Predictors of efficacy after stereotactic radiosurgery for medial temporal lobe epilepsy

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ABSTRACT

Background: Stereotactic radiosurgery (RS) is a promising treatment for intractable medial temporal lobe epilepsy (MTLE). However, the basis of its efficacy is not well understood.

Methods: Thirty patients with MTLE were prospectively randomized to receive 20 or 24 Gy 50% isodose RS centered at the amygdala, 2 cm of the anterior hippocampus, and the parahippocampal gyrus. Posttreatment MRI was evaluated quantitatively for abnormal T2 hyperintensity and contrast enhancement, mass effect, and qualitatively for spectroscopic and diffusion changes. MRI findings were analyzed for potential association with radiation dose and seizure remission (Engel Ib or better outcome).

Results: Despite highly standardized dose targeting, RS produced variable MRI alterations. In patients with multiple serial imaging, the appearance of vasogenic edema occurred approximately 9–12 months after RS and correlated with onset of seizure remission. Diffusion and spectroscopy-detected alterations were consistent with a mechanism of temporal lobe radiation injury mediated by local vascular insult and neuronal loss. The degree of these early alterations at the peak of radiographic response was dose-dependent and predicted long-term seizure remission in the third year of follow-up. Radiographic changes were not associated with neurocognitive impairments.

Conclusions: Temporal lobe stereotactic radiosurgery resulted in significant seizure reduction in a delayed fashion which appeared to be well-correlated with structural and biochemical alterations observed on neuroimaging. Early detected changes may offer prognostic information for guiding management. *Neurology*® 2010;74:165–172

GLOSSARY

ADC = apparent diffusion coefficient; **CI** = confidence interval; **CVLT-LDFR** = Long Delay Free Recall score of the California Verbal Learning Test; **FOV** = field of view; **MTLE** = medial temporal lobe epilepsy; **NAA** = *N*-acetylaspartate; **QOLIE-10**= Quality of Life in Epilepsy 10 inventory; **RS** = stereotactic radiosurgery; **TE** = echo time; **TMT** = Trail Making Test; **TR** = repetition time; **WMS** = Wechsler Memory Scale–Revised.

Stereotactic radiosurgery (RS) is currently under evaluation as an alternative to open surgery for mesial temporal lobe epilepsy (MTLE). Outcome in terms of seizure remission is variable.[1-9] Recent European reports have demonstrated good long-term outcomes in larger series of patients.[2,5] Similarly, we recently published high rates of seizure control after Gamma Knife® RS in a prospective multicenter pilot trial.[10] In this study, 2 RS doses were compared; the overall seizure remission rate was 69% during the third follow-up year after treatment which is comparable to that reported for resective temporal lobectomy.[11]

While preliminary data on efficacy of RS exist, several important questions remain to be answered. One potential limitation of RS for MTLE is the 12- to 24-month latency from treatment to seizure remission.[4] The antiepileptic effect of RS is much slower than remission of other conditions such as neoplasms or trigeminal neuralgia.[7,12-14] As there is a morbidity and even a small mortality of uncontrolled seizures,[15-18] an early marker of efficacy would be clinically useful, allowing interventions such as early open surgical "escape" resection to be judi-

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ciously applied. Furthermore, the mechanism by which RS renders an anticonvulsant effect is incompletely understood. While the cognitive effects of open surgery for MTLE have been extensively studied,[19-21] they have not been adequately delineated for RS.[22]

In order to address these issues, we report in detail the serial MRI radiographic changes in our prospective, multicenter study of RS for MTLE.[23] We chronicle the time course of the RS-induced changes and their relationships to RS dose, subsequent seizure remission, and changes on neuropsychometric testing.

METHODS Human investigation approval, inclusion and exclusion criteria, RS protocol, and initial efficacy and safety of our multicenter, prospective trial of RS for MTLE are detailed elsewhere.[23] Briefly, subjects had pharmacoresistant complex partial seizures and underwent standardized, presurgical evaluation that confirmed the presence of unilateral mesial temporal sclerosis (defined as either asymmetric increased hippocampal T2 signal or hippocampal atrophy) concordant with ipsilateral video-EEG lateralization confirming unilateral temporal lobe seizures.

Subjects were randomized to RS treatment with either a 20 Gy or 24 Gy dose containing a 50% isodose volume ranging from 5.5 to 7.5 mL comprising the amygdala, anterior 2 cm of hippocampus, and parahippocampal gyrus. Subjects were stratified according to center and gender. Radiation safety factors limited dose to a maximum of 10 Gy to the nearby brainstem and 8 Gy to the optic nerves and chiasm.

Standard protocol approvals, registrations, and patient consents. The study was approved by the NIH–National Institute of Neurological Disorders and Stroke, by the University of California, San Francisco Committee on Human Research, and by the respective institutional review boards at each of the other 6 treatment centers. Written informed consent was obtained from all patients.

MRI analysis. All subjects underwent brain MRI at baseline, 12 and 24 months after treatment, and also at any other time at physician discretion. A highly standardized protocol for MRI was carried out as follows: 1) T1 sagittal localizer (repetition time [TR] = 600; field of view [FOV] = 22); 2) T2 axial images (TR = 2,500; echo time [TE] = 30/80; FOV = 22 × 16); 3) fast spin echo coronal image (TR = 4,000; TE = 102; FOV = 22 × 16); 4) MPGR coronal (TR = 787; TE = 25; flip angle = 20°; FOV = 22 × 16); 5) 3-mm coronal interleaved fluid-attenuated inversion recovery 2 (TR = 36; flip angle = 35°; FOV = 22 × 16); 6) 3-dimensional-SPGR coronal (TR = 36; flip angle = 35°; FOV = 22 × 16; slice thickness 1.5 mm and in-plane resolution of 0.9 mm); 7) 3-dimensional-SPGR coronal with gadolinium; 8) echoplanar–diffusion-weighted imaging (TR = 8,000; TE min; 1 shot 166.67; FOV = 36 × 27; 5 mm skip 0; matrix 256 × 128; b = 1,000). MRIs were reviewed centrally by evaluators blinded to dose and clinical condition (E.F.C., M.O., W.P.D.).

To assess the severity of vasogenic edema, we used complementary quantitative and qualitative techniques. The volumes of T2 hyperintensity and T1 contrast enhancement were measured using digital calipers on a PACS station. Volumes (cc) were approximated using the formula for an ellipsoid: $4/3\pi$ A × B × C, where A, B, and C are the mediolateral, dorsoventral, and anteroposterior dimensions (cm). Given the variability of radiographic responses between patients after RS, the volumes were normalized by values obtained at 12 months after RS and plotted as a function of time.

To capture the neuroanatomic extent and the clinical severity of changes, volume measurements were supplemented with objective, standardized severity scales ranking the anatomic extent of T2 hyperintensity and the degree of mass effect into 6-point ranges.[24] The hyperintensity score rated T2 change severity (0 = none, 1 = confined to temporal lobe, 2 = temporal lobe + basal ganglia, 3 = temporal lobe + basal ganglia + [parietal lobe or occipital lobe], 4 = temporal lobe + basal ganglia + [parietal and occipital lobes], 5 = temporal lobe + basal ganglia+[parietal and occipital lobes] + frontal lobe). The mass effect scale rated edema in terms of swelling (0 = none, 1 = slight swelling, 2 = moderate local swelling without narrowing and 3 = with narrowing of the ambient cistern, 4 = important cerebral swelling with midline shift <10 mm, 5 = major cerebral swelling with midline shift ≥10 mm).

Apparent diffusion coefficient (ADC) was measured from the hippocampus and temporal stem. The ADC measures the magnitude of diffusion (of water molecules) within cerebral tissue. Diffusion-weighted datasets were acquired using a single-shot, echoplanar technique (b values of 0 and 1,000 s/mm^2), from which maps of ADC were calculated with software provided by the system manufacturer (GE Healthcare, Milwaukee, WI).

Multi-time point spectroscopic data were acquired from both mesial temporal lobes using a single-voxel (8 mL), point-resolved spectroscopic technique (TE = 135 msec; TR = 1,600 msec). The postgadolinium T1-weighted 3-dimensional SPGR was used to prescribe the PRESS selected volume. Briefly, the data were filtered with a Lorentzian function and Fourier transformed, resulting in an array of spectra. The spectra were corrected for baseline variations, phase shifts, and frequency shifts within the region of each peak, employing a priori information about the relative location of each metabolic peak. Voxels were selected from the RS target region in the medial temporal lobe and compared to unaffected homologous control voxels from the contralateral hemisphere. Choline, creatine, *N*-acetylaspartate (NAA), lactate, and lipid resonance peaks in chosen voxels were visually identified.

Seizure remission. Seizure remission was determined from standardized, physician-supervised seizure diaries. Seizure remission was defined as having no seizures (with or without auras, comparable to Engel Ib or better outcome[25]) during the year-long period between 24 and 36 months.

Neuropsychology. Neuropsychological testing results acquired at baseline and at 12 and 24 months postoperatively were evaluated in relation to peak MRI changes. The Long Delay Free Recall score of the California Verbal Learning Test (CVLT-LDFR)[26] and the delayed recall score of the Logical Memory subtest from the Wechsler Memory Scale–Revised (WMS-R DR)[27] provided measures of noncontextual and contextual verbal memory.[19] Assessments of global cognitive function were carried out with the use of the Trail Making Test (TMT)[28] and quality of life was assessed with the Quality of Life in Epilepsy 10 inventory (QOLIE-10).[29]

Statistical analysis. Nonparametric Mann-Whitney tests were used to statistically evaluate associations between variables such as volumes of T2 edema and T1 contrast enhancement, and seizure remission. Spearman correlations were used to evaluate

associations between neuroimaging changes and neuropsychological findings. Statistical significance was determined at p values < 0.05.

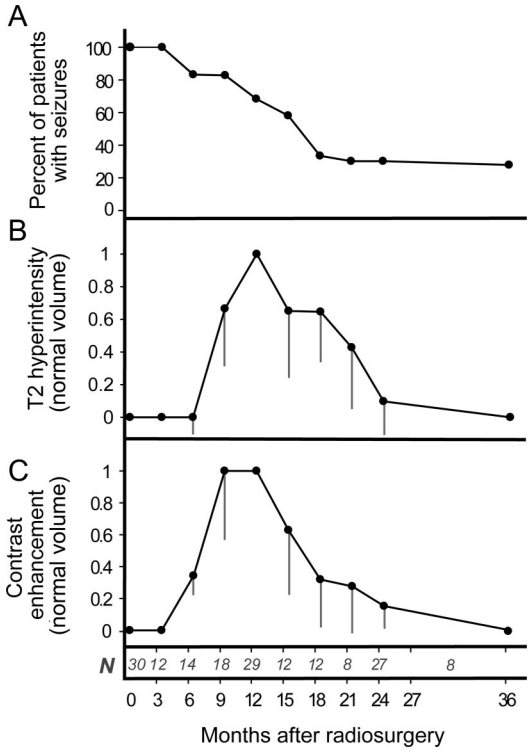
RESULTS Thirty subjects were randomized and treated. Three subjects did not complete the 36-month study: one subject was lost to follow-up (20 Gy), one required urgent temporal lobectomy at 15 months for dexamethasone-resistant papilledema following radiosurgery (24 Gy), and another was not seizure-free at 24 months and requested temporal lobectomy (20 Gy). The 2 subjects that underwent temporal lobectomy were considered as "no remission." Seizure remission was defined as complete seizure control during the 1-year period between 24 and 36 months after treatment. In this study, 20 of 29 (69%) patients were considered to be in seizure remission (the patient who was lost to follow-up was excluded). Although a greater proportion of patients who received 24 Gy (76.9%) were seizure-free compared to 20 Gy (58.8%), the difference did not reach statistical significance.[23]

Neuroimaging. Figure 1 demonstrates the time course of the RS-induced radiologic changes in relationship to clinical responses of seizures. MRI scans were obtained for all subjects at 12 and 24 months, and the intervening additional MRIs were done at discretion of the treating physician. The most striking effect was the degree of abnormal T2 hyperintensity associated with vasogenic edema. In those patients with multiple serial MRI, T2 hyperintensity appeared within the medial temporal lobe beginning around the ninth postoperative month and peaked in intensity at 12 months, corresponding to a decline in the proportion of patients experiencing complex partial seizures. Contrast enhancement followed a similar time course, except that it preceded T2 changes and diminished quickly after months 9–12. Enhancement was typically ring-enhancing and centered over the target region. Serial MRI changes are illustrated for a representative subject in figure 2.

The distribution of T2 hyperintensity, contrast enhancement, and hyperintensity severity and mass effect scales are shown in figure 3, also comparing 20 Gy vs 24 Gy at 12 and 24 months. In general, 24 Gy doses induced significantly larger responses than 20 Gy when measured at 12 months. At 24 months, however, these differences were not significant. Notably, the T2 hyperintensity volume at 12 months did not predict subsequent volumes at 24 months (Spearman nonparametric correlation, $p = 0.99$), demonstrating that the radiosurgical response is a monophasic, subacute lesion.

As graded by the T2 hyperintensity severity (HIS) scale, at 12 months substantial variability existed in the extent of edema (figure 3C), ranging from none to extensive white matter changes extending from the temporal lobe to occipital lobe. No signs of abnormal T2 hyperintensity were observed in the brainstem. Over the following 12–15 months, the degree of abnormal T2 hyperintensity subsided considerably. The course of mass effect was similar to hyperintensity changes, demonstrated by the correlation between mass effect and T2 severity scores at 12 months (Spearman correlation p value $= 0.002$). As with the edema, a large degree of variability existed for the mass effect. As it resolved, the swollen medial temporal lobe transitioned to a slightly atrophic morphology.

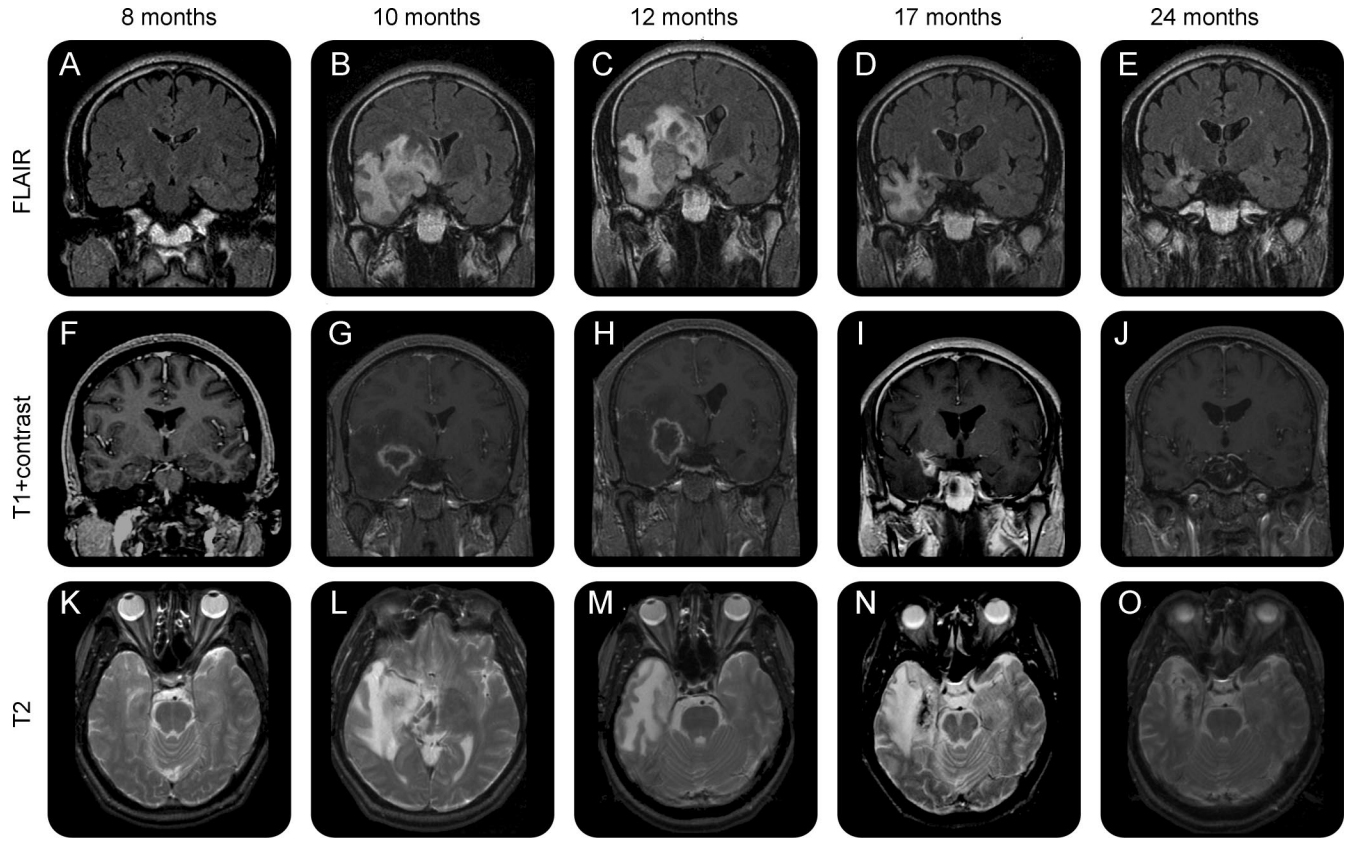
Figure 1 **Time course of incidence of seizure remission (seizure-free with or without auras)**



(A) The mean volumes of T2 hyperintensity (B) and contrast enhancement (C) were normalized by values obtained at 12 months after RS for each patient and the mean is plotted as function of time (gray lines are SEM). *N* indicates the number of patients who underwent neuroimaging between each examination interval since neuroimaging was standardized for 12- and 24-month visits and by physician request at other intervals.

Diffusion and MRS. ADC values from the ipsilateral temporal lobes were approximately twice as high as the contralateral temporal lobes at 12 months (n = 14, median difference in ADC [ipsilateral-contralateral] = 934; $p < 0.001$, Wilcoxon signed rank test). Typically, the temporal lobe and surrounding areas demonstrated increased ADC values consistent with the transient vasogenic edema observed in T2 imaging. However, a

Figure 2 Development of radiologic changes in a representative patient treated with a 24-Gy dose



Fluid-attenuated inversion recovery coronal (A–E), T1 coronal with gadolinium (F–J), T2 axial (K–O). Abnormal T2 prolongation involving the right frontal and temporal lobes demonstrating central heterogeneity at the level of the right medial temporal lobe. Severe vasogenic edema resulting in a mild increase in midline shift. The central area of heterogeneity has peripheral enhancement. By 12 months, the swelling of the temporal lobe resulted in almost 1 centimeter of midline shift on the coronal view. The T2 abnormality is largely limited to the white matter. The corresponding volume of abnormal T2 hyperintensity is 703 mL, the volume of contrast enhancement is 31.4 mL, the T2 hyperintensity anatomic extent score is 5 (extends to parietal and frontal lobes), and the mass effect score is 3 (local swelling with narrowing of the ambient cistern). At 24 months, there was significant reduction in the extent of T2 hyperintensity (102 mL, score 1), with residual T2 prolongation only in the right anterior parahippocampal gyrus, fusiform gyrus, and extending superiorly along the right temporal stem into the inferior subinsular cortex. There was interval decrease in mass effect at 24 months (mass effect score = 0). The right temporal lobe now appears atrophic compared to the left temporal lobe.

heterogenous pattern with focal areas of reduced diffusion was also observed at the target site (figure 4A), indicating ongoing ischemia and local metabolic alterations at a relatively long timepoint after treatment.

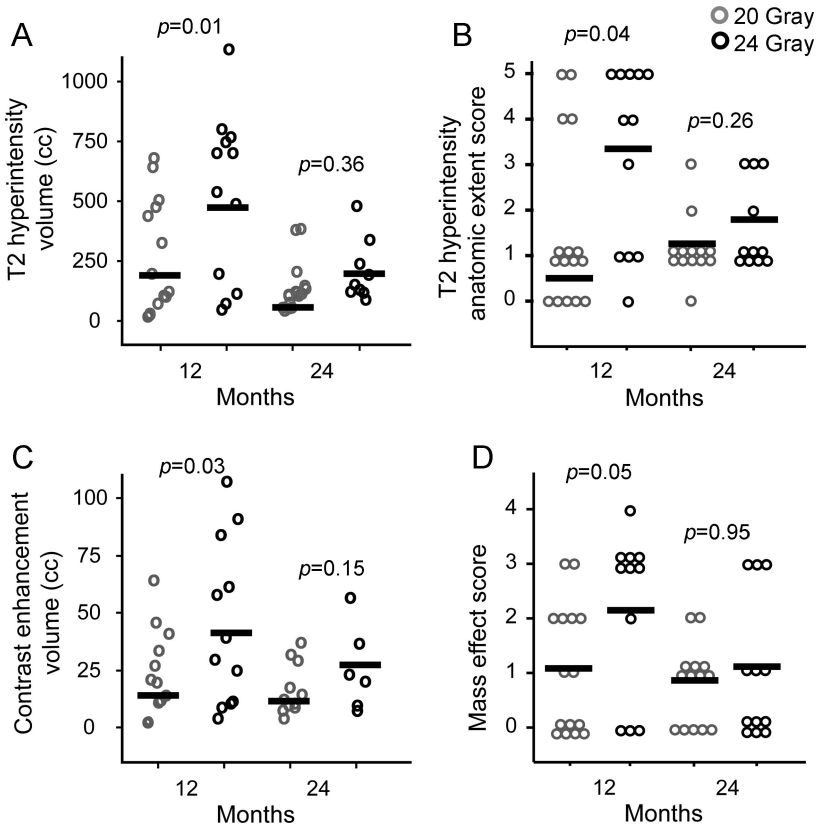
Proton spectroscopy was available in 5 patients (pretreatment = 4 scans, postoperative months 8–11 = 4, month 12 = 5, month 24 = 4 scans, total = 19 scans). Pretreatment levels of choline, creatine, and NAA were either normal or slightly reduced in the ipsilateral mesial temporal lobe compared qualitatively to the contralateral side on pretreatment MRS. At 12 months, choline, creatine, and NAA peaks were essentially absent and a highly elevated lactate peak appeared at the center of the surgical target (figure 4B).

Predictors of seizure remission. Beyond neuroimaging variables, we also examined treatment variables to evaluate which findings were best associated with subsequent seizure remission. The association between remission and treatment volume at the 50% isodose line ($p = 0.08$), or the volume of the surgical target with remission ($p = 0.12$) did not reach significance.

In contrast, larger volumes of T2 hyperintensity and contrast enhancement at 12 months were strongly associated with subsequent seizure remission in the period evaluated between 24 and 36 months (figure 5). The specificity of T2 hyperintensity volume with cutoff at >200 mL was 100% for predicting eventual seizure remission, with sensitivity = 65%, positive predictive value = 100% (95% confidence interval [CI] = 75%–100%), and negative predictive value = 42% (95% CI = 0.15–0.72).

Neuropsychology. We examined the relationship between magnetic resonance changes and language or global cognitive functions. We found no correlation between T2 hyperintensity volumes and changes in learning and memory or global cognition at either 12 or 24 months (CVLT-LDFR, WMS-R DR, TMT-A and TMT-B; Spearman rank correlation, $p > 0.45$).

Figure 3 Quantification of radiographic alterations stratified by dose



Distribution by stereotactic radiosurgery dose of (A) T2 volumes, (B) qualitative severity scores of T2 neuroanatomic extent, (C) contrast enhancement volumes, and (D) mass effect. Bars = mean. p Values from Mann-Whitney tests.

Interestingly, improvement in quality of life was correlated with greater T2 hyperintensity volumes at 12 months (QOLIE-10; coefficient = 0.47, 95% CI = 0.09–0.73, $p = 0.01$). We interpret this finding as a reflection of higher seizure remission in the responder group, since QOLIE-10 scores strongly follow seizure remission patterns.[23]

However, in the subset of patients with RS in the dominant hemisphere (n = 13), we found that worsening of the memory and language scores evaluated at 12 months appeared to have weak but insignificant correlation with concurrently measured peak T2 hyperintensity volumes (WMSR-DR, Spearman correlation coefficient = −0.55, $p = 0.05$; CVLT-LDFR = −0.53, $p = 0.06$; BNT = −0.47, $p = 0.10$).

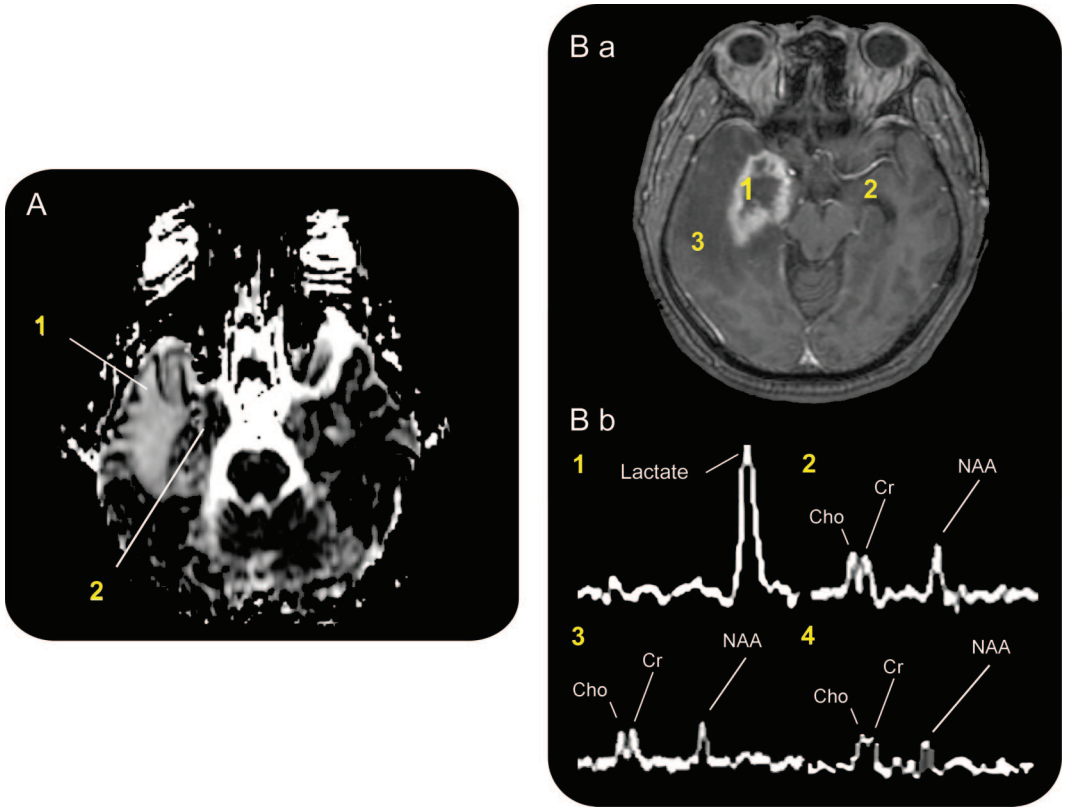
T2 hyperintensity volumes at 12 months did not correlate with long-term memory and language outcomes at 24 months (WMSR-DR, $r = 0.02$, $p = 0.92$; CVLT-LDFR = 0.03, $p = 0.94$; BNT = −0.11, $p = 0.71$). This was confirmed by the lack of difference in T2 changes in the subgroup of dominant hemisphere patients who were classified as significantly impaired (as determined by relative change indices)[10] compared to those who were not impaired (Mann-Whitney test, $p = 0.59$). Changes in global cognitive function at 24 months did not reveal an association with T2 hyperintensity volumes (TMT-A, $p = 0.86$; TMT-B, $p = 0.15$).

DISCUSSION Our recently published pilot trial demonstrated that Gamma Knife® RS for MTLE was a well-tolerated procedure with seizure remission rates similar to those published for standard open temporal lobectomy. In the current report, we examined the development of the RS-induced radiologic changes and their association with clinical outcomes. We found that MRI indicators of vasogenic edema occurred approximately 9 months after RS and showed a significant relationship with seizure remission. Evidence of vasogenic changes, as well as diffusion and biochemical alterations detected by spectroscopy, are consistent with a mechanism of temporal lobe radiation injury mediated by local vascular insult and tissue necrosis. The extent of these alterations at 12 months was dose-dependent and predicted seizure remission in the third year of follow-up. The extent of the radiographic lesion did not correlate with long-term or sustained impairments in measures of language function or neurocognition.

Our results help to explain the outcomes reported in previous trials of RS for MTLE. With few exceptions, high-dose protocols (>20 Gy) yielded better short-term seizure remission than lower dose protocols.[8] In the current report, high-dose RS treatments resulted in larger radiologic changes; accordingly, the presence of a "significant" T2 hyperintensity lesion (volume >200 mL) at the 12-month postoperative mark strongly predicted good seizure and quality of life outcomes.

While the neuroimaging changes documented in the current study are consistently associated with seizure control, the mechanisms by which RS reduces or eliminates seizures are unclear. Diffusion and proton spectroscopic data may help in this task, as well as shed light on the findings of "radionecrosis" in general. ADC maps at 12 months showed increased perilesional diffusion consistent with vasogenic edema, and within the target, decreased diffusion, consistent with the development of cytotoxic edema as seen with ischemia. Proton spectroscopic data support this interpretation: losses of NAA, choline, and creatine peaks and the development of lactate within the target indicated lack of normal oxidative metabolism, and thus, ischemic loss of neuronal parenchyma. Therefore, our data demonstrated a progression of ischemic vascular injury with subsequent necrosis, leading to increased vascular permeability, vasogenic edema within and around the radiosurgical target, and finally focal encephalomalacia. These findings are somewhat unexpected, since

Figure 4 Potential mechanisms of radiosurgery for medial temporal lobe epilepsy revealed by magnetic resonance diffusion and spectroscopy



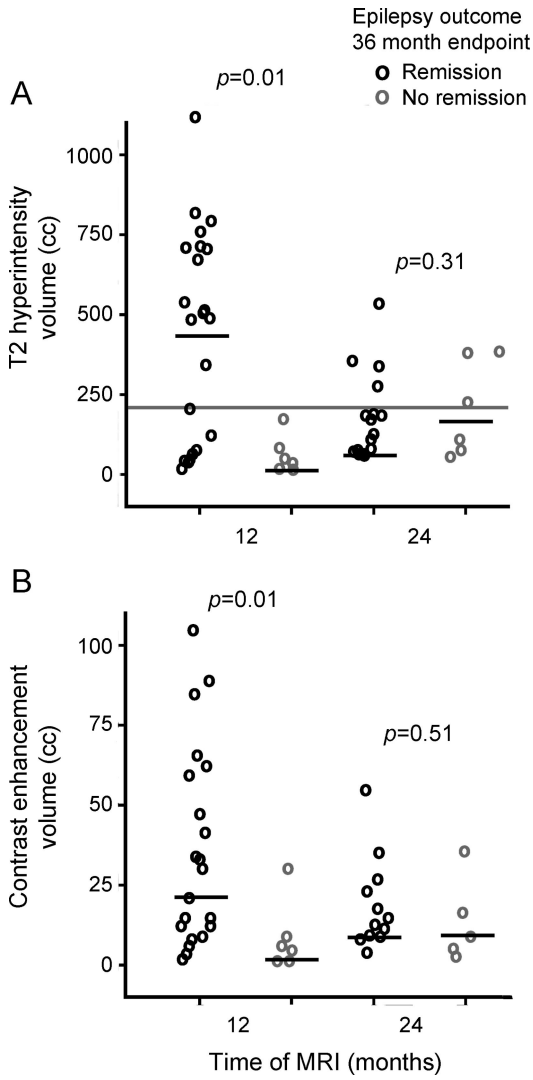
(A) Diffusion magnetic resonance at 12 months after treatment shows increased diffusion throughout the temporal lobe (1). There is also an area of decreased diffusion, and heterogeneity in the medial temporal lobe (2) suggesting ongoing delayed ischemic changes. (B) Proton magnetic resonance spectroscopy. T1-weighted axial MRI after gadolinium administration for spectroscopy voxel measurements (B.a). Spectra obtained for individual voxels (1 mL) selected in the following areas (B.b): (1) radiosurgery target region in mesial temporal lobe at 12 months, (2) contralateral mesial temporal lobe at 12 months, (3) peri-target region edema at 12 months, and (4) target region in mesial temporal lobe before radiosurgery treatment (not shown, but same position as (1) before treatment). The right medial temporal lobe demonstrates a prominent lactate peak in the area of contrast enhancement, and the near absence of the *N*-acetylaspartate signal compared to other regions or before treatment.

preclinical investigations with the use of rat models of limbic epilepsy demonstrate that seizure reduction is not associated with tissue necrosis or a concomitant loss of neurons,[30-32] though most animals achieved improvement rather than remission of seizures. On the other hand, in humans, seizure remission after RS of other epileptic lesions—hypothalamic hamartomas or vascular malformations—does not require radiologic changes consistent with radionecrosis.[33,34] Similarly, histopathology of hippocampal specimens obtained from open temporal lobectomy after failed RS for MTLE[1,3,7] demonstrates perivascular sclerosis and hyalinization, rather than necrosis. However, since these specimens were obtained from unsuccessful RS, they may not be sufficient to explain the changes required for successful RS in MTLE. Our data indicate that RS does not result in remission of temporal lobe seizures unless there is significant injury to neural tissue in the presumed seizure focus. Whether there is an antiepileptic effect in the human temporal lobe that does not require neuronal damage has not been demonstrated.

Although our data provide guidance in the prediction of seizure remission by 12-month neuroimaging criteria, they do not explain the biologic variability among patients exposed to very similar treatment protocols. Of course, the factors that predict failure of standard temporal lobectomy may also apply to RS, including incomplete hippocampal "resection" or bilateral disease. On the other hand, sensitivities to radiation may differ among patients. Radiation injury mediated by vascular endothelial insult may be affected by genetic factors, such as DNA repair mechanisms, or even acquired conditions such as intracranial atherosclerosis.

The lack of neurocognitive impairments that correspond to peak neuroimaging changes has implications in the overall morbidity of RS. The

Figure 5 **Radiographic predictors of seizure freedom after radiosurgery for medial temporal lobe epilepsy**



Dose effects on T2 hyperintensity volumes (A) and contrast enhancement volumes (B) at 12 and 24 months after radiosurgery in relationship to seizure remission between postoperative months 24 and 36. Black bars denote means. In (A), gray bar demonstrates cutoff threshold volume denoting 100% specificity in predicting seizure remission. *p* Values from Mann-Whitney tests.

development of transient, perilesional edema is expected after RS, but short-term cognitive morbidities have not been described.[22] Studies of cognition or behavior after RS for tumors,[35] vascular malformations,[36] hypothalamic hamartomas,[34] or mesial temporal lobe epilepsy[4,23,37] all demonstrate stabilization, relative sparing, or improvements in various markers of cognitive function, but these studies focus on final outcomes with little emphasis on interim or peak effects. Studies of patients treated with RS for metastatic tumors show that the majority of survivors, most of whom are impaired in categories of executive function, motor dexterity, or learning and memory at presurgical baseline, demonstrate stability or improvements 200 days following treatment[35]; however, the majority of subjects died of their disease. Patients tested 1 year after RS for vascular malformations demonstrated no significant changes.[36] We found a weak trend between the severity of temporal lobe edema and measures of language function when involving the dominant hemisphere, though the study was not powered to make definitive conclusions. A larger trial currently underway will address this issue in detail.

AUTHOR CONTRIBUTIONS

Statistical analyses: Edward Chang, Mark Quigg, Kathleen Lamborn. Data collection: Edward Chang, Mark Quigg, Michael Oh, Mariann Ward, Nicholas Barbaro. Data analysis: Edward Chang, Kathleen Lamborn, Mark Quigg, Donna Broshek. Preparation and editing of manuscript: Edward Chang, Mark Quigg, William P. Dillon, Mariann Ward, Kenneth Laxer, Donna Broshek, Nicholas M. Barbaro.

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DISCLOSURE

Dr. Chang reports no disclosures. Dr. Quigg has served on a speakers' bureau for GlaxoSmithKline and received research support from the NIH/NINDS [R01NS039280–01 (Treatment Site PI, Study Co-PI)]. Dr. Oh reports no disclosures. Dr. Dillon serves on a scientific advisory board as head of the core lab for Coaxia, Inc.; serves as Senior Editor of the *American Journal of Neuroradiology*; receives honoraria for speaking or educational activities not funded by industry; and estimates that 100% of his clinical effort is spent on neuroimaging. M.M. Ward reports no disclosures. Dr. Laxer serves on scientific advisory boards, speakers' bureaus, and received speaker honoraria from GlaxoSmithKline, UCB, and Pfizer Inc.; serves as a consulting editor for *Epilepsy Research*; serves as consultant to Lundbeck Inc. (formerly Ovation) and Chairman of Independent Data Monitoring Committee; and receives research support from Genentech, Inc. and the NIH [RO1-NS031966 (PI)]. Dr. Broshek reports no disclosures. Dr. Barbaro has received research support from Elekta AB (Stockholm, Sweden) and from the NIH/NINDS [NS39280–03 (PI)].

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