ABSTRACT

Background and Purpose: Glioblastoma Multiforme (GBM) is associated with debilitating physical and psychosocial side effects. Voluntary exercise recommended as an adjunct therapy is often limited by physical and neurological impairments. The potential impact of aerobic and muscle strengthening neuromuscular electrical stimulation (termed concurrent NMES) exercise (4 weeks, 2-5x/week, 30 mins-1 hr) delivered to the lower limbs in patients with GBM has not been examined. This case study explores the impact of a short-term concurrent NMES intervention progressing to NMES and supervised voluntary exercise (aerobic and resistance training) over a 10-week period in a patient with GBM undergoing adjuvant treatment.

Case description: The case was a 61-year-old male with GBM who had completed radiotherapy treatment (40Gy) and was under-going adjuvant chemotherapy. Eastern Cooperative Oncology Group (ECOG) level was 3. Assessments were conducted at baseline, and at week-4 and 10 of the intervention. Outcomes included 30 second sit to stand (30STS), timed up and go (TUG), European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), and Godin Leisure-Time Questionnaire.

Outcomes: The intervention was well tolerated, with >70% NMES exercise adherence over 10 weeks and progression to combined NMES and voluntary exercise at week 5. No adverse events were reported. Despite self-reported increases in fatigue levels, clinically meaningful improvements were observed at week 4 and 10 for 30STS, TUG and Physical QoL. Self-report physical activity levels increased at week 10.

Discussion: In this first clinical case report, a 10-week NMES/voluntary exercise intervention led to improvements in physical and QoL outcomes. This initial evidence suggests NMES exercise is safe and feasible and may act as a bridge to voluntary exercise. NMES demonstrated

promise as an effective supportive intervention in the management of GBM. Future clinical trials are required to expand these initial findings.

Key Words: neuromuscular electrical stimulation; cancer rehabilitation; exercise; supportive care

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain malignancy, accounting for 48% of all malignant brain and other central nervous system (CNS) tumours in adults (1). Incidence rates are low when compared with other solid tumours, with annual age-adjusted incidence rates in the US of 3.21 per 100,000 persons (1). However, GBM remains incurable and survival rates at five years are very low (~5%), with a median survival time from diagnosis of 15 months (2, 3). GBM is primarily diagnosed in older adults (median age at diagnosis 64 years) and a higher incidence rate is reported in men (4–6). Both lifestyle and environmental risk factors have been associated with GBM development (7), although prior therapeutic radiation is the only proven exposure risk factor (8, 9). Despite advances in antineoplastic treatments, GBM remains a difficult cancer to treat. Current standard treatment regimens for newly diagnosed GBM require a multimodal approach, including surgical resection if possible, followed by radiotherapy plus concomitant and adjuvant temozolomide based chemotherapy (10).

GBM and its management often result in debilitating cognitive, emotional and physical effects which can have a profound impact on quality of life (QoL) for patients and their families and can limit independence. Sequalae vary depending on tumour location. Neurological deficits include impaired balance and coordination, seizures, headaches and memory loss, all of which

can make voluntary exercise challenging (11). Fatigue, while common in patients with cancer, has been reported as up to 50% more severe in GBM patients when compared with normative levels in cancer patients and is one of the most distressing symptoms (12, 13). Functional changes have also been described, with cardiorespiratory fitness and strength levels in postsurgical GBM patients reported as ~60% lower than that of age and sex matched sedentary normative values (12, 13). Given these observations and the poor prognosis associated with the disease, it is important to identify therapies which are safe and can optimise QoL and maintain functional independence.

Exercise (150 mins/week aerobic exercise + 2x/week resistance training) is currently recommended for all cancer survivors as an adjunct therapy and to help counteract physical impairments (14). Most likely due to the complex nature of GBM, few exercise-based clinical trials have been carried out to evaluate its safety and effectiveness in this cohort. Established clinical research from which current exercise guidelines in oncology are based, demonstrates safety and effectiveness in other cancer cohorts, providing a strong rationale to support exercise prescription in GBM patients. However, primary brain tumour patients are noted to struggle with exercise participation largely due to the aggressive nature of the disease. Common exercise limiting symptoms include proximal muscle weakness, neurological deficits such as balance, and coordination issues due to peritumoral vasogenic oedema (9), pronounced physical deconditioning and chronic fatigue (15). This highlights the need for safe, pragmatic and shorter-term alternatives to augment or prevent decline in physical function and QoL.

Neuromuscular electrical stimulation (NMES) generates muscle contractions via electrical impulses delivered to motor nerves. It is delivered using surface electrodes placed on target muscle groups using a handheld device with the user typically in a seated or supine position

(16). High frequency NMES (HF-NMES, 20-100 Hz) has been extensively used in different areas of rehabilitation and sports training to augment muscle function and structure over periods of ~4 weeks (3x/week) (17, 18). Emerging evidence now supports the use of low frequency NMES (LF-NMES, 3-12 Hz) for enhancing cardiorespiratory fitness (CRF) in healthy populations over a similar time period (12 sessions over 4 weeks) (19, 20) and has been shown to improve CRF and strength in deconditioned clinical populations with low functional capacity over 6-8weeks (21, 22). This provides strong rationale for the use of both LF and HF-NMES protocols (concurrent NMES) targeting the lower limbs (quadriceps and hamstrings) in early stage cancer rehabilitation. Of note, previous attempts to use NMES in cancer rehabilitation applied/adapted HF-NMES protocols from orthopaedic and neurological rehabilitation settings and proved largely unsuccessful at improving functional and strength outcomes (23). These negative outcomes have been linked to inappropriate NMES protocol design and poor adherence with the intervention (24).

Recently, a personalised and progressive concurrent approach has been proposed in adult cancer survivors (25). This approach has been developed to target the pronounced deterioration seen in the neuromuscular and cardiovascular systems during and following cancer treatments (11, 12, 26). Improvements in functional strength and aerobic exercise capacity were reported following 4 – 8 weeks of concurrent NMES exercise delivered to the quadriceps and hamstring muscles in a small heterogeneous group of cancer survivors (25). Notably, the greatest improvements were seen in the most deconditioned patients, a finding previously reported in the literature (27). Furthermore, some patients progressed to voluntary exercise programmes upon completion. As such NMES exercise may have an important role to play in the effective management of GBM, in those who may be experiencing exercise limiting symptoms. However, no clinical case study or any early phase clinical trials exist investigating the impact

of a short-term personalised and progressive NMES exercise programme followed by a combined NMES and supervised voluntary exercise intervention to improve outcomes in GBM patients. Here we report for the first time the safety, feasibility and impact of a progressive, concurrent NMES (LF and HF) and voluntary exercise programme in a GBM patient undergoing adjuvant treatment. The first 4 weeks involved a personalised and progressive concurrent NMES exercise intervention. The following 6 weeks involved a personalised and progressive concurrent NMES exercise intervention plus 1 supervised voluntary exercise session per week.

METHODS

Study design & Patient

This was a case study in which we followed the patient for a period of 10-weeks with three measurement time points. Objective physical measures and patient reported outcomes (PROs) were recorded at baseline, week 4 upon completion of the NMES exercise intervention and week 10 upon completion of the combined NMES/voluntary exercise intervention.

This case study describes a 61-yr-old male (height = 184 cm, weight = 113.4 kg) with a histological diagnosis of GBM. The patient is married, is a non-smoker, and was retired at the time of study entry. He was diagnosed with multifocal cerebellar GBM in January 2018. The diagnosis was made during surveillance of a meningioma, identified in 2016. The patient underwent surgery in January 2018 whereby a tissue biopsy was obtained for histological diagnosis, but no debulking surgery was possible. Cancer treatment involved 3 weeks of hypo-fractionated cranial external beam radiotherapy followed by 6 cycles of adjuvant chemotherapy. Radiotherapy commenced in February 2018 with a dose of 40 Gy (daily fractions of 2.67 Gy, Monday – Friday) over 3 weeks. Chemotherapy commenced after

radiotherapy. The patient received a standard temozolomide chemotherapy regime comprising of six, 28-day cycles. Temozolomide was administered orally once daily (150mg/m^2) for days 1 – 5, followed by 23 days of treatment interruption. The patient reported regular bouts of nausea 3 – 4 days after completion of each chemotherapy cycle. In addition, at the time of study entry the patient was administered dexamethasone (2mg) every second day. This standard dose was increased during periods of significant balance impairment.

Previous medical history includes Leukaemia diagnosed aged 15 and myocardial infarction aged 50. Treatment for Leukaemia at that time included chemotherapy and whole brain radiotherapy. Prior to GBM diagnosis the patient regularly attended the gym (2x/week) and played golf 1x/week. He now requires carer support daily (1.5 – 2 Hrs). Due to disease progression, the patient suffers from a significant balance impairment which limits unsupervised exercise participation. As such, he requires a four-wheeled walking aid to mobilise. The patient's level of function on the Eastern Cooperative Oncology Group scale was 3 (ECOG, scale 0-5, 3 - Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours). The NMES/voluntary exercise intervention began 9 days prior to his 4^{th} cycle of chemotherapy and following referral from his physiotherapist. The patient completed cycles 4 and 5 of his treatment regime during the course of the study (Figure 1). Cycle 6 was expected to be completed 1 week prior to the end of the study period but was withheld due to thrombocytopenia (110 x 10^9/litre) and fatigue.

This study protocol was approved by the University and the Hospital Research Ethics Committees and the patient provided written informed consent.

NMES intervention

The unsupervised home-based concurrent NMES exercise intervention, developed to target functional muscle strength and aerobic exercise capacity in cancer patients, has previously been described in detail (25). In brief, the personalised and progressive NMES exercise intervention was delivered using a 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 2). The patient trained without supervision at home using a standard weekly progressive prescription progressing from 2 x 30 min sessions/week to 5 x 1 hr sessions/week (Table 1). The session duration of LF-NMES progressed weekly (15-45 mins), but HF-NMES session duration remained constant at 15 mins. The programme delivered two-phases during each session (Phase 1 - LF-NMES: 4Hz, 620μs, 15-45 mins, Phase 2 - HF-NMES: 20Hz, 500μs, 15 mins). The patient was instructed to train for 4-weeks with NMES (2-5x/week) only, followed by 6 weeks of NMES (5x/week) + voluntary exercise (1x/week).

To determine the initial NMES exercise intensity, the patient completed 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 unit was demonstrated.

Exercise intervention

The supervised exercise intervention (Fit for Life), which is routinely offered as part of a clinical service for oncology patients, included 1 x 60-minute exercise session/week for 6 weeks, supervised by a qualified exercise professional. Each supervised session consisted of

individually tailored cardiovascular, resistance and balance exercises (Table 2). The training programme was adapted and progressed weekly based on subjective functional and psychological feedback from the patient. Educational sessions (30-minutes) were delivered after each exercise session by relevant qualified health professionals including a clinical psychologist, dietician, occupational therapist and physiotherapist. Sessions included exercise pacing (x2), healthy eating (x2), stress management (x1), and behaviour change (x1).

Outcome measures

Physical function

Functional muscle strength

Lower limb functional muscle strength was assessed using the 30 second Sit to Stand test (30STS). The patient was required to stand up from and sit down on a 45cm padded chair with no arm-rests as many times as possible in 30 seconds. The use of hands to help stand was allowed if required (28). Two trials were completed separated by 1 minute of rest. The average of both attempts was recorded. A change in 30STS score of 2 reps was considered the minimal clinically important difference (MCID) (29).

Functional mobility

Functional mobility was assessed via the Timed Up and Go Test (TUG). The patient was required to stand up from a 45 cm chair, walk 3 m, turn around, walk 3 m back and sit down again, walking at a preferred pace. The use of a walking aid was allowed. The test was completed twice, with the best score being recorded. A change of 3 sec in TUG time was considered the MCID (30).

Patient-reported outcomes

Physical activity levels

Physical activity levels were assessed using the Godin Leisure Time Questionnaire (GLTEQ). The patient self-reported the frequency and duration of mild moderate and strenuous exercise over a 1-week period. A leisure score index was calculated by multiplying the frequency (x/week) of strenuous, moderate and light intensity exercise of more than 15 mins by 9, 5 and 3 respectively. A higher score is indicative of a higher level of leisure time exercise. The patient was instructed to report exercise out with the Fit for Life intervention.

Fatigue

The Brief Fatigue Inventory was used to assess current and past (last 24 hrs) levels of fatigue. It is comprised on 9 questions under 4 headings. Each question was rated on a scale 1-10. A mean BFI score of 0, 1-3, 4-6 and 7-10 indicates no fatigue, mild fatigue, moderate fatigue and severe fatigue respectively (31).

Quality of life

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 (Global QoL and five function domains: physical, emotional, social, role, cognitive). Scores ranged from 0 to 100 with a higher score representing a higher level of Global QoL and functioning. Change in domain score of 5-10 was considered the MCID (32).

RESULTS

No adverse events occurred during the NMES or NMES/voluntary exercise interventions. The patient completed a total of 10 of the 14 unsupervised NMES sessions during the 4-week intervention period (71% adherence). Reasons for missed sessions included chemotherapy side effects such as fatigue. An additional 13 NMES sessions were completed over the 6-week NMES/voluntary exercise period. The patient was able to demonstrate small progressions in NMES exercise intensity across the study, from the first to last session and recorded maximum stimulator output achieved during training sessions in a self-report diary. The patient reported increased sensitivity and muscle discomfort during NMES in the days immediately following chemotherapy, leading to reductions in the NMES intensity he administered. However, these symptoms usually subsided 5 days post chemotherapy.

All voluntary exercise sessions were attended during the 6-week period. The patient tolerated voluntary exercise well, completing the prescribed exercises during each session. He did suffer from balance issues during week 3 which affected some exercise participation. Balance issues had subsided by the following week after increased dexamethasone dose.

Physical function

Objective assessments of physical function demonstrated improvements in lower limb functional strength and functional mobility at both 4-week and 10-week time points (Table 3). Following the 4-week NMES intervention, lower limb strength as measured by 30STS had improved by 17% (+1 rep). This was accompanied by a 24% (-6.23 s) improvement in functional mobility as measured with TUG. Following the 6-week NMES/voluntary exercise intervention lower limb strength had improved by an additional 14% (+1 rep) with functional mobility improving by an additional 10.5% (- 2.02 s).

Fatigue

Fatigue levels increased across the intervention period. Fatigue levels increased by 14% (5.44 to 6.22) between baseline and 4-weeks. During the NMES/Fit For Life intervention fatigue levels increased by an additional 25% (6.22 to 7.77).

Quality of Life

Change in QoL domains is reported in point change. Global quality of life increased by 17 points (50 to 67) between baseline and 4-weeks. At 10-weeks global QoL reduced again by 17 points, returning to baseline score (67 to 50). Physical QoL increased by 14 points between baseline and 4-weeks (13 to 27) and increased a further 20 points at 10-weeks (27 to 47). Role QoL increased by 16 points between baseline and week 4 (17 > 33) and increased a further 17 points between week 4 and week 10 (33 to 50). Emotional QoL and Cognitive QoL did not change between baseline and week 4. At week 10 Emotional QoL had regressed (58 to 50), whilst Cognitive QoL had increased by 33 points (17 to 50).

DISCUSSION

The results achieved in this case study provide preliminary evidence of the safety and feasibility of NMES exercise in a patient with GBM undergoing adjuvant treatment. The intervention was associated with clinically meaningful improvements in physical function and QoL domains of physical, role and cognitive. This case study identifies concurrent NMES as a novel supportive intervention that may improve physical function and offer a bridge to voluntary exercise for individuals with GBM who may otherwise be limited by their compromised functional ability.

Both NMES exercise and subsequent combined NMES/voluntary exercise appeared to be safe and feasible as a progressive exercise schedule. No serious adverse events were reported. Mild muscle discomfort during stimulation sessions in the days following chemotherapy was reported, a finding previously identified in the literature in cancer survivorship (25). This discomfort subsided 4 – 5 days post chemotherapy treatment with an intermittent effect on NMES intensity parameters tolerated. The patient attained 71% adherence (10 of the 14 NMES sessions) during the 4-week NMES intervention. 100% voluntary exercise adherence during the subsequent 6-week combined intervention period was recorded. The patient was advised to complete 5 sessions/week from week 4-10 (30 sessions), with a weekly minimum dose of 3 sessions/week (18 sessions) recommended. Thirteen NMES sessions were completed over this 6-week period giving 72% adherence (13 of the minimum 18 sessions advised) with NMES at this time point. The primary reason reported for missed NMES sessions was illness.

A flexible approach to prescription was adopted due to daily fluctuations in functioning. It has been suggested that an adaptive approach may help facilitate better adherence in patients with cancer (33). In the current study, the target NMES prescription was not met. However, clinically meaningful improvements in physical function and QoL were observed with the completion of a low dose (~2x/week). Similarly, a study involving chronic heart failure patients (CHF) with functional status (New York Heart Association class III/IV) similar to that of the patient in this case study (ECOG 3) observed improvements in functional capacity and QoL using a low dose HF-NMES protocol (2 x 50 min/week) over 7 weeks. Together this suggests that a lower NMES dose than that commonly prescribed in the literature (1hr, 5x/week) may be adequate to achieve improvements for severely deconditioned patients.

It is well documented that over cumulative cancer treatment periods, patients may experience a deterioration in physical function (26). These deficits can be pronounced, and in GBM patients given the aggressive nature of both disease and treatment results in reduced muscle strength, functional mobility and limited independence (15). In addition, when combined with prescribed medications such as dexamethasone (side effects: proximal muscle weakness & weight gain), problems can accumulate and be long lasting. Voluntary exercise, while proven effective for minimising side effects across the cancer continuum, may not be a viable strategy for all patients due to chronic fatigue and/or pronounced deconditioning. NMES provides a pragmatic alternative to help build or maintain physical function prior to progression into a voluntary exercise-based programme. Our case study demonstrated improvements in both functional muscle strength and functional mobility after the 4-week NMES exercise intervention. This finding is in line with a recent report in a small heterogenous group of adult cancer survivors who completed the same NMES exercise intervention (25). This is an important clinical finding since improvements occurred at a time when decrements in physical function might otherwise have been expected.

At week 10, following introduction to combined NMES and voluntary exercise at week 5, functional muscle strength and functional mobility improved further. A primary goal of NMES exercise should be to minimise functional deficits so that progression, where appropriate, to supervised voluntary exercise can be achieved. Current exercise guidelines are based on evidence from other cancer cohorts. There is strong theoretical rationale to support voluntary exercise for the management of GBM symptoms since it can target cognitive, emotional and physical impairments and has very few side effects when appropriately prescribed in neuro-oncology (13). However, tapering the NMES exercise prescription from NMES exercise to NMES + voluntary exercise and on to voluntary exercise may lead to greater benefits in GBM

patients who are generally deconditioned. NMES can be used as a supplementary early stage intervention during a progressive voluntary exercise programme.

Due to the complexity of clinical presentations in patients with GBM, multi-modal approaches (non-pharmacological & pharmacological) to rehabilitation must be considered. The patient in the current study experienced significant balance impairments which effected voluntary exercise participation and walking confidence. Such neurological deficits can be due to peritumoral vasogenic oedema and are improved following an increase in dexamethasone dose (9). However, long-term, high dose corticosteroid regimes are associated with deleterious changes which should be considered and mitigated against during programme development. Windholz et al. (34), observed poorer baseline function in cancer survivors recently treated with steroids and reported a non-significant trend towards an improvement in 6-minute walk distance in these patients using HF-NMES (50Hz, 30 mins, 7 days/week, 6 weeks). However, in the current study the interaction between NMES and corticosteroids is not reported, and future studies are warranted.

Given the poor prognosis associated with GBM, the development of interventions which lead to improvements in QoL are greatly welcome. In this case study, after the 4-week NMES exercise intervention we observed changes in QoL with Global QoL and Role and Physical QoL subscales increasing and exceeding the MCID threshold (32). In addition, these improvements occurred despite the patient undergoing active chemotherapy across the intervention period. However, at week 10, despite Physical and Role QoL subscales increasing further and Cognitive QoL increasing, Global QoL had returned to baseline levels. The Emotional QoL subscale deteriorated during this time interval. In addition, increased fatigue, noted across the intervention period, is known to negatively impact QoL in patients with cancer

(35). Subjective feedback from the patient did highlight severe fatigue during week 10 testing. This coincided with the withholding of the patients final temozolomide treatment cycle due to thrombocytopenia (110 x 10^9/litre) and fatigue.

Of note, the patient's physical activity (PA) levels remained the same over the 4-week NMES intervention period but increased during the 6-week period of NMES + voluntary exercise, despite increased fatigue and lower Global QoL rating. This result contrasts with a recent report demonstrating decreased PA levels following the same voluntary exercise programme as this case study but without NMES in a heterogenous groups of cancer survivors undergoing chemotherapy.(36).

Case studies involving a single individual have inherent limitations. It is possible that this patient was a high responder to the intervention. In addition, since the patient participated in the 6-week voluntary exercise programme along-side the NMES intervention, it is difficult to attribute the results to one particular intervention. However, the experienced oncology physiotherapist who lead the class felt that there was an additional gain from the NMES intervention when comparing with GBM patients who had completed previous classes without NMES exercise. The patient had an existing and supportive social network which can be viewed as an important source of motivation and encouragement to participate in voluntary exercise (37). The same benefits may not be realised amongst all patients with GBM. Randomised controlled trials are required to elucidate these findings and determine if they can be reproduced consistently in patients with GBM.

In conclusion, this case study provides preliminary evidence of the safety and feasibility of a 10-week NMES + voluntary exercise intervention in a patient with GBM concurrently

receiving chemotherapy. Given the magnitude of the improvements observed, the use of NMES as a supportive intervention in the management of GBM may be warranted to enhance physical function and aspects of QoL. Furthermore, NMES-based exercise may act as a bridge to voluntary exercise participation when used in early stage rehabilitation for individuals who are functionally compromised. The results of this case study provide strong rationale for the development of future clinical trials to confirm these preliminary results prior to the clinical implementation of this technology.

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Table Legend

Table 1. Standard LF & HF NMES exercise prescription and progression guidelines

Table 2. Sample personalised aerobic and resistance exercise programme prescribed as part of the Fit for Life programme

Table 3. Absolute scores and percentage change in measures of functional muscle strength and functional mobility. Changes in quality of life are reported as point change.

Figure Legend

Figure 1. Experimental design showing 4-week NMES intervention, 6-week NMES/voluntary exercise intervention, assessment time points, and treatment cycles.

Figure 2. Wearable neoprene garments and electrode placement

Table 1.

Time	Phase	Standard Progression (duration/on:off)	Session frequency (No. /week)
Wk 1	LF-NMES	15 min continuous	
	HF-NMES	15 min: 2 s ON: 15 s OFF	2
Wk 2	LF-NMES	20 min continuous	
	HF-NMES	15 min: 5 s ON: 15 s OFF	3
Wk 3	LF-NMES	25 min continuous	
	HF-NMES	15 min: 5 s ON: 10 s OFF	4
Wk 4	LF-NMES	30 min continuous	
	HF-NMES	15 min: 5s ON: 10 s OFF	5
Wk 5	LF-NMES	35 min continuous	
	HF-NMES	15 min: 5s ON: 10 s OFF	3 – 5
Wk 6	LF-NMES	35 min continuous	
	HF-NMES	15 min: 5s ON: 10 s OFF	3 – 5
Wk 7	LF-NMES	40 min continuous	
	HF-NMES	15 min: 5 s ON: 10 s OFF	3 – 5
Wk 8	LF-NMES	45 min continuous	
	HF-NMES	15 min: 5 s ON: 10 s OFF	3 – 5
Wk 9	LF-NMES	45 min continuous	
	HF-NMES	15 min: 5 s ON: 10 s OFF	3 – 5
Wk 10	LF-NMES	45 min continuous	
	HF-NMES	15 min: 5 s ON: 10 s OFF	3 – 5

Table 2.

Exercise	**Sets**	**Intensity (reps/time)**	
Motomed cycling	X1	8-10 mins	Gear II
Bicep curls	X2	20-30 each arm	Controlled eccentric phase
Standing balance*	X3	10-15 secs	Eyes closed
Sit to stand	X1	5-20	Bed height 18.5-19in
Shuttle walks*	X1	30-50 m	With frame
Knee extension	X2	10-20	5 sec hold
Overhead ball press	X2	10-20	2kg ball

*balance difficulties experienced week 3

Table 3.

Measure	Baseline	4 weeks	10 weeks	Change Baseline to 4 weeks (%) *	Change 4 weeks to 10 weeks (%) *
Physical function					
Timed up & go (s)	25.43	19.20	17.18	24*	10.5*
Sit to stand	6	7	8	17*	14*
Physical activity level					
Godin leisure score index	9	9	35	0*	288*
Quality of life					
Physical	13	27	47	14	34
Role	17	33	50	16	33
Emotional	58	58	50	0	-8
Cognitive	17	17	50	0	33
Social	83	83	83	0	0
Global QoL scale	50	67	50	17	0
Fatigue					
Global BFI	5.44	6.22	7.77	14*	25*

*Indicates % change. All other values based on point change

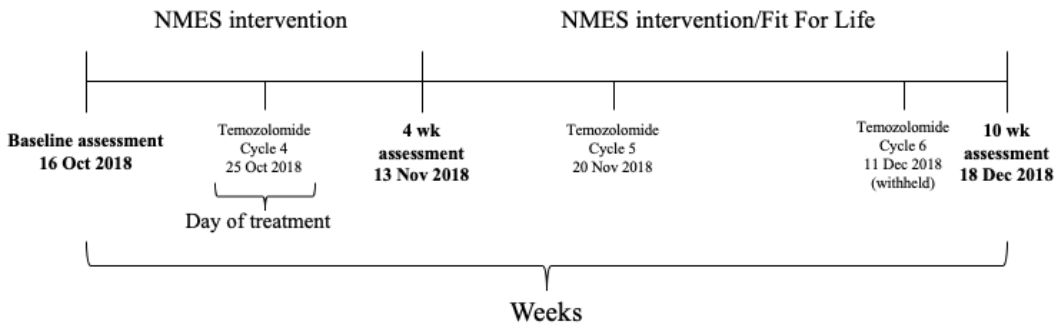
NMES intervention
NMES intervention/Fit For Life
Baseline assessment
16 Oct 2018
Temozolomide
Cycle 4
25 Oct 2018
Day of treatment
4 wk
assessment
13 Nov 2018
Temozolomide
Cycle 5
20 Nov 2018
Temozolomide
Cycle 6
11 Dec 2018
(withheld)
10 wk
assessment
18 Dec 2018
Weeks

Figure 1.

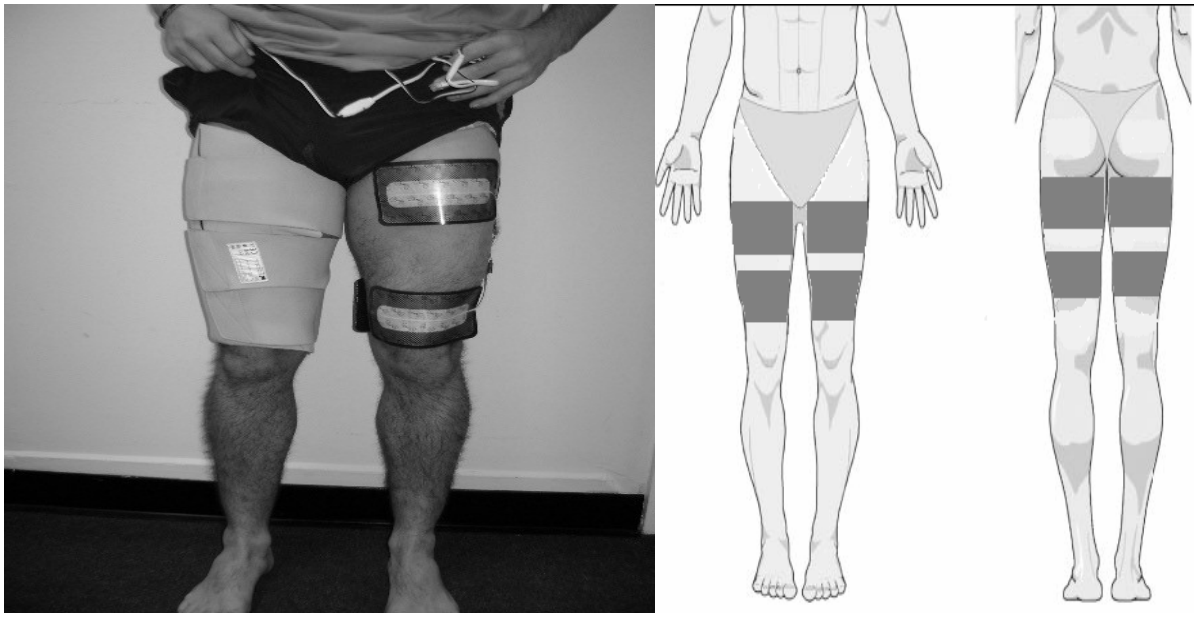

Figure 2.