Intellectual and Academic Outcome Following Two Chemotherapy Regimens and Radiotherapy for Average-Risk Medulloblastoma: COG A9961

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Purpose. Assess the intellectual and academic outcomes as well as risk factors associated with treatment for average-risk medulloblastoma in childhood using 23.4 Gy of craniospinal radiotherapy plus adjuvant chemotherapy. ***Methods.*** From an overall sample of 379 enrolled in the parent study (COG A9961), 110 patients received a total of 192 assessments over more than 5 years with standardized IQ and academic achievement tests. Random coefficient models of the various outcomes were developed that incorporated covariates including chemotherapy regimen, age at diagnosis, sex, initial Full Scale IQ, and mutism. ***Results.*** Participants in this study were found to be comparable to the overall sample in all demographic, disease, and treatment factors, except there were more gross total resections in the subsample undergoing intellectual and academic assessment. Major findings include significant decline in both intellectual and academic domains over time that were greater in children who were younger at diagnosis and had higher initial intelligence test scores. Children with mutism were at higher risk for initial effects on intelligence. No effects of sex were found. ***Conclusion.*** These results show progressive decline over several years post-treatment in standardized intellectual and academic scores. Despite recent improvements in therapies for these children, most notably a decrease dose of craniospinal radiation, they remain at risk. The pursuit of less toxic treatments, particularly for younger children, should continue. Neuropsychological surveillance should be routine at centers treating children with brain tumors. Pediatr Blood Cancer 2013;60:1350–1357.
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INTRODUCTION

Treatment for children 3 years or greater with non-disseminated totally or near totally resected medulloblastoma, so-called average-risk disease, has evolved over the past decade [1]. Because of neurodevelopmental risks associated with what was once standard (36 Gy) craniospinal radiotherapy, and evidence that treatment with lower doses of craniospinal radiotherapy (23.4 Gy) plus chemotherapy during and after radiotherapy, results in survival rates that compare favorably to treatment with higher dose radiotherapy with or without chemotherapy, accepted treatment consists of lower-dose craniospinal radiotherapy and chemotherapy. Reducing damage to healthy surrounding tissue has also been a focus of more recent therapeutic approaches. Focal and conformal radiotherapy to more precisely target diseased tissue, as well as new technologies (e.g., proton beam radiotherapy) have become increasingly utilized in attempts to spare healthy tissue. In addition to providing comparable disease control and survival, there is evidence of less neurocognitive morbidity in children treated with lower doses [2,3]. Ris et al. [2] reported an estimated loss of 4.3 Full Scale IQ points per year, while Mulhern et al. [3] estimated that there was a 10–15 IQ point benefit to younger children treated with the reduced dose craniospinal radiation.

Neurocognitive effects have been linked to both gross [4] and microscopic [5] changes in white matter integrity. Mulhern et al. [4] found that the amount of normal appearing white matter correlated inversely with cognitive functioning, including IQ, in a sample of 42 patients treated with craniospinal radiotherapy. Mabbott et al. [5] found multiple areas of cerebral white matter damage after treatment with craniospinal radiotherapy, and this was associated with lower IQ. The pathophysiology of long-term disturbances in neuropsychological functioning and development is not limited to white matter injury. Although incompletely understood, it probably involves apoptotic cell death and secondary cell death mediated by hypoxic-ischemic and inflammatory responses, culminating in damage to the intimal lining of the cerebral vasculature, disruption of the blood–brain barrier, and direct damage to cerebral white matter as well as damage to neural progenitor cells in neuronal niches [6,7]

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Effects on intellectual development are associated with both radiation dose and age, with younger children treated with higher doses being most at risk for eventual declines in IQ up to 4 years post-treatment [8]. One study reported different trajectories in intellectual development for older and younger patients [9]. Older patients (mean age at diagnosis = 11 years) showed early preservation followed by later decline while younger patients (mean age at diagnosis = almost 6 years) showed early decline followed by later stabilization of IQ.

Research on cerebellar mutism suggests that this may be a heretofore underappreciated factor in accounting for late effects. Cerebellar mutism is characterized by acute onset of mutism 1–2 days after surgery, ataxia, emotional lability, irritability, and high pitched cry. Robertson et al. [10] found that the incidence of mutism following surgery for medulloblastoma may be as high as 24%. In some cases recovery is slow and incomplete, and Grill et al. [11] reported lower Verbal IQ, Performance IQ, and fine motor deficits in patients with mutism compared to those without mutism.

This study contributes to a growing literature describing outcomes associated with modern RT protocols involving reduced craniospinal dose. The uniquely large sample and application of sophisticated multivariate modeling also allowed a simultaneous investigation of multiple putative predictors, such as age, sex, mutism, and baseline functioning. We hypothesized that: (1) our sample of patients treated for average-risk medulloblastoma would show an overall decline in IQ and achievement scores over time; (2) younger patients at treatment would show more decline than older patients; and (3) those exhibiting mutism would have poorer IQ and achievement outcomes than those without mutism. Although not posing specific hypotheses, we were also interested in exploring other possible predictors of outcome, such as sex and baseline level of functioning.

PATIENTS AND METHODS

The joint Pediatric Oncology Group/Children's Cancer Group (now the Children's Oncology Group: COG) prospective phase III clinical trial (A9961) of craniospinal radiotherapy (CSR) and adjuvant chemotherapy opened for enrollment in December 1996. It provided an ideal opportunity to prospectively study neurocognitive late effects in the largest sample yet reported of children treated with 23.4 Gy CSR. Children ages 3–21 years of age newly diagnosed with Average Risk Medulloblastoma (3 years of age or older with totally or near totally resected, nondisseminated disease) were eligible, and the study accrued 421 patients. All patients were treated with craniospinal dose of 23.4 Gy with a 32.4 Gy boost to the posterior fossa. Concomitant vincristine was administered during radiation therapy (RT), and patients were randomized to one of two adjuvant chemotherapy regimens beginning 6 weeks post-RT. Regimen A consisted of oral lomustine (CCNU), intravenous cisplatin (CDDP), and intravenous vincristine (VCR). Regimen B included intravenous cyclophosphamide (Cyclo), CDDP, and intravenous VCR. The 5-year progression-free survival rates for the treatment approaches were $82 \pm 2.8\%$ for regimen A, and $80 \pm 3.1\%$ for regimen B, which compares favorably with those reported in conventional therapy [1].

Sample

The neurocognitive component of A9961 was conducted on a subset of Pediatric Oncology Group and Children's Cancer Group member institutions that had identified psychologists and agreed at the outset of the trial to complete the study measures. Four hundred twenty-one patients were enrolled on A9961 with 42 subsequently excluded following central review. Of the 379 remaining patients, 110 (26%) had at least baseline intellectual testing completed and 75 (18%) had at least a baseline assessment of academic achievement and are included in the intellectual testing study sample (ITSS) and academic achievement study sample (AASS), respectively. Table I shows the frequency of evaluations for the ITSS and AASS groups. Clinical and demographic characteristics for ITSS and AASS are summarized in Table II. None of these characteristics were significantly associated with therapeutic regimen ($P > 0.05$). In most respects, the study samples were representative of the overall sample. However, the ITSS had significantly more gross total resections resulting in no residual tumor compared to those excluded from the analysis who had a larger percentage of radical subtotal resections (>95% of the tumor resected), resulting in slightly more residual tumor (<1.5 cm^2; $P = 0.025$). Of the 379 eligible patients, few had brain stem involvement (15%) and significantly fewer of these were part of ITSS and AASS ($P = 0.003$ and $P = 0.042$, respectively). Parents provided consent for the testing as part of the overall consent to participate in COG protocol A9961 in

TABLE I. Frequency and Timing of Intellectual and Academic Achievement Assessments

Number of times assessed	Intellectual testing, N (%)	Academic achievement, N (%)	Timing of assessments in years from completion of radiation ±6 months	Intellectual testing, N (%)	Academic achievement, N (%)
1	52 (47)	37 (49)	Baseline[a]	110 (57)	75 (59)
2	35 (32)	25 (33)	1	10 (5)	7 (6)
3	22 (20)	12 (16)	2	37 (19)	15 (20)
4	1 (1)	1 (2)	3	5 (3)	3 (2)
			4	7 (4)	3 (2)
			5	15 (8)	11 (9)
			6	8 (4)	3 (2)

[a]Diagnosis to 9 months post-radiation.

TABLE II. Comparison of Demographic and Clinical Characteristics in the Intellectual Testing Subsample and Academic Achievement Subsample Versus the A9961 Patients Who Did Not Participate

	At least baseline intellectual testing, included in analysis (N = 110)	No baseline intellectual testing, not included in analysis (n = 269)	At least baseline academic achievement testing, included in analysis (n = 75)	No baseline academic achievement testing, not included in analysis (n = 304)
Sex				
Male				
N	57	166	42	181
Percent	51.8	61.7	56.0	59.5
Female				
N	53	103	33	123
Percent	48.2	38.3	44.0	40.5
Treatment regimen				
A				
N	57	130	41	146
Percent	51.8	48.3	54.7	48.0
B				
N	53	139	34	158
Percent	48.2	51.7	45.3	52.0
Extent of resection				
No tumor sampling/no surgery				
N	0	1	0	1
Percent	0	0.4	0	0.3
Subtotal resection				
N	2	10	2	10
Percent	1.8	3.7	2.7	3.3
Radical subtotal resection				
N	12	60	9	63
Percent	10.9	22.3	12.0	20.7
Gross total				
N	96	198	64	230
Percent	87.3	73.6	85.3	75.7
Amount of residual tumor				
None/not visible				
N	90	182	59	213
Percent	81.8	67.7	78.7	70.1
$\leq$1.5 cm^2				
N	10	53	7	56
Percent	9.1	19.7	9.3	18.4
>1.5 to $\leq$3.0 cm^2				
N	0	1	0	1
Percent	0	0.4	0	0.3
Tumor present, but not measurable				
N	4	17	4	17
Percent	3.6	6.3	5.3	5.6
Equivocal for tumor				
N	6	16	5	17
Percent	5.5	5.9	6.7	5.6
Cerebellar mutism syndrome				
Yes				
N	24	60	13	71
Percent	21.8	22.3	17.3	23.4
No				
N	84	203	60	227
Percent	76.4	75.5	80.0	74.7
Unknown				
N	2	6	2	6
Percent	1.8	2.2	2.7	2.0
Brain stem involvement				

(*Continued*)

TABLE II. (*Continued*)

	At least baseline intellectual testing, included in analysis (N = 110)	No baseline intellectual testing, not included in analysis (n = 269)	At least baseline academic achievement testing, included in analysis (n = 75)	No baseline academic achievement testing, not included in analysis (n = 304)
Yes				
N	6	47	5	48
Percent	5.5	17.5	6.7	15.8
No				
N	104	222	70	256
Percent	94.5	82.5	93.3	84.2
Age at diagnosis				
Median	7.38	8.14	8.16	7.79
Min	3.44	3.10	4.28	3.10
Max	16.82	19.49	16.17	19.49

accordance with each institution's Institutional Review Board requirements.

Intellectual and Academic Achievement Testing

The A9961 neurocognitive assessment schedule called for an evaluation to be completed between 3 and 6 months post-RT, as well as two follow-up assessments completed at 2 and 5 years post-study entry. During the study, some of the assessments were taken according to the planned schedule and others were taken at varying time points. In order to make maximum use of the available data, analyses included patients who had at least one assessment between diagnosis and 9 months after completion of radiation (the baseline test). This is justified on the basis of research showing the emergence of significant late-effects of radiation after 9 months post-RT (Ris et al.[2]). The number of times assessed and timing of these assessments are contained in Table I. Table III shows the observed scores for each year after radiation therapy.

The test battery in the original COG A9961 protocol included age-appropriate, gold standard measures of general intellect (Wechsler Preschool and Primary Scales of Intelligence-Revised, Wechsler Intelligence Scale for Children-Third Edition, Wechsler Adult Intelligence Scale-Revised, Wechsler Adult Intelligence Scale-Third Edition), academic achievement (Wide Range Achievement Test-Third Edition), visuomotor integration (Beery Visual Motor Integration Test), adaptive functioning (Vineland Adaptive Behavior Scale), and social-emotional status (Child Behavior Checklist). However, the most complete data were for the intellectual tests and academic measures and so this report will concentrate on only Full-Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) outcomes from the intellectual tests and reading, spelling, and arithmetic outcomes from the academic achievement tests. Per protocol, intellectual testing was completed first followed by academic testing. However, adherence to this order was not specifically documented as testers were free to use clinical discretion to maximize the validity of the results.

Statistical Methods

Differences in demographic and clinical characteristics were investigated using exact chi-squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Random coefficient models [12] (RCMs) were used to estimate the change in neurocognitive outcomes over time and to investigate the effect of covariates on the estimated change. RCMs are an approach for analyzing multiple assessments on each patient over time. These models take into account that measurements on the same patient are correlated. RCMs allow for unbalanced data and use all available data. Although this study planned assessments at 3–6 months post-radiation and at 2 and 5 years after study enrollment, patients were assessed at a variety of times during the study. Time of the

TABLE III. Observed Intellectual and Achievement Scores

Timing of assessments in years from completion of radiation ±6 months	FSIQ[a] mean (SD)	VIQ mean (SD)	PIQ mean (SD)	Reading mean (SD)	Spelling mean (SD)	Arithmetic mean (SD)
Baseline[b]	96.2 (16.9)	98.6 (16.0)	93.2 (17.4)	98.8 (16.6)	97.1 (17.3)	94.7 (18.6)
1	96.0 (21.3)	100.0 (23.1)	92.5 (17.9)	98.0 (18.8)	102.4 (15.4)	96.0 (20.8)
2	90.1 (17.4)	91.5 (17.6)	90.8 (16.5)	97.8 (15.9)	96.8 (16.3)	93.7 (17.4)
3	99.5 (15.8)	99.6 (11.0)	97.3 (18.4)	92.7 (13.3)	93.0 (14.9)	105.0 (8.5)
4	79.6 (14.9)	83.0 (11.8)	79.4 (19.3)	103.0 (1.73)	93.0 (12.7)	95.7 (23.2)
5	93.5 (13.5)	94.5 (15.2)	92.7 (15.0)	94.0 (17.8)	88.4 (14.9)	92.2 (10.5)
6	75.6 (12.4)	79.9 (12.1)	78.0 (13.1)	78.5 (21.9)	75.0 (12.5)	68.0 (3.0)

[a]Intellectual and achievement scores presented as standardized scores with mean of 100 and SD of 15; [b]Diagnosis to 9 months post-radiation.

assessment used in the analysis was calculated in years from the end of radiation. All assessments were used in the model construction.

Separate models were created for each neurocognitive outcome. Treatment regimen, sex, and cerebellar mutism were treated as dichotomous variables in the models. Age at diagnosis was analyzed both as a continuous covariate and as a categorical variable divided at the age of 7 to enhance comparison with previous studies. Profile plots with spline smoothing were created prior to analysis to identify outliers and to visually inspect patterns in the change in outcome over time. We focused on the pattern of change in the first 2 years as 75% of the data was within this interval. There was no evidence of deviations from linearity that caused concern, so for all outcomes a linear change was assumed. Patients that had only the baseline measurement (i.e., only one score) were not excluded, although these patients only contributed to the estimation of the intercept. Statistical significance for an intercept or slope term was set at $P < 0.05$. The analyses for this study were carried out using PROC MIXED in the SAS statistical package, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Results from the longitudinal models revealed significantly lower FSIQ (96.0 points; $P = 0.020$), PIQ (93.5 points; $P = 0.0002$), and arithmetic scores (94.9 points; $P = 0.021$) at baseline compared to the normative mean of 100. Further there was a significant decrease in the FSIQ following radiation (-1.9 points/year; $P \leq 0.0001$), as well as significant declines in Verbal IQ (VIQ; -1.9 points/year; $P \leq 0.0001$), Performance IQ (PIQ; -1.7 points/year; $P \leq 0.001$), Reading (-1.5 points/year; $P = 0.047$), and Spelling (-2.1 points/year; $P = 0.004$).

Chemotherapy regimen B was significantly associated with worse scores at baseline compared with regimen A for FSIQ

(92.3 vs. 99.6, $P = 0.028$), VIQ (94.2 vs. 102.1, $P = 0.013$), and Reading (94.1 vs. 102.4, $P = 0.033$), but there were no significant differences in slope. To investigate whether the difference in chemotherapy regimens at baseline was an artifact of extreme outliers, the data were reanalyzed without these scores and there was no longer a significant difference in the FSIQ estimated baseline, but there remained significant differences at the intercept for VIQ and Reading. Further, children treated with regimen A experienced a significant decline in Math scores over time (A: -2.7 points/year vs. B: -0.29 points/year, $P = 0.050$).

Because the difference at baseline was unexpected, the differential early toxicities in these two regimens were explored as they may have accounted for these differences in test scores. For the purposes of these analyses, toxicities were categorized as hematologic, nervous system, performance score, and infection using CTCAE (Common Terminology Criteria for Adverse Events) grades for the chemotherapy course closest to the timing of the baseline assessment. For each toxicity categorization, a toxicity was defined as occurring if the patient experienced any grade. The results of these analyses indicate that nervous system toxicity was strongly related to baseline intellectual and achievement scores ($P = 0.0068$ and $P = 0.0030$ for Full Scale IQ and Reading, respectively). However, when the random coefficient models were re-run with nervous system toxicity as a covariate, treatment regimen remained significantly correlated with baseline scores in most models. It cannot be ruled out, as well, that the significant relationship between nervous system toxicity and baseline scores merely reflects neurologic deficits that these patients had at baseline that were not chemotherapy toxicities, *per se*. Therefore, since differences in treatment groups at baseline could not be accounted for, all subsequent models controlled for regimen.

TABLE IV. Demographic and Clinical Predictors of Intellectual Outcomes

| | | FSIQ | | | | | VIQ | | | | | PIQ | | | |
| | | Intercept | | Slope | | | Intercept | | Slope | | | Intercept | | Slope | |
	N[a]	Estimate	SE	Estimate	SE	N[a]	Estimate	SE	Estimate	SE	N[a]	Estimate	SE	Estimate	SE
Overall sample	106	96.0	1.7	-1.9^b	0.45	109	98.3	1.6	-1.9^b	0.42	109	93.5	1.7	-1.7^b	0.48
Sex															
Female	51	97.1	2.4	-2.2^b	0.63	52	98.8	2.3	-2.1^b	0.59	53	94.5	2.4	-2.0	0.68
Male	55	95.0	2.3	-1.6^b	0.65	57	97.7	2.2	-1.5^b	0.60	56	92.8	2.3	-1.4^b	0.72
Mutism															
Yes	23	89.1^c	3.5	-2.8^b	0.86	23	92.9	3.4	-2.6^b	0.78	24	86.5^c	3.5	-2.2^b	0.95
No	81	97.8	1.9	-1.6^b	0.53	84	99.9	1.8	-1.6^b	0.51	83	95.4	1.9	-1.5^b	0.59
Baseline FSIQ															
<100	61	84.3^c	1.3	-1.0	0.53	64	88.6^c	1.5	-0.72	0.49	64	82.3^c	1.4	-1.2	0.61
≥100	45	111.8	1.6	$-2.7^{b,c}$	0.58	45	111.5	1.8	-2.8^b	0.53	45	110.0	1.7	-2.8^b	0.66
Age															
<7	48	94.0	2.5	-2.9	0.63	49	94.8	2.3	-2.6^b	0.58	49	92.4	2.5	$-3.1^{b,c}$	0.67
≥7	58	97.9	2.3	-0.96	0.60	60	100.9	2.1	-1.0	0.58	60	94.5	2.3	-0.50	0.64
Extent of resection															
Gross total	93	96.0	1.8	-2.0^b	0.38	95	98.6	1.7	-1.9^b	0.36	95	93.3	1.8	-1.8^b	0.42
Subtotal/radical subtotal	13	98.0	4.9	-1.6	0.91	14	96.5	4.6	-1.3	0.87	14	97.8	4.9	-1.5	1.0

SE, standard error. [a]Small differences in sample sizes reflect missing data preventing derivation of all scores for a participant; [b]Statistically significant decline compared to zero (no decline) at the $P < 0.05$ level; [c]Statistically significant difference between the two groups at the $P < 0.05$ level.

Analysis of Intellectual Performance

Table IV reports the results of univariate analyses investigating the effects of demographic and clinical characteristics on intellectual performance after adjusting for differences due to treatment regimen. Patients who experienced some level of mutism had a significantly lower estimated FSIQ and PIQ baseline compared to patients without mutism ($P = 0.039$ and $P = 0.036$, respectively) and experienced significant declines in all three intellectual outcomes although not significantly different at the $P = 0.05$ level from those with no mutism. FSIQ, VIQ, and PIQ scores of younger patients decreased faster than the older patients ($P = 0.014$, $P = 0.012$, $P = 0.023$, respectively). Age at diagnosis divided at the age of 7 years showed similar results, although when age was categorized in this way, the slope for VIQ did not attain significance. Patients with a higher baseline FSIQ score showed a significantly faster rate of decrease in FSIQ ($P = 0.047$). There were no significant differences in the estimated baseline scores or slopes by gender or extent of resection.

Analysis of Academic Achievement

Patients with mutism experienced significant declines in all three academic achievement outcomes, and Reading scores declined significantly faster than for those with no mutism (-4.3 points/year vs. -0.49 points/year, $P = 0.012$). Age at diagnosis as a continuous variable was significantly correlated with changes in Reading scores with younger patients experiencing a steeper decline over time ($P = 0.016$). Younger patients experienced significant declines in Spelling scores although not statistically significant from older patients. Table V displays results of academic achievement outcomes by age at diagnosis divided at the age of 7 years. There were no significant sex or extent of resection effects.

DISCUSSION

The results of this study indicate significant decline in intellectual functioning over 5 years of an estimated 1.7 points per year in this sample of children treated for average-risk medulloblastoma. This is approximately half the rate of decline reported in another, non-overlapping sample from the Children's Cancer Group (CCG) [2]. This may be accounted for by differences between these two studies, including both a younger mean age and greater variability in IQ instruments used in the 2001 study. Furthermore, the current findings derive from a much larger sample, and the rate of decline reported here is in close agreement with that reported by Mulhern et al. [13].

Similar to the IQ scores, declines in standardized academic achievement scores were found. Confirming our hypothesis, a risk factor for declines included younger age at treatment (FSIQ, VIQ, PIQ, and Reading). Higher baseline IQ (FSIQ) was also associated with greater decline. Sex was not associated with declining intellectual or academic scores. Chemotherapy regimen (FSIQ, VIQ, and Reading) and mutism (FSIQ, PIQ) were associated with differences at baseline. The latter finding suggests that children who experience post-surgery mutism are at increased risk for initial effects with the rate of decline thereafter being consistent with that of children who do not experience mutism. Mutism, though, may place children at risk for later decline in reading skills, providing partial support for our hypothesis. This finding contributes to a growing literature identifying mutism, which was found in 22% of our sample, as an important risk factor in neurocognitive outcome [11,14]. It is important to note that verbal skills were not selectively impacted by mutism. In fact, non-verbal abilities reflected in PIQ were most affected and may relate to associated symptoms of mutism, such as attentional dysregulation and executive dysfunction. Age at diagnosis was confounded with

TABLE V. Demographic and Clinical Predictors of Academic Achievement

| | | Reading | | | | | Spelling | | | | | Arithmetic | | | |
| | | Intercept | | Slope | | | Intercept | | Slope | | | Intercept | | Slope | |
	N[a]	Estimate	SE[b]	Estimate	SE	N[a]	Estimate	SE	Estimate	SE	N[a]	Estimate	SE	Estimate	SE
Overall sample	74	98.8	1.9	−1.5	0.73	71	97.8	1.9	−2.1	0.69	75	94.9	2.1	−1.3	0.76
Sex															
Female	32	98.9	2.9	−1.2	1.2	33	99.0	2.9	−2.3[c]	1.0	33	95.1	3.2	−2.1	1.1
Male	42	97.7	2.6	−1.6	1.0	38	96.1	2.7	−1.8	1.0	42	94.1	2.8	−0.43	1.0
Baseline FSIQ															
<100	43	91.9[d]	2.2	−0.81	0.87	41	91.1[d]	2.4	−1.8	0.89	43	87.1[d]	2.5	−0.33	0.94
≥100	31	107.2	2.7	−2.6	1.2	30	106.1	2.8	−2.4	1.2	32	104.6	2.9	−2.1	1.2
Mutism															
Yes	12	99.9	4.9	−4.3[c,d]	1.3	12	96.1	5.0	−3.0[c]	1.2	13	87.6	4.8	−2.6[c]	1.3
No	60	97.4	2.3	−0.49	0.73	58	97.8	2.3	−1.6[c]	0.80	60	96.7	2.3	−1.0	0.89
Age															
<7	21	95.1	3.5	−2.6[c]	1.2	20	93.3	3.7	−2.4	1.1	22	92.2	3.9	−1.5	1.1
≥7	53	99.2	2.2	0.63	0.94	51	99.0	2.3	−1.8	0.96	53	95.2	2.6	−0.76	1.1
Extent of resection															
Gross total	63	98.3	2.2	−1.7[c]	0.75	61	97.9	2.2	−2.2[c]	0.72	64	95.1	2.3	−1.4	0.84
Subtotal/radical subtotal	11	98.7	5.2	−0.19	1.5	10	96.1	5.5	−1.2	1.8	11	91.8	5.6	0.15	1.9

[a]Small differences in sample sizes reflect missing data preventing derivation of all scores for a participant; [b]SE, standard error; [c]Statistically significant decline compared to zero (no decline) at the $P < 0.05$ level; [d]Statistically significant difference between the two groups at the $P < 0.05$ level.

mutism as those with mutism tended to be somewhat younger than those without mutism (although not significantly so). This study did not have sufficient power to parse the variance attributable to these two factors.

The difference at the end of RT between the two chemotherapy regimens is difficult to explain. Regimen B was associated with greater toxicity (hematologic and infection) throughout treatment [1], and it was this regimen that had the lower baseline score. Since chemotherapy was initiated 6 weeks post-RT and baseline measurements were taken between diagnosis and 9 months post-RT, differential toxicities could conceivably account for this initial difference in IQ. However, post hoc analyses of the full range of toxicities and their relation to baseline testing did not support this conclusion. Statistical artifact was also explored by removing extreme scores, which resulted in some (FSIQ) but not all (VIQ and Reading) outcomes failing to reach significance. Therefore, the question of why there was a difference in scores at baseline remains unanswered although it may be a failure of random assignment to equate the two chemotherapy groups on initial intellectual and academic functioning.

As was reported by Ris et al. [2], higher intellectual functioning at the time of treatment was associated with greater decline, although these children maintained higher scores over follow-up than did those with lower intellectual functioning. This is consistent with the buffering effect of cognitive reserve as formulated by Dennis [15] and Stern [16], that is, outcome following an insult to the brain is maximized in the context of higher premorbid cognitive abilities. Younger age at treatment has been found to be a robust risk factor in the late-effects literature and our findings re-emphasize the importance of developing effective treatments for this disease that are less toxic to the developing central nervous system. While the reduced dose of CSR used in this study (23.4 Gy) in comparison to higher doses used in other studies would appear to attenuate intellectual decline, the estimated loss of over half a standard deviation by 5 years post treatment is still substantial and associated with academic and, likely, a cascade of neurobehavioral morbidity later in life.

Some differences in our findings compared to those of another report on a similar sample [13] bear explanation. While Mulhern et al. [13] failed to find a significant difference in IQ between average-risk (treated with 23.4 Gy CSR) and high-risk (treated with 39.6 Gy CSR) groups, and no statistically significant decline in IQ in the average-risk group, patients in the Mulhern et al. study were treated with three-dimensional conformal radiotherapy while nearly all of our patients were treated with conventional two-dimensional radiotherapy. Therefore, our patients may have received somewhat higher doses to larger volumes in the posterior fossa.

The limitations of our study include low rate of testing of eligible participants in A9961, variability in both follow-up and timing of completed assessments, and age-related variance in the testing instruments. Low testing rates are attributable to several factors including failure to refer to a psychologist/neuropsychologist at centers lacking comprehensive brain tumor clinics, failure of third party payers to cover the costs of the evaluation, and decreased motivation on the part of the family with increased time from treatment. Still, the overall sample size of 110 undergoing a total of 192 assessments is an unusually large, homogeneous sample of children with average-risk medulloblastoma receiving contemporary treatments.

Multivariate techniques, such as random coefficient modeling used here, are able to make maximum use of the available data despite a high rate of missingness. Straightforward interpretation of such results, though, requires the assumption that missingness is independent of outcome, an assumption that cannot be confirmed. For example, it may be that those patients who return for testing have suffered either more or less impairment than those who were not available for testing, in which case missingness and outcome would be related. Alternatively, it may be that other factors, such as the availability of a psychologist/neuropsychologist to do the testing at a particular institution determined whether follow up testing was completed, in which case missingness and outcome would be unrelated.

Another challenge in longitudinal research is measurement error introduced by transitions in tests as the sample ages. In the current study, out of 20 such transitions, the majority (60%) consisted of changing from the WPPSI-R to the WISC-III. However, since the WISC-III tends to yield slightly higher IQ scores than the WPPSI-R [17] the effect would be null biasing (i.e., to underestimate decline over time).

In conclusion, while the current study was restricted to patients with average-risk medulloblastoma, all of whom received 23.4 Gy CSR, these results add to the growing empirical support for the neurocognitive benefits of reduced dose protocols. Most of what we know about long-term neurobehavioral toxicities of RT is based on therapies in which larger volumes of brain are exposed to higher doses. Conclusions drawn from this literature my have limited generalizability to contemporary and future cohorts of children treated for brain tumors. For younger children and infants, in particular, who are at higher risk for such complications, deferred radiotherapy [18,19], lower doses of craniospinal radiotherapy, hyperfractionated radiotherapy [20], and proton beam therapy further limiting the volume of local boost radiotherapy and scatter to the temporal lobes [21] offer the promise of further reduction in adverse late effects.

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