Long-Term Follow-Up of Children Treated for High-Grade Gliomas: Children's Oncology Group L991 Final Study Report

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A B S T R A C T

Purpose

High-grade gliomas of the CNS are characterized by poor treatment response and prognosis for long-term survival. The Children's Oncology Group (COG) L991 study investigated the neuropsychological, behavioral, and quality of life (QoL) outcomes after treatment on the Children's Cancer Group (CCG) trial for high-grade gliomas (CCG-945).

Patients and Methods

Fifty-four patients (29 males, 25 females) with a median age of 8.8 years at diagnosis (range, 0.2 to 19.5 years) were enrolled at 25 institutions in North America, representing 81% of available survivors; median length of follow-up was 15.1 years (range, 9.5 to 19.2 years), and median age at study evaluation was 23.6 years (range, 11.3 to 36 years). Standardized tests of neuropsychological functioning and QoL were performed. Descriptive statistics summarized principal findings, and one-way analysis of variance identified potential predictors of outcomes.

Results

With an average follow-up time of 15 years, survivors demonstrated intellectual functioning within the low-average range. Executive functioning and verbal memory were between the low-average and borderline ranges. In contrast, visual memory and psychomotor processing speed were between the borderline and impaired ranges, respectively. Approximately 75% of patient reported overall QoL within or above normal limits for both physical and psychosocial domains. Nonhemispheric tumor location (midline or cerebellum), female sex, and younger age at treatment emerged as independent risk factors.

Conclusion

These results serve as a benchmark for comparison with future pediatric high-grade glioma studies, in addition to identifying at-risk cohorts that warrant further research and proactive interventions to minimize late effects while striving to ensure survival.

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INTRODUCTION

Primary CNS malignancies are second in incidence to acute lymphoblastic leukemia in children and adolescents, with approximately 2,400 newly diagnosed pediatric patients each year in the United States.¹ Advances in diagnostic modalities, pediatric randomized clinical trials, and increasingly aggressive treatment protocols have improved the 5-year survival rates of children with CNS tumors from 58% in the late 1970s to 73% in 2000.² At present, greater than 60% of children diagnosed with brain tumors are currently expected to survive into adulthood.³ Consequently, the neuropsychological and behavioral outcomes of pediatric patients are receiving increasing attention, as multimodality treatments increase the probability of long-term survival.

Specific treatments for pediatric CNS tumors differ considerably by tumor location and histology; however, most regimens incorporate combinations of neurosurgery, chemotherapy, and irradiation to the entire neuraxis or to the tumor bed. Chemotherapeutic agents used in treatment regimens place children at increased risk for both early and late nervous system sequelae.⁴ Cranial irradiation has been associated with deficits in intelligence, attention, memory, motor skills, processing speed, and visual-spatial skills secondary to white matter changes, particularly in the frontal cortex.⁴⁻⁶ Moreover, younger children at diagnosis have demonstrated more pronounced intelligence quotient (IQ) and functional deficits,⁷ whereas tumor location, resectability, recurrence, and family socioeconomic

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status have also been shown to affect intellectual functioning, academic achievement, and behavioral adaptation.⁸

High-grade gliomas are a group of CNS tumors characterized by heterogeneity and a typically poor treatment response and prognosis for survival.⁹ The present study, Children's Oncology Group (COG) L991, was developed as a long-term follow-up of patients enrolled onto the Children's Cancer Group (CCG) 945 trial, which is the largest, multicenter, randomized therapeutic trial for children with high-grade gliomas. The present outcomes study is the first investigation, to our knowledge, of the neuropsychological, quality-of-life (QoL), social-emotional, and behavioral late effects arising from multimodality treatment for this pediatric disease. Secondary aims include determining the differential impact of various risk factors on patient outcomes, such as age at diagnosis, pathology, tumor location, extent of resection, sex, and time since completion of treatment.

PATIENTS AND METHODS

Two hundred fifty patients, younger than age 21 years at diagnosis, were enrolled onto the therapeutic trial between 1985 and 1992. Detailed descriptions of patient characteristics, disease parameters, and methods of treatment have been previously reported.⁹⁻¹⁶ Children 36 months of age and older at study entry were randomly assigned to one of two treatment arms, both of which included radiotherapy 54 Gy in 1.8-Gy fractions directed to the tumor volume with 2-cm margins. The control regimen, regimen A, consisted of weekly vincristine during involved-field irradiation followed by eight cycles of lomustine, vincristine, and prednisone administered every 6 weeks. The experimental regimen, regimen B, involved two cycles of the eight-drugs-in-1-day (8-in-1) chemotherapy regimen (lomustine, vincristine, hydroxyurea, procarbazine, cisplatin, cytarabine, dacarbazine, and methylprednisolone), followed by irradiation given at the same volume and dose and then by eight cycles of 8-in-1 maintenance chemotherapy. Patients younger than 36 months at diagnosis were nonrandomly assigned to the 8-in-1 treatment regimen and did not receive radiotherapy. Patients with primary spinal cord high-grade gliomas age 36 months and older were nonrandomly assigned to receive 8-in-1 with 36 Gy of irradiation to the craniospinal axis.

All surviving patients who completed multimodality therapy on CCG-945 were eligible to participate in the COG L991 outcomes study, including patients who had experienced relapse and required additional treatment. Patients provided signed informed consent before enrollment on institutional review board–approved protocols in compliance with the Declaration of Helsinki.

Measures

Patients were administered a battery of standardized tests either by a licensed psychologist or, in some cases, by a psychology trainee under the supervision of a licensed psychologist at their respective local institutions. Age-stratified normative standards for the neuropsychological, social-emotional, behavioral, and QoL assessment instruments were used (Appendix, online only).

Statistical Analyses

To assess for potential selection bias, χ^2 analyses were performed to compare demographic and clinical characteristics of the 54 patients enrolled onto this study with those of 25 surviving patients who were enrolled onto CCG-945 but not COG L991. There was no indication of selection bias based on age, sex, race, extent of resection, and tumor location. Individual test performances were compared with the normative test means for each measure using one-sample *t* tests. One-way analysis of variance tests were conducted to determine the differential impact of the following risk factors: age at diagnosis, race, sex, tumor pathology, extent of resection, tumor location, treatment regimen, relapse status, and months of follow-up. For predictors with more than two levels, when a main effect was found, a Tukey post hoc test was conducted to identify significant differences between the groups. Two-sided analysis was used in all comparisons, and a *P* < .05 was considered statistically

significant for all instruments except for the Delis-Kaplan Executive Function Test (DKEFS), the California Verbal Learning Test (CVLT), and the Rey Complex Figure Test, where an α level of *P* < .01 was established to minimize the chance of a type I error, given the multiple comparisons. For the Neurobehavioral Function Inventory (NFI), matched-pair *t* tests were conducted to examine differences in family and patient ratings on the six subscale scores.

RESULTS

Fifty-four survivors were enrolled between 2001 and 2005 at 25 institutions across North America, representing 81% of the available survivors (54 of 79 survivors). Thirteen survivors declined participation, and 12 could not be located by the treating institutions. The study sample included 29 males and 25 females with a median age of 8.8 years (range, 0.2 to 19.5 years) at diagnosis; median length of follow-up was 15.1 years (range, 9.5 to 19.2 years); and median age at study evaluation was 23.6 years (range, 11.3 to 36 years; Table 1).

Intelligence

Mean intellectual functioning was measured to be within the low-average range for Full Scale IQ (FSIQ), Verbal IQ (VIQ), and

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients	%
Age at diagnosis, years		
Median	8.8	
Range	0.2-19.5	
Age at testing, years		
Median	23.6	
Range	11.3-36.0	
Length of follow-up, years		
Median	15.1	
Range	9.5-19.2	
Sex		
Male	29	53.7
Female	25	46.3
Race		
White	44	81.5
Latino	7	13.0
African American	1	1.9
Mixed	2	3.7
Disease location		
Left cerebral hemisphere	24	44.4
Right cerebral hemisphere	12	22.2
Posterior fossa	7	13.0
Midline	7	13.0
Spine	4	7.4
Extent of resection		
Partial	5	9.3
Subtotal	11	20.4
Total	34	63.0
Biopsy	4	7.4
Treatment arm		
A (standard arm)	23	42.6
B (experimental arm)	17	31.4
Nonrandomized B (nonrandom assignment to experimental arm)	14	26.0
Pathology		
High-grade glioma	30	55.6
Discordant tumor	24	44.4

Performance IQ (PIQ) on the Wechsler Abbreviated Scale of Intelligence (Table 2).

Predictor variables were initially determined using VIQ, PIQ, and FSIQ as outcome measures. A sex main effect was found for VIQ ($F = 5.42, P = .02$). Female patients obtained lower VIQ (mean score, 74.9) compared with male patients (mean score, 87.9). In addition, age at treatment was significantly associated with both FSIQ ($F = 4.87, P = .03$) and PIQ ($F = 5.28, P = .026$). Patients younger than 3 years at treatment obtained lower FSIQ scores (mean score, 70.0) compared with older patients (mean score, 86.1). Younger patients also reported lower PIQ (mean score, 71.4) than patients older than age 3 years at the time of treatment (mean score, 86.7). Tumor location main effects were associated with FSIQ ($F = 3.25, P = .03$) and VIQ ($F = 3.96, P = .01$). Tukey post hoc tests indicated significantly higher FSIQ and VIQ in patients with spinal cord tumors (mean scores, 100.3 and 103.3, respectively) than those treated for tumors in the posterior fossa (mean scores, 64.9 and 66.1, respectively).

Verbal Learning and Memory

Verbal learning and memory was within the low-average range on the CLVT. Short Delay Recall remained in the low-average range but declined to the borderline range after a 20-minute long delay. Recognition Memory improved to the low-average range.

Tumor location main effects were found for the following three scales of the CVLT: Overall Learning ($F = 3.88, P = .015$; trend), Short Delay Free Recall ($F = 3.95, P = .014$; trend), and Short Delay Cued Recall ($F = 4.74, P = .006$). Tukey post hoc tests indicated significant differences in Overall Learning between spinal cord (mean score, 54.0) and posterior fossa (mean score, 25.6) patient subgroups; in Short Delay Free Recall between spinal cord (mean score, 0.5) and midline (mean score, -2.4) patient subgroups; and in Short Delay Cued Recall between spinal cord (mean score, 0.1) and midline patient subgroups (mean score, -3.0).

Visual-Spatial and Visual Memory

Mean performance on the Rey Complex Figure Test, a combined measure of visual-spatial constructional planning and motor integration, was within the impaired range indicating severely affected skills. When subsequently asked to redraw the design from memory, the study sample demonstrated a borderline ability in both short- and long-delay recall conditions, as well as on the recognition trial.

Executive Functioning

Performances on the executive functioning subtests from the DKEFS varied from the low-average to borderline ranges. Tumor location main effects were determined for the following subtests of the DKEFS: Color-Word Interference Test (Word Reading, $F = 5.7, P = .0024$; Inhibition, $F = 5.99, P = .0019$; Inhibition/Switching, $F = 7.27, P < .001$), and Trail Making Test (Number Sequencing, $F = 0.43, P = .013$, trend; Number-Letter Switching, $F = 4.56, P = .0079$). Significant differences were noted between spinal cord and posterior fossa patient subgroups on all five subtests and between spinal cord and cerebral hemisphere patient subgroups in all three Color-Word Interference subtests. There was a significant overall tumor location main effect for the correct number of sorts in the Sorting Test ($F = 4.72, P = .0072$) and an indication of trend in Sort Descriptions ($F = 4.13, P = .014$) and in Color Naming of the Color-Word Interference Test ($F = 4.27, P = .0103$). However, for all three measures,

Tukey tests comparing all four patient subgroup means did not yield significant findings for any of the paired means.

Psychomotor Processing Speed

Psychomotor processing speed on the Symbol Digit Modalities Test was found to be the most severely affected higher cortical function as documented by the impaired study sample mean. Tumor location main effects were observed for psychomotor processing speed on the Symbol Digit Modalities Test ($F = 4.30, P = .0097$). Tukey post hoc analysis indicated a significant difference in processing speed between patients with spinal cord tumors (mean score, -0.74) and both patient groups with posterior fossa and midline tumors (mean scores, -3.51 and -3.55, respectively).

QoL

QoL is a value compromised of psychological and social functioning, along with any physical discomfort and disability. Despite documented functional variability, responses on the Short Form-36 Health Survey (version 2.0) and Child Health Questionnaire indicated overall physical and psychological QoL to be solidly within the average range.

Combined analysis using the overall QoL summary scores from the Child Health Questionnaire and Short Form-36 indicated that sex was the single best predictor of physical health ($P = .05$). Female patients (mean score, 42.8) reported poorer overall physical QoL when compared with male patients (mean score, 49.7). There were no predictor variables associated with the overall psychological QoL scale.

Social-Emotional and Behavior Functioning

Both patients and their caregivers (parents, 89%; spouses or siblings, 11%) completed the NFI to assess social-emotional and behavioral functioning. The consistency between reports from patients and these secondary data sources was calculated for each subscale by differences in matched-pair T scores, with higher scores indicating greater disparities (Table 3). There were no significant differences between family and patient mean scores for the Motor, Somatic, Depression, and Aggression subscales. The Communication subscale revealed a significant difference between family reports (mean score, 58.87) compared with patient endorsements (mean score, 51.68) of problems ($t = 4.16, P < .01$). The Attention/Memory subscale demonstrated a significant difference between family perceptions (mean score, 50.71) compared with patient reports (mean score, 46.19) of difficulties ($t = 2.78, P < .01$).

Analyses to identify potential predictors of lowered social-emotional and behavioral functioning were conducted using the six subscales of the NFI as outcome measures. Univariate analysis revealed that sex was significantly associated with scores on the Depression subscale. Family members of female patients (mean score, 45.7) perceived more frequent problems involving depression than family members of male patients (mean score, 43.7; $F = 7.24, P = .01$).

DISCUSSION

We report, to our knowledge, the first systematic investigation of neuropsychological functioning, behavior, and QoL in long-term survivors treated for childhood high-grade gliomas. Our sample included patients previously treated on the largest randomized clinical trial for

Table 2. Neuropsychological Functioning, Behavior, and Quality-of-Life Test Results

Test	No. of Patients	Score		Patients Below Normal Limits	
		Mean	SD	No.	%
Intelligence					
WASI Full Scale IQ	49	83.14*	20.56	25	51.0
WASI Performance IQ	50	83.96*	18.82	25	50.0
WASI Verbal IQ	50	82.18*	20.44	28	56.0
Psychomotor processing speed					
SDMT	47	−2.59*	1.49	42	89.4
Verbal learning and memory					
CVLT Total Score Trials 1-5	47	37.53*	13.91	25	53.2
CVLT Short Delay Free	47	−1.20*	1.53	22	46.8
CVLT Short Delay Cued	47	−1.41*	1.57	23	48.9
CVLT Long Delay Free	47	−1.37*	1.51	25	53.2
CVLT Long Delay Cued	47	−1.40*	1.58	23	48.9
CVLT Recognition Memory	46	−0.80	2.40	20	43.5
Visual-motor integration and visual memory					
RCFT Copy	45	26.21*	9.15	24	53.3
RCFT Immediate Recall	43	31.58*	15.22	31	72.1
RCFT Delayed	44	28.98*	13.18	33	75.0
RCFT Recognition Total	44	32.64*	13.53	31	70.5
Executive functioning					
DKEFS Trail Making Test					
Visual Scanning	45	4.96*	4.11	26	57.8
Number Sequencing	45	5.04*	4.30	25	55.6
Letter Sequencing	45	4.36*	4.20	29	64.4
Number Letter Switching	43	4.42*	3.87	30	69.8
Motor Speed	45	6.22*	4.23	21	46.7
DKEFS Verbal Fluency Test					
Letter Fluency	47	6.68*	4.09	28	59.6
Category Fluency	47	7.23*	4.33	21	44.7
Category Switching, Correct Responses	47	7.23*	4.60	23	48.9
Category Switching Accuracy	47	7.23*	3.88	20	42.6
DKEFS Design Fluency					
Filled Dots: Total Correct	44	7.34*	2.56	14	31.8
Empty Dots: Total Correct	44	7.20*	2.94	21	47.7
Switching: Total Correct	44	7.32*	3.38	17	38.6
Design Fluency: Total Correct	44	7.07*	3.24	18	40.9
DKEFS Color–Word Interference Test					
Color Naming	45	4.44*	3.82	31	68.9
Word Reading	44	4.70*	4.40	32	72.7
Inhibition	43	4.40*	4.13	31	72.1
Inhibition/Switching	42	4.62*	3.78	31	73.8
DKEFS Sorting Test					
Description	36	6.44*	3.48	16	44.4
Correct Sorts	39	6.51*	3.60	18	46.2
DKEFS Tower Test					
Tower	42	7.64*	4.15	16	38.1
Social-emotional and behavioral functioning					
NFI Patient Aggression	36	44.47*	6.23	11	30.6
NFI Patient Communication	36	50.58	10.29	7	19.4
NFI Patient Depression	36	44.56	9.91	12	33.3
NFI Patient Memory/Attention	36	44.67	11.39	10	27.8
NFI Patient Motor	36	46.97	9.09	6	16.7
NFI Patient Somatic	36	45.83	8.17	7	19.4
NFI Family Aggression	35	46.69	8.04	7	20.0
NFI Family Communication	35	60.46*	13.62	2	5.7
NFI Family Depression	35	48.80	10.13	6	17.1
NFI Family Memory/Attention	35	52.09	10.19	3	8.6
NFI Family Motor	35	52.63	11.57	5	14.3
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Table 2. Neuropsychological Functioning, Behavior, and Quality-of-Life Test Results (continued)

Test	No. of Patients	Score		Patients Below Normal Limits	
		Mean	SD	No.	%
NFI Family Somatic	35	48.54	10.72	7	20.0
Quality of life					
Psychosocial	45	47.87	11.72	11	24.4
Physical	45	46.3	11.56	10	22.2

NOTE. Scoring for the tests was as follows: WASI, standard scores: mean, 100; SD, 15; SDMT, z scores: mean, 0; SD, 1; CLVT, total, T scores: mean, 50; SD, 10; CVLT, indices, z scores: mean, 0; SD, 1; RCFT, copy, raw scores: 36 points total; RCFT, indices, T scores: mean, 50; SD, 10; DKEFS, subtests, scaled scores: mean, 10; SD, 3; NFI, indices, T scores: mean, 50; SD, 10; Short Form-36 and Child Health Questionnaire indices, T scores, mean, 50; SD, 10.

Abbreviations: CVLT, California Verbal Learning Test; DKEFS, Delis-Kaplan Executive Functioning System; IQ, intelligence quotient; NFI, Neuropsychological Functioning Inventory; RCFT, Rey Complex Form Test; SD, standard deviation; SDMT, Symbol Digit Modalities Test; WASI, Wechsler Abbreviated Scale of Intelligence.

*Significant results of one-sample *t* test comparison with test norms ($P < .001$).

such children. After an average follow-up of 15 years, survivors enrolled onto the present outcomes study COG L991 demonstrated mean intellectual functioning within the low-average range. Half of this study sample performed within or above normal limits. Executive functioning and verbal learning and memory were between the low-average and borderline ranges, with similar distributions as noted earlier. In contrast, visual learning and memory and psychomotor processing speed were measured to be within the borderline and impaired ranges, respectively, with approximately 75% to 90% of the survivors below normal limits in both domains. In marked contrast, QoL was reported to be solidly within normal limits for more than 75% of the survivors. This apparent discrepancy between lower neuropsychological functioning and higher QoL could be interpreted as a denial of documented disabilities; however, the robust correlations between patient and caregiver reports on the NFI for Depression, Aggression, Motor, and Somatic domains suggest that many survivors are accurately reporting adjustment to many aspects of daily functioning despite frank limitations. The significant disparities found in the two domains of Communication and Attention/Memory provide a focus for interventions by increasing survivor awareness and guiding educational and remediation programs for long-term survivors.

Nonhemispheric tumor location (midline or posterior fossa), female sex, and young age at treatment emerged as independent risk factors for lower neuropsychological, QoL, social-emotional, and behavioral functioning. These identified predictor variables provide direction and focus for targeted assessment and early interventions with these at-risk groups. Explanations for the present findings of lowered

memory and processing speed in patients with midline tumors include damage to vital structures such as the basal ganglia, anterior corpus callosum, thalamus, caudate nucleus, and adjacent white matter tracts, along with the hypothalamic-pituitary axis and fronto-striato-thalamic circuits, which can affect abilities in these specific domains of functioning.¹⁷⁻²⁰

Posterior fossa lesions included tumors predominantly arising from the cerebellar hemispheres, vermis, and brainstem. Patients treated for tumors in the posterior fossa demonstrated the most severe cognitive and behavioral problems, which involved intelligence, learning, executive functioning, and processing speed. The role of the cerebellum in motor functioning has been well studied; however, emerging research describes connections between the cerebellum and the cerebral hemispheres (ie, frontal lobes) that regulate selective and sustained attention, as well as information processing speed, intelligence, language, and memory skills. In addition, posterior fossa tumors can commonly lead to hydrocephalus, which may negatively impact brain development by increased intracranial pressure, causing injury to the periventricular white matter.²¹⁻²⁸

Females in this study demonstrated significantly lower verbal intellectual abilities compared with males. Follow-up studies of childhood acute lymphoblastic leukemia survivors have demonstrated that female sex is a risk factor for lower intelligence and verbal memory skills after treatment.²⁹⁻³⁴ However, this disparity has not been well demonstrated within the pediatric brain tumor population. Sexual dimorphism in cerebral development may play a role given males' generally increased cerebral volume by age, in addition to differences in other structures such as the hippocampus, amygdala, and gray and white matter volume between the sexes; however, a recent review was not able to establish a link between radiation-induced damage and sex.³⁵ One study of 43 children with average-risk medulloblastoma treated with reduced-dose craniospinal radiotherapy and chemotherapy noted that girls demonstrated a significant decline in VIQ compared with boys ($P = .008$).³⁶ The authors qualify the finding by noting their longitudinal modeling, which used predicted IQ scores and averages for each individual, as well as the disproportionate number of 34 boys versus nine girls.

Female patients in our study also reported lower physical QoL, and their caregivers endorsed more depressive symptoms compared with those reporting on male patients. This finding is consistent with

Table 3. Comparisons Between Patient and Caregiver Reports of the Neuropsychological Functioning Inventory

Scale	Degrees of Freedom	Family Mean T Score	Patient Mean T Score	<i>t</i> Value
Communication	30	58.87	51.68	4.16*
Motor	30	51.39	48.32	1.96
Attention/memory	30	50.71	46.19	2.78*
Somatic	30	48.19	46.84	0.80
Depression	30	48.23	46.06	1.35
Aggression	30	45.87	45.03	0.61

* $P < .01$.

other recently published reports and provides ample support for targeted early intervention for physical therapy and psychosocial support for female patients treated for high-grade gliomas.^{37,38} Patients less than 3 years of age at time of treatment had significantly lower global intellectual abilities and nonverbal intelligence, findings that are consistent with previously published literature.^{6,8,39-44} This finding underscores the heightened sensitivity of the developing CNS to aggressive brain tumors and treatments, especially considering the nonrandom assignment of the youngest patients to the experimental 8-in-1 treatment regimen without radiotherapy.

The present outcomes study had limitations. There were no records of levels of functioning before, or soon after, completion of tumor treatment. Consequently, survivors were evaluated in comparison to age-stratified norms established for each measure, rather than by serial assessment to compare these findings with prior levels of functioning. Additionally, the use of a matched comparison group (ie, race, education, socioeconomic status) is the preferred approach to detecting significant differences, although the normative samples for the instruments used in this study are typically well defined with respect to age, sex, and geographic location. A large percentage of survivors (44%) assessed in this study originally classified as having high-grade gliomas were subsequently found on central re-review to have discordant diagnoses (predominantly low-grade gliomas). The implications of the high rate of discordant diagnoses, particularly in children less than 6 years of age, resulted in a proportion of children being overtreated with irradiation and intensive chemotherapy. The 10-year event-free and overall survival rates of such children less than 6 years of age were no better than 58%, suggesting that there was indeed something more ominous about the pathology in at least a proportion of these young children.

Further research is required to elaborate the outcomes of patients with high-grade gliomas that arise in the midline or the posterior fossa, as well as to clarify the specific neuroanatomic structures and pathways that become preferentially altered to these regions during the treatment and recovery process. Similarly, larger, prospective research studies are warranted to confirm our findings that female children treated for CNS tumors are at increased risk for neuropsychological, QoL, and emotional difficulties, as well as to enhance the understanding of sex-mediated mechanisms of tumor- and treatment-related injuries. Evaluating changes in structural and functional connectivity

by sex, as well as in the posterior fossa and midline regions, noninvasively via magnetic resonance imaging (MRI) can potentially provide insights and serve as biomarkers of neuropsychological outcomes in children undergoing brain tumor therapy. White matter fiber pathways (structural connectivity) and functional brain regions (functional connectivity) can be mapped using diffusion tensor imaging and functional connectivity MRI (also known as resting state functional MRI).⁴⁵⁻⁴⁷ Functional connectivity MRI can be used as a tool to survey the broad topography and global properties of brain architecture; in contrast, diffusion tensor imaging can more specifically elucidate specific anatomic pathways being altered.^{48,49}

Because current and pending high-grade glioma treatment protocols are incorporating combinations of aggressive tumor resections, followed by complex multimodality treatment regimens, collecting prospective data on these at-risk populations would promote the implementation of targeted remedial interventions ranging from behavioral training to psychopharmacologic treatments to improve attention, executive functioning, and memory. The persistent surveillance of pediatric patients treated for high-grade glioma is highly recommended as standard of care, to assist medical and rehabilitative decision making to minimize the impact of late effects, while striving to ensure long-term survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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