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Investigating Verbal and Visual Auditory Learning after Conformal Radiation Therapy for Childhood Ependymoma

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Abstract

Purpose—The primary objective of this study was to determine if children with localized ependymoma experience a decline in verbal or visual-auditory learning after conformal radiation therapy (CRT). The secondary objective was to investigate the impact of age and select clinical factors on learning before and after treatment.

Methods and Materials—Learning in a sample of 71 patients with localized ependymoma was assessed with the California Verbal Learning Test (CVLT-C) and the Visual-Auditory Learning Test (VAL). Learning measures were administered before CRT, at six months and then yearly for a total of five years.

Results—There was no significant decline on measures of verbal or visual-auditory learning after CRT; however, younger age, more surgeries and CSF shunting did predict lower scores at baseline. There were significant longitudinal effects (improved learning scores after treatment) among older children on the CVLT-C and children that did not receive pre-CRT chemotherapy on the VAL.

Conclusion—There was no evidence of global decline in learning after CRT in children with localized ependymoma. Several important implications from the findings include: 1) identification of and differentiation among variables with transient versus long-term effects on learning; 2) demonstration that children treated with chemotherapy prior to CRT had greater risk of adverse visual-auditory learning performance, and; 3) establishment of baseline and serial assessment as critical in ascertaining necessary sensitivity and specificity for the detection of modest effects.

Keywords

ependymoma; brain tumor; radiotherapy; memory; pediatrics

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INTRODUCTION

Advances in conformal radiation therapy (CRT) have lowered the risk of cognitive decline in pediatric brain tumor patients by minimizing exposure of healthy brain tissue to irradiation.¹⁻⁴ CRT uses 3-dimensional imaging and specialized software to concentrate the prescribed dose to the tumor while sparing surrounding healthy tissue.³ Research has linked higher doses of radiation to longitudinal decline in IQ, memory, attention and academic achievement.²⁻⁴ These adverse effects are more pronounced with conventional radiation therapy versus CRT.⁵⁻⁸ Cognitive decline after irradiation has been attributed to a slower rate of knowledge acquisition versus loss of intellectual skill.⁹⁻¹⁰

A prior study examining neurocognitive outcome in children with ependymoma treated with CRT found that children under 3 years of age at the time of CRT had significantly lower intellectual function scores at baseline compared to children over 3 years.³ However, these differences were no longer significant at the 48 month follow-up time point since the younger cohort exhibited an increase in IQ over time.³ No significant declines in memory, academic achievement or adaptive behavior were found at the 24 month follow-up time point; although only a portion of the cohort completed all measures of memory, learning and academic achievement.³

CRT has demonstrated the potential to reduce *global* cognitive decline following treatment; however, the possibility of decline in other neurocognitive domains remains to be determined.^{2,3,11-15} Preliminary evidence of subtle difficulties in reading, attention and memory following irradiation in the treatment of ependymoma have been reported.¹⁵⁻¹⁶ We recently found that children with ependymoma experienced modest declines in reading but not math or spelling after CRT.¹⁶ Another study of children treated with conventional irradiation for infratentorial ependymoma revealed reading difficulties after treatment, as well as visuospatial, memory and attention deficits, despite the lack of significant deterioration in aggregate IQ scores following treatment.¹⁵

Childhood ependymoma typically emerges at an earlier age than other localized tumors such as craniopharyngioma and astrocytoma, which may create additional risk as young age is a robust predictor of adverse neurocognitive outcome.^{4,17-21} Studies investigating outcome in children with ependymoma have found young age to predict lower mean scores on measures of intellectual function, although young age has not necessarily been found to predict decline in intellectual function after treatment.^{3,8,15}

For the current study, verbal and visual-auditory learning were serially assessed in children with localized ependymoma. Patients were treated with smaller-than-conventional volumes with the objective of sparing normal tissue. It was our hypothesis that the use of CRT would not result in significant longitudinal decline in verbal or visual-auditory learning after treatment. A secondary goal was to examine the effect of age and other select clinical factors on neurocognitive outcome. Despite advances in CRT, age was predicted to exert a modest but significant effect on *rate of learning* after treatment. Hypothetically, older children were expected to exhibit a more rapid rate of learning over time than younger children. To our knowledge, no prior studies have examined and compared rate of longitudinal verbal and visual-auditory learning in a prospective manner over a five year span. Recent advances in treatment have reduced the likelihood of more pervasive and conspicuous deficits in the form of global neurocognitive decline(s) after treatment.²⁻¹⁰ Therefore, future studies will need to adapt to treatment advances by employing investigative methods more sensitive to the detection of specific and less conspicuous side effects. The investigative methods used in this study could serve as a potential benchmark for future studies.

PATIENTS AND METHODS

Patients

Seventy-one pediatric patients with localized primary ependymoma were enrolled on a phase II trial of CRT between July 1997 and August 2007. The study was approved by the Institutional Review Board and written informed consent was obtained prior to participation. Criteria for enrollment included diagnosis of localized ependymoma without metastasis, age range between 1 and 21 years at the time of irradiation, no prior irradiation, no ongoing chemotherapy and adequate performance status (ECOG performance grade 0-2).²² Participants ranged from 1 to 15 years of age at the start of CRT (mean age = 5.59 ± 3.82). The median length of follow-up was 59.6 months (range = 11.7 - 92.0). No participants were excluded due to motor, vision or hearing impediments that would have prohibited testing. Patients who experienced treatment failure were not included in the study. Clinical and demographic characteristics are in Table 1.

CRT

All patients received CRT, including intensity-modulated radiation therapy, over six weeks with dosage fractionated to 1.8 Gy per day. Total dose ranged from 54 Gy to 59.4 Gy; children ≤ 18 months received 54 Gy after gross-total resection. Target volume definitions and treatment parameters are reviewed in prior studies.^{3,12}

Clinical Variables

All patients underwent systematic tumor resection before CRT. Patients that developed progressive disease were removed from the study. Approximately 20% of patients received chemotherapy prior to irradiation (typically a multiagent regimen of cyclophosphamide, cisplatin, carboplatin, etoposide, and/or vincristine). Hydrocephalus was identified on neuroimaging performed at the time of diagnosis.

Measures of Verbal and Visual Auditory Learning

Neurocognitive testing was performed before CRT, six months after CRT, and yearly after CRT. Verbal learning was assessed with the California Verbal Learning Test — Children's Version (CVLT-C).²³ This task presents a word list over five trials; the total recall score for trials 1-5 was used. Age-standardized scores were derived with a mean of 50 and standard deviation of 10. Higher scores indicate better performance. Visual learning was assessed with the Visual-Auditory Learning Test (VAL) from the Woodcock-Johnson Tests of Cognitive Ability: Revised.²⁴ The VAL is an associative learning task of word-symbol pairings. Age-standardized scores are derived with a mean of 100 and standard deviation of 15. Higher scores indicate better performance.

Assessment of Intellectual Function

Intellectual function estimates were obtained using the mental index of the Bayley scales or the three subtest administration (Block Design, Information and Similarities subtests) of the age-appropriate Wechsler scale.²⁵⁻²⁷ The mean baseline IQ score for the sample was in the average range (Mean = 102).

Statistical Analyses

All Table 1 variables were included in regression analyses, except for tumor laterality as the majority of participants had midline tumors. Linear models best fit the data. Baseline scores and mean rate of longitudinal change on the CVLT-C and VAL were examined using linear mixed-effects models with random coefficients.²⁸ The intercept of the regression line is the baseline score and slope is the average rate of change per month (Table 2). One set of

analyses was completed for the CVLT-C and another for the VAL. To correct for multiple comparisons, the significance level was set at $p \leq .01$, with $p \leq .05$ considered statistical trends.

Multiple regression analyses used a backward selection method whereby all variables with a $p \leq .01$ for the slope were retained as both an intercept and slope term. Variables were also retained if their removal significantly reduced overall model fit ($p \leq .01$). Continuous covariates were split at their median value for inclusion in models (e.g., age at CRT). For multiple regression analyses, only those with infratentorial tumor location, which comprised 73% of the sample, were included to maintain necessary power and homogeneity for analyses. However, infratentorial versus supratentorial tumor location was examined with univariate analyses (Table 2). Correlations among variables in multiple regression analyses were run to help determine the presence of multicollinearity.

Given that learning measures were only administered to children 5 or older, baseline scores at the start of CRT were not available for children under 5. Therefore, adjustments were made to the simple linear model to use scores at the time of first eligible testing as baseline values for children less than age 5 years at the start of CRT (see Appendix). Univariate analyses assessed practice effects by comparing performance between participants with fewer evaluations (≤ 4) to those with more evaluations (> 4). Analyses were conducted by the biostatistician coauthors using SAS software.²⁹

RESULTS

Memory Outcomes

Mean scores on the CVLT-C (43.78) and VAL (91.86) were in the average range at the start of CRT. There was no evidence of decrease in CVLT-C and VAL scores over time following CRT. In contrast, a trend for increase was found on the CVLT-C ($.12 \pm .041$ points/month; $p = .03$) and a significant increase on the VAL ($.20 \pm .054$ points/month; $p = < .01$) over the five year follow-up time period.

Testing for Practice Effects

The results revealed no difference in the rate of improvement between those with more (> 4) versus fewer assessments (≤ 4) on either the CVLT-C ($p = .32$) or the VAL ($p = .66$). The findings are not suggestive of practice effects.

Demographic and Clinical Predictors of Memory Scores

Univariate—Univariate analyses tested the individual effects of all variables on the CVLT-C and VAL (Table 2). No decline in longitudinal learning scores (slope) was observed for either the CVLT-C or the VAL. For the CVLT-C, there was a trend for a greater number of surgeries to predict lower baseline scores (Figure 1a). Older age, starting CRT within 2 months of initial surgery, supratentorial tumor location, and the absence of shunt predicted a significant increase in CVLT-C scores over time. The rate of increase was greater in older children versus younger children. Older children had significantly higher CVLT-C scores five years after treatment than younger children (Figure 1b).

For the VAL, CSF shunt predicted significantly lower scores at baseline. There was a trend for a greater number of surgeries to predict lower scores at baseline. Older age, male gender, infratentorial tumor location, a greater number of surgeries, absence of pre-CRT chemotherapy, and the presence of hydrocephalus and CSF shunts predicted a significant increase in VAL scores over time. Analyses revealed that although the presence of shunt and a greater number of surgeries predicted lower scores at baseline on the CVLT-C and VAL,

they no longer predicted significant differences five years after treatment since these characteristics were also associated with a more rapid rate of increase in VAL scores over time. Children who received pre-CRT chemotherapy exhibited little to no increase in their VAL scores over time. In contrast, children who did *not* receive pre-CRT chemotherapy exhibited a significant increase in VAL scores over time. There was a trend for those who did not receive pre-CRT chemotherapy to have higher scores on the VAL five years after treatment compared to those who received pre-CRT chemotherapy.

Multiple Regression—No clinically significant or meaningful correlations were found between predictor variables, suggesting an absence of multicollinearity between predictors. For the CVLT-C, multiple regression analyses (Table 3) found that older children (≥ 5) had significantly higher scores at baseline (+7.45 points) than younger children (< 5). A trend was found for children without shunt to have higher baseline scores (+5.86 points) than children with shunt. For the VAL, older children (≥ 5) had significantly higher baseline scores (+17.08 points) than younger children (< 5), and children with fewer surgeries (< 2) had significantly higher baseline scores (+13.06 points) than children with more surgeries (≥ 2). There were no significant slope effects.

DISCUSSION

The results of this study support the primary hypothesis that patients treated with smaller-than-conventional volumes using CRT do not exhibit longitudinal decline in verbal or visual-auditory learning after treatment. These findings are notable as longitudinal declines in learning and intellectual functioning are associated with conventional radiation therapy.
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Evidence supporting the secondary hypothesis that older children would exhibit a more rapid rate of learning over time than younger children was evident for verbal learning but not visual-auditory learning. Multivariate analyses revealed older children had better verbal learning at baseline, and univariate analyses revealed older children had more rapid improvement in verbal learning over time and significantly higher verbal learning scores five years after CRT than younger children. Risk factors were identified that predicted worse learning at different stages of treatment. Patients with multiple tumor resections and CSF shunts had worse verbal and visual-auditory learning at baseline. However, the effects of these specific clinical factors were temporary as they no longer predicted differences five years after treatment.

Risk factors identified near the time of diagnosis also varied in their transient versus long-term effect on learning. Specifically, younger age tended to predict lower scores at baseline as well as smaller rates of increase in learning scores over time. A greater number of surgeries and CSF shunts were associated with lower scores at baseline only, as these scores tended to improve over time, suggestive of recovery from insult associated with tumor mass effect and initial surgical management. These findings support the idea that change in learning can result from both perioperative risk factors with more acute and transient effects, as well as more stable and long-term CRT related side effects that impede learning in younger children.

Supratentorial tumor location was not a risk factor for learning outcome. Prior studies examining the effects of supratentorial versus infratentorial tumor location have been mixed. Some studies have found no increased risk for supratentorial tumor location, while others have found increased risk when the effects of CRT were investigated using detailed radiation dosimetry.^{2,3,13} The treatment of supratentorial tumors leaves brain areas critical to learning new information (e.g., hippocampal-mammillary circuits) vulnerable to radiation

exposure.³⁰ These mixed findings are likely due to varied methodology and sample characteristics across studies.^{2,3,13}

The findings revealed a trend for pre-CRT chemotherapy to have an adverse effect on rate of visual-auditory learning after treatment. This trend was not present for verbal learning. The aggregate effect over time resulted in the pre-CRT chemotherapy subgroup having worse visual-auditory learning five years after therapy compared to children who did not receive pre-CRT chemotherapy. These results suggest that visual auditory learning may be more vulnerable to the adverse effects of pre-CRT chemotherapy than verbal learning. Prior studies have documented increased vulnerability of visual memory to the adverse effects of chemotherapy in children with acute lymphoblastic leukemia treated with intrathecal chemotherapy only.^{31,32} In this study, visual-auditory learning was more susceptible to a greater number of risk factors than verbal learning (e.g., pre-CRT chemotherapy, and more surgeries adversely effected visual-auditory learning to a greater extent than verbal learning). This trend for increased risk in visual-auditory learning may help explain why children with localized ependymoma are at greater risk for reading difficulties following CRT.¹⁵⁻¹⁶ Given that the VAL was developed to assess skills that parallel those used in reading, with associative-paired learning akin to the pairing of letter combinations and their associated phonological representations, disruption of visual-auditory learning may, in part, help elucidate recent findings of increased risk for reading difficulties.¹⁴⁻¹⁶ Given that pre-CRT chemotherapy was equally distributed across both the younger and older age subgroups, pre-CRT findings cannot be attributable to age effects. The possibility of an interaction effect stemming from the use of chemotherapy prior to CRT, which left children more vulnerable to neurocognitive late effects, may have contributed to this finding and warrants investigation in future studies.³³⁻³⁶

The results from this study underscore the critical importance of baseline testing, particularly since learning scores were typically within the average range despite significant subgroup differences. Therefore, the modest yet significant effects found in this study would not have been detected without careful baseline measurement and comparison. The study found increased vulnerability in learning for younger children both at the start of treatment and after treatment as evidenced by diminished rate of learning following CRT. The greater susceptibility of visual-auditory learning to disruption may help explain findings of greater risk for reading deficits among children with localized ependymoma after CRT. The increased vulnerability of younger children to late effects has been suggested in the literature, with one explanation being that younger children experience greater loss of white matter volume following irradiation compared to older children.³⁷⁻⁴⁰ It has also been suggested that visual memory may be disproportionately affected following white matter injury early in life, particularly as the right hemisphere may contain greater volume of white matter.⁴¹⁻⁴⁴ In sum, the findings provide strong evidence that CRT increases the likelihood of a positive neurocognitive outcome for patients with ependymoma, although some subgroups including younger children, those receiving pre-CRT chemotherapy, and those with more perioperative complications may be at increased risk and should be carefully considered during treatment planning and discussion with caregivers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Note: Significant differences were present at baseline but were no longer present by the five year follow-up time point; normative mean ($\pm$ SD) of 50 ± 10

Figure 1a.
Longitudinal Change in Verbal Learning in Childhood Ependymoma. Significant Differences in Verbal Learning at Baseline

Note: Significant differences were not present at baseline but did emerge by the five year follow-up time point; normative mean ($\pm$ SD) of 50 ± 10

Figure 1b.
Longitudinal Change in Verbal Learning in Childhood Ependymoma. Significant Differences in Verbal Learning 5 years post-CRT

Table 1

Patient Demographic and Clinical Characteristics (N = 71)

	N	%
Gender		
Female	35	49.3
Male	36	50.7
Tumor Location		
Infratentorial	52	73.2
Supratentorial	19	26.8
Hydrocephalus		
No	23	32.4
Yes	48	67.6
CSF Shunting		
No	49	69.0
Yes	22	31.0
Pre-CRT Chemotherapy		
No	56	78.9
Yes	15	21.1
Pre-CRT Extent of Resection		
GTR or NTR	65	91.6
STR	6	8.5
Total Number of Pre-CRT Surgeries		
1	44	62.0
2-4	27	38.0
Tumor Laterality		
Midline	49	69.0
Left	9	12.7
Right	13	18.3

	Mean $\pm$ SD	Range
Age at CRT (Years)	5.59 $\pm$ 3.82	1.06 – 15.37
Time from Diagnosis to CRT (Years)	0.54 $\pm$ 1.07	0.05 – 5.80

Acronyms: CSF= cerebrospinal fluid; CRT= conformal radiation therapy; GTR = gross-total resection; NTR = near-total resection; STR = sub-total resection.

Table 2

Demographic and Clinical Predictors of CVLT-C and VAL (N = 71)

Variable	Subgroup	N	Baseline Intercept	SE	p-value	Slope	SE	p-value	Change per month	Score	SE	Estimated 5 year score	p-value
California Verbal Learning Test — Children's Version (CVLT-C)													
Age at CRT	≥ 5 years	34	45.56	2.00	ns	.154	.051	ns	<.01	54.79	2.38	.01	
	< 5 years	37	43.50	2.46	ns	.025	.075	ns		44.97	3.06	ns	
Diagnosis to CRT	≥ 2 months	33	43.12	2.28	ns	.067	.064	ns		47.13	2.85	ns	
	< 2 months	38	44.77	2.05	ns	.148	.058	ns	.01	53.65	2.65	ns	
Gender	Female	35	44.83	2.25	ns	.116	.065	ns		51.82	2.87	ns	
	Male	36	43.26	2.08	ns	.100	.060	ns		49.25	2.82	ns	
Tumor Location	Infratentorial	52	45.50	1.76	ns	.067	.050	ns		49.53	2.33	ns	
	Supratentorial	19	40.74	2.73	ns	.203	.080	ns	.01	52.92	3.88	ns	
Number of Surgeries	1	44	46.41	1.81	.04	.071	.053	ns		50.68	2.51	ns	
	≥ 2	27	40.35	2.36	ns	.159	.069	ns	.02	49.86	3.31	ns	
Hydrocephalus	No	23	41.64	2.60	ns	.178	.075	ns	.02	52.34	3.49	ns	
	Yes	48	45.31	1.88	ns	.072	.054	ns		49.65	2.47	ns	
Shunt	No	49	44.88	1.79	ns	.124	.052	ns	.01	52.31	2.41	ns	
	Yes	22	42.03	2.83	ns	.083	.079	ns		47.02	3.51	ns	
Pre CRT Chemotherapy	No	56	44.99	1.66	ns	.093	.048	ns	.05	50.60	2.24	ns	
	Yes	15	40.12	3.49	ns	.180	.109	ns		50.93	4.88	ns	
Visual Auditory Learning (VAL)													
Age at CRT	≥ 5 years	34	97.93	3.29	ns	.178	.065	ns	<.01	108.58	3.32	ns	
	< 5 years	37	89.18	3.77	ns	.176	.099	ns		99.74	4.22	ns	
Diagnosis to CRT	≥ 2 months	33	88.58	3.62	ns	.190	.081	ns	.02	99.95	3.81	ns	
	< 2 months	38	97.49	3.29	ns	.175	.074	ns	.02	108.00	3.55	ns	
Gender	Female	35	92.27	3.60	ns	.149	.080	ns		101.20	3.74	ns	
	Male	36	94.61	3.42	ns	.208	.073	ns	<.01	107.10	3.66	ns	
Tumor Location	Infratentorial	52	94.94	2.91	ns	.160	.064	ns	.01	104.52	3.09	ns	
	Supratentorial	19	89.56	4.64	ns	.223	.103	ns	.03	102.93	5.14	ns	
Number of Surgeries	1	44	97.86	3.02	.02	.147	.068	ns	.03	106.68	3.26	ns	

Variable	Subgroup	N	Baseline Intercept	Change per month			Estimated 5 year score		
				p-value	Slope	SE	p-value	Score	SE
Hydrocephalus	≥ 2	27	86.21	ns	.226	.089	.01	99.79	4.27
	No	23	97.08	ns	.208	.094	.02	109.59	4.51
Shunt	Yes	48	91.54	ns	.169	.068	.01	101.67	3.20
	No	49	97.47	.01	.148	.063	.02	106.37	3.13
Pre CRT Chemotherapy	Yes	22	84.46	ns	.244	.095	.01	99.13	4.54
	No	56	94.04	ns	.212	.058	<.01	106.75	2.76
	Yes	15	91.40	ns	.037	.134	ns	93.62	6.01

CRT = conformal radiation therapy; ns = not significant

Table 3
Multiple Regression Analyses Predicting Baseline CVLT-C and VAL scores (*N* = 52)

Term	Variable	Parameter	Estimate	SE	p-value
<i>California Verbal Learning Test — Children's Version (CVLT-C)</i>					
Intercept		α_0	38.63	2.70	<.01 ^{*a}
	Age at CRT (<5 vs. ≥ 5)	α_1	7.45	2.61	<.01 [*]
	Shunt (no shunt vs. shunt)	α_2	5.86	2.68	.03
<i>Visual Auditory Learning (VAL)</i>					
Intercept		α_0	81.22	3.96	<.01 ^{*b}
	Age at CRT (<5 vs. ≥ 5)	α_1	17.08	3.83	<.01 [*]
	Number of Surgeries (1 vs. >1)	α_2	13.06	3.87	<.01 [*]

^a compared with normative mean of 50

^b compared with normative mean of 100; baseline is defined as the start of CRT for those ≥ 5 years of age at the start of CRT, and the first evaluation after the age of 5 for those <5 years at the start of CRT.

^{*} p ≤.01.