13 years	N/A
Zhao *et al*, 2016	Pilot controlled trial	N=20 (11 MPACT; 9 control) Mean age: 57 years	N/A

DE, delayed exercise; DLI, delayed lifestyle intervention; EE, early exercise; EN–AF, exercise and nutrition intervention after radiotherapy; EN–DUR, exercise and nutrition intervention during radiation therapy; ILI, immediate lifestyle intervention; MPACT, maintaining physical activity during treatment; PLA, placebo; PRET, progressive resistance exercise training; PROCR, protein and creatine; TP, standardized therapeutic exercise protocol.

2.4.1 Intervention details

Nine studies implemented resistance (or strength) training exercises and three studies combined resistance and aerobic training (Samuel, Maiya, Babu, & Vidyasagar, 2013; Wang et al., 2018; Zhao et al., 2016). The duration of the interventions ranged from 3 weeks (Sandmæl et al., 2017) to 14 weeks (Zhao et al., 2016), while the majority of interventions lasted 12 weeks in length (Capozzi et al., 2015; Capozzi et al., 2016; Lønbro, Dalgas, Primdahl, Johansen et al., 2013; Lønbro, Dalgas, Primdahl, Overgaard et al., 2013; Lonkvist et al., 2017; McNeely et al., 2008, 2004; Rogers et al., 2013). Five interventions provided initial participant supervision of exercise sessions and transitioned to independent, unsupervised exercise sessions (Rogers et al., 2013;

Wang et al., 2018; Zhao et al., 2016). Five interventions gave fully supervised exercise sessions (Lonkvist, Vinther et al., 2017; McNeely et al., 2008, 2004; Samuel et al., 2013; Sandmæl et al., 2017), and two provided concurrent supervised and unsupervised exercise sessions (Capozzi, Boldt, et al., 2015; Capozzi et al., 2016).

2.4.2 Review of safety

In the studies reviewed, overall issues with safety seem to be minimal. Adverse events were reported by three of the twelve studies (McNeely et al., 2008, 2004; Rogers et al., 2013). In two of the three articles to report adverse events, it appears they were unrelated to the exercise intervention (McNeely et al., 2004; Rogers et al., 2013). McNeely and colleagues (McNeely et al., 2008) reported that one participant withdrew from the study as a result of sustaining a soft-tissue injury to the scapular region.

2.4.3 Recruitment and adherence

Feasibility (i.e. recruitment rate, adherence to the exercise intervention, and adverse events) was the primary outcome in seven studies (Capozzi et al., 2015; Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013; Lonkvist, Lønbro, et al., 2017; McNeely et al., 2004; Rogers et al., 2013; Sandmæl et al., 2017; Wang et al., 2018). Recruitment rates ranged from 22% to 82% and were reported in ten of the twelve studies (Capozzi et al., 2015; Capozzi et al., 2016; Lønbro, Dalgas, Primdahl, Johansen et al., 2013; Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013; Lonkvist, Vinther, et al., 2017; McNeely et al., 2008, 2004; Rogers et al., 2013; Sandmæl et al., 2017; Wang et al., 2018). Exercise intervention adherence rates ranged from 45% to 97% and were reported in all but one study (Samuel et al., 2013). Capozzi et al., whom in part, investigated the effects of a ‘lifestyle intervention’ while undergoing treatment (Capozzi et al., 2016), reported a substantially lower adherence rate (45%) in comparison to similar interventions that were 77% (Lonkvist, Vinther, et al., 2017), and 72% (Zhao et al., 2016), respectively. It is difficult to report on the differences between studies, but HNC treatments pose many barriers that limit adherence, an important consideration when designing future studies.

2.4.4 Effects of exercise in people affected by head and neck cancer

The main and reoccurring outcomes that seem to be repeated in the twelve studies examined include muscular strength, anthropometric measurements, fatigue management, and HRQL. Despite the diversity of different assessment tools, which makes comparing results difficult, the following sections will now report on the potential benefits from exercise training interventions during and following treatment.

2.4.4.1 Muscular strength

Muscular strength was investigated in nine studies. Four interventions evaluated muscular strength using handgrip dynamometry and found no differences (Capozzi et al., 2015; Capozzi et al., 2016; Rogers et al., 2013; Wang et al., 2018). The exploratory randomized controlled trial by Capozzi et al., found that both groups (immediate lifestyle intervention vs delayed lifestyle intervention) had no difference in muscular strength from baseline to 12 weeks, and baseline to 24 weeks following a 12-week individualized exercise program (Capozzi et al., 2016).

Lønbro and colleagues (Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013) compared a 12 weeks of progressive resistance training plus protein and creatine supplementation versus progressive resistance training alone, and found that isometric and isokinetic knee extensor strength increased significantly over time, however no differences between groups. In their succeeding body of work, Lønbro and colleagues (Lønbro, Dalgas, Primdahl, Johansen, et al., 2013) compared 12 weeks of progressive resistance training initiated 8 weeks after treatment versus 20 weeks after treatment, and found isometric knee extensor strength significantly improved over self-chosen physical activity, with similar results observed in isokinetic knee flexion. Zhao and colleagues (Zhao et al., 2016) allocated HNC patients to a 14-week functional resistance training and walking program designed to maintain physical activity during cancer treatment and observed a significant mean decrease in knee extensor strength.

Two studies reported on muscular strength using the 1-repitition maximum test. Lonkvist et al. (Lonkvist, Vinther, et al., 2017) reported a significant decrease in chest press, while leg press remained unchanged following 12-weeks of progressive resistance training while receiving RTx with concomitant chemotherapy. McNeely et al. (McNeely et al., 2008) examined the effects of a progressive resistance exercise training programme versus standardized therapeutic exercise and found progressive resistance exercise to be superior in developing upper extremity strength and upper extremity endurance measured by a 50% submaximal seated row test.

2.4.4.2 Muscle mass

Muscle mass was reported only by Sandmæl and colleagues in their randomized pilot trial comparing progressive resistance training and oral nutritional supplementation during and after RTx (Sandmæl et al., 2017). There was no difference assessed in muscle mass between the groups from baseline to the final assessment. A trend towards limiting the loss of muscle mass in the exercise group compared to patient controls both during and after treatment was reported. However, due to the feasibility nature of the study, authors were not powered to detect a interaction effect.

2.4.4.3 Fatigue

Three studies reported positive effects on self-reported fatigue management utilizing physical exercise programmes (McNeely et al., 2008; Rogers et al., 2013; Wang et al., 2018). Using resistance bands over a 12-week training program while undergoing treatment, Rogers et al. (Rogers et al., 2013) reported improved fatigue in the FACIT-F questionnaire, finding a medium effect size over controls.

Fatigue was reported in two studies following cancer therapy with the use of physical exercise interventions (McNeely et al., 2008; Wang et al., 2018). McNeely et al. (McNeely et al., 2008) detected no difference in fatigue using the Functional Assessment of Cancer Therapy-Anemia scale, however reported a trend in favor of progressive resistance exercise compared to standardized therapeutic exercise. Interestingly, the mean score at baseline for both groups were below the clinically relevant fatigue threshold at baseline, and above the clinically relevant threshold after training, however, did not detect a minimal clinically important change. Wang et al. (Wang et al., 2018) found both statistical and clinically important differences using the Brief Fatigue Inventory following a 6-week physical activity intervention.

2.4.4.4 Health-related quality of life

Four studies reported on changes in HRQL in patients over the course of cancer treatment (Lonkvist, Vinther, et al., 2017; Rogers et al., 2013; Samuel et al., 2013; Zhao et al., 2016). One study reported changes in HRQL in patients participating in progressive resistance training undergoing concomitant chemoradiotherapy (Lonkvist, Vinther, et al., 2017). Global health status, emotional, cognitive, and social functioning using the EORTC QLQ-C30 and QLQ-H&N35

appeared to decline during the 12-week programme, however returned to baseline values at 5-months post-treatment (Lonkvist, Vinther, et al., 2017). Rogers et al. detected medium and small effect size improvements for the intervention versus the control group using the FACT-G scale at 6 weeks and 12 weeks, respectively (Rogers et al., 2013). Samuel et al. reported improved HRQL using the SF-36 after 6 weeks of an individually tailored walking and active exercise programme (Samuel et al., 2013). Following 6 weeks of exercise training, the physical component score remained nearly the same in the exercise group, while in the control group there was a decrease. Similarly, there was a significant decrease in the mental component score after 6 weeks in the control group, while there was a significant increase in the exercise group (Table 2.2).

Zhao et al. also measured the impact of their intervention using the SF-36 form (Zhao et al., 2016). When evaluating changes from baseline, maintaining physical activity during cancer treatment compared to controls tended to decline less at 7 weeks, and improved greater at 14 weeks, respectively (Zhao et al., 2016).

Three studies reported on changes in HRQL following treatment. Two studies measured the impact of their intervention on HRQL in participants which cancer diagnosis had been managed by definitive surgical resection (McNeely et al., 2008, 2004). Surprisingly, the pilot study of McNeely et al. found a decreasing trend in HRQL score of both groups (progressive resistance exercise training vs control) from baseline to after the 12-week intervention period, however was not statistically significant (McNeely et al., 2004). In their ensuing study, McNeely and colleagues reported that 12-weeks of programmed exercise did help to manage HRQL. Although there was no statistical difference in HRQL, a clinically meaningful improvement was found in favor of progressive resistance exercise training over standardized therapeutic exercise using the FACT-An and FACT-G scales (McNeely et al., 2008).

One study reported on changes in HRQL over a 12-week progressive resistance training programme following curative RTx with/without chemotherapy (Lønbro, Dalgas, Primdahl, Johansen, et al., 2013). Using the EORTC QLQ-C30, Lønbro et al. found that overall HRQL improved significantly more in the group given the intervention 8 weeks following treatment compared to the group that began 20 weeks post-treatment when compared from baseline to week 12 (Lønbro, Dalgas, Primdahl, Johansen, et al., 2013).

HRQL was assessed using the FACT-An and FACT Head/Neck Symptom Index-22 in participants enrolled into an exercise programme at the initiation of, or following radiation

with/without chemotherapy (Capozzi et al., 2016). Across 24 weeks, declines in both the FACT-An and FACT Head/Neck Symptom Index-22 were present, with scores returning to baseline values by 24 weeks (Capozzi et al., 2016).

2.4.5 Summary of current research

The utilization of exercise interventions in HNC rehabilitation is an emerging field. Existing studies support strength training interventions for patients with HNC both during and following cancer treatment, but no clear consensus on the optimal initiation of such programs has been reached. Exercise prescription also remains underdeveloped in this population, which may be due to a lack of adequately powered randomized controlled trials and studies of poor quality. Therefore, future research is necessary to determine different interventions, and their impact on HNC patients.

Conventional strength training is characterized by dynamic volitional muscle actions against external loads and typically performed using free weights, cable pulleys, elastic bands and exercise machines. Recent literature has outlined progressive overload, specificity, variation, and rest/recovery as the foremost principals of progressive strength training (Ratamess et al., 2009), that if applied appropriately, may optimize neuromuscular adaptations and improve HRQL. However, given the multitude of training variables that can be manipulated to obtain specific adaptations (e.g. moderate to high loading coupled with relatively high volume and short rest intervals to elicit muscular hypertrophy, or heavy loading at a high velocity to elicit muscular force), applying generic training principles to patients and survivors of HNC may limit the full potential in such a population. As such, alternative training strategies can be applied to develop neuromuscular adaptations.

Among them, neuromuscular electrical stimulation (NMES) is one such alternative, which has previously demonstrated efficacy in increasing skeletal muscle hypertrophy, muscle strength, and cardiovascular fitness (Brüggemann et al., 2017; Fan et al., 2012; Gondin et al., 2010; O'Connor & Caulfield, 2018; Vieira et al., 2014). Another potential alternative is eccentric–emphasised muscle actions, which have been shown to induce favorable muscular development such as muscular hypertrophy (Maeo, Shan, Otsuka, Kanehisa, & Kawakami, 2018), force production (Lepley, Wojtys, & Palmieri-Smith, 2015), and neuromuscular control (Lepley,

Lepley, Onate, & Grooms, 2017) when compared to similar forces in its concentric counterpart. These two modalities will now be briefly discussed below.

2.5 Neuromuscular electrical stimulation

2.5.1 Introduction of neuromuscular electrical stimulation

Unlike other electrical stimulation modalities such as transcutaneous electrical stimulation, that is commonly used for pain relief, NMES has been acknowledged as an efficient modality leading to significant improvements in muscle properties, and has demonstrated to be beneficial across a variety of populations (Brüggemann et al., 2017; O'Connor, Caulfield, & Lennon, 2018), including able-bodied individuals and athletes for sports training [although out of the scope of this practice (for a review, see Gondin et al., 2011)], and rehabilitation settings. For example, recently conducted randomized controlled trials have demonstrated that early application of NMES has been found to effectively attenuate the loss of muscle strength and improve functional performance of the quadriceps femoris muscle following total knee arthroplasty and anterior cruciate ligament reconstruction (Feil, Newell, Minogue, & Paessler, 2011; Stevens-Lapsley, Balter, Wolfe, Eckhoff, & Kohrt, 2011). Several other studies have tested the impact of NMES training programmes. In patients with chronic obstructive pulmonary disease, for example, NMES of the quadriceps femoris led to increased exercise performance, peripheral muscle function, and HRQL following an 8-week training period (Vieira et al., 2014). More so, in critically ill patients confined to bed rest, NMES of the quadriceps femoris led to significantly reduced muscle mass loss as assessed with ultrasound (Gerovasili et al., 2009). In cancer rehabilitation, the use of NMES is an emerging field with limited studies (O'Connor et al., 2018). Current evidence suggests that NMES is effective for improving HRQL in cancer survivors (O'Connor et al., 2018), although conflicting findings in patients receiving palliative chemotherapy suggest differently (Maddocks et al., 2013). Furthermore, the effects of NMES on objective measures (i.e. strength, body composition, muscle function) are less clear (O'Connor et al., 2018). Only a select number of cancer types have been investigated, including breast cancer (Belmonte et al., 2011), non-small cell lung cancer (Maddocks et al., 2013, 2009), metastatic lung cancer (Crevenna, Marosi, Schmidinger, & Fialka-Moser, 2006), low rectal cancer (Kuo et al., 2015), foregut cancers (Strasser et al., 2009), and HNC (Lin et al., 2011). Although Lin et al. used people affected by HNC, functional electrical stimulation was delivered only over the suprahyoid muscles to assess the effects of swallowing

function in nasopharyngeal carcinoma patients. Nevertheless, it seems plausible that supervised NMES programmes to improve performance of the neuromuscular system has applicability for people affected by HNC to limit the complications associated with cancer treatment and improve HRQL.

2.5.2 Physiological considerations of neuromuscular electrical stimulation

Muscular contractions evoked by NMES demonstrate a unique motor unit recruitment profile, which differs in several spatial and temporal summation characteristics compared to volitional dynamic muscle actions. According to the well-established Henneman's size principal of voluntary contractions, motor units are recruited in an orderly fashion from small (which are typically slower and less fatigable) to large (faster and more fatigable) (Henneman, Somjen, & Carpenter, 1965). In contrast, the electrical impulses generated by NMES evoke action potentials in the intramuscular motor axon terminal branches located within the electrical field along with outermost sensory nerve endings (Spector et al., 2016). In other words, NMES recruits motor units in a superficial and nonselective pattern (Spector et al., 2016), especially in the quadriceps femoris, where it has been demonstrated that larger motor units are located superficially (Knight & Kamen, 2005). Overall, this unique sequence of motor unit recruitment increases the rate and amount of muscle fatigue. As the current intensity of NMES is increased, deeper motor units are recruited (Spector et al., 2016). That is, the higher the intensity of NMES, the greater the proposed improvements are likely to be.

Feedback mechanisms from afferent nociceptors in the skin however induce a level of discomfort that may limit high stimulation intensities, therefore resulting in an inability to reach high force levels (Maffiuletti, 2010). Muscular forces generated by NMES contractions are usually far from the level of force produced during a maximal isometric voluntary contraction (MIVC) as a consequence (Vanderthommen & Duchateau, 2007). Previous research has observed that on average, NMES-evoked contractions at individual pain thresholds (i.e. maximal) in the quadriceps typically correspond to 40–60% MIVC (Lieber & Kelly, 1991; Theurel, Lepers, Pardon, & Maffiuletti, 2007). However, available results have varied between NMES-evoked forces corresponding from 25% to 90% MIVC (Vanderthommen & Duchateau, 2007), indeed demonstrating that NMES is less effective than voluntary contractions in developing high contraction forces. The latter results may be attributed to a highly trained and motivated cohort

who can tolerate tremendously high current intensities, that are not reproducible in clinical settings. The lack of understanding physiological specificities in response to its many parameters, in particular characteristics of the electrical current (e.g. pulse duration and frequency), is perhaps another major barrier to successfully implementing NMES in clinical settings (Spector et al., 2016). However, and although often debated, it has been suggested that to achieve a NMES-evoked contraction similar to that of a sustained voluntary muscle contraction, pulse frequencies of 35–75 Hz should be utilized (Spector et al., 2016). As such, there is no known consensus on an optimal NMES training programme (Spector et al., 2016). Moreover, the limited amount of studies that have provided NMES treatment to cancer survivors specifically, lacked standardisation in programme prescription and progression (O'Connor et al., 2018). Additionally, NMES cannot improve coordination between working muscles and therefore does not facilitate learning specific coordination and motor control of complex movements (Paillard, 2008). Hence, combining NMES in adjunct with volitional muscle actions may allow for greater adaptations in the neuromuscular system, and also motor control during voluntary movement (Paillard, 2008), which are important aspects in activities of daily living and functional independence.

2.5.3 Application of neuromuscular electrical stimulation for survivors of HNC

NMES involves the application of electrical impulses disseminated through surface electrodes at a level that induces controlled skeletal muscle contractions (Hultman, Sjöholm, Jäderholm-Ek, & Krynicki, 1983), and usually placed on major muscle groups (e.g. quadriceps femoris) (O'Connor et al., 2018). Despite the potential limitations of NMES described above, its physiological adaptations offer important benefits for the use in cachexic patients, particularly those affected by HNC. Similar to strength training with voluntary contractions, NMES can increase maximal muscle force in voluntary contractions following several bouts of strength training, which is mainly attributed to neural adaptations (i.e. an increased capacity to activate motor units) but without overt muscle hypertrophy (Hortobágyi & Maffiuletti, 2011), and through structural adaptations (i.e. muscle hypertrophy) which commonly appear after 6–8 weeks. However, the ability of NMES to recruit a relatively high proportion of large, high-force motor units at relatively low contraction intensities in comparison to voluntary muscle contractions is particularly important in conditions characterized by skeletal muscle weakness and muscular atrophy (i.e. cancer cachexia), in which high-force muscle fibers are typically more affected

(Morrissey, 1988). Due to the possible inability of HNC survivors to generate contractions sufficient enough to promote strength gains shortly after post-treatment, NMES training programs may elicit superior improvements in maximal voluntary strength, muscle mass, and exercise capacity when compared to traditional rehabilitation interventions used for survivorship in HNC (i.e. strengthening, cardiovascular, and flexibility strategies).

2.6 Eccentric muscle actions

2.6.1 Introduction of eccentric muscle actions

Our current knowledge of muscle energetics is often referred to the early work of W.O. Fenn, who first established that the energy cost of force production is: 1) increased when work is performed during muscle shortening; and 2) reduced when work is performed during muscle lengthening (Fenn, 1924). An eccentric muscle contraction occurs when the force applied to a muscle exceeds the momentary force produced by the muscle itself which results in a lengthening action (Douglas, Pearson, Ross, & McGuigan, 2017). In contrast, muscle shortens during a concentric contraction. Concentric muscle contractions initiate dynamic movements while eccentric muscle contractions slow or stop them. Together, eccentric and concentric actions form a muscle function referred to as the stretch shortening cycle, a phenomenon naturally occurring in everyday able-bodied human motor tasks (i.e. ground locomotion). But eccentric contractions are uniquely different from concentric contractions in terms of both molecular and neurological mechanisms and remain less understood. Although it is unlikely that a single theory can explain the various observations of eccentric muscle contractions, possible mechanisms include a greater actin-myosin interaction at the cross-bridge level compared to concentric or isometric contractions, as well as the activation of force modulating structural proteins such as titin (Baroni, Ronei, Herzog, & Vaz, 2015; Douglas et al., 2017). It has also been suggested that neural inhibition is greater in eccentric compared to concentric maximal voluntary contractions (Baroni et al., 2015; Enoka, 1996). However, one theory that has remained well established for nearly a century is that, during eccentric contractions, the force production of human skeletal muscle is increased (Fenn & Marsh, 1935). Thus, there are two defining characteristics to eccentric muscle contractions that make them possible to employ in HNC training interventions: 1) force production is distinctively high; and 2) the energy required to produce force is distinctively low (Lastayo, Marcus, Dibble,

Frajacomo, & Lindstedt, 2014). In other words, this allows participants to perform the same amount of work at lower perceived efforts than concentric training.

2.6.2 Defining properties of eccentric exercise for head and neck cancer survivors

Indeed, because of the side-effects of cachexia as a consequence of RTx ± concomitant chemotherapy for HNC, it seems apparent that exercise capable of producing high force with minimal energy output are ideal characteristics for strength training interventions in this population. Consequently, these side-effects contribute to a reduction in functional capacity and HRQL. As a means of combatting these declines, training interventions including eccentrically-emphasized training methods seem applicable since their use have demonstrated favorable muscular adaptations, including superior improvements in muscle strength and structural (i.e. muscle thickness) outcomes when compared to conventional strength training (Raj et al., 2012). Assessing and understanding the defining properties, safety, feasibility, and application of eccentric exercise may be an asset in HNC.

2.6.2.1 Strength adaptations

Eccentric training programmes have resulted in strength improvements across various modes of strength measures (i.e. eccentric, concentric, and isometric), regardless of the type of eccentrically-emphasized training (i.e. eccentric isokinetic or isotonic) (Baroni et al., 2015). For example, Baroni et al. investigated the effects of a 12–week eccentric training program of the knee extensors on an isokinetic dynamometer and found a 29%, 24% and 15% increase in eccentric, isometric, and concentric strength, respectively (Baroni et al., 2013). Meanwhile, Santos and colleagues reported increases in isometric (10%) and eccentric strength at 30°/s (20%) and 120°/s (13%) following 6 weeks (12 sessions) of eccentric isokinetic training, respectively (Hanashiro, Ávila, Santos, Salvini, & Camargo, 2010). Further, similar findings have been reported in other muscle groups. For example, Pensini et al. reported significantly increased maximal eccentric (16%), isometric (30%) and concentric (14%) torque following a 4 week eccentric training programme (Pensini, Martin, & Maffiuletti, 2002). These results are supported by other studies investigating the effects of eccentric knee extensor training programmes, which have yielded similar results [See (Baroni et al., 2015) for a recent review].

2.6.2.2 Structural adaptations

In addition, evidence exists that eccentrically-emphasized muscle actions provide a greater stimulus for hypertrophy than its concentric counterpart (Roig et al., 2009). Commonly used to examine the hypertrophic response in a multitude of studies is the measurement of cross-sectional area (CSA) using ultrasonic imaging (Baroni et al., 2015; Lieber & Friden, 2000). A popular anatomical location to measure CSA is the quadriceps femoris, since they have an important function in performing locomotor tasks such as walking, as well as its common inclusion in clinical outcomes and research settings (Gruet et al., 2014). Previous studies have observed significant increases in quadriceps muscle thickness after eccentric training programmes. For example, Baroni and colleagues, reported significant increases in muscle thickness in the vastus lateralis and rectus femoris by around 7–10%, respectively, following 12 weeks of isokinetic eccentric training (Baroni et al., 2013), with similar increases found in the vastus medialis (Blazevich, Cannavan, Coleman, & Horne, 2007). Comparable results have also been found in older adults, many of whom experience sarcopenia and functional declines (LaStayo, Ewy, Lindstedt, Johns, & Pierotti, 2011). Among studies reviewed, authors observed increases in vastus lateralis muscle thickness by up to 60% with eccentric training programmes lasting between 11–16 weeks (LaStayo et al., 2011; Raj et al., 2012).

2.6.3 Exercise-induced muscle damage

Despite their seemingly superior characteristics over concentric muscle actions, high-force eccentric contractions are associated with exercise-induced muscle damage. Indeed, if carried out vigorously enough all forms of exercise (i.e. concentric or isometric) can become painful, and muscles become fatigued. However, within a short time frame (i.e. 1–2 hours) muscles typically recover (Uwe Proske & Allen, 2005). Performing repetitive unaccustomed eccentric exercise is associated with delayed onset-muscle soreness, which has been described as the stiff, aching soreness felt during movement or palpation of the affected tissue (Douglas et al., 2017; Proske & Morgan, 2001). Exercise-induced muscle soreness appears in the hours following cessation of eccentric exercise, peaks between 24–72 hours, and eventually disappears between 5–7 days (Cheung, Hume, & Maxwell, 2003). There is clear evidence suggesting that initial exercise–induced muscle damage is a result of disruption to the sarcomeres as well as impairment of the excitation–coupling process (LaStayo et al., 2003; Proske & Morgan, 2001). Such disruptions may

cause several other short term changes in peripheral responses, including a decline in voluntary and evoked muscle force, inflammation, and oedema, as well as changes in the central nervous system, including impairment in voluntary activation (i.e. increased central fatigue) (Goodall et al., 2017). Although there are negative short-term consequences to eccentric muscle contractions, particularly when performed at high intensities, eccentric exercise can result in protective effects against subsequent bouts of lengthening contractions lasting from several weeks to months (Douglas et al., 2017; Goodall et al., 2017). This phenomenon, referred to as the repeated bout effect, is known to progressively attenuate exercise-induced muscle damage in successive and similar bouts of eccentric exercise (Douglas et al., 2017). Nevertheless, there are a number of mechanisms contributing to eccentric work including neural, mechanical, and cellular adaptations (for a review, see Douglas et al., 2017), that presumably far outweigh the acute responses associated with eccentric exercise.

2.6.4 Safety, feasibility, and application of eccentric overloading in survivors of HNC

The safety and feasibility of eccentric exercise training has been demonstrated in a diverse sample of individuals in rehabilitative settings. For example, eccentric exercise training programmes have been observed in patients after anterior cruciate ligament reconstruction (Gerber et al., 2007), persons with Parkinson's disease (Dibble, Hale, Marcus, Gerber, & LaStayo, 2006), patients with advanced COPD (Rocha Vieira et al., 2011), and elderly cancer survivors (LaStayo, Larsen, Smith, Dibble, & Marcus, 2010).

Because treatment for HNC frequently results in muscle wasting, muscle weakness, and increased fatigue, using eccentric training methods to mitigate these effects and improve physical performance and HRQL seems reasonable. This is mainly attributed to the potential of generating high force contractions at a relatively lower energy cost and perceived exertion than what would be required to perform concentric muscle actions. There is no question that muscle lengthening under an external load results in structural damage, particularly when unfamiliar (Baroni et al., 2015). However, it is not unreasonable to think that eccentric contractions, if introduced cautiously and progressively, must result in such a response. Indeed, eccentric overloading can be a viable option to conventional training for HNC survivors as it appears to induce superior muscular adaptations including neural, hypertrophic, and strength improvements (Baroni et al., 2015).

2.7 Statement of the problem

Early research (see Table 2.2) has shown some success in the use of generic, conventional physical exercise to relieve many of the side effects for HNC survivors (Capozzi, Nishimura, et al., 2015). Typically, when the correct training principals are adhered to, muscle strength and muscle mass are effectively enhanced. However, conventional strength training variables may be less effective in eliciting positive outcomes in clinical populations. In particular, individuals who receive treatment for HNC can experience profound side-effects that often contribute to the risk of cancer-related cachexia. It is not unreasonable to speculate that this patient population will experience a reduced exercise-capacity in such a way that limits their ability to produce muscle force sufficient enough to preserve muscle function and/or lack the energy required to do so. Furthermore, cancer treatment may cause an increased perception in fatigue and a reduction in overall physical function and HRQL.

Given the above discussion, it seems generic strength training prescriptions may be less applicable to increase muscle strength and mass in individuals affected by HNC treatment. Therefore, the effectiveness of alternative strength training regimens require investigation. In typical research settings, eccentric overloading involves machine assisted (i.e. an isokinetic dynamometer) concentric movements that are sequentially lowered (eccentrically) by participants. Although this form of training is reliable and commonly used in research facilities, it is far less applicable in real-world situations. A more practical way of obtaining eccentric overload is through accentuated eccentric loading, whereby an external load is eccentrically lowered with one limb and concentrically lifted with two limbs (Wagle et al., 2017). Hence, this form of eccentric overload training involves a relatively underloaded concentric phase and overloaded eccentric phase. Also, by implementing this strategy, our protocol can be done at home without supervision (once participants are familiarized) as it requires relatively little equipment.

It is clear the literature indicates that both NMES and eccentric overload training independently induce favorable muscular adaptations, however the combined effects of these training modalities is limited. Also, no study has attempted to optimize the type of exercise prescribed to survivors of HNC by investigating alternatives to strength training.

In addition to the lack of optimized exercise prescription in survivors of HNC, research on the measurement of neuromuscular function or fatigue following exercise is limited. Few studies in total (< 10) have been published on the topic, none of which investigate the mechanisms of

neuromuscular function or fatigue as a result of exercise in HNC survivors; see Twomey et al. for a brief synopsis (Twomey, Martin, et al., 2018). The general consensus of these findings was that (i) central mechanisms may be a greater contributor in the cessation of exercise and (ii) there is less of disturbance to contractile proprieties (i.e. limited contribution of peripheral fatigue) (Twomey, Martin, et al., 2018). However, people affected by HNC are faced with unique side-effects that may contrast these findings. Hence, there is a gap in the literature that requires further insight into the central and peripheral properties of neuromuscular function and exercise-induced fatigue in people affected by HNC.

Herein, the aim of this work was two-fold. In Chapter Three, we assessed the impact of treatment for HNC on neuromuscular function and fatigability in the knee extensors and patient-reported outcomes. In Chapter Four, our main aim was to assess the feasibility of an experimental strength training intervention involving a combination of eccentric overloading and NMES, and a conventional strength training intervention that was similar in frequency and total number of contractions. The second aim was to provide preliminary efficacy for the experimental and conventional strength training interventions regarding muscle strength and muscle CSA of the knee-extensors.

Chapter Three: Neuromuscular Function and Fatigability in People Diagnosed with Head and Neck Cancer Before Versus After Treatment

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Running Title: Effects of radiation therapy on neuromuscular function

3.1 Abstract

Background: Treatment for head and neck cancer (HNC) is associated with multiple side-effects and deleterious consequences including reductions in body mass, physical function and health-related quality of life (HRQL). Little is understood about alterations in neuromuscular function and fatigability induced by radiation therapy (RTx).

Objective: This study aimed to assess the impact of RTx ± concomitant chemotherapy as curative-intent treatment for HNC on neuromuscular function and fatigability in the knee extensors, performance time, and patient reported outcomes.

Methods: Ten people with HNC (4 female; 50 ± 9 years) competed a neuromuscular assessment protocol before (post-operative: n=7) and after (56±30 days) completion of RTx (RTx with concomitant chemotherapy: n=8). Lab assessments included anthropometrics, self-reported fatigue (Functional Assessment of Chronic Illness Therapy–Fatigue), HRQL (Functional Assessment of Cancer Therapy–Head & Neck) and a neuromuscular assessment [involving maximal isometric voluntary contractions (MIVC) in the knee extensors and electrical stimulation of the femoral nerve] before and during an intermittent cycling test.

Results: Paired-sample t-tests were performed to test for within-group differences. From before to after treatment, MIVC was reduced (530 ± 179 vs. 421 ± 131 N; P = 0.002), as was potentiated twitch force (172 ± 49 vs. 144 ± 46 N; P < 0.001), and muscle cross-sectional area in the vastus lateralis (19.49 ± 6.40 vs. 15.55 ± 6.69 cm^2; P = 0.01) and rectus femoris (6.29 ± 2.47 vs. 4.93 ± 1.90 cm^2; P = 0.004). Time to volitional exhaustion was reduced from 966 ± 269 s to 823 ± 239 s (P = 0.008) and peripheral, rather than central processes contributed to a reduction in maximal force due to cycling exercise. After treatment, the severity of self-reported fatigue increased (P = 0.041) and HRQL decreased (P = 0.012), which was significantly correlated with MIVC force (P = 0.049).

Conclusion: Our results provide evidence of neuromuscular decrements in HNC patients following treatment, that may be explained, largely, by peripheral perturbations. Future research may consider targeting neuromuscular outcomes and HQRL measures with resistance training interventions in HNC survivors.

Words: 337

Keywords: Central fatigue, peripheral fatigue, maximal isometric voluntary contraction, cancer rehabilitation, exercise oncology

3.2 Introduction

Neoplasms that arise from different anatomic subsites in the head and neck region, and include oral cavity, laryngeal, nasopharyngeal, oropharyngeal and hypopharyngeal carcinomas are collectively known as head and neck cancer (HNC). Head and neck squamous cell carcinomas account for more than 90% of all head and neck malignancies, are the sixth most common cancer worldwide, and account for more than 830,000 new cases and 430,000 deaths annually (Bray et al., 2018; Cramer et al., 2019). While HNC has historically been linked to tobacco and alcohol consumption among older adults, infection of human papillomavirus (HPV) has recently become an important factor in the epidemiology of HNC, particularly of the oropharynx (Chaturvedi et al., 2011). People affected by HPV-positive HNCs have different demographic characteristics, including higher incidences in men and are younger in mean age at diagnosis (Cramer et al., 2019), and have a favourable prognosis compared to patients with HPV-negative tumours (Ang et al., 2010). Although substantial progress has been made in modern HNC disease management, approximately 60% of patients are diagnosed when the malignancy has developed into locally advanced disease and are usually treated with multimodal therapies (Adelstein et al., 2017; Uta et al., 2018). Radiation therapy (RTx) remains an integral part of curative-intent treatment for HNC and is scheduled as: (i) definitive curative treatment (i.e., total dose 66 – 70 Gy, delivered for 30 – 33 treatments over ~6 weeks); or (ii) after surgery, as adjuvant treatment with/without concomitant chemotherapy (Iacovelli et al., 2018).

Given that several critical structures in the head and neck region are subject to damage from RTx, (i.e. muscles involved in deglutition, salivary glands, and taste receptors), patients with HNC present unique late and long-term challenges (Peach et al., 2018; Rathod et al., 2015). In particular, these challenges contribute to a negative energy balance, which can cause severe and unintentional weight loss (i.e. > 5%), the main clinical parameter for the diagnosis of cancer cachexia (Fearon et al., 2011). Cancer cachexia is a common consequence of cancer therapy that occurs in 30% to 82% of patients with HNC (Jager-Wittenaar et al., 2007; Silver et al., 2007). Cancer cachexia is characterized by skeletal muscle atrophy that is associated with impaired muscle strength and functional (or physical) performance, reduced health-related quality of life (HRQL), and an increased perception of fatigue (Evans et al., 2008). Cancer cachexia in patients with HNC may be due to treatment side effects (Lonkvist, Vinther, et al., 2017), or directly from tumour burden (Couch et al., 2015; Der-Torossian et al., 2013), and may be accompanied by

several neuromuscular complications associated with cancer [see (Grisold et al., 2016) for a review]. Together these impairments can impact physical capabilities, substantially diminishing functional independence. However, few studies have assessed the measurement of neuromuscular function and performance fatigability in cancer populations (Twomey, Aboodarda, et al., 2017), and particularly not after a specific cancer treatment. Accordingly, a thorough investigation may inform a better understanding of these mechanisms to advance methods for disease management and promote enhanced HRQL and overall well-being in cancer patients.

Performance fatigability refers to objective decrements in task or motor performance (Kluger, Krupp, & Enoka, 2013). In order to investigate performance fatigability, our lab has developed a cycle ergometer (Doyle-Baker et al., 2018), that when combined with electrical stimulation paradigms [for a review, see (Millet et al., 2012)], allows for the investigation of the central and peripheral components of neuromuscular function before, during, and immediately after cycling exercise. Previous research has identified that central mechanisms may have a greater contribution than peripheral mechanisms (i.e. muscle contractile properties) in the decision to terminate a performance task in survivors of cancer (Cai et al., 2014; Kisiel-Sajewicz et al., 2013; Yavuzsen et al., 2009), however, only sustained single-joint isometric contractions have been investigated. Due to the demands of RTx for HNC, this population are faced with unique side effects including the loss of lean body mass and muscle strength (Jager-Wittenaar et al., 2011), therefore, compared to different cancer diagnoses and anti-cancer therapies, the same neuromuscular alterations may not apply. Understanding alterations in neuromuscular function as a crucial aspect of functional well-being and independence is a priority for future research.

Thus, the aims of this study were two-fold. First, we aimed to investigate the impact of RTx as curative-intent treatment for HNC on maximal force, muscle cross-sectional area (CSA) and patient-reported outcomes including HRQL and fatigue. Second, we aimed to investigate central and peripheral aspects of performance fatigability during and after an intermittent cycling test to exhaustion. It was hypothesized that maximal force and CSA of the knee extensors would decrease after the treatment period, and that time to volitional exhaustion during intermittent cycling and HRQL would be reduced, while the severity of fatigue for a given workload is increased.

3.3 Methods

3.3.1 Ethical approval

All experimental procedures were conducted in accordance with the *Declaration of Helsinki*, with the exception of registration in a database. This study was approved by the Health Research Ethics Board of Alberta – Cancer Committee (ID: HREBA.CC-16-0744). Written informed consent was provided by all volunteers prior to participation.

3.3.2 Participants and eligibility

Ten people diagnosed with HNC (mean ± SD; age: 50 ± 9; stature 172 ± 9 cm; 4 female) were recruited through the head and neck tumor clinic at HNC patient-education sessions at the Tom Baker Cancer Center (Calgary, AB), in collaboration with a senior radiation oncologist. A member of the research team gave a short presentation about the study, and interested patients gave permission to be contacted with additional study information. Potential participants were able to discuss the study and any questions or concerns with a member of the research team over the phone and/or email. Once patients confirmed that they were willing to participate, a time and date were set for the first laboratory visit. Participants were eligible if they met the following criteria: (1) a verified clinical diagnosis of head and neck cancer (stage I-IV) with the primary tumor in the oral cavity, pharynx, larynx, paranasal sinuses, or salivary glands; (2) due to receive RTx ± concomitant chemotherapy (3) aged 18–75 years; (4) able to walk without assistance; (5) received Canadian Society for Exercise Physiology-Certified Exercise Physiologist (CSEP-CEP) approval via The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and/or physician approval; and (6) willing/able to travel to the University of Calgary. Exclusion criteria were: (1) comorbidities that could confound the ability to participate in laboratory tests (e.g. other malignancies, neuromuscular, musculoskeletal or vascular conditions affecting the lower extremities, such as radiculopathy or myopathy, (where the research team were consulted for individual cases); (2) presence of a percutaneous endoscopic gastrostomy; and (3) unable to follow verbal instructions in English. Participants were instructed to refrain from consuming both caffeine and alcohol for a minimum of 12 h prior to experimental sessions and participating in intense exercise for 24 h.

3.3.3 Experimental design

Participant enrollment began in March 2017 and ended in February 2019. Volunteers (post-operative: n = 7 of 10 participants; RTx with concomitant chemotherapy: n = 8 of 10 participants) visited the laboratory on two separate occasions to complete a neuromuscular assessment protocol before (5 ± 5 days) and after (56 ± 30 days) RTx. Individual laboratory visits were scheduled at the same time of day (± 2 hours) to account for diurnal variations in muscle contractile properties (Tamm et al., 2009). During the first visit an in-person discussion was conducted by the study coordinator to inform participants of the purpose of the investigation, testing procedures, associated risks, and potential benefits. Informed consent was reviewed such that the information presented was comprehensible and participants understood that their participation was entirely voluntary. Participants completed neuromuscular assessments involving MIVCs in the knee extensors and electrical stimulation of the femoral nerve performed on both: (i) a standardized isometric chair; and (ii) a custom-built ergometer (Figure 1a) before, during, and immediately after cycling to assess performance fatigability, and was replicated in the subsequent trial (after RTx), with further details described in later sections.

3.3.3.1 Health screening

Participants completed a PAR-Q+ and were screened for contradictions that restricted maximal effort knee extensor contractions or cycling performance. Participants were also screened for hypertension and cardiac abnormalities, determined by resting blood pressure and electrocardiography measurements, respectively. If the participant displayed a resting blood pressure ≤ 144/94 mmHg, resting heart rate ≤ 90 bpm and normal sinus rhythm, respectively, and no further concerns that warranted physician approval, then they were cleared by a CSEP-CEP and continued the procedures descried below, in the order in which they were completed:

3.3.3.2 Patient-reported outcomes

Perception of fatigue was measured using the Functional Assessment of Chronic Illness Therapy – Fatigue, Version 4 (FACIT-F) questionnaire where higher scores indicate better status. The FACIT-F scale consists of a 13-item, unidimensional measure of fatigue (Yellen et al., 1997) with each item answered on a five-point scale from 0 (maximum fatigue) to 52 (minimum fatigue). A score of ≤ 34 was used to classify 'clinically significant fatigue' (Alexander et al., 2009; Van Belle et al., 2005), and a change in > 4 to identify those with a minimal clinically important

difference (MCID) (Elting et al., 2008). The FACIT-F scale has been previously used to investigate patient-reported outcomes among HNC (L. Rogers et al., 2013), with proven reliability to clinical outcomes (D. F. Cella et al., 1993). HRQL was measured using the Functional Assessment of Cancer Therapy – Head & Neck, Version 4 (FACT-H&N) questionnaire. The FACT-H&N questionnaire consists of a 38-item instrument with an 11-item subscale specific to head and neck concerns, and 27 questions in four other domains: physical well-being (7), social/family well-being (7), emotional well-being (6), and functional well-being (7) (Ringash et al., 2008). Each item was answered on a five-point scale from 0 (worst possible HRQL) to 144 (best possible HRQL). A clinically significant change in FACT-H&N score was represented by a difference of about ≥ 6 to rate feeling better, and about ≤ 12 as feeling worse (Ringash et al., 2004).

3.3.3.3 Anthropometry

A Detecto-Medic scale (Detecto Scales Inc., Brooklyn, NY) was used to measure body mass and height, respectively. Skinfold thicknesses were measured via a Holtain Tanner Skinfold Caliper (Holtain Ltd., Crymych, UK) to predict relative body fat percent (BF%) using the Jackson & Pollock 4-site skinfold technique (A. S. Jackson & Pollock, 1978; A. S. Jackson, Pollock, & Ward, 1980), on the right side of the body to the nearest 0.2 mm, and measured in triplicates unless 2 of 3 skinfolds were ≤ 0.4 mm apart, at the following sites: (1) triceps, halfway between the acromion- and olecranon-process; (2) suprailiac, superior to the iliac crest at the mid-axillary line; (3) abdominal, 5 cm lateral of the umbilicus; and (4) thigh, halfway between the inguinal crease and proximal patella.

3.3.3.4 Muscle CSA

Using B-mode ultrasonography (GE Medical Systems LOGIQ E9, Wauwatosa, WI), muscle CSA was captured in the axial plane of the vastus lateralis and rectus femoris with a 13-MHz linear array transducer. During the measurements, participants were instructed to adopt a fully relaxed, supine position with their legs extended. One axial perpendicular line was marked with semi-permanent ink at 50% of the distance between the greater trochanter and the lateral epicondyle of the knee. A liberal amount of water-soluble gel was applied to a probe to help maintain a consistent pressure and avoid compression of the muscle to ensure clear images were captured. To obtain muscle CSA, consecutive two-dimensional (2-D) images were acquired with

the probe placed perpendicular to the skin while following a lateral-to-medial direction positioned over the previously marked line. A minimum of three acceptable images were acquired (i.e. the image displayed identifiable borders for the vastus lateralis and rectus femoris). This technique of ultrasound imaging and manual tracing for image analysis is a valid and reliable method for assessing quadriceps atrophy and hypertrophy (Scott et al., 2017).

3.3.3.5 Neuromuscular assessment at rest

Preceding the intermittent cycling test, determination of supramaximal femoral nerve electrical stimulation (FNES) intensity took place on the isometric chair. Participants then began a preparatory set that involved five submaximal voluntary isometric knee extension contractions of approximately 5-s in duration, with 5-s rest between contractions. Participants were instructed to gradually increase the force of subsequent contractions, working up to one 'near-maximal' contraction based on perceived effort and by referencing real-time visual feedback displayed on a large monitor positioned ~1 m in front of the participant. Next, participants performed a neuromuscular assessment beginning with two MIVCs with no stimulations and recorded as maximum voluntary force. Where two MIVCs differed by ≥ 5%, a third was performed. Subsequently, two additional MIVCs were performed with single pulse FNES during and then at rest within 2-s after a single MIVC to determine voluntary activation (VA) (Merton, 1954) and potentiated knee extensor twitch force, respectively. Each of the maximal contractions were separated by 60-s rest and performed under strong verbal encouragement. Participants were then transferred to the cycle ergometer (see next section).

3.3.3.6 Intermittent cycling test and performance fatigability

This investigation employed a recently validated cycling ergometer to perform whole body (cycling) exercise that allowed for the instantaneous and intermittent assessment of neuromuscular fatigue during and after cycling (Doyle-Baker et al., 2018). Participants began on the cycle ergometer by completing a series of MIVCs identical to those performed on the isometric chair before beginning the intermittent cycling test (Figure 3.1b), and has been described in detail elsewhere (Doyle-Baker et al., 2018). The intermittent cycling test consisted of 3-min stages performed at pre-determined power outputs that were scaled to individual body mass identified at the initial laboratory visit. The increments in power output increased 0.3 $W \cdot kg^{-1}$ for the first four

stages, 0.4 W·kg^{-1} for the following five stages, and by 0.5 W·kg^{-1} for any subsequent stages. Participants cycled at a self-selected cadence (≥ 60 rpm) during the initial trial as the only real-time feedback they received during cycling and was recorded for replication during the subsequent trial. During cycling participants were permitted to drink water ad libitum. At the end of each 3-min stage, the pedals were locked so that the participants testing knee was at a 90º angle allowing for an intermediate neuromuscular assessment (20-s duration). As shown in Figure 3.1a, this consisted of a single MIVC with FNES before the pedals were unlocked to allow the participant to resume cycling at their target cadence at the pre-determined higher power output. Following volitional exhaustion from cycling performance i.e. task failure (rpm < 60), a post-exercise neuromuscular assessment was performed immediately and after 20-s recovery, respectively (Figure 3.2b). Participants were outfitted to continuously measure heart rate, and the rating of perceived effort (Borg, 1982) and dyspnea were assessed every 3-min. The reliability of this protocol has previously been assessed in our laboratory in a cohort of healthy individuals (Doyle-Baker., 2018).

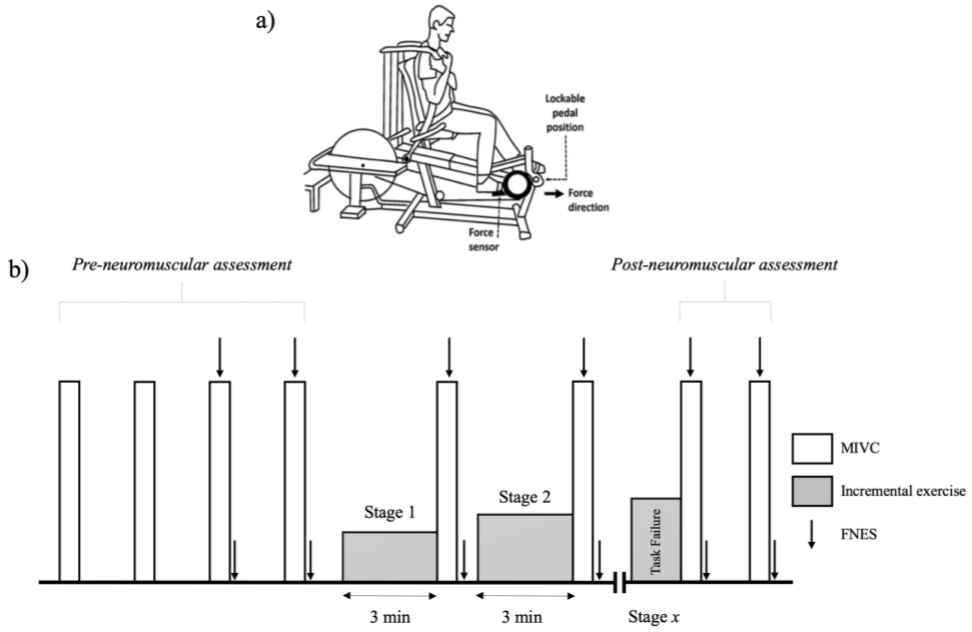

Figure 3.1: (panel **a**) The ergometer used for maximal incremental cycling and neuromuscular assessments. The position of the pedal is locked in isometric mode. The arrow indicated the direction of force applied by the knee extensors at ~90º; and (panel **b**) description of the incremental maximal cycling test showing when neuromuscular assessments were measured. The neuromuscular assessments involved a knee extensor MIVC with FNES delivered during and within 2-s after MIVC to determine VA and peripheral fatigue. MIVC, maximal isometric voluntary contraction; FNES, femoral nerve electrical stimulation.

3.3.4 Experimental set-up

3.3.4.1 Force and electromyography recordings

On the isometric chair (custom-built from a Kin-Com dynamometer frame), a calibrated load cell (LC101-2 K, Omegadyne, Sunbury, OH) was used to measure knee extensor force during voluntary and evoked contractions. The load cell was fixed to the isometric chair and connected to a noncompliant cuff attached to the ipsilateral testing leg, superior to the malleoli, that was individually adjusted to be positioned directly behind the point of applied force. Participants sat upright in the chair, with the hips and knees at 90º flexion. Two noncompliant straps that were that were fastened diagonally across the thorax and one across the abdomen constrained participants from extraneous movements of the upper body. Participants were encouraged to place their hands across their chest, grasping the opposite shoulder strap for support.

On the ergometer, voluntary and evoked force was measured using a wireless pedal force analysis system (Power-Force Model PF1.0.0, Radlabor GmbH, Freiburg, Germany) located between the pedal and crank. The ergometer permitted the pedals to be locked instantly in a fixed position such that participants hip angle was ~ 100º and knee and ankle of the tested limb were ~ 90º while seated upright, and both cranks parallel to the ground. This allowed participants to perform a contraction of the knee extensors whereby the force was measured in line with the crank (Figure 3.1a). Participants were secured with noncompliant straps across the trunk to limit extraneous movements of the upper body. Force was sampled at 500 Hz and recorded using Imago Record (version 8.50, Radlabor GmbH). To provide real-time visual force feedback, the PowerForce signal was transmitted to a PowerLab system (16/35, ADInstruments, Bella Vista, Australia) using a 16-bit A/D card (NI PCI-6229, National Instruments, Austin, TX) and connector block (BNC-2111, National Instruments).

Surface electromyography (EMG) activity was recorded from the muscle bellies of the vastus lateralis (VL), rectus femoris (RF), and the long head of the biceps femoris with pairs of single-use self-adhesive electrodes (10-mm diameter, Meditrace, Covidien, Mansfield, MA) according to *SENIAM* guidelines (Hermens et al., 2000), and a reference electrode over the patella. Electrode placement was reinforced with hypoallergenic surgical tape (3M Transpore, St. Paul, MN) to ensure they would remain in contact for the duration of the experiment. The skin was shaven, lightly abraded, and cleaned with isopropyl alcohol swabs to ensure low impedance (< 10 kΩ). The electrodes were used to measure the compound muscle action potential (M wave) elicited

by FNES. Raw EMG signals were analog-to-digitally converted, amplified with an octal bio-amplifier (ML138, ADInstruments; common mode rejection ratio = 85db, gain = 500), band-pass filtered (5–500 Hz), sampled (2000 Hz), acquired, and later analyzed off-line (LabChart v8 software, ADInstruments).

3.3.4.2 Femoral nerve electrical stimulation

Single transcutaneous electrical muscle stimuli (1 ms pulse width) were delivered to the knee extensors of the ipsilateral testing limb using a constant-current stimulator (DS7AH, Digitimer, Ltd., Hertfordshire, UK). The cathode (10 mm diameter, Meditrace 100) was positioned high in the femoral triangle and secured with gauze and hypoallergenic tape to apply pressure. The anode (50 × 90 mm rectangular electrode; Durastick Plus, DJO Global, Vista, CA) was placed midway between the greater trochanter and iliac crest. Single stimuli were delivered to the relaxed muscle beginning at 10 mA and increasing by 10 mA until plateaus occurred in twitch peak force and VL M-wave amplitude. Supramaximal FNES was ensured by increasing the intensity at this plateau by 30% to ensure full spatial recruitment of knee extensor motor units (mean current, before RTx 152 ± 76 mA; after RTx 139 ± 47 mA).

3.3.5 Data analysis

3.3.5.1 Neuromuscular parameters

Force for all MIVCs during neuromuscular assessments were recorded as the greatest 500 ms average before stimulation. Muscle contractility from each single electrical stimulus was assessed for potentiated twitch amplitude (Q_{pot}), maximum rate of force development (MRFD), and maximum relaxation rate. VA measured through the twitch interpolation technique was assessed by comparing the amplitude of the superimposed twitch (SIT) during MIVC with the amplitude of the corresponding Q_{pot} using the equation: $VA\ (\%) = [1 – (SIT/Q_{pot}) \times 100]$ (Merton, 1954). Electrically evoked EMG responses (M wave) in the VL and RF were analyzed from the peak-to-peak amplitude following each supramaximal FNES and was determined from the selection of data encompassing the biphasic wave. Following any stimulation artifacts, data selection of M wave began at the first deviation from zero and ended on the return to zero after the biphasic wave. The EMG root mean square (RMS-EMG) from VL and RF was measured as the greatest 500 ms average before stimulation. All parameters were assessed on the isometric chair

pre-cycling, and on cycling ergometer pre-cycling, after each completed 3 min stage, and immediately post-cycling (at volitional exhaustion). Because participants reached volitional exhaustion at different time points, we used the last neuromuscular assessment completed by all participants (i.e. after the 2nd stage of cycling) in later analysis as a common time point for all participants.

3.3.5.2 Muscle CSA

Muscle CSA of the constructed VL and RF images were measured using a computerized, public domain planimetry software program (ImageJ, National Institutes of Health, Bethesda, MD) by following the muscle fascia with an 800-dpi mouse (Magic Mouse, Apple, Cupertino, CA). The planimetry software was calibrated with fixed distance scales displayed in the ultrasound images and three acceptable CSA images were measured thrice, in sequence. The mean of the CSA from each image was considered.

3.3.6 Statistical analysis

Data are reported as mean ± standard deviation (SD) or as median and interquartile ranges (IQRs), frequency, and percentages as appropriate. The assumptions of normality and sphericity were tested using a Shapiro–Wilk test and Mauchly's test, respectively. If the assumption of Sphericity was violated, the Greenhouse–Geisser correction was applied when necessary. Differences in responses to intermitted cycling were analysed using a two-way repeated measure analysis of variances (ANOVA), i.e. time (3: pre-test, last common stage completed, post-test) × treatment (2: before receiving RTx, after receiving RTx). Bonferroni corrections for *post hoc* analysis was used if ANOVA indicated significant main or interactions effects. Paired-samples *t*-tests were performed to assess effects for neuromuscular function and anthropometric parameters, total time to volitional exhaustion during cycling. Nonparametric Wilcoxon signed-ranks tests were used to determine if patient-reported outcomes (HRQL and fatigue) differed significantly when compared before- versus after RTx. Effect sizes were calculated to provide a quantitative measure of the magnitude of the reported effects. Partial eta squared (η_{p2}) was used as an estimate of effect size for main and interaction effects of ANOVA. Interpretation of the size of the effect was cautiously considered as $\eta_{p2} = 0.01$ is small, $\eta_{p2} = 0.06$ is medium and $\eta_{p2} = 0.14$ is large (Cohen, 1988). Cohen's d_{av} was used to describe the standardized mean difference of an effect

paired-samples *t*-tests. Interpretation of the size of the effect was considered as $d = 0.2$ is small, $d = 0.5$ is medium and $d = 0.8$ is large (Cohen, 1988). Finally, the effect size for the Wilcoxon signed-ranks tests were calculated as: r = Z/SQR(*n*). Statistical significance was set at $P < 0.05$. All statistical procedures were conducted using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

3.4 Results

3.4.1 Flow of participants

Participant characteristics are summarized in Table 3.1. The flow of participants is illustrated in Figure 3.2.

Table 3.1: Participant characteristics.

Variables (*n* = 10)	
Age, mean (SD)	50 (9)
Sex, *n* (%)	
Female	4 (40%)
Male	6 (60%)
Primary tumor site, *n* (%)	
Larynx	1 (10%)
Oral cavity	2 (20%)
Oropharynx	5 (50%)
Nasopharynx	1 (10%)
Salivary glands	1 (10%)
Stage, *n* (%)	
I–II	6 (60%)
III–IV	0
Unknown	4 (40%)
Treatment, *n* (%)	
Major surgery (before RTx)	7 (70%)
Radiation therapy alone	2 (20%)
Concomitant chemotherapy	8 (80%)
HPV status, *n* (%)	
Positive	5 (50%)
Negative	5 (50%)

RTx, radiation therapy; HPV, human papillomavirus

Ten participants were included for final analyses. Unfortunately, recruitment was low likely due to the unique and debilitating consequences associated with HNC and its treatment. During the initial lab visit, four individuals were excluded from all physical testing due to contradicted health-

screenings. Six participants who completed the lab visit before treatment did not complete testing after receiving treatment (Figure 3.2).

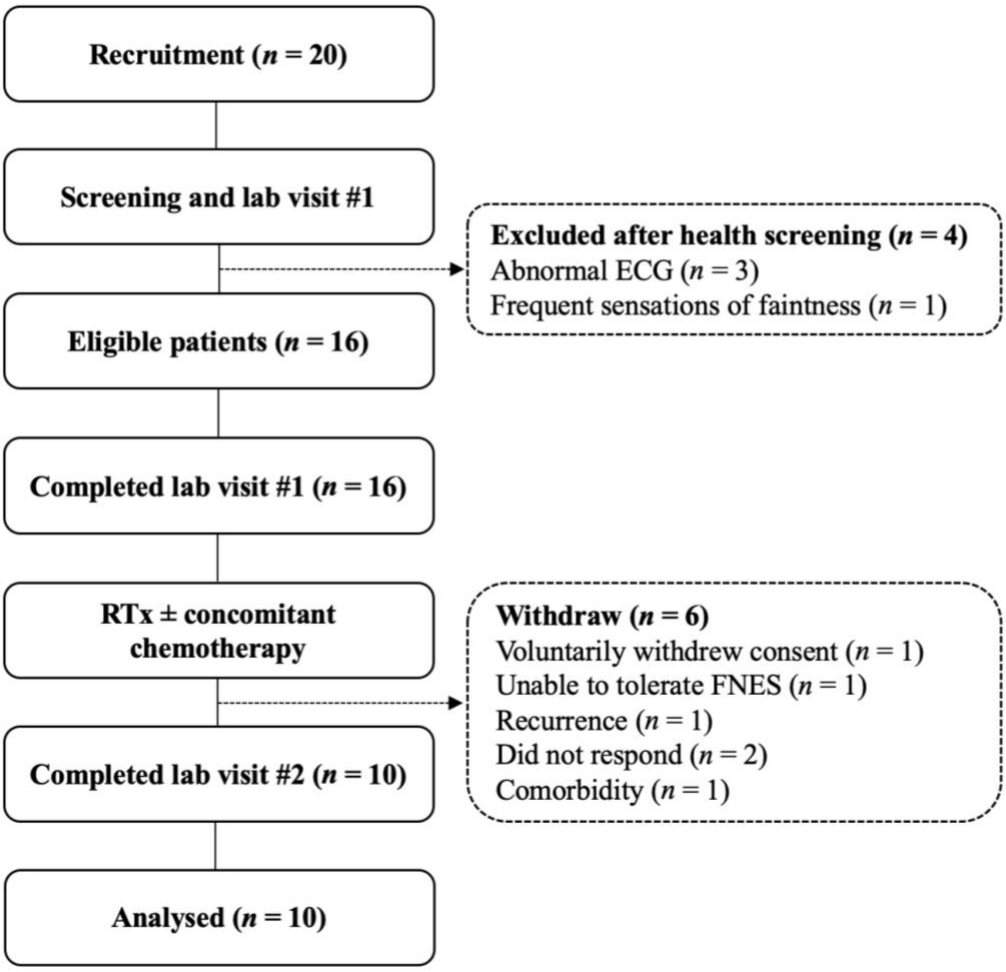

Figure 3.2: Participant flow diagram. ECG, electrocardiogram; RTx, radiation therapy.

3.4.2 Neuromuscular function

A significant decrease occurred between sessions in knee extensor MIVC force by 18 ± 13% ($T_{(9)}$ = 4.327, P = 0.002, d = 0.73), and in Q_{pot} by 16 ± 8% ($T_{(9)}$ = 6.47, P < 0.001, d = 0.62), respectively (Figure 3.3), while VA remained unchanged (Figure 3.3, 91 ± 5 [before] to 95 ± 4% [after]; $T_{(9)}$ = -1.901, P = 0.09, d = 0.93). Regarding RMS-EMG for VL (0.501 ± 0.128 [before] and 0.562 ± 0.394 mV·ms^{-1} [after]) and RF (0.336 ± 0.169 [before] and 0.375 ± 0.154 mV·ms^{-1} [after]), no difference was found (VL: $T_{(9)}$ = -0.757, P = 0.468, d = 0.20; RF: $T_{(9)}$ = -0.782, P = 0.455, d = 0.25). Likewise, the peak-to-peak amplitude of the VL M-wave response showed no difference from before to after treatment (11.1 ± 4.7 to 9.4 ± 6.1 mV; $T_{(9)}$ = 1.213, P = 0.256, d =

0.34). However, a significant decrease was detected in the RF M-wave response from before to after treatment by 36 ± 30% from 9.6 ± 5.4 to 5.3 ± 2.1 mV ($T_{(9)}$ = 3.572, P = 0.006, d = 1.22).

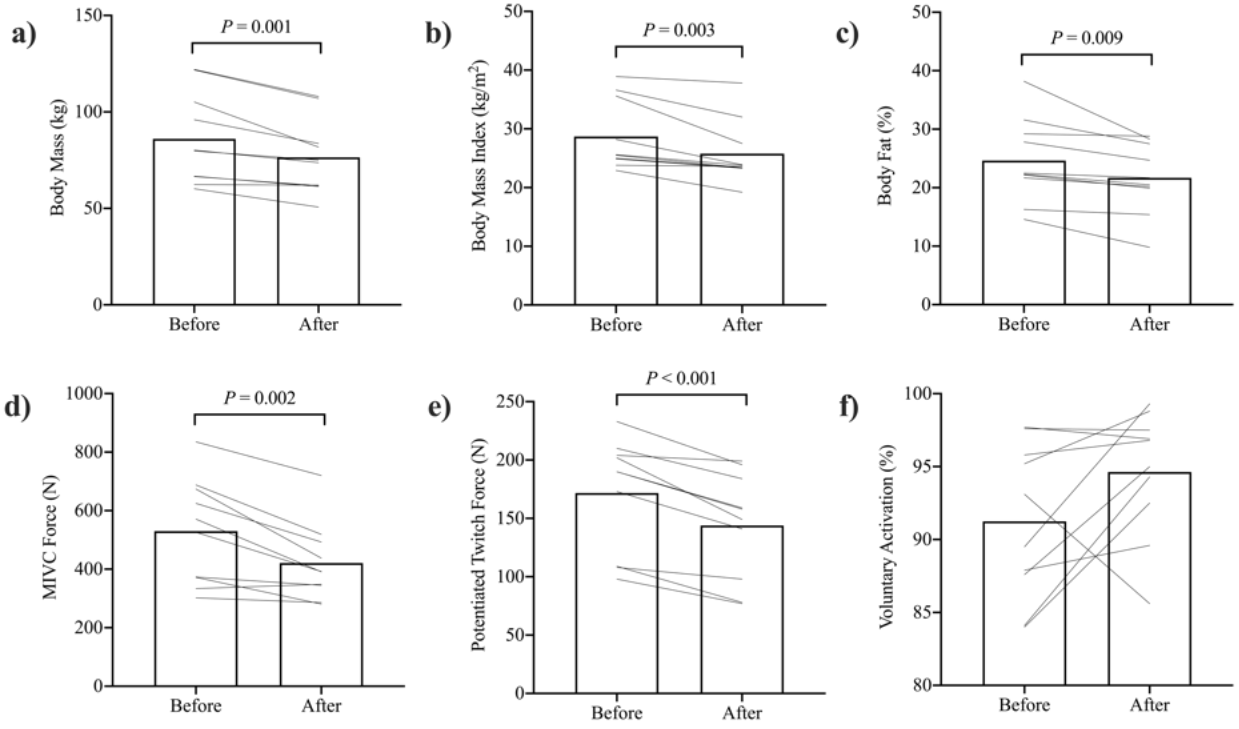

Figure 3.3: *A schematic illustrating: (panel **a**) body mass; (panel **b**) body mass index; (panel **c**) percent body fat; (panel **d**) maximal isometric knee extensor force (MIVC); (panel **e**) potentiated twitch force of knee extensors; and (panel **f**) voluntary activation before versus after treatment.*

3.4.3 CSA and body composition

Figure 3.4 a shows VL muscle CSA, which decreased significantly from before treatment to after treatment by 21 ± 18% ($T_{(8)}$ = 3.380, P = 0.01, d = 0.64, Figure 3.4a). In addition, RF muscle CSA significantly decreased by 20 ±14% ($T_{(8)}$ = 3.988, P = 0.004, d = 0.66) from before to after RTx (Figure 3.4b). As shown in Figure 3.3, body mass decreased significantly from before to after RTx by 10 ± 6% from ($T_{(9)}$ = 4.519, P = 0.001, d = 0.47). Body mass index and estimated body fat % also decreased by 10 ± 7% ($T_{(9)}$ = 4.519, P = 0.003, d = 0.54), and 12 ± 10% ($T_{(9)}$ = 4.983, P = 0.009, d = 0.47), respectively (Figure 3.3).

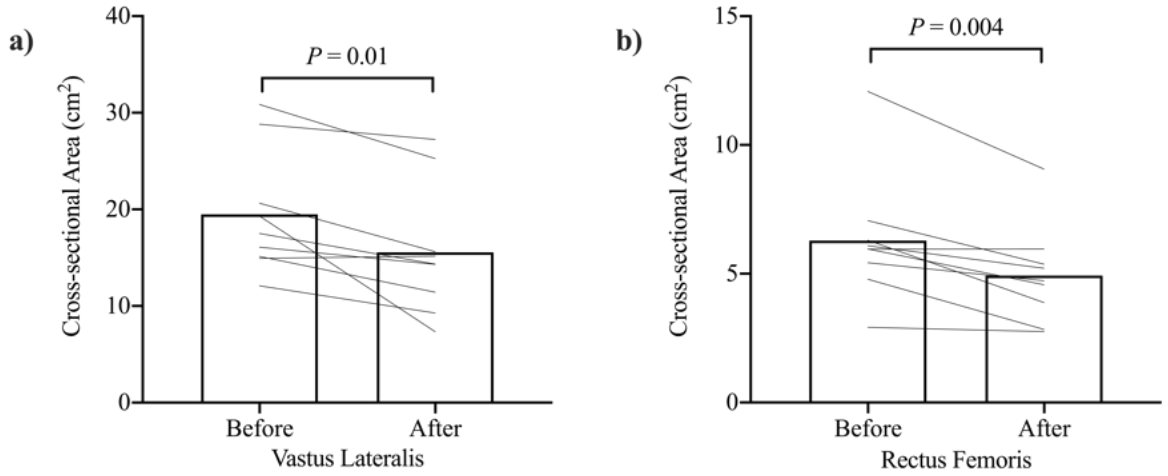

Figure 3.4: (panel **a**) vastus lateralis muscle cross-sectional area; and (panel **b**) rectus femoris muscle cross-sectional area.

Table 3.2: Comparisons of patient-reported health-related quality of life and fatigue scores from baseline to after treatment, $n = 10$.

Measure	Before Treatment		After Treatment			
	Median	IQR	Median	IQR	*P* value	*Effect size*[a]
FACT-H&N physical	26	23-28	22	18-24	0.011	-0.81
FACT-H&N social	25	23-27	24	24-26	0.359	-0.29
FACT-H&N emotional	20	18-21	23	17-23	0.309	-0.32
FACT-H&N functional	21	17-26	20	15-24	0.219	-0.39
FACT-H&N subscale	35	32-39	25	20-31	0.007	-0.85
FACT-H&N total	126	115-135	115	90-124	0.012	-0.79
FACIT-F	39	30-52	35	26-42	0.041	-0.65

IQR, interquartile range; FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy – Fatigue Questionnaire.
[a] r=Z/SQR(n).

3.4.4 Perceived HRQL and fatigue

As shown in Table 3.2, the total FACT-H&N score decreased 13 ± 12%, by a mean of 16 ± 14 points (Z = -2.499, P = 0.012, r = -0.79) from before to after treatment, that on average, exceeded the MCID. The Physical Well-being (Z = -2.552, P = 0.011, r = -0.81) and HNC specific (Z = -2.689, P = 0.007, r = -0.85) subscales showed a statistically significant worsening from baseline, while Social/Family Well-being (Z = -0.917, P = 0.359, r = -0.29) Emotional Well-being (Z = -1.017, P = 0.309, r = -0.32), and Functional Well-being (Z = -1.230, P = 0.219, r = -0.39) domains remained the same. The FACIT-F score reduced by 21 ± 33%, by a mean of 9 ± 11 points

(Z = -2.041, P = 0.041, r = -0.65) from before to after treatment, that on average, also exceeded the MCID.

3.4.5 Effects of the intermittent cycling test

3.4.5.1 Performance time

Paired samples *t*-test analysis of time to volitional exhaustion during maximal cycling showed a significant decrease from before to after RTx by 15 ± 12% from 966 ± 269 s to 823 ± 239 s ($T_{(9)}$ = 3.414, P = 0.008, d = 0.62). The corresponding mean power output achieved at volitional exhaustion was 146 ± 40 W before treatment, and 123 ± 38 W after treatment ($T_{(9)}$ = 1.847, P = 0.098, d = 0.62).

3.4.5.2 Muscle contractile responses

As anticipated and illustrated in Figure 3.5, maximal voluntary force decreased during the cycling test (main effect of time: $F_{2,18}$ = 17.46, P < 0.001, η_{p2} = 0.66), where post hoc analysis indicated a decrease in MIVC of 4 ± 27% from pre-cycling to the last common stage completed (P = 0.003, d = 0.40) and decrease in MIVC of 28 ± 24% from pre-cycling to post-cycling (P = 0.001, d = 1.14). Also, as a result of cycling, there was a main effect of time in the decrease of potentiated evoked force ($F_{2,18}$ = 36.03, P < 0.001, η_{p2} = 0.80), where post hoc analysis revealed a change from pre cycling to the last common stage completed (–19 ± 28%; P = 0.02, d = 0.70) and from pre-cycling to volitional exhaustion (–55 ± 17%; P < 0.001, d = 2.03), respectively.

3.4.5.3 Voluntary activation

No main effect of treatment ($F_{1,9}$ = 0.879, P = 0.373, η_{p2} = 0.09), treatment × time ($F_{2,18}$ = 0.089, P = 0.915, , η_{p2} = 0.01), or main effect of time ($F_{2,18}$ = 1.1716, P = 0.208, η_{p2} = 0.16) were found for VA (Figure 3.5).

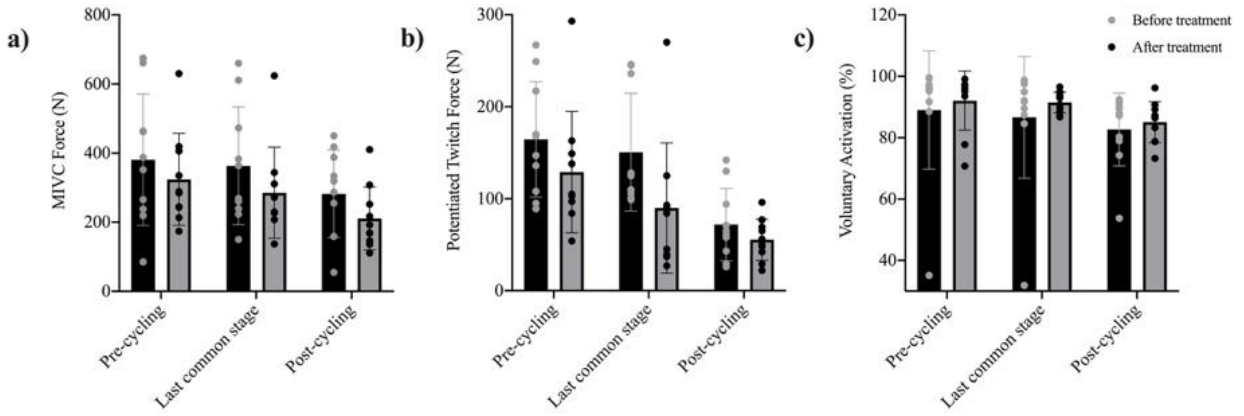

Figure 3.5: (panel a) maximal isometric voluntary contraction (MIVC); (panel b) Potentiated twitch force; (panel c) Voluntary activation.

3.4.5.4 Exploratory analyses

As illustrated in Figure 3.6, we assessed the relationship between the changes in patient-reported measures (FACT-H&N total and FACIT-F) and characteristics of muscle function (MIVC, Q_{pot} and CSA) using bivariate correlations. In general, worse HRQL and fatigue severity was not correlated with worsening of our main outcomes (Figure 3.6). However, there was a significant correlation between overall HRQL (FACT-H&N) and maximal force generation of the knee extensors (r = 0.63, P = 0.049).

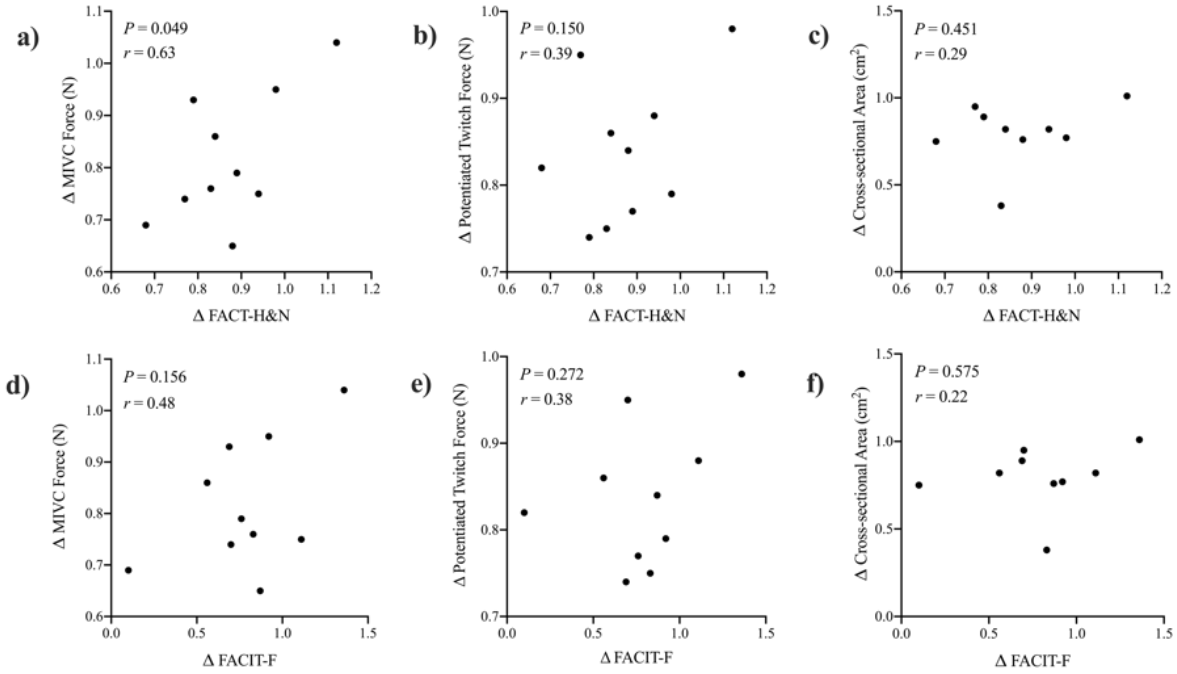

Figure 3.6: *Correlation between: (panel **a**) FACT-H&N and MIVC force; (panel **b**) FACT-H&N and potentiated twitch force; (panel **c**) FACT-H&N and cross-sectional area; (panel **d**) FACIT-F and MIVC force; (panel **e**) FACIT-F and potentiated twitch force; (panel **f**) FACIT-F and cross-sectional area. FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck Questionnaire; MIVC, maximal isometric voluntary contraction; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Questionnaire.*

Moreover, we explored if there was a relationship between patient-reported outcomes and measures of performance fatigability. No correlations were found between MIVC and Q_{pot} force at both the last common stage and post-cycling. There were significant correlations between the decrease in HRQL and the decrease in exercise time (r = 0.65, P = 0.041), plus the increase in fatigue severity (decreased FACIT-F) and the decrease in exercise time (r = 0.77, P = 0.009) (Figure 3.7).

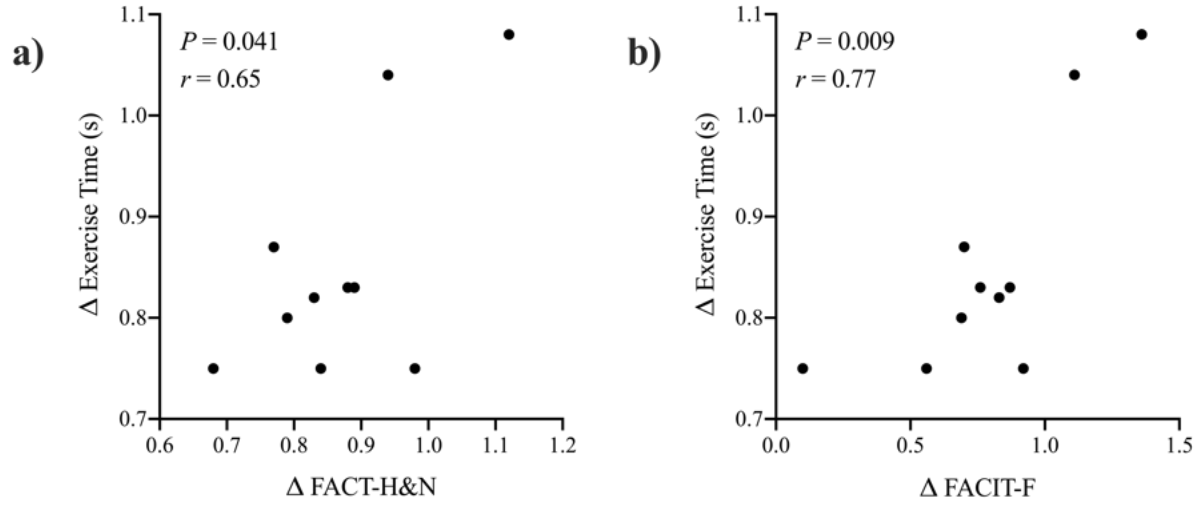

Figure 3.7: Correlation between: (panel **a**) the change in FACT-H&N and change in exercise time; and (panel **b**) the change in FACIT-F and changes in exercise time. FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck Questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Questionnaire.

3.5 Discussion

The main aim of the present study was to examine the changes in maximal force, muscle CSA, and patient-reported outcomes, and to investigate performance fatigability of the knee extensors during and after an intermittent cycling test to volitional exhaustion in people who completed treatment for HNC. To our knowledge, this is the first study to investigate contractile

and electromyographic changes during and immediately after a maximal cycling test to explore performance fatigability in people treated for HNC. The main findings were as follows: 1) impairment of neuromuscular function was observed after cancer treatment for HNC due to peripheral factors (evidenced by a significant decline in potentiated twitch force at rest and muscle CSA); and 2) the decrease in the force generating capacity of the knee extensors with cycling exercise was mainly due to peripheral disturbances (evidenced by a progressive decline in evoked force), and likely contributed to the cessation of dynamic exercise. This study also showed that following treatment for HNC, patients experienced increased fatigue severity and reduced HRQL, evidenced by a mean decrease of 9 ± 11 points, and 16 ± 14 points on the FACIT-F and FACT-H&N questionnaires, respectively. These findings support our research hypothesis that decrements in knee extensor force and muscle CSA would occur in HNC patients following RTx ± concomitant chemotherapy and provide the first quantification of the alterations.

3.5.1 Muscle contractility at rest

In the current investigation, we used muscle stimulation paradigms and EMG to study the potential mechanisms responsible for a loss in skeletal muscle strength following cancer treatment for patients with HNC. Our results demonstrated that peripheral mechanisms are predominately responsible for the observed decrease in maximal voluntary force production after RTx, whereas neural contributions seemed to be less of a factor. This was demonstrated by a 17% reduction in mechanical force of the knee extensors at rest (Figure 4) and supported by a drop in RF M-wave amplitude.

The twitch interpolation method, which estimates the amount of neural drive an individual voluntarily recruits to the muscle, and a measure of central fatigue when a reduction occurs (Gandevia, 2001) has previously shown validity to assess maximal VA of the knee extensors (G. Y. Millet, Martin, Lattier, & Ballay, 2003). Utilizing this technique in the current study elicited no change in VA at rest (Figure 4). Due to the relatively high VA observed in the current study (91 ± 5% before– and 95 ± 4% after–RTx), which is similar to at rest knee extensor VA in healthy individuals (Goodall et al., 2009), a ceiling effect could have contributed to the current results. The ceiling effect associated with measurements of VA is supported by previous studies in healthy (Dekerle, Greenhouse-Tucknott, Schafer, Wrightson, & Ansdell, 2018) and injured (Dongés, Boswell-Ruys, Butler, & Taylor, 2019) people. Nevertheless, due to the contribution of peripheral

disruptions to contractile muscle function after receiving RTx for HNC, it is likely that a decrease in the peripheral neuromuscular system contributed greater to reduced MIVC force than an impairment to central drive at rest.

The ~20% reduction in muscle CSA of the knee extensors (Figure 4) likely explains why maximal voluntary and mechanical force displayed significant reductions after treatment (Figure 3). Similar to our study, Sandmael et al. assessed skeletal muscle mass before the start, and at the end of RTx treated HNC patients and found a significant reduction in muscle mass at the third lumbar region (Sandmæl et al., 2017). Anatomically different in comparison to the current study, skeletal muscle mass of the third lumbar vertebra highly correlates with total body skeletal mass (Shen et al., 2004), thus can provide precise estimates of muscle wasting (Sandmæl et al., 2017). Indeed, cancer cachexia is a debilitating wasting syndrome characterized by decreased muscle anabolism and increased catabolism, and results in muscle atrophy, with mounting evidence that skeletal muscle depletion results in neuromuscular impairments (Larsson et al., 2018). Previous investigations have demonstrated comparable findings, in that the loss of lean body mass was significantly associated with reduced physical function and functional independence (Silver et al., 2007). However, this association was assessed by patient-reported questionnaires and although the clinical relevance of such measurements remains an important outcome, these studies lacked objective measurements of functional performance. It has been found previously that there is a strong association between cachexic HNC patients and low functional status measured by hand grip strength (Orell-Kotikangas et al., 2017). Despite handgrip strength being a valid measure to assess muscle function (Orell-Kotikangas et al., 2017), the design of the current study and that of Orell-Kotikangas prevents a direct comparison.

3.5.2 Perceptions of fatigue and HRQL

As hypothesized, we found that RTx for patients with HNC results in statistically and clinically significant changes in both the severity of perceived fatigue and worse HRQL following treatment. A reduction in > 4 units is considered clinically significant with the FACIT-F scale (Elting et al., 2008), which occurred in the present study (Table 1). Additionally, a reduction of about 12 units with the FACT-H&N scale are considered as a clinically significant change (Ringash et al., 2008), and an overall difference in HRQL of 16 points after treatment was observed in the current study (Table 1). Although we did not directly measure the influence of specific

treatment-related toxicities on perceived fatigue and HRQL, the current study did produce a correlation between the decrease in overall HRQL (total FACT-HN score) and the decrease in maximal knee extensor muscle strength (Figure 6). Likewise, a significant correlation was identified between the decrease in HRQL and exercise time to volitional exhaustion, and between increased perceived fatigue and exercise time to volitional exhaustion (Figure 7). Due to our low sample size however, these results should be interpreted with caution until replicated in larger studies. Regardless, our results align with previous observations that have identified similar associations between cancer treatment for HNC and patient-reported outcomes (Sawada et al., 2012).

3.5.3 Intermittent cycling test

By applying our labs recently validated intermittent cycling test to our methodology, we were able to characterize the etiology of neuromuscular fatigue of people diagnosed with HNC before and after cancer treatment for the first time by assessing (i) measures of voluntary and mechanically evoked force; (ii) voluntary activation; and (iii) EMG parameters of the knee extensors. Our results showed that after treatment, time to volitional exhaustion decreased by over 2 min on average. We anticipated that before treatment, maximal knee extensor force would not decrease from pre-cycling to the last common stage (2nd stage of cycling), but would do so after treatment as this was relatively low intensity cycling. However, this was not the case as evidenced by the absence of a treatment × time interaction. The lack of decrease and relatively large variation in maximal voluntary force (5 ± 36%) from baseline to the last common stage before treatment may be due to large individual variation and may speak to the diversity of this population. That is, where some individuals had reached 'near maximal' at rather low power outputs (52 ± 15 W) after performing the last common stage of cycling (2nd stage or 360 sec of cycling), others may have experienced somewhat of a 'warm up' effect. At volitional exhaustion, the magnitude of neuromuscular fatigue did not differ from before to after treatment, despite the substantially lower exercise time between these conditions.

Percutaneous electrical stimulation of the motor nerve of individual muscles, thus bypassing the influence of central nervous system, are used to inform localized changes in muscle contractility. The consequential mechanical twitch force and M-wave are recorded and used to determine potential sites of peripheral fatigue within the neuromuscular system (Place, Yamada,

Bruton, & Westerblad, 2010). In the current study, a decrease in the amplitude of potentiated twitch force occurred during intermittent cycling both before treatment (–7% at the last common stage and –56% post-cycling) and after treatment (–32% at the last common stage and –54% post-cycling). We also observed a 42% reduction in the amplitude of M-wave in the RF, however, this was only detected post-cycling, after treatment only. In contrast, M-wave proprieties of VL demonstrated no change. Due to the lack of reduction in M-wave amplitude, it may be interpreted that (i) reduced time to volitional exhaustion; and (ii) decreased force production during fatiguing exercise in the current study is the result of changes in Ca^{2+} release, Ca^{2+} sensitivity and/or force produced by the cross-bridges engaged (Place et al., 2010). However, it should be noted that EMG outcome measures can be less reliable than force parameters (Doyle-Baker et al., 2018), such as they are susceptible to contamination like changes in temperature and sweat.

In the present study, there were no evident contributions to the development of central fatigue throughout the cycling test, evidenced by no change in VA at the last common stage completed or post-cycling. Further, RMS-EMG activity can inform central mechanisms in addition to VA, where an increased workload indicates greater motor unit firing rates, that work to counteract fatigue of the exercising muscles (Bigland-Ritchie, Furbush, & Woods, 1986). No change in RMS-EMG was found, indicating that muscle activity remained relatively constant throughout the cycling test.

Despite previous research demonstrating an association between RTx dose to discrete structures of the central nervous system and treatment-related fatigue scores (Ferris et al., 2017), which could have been associated with a higher contribution of central fatigue (i.e. a reduction in VA), it was not a clear factor in the current study. Rather, the contribution of peripheral factors influenced changes in voluntary force production both at rest and during intermittent cycling. Nevertheless, the association between reduced functional status and diminished muscle contractile proprieties could be explained by the fact that 90% of participants in the current study became cachexic according to current classifications (Fearon et al., 2011), although the magnitude of peripheral fatigue development following exercise termination tended to be the same despite a significant drop in time to volitional exhaustion. Investigating neuromuscular parameters in HNC patients can inform us about central/peripheral contributions to neuromuscular function and locomotor fatigability. This may help to inform the development of future physical training interventions; however, they do not explain why patients experience significant perceptions of

fatigue at rest. Further studies should be conducted to evaluate neuromuscular contributions in cachexic populations.

3.5.4 Limitations

Although our cycling ergometer is a methodological advancement in the way of neuromuscular measurements during exercise (Doyle-Baker et al., 2018), we are still only assessing neural and contractile parameters during isometric contractions, as with the majority of fatigue studies. As such, it would be beneficial for future research to quantify muscle fatigue during dynamic contractions. Nevertheless, the neuromuscular assessments in the current study commenced immediately (within 1-s) following cycling bouts and only required approximately 10 to 15 seconds. It is unlikely that the time delay to resume cycling had any significant effect on recovery. Due to our recruitment strategy, a proper familiarization session to acquaint participants with the test procedures and equipment was not feasible. Although two highly trained research personnel were present at all sessions to coach participants through the techniques used in the current study, a familiarization session is usually recommended, and we recognize this as a study limitation. Finally, the main limitation is that, due to unanticipated difficulties with recruitment despite an extended recruitment period, only 10 participants completed both lab visits. As such, the study may have been underpowered to detect smaller effects, although we note that many before versus after treatment effects were large due to the severity of RTx and its associated side effects. Our small sample size also meant that we were unable to perform any sub-group analysis for example, HPV-positive vs. HPV-negative patients.

3.6 Conclusion

In conclusion, the results of this study demonstrate that neuromuscular function is impaired following RTx for HNC and cycling exercise to volitional exhaustion results in greater peripheral disturbances to the neuromuscular system rather than central mechanisms. In both cases, the reduced capacity to produce maximal force of the knee extensors was explained by a decrease in evoked force in response to percutaneous electrical stimulation rather than a decrease in neural drive. Also, HRQL and fatigue severity are negatively impacted following anti-neoplastic treatment for HNC. These results confirm that physical function is substantially reduced in people who completed RTx ± concomitant chemotherapy for HNC. Future directions in this population

should focus on physical training interventions that target improvements in neuromuscular function, with the overall aim of improving HRQL.

Chapter Four: Feasibility and Preliminary Efficacy of Eccentric Overloading and Neuromuscular Electrical Stimulation to Improve Muscle Strength and Muscle Mass After Treatment for Head and Neck Cancer

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Running Title: Effects of a novel strength training program on neuromuscular function

4.1 Abstract

Background: Treatment for head and neck cancer (HNC) is often associated with a significant and involuntary loss of body weight, which is mainly due to muscle wasting. As a consequence, it is common for these patients to experience declines in muscle strength, which has a negative impact on functional performance, health-related quality of life (HRQL) and fatigue. Early evidence suggests strength training is beneficial following treatment for HNC. We hypothesized that exercise prescription could be optimized to promote improvements in muscle strength and mass.

Objectives: First, to determine the feasibility of a 12-week eccentric overloaded combined with neuromuscular electrical stimulation (NMES) strength training program among survivors of HNC. Second, to investigate the differences over time (pre- and post-intervention), and between groups (2: experimental [EXP] and conventional [CON] strength training) regarding muscle strength and muscle cross-sectional area (CSA) of the knee-extensors.

Methods: Twenty-two participants were randomized to either the EXP (n = 11) or CON (n = 11) interventions. Feasibility outcomes were quantified as rates of accrual, completion, adherence and compliance. Patient-reported HRQL and fatigue, functional performance, and a neuromuscular assessment involving maximal isometric voluntary contractions (MIVCs) and electrical stimulations of the femoral nerve performed before and during an intermittent cycling test were assessed at pre-intervention and post-intervention.

Results: Eighty-six percent of participants completed the intervention and overall adherence was 88%. NMES intensity and unilateral squat load significantly increased over 12-weeks. MIVC increased by 22 ± 23% post-intervention, and muscle cross-sectional area increased by 19 ± 23% and 17 ± 22% in the vastus lateralis and rectus femoris, respectively. Regardless of intervention, cycling performance increased 18 ± 13%. The cycling protocol induced substantial decreases in MIVC and resting potentiated twitch force (–38%, –55%), respectively. Improved HRQL and reduced fatigue severity also demonstrated clinically relevant improvements.

Conclusion: A fully supervised eccentric overloading and NMES training program is feasible for survivors of HNC. However, conventional strength training strategies should not be overlooked. Future research should feature fully powered trials and focus on timing of the intervention.

Words: 334

Keywords: Central fatigue, peripheral fatigue, cancer rehabilitation, exercise oncology, neuromuscular electrical stimulation, accentuated eccentric loading

4.2 Introduction

Cancer therapy for head and neck cancer (HNC) frequently results in a considerable amount of involuntary weight loss that averages between 6–12% of pre-treatment body mass (Lønbro, Dalgas, Primdahl, Johansen, et al., 2013; Silver, Dietrich, & Murphy, 2007). Modern anti-cancer regimens have substantially improved outcomes, for example intensity modulated radiation therapy (Gulliford et al., 2012; Rathod et al., 2013). However, the majority of patients with HNC still experience deleterious side effects from radiation therapy (RTx) and/or chemotherapy, such as mucositis, xerostomia, dysphagia, and fatigue, that may be caused by the malignancy itself, but are primarily a result of RTx (Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013; Sandmæl et al., 2017). These side effects impair swallowing function to an extent that results in caloric restriction and malnutrition, and ultimately leads to unintentional weight loss (Sandmæl et al., 2017; Silver et al., 2007). It has been reported muscle wasting (i.e. cancer cachexia) is responsible for more than 70% of the weight loss (Silver et al., 2007). In our unpublished previous work, which examined knee-extensor muscle function in participants pre to post RTx ± concomitant chemotherapy, we reported an 18% decrease in strength measured by maximal isometric force, and a 21% decrease in muscle cross-sectional area (CSA). This was also reflected in functionally relevant measures (e.g. a reduction of 15% in performance time during an incremental cycling test). Furthermore, the loss of muscle strength was correlated with a reduction in HRQL and increase in fatigue (Chapter Three).

Existing research indicates that exercise interventions mitigate the side effects of cancer treatment in HNC patients by helping to counteract muscle wasting, manage fatigue, regain strength and improve HRQL after treatment (Capozzi, Nishimura, McNeely, Lau, & Culos-Reed, 2015). Although there are relatively few studies on the topic, previous trials of exercise interventions in people with HNC both during and after treatment have demonstrated positive outcomes in favor of exercise training (Capozzi et al., 2016; Lønbro, Dalgas, Primdahl, Johansen et al., 2013; Lonkvist et al., 2017). However, physical exercise for people with HNC is an emerging field, and although strength training should be the focus of the intervention due to the unique side effects of HNC treatment, only the effects of conventional strength (or resistance) training have been assessed. That is, strength training where dynamic voluntary muscle contractions are performed against external loads (Ratamess et al., 2009), including concentric and eccentric muscle actions. While conventional strength training is beneficial to attenuate cancer-related

cachexia (Al-Majid & Waters, 2008), HNC patients are faced with prolonged side effects following treatment, such as negative energy balance (Lønbro, Dalgas, Primdahl, Johansen et al., 2013), reduced exercise capacity (Chapter Three), and functional limitations that could further impact recovery (Peach et al., 2018; Silver et al., 2007). Hence, there is a need to optimize exercise prescription in patients with HNC. Future research will benefit from exploring the effectiveness of alternative strength training interventions.

One of these alternative modalities is eccentric muscle contractions, which involves the active lengthening of muscle under an external load (Douglas et al., 2017). It has been widely evidenced that exercise involving eccentric muscle actions provide a greater effect on muscle strengthening and hypertrophic responses compared to concentric or isometric contractions because of the potential for high force production (Baroni et al., 2015; Douglas et al., 2017). Another aspect that favors eccentric training is that it requires a distinctively low energy cost compared to its concentric counterpart (Lastayo et al., 2014). A practical way of eliciting eccentrically-focused training is accentuated eccentric loading, which prescribes both eccentric (where the contraction is overloaded) and concentric (where the contraction is underloaded) movements, with relatively little interruption to the natural mechanics of performed exercise (Wagle et al., 2017). Because of these characteristics, eccentric training has been studied extensively as an interventional strategy, with the consensus that muscle strength and muscle size parameters are more effective compared to concentric or isometric exercise in muscle performance, injury prevention, and rehabilitation settings (Lastayo et al., 2014).

Another modality that may favor neuromuscular adaptations is electromyostimulation or neuromuscular electrical stimulation (NMES), which involves a sequence of electrically-evoked contractions that are delivered through surface electrodes to superficial skeletal muscles (Maffiuletti, 2010). The advantages of NMES for improving muscle strength and muscle mass have been published in numerous randomized controlled trials, and it is recommended in rehabilitation programs for patients with several conditions, particularly musculoskeletal disorders (Feil et al., 2011; Gerovasili et al., 2009; Vaz et al., 2013) (as outlined in detail in section 2.5 Neuromuscular electrical stimulation). NMES in oncological settings is relatively new, however, early evidence seems to support its application in cancer survivorship (O'Connor et al., 2018). The well-established effects of eccentric overloading and NMES may provide superior improvements in developing muscle strength and muscle mass when compared to conventional strength training

in this population. As such, a combined approach using both modalities may be complimentary to one another.

Therefore, to assess whether the exercise prescription for people who have completed treatment for HNC could be optimized, we developed an experimental strength training intervention involving a combination of both accentuated eccentric loading and NMES in the knee extensors, and a conventional training intervention that was similar in frequency and total number of contractions. The primary aim of this randomized pilot trial was to assess feasibility (overall recruitment, adherence, completion and compliance to the interventions). The secondary aim was to provide preliminary efficacy for the experimental strength training intervention (EXP) versus conventional strength training (CON) on maximal isometric force and muscle CSA of the knee extensors in people who had completed treatment for HNC.

4.3 Methods

4.3.1 Study design

This was a single-centre, two-arm, randomized controlled trial. Participants attended the Human Performance Lab (Faculty of kinesiology, University of Calgary, Alberta, Canada) at baseline, (after treatment for HNC), and post-intervention. Figure 4.1 represents the flow of participants and overall design of the study. All experimental procedures were conducted in accordance with the *Declaration of Helsinki*, with the exception of registration in a database. This study was approved by the Health Research Ethics Board of Alberta – Cancer Committee (ID: HREBA.CC-16-0744). Written informed consent was provided by all volunteers after they were informed of all the procedures, potential benefits, and associated risks of the study, and prior to any participation of assessments and interventions. This study was retrospectively registered on ClinicalTrials.gov: NCT04013178.

4.3.2 Recruitment

As described in Chapter Three, volunteers were recruited through the head and neck tumor clinic at HNC patient-education sessions at the Tom Baker Cancer Center (Calgary, AB), in collaboration with a senior radiation oncologist. Participant enrollment began in October 2017 and ended in February 2019. A member of the research team gave a short presentation about the study, and interested patients gave permission to be contacted with additional study information.

Participants had the option to participate in a laboratory visit before RTx, as described in Chapter Three, but this was not required to be eligible for the exercise intervention offered after RTx in this study. People who indicated that they would be interested in receiving more information about the study were contacted approximately 4 weeks after their final RTx session and were invited to the laboratory based on current health status e.g. volunteers were advised that their weight should have stabilized, and were postponed if the participant or study team were concerned that the testing protocol would aggravate any ongoing pain.

4.3.3 Participants

Eligible participants met the following inclusion criteria: (1) a verified clinical diagnosis of HNC (stage I-IV) with the primary tumor in the oral cavity, pharynx, larynx, paranasal sinuses, or salivary glands; (2) completed curative RTx ± concomitant chemotherapy (3) no comorbidities that could confound the ability of participation in both laboratory testing and training (including but not limited to current malignancies, neuromuscular, musculoskeletal or vascular conditions affecting the lower extremities, such as radiculopathy or myopathy, where the clinical team were consulted for individual cases); (5) aged > 18 years; (6) willing and able to travel to the University of Calgary (Calgary, AB); (7) received Canadian Society for Exercise Physiology-Certified Exercise Physiologist (CSEP-CEP) approval via The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and/or physician approval; and (8) able to follow verbal instructions in English. Twenty-two people (mean ± SD; age: 52 ± 9; stature 174 ± 11 cm; mass: 76 ± 18 kg; 8 female) who completed RTx (i.e. 30 – 33 treatment delivered over ~6 weeks, 5 fractions/week) ± concomitant chemotherapy for HNC volunteered to participate in this study. Of the 22 volunteers, 15 had undergone surgery (i.e. RTx was adjuvant therapy), and 18 had received chemotherapy (cisplatin) concomitant to RTx (see Table 4.1 for a detailed description of participant characteristics).

4.3.4 Randomization and blinding

The randomization process was conducted by an assistant researcher not involved in treatment interventions or study outcomes. Participants were randomly allocated to the EXP or CON group after the baseline laboratory assessment was completed. Randomization was performed using an open-source, Web-based minimization program (MinimPy) (Saghaei &

Saghaei, 2011). Participants were stratified by sex (male/female), age (< 60/≥ 60), tumor type (oropharyngeal/non-oropharyngeal), chemotherapy (no/yes) and major surgery (no/yes), then assigned to the intervention that created the least imbalance. Due to the nature of the interventions (EXP and CON), blinding participants and the study team to treatment allocation was not feasible.

4.3.5 Laboratory visits

Before the intervention, participants (n = 22) visited the laboratory 57 ± 30 days after RTx. After the intervention, participants (n = 19) repeated the laboratory visit a minimum of 72 hours following the final exercise session to allow for a sufficient recovery, and to ensure muscle damage/swelling did not affect results (Schoenfeld et al., 2018). Participants were asked to avoid both caffeine and alcohol consumption, and the performance of strenuous exercise in the 24 hours preceding each laboratory visit.

All laboratory protocols were tested in our previous work (Part I) and was identical to those used in the current study. Briefly, on the initial lab visit, after RTx, a health screening was conducted (see 3.3.3 Experimental design). The remaining assessments were identical before and after the intervention, and comprised of (in order) patient-reported outcomes, including the Functional Assessment of Chronic Illness Therapy – Fatigue, Version 4 (FACIT-F) questionnaire and Functional Assessment of Cancer Therapy – Head & Neck, Version 4 (FACT-H&N) questionnaire (see 3.3.3.2 Patient-reported outcomes). Next, participants body mass and body height were measured, as well as skinfold thicknesses to predict relative body fat percent (see 3.3.3.3 Anthropometry), and muscle CSA thereafter (see 3.3.3.4 Muscle CSA). Afterwards, participants were prepared to undergo an assessment of neuromuscular function on a standardized isometric chair (3.3.4.1 Force and electromyography recordings), which began with the determination of supramaximal femoral nerve electrical stimulation and subsequently followed a warm-up period, and a neuromuscular evaluation that included measurements of maximal voluntary force, voluntary activation and potentiated twitch amplitude of the knee extensors (see 3.3.3.5 Neuromuscular assessment at rest). Finally, participants completed an incremental cycling test to measure performance fatigability that included neuromuscular assessments before, during and immediately following volitional exhaustion (3.3.3.6 Intermittent cycling test and performance fatigability). The stimulation current elicited over the femoral nerve or all participants before training was 160 ± 57 mA and after training was 161 ± 74 mA.

As an addition to the neuromuscular assessments used in Chapter Three, we included a functionally relevant test of lower limb muscular endurance. The 30-s sit-to-stand test has been used in numerous studies to investigate functional (or physical) performance levels (Millor, Lecumberri, Gómez, Martínez-Ramírez, & Izquierdo, 2013). We assessed functional lower body performance that resemble activities of daily living (i.e. performing locomotor tasks), using the 30-s sit-to-stand test, conducted before the first and after the last training sessions. This was measured as the number of times a participant could stand from a seated position in 30 s. This method has been previously used in survivors of HNC (Capozzi et al., 2016; Lønbro et al., 2013; Lonkvist et al., 2017).

4.3.6 Treatment arms

Both training interventions took place in the Thrive Centre (Faculty of Kinesiology, University of Calgary, AB), a fitness facility for people affected by cancer. Where possible, participants were scheduled to perform 36 sessions over 12-weeks, planned thrice weekly, on non-consecutive weekdays to ensure optimal recovery between sessions (Lonkvist et al., 2017). If committing to a training frequency of three sessions per week was not possible, participants could opt to attend twice per week (24 planned sessions over 12 weeks). This is aligned with previous study designs in HNC patients (Lonkvist et al., 2017), and is an important consideration if the goal is increasing muscular strength (Grgic et al., 2018) and muscle hypertrophy (Schoenfeld, Ogborn, & Krieger, 2016). Participants were given the opportunity to attend 'make-up' training sessions added to the end of the training intervention if there was a conflict in scheduled personal or public holidays and/or illness or ongoing medical appointments. Mean completion time was calculated as the number of weeks participants took to complete their intervention. One participant in the CON group could only commit to two training sessions per week and as such, 24 sessions over 12-weeks were scheduled. Adherence was evaluated as the total number of sessions attended as a percentage of the total number of sessions scheduled. The exercise intervention was delivered in a small-group setting, and participants in both treatment arms were supervised by the same exercise specialist (a CSEP-CEP with cancer-specific training). To ensure the overall wellbeing of the participant, and to monitor that the intervention did not increase fatigue severity, participants were asked to quantify their fatigue before and after each supervised training session using a rating-of-fatigue scale (Micklewright, St Clair Gibson, Gladwell, & Al Salman, 2017).

4.3.7 Interventions

4.3.7.1 Experimental group

Participants allocated to the experimental intervention performed accentuated eccentric loading by eccentrically focused single leg squats, followed by NMES. NMES was delivered via a portable battery powered electrical stimulator device (Compex SP 2.0, Compex, Vista, CA). Eccentrically focused single leg squats were performed as 2 sets × 8 repetitions, which involved overloaded eccentric contractions and relatively underloaded concentric contractions performed bilaterally so that the weight was evenly distributed. Specifically, participants lowered the weight unilaterality using a slow to moderate velocity before making contact with a flat bench or chair to initiate the concentric phase, which was adjusted such that the hip-joint was parallel without sacrificing neutrality of the spine and neck, and non-alternating between contralateral limbs. NMES was applied using Compex Performance self-adhesive electrodes to deliver stimulations bilaterally to the knee extensors. Single negative electrodes (5 cm × 10 cm) were placed proximally on the knee extensors, close to the insertion point, while pairs of positive electrodes (5 × 5 cm) were placed over the vastus lateralis proximally and the vastus medialis distally, according to the recommendations of the manufacturer (https://www.compexstore.com/?from=en). Sixty-six bi-lateral NMES contractions were delivered using a frequency of 40 Hz, as well as a pulse duration of 180 μs, and a contraction-relaxation period of 5 s bursts of stimuli, 10 s rest period, ramp-up time of 1.5 s, and ramp-down time of 0.75 s. Stimulating characteristics were selected from the commercially available 'muscle building' Compex program and expressed as a value from 0 – 999 (arbitrary units [a.u.]; where peak current is 120 mA). Participants were encouraged to set the current intensity to the maximally tolerated level ensuring a visible muscle contraction, and to increase the intensity if it became more tolerable over time. When the electrical stimuli began, participants performed alternating voluntary concentric knee extensor contractions, while keeping the knee slightly bent. These instructions were chosen based on the manufacturer's instructions (*Integrating Electro Muscle Stimulation Into Fitness Training Level 1*, 2016), and recommended for optimal application of NMES (Maffiuletti et al., 2018). Peak intensities were recorded after each session of NMES.

4.3.7.2 Conventional group

Dynamic strength training was prescribed to the CON group as the active control. Total volume (sets × repetitions × load) has been reported as one of the main variables to influence muscular adaptations (Schoenfeld, Ogborn, & Krieger, 2017), with previous studies demonstrating a dose-response relationship between volume and hypertrophy (Krieger, 2010; Lasevicius et al., 2018; Schoenfeld et al., 2017). Therefore, we designed the training protocols to ensure that the frequency of training and the total number of contractions (i.e. sets and repetitions) were similar per session in EXP and CON programs. In EXP, 66 NMES contractions and 2 sets × 8 repetitions of single-leg squats were performed, totaling 82 contractions in total during each session. In CON, participants performed 5 different dynamic strength training exercises of 2 sets × 8 repetitions, totaling 80 contractions total. The progression of intensity was monitored as an increase in load. Participants completed a series of dynamic exercises targeting the knee extensors and performed five exercises of two sets × eight repetitions using a controlled slow to moderate velocity, with 1 – 3 min rest between sets. A select number of both compound and isolated movements using body weight, dumbbells, elastic bands (TheraBand, Akron, OH) and machine-based resistance exercises were prescribed based on individual ability and exercise tolerance to accommodate for a diverse group of individuals.

4.3.7.3 Exercises performed by both treatment arms

Participants in both interventions completed the same standardized warm-up (dynamic, light aerobic movement) and cool-down (static stretching of major muscle groups). Both groups also performed the same (or similar, based on any modifications) exercises after completing their specific knee extensor program. These exercises targeted major lower limb antagonistic and synergistic muscles (e.g. hamstrings, erectors, gluteus, gastrocnemius and soleus) and upper limb muscles, primarily to ensure overall wellbeing and promote full-body functioning. Particularly, special attention was aimed to progressive strength training of the glenohumeral joint with the objective of reducing pain, increasing range of motion, and promoting muscular strength of the shoulder complex and other scapula stabilizing muscles, as people that receive surgical procedures and/or RTx for HNC frequently experience shoulder dysfunction (Carvalho, Vital, & Soares, 2012). The muscle groups strengthened were rhomboids (scapular retraction), levator scapulae (scapular elevation), infraspinatus and posterior deltoids (external rotation), and middle deltoids

and subscapularis (glenohumeral/scapular abduction). These muscle groups were chosen based on their common inclusion in training interventions for shoulder pain and dysfunction in HNC survivors (McNeely et al., 2008, 2004). Participants performing any voluntary exercise were instructed to do so to tolerance, and where achievable. Where an existing side-effect of treatment (e.g. spinal accessory nerve damage) or pre-existing injury (e.g. knee replacement) limited the performance of an exercise, the exercise was modified or substituted. Loads were chosen based on the principle that the weight selected allowed for a set to be completed before failure (i.e. it was perceived that 1 – 2 additional repetitions could be performed), with any exercise being stopped with the breakdown of technique. To quantify this perception, we corresponded this sensation to a rate of perceived exertion of approximately 13 – 15 of 20 (described as "somewhat hard" to "hard") (Borg, 1982). This progression model was formulated in accordance to guidelines from the American College of Sports Medicine (Ratamess et al., 2009) and cancer-specific guidelines (Schmitz et al., 2010).

4.3.8 Data analysis

4.3.8.1 Feasibility

Analyses included feasibility outcomes: accrual (the percent of patients enrolled in our study), completion (the number of participants randomized vs. number who finished the intervention), adherence (the number of training sessions scheduled vs. number attended), and compliance to NMES and eccentric strength training (including evidence of progression over time). Feasibility outcomes were not based on an a priori criteria. The number and nature of any adverse events were also considered.

4.3.8.2 Neuromuscular parameters

Muscle CSA, maximal voluntary contraction and muscle stimulation paradigms were analyzed using identical techniques to that previously described (see 3.3.5.1 Neuromuscular parameters, respectively). In regard to the cycling test, maximal voluntary force, potentiated evoked force, voluntary activation, M-wave and root mean square EMG activity of the vastus lateralis and rectus femoris collected during the last stage (i.e. second stage) completed by all participants was normalized to the pre-cycling values measured on the cycling ergometer. This normalized data is referred to the 'last common stage' in later reporting. Similarly, the data

collected at volitional exhaustion was normalized to the pre-cycling values measured on the cycling ergometer and is referred to 'post-cycling' in later reporting.

4.3.8.3 NMES training intensities

The peak stimulation intensities that were obtained after each session in the EXP group were averaged over each individual training session. The averages from week 3, 6, 9, and 12 were calculated and used to evaluate differences over time.

4.3.9 Statistical analysis

In order to power the study to detect a difference in a repeated-measures ANOVA for the interaction of group (2: CON, EXP) × time (before receiving intervention, after receiving intervention), a power analysis was conducted for the efficacy outcome of MIVC force using G*power version 3.1 software program (Franz, Erdfelder, Lang, & Buchner, 2007). We used a large effect size of (partial eta squared 0.14) due to the large effect of RTx on MIVC force (~20% decrease) and therefore large potential for improvement. Based on a power of 80%, significance level of 5%, a total sample size of 54 individuals (27 participants each group) would be required to detect this effect. Based on a similar recruitment strategy at the same site, Capozzi and colleagues (Capozzi et al., 2016) assessed 448 HNC patients for eligibility over a 19-month recruitment period, where 60 participants were randomized and the loss to attrition was 30% (42 of 60 participants). Therefore, we anticipated that accrual would be close to the required sample size of 54 after a similar recruitment period. However, this was not the case, and although the study is powered to detect a main effect of time (included in later reporting), it is not powered to detect a group × time interaction using the planned statistical analysis (Supplementary Table A). Therefore, to evaluate differences in groups, the focus in the results section is on mean differences and the standardized mean difference; SMD). Interpretation of the SMD was considered as follows: 0.2 is small, 0.5 is medium and 0.8 is large (Cohen, 1988). For patient-reported outcomes, the reported minimally clinically important difference (MCID) was also used to evaluate any differences over time or between groups. All data was visually inspected for normal distribution by q-q-plots, histograms, and box plots. The assumptions of normality and sphericity were tested using a Shapiro–Wilk test and Mauchly's test, respectively. If the assumption of Sphericity was violated, the Greenhouse–Geisser correction was applied when necessary. A one-way ANOVA

with repeated measures (week 3, week 6, week 9, and week 12) was performed to determine differences between the average values of NMES intensities. Bonferroni corrected t-tests were conducted as post hoc analysis if the ANOVA indicated a significant effect. Effect sizes were calculated to provide a quantitative measure of the magnitude of the reported effects. Partial eta squared (η_{p2}) was used as an estimate of effect size for ANOVA. Interpretation of the size of the effect was cautiously defined as follows: $\eta_{p2} = 0.01$ is small, $\eta_{p2} = 0.06$ is medium and $\eta_{p2} = 0.14$ is large (Cohen, 1988). Statistical significance was set at $P < 0.05$. All statistical procedures were conducted using SPSS software version 25.0 (IBM Corp., Armonk, NY).

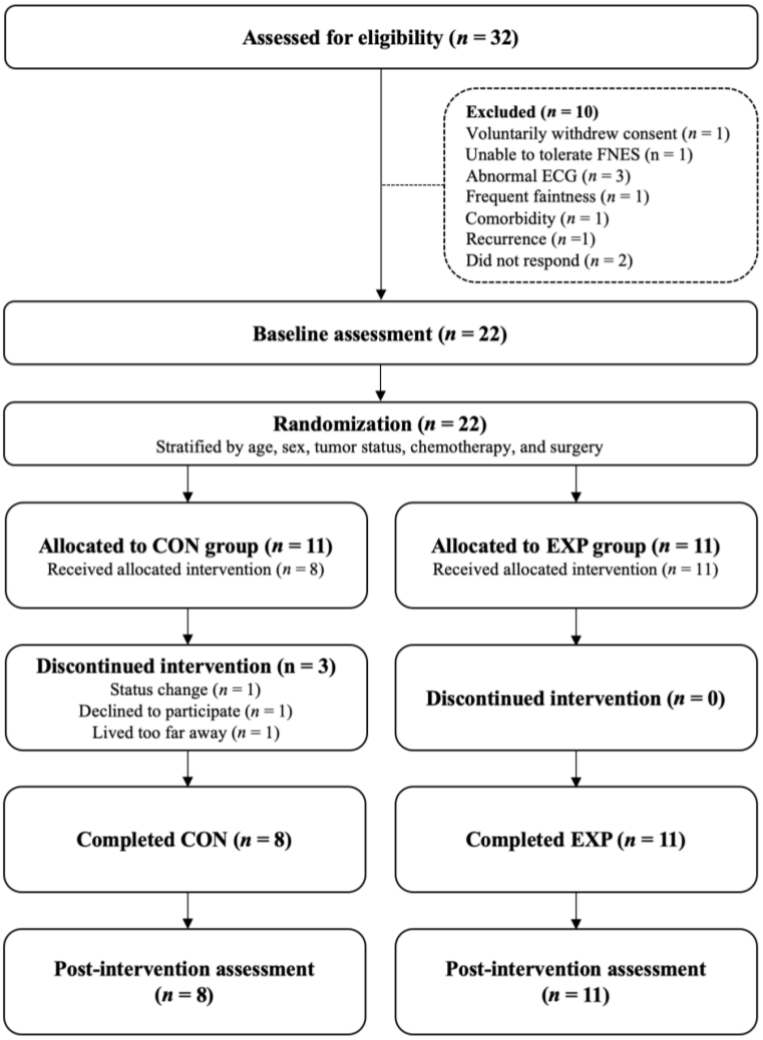

Figure 4.1: Overall study design. ECG, electrocardiogram; CON, conventional strength training group; EXP, experimental strength training group.

4.4 Results

4.4.1 Feasibility outcomes

4.4.1.1 Accrual

Over the course of the recruitment period we attended 43 patient-education sessions and as a result, a total of 237 patients were approached to participate. Of these patients, 51% (121 of 237) declined to be contacted to take part in the study with the most common reason due to travel distance. In the remaining 49% of patients (n = 116) who provided contact details, 9 did not meet the inclusion criteria, due to being aged > 75 years (n = 2), an existing comorbidity (n = 5), and could not understand or follow instructions in the English language (n = 2). Additionally, 32% of patients (75 of 237) were excluded because they could not be contacted (n = 63), lived too far away (n = 5), had no time (n = 4), were not interested with no specific reason (n = 3), or died (n = 1). The overall accrual of those who attended the education-sessions was 13.5% (32 of 237 patients). Unfortunately, we are not able to provide the recruitment rate based on the number of eligible patients, because over half did not provide a reason that they did not want to be contacted.

4.4.1.2 Completion

As illustrated in Figure 4.1, a total of 32 people who had completed RTx for HNC attended the laboratory and were assessed for inclusion during the recruitment period. Of those, 69% (22 of 32 patients) completed the pre-intervention assessment and began the 12-week intervention (see Table 4.1 for participant characteristics). However, three people discontinued, not due to one particular reason (Figure 4.1), resulting in a total completion rate of 86% (19 of 22 participants). Completion rate of the 12-week program in CON was 82% (9 of 11 participants) and 100% (11 of 11 participants) in the EXP group. Overall mean completion time for the intervention was 12.8 ± 1.6 weeks (13.2 ± 2.2 weeks and 12.6 ±1.2 weeks for CON and EXP, respectively).

4.4.1.3 Adherence

Overall program adherence during the 12 weeks was 88 ± 12% (588 of 672 sessions), 81 ± 15% (223 of 276 sessions) for CON, and 92 ± 8% (365 of 396 sessions) for EXP.

Table 4.1: Baseline characteristics of participants.

Variable	Experimental (n = 11)	Conventional (n = 11)	Combined (n = 22)
Demographic/anthropometric, mean ± SD			
Age, years	53 ± 7	50 ± 11	52 ± 9
Body mass (kg)	78.1 ± 16.9	73.0 ± 18.9	75.9 ± 17.5
Height (cm)	174.2 ± 11.8	173.6 ± 9.8	173.9 ± 10.7
BMI (kg/m2)	25.7 ± 5	32.9 ± 4.4	25 ± 4.7
Estimated body fat (%)	21.9 ± 6.2	18.9 ± 6	20.6 ± 6.1
Sex, n (%)			
Male	8 (73)	6 (55)	14 (64)
Female	3 (27)	5 (45)	8 (36)
Primary tumor site, n (%)			
Larynx	0	1 (9)	1 (5)
Oral cavity	3 (27)	1 (9)	4 (18)
Oropharynx	8 (73)	5 (45)	13 (59)
Nasopharynx	0	1 (9)	1 (5)
Salivary glands	0	3 (27)	3 (14)
Stage, *n* (%)			
I-II	5 (45)	5 (45)	10 (45)
III-IV	3 (27)	1 (9)	4 (18)
Unknown	3 (27)	5 (45)	8 (36)
Treatment, n (%)			
Major surgery (before RTx)	7 (64)	8 (73)	15 (68)
Radiation therapy alone	0	0	0
Concomitant chemotherapy	9 (82)	9 (82)	18 (82)
HPV status, n (%)			
Positive	8 (73)	5 (45)	13 (59)
Negative	3 (27)	6 (54)	9 (41)

BMI, body mass index; HPV, human papillomavirus; RTx, radiation therapy

4.4.1.4 Adverse events

No adverse events during or after training, and no adverse events during or after testing were observed.

4.4.1.5 Compliance to NMES and eccentric training

Analysis of one-way ANOVAs detected a significant main effect of time ($F_{1.569,15.686}$ = 11.28, P = 0.002, η_{p2} = 0.53) across the average stimulation intensity participants were able to maximally tolerate across week 3 to week 12 (Figure 4.2b). To further support the evaluation of NMES intensity, the difference in peak stimulation output between single training sessions at similar points (Figure 4.2a) confirmed a main effect of time ($F_{1.899,18.993}$ = 11.18, P < 0.001, η_{p2} = 0.53). The mean weight loading for unilateral squats significantly improved by 10 ± 5 kg ($F_{3,0}$ = 31.38, P < 0.001, η_{p2} = 0.76), between week 3 and week 12.

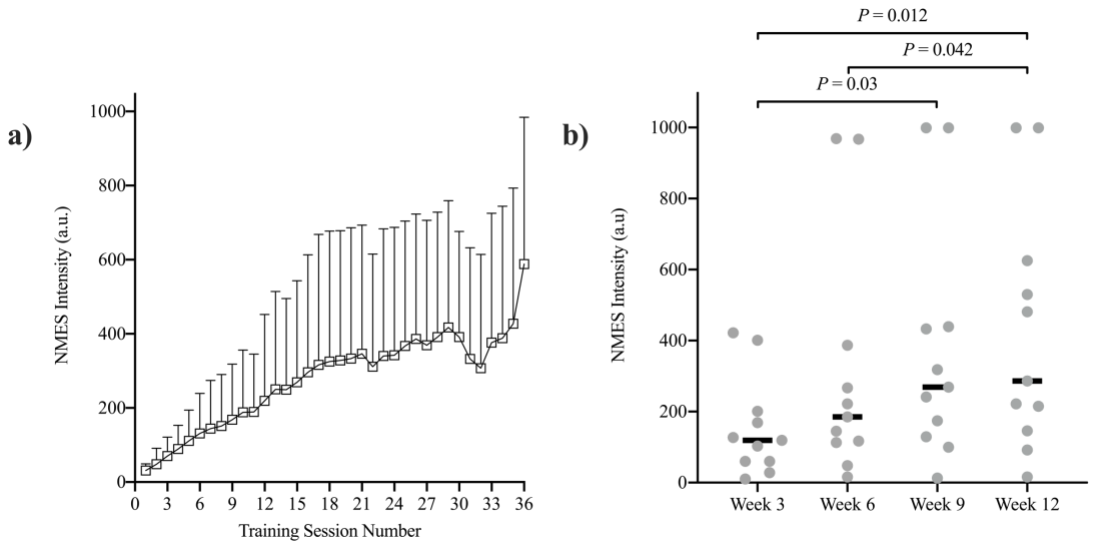

Figure 4.2: Neuromuscular electrical stimulation intensities. (Panel **a**) daily intensities over the 12-week program; (Panel **b**) Average weekly intensities over the 12-week program.

4.4.1.6 Compliance to conventional training

In the CON group, all but one participant progressed substantially (in terms of increased load, and progression to more difficult movements e.g. from static lunge to Bulgarian split squat) over the course of the intervention. All participants in the EX group made similar improvements, and the data for NMES stimulation intensity were considered in detail.

4.4.2 Neuromuscular function

Maximal force generating capacity of the knee extensors (Figure 4.3a) increased from before to after the intervention by 22 ± 23% (from 427 ± 106 to 507 ± 102 N; main effect of time: $F_{1,17} = 15.93$, $P < 0.001$, $\eta_{p2} = 0.48$). The data suggest that the EXP and CON interventions resulted in similar improvements in MIVC force (Table 4.2). Despite the increase in voluntary force, evoked force (potentiated twitch force, Figure 4.3b) did not increase from before to after the intervention ($F_{1,17} = 1.2$, $P = 0.299$, $\eta_{p2} = 0.06$). In addition, voluntary activation did not change over time ($F_{1,17} = 0.48$, $P = 0.499$, $\eta_{p2} = 0.03$).

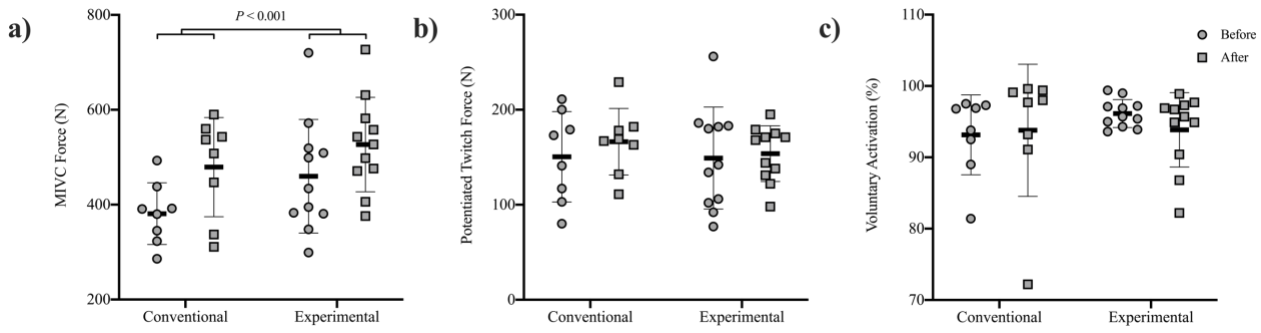

Figure 4.3: Difference in: (panel **a**) maximal isometric muscle force; (panel **b**) potentiated twitch force; and (panel **c**) voluntary activation following a 12-week strength training program. MIVC, maximal voluntary isometric contraction.

4.4.3 Anthropometrics

As shown in Figure 4.4, vastus lateralis and rectus femoris muscle CSA increased by 19 ± 23% and 17 ± 22%, respectively (main effect of time: $F_{1,17}$ = 10.7, P = 0.004, η_{p2} = 0.3 and $F_{1,17}$ = 10.1, P = 0.006, η_{p2} = 0.37, respectively). However, there is little evidence to suggest that one intervention resulted in larger improvements than the other (Table 4.2). Further, no main effects of time were found in other anthropometric measures including body mass ($F_{1,17}$ = 0.11, P = 0.74, η_{p2} = 0.01), BMI ($F_{1,17}$ = 0.02, P = 0.891, η_{p2} = 0.001), and estimated percent body fat ($F_{1,17}$ = 3.89, P = 0.065, η_{p2} = 0.19) (Supplementary Table A).

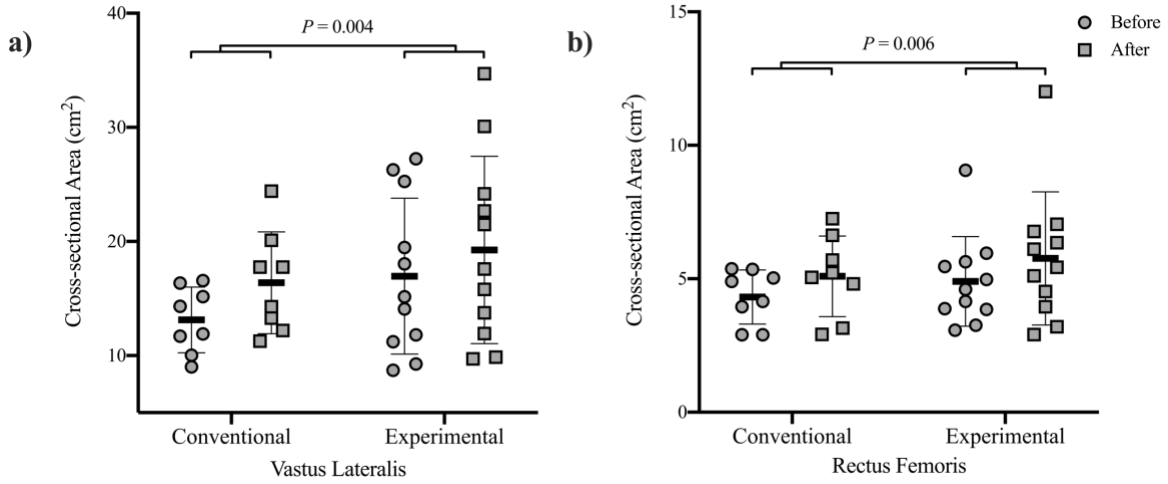

Figure 4.4: Difference in cross-sectional area following a 12-week strength training program; **a**) vastus lateralis, **b**) rectus femoris.

4.4.4 Patient-reported outcomes

Figure 4.5 shows changes in HRQL and perceived fatigue from before to after the 12-week training interventions. FACT-H&N (total score) improved overtime ($F_{1,17}$ = 41.78, P < 0.001, η_{p2} = 0.71), with a mean increase of 13 ± 10 points from pre- to post-intervention (where the improved MCID is represented by ≥ 6 points). A main effect of time for several subscales of the FACT-H&N were observed, including physical well-being ($F_{1,17}$ = 22.47, P < 0.001, η_{p2} = 0.57), emotional well-being ($F_{1,17}$ = 6.00, P = 0.025, η_{p2} = 0.26), functional well-being ($F_{1,17}$ = 36.83, P < 0.001, η_{p2} = 0.68), and the HNC-specific subscale ($F_{1,17}$ = 17.11, P = 0.001, η_{p2} = 0.50), while social well-being did not differ ($F_{1,17}$ = 1.41, P = 0.252, η_{p2} = 0.08). More so, the severity of perceived fatigue (FACIT-F score) improved over time ($F_{1,17}$ = 10.79, P = 0.004, η_{p2} = 0.39). Clinically, this change was also relevant as the score increased by 6 ± 8 points (MCID = > 4 points) from pre- to post-intervention (where an increase in FACIT-F score indicates lower fatigue severity). Patient-reported outcomes are presented in Table 4.2.

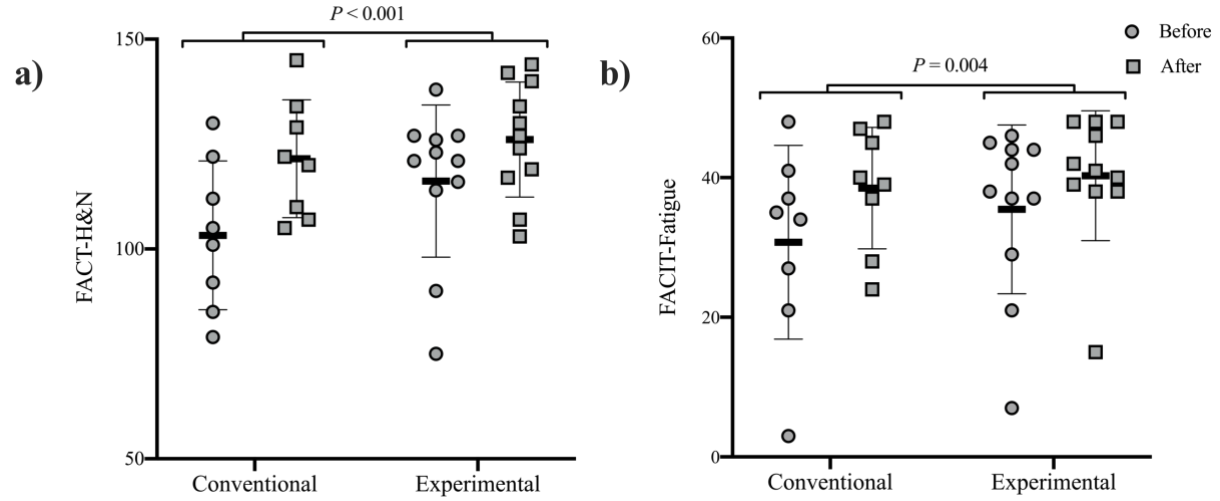

Figure 4.5: Individual changes in patient-reported outcomes following 12-weeks of strength training (panel **a**) Functional Assessment of Cancer Therapy – Head and Neck Questionnaire; (panel **b**) Functional Assessment of Chronic Illness Therapy – Fatigue Questionnaire.

4.4.5 Functional performance outcomes

After completing the 12-week intervention, participants were able to perform an additional 4 ± 4 stands (main effect of time: $F_{1,17}$ = 18.36, P = 0.001, η_{p2} = 0.52).

4.4.6 Responses to the intermittent cycling test

Cycling performance increased from before to after the 12-week program (main effect of time: $F_{1,17} = 48.67$, $P < 0.001$, $\eta_{p2} = 0.74$) as time to volitional exhaustion was improved by 157 ± 105 s (18 ± 13%), and seemed to be better in CON compared to EXP (SMD = 0.72; Table 4.2). *Force*: Normalized maximal voluntary force during the last common neuromuscular assessment did not differ from before to after the intervention (main effect of time: $F_{1,17} = 0.67$ $P = 0.894$, $\eta_{p2} = 0.04$). Figure 4.6 illustrates that although force was substantially reduced at the point of volitional exhaustion both before and after the intervention (Supplementary Table B), no main effect of time was detected ($F_{1,17} = 4.06$, $P = 0.06$, $\eta_{p2} = 0.19$).

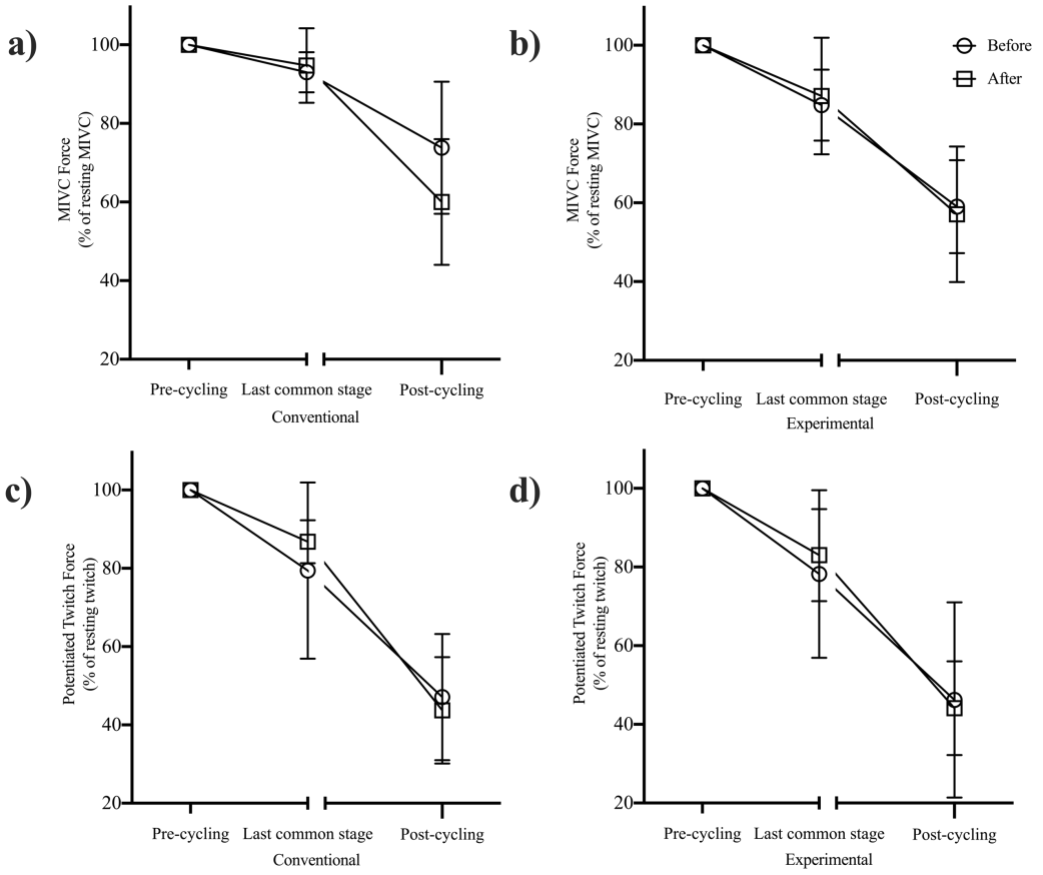

Figure 4.6: Voluntary and evoked knee extensor force during neuromuscular assessments throughout the cycling test. Values were normalized as a percent of pre-cycling measurements. (panel **a**) MIVC before vs. after CON training; (panel **b**) MIVC before vs. after EXP training; (panel **c**) Potentiated twitch force before vs. after CON training; and (panel **d**) potentiated twitch force before vs. after EXP training. MIVC, maximal isometric voluntary contraction; CON, conventional training group; EXP, experimental training group.

As with voluntary force, potentiated twitch force was not different after the last common stage of cycling (main effect of time: $F_{1,17}$ = 0.06, P = 0.813, η_{p2} = 0.003) from before to after the intervention. A substantial decrease from pre-cycling in potentiated evoked force was also evident at the point of volitional exhaustion both before and after the intervention (Figure 4.6). However, this decrease was not different for the main effect of time ($F_{1,17}$ = 1.23, P = 0.283, η_{p2} = 0.07).

There were no significant differences in vastus lateralis and rectus femoris M-wave amplitude at the last common stage or post-cycling from before to after the intervention, and no significant differences in the group × time interaction (Supplementary Table B).

4.4.7 Central responses

Voluntary activation was not different from before to after the intervention at the last common stage (main effect of time: $F_{1,17}$ = 0.12, P = 0.729, η_{p2} = 0.01) or at post-cycling (main effect of time: $F_{1,17}$ = 1.51, P = 0.236, η_{p2} = 0.08). Additionally, there was no difference between EXP and CON after the last common stage or post-cycling (Supplementary Table B). RMS-EMG values were different from before to after the training intervention (Supplementary Table B).

Table 4.2: Mean and standardized mean differences of anthropometrics, patient-reported outcomes, functional performance, and neuromuscular function.

Outcome	Conventional Group (n = 8)			Experimental Group (n = 11)			Standardized Mean Difference
	Pre-Intervention	Post-Intervention	Mean Difference	Pre-Intervention	Post-Intervention	Mean Difference	
Body composition							
Body mass, kg	73.0 ± 17.7	72.8 ± 15.2	–0.2 ± 3.9	78.1 ± 16.9	78.9 ± 17.9	0.8 ± 3.7	-0.26
BMI, kg/m$_2$	23.9 ± 4.1	23.7 ± 3.3	–0.3 ± 1.7	25.7 ± 5.0	25.9 ± 6.2	0.2 ± 1.3	-0.33
Percentage fat	18.9 ± 5.6	17.7 ± 4.4	–1.3 ± 3.0	21.9 ± 6.2	20.8 ± 6.0	–1.1 ± 2.0	-0.08
CSA							
VL, cm$_2$	13.1 ± 2.7	16.4 ± 4.2	3.2 ± 3.1	17.0 ± 6.9	19.3 ± 8.2	2.3 ± 3.9	0.27
RF, cm$_2$	4.3 ± 1.0	5.1 ± 1.4	0.77 ± 1.05	4.9 ± 1.7	5.8 ± 2.5	0.9 ± 1.1	-0.08
Patient-reported outcomes							
FACT-H&N physical	19 ± 5	26 ± 2	7 ± 4	22 ± 5	25 ± 4	3 ± 4	1.00
FACT-H&N social	24 ± 3	24 ± 4	0 ± 2	24 ± 3	25 ± 3	1 ± 2	-0.50
FACT-H&N emotional	19 ± 3	21 ± 2	2 ± 3	20 ± 4	22 ± 2	2 ± 3	0.00
FACT-H&N functional	18 ± 6	23 ± 4	5 ± 3	19 ± 6	23 ± 5	4 ± 3	0.33
FACT-H&N subscale	23 ± 4	28 ± 5	5 ± 2	31 ± 4	32 ± 5	1 ± 4	1.00
FACT-H&N total	103 ± 17	122 ± 13	18 ± 9	116 ± 18	126 ± 14	10 ± 9	0.80
FACIT-F	31 ± 13	39 ± 8	8 ± 9	35 ± 12	40 ± 9	5 ±7	0.38
Functional performance							
Sit-to-stand, repetitions	14 ± 2	19 ± 5	5 ± 4	18 ± 6	21 ± 6	3 ± 3	0.50
Performance time, s	761 ± 174	961 ± 225	201 ± 83	1016 ± 186	1141 ± 275	125 ± 107	0.72
Neuromuscular parameters							
MIVC, N	381 ± 61	479 ± 98	98 ± 64	460 ± 119	527 ± 100	67 ± 101	0.35
Potentiated twitch, N	151 ± 45	166 ± 33	16 ± 29	149 ± 54	154 ± 29	5 ± 48	0.27
Voluntary activation, %	94 ± 4	94 ± 4	0 ± 9	96 ± 2	94 ± 5	–2 ± 5	0.29
VL M-wave amp, mV	10.06 ± 5.91	11.16 ± 7.37	1.10 ± 3.62	6.77 ± 4.43	9.19 ± 5.27	2.42 ± 3.38	-0.37
RF M-wave amp, mV	5.44 ± 2.02	5.79 ± 0.82	0.35 ± 1.46	5.15 ± 2.64	6.45 ± 2.16	1.29 ± 3.56	-0.33
VL RMS-EMG, mV	0.554 ± 0.337	0.787 ± 0.958	0.233 ± 0.616	0.482 ± 0.299	0.496 ± 0.289	0.014 ± 0.243	0.47
RF RMS-EMG, mV	0.402 ± 0.185	0.464 ± 0.193	0.062 ± 0.143	0.379 ± 0.178	0.432 ± 0.194	0.053 ± 0.178	0.05

BMI, body mass index; CSA, cross-sectional area; VL, vastus lateralis; RF, rectus femoris; FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck Questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Questionnaire; MIVC, maximal voluntary isometric contraction, M-wave, compound muscle action potential; amp, amplitude; RMS-EMG, root means square of electromyography

4.5 Discussion

The primary aim of this randomized pilot trial was to evaluate the feasibility of an optimized, experimental strength training intervention involving a combination of eccentric overloading and NMES compared to a conventional training intervention similar in frequency and contraction number. The secondary aim was to provide efficacy for the experimental program and conventional program on maximal isometric force and muscle CSA in the knee extensors. The main findings were that: 1) eccentric overloading and NMES in RTx treated survivors of HNC seem to be feasible, safe, and well tolerated despite recruitment difficulties limiting the ability to make firm conclusions; and 2) an experimental intervention results in similar (and substantial) improvements in muscle function and muscle structure compared to conventional strength training. Quantifying physical/functional parameters is also an important outcome when considering endpoints of strength training programs. Therefore, after 12 weeks of strength training, maximal isometric muscle strength showed a more than 20% increase while muscle CSA increased by nearly the same, regardless of group. In addition, patient reported HRQL improved by approximately double the MCID, while fatigue severity substantially improved. Finally, this study showed that performance fatigability of the knee extensors during and after an intermittent cycling test to volitional exhaustion was not changed despite time to volitional exhaustion (i.e. exercise tolerance) was significantly increased by more than 2 minutes on average.

4.5.1 Feasibility and efficacy

With regards to feasibility, the overall adherence of approximately 88% was excellent. Adherence in the current study is comparable to previously reported adherence rates of 97% and 95%, respectively, in HNC training studies initiated after RTx (Lønbro, Dalgas, Primdahl, Johansen, et al., 2013; Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013), although a direct comparison is difficult considering the limited supervision in the studies of Lønbro et al. To the best of our knowledge, only two other studies have initiated an exercise program focused on strength training after RTx, both which compared the differences between an intervention initiated during RTx vs. after RTx. As a comparison, 94% adherence was reported in one study (Sandmæl et al., 2017), while Capozzi et al. reported a mean adherence of 62% after RTx (Capozzi et al., 2016). In consideration of the difference between the current study and previous work of Capozzi et al., the high adherence rate in this research is conceivably due to the fully supervised program.

Likewise, the completion rate of 86% in the current study is excellent, which in comparison, is similar to the work of Lønbro and colleagues (Lønbro, Dalgas, Primdahl, Johansen, et al., 2013; Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013), who reported completion rates of 70% and 83% (55 of 66 participants), respectively. Similarly, Capozzi et al. reported a 79% completion rate (23 of 29 participants) in their delayed intervention (Capozzi et al., 2016). These results contrast with that of Sandmæl et al., who reported a completion rate of only 52% (11 of 21 patients). The high completion rate in this study may speak to the degree of flexibility offered, and what we consider an advantage of our program.

Although we were able to provide evidence of efficacy for a novel strength training intervention after RTx for HNC, the overall recruitment rate of 13% in the current study appears to be lower when compared to other interventional studies in HNC conducted after treatment, partly because it is calculated based on the number of people who received the recruitment presentation rather than the number who would have been eligible. In the two studies of Lønbro et al., a recruitment rate of 28% (DAHANCA 25A) and 22% (DAHANCA 25B), respectively, were reported (Lønbro, Dalgas, Primdahl, Johansen, et al., 2013; Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013). Capozzi et al. reported a recruitment rate of 56% of eligible patients (Capozzi et al., 2016). However, this is due to the ability to track the number of eligible patients (a limitation of the present study). For example, 448 patients received information/were assessed for eligibility in the study of Capozzi et al., and with an accrual of 60 patients, this is an overall accrual of 13% Assuming that the reasons for ineligibility would be roughly the same between time periods, our recruitment is similar to that reported by Capozzi et al. Nevertheless, recruitment difficulties would limit the success of a fully powered randomized controlled trial at this particular site, and recruitment strategies should be considered carefully in future studies.

4.5.2 Applicability of the experimental training program

With regard to muscle strength and muscle CSA, both EXP and CON groups improved after 12 weeks of supervised training. MIVC increased by a mean of 22%, and muscle thickness in the vastus lateralis and rectus femoris increased 19% and 17%, respectively. These results suggest that a combined training program involving separate accentuated eccentric loading and NMES does not provide a greater stimulus to improvements in the neuromuscular system compared to conventional strength training. However, these findings should be interpreted with

caution due to the fact we did not meet the adequate sample size required to detect significant group by time effects. Conventional strength training methods are a valuable tool that should not be overlooked in RTx treated survivors of HNC. Conventional strength training is a valuable tool that should not be overlooked.

Nevertheless, these results are encouraging for the application of eccentric overloading and NMES as it offers greater flexibility to future training programs in patients where conventional strength training is not tolerable or is a contraindication. For example, in studies that have investigated the optimal timing of an exercise intervention for HNC care (Capozzi et al., 2016; Sandmæl et al., 2017), a noticeable difference favoring adherence when an exercise intervention is initiated after compared to during treatment was observed. This may speculatively be due to the deleterious consequences these individuals are challenged with during cancer treatment. Importantly, the experimental approach has the potential to improve muscle function and structure at lower intensities, as NMES is generally delivered at higher frequencies than voluntary contractions (Spector et al., 2016), preferentially activating larger type II motor units (Maffiuletti et al., 2018), contrary to the size principle (Henneman et al., 1965). As such, the application of our experimental program initiated during cancer treatment, could, conceivably be more beneficial in limiting muscle wasting and result in improved adherence rates compared to conventional methods of strength training. In the future, adequately powered randomized controlled trials are required to test this theory. One pitfall of NMES is that it cannot improve coordination and, therefore, limits the potential for learning specific movement patterns (Paillard, 2008). Facilitating motor learning can be an important aspect in gaining a greater degree of functional independence. Therefore, another important consideration moving forward could be the application of NMES in adjunct to voluntary, dynamic strength training in RTx treated survivors of HNC.

4.5.3 Patient-reported Outcomes

In the current investigation, participants HRQL and perceptions of cancer-related fatigue were both statistically and clinically improved following 12 weeks of strength training (Figure 4.5). An increase of 13 points (total score) on the FACT-H&N questionnaire was observed in the current study, which exceeds the clinically important difference of ≥ 6 points in this outcome (Ringash et al., 2004). Also, patient-reported perceptions of fatigue on the FACIT-F questionnaire improved by 6 ± 8 points overall, exceeding the minimal clinically important difference of 4 points.

A possible explanation the increase in self-reported outcomes may include regression to the mean, particularly due to the absence of a 'no-exercise' control group. However, the increases in patient-reported HRQL and fatigue after 12 weeks of strength training in the current study are similar in magnitude to the decreases observed following completion of cancer therapy in HNC. In particular, in our previous work we reported a decrease of 16 points and 9 points in self-perceived HRQL and fatigue, respectively (Chapter Three). Therefore, it seems that 12 weeks of supervised strength could reverse a large portion of these outcomes as reported using similar training interventions (Lønbro et al., 2013). Our results detected HRQL improvements in favor of CON, particularly in the physical and symptom specific subscales. However, baseline scores of the two specific measures were much lower in CON, suggesting a large potential for improvement in this group. More so, the symptom specific subscale addresses symptoms directly related to the effects of treatment, e.g. 'My mouth is dry' which is rated on a Likert scale from 0 described as 'not at all' to 4 as 'very much' (Ringash et al., 2004). It is unlikely that physical exercise training would impact these sensations over a 12-week intervention and is therefore, likely due to chance (Table 4.2).

4.5.4 Neuromuscular function and fatigability

Surprisingly, when potentiated resting twitch was evaluated, we were unable to detect an increase in mechanically evoked force after the training period (Figure 4.3b). Due to the lack of central influence, i.e. increase in voluntary activation, we assumed that peripheral components would contribute greater to the 22% improvement in MIVC force. However, this was not the circumstance, and likely a result of low statistical power and large standard deviation. Similar to the results in our previous work (see 3.4.5 Effects of the intermittent cycling test), maximal isometric force and potentiated evoked force in the current study was substantially reduced after incremental cycling to volitional exhaustion (Figure 4.6). After normalizing the cycling test outcomes to a percent of pre-cycling, the development of neuromuscular fatigue did not differ over time as a result of incremental cycling to volitional exhaustion. Despite the lack of statistical evidence, the magnitude in which peripheral muscle fatigue developed post-cycling was large (evidenced by the ~55% reduction in potentiated evoked force) and was similar from before to after the intervention (Figure 4.6).

4.5.5 HNC: associations with previous literature

The results of the current study are consistent with previous studies that have investigated strength training interventions in survivors of HNC that have been treated with RTx, showing that conventional strength training was effective for increasing muscle strength and lean body mass (Lønbro et al., 2013). We report maximal isometric strength of the knee extensors in CON increased an average of ~26%, which are aligned with previous changes of ~20% in isometric and isokinetic knee extensor strength (Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013), although a direct comparison may be difficult due to different intervention specifics (i.e. nutritional supplementation and training principles), testing methods and study protocols. However, where previous investigations have already shown promise in mitigating the effect of muscle wasting and improving HRQL in RTx treated survivors of HNC (Capozzi et al., 2016; Lønbro, Dalgas, Primdahl, Overgaard, et al., 2013), these studies were limited to conventional strength training principles only. Therefore, we attempted to manipulate exercise selection in an attempt to elicit superior outcomes in muscle strength and muscle size. To the best of our knowledge, this is the first study to investigate the effects of eccentric overloading and NMES and compare it to conventional strength training on muscle strength and muscle CSA of the knee extensors. In doing so, the experimental design of current study was intended to use non-invasive strategies. In other words, the training program could potentially be applied outside of research settings, such as rehabilitation facilities or even safely at home without supervision. As such, we opted to implement accentuated eccentric loading, a more practical training method than isokinetic dynamometers commonly used in laboratory studies (Baroni et al., 2015), and current characteristics commonly applied by most commercialized NMES products (https://ca.compexstore.com/en).

4.5.6 NMES: associations with previous literature

The application of NMES in cancer rehabilitation is a novel approach (O'Connor et al., 2018), with many studies having markedly distinct intervention characteristics from the current study. The duration of many interventions in cancer survivors alone makes it difficult for comparison with this study, as the reported number of delivered treatments range from 4 sessions (Strasser et al., 2009) to 15 sessions (Lin et al., 2011). In patients with non-small lung cell cancer, NMES was applied over an 11-week period vs. a true control group during chemotherapy

treatment, however no significant differences were found in knee extensor muscle strength or body composition (Maddocks et al., 2013). However, there is not a lack of quality studies investigating the application of NMES to improve strength or physical function. For example, the findings in this research are similar to previous comparative studies assessing the effectiveness of NMES, demonstrating no advantage in maximal isometric force of the knee extensors between an experimental NMES program and exercise control group in patients with knee osteoarthritis (Elboim-Gabyzon, Rozen, & Laufer, 2013). In contrast, the application of NMES appears to be beneficial to improve muscle weakness and atrophy of the quadriceps muscles in people who receive anterior cruciate ligament surgery (Hauger et al., 2018). The dissimilar findings among NMES-based programs are most likely due to the difference in methodologies across investigations. A more systematic and unified approach to NMES therapy is required, as discussed previously (Maffiuletti et al., 2018) to optimize outcomes in clinical populations.

4.5.7 Study limitations

A potential limitation in the current study was that laboratory testing, interventional procedures and data analysis were conducted by the first author, when having blinded outcome assessors would reduce the potential for experimenter bias. However, it is possible that this contributed to the excellent adherence and completion rates. In addition, the same investigator provided instruction to both groups, although also an important consideration to deliver consistency in the application of treatment protocols. Given the fact we attempted to optimize a training intervention on muscle strength and lean body mass, it may be considered that the absence of nutritional supplementation may be a limitation. Given the beneficial effects nutritional supplementation can have on a variety of clinical populations (Fairman et al., 2019), it seems reasonable implementation of an ergogenic aid could have augmented the effects of strength training on muscle performance. However, and to the best of our knowledge, every HNC patient at the Tom Baker Cancer Centre is appointed a registered dietician whom works closely with patients to ensure their nutritional requirements are being fulfilled.

The design of this trial also did not include a ‘no exercise’ control group. The lack of representation of a ‘no exercise’ control limits our ability to determine if our findings were fully representative of the exercise protocols versus the natural time course of recovery. Nevertheless, the improvements in muscle strength and mass are unlikely to be due to regression to the mean

over 3 months, and other studies have reported that typically, HRQL and fatigue are still reduced even up to 12 months after treatment. In terms of interventional design, we also lack the ability to determine which modality (NMES or eccentric overloading) in the experimental group has the most impact. Future studies can benefit from a larger sample size and multi-center sites. Further, we did not attempt to control for exercise outside of the intervention. Although participants were not offered any advice on what to do outside of their training sessions, they were permitted to participate in any self-chosen exercise which was individually recorded and subsequently submitted concluding study association. For the application of NMES, previous recommendations have called to exclude users unable to generate forces > 15% of maximal voluntary contractions (Maffiuletti et al., 2018), although wide-pulse high-frequency NMES (> 80 Hz) may be effective to increase muscle strength in that case (Neyroud et al., 2019). Although this was not measured as participants were not secured to a dynamometer during contractions, it was nevertheless ensured that participants maintained a visible muscle contraction. Finally, due to our small sample size we were unable to explore sub-group analyses between HPV-positive and negative participants.

4.6 Conclusion

In summary, this is the first study to show that an eccentric overloading and NMES training program is feasible and well tolerated in survivors of HNC. Despite poor accrual at this site, adherence and competition rates were excellent. Additionally, these results demonstrate that 12 weeks of supervised strength training induce muscular strength gains and muscle hypertrophy, while improving perceptions of HRQL, and reducing fatigue severity. While the use of conventional strength training as a modality to increase muscle strength and muscle CSA should not be overlooked, especially in regard to interventional strategies after RTx, the application of eccentrically overloaded training and NMES may be effective alternatives when conventional training is not tolerable or a contraindication. More so, this experimental intervention is easily reproducible for real-word situations, such as at home as it requires the use of no additional space. In the future, exercise specialists should assess patient status on a case to case basis. Future investigations with the current study population should focus on timing of our experimental intervention and nutritional supplementation to improve functional independence and overall HRQL.

4.7 Conflict of interest

The authors report no conflicts of interest in this study.

4.8 Acknowledgements

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Chapter Five: Discussion

5.1 Discussion

First, this thesis explored the impact of cancer treatment on survivors of HNC regarding the mechanisms of neuromuscular function, performance fatigability, and HRQL and perceived fatigue. Second, we assessed the feasibility of a novel strength training protocol combining eccentric overloading and NMES (experimental program), and a conventional strength training program of similar frequency and number of contractions. Last, this work aimed to provide efficacy for the experimental program and conventional program on maximal muscle force and muscle CSA of the knee extensors. This body of work is the first comprehensive evaluation of neuromuscular function and performance fatigability in RTx treated survivors of HNC (i): after cancer therapy; and (ii) after a training protocol combining eccentric overloading and NMES, and conventional strength training program for survivors of HNC. The following sections will provide a brief summary of the main findings from each original manuscript, discuss the overall strengths and limitations of the current research, and conclude with future implications for interventional strategies in HNC.

5.2 Summary of results

5.2.1 Chapter Three

The study presented in Chapter Three was the first study to investigate contractile and electromyographic changes at rest, during, and immediately following a maximal cycling test to explore neuromuscular function and performance fatigability in people who completed RTx ± concomitant chemotherapy for HNC. The primary hypothesis was that maximal force and muscle CSA of the knee extensors would decrease after the treatment period. The secondary hypothesis was that exercise performance time and perceived HRQL would decrease, and fatigue severity would increase. The 18% decrease in maximal muscle force and 20% reduction in muscle CSA of the knee extensors after treatment confirmed our hypothesis that neuromuscular function would be impaired following cancer treatment for HNC. The observed decrease in mechanically evoked force at rest without a decrease in voluntary activation suggests that peripheral disturbances contribute greater to a decline in muscle force than central factors in RTx treated survivors of HNC. Also, analyses investigating the changes in patient-reported outcomes (HRQL and fatigue) confirmed that HRQL decreases and fatigue severity increases. These results also established that

these symptoms are significantly corelated with reduced exercise performance time. The findings from this study indicate that future physical training interventions should target improvements in neuromuscular function, predominately exercises that are targeted to promote improvements in muscle mass and muscular strength, with the overall aim of improving HRQL.

5.2.2 Chapter Four

The study presented in the fourth chapter was the first randomized pilot trial to evaluate the feasibility of an experimental strength training intervention involving a combination of eccentric overloading and NMES and a conventional training intervention similar in frequency and volume in survivors of HNC. The secondary aim was to investigate the effectiveness of both interventions on maximal isometric force and muscle CSA in the knee extensors. The main results demonstrated that eccentric overloading and NMES seem to be safe and well tolerated in survivors of HNC who have been treated with RTx, evidenced by the high compliance of both unilateral squats and NMES intensity, respectively. Also, adherence and completion of both groups was rated excellent with 88% and 86%, respectively.

Analyses investigating muscle strength and muscle mass indicated a more than 20% increase in MIVC after the intervention, while muscle thickness in the vastus lateralis and rectus femoris increased 19% and 17%, respectively, in both groups. Participants in both groups also reported improved HRQL that was approximately double the MCID, and reduced fatigue severity. The findings from this study indicate that although conventional strength training should not be overlooked, the application of eccentric overloading and NMES offer flexibility for future exercise interventions in patients where high-intensity conventional strength training is not tolerable or is a contraindication.

5.3 Limitations

This well-designed investigation is not without several limitations. Additional to those limitations mentioned previously in individual chapters, the low recruitment rate and therefore small sample size in both Chapters is a major limitation. Also, as with most physical activity studies there is a risk for selection bias (e.g. people with a previous history of exercise may be more interested in enrolling), therefore, the sample obtained may not be representative of the entire population. For example, there was a higher presence of HPV-positive patients compared to HPV-

negative patients in this study. People in this HPV-positive sub-group, many of whom are younger are more likely to engage in physical activity and exercise on a regular basis, whereas those people who identify as HPV-negative patients tend to be older adults with a history of high rates of alcohol and tobacco consumption (Cramer et al., 2019).

Furthermore, no qualitative research was conducted to evaluate participants experience throughout their involvement in the training program. This could have been beneficial from changes in muscle function and structure, and also from the standpoint of participants caregivers, as well as the family that support them. Because this study was designed as a pilot trial, the services in the current study were offered exclusively at a single study site. Some of the most common barriers to facility-based exercise programs in this population has been reported as the distance, cost, and time of travelling (Mina et al., 2018). Consequently, there was no consideration for rural patients of HNC in the present investigation. Last, these findings are currently not designed to be pragmatic. As such, future research could consider how this program could be applied elsewhere. Future studies would require larger, multicenter trails to determine the practicality of physical training interventions in survivors of HNC.

5.4 Future implications for exercise interventions in survivors of HNC

Future investigations should focus on the timing of the experimental intervention presented in this work. As patients of HNC are at a high-risk of developing cachexia, the combination of eccentric overloading and NMES could aid in mitigating the side-effects of treatment if initiated at the commencement of cancer therapy. For example, this intervention requires a relatively low demand for energy cost and potential for high force output, important considerations in program design when patients frequently fail to meet nutritional guidelines, thus having to rely on the use of feeding tubes. Also, as this novel intervention requires the need for little equipment and space, and the non-cumbersome nature of the NMES device, it could be applied in both clinical environments and unsupervised at-home environments. Future studies and high-risk cachexic patients could benefit from an interventional strategy of this kind.

Further, to eliminate the selection bias identified aforementioned, future studies could benefit from multi-modal recruitment strategies. Also, physician and oncologist referrals could potentially allow for a higher sample-size and also the chance for a more diverse study population.

5.5 Conclusion

In final summary, we demonstrated that neuromuscular function is impaired following RTx for HNC. The reduced capacity to produce maximal force of the knee extensors was explained by a decrease in mechanically evoked force in response to electrical stimulation rather than a decrease in neural drive, which is also evident during a maximal cycling test.

In our pilot-controlled trial we demonstrated that a training intervention combining eccentric overloading and NMES after cancer treatment is patients of HNC is feasible. In this sample of participants, it was safe, well tolerated, and resulted in substantial improvements in maximal voluntary muscle force and muscle hypertrophy. This novel approach to exercise intervention strategies offers greater flexibility to future training programs, particularly where conventional strength training is not tolerable or is a contraindication in cachexic populations.

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Supplementary Material

Table A: Outcomes of neuromuscular function, patient-reported questionnaires and anthropometrics by group.

	Conventional Group (n = 8)		Experimental Group (n = 11)		Time Effect			Interaction Effect (Group × Time)		
Outcome	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention	$F_{(1,17)}$	P	η_p2	$F_{(1,17)}$	P	η_p2
Body composition										
Body mass, kg	73.0 ± 17.7	72.8 ± 15.2	78.1 ± 16.9	78.9 ± 17.9	0.114	0.74	0.007	0.297	0.593	0.017
BMI, kg/m2	23.9 ± 4.1	23.7 ± 3.3	25.7 ± 5.0	25.9 ± 6.2	0.019	0.891	0.001	0.359	0.557	0.021
Percentage fat	18.9 ± 5.6	17.7 ± 4.4	21.9 ± 6.2	20.8 ± 6.0	3.888	0.065	0.186	0.012	0.915	0.001
CSA										
VL, cm2	13.13 ± 2.69	16.38 ± 4.18	16.96 ± 6.84	19.25 ± 8.21	10.74	0.004	0.387	0.32	0.579	0.018
RF, cm2	4.32 ± 0.95	5.09 ± 1.41	4.90 ± 1.68	5.76 ± 2.49	10.06	0.006	0.372	0.031	0.862	0.002
Patient-reported outcomes										
FACT-H&N physical	19 ± 5	26 ± 2	22 ± 5	25 ± 4	22.468	< 0.001	0.569	4.294	0.054	0.202
FACT-H&N social	24 ± 3	24 ± 4	24 ± 3	25 ± 3	1.408	0.252	0.077	1.424	0.381	0.045
FACT-H&N emotional	19 ± 3	21 ± 2	20 ± 4	22 ± 2	6.003	0.025	0.261	0.019	0.892	0.001
FACT-H&N functional	18 ± 6	23 ± 4	19 ± 6	23 ± 5	36.825	< 0.001	0.684	0.918	0.351	0.051
FACT-H&N subscale	23 ± 4	28 ± 5	31 ± 4	32 ± 5	17.112	0.001	0.502	7.207	0.016	0.298
FACT-H&N total	103 ± 17	122 ± 13	116 ± 18	126 ± 14	41.778	< 0.001	0.711	3.666	0.073	0.177
FACIT-F	31 ± 13	39 ± 8	35 ± 12	40 ± 9	10.786	0.004	0.388	0.587	0.454	0.033
Functional performance										
Sit-to-stand, repetitions	14 ± 2	19 ± 5	18 ± 6	21 ± 6	18.363	0.001	0.519	0.97	0.339	0.054
Performance time, s	761 ± 174	961 ± 225	1016 ± 186	1141 ± 275	48.673	< 0.001	0.741	2.634	0.123	0.134
Neuromuscular parameters										
MIVC, N	381 ± 61	479 ± 98	460 ± 119	527 ± 100	15.924	0.001	0.484	0.57	0.461	0.032
Potentiated twitch, N	151 ± 45	166 ± 33	149 ± 54	154 ± 29	1.15	0.299	0.063	0.337	0.569	0.019
Voluntary activation, %	94 ± 4	94 ± 4	96 ± 2	94 ± 5	0.477	0.499	0.027	0.477	0.499	0.027
VL M-wave amp, mV	10.06 ± 5.91	11.16 ± 7.37	6.77 ± 4.43	9.19 ± 5.27	4.457	0.05	0.208	0.636	0.436	0.036
RF M-wave amp, mV	5.44 ± 2.02	5.79 ± 0.82	5.15 ± 2.64	6.45 ± 2.16	1.485	0.24	0.08	0.489	0.494	0.028
VL RMS-EMG, mV	0.554 ± 0.337	0.787 ± 0.958	0.482 ± 0.299	0.496 ± 0.289	1.323	0.266	0.072	1.033	0.324	0.057
RF RMS-EMG, mV	0.402 ± 0.185	0.464 ± 0.193	0.379 ± 0.178	0.432 ± 0.194	2.174	0.159	0.113	0.015	0.905	0.001

BMI, body mass index; CSA, cross-sectional area; VL, vastus lateralis; RF, rectus femoris; FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck Questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Questionnaire; MIVC, maximal voluntary isometric contraction, M-wave, compound muscle action potential; amp, amplitude; RMS-EMG, root means square of electromyography

Table B: Cycle ergometer outcomes by group.

	Conventional Group (n = 8)		Experimental Group (n = 11)		Time Effect			Interaction Effect (Group × Time)		
Outcome	Pre-Intervention	Post-Intervention	Pre-Intervention	Post-Intervention	$F_{(1,17)}$	P	η_{p2}	$F_{(1,17)}$	P	η_{p2}
Last common stage, % Pre-cycling										
MIVC	93 ± 5.1	94.7 ± 9.5	84.8 ± 9	87.1 ± 11.8	0.665	0.426	0.038	0.018	0.894	0.001
Potentiated twitch	79.4 ± 22.5	86.8 ± 5.5	78.2 ± 21.3	83 ± 11.7	1.227	0.283	0.067	0.058	0.813	0.003
Voluntary activation	98.3 ± 10.2	96.6 ± 4.1	97.1 ± 4	97.3 ± 6.1	0.124	0.729	0.007	0.172	0.684	0.01
VL M-wave amp	104.2 ± 9.1	102.9 ± 5.5	84.5 ±26.2	100.2 ± 6.6	2.001	0.175	0.105	2.793	0.113	0.141
RF M-wave amp	104.3 ± 12.7	104.1 ± 10.4	91.7 ± 21.6	98.6 ± 8.2	0.524	0.479	0.032	0.581	0.457	0.035
VL RMS-EMG	109.2 ± 19.5	114.2 ± 15.5	92.4 ± 21.6	99.4 ± 15.9	0.873	0.363	0.049	0.023	0.883	0.001
RF RMS-EMG	103.3 ± 25.2	106.5 ± 19.1	110.9 ± 37.9	99.5 ± 16.4	0.221	0.645	0.013	0.709	0.411	0.04
Post-cycling, % Pre-cycling										
MIVC	73.8 ± 16.8	59.9 ± 16.3	59 ± 11.8	57.1 ± 17.2	4.061	0.06	0.193	2.309	0.147	0.12
Potentiated twitch	47.1 ± 16.1	43.7 ± 13.6	46.2 ± 24.8	44.1 ± 11.9	0.379	0.546	0.022	0.021	0.886	0.001
Voluntary activation	92.5 ± 12.3	90.2 ± 11.7	91.5 ± 10.2	85.1 ± 16.5	1.509	0.236	0.082	0.307	0.587	0.018
VL M-wave amp	117.3 ± 22.5	105.2 ± 10.1	98.3 ± 26.9	108.7 ± 12.2	0.02	0.889	0.001	3.391	0.083	0.166
RF M-wave amp	102.7 ± 23.8	111.2 ± 23.2	96 ± 26	105.3 ± 10.5	2.047	0.172	0.113	0.039	0.846	0.002
VL RMS-EMG	107.7 ± 15.5	107.2 ± 21.6	96.9 ± 28.3	77.9 ± 31.6	0.816	0.379	0.046	0.737	0.403	0.042
RF RMS-EMG	109.4 ± 40.4	94.4 ± 29.5	107.2 ± 38.6	95 ± 29.6	1.536	0.232	0.083	0.017	0.899	0.001

MIVC, maximal isometric voluntary contraction; VL, vastus lateralis; RF, rectus femoris; M-wave, compound muscle action potential; amp, amplitude; RMS-EMG, root means square of electromyography