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Microstructural Changes in Hippocampal Subfields and Neurocognitive Decline After Fractionated Brain Radiation Therapy

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Abstract

Purpose: Irradiation of the hippocampus (HC) during treatment for primary brain tumors contributes to neurocognitive decline. Although whole HC-sparing techniques have mitigated some toxicity, the HC comprises multiple subfields which subserve different components of memory. We evaluated longitudinal, dose-dependent volumetric changes in HC subfields after fractionated radiotherapy (RT) and determined their associations with verbal and visuospatial memory performance.

Methods: Ninety adults with primary brain tumors received fractionated intensity-modulated RT or proton therapy. High-resolution 3D T1 and FLAIR MRI and a comprehensive neurocognitive battery were obtained at baseline and 3, 6, and 12-months post-RT. Bilateral HC and their subfields were segmented using robust, validated, automated parcellation software. Linear mixed-effects (LME) models quantified (1) time-dependent atrophy, (2) dose-volume relationships, and (3) subfield-memory associations, adjusting for censored volume, age, and sex.

Results: Total hippocampal volume declined by 2.8% at 3 months, 4.3% at 6 months, and 4.1% at 12 months (all $p < 0.05$ vs baseline). Left-sided structures exhibited greater percentage volume loss at 3- and 6-months post-RT than right-sided subfields. Dose-dependent atrophy was significant at 12 months in the left hippocampus and across all time points in the right hippocampus. Twelve right-sided and two left-sided subfields exhibited dose-responsive atrophy for one or more time points. Preserved volumes of the left hippocampal-amygdala transition area (HATA) and left hippocampal tail predicted higher Hopkins Verbal Learning Test-Revised (HVLT-R) total recall scores, whereas preservation of these subfields and the left presubiculum body predicted higher delayed recall scores. Preserved volumes of right subicular structures (subiculum body, parasubiculum) and left HATA predicted Brief Visuospatial Memory Test-Revised (BVMT-R) total and delayed recall scores, respectively.

Conclusion: Fractionated RT induces progressive, dose-related atrophy in discrete hippocampal subfields, with earlier and steeper dose–response curves observed on the right. Specific subfields (left hippocampal tail, left presubiculum body, right parasubiculum) are both radiosensitive and critical for memory preservation. Subfield-sparing planning objectives may optimize cognitive outcomes when whole-HC avoidance is not feasible.