Case Study

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Exercise Improves Physical Function and Mental Health of Brain Cancer Survivors: Two Exploratory Case Studies

Gregory T. Levin, PhD[1,2], Kenneth M. Greenwood, PhD, DPsych[2,3], Favil Singh, PhD[2], Daphne Tsoi, MBBS, MSc, FRACP[4], and Robert U. Newton, PhD[2]

Abstract

Background. Malignant brain tumors are unpredictable and incurable, with 5-year survival rates less than 30%. The poor prognosis combined with intensive treatment necessitates the inclusion of complementary and supportive therapies that optimize quality of life and reduce treatment-related declines in health. Exercise therapy has been shown to be beneficial in other cancer populations, but no evidence is available for brain cancer survivors. Therefore, we report results from 2 preliminary cases. *Methods*. Two female patients diagnosed with glioblastoma multiforme and oligodendroglioma participated in a structured and supervised 12-week exercise program. The program consisted of two 1-hour resistance and aerobic exercise sessions per week and additional self-managed aerobic sessions. Outcome measures of strength, cardiovascular fitness, and several psychological indicators (depression, anxiety, and quality of life) were recorded at baseline, after 6 weeks and at the conclusion of the intervention. *Results*. Exercise was well tolerated; both participants completed all 24 sessions and the home-based component with no adverse effects. Objective outcome measures displayed positive responses relating to reduced morbidity. Similar positive responses were found for psychological outcomes. Scores on the Hospital Anxiety and Depression Scale showed clinically meaningful improvements in depression and total distress. *Conclusion*. These findings provide initial evidence that, despite the difficulties associated with brain cancer treatment and survivorship, exercise may be safe and beneficial and should be considered in the overall management of patients with brain cancer.

Keywords

neuro-oncology, depression, anxiety, exercise oncology, comprehensive cancer care

Introduction

Brain cancer is a devastating and highly debilitating form of cancer. In 2014, there were an estimated 23 000 new cases of brain and nervous system cancers in the United States alone.[1] This number is fairly low compared to the incidence of breast or prostate cancer but is particularly challenging because of the poor prognosis for brain tumors; approximate 5-year survival rates are less than 30%,[2] and there is a mean survival time of approximately 15 months for glioblastoma, the most common malignant brain tumor.[3] Moreover, brain cancer is one of very few tumor sites that have not seen a decline in mortality over the past 20 years.[4]

The impact of brain cancer and its associated treatments often results in impaired physical capabilities, mild or major cognitive dysfunction, and compromised psychological well-being.[5,6] Therefore, adjuvant and supportive care that facilitates an improved quality of life and reduces these adverse effects should be considered for brain cancer survivors (we use the term *survivor* in accordance with the definition by National Coalition for Cancer Survivorship as someone who has been diagnosed with cancer and is still alive, regardless of the stage of their disease or the treatment that they are receiving).[7] A large body of evidence has emerged to support the prescription of exercise as a therapeutic and supportive form of care for cancer survivors. Indeed, the American College of Sports Medicine (ACSM) and the American Cancer Society (ACS) are among the many international organizations that have specific exercise guidelines for cancer survivors.[8,9] These guidelines were,

[1]University of Calgary, AB, Canada
[2]Edith Cowan University, Perth, WA, Australia
[3]Capital Medical University, Beijing, PRC
[4]St John of God Hospital, Subiaco, WA, Australia

Corresponding Author:
Gregory T. Levin, Cumming School of Medicine, Department of Oncology, University of Calgary, Holy Cross Site, 2202 2nd St, S W Calgary, AB T2S 3C1, Canada.
Email: gregory.levin@ucalgary.ca

however, compiled from research outcomes comprising breast, prostate, colon, hematological, and gynecological cancers. Therefore, the potential beneficial impact of exercise for brain cancer survivors remains unknown. Nonetheless, previous research has pointed toward a relationship between exercise engagement and survival time in recurrent glioma patients.[10] Additionally, Cormie et al[11] recently presented a theoretical perspective of the potential impacts of including exercise as a form of supportive care for neuro-oncology survivors.

Therefore, this report aims to contribute to empirical evidence by describing the outcomes of 2 distinct case studies of brain cancer survivors who undertook a 12-week structured and supervised exercise program by highlighting clinically important outcomes, including the ability to tolerate and adhere to the exercise program.

Methods

Participants

Two case studies have been drawn from a larger feasibility trial that aimed to examine exercise for the management of depression in depressed cancer survivors.[12] These were the only 2 brain cancer survivors within the trial who met inclusion criteria for participation: (1) able to understand written English; (2) able to walk 400 m unassisted; (3) family physician consent confirming no musculoskeletal, cardiovascular, or neurological limitations; and (4) elevated depressive symptoms at baseline. This case study examination is unique because the 2 participants were diagnosed with different brain tumors and were at various stages within their cancer care continuum. Participant A (58 years old, 163 cm, 66.4 kg, 62 months postdiagnosis) was first diagnosed with low-grade glioma in the right frontal lobe in 2007, which was treated with surgical resection. She underwent repeat resection in 2012 for recurrent disease followed by radiotherapy. Her disease at this time transformed to grade III anaplastic oligodendroglioma. On commencement of the exercise program, her medications included thyroxine, lamotrigine, sertraline, calcium, and latanoprost. Participant A was 288 months postdiagnosis for clinical depression and had a history of pharmacotherapy and psychotherapy, including current antidepressant medication. Participant B (61 years old, 164 cm, 59.4 kg, 5 months postdiagnosis) was diagnosed with right frontal lobe glioblastoma multiforme in December 2012. She received standard treatment consisting of surgical excision followed by concurrent radiotherapy with temozolomide chemotherapy. She developed progressive disease despite these treatments. She was receiving intravenous bevacizumab fortnightly when she entered the exercise trial. Her other medications included levetiracetam, dexamethasone, omeprazole, vitamin D, and temazepam. Participant B had not been clinically diagnosed with depression but presented with severe symptomatology according to the Hospital Anxiety and Depression Scale (HADS; see Table 1). Neither participant had any other diagnosed illness or chronic disease. Both were female, married, and educated to a bachelor's degree level. Both participants were supportive of the research and provided written informed consent.

Exercise Intervention

A 12-week exercise intervention, performed twice weekly, was supervised by an accredited exercise physiologist. Each supervised exercise session consisted of 20 minutes of moderate to vigorous aerobic exercise (eg, treadmill, cycling ergometer, rowing ergometer) and 40 minutes of resistance training. The resistance training targeted all the major upper- and lower-body muscle groups, using the following 9 exercises: chest press, leg press, lateral pulldown, knee extension, knee flexion, seated row, lateral shoulder raises, step up, and bicep curls. The load of external resistance was established in the first 2 weeks and subsequently increased to ensure that the participants always performed at a specified intensity. In the first 2 weeks, participants performed 2 sets of 12 repetitions (2×12), followed by 3×10 for 4 weeks, 3×8 for 3 weeks, and 4×6 for the final 3 weeks. The 2 supervised exercise sessions were supplemented with additional home-based aerobic exercise. Participants were encouraged to accumulate a total of 150 minutes of aerobic exercise, not including their 2 resistance training sessions, to meet recommended physical activity guidelines of 150 min/wk.[8] A home-based activity log was provided at baseline and monitored regularly.

Outcome Measures

Objective physical and physiological measures, along with subjective patient-reported outcomes (PROs), were recorded at baseline, after 6 weeks, and again after completion of the 12-week program. All measures were collected in a single 90-minute session at the university health and wellness institute. All measures were taken in the same order at each testing session.

Physical and Physiological Measures

Aerobic adaptations. To examine cardiovascular adaptations to exercise, oxygen consumption (VO_2) and heart rate (HR) responses were measured during the first 2 stages of a modified Bruce Treadmill protocol.[13] These stages correspond to velocities of 2.7 and 4.0 km/h at gradients of 10% and 12%, respectively. Oxygen uptake was measured through indirect calorimetry (Parvo Metabolic Measuring System, Sandy, UT). Additionally, the participants performed a 400-m long corridor walk test, which can be used as a measure of physical function and act as a surrogate

Table 1. Outcome Measures Reported for Each Assessment Point for Both Participants.

	Participant A			Participant B		
	Baseline	6 Weeks	12 Weeks	Baseline	6 Weeks	12 Weeks
VO_2 (ml/kg/min)						
Rest	3.45	5.36	4.99	5.47	4.78	5.45
Stage 1	14.51	15.56	13.75	15.13	15.34	15.65
Stage 2	22.32	21.35	19.27	20.79	18.91	20.32
Heart rate (bpm)						
Rest	79	74	72	93	81	74
Stage 1	101	97	93	103	96	86
Stage 2	119	115	111	110	109	103
Functional fitness						
400 m walk (s)	258.6	251.8	248.7	250.5	241.6	231.3
Strength (kg)						
Chest press 1-RM	17.5	20.0	20.0	12.5	17.5	20.0
Leg press 1-RM	76.5	76.5	90.0	49.5	58.5	72.0
Body composition						
Lean mass (kg)	39.1	38.1	36.9	36.5	36.5	37.9
Fat mass (kg)	25.3	25.7	26.1	21.4	19.8	18.7
Percentage body fat (%)	38.0	39.0	40.1	35.9	34.1	32.0
MHC: SF-36	34.70	28.91	33.68	27.39	28.64	54.77
PHC: SF-36	47.52	46.86	50.65	46.24	41.51	38.36
HADS	23	18	14	24	27	13
HADS-D	10	8	6	12	15	6
HADS-A	13	10	8	12	12	7
SWLS	11	19	29	7	5	17
CASES	115	119	149	110	111	156
PSQI	16	17	12	12	14	15
Exercise engagement						
Total (min/wk)	240	405	220	180	250	450
Exercise intensity (min/wk)						
Mild	0	105	100	60	90	315
Moderate	60	60	0	120	160	135
Strenuous	180	240	120	0	0	0

Abbreviations: VO_2, oxygen consumption; bpm, beats per minute; 1-RM, 1 repetition maximum; MHC, mental health composite; PHC, physical health composite; SF-36, Short Form 36; HADS, Hospital Anxiety and Depression Scale; HADS-D, HADS depression subscale; HADS-A, HADS anxiety subscale; SWLS, Satisfaction with Life Scale; CASES, Cancer Self-Efficacy Scale; PSQI, Pittsburgh Sleep Quality Index.

measure of aerobic capacity.[14,15] Performance was assessed by measuring the time taken to complete this task.

Muscle strength and body composition. Maximal concentric muscle strength was assessed for the upper (chest press) and lower (leg press) body using the 1 repetition maximum (1-RM) method.[16] Participants performed a graded warm-up consisting of one set of 6 repetitions at a light weight, followed by a second set of 3 lifts at a heavier weight. Thereafter, single lift sets were performed until reaching the 1-RM; the weight that could be lifted only once with correct form and technique.[14] All 1-RMs were determined within 5 attempts. Changes in total body lean muscle and fat mass composition and percentage body fat were assessed using dual energy X-ray absorptiometry (DXA, Hologic Discovery A, Waltham, MA).

Patient-Reported Outcomes. Several well-validated questionnaires examined psychosocial outcomes. Measures included quality of life, depression, anxiety, total distress, satisfaction with life, cancer-specific self-efficacy, and sleep quality.

Quality of life was recorded using the Short Form-36 v2 (SF-36),[17] which comprises 8 subscales of the SF-36, and the 2 composite scores of physical (PHC) and mental (MHC) health are reported. These composite scores are presented for comparison to the normalized mean *T* score of 50 and a standard deviation of 10.[18] Depression (HADS-D), anxiety (HADS-A), and total distress were all recorded using the HADS.[19] Although the HADS is a single 14-question scale, the use of the individual subscales to assess anxiety and depression independently is well supported.[20] Satisfaction with life was measured using the brief 5 questions of the

Satisfaction With Life Scale (SWLS).[21] The ability to manage living with cancer was measured using the Lewis Cancer Self-Efficacy Scale (CASES).[22,23] This questionnaire comprises 17 items (eg, "I am able to manage what is being asked of me despite the cancer") that are scored on an 11-point Likert scale ranging from 0 (*not at all confident*) to 10 (*very confident*). In accordance with the authors' instructions, participants were asked to rate their level of confidence to manage or cope with cancer-related problems for that particular day. Higher scores represent increased self-efficacy. Finally, the Pittsburgh Sleep Quality Index (PSQI), which measures sleep outcomes over the previous 1-month period was used to assess changes in sleep quality.[24]

Physical Activity and Exercise Adherence. A modified version of the Godin Leisure Time Exercise Questionnaire was used to determine physical activity levels.[25] This questionnaire asks participants to record how often they performed exercise in the previous week and to categorize the intensity of each session as mild, moderate, or strenuous. Two modifications were made to the original questionnaire to accurately quantify exercise activity. First, the minimum time requirement was lowered from 15 to 10 minutes, which is more in line with current exercise guidelines suggested by the ACSM.[26] Second, the average duration of each session was reported. These changes allowed for the determination of whether an individual was meeting international physical activity guidelines for cancer survivors.[8] Exercise adherence was measured by comparing the total number of sessions attended with the number scheduled over the 12 weeks.

Results

Objective assessments showed improvements in physical health indicators in both participants; however, the patterns of improvement were not always similar (Table 1). Both participants showed an improvement in cardiovascular efficiency demonstrated by the comparatively lower HR at each stage across time and a reduction in time to complete the 400-m walk test. However, they displayed variable oxygen consumption responses. Maximal strength, summed as the total of the upper- and lower-body exercise tests, increased by 17% and 48%, regardless of the variable body composition responses. Subjective PROs also varied between the 2 participants. However, over the entire 12-week program, there was a consistent improvement for all mental health outcomes. Both participants showed clinically meaningful reductions in depression, anxiety, and total distress, reducing symptomatology below cutoff scores used to represent clinical caseness.[27] This change occurred with concomitant increases in satisfaction with life (SWLS) and cancer coping self-efficacy (CASES). Little change was noted for sleep quality, and both participants consistently reported scores above 5, which is used to indicate sleep disturbance.[24]

It is important to note that no adverse events occurred throughout the intervention. Both participants demonstrated 100% adherence, attending all 24 scheduled sessions. Furthermore, participant A completed an additional 35 home-based aerobic sessions, 16 in the first 6 weeks and 19 in the following 6 weeks. Participant B completed an additional 44 sessions over the 12 weeks, 22 in each 6-week period. Both participants were highly active at baseline, but still managed to increase their exercise engagement for the first 6 weeks; thereafter, participant A declined below baseline levels, whereas participant B continued to increase, more than doubling her total physical activity minutes compared with baseline levels.

Discussion

The aim of this report was to examine whether a 12-week structured and supervised exercise program was beneficial and of clinical benefit within a supportive care framework for cancer survivors with brain tumors. Two unique participants, who presented with common tumors and at vastly different stages of prognoses, participated in a similar exercise program, individualized only by intensity but not by exercise selection. The results achieved by both participants present initial evidence indicating that physical and mental health is enhanced after commencing a supervised, structured, and professionally led exercise program.

In line with expectations from a structured and supervised exercise program, both participants increased muscle strength and cardiovascular fitness. These findings are clinically important for several reasons. First, both participants were already active and meeting physical activity recommendations set by the ASCM for cancer survivors.[8] Therefore, based on the dose-response theory, the 2 participants had a reduced capacity for physical improvement compared with inactive survivors,[26,28] which may account for the relatively low percentage increase in maximal strength shown by participant A. Second, the medications prescribed for the 2 participants as well as the ongoing chemotherapy (bevacizumab) for participant B are known to have deleterious effects on physical function and fitness. It is well documented that patients undergoing chemotherapy and radiation therapy experience treatment-related symptoms (eg, fatigue, reduced strength, and reduced fitness),[29-31] and when used in combination, these effects are magnified and can be long lasting.[32] Both these participants had previous exposure to cranial radiotherapy and participant B also had multiple sessions of chemotherapy. Additionally, both participants were taking prescribed antiepileptic medications (lamotrigine and levetiracetam), which also commonly present lead to symptoms of headaches, nausea, and fatigue.[33] These medications and adverse effects have a multiplicative effect in reducing the capacity for physical activity. Therefore, the improvements for these 2 participants likely

occurred when decrements in cardiorespiratory fitness and muscle strength may otherwise have been expected. Notably, the continued engagement in moderate to vigorous exercise may have the potential not only to decrease morbidity, but also decrease mortality. Previous research by Ruden et al[10] illustrated that engaging in regular higher-intensity exercise was associated with increased survival for survivors of recurrent brain cancer. However, the current trial was not designed with survival as an end point.

Current evidence suggests that screening and treating depression in patients with brain cancer should be a primary concern for comprehensive care.[34] Distress has been classified as the sixth vital sign, and best-practice cancer care should attend to the emotional and psychosocial needs of each patient.[35] Previous reports indicate that approximately 50% of neurological cancer survivors suffer with elevated distress.[36] The 2 participants were included within the larger trial particularly because they were distressed; nonetheless, in this regard, they are likely very representative of the clinical population. The 2 participants both had clinically meaningful reductions in depression and total distress, measured using the HADS,[27,34] after the 12-week exercise intervention. These outcomes are in line with evidence that exercise reduces depression in depressed individuals[37] as well as comorbid depression in people with cardiovascular disease[38] and are unlikely to be attributed to any response from medications because these were consistent before and during the intervention period.

There was also a large and clinically meaningful categorical shift in satisfaction with life. The scale allows a range of 5 to 35. Categorical scoring zones have been provided by the authors, with each 5-point block (eg, 5-9, 21-25) representing an increased level of satisfaction with life[21]; a score of 20 is classified as the neutral threshold value for this scale.[39] At baseline, both participants scored on the lower end of the scale (11 and 7), but by the conclusion of the exercise intervention, participant A increased 3 categorical levels, exceeded the neutral threshold, and fell within the "high" category. Participant B increased 2 categorical levels from "extremely dissatisfied" to "slightly below average" and was just 1 point short of reaching the neutral threshold.

Interestingly, the improvements in objective physical assessments as well as the improved mental health measures occurred independently of self-rated physical health (PHC from the SF-36), which remained relatively stable for participant A and declined considerably for participant B. Specifically, for participant A, this may have been partly a result of overtraining because she reported increased fatigue. Therefore, after 6 weeks participant A was advised by the exercise physiologist to reduce her total exercise load. The decline in PHC SF-36 score for participant B may be explained by the ongoing pharmacotherapy, which caused unexpected adverse events such as nosebleeds because of blood thinning. This suggests that a general measure of health-related quality of life may not be an appropriate or clinically meaningful PRO to assess the effectiveness of an exercise program in neuro-oncology patients, who can have rapidly changing subjective opinions of their health status based on compromised immune systems and increased risk of illness or negative prognostic feedback from treating clinicians.

This exercise program was supported by the treating oncologist of both participants as well as their respective family physicians. This process of approval by clinicians should be considered as best practice to ensure that there are no contraindications to exercise. While recuperating from cancer treatment, the introduction or continuation of physical activity to enhance recovery, reduce toxicity, increase physical function, and improve health-related quality of life has been recommended by the ACSM[8] and further endorsed by the ACS.[9] The findings reported above, along with new and emerging evidence, suggests that exercise is safe and beneficial for even the most complex cancer cases, including patients with bone metastases[40] and those with poor prognoses, including pancreatic cancer patients.[41]

In summary, the outcomes from this report are intended to build a level of evidence regarding the benefits of exercise for cancer survivors with brain tumors. However, both participants were active at baseline, which may limit the generalizability of these findings. Moreover, the duration of the intervention was relatively short. Nonetheless, for these particular survivors, there were some important and clinically relevant outcomes. If exercise is to be included as standard care, it is essential to build on these results and determine whether patients with brain cancer continue to improve over longer periods of time and whether they are able to maintain the adherence levels seen in this study. These 2 cases illustrate that, in some cases, exercise is a beneficial form of supportive care, improving compromised mental health and enhancing physical capacity for brain cancer survivors, regardless of whether they are in palliative care or have exceeded the median expectations for survival. However, more evidence, including larger clinical and controlled trials, is required before these results can be broadly translated into clinical practice for all brain cancer survivors.

Declaration of Conflicting Interests

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