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ORIGINAL REPORT

Attainment of Functional and Social Independence in Adult Survivors of Pediatric CNS Tumors: A Report From the St Jude Lifetime Cohort Study

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ABSTRACT

Purpose

Beyond survival, achieving independence is a primary goal for adult survivors of pediatric CNS tumors. However, the prevalence of and risk factors for failure to achieve independence, assessed with multiple concurrent indicators, have not been examined.

Patients and Methods

Functional and social independence was assessed in 306 survivors (astrocytoma [n = 130], medulloblastoma [n = 77], ependymoma [n = 36], and other [n = 63]; median current age, 25.3 years [range, 18.9 to 53.1 years]; time since diagnosis, 16.8 years [range, 10.6 to 41.8 years]). Six observed indicators were used to identify latent classes of independence, which included employment, living independently, assistance with personal care, assistance with routine needs, obtaining a driver's license, and marital status. Physical performance impairments were defined as scores < 10th percentile on measures of aerobic capacity, strength, flexibility, balance, mobility, and adaptive function. Multinomial logistic regression estimated odds ratios (ORs) and 95% CIs were calculated for associations of disease/treatment exposures and impairments in physical performance with nonindependence.

Results

Three classes of independence were identified as independent (40%), moderately independent (34%), and nonindependent (26%). In multivariable models, craniospinal irradiation (OR, 4.20; 95% CI, 1.69 to 10.44) and younger age at diagnosis (OR, 1.24; 95% CI, 1.14 to 1.35) were associated with risk of nonindependence versus independence. Beyond impaired IQ, limitations in aerobic capacity (OR, 5.47; 95% CI, 1.78 to 16.76), flexibility (OR, 3.66; 95% CI, 1.11 to 12.03), and adaptive physical function (OR, 11.54; 95% CI, 3.57 to 37.27) were associated with nonindependence versus independence. Nonindependent survivors reported reduced physical but not mental health-related quality of life compared with independent survivors.

Conclusion

Sixty percent of survivors of pediatric CNS tumors do not achieve complete independence as adults. Reduction in intensity of primary therapies and interventions that target physical performance and adaptive deficits may help survivors to achieve greater independence.

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INTRODUCTION

CNS tumors account for approximately 20% of malignancies diagnosed in children < 19 years of age, with an incidence of 5.7 per 100,000 in the United States.[1] With advances in treatment and supportive care, 5-year survival rates have increased from < 60% in 1980 to approximately 74% today,[2] yet the consequences associated with long-term survival of a CNS tumor remain considerable. Deleterious effects of tumor location within the CNS and CNS-directed therapies include increased risk for late mortality, subsequent neoplasms, endocrinopathies, musculoskeletal abnormalities, sensory and neurologic deficits, neurocognitive impairment, and physical performance limitations, among others.[3-7]

ASSOCIATED CONTENT

Appendix
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Because large numbers of survivors of CNS tumors are now aging into adulthood, the inability of many to achieve independence is becoming increasingly apparent. Independence can be characterized by participation in functional activities (self-care, independent living), social engagement (partnership/marriage), and the establishment of economic autonomy from caregivers (education, employment). Results from the Childhood Cancer Survivor Study indicate that unemployment is 2.4 times greater among survivors of CNS tumors compared with siblings,[8] 78% never being married or living as married,[9] and 87% less likely to live independently than survivors of Hodgkin Lymphoma.[10] The International Classification of Functioning, Disability, and Health recognizes that personal physical factors (ie, physiologic functions of body systems) influence the execution of activities (eg, activities of daily living) and societal participation.[11] Survivors of CNS tumors have well-documented personal deficits in strength, balance, and fitness, and these have been associated with discrete aspects of social participation/independence.[7] Past studies have examined markers of independence in isolation without considering that individual indicators of independence often co-occur. Identification of specific patterns or degrees of functional independence (eg, independent, nonindependent) and associated factors may help to inform recommendations for clinical care and intervention-based approaches. In addition, although failure to attain independence in adulthood has been associated with poorer quality of life and psychological distress in noncancer populations,[12] this has not been examined in survivors of pediatric CNS tumors.

The aims of the current study were to provide a comprehensive assessment of independence in survivors of CNS tumors by identifying profiles of functional and social independence using multiple concurrent indicators, examining the contribution of physical performance status to failure to achieve independence, and assessing the effect on survivors' health-related quality of life.

PATIENTS AND METHODS

Participants

Participants included 306 adult survivors of childhood CNS tumors who completed baseline evaluations as part of the St Jude Lifetime Cohort Study (SJLIFE). SJLIFE—a dynamic cohort of childhood cancer survivors—is designed to facilitate a longitudinal evaluation of health outcomes. The study design has been previously described.[13] For these analyses, participants were treated for a CNS tumor at St Jude Children's Research Hospital (SJCRH), are currently ≥ 18 years of age, and are ≥ 10 years since their original diagnosis. The SJLIFE protocol was approved by the SJCRH institutional review board, and participants provided written informed consent. Survivors were excluded if they had a neurologic disorder or injury unrelated to their primary cancer diagnosis or its treatment and known to affect functional independence (Fig 1).

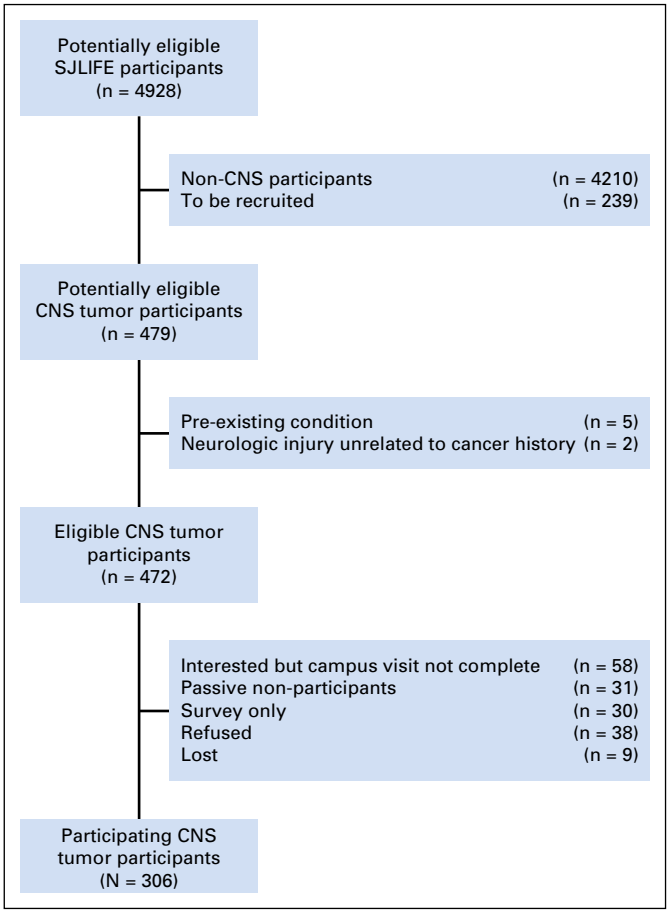

Fig 1. Study flow diagram. SJLIFE, St Jude Lifetime Cohort Study.

Primary Outcome

Functional and social independence were assessed by six observed indicators, selected on the basis of individual item face validity, use of similar constructs in past studies, and validated measures.[10,14-17] These indicators were defined as independent living (yes: lives with spouse/partner or alone; no: lives with parents or other relatives [not including minor children]); employment (full time: working full time, caring for home or family, student; part time: working part time; unemployed: not currently working, unemployed and looking for work, unable to work because of disability or illness, retired); marital status (never married: single, never married; history of marriage: married, living as married, widowed, divorced, separated or no longer married or living as married); assistance with personal care needs, such as eating, bathing, dressing, or getting around one's home (yes, no); assistance with routine needs, such as everyday chores, necessary business, shopping, and other purposes (yes, no); and current driver's license (yes, no). Being unmarried or not living with a partner does not suggest the absence of social relationships but may limit the extent of an individual's social network. Likewise, not having a driver's license does not equate to social isolation but suggests greater dependence on others for social engagement.[16] Because indicators of independence can be reliably observed by significant others, we accepted responses from surveys that were completed by direct as well as proxy report.

Secondary Outcomes

Quality of life. Health-related quality of life (HRQOL) was assessed using the Medical Outcomes Survey 36-Item Short Form,[18] which provides two composite scores (physical and mental) and subscale scores for eight domains (general health, role physical, physical function, bodily pain, vitality, mental health, social function, and role emotional). Age- and sex-specific normative data were used to calculate T scores (mean, 50; standard deviation [SD], 10). Scores ≤ 40 were classified as poor HRQOL.

Psychological distress. Psychological distress was measured with the Brief Symptom Inventory 18,[19] an 18-item questionnaire that uses a 5-point Likert response format to assess the presence of distress symptoms over the past 7 days. The measure provides an overall index of global

psychological distress as well as subscales for anxiety, depression, and somatization. Sex-specific T scores (mean, 50; SD, 10) were calculated using normative data from a sample of adults in the northeastern United States. Scores ≥ 90th percentile (T score ≥ 63) were classified as representing acute distress.

Exposures

Disease and treatment exposures. Consistent with previously published SJLIFE procedures,[13] medical record abstraction was performed to codify disease and treatment exposures, including primary tumor location (infratentorial, supratentorial), surgical resection (none, biopsy, partial, gross total), hydrocephalus with shunt placement, and agent-specific chemotherapeutic exposure (yes, no). Mean radiation dose to four segments of the brain (posterior fossa, temporal, parieto-occipital, frontal) was estimated using established methods by the radiation physicists at MD Anderson Cancer Center.[5]

Physical performance. Physical performance measures were completed during a 2-hour dedicated assessment by master's level–certified clinical exercise physiologists (American College of Sports Medicine) and one physical therapist. This group performs inter- and intrarater reliability yearly for all measures. Participants were given standardized instructions and sufficient rest between tests to account for fatigue. Impairment on each outcome was defined as performance < 10th percentile (> 1.3 SD below the mean) using age- and sex-specific data from community comparisons.[20]

Aerobic capacity. Aerobic endurance was assessed with the 6-minute walk test according to American Thoracic Society guidelines.[21] Heart rate, oxygen saturation, and the Borg Rating of Perceived Exertion were recorded at baseline; at 2, 4, and 6 minutes, and after a 2-minute recovery. The outcome was distance (in meters) walked in 6 minutes.[22]

Strength. Isokinetic knee extension and ankle dorsiflexion strength were measured while sitting (System 4 dynamometer; Biodex Medical Systems, Shirley, NY). Strength was recorded as peak torque (Newton meters per kilogram) of five repetitions at 60° per second. Isometric handgrip strength was measured using a hand-held dynamometer (Jamar; Patterson Medical, Warrenville, IL).[23] The maximum value (in kilograms) from two trials was used for analysis.

Flexibility. Low-back and hamstring flexibility was assessed using a Flex-Tester sit and reach box (Novel Products, Rockton, IL). The better of two trials (in centimeters) was used for analysis.[24]

Balance. Balance was evaluated using the Sensory Organization Test (NeuroCom SMART EquiTest, Natus Medical, Pleasanton, CA). Percentage of time spent inside a 12.5° sway envelope was recorded.[25,26]

Mobility. The Timed Up and Go test was used to assess mobility. Participants began seated in a standard chair and were instructed to rise, walk 3 m, turn, return to the chair, and sit. Time to complete the test was recorded.[27]

Adaptive physical function. The Physical Performance Test,[28] seven-item version, was used to evaluate activities of daily living. Participants were timed while writing a sentence, simulating eating, transferring an object to a shelf, dressing, retrieving an object from the floor, standing and turning, and walking. The score out of a maximum of 28 was recorded.

Covariates

Physical health status. Chronic health conditions were classified using a modified version of the Common Terminology Criteria for Adverse Events (version 4.03) specific to childhood cancer survivors.[29] We included the following organ systems (specific variables): cardiac (cardiomyopathy), pulmonary (corrected diffusing capacity of lung for carbon monoxide), endocrine (growth hormone deficiency, luteinizing hormone/follicle-stimulating hormone deficiencies, thyroid-stimulating hormone deficiency, adrenocorticotropic hormone deficiency), and neurologic (stroke, hemiplegia, paraplegia).

Intelligence. General intelligence was assessed using the matrix reasoning and vocabulary subsets from the Wechsler Abbreviated Scale of Intelligence,[30] which provides an abbreviated intelligence score (mean, 100; SD, 15) on the basis of age-specific national normative data. Scores < 10th percentile were considered impaired (standard score ≤ 81). Attention, memory, and executive functions also were assessed; domain-specific impairments were classified using previously published methods in our cohort.

Statistical Analysis

χ^2, Fisher's exact, and *t* tests were used to compare demographic and treatment characteristics between participants and nonparticipants. Latent class analysis (LCA) using the six indicators of independence was used to identify classes of independence without prespecification of a set number of classes.[31,32] Models were fit with one to four classes, and multiple fit indices were evaluated to select the optimal class number, including the Bayesian information criterion (BIC), Vuong-Lo-Mendell-Rubin likelihood ratio test, entropy, and minimum posterior probability.[33,34] Optimal fit emphasis was placed on adjusted Bayesian information criterion, adjusted Vuong-Lo-Mendell-Rubin *P* value, and substantive meaning. We required that the smallest class size be ≥ 10% to permit sufficient power for subsequent multivariable analyses. To confirm the robustness of class selection, we applied a similar LCA approach to a second population of acute lymphoblastic leukemia survivors who also received CNS-directed therapies. The proportion of survivors in each class with observed indicators of independence were examined and compared using χ^2 tests. Multivariable log-binomial models were used to examine associations between treatment exposures and physical performance variables with classes of functional independence; odds ratios (ORs) and 95% CIs were calculated. For models that examined associations between classes of independence and quality of life and psychological distress outcomes, adjusted means and standard errors were calculated, and generalized linear regression models were used. A Bonferroni correction was applied to analyses of HRQOL and psychological distress, and $P = .0035$ was considered significant. Analyses were completed using SAS 9.3 statistical software (SAS Institute, Cary, NC).

RESULTS

Of 472 potentially eligible CNS tumor survivors, 306 (65%) returned to SJCRH for a risk-based medical evaluation (Fig 1). Participants were, on average, 26.3 years of age and 17.6 years since their original diagnosis and were more likely than nonparticipants to be diagnosed with medulloblastoma (25% *v* 16%; Table 1). Approximately one third of participants received focal irradiation and one third craniospinal irradiation (CSI). Eighty-one percent of survivors completed study questionnaires independently; 19% were completed by significant other proxy report.

Three meaningful classes of functional independence were identified through LCA and reflected varying degrees of independence: independent (40%), moderately independent (34%), and nonindependent (26%). Appendix Table A1 (online only) lists the model fit indices for one through four classes. A similar three-class structure was observed for survivors of acute lymphoblastic leukemia treated with CNS-directed therapies (Appendix Tables A2 to A4, online only). Figure 2 shows the distribution of the six primary indicators by class of independence. A larger proportion of nonindependent survivors required assistance with personal care (independent, 1%; moderately independent, 2%; nonindependent, 27%; $P < .001$) or routine needs (independent, 11%; moderately independent, 4%; nonindependent, 78%; $P < .001$) and did not

Table 1. Demographic and Treatment Characteristics of Participant and Nonparticipant CNS Tumor Survivors

Characteristic	Participants, No. (%)	Nonparticipants, No. (%)	*P*
No. of participants	306	166	
Demographic			
Age at study, years			
Mean (SD)	26.3 (5.1)	—	—
Median (range)	25.3 (18.9-53.1)	—	—
Sex			.840
Male	174 (56.9)	96 (57.8)	
Female	132 (43.1)	70 (42.2)	
Ethnicity			.530
Non-Hispanic white	252 (82.3)	131 (78.9)	
Non-Hispanic black	50 (16.3)	33 (19.9)	
Hispanic	2 (0.7)	—	
Other	2 (0.7)	2 (1.2)	
Cancer-related characteristic			
Diagnosis			.002
Astrocytoma	130 (42.5)	79 (47.6)	
Medulloblastoma	77 (25.2)	27 (16.3)	
Ependymoma	36 (11.8)	12 (7.2)	
Craniopharyngioma	21 (6.9)	4 (2.4)	
Other low-grade glioma	12 (3.9)	13 (7.8)	
Germ cell tumors	10 (3.3)	13 (7.8)	
Other	20 (6.5)	18 (10.8)	
Age at diagnosis, years			
Mean (SD)	8.7 (4.6)	8.5 (4.9)	.600
Median (range)	8.6 (0.1-22.7)	8.0 (0.2-19.7)	
Interval since diagnosis, years			
Mean (SD)	17.6 (5.0)	—	—
Median (range)	16.8 (10.6-41.8)	—	—
Decade of diagnosis			.560
1960s	1 (0.3)	0 (0.0)	
1970s	5 (1.6)	4 (2.4)	
1980s	57 (18.6)	34 (20.5)	
1990s	194 (63.4)	94 (56.6)	
2000s	49 (16.0)	34 (20.5)	
Treatment exposure			
Mean CRT dose, Gy (SD)			
Posterior fossa	40.155 (24.071)	38.057 (24.158)	.490
Temporal	45.576 (20.088)	43.965 (15.775)	.490
Parieto-occipital	27.906 (20.740)	32.504 (23.087)	.110
Frontal	22.829 (20.183)	23.711 (18.514)	.740
Tumor location			.470
Supratentorial	153 (50.0)	86 (51.8)	
Infratentorial	147 (48.0)	74 (44.6)	
Spinal cord	6 (2.0)	6 (3.6)	
Surgical resection			.480
None	44 (14.4)	30 (18.1)	
Biopsy	42 (13.7)	21 (12.7)	
Partial	73 (23.9)	31 (18.7)	
Gross total	147 (48.0)	84 (50.6)	
Shunt			.270
No	187 (61.1)	110 (66.3)	
Yes	119 (38.9)	56 (33.7)	
Cranial radiation therapy			.100
None	103 (33.7)	72 (43.4)	
Focal	103 (33.7)	45 (27.1)	
Craniospinal	100 (32.7)	49 (29.5)	
Chemotherapy			.340
No	193 (63.1)	112 (67.5)	
Yes	113 (36.9)	54 (32.5)	

Abbreviations: CRT, conformal radiation therapy; SD, standard deviation.

have a driver's license (independent, 13%; moderately independent, 8%; nonindependent, 95%; $P < .001$). However, moderately independent survivors had comparable rates of employment, driving, and independence with routine and personal needs yet differed from those in the independent class in their inability to live alone ($P < .001$) and history of marriage ($P < .001$).

In multivariable models, treatment with CSI was associated with a 4.2-fold increased likelihood of nonindependence (OR, 4.20; 95% CI, 1.69 to 10.44). Hydrocephalus with shunting (OR, 2.57; 95% CI, 1.31 to 5.05) and younger age at diagnosis (OR, 1.24; 95% CI, 1.14 to 1.35) also were associated with an increased likelihood of survivors being nonindependent compared with independent (Table 2). Appendix Table A5 (online only) lists diagnostic and treatment characteristics by latent class. Appendix Table A6 (online only) lists a comparison of class 2 (moderately independent) and class 3 (nonindependent) with respect to treatment exposures.

In multivariable models that considered associations between physical performance and failure to achieve independence (Table 3), measures of aerobic capacity (OR, 5.47; 95% CI, 1.78 to 16.76), leg strength (OR, 15.28; 95% CI, 2.61 to 89.56), flexibility (OR, 3.66; 95% CI, 1.11 to 12.03), and adaptive physical function (OR, 11.54; 95% CI, 3.57 to 37.27) were associated with an increased likelihood of nonindependence in survivors. These estimates were observed after adjustment for concurrent chronic health conditions and intellectual impairment. Of note, nonindependent survivors were more likely to have severe impairment in the domains of attention, memory, and executive function (Appendix Table A7, online only). Appendix Table A8 (online only) lists a comparison of class 2 (moderately independent) and class 3 (nonindependent) with respect to physical performance measures.

Degree of functional independence was associated with HRQOL but not with emotional distress symptoms (Table 4; Appendix Table A9, online only). Survivors who were nonindependent reported reduced physical HRQOL in some but not all domains (physical function, $P < .001$; role limitations as a result of general health, $P < .001$) compared with independent survivors.

DISCUSSION

To our knowledge, this study is the first to comprehensively examine the ability of survivors of childhood CNS tumors to achieve independence as adults. By using multiple concurrent indicators, we identified three phenotypes that reflect varying degrees of functional and social independence. Only 40% of long-term survivors in our population achieved complete independence in adulthood. In this sample, nonindependent survivors were more likely to be living dependently, unemployed, require assistance with personal care and routine needs, unable to drive, and unmarried. However, we identified a substantial proportion (34%) as moderately independent. The identification of interventions and support to help this latter population to achieve autonomy is important as their caregivers, most commonly their parents, age.

Treatment with CSI conferred a four-fold increased likelihood of nonindependence. This finding is not particularly surprising given the well-established cognitive morbidities associated with CSI, particularly among those exposed at younger ages.[6,35] Tumors such as medulloblastomas are now classified by prognostic

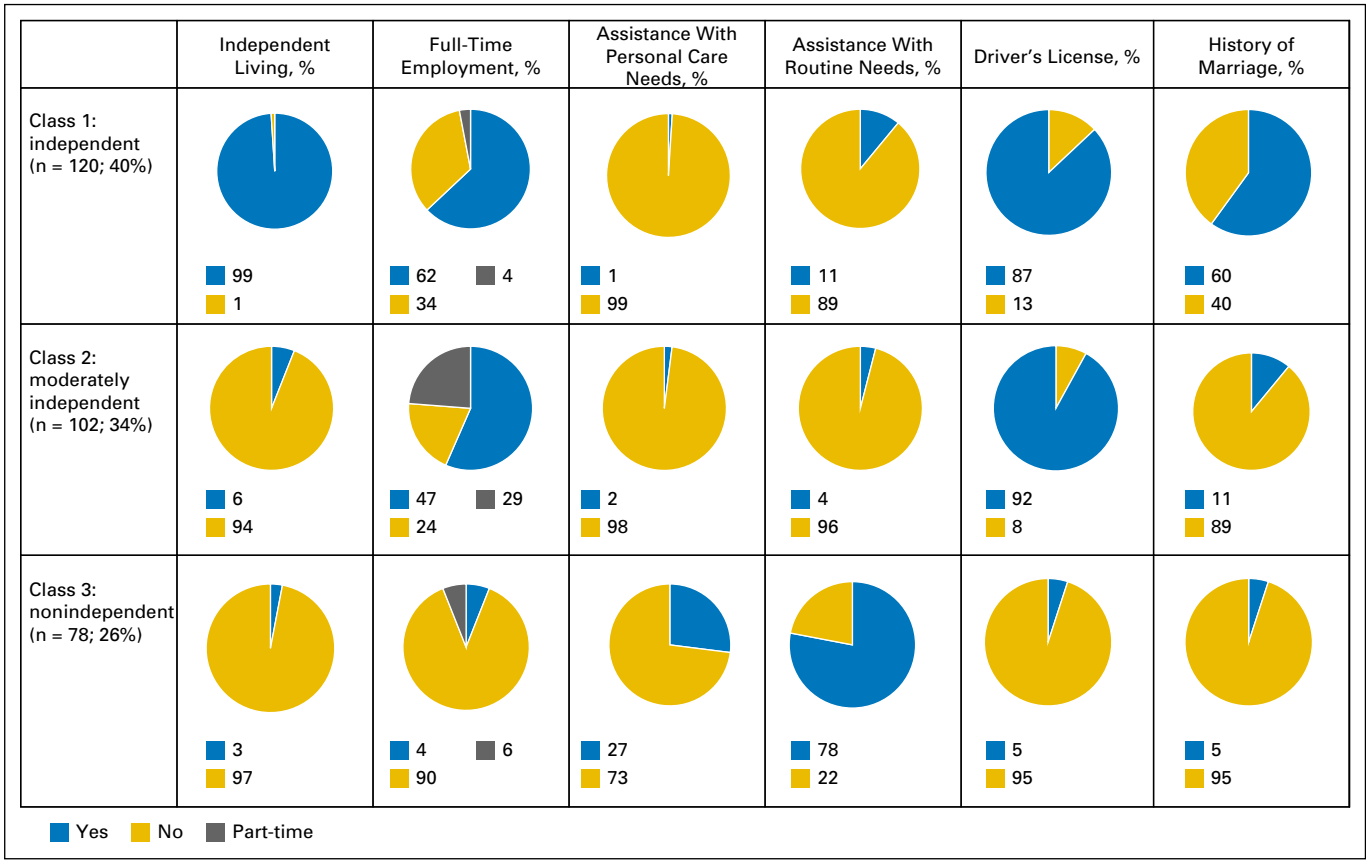

Fig 2. Indicators of functional and social independence by latent classes.

molecular characteristics. Such improved stratification may allow for the identification of favorable populations, such as the wingless (WNT) subgroup of medulloblastoma, in whom reductions in CSI exposure may be achieved without compromising tumor control. In fact, the current data suggest that a smaller proportion of survivors treated in more recent decades are nonindependent

Table 2. Associations Between Treatment Exposures and Failure to Achieve Independence

	Independent Class 1		Moderately Independent Class 2 *v* Class 1		Nonindependent Class 3 *v* Class 1	
Treatment Exposure	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Cranial radiation therapy						
None	50 (41. 7)	—	35 (34.3)	1.00	16 (20.5)	1.00
Focal	36 (30.0)	—	40 (39.2)	1.28 (0.63 to 2.59)	25 (32.1)	1.60 (0.69 to 3.77)
Craniospinal	34 (28.3)	—	27 (26.5)	1.45 (0.65 to 3.23)	37 (47.4)	**4.20 (1.69 to 10.44)**
Tumor location						
Infratentorial	57 (47.5)	—	45 (44.12)	1.00	44 (56.4)	1.00
Supratentorial	60 (50.0)	—	55 (53.92)	1.11 (0.56 to 2.19)	33 (42.3)	1.54 (0.70 to 3.36)
Spinal cord	3 (2.5)	—	2 (1.96)	0.74 (0.09 to 6.16)	1 (1.3)	0.50 (0.03 to 7.24)
Surgical resection						
None/biopsy	29 (24.2)	—	37 (36.27)	1.00	19 (24.4)	1.00
Partial	28 (23.3)	—	22 (21.57)	0.54 (0.24 to 1.26)	20 (25.6)	1.00 (0.39 to 2.59)
Gross total	63 (52.5)	—	43 (42.16)	0.46 (0.22 to 0.99)	39 (50.0)	0.90 (0.37 to 2.18)
Shunt						
No	85 (70.8)	—	63 (61.8)	1.00	35 (44.9)	1.00
Yes	35 (29.2)	—	39 (38.2)	1.62 (0.87 to 3.02)	43 (55.1)	**2.57 (1.31 to 5.05)**
Sex						
Female	53 (44.2)	—	43 (42.2)	1.00	33 (42.3)	1.00
Male	67 (55.8)	—	59 (57.8)	0.99 (0.55 to 1.79)	45 (57.7)	0.87 (0.45 to 1.68)
Mean age at diagnosis, years (SD)	10.63 (4.3)	—	8.26 (4.5)	0.98 (0.90 to 1.06)	6.38 (4.3)	**1.24 (1.14 to 1.35)**
Mean age at evaluation, years (SD)	28.33 (5.5)	—	24.63 (4.1)	1.02 (0.94 to 1.11)	25.49 (4.5)	0.95 (0.88 to 1.02)

NOTE. Single multivariable model presented with all adjusted variables shown. Boldface indicates statistical significance.
Abbreviations: OR, odds ratio; SD, standard deviation.

Table 3. Associations Between Physical Performance and Intellectual Deficits and Failure to Achieve Independence

Impairment	Independent Class 1		Moderately Independent Class 2 *v* Class 1		Nonindependent Class 3 *v* Class 1	
	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Aerobic						
Six-Minute Walk Test						
≥ 1.3 SD	108 (92.3)	—	96 (94.1)	1.00	34 (55.7)	1.00
< 1.3 SD	9 (7.7)	—	6 (5.9)	0.99 (0.31 to 3.13)	27 (44.3)	**5.47 (1.78 to 16.76)**
IQ ≤ 81						
No	103 (88.0)	—	86 (86.9)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.1)	1.30 (0.53 to 3.23)	48 (70.6)	**11.90 (4.47 to 31.67)**
Strength						
Hand grip						
≥ 1.3 SD	112 (94.9)	—	88 (86.3)	1.00	55 (74.3)	1.00
< 1.3 SD	6 (5.1)	—	14 (13.7)	**5.27 (1.62 to 17.09)**	19 (25.7)	3.42 (0.89 to 13.13)
IQ ≤ 81						
No	103 (88.0)	—	86 (86.9)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.1)	1.12 (0.44 to 2.86)	48 (70.6)	**16.03 (6.30 to 40.81)**
Knee extension (60 degrees per second)						
≥ 1.3 SD	110 (98.2)	—	88 (94.6)	1.00	39 (67.2)	1.00
< 1.3 SD	2 (1.8)	—	5 (5.4)	2.48 (0.44 to 13.98)	19 (32.8)	**15.28 (2.61 to 89.56)**
IQ ≤ 81						
No	103 (88.0)	—	86 (86.9)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.1)	1.08 (0.40 to 2.90)	48 (70.6)	**15.42 (5.47 to 43.44)**
Flexibility						
Sit and reach test						
≥ 1.3 SD	103 (88.8)	—	95 (37.7)	1.00	54 (83.1)	1.00
< 1.3 SD	13 (11.2)	—	7 (6.9)	0.65 (0.23 to 1.84)	11 (16.9)	**3.66 (1.11 to 12.03)**
IQ ≤ 81						
No	103 (88.0)	—	86 (86.9)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.1)	1.31 (0.53 to 3.25)	48 (70.6)	**19.59 (7.56 to 50.76)**
Dorsiflexion (60 degrees per second)						
≥ 1.3 SD	105 (94.6)	—	88 (95.7)	1.00	52 (92.9)	1.00
< 1.3 SD	6 (5.41)	—	4 (4.35)	0.90 (0.23 to 3.50)	4 (7.14)	1.75 (0.35 to 8.72)
IQ ≤ 81						
No	103 (88.0)	—	86 (86.87)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.13)	1.11 (0.42 to 2.94)	48 (70.6)	**17.65 (6.54 to 47.62)**
Dorsiflexion (90 degrees per second)						
≥ 1.3 SD	106 (95.5)	—	88 (95.65)	1.00	49 (87.5)	1.00
< 1.3 SD	5 (4.5)	—	4 (4.35)	1.16 (0.28 to 4.86)	7 (12.5)	2.18 (0.46 to 10.44)
IQ ≤ 81						
No	103 (88.0)	—	86 (86.87)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.13)	1.10 (0.41 to 2.93)	48 (70.6)	**16.68 (6.19 to 44.93)**
Balance						
Sensory Organization Test						
≥ 1.3 SD	82 (72.6)	—	73 (76.8)	1.00	19 (36.5)	1.00
< 1.3 SD	31 (27.4)	—	22 (23.2)	0.97 (0.47 to 1.98)	33 (63.5)	2.51 (0.96 to 6.53)
IQ ≤ 81						
No	103 (88.0)	—	86 (86.9)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.1)	1.10 (0.43 to 2.82)	48 (70.6)	**15.16 (5.55 to 41.39)**
Mobility						
Timed Up and Go test*						
≥ 1.3 SD	116 (100.0)	—	102 (100.0)	1.00	69 (100.0)	1.00
< 1.3 SD	0 (0.0)	—	0 (0.0)	—	0 (0.0)	—
IQ ≤ 81						
No	103 (88.0)	—	86 (86.9)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.1)	—	48 (70.6)	—
Adaptive physical function						
Physical Performance Test†						
≥ 1.3 SD	110 (94.0)	—	91 (89.2)	1.00	22 (36.7)	1.00
< 1.3 SD	7 (6.0)	—	11 (10.8)	2.50 (0.80 to 7.80)	38 (63.3)	**11.54 (3.57 to 37.27)**
IQ ≤ 81						
No	103 (88.0)	—	86 (86.9)	1.00	20 (29.4)	1.00
Yes	14 (12.0)	—	13 (13.1)	1.15 (0.46 to 2.89)	48 (70.6)	**8.91 (3.20 to 24.78)**

NOTE. Six separate multivariable models are presented. Each model is adjusted for age; sex; ethnicity; and other comorbid conditions, including neurologic, pulmonary, cardiac, and endocrine. Boldface indicates statistical significance.

Abbreviations: IQ, intelligence quotient; OR, odds ratio; SD, standard deviations.

*None of the participants who completed the Timed Up and Go test were < 1.3 SD below the population mean.

†Provides a measure of simulated activities of daily living.

Table 4. Associations Between Latent Classes of Independence and Impaired Health-Related Quality of Life (HRQOL)

	Independent	Moderately Independent		Nonindependent	
Impairment	Mean (SE)	Mean (SE)	*P*	Mean (SE)	*P*
Physical summary	48.8 (1.22)	47.9 (1.33)	.67	**38.5 (1.33)**	**< .001**
Mental summary	46.7 (1.62)	46.4 (1.76)	.97	48.8 (1.75)	.58
Physical function	47.2 (1.31)	46.3 (1.43)	.72	**35.5 (1.41)**	**< .001**
Role physical	47.5 (1.41)	47.3 (1.54)	.99	**37.4 (1.53)**	**< .001**
Body pain	49.9 (1.40)	49.7 (1.52)	.99	48.4 (1.48)	.70
General health	47.9 (1.58)	45.3 (1.73)	.18	41.9 (1.71)	.01
Vitality	49.7 (1.44)	50.4 (1.58)	.87	48.3 (1.55)	.73
Social function	46.1 (1.54)	45.1 (1.68)	.75	41.7 (1.63)	.08
Role emotional	44.4 (1.63)	45.2 (1.77)	.87	42.9 (1.77)	.73
Mental health	48.9 (1.49)	46.8 (1.63)	.30	48.4 (1.62)	.97

NOTE. Models adjusted for age; sex; ethnicity; education; other comorbid conditions, including neurologic, pulmonary, and endocrine; and IQ. Boldface indicates statistical significance.
Abbreviation: SE, standard error.

(Appendix Table A10, online only), which potentially corresponds to changes in cranial radiation dose and delivery parameters (ie, three-dimensional conformal radiation therapy).

This analysis identified both new targets (physical performance) and established targets (cognition) for intervention. Moderately independent survivors comprise a group potentially amenable to physical performance interventions designed to promote greater independence because intellectual impairment was largely unrelated to independence in this group, but large effect estimates (ie, ORs $\geq$ 2.5) were observed for associations between strength and adaptive function. Exercise programs have been shown to have positive effects on independence and adaptive living skills in adults with dementia,[36-38] and strength training has been shown to preserve independence in older adults.[39] We previously reported that survivors of pediatric brain tumors with physical performance limitations had restricted access to their physical environment.[40] Efforts to improve physical performance deficits and reduce individual-level barriers associated with access to the environment may promote greater independence. Vocational rehabilitation efforts may be appropriate for survivors who are unable to acquire employment because childhood cancer survivors who receive job search assistance and on-the-job support are four times more likely to be employed after receipt of such services.[41]

Physical performance deficits, including aerobic capacity, strength, flexibility, and mobility, were significantly associated with classification in the nonindependent class in which intellectual deficits also had a substantial effect on this poor outcome. More than 60% of survivors in this class showed severe impairment on measures of attention, memory, and executive function, which is consistent with an earlier report from our group; in that report we considered measures of independence separately and found that survivors of CNS tumors with impaired neurocognitive function were less likely to graduate from college and live independently.[6] The current results suggest that for this identified group of nonindependent survivors of CNS tumors, multimodal interventions that target both cognitive and physical performance deficits are warranted. In fact, interdisciplinary rehabilitation programs for the treatment of postacute traumatic brain injury in adults are generally effective at improving outcomes.[42] However, for this group of survivors, some aspects of independence may be unattainable (eg, driver's license in the presence of seizures), and interventions may need to focus on long-term supportive care both within and outside the home, including psychosocial support for primary caregivers of these survivors.

The results should be considered in the context of several limitations. A larger proportion of survivors of medulloblastoma were participants than nonparticipants. Because this diagnostic group is most likely to receive CSI, the results may overestimate the prevalence of nonindependence. Conversely, nonparticipants may have been unable to return to SJCRH because of reduced independence, so the results may underestimate the prevalence of nonindependence. Taken together, the effect of nonparticipation on the direction of our effect estimates is unclear. Future research is needed to understand the longitudinal trajectory of independence in survivors as well as the effect of changes in front-line therapies on degree of independence. Because survivors in this sample were a mean age of 26 years, they may acquire greater independence from their primary caregivers as they continue to transition through adulthood; however, with the heighten risk of developing chronic health conditions[43] and frailty,[44] survivors' independence also may be compromised as they age. Finally, future research should incorporate the use of validated measures of independence and disability because normative population data may provide additional information about the magnitude of risk of nonindependence among survivors.

In conclusion, the findings show that for children with CNS tumors, 5- or even 10-year survival is not enough. The ultimate goal should be to deliver therapies that maximize both survival and opportunities for functional and social independence throughout the lifespan.

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Disclosures provided by the authors are available with this article at jco.org.

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Appendix

Table A1. Latent Class Analysis Model Fit Indices for Latent Classes of Independence Among CNS Tumor Survivors

Model	BIC	Adjusted BIC	VLMR *P*	Adjusted VLMR *P*	Entropy	Minimum Posterior Probability	Smallest Class, %
1-Class solution	2,287.02	2,264.82	—	—	—	—	100.0
2-Class solution	2,044.42	1,996.85	< .0010	< .0010	0.858	0.92	26.7
3-Class solution	2,027.92	1,954.97	.0342	.0367	0.731	0.84	26.0
4-Class solution	2,035.35	1,937.03	.0012	.0013	0.780	0.88	18.3

Abbreviations: BIC, Bayesian information criterion; VLMR, Vuong-Lo-Mendell-Rubin.

Table A2. Characteristics of SJLIFE ALL Cohort

Characteristic	No. (%)
Age at diagnosis, years	
Mean (SD)	6.56 (4.38)
Range	0.20-19.48
0-5	582 (57.80)
6-10	243 (24.13)
11-15	146 (14.50)
16-20	36 (3.57)
Time from diagnosis, years	
Mean (SD)	24.89 (7.94)
Range	10.49-47.74
10-20	355 (35.25)
21-30	418 (41.51)
31-40	209 (20.75)
41-50	25 (2.48)
Age at evaluation, years	
Mean (SD)	31.45 (8.14)
Range	18.43-59.70
18-20	74 (7.35)
21-30	440 (43.69)
31-40	349 (34.66)
41-50	129 (12.81)
> 50	15 (1.49)
Sex	
Female	497 (49.35)
Male	510 (50.65)
Cranial radiation therapy dose	
No cranial radiation therapy	428 (42.50)
< 18 Gy	23 (2.28)
18-24 Gy	470 (46.67)
> 24 Gy	83 (8.24)
Dose unknown	3 (0.30)
High-dose IV methotrexate	
No	364 (36.15)
Yes	643 (63.85)
Intrathecal methotrexate	
No	0 (0)
Yes	1,007 (100)
High-dose cytarabine	
No	930 (92.35)
Yes	77 (7.65)
Intrathecal cytarabine	
No	206 (20.46)
Yes	801 (79.54)

NOTE. (n = 1,007).
Abbreviations: ALL, acute lymphoblastic leukemia; IV, intravenous; SD, standard deviation; SJLIFE, St Jude Lifetime Cohort Study.

Table A3. Latent Class Analysis Model Fit Indices for SJLIFE ALL Cohort

Model	BIC	Adjusted BIC	VLMR *P*	Adjusted VLMR *P*	Entropy	Minimum Posterior Probability	Smallest Class, %
1-Class solution	5,611.49	5,589.26	—	—	—	—	100.0
2-Class solution	5,243.03	5,195.39	< .0010	< .0010	0.647	0.893	36.7
3-Class solution	5,122.27	5,049.22	< .0010	< .0010	0.724	0.792	13.6
4-Class solution	5,119.73	5,021.27	.0295	.0310	0.728	0.837	6.1
5-Class solution	5,143.28	5,019.45	.0259	.0271	0.788	0.752	2.0

Abbreviations: ALL, acute lymphoblastic leukemia; BIC, Bayesian information criterion; SJLIFE, St Jude Lifetime Cohort Study; VLMR, Vuong-Lo-Mendell-Rubin.

Table A4. Classes of Functional Independence in SJLIFE ALL Cohort

Indicator	Latent Class, No. (%)		
	Independent	Moderately Independent	Nonindependent
History of marriage			
No	110 (18.1)	218 (95.6)	64 (50.4)
Yes	497 (81.9)	10 (4.4)	63 (49.6)
Independent living			
Independent	558 (94.7)	20 (9.2)	48 (38.1)
Nonindependent	31 (5.3)	197 (90.7)	78 (61.9)
Employment			
Full time	491 (82.5)	120 (54.3)	7 (5.4)
Part time	28 (4.7)	63 (28.5)	2 (1.5)
Unemployed	76 (12.7)	38 (17.2)	121 (93.1)
Assistance with personal care needs			
Yes	0 (0.0)	0 (0.0)	21 (15.4)
No	631 (100)	227 (100)	115 (84.6)
Assistance with routine needs			
Yes	7 (1.1)	0 (0.0)	67 (49.6)
No	624 (98.9)	226 (100)	68 (50.4)
Driver's license			
Yes	621 (98.4)	199 (87.3)	53 (40.0)
No	10 (1.6)	29 (12.7)	83 (60.0)

Abbreviations: ALL, acute lymphoblastic leukemia; SJLIFE, St Jude Lifetime Cohort Study.

Table A5. Diagnosis and Treatment Characteristics by Classes of Independence Among CNS Tumor Survivors

Characteristic	Class, No. (%)			*P*
	Independent	Moderately Independent	Nonindependent	
Diagnosis				.006
Medulloblastoma	25 (20.8)	19 (18.6)	32 (41.0)	
Ependymoma	11 (9.2)	16 (15.7)	9 (11.5)	
Astrocytoma	55 (45.8)	45 (44.1)	28 (35.9)	
Craniopharyngioma	6 (5.0)	10 (9.8)	4 (5.1)	
Other low-grade glioma	9 (7.5)	2 (2.0)	1 (1.3)	
Germ cell tumor	4 (3.3)	4 (3.9)	1 (1.3)	
Other	10 (8.3)	6 (5.9)	3 (3.9)	
Cranial radiation therapy				.005
None	50 (41.7)	35 (34.3)	16 (20.5)	
Focal	36 (30.0)	40 (39.2)	25 (32.1)	
Craniospinal	34 (28.3)	27 (26.5)	37 (47.4)	
Tumor location				.590
Supratentorial	60 (50.0)	55 (53.9)	33 (42.3)	
Infratentorial	57 (47.5)	45 (44.1)	44 (56.4)	
Spinal cord	3 (2.5)	2 (2.0)	1 (1.3)	
Surgical resection				.280
None/biopsy	29 (24.2)	37 (36.3)	19 (24.4)	
Partial	28 (23.3)	22 (21.6)	20 (25.6)	
Gross total	63 (52.5)	43 (42.2)	39 (50.0)	
Age at diagnosis, years				< .001
0-3	7 (5.83)	21 (20.6)	27 (34.6)	
4-7	44 (36.7)	35 (34.3)	26 (33.3)	
8-11	32 (26.7)	25 (24.5)	19 (24.4)	
12-15	37 (30.8)	21 (20.6)	6 (7.7)	

Table A6. Associations Between Treatment Exposures and Failure to Achieve Independence (Class 2 *v* Class 3) Among CNS Tumor Survivors

Treatment Exposure	Moderately Independent *v* Nonindependent, OR (95% CI)
Cranial radiation therapy	
None	1.00
Focal	**0.80 (0.35 to 1.82)**
Craniospinal	**0.35 (0.14 to 0.86)**
Tumor location	
Infratentorial	1.00
Supratentorial	1.39 (0.64 to 3.00)
Spinal cord	2.06 (0.13 to 32.2)
Surgical resection	
None/biopsy	1.00
Partial	0.54 (0.22 to 1.36)
Gross total	0.52 (0.22 to 1.21)
Shunt	
No	1.00
Yes	0.63 (0.33 to 1.20)
Sex	
Female	1.00
Male	1.15 (0.60 to 2.19)
Age at diagnosis	**1.20 (1.10 to 1.32)**
Age at evaluation	**0.88 (0.81 to 0.97)**

NOTE. Single multivariable model presented with all adjusted variables shown. Boldface indicates statistical significance.
Abbreviation: OR, odds ratio.

Table A7. Number and Proportion of CNS Tumor Survivors With Severe Impairment in Attention, Memory, and Executive Function Across Latent Classes

Impairment	Class 1, No. (%)	Class 2, No. (%)	Class 3, No. (%)	*P*
Attention				**< .001**
Not impaired	91 (75.8)	75 (73.5)	15 (19.2)	
Impaired	23 (19.2)	21 (20.6)	54 (69.2)	
Unknown	6 (5.0)	6 (5.9)	9 (11.5)	
Memory				**< .001**
Not impaired	91 (75.8)	69 (67.6)	26 (33.3)	
Impaired	24 (20.0)	27 (26.5)	48 (61.5)	
Unknown	5 (4.2)	6 (5.9)	4 (5.1)	
Executive function				**< .001**
Not impaired	77 (64.2)	61 (59.8)	10 (12.8)	
Impaired	38 (31.7)	35 (34.3)	64 (82.1)	
Unknown	5 (4.2)	6 (5.9)	4 (5.1)	

NOTE. Boldface indicates statistical significance.

Table A8. Associations Between Physical Performance and Intellectual Deficits and Failure to Achieve Independence (Class 2 *v* Class 3) Among CNS Tumor Survivors

Impairment	Moderately Independent *v* Nonindependent, OR (95% CI)
Aerobic	
Six-Minute Walk Test	
≥ 1.3 SD	1.00
< 1.3 SD	**0.18 (0.06 to 0.58)**
IQ ≤ 81	
No	1.00
Yes	**0.11 (0.04 to 0.28)**
Strength	
Hand grip	
≥ 1.3 SD	1.00
< 1.3 SD	1.54 (0.47 to 5.06)
IQ ≤ 81	
No	1.00
Yes	**0.07 (0.03 to 0.18)**
Knee extension (60 degrees per second)	
≥ 1.3 SD	1.00
< 1.3 SD	**0.16 (0.04 to 0.67)**
IQ ≤ 81	
No	1.00
Yes	**0.07 (0.03 to 0.20)**
Flexibility	
Sit and reach test	
≥ 1.3 SD	1.00
< 1.3 SD	**0.18 (0.05 to 0.63)**
IQ ≤ 81	
No	1.00
Yes	**0.07 (0.03 to 0.17)**
Dorsiflexion (60 degrees per second)	
≥ 1.3 SD	1.00
< 1.3 SD	0.51 (0.10 to 2.69)
IQ ≤ 81	
No	1.00
Yes	**0.06 (0.02 to 0.17)**
Dorsiflexion (90 degrees per second)	
≥ 1.3 SD	1.00
< 1.3 SD	0.53 (0.11 to 2.58)
IQ ≤ 81	
No	1.00
Yes	**0.07 (0.02 to 0.18)**
Balance	
Sensory Organization Test	
≥ 1.3 SD	1.00
< 1.3 SD	0.39 (0.15 to 1.01)
IQ ≤ 81	
No	1.00
Yes	**0.07 (0.03 to 0.20)**
Mobility	
Timed Up and Go test*	
≥ 1.3 SD	1.00
< 1.3 SD	—
IQ ≤ 81	
No	1.00
Yes	—
Adaptive physical function	
Physical Performance Test†	
≥ 1.3 SD	1.00
< 1.3 SD	**0.22 (0.08 to 0.59)**
IQ ≤ 81	
No	1.00
Yes	**0.13 (0.05 to 0.34)**

NOTE. Six separate multivariable models are presented. Each model is adjusted for age; sex; ethnicity; and other comorbid conditions, including neurologic, pulmonary, cardiac, and endocrine. Boldface indicates statistical significance.

Abbreviations: IQ, intelligence quotient; OR, odds ratio; SD, standard deviation.

*None of the participants who completed the Timed Up and Go test were < 1.3 SD below the population mean.

†Provides a measure of simulated activities of daily living.

Table A9. Associations Between Latent Classes of Independence and Psychological Distress Among CNS Tumor Survivors

	Depression		Anxiety		Somatization		Global Distress	
Latent Class	Mean (SE)	*P*	Mean (SE)	*P*	Mean (SE)	*P*	Mean (SE)	*P*
Independent	50.4 (1.49)		47.9 (1.35)		51.2 (1.34)		49.4 (1.55)	
Moderately independent	52.9 (1.62)	.22	49.4 (1.47)	.53	52.0 (1.46)	.84	51.5 (1.69)	.35
Nonindependent	52.3 (1.58)	.58	48.6 (1.44)	.93	56.4 (1.43)	.01	52.9 (1.65)	.20

NOTE. Adjusted means are shown. Models adjusted for age; sex; ethnicity; education; other conditions, including neurologic, pulmonary, and endocrine; and IQ.
Abbreviation: SE, standard error.

Table A10. Number and Proportion of CNS Tumor Survivors Across Latent Classes by Decade of Diagnosis

	Latent Class, No. (%)		
Decade of Diagnosis	Independent	Moderately Independent	Nonindependent
1960-1989	28 (44.4)	7 (11.1)	28 (44.4)
1990-1999	72 (37.7)	74 (38.7)	45 (23.6)
≥ 2000	20 (43.5)	21 (45.7)	5 (10.9)