

PREDICTING THE UNPREDICTABLE: STEREOTACTIC RADIOSURGERY AND TEMPORAL LOBE EPILEPSY

Predictors of Efficacy After Stereotactic Radiosurgery for Medial Temporal Lobe Epilepsy. Chang EF, Quigg M, Oh MC, Dillon WP, Ward MM, Laxer KD, Broshek DK, Barbaro NM; Epilepsy Radiosurgery Study Group. *Neurology* 2010;74(2):165–172. **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.

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COMMENTARY

In multiple prior publications, stereotactic radiosurgery (SRS), at adequately high doses, has been shown to achieve rates of seizure control that rival surgical resections in the treatment of focal epilepsy (1). In early animal models, it was also postulated that the antiepileptic effect of SRS might be achieved at subnecrotic doses, which raised the intriguing possibility of using SRS in functional areas of the brain, such as the dominant hippocampus, to control seizures without causing neuropsychological decline (2). Early enthusiasm for a minimally invasive, nonsurgical treatment for focal epilepsy was tempered by the appearance of striking imaging changes in the brain, including ring-enhancing lesions, multilobar edema, and midline shift, resulting in high rates of headaches that necessitated steroid treatment and even early surgery in a small subset of patients with worrisome symptoms. Likewise, it became clear that for SRS to be effective, the region of onset must be clearly delineated, which is not always the case in a network disease, such as epilepsy. In addition, the volume of the ictal onset zone must be sufficiently small that delivering a high enough dose of therapeutic radiation will not likely cause symptomatic radiation necrosis. The maximal treatment volume in this current study was 7.5 mL. For this reason, hypothalamic hamartomas and mesial temporal lobe epilepsy are ideal candidates for SRS.

Although SRS is frequently employed at certain centers throughout the world to treat focal epilepsy, the technique has not gained widespread acceptance in the United States. Chang et al., the authors of this NIH sponsored randomized study, are to be commended for organizing such a well thought-out multicenter study, in an attempt to address not only the question of efficacy, but also the relationships among efficacy, dose, side effects, and cognitive outcome. While this article, as well as a recently published companion article (3), provides a bounty of useful data, ultimately the accrual of patients was low and hence the power of these studies is not quite sufficient to definitively address the most pressing issues.

The main goals of the study were first to determine which dose, 20 or 24 Gy, would lead to greater rates of seizure freedom and second to assess whether the degree of radiographic change could predict outcome. Although the trend toward better outcome with the higher dose is apparent, the power of the study was inadequate to show statistical significance. Indirect evidence demonstrating that a higher dose leads to more radiographic change and that more radiographic change leads to better outcome is clearly present. Unfortunately, the degree of radiographic change is extremely variable and unpredictable. Nevertheless, in spite of inadequate power to achieve the main goal of the study and large fluctuations in radiographic change in the brain, the authors attempt to convince the reader that SRS may lead to better cognitive outcome for patients with

mesial temporal lobe epilepsy. This conclusion appears unsubstantiated at this juncture.

Using magnetic resonance spectroscopy, the authors unambiguously demonstrated that SRS at 24 Gy causes neurons to die and elicits ischemia in the treated brain. Hence, SRS should be considered ablative, rather than neuromodulatory. However, Chang et al. emphasize that verbal memory decline was only demonstrated in 25% of dominant hippocampal treatments, which the authors claim compares favorably with resective surgery, after which as many as 60% of patients exhibit verbal memory decline (4). Although the investigators state in the abstract that radiographic changes were not associated with verbal memory decline for the entire population of patients, they point out in the results section that for dominant hemisphere cases a “weak but insignificant correlation” in decreased memory and language scores was found on two different tests ($p = 0.05$ and $p = 0.10$). Given the small number of patients, this finding would likely become quite significant with a larger “*N*.” With only 13 dominant hemisphere patients completing the study, it again raises the question of whether sufficient power exists to adequately address the issue of memory. In addition, it has been well documented that verbal memory decline is much more prevalent in dominant resections, whereas verbal memory improvement is found in nondominant resections, assuming patients are rendered seizure free (5). Hence, assessing verbal memory in the group as a whole and not separating them into dominant versus nondominant for statistical purposes is spurious and likely reflects the need to pool patients, given the small numbers recruited for this study.

One wonders why recruitment was so small for this minimally invasive nonsurgical cure for epilepsy. Several reasons come to mind. Perhaps the public, who fear the noncarcinogenic miniscule doses of radiation emitted from their cell phones, is not so ready to have high-dose gamma rays shot into their brains to treat a chronic disease? Perhaps the epilepsy surgeons would rather perform an elegant, low-risk operation during which they have complete control over the amount of tissue removed, rather than trusting a poorly understood process that leads to widely variable amounts of radiographic signal change, which can neither be predicted nor controlled. Either way, the role that SRS will play in treatment algorithms for focal epilepsy remains a mystery.

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