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**Personalised and progressive neuromuscular electrical stimulation (NMES) in patients with
cancer – a clinical case series**

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ABSTRACT

Purpose

Neuromuscular electrical stimulation (NMES) may be a pragmatic short-term alternative to voluntary exercise to augment cancer rehabilitation. However, previous attempts to use NMES as an exercise modality in this cohort have been unsuccessful, largely due to the use of NMES protocols that were developed for other rehabilitation contexts. We assessed the effects of a personalised and progressive NMES exercise intervention, designed with early stage cancer rehabilitation in mind, on exercise capacity, lower body functional strength and quality of life in (QoL) in patients who are currently undergoing or have recently completed treatment for cancer.

Methods

Ten adult patients were recruited. A personalised and progressive NMES exercise intervention was implemented in each case over a 4 – 8-week period. The 30 seconds sit to stand test (STS), 6-minute walk test (6MWT), and EORTC QLQ C-30 were performed pre-and post-intervention. Patients completed semi structured interviews post intervention to explore their experiences and views on the intervention, and its impact on their daily lives.

Results

Six of the 10 recruited patients completed the intervention and completed pre-and post-assessments. Four of 6 patients improved STS, 5 of 6 patients improved 6MWT and 4 of 6 patients improved Global QoL. Perceived benefits included improved muscle strength and more confidence when walking.

Conclusion

A personalised and progressive NMES exercise intervention appears safe and may improve functional capacity and QoL in adults who are undergoing or have recently completed treatment for cancer.

Replication of these results in a controlled prospective study is warranted prior to clinical implementation.

Keywords: neuromuscular electrical stimulation, adult cancer survivors, rehabilitation, oncology, physical function

BACKGROUND

Most cancer survivors will experience a plethora of physical and psychosocial side effects during and following antineoplastic treatment. Many of these complications can reduce functional capacity and exacerbate health related quality of life (HR-QoL) and limit independence [1, 2]. A large body of evidence demonstrates the safety and efficacy of voluntary exercise in adult cancer survivors across the cancer care continuum for counteracting many of these side effects [3–5]. As such, international guidelines recommend cancer survivors avoid inactivity, and achieve a weekly exercise prescription of 150 minutes of moderate intensity aerobic exercise, and 2-3 resistance training sessions [6]. However, depending on treatment and disease stage, some patients may be excluded from exercise if deemed to be at risk of harm (e.g. bone metastases) [7], whilst others may feel incapable of exercising due to pronounced physical deconditioning and chronic fatigue. Thus, physical inactivity is commonly reported amongst cancer patients during and following adjuvant cancer treatment.

Neuromuscular electrical stimulation (NMES) could be a pragmatic alternative to voluntary exercise in these cases. NMES generates muscle contractions via electrical impulses which are delivered to motor nerves using surface electrodes placed over target muscle groups, typically using a handheld battery powered stimulation unit [8]. Many studies have demonstrated that repeated unsupervised application of NMES in healthy and clinical populations may result in improvements in muscle strength [9, 10]. However, despite a growing body of evidence in its favour, its clinical implementation still remains difficult [11]. This can, in part be linked to the discomfort associated with electrically evoked muscle contractions. The use of large electrodes can somewhat attenuate this discomfort by optimising current delivery [12]. In addition, a slow, progressive and individualised prescription may be pragmatic in clinical cohorts to habituate users to the unaccustomed sensation [13]. Nevertheless, adherence to home-based NMES exercise remains poor, highlighting the need for

novel methods of delivering NMES exercise, particularly amongst clinical populations, which can progressively habituate users and allow for prolonged application.

Early attempts to implement NMES exercise into the rehabilitation of cancer survivors have been largely unsuccessful. A recent review [14], reported that NMES exercise in adults cancer survivors, although potentially beneficial for improving HR-QoL, had no significant effect on functional and strength outcomes. The authors associated this with poor adherence to home based interventions, and inappropriate NMES exercise prescription [14]. Much of the recent focus in the literature relating to NMES exercise for cancer survivors has been on application/adaptation of NMES protocols that have been commonly used to promote muscle strengthening in orthopaedic and neurological rehabilitation settings. These protocols, which use high frequency-NMES (>20Hz, HF-NMES) to induce tetanic isometric contractions, are effective for improving muscle strength, yet have a negligible effect on cardiorespiratory fitness [15].

Recently, low frequency NMES (3-12Hz, LF-NMES) has emerged as an effective means of augmenting cardiovascular fitness in healthy and clinical populations [16, 17]. In those clinical populations with low functional capacity such as chronic heart failure, modest improvements in muscle strength have also been observed despite the NMES prescription not being designed to target this aspect of fitness [18]. Considering the marked and significant impairment in the neuromuscular and cardiovascular systems following cancer treatment [2, 6], a concurrent approach which considers muscle strength and cardiovascular fitness equally is warranted. Concurrent NMES, involving a LF-NMES and HF-NMES phase has previously been evaluated in a healthy elderly population with improvements in strength and aerobic exercise capacity reported [19]. However, to date, no studies have incorporated a personalised and progressive concurrent NMES exercise programme in cancer survivors.

Therefore, this case series was aimed at determining the feasibility, safety and effects of a personalised and progressive concurrent NMES exercise programme on functional capacity and HR-QoL in patients who are undergoing or have recently finished adjuvant cancer treatment.

METHODS

Design and Patients

This was a pilot case series in which we followed patients for a period of 4 – 8 weeks, with two measurement time points. Measurements of functional capacity and HR-QoL were recorded at baseline and post NMES exercise intervention. User experience of NMES exercise were recorded after the intervention.

Following institutional ethical approval, ten patients (6 female, 4 male) were recruited between February 2018 and July 2018, from those referred by their treating physicians at Clinica Oncoavanze: a private oncology clinic in Seville, Spain. The patients recruited included; 1) those with an Eastern Cooperative Oncology Group (ECOG) performance status of >1 and deemed by their oncology care teams to have impaired physical function, 2) who's participation in voluntary exercise was contraindicated, 3) those who felt unable to participate in voluntary exercise programmes, or 4) had physical limitations which affected instrumental activities of daily living (ADL's) (e.g. tasks such as doing household chores, grocery shopping, using public transportation) [20]. Patients were excluded if; 1) they had serious cardiac arrhythmias, 2) any cognitive impairment which may affect their ability to apply NMES safely unsupervised, 3) deep vein thrombosis within the last 6 months, or 4) metastatic lesions to the femur. Although a cardiac pacemaker is considered a contraindication, emerging evidence suggests patients with a pacemaker can use lower limb NMES safely [21].

Therefore, pacemaker patients were considered if given clearance from their cardiologist. Patients were fully informed of all experimental procedures prior to giving written informed consent.

NMES intervention

A personalised and progressive concurrent NMES exercise programme was designed which could target functional muscle strength and aerobic exercise capacity. Stimulation was delivered using a battery powered, hand held muscle stimulation unit (INKO RS, BioMedical Research Ltd, Galway, Ireland), and four adhesive gel electrodes (17 x 10.3cm) placed on each leg (x2 proximal and distal quadriceps, x2 proximal and distal hamstrings) and applied via a pair of neoprene garments which were secured by velcro straps (Figure 1).

Patients were instructed to train with NMES, unsupervised, at home. Patients were instructed to complete sessions seated or lying down, with light knee flexion to increase comfort. Session frequency was progressed weekly, from 2x/week in week 1, to 5x/week in week 4 remaining constant thereafter. Due to day to day variability in physiological, functional and psychological factors [22], patients were instructed to try and achieve the prescribed number of sessions, and record reasons for missed sessions. Each patient used a training diary to record session data (date, time, maximum intensity reached, session rating of perceived exertion (RPE). The stimulator was programmed to deliver 2 separate phases (termed concurrent NMES) [13]. The current waveform for phase 1 (LF-NMES programme) was designed to generate rhythmical sub-tetanic isometric contractions using bursts of 4 pulses (pulse width: 620 μ s) delivered at a fixed frequency of 4Hz for a duration of 13 – 45 minutes. Phase 2 (HF-NMES programme), was designed elicit a series of tetanic strengthening isometric contractions using a burst of 4 pulses (pulse width: 500 μ s) delivered at a fixed frequency

of 20Hz, for a duration of 15minutes. The on:off duty cycle for the HF-NMES programme progressed weekly over 4 weeks (Table 1). Patients were instructed to achieve the maximum tolerable intensity and increase intensity throughout the session if possible. Patients were instructed to not co-contract the target muscles during stimulation.

Personalised and progressive NMES

Due to tolerability being a major determinant of the response to NMES [23], a progressive and personalised prescription was developed. A standard session progression was used as a guide and individualised weekly in response to information gathered from face to face meetings with each patient. This included subjective feedback and training diary information (sessions completed, stimulation intensity progression, session RPE). The standard progression guide of both phases and individualised patient progressions are reported in Table 1. An intermittent delivery of the LF-NMES programme (Figure 2A) was used for each patient in week 1 (Phase 1). In week 2 patients progressed to either an extended intermittent protocol (Phase 2), or to continuous delivery (Phase 3). This occurred when the patient felt they had become suitably habituated to the stimulation and indicated they could tolerate continuous LF-NMES. Reduction of the pulse width from 620 to 300 μ s was used as the means of introducing relative 'rest' periods to the intermittent programme (Figure 2A). Progression in the LF-NMES session protocol involved increased weekly session duration (5 – 10 minutes per week). In the HF-NMES protocol, the duty cycle (on:off cycle) increased weekly from 2s:15s to 5s:15s to 5s:10s and constant thereafter as previously reported (Figure 2B) [24]. To maximise the compliance with the intervention, weekly phone calls were completed to identify and solve problems and prompt continued increase in stimulation intensities as tolerated.

To determine the initial stimulation intensity, patients performed a 10-stage incremental NMES protocol during which the stimulation intensity was increased every 3 minutes in equal increments of 14mA from a starting point of 14mA. This session also acted as a familiarisation session whereby the safe and correct use of the units was demonstrated.

Physical and Psychological outcomes

To assess the effectiveness of NMES, we carried out physical and psychological assessments before the start of home-based NMES training and after the intervention. Physical assessments included functional muscle strength, and aerobic exercise capacity assessment. Psychological assessment measured HR-QoL. Feasibility and safety and user experience were determined following the intervention using semi-structured interviews.

Physical assessment

Functional muscle strength

Lower limb functional muscle strength was assessed using the 30 second repeated sit- to stand test (STS). The STS required patients to stand up from, and sit down on a 45cm padded chair with no armrests as many times as possible in 30 s. Patients could use their hands to help them stand if required [25] and were provided standardised verbal encouragement to continue to sit and stand throughout the test. Patients completed two trials separated by 1 minute of rest. The average of both attempts was recorded.

Functional exercise capacity

Functional exercise capacity was assessed using a 6-minute walk test (6MWT) along a 20m indoor corridor. Patients were instructed to walk as far as possible in the 6-minutes, back and forth along

the corridor, turning briskly around the markers at each end. Patients could slow down, stop and rest if necessary. Standardised moderate verbal encouragement was provided every 2 minutes by the same investigator to each patient. The distance walked in 6 minutes was recorded to the nearest meter.

Psychological assessment

HR-QoL

The multidimensional European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to assess HR-QoL. Using the EORTC scoring manual, a linear transformation was used to standardise the raw score, so that scores ranged from 0 to 100. A higher score represents a higher level of Global QoL and functioning. A change in subscale score of 5-10 was considered the minimal clinically meaningful change [26].

User experience

Patients were invited to complete semi-structured interviews to explore their experiences and views on the intervention, and its impact on their daily lives. Questions were open ended and were tape-recorded. Recordings were transcribed verbatim.

Data management and Analysis

Due to the limited number of patients included in this study, data are presented individually and trends in outcomes are narratively summarised. Descriptive statistics (% change) are used for functional muscle strength and aerobic exercise capacity to describe changes in the functional status of patients.

RESULTS

Completion of the study was achieved by 6 of the 10 recruited patients (Table 2). Nine patients received baseline assessments and 8 began the home-based intervention. One patient who had an implanted pacemaker received initial clearance to participate from his cardiologist, however, withdrew after baseline assessments due to further concerns expressed by the cardiologist. One patient withdrew after one week, citing lack of time, whilst a further patient withdrew after two weeks of the NMES exercise intervention, citing muscle discomfort following stimulation. One patient reported muscle soreness the day after NMES use, which subsided within 2 days. No serious adverse events were reported. Three patients completed 4 weeks, and 3 patients completed 8 weeks. Measurement time points for 8wk patients included 4wk functional testing, however, this is not reported.

Physical function

After NMES exercise, lower limb functional muscle strength had improved in 4 of 6 patients (Table 3A). Percentage increase in STS score ranged from 13% to 67%. Patient 3 was the exception to this observation and showed an 8% decrease. Patient 5 STS score did not change. Improvements in aerobic exercise capacity were observed in 5 of 6 patients. Percentage increases in 6MWT distance ranged from 2% to 160%. Patient 3 distance decreased by 12%. At baseline Patient 1 required the use of a walking aid to complete the 6MWT. After 4 weeks of NMES, she had shown a 16% increase in 6MWT distance (112m vs 130m) (Not reported), completing the test unaided, with rest periods. At 8 weeks, her distance had increased a further 124% (112m vs 291m), unaided, with no rest periods

Quality of Life

Global QoL improved in 4 of 6 patients. Score increase ranged from 7 to 33 points. Patient 1 Global QoL decreased by 100%, whilst Patient 3 Global QoL remained the same after the NMES intervention. Four of 6 patients reported improved Physical QoL, with score increase ranging from 7 to 34. Role QoL increased in 3 patients, decreased in 1 and remained unchanged in 2. Scores in the other sub-scales were mostly unchanged (Table 3B).

Acceptability and user experience

One patient completed the prescribed LF-NMES session frequency, with Patient 6 completing more sessions than prescribed (18 sessions). Patient 1 missed 8 sessions, Patient 2 missed 3 sessions, whilst Patients 3 and 4 missed 1 session. Patient 5 missed 17 sessions. No patients prescribed HF-NMES achieved the target number of sessions prescribed (Table 4). Six patients completed qualitative interviews. The perceived benefits of the NMES exercise intervention were: greater muscle strength which made undertaking activities of daily living (e.g. climbing stairs) easier, and increased ability and confidence when walking alone (Panel). One patient reported some muscle soreness after initial use, which subsided. No other negative experiences were reported.

Panel. Illustrative quotes from the qualitative interviews about the perceived effect of the NMES exercise intervention

"I improve little by little...I feel that my legs are stronger and I can move better...I don't feel as fatigued as I used to and I feel safer when walking...6 weeks ago I always needed to hold onto my husband when we were out walking...but I don't need to know when I go out and I feel safe going out alone"

(Woman, 63 years)

“I really like it...my legs have more strength, especially straight after using the unit...I walk better and more confidently...I have fallen 4 to 5 times before using the unit...but I haven’t since I started...I have stumbled, but I have been able to control it and not fall over...better leg strength has allowed me to swim better in my pool, something that was difficult before” (Woman, 67 years)

“I feel like I have more strength...I feel better but I experienced some muscle soreness...I feel like I had done a workout...the pain was not limiting but just noticeable. I feel like I can walk more...I would advise others to use it, especially those with limits...it’s important for people to exercise and stim is easy as its minimalist and not a large amount of equipment” (Man, 46 years)

DISCUSSION

The results presented in this study support the use of a personalised and progressive concurrent NMES exercise intervention as a feasible and safe intervention in adult cancer survivors. A concurrent NMES programme may facilitate improvements in functional exercise capacity and functional muscle strength after just 4 weeks. In addition, there appears to be a dose response relationship between NMES exercise volume and functional improvements. The functional improvements were accompanied by subjective improvements in HR-QoL and self-report improvements in lower limb strength and increased confidence when walking unaided (Panel)

Similar to previous reports which have demonstrated NMES exercise to be safe, even in those with metastatic disease, and undergoing intensive chemotherapy and allogenic/autologous stem cell transplantation [27, 28] we reported no serious adverse events. Only one patient withdrew due to muscle discomfort which was reported in her second week of use. Tolerance to NMES exercise is individual-specific with around 10% of older adults and those with chronic diseases being unable to

tolerate NMES exercise [29, 30]. In cancer patients, this estimate may be higher particularly amongst those undergoing treatment, which may exacerbate tolerance. Three patients who completed the study reported increased sensitivity to stimulation for 2-3 days following their cancer treatment. In addition, the patient who withdrew did so after two weeks, and shortly after a chemotherapy cycle. Furthermore, her withdrawal came after informal feedback in week 1 which highlighted enjoyment of the programme, no muscle discomfort and subjective improvements in physical function. Together this suggests that although NMES exercise appears safe during treatment, stimulation intensities in the days following treatment may require greater modification, possibly to levels below motor threshold or no stimulation on these days if adherence is a concern.

A progressive deterioration in physical function is commonly reported in cancer patients during treatment [1]. Voluntary exercise is a proven strategy for minimising the loss of aerobic and muscular fitness [6]. NMES exercise may be a pragmatic alternative for those unable to exercise, with 4 of the 6 patients in the current study demonstrating improvements in functional muscle strength, and 5 of 6 patients improving aerobic exercise capacity. Patient 4 increased 6MWT by 7m, which is below the 14m considered the minimal clinically meaningful change [31]. In addition, the STS score of Patient 5 remained the same at 8 weeks of NMES exercise. Both results can be considered a maintenance in physical function and viewed as a positive result whilst undergoing cancer treatment. Patient 1, who was the most deconditioned at baseline, demonstrated some of the largest improvements in both outcomes (STS: 67% and 6MWT: 160%). At baseline, she required a walking aid to complete the 6MWT. However, at 8wk post testing she was capable of completing the 6MWT unaided. These improvements in Patient 1 are not surprising since previous observations suggest that the most deconditioned patients are likely to obtain the most benefit from NMES exercise [32]. These

results are encouraging given that walking and body transfers are two commonly affected activities of daily living in cancer patients [20].

At baseline Patient 3 recorded the highest 6MWT distance. He was prescribed only LF-NMES to try and maintain walking capacity. However, after 4 weeks he recorded 70m less. Glioblastoma is an aggressive brain cancer which is commonly associated with motor deficits such as ataxia and gait impairment [33]. At the time of post testing, the patient reported weakness and general malaise. Additionally, he had received 1 cycle of temozolomide, and was receiving regular dexamethasone, both of which may have contributed to muscle weakness [34]. Previous LF-NMES protocols (5x1hr sessions/week) evaluated in other clinical populations have led to significant improvements in 6MWT distance [18]. Therefore, the prescribed training dose and progression in the current study may have been inadequate to minimise the progressive physical deterioration which can accompany treatment for this aggressive tumour type.

In response to treatment side effects, the psychological condition of cancer patients can significantly deteriorate [35]. Exercise based interventions have proven effective in mitigating reductions in HR-QoL. A recent review has suggested that NMES exercise may be an effective intervention for improving HR-QoL [14]. Our results show that 4 of 6 patients improved Global QoL and Physical functioning QoL. These results are promising considering cancer patients can experience day to day variations in physiological, functional and psychological factors [22], which may impact on QoL during treatment. In addition, higher QoL measured at the end of treatment is associated with higher post treatment exercise attendance [36]. Patient 6, who exhibited the largest change in Global QoL (+33) was the only patient who was not on active treatment, having completed her last cycle, 4 weeks

previously. It is possible that the completion of her treatment schedule, the short duration of her illness and the NMES exercise intervention may have led to a higher improvement in QoL. Informal feedback from Patient 6, informed us of her progression into supervised aerobic and resistance training. Similarly, Patients 2 and 4 reported their intentions to progress into supervised and unsupervised voluntary exercise, further demonstrating increased motivation to maintain activity levels after NMES exercise.

Strengths and Limitations

The main strength of this study is that to the best of the investigators knowledge this is the first report of an individually prescribed and progressed NMES exercise intervention in cancer patients. The main limitation is the small number of patients involved which limits the extent of which conclusions can be drawn. However, these results provide rationale for future research.

CONCLUSIONS

To our knowledge this case series is the first report of a successful personalised and progressive NMES exercise intervention to augment aerobic and muscular fitness in cancer patients. The findings indicate that NMES may be an effective strategy for those who are undergoing or have recently completed treatment for cancer. Importantly, NMES exercise may act as a bridge to voluntary exercise for those whose progressive physical deterioration during and following treatment limits their voluntary exercise capabilities. Future research in this area is warranted to confirm these findings prior to clinical implementation.

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References

1. Courneya KS, Friedenreich CM (2001) Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med* 23:263–272 . doi: 10.1207/S15324796ABM2304_5
2. Schneider CM, Hsieh CC, Sprod LK, et al (2007) Cancer treatment-induced alterations in muscular fitness and quality of life: The role of exercise training. *Ann Oncol*. doi: 10.1093/annonc/mdm364
3. Segal R, Zwaal C, Green E, et al (2017) Exercise for people with cancer: a systematic review. *Curr Oncol* 24:e290–e315 . doi: 10.3747/co.24.3619
4. Spence RR, Heesch KC, Brown WJ (2010) Exercise and cancer rehabilitation: A systematic review. *Cancer Treat. Rev.* 36:185–194
5. Gerritsen JKW, Vincent AJPE (2016) Exercise improves quality of life in patients with cancer: A systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* 50:796–803 . doi: 10.1136/bjsports-2015-094787
6. Schmitz KH, Courneya KS, Matthews C, et al (2010) American college of sports medicine roundtable on exercise guidelines for cancer survivors. *Med. Sci. Sports Exerc.* 42:1409–1426
7. Crevenna R (2013) From neuromuscular electrical stimulation and biofeedback-assisted exercise up to triathlon competitions-regular physical activity for cancer patients in Austria.

Eur Rev Aging Phys Act 10:53–55 . doi: 10.1007/s11556-012-0110-8

8. Hultman E, Sjöholm H, Jäderholm-Ek I, Krynicki J (1983) Evaluation of methods for electrical stimulation of human skeletal muscle in situ. *Pflügers Arch Eur J Physiol* 398:139–141 . doi: 10.1007/BF00581062
9. Maffiuletti NA, Roig M, Karatzanos E, Nanas S (2013) Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. *BMC Med* 11:137 . doi: 10.1186/1741-7015-11-137
10. Bax L, Staes F, Verhagen A (2005) Does neuromuscular electrical stimulation strengthen the quadriceps femoris? A systematic review of randomised controlled trials. *Sports Med* 35:191–212 . doi: 10.2165/00007256-200535030-00002
11. Maffiuletti NA, Gondin J, Place N, et al (2017) The Clinical Use of Neuromuscular Electrical Stimulation for Neuromuscular Rehabilitation: What Are We Overlooking? *Arch Phys Med Rehabil*. doi: 10.1016/j.apmr.2017.10.028
12. Doheny EP, Caulfield BM, Minogue CM, Lowery MM (2010) Effect of subcutaneous fat thickness and surface electrode configuration during neuromuscular electrical stimulation. *Med Eng Phys*. doi: 10.1016/j.medengphy.2010.03.004
13. O'Connor D, Caulfield B (2018) The application of neuromuscular electrical stimulation (NMES) in cancer rehabilitation: current prescription, pitfalls, and future directions. *Support care cancer Off J Multinatl Assoc Support Care Cancer*. doi: 10.1007/s00520-018-4269-z
14. O'Connor D, Caulfield B, Lennon O (2018) The efficacy and prescription of neuromuscular electrical stimulation (NMES) in adult cancer survivors: a systematic review and meta-analysis. *Support Care Cancer* 26:3985–4000 . doi: 10.1007/s00520-018-4342-7
15. Minogue CM, Caulfield BM, Reilly RB (2007) What are the electrical stimulation design parameters for maximum VO₂ aimed at Cardio-Pulmonary rehabilitation? In: Annual

International Conference of the IEEE Engineering in Medicine and Biology - Proceedings. pp 2428–2431

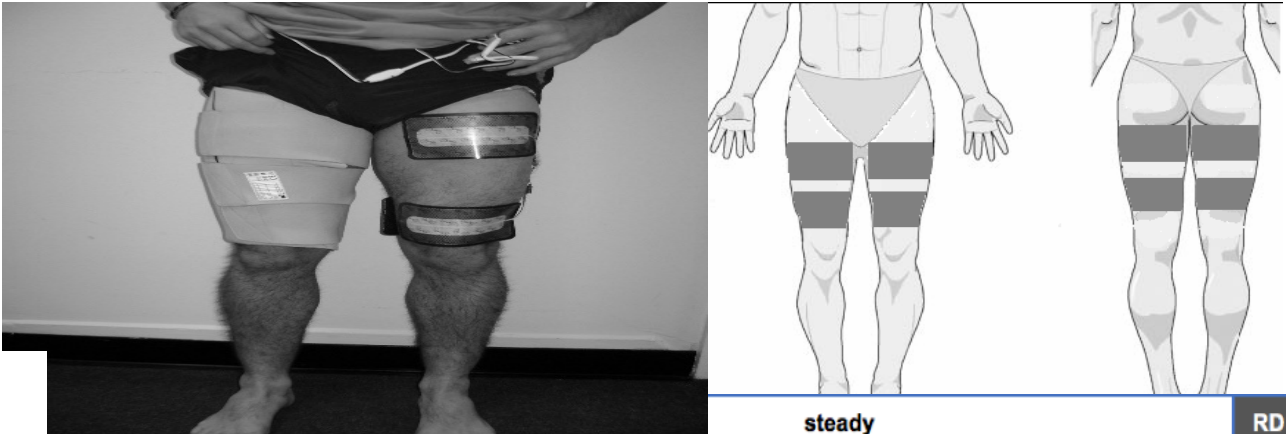
16. Caulfield B, Crowe L, Coughlan G, Minogue C (2011) Clinical application of neuromuscular electrical stimulation induced cardiovascular exercise. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. pp 3266–3269
17. Banerjee P (2011) Can Electrical Muscle Stimulation of the Legs Produce Cardiovascular Exercise? *J Clin Exp Cardiol* 02:134–136 . doi: 10.4172/2155-9880.1000134
18. Banerjee P, Caulfield B, Crowe L, Clark AL (2009) Prolonged Electrical Muscle Stimulation Exercise Improves Strength, Peak VO₂, and Exercise Capacity in Patients With Stable Chronic Heart Failure. *J Card Fail* 15:319–326 . doi: 10.1016/j.cardfail.2008.11.005
19. Caulfield B, Prendergast A, Rainsford G, Minogue C (2013) Self directed home based electrical muscle stimulation training improves exercise tolerance and strength in healthy elderly. *Conf Proc . Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf* 2013:7036–7039 . doi: 10.1109/EMBC.2013.6611178
20. Neo J, Fettes L, Gao W, et al (2017) Disability in activities of daily living among adults with cancer: A systematic review and meta-analysis. *Cancer Treat. Rev.*
21. Cenik F, Schoberwalter D, Keilani M, et al (2016) Neuromuscular electrical stimulation of the thighs in cardiac patients with implantable cardioverter defibrillators. *Wien. Klin. Wochenschr.* 128:802–808
22. Fairman CM, Zourdos MC, Helms ER, Focht BC (2017) A Scientific Rationale to Improve Resistance Training Prescription in Exercise Oncology. *Sport Med* 47:1457–1465 . doi: 10.1007/s40279-017-0673-7
23. Vivodtzev I, Debigar?? R, Gagnon P, et al (2012) Functional and muscular effects of

- neuromuscular electrical stimulation in patients with severe COPD: A randomized clinical trial. *Chest* 141:716–725 . doi: 10.1378/chest.11-0839
24. Maddocks M, Nolan CM, Man WD-C, et al (2016) Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: A randomised double-blind, placebo-controlled trial. *Lancet Respir Med* 4:27–36 . doi: 10.1016/S2213-2600(15)00503-2
 25. Applebaum E V., Breton D, Feng ZW, et al (2017) Modified 30-second Sit to Stand test predicts falls in a cohort of institutionalized older veterans. *PLoS One*. doi: 10.1371/journal.pone.0176946
 26. Maringwa J, Quinten C, King M, et al (2011) Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Ann Oncol*. doi: 10.1093/annonc/mdq726
 27. Crevenna R, Marosi C, Schmidinger M, Fialka-Moser V (2006) Neuromuscular electrical stimulation for a patient with metastatic lung cancer - A case report. *Support Care Cancer* 14:970–973 . doi: 10.1007/s00520-006-0033-x
 28. Bewarder M, Klostermann A, Ahlgrimm M, et al (2018) Safety and feasibility of electrical muscle stimulation in patients undergoing autologous and allogeneic stem cell transplantation or intensive chemotherapy. *Support Care Cancer*. doi: 10.1007/s00520-018-4390-z
 29. Delitto A, Strube MJ, Shulman AD, Minor SD (1992) A study of discomfort with electrical stimulation. *Phys Ther*. doi: 10.1093/ptj/72.6.410
 30. Vivodtzev I, Rivard B, Gagnon P, et al (2014) Tolerance and physiological correlates of neuromuscular electrical stimulation in COPD: A pilot study. *PLoS One* 9: . doi: 10.1371/journal.pone.0094850
 31. Bohannon RW, Crouch R (2017) Minimal clinically important difference for change in 6-

minute walk test distance of adults with pathology: a systematic review. J. Eval. Clin. Pract.

32. Roig M, Reid WD (2009) Electrical stimulation and peripheral muscle function in COPD: A systematic review. Respir. Med. 103:485–495
33. Amidei C, Kushner DS (2015) Clinical implications of motor deficits related to brain tumors†. Neuro-Oncology Pract 2:179–184
34. Batchelor TT, Taylor LP, Thaler HT, et al (1997) Steroid myopathy in cancer patients. Neurology 48:1234–1238
35. Flechtner H, Bottomley A (2003) Fatigue and quality of life: lessons from the real world. Oncologist 8 Suppl 1:5–9 . doi: 10.1634/theoncologist.8-suppl_1-5
36. Bland KA, Neil-Sztramko SE, Kirkham AA, et al (2018) Predictors of attendance to an oncologist-referred exercise program for women with breast cancer. Support Care Cancer. doi: 10.1007/s00520-018-4180-7

(A)



								RD	
PHASE INTENSITY									steady
PHASE DURATION	90s	180s	30s	180s	60s	180s	30s		
PHASE INTENSITY									
PHASE DURATION									
PULSE WIDTH	620µs	620µs	300µs	620µs	300µs	620µs	620µs		
PULSE FREQUENCY	4-pulse train repeated @ 4Hz								
PHASE INTENSITY	RU								RD
PHASE DURATION	90s	300s	60s	300s	60s	300s	30s		
PULSE WIDTH	620µs	620µs	300µs	620µs	300µs	620µs	620µs		
PULSE FREQUENCY	4-pulse train repeated @ 4Hz								

PHASE 2

PHASE 3

(B)

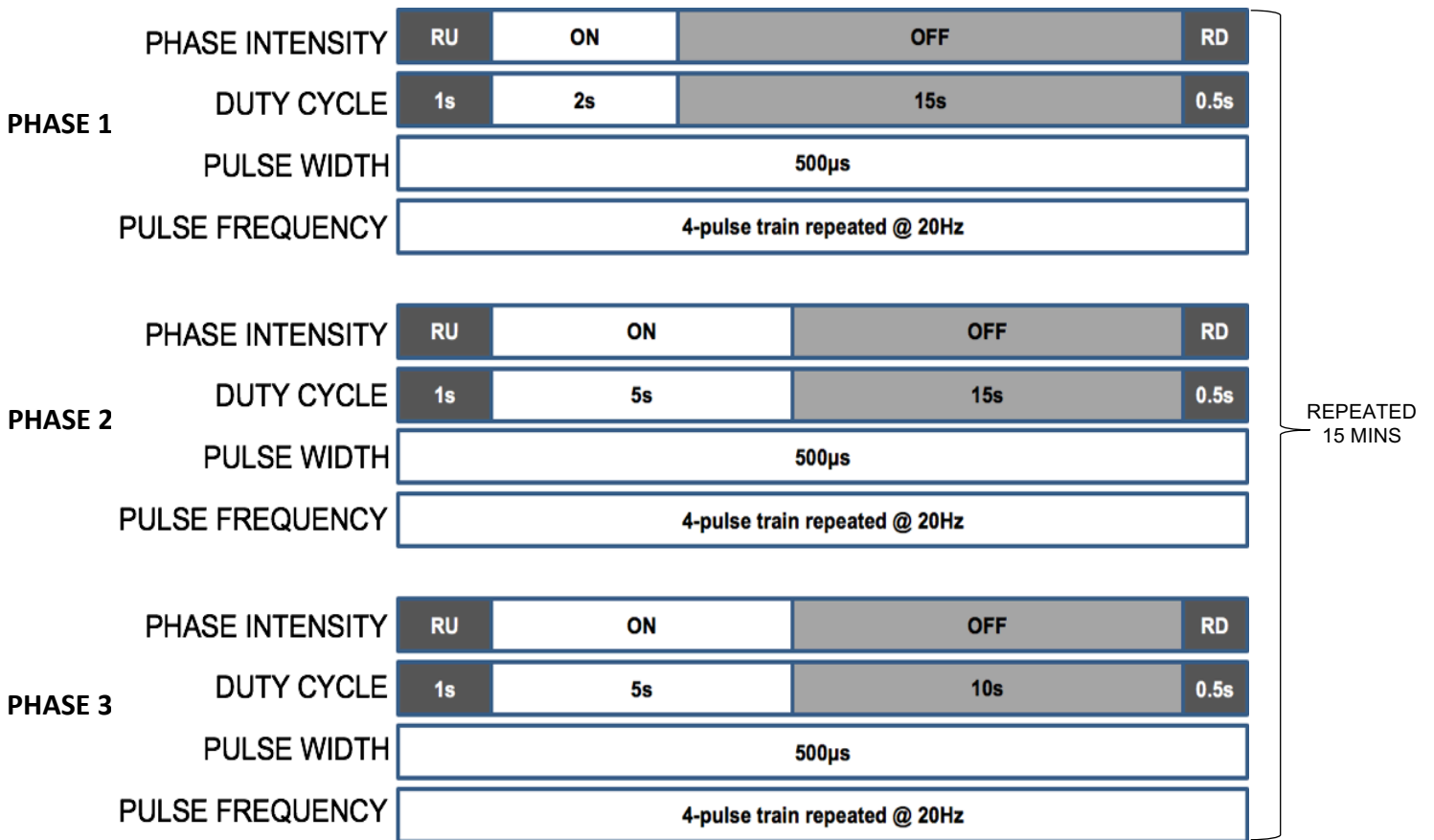


Figure 2. Schematic representation of LF-NMES intermittent delivery (A) and HF-NMES duty cycle (B) progressions

Table 1. Standard prescription and progression guidelines

Time	Phase	Standard Progression (duration/on:off)	Session frequency (No. /week)
Wk 1	LF-NMES	3 x 3 min Ramp	2
	HF-NMES	N/A	2
Wk 2	LFNMES	3 x 5 min Ramp*	3
	HF-NMES	2 s ON: 15 s OFF	3
Wk 3	LFNMES	25 min continuous	4
	HF-NMES	5 s ON: 15s OFF	4
Wk 4	LFNMES	30 min continuous	5
	HF-NMES	5s ON: 10 s OFF	5
Wk 5	LFNMES	35 min continuous	5
	HF-NMES	5s ON: 10 s OFF	5
Wk 6	LFNMES	35 min continuous	5
	HF-NMES	5s ON: 10 s OFF	5
Wk 7	LFNMES	40 min continuous	5
	HF-NMES	5 s ON: 10 s OFF	5
Wk 8	LF-NMES	45 min continuous	5
	HF-NMES	5 s ON: s OFF	5

Ramp protocol: 3 x 5 min* 4Hz, 1.5 min RU, 5 min @ 620 μ s, 1 min @ 100 μ s, 5 min @ 620 μ s, 1 min @ 300 μ s, 5 min @ 620 μ s, 30 s RD. **RU** = Ramp Up, **RD** = Ramp Down

Table 2. Characteristics, socio-demographics, and medical history of patients who completed the study

Patient	1	2	3	4	5	6
Characteristics						
Age (y)	67	67	46	68	67	63
Height (m)	1.61	1.58	1.62	1.63	1.59	1.56
Weight (kg)	67	60	77	85	58	59
BMI (kg/m ²)	25.9	24.0	29.3	32.0	22.9	24.2
Socio-demographics						
Marital status	Married	Divorced	Married	Divorced	Married	Married
Education	High school	University	University	College	College	University
Employment	Working	Retired	Working	Working	Retired	Working
Medical history						
Cancer type	Ovarian	Liver	Glioblastoma	Bladder	HER2+ Breast	NSCLC
Cancer stage/grade	IV	IV	IV	IV	IV	IIIB
Date of diagnosis	Nov 2015	Oct 2017	Feb 2018	Jul 2017	Apr 2018	Feb 2018
Treatment	Chemotherapy	Chemotherapy	Radiotherapy + Chemotherapy	Immunotherapy	Chemotherapy + immunotherapy	Chemotherapy
Treatment status	Active	Active	Active	Active	Active	Complete
Comorbidities	RA	Depression/anxiety Previous cancer diagnosis (Ovarian, 2005)	None	Spinal stenosis	None	None

Abbreviations: HER2+ - human epidermal growth factor receptor 2 positive. NSCLC - Non-small cell lung cancer. BMI – Body Mass index (weight [kg]/height [m²]). RA – Rheumatoid Arthritis

(A)

Table 3. Physical performance assessment results at baseline and post NMES intervention

Patient No.	STS (reps)			6MWT (m)		
	Baseline	Post	% Change	Baseline	Post	% Change
1**	3	5	67	112*	291	160
2**	10	17	70	407	474	17
3	12	11	-8	600	530	-12
4	8	9	13	373	380	2
5**	10	10	0	312	342	10
6	9	13	44	390	433	11

*Indicates walking device used. **indicates 8wk intervention completed.

(B)

Table 3. Global health QoL and functional scales

Patient No.	Global QoL		Physical		Role		Emotional		Cognitive		Social	
	Baseline	Post	Baseline	Post	Baseline	Post	Baseline	Post	Baseline	Post	Baseline	Post
1	50	33	13	53	0	33	83	100	67	67	0	33
2	75	83	80	87	67	100	83	83	83	83	67	67
3	67	67	80	87	67	67	100	100	100	100	100	33
4	42	50	80	80	83	100	58	83	100	67	83	50
5	42	58	93	67	100	33	83	33	67	33	50	67
6	50	83	80	93	67	100	33	67	100	100	50	100

Table 4. Session completion rates and session intensities

Patient No.	Intervention length (wks)	Total no. of completed LF-NMES sessions	Total no. of completed HF-NMES sessions	LF-NMES intensity during sessions (first-last session)*	HF-NMES intensity during sessions (first-last session)*
1	8	26 of 34	26 of 32	42 - 60	40 – 60
2	8	31 of 34	25 of 32	72 – 99	60 - 96
3	4	13 of 14	0 of 12	55 - 76	N/A
4	4	13 of 14	0 of 12	37 – 74	N/A
5	8	17 of 34	15 of 32	50 – 75	40 - 65
6	4	18 of 14	7 of 12	48 - 49	40 – 40

*Intensity reported as % of maximum output (140mA)