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Association between hippocampal dose and memory in survivors of childhood or adolescent low-grade glioma: a 10-year neurocognitive longitudinal study

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Abstract

Background. Hippocampal avoidance has been suggested as a strategy to reduce short-term memory decline in adults receiving whole-brain radiation therapy (RT). The purpose of this study was to determine whether the hippocampal dose in children and adolescents undergoing RT for low-grade glioma was associated with memory, as measured by verbal recall.

Methods. Eighty patients aged at least 6 years but less than 21 years with low-grade glioma were treated with RT to 54 Gy on a phase II protocol. Patients underwent age-appropriate cognitive testing at baseline, 6 months posttreatment, yearly through 5 years posttreatment, year 7 or 8, and year 10 posttreatment. Random coefficient models were used to estimate the longitudinal trends in cognitive assessment scores.

Results. Median neurocognitive follow-up was 9.8 years. There was a significant decline in short-delay recall (slope = –0.01 standard deviation [SD]/year, $P < 0.001$), total recall (slope = –0.09 SD/y, $P = 0.005$), and long-delay recall (slope = –0.01 SD/y, $P = 0.002$). On multivariate regression, after accounting for hydrocephalus, decline in short-delay recall was associated with the volume of right (slope = –0.001 SD/y, $P = 0.019$) or left hippocampus (slope = –0.001 SD/y, $P = 0.025$) receiving 40 Gy (V40 Gy). On univariate regression, decline in total recall was only associated with right hippocampal dosimetry (V40 Gy slope = –0.002, $P = 0.025$). In children <12 years, on univariate regression, decline in long-delay recall was only associated with right (V40 Gy slope = –0.002, $P = 0.013$) and left (V40 Gy slope = –0.002, $P = 0.014$) hippocampal dosimetry.

Conclusion. In this 10-year longitudinal study, greater hippocampal dose was associated with a greater decline in delayed recall. Such findings might be informative for radiation therapy planning, warranting prospective evaluation.

Key Points

1. Survivors of pediatric low-grade gliomas experience decline in memory.
2. Greater hippocampal dose is associated with greater decline in memory.
3. Reducing hippocampal dose may represent a memory preserving treatment strategy.

Importance of the Study

Although hippocampal avoidance has been suggested as a memory preserving strategy for adults with brain metastases undergoing whole-brain radiation, the merit of this strategy in pediatric brain tumor patients is unclear. Pediatric low-grade gliomas represent the most common pediatric brain tumor, and those treated with radiation experience late cognitive deficits, including memory decline. In these patients, we have found that hippocampal dose is associated with memory, as measured by verbal recall. Greater hippocampal dose is associated with greater decline in memory and therefore reducing hippocampal dose in the treatment planning process may result in memory preservation. This finding deserves prospective validation, particularly in the era of proton therapy.

Neurogenesis occurs in the subgranular zone of the dentate hippocampus throughout life.[1,2] Radiation injury to this area is associated with decreased neurogenesis secondary to alterations in the microenvironment and decreased proliferation of progenitor cells.[3] Hippocampal avoidance (HA) has been suggested as a strategy to reduce short-term memory decline, as measured by delayed recall, in adults undergoing whole-brain radiation therapy (RT). A phase II study by the Radiation Therapy Oncology Group (RTOG) has demonstrated that the relative decline in delayed recall from baseline to 4 months can be reduced with HA.[4] Testing this hypothesis further are 2 phase III studies which randomize adults to whole-brain radiation with or without HA; one of these studies recently closed and the preliminary results suggest HA with memantine increases time to neurocognitive failure compared with memantine alone.[5–7]

In contrast to adults, there is limited data on the association between hippocampal dose and memory preservation after cranial RT in children or adolescents. Low-grade gliomas (LGGs) are the most common brain tumors in children, and a subset of these tumors are treated definitively with focal RT.[8] These patients often survive for many years after undergoing RT and develop late neurocognitive deficits.[9] The severity of the neurocognitive deficits correlates with younger age, a greater volume of brain being irradiated, the presence of hydrocephalus, and the presence of a shunt.[9,10] The effect of hippocampal dose on cognitive measures, especially those related to memory, has not been studied in this patient population. Verbal recall is an important measure of memory and has been correlated with other important functional outcomes such as problem solving, independence of everyday functioning, and quality of life.[11,12] Therefore, we investigated whether there was an association between hippocampal dose and verbal recall in survivors of childhood or adolescent LGG treated with focal RT. Unlike clinical variables that cannot be modified, such as age or presentation with hydrocephalus, hippocampal dose can be reduced in the RT planning process, and this may represent a memory-sparing treatment strategy for these patients.

Patients and Methods

Study Population

We identified patients with LGGs receiving focal RT between 1997 and 2010 on a phase II protocol, RT1, at St Jude Children's Research Hospital (ClinicalTrials.gov identifier: NCT00187226). Patients aged ≥6 years but <25 years when treated were eligible for inclusion in the study. Patients younger than 6 years (n = 14) were excluded because RT is increasingly avoided in such patients, if possible.[13] Adolescents were defined as those aged 12 or older. Patients with metastatic disease or prior irradiation were also excluded. Eighty patients met the inclusion criteria. This study represents a secondary analysis of RT1, which was approved by the St Jude institutional review board, and all study participants consented to the study.

Radiation Therapy

RT was delivered with a 3D conformal or intensity-modulated radiation technique to a total dose of 54 Gy in 1.8 Gy fractions over 6 weeks. The gross tumor volume included both the cystic and solid components of the tumor and was defined by T2/fluid attenuated inversion recovery (FLAIR) hyperintensity and T1 enhancement (if present). In patients who underwent surgery before RT, the gross tumor volume was defined as the surgical bed and any residual T2/FLAIR hyperintensity or T1 enhancement. The clinical target volume (CTV) margin was 1 cm. A planning target volume margin of 0.5 or 0.3 cm was used. All patients were treated with photon therapy. Dose volume histogram data were extracted from RT plans (Supplementary Table 1). The hippocampus was contoured retrospectively according to the RTOG 0933 atlas by a board-certified radiation oncologist.[14] Hippocampal contours were largely based on 3D T1 postcontrast MRI sequence with 1 mm to 1.25 mm slices. Axial T2/FLAIR, axial T2, and coronal T1 sequences were also available for review. MRI sequences were fused to CT simulation to delineate the hippocampi on CT and calculate dose delivered to the right and left hippocampus. Hippocampal dose constraints were not utilized at the time of RT planning.

Clinical Follow-Up

All patients underwent prospective disease assessment and neurocognitive assessment. Patients underwent brain MRI and a physical exam every 3 months for the first 2 years, every 6 months through 5 years, and yearly thereafter until 10 years posttreatment. The neurocognitive evaluation is described below.

Neurocognitive Evaluation

Study measures specific to memory, learning, and attention were selected from a comprehensive neurocognitive battery administered at baseline, at 6 months, yearly through year 5, at 7 or 8 years, and at 10 years posttreatment. Verbal memory was assessed using the California Verbal Learning Test–Children's Version (CVLT-C)[15] for children aged 6 to 16 years. There are no age-specific norms for children less than 6 years of age; therefore CVLT-C is not administered in this population. The CVLT-C measure includes 5 presentations of a list of 15 words in 3 categories. Learning is evaluated across 5 trials with immediate recall (CVLT-Total [CVLT-T]); after a distracter list and short delay (CVLT-SD); and after a long delay, during which the examinee is given a nonverbal task for 20 minutes (CVLT-LD). Also tested were (i) the use of semantic clustering as a mnemonic strategy, whereby words from the same category are remembered together, and (ii) discriminability, the ability to pick out true positives from distracters after a long delay. The California Verbal Learning Test Second Edition (CVLT-II)[16] is a comparable version of the test administered to individuals aged ≥17 years; it comprises 16 words from 4 categories and provides the same scores. All scores are age standardized Z-scores, with a mean of 0 and standard deviation (SD) of 1. All selected measures have age-specific norms from large, representative samples. Standardized tables of raw score equivalents for each Z-score across all ages can be found in the CVLT-C and CVLT-II manuals.[15,16] Measures also have appropriately demonstrated reliability and validity.

Study measures specific to sustained attention and processing speed were also analyzed to determine whether functionalities not directly related to the hippocampus were also affected by hippocampal dose. Conners' Continuous Performance Test (CPT)[17] is a computerized measure of sustained attention during which letters are presented individually on a computer screen and the participant must respond by pushing the space bar for all letters except X. CPT omission (failing to respond to a non-X) is a measure of inattention, and the CPT Hit Response Time (CPT HitRT) is a measure of response speed. The task takes 14 minutes and is reported as an age standardized Z-score. Standardized tables of raw score equivalents for each Z-score across all ages can be found in the CPT manual.[17]

Statistics

The neurocognitive outcome variables included: CVLT-T, CVLT-SD, CVLT-LD, semantic cluster, discriminability, CPT omission, and CPT HitRT. Definitions for each of these outcomes are provided in the neurocognitive evaluation section. Random coefficient models were used to estimate the longitudinal trends of these neurocognitive outcomes over time. Each patient was treated as a cluster and the intercept and slope were assumed to be random among patients. The models also included covariates and covariate-by-time interaction terms. Follow-up time was calculated from start of RT to last neurocognitive test. Patients were censored at the time of progression or second malignancy. To be included in the analysis for any given neurocognitive outcome, the participant had to have at least 2 scores for that measure. Clinical covariates were included in the multivariate model if they were significant on univariate regression ($P < 0.05$). Additionally, the dosimetric covariate that was significant on univariate regression ($P < 0.05$) was carried forward to the multivariate model. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to compare models with different dosimetric parameters, with lower AIC and BIC values indicating better models. Separate multivariate models were created for the right and left hippocampus. Statistical analyses were performed with Stata 2015 or SAS v9.4.

Results

Patient Characteristics

The median age at the start of RT was 9.5 years (range, 6–20 y) (Table 1). Most patients had pilocytic astrocytoma (61%, $n = 49$). Half of the tumors were in the hypothalamus and/or optic pathway, and 30% were in the thalamus or midbrain. In terms of surgical resection, 41% of patients underwent a biopsy alone and 38% underwent a subtotal resection (STR). Fifteen patients (19%) had radiographically diagnosed optic-pathway gliomas without histologic confirmation. Most patients (71%) underwent RT as first-line therapy and received no prior chemotherapy. Approximately a third of the patients had hydrocephalus at diagnosis, with all but 3 of these patients requiring a shunt.

Hippocampal Dose and Volume Analysis

As most tumors were in midline structures such as the hypothalamus, optic pathway, thalamus, or midbrain, the dose distributions to the left and right hippocampi were similar (Supplementary Figure 1). The median volume (%) of the right and left hippocampus receiving 20 Gy (V20 Gy) was 100%, with interquartile ranges (IQRs) of 85–100% and 83–100%, respectively. The median right and left hippocampal V40 Gy was 79% (IQR, 35–100%) and 77% (IQR, 40 –100%), respectively.

Neurocognitive Assessments

The median neurocognitive follow-up from the start of RT was 9.8 years (range, 0.46–10.8 y). Baseline neurocognitive measures were obtained at a median of 0.2 months before RT. A total of 3256 neurocognitive measurements were obtained over the 10-year follow-up period. Supplementary Table 2 shows the breakdown of patients with neurocognitive data at each timepoint. At 5 years following RT, 57 patients (71%) underwent CVLT neurocognitive testing and 53 (66%) patients underwent CPT neurocognitive testing. At 10 years following RT, at least 39 patients (49%) underwent most measures of CVLT and CPT neurocognitive testing.

Table 1 Patient characteristics

Variable	Number (%)
Median age at RT in years (range)	9.5 (6–20)
Sex	
Female	44 (55)
Male	36 (45)
Histology	
Pilocytic astrocytoma	49 (61.25)
Optic pathway glioma (radiographic diagnosis)	15 (18.75)
Diffuse astrocytoma	5 (6.25)
Ganglioglioma	4 (5)
Neurocytoma	2 (2.5)
Oligodendroglioma	1 (1.25)
Astrocytoma, not otherwise specified (NOS)	2 (2.5)
Low-grade glioma, NOS	2 (2.5)
Tumor Location	
Hypothalamus/optic pathway	40 (50)
Thalamus/midbrain	24 (30)
Cerebellum	8 (10)
Cerebral hemisphere	8 (10)
Neurofibromatosis Type 1	
No	69 (86.25)
Yes	11 (13.75)
Extent of Surgical Resection	
Biopsy	33 (41.25)
STR	30 (37.5)
Near-total resection	2 (2.5)
No surgery/biopsy (radiographic diagnosis)	15 (18.75)
Number of Surgical Interventions Prior to RT	
0	15 (18.75)
1	46 (57.5)
2	14 (17.5)
3	4 (5)
Chemotherapy Before RT	
No	57 (71.25)
Yes	23 (28.75)
Hydrocephalus at Diagnosis	
Yes	27 (33.75)
No	53 (66.25)
Shunt at Diagnosis	
Yes	24 (30)
No	56 (70)

CVLT-T

Seventy-three patients had at least 2 CVLT-T scores. The decline in CVLT-T was significant (slope = –0.09 SD/y, P = 0.005) (Figure 1). Unadjusted individual patient data are shown in Supplementary Figure 2. On univariate regression, only right hippocampal dose was associated with change in CVLT-T (Table 2). For every percent increase in right hippocampal V40 Gy, CVLT-T decreased by 0.002 SD/year. Treating the entire right hippocampus to 40 Gy (ie, V40 Gy 100%) was associated with 5-year and 10-year reductions in CVLT-T of 0.74 SD and 1.49 SD, respectively (Supplementary Figure 3).

CVLT-SD

Seventy-three patients had at least 2 CVLT-SD scores. The decline in CVLT-SD over time was significant (slope = –0.01 SD/y, $P < 0.001$) (Figure 1). Individual unadjusted patient data are shown in Supplementary Figure 4. On multivariate regression, decline in CVLT-SD was associated with hippocampal dose and hydrocephalus. After accounting for hydrocephalus, both left hippocampal V40 Gy (slope = –0.001 SD/y, P = 0.025) and right hippocampal V40 Gy (slope = –0.001 SD/y, P = 0.019) remained significantly associated with a decline in CVLT-SD (Table 3). For every percent increase in right or left hippocampal V40 Gy, CVLT-SD decreased by 0.001 SD/year. Treating the entire right (Figure 2A and B) or left hippocampus (Figure 2C and D) to 40 Gy was associated with a 5-year and 10-year short-delay recall reduction of 1 SD and 2 SD, respectively, for patients with hydrocephalus, and 0.5 SD and 1 SD, respectively, for patients without hydrocephalus. Although age is an important predictor of cognitive outcome after cranial RT, age at RT was not associated with change in CVLT-SD (slope = 0.0008 SD/y, P = 0.126). Inclusion of age in the multivariate regression model resulted in a nonsignificant slope (Supplementary Table 3).

In order to determine whether hippocampal doses other than 40 Gy improved model fitness, we compared doses that were significantly associated with CVLT-SD on multivariate regression for both the right and the left hippocampus. Only left and right hippocampal V40 Gy and V45 Gy were both associated with CVLT-SD on multivariate regression, and model fitness utilizing V45 Gy was similar to that of the model utilizing V40 Gy, as determined by AIC and BIC values (Supplementary Table 4).

CVLT-LD

Seventy-three patients had at least 2 CVLT-LD scores. The decline in CVLT-LD was significant over time (slope = –0.01 SD/y, P = 0.002) (Figure 1). Unadjusted individual patient data are shown in Supplementary Figure 5. On univariate regression, none of the clinical variables or hippocampal doses were significantly associated with a decline in CVLT-LD (Supplementary Table 5). However, when patients were stratified into pre-adolescents (<12 y) versus adolescents (≥12 y), there was a significant decline in CVLT-LD in the pre-adolescent subgroup (n = 51) (slope = –0.009 SD/y, P = 0.002), which was associated with left or right hippocampal dosimetry (Table 2). For every percent increase in right or left hippocampal V40 Gy, CVLT-LD decreased by 0.002 SD/year. Treating the entire right (Figure 2E) or left hippocampus (Figure 2F) to 40 Gy was associated with a 5-year and 10-year long-delay recall reduction of 0.9 SD and 1.8 SD, respectively.

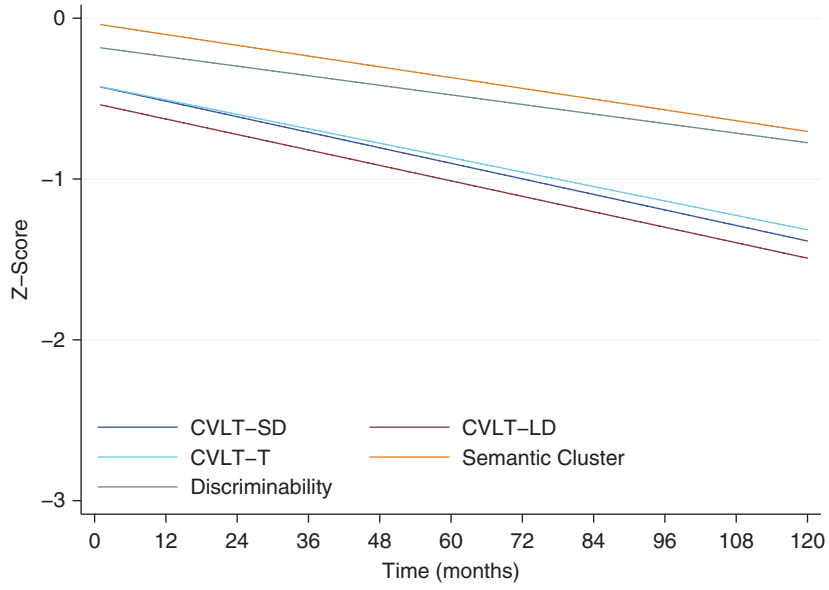

Fig. 1 Regression lines of change in CVLT-SD, CVLT-LD, CVLT-T, semantic cluster and discriminability scores over time without inclusion of any covariates. Unadjusted change in neurocognitive measures over time for individual patients can be found in the supplement.

Table 2 Univariate regression models for CVLT-LD and CVLT-T

Variable	CVLT-LD: Left Hippocampus (age <12 y)		
	Coefficient[α]	SE	*P*-value
Left hippocampal V30 Gy (%)	−0.002	0.001	0.044
Left hippocampal V35 Gy (%)	−0.002	0.001	0.02
Left hippocampal V40 Gy (%)	−0.002	0.001	0.014
Left hippocampal V45 Gy (%)	−0.002	<0.001	0.011
Left hippocampal V50 Gy (%)	−0.002	<0.001	0.033
	CVLT–LD: Right Hippocampus (age <12 y)		
Right hippocampal V30 Gy (%)	−0.002	0.001	0.032
Right hippocampal V35 Gy (%)	−0.002	0.001	0.019
Right Hippocampal V40 Gy (%)	−0.002	<0.001	0.013
Right Hippocampal V45 Gy (%)	−0.002	<0.001	0.016
	CVLT-T: Right Hippocampus		
Right hippocampal V25 Gy (%)	−0.002	<0.001	0.031
Right hippocampal V30 Gy (%)	−0.002	<0.001	0.023
Right Hippocampal V35 Gy (%)	−0.002	<0.001	0.02
Right Hippocampal V40 Gy (%)	−0.002	<0.001	0.025

[α]Coefficient represents the change in Z-score (standard deviation) per year for each percent increase volume of hippocampus receiving the respective dose.
Abbreviations: SE, standard error; CVLT-LD, California Verbal Learning Test–Long Delay; CVLT-T, California Verbal Learning Test–Total Recall; hippocampal V40 Gy, volume of hippocampus receiving 40 Gy.

Table 3 Multivariate regression models for CVLT-SD

Variable	Left Hippocampus		
	Coefficient[α]	SE	*P*-value
Hydrocephalus			
Yes	0		
No	0.106	0.044	0.019
Left hippocampal V40 Gy (%)	−0.001	<0.001	0.025
	Right Hippocampus		
	Coefficient[α]	SE	*P*-value
Hydrocephalus			
Yes	0		
No	0.117	0.043	0.01
Right hippocampal V40 Gy (%)	-0.001	<0.001	0.019

[α]Coefficient represents the change in Z-score (standard deviation) of CVLT-SD per year. When interpreting dose-volume data, coefficient represents the change in Z-score (standard deviation) per year for each percent increase in volume of hippocampus receiving 40 Gy.
Abbreviations: SE, standard error; CVLT-SD, California Verbal Learning Test–Short Delay; hippocampal V40 Gy, volume of hippocampus receiving 40 Gy.

Individual patient data for the pre-adolescent and adolescent subgroups are shown in Supplementary Figure 6. The CVLT-LD scores of adolescents ($n = 22$) did not show a significant decline over time (slope = −0.005 SD/y, $P = 0.234$) and were not associated with hippocampal dose; however, interpretation of this result is limited by the small number of patients in this group.

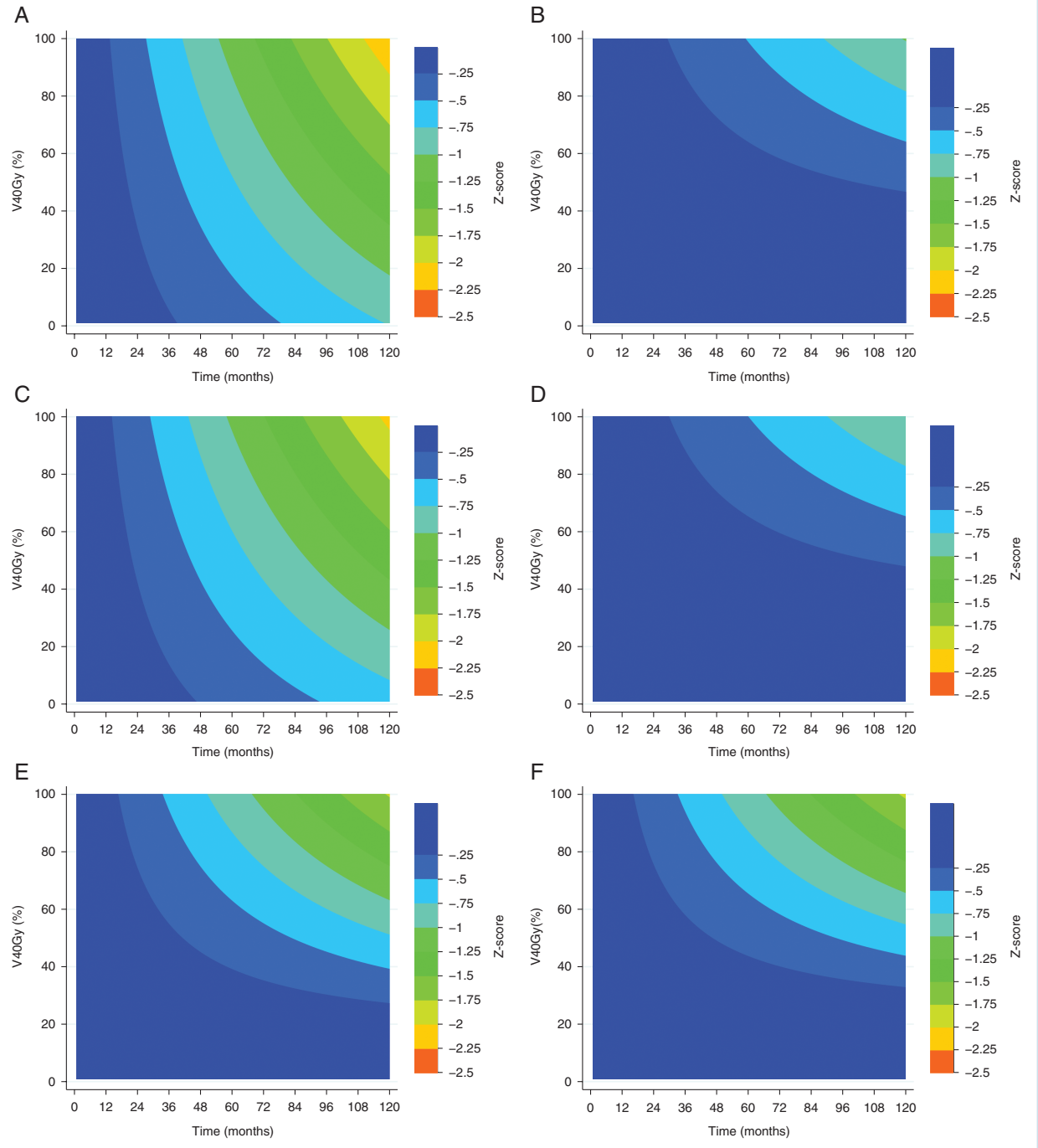

Fig. 2 Contour plot of the difference in CVLT-SD from baseline as a function of time from RT and volume of: (A) *right* hippocampus receiving 40 Gy (%) in patients *with* hydrocephalus, (B) *right* hippocampus receiving 40 Gy (%) in patients *without* hydrocephalus, (C) *left* hippocampus receiving 40 Gy (%) in patients *with* hydrocephalus, (D) *left* hippocampus receiving 40 Gy (%) in patients *without* hydrocephalus. Treating the entire right (Figure 2A and B) or left hippocampus (Figure 2C and D) to 40 Gy was associated with a 5-year and 10-year short-delay recall reduction of 1 SD and 2 SD, respectively, for patients with hydrocephalus, and 0.5 SD and 1 SD, respectively, for patients without hydrocephalus. Contour plot of difference in CVLT-LD from baseline for children <12 years as a function of time from RT and volume of (E) *right* hippocampus receiving 40 Gy (%), and (F) *left* hippocampus receiving 40 Gy (%). Treating the entire right (Figure 2E) or left hippocampus (Figure 2F) to 40 Gy was associated with a 5-year and 10-year long-delay recall reduction of 0.9 SD and 1.8 SD, respectively.

Semantic Cluster and Discriminability

Seventy-four patients had at least 2 semantic cluster and 2 discriminability scores. The decline in semantic cluster was significant (slope = –0.07 SD/y, $P = 0.003$), as was the decline in discriminability (slope = –0.05 SD/y, $P = 0.003$). Unadjusted individual patient data are shown in Supplementary Figure 7. On univariate regression, the only variable associated with semantic cluster was absence of hydrocephalus (slope = 0.11 SD/y, $P = 0.008$). None of the clinical or hippocampal doses were associated with change in the discriminability Z-score on univariate regression.

CPT Omission and CPT HitRT

Sixty-eight patients had at least 2 CPT omission scores and 2 CPT HitRT scores. The change in CPT omission was not significant (slope = 0.025 SD/y, $P = 0.555$), but the change in CPT HitRT was significant (slope = 0.018 SD/y, $P < 0.001$). Unadjusted individual patient data are shown in Supplementary Figure 8. On univariate regression, none of the clinical variables or hippocampal doses were associated with change in CPT omission or change in CPT HitRT.

Discussion

The ability to record day-to-day events and retrieve those memories at a later time arises from 2 linked processes: (i) initial encoding of the new experience and (ii) consolidation of the new experience such that it is optimized for retrieval when cued by an appropriate stimulus.[18] The current understanding of how the brain organizes new memories suggests that the hippocampus is critical to the first process, whereas both the hippocampus and the medial prefrontal cortex might be important in the second process.[19–21] Consistent with this, our long-term neurocognitive data suggest that radiation injury to the hippocampus may negatively affect the ability to encode new information. Patients in whom a greater volume of the hippocampus received 40 Gy experienced a sharper decline in their ability to recall words from an initial list after being presented with a distracting second list, as measured by short-delay recall (CVLT-SD). Greater right hippocampal doses were also associated with a decline in learning (CVLT-T). Overall, these results suggest that the hippocampal dose may be important in long-term cognitive outcomes, particularly for initial memory encoding and protection from interfering information. Notably, functionality not associated with the hippocampus, such as sustained attention and processing speed (measured by CPT omission and CPT HitRT), was not associated with hippocampal dose.

In children younger than 12 years, decline in long-delay recall was also associated with hippocampal dose. These findings suggest that radiation injury to the hippocampus may result in disruption of initial learning, encoding, and protection from interference, particularly in children younger than 12 years. In adolescents aged 12 years or older, this disruption may not be seen if a delay period enables consolidation. The initial encoding process appears to be most related to hippocampal dose, whereas consolidation of new memories might be more dependent on other brain substructures, such as the medial prefrontal cortex and its interactions.[21]

When comparing our results with those from the literature concerning adult patients, 3 important distinctions must be noted. First, the phase II trial of hippocampal avoidance in adults, RTOG 0933, used the Hopkins Verbal Learning Test (HVLT) to assess recall.[4] The HVLT is available only for participants aged 13 years or older. It takes less time to administer than the CVLT and uses 3 trials of 12 words instead of 5 trials of 15 or 16 words.[22] It has no equivalent to CVLT-SD, but it does have a delayed-recall measure that approximates CVLT-LD. Second, the primary outcome on RTOG 0933 was delayed verbal recall at 4 months. We did not assess recall at 4 months because cognitive deficits in children increase with time without a definite plateau. Third, RTOG 0933 was conducted in patients with a median age of 61 years who were undergoing whole-brain radiation for brain metastases. From a neurodevelopment and disease-burden standpoint, this patient population is very different from children with focal LGGs. However, despite these differences, our results are comparable to those in adults in that both suggest an association between hippocampal dose and measures of recall.

These results have important implications for RT planning, especially in the setting of proton therapy and utilization of smaller CTV margins. Proton therapy is increasingly being utilized for pediatric brain tumors[23] due to the dosimetric advantage afforded by the Bragg peak. Although proton therapy does not result in any exit dose, there generally is entrance dose outside of the target volume, and knowing where to place this entrance dose is critical to leveraging the full potential of proton therapy. Our data suggest using beam arrangements to avoid the hippocampi, and in particular, to avoid hippocampal doses equal to or greater than 40 Gy. In addition to proton therapy, the utilization of a smaller CTV margin would further facilitate dose reduction to the hippocampi. Although RT1 employed a CTV margin of 1 cm, recently published results from the Children's Oncology Group study ACNS0221 showed that a CTV margin of 0.5 cm was effective and did not result in any marginal relapses.[24] Proton therapy plans using a CTV margin of 0.5 cm would have a more favorable hippocampal dose-volume profile compared with photon plans utilized on RT1, highlighting that there is significant opportunity for improvement and that modeled neurocognitive outcomes using the RT1 dataset may not necessarily be representative of outcomes after modern-day proton therapy.

Several retrospective studies have correlated hippocampal dose with cognitive function in children; however, none have focused on LGGs or included neurocognitive follow-up beyond 5 years, which is particularly important in this patient population with a 10-year overall survival of 95%.[8] Zureick et al found that left hippocampal V20 Gy equivalent was significantly associated with a decline in immediate verbal memory,

but not in delayed verbal memory, although patients did demonstrate a deficit in delayed verbal memory.[25] Hippocampal dosimetry was analyzed in a heterogeneous pediatric brain tumor population, half of whom received craniospinal irradiation, and the study had a neurocognitive follow-up of 3 years. Merchant et al demonstrated that hippocampal dose was associated with a decline in emotional intelligence quotient in patients with medulloblastoma with a follow-up of 5 years; however, no association between hippocampal dose and verbal recall was reported.[26] Findings from a cohort of 14 pediatric patients with brain tumors treated with proton therapy with 2 years of follow-up suggested that word-pair delayed recall was associated with both left and right hippocampal doses.[27] There are also data suggesting that the hippocampal volume is reduced in survivors of pediatric brain tumors and that this volume reduction is associated with a decline in memory.[28]

In addition to hippocampal dose, hydrocephalus is an important predictor of CVLT-SD. These results are consistent with prior literature.[29–31] Hydrocephalus may affect measures of memory and learning through increased intracranial pressure stretching and distorting neural pathways within the hippocampus.[32,33]

This study has several limitations. It represents a retrospective analysis of neurocognitive data collected prospectively on the phase II protocol RT1. Although data were collected at baseline, at 6 months posttreatment, yearly through year 5 posttreatment, at 7 or 8 years, and at 10 years posttreatment, complete data were not obtained for all patients at every timepoint. However, this is somewhat mitigated by our use of a random coefficient model that can handle data that are missing at random without introducing biases.[34] Although tumor progression, recurrence, and secondary malignancy can also result in cognitive decline, we censored patients at the time of recurrence, progression, or second malignancy to avoid such confounding explanations for our results. Local control data were collected prospectively, as all patients were followed closely on protocol with a brain MRI. Although use of anesthesia has been associated with neurocognitive deficits,[35] data on anesthesia use were not available for analysis. However, it should be noted that the concern regarding anesthesia use is greatest in infants aged ≤3 years, and even within this age group, studies of single and multiple anesthesia exposures have shown mixed results.[35–38] Our study did not include children less than 6 years of age.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

hippocampus | memory | pediatric low-grade glioma

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Authorship statement. Design of study: SA. Statistical analysis: SW and SA. Interpretation of results: all authors. Manuscript writing, critical feedback, and revisions: all authors.

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