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Clinical Investigation: Central Nervous System Tumor

Phase Measurement of Cognitive Impairment Specific to Radiotherapy

Carol L. Armstrong, Ph.D.,[*,†] David M. Shera, Sc.D.,[*,‡] Robert A. Lustig, M.D.,[¶] and Peter C. Phillips, M.D.[*,§]

**Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Department of Pediatrics, [†]Division of Neuro-Oncology, [‡]Division of Biostatistics and Epidemiology, [§]Division of Neurology and Oncology; and [¶]Department of Radiation Oncology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania*

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Summary

Prospective cognitive phase effects from RT were longitudinally studied in treated and untreated brain tumor patients. Memory was parsed using previously known and new tests. The findings from 41 irradiated and 29 nonirradiated patients with supratentorial tumors revealed a decline and recovery of memory dependent on the semantic cortex and the hippocampal memory system only in the irradiated patients. Findings support using brief, disease-sensitive cognitive tests that can replace use of brief general cognitive tests.

Purpose: Memory impairment is an early-delayed effect of radiotherapy (RT). The prospective longitudinal measurement of the cognitive phase effects from RT was conducted on treated and untreated brain tumor patients. The study design investigated semantic vs. perceptual and visual vs. verbal memory to determine the most disease-specific measure of RT-related changes and understanding of the neurotoxicity from RT to the brain.

Methods and Materials: Tests of memory that had previously shown RT-related phasic changes were compared with experimental tests of memory to test hypotheses about cognition targeted to the neural toxicity of RT. The results from 41 irradiated and 29 nonirradiated patients with low-grade, supratentorial tumors were analyzed. The methods controlled for comorbid white matter risk, recurrence, interval after treatment, and age (18–69 years). The effects were examined before RT and at three points after RT to 1 year using a mixed effects model that included interval, group, surgical status, medication use, practice, and individual random effects. Four new tests of memory and other candidate cognitive tests were investigated, and a post hoc analysis of a comprehensive battery of tests was performed to identify the cognitive processes most specific to RT.

Results: The RT effects on memory were identified in the treated group only; among the new tests of memory and the complete neurocognitive battery, the RT effects were significant only for delayed recall ($p < 0.009$) and interval to recognize ($p < 0.002$). Tumor location was not related to the treatment effect. Memory decline was specific to retrieval of semantic memories; a double dissociation of semantic from perceptual visual memory was demonstrated in the RT group.

Conclusions: These results implicate memory dependent on the semantic cortex and the hippocampal memory system. A cognitive measurement that is brief but specific to neural mechanisms is effective and feasible for studies of RT damage. © 2012 Elsevier Inc.

Keywords: Brain neoplasms, Conformal radiotherapy, Radiation injury, Memory, Cognitive disorders

Reprint requests to: Carol L. Armstrong, Ph.D., Children's Hospital of Philadelphia, 3535 Market St., Rm. 1410, Philadelphia, PA 19104. Tel: (215) 590-1709; Fax: (267) 426-5260; E-mail: armstrongc@email.chop.edu

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Introduction

Radiotherapy (RT) in neuro-oncology is associated with damaging side effects in brain physiology, cognition, and mood; however, phase patterns after RT are a factor in neurocognitive dysfunction. Temporal sampling error can result if cognition is measured outside of critical periods. Brief cognitive screening and functionality tests have been insensitive. A comprehensive cognitive assessment can detect the nature and severity of the deficits but might not be feasible in longitudinal studies. Studies of varied neurologic disorders that compared disease-specific with short neurocognitive batteries have shown that only the cognitive predictors closely associated with the known neurologic mechanisms have predicted progression (1). Such a model has emerged for the study of RT effects on cognition—hippocampus-based memory (2). The present study investigated the specificity of memory impairment by way of a systematic comparison of memory processes and materials.

An early-delayed RT memory effect was reproduced reliably as the retrieval of words from long-term memory. The temporal pattern of decline and recovery was seen during the course of 1 year from the pretreatment baseline, during which working memory, verbal fluency, and information processing speed remain stable (3). Previously, we investigated whether executive control of memory and attention might mediate the memory change (4). On ruling out covarying functions, additional investigation of memory was conducted to hone the measurement of RT effects on cognition.

In longitudinal studies of patients who received RT, verbal retrieval was near $z = 0$ immediately before RT, declined, and then recovered to baseline, an effect replicated by an outside laboratory (5). A double dissociation of verbal from visual memory at baseline and 1.5 months after RT completion was also reproduced (3). An early-delayed decline in verbal retrieval and improvement by 1 year was identified in supraspan memory, which activates the ventrofrontal and mesial temporal-hippocampal memory system (6).

To investigate the specificity of the retrieval phenomena, four new memory tests were created. Two were supraspan tests using parallel psychometric methods and perceptual or semantic, visual, or verbal materials: a test of nonsense words (verbal perceptual items) and a test of nameable figures (visual semantic). Longitudinal data from these tests were compared with previously reported (3) tests of words (verbal semantic) and figures (unnameable visual) in a multivariate mixed model. Two tests of recognition memory were created to measure the speed of retrieval. The data were collected prospectively from two groups of patients with low-grade brain tumors, with and without RT.

If RT degraded the ventrofrontal white matter, a decline after RT would be found in retrieval on all supraspan memory tests. We hypothesized that the tests of semantic stimuli would be more sensitive to the RT effects than would the perceptual stimuli because semantic association depends on widespread cortical connectivity, including the hippocampus (7). If RT impeded retrieval efficiency but did not severely damage the hippocampal memory, we could expect a decline in the speed of retrieval (7) measured by recognition.

Methods and Materials

Participants

The patients were adults with primary, low-grade, supratentorial brain tumors recruited during an 11-year period. The low-grade diagnosis was determined by pathologic confirmation using World Health Organization criteria for grades 1 and 2 or by neuroradiologic consensus in the absence of surgery. The patient age range at baseline was 22−66 years. To remove confounding factors causing cognitive impairment, the patients with extensive neuropsychological impairment, amnesia, aphasia, cardiovascular disease, hypertension, diabetes, pulmonary disease, kidney disease, other cancer, or immunocompromise were excluded.

One group had received standard RT after surgical biopsy, resection, or no surgical intervention, and the other group had did received RT. The patients who had undergone surgery were studied 6 weeks postoperatively and just before RT, and the patients without surgery were studied immediately before RT. Those not receiving RT were tested 6 weeks after resection or when available for patients without resection. The patients had been referred by neuro-oncology conferences at the hospitals of the University of Pennsylvania and Thomas Jefferson University. The investigations were performed after approval by the institutional review boards of both hospitals, ensuring ethical standards on human experimentation in accordance with the 1975 Declaration of Helsinki and 2000 revision.

Of 80 eligible patients with serial neuropsychological evaluations beginning at baseline and at one and two years post-treatment, 75 were evaluable (exclusions owing to severe amnesia and widespread cognitive impairment preventing valid measurement of RT-related cognitive outcomes, acute bacterial meningitis, quiescent multiple sclerosis, and psychiatric disorders unrelated to tumor). Four patients withdrew from the study after the evaluation. One patient's tumor recurred 4 months after baseline, leading to death 9 months after baseline. The data from this patient were excluded because of the risk of measuring the effects from the tumor recurrence, rather than from the RT. None of the 70 remaining patients had evidence of tumor recurrence/growth for 1 year after baseline.

Of the 70 patients, 41 irradiated (RT group) and 29 nonirradiated (no-RT) were compared. The tumors were gliomas (65%), neuroendocrine tumors (15%), meningiomas (12%), and other (8%). The rates of surgical intervention were similar between the two groups: 71% of the RT and 79% of the no-RT group. The patients in the RT group included 13 (32%) with right hemisphere, 17 (41%) with left hemisphere, and 11 (27%) with central tumors. Of the no-RT group, 15 (52%) had right hemisphere, 10 (34%) had left hemisphere, and 4 (14%) had central tumors. The median age of the RT group was 42 years (mean, 41.19 $\pm$ 11.76; range, 22−66) and of the no-RT group was 40 years (mean, 40.30 $\pm$ 10.77; range, 24−56). The median education of both groups was 16 years. The RT patients were 85% dextral, 12% sinistral, and 1 mixed dominance. The no-RT patients were 86% dextral and the remaining sinistral. Men comprised 56% of the RT group and 38% of the no-RT group.

Treatment

Computed tomography-based planning was performed. RT was administered using three-dimensionally based conformal plans

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