Gamma Knife thalamotomy for essential tremor

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Object. The purpose of this study was to evaluate the results following Gamma Knife thalamotomy (GKT) for medically refractory essential tremor in a series of patients in whom open surgical techniques were not desirable.

Methods. Thirty-one patients underwent GKT for disabling essential tremor after medical therapy had failed. Their mean age was 77 years. Most patients were elderly or had concomitant medical illnesses. A single 4-mm isocenter was used to target a maximum dose of 130 or 140 Gy to the nucleus ventralis intermedius. Items from the Fahn-Tolosa-Marin clinical tremor rating scale were used to grade tremor and handwriting before and after radiosurgery.

Results. The median follow-up was 36 months. In the group of 26 evaluable patients, the mean tremor score (± standard deviation) was 3.7 ± 0.1 preoperatively and 1.7 ± 0.3 after radiosurgery (p < 0.000015). The mean handwriting score was 2.8 ± 0.2 before GKT and 1.7 ± 0.2 afterward (p < 0.0002). After radiosurgery, 18 patients (69%) showed improvement in both action tremor and writing scores, 6 (23%) only in action tremor scores, and 3 (12%) in neither tremor nor writing. Permanent mild right hemiparesis and speech impairment developed in 1 patient 6 months after radiosurgery. Another patient had transient mild right hemiparesis and dysphagia.

Conclusions. Gamma Knife thalamotomy is a safe and effective therapy for medically refractory essential tremor. Its use is especially valuable for patients ineligible for radiofrequency thalamotomy or deep brain stimulation. Patients must be counseled on potential complications, including the low probability of a delayed neurological deficit. (DOI: 10.3171/JNS/2008/108/01/0111)

Key Words • essential tremor • Gamma Knife • radiosurgery • thalamotomy

Clinical Material and Methods

Essential tremor is the most common adult movement disorder. The hallmark of essential tremor is a progressive kinetic tremor of the arms. Those patients who seek medical attention are often forced to change employment or retire early, since symptoms are progressively disabling and lead to a significant loss of independence. For patients with severe essential tremor refractory to medical therapy, surgery is a viable option. Two alternative procedures for the treatment of disabling tremor include stereotactic radiofrequency thalamotomy and high-frequency DBS. Some patients, however, are poor candidates for invasive surgery, whether due to advanced age, use of anticoagulants, presence of coagulopathy, the presence of other serious medical comorbidities, or a combination of 2 or more of these considerations. In such cases GKT can be considered. The purpose of this study is to evaluate the safety and effectiveness of GKT for essential tremor.

Abbreviations used in this paper: AC = anterior commissure; DBS = deep brain stimulation; GKT = Gamma Knife thalamotomy; MR = magnetic resonance; PC = posterior commissure; VIM = nucleus ventralis intermedius.
Stereotactic radiosurgical thalamotomy was performed using the Model U, B, or C Leksell Gamma Knife. A dose of 130–140 Gy was delivered with a single 4-mm isocenter. Twenty-seven patients underwent a left radiosurgical thalamotomy (that is, dominant side). The right side was used for radiosurgery, a gamma angle of 60–70° was used to create an isocenter volume that more closely matched the shape of the VIM in the anterior–posterior and differentiative gray and white matter structures. Details of the MR imaging parameters are shown in Table 2.

The target in all cases was the VIM contralateral to the most affected limb. The VIM was targeted as follows: 1) anterior–posterior (1/4 of the AC–PC distance plus 1 mm anterior to the PC); 2) laterality (1/2 the width of the third ventricle plus 11 mm from the AC–PC line); and 3) superior–inferior (isocenter placed 2.5 mm superior to the AC–PC line). The laterality of the isocenter was adjusted to keep it medial to the internal capsule. The 20% isodose line of the 4-mm collimator was kept medial to the internal capsule. When the Model B or C Gamma Knife was used, selective beam blocking was performed to restrict the dose toward the internal capsule. A gamma angle of 110° was used to create an isocenter volume that more closely matched the shape of the VIM in the anterior–posterior and superior–inferior coordinates. When the Model U unit was used for radiosurgery, a gamma angle of 60–70° was used and no beam blocking was necessary.

Stereotactic radiosurgical thalamotomy was performed using the Model U, B, or C Leksell Gamma Knife. A maximum dose of 130–140 Gy was delivered with a single 4-mm isocenter. Twenty-seven patients underwent a left radiosurgical thalamotomy (that is, dominant side). The right VIM was targeted when left arm tremor was more prominent. Items from the Fahn-Tolosa-Marin clinical tremor rating scale were used to assess pre- and postoperative tremor (Table 3). The preoperative mean Fahn-Tolosa-Marin tremor score (± standard deviation) was 3.7 ± 0.1; after radiosurgery the mean score fell to 1.7 ± 0.3. The pre- and post-GKT mean handwriting scores were 2.8 ± 0.2 and 1.7 ± 0.2, respectively. The difference between pre- and post-GKT scores for both tremor and writing was found to be statistically significant via the Wilcoxon signed-rank test (tremor p < 0.000015; handwriting p < 0.0002).

After radiosurgery, 18 patients (69%) showed improvement in both action tremor and writing scores, 6 (23%) in only action tremor scores, and 3 (12%) in neither tremor nor writing. In patients who had improvement in both action and writing scores, a reduction in disability was noted. Patients continued to follow their medication regimen until consistent tremor relief was achieved. One patient who experienced tremor relief for several years died of lung cancer 56 months after treatment. Another elderly patient who reported significant improvement in tremor and handwriting after radiosurgery died of lung cancer 29 months after treatment. Transient mild right hemiparesis and dysphagia developed in one patient. A second patient suffered a mild right hemiparesis and speech impairment months after radiosurgery (Fig. 3). An MR imaging study showed a larger than expected volume of contrast enhancement, which resolved over the next 18 months. There were no other complications of the procedure. Thus, the complication rate for this study was 7.7%, with both patients who suffered complications eventually making a good recovery. Multivariate testing showed no correlation with outcome for age, sex, radiation dose, side of thalamotomy, or presence of leg or head tremor.

Discussion

For those patients in whom medical treatment fails to control essential tremor, options include radiofrequency thalamotomy, high-frequency DBS, or GKT. The VIM is the thalamic relay nucleus of the cerebello-thalamocortical pathway mediating cerebellar control of the motor cortex, and all of these procedures have been thought to act by disrupting the function of this pathway. This may be a simplistic interpretation of the mechanism of the therapeutic effect, as DBS appears to facilitate activity of the pathway.

For certain patients (including the elderly, those taking anticoagulants or with coagulopathy, and/or those with medical comorbidities), invasive procedures such as radiofrequency thalamotomy and DBS may present unacceptable risks. As outlined in Table 1, patient age and the pres-
ence of medical comorbidities were the 2 most common factors considered in choosing GKT over other surgical alternatives. The mean patient age of 77 years in this study is older than the mean age of 60 years in our DBS case series. However, the oldest patient in the DBS study was 82 years old and was in good overall health.

In this study, GKT proved to be effective in improving medically refractory essential tremor in a case series involving predominantly elderly patients. In 18 of the cases (69%) both action tremor and writing scores improved, and action tremor scores improved in an additional 6 (23%). Thirteen patients (50%) had either no or only slight intermittent tremor in the affected extremity after GKT, and 90% had some degree of clinically significant tremor improvement. Although we did not score head tremor, many patients with neck, jaw, or head tremor had improvement of that symptom. Overall, the mean Fahn-Tolosa-Marin tremor score improved from 3.7 ± 0.1 to 1.7 ± 0.3 (p < 0.000015). Young et al. published results from 8 cases in which patients with essential tremor underwent GKT and noted an 87.5% rate of clinical improvement (62.5% complete tremor arrest, 25% nearly tremor free) and 12.5% failure rate. Results from that smaller series are comparable to those of the present study.

Fig. 1. Axial (A–C) and coronal (D) MR images. A: Image showing left VIM target (cross-hair). B: Image obtained 3 months post-GKT. The thalamotomy lesion is clearly seen. C: Image obtained 28 months post-GKT. The thalamotomy lesion appears slightly larger. D: Image obtained 28 months post-GKT showing thalamotomy lesion.
We previously reported early results after GKT in 8 patients with essential tremor and noted complete tremor arrest in 75% and > 50% improvement in 25%. The Fahn-Tolosa-Marin grades of tremor, handwriting, and drawing showed improvement after radiosurgery. We hypothesized that radiation beyond the 50% isodose line may affect surrounding kinesthetic cells without destroying them; therefore, the effect of GKT may be due to both direct tissue destruction and alteration of the “tremor region.” We realize that the target effect may reach beyond the volume of the VIM. Similarly, the spread of current in DBS may reach outside the nucleus into the regional thalamus, which could account for the sensory symptoms noted by some patients.

Young et al. later reported long-term results of GKT for the treatment of essential tremor. At 1 year postprocedure, results in 51 patients were evaluated, and in this series 78% were tremor free, 14% were nearly tremor free, and in 8% tremor had not improved. At 4 years postprocedure 71% were tremor free, 18% were nearly tremor free, and treatment had failed in 6%. The mean Fahn-Tolosa-Marin scores for action tremor were 3.4 pre-GKT and 0.7, 0.8, 0.9 at 6, 12, and 48 months post-GKT, respectively. The authors reported mean Fahn-Tolosa-Marin scores for handwriting as 3.1 pre-GKT and 0.7, 0.5, and 0.8 at 6, 12, and 48 months post-GKT, respectively. In the current study, the mean handwriting scores were 2.8 ± 0.2 before GKT and 1.7 ± 0.2 after GKT (p < 0.0002). The mean Fahn-Tolosa-Marin scores for action tremor reported by Young et al. were low even 48 months after radiosurgery. The differences between their scores and those in the present study may be due to differences in target location, inaccuracies in reporting scores, and/or selection bias. Their finding of 89% of patients being tremor free or nearly tremor free at 4 years post-GKT is remarkable but should be interpreted with caution, since follow-up involved only 16 of 51 patients. More studies with higher numbers of patients and longer follow-up would be a valuable addition to the existing literature.

Gamma Knife thalamotomy for suppression of action tremor has not been directly compared with DBS. Benabid et al. implanted thalamic DBS units into 20 patients with tremor, and at 3-month follow-up found that complete or near-complete relief of tremor had been achieved in 75%. At the most recent follow-up the success rate was 61%. Other groups have documented improved outcomes with

<table>
<thead>
<tr>
<th>Grades</th>
<th>Clinical Assessment</th>
<th>Pre-GKT</th>
<th>Post-GKT</th>
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<tbody>
<tr>
<td>tremor</td>
<td>0</td>
<td>no tremor</td>
<td>0  3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>slight: barely perceivable, may be intermittent</td>
<td>0  10</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>moderate: amplitude &lt;2 cm, may be intermittent</td>
<td>0  8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>marked: amplitude 2–4 cm</td>
<td>9  3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>severe: amplitude &gt;4 cm</td>
<td>17  2</td>
</tr>
<tr>
<td>handwriting</td>
<td>0</td>
<td>normal</td>
<td>1  3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>mildly abnormal: slightly untidy, tremulous</td>
<td>1  11</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>moderately abnormal: legible, but w/ considerable tremor</td>
<td>5  6</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>markedly illegible</td>
<td>15  4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>severely abnormal: patient unable to keep pencil/pen on paper w/other hand</td>
<td>4  2</td>
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DBS for essential tremor with at least 2-year follow-up. Complications after DBS procedures include lead breakage, wound infection, electrode migration, and intracranial hemorrhage. Side effects from stimulation include dysarthria, paresthesias, dystonia, balance disturbance, ataxia, and limb weakness. Nevertheless, the ability to adjust or remove a DBS system is an advantage in certain patients; during open surgery, intraoperative physiological data may facilitate better target localization. Several younger patients in our earlier radiosurgery series were good DBS candidates but chose radiosurgery instead to avoid an open operation and placement of hardware. One 56-year-old dental surgeon with familial essential tremor, who had sought consultation at multiple movement disorder centers, chose radiosurgery for himself and his 82-year-old mother after refusing DBS.

Stereotactic radiofrequency thalamotomy for essential tremor has a reported success rate of 73–93%, which again is comparable to GKT. Compared with DBS, however, open thalamotomy may be associated with poorer functional outcome and more adverse effects. In cases of tremor recurrence, further surgery may be necessary. We have
stopped using this lesioning technique in favor of radiosurgical thalamotomy.

Imaging Changes

Review of post-GKT MR images obtained in our patients usually showed a 4- to 5-mm round, well-circumscribed lesion with peripheral contrast enhancement surrounding a low-signal region (Fig. 1). A localized area of high signal (seen on long relaxation-time studies) may be indicative of the peripheral neuronal effect, manifested as an increase in intra- or extracellular water. The 2 patients with complications had different MR imaging findings (Fig. 3). Although the enhancing lesion created in 1 patient was unexpectedly large (Fig. 3A and B), complete resolution was seen in subsequent images. This improvement indicated that the response was related to temporary blood-brain barrier changes and not to permanent radiation necrosis. Indeed, Ohye et al.14 studied the lesion produced by GKT in the treatment of various types of tremor, including 11 cases of essential tremor, and found 2 types. The atypical type had an irregularly shaped area of high signal that usually extended into the internal capsule or medial thalamic region, often involving streaking along the thalamo-capsular border. This appearance is similar to the peripheral effect described above. The formation of this lesion could not be related to patient age, cortical atrophy, and symptom type (tremor, rigidity, or dystonia).

Others have corroborated the finding of 2 distinct types of lesions, one desirable and the other not. Friedman et al.4 found that most GKT lesions at 3 months post radiosurgery were \( \leq 5 \) mm in diameter. They noted, however, that patients with ring-enhancing lesions that measure \( \geq 7 \) mm in diameter at 3 months post-GKT may be at risk of more extensive radiation effects and vasogenic edema. In their experience, the development of symptomatic radiation effects was idiosyncratic and occurred in approximately 20% of patients. Okun et al.15 reported complications in 8 patients who underwent Gamma Knife radiosurgery at higher radiation doses (150–200 Gy) and found significant and persistent T2-weighted and FLAIR signal changes consistent with clinical findings.

Ohye and colleagues13 compared lesion size, treatment time, and clinical response time of GKT before and after reloading of radioactive cobalt. Interestingly, they noted significantly smaller thalamic lesions, shorter irradiation times, and decreased time to clinical effect after reloading of the cobalt sources. They hypothesized that increased dose rate was responsible for the observed phenomena. In our patients, the typical response time was 1–4 months, although 3 patients had significant tremor improvement within 2 days. It has been proposed that up to 2% of the population may be hypersensitive to radiation. At present no testing can identify these individuals, although carriers of the ataxia telangiectasia gene are known to have increased radiation sensitivity. Microelectrode recording for target localization was not used in our study and, in fact, its use would defeat the purpose of using a minimally invasive approach. Sato et al.17 used depth recording in 4 tremor patients to indirectly determine the optimum target in GKT. Not surprisingly, within the expected target area they found rhythmic discharge time-locked to tremor, kinesthetic neurons, or both. The delay to therapeutic effect should not be a major issue for patients, since most of them have been living with essential tremor for many years. More research is required to determine if the “time to effect” can be decreased in a predictable fashion. Further investigation into exactly why the delay occurs is warranted.

Failure and Morbidity

In the current study there were 3 patients (15%) whose symptoms did not respond to GKT. They included a 65-year-old man, a 52-year-old man, and a 71-year-old man, with follow-up at 65, 37, and 9 months, respectively. In the youngest of these 3 patients, prior DBS had failed after an initial lead breakage with revision, and the other 2 patients did not seek additional surgery although 1 was offered DBS. In all 3 the radiosurgery was left-sided and entailed a single dose of 140 Gy. Whether failures were related to targeting, a lesion that was too small and did not affect enough kinesthetic cells or some other factor is not known. Ohye et al.12 discerned an important technical limit of GKT. Although he was managing mostly parkinsonian tremor and only 5 cases of essential tremor, he noted that 5 patients had unsatisfactory outcomes (whether they had parkinsonian tremor or essential tremor was not specified). Some of these patients underwent subsequent open surgery with microelectrode recording. It was found that perilesional tremor-related neurons had escaped irradiation and were viable. Ohye et al. explain that this occurred because they had not chosen the ideal target in an effort to avoid delivering high doses of radiation to the internal capsule.

The complication rate in our study was 7.7%. One patient had a mild right hemiparesis and speech impairment post radiosurgery. Another patient had transient mild right hemiparesis and dysphagia. Both patients subsequently improved, and only 1 of the 2 had mild persistent deficits. Young and colleagues20 reported a permanent complication rate for GKT of 1.3% (2 of 158 patients). One patient had contralateral paresthesias of the face and upper extremity. The other patient had mild weakness of the contralateral extremities and very minimal dysphagia. Siderowf et al.19 reported the case of a 59-year-old man who underwent left GKT for essential tremor and experienced significant procedure-related complications. Although this patient had a good response 1 month postprocedure, he developed progressive rest and action tremor 7–12 months after GKT. In addition, he experienced right-sided dystonia and numbness, as well as choreoathetosis in the right arm. Review of the MR images of patient’s brain obtained at 11 months post-GKT demonstrated an enhancing lesion involving the left thalamus, basal ganglia, and midbrain. Unfortunately, the details of the radiosurgery plan were unavailable.

The Quality Standards Subcommittee of the American Academy of Neurology recently stated disadvantages of GKT, including dependence on anatomical imaging, delay of weeks to months for clinical results to occur, and risk of delayed progressive neurological deficits.25 They concluded that there is insufficient evidence to make recommendations regarding the use of GKT in the treatment of essential tremor.21 The overwhelming majority of post-GKT MR imaging studies depict a lesion in exactly the planned location with the expected appearance. We used targeting identical to what we have used and reported for DBS.7 The
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advantage of radiosurgery is that tremor relief can be provided to patients (particularly the elderly) who would not be good candidates for DBS.

Conclusions

We believe that GKT is an effective therapy for medically refractory essential tremor. Its use is particularly desirable in cases unsuitable for open stereotactic surgery, including those involving patients of advanced age, those with coagulopathy, those being treated with anticoagulation therapy, and those with other medical comorbidities. For such patients, there may be no other acceptable options. Patients must be counseled regarding potential complications, including the low possibility of a delayed neurological deficit. Future research should include controlled, prospective trials to delineate the optimum parameters for GKT (for example, patient selection, radiosurgical dose, dose rate) and to determine the safety and efficacy of GKT as compared with other modalities. Adopting standard outcome measures will be crucial to the effective comparison of results from different research groups.

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References


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