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Clinical Investigation: Central Nervous System Tumor

Hippocampal Dosimetry Predicts Neurocognitive Function Impairment After Fractionated Stereotactic Radiotherapy for Benign or Low-Grade Adult Brain Tumors

Vinai Gondi, M.D.,* Bruce P. Hermann, Ph.D.,† Minesh P. Mehta, M.D., FASTRO,¶ and Wolfgang A. Tomé, Ph.D., FAAPM*,‡,§

*Departments of *Human Oncology, †Neurology, ‡Medical Physics, and §Biomedical Engineering, University of Wisconsin, Madison, WI; and ¶Department of Radiation Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL*

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Summary

Equivalent dose in 2-Gy fractions to 40% of the bilateral hippocampi greater than 7.3 Gy is associated with long-term memory impairment. Modern intensity-modulated radiation therapy techniques can reduce the dose to the bilateral hippocampi below this dosimetric threshold.

Purpose: To prospectively evaluate the association between hippocampal dose and long-term neurocognitive function (NCF) impairment for benign or low-grade adult brain tumors treated with fractionated stereotactic radiotherapy (FSRT).

Methods and Materials: Adult patients with benign or low-grade adult brain tumors were treated with FSRT per institutional practice. No attempt was made to spare the hippocampus. NCF testing was conducted at baseline and 18 months follow-up, on a prospective clinical trial. Regression-based standardized z scores were calculated by using similar healthy control individuals evaluated at the same test−retest interval. NCF impairment was defined as a z score ≤ -1.5. After delineation of the bilateral hippocampi according to the Radiation Therapy Oncology Group contouring atlas, dose−volume histograms were generated for the left and right hippocampi and for the composite pair. Biologically equivalent doses in 2-Gy fractions (EQD_2) assuming an α/β ratio of 2 Gy were computed. Fisher's exact test and binary logistic regression were used for univariate and multivariate analyses, respectively. Dose−response data were fit to a nonlinear model.

Results: Of 29 patients enrolled in this trial, 18 completed both baseline and 18-month NCF testing. An EQD_2 to 40% of the bilateral hippocampi >7.3 Gy was associated with impairment in Wechsler Memory Scale-III Word List (WMS-WL) delayed recall (odds ratio [OR] 19.3; $p = 0.043$). The association between WMS-WL delayed recall and EQD_2 to 100% of the bilateral hippocampi >0.0 Gy trended to significance (OR 14.8; $p = 0.068$).

Conclusion: EQD_2 to 40% of the bilateral hippocampi greater than 7.3 Gy is associated with long-term impairment in list-learning delayed recall after FSRT for benign or low-grade adult brain tumors. Given that modern intensity-modulated radiotherapy techniques can reduce the dose to the bilateral hippocampi below this dosimetric threshold, patients should be enrolled

Reprint requests to: Wolfgang A. Tomé, Ph.D., FAAPM, Department of Human Oncology, University of Wisconsin, 600 Highland Avenue, K4/314 CSC, Madison, WI 53792. USA. Tel: (608) 263-8510; Fax: (608) 263-9167; E-mail: tome@humonc.wisc.edu

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in ongoing prospective trials of hippocampal sparing during cranial irradiation to confirm these preliminary results. © 2013 Elsevier Inc.

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Introduction

Although memory impairment has been a well-documented toxicity of cranial irradiation, a pathophysiologic explanation remains ill defined. One plausible hypothesis, focused on the role of neurogenic stem cells located in the subgranular layer of the hippocampal dentate gyrus, has been proposed on the basis of preclinical data demonstrating that this stem cell compartment is exquisitely sensitive to therapeutic doses of cranial irradiation (1). Preclinical models have demonstrated loss of hippocampal-dependent functions of spatial learning and memory, as tested by water maze tests, as a consequence of hippocampal irradiation (2, 3). However, to date, there is a paucity of clinical data to suggest that radiation dose to the hippocampus leads to long-term memory effects. We sought to address this hypothesis by conducting a prospective observational study of adult patients with benign or low-grade brain tumors treated with fractionated stereotactic radiotherapy (FSRT) and correlating hippocampal dose–volume histogram (DVH) data with long-term neurocognitive function (NCF) impairment.

Methods and Materials

Patient population

Adult patients with diagnoses of pathologically confirmed or clinically suspected benign or low-grade intracranial neoplasms were enrolled in this prospective protocol, approved by the University of Wisconsin Health Sciences Institutional Review Board. Eligible patients were >18 years of age, with no history of prior chemotherapy or radiotherapy. If biopsy or therapeutic resection was performed, patients were enrolled at least 1 week after biopsy and at least 4 weeks after resection.

Fractionated stereotactic radiotherapy

All patients were treated with FSRT by use of an optically guided intracranial radiotherapy system (4, 5). Treatment-planning computed tomography of the head was obtained with the patient in the supine position with custom bite-plate-fiducial-array-complex in place and subsequently fused to a three-dimensional spoiled gradient magnetic resonance imaging scan of the brain with gadolinium contrast medium and appropriate T2/FLAIR sequences. Gross and clinical target volumes were delineated per contemporary clinical practice. Planning target volume was generated by use of a 2-mm margin. Radiotherapy doses and fraction sizes were chosen on the basis of current clinical practice. All low-grade gliomas, meningiomas, and pituitary adenomas were treated to a dose of 50.4 to 54 Gy in 28 to 30 fractions of 1.8 Gy per fraction. All vestibular schwannomas were treated to a dose of either 20 Gy in five fractions of 4 Gy per fraction or 50.4 Gy in 28 fractions of 1.8 Gy per fraction. During treatment planning, no attempt was made to conformally avoid the hippocampus.

DVH analysis of hippocampus

After completion of FSRT, the bilateral hippocampi were delineated by use of a published contouring protocol currently in use in an ongoing cooperative-group Phase II trial of hippocampal avoidance during whole-brain radiotherapy (WBRT) for brain metastasis (Radiation Therapy Oncology Group [RTOG] 0933) (1, 6). This contouring protocol focuses on delineating the dentate gyrus and cornu ammonus, where neural progenitor cells important for memory-related function are believed to be anatomically clustered. This delineation was performed after completion of FSRT to ensure that no inadvertent effort at sparing the hippocampus would be undertaken during treatment planning. DVHs were generated for the left and right hippocampi individually and for the composite bilateral hippocampi. Doses were converted to biologically equivalent doses in 2-Gy fractions (EQD_2) assuming an α/β ratio of 2 Gy. For this analysis, EQD_2 to deciles (D10% to D100%), and the maximum EQD_2 (D_{max}), of individual and combined hippocampal volumes, were determined and tabulated.

Neurocognitive testing

All study participants underwent a battery of neurocognitive function (NCF) tests assessing estimated premorbid and current intelligence, language, visual perception, memory, executive function, and processing speed (Table 1).

The test battery was 60 to 90 minutes long and was conducted at baseline (before FSRT was started) and at 18 months follow-up. A cohort of similarly aged healthy control individuals was also enrolled and administered the NCF test battery at the same test–retest interval. These control individuals were either biologic relatives (brother or sisters) or nonbiologic but sociologically similar relatives (spouses) of the patients. The baseline and retest scores of control individuals were used to derive predicted retest scores, controlling for known sources of error variance in test–retest paradigms (*eg*, regression to the mean, effects of age and education on retest performance). In this fashion, the nature and degree to which experimental patients' test–retest performance was affected could be determined with precision.

Statistical analysis

The experimental and control individuals were compared by use of chi-squared statistics for categoric factors and the F statistic from analysis of variance for continuous factors. Descriptive statistics were generated for patient characteristics and NCF measures. Baseline scores for control individuals were regressed on retest scores with age, years of education, and sex as possible predictors for each cognitive measure. The resulting equations