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Phase Measurement of Cognitive Impairment Specific to Radiotherapy

Carol L. Armstrong, Ph.D.,

Children's Hospital of Philadelphia, Division of Neuro-Oncology, University of Pennsylvania School of Medicine, Department of Pediatrics, Philadelphia, PA, U.S.A.

David M. Shera, Sc.D.,

University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Biostatistics and Epidemiology, Philadelphia, PA, U.S.A.

Robert A. Lustig, M.D., and

University of Pennsylvania School of Medicine, Department of Radiation Oncology, Philadelphia, PA, U.S.A.

Peter C. Phillips, M.D.

Children's Hospital of Philadelphia, Division of Neuro-Oncology, University of Pennsylvania School of Medicine, Department of Neurology, Philadelphia, PA, U.S.A.

Abstract

Purpose—Memory impairment is an early-delayed effect of radiotherapy. Prospective longitudinal measurement of cognitive phase effects from radiotherapy (RT) was conducted on treated and untreated brain tumor patients. Study design investigated semantic versus perceptual, and visual versus verbal, memory to determine the most disease-specific measure of RT-related change and understanding of the neurotoxicity from radiotherapy to brain.

Methods and Materials—Tests of memory that previously showed RT-related phasic changes were compared to experimental tests of memory to test hypotheses about cognition targeted to the neural toxicity of RT. Results from 41 irradiated and 29 nonirradiated patients with low-grade, supratentorial tumors were analyzed. Methods controlled for co-morbid white matter risk, recurrence, time post treatment, and age ($>18<69$). Effects were examined pre-RT and at three time points post-RT to one year using a mixed effects model including time, group, surgical status, medications, practice, and individual random effects. Four new tests of memory and other candidate cognitive tests were investigated, as well as post-hoc analysis of a comprehensive battery of tests, to identify the cognitive processes most specific to RT.

Results—RT effects on memory were identified in the treated group only; among the new tests of memory and complete neurocognitive battery, the RT effects was significant only for delayed recall ($p<.009$) and time to recognize ($p<.002$). 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.

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Corresponding author: Carol L. Armstrong, Children's Hospital of Philadelphia, 3535 Market Street, Rm. 1410, Philadelphia, PA 19104, Tel: 215-590-1709, armstrongc@email.chop.edu.

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Conclusions—Results implicate memory dependent on semantic cortex and the hippocampal memory system. Cognitive measurement that is brief but specific to neural mechanisms is effective and feasible for studies of RT damage.

Keywords

brain neoplasms; conformal radiotherapy; radiation injury; memory; cognitive disorders

Radiation therapy (RT) in neuro-oncology is associated with damaging side-effects in brain physiology, cognition, and mood, but phase patterns after RT is a factor in neurocognitive dysfunction. Temporal sampling error can result if cognition is measured outside critical periods. Brief cognitive screening and functionality tests have been insensitive. Comprehensive cognitive assessment can detect the nature and severity of deficits, but may not be feasible in longitudinal studies. Studies of varied neurological disorders that compared disease-specific with short neurocognitive batteries have shown that only the cognitive predictors closely associated with the known neurological mechanisms predicted progression(1). Such a model has emerged for study of radiotherapy effects on cognition – hippocampus-based memory(2). This study investigates the specificity of memory impairment via systematic comparison of memory processes and materials.

Early-delayed RT memory effect was reproduced reliably as retrieval of words from long-term memory. The temporal pattern of decline and recovery is seen over the course of a year from pre-treatment 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). Upon ruling out covarying functions, further investigation of memory was conducted to hone measurement of RT effects on cognition.

In longitudinal studies of patients who received RT, verbal retrieval was near $z=0$ immediately before RT, declined, then recovered to baseline, an effect replicated by an outside laboratory(5). Double dissociation of verbal from visual memory at baseline and 1.5 months post-completion of RT was also reproduced(3). Early-delayed decline in verbal retrieval and improvement by one 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 namable figures (visual semantic). Longitudinal data from these tests are compared with previously reported(3) tests of words (verbal semantic) and figures (unnamable visual) in a multivariate mixed model. Two tests of recognition memory were created to measure speed of retrieval. 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, decline after RT would be found in retrieval on all supraspan memory tests. We hypothesized that tests of semantic stimuli are more sensitive to RT effects than perceptual stimuli because semantic association depends on widespread cortical connectivity including hippocampus(7). If RT impeded retrieval efficiency, but did not severely damage hippocampal memory, we expected a decline in the *speed* of retrieval(7) measured by recognition.

Methods

Participants

Patients were adults with primary, low-grade, supratentorial brain tumors recruited over 11 years. Low-grade diagnosis was based on pathological confirmation using World Health Organization criteria for grades I and II, or neuroradiologic consensus in the absence of surgery. Actual patient age at baseline was 22–66 years. To remove confounding factors causing cognitive impairment, patients with extensive neuropsychological impairment, amnesia, aphasia, cardiovascular disease, hypertension, diabetes, pulmonary disease, kidney disease, other cancer, or immunocompromise were excluded.

One group – XRT – received standard RT after surgical biopsy, resection, or no surgical intervention, and the other did not receive RT – No-XRT. Patients with surgery were studied six weeks after surgery and just before RT, and patients without surgery were studied immediately before RT. Those not receiving RT were tested six weeks after resection, or when available in cases without resection. Patients were referred by Neuro-Oncology conferences at the hospitals of the University of Pennsylvania and Thomas Jefferson University. Investigations were performed after approval by the Institutional Review Boards of both hospitals, which ensured ethical standards on human experimentation in accordance with the 1975 Declaration of Helsinki and revision in 2000.

Of 80 eligible patients with serial neuropsychological evaluations beginning at baseline and two yearly evaluations, 75 were evaluable (exclusions due to severe amnesia and widespread cognitive impairment preventing valid measurement of xrt-related cognitive outcomes, acute bacterial meningitis, quiescent multiple sclerosis, and psychiatric disorders {2} unrelated to tumor. Four patients self-excluded after evaluation. One patient's tumor recurred four months after baseline leading to death nine months after baseline; data from this patient was excluded because of risk of measuring tumor recurrence, rather than xrt, effect. None of the 70 remaining patients had evidence of tumor recurrence/growth for one year after baseline.

Groups of 41 irradiated (XRT) and 29 nonirradiated (No-XRT) patients were compared. Tumors were gliomas (65%), neuroendocrine tumors (15%), meningiomas (12%), and other (8%). Rates of surgical intervention were similar between the groups: 71% of XRT, 79% of No-XRT. XRT included 13 (32%) right, 17 (41%) left hemisphere lesions, and 11 (27%) central tumors. Of No-XRT, 15 (52%) had right, 10 (34%) had left, and four (14%) had central tumors. Median age of XRT was 42 years (mean=41.19, SD=11.76; range=22–66), and of No-XRT was 40 (mean=40.30, SD=10.77; range=24–56). Median education of both groups was 16 years. XRT patients were 85% dextral, 12% sinistral, and one mixed dominance. No-XRT patients were 86% dextral and the remaining sinistral. Males comprised 56% of XRT, and 38% of No-XRT.

Treatment

CT based planning was performed. RT was administered using 3D-based conformal plans, and optimal photon energy based on dose distribution within the clinical target volumes and maximal sparing of normal brain parenchyma. The median low-grade glioma dose of 54.0 Gy (mean=54.3 Gy) was delivered in fractions of 1.8–2.0 Gy per treatment day over 4.5 to 7.0 weeks (total dose range, 46 Gy (4 pituitary tumors) - 63 Gy (1 grade II astrocytoma)). Treatment of patients with other tumor histology was planned and delivered similarly. Two patients received chemotherapy concurrently with RT and three patients began chemotherapy at the second time point. One patient from each group was treated with chemotherapy before study baseline.

Neuropsychological assessment

A four hour battery (for detailed description(8)) included standardized tests of *motor control, attention, language, cognitive processing speed, verbal working memory, verbal long-term memory, visuospatial perception, visual working memory, visual long-term memory, and reasoning and set shifting*. Four equivalent forms of memory tests reduced practice effects.

Data points were:

1. Baseline – 4–6 weeks after surgery, immediately before RT,
2. 1.5 months after completing RT,
3. 4.5 months after completing RT,
4. 1 year after baseline.

Prior within-subject longitudinal studies showed detrimental cognition effects from RT in a verbal semantic memory test of words (Rey Auditory Verbal Learning Test (RAVLT)), that measures learning/encoding over five trials (T1-5), retrieval after word interference (T6), and consolidation (retrieval after delay; T7). The Biber Figure Learning Test measured visual perceptual memory, using the same variables (BFLT T1-5, T6, T7), and tested the dissociation from the RT-sensitive memory test (RAVLT). To reduce practice effects, patients received the same form of each memory test at baseline, and then equivalent forms were pseudorandomized.

Experimental Tests of Memory

We piloted new memory tests for structural analysis of whether RAVLT was sensitive to RT because of its semantic or perceptual nature.

{1} We created a test of visual semantic memory, mirroring the supraspan paradigm and indices (Icon Memory T1-5, T6, T7). Icon Memory items were simply structured icons used by international travelers (e.g., symbols for bed, dollar). Selected icons were as simple to draw as the Biber figures, in order to equate output interference.

{2} We developed a supraspan test of verbal perceptual memory (Pseudoword T1-5, T6, T7) to measure phonological memory. Stimuli were one-syllable pseudowords that are pronounceable consonant-vowel-consonant trigrams with little similarity to real words. To reduce difficulty, 12 items were used instead of 15 as in other supraspan tests.

{3, 4} We developed two tests to measure speed and accuracy to recognize familiar words and pictures(9): Word Recognition (WordRec), and Picture Recognition (PictRec). This classic hippocampal recognition paradigm randomly presented 60 target words or pictures for study; then subjects attempted to recognize “old” from 60 “new” items. There was no overlap in namability of stimuli among tests.

Additional tests

All principal measures from a comprehensive test battery with a large number of missing scores were eliminated from analyses; 37 different neuropsychological measures remained(8). Tests of attention, working memory, and processing speed were of particular interest because of possible sensitivity to RT: Symbol Digit Modalities (Symbol Digit), Digit Span, Visuospatial Span, Word Span, and Paced Auditory Serial Addition Test (PASAT, requires sustained attention). The null hypothesis was that these cognitive functions would not demonstrate early-delayed decline and recovery that was hypothesized for tests of associative memory.

Statistical Analysis

Early-Delayed Cognitive Deficit due to RT: Each cognitive score was fit with a mixed effects model using random intercepts for each subject and fixed main effects for time, XRT/No-XRT (RT variable), the hypothesized Early-Delayed RT Response Pattern, and Resection/Biopsy (full, partial, biopsy, none). Early-Delayed RT Response Pattern was defined as decline from baseline by 1.5 months post-RT, and recovery by 4.5 months post-RT. Fixed interaction effects included RT with time, the hypothesized pattern, and resection/biopsy. Because the mixed effects model fits a random intercept for each subject, variables that are constant over time (e.g., baseline score, tumor grade, tumor location) effectively model the random intercepts.

Medications that can affect cognitive scores were included in the model as four dichotomous time varying covariates: anti-hypertensives, anti-seizure, steroids, or anti-depressants. One patient took an opioid-based analgesic for one time point.

The primary interest was the regression coefficient for the interaction of RT status by the hypothesized Early-Delayed Response Pattern, after adjusting for all other variables. A significant result indicated a differential, early-delayed effect of RT on that cognitive measure. Following the fit of the full model, a backward stepwise selection procedure with a high threshold for removal ($p > .15$) was employed to remove variables. The main effect terms of time, the Early-Delayed Response Pattern, and RT were retained as long as the interaction terms were still in the model. At the end of the process, variables remaining in the model were considered predictive.

The same longitudinal methods applied to cognitive and clinical secondary outcome variables. Because some secondary outcome variables were later included in the battery of tests, these analyses had smaller sample sizes.

Results

Early-Delayed Cognitive Deficit

Table 1 gives the estimated coefficients for the interaction between RT variables and the Early-Delayed Response Pattern. The model for each outcome also included the values for time, RT by time, biopsy, partial resection, full resection, location, and medications.

Two findings were significant when treatment status was controlled; full results are given in Table 1. The RT effect was significant for RAVLT T7 ($p = .009$), which represents retention of the word list in long-term memory over 30-minute delay. The XRT group declined six weeks post-RT in RAVLT T7; Cohen's d was 0.50. XRT scores recovered, but the No-XRT group demonstrated no decline and recovery (Figure 1). Patients who received chemotherapy during part of the year had scores between .04 and .32 standard deviations of the group mean, and thus not different. Patients with and without surgery did not differ in xrt status.

Figure 1 compares the patterns of word versus figure recall. RAVLT T6, showed a trend level decline in the XRT group, followed by recovery ($p = 0.045$), and supports the finding that retrieval, more than learning, of words shows an RT effect. The RAVLT T1-5 variable measured the effect of learning the words, with a significance level of $p = 0.081$. No other memory tests demonstrated early-delayed decline and recovery (Table 1).

PictRec Reaction Time (Figure 2a) had a significant treatment group by Early-Delayed Pattern value ($p = .0017$), defined by a Bonferroni adjusted threshold of $(.05/32 = .0016)$. Reaction Time to recognize the pictures quickened over time in No-XRT, as expected based

on recovery from surgery and practice effect. In contrast, XRT showed no change in reaction time and failure to improve at the early-delayed time point, ergo slowed reaction time (Figure 2b).

Tumor Location

The mixed effects model fits a random intercept for each subject, so that tumor location, constant over time in these non-recurring groups, was effectively modeled by the random intercepts. However, because tumor location is often suspected as biasing cognitive effects of radiotherapy, we examined tumor location. Chi Square analysis of left or right hemispheric location of tumor between the two groups was $\chi^2=0.758$ ($p=0.57$), which permits accepting the null hypothesis that the RT effect was independent of hemispheric tumor location. Frontal versus nonfrontal location was not significantly different between the groups ($\chi^2=0.052$, $p>0.90$), nor was frontotemporal versus other location ($\chi^2=0.986$, ns).

Discussion

Results identified biphasic RT effects on memory processes. Although there is now consensus that the hippocampus responds to RT, cognitive measurement of RT toxicity has not been definitively associated with the role of hippocampus in memory. Tests of memory were created through systematic parsing of memory processes, in order to identify disease-specific tests of hippocampal-mediated memory, and to confirm that there is no material-specific effect of RT-related memory outcomes due to bias from tumor locus.

Among the entire battery, two tests of retrieval from semantic long-term memory declined and recovered only in the RT-treated group. The pattern was not seen in other cognitive processes, such as working memory, encoding, processing speed, or attention. Only measures of semantic retrieval - word retrieval and recognition of namable pictures - showed the RT pattern. The involvement of delayed memory retrieval is consistent with the memory consequences of the downregulation of hippocampal and glial neurogenesis, oxidative stress, and mechanisms of neural inflammation observed in animal models(10).

Specificity of Memory

Results did not support RT injury to memory retrieval generally. Among four supraspan tests (meaningful words, pseudowords, geometric figures, nameable figures), only meaningful words showed the effect. We confirmed a double dissociation from visual memory for XRT, and the same visual memory increase in No-XRT. This persistent finding may be attributed to the brain's more robust visual, than verbal memory in the brain(11), causing post-treatment recovery and rate of learning to be stronger for visual images than for words. The RT effect was characterized as affecting semantic memory processes, rather than visual- or verbal-specific memory material selectively. Retrieving semantic memories depends on both cortical memory networks and the hippocampal memory system.

If retrieval efficiency(7) was the mechanism of response to RT, both word and picture recognition would decline. The data were not supportive: reaction times showed the early-delayed RT pattern only in the irradiated patients and only in picture recognition (Figure 2a). Dual coding theory states that picture recognition engages both cerebral hemispheres, while word recognition shows a robust left hemisphere effect(12). The slowing in the recognition of pictures is consistent with a bihemispheric response to RT in patients with multi-focal lesions and diffuse irradiation spread(13)

RT impairment was only in retrieval, in both supraspan and recognition tests. Optimal retrieval can be delayed for minutes-to-hours and involves reiterative consolidation; short-

term memory endures for seconds and is related to sensory and working memory processes. Encoding and storage of new memories, as well as retrieval of memories from long-term memory, are the domain of the hippocampal formation and medial temporal lobe(14,15). Short-term memory tests may be erroneously used as a surrogate for hippocampal dysfunction. While the prefrontal lobe, the region of multi-modal working memory and control, works in conjunction with medial temporal lobe-hippocampus to encode(6), clinical tests of short-term memory are insufficiently sensitive to the hippocampus. Neither this nor prior studies support the sensitivity of working memory to RT(4,8).

Retrieval of meaningful words and namable pictures requires reconstruction of attributes from cortical semantic networks. Only familiar words that are explicitly and implicitly associated in cortical memory networks, and namable pictures that require bihemispheric activation to retrieve, predicted the RT model. This finding implicates the hippocampus in RT effects: the final pathway for widespread semantic networks involved in post-encoding retrieval is the back propagation of signal from hippocampus to temporal cortex(16). Despite lack of bias in the groups in tumor location, the cortex-to-hippocampus streams are implicated, consistent with the diffuse nature of radiation scatter in groups with varied tumor foci.

RT memory toxicity is a spectrum of cellular toxicities. White matter abnormal signal on MRI that may resolve within the first year of treatment(13,17). Irradiation causes interference in endothelial and glial adult cell cycles(17). Depressed neurogenesis of subependymal glial and hippocampal neuroblast stem cells in adult animals(18) and smaller hippocampal volumes in children(19) demonstrate the early-delayed phase pattern. Immune-mediated RT inflammatory processes are also associated with memory impairment(10,20).

Radiotherapy and Neurocognitive Measurement

Efforts to identify efficient tests of the neurocognitive costs or benefits of RT may be informed by these results. Batteries that are thought to be generally sensitive, but brief, consistently fail to demonstrate the specificity and sensitivity to the physiological mechanisms of the disease (cf (1)). RT-specific memory tests of delayed word retrieval and picture recognition reaction time may be more inclusive of radiation injury to cortex, rather than brief but diverse cognitive tests.

There are several limitations of this study. Icon Memory showed a skewed normal distribution; most subjects perform at ceiling, and it may be insensitive to RT. We could not randomize treatment conditions, or individually match patients, though risk for confounds from other sources of white matter damage was reduced by exclusion criteria. Other sources of variability are the variety of primary tumor types and locations, and the range of radiation doses. Although four of the six memory tests are validated (RAVLT, BFLT, PictRec and WordRec), Pseudoword and Icon are not, though pilot work created equivalent item associability and equivalent forms, and prevented duplication of semantic items among the six tests. The RT effect was not large though it has been constant across studies, and may be consistent with the reversible biological mechanisms of injury that diminish, but do not ablate, neural processes.

Conclusions

The significance of these findings is that hippocampus involvement in cognitive injury from radiotherapy is now reasonably convincing. The findings suggest an additional general effect on memory networks of the neocortex. The in-depth analysis of memory processes shows that early-delayed RT effects upon cognition are specific to reconstruction of *semantic* memory. As in prior studies, the effect size was 0.50. Studies are needed that

correlate neuroimaging markers with cognition. Good cognitive tests of neural responses are needed for understanding clinical course, early detection of cognitive change, and response to neuroprotective treatments.

Summary

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

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Figure 1. Dissociation of word and figure memory slopes in XRT (solid lines) and No-XRT (dashed) groups – delayed recall Means.

2a

2b

Figure 2.

a: Picture Recognition Reaction Time for Hits

b: Picture Recognition Accuracy (hit rate)

Table 1

Results of modeling of early delayed XRT response pattern

Outcome	Estimate	Standard Error	t Value	P Value	Significance
RAVLT T1-5	-3.56	2.00	-1.78	0.0808	
RAVLT T6	-1.31	0.64	-2.04	0.0454	*
RAVLT T7	-1.68	0.62	-2.69	0.0094	**
BFLT T1-5	-8.67	5.80	-1.50	0.1414	
BFLT T6	-0.35	1.78	-0.20	0.8443	
BFLT T7	0.00	1.30	0.00	0.9979	
Symbol Digit	-2.66	1.72	-1.54	0.1278	
PASAT mean	-8.86	16.06	-0.55	0.5816	
Pseudoword T1-5	-8.25	5.14	-1.60	0.1203	
Pseudoword T6	-1.03	1.72	-0.60	0.5534	
Pseudoword T7	-1.77	1.90	-0.93	0.3602	
Icon Memory T1-5	-2.53	1.91	-1.32	0.1971	
Icon Memory T6	-1.00	0.68	-1.46	0.1546	
Icon Memory T7	-0.06	0.91	-0.07	0.9487	
Pict Rec hit rate	-0.03	0.03	-1.09	0.2884	
Pict Rec reaction time	60.63	18.47	3.28	0.0017	**
Word Rec hit rate	-0.05	0.06	-0.93	0.3657	
Word Rec reaction time	123.96	135.22	0.92	0.3610	

* <.05

** <.01