Stereotactic radiosurgery for Treatment of Epilepsy

Mark Quigg, MD, MSc; Nicholas M. Barbaro, MD

Stereotactic radiosurgery, known for efficacy in the noninvasive treatment of tumors or arteriovenous malformations that are otherwise difficult to access through traditional surgery, is an emerging technology in the treatment of focal epileptic lesions. Recent studies in the treatment of hypothalamic hamartoma and mesial temporal lobe epilepsy further suggest that seizures in these medically intractable syndromes remit at clinically significant rates with stereotactic radiosurgery. Further studies will be required to determine whether efficacy attains that of traditional surgery while offering a noninvasive technique with potentially lower morbidity.

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sional tissue through radionecrosis is not required for amelioration of seizures or their experimental surrogates. Second, seizure response, either in successful remission or in a paradoxical worsening, varies with target, dose, or postoperative duration. Third, the treatment target, dose, and volume remain empirically determined, and scaling up from experimental models to humans is not straightforward.

It is not known how gamma irradiation produces an antiepileptic effect. Sensitivity to ionizing irradiation is largely dependent on mitotic rate; therefore, neurons are relatively radioresistant. In flurothyl-kindled mice, although total brain irradiation terminates seizure-induced mitotic activity in hippocampal dentate gyri, irradiated mice have no changes in seizure threshold or clinical seizure phenotype. Therefore, the differences in mitotic activity in epileptic areas may not underlie antiepileptic effect.4 Tissue necrosis is not necessary.3-6 Histologic examination of irradiated rat hippocampi shows changes of experimental hippocampal sclerosis rather than changes typical of acute or chronic severe radiation injury.3-6

Although neurons themselves are resistant to radionecrosis, supporting structures—vasculature and glia—are not. The major pathological findings after irradiation consist of endothelial damage to small blood vessels and astrocytic reactions. One hypothesis, therefore, is that neuronal damage results from ischemia caused by vascular inflammation.

Other hypotheses suggest that irradiated neuronal circuits undergo neuromodulation that renders an anticonvulsant effect (or, sometimes, a paradoxically proconvulsant effect). Differential susceptibility to irradiation or ischemia among different neuronal populations within epileptogenic circuits may account for this phenomenon.7

Given these possible mechanisms, studies with the use of well-validated models of partial epilepsy address some of the questions of target, administration, time course, and clinical sequelae. These models include electrically kindled rats38 studied through surrogate markers of triggered seizure threshold and severity, as well as rat models that experience spontaneous seizures induced either by kainic acid5,6 or by electrically provoked, self-sustained limbic status epilepticus.4

The earliest of these series established that there might be a proconvulsant or anticonvulsant effect of GKS that varies with postoperative duration or dose. Kindled rats with doses of 25 Gy or less to the amygdala experience clinically more intense seizures.8 Kindled rats treated with 40 Gy to a single hippocampus initially experience a decrease in seizure threshold compared with controls within the first month. Thereafter, however, treated animals develop increased seizure thresholds.3

Other experiments established relationships between dose and latency with experimental spontaneously occurring seizures.46 In animals monitored for 6 weeks, doses of 80 and 100 Gy cause seizure reductions within 2 to 4 weeks postoperatively, whereas lesser doses cause reductions of slower onset.5 Increasing doses of radiosurgery correlate with higher percentages of rats that became seizure-free.6 Other studies indicate that there is a threshold effect, with single treatments of 30 Gy being as effective as 60 Gy in reducing seizures.5 This suggests that, once a tissue-damaging level has been reached, there is little advantage in increasing the radiation dose. Long-term electroencephalogram monitoring for periods of up to 10 months establishes that the anticonvulsant effects of GKS are durable.4

In summary, it seems clear from the preclinical literature that there is a dose-dependent response to radiation. These experiments help define a therapeutic window of treatment dose bounded by ineffectiveness, paradoxical exacerbation, or delayed remission at the lower doses and by tissue necrosis at higher doses. Evaluation of human studies, therefore, requires particular attention to treatment dose, volume, and target.

### TREATMENT OF LESIONAL EPILEPSY

The anticonvulsant benefits of GKS were first observed as additional benefits during its use as a treatment of tumors or arteriovenous malformations (AVMs).10-14

#### Supratentorial Tumors

Given the variety of types, pathological features, and locations of central nervous system tumors, the studies of effects of GKS on tumor-associated epilepsy are few. Schrottner et al,9 however, concentrated on patients with medically intractable epilepsy resulting from tumors, dividing 24 patients into 2 groups by the amount of radiation directed to surrounding tissue. Outcome was retrospectively ranked at mean duration of approximately 2 years as “excellent” (Engel class 1 or 2) or not. Patients in the high-dose group achieved a 66% improvement rate compared with 42% for the low-dose group. Because all patients achieved tumor control with GKS (thus removing tumor response as a potential confounder), the differing rates of seizure improvement suggest that higher GKS doses are important in modifying epileptogenic changes in cortex adjacent to tumor.

#### Arteriovenous Malformations

The potential efficacy of GKS in the treatment of symptomatic localization-related epilepsies is most evident in the treatment of AVM10-14 (Table 1). Representative is the large series accumulated by Steiner et al,11 who reported that seizures remit after GKS in 69% of patients with AVM and epilepsy. Subsequent studies of both proton beam treatment and GKS show a combined rate of seizure remission of approximately 70% (Table 1). A recent large case series emphasized that the incidence of seizure remission is better with smaller AVMs.13 However, Steiner et al11 noted that seizures remitted independent of radiologic remission of the AVM, a finding that suggests that the effects of irradiation near the lesion, rather than the improvement of the AVM itself, may be important in control of seizures after GKS.

#### Cavernous Malformations

With the favorable results encountered in treatment of seizures associated with AVMs and tumors, investiga-
tors began to explore the efficacy of GKS in other epileptic lesions. Table 1 shows a summary of the efficacy of GKS in the treatment of seizures associated with cavernous malformations. In general, seizure remission is lower than that encountered in cases after treatment of AVMs. The effect of dose to adjacent brain around the margin of the cavernous malformation, thought important in the case of tumors and possibly AVMs, has not been systematically studied in terms of seizure control (although higher doses may have more problems with radiotoxicity and lower doses with rebleeding). Excess morbidity in terms of postoperative hemorrhage remains a concern. For example, the early Swedish experience determined that GKS did not appreciably alter the natural course of cavernous malformation while exposing patients to radiation-induced complications that exceeded by 7 times those expected for the same dose for AVMs. A recent retrospective comparison concluded that traditional open resection resulted in better seizure control and rebleeding avoidance than did GKS.

Hypothalamic Hamartomas

Hypothalamic hamartomas are an important cause of an epileptic encephalopathy marked by medically intractable gelastic and other seizures with behavioral and cognitive decline. Although HHS are difficult to excise with the use of standard surgical techniques, GKS has the advantage of providing noninvasive access while sparing adjacent tissue.

Table 1. Seizure Remission After Stereotactic Radiosurgery of Arteriovenous Malformations, Hypothalamic Hamartomas, and Cavernous Malformations

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Duration of Follow-up b</th>
<th>Outcome c</th>
<th>Remission, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arteriovenous malformations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heikkinen et al, 1989</td>
<td>29</td>
<td>2-6 y</td>
<td>Cessation</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Steiner et al, 1992</td>
<td>59</td>
<td>24-96 mo</td>
<td>Cessation</td>
<td>41 (69)</td>
</tr>
<tr>
<td>Gerszten et al, 1996</td>
<td>15</td>
<td>47 mo</td>
<td>Cessation</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Kurita et al, 1998</td>
<td>35</td>
<td>43 mo</td>
<td>Cessation</td>
<td>28 (80)</td>
</tr>
<tr>
<td>Schäuble et al, 2004</td>
<td>65</td>
<td>4 y</td>
<td>EC, &lt; 4</td>
<td>48 (74)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>203</td>
<td></td>
<td></td>
<td>144 (71)</td>
</tr>
<tr>
<td><strong>Cavernous malformations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bartolomei et al, 1999</td>
<td>49</td>
<td>24 mo</td>
<td>EC, 1</td>
<td>26 (53)</td>
</tr>
<tr>
<td>Kim et al, 2005</td>
<td>12</td>
<td>30 mo</td>
<td>Cessation</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Liscak et al, 2005</td>
<td>44</td>
<td>48 mo</td>
<td>Cessation</td>
<td>20 (45)</td>
</tr>
<tr>
<td>Liu et al, 2005</td>
<td>28</td>
<td>5.4 y</td>
<td>EC, &lt; 4</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Shih and Pan, 2005</td>
<td>16</td>
<td>46 mo</td>
<td>Cessation</td>
<td>4 (25)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>149</td>
<td></td>
<td></td>
<td>74 (50)</td>
</tr>
<tr>
<td><strong>Hypothalamic hamartomas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Régis et al, 2000</td>
<td>10</td>
<td>28 mo</td>
<td>Cessation</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Unger et al, 2002</td>
<td>4</td>
<td>12-68 mo</td>
<td>Cessation</td>
<td>0</td>
</tr>
<tr>
<td>Selch et al, 2005</td>
<td>3</td>
<td>17 mo</td>
<td>EC, 1</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Barajas et al, 2005</td>
<td>3</td>
<td>30-50 mo</td>
<td>Cessation</td>
<td>0</td>
</tr>
<tr>
<td>Régis et al, 2006</td>
<td>27</td>
<td>&gt; 3 y</td>
<td>Cessation</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Mathieu et al, 2006</td>
<td>4</td>
<td>22 mo</td>
<td>Cessation</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>51</td>
<td></td>
<td></td>
<td>16 (31)</td>
</tr>
</tbody>
</table>

Abbreviation: EC, Engel class.

a The study by Heikkinen et al used a proton beam accelerator and the study by Selch et al used a linear accelerator; all other studies used the Gamma Knife (Elekta AB, Stockholm, Sweden).
b Reported as mean or range.
c Definition of clinical seizure improvement.
d Pediatric patients only.

Table 1 shows a summary of radiosurgical treatment of HHS. Although the combined rate of 27% appears low, seizure remission alone underestimates the positive impact on overall morbidity and custodial care required in these cases of severe epilepsy. Behavioral outcomes have not been rigorously quantified, but every report on HHS in Table 1 notes that most patients experience marked improvement in behavior, sleep quality, and learning. In some cases, the treatment enables relatively normal participation in school.

A European, multicenter, prospective trial of GKS for HHS has enrolled 60 patients, 27 of whom have exceeded 3 years of follow-up. This study emphasizes the temporal evolution of seizure changes during the postoperative period. Within the first 2 months a slight improvement in seizure rate typically occurs. Seizures transiently worsen in frequency before reduction and remission occur. Behavioral improvements, along with electroencephalogram normalization, tend to occur in a more linear fashion. Morbidity is low, with no ill effects except for 1 instance of poikilothermia noted among the cases reported in Table 1. Some data also emphasize the importance of the marginal dose of radiation as noted in tumors and AVMs. Patients treated with doses exceeding 17 Gy to the margin of HHS have greater rates of seizure remission than those receiving less than 13 Gy. Use of GKS may be one of several nontraditional surgical approaches that can improve what is otherwise a devastating epileptic encephalopathy.
TREATMENT OF PHYSIOLOGIC EPILEPSIES

Mesial Temporal Lobe Epilepsy

Mesial temporal lobe epilepsy consists of atrophy, specific neuronal loss, and gliosis within the limbic system, most notably within the amygdala-hippocampus. Mesial temporal lobe epilepsy is the most frequent cause of medically intractable epilepsy in adults. The rationale for its treatment with GKS is less compelling than in the disorders discussed earlier because MTLE is amenable to open surgery.

Open surgery, however, has a small, but real, risk of perisurgical complications such as bleeding, infection, and postoperative pain. Second, open surgery is expensive. Although a formal cost comparison for epilepsy treatment has not been done, the average cost per patient for open microsurgery was nearly 50% more than that for GKS for treatment of similar disorders. Third, some of the reported adverse events of temporal lobectomy involve changes in results of neuropsychological testing. Fourth, some patients are reluctant to undergo elective open surgery with required inpatient stay and general anesthesia despite proven efficacy. Thus, GKS may offer a noninvasive alternative to open surgery in the pursuit of less postsurgical morbidity and less cost.

Unfortunately, initial attempts at epilepsy radiosurgery in Sweden were not encouraging.28 Barcia et al29 in 1994 described 11 patients treated for “idiopathic focal epilepsy”; only 4 became seizure-free. Régis and colleagues30 revived interest in GKS for MTLE in 1995 when their pilot studies showed high rates of seizure remission. Table 2 summarizes published cases; notably, all differ in treatment protocols and results, with most failing to achieve complete remission from seizures. 31-36 The variability in results of GKS therapy for MTLE underscores the difficulties in the determination of basic variables of anatomic target, dose, and target volume.

Anatomic targets in GKS for MTLE are the least variable factor. All of the studies in Table 2 specify that the 50% isodose volume contains regions thought most important in the generation of mesial seizures: the amygdala, the head and anterior body of the hippocampus, and the parahippocampal gyrus (Figure 1). Dose and target volume are more variable. Comparison of the studies listed in Table 2 suggests that low-dose protocols are less successful than higher-dose protocols. Volumeresponse curves from preliminary studies by Régis demonstrate a relatively steep curve that separates ineffective treatment from excessive toxicity stemming from radiation-provoked edema (Figure 2) (Jean Régis, MD, oral and written communication, October 17, 2005).

Régis et al36 outlined the typical postoperative course, and in most respects it follows the polyphasic course described after GKS for HHS.24 No significant clinical or neuroimaging changes occur until 9 to 12 months after surgery.30,34,36,37 Nearly all patients experience transient exacerbations in auras before seizures decrease or remit.36 The most dramatic drop in seizure rate occurs between 12 and 18 months, coinciding with the development and resolution of maximal changes on magnetic resonance images (Figure 3).

Other morbidities reported by Régis et al36 include visual field deficits in 52% of patients, mostly quadrant-anopia as usual after standard anterior temporal lobectomy. One subject had a hemianopia (indicating direct involvement of the optic tract) and another had mixed deficits.36 Other “transient minor morbidities” consisted of headache, nausea, vomiting, and depression. Headache requires special comment because it coincides in some subjects with postoperative edema.36 Corticosteroids, given in response to headache, visual field changes, or magnetic resonance imaging changes, were used in most of the patients included in Table 2, but no clear evidence supports specific guidelines for corticosteroid initiation, its effectiveness in treating symptoms, or its effects on eventual seizure remission. In fact, Régis et al36 reported that 38% of subjects were not treated with corticosteroids at any point in the postoperative course.

One important factor in consideration of GKS compared with open surgery is that the delayed effect of treatment may expose patients to the continued morbidity of ongoing seizures, including sudden unexpected death in epilepsy and traumatic injury. Two deaths occurred during the latency period in a case series of 5 patients treated with “low-dose” radiation (Table 2). Allowing enough time for maturation of the radiosurgical lesion may have allowed some patients treated with lower doses to demonstrate remission, given that animal models treated with lower doses demonstrated improvements at a slower rate than those treated with higher doses.36 Future trials of GKS may need to consider supplementary seizure pro-

Table 2. Seizure Remission Rates (Defined as Engel Class 1) of Stereotactic Surgery for Mesial Temporal Lobe Epilepsy

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Dose, Gy</th>
<th>Volume, mL</th>
<th>Lower Limit of Follow-up, mo</th>
<th>Remission, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Régis et al31</td>
<td>7</td>
<td>25</td>
<td>6.3-6.9</td>
<td>24</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Cmelak et al25b</td>
<td>1</td>
<td>15</td>
<td>NS</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Kawai et al33</td>
<td>2</td>
<td>18</td>
<td>6.2-8.7</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Srikiwilaikul et al34</td>
<td>5</td>
<td>20</td>
<td>6.1-8.7</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>McDonald et al36</td>
<td>5</td>
<td>20-24</td>
<td>4.3-5.2</td>
<td>27</td>
<td>NA</td>
</tr>
<tr>
<td>Régis et al36</td>
<td>21</td>
<td>24</td>
<td>5.5-9.0</td>
<td>24</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td>19 (46)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NS, not specified.

a All studies used the Gamma Knife (Elekta AB, Stockholm, Sweden). Treatment dose and volumes are estimated at the 50% isodose limit.

b Linear accelerator; dose and volume at 57% isodose limit.
phylaxis during the period of transient exacerbation of auras and seizures.

Beyond seizure efficacy, studies have begun to evaluate secondary outcome measures such as cognition and quality of life. Epileptic rats demonstrate no behavioral effects attributable to GKS. In humans, 3 reports of neuropsychological outcome after GKS for MTLE are available: the previously noted prospective, multicenter trial and 2 studies of small series of participants. Prospective trial results report no mean neurocognitive changes through a 2-year follow-up period. Similarly, Srikijvilai et al reported no group mean changes at 6 months of follow-up, although some individuals showed decline in at least 1 cognitive domain. McDonald et al reported on 27-month follow-up in 3 participants who underwent dominant-hemisphere low-dose GKS treatment. No long-term consistent changes in neurocognitive measures were found, although each patient showed decline in a measure of verbal memory. They concluded that neurocognitive changes after GKS appeared similar to those of anterior temporal lobectomy.

In summary, GKS for MTLE appears to have promise, but dose and relative benefits have yet to be clearly demarcated from those of open surgery. A National Institutes of Health–sponsored multicenter pilot study on the safety of GKS for MTLE has recently been completed. In that study, patients who would normally qualify for anterior temporal lobectomy for unilateral MTLE were randomized to either a 20- or 24-Gy dose. A total of 30 subjects were enrolled and followed up for 3 years. Preliminary results are promising, with safety well within that expected after routine GKS with favorable efficacy and neuropsychological profiles.

Other Nonlesional Epilepsies

There are no published data on the use of GKS for nonlesional neocortical loci. Because localization of seizure onset in these cases usually requires invasive techniques, the noninvasive nature of GKS loses some advantage. One may speculate that, if noninvasive localization and brain mapping were rigorous enough to identify loci and function of the neocortex, GKS may have a future role.
Resection of the corpus callosum decreases the severity and number of primary generalized or rapidly propagating secondarily generalized seizures in patients who are not otherwise good surgical candidates. Small case series report that improvement in seizures after GKS resection of the corpus callosum was comparable to that reported after open callosotomy, with lack of notable complications. The future role of GKS in corpus callosotomy may be more difficult to determine because the effectiveness of vagal nerve stimulation makes surgery a less attractive option.

CONCLUSIONS

In summary, GKS offers an alternative to open surgery in selected patients with epilepsy caused by mass lesions such as tumors or AVMs. The choice between open and noninvasive surgery, however, should still be guided by the difficulties presented by the lesion rather than to any epilepsy-specific characteristics of either surgical technique. On the other hand, GKS for the seizures arising from cavernous malformations appears to have a less than enthusiastic endorsement, given some studies’ findings of excessive rebleeding. In contrast, GKS for HHs appears promising given the combination of inaccessibility to traditional surgery, severe morbidity of gelastic epilepsy, and good safety profile.

Finally, recent trials suggest that certain protocols of GKS for MTLE may offer a noninvasive alternative to open surgery while yielding similar rates of seizure remission and favorable neuropsychological outcomes. Further work is needed to clarify whether remission rates or neurocognitive outcomes after GKS are comparable to those after anterior temporal lobectomy. One distinct disadvantage of GKS is the latency period required while the radiosurgical lesion develops. However, the noninvasive nature of GKS may prove to be an advantage to those who fear craniotomy or those with comorbid medical conditions that may prevent full anesthesia.

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Correspondence: Mark Quigg, MD, MSc, Department of Neurology, PO Box 800394, HSC, University of Virginia, Charlottesville, VA 22908 (quigg@virginia.edu).

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REFERENCES


