2023

A feasibility, safety, and efficacy evaluation of supervised aerobic and resistance exercise for patients with glioblastoma undertaking adjuvant chemoradiotherapy

Anna K. Nowak

Robert U. Newton
Edith Cowan University

Travis Cruickshank

Prue Cormie

Georgia K. Halkett

See next page for additional authors

10.1093/nop/npad006

Nowak, A. K., Newton, R. U., Cruickshank, T., Cormie, P., Halkett, G. K., Tsoi, D., & Galvão, D. A. (2023). A feasibility, safety, and efficacy evaluation of supervised aerobic and resistance exercise for patients with glioblastoma undertaking adjuvant chemoradiotherapy. Neuro-Oncology Practice, 10(3), 261-270. https://doi.org/10.1093/nop/npad006

Neuro-Oncology Practice

10(3), 261–270, 2023 | https://doi.org/10.1093/nop/npad006 | Advance Access date 3 February 2023

A feasibility, safety, and efficacy evaluation of supervised aerobic and resistance exercise for patients with glioblastoma undertaking adjuvant chemoradiotherapy

Anna K. Nowak‡, Robert U. Newton‡, Travis Cruickshank, Prue Cormie, Georgia K.B. Halkett, Daphne Tsoi and Daniel A. Galvão

Medical School, University Western Australia, Perth, Western Australia, Australia (A.K.N.); Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia (A.K.N.); Exercise Medicine Research Institute, Edith Cowan University, Perth, Western Australia, Australia (R.U.N., T.C., D.A.G.); School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia (R.U.N., T.C., D.A.G.); School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Queensland, Australia (R.U.N.); Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia (P.C.); School of Nursing, Midwifery and Paramedicine, Curtin University, Perth, Western Australia, Australia (G.K.B.H.); St John of God Hospitals Subiaco and Murdoch, Perth, Western Australia, Australia (D.T.);

Corresponding Author: Robert U. Newton, PhD, Exercise Medicine Research Institute, Edith Cowan University, 270 Joondalup Drive, Joondalup, 6027 WA, Australia. (r.newton@ecu.edu.au).

‡Joint first authors.

Abstract

Background. While therapeutically effective, chemoradiotherapy treatment for high-grade glioma (glioblastoma) is often accompanied by side effects. Exercise has been demonstrated to alleviate the adverse effects of such treatments in other cancers. We aimed to evaluate the feasibility and preliminary efficacy of supervised exercise incorporating autoregulation.

Methods. Thirty glioblastoma patients were recruited, five declined exercise and 25 were provided with a multimodal exercise intervention for the duration of their chemoradiotherapy treatment. Patient recruitment, retention, adherence to training sessions and safety were evaluated throughout the study. Physical function, body composition, fatigue, sleep quality, and quality of life were evaluated before and after the exercise intervention.

Results. Eight of the 25 participants commencing exercise withdrew prior to completion of the study (32%). Seventeen patients (68%) demonstrated low to high adherence (33%–100%) and exercise dosage compliance (24%–83%). There were no reported adverse events. Significant improvements were observed for all trained exercises and lower limb muscle strength and function with no significant changes observed for any other physical function, body composition, fatigue, sleep, or quality of life outcomes.

Conclusions. Only half of glioblastoma patients recruited were willing or able to commence, complete or meet minimum dose compliance for the exercise intervention during chemoradiotherapy indicating the intervention evaluated may not be feasible for part of this patient cohort. For those who were able to complete the exercise program, supervised, autoregulated, multimodal exercise was safe and significantly improved strength and function and may have prevented deterioration in body composition and quality of life.

Keywords:

adherence | function | QOL | muscle | strength

High-grade gliomas (glioblastoma) are a devastating primary central nervous system malignancy that affects individuals of all ages. Treatment of glioblastoma patients typically involves surgical resection of the tumor, radiotherapy, and chemotherapy.[1] These treatments have been demonstrated to significantly improve median survival time in patients with grade III and IV glioblastoma.[1–4] However, significant side effects, including excessive fatigue, poor sleep, appetite loss, constipation, and physical function impairments occur during radiotherapy, and are more common and have an additional impact on quality of life during chemoradiotherapy.[2,5] Adjunctive therapies that counteract side effects are needed to improve function, quality of life, and potentially even treatment adherence and overall survival.

There is accumulating evidence that exercise can counteract the toxicities of radiotherapy and chemotherapy thereby improving physical function, fatigue, mood, quality of life, treatment adherence, and overall efficacy.[6,7] Studies in breast cancer patients undertaking chemotherapy have reported better sleep, body composition, mood, strength, aerobic capacity, and quality of life outcomes after exercise.[8–10] The positive effects of exercise during chemotherapy have also been documented in colorectal cancer patients with Waart et al.[11] reporting significant improvements in aerobic fitness and reduced fatigue in patients with colorectal cancer engaging in exercise during chemotherapy. Significant improvements in fatigue, mental health, muscle strength, balance, and quality of life have also been documented in ovarian cancer patients receiving exercise during chemotherapy.[12] Specific to brain cancers, there is evidence of improvements in quality of life, cardiorespiratory fitness and body composition in patients with grade II, III, and IV gliomas for exercise implemented as rehabilitation after chemoradiotherapy.[13,14]

Most recently, Eisenhut et al.[15] reported on the effects of aerobic training or resistance training compared to active control in patients with grade III and IV glioma undergoing chemoradiotherapy after neurosurgery. Interestingly they found superior benefits for aerobic training and active control compared to resistance training for depression, stress, and anxiety measures and neither of the exercise interventions improved physical fitness and actually increased fatigue.[15] This is in considerable contrast to previous findings briefly outlined above across a range of cancers during and after treatment and certainly necessitates further research into exercise as a medicine to combat unwanted side effects in glioblastoma patients undertaking chemoradiotherapy. Feasibility (recruitment, retention, safety, adherence compliance) to the exercise interventions was not reported by Eisenhut et al.[15] and this remains of clinical interest given that these patients are quite unwell.

There is limited and conflicting research into the therapeutic effects of exercise for glioblastoma patients undertaking radiotherapy and chemotherapy. The purpose of this study was to evaluate the feasibility and preliminary efficacy of a structured, multimodal, supervised exercise intervention for glioblastoma patients undertaking chemoradiation treatment.

Materials and Methods

Study Design

The present investigation was an exploratory study on the feasibility and preliminary efficacy of a structured exercise intervention on physical function, body composition, fatigue, sleep quality, and quality of life in individuals with high-grade glioma undertaking adjuvant chemoradiotherapy. The pilot study aimed to include at least 15 participants. Formal sample size calculations were deemed not necessary for this pilot feasibility study. Individuals enrolled in the study were assessed before and after the structured exercise intervention (~6 weeks).

Participants

Thirty patients with glioblastoma were recruited for this multisite trial by oncologists at Sir Charles Gairdner Hospital, St John of God Hospital Murdoch and Subiaco, and a study coordinator at Edith Cowan University over 21 months from April 2014 to December 2015. Inclusion criteria were as follows: (1) patients with glioblastoma scheduled to receive chemoradiotherapy; (2) the ability to understand written and verbal instructions; and (3) the capacity to perform aerobic and resistance training exercise as determined by the patient's oncologist in consultation with the clinical exercise physiologists. Exclusion criteria included: (1) Eastern Cooperative Oncology Group (ECOG) performance status >1 and (2) concomitant neurological, musculoskeletal, or cardiovascular disorders that would prevent exercise participation.

Study Approval, Registration, and Patient Consent

Ethical approval for this study was granted by Edith Cowan University, Sir Charles Gairdner Hospital, and St John of God Hospital Human Research Ethics Committees (11142, 2014-010, 690 respectively). Written informed consent was provided by all participants.

Study Procedures

Patients were evaluated at Edith Cowan University within 1 week of commencing and completing the chemoradiotherapy/multimodal exercise program. To ensure the reliability of collected data: (1) the same assessors were used at pre and post-testing sessions; (2) patients were assessed at the same time of day (within ± 2 h) at both testing time points; (3) patients were familiarized with testing procedures prior to administration; and (4) patients refrained from alcohol and mentally and physically exhausting activities 24 h prior to administration of test procedures.

Primary Outcome

Feasibility.——Feasibility was evaluated by examining patient recruitment, retention, safety, adherence, and compliance with the exercise program. The recruitment of patients for the exercise program was evaluated by assessing recruitment logs. The retention of patients was measured as the percentage of individuals who completed the intervention. Safety was evaluated by reviewing the incidence and severity of any adverse events which were recorded on a form completed by the supervising clinical exercise physiologist. Patient adherence (completed vs scheduled sessions) and compliance (prescribed vs actual exercise dosage completed) to the exercise program were evaluated using exercise logs recorded by clinical exercise physiologists and patients. The threshold for minimal exercise dosage compliance was set at 33%.

Secondary Outcomes

Body composition.——Dual-energy X-ray absorptiometry (DEXA) was used to examine changes in the whole body and regional lean tissue mass, fat mass, and fat percentage.[16]

Fatigue.——Changes in cancer-related fatigue was assessed using the functional assessment of chronic illness therapy-fatigue (FACIT-F).[17]

Physical function.——Cardiorespiratory endurance, muscular power, and muscular strength were examined using the 400-m walk test, 6-m walk test (normal, fast, and backwards), chair rise test and, a one-repetition maximum leg press test.[16]

Quality of life.——Quality of life was assessed using the Short Form 36 (SF-36) Version 2.[18]

Sleep quality.——Sleep quality was evaluated using the Pittsburgh Sleep Quality Index.[19]

Exercise Training Program

The exercise intervention was mixed mode comprised of both aerobic and resistance training. This design was informed by current guidelines[20] combined with our previous exercise trials in cancer patients[16,21] and was supervised by clinical exercise physiologists. Aerobic exercise training consisted of moderate to vigorous cardiovascular exercise (~60%–85% of estimated maximum heart rate) for 20 to 30 min on treadmill, cycle, and rowing ergometers. Resistance exercise training consisted of moderate to vigorous upper and lower body, isotonic machine-based resistance exercises (60%–85% of 1RM). Patients performed 6–12 repetitions of 2–4 sets for each resistance exercise. Once the patient could complete more than the prescribed number of repetitions the resistance was increased by 5%–10% for subsequent sets and sessions as tolerated. Training sessions were delivered in small groups (1–4 patients) twice weekly for 1 h at outpatient exercise clinics (specialist clinics with facilities and equipment for patient assessment and exercise medicine implemented by accredited exercise physiologists) across the Perth metropolitan area (northern, eastern, western, and southern quadrants). At each session, the patient was asked how they were feeling at the start and during the workout and the number of exercises, sets, repetitions and resistance would be adjusted accordingly, a process termed "autoregulation".[20]

Statistical Analysis

Demographic data are presented as means and standard deviations. Normality assumptions were assessed using Shapiro–Wilk tests. Changes in physical function, sleep quality, body composition, and quality of life outcomes was assessed using mean values pre and post intervention period with paired *t* tests. As this was a non-randomized, small-scale trial, a complete-case analysis was used. Statistical significance was set at $P \leq .05$. All statistical analyses were undertaken using IBM SPSS Version 25 (Armonk, NY, United States).

Results

Demographic descriptors of the patients are presented in table 1. Thirty patients, six women (20%), volunteered (age: mean 51.03 ± 2.32 years, median 53 [IQR = 43–63] years) and consented to participate in the study, and all had Grade IV glioma (glioblastoma). Of these, five agreed to undergo testing, but would not participate in the exercise intervention. Of the 25 that commenced the exercise intervention, eight withdrew (32%) prior to the post-intervention assessment time point due to side effects associated with radiotherapy and chemotherapy treatments, including nausea, excessive fatigue, bodily pain, and seizures. None withdrew due to exercise adverse events or other factors related to the exercise intervention or assessments. Patient and carer perspectives of the exercise program have been published elsewhere[22] reporting positive perceptions and experiences of participating in exercise during chemoradiotherapy; however, some challenges were experienced.[22]

Exercise Intervention Adherence and Compliance

Patients who commenced the exercise intervention and remained in the study to complete the post-intervention assessments ($N = 17$) demonstrated low (33%) to high (100%) adherence to the exercise training intervention as measured by the number of attempted and possible training sessions which varied for each patient due to time of recruitment and duration of treatment ranging 3/9 to 21/21 sessions. On average, study participants who completed the intervention attended 90% of their possible training sessions. Compliance with the prescribed exercise dosage also ranged from low (24%) to high (83%) with an average

Table 1. Demographics and Medications at Baseline

Outcome Measure	Recruited (n=30) Mean ± SD	No Exercise or Withdrew (*n* = 13) Mean ± SD	Completed (*n* = 17) Mean ± SD
Age (yr)	51.03 ± 2.32	47.61 ± 14.10	55.82 ± 8.90
Female, N (%)	6 (20.0%)	3 (23.1%)	5 (29.4%)
Married, N (%)	24 (80.0%)	12 (92.3%)	15 (88.2%)
Tertiary education, N (%)	10 (33.3%)	6 (46.2%)	6 (35.3%)
Height (cm)[a]	171.3 (166.3, 179.3)	169.0 (148.3, 189.8)	172.11 ± 7.62
Weight (kg)	81.70 ± 14.26	85.04 ± 17.39	80.21 ± 12.93
Corticosteroid use, N (%)	10 (33%)	4 (30.8%)	6 (35%)
No. of comorbidities	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.12 ± 0.39
Epilepsy	17 (56.7%)	6 (46.2%)	9 (52.9%)
Anti-epileptic medication	9 (30.0%)	7 (53.8%)	5 (29.4%)
Received combined chemoradiotherapy	30 (100%)	13 (100%)	17 (100%)

[a]Data were non-normally distributed; median and ± IQR are presented, Wilcoxon Signed Rank Test were applied.

for the group being 43%. Two patients did not meet the 33% threshold of prescribed exercise dosage compliance being 24% and 26% and one patient was borderline on 34%.

Adverse Events

There were no reported adverse events associated with the exercise intervention or assessments in this trial.

Changes in Secondary Outcomes

Throughout the intervention period, patients demonstrated significant improvements in most resistance exercises (figure 1). Participants also demonstrated a significant increase in 1RM leg press strength and improvement in repeated chair rise time pre to post intervention (table 2). No significant changes were observed for fatigue, sleep quality, body composition, quality of life and the remaining physical function outcome measures. Individual percentage changes for the physical function tests are presented in figure 2. A follow-up analysis was completed with the two patients who did not meet the minimum exercise dosage threshold removed. This resulted in significant mean improvement for 1RM leg press ($P = .000$), repeated chair rise ($P = .003$), 6 m usual walk ($P = .001$), and 6 m fast walk ($P = .008$).

Discussion

This study evaluated the feasibility and preliminary efficacy of a structured, multimodal exercise intervention for glioblastoma patients undertaking combination adjuvant therapy. There were three important findings: (1) only half of the patients recruited were willing or able to commence, complete or meet minimum dose compliance for the exercise intervention indicating that the intervention evaluated may not be feasible for a considerable portion of this patient cohort; (2) for those who completed the exercise program, adherence ranged between 33% and 100% (mean of 78%) and compliance to the prescribed exercise dosage ranged from 24% to 83% (mean of 43%); (3) both lower body muscle strength and chair rise performance improved over the intervention with no decline in body composition, fatigue, sleep quality, or quality of life; and (4) no serious study-related adverse events, including exercise-induced seizures were observed.

There are still no proven therapies that relieve or ameliorate side effects associated with chemoradiotherapy treatment for people with glioblastoma. Furthermore, corticosteroid use during chemoradiotherapy is common in this population (33% in current study) and is known to have adverse effects on sleep quality, to promote appetite and weight gain, as well as lead to the development of proximal myopathy.[23] Some of these side effects, including fatigue (33% experience grade 2 fatigue or above), insomnia, appetite loss, and constipation may be ameliorated or stabilized by exercise, although one study suggests both aerobic and resistance training may exacerbate fatigue in patients with high-grade glioma undergoing chemoradiation therapy.[15] While we did not observe positive effects for sleep, fatigue or quality of life outcomes following exercise training in this cohort of glioblastoma patients, it is noteworthy that these outcomes did not decline, which has been documented in observational studies.[24,25] The most probable reason is that the dose and/or mode of exercise training was not appropriate for improving these outcomes in high-grade glioma patients. It is also possible that exercise training is unable to improve these clinical outcomes in high-grade glioma patients. These tentative explanations need investigation in future studies.

The glioblastoma patients in this study demonstrated low (33%) to high (100%) adherence as measured by attendance at planned exercise training sessions with a group average of 78%. Previous studies by Baima et al.[14] and Gehring et al.[13] have reported adherence rates of 64% and 79% respectively for glioblastoma patients

Neuro-Oncology Practice

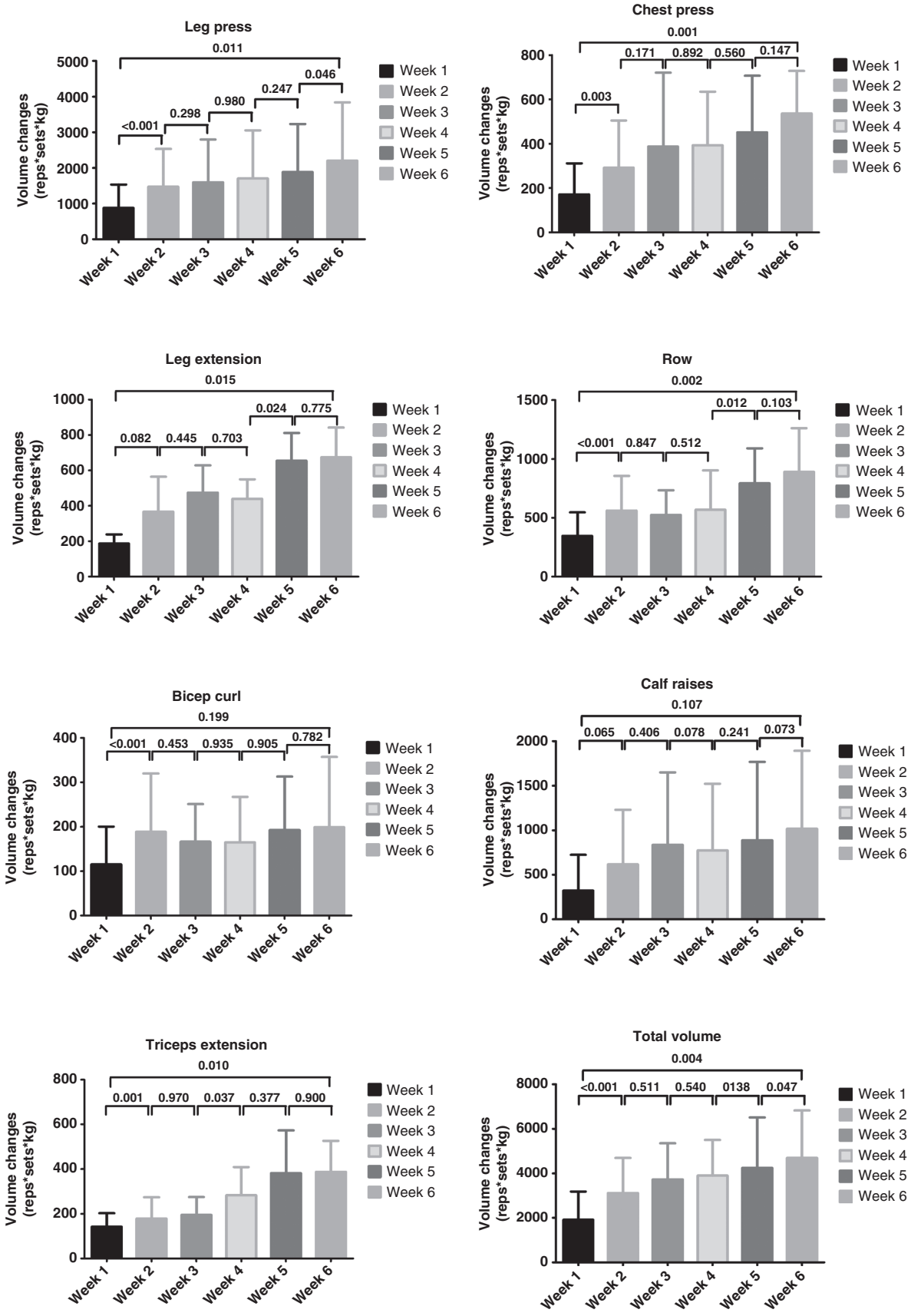

Fig. 1. Resistance training volume for individual exercises and total over the 6-week intervention.

Table 2. Changes in Secondary Outcomes

Outcomes Measure	Pretrial	Post-trial	*P*
Physical function			
1RM leg press (kg)[a]	103.6 ± 39.2	118.0 ± 47.6	**0.024**
Chair rise test (sec)[a]	10.70 ± 1.91	10.09 ± 2.22	**0.047**
400 M walk test (sec)[b]	230.4 (203.4, 264.3)	223.7 (205.8, 265.3)	0.778
6 M normal walk test (sec)[a]	4.38 ± 0.65	4.23 ± 0.68	0.319
6 M fast walk test (sec)[a]	3.07 ± 0.36	2.95 ± 0.50	0.105
6 M backwards walk test (sec)[a]	14.49 ± 6.15	14.73 ± 8.23	0.832
Body composition			
Lean tissue mass (kg)[a]	53.78 ± 9.68	53.60 ± 9.81	0.713
Fat mass (kg)[b]	22.86 (18.81, 26.41)	22.82 (18,61, 30.39)	1.000
Fat percentage (%)	29.82 ± 8.00	30.41 ± 8.48	0.293
Total mass (kg)[a]	80.74 ± 14.43	81.21 ± 14.78	0.466
Fatigue			
FACIT-F[a]	39.79 ± 5.75	37.43 ± 6.25	0.281
Sleep quality			
Pittsburgh sleep quality Index global score[a]	11.71 ± 6.2	11.21 ± 4.48	0.735
Health related quality of life[*]			
Physical functioning[b]	85.00 (60.00, 95.00)	85.00 (60.00, 100.00)	0.755
Role physical[a]	39.12 ± 23.44	48.75 ± 36.99	0.226
Bodily pain[b]	84.00 (74.00, 100.00)	84.00 (70.00, 100.00)	0.694
General health[a]	62.22 ± 22.33	60.52 ± 25.12	0.774
Vitality[a]	54.61 ± 17.87	46.67 ± 30.05	0.228
Social functioning[a]	58.61 ± 24.32	66.11 ± 28.39	0.199
Role emotional[b]	48.16 (34.69, 52.14)	45.30 (31.58, 58.29)	0.984
Mental health[a]	72.34 ± 19.13	72.12 ± 19.67	0.953
Physical component score[a]	46.78 ± 7.27	47.73 ± 8.51	0.608
Mental component score[a]	46.09 ± 10.79	45.90 ± 13.26	0.945

*All items on the SF-36 are scored such that a higher score denotes a more favorable health state.
aData were normally distributed; mean and ± standard deviation (SD) are presented, Paired *t* tests were applied.
bData were non-normally distributed; median and ± IQR are presented, Wilcoxon Signed Rank Test was applied.

undertaking short-term and long-term home-exercise interventions, albeit at different treatment timepoints. Compliance with the prescribed exercise dosage was also wide ranging from 24% to 83% (mean of 43%) and to the best of our knowledge this is the first study in glioblastoma patients to report actual dosage compliance. We have previously reported exercise dosage compliance of between 19% and 99% (mean of 77%) for prostate cancer patients with advanced bone metastatic disease over a 12 week intervention.[26] In another of our trials in patients with cancer of the pancreas undergoing chemotherapy, we reported compliance of 55% over 12 weeks of exercise.[27] The glioblastoma patients in the current study were undergoing chemoradiation however there appear to be other factors, likely declining health, contributing to their even lower average exercise dosage compliance. By comparison, a trial of home-based, virtually supervised exercise therapy in patients with type 2 diabetes resulted in 95% exercise compliance.[28] The exercise program was designed to be undertaken in groups to enhance peer support, motivation, and enjoyment. However, due to patient preference, symptoms, and availability, some patients completed some sessions on an individual basis which may have reduced adherence and compliance although it should be noted that all exercise sessions were supervised by a clinical exercise physiologist to support, monitor, and motivate the patients. Autoregulation was implemented in this trial whereby on a presentation for a given exercise session, the clinical exercise physiologist would consult with the patient to determine their capacity to exercise with regression or progression of the planned session. Although it was not possible to assess this empirically, this may have facilitated attendance and exercise dosage with the patient's knowledge that each exercise session could be adapted according to their physical and psychological "readiness" to train.

It should be noted that the number of men recruited to this study was four times that of women and yet the gender incidence of glioblastoma is 1.6 men to women.[29] The

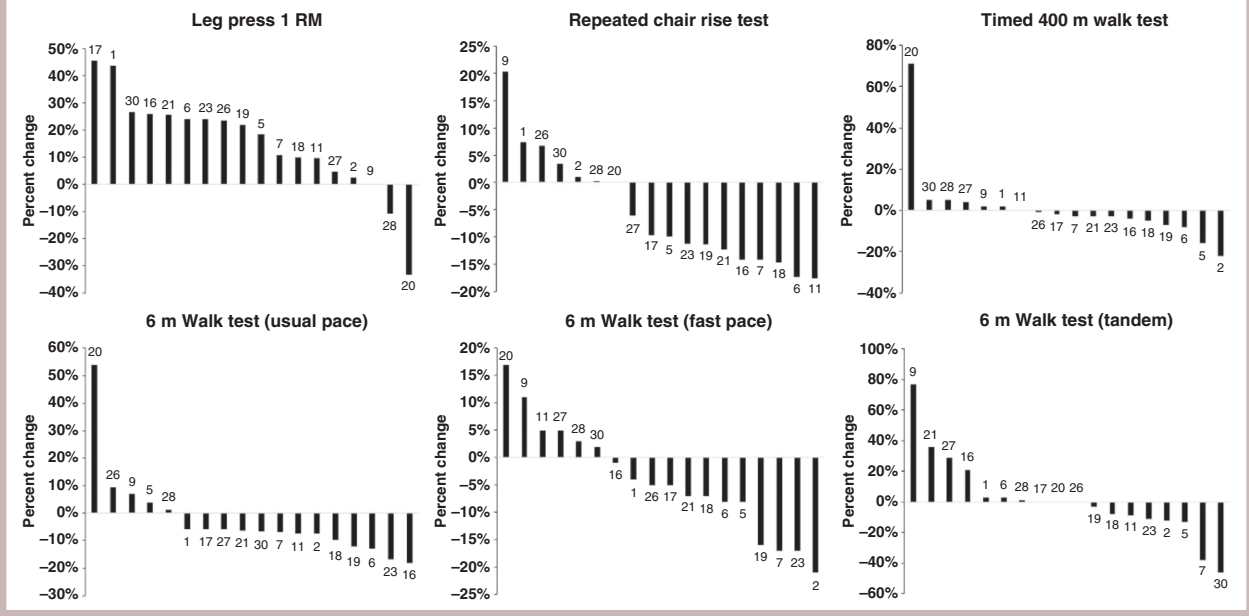

Fig. 2. Percentage change for individual participants for the functional capacity tests. *Note*: Patients #9 and #20 were excluded from secondary analysis.

reasons for this are highly speculative but may indicate a greater motivation of men with glioblastoma to engage in exercise training or alternatively a greater willingness of female carers to facilitate attendance at exercise training.

Importantly, there were no serious adverse events throughout the study. In particular, we observed no seizures during clinical testing or the moderate-intensity exercise intervention. This is of relevance as high-intensity exercise has been suggested to increase the likelihood of seizures. This finding together with previous reports indicate that clinic- and home-based exercise interventions are safe and well tolerated by glioblastoma patients during and after chemotherapy and radiation treatments, however adherence and compliance vary considerably, and this is likely indicative of patients who are less well and not tolerating the chemoradiation therapy. The question of feasibility is very much dependent on individual patient status. While all had the same grade of glioma (grade IV—glioblastoma) and were receiving very similar chemoradiation, some patients attended every scheduled exercise session and could comply with 83% of the exercise prescribed while others felt they could not exercise at all or completed as little as 24% of the exercise prescription, even though it was individualized to their capacity.

Whilst our small sample size and lack of a randomized comparator meant that we were unable to draw any firm conclusions from the quality of life results, we note that some quality of life parameters numerically improved (Role limitations due to physical health, Social functioning) whilst Vitality (energy/fatigue) numerically declined. This may lend further support to the findings of Eisenhut et al.[15] that ratings of fatigue by these patients receiving chemoradiation therapy might not be ameliorated by exercise, although this is speculative given the changes were not statistically significant. Inclusion of a comparator group in future trials will be key to understanding any impact of exercise on maintaining or reducing deterioration in quality of life during treatment. It should be reiterated that all of the patients were undergoing therapy that is reported to result in clinically significant declines in quality of life, strength, and physical function[2,5] so the finding of no such decline in the current study is encouraging. However, as can be observed from figure 2, some patients did decline in several of the physical function tests and two of these, patient #9 and patient #20 were below the compliance threshold. It is likely that worsening health and increasing side-effects of treatment are impacting and the low dose of exercise is insufficient to ameliorate.

Deficits in muscle strength are common and contribute to physical impairments in glioblastoma patients. Keilani et al.[30] have previously reported significant deficits of strength in quadriceps and hamstring muscle groups and associated impairments in physical function in glioblastoma patients after chemoradiation. We found that exercise significantly improves muscle strength in glioblastoma patients undertaking chemoradiation as assessed by maximal leg press, a highly functional benefit and this was further evidenced by the improvement in repeated chair rise performance. Our glioblastoma patients also demonstrated a significant increase in total volume lifted during training sessions indicating they were adapting to the training stimulus and increasing their exercise capacity. This is the first study to demonstrate muscle strength gains in this patient population, an important clinical outcome. Eisenhut et al.[15] reported no change in maximal strength although this was assessed by handgrip which might not be reflective of training adaptations.

The exercise program did not alter body composition in these glioblastoma patients, such as lean tissue mass, which has been previously reported to increase in patients with prostate[31] and breast cancer[6] as a result of resistance exercise. This is possibly due to insufficient exercise dosage over such a short intervention (6 weeks) however, it is important to note that muscle mass did not decrease as is typical for cancer patients over the course of chemotherapy and/or radiation therapy[32] including those with glioblastoma.[33] It could also be theorized that the treatments the patients are receiving, particularly corticosteroids, may interfere with their ability to increase muscle mass, so it remains possible that if studied for a longer period, participants might have exhibited a measurable increase in muscle mass. Future trials of longer duration and larger sample sizes are required to elucidate this. Toxicities of chemoradiation accumulate and so the greatest negative impact would be expected at the 6-week assessment in patients under usual care. The exercise program appears to have ameliorated declines, but it would have been interesting to continue the intervention post-treatment for rehabilitation as larger improvements may have been observed.

The exercise program implemented was mixed mode incorporating both aerobic and resistance training. We have recently reported compromised muscle hypertrophy in men with prostate cancer receiving hormone therapy on a similar combination program compared to those not performing any aerobic exercise.[31] It is possible that the "interference effect" of aerobic exercise suppressing the hypertrophic drive of resistance training[34] is evident in patients with glioblastoma undertaking chemoradiation. This postulation certainly requires further investigation as maintaining or increasing muscle mass in patients with glioblastoma may be a priority over cardiorespiratory fitness. In particular, for those patients with or at risk of sarcopenia, given low muscle mass is associated with greater treatment toxicities, side effects and dosage reduction[35] as well as poorer survival[36] exercise prescription of resistance training only may be more beneficial for improvement in body composition, strength and function as well as potentially better compliance due to lower patient burden.

With the secondary analysis omitting the two patients below exercise dosage threshold, there was a significant improvement in 6 m normal and fast walking speed, but no other significant changes. Walking ability over the longer distance of 400 m did not change and this was unexpected given the aerobic training conducted which even included walking exercise but this has been observed in this population in other research.[15] Our findings are nevertheless still clinically relevant. Previous studies have reported reduced cardiorespiratory endurance and muscular power in patients with glioblastoma as a result of treatment.[37] We found no evidence of deterioration of these performance qualities during treatment in our study participants. This finding suggests that regular exercise engagement whilst undertaking chemoradiation may prevent a treatment-related decline in physical function and cardiorespiratory endurance which is an important outcome of this study. As a consequence, this may explain why quality of life was preserved in these patients rather than the declines previously reported to result from chemotherapy and/or radiation therapy.[38] However, additional randomized controlled studies are needed to confirm these conclusions.

It is noteworthy that this study had a high dropout rate, with 32% percent of recruited participants withdrawing prior to the completion of the study. Participant dropout was attributed to side effects associated with chemoradiation treatments, including nausea, excessive fatigue, bodily pain, and seizures. This figure is higher than previously reported work, in particular a home-based aerobic exercise study reported a dropout rate of 10.6% over a six-month period[13] and supervised aerobic (10.0%) or resistance exercise (9.1%).[15] The notably higher dropout rate in the present study may be attributed to the inclusion of patients with greater disease severity. In particular, the present study only included participants with high-grade glioma, whereas Gehring et al.[13] included a large percentage of participants with low-grade glioma (64% of the cohort) and Eisenhut et al.[15] with 24% grade III and 76% grade IV. It is possible that exercise interventions are less feasible for individuals with high-grade glioma due to mitigating disease and treatment-related symptoms, including nausea, fatigue, pain, and seizures. The higher dropout rate observed in the present study may also be explained by different exercise delivery methods. Gehring et al.[13] delivered aerobic exercise sessions remotely in the home environment, whereas the present study delivered exercise sessions in specialized exercise oncology clinics. Delivery of exercise in the home environment rather than a specialist center may enhance the feasibility of exercise by reducing the travel and time burden for glioma patients. Eisenhut et al.[15] implemented supervised single-mode exercise of either aerobic or resistance training so it may be that the multimodal intervention in the current study was excessive for some participants. The aforementioned points and observations are relevant for clinical practice and health service delivery and suggest that home-based exercise is more feasible for glioma patients and exercise prescription may need to be more nuanced, although this needs to be explored more thoroughly in high-grade glioma patients.

Several limitations and strengths must be considered when interpreting our findings. First, we did not include a control group, which limits our ability to draw definitive conclusions on the utility of exercise to ameliorate treatment-related adverse effects in glioblastoma patients. Second, our findings were derived from a small sample of glioblastoma patients limiting the generalizability of our findings to the wider glioblastoma community. Third, half of the patients could not complete or did not meet compliance threshold to the exercise program limiting our ability to detect the meaningful effects of the exercise. Fourth, it is likely that both referring physicians and patients exhibited selection bias toward participation in an exercise trial and so this sample may not be representative of the patient population. Strengths of the study include the uniqueness of this clinical population undertaking chemoradiation treatments and that we were even able to recruit 30 patients with grade IV brain cancer to an exercise trial. We are the first to report improved strength and physical function as well as feasibility through in-depth analysis of patient recruitment,

retention, safety, adherence and compliance, including true exercise dosage.

Conclusion

Our findings can be interpreted as initial evidence that this supervised, multimodal, autoregulated, exercise intervention delivered during chemoradiation is feasible for around half of the patients and appears to be safe when delivered in an exercise clinic under professional supervision. Furthermore, exercise as implemented improves muscle strength and functional capacity in particular for those patients that complete a minimum exercise dosage. Further, the exercise program might prevent deterioration in fatigue, sleep, body composition, physical function, and quality of life in glioblastoma patients during a period of chemoradiation. Future randomized controlled trials with larger sample sizes, more sophisticated and targeted exercise prescriptions with different modes, dosages, settings, and supervision are required to confirm and expand on these findings in particular to address compliance and feasibility.

Acknowledgment

We acknowledge assistance from clinicians with patient recruitment (Dr Anne Long, Dr Arman Hasani). We gratefully acknowledge funding from the Sir Charles Gairdner Hospital Research Advisory Committee which made this work possible. We also acknowledge the participants and their families for their time and involvement in this study.

Funding

No external funding for this work was provided.

Conflict of Interest

Anna Nowak reports research funding to institution (AstraZeneca, Douglas Pharmaceuticals); Consultant or advisory positions (Bayer pharmaceuticals, Roche Pharmaceuticals, Boehringer Ingelheim, Merck Sharp Dohme, Douglas Pharmaceuticals, PhaarmAbcine); and Travel funding (Boehringer Ingelheim, AstraZeneca).

Prue Cormie is the Founder and Director of EX-MED Cancer Ltd, a not-for-profit organization that provides exercise medicine services to people with cancer. Prue Cormie is the Director of Exercise Oncology EDU Pty Ltd, a company that provides fee for service training courses to upskill /.;;/;. exercise professionals in delivering exercise to people with cancer.

Robert Newton reports research funding to institution (Abbvie, AstraZeneca, Ipsen Pharmaceutical Pty) and Travel funding (Abbvie).

References

1. Stupp R, Brada M, Van Den Bent M, et al. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2014;25(suppl_3):iii93–iii101.
2. Stupp R, Mason WP, Van Den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987–996.
3. Stupp R, Hegi ME, Mason WP, et al; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10(5):459–466.
4. van den Bent MJ, Baumert B, Erridge SC, et al. Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. *Lancet.* 2017;390(10103):1645–1653.
5. Taphoorn MJ, Stupp R, Coens C, et al; European Organisation for Research and Treatment of Cancer Brain Tumour Group. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. *Lancet Oncol.* 2005;6(12):937–944.
6. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol.* 2007;25(28):4396–4404.
7. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. *J Clin Oncol.* 2015;33(17):1918–1927.
8. McNeely ML, Campbell KL, Rowe BH, et al. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *Can Med Assoc J.* 2006;175(1):34–41.
9. Courneya KS, Segal RJ, McKenzie DC, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med Sci Sports Exerc.* 2014;46(9):1744–1751.
10. Courneya KS, McKenzie DC, Mackey JR, et al. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst.* 2013;105(23):1821–1832.
11. van Waart H, Stuiver MM, van Harten WH, et al. Recruitment to and pilot results of the PACES randomized trial of physical exercise during adjuvant chemotherapy for colon cancer. *Int J Colorectal Dis.* 2018;33(1):29–40.
12. Mizrahi D, Broderick C, Friedlander M, et al. An exercise intervention during chemotherapy for women with recurrent ovarian cancer: a feasibility study. *Int J Gynecol Cancer.* 2015;25(6):985–992.
13. Gehring K, Kloek CJ, Aaronson NK, et al. Feasibility of a home-based exercise intervention with remote guidance for patients with stable grade II and III gliomas: a pilot randomized controlled trial. *Clin Rehabil.* 2018;32(3):352–366.
14. Baima J, Omer ZB, Varlotto J, et al. Compliance and safety of a novel home exercise program for patients with high-grade brain tumors, a prospective observational study. *Support Care Cancer.* 2017;25(9):2809–2814.
15. Eisenhut L, Sadeghi-Bahmani D, Gerber M, et al. Effects of two types of exercise training on psychological well-being, sleep and physical fitness in patients with high-grade glioma (WHO III and IV). *J Psychiatr Res.* 2022;151:354–364.

16. Newton RU, Taaffe DR, Spry N, et al. A phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer. *BMC Cancer*. 2009;9:210.
17. Peters KB, West MJ, Hornsby WE, et al. Impact of health-related quality of life and fatigue on survival of recurrent high-grade glioma patients. *J Neurooncol*. 2014;120(3):499–506.
18. Bosma I, Reijneveld JC, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. *Neuro Oncol*. 2009;11(1):51–58.
19. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
20. Hayes SC, Newton RU, Spence RR, et al. The Exercise and Sports Science Australia position statement: exercise medicine in cancer management. *J Sci Med Sport*. 2019;22(11):1175–1199.
21. Galvao DA, Taaffe DR, Spry N, et al. Exercise preserves physical function in prostate cancer patients with bone metastases. *Med Sci Sports Exerc*. 2018;50(3):393–399.
22. Halkett GKB, Cormie P, McGough S, et al. Patients and carers' perspectives of participating in a pilot tailored exercise program during chemoradiotherapy for high grade glioma: a qualitative study. *Eur J Cancer Care (Engl)*. 2021;30(5):e13453.
23. Armstrong TS, Ying Y, Wu J, et al. The relationship between corticosteroids and symptoms in patients with primary brain tumors: utility of the Dexamethasone Symptom Questionnaire-Chronic. *Neuro Oncol*. 2015;17(8):1114–1120.
24. Perry JR, Laperriere N, O'Callaghan CJ, et al; Trial Investigators. Short-course radiation plus temozolomide in elderly patients with glioblastoma. *N Engl J Med*. 2017;376(11):1027–1037.
25. Flechl B, Sax C, Ackerl M, et al. The course of quality of life and neurocognition in newly diagnosed patients with glioblastoma. *Radiother Oncol*. 2017;125(2):228–233.
26. Fairman CM, Nilsen TS, Newton RU, et al. Reporting of resistance training dose, adherence, and tolerance in exercise oncology. Article. *Med Sci Sports Exerc*. 2020;52(2):315–322.
27. Luo H, Galvao DA, Newton RU, et al. Evaluation of a clinic-based exercise program in patients with pancreatic cancer undergoing nonsurgical treatment. *Med Sci Sports Exerc*. 2023;55(1):9–19.
28. Scott SN, Shepherd SO, Andrews RC, et al. A multidisciplinary evaluation of a virtually supervised home-based high-intensity interval training intervention in people with type 1 diabetes. *Diabetes Care*. 2019;42(12):2330–2333.
29. Carrano A, Juarez JJ, Incontri D, et al. Sex-specific differences in glioblastoma. *Cells*. 2021;10(7). doi:10.3390/cells10071783.
30. Keilani M, Krall C, Marosi C, et al. Strength of skeletal muscle and self-reported physical performance in Austrian glioblastoma-patients. *Wien Klin Wochenschr*. 2012;124(11-12):377–383.
31. Newton RU, Galvao DA, Spry N, et al. Exercise mode specificity for preserving spine and hip bone mineral density in prostate cancer patients. *Med Sci Sports Exerc*. 2019;51(4):607–614.
32. Lonkvist CK, Vinther A, Zerahn B, et al. Progressive resistance training in head and neck cancer patients undergoing concomitant chemoradiotherapy. *Laryngoscope Investig Otolaryngol*. 2017;2(5):295–306.
33. Bertoli S, Battezzati A, Petruzzi A, et al. Anthropometrics and body composition in adults with high-grade gliomas: effects of disease-related variables. *Nutr Cancer*. 2018;70(3):431–440.
34. Wilson JM, Marin PJ, Rhea MR, et al. Concurrent training: a meta-analysis examining interference of aerobic and resistance exercises. *J Strength Cond Res*. 2012;26(8):2293–2307.
35. Pin F, Couch ME, Bonetto A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. *Curr Opin Support Palliat Care*. 2018;12(4):420–426.
36. Cespedes Feliciano EM, Chen WY, Lee V, et al. Body composition, adherence to anthracycline and taxane-based chemotherapy, and survival after nonmetastatic breast cancer. *JAMA Oncol*. 2020;6(2):264–270. doi:10.1001/jamaoncol.2019.4668
37. Jones LW, Friedman AH, West MJ, et al. Quantitative assessment of cardiorespiratory fitness, skeletal muscle function, and body composition in adults with primary malignant glioma. *Cancer*. 2010;116(3):695–704.
38. Kassam Z, Mackay H, Buckley CA, et al. Evaluating the impact on quality of life of chemoradiation in gastric cancer. *Curr Oncol*. 2010;17(4):77–84.