Late cognitive and radiographic changes related to radiotherapy
Initial prospective findings

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Abstract—Background: Assumptions about the damaging effects of radiotherapy (XRT) are based on studies in which total dose, dose fraction, treatment volume, degree of malignancy, chemotherapy, tumor recurrence, and neurologic comorbidity interact with XRT effects. This is a prospective, long-term study of XRT effects in adults, in which total dose and dose fraction were constrained and data related to tumor recurrence and neurologic comorbidity (e.g., hypertension) were excluded. Methods: The effects of XRT on the cognitive and radiographic outcomes of 26 patients with low-grade, supratentorial, brain tumors yearly from baseline (6 weeks after surgery and immediately before XRT) and yearly to 6 years were examined. Radiographic findings were examined regionally. Results: Selective cognitive declines (in visual memory) emerged only at 5 years, whereas ratings of clinical MRI (T2 images) showed mild accumulation of hyperintensities with post-treatment onset from 6 months to 3 years, with no further progression. White matter atrophy and total hyperintensities demonstrated this effect, with subcortical and deep white matter, corpus callosum, cerebellar structures, and pons accounting for these changes over time. About half of the patients demonstrated cognitive decline and treatment-related hyperintensities. Conclusions: There was no evidence of a general cognitive decline or progression of white matter changes after 3 years. Results argue for limited damage from XRT at this frequently used dose and volume in the absence of other clinical risk factors.

Radiotherapeutic damage is characterized by multiple phases including the acute, subacute, and late delayed.1-3 Late-delayed changes have been reported as early as 1 year and as late as 20 years after treatment. Current techniques have decreased the toxic burden to normal tissue,3 and radiation necrosis has become rare. However, there is abundant evidence that cognitive deterioration occurs in adults4-6 and children7,8 who receive restricted fields or whole brain irradiation (XRT), despite little or no neurologic impairment. There is little agreement on the time course of the late-delayed changes.

Previous studies suggest that no significant deterioration on either neuroimaging or neuropsychological testing occurs before 18 months after XRT.6,7,9-16 Malignancy is a confounding factor due to paraneoplastic phenomena. Retrospective studies show that XRT-related dementia is characterized as progressive subcortical dementia,17,18 and occurred in 2% of adult patients with cured metastatic brain tumors treated with whole brain XRT.19 Findings have ranged from little cognitive deterioration in adults at 4 years after treatment2 to mental retardation as early as 2 years in children (although some surviving untreated children also met criteria for mental retardation).20 Many studies, though limited by their retrospective designs, report 20% to 80% of patients with some degree of cognitive impairment on formal testing from 2 to 20 years later.20-22

We measured the course of cognitive decline and radiographic change over 6 years of the late-delayed phase of XRT effects. Patient selection was considered critical to understanding XRT effects; patients were recruited whose cognitive functioning was not confounded by malignancy or concomitant neurologic complication, and who would receive 100% of dose to the cortex.

Methods. Patient selection and characteristics. We studied patients with primary, low-grade supratentorial brain tumors (gliomas [WHO grades I and II], pituitary and pineal tumors, and noninvasive meningiomas), treated

See also pages 8, 48, and 121
with standard XRT after surgical biopsy, resection, or no surgical intervention. Patients were recruited for inclusion in a longitudinal study by neuro-oncology physician referral or the brain tumor conferences of the Hospital of the University of Pennsylvania and Thomas Jefferson University Hospital in Philadelphia. Informed consent was obtained through discussion regarding the nature of the procedures and study.

Tumor grading was based on pathologic or neuroradiologic findings in the absence of surgery. Additional inclusionary criteria were life expectancy of at least 3 years and age between 18 and 69 years. Exclusionary criteria included extensive neuropsychological impairment, amnesia (i.e., inability to learn new material), aphasia (i.e., inability to understand task instructions or express thoughts fluently), neurologic comorbidity (e.g., meningitis), or history of coronary artery disease, hypertension, diabetes, pulmonary disease, kidney disease, other cancer, and immunosuppressive disease.

Of the 55 patients who had been in the longitudinal study for at least 1 year, 33 patients were irradiated. Three patients were excluded after the initial neuropsychological evaluation. One patient was excluded who had a large meningioma, severe memory encoding and retrieval deficits, and impairment in three cognitive domains. One patient was excluded after developing bacterial meningitis from an infected shunt. A third patient had a 1-cm meningioma arising from the anteroinferior portion of the falx, and severe and widespread cognitive deficits that were thought to represent an etiology unrelated to her tumor. Three more patients excluded themselves after the initial neuropsychological evaluation for personal reasons. One patient had tumor regrowth 1.5 years after baseline, so the data of this patient were also excluded from any analysis. The remaining 26 patients included 13 patients who had received neuropsychological evaluation 6 years after treatment. Some patients were tested up to 10 years after treatment, but there were an insufficient number of cases to group them by later time points. One patient was diagnosed with diabetes and hypertension about 5 years after entry into the study and the results from that point on were excluded from analyses, although we continued to follow this patient. This patient demonstrated rapid and major atrophy, white matter hyperintensities, and eventually thalamic and pontine infarcts beginning 1 year after diagnosis of uncontrolled diabetes and hypertension. Cognitive scores for this patient also demonstrated rapid and major declines. Three other patients had tumor recurrence, and their data were included in the analyses until the date of the radiographic diagnosis of recurrence, although we continued to follow them. The number of cognitive data points and radiographic scans used in the final analyses are displayed in table 1. An additional set of MRI scans was added for which there was no corresponding cognitive test points, and this larger set of scans was analyzed separately. The number of scans over time included in this analysis is also shown in figure 1.

A total of 26 patients were included in the comparisons over time of the cognitive changes, but a total of 22 patients were included in the analyses of the radiographic changes due to the unavailability of some scans such as baseline scans. The patient groups were composed of gliomas (65%), neuroendocrine tumors (15%), meningiomas (12%), and other (8%). The group was composed of 13 left hemisphere and 7 right hemisphere lesioned patients, as well as 6 patients whose tumors were not lateralized. The median age was 42.5 years, and the mean age was 41.12 (SD = 11.83). The mean education was 15.31 years (SD = 2.56); 23% did not continue their education beyond high school, 42% had some college or were college graduates, and 35% had some postgraduate education. Patients were primarily dextral (81%), with 15% sinistral, and 1 patient with mixed dominance. Men comprised 58% of the group.

The data of the 22 nonirradiated patients, whose recruitment began later, were not sufficiently longitudinal to provide a control group at this time.

Radiotherapy. XRT was administered similarly at both institutions by the use of megavoltage machines, with the selection of optimal photon energy based on dose distribution within the clinical target volumes and maximal sparing of normal brain parenchyma. The criterion for including a tumor type was that the total XRT dose would be significant to the cortex and subcortical areas that are critical for cognition. Pineal and pituitary tumors met this criterion. Pineal and pituitary tumors met this criterion. As an example, dose reconstruction for one study patient with a pineal tumor showed that the parietal lobe received the lowest dose (21% to 52% of total dose of 5580 Gy), the occipital lobe received 57% to 63%, the temporal lobe received 73% to 99%, the frontal lobe received 73% to 79%, the corpus callosum received 97% to 102%, the cerebellum received 83% to 86%, the basal ganglia received 97% to 106%, the thalamus received 99% to 101%, and the

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Table 1 Number of patients included in each year of study excluding time points after recurrence and development or comorbidity

<table>
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<tr>
<th>Outcome measure</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
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<td>26</td>
<td>14</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>9</td>
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<td>22</td>
<td>22</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

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Figure 1. Average MRI ratings for global measures over 6 years (excluding reoccurrence and hypertensive data points). Black squares represent average white matter atrophy rating; white circles represent average hyperintensity rating; black triangles represent average gray matter atrophy rating. Higher scores represent a greater number of abnormalities visible on MRI.
anterior cingulate received 98% of the total dose. A mean low-grade glioma dose of 55.6 Gy (range = 54 to 63 Gy), a mean pituitary dose of 46 Gy, and mean meningioma dose of 54.6 Gy (range = 54 to 55.8 Gy) were delivered in fractions of 1.8 to 2.0 Gy per treatment day over 4.5 to 7.0 weeks. Two patients received bischloronitrosourea (BCNU) concurrently with XRT, and one completed BCNU before XRT.

Neuropsychological assessment. An extensive test battery was administered in a single 4-hour session that included a neuropsychological interview by a neuropsychologist or by doctoral psychology students and postdoctoral fellows under the supervision of a neuropsychologist (C.L.A.). Rests were provided as needed.

The battery included standardized neuropsychological indices from the domains of motor function (Praxis, Finger Tapping Test29 [Right and Left]), attention (selective visual attention [Bells Test24], Auditory Selective Attention Test,25 sustained visual attention [Continuous Performance Test24]), language (Sentence Repetition Test27 [total correct], Controlled Oral Word Association Test,27 Animal Naming Test27 [category fluency]), cognitive processing speed (Paced Auditory Serial Addition Test30 [PASAT], Symbol Digit Modalities Test30 [oral version]), verbal memory (Digit Span Test21 [Forward], Word Span Test,29 Rey Auditory Verbal Learning Test29 [Learning (total for Trials 1 to 5), Post-Interference Retrieval (T6), Retention (T6/T5), Delayed Recall (T7), Retention after Delay (T7/T6), Total Recognition Hits, Total Recognition False Alarm Responses]), visuospatial perception (Road Map Test31, Visual Pursuits Test23 [number of items completed, percent accurate responses], Rey Osterrieth Complex Figure Test23 [copy of figure]), visual memory (Visual Memory Span Test23 [Forward], Revised Benton Visual Retention Test22 [total correct], Rey Osterrieth Complex Figure Test23 [immediate recall, delayed recall], Biber Figure Learning Test23 [Learning (total for Trials 1 to 5), Post-Interference Retrieval (T6), Retention (T6/T5), Delayed Recall (T7), Retention after Delay (T7/T6), Total Recognition Hits, Total Recognition False Alarm Responses]), and conceptual set shifting (Wisconsin Card Sorting Test [number of categories achieved, perseverative errors]).

The data points for this study were: baseline (4 to 6 weeks after surgery and just prior to beginning XRT), 1 year after baseline, and yearly for 6 years after treatment. All patients were tested at baseline and at subsequent test points on the identical set of tests. However, to partially control for practice effects, multiple forms34 were used randomly across contact points for the Auditory Selective Attention Test (2 forms), Rey Auditory Verbal Learning Test (4 forms), Complex Figure Test (2 forms), Revised Benton Visual Retention Test (3 forms), and Biber Figure Learning Test (4 forms). Over the course of the study, some changes in the test battery were made to answer evolving study hypotheses about the effects of XRT.2 Some tests that were insensitive or psychometrically poor were eliminated to “make room” for new tests. However, the within-subject design determined that the battery taken by an individual remained unchanged from baseline.

All missing data were due to the above research design issue and technical failure. Those principal measures with the largest number of missing values were eliminated from further analysis. A total of 37 different neuropsychological measures remained for analysis. In addition to individual neuropsychological test indices, a single measure of cognitive performance at each contact point was computed. This measure was defined as the intrasubject variation in cognitive performance among all tests, calculated in three ways. The three measures of cognitive variation were derived by applying normative values to a patient’s test score, converting it to a standard z-score, and then calculating: 1) the maximum variation—the total range of z-scores by subtracting the minimum z-score from the maximum z-score; 2) the 90% range—the z-score range from the 5th percentile to the 95th percentile; and 3) the 80% range—the z-score range from the 10th percentile to the 90th percentile. We hypothesized that if late-delayed radiation damage was not based on the vulnerability of certain brain regions, or if the effects of XRT were not anatomically systematic because of differing tumor locations and dose distributions, or if other patient characteristics contributed to variability in susceptibility to XRT damage, then specific tests might not be sufficiently sensitive. Our rationale for using a measure of variability was that it would encompass all the instability within a patient’s performance. The percentile distributions were used to eliminate biasing of the results due to scores that were at the extremes of the patients’ data distribution, or to the non-normal distributions of some test scores. The total z-score range was included to maximize the potential sensitivity of the variability measurement.

Neuropsychological measures that were hypothesized a priori to be sensitive to late-delayed XRT damage were limited to the measures that demonstrated a treatment effect in our studies of the early-delayed radiation effect.34,35 These were the postencoding retrieval measures from the Rey Auditory Verbal Learning Test, indices that had demonstrated a selective decline at the early-delayed radiotherapy phase. The remaining neuropsychological measures were also analyzed.

Neuroimaging. All available clinical MRI scans were gathered for each patient, requiring the amassing of scans from several hospitals and imaging centers. Although this resulted in varying TR/TE lengths and sequences, it also resulted in a more complete set of data for patients who often received surgery, radiation treatments, and follow-up examinations with different doctors and centers. In all cases, multiple slice, contiguous spin-echo images were performed on a 1.5 T superconducting magnet.

MRI images were rated by a single neuroradiologist (J.V.H) who was informed of the patient’s age but was blinded to treatment status (XRT vs no irradiation) and time after treatment. All MR scans were judged by increased signal intensity on T2-weighted axial images. Hypointensities were rated for severity using a 7-point scale reflecting the magnitude of the white matter disease: (0) no focal hypointensities, (1) 1 to 3 small scattered foci, (2) 1 to 3 large focal hypointensities, (3) confluent hypointensities, (4) periventricular cloaking defined as a hyperintense band of variable thickness with smooth lateral margins surrounding the ventricles, (5) periventricular cloaking plus widespread white matter disease, (6) homogeneously, diffusely abnormal white matter defined as hypointensity extending from the ventricular lining to the cortico-medullary junction involving most of the white matter. In addition, a 4-point rating scale was used to rate the atrophy of the white and the gray matter separately:
were found in the PASAT (F(1,73) = 8.27, p < 0.005). Notably, only two parameters—total for Trials 1 to 5 (F(1,44) = 16.17, p < 0.0002), Post Interference Retrieval-T6 (F(1,44) = 27.54, p < 0.0001); and Delayed Recall-T7 (F(1,44) = 8.78, p < 0.005). Notably, only measures of learning and absolute recall reached significance, and not the relative measures of retention. Figure 3 depicts the XRT-related cognitive declines. Individual analyses demonstrated the selective nature of the cognitive impairments. We examined the percentage of patients who were clinically impaired, using one z-score less than the mean.

Results. Neurocognitive findings. Seven of the 37 neuropsychological indices showed significant slopes of improvement over 6 years, 6 of which showed a significant linear pattern. The measures of improvement (table 2) were found in the PASAT (F(1,73) = 16.72, p < 0.0001), Immediate Recall (F(1,71) = 6.30, p < 0.01) and Delayed Recall (F(1,70) = 4.80, p < 0.03) of the Complex Figure. Controlled Oral Word Association Test (F(1,72) = 4.08, p < 0.05), Sentence Repetition (F(1,61) = 13.58, p < 0.0005), Symbol Digit Modalities (F(1,74) = 8.27, p < 0.005), and Auditory Selective Attention Test (F(1,74) = 3.82, p < 0.05). If we use a liberal correction factor to control for multiple comparisons, accepting an alpha of 0.005, then three measures remain significant. Two examples of the characteristic slopes of improvement are shown in figure 2.

A second pattern was found that suggested improvement until a decline at 5 years after XRT, and this pattern was thought to reflect the late-delayed damaging effects of treatment (see table 2). Three measures from the Biber Figure Learning Test demonstrated improvement and then decline on curvilinear analyses: Learning—total for Trials 1 to 5 (F(1,44) = 16.17, p < 0.0002); Post Interference Retrieval-T6 (F(1,44) = 27.54, p < 0.0001); and Delayed Recall-T7 (F(1,44) = 8.78, p < 0.005). Notably, only measures of learning and absolute recall reached significance, and not the relative measures of retention. Figure 3 depicts the XRT-related cognitive declines. Individual analyses demonstrated the selective nature of the cognitive impairments. We examined the percentage of patients who were clinically impaired, using one z-score less than the mean.

Analyses. A mixed model repeated analysis of variance using the Statistical Analysis System (SAS) was used to analyze the data, with the advantage that the model adjusts estimates for missing observations. The linear and quadratic trends in neuropsychological test indices, cognitive variation score, and MRI ratings over 6 years after treatment were analyzed. To look for consistent trends over time, the linear slopes over time for each subject on each cognitive measure, the variation scores, and each anatomic variable were obtained from the mixed model program and used in a correlation matrix for the purpose of identifying correlated slopes of change over time. Demographic variables of age, education, and sex, as well as fatigue and depression, were entered as a first step in a secondary mixed model program, and the linear and curvilinear trends on the cognitive measures were entered as a second step to see if cognitive effects existed beyond the demographic variables.

Recall (F(1,71) = 4.08, p < 0.05), Sentence Repetition (F(1,61) = 13.58, p < 0.0005), Symbol Digit Modalities (F(1,74) = 8.27, p < 0.005), and Auditory Selective Attention Test (F(1,74) = 3.82, p < 0.05). If we use a liberal correction factor to control for multiple comparisons, accepting an alpha of 0.005, then three measures remain significant. Two examples of the characteristic slopes of improvement are shown in figure 2.

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the mean as the criterion for impairment. Results indicate
that the rate of clinical impairment in the group dimin-
nished after high levels at baseline (25% to 44%), with the
lowest level of impairment reached at year 4 (0%); this
result parallels the analysis of variance results. By year 5
(20% to 40%) and year 6 (20% to 67%) impairment levels
increased again. The mean decline in each cognitive score
was less than 1 SD at years 5 and 6.

Measures of fatigue and depression were examined for
significant effects over time. Neither the Fatigue Severity
Scale (linear $p = 0.27$, curvilinear $p = 0.75$), Beck Depres-
sion Inventory (linear $p = 0.88$, curvilinear $p = 0.13$), nor
MMPI-2 Depression Scale (linear $p = 0.93$, curvilinear $p = 0.69$) showed change. Age, gender, and fatigue when covar-
ied with the significant cognitive variables, also did not
account for a significant amount of the variance over time.
Although education did account for some of the variance in
the changes in the three Biber variables, the cognitive
changes over time remained (Biber Learning—
total for Trials 1 to 5 ($F(1,30) = 7.10, p = 0.02$); Biber Post Inter-
ference Retrieval-T6 ($F(1,30) = 13.18, p = 0.001$); Biber De-
layed Recall-T7 ($F(1,30) = 4.56, p = 0.05$)). Patients with
extra-axial tumors (pituitary adenomas: $n = 2$ at year 4, 1
at year 5, and 3 at year 6) had mean scores that were
similar to or better than the mean for the group.

The cognitive variation measure yielded no effect of
irradiation over the 6 years after treatment. The 3 mea-
sures of cognitive variation demonstrated (z range $F(1,74) = 6.43, p < 0.01$; 90% range $F(1,74) = 4.65, p < 0.03$; 80% range $F(1,74) = 3.79, p < 0.06$) that
showed that each of the cognitive variation mean scores
were greatest at baseline and generally declined over the
next few years, with no clear increase at 6 years (figure 4).

### Table 2 Significant trends in cognition over 6 years after
treatment with XRT

<table>
<thead>
<tr>
<th>Test Index</th>
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<th>Curvilinear</th>
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<td>Improvements</td>
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<td>Auditory Selective Attention Test</td>
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<td>Paced Auditory Serial Addition Test (PASAT)</td>
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<td>Sentence Repetition Test</td>
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<td>Symbol Digit Modalities Test—oral version</td>
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<td>0.91</td>
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<tr>
<td>Rey Osterrieth Complex Figure Test</td>
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<tr>
<td>Immediate Recall</td>
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<td>0.01</td>
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<tr>
<td>Delayed Recall</td>
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<td>0.03</td>
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<tr>
<td>Declines</td>
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<td>Biber Figure Learning</td>
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<tr>
<td>Total for Trials 1 to 5</td>
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<tr>
<td>Post Interference Retrieval (T6)</td>
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<tr>
<td>Delayed Recall (T7)</td>
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<tr>
<td>Continuous Performance</td>
<td>0.18</td>
<td>0.04</td>
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**Figure 3. Significant cognitive declines over 6 years (ex-
cluding recurrence and hypertensive data points). (A) Biber
Learning (total for Trials 1 to 5) total score. (B) Biber Post Interference Retrieval (T6) and Biber Delayed
Recall (T7) scores. Black squares represent Biber T6
scores; white circles represent Biber T7 score.**

**MRI ratings.** The changes over time in the mean white
matter atrophy, mean hyperintensity, and mean gray mat-
ter scores are shown in figure 1. For the same set of pa-
tients for whom the cognitive data were available at the
same time points, the White Matter Atrophy ($F(1,53) = 5.62, p < 0.02$) and the Hyperintensities ($F(1,53) = 5.97,
$p < 0.02$) ratings demonstrated curvilinear effects over
time. The mean Gray Matter Atrophy rating showed no
change over time ($p = 0.24$). These analyses were followed
by analyses of our seven regional subgroups. Both linear
and curvilinear changes in regional subgroup 1 were found
(linear $F(1,55) = 8.49, p < 0.005$) and curvilinear $F(1,55) = 7.16, p < 0.01$). Regional subgroup 1 was composed of the
bihemispheric subcortical white matter including the cen-
trum semiovale, periventricular areas, and internal cap-
sules. This regional subgroup appeared to account for the
changes over time in the Hyperintensities variable. Within
this subgroup, the left frontal white matter (curvilinear
$F(1,55) = 9.31, p < 0.004$), left centrum semiovale (linear
$F(1,55) = 8.57, p < 0.005$), and left periventricular
white matter ratings (linear $F(1,55) = 9.71, p < 0.003$; curvi-
linear F(1,55) = 7.78, p < 0.007) increased over time (see figure 5).

A second set of analyses was done with all the clinical MRI collected on the same set of patients. This analysis examined the radiographic changes independent of cognitive data points. For this analysis there were 171 MRI scans that had been rated using our rating systems, vs a total of 81 that corresponded with the cognitive data points. Again, the mean white matter atrophy and white matter hyperintensities showed linear and curvilinear increases (see figure 5). White matter atrophy appeared to peak about 2 1/2 to 3 years (30 to 35 months) after treatment, with the exception of an unsustained additional peak at about 5 years after treatment (linear F(1,141) = 38.80, p = 0.0001). White matter hyperintensities also showed a peak at 30 to 35 months, which was the strongest effect (linear F(1,141) = 27.61, p = 0.0001). Hyperintensities were predominantly in the immediate region of the tumor locus, with rare exceptions. Regional subgroup 1 again showed the largest effect (F(1,141) = 33.97, p < 0.0001), accounted for by both left and right frontal white matter, left and right centrum semiovale, and left and right periventricular areas. Regional subgroup 2 comprised three parts of the corpus callosum (F(1,141) = 8.23, p = 0.005), regional subgroup 4 comprised cerebellar structures (F(1,141) = 4.31, p < 0.04), and regional subgroup 6 comprised the pons (F(1,141) = 5.84, p = 0.03); all showed some contribution to the variance in white matter hyperintensities over time. In all analyses, data were removed at the time when recurrence was radiographically identified, and for the patient with secondary effects from hypertension and diabetes.

Individual analyses showed that 54% of the 26 patients demonstrated some progression in the rated score of white matter hyperintensities over time, although the progression was often not continuous. Individual progression was identified if a score increased in relation to the pre-XRT baseline that was not related to recurrence or growth of the tumor, defined as a temporal and spatial proximity to the time of growth and tumor location. Two of the three patients who received BCNU developed XRT-related white matter abnormalities that emerged before 1 year and, in both cases, the BCNU overlapped with XRT and continued after. A third patient, who also received BCNU but completed treatment before starting radiotherapy, did not show evidence of white matter abnormalities.

Of the remaining 12 (46%) patients who demonstrated white matter hyperintensities that were associated with XRT excluding BCNU, 5 (42%) showed some increase in scores in the white matter whose onset preceded 1 year after XRT (between 5.1 to 10.7 months after initiation of XRT). White matter abnormalities increased or had onset between 1 and 2 years in 4 of 12 (33%) patients who showed XRT-related changes, and at approximately 36 months in 3 of 12 (25%) patients. No progression occurred after 3 years after treatment during the course of time included in this report.

Correlation of MRI and cognitive findings. The slopes of late treatment-related cognitive decline did not correlate significantly with the slopes of increasing radiographic hyperintensities. This was primarily because the increase in hyperintensities increased until a peak around 30 to 36 months after treatment, but cognitive function was improving at this same time. No further increase in hyperintensities was found when the selective cognitive measures showed significant declines at 4 years (see figures 1 and 3).

Discussion. A late-delayed effect of XRT damage was demonstrated by declines in selective cognitive functions that began 5 years after XRT. The selectivity of the cognitive decline is initial evidence that widespread cognitive impairment or dementia does not occur precipitously after XRT in adult low-grade brain tumor patients without risk factors for vascular damage. The chronic clinical period, 1 to 5 years
after treatment, is thought to be based on deterioration of vascular structure and secondary parenchymal degeneration that can result in loss of resistance to various types of stress. We found elevated fatigue but no other indicators of predictable cognitive decline during this period. There was relatively little cognitive decline during the late clinical period (>5 years after treatment) in our patients who were screened for vascular risk factors before enrollment in the study. In contrast, the patient with uncontrolled diabetes and hypertension with onset 5 years after treatment demonstrated precipitous cognitive and radiographic changes. Another prospective study of late-delayed cognitive change in adults with low-grade and anaplastic brain tumors found no evidence of predictable decline in cognition 4 years after treatment. In this study, two patients improved significantly, one remained stable, and one, who had resection of a right temporal anaplastic oligodendroglioma, XRT, and IV nitrosoureas, showed mild leukoencephalopathy in the radiated field and onset of global cognition deterioration 6 months after beginning XRT. Thus, prospective studies agree that partial field radiotherapy alone with current treatment methods (approximately 55 Gy in fractions of 1.8 Gy over 6 weeks) does not, without other risk for morbidity, carry a burden of cognitive decline in adults for at least 4 years after treatment.

The cognitive measures of late vulnerability to XRT were not those that marked the early-delayed effects of XRT, suggesting differential pathophysiological mechanisms for these two phases. The early-delayed effect appears mediated by temporary demyelination. The pathologic mechanism for the late-delayed effect may be caused by damage to cerebral blood vessels based on the radiosensitivity of endothelium, as well as empirical and case reports of vascular vulnerability to XRT. A selective decline in visual memory, in contrast to the unimpaired or improved measures of verbal memory, attention, language, complex processing speed, motor function, visuospatial perception, and problem solving, could be associated with this mechanism. The visual memory tests (Biber) used in this study required the learning and retrieval of novel though regular shapes and more “shallow” processing of the structural features of the simple designs, whereas the verbal memory tests contain word stimuli of high frequency and familiarity that are “deeply” processed. Current memory theory proposes that novel stimuli, such as those in the Biber, require the hippocampus-based configural memory system, whereas semantically driven data are processed by the neocortical associative semantic memory networks. The continuing slope of improvement in the Biber for 4 years followed by a decline at year 5 suggests that the configural memory system, with its theorized basis in the hippocampal memory system, is sensitive to late-delayed physiologic effects. Slow progression of residual radiation damage and formation of dense fibrous tissue caused by hypoperfusion characterize the late clinical period, and ischemic injury in the subcortical and deep white matter is the most abundant evidence of late XRT damage. The potential biologic basis for the sensitivity of visual memory to XRT is the sensitivity of the CA1 neurons of the hippocampus to ischemia, and the CA3 region to repeated stresses of various kinds.

There is also converging evidence for the expected rate of white matter abnormalities seen on MRI. A minimal degree of leukoencephalopathy was found around the tumor sites, primarily in the subcortical and deep white matter, with smaller changes in the corpus callosum, cerebellar structures, and the pons. Although 54% of our series of patients showed minimal white matter hyperintensities (WMH), a larger study of mixed tumor grades reported 46% with WMH after 1 year after treatment. We did not find the hyperintensities to progress beyond 3 years after treatment, which has also been reported in other studies. One exception is a report of progressive cerebral atrophy in 61% of small-cell lung cancer patients up to 8 years after treatment. However, small-cell lung cancer patients are known to have high rates of cognitive impairment before treatment because of paraneoplastic effects, brain metastases in some cases, higher fractions of XRT (2 to 3 Gy), and concurrent chemotherapy.

WMH preceded the onset of cognitive decline; the accrual of mild WMH reached a peak 2 to 3 years after XRT while cognitive functions were still improving. This is predicted by the threshold effect: a critical burden of white matter abnormalities must accumulate before adverse cognitive effects become evident. Lack of correlation between cognitive measures and normal appearing white matter volume in children with cerebellar tumors and craniospinal XRT has also been reported.

Adult age and depression were not associated with cognitive decline in our study, but other factors that can present high risk in interaction with XRT include chemotherapy immediately before, during, or after XRT, malignancy, risk for vascular injury (e.g., hypertension, diabetes, hypercholesterolemia), and very young age. The addition of other risk factors may prognosticate a separate group of patients who are likely to develop both radiographic and cognitive decline within 5 years of treatment. This determination will require direct comparison of groups of patients with and without risk factors.

Another constraint of our study was the small number of patient visits available after the first 2 years after XRT. The decrease in sample size is partially attributable to loss of contact with patients when they moved (10.2%), refusal to continue in the study when they returned to work (9.1%), and death (7.8%). Another limitation is the lack of a low-grade tumor control group. Some of these limitations can be addressed as we continue to accrue and follow patients over a 10- to 20-year period. However, these results indicate that we cannot extrapolate the degree of cognitive and radiographic damage from
whole brain XRT or from higher doses to that caused by restricted field XRT given to patients with low-grade brain tumors. The reduction of noise through the patient selection methods and the emphasis on prospective studies has permitted us to describe the XRT-related changes from moderate dose, restricted field treatment, that are not due to malignancy, chemotherapy, or other clinical factors that also cause vascular brain damage or radiographic changes.

References

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Intrathecal methotrexate affects cognitive function in children with medulloblastoma

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Abstract—Background: Cognitive impairment occurs after malignant brain tumor treatment in children, following brain radiotherapy and systemic and intrathecal chemotherapy. Objectives: 1) To compare two groups of children who underwent surgery for cerebellar medulloblastoma with their cousins and siblings, assessing intelligence, executive function, attention, visual perception, and short-term memory. Both groups were treated with the same combined radiotherapy–chemotherapy, but differed in that only one group received intrathecal methotrexate (MTX+/H11001). 2) To relate these measures to MRI findings (leukomalacia). Results: The two groups performed worse than their control subjects in all tests. The MTX+/H11001 group younger than 10 years performed significantly worse in all tests, particularly executive ones. The group older than 10 years performed significantly worse only in short-term memory. Younger patients without MTX performed significantly worse than controls only in some neuropsychological measures; there were no differences between older patients and control subjects. Only in the MTX+ group was there a direct correlation between extent of leukomalacia and performance in some tests. Conclusions: The administration of intrathecal methotrexate to children with medulloblastoma worsens the cognitive deficits induced by chemotherapy and radiotherapy. The use of intrathecal methotrexate in the treatment of medulloblastoma and other malignancies should be reassessed.

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Medulloblastoma, the most common malignant CNS tumor in childhood, mainly occurs in the posterior fossa, where 50% of all childhood brain tumors develop. Children with medulloblastoma and other malignant brain tumors are at risk for late CNS sequelae from external radiotherapy and systemic and intrathecal chemotherapy. The resulting cognitive impairment is often disabling and persists throughout life. This impairment manifests as decline in IQ, poor scholastic achievement, and a series of neuropsychologic deficits that are often aggravated by endocrinologic damage. It is important, therefore, to accurately assess the cognitive sequelae of brain tumor treatment to guide the development of risk-adapted therapies. This is particularly germane in children with medulloblastoma for whom current research aims to replace radiotherapy with chemotherapy or at least reduce the overall radiation dose. We report neuropsychological assessment in two groups of children with cerebellar medulloblastoma. Both received the same combined radiotherapy–chemotherapy after surgery, but differed in that one only group received intrathecal methotrexate. We (1) assessed differences between the groups in terms of...