Int J Radiat Oncol Biol Phys. 2023 May 23;S0360-3016(23)00515-1.
doi: 10.1016/j.ijrobp.2023.05.026. Online ahead of print.

Dose-dependent atrophy in bilateral amygdalae and nuclei after brain radiotherapy: Association with mood and memory outcomes on a longitudinal clinical trial

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PMID: 37230430 DOI: 10.1016/j.ijrobp.2023.05.026

Abstract

Background: Amygdalae, bilateral almond-shaped structures located anterior to the hippocampi, are critical to limbic system functions of emotional processing and memory consolidation. The amygdalae are heterogeneous, composed of multiple nuclei with distinct structural and functional properties. We prospectively assessed associations between longitudinal changes in amygdala morphometry, including component nuclei, and functional outcomes in primary brain tumor patients receiving radiation therapy (RT).

Methods: On a prospective longitudinal trial, patients (n=63) underwent high-resolution volumetric brain MRI and testing for mood (Beck Depression Inventory [BDI]; Beck Anxiety Inventory [BAI]), memory (BVMT-Total/Delayed Recall; HVLT-Total/Delayed Recall) and health-related quality of life (hrQOL) outcomes (FACT-Br Social/Emotional Well-being) at baseline, 3, 6, and 12-months post-RT. Amygdalae, including eight nuclei, were auto-segmented bilaterally using validated techniques. Linear mixed effects models assessed longitudinal change in amygdalae/nuclei volumes, and association with dose and outcomes. Wilcoxon rank sum tests compared amygdala volume change between subject groups with worse and stable outcomes at each timepoint.

Results: We found atrophy in the right amygdala at 6 months (p=0.001) and the left amygdala at 12 months (p=0.046). Higher dose was associated with atrophy of the left amygdala (p=0.013) at 12 months. Right amygdala showed dose-dependent atrophy at 6 months (p=0.016) and 12 months (p=0.001). Worse BVMT-Total, HVLT-Total and HVLT-Delayed performance was associated with smaller left lateral (p= 0.014, p=0.004, p=0.007) and left basal (p=0.034, p=0.016, p=0.026) nuclei volumes. Increased anxiety at 6 months was associated with greater combined (p=0.031) and right (p=0.007) amygdala atrophy. Greater left amygdala atrophy (p=0.038) was noted in patients with decreased emotional well-being at 12 months.

Conclusions: Bilateral amygdalae and nuclei undergo time- and dose-dependent atrophy after brain RT. Atrophy in amygdalae and specific nuclei was associated with poorer memory, mood, and

emotional well-being. Amygdalae-sparing treatment planning may preserve neurocognitive and neuropsychiatric outcomes in this population.