Radiosurgery for Medial Temporal Lobe Epilepsy Resulting from Mesial Temporal Sclerosis

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SYNOPSIS: Mesial temporal lobe epilepsy associated with mesial temporal sclerosis (MTS) is perhaps the most well-defined epilepsy syndrome that is responsive to structural interventions such as surgery. When temporal lobe epilepsy is caused by underlying MTS, seizure improvements with open microsurgical resections have been reported in 65–90% of patients [5, 7, 23-27]. Though morbidity and mortality in these procedures are typically low, open resection, as with any open technique, is associated with an increased risk of infection, blood loss, ischemic events, and postoperative hemorrhage, as well as prolonged hospital stay. Several clinical studies evaluating the morbidity and mortality associated with open microsurgery for temporal lobe epilepsy have reported that approximately 5% to 23% of patients experience a postoperative symptomatic neurological deficit [8,11,12,15,16]. In recent years, several minimally invasive techniques have arisen that provide

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This is the author's manuscript of the article published in final edited form as:
Gianaris, T., Witt, T., & Barbaro, N. M. (2016). Radiosurgery for Medial Temporal Lobe Epilepsy Resulting from Mesial Temporal Sclerosis. Neurosurgery Clinics of North America, 27(1), 79–82. http://doi.org/10.1016/j.nec.2015.08.011

additional options for the treatment of MTS while potentially avoiding many of open surgery's associated risks. By evading these risks, they also open up treatment options to patients that would otherwise be poor surgical candidates based on tumor size or location [6,19]. Radiosurgery is one of the most intensively studied of these alternatives and has found a growing role in the treatment of medial temporal lobe epilepsy.

KEY POINTS:

- Radiosurgery for mesical temporal sclerosis (MTS)-associated medial temporal love epilepsy (MTLE) is an attractive option because it is relatively noninvasive, with lower morbidity than major surgery.
- Conventional open temporal lobectomy surgery may also be pursued if the initial radiosurgical treatment is ineffective and after sufficient time has been permitted for the delayed radiosurgical antiepileptic effect after 3 years.
- The main known disadvantage of radiosurgery at present is the delayed response for seizure control, during which time patients continue to suffer from the sequelae of seizures.
- Future research into this treatment modality will ideally make individualized patient treatment more feasible and attainable, allowing the neurosurgical community to more effectively manage and treat medial temporal lobe epilepsy.

Introduction

Radiosurgery is the precise application of focused radiation to targeted brain with the aid of stereotactic guidance [1-27]. Radiosurgery is particularly well suited for treatment of MTS leading to medial temporal lobe epilepsy because MTS typically exhibits radiographic changes on MRI, allowing this focused radiation to be directed to a specific, small region of pathology, sparing the rest of the brain from harmful radiation [24]. Regis and colleagues were able to demonstrate the safety of focused radiosurgery for medial temporal lobe epilepsy while still delivering doses effective enough to reduce seizure frequency, whereas a prospective multicenter European study using the Gamma Knife proprietary radiosurgery tools found similar efficacy rates for seizure reduction with a dose of 29 Gy when comparing radiosurgery to the gold standard of conventional microsurgery for epilepsy after 2 years with similar morbidity and mortality [28].

A similar multicenter trial studying a direct comparison of radiosurgery to resection for MTLE has shown in pilot studies that a dose of 24 Gy to the medial temporal lobe was able to eliminate seizures in 85% of patients at 2 years of follow up as well [29]. In this pilot study, patients were treated with 2 different radiation doses (20 or 24Gy) and there was significant seizure remission in both groups at 12 months (58.8% and 76.9% respectively), with no dose-based or seizure remission-based changes in headaches, visual field defects, and the use of steroids. Although these studies thus far only have time points at 1 and 2 years, recent research in France looking at outcomes of 5 and 8 years has demonstrated continued seizure reduction remission after radiosurgery, although at a lower rate, finding 47% remission at 5 years and 60% at 8 years [30,31]. In addition, there may be benefits with respect to memory and language preservation.

Risks of Treatment

Although these studies have shown that radiosurgery is effective with minimal morbidity and mortality at time points of greater than one year, radiosurgery, unlike open resection, has a lag time after treatment before patients begin to see the effects of therapy and, in the near-term, patients are still exposed to the risks of continued seizures as well as the risks of radiation. Typically, patients treated with radiosurgery can achieve seizure reduction at 9–12 months and possible complete cessation of seizures between 18 and 24 months after radiosurgery treatment [28]. In addition, a transient increase in partial seizures (auras) can be noted at approximately the same time that complex seizures decrease with radiosurgery and many of them require a transient period of steroid administration for the radiation-induced edema [28]. Srikijvilaikul and colleagues found two deaths during this latency period in a small case series of five patients treated with 20 Gy before seizure remission, likely complications of ongoing seizures [33]. Quigg and colleagues found that language (Boston Naming Test), verbal memory (California Verbal Learning Test and Logical Memory Subtest of the Wechsler Memory Scale-Revised), cognitive efficiency, and mental flexibility (Trail Making Test), and mood (Beck Depression Inventory) did not differ from baseline after radiosurgery, demonstrating long-term neurocognitive safety using established scoring scales, despite the increased potential for necrosis [33].

Radiosurgery for MTLE is not without risks and long-term effects; radiation necrosis has been demonstrated by several studies and case reports. Hensley-Judge and colleagues [34] found postoperative visual field deficits in 15 of 24 (62.5%) patients, all homonymous superior quadrantanopsias, proportions similar to historical comparisons from open surgery for MTLE. Another case series demonstrated two of seven patients, status post radiosurgery for MTS presenting with symptomatic radiation necrosis, required resection after 5 and 10 years [35]. Additionally, there is some concern in the long term for radiosurgery-associated ‘radiation-induced’ malignancies, though these

reported cases are rare, and none has been reported following therapy for MTS [36-39]. While it has initially been studied as a primary modality for MTS treatment, radiosurgery is also being investigated as a treatment for refractory epilepsy after temporal lobe resection. Yen and colleagues found significant seizure reduction in a case series of 4 patients who underwent radiosurgery following temporal lobe resection[40]. There was reduction of seizure frequency at 6 months after radiosurgery for refractory epilepsy after temporal lobe resection as well as improved neuropsychological profiles, including memory function and quality of life, lasting up to the 2-year follow-up exam.

Mechanism of Action and Histopathology

Conversely, open resective surgery following radiosurgery has, as a side benefit, provided an opportunity to understand the mechanism of action of radiosurgery on a histopathologic level. In two separate studies, Kawai and colleagues and Srikijvilaikul and colleagues found histologic changes, including necrotic foci with vessel wall thickening and fibrinoid and hyaline degeneration, in a patient treated with 18 Gy, as well as perivascular sclerosis, and macrophage infiltration upon resection and evaluation of a patient treated with 20 Gy [32, 41]. Cmelak and colleagues reported no radiation-induced histopathologic changes in tissues treated with 15 Gy of radiosurgery, suggesting that some histological damage may be needed for effective seizure control [42-45]. Chang and colleagues found vasogenic edema appeared approximately 9-12 months after radiosurgery on serial MRI scans and correlated with the onset of seizure remission, further corroborating this hypothesis [46]. Barbaro and and colleagues suggested that the mechanisms may be some combination of neuromodulation and true neuronal destruction, with some animal studies demonstrating improvement in seizures without evidence of necrosis, whereas others have shown direct structural, destructive lesions in the tissue zone to correlate better with outcome, perhaps because of some contribution from ischemic factors [29, 446, 47]. The concrete mechanism of radiosurgery, destructive or otherwise, warrants further study.

Summary

In summary, radiosurgery for MTS-associated MTLE is an attractive option because it is relatively noninvasive, with lower morbidity than major surgery. Conventional open temporal lobectomy surgery may also be pursued if the initial radiosurgical treatment is ineffective and after sufficient time has been permitted for the delayed radiosurgical antiepileptic effect after 3 years [28]. Its main known disadvantage at present is the delayed response for seizure control, during which time patients continue to suffer from the sequelae of seizures. Future research into this treatment modality will ideally make individualized patient treatment more feasible and attainable, allowing the neurosurgical community to more effectively manage and treat medial temporal lobe epilepsy.

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