ADVANCES IN THE RADIOSURGICAL TREATMENT OF EPILEPSY

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Radiosurgery is the precise application of focused radiation to a targeted volume area within the brain, which has been identified on MRI. With recent advances, radiosurgical treatment is now being evaluated as an alternative treatment to open resective surgery for intractable epilepsy. Recent prospective trials suggest that radiosurgery may be an effective and safe treatment for medically intractable epilepsy associated with mesial temporal sclerosis, cavernous malformations, and hypothalamic hamartomas.

Radiosurgery involves the application of focused radiation to a discrete target area of the brain, as determined by MRI (1). Initially conceptualized by Leksell for use in functional neurosurgery, radiosurgical treatment for neurologic disorders is now also an option for several neoplastic and vascular indications (2,3). Differing from standard-dose fractionated radiotherapy, radiosurgery allows the neurosurgeon to deliver a precise and accurate amount of radiation to a smaller volume, without affecting nearby normal parenchyma and with minimal risk to neurological function (1,4–6). Radiosurgery is now being applied as different modalities including linear accelerator (LINAC), Gamma Knife, and proton beam stereotactic radiosurgery.

Patients with pharmacoresistant seizures frequently are referred for surgical treatment, and approximately half of them are found to be candidates for surgical resection of the seizure focus (7). For patients with concordant semiology as well as EEG and imaging indicating mesial temporal lobe seizure onsets, microsurgical resection of mesial temporal lobe structures can be performed with low morbidity and even lower mortality (6). However, open procedures have inherent risks, including damage to the brain, hemorrhage, blood loss, infection, and risks associated with general anesthesia. Several clinical studies evaluating the morbidity of temporal lobe microsurgery report that 5–23% of epilepsy patients undergoing open surgery had a postoperative symptomatic neurologic deficit (8–10). Radiosurgery now is being evaluated as an alternative treatment to open resective surgery for intractable epilepsy—specifically for medial temporal lobe epilepsy (MTLE) with mesial temporal sclerosis (MTS), gelastic epilepsy associated with hypothalamic hamartomas, and epilepsy with vascular malformations (1,3,5,6,11–29).

Medial Temporal Lobe Epilepsy

MTLE associated with MTS is perhaps the most well-defined epilepsy syndrome that is responsive to surgical intervention, with surgical cure expected in 65–90% of patients (2,7,30–37). This form of adult intractable epilepsy is particularly amenable to radiosurgery because 80–90% of cases show potential radiographic targets as changes on MRI (5,34). Recently, radiosurgery has been explored as an alternative to open resective surgery for MTS associated MTLE. In the first application of the Leksell Gamma Knife for epilepsy, Regis et al. used radiosurgery on a small number of patients and showed amelioration of seizures with minimal morbidity and mortality (23,24). In a more recent prospective, multicenter European study by Regis et al. gamma knife surgery for MTS resulted in comparable seizure-reduction efficacy rates (65%) for radiosurgery as for conventional surgery at the 2-year follow-up (6). Using a marginal dose of 24 Gy, this study again demonstrated that radiosurgery may be used as an alternative to conventional resective surgery to treat MTLE associated with MTS and improve quality of life with favorable rates of morbidity and mortality.

Currently in the United States, a multicenter pilot trial is being conducted to evaluate the safety of this Gamma Knife procedure in patients with MTLE and to determine the dose to use in a larger phase III trial. The 2-year follow-up results show that 85% of patients treated with 24 Gy (to the 50% isodose line) to the medial temporal lobe (including the amygdala, anterior hippocampus, and nearby cortex) are seizure-free, with minimal morbidity (Barbaro NM, Larson, D, Laxer, KD, Quigg M, Lamborn K, Ward MM, and the Radiosurgery Epilepsy Study Group, unpublished data, 2006). Of interest is the fact that neuropsychological testing showed no decline in cognitive function following treatment, including verbal memory skills for patients

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treated on language-dominant sides. Quality-of-life assessments at 2 and 3 years showed improvements that paralleled freedom from seizures. The pilot trial was not designed to determine the true efficacy of radiosurgery for MTLE. Therefore, a larger phase III trial comparing open surgery with radiosurgery for patients with clinically and radiographically defined MTS is planned.

The beneficial effects of radiosurgery are not displayed immediately. Most patients achieve seizure reduction at 9–12 months and complete cessation of seizures between 18 and 24 months after radiosurgical treatment. Typically, a transient increase in partial seizures (auras) is noted at approximately the same time as complex seizures decrease (6). Some patients may require corticosteroids to treat the radiation-induced edema associated with the initial radiosurgical effect (i.e., for 10–15 months post-treatment) (6, Barbaro NM, personal observation). Patients are at risk for seizure-related complications, including death, during the period between treatment and cessation of seizures (39).

Successful radiosurgical treatment has been shown to be target-related. Recently, Regis et al. (6,16,23,24) radiosurgically targeted the mesial temporal lobe structures (including amygdala, anterior hippocampus, and nearby entorhinal cortex) in a series of patients, whereas Kawai et al. (6,16,23,24) confined their treatment to the amygdala or hippocampus. Each series reported contrasting rates of efficacy in ameliorating medial temporal lobe seizures with radiosurgery; it appears that targeting the entire mesial temporal lobe may be a more effective method of reducing seizures with radiosurgical methods. Although target definition may be variable among different neurosurgeons, radiosurgery for MTS-associated MTLE is an attractive option because of its low morbidity and mortality. Furthermore, conventional open temporal lobectomy still can be pursued if the initial radiosurgical treatment is ineffective, once sufficient time (3 years) has passed to determine whether the delayed radiosurgical antiepileptic effect will occur (6).

Recent dose studies with small numbers of patients suggest that a lower marginal dose of 20 Gy may be less effective in reducing seizures. One gray (Gy) is the absorption of 1 J/kg of tissue mass. Cmelak et al. report unsuccessful seizure reduction with radiosurgery using a 15-Gy dose in one patient (38). Kawai and colleagues also report two cases of radiosurgery that resulted in an unsuccessful antiepileptic effect with a dose of 18 Gy (16). Finally, Srikijvilaikul et al. report a series of five patients with failed Gamma Knife radiosurgical treatment for seizure control with a 20-Gy marginal dose (39). Within the current U.S. pilot trial, the 20-Gy dose resulted in approximately 60% of patients becoming seizure free at 2 years following Gamma Knife treatment. Clearly, larger numbers of patients followed over longer periods of time would be required to determine the true percentage of seizure-free outcomes with this dose. However, it is unlikely to occur, as the higher 24-Gy dose appears to be safe and is likely more effective.

Histological Evaluation of Radiosurgical Treatment for MTLE

Histological examination of radiosurgically treated human mesial temporal tissue for MTLE has been limited; however, some histological reports of patients who subsequently underwent resection because of lack of seizure control have been published (16,38,39). Using a subtherapeutic dose of 15 Gy, Cmelak et al. noted no radiation-induced histopathologic changes after radiosurgery (38). In a study by Kawai and colleagues involving two patients treated with 18-Gy subtherapeutic dose, one patient was noted to have a necrotic focus with some prominent vascular changes consisting of vessel wall thickening, fibrinoid, and hyaline degeneration, while the other patient showed no necrosis or vascular changes (16). Treated with a higher, yet subtherapeutic dose of 20 Gy, all five patients in a study by Srikijvilaikul et al. showed necrosis, perivascular sclerosis, and macrophage infiltration on resection and histologic evaluation (39). These observations suggest that in humans, significant histologic changes may only be observed in radiosurgical doses greater than or equal to 20 Gy. Such radiobiologic and histologic changes may be required for a full antiseizure effect. Thus, a dose that produces some tissue damage without producing an excessive response, likely 24 Gy, is the optimal effective dose in the radiosurgical treatment of MTLE (6,23,24).

Hypothalamic Hamartomas Associated with Gelastic Epilepsy

Hypothalamic hamartomas are rare lesions with a prevalence of 1–2 in 100,000 individuals; they are commonly associated with precocious puberty, developmental cognitive delay, and gelastic epilepsy (25,40). These hamartomas are ectopic tissue consisting of glia, neurons, and fiber bundles. Surgical resection of hypothalamic hamartomas has been reported to improve control of gelastic seizure activity; however, because of the technical difficulties involved in reaching the deep lesion, open microsurgical resection of this critical area can be difficult, incomplete, and associated with complications, such as motor, visual, and hypothalamic deficits (25,40–43).

Recent reports suggest that radiosurgery may be an excellent treatment option for patients with hypothalamic hamartomas. Unger et al. report two patients treated with low-dose radiosurgery for hypothalamic hamartomas who had significant seizure improvement after 36 and 54 months. (29). As mentioned earlier, this delay is consistent with the therapeutic effects of radiosurgery for other conditions. In a recent retrospective multicenter study, Regis et al. report 10 patients treated with 18 Gy who had improvement in seizures after

radiosurgical treatment of hypothalamic hamartomas (25). In a larger series, 19 out of 30 patients were shown to have short-term improvements in 6 months of follow-up; however, further follow-up data are still being evaluated in this series (27). Thus, radiosurgery may be an appealing alternative for treatment of patients with these lesions, with microsurgical resection still available for patients who fail to respond to the less invasive therapy. Further investigations with larger series and longer, prospective follow-up must be conducted to establish the true safety and efficacy of this treatment option. The optimal dose is based on limited literature, as cited, it is likely 18 Gy. Similar to other uses of radiosurgery, the effects of radiosurgery for hypothalamic hamartomas are commonly seen 6–16 months after treatment.

Cavernous Malformation Associated with Epilepsy

Cavernous malformations are congenital vascular abnormalities that can cause hemorrhage or neurologic deficits, but more commonly manifest as recurring seizures (26,44). The incidence of medically intractable epilepsy associated with cavernous malformations is not yet established (26), and radiosurgical treatment is controversial because clear evidence of protection from hemorrhage is yet to be established (15,18,26). Although open microsurgical treatment of cavernous malformations remains the standard efficacious therapy, a recent series by Regis et al. suggests a role for radiosurgery in the treatment of seizures associated with cavernous malformations near "highly functional cortex," which because of their location may preclude open resection (26). Using a mean dose of 19 Gy, 53% of 49 patients with refractory seizures became seizure free, and 20% of those treated were significantly improved at 2 years (26)—demonstrating that epilepsy associated with cavernous malformations near eloquent cortex may be treated with radiosurgery to reduce seizure frequency. Given both the low bleeding risk in cortical regions and the common presentation of medically intractable seizures with cavernous malformations (45), patients seeking an alternative to microsurgical resection with decreased morbidity may opt for radiosurgical treatment. In addition to cavernous malformations near eloquent cortex, radiosurgery for deep-seated cavernous malformations that are not amenable to open procedures may be suitable for patients with medically intractable seizures. Unfortunately, these deeply located lesions have a higher risk of clinical bleeding, which is associated with a poorer neurologic outcome (45); the effect of radiosurgery on this risk is still unclear (15,18,26). Without clear evidence of the effect of radiosurgery on bleeding risk, microsurgical resection remains the standard therapy for cavernous malformations.

Long-term Radiosurgical Complications

The true incidence of long-term complications following radiosurgery is not yet known. There are reported cases of "radiation induced" malignancies associated with radiosurgery, but these reported cases are extremely rare (6,46–49). Because radiation-induced neoplasms require decades to develop, investigations involving much longer periods of follow-up than currently have been reported must be carried out to appreciate fully the possible long-term complications. A conservative estimate based on available literature suggests a rate of 3% in 30 years.

The Antiepileptic Radiosurgery Mechanism

Although radiosurgery has been shown to reduce seizures in various forms of medically intractable epilepsies, the mechanism by which this abatement occurs is unclear, although several possible mechanisms have been proposed. As glial cells are more radiosensitive than neurons, Barcia-Salorio proposed low-dose radiosurgery may reduce glial scar formation, allowing increased dendritic sprouting, improved cortical reorganization, and, consequently, fewer seizures (12). Although the clinical results of the most recent human studies suggest that the therapeutic efficacy of radiosurgery is linked to necrosis of mesial temporal structures, proof for this concept would need to come from direct observation of tissue samples from patients for whom radiosurgery has resulted in seizure control. Such observations are unlikely to occur, because only patients with persistent seizures would be expected to undergo open resective surgery.

Surrogate markers of radiation effects, such as imaging changes on MRI, thus far have shown mixed results. With most patients, radiation-induced edema becomes evident on MRI 9–15 months following radiosurgery. These radiographic changes are usually time-limited and often are followed by focal atrophic changes. Thus, MRI changes may not be diagnostic of true radiation necrosis. As with MTLE, the actual mechanism by which high-dose radiation reduces neuronal hyperexcitability likely will not be found from human studies, as tissue biopsy is not likely in patients who achieve seizure control.

Low-Dose Radiosurgery and Treatment Efficacy

Although preclinical evidence and the results from two early human trials suggested that control of seizures might be possible with doses of radiosurgery that were lower than those typically applied to tumors (11,14), recent case reports describe the failure of low-dose radiosurgery to control seizures (16,38,39). While failure of seizure control is easy to identify, it is a much more difficult task to determine that the failure is due to an insufficient radiosurgery dose. The time dependence of radiosurgical effects is also a confounding factor that has not been fully explored. Among various radiosurgical treatment centers, a consensus has not yet been reached regarding the time period at which radiosurgical treatment should be determined to have "failed" (28). As noted, recent prospective results suggest that radiosurgery may have results very similar to resection for which

~30% of patients will continue to have seizures (6). However, the reported failures of low-dose radiosurgery are case reports and as of yet, do not demonstrate a failure rate of ≥30%. Radiosurgery patients who did not show adequate seizure reduction commonly had radiation doses of 20 Gy or less, and these patients showed little evidence of radiation-induced necrosis in their pathologic specimens (16,38,39). Thus, the best evidence to date from human and animal experiments suggests that there is a steep dose–response effect for seizure reduction, that some neuronal damage is required to produce seizure abatement, and that the dose required to eliminate seizures is very close to the absolute tolerability of human brain tissue.

Conclusions

Recent data suggest radiosurgery indeed is effective in reducing epileptiform activity and seizures associated with several forms of medically intractable epilepsy, including MTLE as well as epilepsy from hypothalamic hamartomas and vascular malformations. Prospective trials with larger numbers of patients will be required to establish radiosurgery as a standard therapy for MTLE. As the true long-term toxicity of radiosurgery is not known, patients treated with this modality will need to be carefully followed.

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