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Physical functional capacity of patients with glioma prior to adjuvant radiation: preliminary descriptive study

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Abstract

Background. Few studies have assessed physical functioning in glioma patients with grade II, III, and IV glioma prior to undergoing adjuvant radiation with or without chemotherapy. The aim of this study was to describe the baseline physical functioning capacity of patients with glioma prior to adjuvant therapy compared to validated cutoffs required to maintain independence.

Methods. This study is a cross-sectional study that recruited patients with grade II, III, and IV glioma (n = 33) undergoing adjuvant radiation with or without chemotherapy. The six-minute walk, thirty-second sit-to-stand, and timed "Up & Go" assessments were used to describe baseline physical functioning. Perceived quality of life from the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) version 3.0 was used to quantify the quality of life.

Results. Mean distance walked in the six-minute walk test was 416.2 m (SD 137.6 m) with a mean of 12.2 stands (SD 3.4 stands) achieved during the thirty-second sit-to-stand. Median time to complete the timed "Up & Go" assessment was 7 s (interquartile range: 3 s). One-sample *t* tests suggest walking distance and chair stands were significantly lower than cutoff criterions to maintain independent living, $t(32) = -5.96$, $P < .001$, bias-corrected accelerated 95% CI [370.7-460.4], and $t(32) = -4.60$, $P < .01$, bias-corrected accelerated 95% CI [11.0-13.4], respectively. Wilcoxon signed-rank test identified significantly shorter median time taken to complete the timed "Up & Go" test compared to the cutoff criterion ($z = -4.43$, n = 33, $P < .01$).

Conclusion. This study suggests glioma patient's aerobic endurance and lower limb strength are below criterion cutoffs recommended to maintain independent living. Timed "Up & Go" scores did not exceed the criterion cutoff, indicating respectable levels of mobility.

Keywords

assessments | functional capacity | glioma | independence | quality of life

Primary brain tumors and subsequent treatment can impact physical functioning. In 2017, in Australia, older adults (defined as the general population over 65 years of age) account for 46% of all glioma diagnoses.[1] Current treatment for gliomas varies with histological grade and is tailored to age, diagnosis, the presence of comorbidities, and performance status.[2] As a result, goals of treatment may vary, but broadly aims are to prolong survival, preserve neurological function, and maintain quality of life.

Physical, cognitive, and emotional changes are common and vary according to various treatment-related and patient-related factors. These may manifest as declines in executive function, strength, and aerobic capacity, with increased levels of fatigue and depression.[3,4] Declines in physical capacity are comparable to the deconditioning observed in the aging population and can impact physical capacity to perform activities of daily living, independence, and quality of life.[5] For these reasons, there is a pressing need to explore management options to address side effects affecting physical capacity, independence, and quality of life. Clinical research indicates exercise has a potential role in this regard.

In the last decade, the therapeutic benefits of exercise throughout the cancer care continuum have been investigated. A recent systematic review concluded that structured exercise following cancer diagnoses has a significant protective effect against cancer-specific mortality and recurrence.[6] Other therapeutic benefits include improvements in body composition, strength and aerobic fitness, physical capacity, and quality of life.[7–10] Much of this research was conducted in more common cancers such as breast, prostate, and colon. Research investigating the benefits of individualized exercise within the glioma population is scarce. General exercise guidelines may not apply to the unique pathophysiology, therapeutic management, and symptom-burden experienced in the glioma population.

As the exercise-oncology literature evolves, it is shifting away from generic guidelines in favor of a more focused approach, matching each patient's goals to their current physical capacity.[11] Limited data are available to describe the "baseline" physical capacity of patients with glioma before receiving adjuvant cancer therapy.[5,12] However, some existing research indicates that exercise behavior may be associated with improved median survival.[13] From a rehabilitative perspective, the assessment of physical capacity is fundamental to identify those at risk of mobility difficulties and falls and is a guiding pre-requisite for an individualized exercise prescription.

To evaluate baseline physical capacity, standardized performance-based assessments of aerobic endurance, lower body strength, and mobility (the six-minute walk, thirty-second sit-to-stand, and timed "Up & Go" tests, respectively) were implemented. Assessments of physical capacity were selected as they represent both clinical and research relevant areas of focus for health care professionals involved in the prescription and delivery of exercise interventions. Although application of these assessments remains novel within the glioma population, they are frequently applied within the exercise-oncology practice and literature. In addition, normative values for these assessments have been published within both healthy and clinical populations allowing health care professionals to quantitatively interpret and compare each patient's results relative to others of a similar age or medical condition. In turn, these results may provide information required for individualized goal development, exercise prescription, intervention effectiveness, monitoring, and patient care throughout cancer treatment.

The six-minute walk test is a submaximal assessment of aerobic endurance commonly used in clinical practice and research as it does not require any specialized equipment or training to implement, providing a more feasible assessment of aerobic endurance compared to other maximal or submaximal assessments. It has been used in patients with varying cardiopulmonary diseases,[14] neurological conditions including stroke,[15] Parkinson's,[16] and Alzheimer's,[17] as well as within cancers of the breast,[18] prostate,[19] and high-grade gliomas.[20,13] The six-minute walk test has reported a high test-retest reliability within the cancer population (interclass correlation coefficient [ICC] = 0.93, 95% confidence interval [CI] 0.86-0.97).[21]

The delivery of the six-minute walk test is standardized using protocols published by the American Thoracic Society.[22] At their own pace, patients are to cover as much distance as possible within 6 min by continuously walking over a hard surface between two cones set 30 m apart. The test score is the distance covered in meters, termed the six-minute walk distance. Walk distances have demonstrated moderate to strong correlations with peak oxygen uptake,[23] physical capacity and mobility components,[24] levels of physical activity,[25] and is a robust predictor of mortality[26] in a wide range of clinical settings. To facilitate direct comparisons of walk distance, a normative value was selected from the published literature that followed the American Thoracic Society six-minute walk test protocol. As a result, a normative value of 559 m[27] was used in this study. Although other published literature on the elderly has reported similar normative values,[28] the use of different protocols limits direct comparison.

The thirty-second sit-to-stand test is used to assess lower body strength and was performed according to the test manual described by Jones et al.[29] Patients are asked to rise from a seated position and stand in a fully extended standing position as many times possible in 30 s. The score is the total number of correctly executed stands completed within the allocated timeframe. Due to its simplicity and role in assessing common everyday activities including getting in and out of a chair, stair climbing, and maintaining balance, it is implemented within a range of populations including the elderly,[29] stroke,[30] and cancer patients.[31] The thirty-second sit-to-stand test has a high test-retest reliability (ICC = 0.84), correlating strongly with one-repetition maximum leg press scores and is able to discriminate between high-active and low-active adults.[29] Older adults that demonstrated lower sit-to-stand performances were associated with nearly twice the likelihood of experiencing a fall-related injury[32] and report higher need of assistance with activities of daily living.[33] Rikli and Jones[34] proposed a cutoff value of 15 stands for women and 16 stands for men as a criterion score for maintaining independent functioning in later life. For the purposes of this study, we used the proposed cutoff for women as a more conservative measure for comparison against our sample of glioma patients.

The timed "Up & Go" test is a measure of functional mobility, balance, and falls risk developed by Podsiadlo and Richardson.[35] The test takes only seconds to perform, requires no special equipment or training, and captures important mobility components, including transfer ability, gait, and turning movements. It has been studied in the elderly,[36] patients with neurological conditions such as Parkinson's disease[37] and cancer patients.[38] At their own pace, patients are asked to rise from a seated position without using armrests, walk to a cone 3 m away, turn, walk back, and sit down again. The test score is the time in seconds to complete the test. Within the literature, however, there is a variation in cutoff values reported to identify patients with functional impairments.[39] For example, in community-dwelling older adults, the timed "Up & Go" test has been shown to strongly predict disabilities in activities of daily living, including the ability to get in and out of bed and walk around the house. 40 Further, difficulties in higher level tasks such as money management have been demonstrated in older adults who required more than 13 s to complete the timed "Up & Go" test with older adults that completed the test in more than 20 s demonstrating further disability and difficulty.[40] While a cutoff point of 13.5 s has been identified as having 87% sensitivity and specificity in correctly identifying those with increased falls risk.[41] Further Bischoff et al.[42] promote 12 s as a clinical cutoff point for normal mobility, functioning, and reduced falls risk.

The timed "Up & Go" test has a high intra-rater and inter-rater reliability (ICC = 0.92-0.96)[43] with a reported moderate (ICC = 0.56)[44] to high (ICC = 0.99)[35] test-retest reliability, possibly caused by a change in sample stability or potential learning effects between trails.[45] However, construct validity has been supported through a range of moderate to strong correlations with essential functional measurements including gait speed, postural sway, step length, and stair test.[43] For the purpose of this study, the 13.5-s cutoff[41] was selected due it its ability to identify the risk of mobility issues and falls and being a conservative estimate between two opposing values.

The purpose of this study was to describe the baseline physical functioning capacity of patients with glioma prior to adjuvant therapy. We also explored the correlations between physical capacity and quality of life. We consider the following hypotheses: (1) Patients with glioma after surgery will have physical functioning different from the physical functioning normative values of the older adult population; (2) Better physical functioning will be positively associated with greater perceptions of quality of life.

Methods

Descriptive data reported are part of a larger pilot study exploring the feasibility of implementing an exercise intervention in patients with glioma undergoing adjuvant radiation with or without chemotherapy. Inclusion criteria were: (a) histologically confirmed World Health Organization (WHO) grade II, III, and IV glioma; (b) age greater than 17 years old; (c) Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2; (d) intention to receive radiation therapy; (e) treating oncologist approval; and (f) ability to communicate in English. The study followed institutional guidelines provided by each participating hospital and was approved by their respective Ethics Committees HREC/17/QPEC/43 and HREC/14/LPOOL/408. All participants provided written informed consent.

Procedures

Participants were identified and screened for eligibility during outpatient clinic consultations at their primary hospital. Following oncologist approval, the research team discussed and provided participants an overview of the study. Consenting patients completed physical functional assessments to examine aerobic capacity, lower limb strength, and balance followed by subjective quality of life assessment. Relevant clinicopathological data were also recorded.

Assessments

Three tests were used to assess physical capacity and were selected for ease of administration and scoring requiring minimal space and equipment requirements within a clinical environment. These tests represented both the key physical parameters and functions of independent living including mobility (eg, walking) and transferring (eg, rising from a chair). The six-minute walk test is a reliable and valid submaximal assessment of aerobic endurance; the distance walked in 6 min was recorded to the nearest meter.[22] The thirty-second sit-to-stand test, shown to be a valid and reliable measure of lower body strength test, was administered.[29] The number of stands achieved in 30 s was counted. The timed "Up & Go" test has demonstrated high construct validity with log-transformed assessments of balance and was administered accordingly.[35] Time to complete the test was recorded in seconds. Normative value cutoffs represent the value required to maintain functions of daily living within an adult population independently, safely, and without fatigue.[34] For comparisons, cutoffs were 559 m, 15 stands, and 13.5 s, respectively.[27,34,41]

Health-related quality of life was measured using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) version 3.0 and scored according to guidelines.[46] The QLQ-C30 contains 30 items across five functional scales (physical, role, emotional, cognitive, and social), nine symptom scales (fatigue, nausea and vomiting, and pain), and one global health status/quality of life scale. After linear transformation, the global health status is scored from 0 to 100. A higher global health status score represents a better perception of quality of life.

Statistical analysis

Baseline physical capacity and quality of life are reported as means and standard deviations if assumptions of normality were met, or as median and interquartile range if violated. Where missing data occurred, Little's missing completely at random (MCAR)

test was used to determine the pattern of missing data. Little's MCAR test was not significant ($\chi^2(4) = 2.45$, $P = .65$), suggesting that missing data pattern was non-systematic. Given the non-systematic pattern of missing data, listwise deletion was implemented. When assumptions of normality were met, a one-sample *t* test was used to compare physical capacity to criterion cutoff values. The Wilcoxon signed-rank test for one sample was used when assumptions of normality were not met. Similarly, Pearson's correlation coefficient or Spearman's rank correlation coefficient were used to assess the relationship between physical capacity and quality of life with bias-corrected accelerated 95% CI estimated using 1000 bootstrapped samples. An alpha value (accepted as $\alpha = 0.05$, two-tailed) was used to determine the significance. Statistical analyses were conducted using SPSS (IBM SPSS Statistics Version 25.0; IBM) for Macintosh.

Results

A total of 33 participants aged 29–72 years were recruited from April 2015 to July 2019. Patients' baseline demographics and clinical characteristics are shown in Table 1.

Overall, 33 (100%) patients completed the six-minute walk, thirty-second sit-to-stand, and timed "Up & Go" tests. However, only 29 (88%) of patients completed the QLQ-C30 questionnaire. The mean distance walked in the six-minute walk test was 416.2 m (SD 137.6 m) with a mean of 12.2 stands (SD 3.4 stands) achieved during the thirty-second sit-to-stand were (Figure 2a, b). Median time to complete the timed "Up & Go" assessment was 7 s (interquartile range: 3 s) (see Figure 2c). The mean quality of life score was 60.6 (SD 21.2). Quality of life data were missing for four cases. Of these, three cases were female, two had a performance status of "0," and two had a performance status of "1." Causes of missing data include withdrawal from the study due to disease progression (n = 2), patient losing the questionnaire (n = 1), and questionnaires not returned to study researchers (n = 1).

The mean distance covered during the six-minute walk test in this sample was significantly lower than the 559-m cutoff, $t(32) = -5.96$, $P < .001$, bias-corrected accelerated 95% CI [370.7-460.4], with an absolute mean difference of 142.9 m. Likewise, the mean number of stands achieved during the thirty-second sit-to-stand in this sample were significantly lower from cutoff criterion of 15 stands, $t(32) = -4.60$, $P < .01$, bias-corrected accelerated 95% CI [11.0-13.4] with an absolute mean difference of 2.8 stands. Wilcoxon signed-rank test identified significantly shorter median time taken to complete the timed "Up & Go" test compared to the cutoff criterion of 13.5 s, $z = -4.43$, $P < .01$. There was no meaningful relationship between meters walked and perceived quality of life ($r = -0.02$, bias-corrected accelerated 95% CI [–0.56 to 0.66], $P = .90$, n = 29). There was a positive moderate relationship between the thirty-second sit-to-stand and perceived quality of life ($r = 0.42$, bias-corrected accelerated 95% CI [–0.05 to 0.75], $P = .02$, n = 29). The Spearman correlation coefficient between the timed "Up & Go" and perceived quality of life score was negative and weak ($r_s = -0.15$, bias-corrected accelerated 95% CI [–0.53 to 0.27], $P = .45$, n = 29).

Discussion

The primary aim of this study was to describe physical functioning in a sample of patients with glioma after surgical intervention and before radiation therapy. The results of this study indicate patient's aerobic endurance and lower limb strength were below criterion cutoff recommended to maintain independent living. Importantly, timed "Up & Go" scores did not exceed the criterion cutoff, indicating respectable levels of mobility within the current sample.

In our sample, the mean distance walked during the six-minute walk test was comparable to findings of previous studies investigating functional capacity in similarly aged patients with glioma (Figure 1a).[13,20] Furthermore, performance of our sample was significantly below the 559-m cutoff reported for community-dwelling 60- to 69 years old and cutoffs for maintaining independent living.[27,34] In fact, 30 (90.9%) participants were below the cutoff (Figure 2a). Based on these results, our sample presented with an aerobic endurance similar to those of community-dwelling adults aged 80- to 89 years old[34] prior to undergoing adjuvant therapy, a value approximately 40 years older than our sample mean.

Similarly, we report a significant difference between the chair stands achieved in our sample and the 15-chair-stand criterion cutoff. In fact, 23 (69.7%) participants were below the cutoff (Figure 2b), suggesting possible deficits in lower limb strength. Although declines in strength reflect normal age-related changes, our data suggest these participants have lower extremity strength equivalent to elderly 80-89 years of age (Figure 1b).[29,47] Clinically, the thirty-second sit-to-stand test is a good indicator of lower body strength in older adults, demonstrating a strong association with knee extensor and flexor strength, walking speed, stair climbing ability, and balance.[34,48] Our results suggest that glioma patients are at a greater risk of impaired lower limb strength.

The timed "Up & Go" test is a tool used to assess motor function, postural control, and risk of falls in the geriatric population. The criterion cutoff of 13.5 s is used where a completion time greater than the cutoff indicates increased risk of mobility issues and falls. In this study, 32 (97%) of the participants were below the cutoff, with only one participant (3%) completing the assessment in 27 s (Figure 2c). These results suggest participants were not at risk for mobility or falls and are comparable to a previously published descriptive meta-analysis on apparently healthy elders.[49] However, caution is warranted when interpreting this result as several factors may at play. Firstly, there is no consensus within the literature as to which "cutoff" times are the most appropriate to use. Some authors set "greater than 10 s" as the cutoff for mobility and falls, whereas others suggest that a time "greater than 20 s" to be the more appropriate cutoff.[39,41] For the purposes of this study, the 13.5-s cutoff was selected due it its ability to identify the risk of mobility and falls and being a conservative estimate

Table 1. Baseline Patient Demographic and Clinical Characteristics (n = 33).

Characteristics	Mean (SD)	n (%)
Age, y	49.0 (13.4)	
Height, cm	175.6 (11.0)	
Body mass, kg	91.1 (21.7)	
Body mass index, kg/m^2	29.4 (5.9)	
Time since diagnosis, days	26.0 (15.0)[a]	
Gender		
Female		12 (36)
Male		21 (64)
ECOG		
0		20 (61)
1		12 (36)
2		1 (3)
WHO tumor grade		
II		6 (18)
III		5 (15)
IV		22 (67)
Tumor histology		
Astrocytoma		10 (30)
Oligodendroglioma		1 (3)
Glioblastoma		22 (67)
Surgery (extent of resection)		
Biopsy		4 (12)
Sub-total resection		21 (64)
Gross-total resection		8 (24)
Radiation protocol		
Receiving radiation		33 (100)
Radiation with concurrent chemotherapy		25 (76)
Radiation with sequential chemotherapy		2 (6)
Radiation without chemotherapy		6 (18)
Supportive agents		
Receiving anti-epileptic medication (levetiracetam)		
Yes (mg/daily)	500.0 (375.0)[a]	15 (46)
No		18 (55)
Receiving corticosteroids (dexamethasone)		
Yes (mg/daily)	4.0 (1.0)[a]	9 (27)
No		24 (73)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization.
Data are presented as mean and SD or as n (%) except where indicated.
[a]Data reported as median and interquartile range.

between two opposing values. Secondly, the mean age in our sample was below the target age range for this assessment, possibly lending to the shorter completion times.[50] Thirdly, given our study cohort predominantly had ECOG performance status of 0-1, this may not be representative of more frail patients who would otherwise be at risk of mobility deficits and falls.

A second objective was to examine whether functional measures correlated with perceived quality of life. Here, we found that in general, being able to complete more stands was associated with better quality of life. These results suggest that muscular strength in the lower limbs is associated with the ability to perform activities which are reflective of independent daily living, including stair

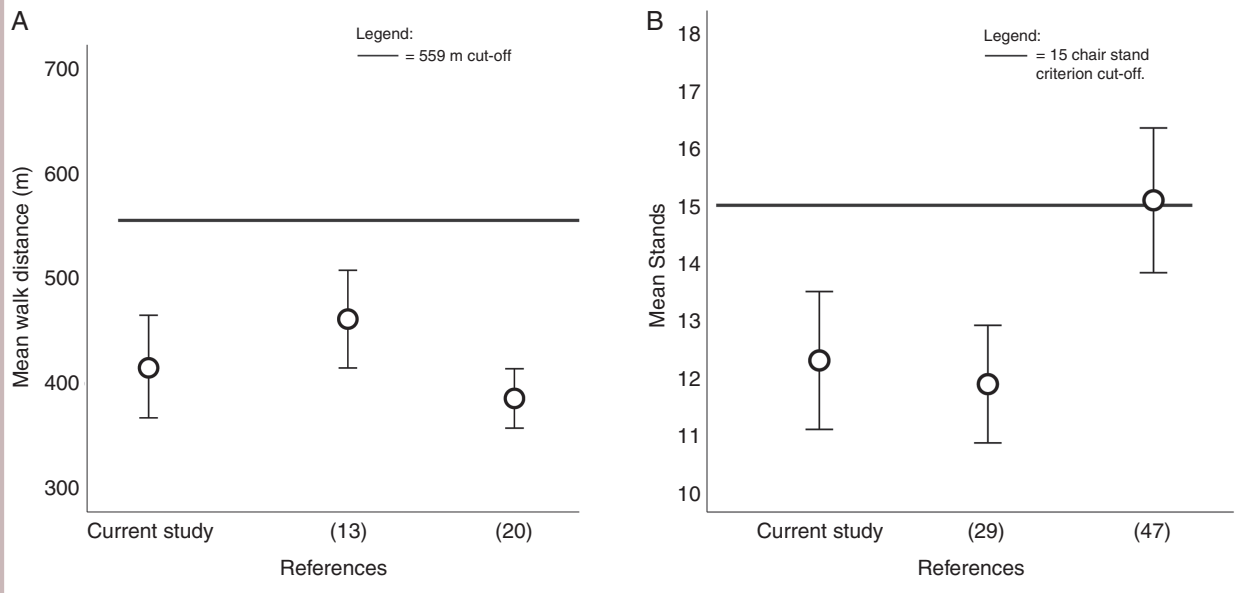

Figure 1. (a) Error plot illustrating the distribution of mean and 95% confidence intervals for six-minute walk test distance in our sample of glioma patients compared with walk distances in two other published glioma studies.[20,13] Despite recruiting glioma patients of similar age, all studies report a mean walk distance below the 559-m cutoff. Jones et al.[20] reported a mean walk distance of 390.0 m (SD 93.0 m). Ruden et al.[13] reported a mean walk distance of 448.0 m (SD 135.0 m), while this study reported a mean walk distance of 416.2 m (SD 137.6 m). Further study characteristics are provided in Supplementary Table 1. (b) Error plot illustrating the distribution of mean and 95% confidence intervals for stands completed within the thirty-second sit-to-stand in our sample of glioma patients compared to healthy community-dwelling 80- to 89 years old.[29,47] Jones et al.[29] reported a mean of 11.9 stands (SD 3.2 stands) and Tveter et al.[47] reported a mean of 15.4 stands (SD 3.3 stands), while this study reported a mean of 12.2 stands (SD 3.3 stands). Further study characteristics are provided in Supplementary Table 1.

climbing and rising from a chair. Ultimately, these transfer skills may be important factors impacting quality of life. There were no associations of importance between the six-minute walk and the timed "Up & Go" assessments and quality of life. The lack of association between aerobic endurance and timed "Up & Go" assessments may be due to the questionnaire chosen to measure the quality of life. Previous studies reporting association between the six-minute walk test and quality of life have used the FACT (Functional Assessment of Cancer Therapy) Brain Cancer questionnaire.[7,20] Consistent with our primary hypothesis, our assessments indicate a lack of lower limb strength and poor aerobic endurance overall in this group of patients; however, mobility appears to be functional. Our secondary hypothesis was not supported as only the thirty-second sit-to-stand showed any association with quality of life.

Study Limitations

This study has a number of limitations. Firstly, recruitment bias may affect the generalizability of the results. Secondly, given our selection criteria and the performance status of our population, the generalizability of these results is limited to participants with good performance status. Finally, correlations generated in this study are based on cross-sectional analysis, providing insight into correlations between physical capacity and quality of life; however, it is not possible to establish a causal relationship using this approach. Further caution is required when interpreting the comparisons within the study due to the number of univariate statistical analyses undertaken within a small sample size and no adjustments to the significance level used (eg, no Bonferroni adjustment). This analysis was intended as a preliminary description to identify possible deficits in functional capacity that may impact long-term functioning and quality of life in glioma patients. Future research should build on this analysis by using a sufficiently powered sample size and multivariate analysis undertaken over a longer duration to confirm and expand the results of this study. Additionally, investigations should continue to focus on clinically relevant outcomes and their correlates with poorer functional capacity to identify outcomes that may contribute to poorer quality of life.

In summary, our results indicate that even in a group of relatively young patients with good performance status able to participate in an exercise intervention after surgery for glioma, poor aerobic endurance, and reductions in lower limb strength were apparent. These deficits are similar to those observed in community-dwelling 80- to 89 years old. Although the timed "Up & Go" test was below criterion cutoff, these results should be interpreted with caution as our sample age was below the average age used to test the timed "Up & Go" test. Our study also reports a moderate association between lower body strength and

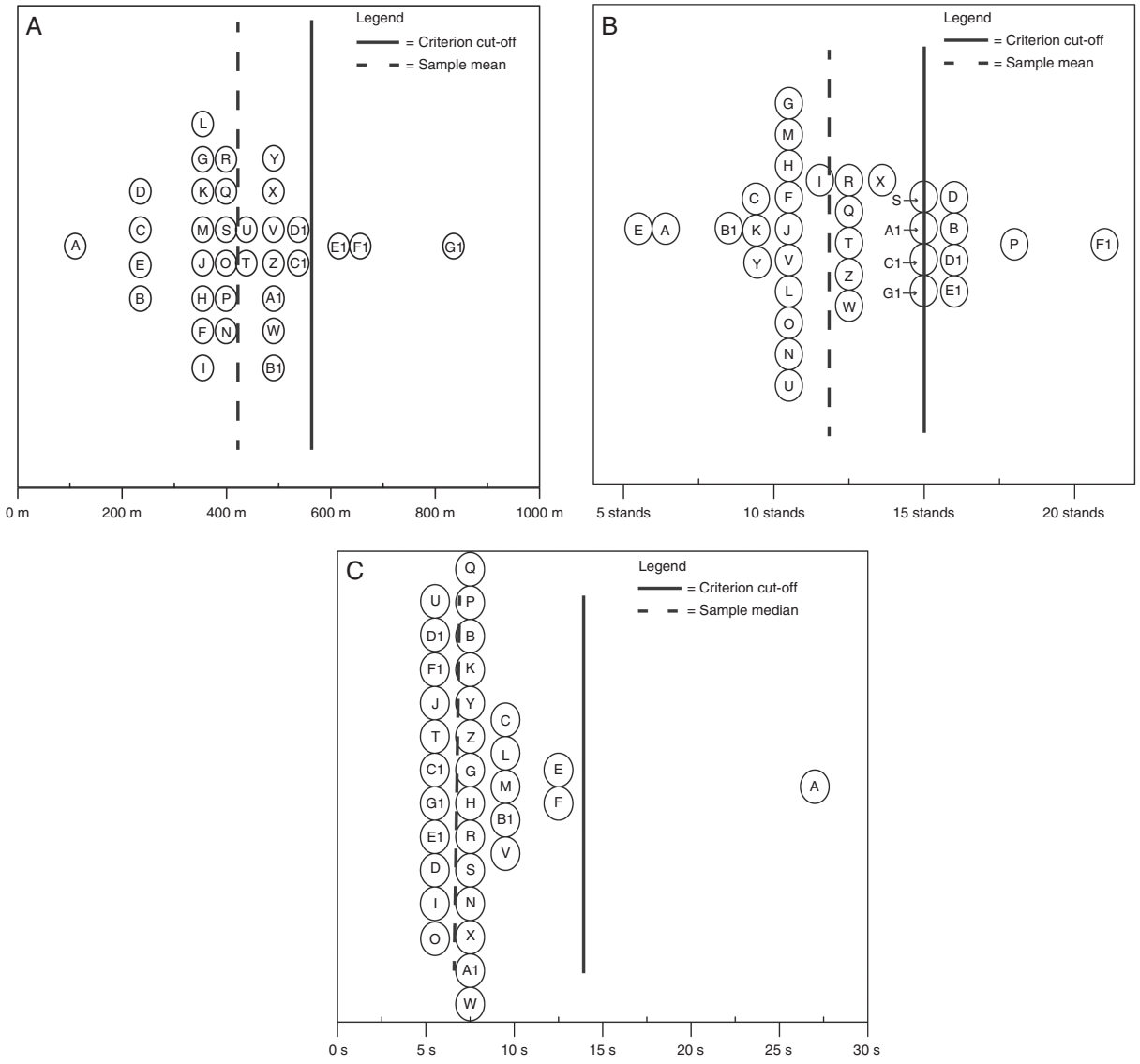

Figure 2. (a) Dot plot of mean score and criterion cutoff for the six-minute walk test with cutoff of 559 m. As a descriptive tool, patient data are de-identified and labeled from A to G1 facilitating cross-assessment comparisons. For example, "Case D" scored below the cutoff for the six-minute walk test, but above for the thirty-second sit-to-stand test, indicating a possible deficit in aerobic endurance, but respectable lower limb strength. Data for all cases, sample mean, and criterion cutoff are provided in Supplementary Table 2a. (b) Dot plot of mean score and criterion cutoff for the thirty-second sit-to-stand test with criterion cutoff of 15 stands. Data for all cases, sample mean, and criterion cutoff are provided in Supplementary Table 2b. (c) Dot plot of median score for the timed "Up & Go" test with criterion cutoff of 13.5 s. Data for all cases, sample median, and criterion cutoff are provided in Supplementary Table 2c.

quality of life. There is a need to provide rehabilitation and management services including exercise to improve functional capacity and other important end points in glioma patients. As a result, our research group is investigating the feasibility and safety of individualized exercise during adjuvant therapy. Quantitative assessments of functional capacity and supervised tailored exercise interventions may complement existing management therapies, possibly minimize the strength and cardiovascular deficits, and assist with the shift toward person-centered care.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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