

Metabolic Alterations: A Biomarker for Radiation-Induced Normal Brain Injury—An MR Spectroscopy Study

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Purpose: To assess if interval changes in metabolic status in normal cerebral tissue after radiation therapy (RT) can be detected by 2D CSI (chemical shift imaging) proton spectroscopy.

Materials and Methods: Eleven patients with primary brain tumors undergoing cranial radiation therapy (RT) were included. 2D-CSI MRS was performed before, during, and after the course of RT with the following parameters: TE/TR 144/1500 ms, field of view (FOV) 24, thickness 10 mm, matrix 16 × 16. The metabolic ratios choline/creatine (Cho/Cr), N-acetylaspartate (NAA)/Cr, and NAA/Cho in normal brain tissue were calculated.

Results: NAA/Cr and Cho/Cr were significantly decreased at week 3 during RT and at 1 month and 6 months after RT compared to values prior to RT ($P < 0.01$). The NAA/Cr ratio decreased by -0.19 ± 0.05 (mean \pm standard error [SE]) at week 3 of RT, -0.14 ± 0.06 at the last week of RT, -0.14 ± 0.05 at 1 month after RT, and -0.30 ± 0.08 at 6 months after RT compared to the pre-RT value of 1.43 ± 0.04 . The Cho/Cr ratio decreased by -0.27 ± 0.05 at week 3 of RT, -0.11 ± 0.05 at the last week of RT, -0.26 ± 0.05 at 1 month after RT and -0.25 ± 0.07 at 6 months after RT from the pre-RT value of 1.29 ± 0.03 . Changes in Cho/Cr were correlated with the interaction of the radiation dose and dose-volume at week 3 of RT, during the last week of RT ($P < 0.005$), and at 1 month after RT ($P = 0.017$).

Conclusion: The results of this study suggest that MRS can detect early metabolic changes in normal irradiated brain tissue.

Key Words: irradiation; normal brain; magnetic resonance spectroscopy

J. Magn. Reson. Imaging 2009;29:291–297.

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EVERY YEAR about 22,000 new cases of primary benign and malignant brain neoplasms are diagnosed in the United States (1). The incidence of both malignant and benign tumors of the central nervous system has been increasing in the older population, while remaining stable or even decreasing in younger individuals (2). Cranial radiation therapy (RT) is widely used to retard tumor growth and proliferation. Cranial RT is known to affect the central nervous system, resulting in delayed neurological complications (3–5) and neurocognitive deficits in long-term survivors. The incidence of radiation necrosis after conventional therapy ranges from 5%–24% (6). The delayed neurological symptoms include functional and cognitive impairments, including deficits in learning, working memory, executive function, vision, and motor function (7–10), and eventually dementia. On conventional MRI the effects of radiation on brain tissue are evident in some patients as early as 2–6 months after completion of RT as signal abnormality in white matter (5). These changes are defined as early delayed radiation-induced injuries. Periventricular white matter abnormality is observed, but usually not until 12–18 months post-RT (5,11). Changes observed in animal models (12–14) and postmortem human brain specimens (15) include brain inflammation, demyelination of white matter, breakdown of the blood-brain barrier, and an array of neurotoxic effects (16). Retrospective studies have noted a spatial relationship between local RT dose and the changes seen on computed tomography (CT) / magnetic resonance imaging (MRI) (5,17). Furthermore, a previous study revealed that after RT, normal-appearing large white matter bundles such as genu and splenium of the corpus cal-

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Contract grant sponsor: National Institutes of Health (NIH); Contract grant numbers: 3 PO1 CA59827, R21 CA11369901, PO1 CA8578.

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Received June 22, 2008; Accepted October 8, 2008.

DOI 10.1002/jmri.21657

Published online in Wiley InterScience (www.interscience.wiley.com).

Table 1
Patients Demographics, Primary Diagnosis, and Radiation Dose

Patients	Age(year)/sex	Diagnosis	Prescribed dose (Gy)	Fx size (Gy) x number of Fx
1	33/M	Grade II gemistocytic astrocytoma	59.4	1.8 × 33
2	64/M	Pituitary macroadenoma	50.4	1.8 × 28
3	55/M	Sphenoid wing meningioma	54.0	1.8 × 30
4	29/M	Craniopharyngioma	55.8	1.8 × 31
5	25/F	Low grade glioma	54.0	1.8 × 30
6	71/M	Null cell pituitary adenoma	50.4	1.8 × 28
7	30/M	Grade II oligoastrocytoma	54.0	1.8 × 30
8	39/M	Grade II mixed oligoastrocytoma	59.4	1.8 × 33
9	44/M	Pituitary macroadenoma	50.4	1.8 × 28
10	55/M	Grade II astrocytoma	54.0	1.8 × 30
11	33/M	Pituitary macroadenoma	50.4	1.8 × 28

Fx, fraction.

losum show progressive structural degradation that is evident initially in high-dose regions and later becomes evident beyond the high-dose regions (18).

Magnetic resonance spectroscopy (MRS), a technique for noninvasive measurement of chemical substances (metabolites) in the brain, has proven to be a useful tool in the evaluation of recurrent contrast-enhancing lesions in patients previously treated for primary neoplasms by helping to differentiate recurrent tumor from radiation necrosis (19–21). It is useful as a prognostic tool during tumor treatment (22), in evaluation of changes in the brain after prophylactic RT for acute leukemia (23,24), and in assessment of late delayed radiation-induced effects (25,26). However, to our knowledge only a few prospective studies evaluating interval changes in metabolic activity in normal-appearing brain parenchyma during and following cranial RT for primary brain neoplasm have been published. Most used is single voxel 1H-MRS technique with only a limited part of the brain evaluated and only at one or two timepoints during and after irradiation (27–30). Few reports describe interval follow-up using two-dimensional (2D) multivoxel spectroscopy (31) or 3D spectroscopic imaging (32).

Our ultimate goal is to predict delayed neurological sequelae of cranial RT by early assessment of metabolic alterations in normal appearing brain using 2D chemical shift imaging MRS (2D CSI MRS). We hypothesized that structural degradation in cerebral tissue after RT would be predicted by early changes in metabolic activity detectable by MRS before the development of neurocognitive symptoms or anatomic changes seen on conventional MRI.

In this prospective study we studied patients with relatively stable tumors that were treated with conventional fractionated RT at ordinary doses and did not have obvious new radiation-induced radiographic abnormalities or evidence of early tumor growth after RT, with the goal of evaluating early delayed RT effects on normal-appearing brain.

MATERIALS AND METHODS

This prospective study involving MRI and 2D CSI MRS was approved by the local Institutional Review Board.

All patients provided informed consent. Patients with either low-grade glioma or benign tumors without previous cranial irradiation were eligible. Eleven patients (10 men, 1 female, age range 25–71 years, mean 44 years of age) were enrolled. Their primary tumors were low-grade gliomas (5), pituitary adenomas (4), meningioma (1), and craniopharyngioma (1) (Table 1). All patients underwent standard 3D conformal fractionated RT, resulting in partial brain irradiation (Fig. 1). All patients were treated 1.8 Gy daily, Monday to Friday, for 28–33 fractions, resulting in 50.4–59.4 Gy to the tumor. MRI/MRS scans were acquired prior to RT, at 3 and 6 weeks during RT, and 1 month and 6 months after the completion of RT to evaluate the impact on radiation to normal brain tissue outside the tumor.

The conventional MRI brain protocol included: sagittal and axial T2-weighted and postgadolinium T1-weighted images, axial T2-weighted FLAIR (fluid attenuated inversion recovery), T2-weighted images, diffusion-weighted images, and postgadolinium T1-weighted coronal images. Spectroscopic data were acquired using point-resolved (PRESS) 2D CSI performed on a 1.5T scanner (LX EchoSpeed, GE Medical Systems, Milwaukee, WI) with the following parameters: Probe-P, extended dynamic range, TE/TR 144/1500 msec, field of view (FOV) 24, thickness 10 mm, matrix 16 × 16, 1 NEX, with use of saturation bands outside the FOV. The scan time was 6:30 minutes. The PRESS region was centered over the midportion of the tumor and included normal-appearing brain tissue on both sides of the tumor. The size of the PRESS region varied from 8 × 3 cm² to 8 × 10 cm², depending on the location of the tumor allowing for coverage of regions receiving both high and low dose RT. The metabolic spectra were analyzed using the vendor software (Funtool 2, GE) with manual adjustment of metabolic peak boundaries. Only spectra of 2D CSI voxels from normal-appearing brain tissue outside the tumor were analyzed in this study. In each patient, spectra from a minimum of 14 voxels obtained from scans during and after RT were paired with corresponding voxels from scans prior to RT to assess changes in metabolite levels. No voxels from cerebellum or pons were included in the calculations. The metabolites of N-acetylaspartate (NAA), choline (Cho), and creatine (Cr) were evaluated, and the metabolic ratios NAA/Cr,

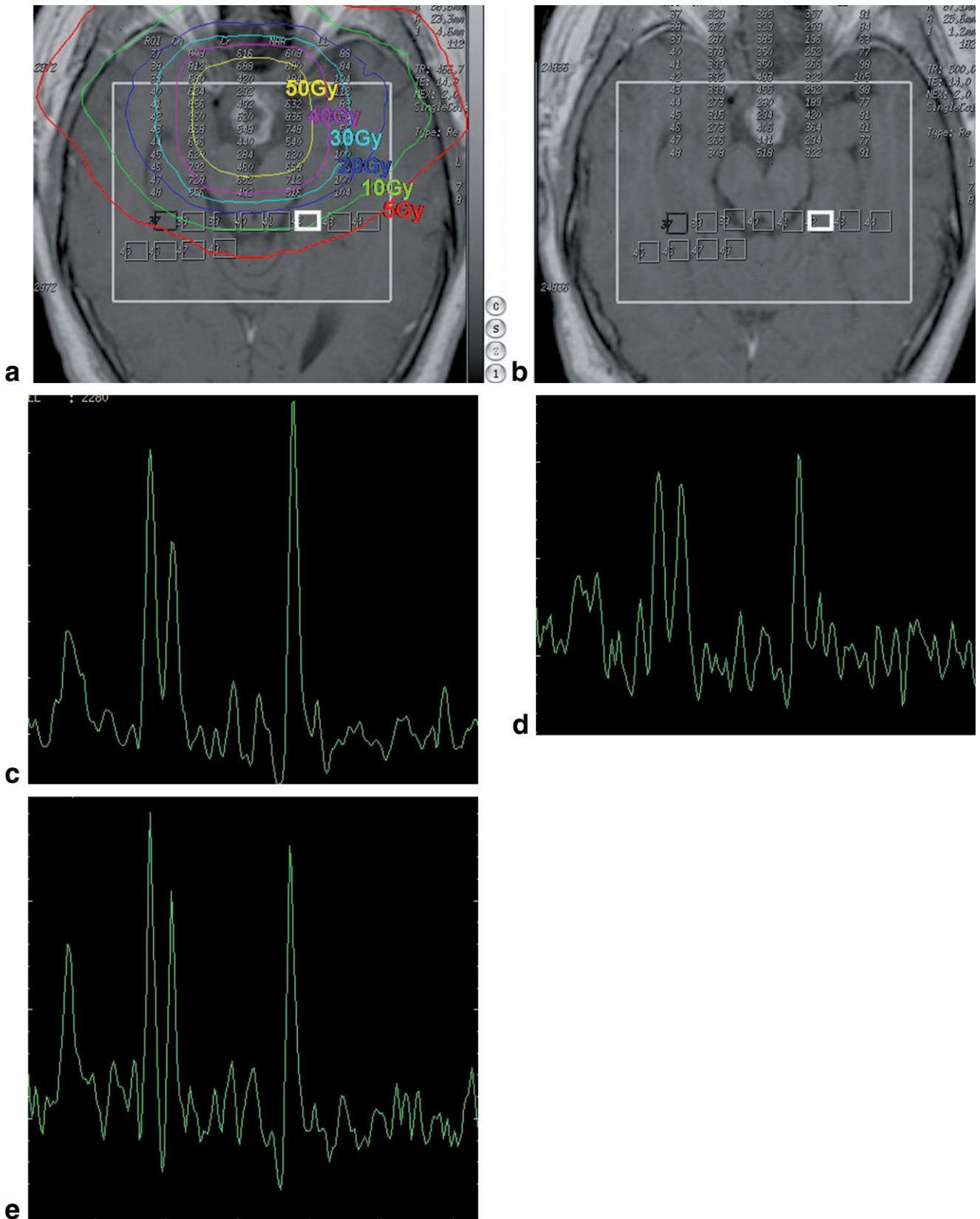


Figure 1. a-e: Axial post-Gd-DTPA T1-weighted images before RT (a) and 6 months after the completion of RT (b). The radiation isodose contours are overlaid on post Gd-DTPA T1-weighted images (a). The large white boxes represent the VOIs for MRS acquisition, and small white boxes depict the individual VOIs for spectral analysis. The three representative spectra prior to RT (c), at 3 weeks of RT (d), and 6 months after RT (e) were from the corresponding bright white boxes in top panels. Color contours denote isodose lines of radiation.

Cho/Cr, and NAA/Cho were calculated. The metabolic maps were digitally transferred for additional analysis using FIAT (33), an integrated functional image analysis software package developed in-house. FIAT is equipped with a range of tools and features that allow coregistration, mathematical manipulations, and evaluation of quantitative information.

We determined the areas under the metabolite peaks and calculated the metabolite ratios in normal-appearing brain parenchyma outside the tumor on conventional pre- and postcontrast-enhanced T1-weighted, T2-weighted, and FLAIR MRI. Timepoints studied were at the baseline before RT, at 3 weeks and 6 weeks during RT, and at 1 and 6 months after radiation treatment.

Statistical Methods

The temporal changes of the metabolic ratios of Cho/Cr, NAA/Cr, and NAA/Cho during and after RT were compared to ones prior to RT by paired *t*-test. Bonferroni correction was used for multiple comparisons, and thereby a *P*-value of <0.0125 ($= \alpha/n = 0.05/4$) was considered statistically significant. The correlations between the changes in the metabolic ratios and radiation doses as well as the dose volumes were assessed by linear regression, and again a *P*-value of 0.0125 was considered statistically significant. The dose-volume was defined as the volume of brain tissue that received a dose greater than 40 Gy ($V_{>40}$) at the completion of RT were used for the analysis as the effect of dose-volume.

RESULTS

Patient demographics, primary diagnosis and radiation dosage are given in Table 1. All patients had stable disease, ie, no interval change in tumor size, configuration, contrast enhancement, or peritumoral edema in the follow-up period following completion of RT.

Three patients did not have the 6-month follow-up exam. In two other patients the anatomic locations of the 2D MRS region acquired at either the 1-month or 6-month follow-up were not adequately aligned with the pre-RT 2D MRS region, and thus these specific MRS data timepoints were excluded from the final analysis.

MRI Findings

No interval change in size, configuration, or enhancement of the tumor to suggest progression were noted in the examined patients. Among the 11 patients studied, no definite radiation-induced lesions were evident by visual inspection of T2-weighted, FLAIR, and postgadolinium T1-weighted images up to 6 months after RT. All patients with low-grade glioma had hyperintense signal on T2-weighted FLAIR images in the tumor and in its vicinity that did not significantly change during the 6-month follow-up interval. In one patient with glioma, mild scattered focal areas of increased T2/FLAIR signal abnormalities were present in the centrum semiovale and periventricular white matter prior to RT, consistent with old ischemic changes. These areas demonstrated no change over the 6 months of follow-up. No new areas

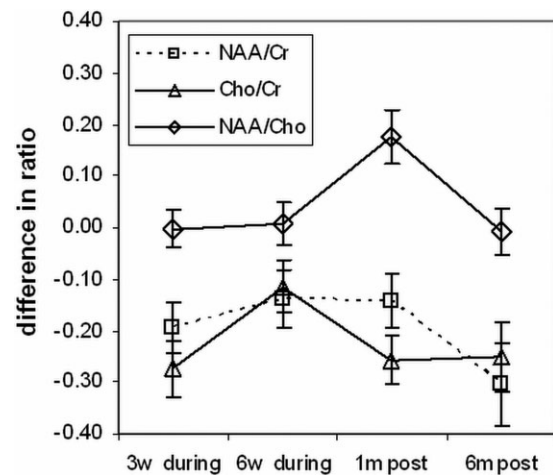


Figure 2. Differences of ratios of NAA/Cr (square), Cho/Cr (triangle), and NAA/Cho (diamond) at week 3 and week 6 during RT, and 1 month and 6 months after the completion of RT compared to the values prior to RT. Significant interval changes were observed in NAA/Cr and Cho/Cr during and after RT and in NAA/Cho at 1 month after RT. Error bar: standard error of the mean.

of signal abnormalities or pathological contrast enhancement suggestive of radiation-induced abnormalities were present in the follow-up images. In patients with pituitary adenomas and in the patient with cranio-pharyngioma no signal abnormalities outside the tumor were present before treatment, and no interval change was seen during the 6 months of follow-up. The patient with a meningioma demonstrated postsurgical changes with no interval changes in T2 and FLAIR signal abnormalities over time.

MRS Findings

In this analysis, only voxels of normal-appearing brain tissue were considered (Fig. 1). The quantity of patients available for each timepoint was as follows: pretreatment, 11 patients; week 3 of RT, 10 patients; last week of RT, 9 patients; 1 month post-RT, 9 patients; and 6 months post-RT, 7 patients. The metabolic ratios of NAA/Cr, Cho/Cr, and NAA/Cho in normal-appearing brain tissue prior to RT were 1.43 ± 0.04 (mean \pm SE), 1.29 ± 0.03 , and 1.18 ± 0.03 , respectively.

The metabolic ratios NAA/Cr and Cho/Cr in normal-appearing brain tissues showed significant decreases at week 3 of RT compared to the pre-RT values (Fig. 2). The NAA/Cr ratio decreased by -0.19 ± 0.05 at week 3 during RT ($P < 0.005$), by -0.14 ± 0.06 at the last week of RT ($P = 0.02$), by -0.14 ± 0.05 ($P < 0.01$) 1 month after the completion of RT, and by -0.30 ± 0.08 6 months after RT ($P < 0.0001$, Fig. 2) compared to the pre-RT values. The Cho/Cr ratio decreased by -0.27 ± 0.05 at week 3 during the RT ($P < 0.0001$), by -0.11 ± 0.05 at the last week of RT ($P = 0.025$), by -0.26 ± 0.05 1 month after the completion of RT ($P < 0.0001$), and -0.25 ± 0.07 6 months after RT ($P < 0.001$) compared to the pre-RT ratios (Fig. 2). The NAA/Cho did not change significantly during the RT, but increased significantly 1 month after RT by 0.18 ± 0.05 ($P < 0.001$)

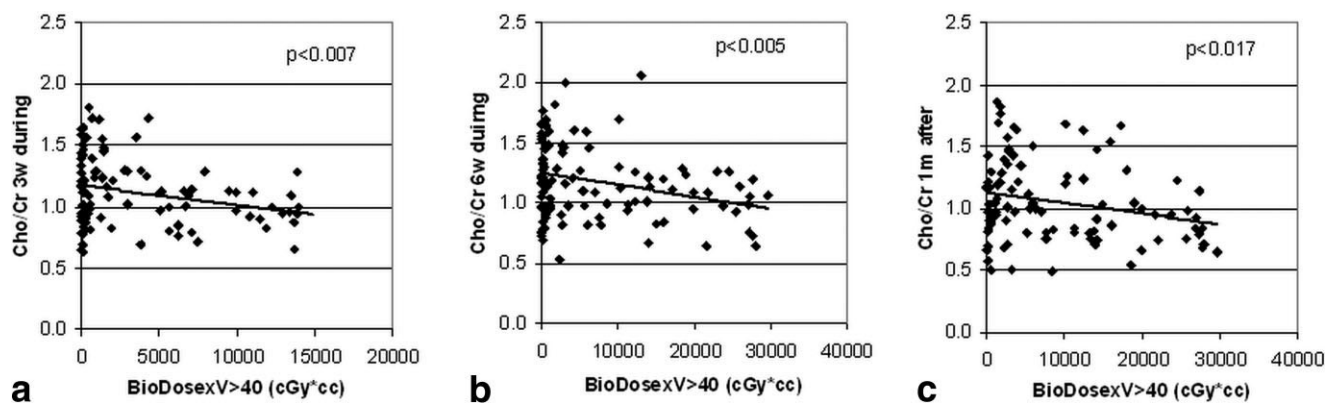


Figure 3. The relationships between the product of the local doses received at the time and the brain volume receiving high doses (>40 Gy) and the ratios of Cho/Cr at week 3 (a) and week 6 (b) during RT and 1 month after the completion of RT (c), suggesting the interaction effect of the dose and the dose-volume on the metabolite.

and eventually returned to the pre-RT baseline value at 6 months after RT (Fig. 2).

None of the changes in the metabolic ratios during and after RT correlated with the local radiation dose ($P > 0.05$). However, the ratio Cho/Cr correlated with the product of biologically corrected dose (equivalent to 2 Gy per fraction with $a/b = 2.5$) received at the time and the dose-volume, and this correlation was significant at week 3 of RT ($P = 0.007$), at the last week of RT ($P = 0.005$), and at 1 month after the completion of RT ($P = 0.017$). This relationship suggests that RT has a greater effect on metabolites when a larger volume receives the high doses (Fig. 3). Even using the Bonferroni correction, the correlation was significant at week 3 and the last week of RT, and marginally significant at 1 month after RT. By 6 months after the completion of RT the correlation was abolished ($P > 0.05$).

DISCUSSION

Late radiation injury is the major, dose-limiting complication of brain irradiation, causing delayed neurological complications and deficits in long-term survivors (6–10). It has been suggested that MRS may serve as a sensitive imaging tool to noninvasively detect neurochemical changes as evidence of neurotoxicity in the irradiated brain (23,24,26–29,31,32). The present study demonstrates that significant alterations in brain metabolites occur in normal-appearing human brain parenchyma early during RT and that interval progression of some of these changes occurs over at least a 6-month period. This is especially evident by the interval decrease in NAA/Cr ratios from the pretreatment values of 1.39 by -0.19 at 3 weeks of RT and the progressive decline by -0.30 at 6 months after the completion of RT. It is conceivable that the observed decreases in NAA/Cr and Cho/Cr ratios are partly attributable to an increase in Cr; however, we expect the drops in NAA and Cho levels to be genuine based on visual inspection of the spectra and the fact that Cr has often been used as an internal standard in other studies. The presumption that NAA decreases following radiation is also supported by a previous study that demonstrated a decrease in whole-brain NAA immediately

after prophylactic whole-brain RT in patients with lung cancer (30). In addition, a decrease in the NAA concentration with no change in the Cr concentration has been demonstrated previously in studies of irradiated brain (26–28). The metabolite NAA is predominantly present in neurons and believed to represent a marker of neuronal density and function. Creatine is a marker of energy metabolism and is considered to be fairly stable under most conditions even if some reports question the stability of Cr in tumors, hypoxia, and other confounding factors (27,29). However, with the assumption that Cr is stable, the metabolite is often used as a denominator in ratio calculations. Therefore, the decrease in the NAA/Cr ratio is most likely due to neuronal damage, neuronal cell death due to apoptosis, and neuronal dysfunction secondary to the irradiation rather than an elevation of the creatine, which also would result in a decreased NAA/Cr ratio (4). Other explanations such as neuronal response to blood–brain barrier breakdown, edema, damaged oligodendrocytes, demyelination, release of cytokines, and exposure to inflammatory cells have also been suggested (34–36).

While several studies overall have demonstrated a decrease in NAA after brain irradiation, there is some controversy in the literature over the interval change of the Cho metabolite. The Cho compound is correlated with cell membrane biosynthesis and metabolic turnover in proliferative tissue (31). Observations of decreases in both Cho and Cr compounds, as well as the decreased Cho/Cr ratio consistent with the present study, have been reported previously (23,32,37). We observed a decrease in Cho/Cr ratio early during RT, and it remained decreased for the first 6 months after RT, in agreement with previous reports (23,37). The decrease of Cho/Cr below pretreatment levels at 6 months is also in accord with a previous study using 3D MRS in which the authors demonstrated an initial increase 2 months after RT followed by a decline below pretreatment levels in patients receiving doses up to 50 Gy (32). It has been suggested that the decrease in Cho seen in normal-appearing brain tissue might be due to membrane damage in the myelin or the myelin-producing oligodendrocytes, accompanied by impaired tissue perfusion (25). A previous diffusion tensor study

showed that demyelization becomes more evident over time; these changes are seen at 1 month and progresses up to 6 months after the end of RT (18). The decreases that we observed in Cho/Cr after RT might reflect this damage to irradiated normal-appearing brain secondary to the radiation. The damage to the normal-appearing brain appears to stabilize over time with no further decline in the Cho/Cr ratio at 6 months follow-up, at least in patients receiving a dose of no more than 50 Gy. Our findings of interval significant decrease in NAA/Cr and Cho/Cr ratios are also in agreement with one of the few previous reports of metabolic changes after prophylactic irradiation in patients with acute lymphoblastic leukemia (23). That study demonstrated a progressive decrease in NAA/Cr and Cho/Cr ratios with increased time since diagnosis. They found that the lower NAA/Cr and Cho/Cr was associated with the presence of hemosiderin but not with imaging findings of leukoencephalopathy. Another study, of children who received RT for childhood leukemia or primary brain tumors (24), found no interval differences in NAA/Cr or Cho/Cr, in contrast to our study and other previous studies (23,28). The differences between the findings presented here and previous studies of young children (23,24) could possibly be explained by differences in cellular metabolism or radiation sensitivity of the young brain compared to older individuals. Also, recent animal studies have demonstrated significant differences in brain metabolite concentrations in irradiated rat brain (38) accompanied by worsening on behavioral tests in the irradiated rats compared to sham-irradiated rats 54 weeks after RT (39).

Our study indicates that both the NAA and Cho metabolites decrease during and early after RT. The progressive reduction in NAA over time suggests that the process of neuronal damage continues long after the completion of RT. However, to further evaluate changes in the metabolites and especially to see if the changes we describe in metabolite ratios could be due to an increase in Cr, future studies should focus on more quantitative analysis of absolute metabolite levels. Future studies will also reveal if these metabolic changes continue to progress after 6 months and if they correlate with the late delayed white matter signal abnormalities commonly seen on MRI.

Overall our study did not demonstrate any significant dose dependence in normal-appearing brain tissue. This is in contrast to a few existing reports on dose-dependent changes in metabolic ratios (32,40). However, the present study demonstrated that Cho/Cr ratios from week 3 during the course of RT and 1 month after the completion of RT were significantly correlated with the product of biologically corrected dose received at the time and the volume of the brain that received high doses. These findings suggest that there is an interaction effect of the dose and the dose-volume on the metabolites. Possible explanations for our finding of no relationship between changes in metabolites and RT dose include our limited number of patients, limited data collection, and limited signal-to-noise ratio. Another possible explanation is the heterogeneity of our sample, especially in brain regions studied, but also in tumor histopathology. The reduction in NAA could be

secondary to other neurotoxicities from RT, for example, blood-brain barrier opening or white matter demyelination. Blood-brain barrier opening occurs early with doses as small as 30 Gy, and it results in abnormal entry of chemicals from the blood into brain tissue. In white matter, early focal and dose-dependent changes in diffusion followed by diffuse changes have been reported (18). The future work will analyze the relationship between the blood-brain barrier, white matter injury, and neuronal injury to determine the temporal evolution of radiation-induced cerebral injury as well as early indicators of this injury.

While it would be of interest to correlate MRS changes to changes in cognitive function as demonstrated by neurocognitive tests, we did not feel that our data were sufficient for this analysis. The heterogeneous locations of the tumors resulted in different localizations of the 2D spectroscopic VOIs that generated data from various brain regions. Data were obtained in some of our patients from the temporal lobe and in others from the frontal lobe, but in no cases from both regions, and therefore comparison with metabolic ratios and neurocognitive tests became implausible.

The heterogeneous tumor histopathology could be considered a limitation of this study. However, none of the tumors demonstrated any change over the period of study, nor was there any change in peritumoral edema in those cases where this was present. We did not study the tumor or the edema but placed ROIs only in normal-appearing brain. Another potential source of difference compared to previous reports is tumor diagnosis. We studied only patients with low-grade gliomas and low-grade tumors to have a sample likely to remain stable over the period of study. None of these patients had ongoing steroid treatment, which might confound the study of patients with high-grade gliomas.

We chose to use the 2D CSI MRS with the PRESS technique and an intermediate echo time of 144 ms to cover a larger irradiated area. We did not use a limited single voxel spectroscopy technique (SVS) even though SVS may be favorable for quantification of metabolites. For future work we plan to add SVS with short echo time for quantification of individual metabolites over time and to determine if the changes seen in the metabolites might be due to gliosis by analysis of the myoinositol resonance at short echo time. In the present study, regional variations in spectra were not considered. However, inspection disclosed no changes in the location of the spectral regions for 6 months after RT occurred. In addition, changes in T1 and T2 relaxation times of metabolites were also not considered in this study. However, we have not calculated the individual metabolite concentrations, only the metabolic ratios. In the future we aim to expand our study to evaluate metabolite changes occurring over a longer time period by following the present patients up to 18 months to evaluate late delayed effects of RT.

Studies of normal volunteers or of nonirradiated brain regions would permit evaluation of scanner stability over time to verify stability of the metabolic ratio measurements. We did not study normal volunteers or nonirradiated regions and thus cannot exclude the possibility that scanner instability could account for some

of the changes seen. We plan to include normal volunteers in future work.

In conclusion, the results of this prospective study suggest that occult injury to the normal brain begins during RT and remains evident for at least 6 months. This study also supports the hypothesis that MRS is sensitive for early detection of metabolic changes in normal brain tissue undergoing radiation. The ability of MRS to detect progressive neuronal injury suggests that MRS might be able to compare the effects of different RT regimens and to evaluate neuroprotective therapies with the potential to minimize the neurotoxicity of brain RT.

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