

Weekly Hippocampal Diffusion Changes During Partial-Brain Radiation Therapy for High- Grade Glioma: Associations With Dose and Early Memory Change

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Abstract

Purpose

To characterize the weekly trajectory of hippocampal diffusion during fractionated partial-brain radiation therapy (RT) for high-grade glioma and determine whether the magnitude of change is associated with planned hippocampal dose.

Methods

45 adults enrolled in a prospective observational imaging study and treated with 60 Gy in 30 fractions with concurrent temozolomide. Diffusion MRI was obtained before RT and weekly during treatment. Relative bilateral hippocampal apparent diffusion coefficient (ADC) change and fractional anisotropy (FA) were evaluated longitudinally. Linear mixed-effects models included treatment week and planned mean bilateral hippocampal dose as fixed main effects

Results

Hippocampal ADC increased progressively from a median relative change of 0.5% at Week 1 to 12% (IQR, 6%-18%) at Week 6. The ADC time coefficient was + 2.2 percentage points per week (95% CI, 1.8–2.5; $P < 0.001$). After accounting for week, higher planned mean hippocampal dose was associated with greater ADC change (+ 0.81 percentage points/Gy; 95% CI, 0.76–0.93; $P < 0.001$). FA remained stable through Week 3 and declined during Weeks 4–6.

Conclusion

Weekly diffusion MRI demonstrates a progressive, dose-associated hippocampal response during fractionated RT, supporting hippocampal ADC as a candidate treatment-phase imaging phenotype for prospective validation.

Introduction

Radiation therapy (RT) is a cornerstone of treatment for high-grade glioma (HGG), but irradiation of normal brain can contribute to neurocognitive morbidity [1–5]. The hippocampus is of particular interest because of its role in learning and memory and the radiosensitivity of the dentate-gyrus neurogenic niche [6–14].

Diffusion-weighted and diffusion-tensor MRI provide quantitative measures sensitive to tissue-water mobility and microstructural organization. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) are candidate response measures, although neither is specific to a single cellular injury process [15,

16]. Clinical studies have demonstrated radiation-related diffusion abnormalities during and after brain RT, including treatment-phase changes in parahippocampal white matter and later hippocampal, cortical, and limbic changes [17–21]. Voxel-based analyses have linked regional brain dose to later neurocognitive decline [22], and white-matter DTI studies have shown dose-associated injury [23, 24]. Hippocampal dose has also been associated with long-term associative-memory decline [25], while regional diffusion analyses suggest substantial heterogeneity in white-matter radiosensitivity [26]. However, the weekly diffusion trajectory within the hippocampus itself during fractionated partial-brain RT remains poorly characterized.

We therefore characterized weekly hippocampal ADC and FA trajectories during partial-brain RT for HGG and evaluated their association with planned hippocampal dose. A secondary exploratory analysis examined whether baseline-to-Week-6 diffusion change was associated with early memory change.

Methods and Materials

Patient Cohort and Study Design

Adult patients aged ≥ 18 years with histologically confirmed HGG and Karnofsky Performance Status ≥ 60 were enrolled in the prospective, single-arm observational imaging study “Serial Advanced Magnetic Resonance Imaging (MRI) for Guidance of Personalized Adaptive Radiotherapy for High Grade Glioma” (UT MD Anderson protocol PA17-0844; NCT04771806). The study opened April 1, 2019, was approved by the UT MD Anderson Institutional Review Board, and required written informed consent. This secondary analysis included 45 patients with evaluable serial diffusion imaging; the exact last accrual date for this 45-patient analytic cohort was not retained in the available analytic materials. All received 60 Gy in 30 fractions over 6 weeks using IMRT or VMAT with concurrent temozolomide followed by adjuvant temozolomide. Multiparametric MRI was obtained before RT and weekly during treatment.

Cognitive Testing

Learning and memory were assessed at baseline and Week 6 with the examiner-administered Cogstate C3 battery using standardized task instructions [27]. Tests included One Card Learning (OCL), Face Name Matching (FNMT), First Letter Name Recall (FNLT), Face Seen Before (FSBT), and Behavioral Pattern Separation-Object (BPTX). The examiner facilitated standardized administration and comprehension; formal blinding to imaging and dose metrics was not documented in the retained study materials. Raw scores were converted to within-sample z scores, and the composite memory score averaged the BPTX Lure Discrimination Index, FNMT, and OCL z scores. Change was calculated from baseline to Week 6. Normative and reliable-change outputs were not available in the retained analytic dataset; potential practice effects are considered in the Discussion [28].

MRI Acquisition, ROI Delineation, and Diffusion-Metric Generation

Weekly MRI was performed on a 1.5-T Siemens Aera scanner. The protocol included 3D T1-weighted MPRAGE (TR/TE/TI, 2100/3.04/1100 ms; voxel size, 0.5×0.5×1.0 mm³) and DTI using 64 diffusion-encoding directions at b = 1000 s/mm² with b = 0 acquisitions (TR/TE, 4500/76 ms; voxel size, 2×2×2.5 mm³). Additional acquisition and preprocessing details are provided in the Supplementary Methods. Hippocampi were manually contoured at each time point on high-resolution T1-weighted MRI by one experienced radiation oncologist using published anatomic guidelines [29]. No automated contour propagation was used. DWI preprocessing included denoising, skull stripping, eddy-current and inter-volume motion correction, and registration to b = 0 and T1-weighted images. ADC maps were generated by mono-exponential fitting and FA maps by tensor fitting.

Median ADC and FA were extracted from the combined bilateral hippocampal ROI at baseline and weekly. Relative ADC change and absolute FA change were defined as:

$$\text{Relative ADC change (\%)} = 100 \times [(ADC_t - ADC_{baseline}) / ADC_{baseline}]$$

$$\text{Absolute FA change (\%)} = 100 \times (FA_t - FA_{baseline})$$

Baseline relative ADC change was 0% by definition. For descriptive cognitive comparisons, absolute FA change was multiplied by 100 for presentation; mixed-effects FA coefficients are reported in unscaled raw FA units. A low-dose left cerebellar-tonsil ROI served as a limited internal measurement reference, not a biologic control.

Radiation-Dose Extraction

The planned three-dimensional dose distribution was obtained from RayStation. Baseline hippocampal ROIs were registered to the planning dataset using rigid registration with deformable refinement. The prespecified dosimetric variable was bilateral mean hippocampal dose, defined as the average of left and right hippocampal mean doses.

Statistical Analysis

Continuous variables are reported as medians with ranges or interquartile ranges and categorical variables as counts and percentages. Early cognitive decline was operationally defined as a ≥ 1-SD decrease from baseline to Week 6; cognitive comparisons were exploratory and not multiplicity-adjusted. Relative ADC changes at Weeks 2–6 were compared with Week 1 using paired Wilcoxon signed-rank tests with Holm correction; FA was compared with baseline. Baseline-to-Week-6 diffusion changes were compared between stable/improved and decline groups using Mann-Whitney U tests.

Longitudinal diffusion trajectories were evaluated with linear mixed-effects models using week as a fixed effect and a patient-specific random intercept. Dose-association models additionally included bilateral mean hippocampal dose as a fixed main effect. No week-by-dose interaction was included; thus the dose coefficient estimates the association between planned dose and diffusion-change magnitude

across repeated observations after accounting for week, not modification of the weekly rate of change. Models used restricted maximum likelihood and all available repeated observations without imputation. Statistical analyses were performed in SPSS Statistics, version 29 (IBM Corp., Armonk, NY, USA).

AI-Assisted Manuscript Preparation

OpenAI ChatGPT was used during manuscript preparation to assist with language editing, organization, and reference-format checking. It was not used to generate or analyze study data or perform statistical analyses. All scientific content, interpretations, and references were reviewed by the authors, who take responsibility for the final manuscript.

Results

Patient Characteristics

The imaging cohort included 45 adults with HGG (median age, 62 years; range, 25–70); 48.9% were female. Glioblastoma accounted for 40/45 cases (88.9%), so the findings primarily reflect a glioblastoma cohort rather than the broader histopathologic spectrum of HGG. All patients received and completed 60 Gy in 30 fractions over 6 weeks with concurrent temozolomide followed by adjuvant temozolomide. Additional baseline characteristics are summarized in Table 1.

Table 1

Patient, tumor, and treatment characteristics (full imaging cohort, n = 45) Unless otherwise specified, characteristics refer to the full imaging cohort. All 45 patients received and completed 60 Gy in 30 fractions (2 Gy per fraction) over 6 weeks of partial-brain RT using IMRT/VMAT, with concurrent TMZ followed by adjuvant TMZ. Paired Week-6 cognitive outcomes were available for n = 24.

Variable	
Age (median, range)	62 (25–70)
Sex (female)	22/45 (48.9%)
Educational years	16 (12–20)
Tumor side (right)	30/45 (66.7%)
Lobe	19 (42.2%)
Frontal	8 (17.8%)
Parietal	11 (24.4%)
Temporal	6 (13.3%)
Occipital	1 (2.2%)
Cerebellum	
Histology	40 (88.9%)
GBM	3 (6.7%)
IDH mut grade 4 astrocytoma	1 (2.2%)
IDH mut grade 3 astrocytoma	1 (2.2%)
H3K27M high grade glioma	
Gross total resection	39 (86.7%)
Clinical target volume, median (range), cm ³	156 (73–274)
Mean bilateral hippocampal dose (Gy)	
Mean ± SD	14.7 ± 3.6
Median (range)	15.7 (6.7–21.6)
Concurrent TMZ	45 (100%)
Adjuvant TMZ	45 (100%)
Steroids during RT	6 (13.3%)
Antiepileptic medication use during RT	12 (26.7%)

Variable	
Completed Week-6 cognitive evaluation	24 (53.3%)
Radiation therapy course	60 Gy in 30 fractions (2 Gy/fraction) over 6 weeks using IMRT/VMAT; completed by 45/45 patients

Hippocampal DWI Changes During RT

Hippocampal ADC increased progressively during RT, from a median relative change of 0.5% at Week 1 to 12% (IQR, 6–18%) at Week 6; Weeks 2–6 differed from Week 1 after Holm correction (all $P < 0.001$). The full weekly trajectory is shown in Fig. 1.

Median hippocampal FA was 0.181 at baseline and 0.165 at Week 6. The median hippocampal FA did not differ significantly from baseline through Week 3 but was lower at Weeks 4–6 (all $P < 0.001$), indicating a later treatment-phase decline than the ADC change (Fig. 1).

Hippocampal volume showed no significant change from baseline to Week 6 (mean, 4.0 cm³ vs 3.97 cm³; $P = 0.375$).

In the retained mixed-effects model, the ADC time coefficient was + 0.022 fractional units per week (95% CI, 0.018–0.025; $P < 0.001$), equivalent to + 2.2 percentage points per week. The FA time coefficient was – 0.0022 raw FA units per week (95% CI, -0.0042 to -0.0001; $P = 0.038$).

Association Between Hippocampal Dose and Diffusion Change

After accounting for week in the retained mixed-effects model, higher mean bilateral hippocampal dose was associated with greater ADC change across repeated on-treatment observations (β =+0.0081 fractional units per Gy; 95% CI, 0.0076–0.0093; $P < 0.001$), equivalent to + 0.81 percentage points per Gy in the modeled ADC outcome. This coefficient describes a dose-associated difference in change magnitude and not a dose-by-time interaction. FA showed a weaker inverse association with dose (β =-0.0009 raw FA units per Gy; $P = 0.017$) (Fig. 2).

Exploratory univariable comparisons did not identify statistically significant associations between hippocampal ADC change and age ($r = 0.25$, $P = 0.13$), sex ($P = 0.46$), steroid use ($P = 0.072$), antiepileptic use ($P = 0.75$), or broad tumor location (frontal vs non-frontal, $P = 0.064$). These analyses do not exclude residual confounding.

In a separate slope analysis of the left cerebellar tonsil reference ROI, mean dose was not associated with the patient-specific ADC slope (β =+0.0002 fractional units per Gy per week; 95% CI, -0.001 to + 0.002; $P = 0.71$) (Supplementary Figure S1). This finding is interpreted only as a limited internal reference and not as evidence that the cerebellum is intrinsically less radiosensitive.

Exploratory Association Between Baseline-to-Week-6 Diffusion Change and Cognition

Paired baseline and Week-6 neurocognitive data were available for 24/45 patients (53.3%), and cognitive analyses were restricted to these 24 patients. The remaining 21 patients did not have a paired Week-6 cognitive outcome in the retained analytic output; exact baseline-only counts and reasons for missing paired follow-up were not retained and are not inferred. A cohort-flow diagram is provided in Fig. 3. Completers had a median age of 55 years (range, 27–70) and 41.6% were female. Existing standardized-mean-difference comparisons showed no major imbalance in most measured characteristics, although completers had modestly higher hippocampal dose and ADC change (Supplementary Figure S2).

In exploratory dichotomized analyses, baseline-to-Week-6 relative ADC increase was greater in patients meeting the ≥ 1 -SD decline definition for OCL (median 16.5% vs 10%; $P = 0.013$) and for the composite memory score (18.5% vs 10%; $P = 0.017$). Other individual cognitive tests were not statistically significant (Table 2). These unadjusted comparisons should not be interpreted as validated thresholds or as proof of persistent neurocognitive toxicity.

Table 2

Hippocampal ADC change and neurocognitive outcomes Relative hippocampal ADC change from baseline to Week 6 is compared between patients with stable/improved versus declined performance for each Cogstate memory test and the composite memory score.

Neurocognitive Test	Stable/Improved (n)	% Δ ADC (median, range)	Declined (n)	% Δ ADC (median, range)	p-value
OCL	10	10% (4–19%)	14	16.5% (7–27%)	0.013
BPTX	17	11% (4–27%)	7	18% (4–27%)	0.209
FNMT	12	12.5% (4–21%)	12	11.5% (4–27%)	0.843
FNLT	12	12.5% (4–27%)	12	11.5% (6–27%)	0.671
FSBT	11	13% (4–22%)	13	12% (4–27%)	1
Composite	12	10% (4–22%)	12	18.5% (8–27%)	0.017

Baseline-to-Week-6 FA change was not significantly associated with decline on any individual cognitive test or the composite memory score (Supplementary Table S1).

Discussion

Our main finding is that hippocampal diffusion changes can be detected and followed during the course of fractionated RT. Weekly MRI showed a progressive increase in ADC over the six weeks of treatment, rather than a change observed only between baseline and the end of RT. Higher planned hippocampal

dose was also associated with greater ADC change, supporting an association between radiation exposure and the observed diffusion changes. The cognitive findings are secondary and provide preliminary context for the possible functional relevance of these imaging changes.

Prior studies established that diffusion MRI can detect evolving radiation effects during treatment, but predominantly in normal-appearing white matter. Nagesh et al. demonstrated dose-dependent diffusion changes in the corpus callosum during and after cranial RT [30], and Hope et al. reported dose-dependent diffusivity changes in normal-appearing white matter during chemoradiotherapy for HGG [31]. Chapman et al. subsequently showed treatment-phase DTI changes in the parahippocampal cingulum associated with later cognitive outcomes [18]. More recent studies identified early post-RT hippocampal quantitative MRI abnormalities and longitudinal regional ADC increases after cranial irradiation [17, 19, 20]. The present study extends this literature by resolving the hippocampal response itself at weekly intervals throughout a conventional 6-week partial-brain course.

The absence of significant hippocampal volume change during the same interval supports the possibility that diffusion imaging captures an earlier treatment response than conventional volumetry. Seibert et al. demonstrated dose-dependent hippocampal volume loss approximately 1 year after partial-brain RT [32], and Le Fèvre et al. similarly linked hippocampal dose with subsequent atrophy in glioblastoma [14]. Early diffusion change and later structural change may therefore represent different phases along a continuum of hippocampal radiation response, although the present data do not establish that ADC change predicts later atrophy.

The biological substrate of increasing hippocampal ADC is likely multifactorial. ADC reflects tissue-water mobility rather than a single injury mechanism, and the hippocampus contains neuronal, glial, vascular, and adjacent white-matter compartments [13]. Experimental studies demonstrate radiation-induced neural precursor-cell dysfunction, persistent inflammatory responses within the hippocampal stem-cell niche, and MRI-detectable hippocampal abnormalities after irradiation [33–35]. Neuroinflammation, microvascular effects, suppression of neurogenesis, cellular remodeling, and altered extracellular water may therefore contribute at different stages. The later decline in FA may reflect a different tissue compartment or time scale; prior FA literature after cranial RT has predominantly involved white-matter tracts [23, 24, 26].

The dose association provides a second dimension to the longitudinal ADC signal. After accounting for treatment week, greater planned mean bilateral hippocampal dose was associated with a larger magnitude of ADC change across repeated observations. Because the model did not include a dose-by-time interaction, this should not be interpreted as evidence that higher dose accelerates the weekly rate of ADC change. Rather, greater radiation exposure was associated with a larger treatment-phase diffusion response. The convergence of a temporal trajectory and a dose association makes hippocampal ADC an attractive quantitative tissue-response phenotype. Future studies should determine whether patients receiving similar physical doses nevertheless show meaningfully different ADC trajectories, potentially reflecting interpatient variation in normal-tissue radiosensitivity.

The exploratory cognitive findings provide a potential functional context. Independent clinical studies have linked hippocampal dose to later memory impairment. In adults, Gondi et al. reported a dose-response relationship between bilateral hippocampal exposure and delayed-recall impairment after fractionated stereotactic RT [36]. In 124 children treated for medulloblastoma on SJMB03, Acharya et al. found that each 1-Gy increase in mean hippocampal dose was associated with approximately 23%-26% higher odds of clinically meaningful associative-memory decline [25]. In our smaller adult HGG subset, greater baseline-to-Week-6 relative ADC increase was associated with early decline in OCL and the composite memory score. These populations and time scales differ substantially, and our data do not establish mediation. Nevertheless, they motivate a testable dose→ADC-response→cognition framework that should be evaluated prospectively with continuous cognitive outcomes and longer follow-up.

Memory toxicity is also unlikely to be confined to the hippocampus. Qian et al. linked post-RT microstructural injury in limbic white-matter pathways to memory performance [21], while Sleurs et al. identified distributed dose-sensitive regions associated with neurocognitive decline [22]. Hippocampal ADC should therefore be viewed as one measurable component of a broader memory-network response rather than a comprehensive marker of cognitive injury.

Limitations include the modest, predominantly glioblastoma cohort and incomplete source-level clinical data. Direct tumor or peritumoral-edema involvement of the hippocampus was not systematically coded, and tumor/resection-cavity proximity, early progression, seizure burden, steroid exposure, and other acute clinical factors could not be fully modeled. Analyses used combined bilateral rather than side-specific dosimetry, and raw absolute ADC outputs were not retained. Formal contour reproducibility metrics, examiner-blinding documentation, random-slope models, residual/influence diagnostics, and partial-volume sensitivity analyses were unavailable. Minor sequence-level variation occurred across protocol instances. The cerebellar tonsil was only a limited measurement reference because its tissue composition, geometry, susceptibility/partial-volume characteristics, and dose distribution differed from those of the hippocampus. Cognitive analyses were restricted to 24 patients, were unadjusted for multiplicity, used within-sample z scores rather than reliable-change metrics, and may be affected by practice effects [28] and other acute treatment or clinical influences. These early cognitive associations do not establish persistent neurocognitive impairment.

The major strength of this study is the ability to observe normal-tissue diffusion response repeatedly during radiation delivery. Prospective validation should first establish the reproducibility of early hippocampal ADC changes, particularly during Weeks 2–4, and their relationship to cumulative delivered dose. Subsequent studies should test whether patient-specific ADC trajectories predict later cognitive or volumetric outcomes beyond dose and clinical factors. Only after such incremental predictive value is established should ADC-guided neuroprotective or response-adaptive strategies be considered.

Conclusions

Serial diffusion MRI demonstrated a progressive, dose-associated hippocampal ADC response during 6 weeks of partial-brain RT. These findings identify hippocampal ADC as a measurable treatment-phase tissue-response phenotype and support prospective validation of early ADC trajectories against delivered dose, later structural change, and neurocognitive outcomes.

Declarations

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

The parent study (UT MD Anderson protocol PA17-0844; NCT04771806) was approved by the UT MD Anderson Institutional Review Board.

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

Supplementary Fig. 2

Standardized mean differences comparing patients with versus without paired Week-6 cognitive follow-up across available demographic, clinical, dosimetric, and imaging variables. This existing analysis does not substitute for a sensitivity analysis of the longitudinal imaging model restricted to the 24 cognitive completers.

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Author Contribution

O.H. conceived the study question, developed the original study concept, performed the statistical analysis, interpreted the results, and led the drafting of the manuscript. B.P. performed DTI data processing and imaging analysis and contributed to data curation and interpretation. J.S.W., K.R.N., and the neuropsychology team contributed to acquisition, processing, and interpretation of the neurocognitive data, development and oversight of the cognitive assessment methodology, and critical

revision of the manuscript. E.K., A.E., S.T., H.L., W.T., C.S., T.S., and C.W. contributed to data collection, data curation, and review of the manuscript. M.C.T., T.H.B., W.J., D.N.Y., M.F.M., A.J.G., S.L.M., and J.L. contributed to clinical data collection, clinical interpretation, and critical review of the manuscript. C.C. provided senior supervision and mentorship, oversaw the study, verified the integrity and provenance of the study data, contributed to data analysis and interpretation, and had overall responsibility for the study data and final manuscript review. All authors contributed to drafting and/or critically revising the manuscript, reviewed the final version, and approved it for submission.

Data Availability

The analytic data underlying this article are not publicly available. Deidentified data may be made available by the corresponding author upon reasonable request and subject to institutional approvals.

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Figures

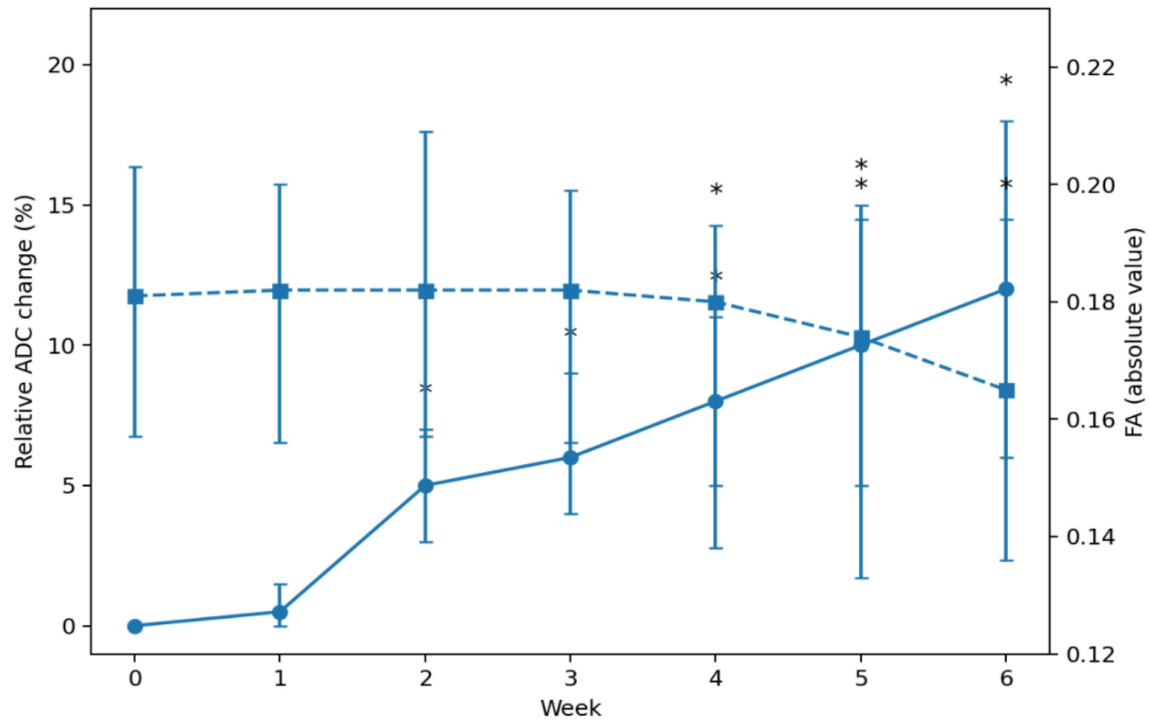


Figure 1

Weekly hippocampal diffusion changes during radiation therapy.

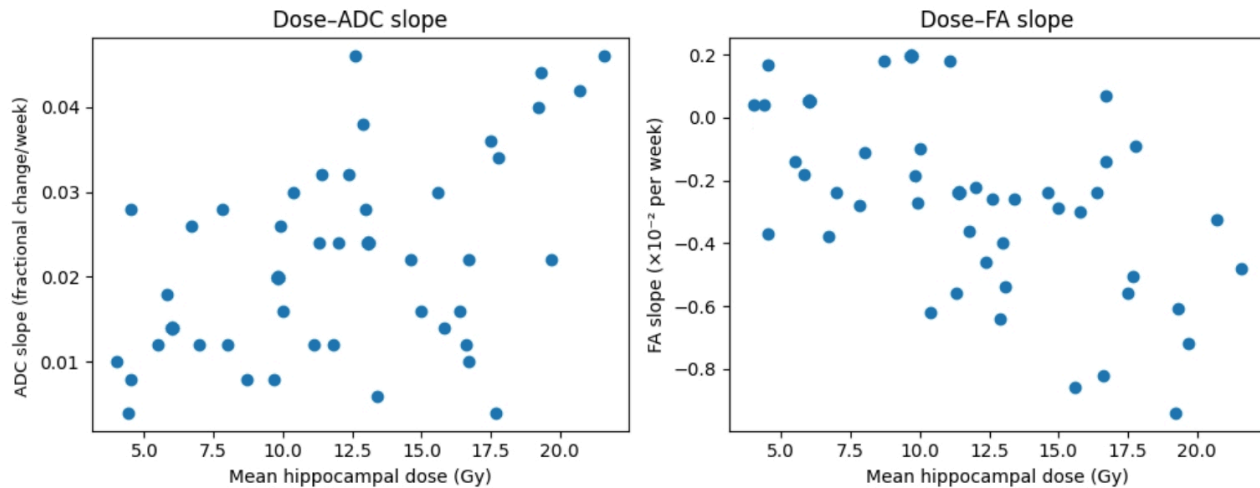


Figure 2

Descriptive association between mean hippocampal dose and patient-specific diffusion-change slopes during radiation therapy. Scatterplots show patient-specific ADC (A) and FA (B) change slopes versus mean bilateral hippocampal dose. No fitted regression lines are shown; inferential results are based on the mixed-effects model with week and dose as main effects and no week-by-dose interaction.

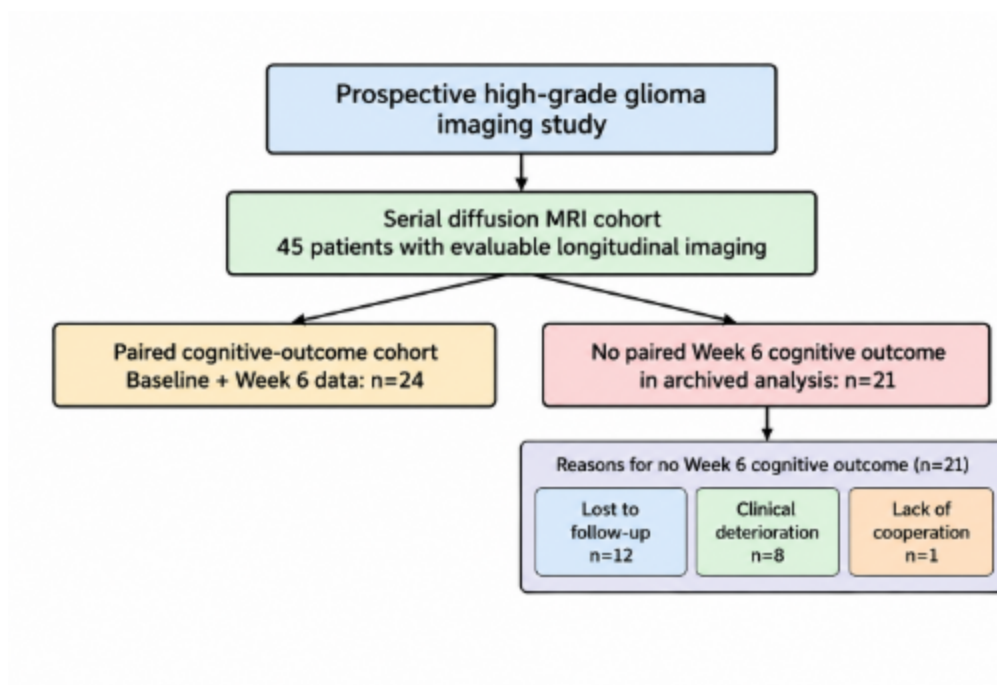


Figure 3

Cohort flow and availability of paired cognitive outcome data.

Supplementary Files

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