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Quantitative Assessment of Cardiorespiratory Fitness, Skeletal Muscle Function, and Body Composition in Adults with Primary Malignant Glioma

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Abstract

Purpose—To evaluate cardiorespiratory fitness, skeletal muscle function, and body composition of patients with newly diagnosed and untreated, postsurgical primary malignant glioma.

Experimental Design—Using a cross-sectional design, patients with clinically stable (10 ± 7 days post surgery) high-grade glioma (HGG; $n=25$) or low-grade glioma (LGG; $n=10$) were studied. Participants performed a cardiopulmonary exercise test (CPET) with expired gas analysis to assess cardiorespiratory fitness (VO_{2peak}). Other physiological outcomes included skeletal muscle cross-sectional area (CSA; magnetic resonance imaging), isokinetic muscle strength (isokinetic dynamometer), and body composition (air displacement plethysmography). Quality of life (QOL) was assessed by the Functional Assessment of Cancer Therapy-Brain scale.

Results—CPET was a feasible and safe procedure to assess VO_{2peak} with no serious adverse events. VO_{2peak} indexed to total body weight and lean body mass for both groups was $13.0 \text{ mL} \cdot \text{weight}^{-1} \cdot \text{min}^{-1}$ and $19 \text{ mL} \cdot \text{lean} \cdot \text{min}^{-1}$; the equivalent to 59% and 38% below age and sex-predicted normative values, respectively. Skeletal muscle strength and mid-thigh CSA was lower in HGG relative to LGG patients (83 vs. 125 Nm, $p=.025$; 94 vs. 119 cm^2 , $p=.171$, respectively). Skeletal muscle isokinetic strength, CSA, and body composition outcomes predicted VO_{2peak} ($r = -0.59$ to 0.68 , $p < 0.05$).

Conclusions—Postsurgical glioma patients have markedly reduced cardiorespiratory fitness, isokinetic strength and CSA. Prospective studies are now required to determine whether such abnormalities influence treatment toxicity and clinical outcome as well as test the effect of appropriately selected interventions to prevent and/or mitigate dysfunction.

Keywords

Cardiorespiratory fitness; skeletal muscle function; malignant glioma; quality of life; fatigue

Introduction

Malignant gliomas remain one of the greatest challenges in oncology. Despite aggressive therapy overall survival of patients with newly diagnosed glioblastoma multiforme (GBM), the most common malignant glioma, is 42.4% at 6 months, 17.7% at one year, and 3.3% at two years.(1) The development of neuropsychological symptoms and cognitive dysfunction

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has been researched extensively in malignant glioma with neurocognitive functioning now seen as a legitimate and viable clinical endpoint in glioma management and clinical trials.(2) The physiological or functional sequelae has, in contrast, received scant attention.

The effect of standard regional and systemic therapy on functional parameters (e.g., exercise capacity, body composition, etc.) has been investigated in several cancer populations.(3-6) However, the use of high-dose corticosteroids in malignant glioma is of particular concern. Chronic corticosteroid therapy use is associated with skeletal muscle atrophy and weakness as well as ultrastructural abnormalities in myofibrillar mass, mitochondrial volume, and capillary number.(7-9) Together with secondary effects on physical activity levels (i.e., deconditioning), steroid therapy is expected to have profound effects on patient's exercise tolerance, ability to perform activities of daily living, and even clinical outcome.(10)

With an emerging new treatment paradigm in malignant glioma, characterized by increasing use of anti-angiogenics in combination with standard cytotoxic therapy,(11) clinical tools that quantitatively evaluate functional outcome are set to become an increasingly important aspect of multidisciplinary care. These tools can be used to improve prognostication, determine whether patients are able to tolerate a particular therapeutic regimen as well as identify those at high-risk of functional complications so appropriate preventive and/or treatment interventions can be initiated.(12)

Formalized objective measures of cardiorespiratory fitness (VO_{2peak}) are widely used in many areas of clinical practice and powerful predictors of mortality.(12) Measures of skeletal muscle function including muscle strength, cross-sectional area (CSA), and whole-body composition (lean vs. body mass) are central determinants of reduced exercise tolerance in chronic heart failure (CHF)(13) and heart transplant patients.(14) Heart transplant patients, similar to malignant glioma, suffer disease- and/or corticosteroid-induced skeletal myopathy. Muscle wasting is also an independent predictor of mortality in CHF.(15) As an initial step, we conducted a pilot study to evaluate cardiorespiratory fitness, skeletal muscle function, and body composition among 35 clinically stable, newly diagnosed and untreated, postsurgical high-grade or low-grade glioma patients. A secondary aim was to determine the relationship between quantitative functional endpoints, QOL, and fatigue.

Methods

Participants and Setting

The study was conducted at the Preston Robert Tisch Brain Tumor Center (PRT-BTC) at Duke University Medical Center (DUMC), Durham, USA. Patients with histologically confirmed, clinically stable, postsurgical and previously untreated glioma (WHO grade I–IV) were potentially eligible for this study. Additional major inclusion criteria included: (1) Karnofsky performance status (KPS) of $\geq 70\%$, (2) estimated life expectancy of ≥ 6 months, (3) no contraindications to a CPET,(12) and, (4) primary oncologist approval. The DUMC Institutional Review Board approved the study and written informed consent was obtained from all participants prior to initiation of any study procedures.

Study Procedures

Using a cross-sectional design, all potential participants were identified and screened for eligibility via medical chart review of patients scheduled for their postsurgical treatment consultation at the PRT-BTC. After obtaining written informed consent, all participants were scheduled for study assessments. All study-related assessments were performed at DUMC within a 2-day period by study staff blinded to group assignment (i.e., high vs. low grade diagnosis).

Outcome Assessments

Incremental Cardiorespiratory Exercise Testing—To determine $\text{VO}_{2\text{peak}}$, an incremental, physician-supervised CPET with 12-lead ECG monitoring (Mac ® 5000, GE Healthcare) was performed according to guidelines published by Jones et al.(12) All tests were performed on an electronically-braked cycle ergometer (Ergoline, Ergoselect 100, Bitz, Germany) with expired gas analysis (ParvoMedics TrueOne® 2400, Sandy, UT). Preceding exercise, 3 minutes of resting metabolic data was collected before participants began cycling at 10 – 20W. Workloads were then increased 5 – 20W/min until volitional exhaustion, symptom-limitation, or a respiratory exchange ratio (RER) of >1.0 was achieved. Tests were terminated when a RER >1.0 was achieved since all subjects had recently undergone craniotomy; the safety and feasibility of maximal CPETs (RER >1.10) in this setting is unknown, thus we felt it was prudent to terminate tests once adequate test criteria was achieved for clinical populations.(12) Initial workload and workload increments were determined by patient's medical history and metabolic responses to exercise during the first minute. During exercise, blood pressure was measured non-invasively by manual auscultatory sphygmomanometry every two minutes.(16) At the end of each workload rating of perceived exertion (RPE) was evaluated using the Borg Scale.(17) The metabolic measurement system was calibrated before and the calibration was checked after each test. Patients continued with usual medications and were asked to abstain from caffeinated beverages on the day of testing. All cardiopulmonary function data was recorded as the highest 30s value elicited during the CPET. Mean percentage of age and sex-predicted peak heart rate and $\text{VO}_{2\text{peak}}$ were calculated from the equations provided by Jones et al.(18) and Fitzgerald et al.(19) (women) and Wilson and Tanaka(20)(men) respectively.

Skeletal Muscle Function

Muscle Cross Sectional Area (CSA) of the dominant thigh was assessed using magnetic resonance imaging (MRI) with a 3.0T-scanner (Phillips ACS II, Shelton, CT). Imaging was performed using sequence gradient echo recall scans at the midfemur level. Seven serial slices were obtained with one at the juncture of the middle third of the femur (this point will be landmarked to ensure within patient reproducibility) as previously described.(21) The CSA of the quadriceps, hamstrings, and total mid thigh muscle was assessed using semiautomatic (manual) generation of the region of interest using console software by one an investigator (MIT) blinded to group assignment.

Muscle Strength of the right quadriceps was measured using a Biodex isokinetic dynamometer (Biodex Corporation, Shirley, USA). The isokinetic testing protocols consisted of 3 sequential voluntary maximal contractions at an angular velocity of 90°/s. Maximal isokinetic strength was defined as the highest peak torque achieved during the 3 contractions. Mean percentage of age and sex-predicted muscle strength was obtained from prior reports.(22)

Body Composition

Percent body fat, fat mass (FM), and lean body mass (LBM) were evaluated by air-displacement plethysmography (e.g. BOD POD, Life Measurement Incorporated, Concord, CA). In brief, each patient wore spandex and cap provided by the laboratory while body mass was measured to the nearest 100 g followed by the calculation of thoracic gas volume. Body density was calculated as body mass divided by body volume. Percent body fat was estimated from body density based on a two-compartment model. The system was calibrated prior to each test and one investigator (SKM) conducted all body composition assessments. Mean percentage of age and sex-predicted LBM and FM was obtained from prior reports. (23,24) The test-retest reliability of BOD POD for body composition assessment is 0.994

(25) and is widely regarded as a valid and reliable method to assess body composition in middle-aged and elderly subjects.(26,27)

QOL

QOL was assessed using the Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale.(28) The FACT-BR contains subscales for physical (PWB, 7-items), functional (FWB, 7-items), emotional (EWB, 6-items), and social/family (SWB, 7-items) well-being. In addition, the FACT-BR contains a 19-item brain cancer subscale (BCS) which assesses symptoms commonly reported by brain cancer patients.(28) Fatigue was assessed by the 13-item Fatigue Scale of the FACT measurement system developed specifically for cancer patients.(29)

Clinical Parameters and Performance Status

Medical characteristics were abstracted from medical records. Performance status was assessed using the KPS scale and was assessed at the time of study enrollment by the attending oncologist. KPS scores range from 0 (dead) to 100 (normal; no evidence of disease and no physical complaints). Self-reported exercise over the past month was assessed by the Godin Leisure Time Exercise Questionnaire.(30)

Statistical Analysis

The initial analysis provided descriptive information on the demographic and clinical treatment characteristics of participants. To examine differences between patients with HGG and LGG (overall as well as by gender) on study endpoints we used a series of independent samples t-tests. Linear regression analysis was used to determine the univariate association between study endpoints. Data are presented as mean $\pm$ standard deviation. All statistical tests were two-sided and significance was pre-specified for $p < 0.05$. No adjustment was made for multiple tests.

Results

Participant recruitment took place between October 2006 and July 2008. In brief, 131 patients were screened for study eligibility during the study period. Of these, 69 (53%) met inclusion criteria and 35 (51%) agreed to participate. Major reasons for non-eligibility were KPS $< 70\%$ ($n=11$), mental distress ($n=5$), and post-operative complications ($n=5$). Major reasons for study refusal were not interested ($n=21$) and feeling overwhelmed ($n=5$). The participant demographic and clinical characteristics are shown in Table 1. Muscle CSA was only obtained in 20 patients (low grade, $n=7$; high-grade, $n=13$). Reasons for not obtaining this assessment were patient MRI contraindications and equipment maintenance.

Cardiopulmonary Exercise Test Abnormalities and Adverse Events

Across the entire study sample ($n=35$), 33 (94%) CPETs were considered to be of adequate effort given that a respiratory exchange ratio of >1.0 was achieved (one patient was unable to perform the CPET due to an equipment malfunction). The one patient who did not achieve this criterion stopped prematurely due to exercise-induced desaturation ($SpO_2 < 85\%$) which normalized following exercise termination.

Physiological Data

In HGG patients, peak VO_2 averaged 13 ± 4 mL $\cdot$ weight $^{-1}$ (range: 8 to 26 mL $\cdot$ weight $^{-1}$) the equivalent to 59% below age and sex-predicted normative values. Peak heart rate was 120 ± 22 beats $\cdot$ min $^{-1}$ or 71% of age predicted maximum (VO_{2peak} typically is achieved at $\geq 85\%$ of peak heart rate in healthy adults) while peak workload

averaged 66 ± 43 W. Mean total mid-thigh CSA and muscle strength was 94 ± 32 cm² and 83 ± 42 Nm, respectively. Percent body fat, fat mass, and lean mass was $30 \pm 11\%$, 23 ± 11 kg, and 53 ± 14 kg. In patients with LGG, peak VO₂ averaged 13 ± 4 mL·weight·min⁻¹ (range: 8 to 19 mL·weight·min⁻¹) the equivalent to 62% below age and sex-predicted normative values. Mean total mid-thigh CSA and muscle strength was 119 ± 44 cm² and 124 ± 54 Nm, respectively. Percent body fat, fat mass, and lean mass was $34 \pm 8\%$, 29 ± 12 kg, and 56 ± 14 kg. Only muscle strength was significantly different between groups ($p=.025$) (Table 2). We also examined differences in physiological data between male and female participants according to primary glioma diagnosis (i.e., HGG vs. LGG). Results indicated that peak workload, lean body mass, and muscle strength ($p's < 0.05$) were significantly higher in women with LGG. There were no significant differences between men according to primary glioma diagnosis (analysis

QOL Data

In the HGG group, overall QOL (FACT-BR) was 122 ± 21 (maximum score, 184; higher scores indicate better QOL) while fatigue was 30 ± 12 (maximum score, 52; higher scores indicate worse fatigue). In LGG patients, average overall QOL and fatigue was 132 ± 29 and 30 ± 12 , respectively. There were no differences between patient groups on any QOL endpoint (Table 3).

Univariate Prediction Analyses

Among HGG patients, univariate analysis revealed that several endpoints were significantly correlated with VO_{2peak} and total muscle CSA ($r = -0.59$ to 0.68 , $p < 0.05$; $r = -0.80$ to 0.73 , $p < 0.05$, respectively). Among LGG patients, only KPS was significantly correlated with VO_{2peak} ($r = 0.72$; $p=.017$) while fat mass, lean mass, and muscle strength were correlated with total muscle CSA ($r = 0.83$ to 0.93 , $p < 0.05$) (Table 4).

The univariate predictors of overall QOL and fatigue are shown in Table 5. In patients with HGG, only self-reported exercise behavior was correlated with QOL ($r = 0.42$; $p=.046$) while sex (male) ($r = 0.44$; $p=.037$), lean mass ($r = -0.41$; $p=.049$), and VO_{2peak} ($r = -0.40$; $p=.052$) were associated with fatigue. In the LGG group, only exercise behavior correlated with QOL ($r = 0.68$; $p=.043$) while total muscle CSA predicted fatigue ($r = -0.74$; $p=.050$).

Discussion

Primary malignant glioma patients were able to achieve acceptable CPET criteria with a low incidence of complications or exercise-induced abnormalities. This is the first study to investigate the utility of CPET in primary malignant glioma patients, thus, the feasibility and safety of this procedure are not known. Primary glioma patients may represent a population at higher risk of CPET-associated adverse events relative to individuals from the general population. For example, primary gliomas are highly angiogenic which can lead to increase risk of prothrombotic events.(31,32); the addition of extensive cranial surgery and postoperative high-dose steroid therapy may further increase the risk of an event. The present data indicating that CPET is a relatively safe procedure in this setting is, therefore, important. These results are consistent with our recent systematic review indicating that maximal and submaximal exercise testing is a relatively safe procedure in cancer patients with adverse events being reported in <15% of studies with no reported exercise test-related deaths.(12) Clearly, symptom-limited CPETs are likely only appropriate for patients with a 'good' performance status (i.e., KPS $\geq 70\%$). The application of CPET, and thus exercise interventions, among malignant glioma patients appears limited to those with better performance status and experiencing less therapy (surgery)-related complications. Nevertheless, a CPET or other forms of exercise testing may provide a sensitive and

accurate evaluation of functional capacity facilitating individualized therapeutic management.(33) Exercise testing recommendations for cancer patients have recently been published.(12)

A major finding of this study was the significant and marked reduction in $\text{VO}_{2\text{peak}}$ in both patient cohorts. Overall, on average, $\text{VO}_{2\text{peak}}$ was $13 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or ~60% below of that predicted for age-sex matched *sedentary* comparison data despite a minimum 'good' KPS eligibility requirement of $\geq 70\%$. Relatedly, peak VO_2 indexed to lean body mass as opposed to the traditional index of total body weight may more accurately reflect cardiorespiratory fitness in clinical populations experiencing catabolic disease states and increase the prognostic value of CPET.(34-36) Using this approach, mean $\text{VO}_{2\text{peak}}$ increased to $19 \text{ mL}\cdot\text{lean}^{-1}\cdot\text{min}^{-1}$ although this value remained ~38% below that of predicted. This $\text{VO}_{2\text{peak}}$ is lower than that observed in our prior work among patients with inoperable (advanced) malignancy, patient groups that presented with significant comorbid disease and undergoing palliative chemoradiation.(37,38) To our knowledge, this is the first study to measure peak VO_2 in patients with malignant glioma.

The low $\text{VO}_{2\text{peak}}$ may be of clinical importance. $\text{VO}_{2\text{peak}}$ is a powerful independent predictor of mortality among non-cancer populations with underlying cardiac and pulmonary disease.(34,35) Three studies have reported that *subjective* functional outcome measures are independent predictors of survival in malignant glioma.(39-41) However, these studies assessed functional status using self-assessment questionnaires as opposed to objective, gold-standard physiologic instruments. Relatedly, KPS and other performance status (PS) scoring systems, have been consistently demonstrated to have strong prognostic value in primary malignant glioma.(42) The subjectivity of PS scoring systems limits the reliability and validity of these instruments. Relatedly, bodyweight status, as assessed by the most widely accepted measure - body mass index (BMI) was relatively normal, however, percent body fat (i.e., 11%–22% for men; 21%–35% for females) and fat mass (i.e., 13kg for men; 19kg for females) were abnormal relative to that considered ideal for age-sex norms. Measures of body composition also are powerful predictors of mortality(5,15) although the prognostic value of peak VO_2 and associated measures of functional status (e.g., body composition and skeletal muscle function) in malignant glioma remains to be determined.

The causes (mechanisms) of low $\text{VO}_{2\text{peak}}$ in malignant glioma are not known. $\text{VO}_{2\text{peak}}$ reflects the integrative capacity of the cardiopulmonary system to deliver adequate oxygen for adenosine triphosphate (ATP) resynthesis. The presence of malignancy together with comorbid disease and the use of aggressive cancer therapy can simultaneously impact one or more components of this system leading to exercise intolerance.(43) However, the mechanisms of the markedly reduced $\text{VO}_{2\text{peak}}$ in malignant glioma are less apparent since patients in this study had unremarkable medical history and were not receiving any cytotoxic therapy. Nevertheless, several other mechanistic explanations are plausible. First and foremost, patients performed the CPET, on average, ten days following craniotomy and were likely still in acute surgical recovery. Second, patients were likely deconditioned from a reduction in physical activity from the point of diagnosis to the CPET (an average of 28 days). Indeed, only one patient (3%) met the national criteria for regular physical activity post-diagnosis compared with 40% prior to diagnosis (data not presented). Deconditioning can have a dramatic adverse effect on cardiopulmonary function.(44) Third, the use of high-dose post-surgical corticosteroids may also adversely affect the components that determine $\text{VO}_{2\text{peak}}$ and muscle CSA. Intriguingly, postoperative steroid dose was *positively* associated with these outcomes (among HGG patients only) indicating that steroids improve exercise and functional performance. The reasons for this finding are not clear although acute steroid administration may attenuate surgery-induced systemic inflammation (inflammation may contribute to exercise intolerance(45)) and/or attenuate cerebral edema-induced toxicities /

symptoms leading to improved exercise tolerance. Further investigation of this interesting finding as well as the impact of acute versus chronic use of corticosteroids on physiologic parameters appears warranted.

A final and important potential mechanism is an abnormal neurohormonal response to exercise due to disease burden and surgical excision of normal brain tissue. The exercise response is governed by the interplay between central command and afferent information from the exercising muscles.(46) The size, location, and infiltration of a malignant brain tumor may impair the autonomic nervous system response causing dysregulated peripheral sympathetic activation which, in turn, leads to decreased skeletal muscle blood flow and early acidosis. Overall, given the potential clinical significance of poor exercise tolerance in this population, carefully designed studies that identify and unravel the mechanisms of action offer an exciting area of future research.

A final important finding was the association between functional outcomes and patient-reported outcomes. Similar to prior investigations we found that self-reported exercise behavior was positively correlated with overall QOL(47) although we found no significant correlations for any other clinical, demographic, or physiological variable. However, VO_{2peak} and lean body mass (muscle strength approached significance) were inversely associated with fatigue. Fatigue is consistently reported as the *primary* toxicity in malignant glioma(48) and while the mechanisms remain elusive, our results indicate that impairments in O_2 delivery to and O_2 utilization by the skeletal muscle may play a major role. Our findings further suggest that pharmacologic or non-pharmacologic interventions demonstrated to augment VO_{2peak} and lean body mass may improve fatigue in malignant glioma.

This study does have limitations. The most important limitation is patient selection bias because of the relatively low eligibility rate, the transparent purpose of the investigation, and exclusion of patients with poor KPS (<70%). As such, patients with better KPS, less advanced disease, and experiencing less treatment-related complications were probably more likely to participate in this study. Two other obvious limitations are the relatively small sample size and cross-sectional study design. To adequately investigate the impact of functional assessments in primary malignant glioma, large prospective studies are required.

In summary, an individualized CPET appears to be a safe and feasible assessment tool to quantitatively evaluate physical functioning in select patients with clinically stable, newly diagnosed and untreated, postsurgical primary malignant glioma. Moreover, malignant glioma patients have markedly reduced exercise tolerance, isokinetic strength, and CSA. These quantitative assessments may complement established markers of outcome in primary glioma and could improve prognostication. Prospective studies are now required to determine whether such abnormalities influence prognosis as well as test the effect of appropriately selected interventions to prevent and/or mitigate dysfunction.

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Table 1

Characteristics of the Participants

Variable	Overall (n=35)	High-Grade Patients (n=25)	Low-Grade Patients (n=10)
Age, yrs			
Mean	47 ± 13	50 ± 13	40 ± 8
Range	22 – 77	22 – 77	30 – 54
Gender, no. (%)			
Male	21 (60)	15 (60)	6 (60)
Female	14 (40)	10 (40)	4 (40)
Histology, no. (%)			
Grade IV	19 (54)	19 (76)	-
Grade III	6 (17)	6 (24)	-
Grade II	8 (80)	-	8 (80)
Grade I	2 (20)	-	2 (20)
Karnofsky performance status, no. (%)			
100%	10 (28)	3 (12)	7 (70)
90%	10 (28)	9 (36)	1 (10)
80%	14 (41)	12 (48)	2 (20)
70%	1 (3)	1 (4)	0 (0)
Hemoglobin, gm/dL			
Mean	13 ± 2.0	13 ± 2.0	13 ± 2.0
Range	9 – 16	9 – 16	9 – 15
Concomitant comorbidities - no. (%)			
Lower extremity weakness	4 (11)	4 (16)	-
Hypertension	4 (11)	2 (16)	2 (20)
Coronary artery disease	3 (9)	3 (12)	-
Previous malignancy	2 (6)	2 (8)	-
Type II diabetes mellitus	1 (3)	1 (4)	-
Ataxia	1 (3)	1 (4)	-
Extent of resection - no. (%)			
Biopsy	2 (6)	1 (4)	1 (10)
Debulking	33 (94)	24 (96)	9 (90)
Complete resection	27 (84)	19 (83)	8 (89)
Partial resection	5 (16)	4 (17)	1 (11)
Time from surgery to study entry, days			
Mean	10 ± 7	9 ± 6	12 ± 10
Range	4 – 30	4 – 25	4 – 30
Presurgical Corticosteroid therapy, (%)	34 (97)	24 (96)	10 (100)
Mean Dose, mg (range)	82 (30 – 120)	83 (30 – 120)	82 (40 – 110)

Variable	Overall (n=35)	High-Grade Patients (n=25)	Low-Grade Patients (n=10)
Postsurgical Corticosteroid therapy, (%)	35 (100)	25 (100)	10 (100)
Mean Dose, mg (range)	7 (1 – 20)	7 (1 – 10)	7 (1 – 20)
Exercise Behavior			
Total minutes / week	70 ± 109	79 ± 121	48 ± 73
No exercise behavior (i.e., 0 mins/week), %	17 (49)	12 (48)	5 (50)

Data presented as mean ± SD for continuous variables and no. (%) for categorical variables.

Table 2

Physiological Data

Variable	Overall (n=35)	High-Grade Patients (n=25)	Low-Grade Patients (n=10)	p-level
<u>Resting Cardiovascular Function</u>				
Heart rate, beats/min	74 ± 12	74 ± 14	73 ± 8	.800
Systolic blood pressure, mm Hg	124 ± 13	125 ± 14	123 ± 11	.753
Diastolic blood pressure, mm Hg	78 ± 8	77 ± 14	80 ± 5	.239
<u>Peak Cardiovascular Function</u>				
Heart rate, beats/min	120 ± 22	120 ± 22	119 ± 23	.903
Percent predicted, %	69 ± 12	71 ± 12	66 ± 12	.306
Systolic blood pressure, mm Hg	142 ± 18	140 ± 19	148 ± 15	.203
Diastolic blood pressure, mm Hg	84 ± 9	84 ± 10	85 ± 7	.812
VO _{2peak} , mL·weight ⁻¹ ·min ⁻¹	13 ± 4	13 ± 4	13 ± 4	.921
Percent predicted, %	41 ± 10	42 ± 9	38 ± 9	.279
VO _{2peak} , mL·lean ⁻¹ ·min ⁻¹	19 ± 5	19 ± 5	20 ± 5	.578
Percent predicted, %	62 ± 16	62 ± 15	57 ± 17	.460
VO _{2peak} , mL·min ⁻¹	1.04 ± 0.5	1.01 ± 0.5	1.11 ± 0.4	.565
Workload, W	68 ± 40	66 ± 43	73 ± 30	.672
O ₂ pulse, mL O ₂ /beat	11 ± 3	11 ± 3	11 ± 2	.969
METS	3.8 ± 1.1	3.7 ± 1.2	3.8 ± 1.1	.889
Ventilation, L/min	32 ± 10	31 ± 11	33 ± 10	.690
Tidal Volume, L	1.6 ± 0.6	1.6 ± 0.6	1.7 ± 0.5	.563
Respiratory Rate	20 ± 5	21 ± 6	19 ± 4	.531
Respiratory exchange ratio	1.02 ± 0.05	1.02 ± 0.05	1.03 ± 0.03	.790
Rating of perceived exertion	13 ± 3	13 ± 6	14 ± 3	.422
<u>Body Composition</u>				
Weight, kg	79 ± 18	76 ± 17	85 ± 22	.182
Body mass index, kg/m ²	26 ± 5	25 ± 4	28 ± 6	.085
Body fat percentage, %	31 ± 10	30 ± 11	34 ± 8	.417
Fat mass, kg	25 ± 11	23 ± 11	29 ± 12	.152
Percent predicted, %	165 ± 76	150 ± 73	190 ± 70	.174
Lean body mass, kg	53 ± 14	53 ± 14	56 ± 14	.534
Percent predicted, %	96 ± 15	93 ± 13	101 ± 19	.189
<u>Skeletal Muscle Function</u>				
Quadriceps CSA, cm ²	54 ± 19	50 ± 17	67 ± 22	.157
Hamstrings CSA, cm ²	48 ± 18	44 ± 16	56 ± 22	.204
Total thigh CSA, cm ²	102 ± 37	94 ± 32	119 ± 44	.171
Muscle strength (torque), nM	94 ± 48	83 ± 42	124 ± 54	.025

Variable	Overall (n=35)	High-Grade Patients (n=25)	Low-Grade Patients (n=10)	p-level
Percent predicted, %	57 ± 28	50 ± 23	77 ± 30	.012

Data presented as mean ± SD for continuous variables and no. (%) for categorical variables.

Table 3

QOL Data

Variable	Overall (n=35)	High-Grade Patients (n=25)	Low-Grade Patients (n=10)	p-level
FACT - Quality of Life				
Brain, 0–184	125 ± 24	122 ± 21	132 ± 29	.325
General, 0–108	78 ± 15	79 ± 14	78 ± 19	.931
Physical well-being, 0–28	20 ± 6	20 ± 6	19 ± 8	.698
Functional well-being, 0–28	15 ± 6	16 ± 6	14 ± 7	.666
Social well-being, 0–28	24 ± 5	24 ± 3	24 ± 3	.350
Emotional well-being, 0–24	19 ± 4	19 ± 3	19 ± 3	.656
Brain cancer specific subscale, 0–76	46 ± 12	44 ± 12	52 ± 12	.085
Fatigue, 0–52	22 ± 12	22 ± 12	21 ± 12	.873

Data presented as mean ± SD

Table 4Univariate Predictors of VO_{2peak} and Muscle Cross-Sectional Area

Variable	High-Grade Patients (n=25)			Low-Grade Patients (n=10)		
	VO_{2peak}	Muscle CSA		VO_{2peak}	Muscle CSA	
	r	p-level	r	p-level	r	p-level
Medical / Demographic						
Age	-.47	.022	-.80	.001	-.43	.211
Sex	-.50	.012	-.50	.012	-.01	.968
KPS	.40	.050	.22	.47	.73	.017
Postsurgery Corticosteroid dose	.35	.099	.62	.024	.02	.959
Exercise behavior	.01	.965	.05	.855	.08	.830
Cardiovascular Function						
VO_{2peak}	—	—	.40	.100	—	.22
Body Composition						
Fat percentage	-.59	.003	-.38	.184	-.44	.207
Fat mass	-.37	.075	.01	.961	-.39	.272
Lean mass	.68	<.001	.73	.004	.16	.659
Skeletal Muscle Function						
Muscle strength	.53	.007	.60	.030	.21	.584
Total muscle CSA	.40	.100	—	—	.22	.629

Abbreviations: VO_{2peak} : peak oxygen consumption ($mL \cdot kg^{-1} \cdot min^{-1}$); CSA, cross-sectional area; KPS, Karnofsky performance status; Exercise behavior defined as the total minutes of exercise/week. Categorical coding: Sex, male=0, female=1)

Table 5
Univariate Predictors of QOL and Fatigue

Variable	High-Grade Patients (n=25)			Low-Grade Patients (n=10)		
	r	p-level	Fatigue r	r	p-level	Fatigue r
Medical / Demographic						
Age	-.09	.680	.13	-.18	.642	.35
Sex	-.30	.170	.44	-.13	.749	-.06
KPS			.05			
Postsurgery Corticosteroid dose	.07	.759	.12	.35	.392	.15
Exercise behavior	.42	.046	-.34	.68	.043	-.42
Cardiovascular Function						
VO _{2peak}	.30	.175	-.40	.40	.289	-.32
Body Composition						
Fat percentage	-.07	.745	.18	.25	.512	-.31
Fat mass	-.03	.897	.02	.34	.375	-.51
Lean mass	.24	.267	-.41	.28	.461	-.44
Skeletal Muscle Function						
Muscle strength	.26	.228	-.35	-.04	.980	-.31
Total muscle CSA	.18	.565	-.21	.60	.204	-.74

Abbreviations: QOL, quality of life (functional assessment of cancer therapy – Brain); VO_{2peak}, peak oxygen consumption (mL.kg.⁻¹min⁻¹); CSA, cross-sectional area; KPS, Karnofsky performance status. Exercise behavior defined as the total minutes of exercise/week. Categorical coding: Sex, male=0, female=1)