Tremor is a common movement disorder that can have disabling effects on daily living, impact employment, and reduce quality of life. Medical management strategies are helpful for some patients, but many individuals either become unresponsive to medication or derive no benefit from it. For decades, the VIM nucleus has been ablated to improve contralateral tremor, first using RFT and more recently using DBS, to provide effective and sustained control of essential or parkinsonian tremor. In the early years, target selection was based on indirect visualization of landmarks for the VIM using air or contrast encephalography. After 1980, many centers switched to using CT scanning to improve target selection. However, MRI has supplanted such techniques because of its enhanced contrast and spatial depiction.

Initial ablation of the target nucleus was performed using cryosurgery, hot wax, and agents such as phenol. Such exploratory methods evolved to the more widespread adoption of stereotactic RFT to create a controlled heat lesion of predictable volume. A trend to manage such patients with DBS emerged more than 15 years ago; more recently, the use of focused ultrasound has been promoted to create a heat lesion of the same target.

As the population ages, patients with tremor in whom medical management fails are more likely to undergo surgical management. The most common surgical procedures are RFT and DBS. There are data showing that outcomes of DBS and RFT are similar. Gamma Knife thalamotomy is another option that has been available in recent years. The purpose of this study was to evaluate the clinical outcomes and complications of Gamma Knife thalamotomy in the MRI era.
Stereotactic Radiosurgery Technique

Patient Cohort

For ET, with clinical improvement rates between 70% and 80%, comparable to stereotactic RFT.24 The purpose of the present study was to expand the clinical outcome analysis in a series of patients with disabling tremor, in all of whom target selection had been performed since the incorporation of MRI for target selection.

Methods

This research was approved by the University of Pittsburgh Institutional Review Board. There were no external sources of funding for this study.

Patient Cohort

The study group consisted of 86 patients (51 males and 35 females) whose mean age was 71 years. Two patients (one with ET and one with MS) underwent staged bilateral procedures, bringing the number of overall procedures to 88. In the 48 patients with ET, the mean age was 74 years. In the 11 patients with a diagnosis of MS the mean age was 45 years, and in the 27 patients with PD the mean age was 76 years. All patients were referred for consideration of surgery because of progressive or unresponsive tremor refractory to medical management. In most patients with ET, trials of propranolol and Myrsolines failed. In recent years, trials of topiramate and levetiracetam also failed in most patients. Patients with other signs and symptoms of PD continued to be managed with standard agents such as carbidopa/levodopa. In patients with MS-related tremor, the condition proved generally unresponsive to medical therapy for tremor. There were no specific indications for radiosurgical thalamotomy compared with other surgical options. It was considered in patients thought to be poor candidates for DBS either due to health or diagnosis (that is, MS). Thus, exclusion criteria for other procedures raised the option of radiosurgery. In rare cases patient choice was the indication.

Patients were considered potential surgical candidates if their tremor resulted in significant limitations in activities of daily living including handwriting and eating. Although some patients had bilateral tremor, they reported that the disability of their tremor was greatest in their dominant hand. Preoperative FTM tremor rating scale scores were obtained and showed a wide spectrum of tremor-related disability (Table 1).7

Stereotactic Radiosurgery Technique

During stereotactic radiosurgery, the Leksell model G stereotactic coordinate frame (Elekta AB) was secured to the patient’s head using a local anesthetic supplemented by brief conscious sedation using fentanyl and midazolam. High-resolution MR images were obtained using a 1.5- or 3.0-T scanner. Contrast-enhanced volume acquisition MRI (with images at 1-mm intervals) was performed for stereotactic targeting through the thalamus and midbrain to identify the AC, PC, and the third ventricle. An axial fast inversion recovery sequence was then obtained to better identify the internal capsule and differentiate gray and white matter structures. The target was the posterior and inferior aspect of the VIM of the contralateral limb most affected by tremor. The VIM was targeted as follows: 1) x coordinate: laterality (50% of the width of the third ventricle + 11 mm from the AC-PC line); 2) y coordinate: anterior-posterior (25% of the AC-PC distance + 1 mm anterior to the PC); and 3) z coordinate: superior-inferior (isocenter placed 2.5 mm superior to the AC-PC line). The lateral position 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, C, 4C, or Perfexion Gamma Knife was used, selective beam or sector blocking was performed to restrict the dose in the region of the internal capsule, which can be well visualized by MRI. Magnetic resonance imaging also allows accurate measurement of the thalamic width, which facilitates adjustment of the medial-lateral x coordinate. 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. A maximum dose of 130–140 Gy was delivered with a single 4-mm isocenter.

Follow-Up

We reviewed the medical and imaging records of 86 patients who underwent GKT for treatment of their tremor during the recent 15-year era of MRI-based target selection (1996–2011). Postradiosurgery imaging was conducted routinely at 4 months. Three functional items from the FTM clinical tremor rating scale including tremor amplitude, handwriting ability, and ability to drink from a cup were evaluated in all patients both preoperatively and during follow-up appointments. The clinical ratings were derived from chart notes recorded by the study neurosurgeon or referring neurologist, detailing the amplitude of tremor, ability to drink, and handwriting ability in the form of a handwriting sample. The tremor rating score used was validated by blinded comparison of reviewer scores. However, use of this rating scale during a telephone discussion was believed to be less reliable. We compared the 3 tremor subscores before and after radiosurgery for individual patients and compared group scores among the 3 tremor etiologies.

A p value of 0.05 was set for statistical comparison among tremor types.

Results

The median follow-up after GKT was 11.5 months (range 1–152 months). All reported patients had pre- and postoperative testing. We excluded those without any follow-up appointments and/or those who died prior to a follow-up appointment; 86 patients remained after these
exclusions. Of 97 total patients managed with GKT for tremor between 1996 and 2011, we excluded 11 patients who lacked both a follow-up appointment and were unreachable later by phone, leaving 86 patients for our analysis. Of the 17 patients for whom we recorded phone follow-up data points, only 2 (12%) had no in-person evaluations. Therefore, for these 2 patients information recorded via phone call is the only follow-up data we have. One of these patients was evaluated at 5 years. The remaining 15 patients (88%) who were phoned had their scores used to track changes in functional ability, to update data since the last office-based assessment.

The FTM clinical tremor rating scale was used to assess pre- and postoperative tremor, handwriting, and ability to drink from a cup (Fig. 1). Overall, the preoperative and postoperative mean tremor scores were 3.3 ± 0.8 and 1.8 ± 1.2, respectively (p < 0.00001). The mean handwriting scores were 2.8 ± 0.8 and 1.6 ± 1.0, respectively (p < 0.00001). The mean preoperative drinking scores were 3.1 ± 0.8 and 1.8 ± 1.1, respectively (p < 0.00001) (Table 1). After radiosurgery, 57 patients (66%) exhibited improvement in all 3 assessed scores, 21 patients (24%) had no improvement in any of the assessed scores, 2 patients (2%) in just 1 score, and 16 patients (18%) who were phoned had their scores used to track changes in functional ability, to update data since the last office-based assessment.

Among the 48 patients with ET, the mean preoperative FTM writing score was 2.7 ± 0.8 and mean postoperative writing score was 1.4 ± 1.1 (p < 0.0001). The tremor score was 3.3 ± 0.8 preoperatively and 1.8 ± 1.2 postoperatively (p < 0.00001). The water-drinking score changed from 2.4 ± 0.8 preoperatively to 1.3 ± 0.9 postoperatively (p < 0.003). Mean tremor scores were 3.9 ± 0.3 before treatment and 2.5 ± 1.0 at the most recent follow-up (p < 0.003) (Table 4). Patients in each tremor subset showed similar improvements in functional scores post-GKT. Improvements in FTM score after treatment for all scores (writing, tremor, and drinking) and tremor subsets (ET, PD, or MS) varied from 1.1 to 1.5, with similar scores before and after radiosurgery for the ET and PD subsets. Patients with MS had significantly higher preoperative scores, but analysis demonstrated a similar FTM score improvement after GKT—an improvement of 1.3 in writing score, 1.4 in tremor score, and 1.4 in the drinking score.

Two patients experienced temporary contralateral hemiparesis 6 months after GKT, 1 patient experienced dysphagia after 8 months, and 1 patient described a peripheral burning sensation with left-sided facial numbness.

The thalamotomy lesion that developed in patients diagnosed with ET, 20 (42%) demonstrated either complete resolution or a barely perceivable tremor after GKT. One patient with ET underwent insertion of a contralateral DBS system 2 years later and did well.

Among 27 patients with PD, the mean FTM writing score changed from 2.4 ± 0.6 preoperatively to 1.3 ± 0.9 postoperatively (p < 0.0001). The mean tremor score was 3.0 ± 0.8 before GKT and 1.5 ± 1.1 after GKT (p < 0.0001), and the mean water-drinking score was 2.9 ± 0.8 before treatment and after treatment 1.5 ± 1.0 (p < 0.0001) (Table 3). Analysis of the results for the 11 patients with MS showed mean writing scores of 3.7 ± 0.5 before GKT and 2.4 ± 0.8 after GKT (p < 0.003). Mean tremor scores were 3.9 ± 0.3 preoperatively and 2.5 ± 0.9 postoperatively (p < 0.001). Mean FTM drinking scores were 3.9 ± 0.3 before treatment and 2.5 ± 1.0 at the most recent follow-up (p < 0.003).

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The thalamotomy lesion that developed in patients diagnosed with ET, 20 (42%) demonstrated either complete resolution or a barely perceivable tremor after GKT. One patient with ET underwent insertion of a contralateral DBS system 2 years later and did well.
gery images were obtained routinely at 4 months. The mean contrast-enhanced short-echo time MRI-measured lesion diameter was 5 mm. When contrast-enhanced CT was used for follow-up, a similar lesion size was identified. Surrounding changes on FLAIR imaging were seen in all patients with MRI. Few patients underwent MRI after 1 year, but persistent contrast-enhanced lesions could be seen within Years 1–2, with regression of enhancement after Year 2. Magnetic resonance imaging was requested 4 months following radiosurgery and was not routinely repeated unless new symptoms developed, because in an early cohort of patients the observed lesions remained stable for 2 years and then decreased in size. The patients who experienced any complication had the onset of symptoms beginning at 6 months after thalamotomy. Imaging performed at that time showed evidence of larger contrast-enhancing lesions due to blood-brain barrier disruption with inflammation. These changes later regressed over the next year.

Discussion

Rationale for Radiosurgical Thalamotomy

Currently, thalamic DBS may be the commonest surgical procedure for medically refractory essential or parkinsonian tremor where it is available. The value of DBS in MS-related tremor is not clear because tremor relief is modest and often not lasting. Stereotactic RFT is still performed where DBS may not be available or affordable. Both procedures are rarely performed in patients older than 80 years or those with medical comorbidities in whom RFT is thought to be associated with unacceptable risk. For such patients, stereotactic radiosurgical thalamotomy using the Gamma Knife is an important option. Prior studies, although few in number, have demonstrated a significant improvement in tremor control. However, this procedure remains underutilized. During the last 15 years, target selection has improved as MRI technologies have advanced.

However, it is not just the ability to perform radiosurgery in older patients or those with significant additional risk factors that makes such a minimally invasive strategy attractive. The radiobiological effect of the radiosurgical lesion is unique. The effect consists of a limited central target necrosis (3–4 mm in diameter) where the highest dose is delivered. This central zone is surrounded by a nonnecrotic peripheral or halo effect that may also provide therapeutic benefit to thalamic cells generating tremor. This peripheral effect, which consists of astrogliosis and mild vascular changes (hyalinization of blood vessels), has been well characterized in subhuman primate models of radiosurgery. Indeed, we think that this regional effect allows radiosurgical targeting to result in a larger therapeutic volume than that obtained during radiofrequency or other heat lesioning techniques. This benefit largely addresses the primary criticism of tremor ablative radiosurgery—that is, the lack of intraoperative electrophysiology target confirmation.

Importance of MRI-Based Targeting

As with the majority of functional neurosurgery procedures, precision of anatomical targets is key to successful interventions and avoidance of complications. The critical anatomical structures near the VIM nucleus must be avoided, and with higher-definition MRI sequences, accurate targeting of this region can be performed safely. Computed tomography targeting, however, is still performed today in patients who have pacemakers or other contraindications to MRI. The accuracy of their VIM
Gamma Knife thalamotomy for tremor

targeting is inherently less than it is with MRI, but the thalamotomy can still be performed with relative safety.

Critical Analysis of Results of Radiosurgical Thalamotomy

In the present study, GKT in the modern era of MRI-based targeting proved to be effective in improving medically refractory tremor associated with ET, PD, and MS. In 70 patients (81%), at least one of the assessed scores was improved following GKT. Of these 70 patients, the median follow-up duration before improvement was 4 months.

A previous series of 26 patients with ET undergoing GKT showed that 90% of patients had some degree of tremor improvement, with 50% showing either no or only slight intermittent tremor after GKT.3 The authors of a smaller series of 8 cases in which patients with ET underwent GKT noted an 87.5% rate of clinical improvement (62.5% complete tremor arrest, 25% nearly tremor free).1 A recent prospective multicenter study from Japan of 72 patients (with PD or MS) found that 81% of patients had excellent or good results.8 Results from each of these studies are comparable to those of the present study, in which 81% of the patients demonstrated some degree of clinically significant tremor improvement.

One study of 18 patients (with ET and PD) using doses of 130–140 Gy found significant improvements in FTM scores for activities of daily living but not tremor.9

In each disease subset, GKT provided statistically significant improvements in FTM writing, tremor, and drinking scores. Similar results were seen in patients with ET and PD. Interestingly, patients with MS who underwent GKT had preoperative scores notably higher than those of the ET and PD patients, indicating that the tremor was more severe at the time of referral. Most MS patients had a coarse, jerking tremor, causing them to often bang their arm and hand against a wheelchair armrest or bedrail. Despite this difference, we found that MS patients had FTM scoring improvements similar to the ET and PD subsets of patients. However, the clinical significance of the MS score reductions, from a range of 3.7–3.9 preoperatively to one of 2.4–2.5 post-GKT, is perhaps not as important to the patient functionally as the scoring improvements seen in ET and PD patients (for whom the final post-GKT scores were in the range of 1.2–1.5).

The severity of tremor was lessened, but the ability for the patient to perform tasks was variable depending on other MS-related deficits.

Complication Assessment and Avoidance

The complications we observed in this patient series, though few, raise several issues with regard to GKT. The radiation effect of GKT in some patients caused a larger than required response that led to inflammation and local mass effect on the internal capsule, with subsequent motor or sensory deficits. These deficits were not permanent and responded to a course of high-dose corticosteroids. There was no obvious flaw in technique in any of these patients, but the presence of a larger lesion was only noted after clinical manifestations were observed. It is possible that other patients had such transient expansion of the radiobiological effect but remained asymptomatic.

Maintenance of Tremor Relief

We studied the maintenance of tremor relief over time. In the current study 5 patients (6%) experienced improved symptoms and tremor scores at initial follow-up but the initial benefit waned over time. The median initial follow-up time to improved scores was 4 months, while the median time that scores later worsened was 23 months. These patients included a 70-year-old man, an 85-year-old man, a 90-year-old woman, a 57-year-old woman, and a 71-year-old man. Four such patients had ET and one had MS. These patients represented a unique group who experienced short-term improvement of tremor symptoms after GKT but who did not sustain that level of improvement. At their most recent follow-up, statuses in 3 of these patients had returned entirely to their pre-GKT scores, while scores in the other 2 patients were maintained and were better than those determined before radiosurgery. We think that radiosurgery provides tremor control that is longer lasting than that seen after RFT.

Some patients who undergo RFT develop early symptom recurrence once the perilesional edema effect resolves. Indeed, the final thermal lesion may be too small. In DBS-treated patients, the need to increase the stimulation energy over time is common. The biology of the radiosurgical effect may be the reason why cells involved in tremor remain controlled.

Limitations of the Present Study

The limitations are related to a variability in outcome documentation, because many patients lived at a distance and not all maintained follow-up at our center. This study used patients as their own controls and did not include an additional control group such as best medical therapy or DBS.

Conclusions

In the era of MRI, we found that GKT for tremor in a group of patients who are elderly or high risk if treated with DBS or RFT can have significant benefit. Further clinical experience in the use of GKT for medically refractory tremor is warranted. One question to evaluate is whether a higher dose (for example, 150 Gy) may improve or sustain tremor relief. At present we believe that GKT is an underutilized approach, appropriate for elderly patients with disabling tremor and those with other increased surgical risk factors.

Disclosure

Dr. Kondziolka is a consultant for Elekta AB, and Dr. Lunsford is consultant for and shareholder in Elekta AB.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kondziolka. Statistical analysis: all authors. Administrative/technical/material support: Kondziolka, Kooshkabadi, Lunsford, Tonetti. Study supervision: Kondziolka.
References