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In Reply to Cihan

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To the Editor: We welcome discussion on this important topic and thank Dr Cihan for her comments and useful further review of the literature on hippocampal damage. Moreover, we absolutely agree that radiation therapy is not the only cause of reduction in hippocampal volume. The purpose of our study (1, 2) was to determine whether radiation therapy in brain tumor patients was associated with hippocampal atrophy and whether there was, additionally, a dose-dependent effect. Indeed, we did find radiation dose–dependent atrophy in brain tumor patients. We also demonstrated the power of quantitative magnetic resonance imaging to measure longitudinal hippocampal atrophy in these cancer patients.

As Dr Cihan accurately points out, numerous neurologic conditions have been associated with hippocampal volume loss, several of which are mentioned in our article. Age is one such factor. In our study, radiation dose and age were each significantly associated with atrophy in a multivariable model. It is quite possible that increased statistical power would reveal significant effects for seizures and systemic therapy as well, consistent with findings in patients not undergoing radiation therapy (3, 4). We acknowledge this limitation to the study in our manuscript. Dr Cihan lists additional factors that could potentially affect hippocampal volume, such as prolonged corticosteroid administration and, critically, chemotherapy.

We join Dr Cihan in calling for careful study of several plausible risk factors for hippocampal atrophy. These factors should be additionally studied in multivariable analyses powered to detect interactions. A case report of marked unilateral hippocampal atrophy in a patient with glioblastoma illustrates dramatic hippocampal damage in the context of numerous potential causes, including surgery, radiation therapy, chemotherapy, corticosteroids, antiepileptic medications, and repeated generalized, tonic-clonic seizures (5). Other studies found that hippocampal volumes can be small in patients with brain tumors even before radiation therapy (6) or after bevacizumab even outside the high-dose radiation therapy field (7). Hippocampal volumes were also smaller than expected in survivors of breast cancer who received chemotherapy (4).

Preserving the cognitive abilities of brain tumor survivors will best be accomplished if we understand the effects of each of these possible contributors and how those effects might be mitigated. For radiation, it seems that dose reduction to the hippocampus is a reasonable strategy for investigation. As demonstrated in our present work, quantitative magnetic resonance imaging may prove to be a powerful tool to improve understanding of cancer treatments on hippocampal volume.

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