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Child-related characteristics predicting subsequent health-related quality of life in 8- to 14-year-old children with and without cerebellar tumors: a prospective longitudinal study

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Background. We identified child-related determinants of health-related quality of life (HRQoL) in children aged 8–14 years who were treated for 2 common types of pediatric brain tumors.

Methods. Questionnaire measures of HRQoL and psychometric assessments were completed by 110 children on 3 occasions over 24 months. Of these 110, 72 were within 3 years of diagnosis of a cerebellar tumor (37 standard-risk medulloblastoma, 35 low-grade cerebellar astrocytoma), and 38 were in a nontumor group. HRQoL, executive function, health status, and behavioral difficulties were also assessed by parents and teachers as appropriate. Regression modeling was used to relate HRQoL *z* scores to age, sex, socioeconomic status, and 5 domains of functioning: Cognition, Emotion, Social, Motor and Sensory, and Behavior.

Results. HRQoL *z* scores were significantly lower after astrocytoma than those in the nontumor group and significantly lower again in the medulloblastoma group, both by self-report and by parent-report. In regression modeling, significant child-related predictors of poorer HRQoL *z* scores by self-report were poorer cognitive and emotional function (both *z* scores) and greater age (years) at enrollment ($B = 0.038$, 0.098, 0.136, respectively). By parent-report, poorer cognitive, emotional and motor or sensory function (*z* score) were predictive of lower subsequent HRQoL of the child ($B = 0.043$, 0.112, 0.019, respectively), while age at enrollment was not.

Conclusions. Early screening of cognitive and emotional function in this age group, which are potentially amenable to change, could identify those at risk of poor HRQoL and provide a rational basis for interventions to improve HRQoL.

Keywords: cerebellar astrocytoma, children, medulloblastoma, outcome, quality of life.

A quarter of all childhood tumors develop in the brain, and 60% of these arise in the posterior fossa.[1] About half of long-term survivors of childhood brain tumors have moderate or severe disability,[2,3] experience chronic medical conditions and significant neurocognitive impairment,[4,5] achieve significantly lower educational attainment than the general population,[6] and suffer long-term socioeconomic disadvantage[7] including disadvantage in the work place[8] and impaired health-related quality of life (HRQoL).[9,10] Early identification of factors predicting impaired HRQoL would enable rehabilitation of these patients to be started early and reduce their risk of subsequent impaired HRQoL.

Poorer HRQoL has been associated with factors such as low IQ[11,12] and poor social,[9] physical,[13,14] behavioral,[11] and emotional functioning.[14] Previous studies of HRQoL in survivors have, however, had methodological limitations. Cross-sectional studies have been unable to explore the developmental trajectory of outcome,[15] while longitudinal studies have often been rendered inconclusive by high rates of attrition.[11,16] Comparison groups have usually not been representative of children in the general population because they were selected from siblings or friends.[17] Furthermore, heterogeneity of the study population has limited separation of the multiple factors that may influence HRQoL such as tumor location, type of surgical and adjuvant treatment,[11,18] age at diagnosis and assessment, time from diagnosis, and sex,[3,12] especially in single-center studies.

Finally, many previous studies have described tumor-related factors that are not amenable to change. The diagnosis of a brain tumor cannot be undone to improve HRQoL, and the

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potential benefit of varying tumor treatments on HRQoL (eg, by dose reduction in chemotherapy and/or radiotherapy) is something that can only be assessed reliably in a multicenter, controlled treatment trial that has little or no room for variation in the individual patient except for response to acute toxicity. The well-known associations between brain tumors and their treatments on the one hand and HRQoL on the other hand, therefore, lend themselves only to description of the child's predicament and/or the design of trials for the evaluation of antitumor treatments.

Child-related factors associated with variation in HRQoL scores, whether or not caused by the tumor or its treatment, are potentially amenable to change by interventions targeted at the specific cognitive, social, physical, behavioral, or emotional function of the individual patient or at parental mental health, which may affect both the child's HRQoL and the parental perceptions of it.[19,20]

The present study describes the level and trajectory of HRQoL scores in children diagnosed with low-grade cerebellar astrocytoma or medulloblastoma (the 2 most common types of posterior fossa tumor) who are old enough to report their own HRQoL reliably. The former is usually treated with surgery alone, with 7-year survival as high as 100% in some reports,[21] while the latter requires adjuvant treatment with chemotherapy and radiotherapy. Standard-risk medulloblastoma, with <1.5 cm^3 of residual tumor and no evidence of metastatic spread, was reported to have a 78% 7-year survival in the most recently undertaken European trial.[22]

The aim of the study was to identify child-related factors, potentially modifiable by intervention in the individual patient, and to avoid the limitations of previous studies. Our strategy in this study was therefore to use variables related to the tumor and its treatment only for the purpose of description before proceeding further to identify child-related predictive factors in both tumor and nontumor groups, irrespective of their association with tumor-related factors.

Materials and Methods

Design

A multicenter prospective longitudinal study was undertaken from February 2005 to January 2010.

Patients

Children aged 8–14 years with either "standard-risk" medulloblastoma (ie, <1.5 cm^3 residual tumor and no evidence of metastatic disease) or low-grade cerebellar astrocytoma diagnosed within the preceding 3 years were recruited from 11 of the 20 Children's Cancer and Leukemia Group (CCLG) Children's Cancer Treatment Centers (CCTCs) in England and Wales over a period of 20 months and then studied prospectively for a 24-month period ending in 2010. These centers are the only hospitals providing this type of treatment in the UK. The completeness of the cohort of cases enrolled in the present study was measured by expressing the number of cases enrolled per year as a percentage of the annual rate of diagnosis in all children fulfilling the study inclusion criteria (whether or not offered to the study) and treated at the 11 participating CCTCs over the most recently available 3-year period (1999–2001 data from the UK National Registry of Childhood Tumors, kindly provided by C Stiller, Childhood Cancer Research Group, Oxford) and assuming a 1.3% subsequent annual increase in the rate of diagnosis.[23] The nontumor group was randomly selected from the same year groups of the schools attended by children in the tumor groups. Noninclusion criteria in all groups were premorbid disability or inability to communicate in the English language, but these criteria were not met in any child referred to the study.

All participating children diagnosed with cerebellar tumor had undergone neurosurgical removal of the tumor. Those with medulloblastoma also received adjuvant treatment comprising 6 weeks of daily craniospinal radiotherapy of 23.4 Gy with a boost of 55.8 Gy to the posterior fossa and Packer regimen chemotherapy (weekly vincristine for 8 weeks followed 6 weeks later by eight 6-week cycles of chemotherapy consisting of CCNU and cisplatin plus vincristine, given weekly for 3 weeks).[24] There were no major deviations from this standard treatment.

Measures

The primary outcome was the child's HRQoL, reported by the children and their parents using the Pediatric Quality of Life Inventory (PedsQL),[25] which was selected due to its good psychometric properties, brevity,[26,27] and applicability to both ill and healthy populations[10,18,28]. Other assessments were undertaken as follows: cognitive functioning, assessed using the Wechsler Intelligence Scale for Children-4th UK Edition (WISC-IV UK);[29] parent- and teacher-report of the child's executive function in everyday life using the Behavior Rating Inventory of Executive Function (BRIEF);[30] parent- and child-report of the child's health status using the Health Utilities Index (HUI3);[31] parent-, teacher-, and child-report of the child's behavior using the Strengths and Difficulties Questionnaire (SDQ);[32] and parent-report of their own psychological well-being using the General Health Questionnaire (GHQ-12).[33] Baseline information obtained from parents included premorbid socioeconomic status (SES) based on the UK Office of National Statistics Socio-economic Classification (ONS 2004). Information on clinical neurological status before and after tumor excision was provided by treatment centers.

Procedure

Children fulfilling inclusion criteria were identified from hospital discharge and clinic lists and referred to the study center by the treating clinicians. Written informed consent was obtained from all participating parents and children. Three assessments were undertaken in the family home, to which questionnaires were sent by post in advance, while the WISC was administered at the visit itself. Parents were given comprehensive instructions by phone prior to the visit regarding how they should provide assistance to their child, if the need arose, without influencing their responses to the items. The first of the 3 visits was within the first month after recruitment (T1), with subsequent visits at 12 and 24 months thereafter (T2 and T3). For each home visit, teacher questionnaires were also completed. The protocol for this study was approved by the UK CCLG. Ethical approval was obtained from the Trent Multi-centre Research Ethics Committee, UK.

Statistical Analyses

The power calculation was based on a predicted sample of 90 children at the third year follow-up: a sample size of 3×30 children could detect a difference in HRQoL between each of the 3 groups of 0.74 standard deviations (SDs) with an 80% power at $P < .05$ in a 2 sided t test. Sample size calculations for prediction models are not so easily performed since the required sample size depends on the intercorrelation between factors (unknown in advance) as well as the actual effect sizes being estimated. However, since adding variables into a multiple linear regression model decreases the overall standard error, the overall power was not reduced in modeling.

The group mean and SD PedsQL scores in the nontumor group were used to derive z scores for the participants surviving brain tumors where the mean and SD in the nontumor group was 0 and 1, respectively. In other words, the z scores in the participants treated for brain tumors were expressed in terms of the number of SDs from the mean in the nontumor group. Intergroup differences in PedsQL z scores were calculated, and time changes in HRQoL within groups and comparisons between groups were analyzed using 2-way ANOVA to enable group effects and time trends to be determined independently.

The model for child-related factors predicting HRQoL was then built using data from "complete-cases" (ie, participants in whom both child- and parent-reported HRQoL scores were available at all 3 time points). WISC subscale scores and child-, parent-, and teacher- reports of subscales from the HUI (not teacher-report), SDQ, and BRIEF (not child report) were assigned, according to their content, to 5 theoretically derived domains of function: Emotion, Behavior, Social, Motor and Sensory, and Cognition (see Appendix A). Internal consistency for each domain of functioning was established using Cronbach's alpha. The mean of the sum of the constituent subscale z scores constituted the score for each domain, with all domains scored in the direction of higher scores indicating worse function. Forced entry and backwards stepwise multiple regression analyses were conducted to identify predictors measured at T1 that were associated with child- and parent-reported HRQoL scores at T3, 24 months later.

Predictors entered into the first step of the model were SES, sex, and child's age. Time from tumor diagnosis was not included because it was not associated with HRQoL in the 2 tumor groups considered separately or together in simple linear regression. Predictors that appeared to be more important ($P < .1$) were retained for the second step, in which parental mental health and the 5 domains of child-functioning were added to the model and those with stronger ($P < .1$) associations with HRQoL retained. The regression analysis was then rerun until only predictors for which $P < .1$ remained to provide the final predictive model. All tests were conducted using IBM SPSS version 19.0. All other significance values were at the level of $P < .05$, 2-tailed.

Results

Study Sample

Seventy-six children surviving cerebellar tumors were referred to the study center. Of these, 72 (95%), comprising 37 with medulloblastoma and 35 with astrocytoma, were enrolled into the study at a mean (range) time interval from tumor diagnosis of 15.5 months (range,1–35 months) (Table 1). The annual rate of

Table 1. Child and parent characteristics at enrollment into study

	Medullo $n = 37$	Astro $n = 35$	No Tumor $n = 38$
Mean age in years (range)	10.2 (8–14)	10.4 (8–14)	10.4 (8–14)
Mean age in years at diagnosis (range)	8.8 (6–13)	9.2 (5–14)	N/A
Mean months from diagnosis (range)	16.2 (1–35)	14.7 (1–35)	N/A
Respondent mean age in years (SD)	39.4 (5.5)	41.0 (8.1)	40.5 (5.3)
	n (%)	*n* (%)	*n* (%)
Female	16 (43)	23 (66)	19 (50)
Mother respondent	35 (95)	32 (91)	33 (87)
Single-parent family	8 (22)	3 (9)	5 (13)
Only child	9 (25)	3 (9)	4 (11)
Parent education			
None	1 (3)	2 (6)	2 (5)
School	14 (38)	5 (14)	7 (18)
College	15 (42)	18 (51)	21 (55)
University	6 (16)	10 (29)	8 (21)
Unknown	1 (3)	0	0
SES prediagnosis			
Managerial/professional	11 (31)	22 (63)	18 (47)
Intermediate	14 (39)	8 (23)	7 (18)
Routine and manual	7 (19)	5 (14)	10 (26)
Not working	4 (11)	0	3 (8)
Unknown	1 (3)	0	0

Abbreviations: astro, low-grade cerebellar astrocytoma; medullo, standard-risk medulloblastoma; N/A, not applicable; no tumor, nontumor comparison group; SD, standard deviation; SES, socioeconomic status.

enrollment into the study over the 1.84-year recruitment period was 95% of the estimated (see methods) number of diagnoses of eligible cases at participating centers over that time (number recruited per year/expected number of eligible patients: 20.4/19.6 [104%] for medulloblastoma; 18.8/21.7 [87%] for astrocytoma). Seven of the 72 (10%) tumor survivors became ineligible for inclusion in the analysis because the child had a tumor relapse (5 medulloblastomas, 2 astrocytomas) during the study, leaving 65 in the study. Of the 38 participants in the nontumor comparison group (see methods), 25 were the first random choice, and 7 were the second random choice, the first family having declined to participate. Attrition due to withdrawal from the study (ie, without tumor relapse) occurred in 7 of 65 (11%) of the tumor survivors (3 medulloblastoma, 4 astrocytoma) and in 2 of 38 (5%) cases in the nontumor group. Child and parent demographic characteristics were similar in the 3 groups at recruitment except for an excess of single parents, only children, lower parental educational qualifications, and occupations other than managerial or professional in families of children surviving medulloblastoma (Table 1).

The mean number of adverse clinical neurological features per child increased over the perioperative period from 4.1 to 5.7 for children with medulloblastoma and from 2.7 to 2.9 for those with astrocytoma. Only 4 of 37 (11%) participants with medulloblastoma and 12 of 35 (34%) with astrocytoma had no adverse postoperative clinical features (Table 2). Fifteen (41%) of the medulloblastoma group had not yet completed adjuvant treatment at T1, but mean HRQoL scores between those on and off treatment at T1 were very similar and are therefore shown collapsed into a single group.

Mean HRQoL scores in the whole study sample of 103 participants at T1 were similar to those in the group of 90 complete cases that was used to compare groups and to identify predictors of HRQoL at T3. Both SES and the functional consequences of adverse neurological features, reflected in Health Status subscores (allocated to the Emotion, Behavior, Social, Motor and Sensory function, and Cognitive domains of function, as appropriate) were included in the regression modeling.

HRQoL Scores Over Time by Tumor Diagnosis

Mean child-reported PedsQL *z* scores hardly changed over the whole time period in any of the 3 groups (Fig. 1), increasing by only 0.08 SDs ($P = .70$). Mean parent-reported PedsQL *z* scores increased over the 24-month study period by 0.33 SDs (Fig. 1), but this change was not significant after adjusting for group ($P = .18$). Compared with those of children in the nontumor group, mean (95% CI) HRQoL *z* scores, adjusted for time, were lower in the medulloblastoma and astrocytoma groups both by child report (−2.03 [−1.64 to −2.43]; −1.04 [−0.65 to −1.43] respectively, *P* always <.001) and by parent-report (−3.32 [−2.84 to −3.80]; −1.58 [−1.11 to −2.05] respectively, *P* always <.001). The percentage of children whose PedsQL total scale score (on a scale of 0–100) fell in the category of being "at risk of impaired HRQoL"[26] was greatest in the medulloblastoma group (score <69.7 by self-report in 73%; score <65.4 by parent-report in 85%), intermediate in the astrocytoma group, and lowest in the nontumor group (Fig. 1). The percentage of children at risk of impaired HRQoL fell progressively over time in both tumor groups, although remaining higher than in the nontumor group (Fig. 1).

Child Characteristics Predicting HRQoL

All the derived domains of functioning had good internal consistency with Cronbach's alpha coefficients of >0.7 (Appendix 1). Domain scores (derived from subscale scores on measures other than HRQoL; see Methods) for Emotion, Behavior, Social, Motor and Sensory, and Cognition showed that function on these domains was best in the nontumor comparison group, intermediate in the astrocytoma group, and worst in the medulloblastoma group. The domains of Cognition and Motor and Sensory function showed the biggest absolute difference in domain scores from the nontumor comparison group and also showed the largest changes over the 24 months of the study: this indicated a decrement in cognition function over time and an improvement in motor and sensory function (Table 3). SES,

Table 2. Clinical neurological features before and after tumor resection

	Medulloblastoma $n = 37$		Cerebellar Astrocytoma $n = 35$	
	Preresection *n* (%)	Postresection *n* (%)	Preresection *n* (%)	Postresection *n* (%)
Severe hydrocephalus	17 (46)	4 (11)	12 (34)	4 (11)
Visual impairment	7 (19)	9 (24)	6 (17)	4 (11)
Speech impairment	3 (8)	11 (30)	1 (3)	6 (17)
Upper limb ataxia	19 (51)	19 (51)	12 (34)	9 (26)
Truncal ataxia	23 (62)	24 (65)	7 (20)	8 (23)
Limb weakness	1 (3)	12 (32)	2 (6)	5 (14)
Balance impairment	24 (65)	27 (73)	17 (49)	9 (26)
Walking impairment	15 (41)	18 (49)	11 (31)	10 (29)
Seizures	0	0	2 (6)	0
Cerebellar mutism	0	12 (32)	0	4 (11)
CNS/other infection	0	8 (22)	0	5 (14)
No adverse features	5 (14)	4 (11)	7 (20)	12 (34)
Mean no. of clinical features (SD)	4.1 (2.8)	5.7 (4.1)	2.7 (2.2)	2.9 (3.2)

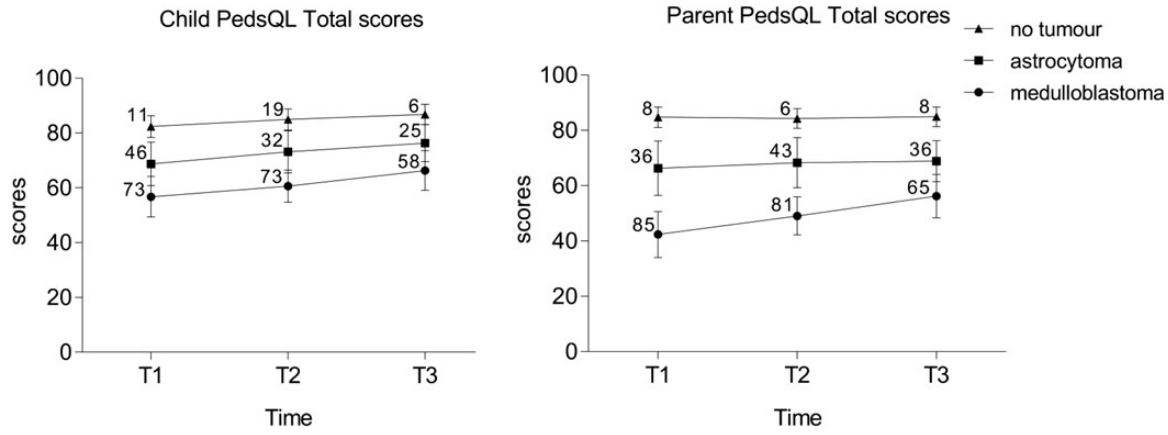

Fig. 1. Quality of Life Inventory mean total scores reported by 90 children and their parents over 24 months. Complete cases (ie, data from participants and their parents at all 3 time points) in 3 groups: standard-risk medulloblastoma ($n = 26$), low-grade cerebellar astrocytoma ($n = 28$), and a nontumor comparison group ($n = 36$). PedsQL = Quality of Life Inventory[25]; Times 1, 2, and 3 were at enrollment, 12 months, and 24 months later, respectively. Higher scores = better functioning. Error bars indicate 95% confidence intervals for the mean. Numbers adjacent to graphs show percentages of children in each group at risk of impaired HRQoL[26] (see text) at the 3 time points.

Table 3. Mean (standard deviation) domains of function *z* scores for all available data at each time point in the 110 study participants

Domain of Function	Mean Domain *z* Scores in All Participants*		
	At Enrollment (T1)	At 12 Months (T2)	At 24 Months (T3)
Emotion			
Medullo	4.03 (4.94)	5.89 (6.10)	3.86 (4.77)
Astro	1.64 (4.01)	3.30 (5.54)	2.57 (4.60)
Comparison	0.06 (3.15)	−0.02 (2.91)	−0.27 (3.35)
Behavior			
Medullo	0.74 (3.87)	1.69 (4.18)	3.20 (5. 04)
Astro	1.24 (4.00)	2.20 (4.12)	3.64 (6.57)
Comparison	0.10 (4.26)	−0.30 (3.87)	−0.04 (4.68)
Social			
Medullo	2.20 (4.33)	1.56 (4.57)	5.04 (6.58)
Astro	0.77 (3.34)	0.64 (4.32)	2.03 (4.82)
Comparison	0.05 (3.96)	−0.02 (3.78)	−0.18 (3.70)
Motor and sensory			
Medullo	27.16 (27.31)	20.34 (26.25)	9.21 (13.88)
Astro	11.82 (25.04)	5.37 (15.04)	3.08 (12.17)
Comparison	0.00 (3.48)	0.00 (4.63)	0.00 (4.06)
Cognition			
Medullo	14.41 (20.68)	17.53 (19.90)	25.14 (19.59)
Astro	10.25 (19.43)	13.93 (21.49)	17.19 (22.13)
Comparison	0.17 (14.03)	−0.46 (13.19)	0.05 (13.24)

In all domains, higher score = worse function. See methods for derivation of domain scores.
Abbreviations: Astro = low-grade cerebellar astrocytoma; Comparison = nontumor comparison group; Medullo = standard-risk medulloblastoma
*Mean domain *z* scores are large in the tumor groups due to lack of variation in the Comparison group.

child's sex, and child's age were included in the first step of the regression analyses, but none of these predictors remained significant as the modeling progressed. After inclusion of the 5 domains of functioning in the regression model, cognitive function, emotional function (both *z* scores) and greater age (years) at enrollment at T1 predicted child-reported HRQoL at T3 ($B = 0.037$, 0.100, 0.136, respectively), accounting for 53% of the variance (Table 4). Cognitive function, emotional function, and motor and sensory function (*z* score) at T1 were predictive of subsequent HRQoL of the child by parent-report at T3 ($B = 0.043$, 0.112, 0.019 respectively) and accounted for 65% of the variance, while age at enrollment was not (Table 5).

Discussion

Group mean HRQoL scores of children aged 8–14 years, who were measured within the first 3 years after diagnosis of standard-risk medulloblastoma or low-grade cerebellar astrocytoma, were persistently significantly poorer than those of their contemporaries in the same schools, with the deficit in HRQoL being greater after treatment for medulloblastoma. The very high percentage of children treated for medulloblastoma with "at risk" HRQoL scores at the end of the 3-year study period emphasizes the very poor initial HRQoL seen in this group. Cognitive and emotional functions were the most powerful child-related characteristics predicting child- and parent-reported HRQoL scores 2 years later, both in these children and in their contemporaries without tumors. Other factors predicting subsequent HRQoL scores were greater age at the first assessment by child self-report and motor and sensory function of the child by parent/proxy report.

The findings in this study provide a rationale for screening of cognitive and emotional function with selected questionnaires, such as the ones used in our study, to identify those potentially modifiable child-related characteristics that identify children likely to be at risk for poor subsequent HRQoL. This could be undertaken

Table 4. Factors at study entry predicting quality of life: child-report 24 months later

	B	95% CI for B	*P*
Step 1 $n = 92$, $R^2 = 0.126$, $R^2_{adj} = 0.075$, $P = .038$			
*SES intermediate	−0.322	−1.128 to 0.485	.430
*SES routine and manual	−0.938	−1.824 to −0.052	.038
*SES not in work	−1.575	−2.867 to −0.282	.018
Child's sex (0 = female, 1 = male)	0.108	−0.562 to 0.777	.750
Child's age (years)	−0.189	−0.369 to −0.009	.039
Step 2 $n = 81$, $R^2 = 0.582$, $R^2_{adj} = 0.529$, $P < .001$			
*SES routine and manual	−0.413	−0.996 to 0.170	.162
*SES not in work	0.065	−0.930 to 1.061	.896
Child's age (years)	−0.137	−0.267 to −0.007	.039
Emotion *z* score	−0.080	−0.161 to 0.001	.053
Behavior *z* score	0.003	−0.117 to 0.110	.951
Social *z* score	−0.052	−0.141 to 0.038	.253
Motor and sensory *z* score	−0.010	−0.022 to 0.003	.127
Cognition *z* score	−0.024	−0.048 to −0.001	.042
Caregiver mental health *z* score	−0.030	−0.258 to 0.199	.797
Final model $n = 81$, $R^2 = 0.534$, $R^2_{adj} = 0.516$, $P < .001$			
Child's age (years)	−0.136	−0.263 to −0.009	.036
Emotion *z* score	−0.100	−0.178 to −0.022	.013
Cognition *z* score	−0.037	−0.053 to −0.020	<.001

*Socioeconomic status relative to the highest category (managerial and professional).
Quality of Life scores were expressed as Pediatric Quality of Life Inventory[25] *z* scores (see methods).

Table 5. Factors at study entry predicting quality of life: parent-report 24 months later

	B	95% CI for B	*P*
Step 1 $n = 94$, $R^2 = 0.091$, $R^2_{adj} = 0.039$, $P = .130$			
*SES intermediate	−0.586	−1.528 to 0.356	.220
*SES routine and manual	−0.877	−1.924 to 0.169	.099
*SES not in work	−1.530	−3.059 to −0.001	.050
Child's sex (0 = female, 1 = male)	−0.183	−0.964 to 0.599	.643
Child's age (years)	−0.194	−0.407 to 0.018	.073
Step 2 $n = 81$, $R^2 = 0.671$, $R^2_{adj} = 0.629$, $P < .001$			
*SES routine and manual	−0.079	−0.723 to 0.565	.807
*SES not in work	0.151	−0.948 to 1.250	.785
Child's age (years)	−0.095	−0.238 to 0.049	.192
Emotion z score	−0.096	−0.185 to -0.007	.036
Behavior *z* score	0.023	−0.102 to 0.149	.711
Social *z* score	−0.080	−0.179 to 0.018	.108
Motor and sensory *z* score	−0.016	−0.029 to −0.002	.025
Cognition *z* score	−0.038	−0.064 to −0.012	.004
Caregiver mental health *z* score	−0.126	−0.378 to 0.126	.323
Final model $N = 81$, $R^2 = 0.644$, $R^2_{adj} = 0.631$, $P < .001$			
Emotion *z* score	−0.111	−0.196 to −0.026	.011
Motor and sensory *z* score	−0.019	−0.032 to −0.006	.004
Cognition *z* score	−0.043	−0.063 to −0.023	<.001

*Socioeconomic status relative to the highest category (managerial and professional).
Quality of Life scores were expressed as Pediatric Quality of Life Inventory[25] *z* scores (see methods).

annually in clinics using brief, easily administered tools.[34,35] Those falling above or below the published cut of scores indicating clinical risk could then undergo a full rehabilitation assessment and be considered for early intervention.

The study incorporated 5 key methodological strengths. First, the age range was designed to include only children old enough to report reliably on their HRQoL[36] and young enough for pediatric HRQoL and other assessments to remain valid through the duration of the study. Second, families were assessed at all 3 time points in more than 90% of recurrence-free participants, so that attrition bias was avoided. Third, a nontumor group of comparable age and educational background was selected in such a way as to be representative of families unaffected by a history of a tumor. Fourth, the inclusion criteria restricted the focus to survivors of tumors in a single brain region, the cerebellum. Fifth, the inclusion of 270 assessments in 90 participants in the longitudinal modeling makes this an unusually large study of a sample with such restrictive inclusion criteria.

The study was powered to show moderate-effect sizes between groups, and the predictive model appeared able to identify those factors exerting substantial predictive power. Regression models containing a small number of factors appropriate to the sample size, such as the final models presented in this paper, would have high power to detect a moderately sized effect (see Methods), but small effects would not be detected and might be missed (type II error). Other, less influential predictors might therefore have appeared in a model generated by an even larger study.

Both the homogeneity of our sample and the importance of the influence of the identified predictors on subsequent HRQoL are supported by the large proportion of variance in HRQoL for which they accounted. By using a range of measures and informants (eg, both parent- and teacher-report of executive function, parent- and child-report of cognition, and direct assessment of cognitive domains), we increased the sensitivity of the model to several aspects of function in both home and school settings. The subsequent conversion of scores to *z* scores and assignment to underlying domains of function (eg, Cognition) minimized the problem of multiple statistical testing. For all these reasons, we believe that the findings are robust. Since the referral base for this study included half of all children's cancer treatment centers in the UK and the number enrolled into the study was 95% of the number of eligible cases expected over the recruitment period, the findings are likely to be generalizable to all 8–14 year old UK children with a recent diagnosis of cerebellar tumor. Indeed, the percentage of those at risk for impaired of HRQoL after medulloblastoma in the present study (58% by self-report at T3) is very similar to what we reported following conventionally fractionated radiotherapy plus chemotherapy in PNET4 survivors across Europe, who were diagnosed at a similar mean age (8.9 years) but over a wider age range (3–21 years) and assessed after a longer interval (7.2 years).[37]

Conversely, the restricted age category and tumor location limit our ability to generalize the findings to other age groups or tumor locations. In younger children and higher risk groups than

our study population, we would expect an even larger predictive influence of cognition on HRQoL because the risk of deficits in processing speed, attention, and working memory has long been identified as increased in younger children and those with higher risk status.[38] However, children with poor neuropsychological function sometimes assess their own HRQoL as being within the range reported by typically developing children. The relationship between age at diagnosis and HRQoL is further complicated by, first, an increasing awareness of loss of previous abilities in children who are older at diagnosis (perhaps accounting for the negative relationship between age and self-reported HRQoL in the present study) and, second, a tendency for children (especially girls) in their teens to report lower HRQoL than when assessed earlier in childhood. Another study would therefore be needed to test these predictions in younger children.

The upward trend in HRQoL self-report scores over time in the nontumor group may reflect normal age-related pressures experienced by children such as the transition from primary to secondary school, which occurs in the UK in the lower part of the age range of our sample.[39] The use of HRQoL *z* scores calculated relative to those of the nontumor group at the same time point adjusted for this common social context. By contrast, the lack of change over time in parent-report scores in the nontumor group exemplifies the difference in the child and parent perspectives, particularly with regard to less observable functioning.[40] Further analysis of the differences between total scores and subscores of parent-, teacher-, and self-report of the outcomes of HRQoL, executive function, health status, and behavioral strengths and difficulties in this study is in progress and will be the subject of a further paper.

Earlier HRQoL scores are likely to correlate highly with subsequent HRQoL scores but were not included in our regression model as potential predictors of subsequent HRQoL because these scores represent the final consequences of underlying child-related characteristics that we hope to change by interventions; establishing that earlier HRQoL predicts subsequent HRQoL would not have brought us closer to that goal. The fact that assessments were done in the child's home contributed to the high retention rate. Any effects of the home setting on WISC scores are likely to be small and similar in tumor and nontumor groups. They should therefore not have biased intergroup comparisons and were adjusted out of the predictive modeling by the use of *z* scores that expressed scores in the tumor groups relative to the range of scores in the nontumor group.

The dominant role, by both child- and parent-report, of cognitive and emotional functioning in predicting subsequent HRQoL and the finding that neither sex, nor parental occupation, nor parental mental health predicted HRQoL is consistent with some previous reports relating to this age group.[9,12,14,18,20] Other previous studies have reported discrepant findings that may be attributable to heterogeneity with respect to participant age, tumor location, and interval from diagnosis or attrition bias.[2,11,41,42]

The importance to HRQoL of neurological deficit, the functional consequences of which were captured in the motor and sensory function domain, was reflected in the predictive role of that domain by parent-report. The higher rate of neurological deficit, including the presence of cerebellar mutism, as expected,[43] in one third in the medulloblastoma group is likely to have contributed to their poorer HRQoL and may reflect the more rapid progression of symptoms of hydrocephalus and other neurological disorders[44] in children with these more rapidly dividing tumors compared with their progression rates in low-grade cerebellar astrocytomas. Their greater increase in these deficits between preoperative and postoperative assessments may be attributable to their more midline location, less well-defined margins, and more vigorous neurosurgical effort to improve survival rates by achieving complete resection.[45]

Current guidelines in the UK suggest that psychological assessment of childhood brain tumor survivors should be undertaken only when concerns about poor HRQoL are raised by teachers or parents,[6] and this problem is not confined to the UK.[46] Identification of difficulties is therefore frequently late, but more timely interventions could be informed by early screening. Specific recommendations for brief screening tests and batteries of tests have been made and shown to be feasible in the context of clinical trials across North America and Europe.[47,48] Cognitive and physical remediation programs have already shown promising results in the short and medium term to enhance academic achievement in this age group, and social-skills training has shown a benefit to HRQoL in preliminary studies of children treated for brain tumors.[49–52] Sustainable low-cost interventions, such as online peer-to-peer support networks,[53] also need to be explored. The long-term benefit of early screening and the intervention that might follow is, however, yet to be established.

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Appendix 1. Domains of function with constituent subscales and internal consistency coefficients

Domain of Function	Constituent Subscales	Cronbach's Alpha
Emotion	SDQ Emotional symptoms (P,C,T)	0.714
	HUI3 Emotional level (P,C)	
Behavior	SDQ Conduct problems (P,C,T)	0.753
	SDQ Hyperactivity and inattention (P,C,T)	
Social	SDQ Peer problems (P,C,T)	0.659
	SDQ Prosocial behavior (P,C,T)	
Motor and sensory	HUI3 Vision level (P,C)	0.8
	HUI3 Hearing level (P,C)	
	HUI3 Speech level (P,C)	
	HUI3 Ambulation level (P,C)	
	HUI3 Dexterity level (P,C)	
	HUI3 Pain level (P,C)	
Cognition	HUI3 Cognition level (P,C)	0.931
	BRIEF Inhibit (P,T)	
	BRIEF Shift (P,T)	
	BRIEF Emotional control (P,T)	
	BRIEF Initiate (P,T)	
	BRIEF Working memory (P,T)	
	BRIEF Plan and organise (P,T)	
	BRIEF Organisation of materials (P,T)	
	BRIEF Monitor (P,T)	
	WISC Verbal (A)	
	WISC Perceptual reasoning (A)	
	WISC Working memory (A)	
	WISC Processing speed (A)	

Cronbach's alpha shown was calculated from subscale scores at enrollment (ie, Time 1).
Abbreviations: A, direct assessment; BRIEF, Behavior Rating Inventory of Executive Function; C, child-report; HUI3, Health Utilities Index; P, parent-report, SDQ, Strengths and Difficulties Questionnaire; T, teacher-report; WISC, Wechsler Intelligence Scale for Children.