Feasibility 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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1 **ABSTRACT**

2 **Purpose:** Treatment of head and neck cancer (HNC) results in severe weight loss, mainly due to loss of lean body
3 mass. Consequently, decreases in muscular strength and health-related quality of life (HRQL) occur. This study
4 investigated the feasibility of a 12-week experimental (EXP) and conventional (CON) strength training intervention
5 delivered after HNC treatment.

6 **Methods:** Participants were randomized to an EXP group ($n=11$) involving eccentric strength training and
7 neuromuscular electrical stimulation (NMES), or a CON group ($n=11$) involving dynamic strength training matched
8 for training volume. Feasibility outcomes included recruitment, completion, adherence and evidence of progression.
9 A neuromuscular assessment involving maximal isometric voluntary contractions (MIVCs) in the knee extensors was
10 evaluated prior to and during incremental cycling to volitional exhaustion at baseline and after the interventions.
11 Anthropometrics and patient-reported outcomes (PROs) were also assessed.

12 **Results:** Although recruitment was challenging, completion was 82% in CON and 100% in EXP. Adherence was 81%
13 in CON and 92% in EXP. Overall, MIVC increased by $19 \pm 23\%$, muscle mass improved $18 \pm 22\%$, cycling exercise
14 time improved by $18 \pm 13\%$, and improvements in HRQL and fatigue were clinically relevant.

15 **Conclusions:** Both interventions were found to be feasible for HNC patients after treatment. Strength training
16 significantly improved maximal muscle strength, muscle mass, and PROs after HNC treatment. Future research should
17 include fully powered trials and consider the use of eccentric overloading and NMES during HNC treatment.

18 **Implications for Cancer Survivors:** Eccentric overloading and NMES may be useful alternatives to conventional
19 strength training after HNC treatment.

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21 **Words:** 250

22
23 **Keywords:** Cancer rehabilitation; Electromyostimulation; Exercise oncology

INTRODUCTION

Anti-neoplastic therapies for head and neck cancer (HNC) frequently result in a considerable amount of involuntary weight loss that averages between 6–12% of pre-treatment body mass [1, 2]. Although modern techniques (e.g. intensity-modulated radiation therapy [3, 4]) have resulted in substantially improved outcomes, the treatment of HNC often causes multiple negative side effects, including mucositis [5], xerostomia [6], and dysphagia [7]. As a consequence, swallowing function is impaired to an extent that results in a reduction in energy intake and malnutrition, and ultimately leads to unintentional weight loss [2, 8]. Muscle wasting (i.e. cancer cachexia) is responsible for more than 70% of the weight loss [2] and is accompanied by decreased muscle strength, physical, and functional limitations [2].

Previous studies have shown that implementing progressive strength (or resistance) training after treatment for HNC helps to mitigate weight loss and muscle wasting by rebuilding lean body mass, muscle strength and functional performance [9, 10]. It can also be beneficial for health-related quality of life (HRQL) [8, 10] and fatigue management [11]. Intervention modalities have been limited to conventional strength training, where dynamic voluntary muscle contractions are performed against external loads [12], including concentric and eccentric muscle actions. However, dietary intake and weight loss can continue to be problematic after HNC treatment completion, and this may contribute to a reduced exercise capacity [13]. Therefore, the effectiveness of conventional strength training programs may be restricted, and there is scope and need to investigate optimizing training modalities that maximizes the stimulus while limiting the associated energy expenditure.

One such alternative is eccentric strength training, which involves the active lengthening of muscle under an external load [14]. It has been evidenced that eccentric overload training leads to muscular adaptations that promote muscle strengthening and hypertrophic responses in athletic populations [15], and in clinical and ageing populations [16], due to the potential for high force production compared to concentric or isometric contractions [14, 17]. Another beneficial aspect of eccentric training is that it requires a distinctively low energy cost [18], i.e. it minimizes energy expenditure, which may be beneficial due to energy conservation issues in HNC patients. A practical way of eliciting eccentrically-focused training is accentuated eccentric loading [19], 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 the performed exercise. Because of these characteristics, eccentric training has been studied extensively as an interventional strategy and has shown efficacy in maximal muscle strength and hypertrophic responses [17] and physical performance [20], including in older cancer survivors [21].

Another modality that may help to maximize the training stimulus in people with HNC is neuromuscular electrical stimulation (NMES), which involves a sequence of electrically-evoked contractions that are delivered through surface electrodes to skeletal muscles [22]. NMES preferentially recruits type II motor units [22], and the advantages of NMES for improving muscle strength and muscle mass have been published in numerous randomized controlled trials [23, 24], and it is recommended in rehabilitation programs for patients with several conditions, particularly musculoskeletal disorders [25–27]. Commercially-available NMES equipment is small and portable and has the potential to be used in home-based interventions. Although the application of NMES in oncological settings is relatively new, some evidence supports its application in cancer survivorship [28]. Hence, the 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.

Because alternative strength training strategies may be beneficial in HNC patients following treatment, we developed a 12-week experimental (EXP) strength training intervention involving a combination of eccentric overloading and NMES in the knee extensors (KEs), and a conventional (CON) strength training intervention, matched in frequency and the total number of contractions. The primary purpose of this study was to investigate the feasibility (recruitment, adherence, completion, and evidence of progression) of 12 weeks of supervised strength training, as well as efficacy outcomes, including neuromuscular function and performance fatigability, muscle cross-sectional area (CSA), and patient-reported outcomes (PROs) in HNC survivors following treatment.

METHODS

Study design

The present study was a single-centre, two-arm, randomized controlled feasibility trial. All experimental procedures were conducted in accordance with the *Declaration of Helsinki*, with the exception of pre-registration in a database. This study was approved by the Health Research Ethics Board of Alberta – Cancer Committee (ID: HREBA.CC-16-0744).

Recruitment

Recruitment was initiated in October 2017 and ended in February 2019. The recruitment strategy was identical to that used in our previous work, where patients with HNC attending a 2-hour education session prior to radiation therapy received a short presentation regarding the study [13]. People who indicated that they would be interested in receiving more information about the study were contacted and invited to participate approximately 4 weeks following their final dose of radiation. Participation was dependent on their current health status (e.g. weight stabilized), and if the participant or study team were concerned that the testing protocol would aggravate any ongoing symptoms, the baseline assessment was postponed.

Eligibility criteria

Eligible participants met the following inclusion criteria: (1) a verified clinical diagnosis of HNC (stage I-IV) and primary tumor in the oral cavity, pharynx, larynx, paranasal sinuses, or salivary glands; (2) completed radiation therapy (i.e. 30–33 treatments delivered over ~6 weeks, 5 fractions/week) $\pm$ 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; (8) able to follow verbal instructions in English; and (9) provided written consent.

Randomization and blinding

Randomization was conducted by an assistant researcher not involved in treatment interventions or study outcomes following completion of all baseline assessments, and performed using an open-source, Web-based minimization program [29]. Participants were stratified by sex (male/female), age ($< 60/\geq 60$), tumour 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, blinding participants and the study team to treatment allocation was not feasible.

Laboratory visits

Participants (see Table 1) attended the Human Performance Laboratory (Faculty of kinesiology, University of Calgary, AB, Canada) to participate in a baseline assessment protocol that was identical to the procedures used in our previous work [13]. The baseline assessment took place 57 ± 30 days after the final radiation dose. Following the intervention, the assessments were repeated a minimum of 72 hours (and maximum 5 days) after the final exercise session to allow for sufficient recovery and to ensure possible muscle damage did not affect the results [30]. A full explanation of the methods used for testing procedures and the experimental setup has been previously described elsewhere [13]. Briefly, a health screening was performed, including resting blood pressure and an electrocardiogram. PROs, including HRQL and fatigue, were evaluated using the Functional Assessment of Cancer Therapy – Head & Neck, Version 4 (FACT-H&N) questionnaire and the Functional Assessment of Chronic Illness Therapy – Fatigue, Version 4 (FACIT-Fatigue) questionnaire. Vastus lateralis and rectus femoris muscle CSA were evaluated using B-mode ultrasonography (GE Medical Systems LOGIQ E9, Wauwatosa, WI), which is a reliable and validated method for assessing quadriceps atrophy and hypertrophy [31]. Neuromuscular function was determined using isometric dynamometry and femoral nerve electrical stimulation [13]. Performance fatigability was evaluated by an incremental cycling test performed on a cycle ergometer [32] that included instantaneous and intermittent maximal isometric voluntary contractions (MIVCs) and electrical nerve stimulation for the assessment of volitional and non-volitional aspects of a reduction in MIVC force, respectively. The mean stimulation current elicited over the femoral nerve at baseline was 160 ± 57 mA, and post-intervention was 161 ± 74 mA. As a measurement of functional (or physical) performance, we assessed the 30 s sit-to-stand test, a functionally relevant protocol that is relevant to activities of daily living [33]. 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 studies in HNC survivors [9, 34, 35]. Participants were asked to avoid both caffeine and alcohol consumption for a minimum of 12 hours, and the performance of strenuous exercise a minimum of 24 hours preceding each laboratory visit.

Treatment arms

Both training interventions took place in the Thrive Centre (Faculty of Kinesiology, University of Calgary), a cancer-specific fitness facility for people affected by cancer. Because strength training frequency is an important consideration if the goal is increasing muscular strength [36] and muscle hypertrophy [37], where possible, participants

were scheduled to perform 36 sessions over 12-weeks, planned thrice weekly, on non-consecutive weekdays. This design is aligned with previous exercise studies in HNC survivors [38]. If committing to three training sessions per week was not possible, participants could attend twice per week. One participant allocated to the CON intervention could only commit to attending twice per week and, therefore, 24 training sessions were scheduled over 12 weeks. The opportunity was made available for training sessions to be added to the end of the training intervention if there was a conflict in scheduled personal or public holidays, illness, and medical appointments. 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 over time, participants were asked to quantify their fatigue before and after each supervised training session using a rating-of-fatigue scale [39]. The number and nature of adverse events were recorded.

Interventions

Experimental group: Participants allocated to the experimental intervention performed eccentrically overloaded unilateral squats followed by NMES. Unilateral squats were performed as 2 sets $\times$ 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 unilaterally 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 delivered via a portable battery-powered electrical stimulator device (Compex SP 2.0, Compex, Vista, CA), and applied using Compex Performance self-adhesive electrodes bilaterally to the KE muscles. Single negative electrodes (5×10 cm) were placed proximally on the KEs, close to the insertion point, while pairs of positive electrodes (5×5 cm) were placed proximally over the vastus lateralis and distally over the vastus medialis, according to the recommendations of the manufacturer (<https://www.compexstore.com/?from=en>). Sixty-six bilateral NMES contractions were delivered using a frequency of 40 Hz, a pulse duration of 180 μ s, 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 the peak current is 120 mA). Participants were encouraged to set the current intensity to the maximally tolerated level and to increase the intensity when it became more tolerable over time. When the electrical stimuli began, participants performed alternating voluntary concentric KE contractions, while keeping the knee slightly bent. This NMES protocol was chosen based on the manufacturer’s instructions [40] and recommended for optimal application of NMES [41]. Peak intensities were recorded after each session of NMES.

Conventional group: Dynamic strength training was prescribed to the CON group as the active control. Total volume (sets $\times$ repetitions $\times$ load) has been reported as one of the main variables to influence muscular adaptations [42], with previous studies demonstrating a dose-response relationship between volume and hypertrophy [42–44]. Therefore, we designed the training protocols to ensure that the frequency of training and the total number of contractions (i.e. sets

× repetitions) in each session were similar between the EXP intervention (e.g. 82 KE contractions as described above) and CON intervention (e.g. 80 KE contractions; performed as 5 different exercises as 2 sets × 8 repetitions). 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. Exercises were performed using a controlled slow to moderate velocity, with 1 – 3 min rest between sets. Progression was monitored as an increase in load.

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 KE 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 well-being 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 radiation therapy for HNC frequently experience shoulder dysfunction [45]. The muscle groups strengthened were rhomboids (scapular retraction), levator scapulae (scapular elevation), infraspinatus and posterior deltoids (external rotation), and lateral part of 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 [46, 47]. 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 the rating of perceived exertion of approximately 13 – 15 of 20 (described as “somewhat hard” to “hard”) [48]. This progression model was formulated in accordance with guidelines from the American College of Sports Medicine [12] and cancer-specific guidelines [49].

Data analysis

Analyses included feasibility outcomes: recruitment (the number of people enrolled vs. the number of people who gave permission to be contacted), completion (the number of participants randomized vs. the number who finished the intervention), adherence (the total number of training sessions scheduled vs. the number attended), and evidence of progression (including NMES intensity and external load used for unilateral squats in EXP, and external load used for bilateral squats in CON). The mean completion time was calculated as the number of weeks participants took to complete their intervention. Analysis of efficacy outcomes (e.g. neuromuscular function, and fatigability, and PROs) have been described in detail elsewhere [13].

Statistical analysis

In order to power the study to detect a difference in the efficacy outcome of maximal muscle strength (MIVC force), a power analysis for a two-way repeated-measures ANOVA for the interaction of group (2: CON, EXP) $\times$ time (2: before the intervention, after the intervention) was conducted using G*power version 3.1 [50]. Using a large effect size of 0.14 partial eta squared (η_p^2) due to the large effect of HNC treatment on muscle strength [13], and hence a large potential for subsequent improvement, a power of 80% and an alpha of 0.05, it was determined that a total sample size of 54 participants (27 in each group) would be required to detect group differences. However, recruitment was much lower than anticipated, and although the study is powered to detect a main effect of time, it is not powered to detect a group $\times$ time interaction. As such, mean differences and standardized mean differences (SMDs) are presented herein, with full statistical reporting (ANOVA) detailed elsewhere (see Supplementary Appendix). Interpretation of the SMD was considered as follows: 0.2 is small, 0.5 is medium and 0.8 is large [51]. For PROs, the minimally important clinical difference (MICD) was also used to evaluate any differences over time or between groups. All data were 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. Effect sizes were calculated to provide a quantitative measure of the magnitude of the reported effects. Partial eta squared was used as an estimate of effect size for ANOVA. Interpretation of the size of the effect was cautiously defined as follows: $\eta_p^2 = 0.01$ is small, $\eta_p^2 = 0.06$ is medium and $\eta_p^2 = 0.14$ is large [51]. All statistical procedures were conducted using SPSS software version 25.0 (IBM Corp., Armonk, NY).

Figure 1 Overall study design and participant flow. ECG, electrocardiogram; CON, conventional strength training group; EXP, experimental strength training group.

RESULTS

Feasibility outcomes

Recruitment. We attended 43 patient-education sessions during the recruitment period. As a result, a total of 237 patients heard about the study during a brief presentation. Fifty-one percent ($n = 121$) declined to be contacted or left the education session prior to talking with the researcher, and 49% ($n = 116$) of patients gave permission to be contacted. Nine of these 116 patients did not meet the inclusion criteria due to: age > 75 years ($n = 2$); having an existing comorbidity ($n = 5$); and unable to follow verbal instructions in English ($n = 2$). Sixty-five percent ($n = 75$) of the patients that gave permission to be contacted were excluded due to the following reasons: 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 ($n = 1$). Overall recruitment was therefore 29.9% (i.e. 32 out of the 107 patients who provided consent to be contacted and were potentially eligible).

Completion. Thirty-two people attended the laboratory and were assessed for eligibility. Figure 1 presents patient flow through the study. Of the participants randomized, three discontinued, leaving overall completion to 86% (19 of 22 participants). In the CON group, 8 participants completed the intervention (82%), and in the EXP group, 11

participants completed the intervention (100%). The mean completion time for participants within both intervention groups was 12.8 ± 1.6 weeks (13.2 ± 2.2 weeks for CON and 12.6 ± 1.2 weeks for EXP).

Adherence. Overall adherence to supervised exercise sessions in both intervention groups was 88% (588 of 672 sessions). Adherence was 81% (223 of 276 sessions) in CON and 92% (365 of 396 sessions) in EXP.

Table 1. Baseline participant characteristics

Variable	Experimental (<i>n</i> = 11)	Conventional (<i>n</i> = 11)	Combined (<i>n</i> = 22)
Demographic/anthropometric, mean $\pm$ SD			
Age (yr.)	53 $\pm$ 7	50 $\pm$ 11	52 $\pm$ 9
Body mass (kg)	78.1 $\pm$ 16.9	73.0 $\pm$ 18.9	75.9 $\pm$ 17.5
Height (cm)	174.2 $\pm$ 11.8	173.6 $\pm$ 9.8	173.9 $\pm$ 10.7
BMI (kg/m ²)	25.7 $\pm$ 5	32.9 $\pm$ 4.4	25 $\pm$ 4.7
Estimated body fat (%)	21.9 $\pm$ 6.2	18.9 $\pm$ 6	20.6 $\pm$ 6.1
Sex, <i>n</i> (%)			
Male	8 (73)	6 (55)	14 (64)
Female	3 (27)	5 (45)	8 (36)
Primary tumour site, <i>n</i> (%)			
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, <i>n</i> (%)			
I-II	5 (45)	5 (45)	10 (45)
III-IV	3 (27)	1 (9)	4 (18)
Unknown	3 (27)	5 (45)	8 (36)
Treatment, <i>n</i> (%)			
Major surgery (before radiation)	7 (64)	8 (73)	15 (68)
Radiation therapy alone	0	0	0
Concomitant chemotherapy	9 (82)	9 (82)	18 (82)
HPV status, <i>n</i> (%)			
Positive	8 (73)	5 (45)	13 (59)
Negative	3 (27)	6 (54)	9 (41)

BMI, body mass index; HPV, human papillomavirus.

Evidence of Progression. Of participants who completed the study, there was clear evidence of progression within both intervention groups (Figure 2). Informal feedback was positive about the use of NMES, and all but one participant was able to gradually progress their maximally tolerated stimulation level over time. In EXP, a gradual progression in weight when performing overloaded unilateral squats was demonstrated, as the increase in external load was 11.5 ± 5.9 kg from the beginning to the end of the intervention. Participants in CON achieved an increase of 18.1 ± 3.7 kg when performing weighted bilateral goblet squats. No adverse events were observed with participation in either intervention.

Figure 2. Progression in different training modalities over 12 weeks of strength training (A–C), including neuromuscular electrical stimulation (NMES) intensities (A); weight of overloaded unilateral squats (B); and weight of bilateral goblet squats performed in the conventional group (C).

Neuromuscular function

From before to after the intervention, the maximal force-generating capacity in the KEs (Figure 3A) increased by $22 \pm 23\%$ (main effect of time: $F_{1,17} = 15.93$, $P < 0.001$, $\eta_p^2 = 0.48$). Despite the increase in voluntary force, 12 weeks of strength training did not increase potentiated twitch force (Figure 3B) or voluntary activation (Figure 3C). SMDs for all neuromuscular data are provided in Table 2.

Body composition outcomes

From before to after the intervention, vastus lateralis and rectus femoris muscle CSA increased by $19 \pm 23\%$ and $17 \pm 22\%$, respectively (main effect of time: $F_{1,17} = 10.7$, $P = 0.004$, $\eta_p^2 = 0.3$ and $F_{1,17} = 10.1$, $P = 0.006$, $\eta_p^2 = 0.37$, respectively), with little evidence to suggest that one intervention resulted in larger improvements than the other (Table 2). No main effects of time were found in our remaining anthropometric measurements, including body mass ($F_{1,17} = 0.11$, $P = 0.74$, $\eta_p^2 = 0.01$), BMI ($F_{1,17} = 0.02$, $P = 0.891$, $\eta_p^2 = 0.001$), and estimated body fat percent ($F_{1,17} = 3.89$, $P = 0.065$, $\eta_p^2 = 0.19$).

Patient-reported outcomes

From before to after the intervention, overall HRQL (FACT-H&N total score) improved both clinically and significantly within both intervention groups by 13 ± 10 points (main effect of time: $F_{1,17} = 41.78$, $P < 0.001$, $\eta_p^2 = 0.71$; Figure 3G), as did fatigue severity by 6 ± 8 points (main effect of time: $F_{1,17} = 10.79$, $P = 0.004$, $\eta_p^2 = 0.39$; Figure 3H). A main effect of time for several subscales of the FACT-H&N were also observed, including physical well-being ($F_{1,17} = 22.47$, $P < 0.001$, $\eta_p^2 = 0.57$), emotional well-being ($F_{1,17} = 6.00$, $P = 0.025$, $\eta_p^2 = 0.26$), functional well-being ($F_{1,17} = 36.83$, $P < 0.001$, $\eta_p^2 = 0.68$), and the HNC-specific subscale ($F_{1,17} = 17.11$, $P = 0.001$, $\eta_p^2 = 0.50$), while social well-being did not differ ($F_{1,17} = 1.41$, $P = 0.252$, $\eta_p^2 = 0.08$).

Figure 3. Changes in secondary outcomes from baseline to after 12 weeks of strength training (A–H). Measurements of neuromuscular function (A–C), including MIVC force (A); potentiated twitch force (B); and voluntary activation (panel C). Performance time (D) from the incremental cycling test. Body composition (E–F), including cross-sectional area in vastus lateralis (E); and cross-sectional area in rectus femoris (F). Patient-reported outcomes (G–H), including FACT-HN (G); FACIT-F (H). MIVC, maximal isometric voluntary contraction; FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck Questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Questionnaire. * Denotes significant time effect ($P < 0.05$).

Incremental cycling test and functional performance

From before to after the intervention, participants increased cycling performance by $18 \pm 13\%$ (main effect of time: $F_{1,17} = 48.67$, $P < 0.001$, $\eta_p^2 = 0.74$; Figure 3D), and the CON group may have improved to a greater extent (SMD 0.72, Table 2). Participants were able to perform an additional 4 ± 4 sit-to-stands (main effect of time: $F_{1,17} = 18.36$, $P = 0.001$, $\eta_p^2 = 0.52$).

Central and peripheral outcome measures: In both groups, 12 weeks of strength training resulted in a significant difference in normalized potentiated twitch force at the last common stage (main effect of time: $F_{1,17} = 6.36$, $P = 0.022$, $\eta_p^2 = 0.27$; Figure 4F, Table S2). There were no changes in voluntary activation, peak-to-peak M-wave amplitude or rms EMG from before to after training (Supplementary Table S2).

Figure 4. Comparison of changes in voluntary and evoked knee extensor force in conventional (CON) and experimental (EXP) strength training groups from baseline to post-intervention during the incremental cycling test (A–F). Volitional and non-volitional outcomes were evaluated at the LCS (the last stage completed both before and after training) and exhaustion (post-cycling). Values are expressed as a percent of the pre-cycling assessment performed on the cycle ergometer. MIVC in CON (A); MIVC in EXP (B); MIVC in CON and EXP (C); potentiated twitch in CON (D); potentiated twitch in EXP (E); and potentiated twitch in CON and EXP (F). MIVC, maximal isometric voluntary contraction; LCS, last common stage. * Denotes significant time effect ($P < 0.05$).

Table 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	0.8 ± 1.1	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-Fatigue	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 rmsEMG, 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 rmsEMG, 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; rmsEMG, root means square of electromyography.

DISCUSSION

The primary purpose of this study was to investigate the feasibility of a strength training intervention involving NMES and eccentric overloading (EXP), alongside a conventional strength training intervention (CON) that was similar in training frequency and the number of contractions. Our results suggest that both interventions were feasible and well-tolerated after HNC treatment, and we note that although recruitment was challenging, participants were able to adhere, progress and complete the intervention. To the best of our knowledge, this is the first study to use alternative strength training techniques (NMES and eccentric overloading) in an attempt to induce favourable muscular adaptations in HNC survivors by maximizing the stimulus while limiting energy expenditure. Our secondary purpose was to provide preliminary results for the efficacy of EXP vs. CON strength training. We report substantial and largely similar improvements in muscle function, muscle CSA, and PROs within both groups, although the small sample size limits our power to statistically examine differences between groups over time.

Feasibility

Adherence and completion. Considering this investigation involved fully supervised exercise sessions, it is difficult to provide a direct comparison of similar studies in HNC survivors that were unsupervised/involved minimal supervision of training programs [9, 10, 34]. Nevertheless, overall adherence in the current study was high (88%), and falls between previously reported adherence rates of 62% [34] and 97% [9] in studies using similar training durations and interventions initiated after HNC therapy. In consideration of the higher adherence in this study compared to that of Capozzi and colleagues [34], which used similar recruitment strategies at the same site, we suggest that it is, in part, due to the level of supervision and flexibility to reschedule training session absences in the present study, versus to a set group training program in the Capozzi et al study. The overall study completion rate was also high (86%) and was similar to that of Lønbro and colleagues [9], who observed a completion rate of 70%. Of the three participants who discontinued the training intervention, decisions were specific to each individual, as illustrated in the flow diagram (Figure 1). Neither group allocation nor the intervention itself influenced the decisions to discontinue the study.

Recruitment. A relatively small percentage of patients who attended the education session prior to radiation therapy and gave permission to be contacted went on to volunteer for the present study (29.9%). This value appears low when compared to similar exercise trials in HNC patients [34], and this is partly because it was calculated based on the overall number of patients who initially expressed interest rather than the number of patients who would have been eligible. In addition, over half the of patients left the education session before completing the consent to contact or talking with a researcher, or declined to participate without providing a reason, a limitation in the current study is our resulting inability to track the total number of eligible participants. In a previous study at this site, Capozzi and colleagues [34] reported a recruitment rate of 55.6%, though people who lived too far away to travel were not included in this estimate because this was considered a study exclusion criteria. Because Calgary serves a wide area, including a number of rural communities, it is reasonable to suggest that many people left the education session or declined to participate due to the required travel distance to the training site. In addition, the presentation was delivered at the end of an education seminar where lots of information was provided to help prepare patients for radiation therapy. It is

likely that this was an overwhelming time for patients and, therefore, being able to present the study after radiation is completed (e.g. during a follow-up appointment) may be a better recruitment strategy. Nevertheless, recruitment difficulties limited the ability to power the study to detect a group $\times$ time interaction, and recruitment procedures should be considered carefully in future fully powered trials.

Evidence of progression. In the EXP group, all but one participant was able to gradually progress their maximally tolerated stimulation intensity over time, and two participants achieved the maximal stimulation output during the 6th week of the intervention (and continued to use this for the remainder of the intervention). However, there is difficulty in detecting similarities to current literature investigating the use of NMES, as there is a large range of electrical stimulation protocols, including differences in frequency, pulse-duration and intensity (for a review, see Maffiuletti et al. [52]), including in cancer rehabilitation [28], with existing studies difficult to interpret due to limited reporting of NMES parameters. Participants also demonstrated improvements in weighted unilateral squats, where all but one participant (a different individual to NMES) exhibited clear evidence of progression. In CON, all participants demonstrated evidence of progression in bilateral goblet squats from start to finish. This occurred even in the most debilitated participants, who were coached beginning with sit-to-stand and were able to progress to a full goblet squat.

Changes in muscular function and muscle mass

Volitional and non-volitional muscle force. We observed significant increases after 12 weeks of strength training in isometric muscle strength of approximately 22% in both groups. These results are consistent with previous studies investigating isometric KE muscle strength after 12 weeks of progressive resistance training in HNC survivors [9, 10]. During the incremental cycling test, MIVC and potentiated twitch force were reduced substantially, as previously reported [14]. After the intervention, the loss of MIVC that occurs during incremental cycling did not differ after the last common stage or at volitional exhaustion (Figure 4). However, after the intervention, the reduction in potentiated twitch force (a measure of muscle contractile ability) was significantly reduced after the last common cycling stage. That is, given the same amount of external work from before to after the intervention, peripheral disturbances were lower after training.

Muscle cross-sectional area. To our knowledge, this is the first study to investigate changes in muscle mass (estimated using ultrasonography) in the KEs after 12 weeks of strength training in HNC survivors. We observed significant improvements in KE muscle CSA in both groups of approximately 18% following strength training (Figure 3E–F). This is a greater increase to that of Sandmæl et al. [8], who reported no difference in change in muscle mass at the site of the third lumbar vertebra using computed tomography following 3 weeks of supervised progressive resistance training program initiated 2 to 4 weeks after the end of radiation therapy for HNC. This may be due to differences in training prescription or intervention duration, or due to differences in the anatomical site.

Changes in patient-reported outcomes

In our previous study [13], we reported that treatment for HNC results in a clinically meaningful reduction in HRQL and increase in the perceptions of fatigue. In the present study, we show statistically and clinically significant improvements in these outcomes (Figure 3C). The lack of a 'no-exercise' control group limited our ability to identify the normal trajectory in these measures, as a gradual improvement in HRQL and fatigue would be expected in the months after HNC treatment [53]. However, participants in the present study returned to baseline values by the end of the intervention. Previous research has shown that, although there is an improvement over time, scores do not return to baseline values until 12-months after cancer treatment [53]. Therefore, it is reasonable to suggest that the strength training interventions accelerated the natural time-course in these measures, considering that exercise is beneficial for cancer-related fatigue [54] and in studies with a no-exercise control, the improvement in HRQL is greater in the group receiving the intervention [10, 34]. Because the decrements in HRQL and fatigue are reversible, it is crucial that this population receive a timely intervention, particularly as HRQL seems to recover substantially slower in the absence of exercise interventions [53].

Implications for practice

Patients in our previous study had a mean (range) weight loss of 10% (1% – 22%) from before to after the end of cancer treatment [13], with weight losses of similar magnitude being reported elsewhere [2, 55]. Similarly, patients lost a significant amount of muscle strength ($-18 \pm 13\%$) and muscle mass ($-21 \pm 16\%$). In the present study, NMES and eccentric overloading were combined in one intervention to promote muscle strength and hypertrophy in HNC survivors because (i) NMES preferentially recruits type II motor units occurs at lower intensities than volitional muscle contractions [22, 56]; and (ii) eccentric strength training allows the muscle to generate high force productions at relatively low energy cost during active lengthening contractions while recruiting motor units non-physiologically. Although the results should be interpreted with caution, the physiological adaptations over 12 weeks appeared to be similar in the experimental and conventional training (i.e. small-medium SMDs; Table 2). These results are encouraging because the application of such modalities offers greater flexibility to future training interventions, particularly in patients where conventional strength training is not tolerable (e.g. frailty or balance difficulties) or is a contraindication (e.g. weight has not stabilized).

Our eccentric overload technique was chosen because it is more practical than eccentric training protocols with isokinetic dynamometers [17] commonly used in laboratory studies. The experimental design of this study used accentuated eccentric loading [19], which requires performing the active lengthening component of an exercise using a single limb and concentric phase with both limbs [16, 57], thus, avoiding the need for any specialized equipment and support. Furthermore, the NMES equipment is portable and commercially available, meaning it could potentially be used in real-world clinical settings. Therefore, the strategies implemented herein could potentially be applied outside of research settings, such as in rehabilitation facilities or even safely at home without supervision (although the feasibility of the latter is yet to be ascertained). Nevertheless, conventional strength training is a valuable tool that should not be disregarded, particularly following HNC treatment as beginning an exercise program at this time is associated with better adherence in some studies [34].

Future directions. An important consideration moving forward could be the application of NMES supplementary to conventional strength training in treated HNC survivors, as one disadvantage of NMES is that it cannot improve coordination, therefore, limits the potential for learning specific movement patterns [58], which is vital when improving functional independence. Furthermore, because previous studies have found that HNC patients find it harder to adhere to strength training during treatment [38, 59], NMES could be investigated as an option to help negate the loss of muscle mass during treatment.

Limitations. Alongside the limitations of this study highlighted earlier (sample size, recruitment strategy and lack of a “no exercise” control), a further limitation of this feasibility study is that the study coordinator was involved with laboratory visits, training interventions, and data analysis. Fully powered trials should include blinding of the outcome assessor to avoid this source of experimenter bias. In addition, by combining the NMES with eccentric training, we are unable to determine the relative contributions of these two strategies. A final limitation is that we did not collect qualitative data on the patient experience of the two interventions, which could help direct future research.

CONCLUSION

In this randomized controlled feasibility trial, we showed that 12-weeks of strength training involving eccentric overloading and NMES is safe, feasible and well-tolerated in HNC survivors. This experimental intervention and a conventional intervention involving dynamic strength training matched in training volume leads to significant increases in muscular adaptations, including muscle strength and muscle hypertrophy, as well as increased HRQL and reduced fatigue severity. These results suggest that this novel training intervention is a viable alternative to conventional strength training, particularly where conventional strength training is not tolerable, is a contraindication or is not feasible for practical reasons (transport, time). Future investigations with the HNC survivors should focus on the timing of this experimental intervention to maintain functional independence and overall HRQL in patients undergoing treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study.

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