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Clinical Outcomes of Gamma Knife Radiosurgery in the Treatment of Patients with Tremors

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Abstract

Patients who suffer from tremors are initially treated with pharmaceuticals. Although medication has proven to be effective in achieving tremor control for some patients, there is still a fraction of patients who seek neurosurgical alternatives due to unacceptable tremor relief or side-effects from the prescribed drugs. Invasive neurosurgical procedures include radiofrequency thalamotomy and in recent years deep brain stimulation. However, patients who have advanced cardiac or respiratory disease, patients who use anticoagulants and patients who are of advanced age are not qualified candidates for neurosurgery. An alternative modality for lesioning intracranial structures is stereotactic radiosurgery using the Gamma Knife. The Gamma Knife is a Cobalt-60 based machine, with 201 separate 4 to18 mm collimator openings that emits multiple gamma rays that converge on a focal point in the brain specified by computer planning. Since its introduction by Leksell, the role of Gamma Knife radiosurgery as a management approach for patients diagnosed with tremors is continuously increasing. This article will review the efficacy of GKRS in the management of tremors, as well as describe the treatment planning and methods associated with this evolving treatment strategy.

Keywords: Gamma Knife; Stereotactic radiosurgery; Essential tremor; Parkinsonian tremor.

Abbreviations: CT, computed tomography; DBS, deep brain stimulation; ET, essential tremor; GKRS, Gamma Knife radiosurgery; GKT, Gamma Knife thalamotomy; MRI, magnetic resonance imaging; PD, Parkinson's Disease; RF, radiofrequency; VIM, ventralis intermedius nucleus.

Introduction

Patients who suffer from tremors are initially treated with medication in the form of beta-blockers, botulinum toxin injections, or anti-seizure drugs [1]. However, these pharmaceuticals are contraindicated for a large number of patients with specific comorbidities and are known to come with many bothersome side-effects [1]. For patients where medication has failed, invasive neurosurgical procedures such as deep brain stimulation (DBS) and radiofrequency (RF) thalamotomy are the next line of treatment for tremor patients. Historically, RF thalamotomy has been the most common invasive neurosurgical procedure in the management of patients who have a disabling tremor [1]. In 1997, The Food and Drug Administration approved DBS of the thalamus as a management approach for parkinsonian and essential tremor [2]. Since that time, numerous published series have reported positive results when using DBS for tremor relief [3]. Although it has proven to be a successful treatment, DBS puts the patient at risk for pulmonary embolism, subcortical hemorrhage, venous infarction, seizure, cerebrospinal fluid leak, skin erosion, and death [2]. In addition, DBS is contraindicated for patients who have advanced cardiac or respiratory disease, who use anticoagulants, and who are of advanced age [3].

Thalamotomy using Gamma Knife radiosurgery (GKRS) is an alternative modality for lesioning intracranial structures. The Gamma Knife's main functional unit is Cobalt-60, which produces multiple gamma rays that are emitted on a focal point in the cranium with precision through 201 separate 4 to 18 mm collimator openings. Gamma Knife thalamotomy (GKT) targets the ventralis intermedius (VIM) nucleus of the thalamus and is able to treat tremors of various etiologies, including essential tremor (ET), parkinsonian tremor, multiple sclerosis (MS) tremor, tremor following a cerebral infarction, and tremor related to encephalitis [1]. Interestingly, treating movement disorders with GKRS is not a new concept and is a procedure first performed by Professor Lars Leksell in the 1960's [4]. Since the advent of computed tomography (CT) scans and later magnetic resonance imaging (MRI), GKRS has evolved significantly in the treatment of patients with tremors. Furthermore, GKRS has been proven to be associated with a relatively low incidence of procedure-related complications and is an attractive management approach for medication intolerable patients who are not qualified candidates for neurosurgery and for patients who prefer the minimally-invasive nature of radiosurgery. Because of those reasons, we present a modern review of the literature analyzing the efficacy of GKT in the management of tremors, as well as describe the treatment planning and methods associated with this treatment option.

Review of gamma knife thalamotomy efficacy

Although ET does not decrease the life expectancy of afflicted

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patients, many suffer debilitating consequences due to the negative effects this condition has on their social and mental wellness [1]. For this reason, determining optimal treatments for specific subsets of patients with ET is imperative for clinicians [1]. Kondziolka et al. [5] treated 31 medical and surgical refractory ET patients with GKT. With a median follow-up of 36 months, the authors reported statistically significant improvements in both the mean tremor score (P < 0.000015) and mean handwriting score (P < 0.0002) following the procedure. Of the evaluable patients, 18 (69%) experienced improvements in their action tremor and handwriting scores, 6 (23%) experienced improvements in their action tremor only, and 3 (12%) did not experience improvements in either variable. Two patients suffered from radiation-related complications, which included transient mild right hemiparesis and dysphagia in one patient and mild right hemiparesis and speech difficulties in the other patient. In a large clinical analysis, Young et al. [6] evaluated 161 patients who underwent GKT for ET at their institution. The mean period of follow-up was determined to be 44 ± 33 months. Throughout this period of time, the authors reported that 81% of patients experienced improvements in drawing scores and 77% of patients experienced improvements in writing scores (P < 0.0001). Radiosurgery-related complications occurred in 14 patients (8.4%), and included difficulties with speech, limited sensory loss contralateral to the side of the procedure, and motor impairments (Table 1).

Treating tremors associated with Parkinson's disease (PD) with GKT is a clinical approach that has gained increased popularity in recent years. Over a seven year period, Duma et al. [7] treated 38 PD patients with GKT. With median follow-up of 30 months, the authors reported that 11 patients (26%) exhibited excellent tremor relief rates, 13 patients (31%) exhibited good tremor relief rates, 4 patients (9.5%) exhibited mild tremor relief rates, and four patients (9.5%) did not experience an improvement in tremor relief rates. One patient reportedly suffered from mild acute dysarthria one week following the procedure. In a separate study by Young et al. [8], 102 patients with PD and 52 patients with ET were evaluated following GKT. After a mean follow-up of 52.5 months, 88.3% of PD patients became fully or nearly tremor free. In addition, approximately 92.1% of ET patients became fully or nearly tremor free one year after GKT. At 48 months post-radiosurgery, 88.3% of these patients maintained excellent levels of tremor control.

In the only prospective cohort study to date, Ohye et al. [9] treated 59 patients with tremor related to PD and 13 patients with ET with GKT. Approximately 53 patients completed at least 24 months of follow-up. In clinical analysis, the authors reported that 43 patients (81.1%) exhibited an excellent or good tremor outcome during follow-up. Interestingly, the authors reported that reduction of tremor severity was delayed in ET patients when compared to PD patients. No permanent complications were related to the radiosurgery procedure. However, one patient experienced transient slight motor weakness approximately three months following the procedure.

Despite the fact that the body of world literature lacks sufficient studies analyzing the efficacy of GKT for MS-related tremor, positive outcomes have been reported in several published series. Mathieu et al. [10] treated six patients with MS-related tremor with GKT. Over a median follow-up of 27.5 months, all six patients in the study reported a significant improvement with their tremor. Complications were reported in one patient, who suffered from transient contralateral hemiparesis that resolved following steroid therapy. Niranjan et al. [11] performed a study where nine patients with ET and three patients with MS-related tremor were treated with thalamotomy using the GK. Eleven patients were monitored following the procedure. With a median follow-up of six months, nine patients (82%) reported excellent tremor control and two patients (18%) reported satisfactory tremor control.

In a separate clinical analysis, Niranjan et al. [12] evaluated the clinical outcomes of patients who underwent RF thalamotomy, GKT, or DBS for tremor relief. Immediately following the procedure, all 11 DBS patients experienced excellent tremor control, and it was reported that only two patients (18.2%) experienced tremor recurrence. Of the 13 patients who underwent RF thalamotomy, five (39%) experienced complete tremor arrest, six (46%) experienced a significant improvement in their tremor, and two (15%) experienced > 50% tremor relief. Of the 12 evaluated GKT patients, 10 (83%) reported excellent tremor relief and two (17%) reported good tremor relief during follow-up.

Gamma knife thalamotomy treatment planning

GKT is a well-established method for treating tremors using a single dose of radiation concentrated at a precise intracranial location. It is accomplished by utilizing a hemispherical array of 201 fixed Cobalt-60 sources, whose concentric radiation beams sum to a considerable dose at the focal point. The patient's head is immobilized within a frame, defining a precise coordinate system. Treatment planning software allows the neurosurgeon or radiation oncologist to map the VIM nucleus and define the treatment location. The radiation dose

1st Author (year)	# Patients Treated	Max GK Dose (Gy)	Period of Follow-Up	Tremor Improvement Rate	Patient Complications	Complication Rate
Kondziolka [5]	31	130-140	Median: 36 months	92%	hemiparesis, dysphagia, dysarthria	7.7%
Young [6]	161	141-152	Mean: 44 ± 33 months	Drawing: 81% Writing: 77%	sensory loss, motor impairments, dysarthria	8.4%
Duma [7]	38	120-160	Median: 30 months	90%	dysarthria	2.6%
Young [8]	PD: 102 ET: 52	120-160	<12-96 months	PD: 88.3% ET: 92.1%	balance disturbance, paresthesias, weakness, dysphagia	1.3%
Ohye [9]	53	130	24 months	81.1%	transient slight motor weakness	1.9%
Mathieu [10]	6	130-150	Median: 27.5 months	100%	hemiparesis	16.7%
Niranjan [11]	11	130-150	Median: 6 months	100%	dysarthria, weakness	9.1%
Niranjan [12]	12	130-150	Median: 24 months	100%	dysarthria, weakness	8.3%

ET = essential tremor; PD = Parkinson's disease

Table 1: Gamma Knife radiosurgery for disabling tremor.

is prescribed such that the 50% isodose line corresponds to the VIM nucleus margin. During planning, care should be taken to minimize the dose to adjacent brain tissue.

The primary goal when using GKT for tremor treatment is to create a lesion in the VIM nucleus while preserving adjacent brain tissue and limiting treatment associated morbidity. Achieving this balance of safety and efficacy requires the administration of a significant dose of radiation to the thalamic target while minimizing the exposure to surrounding tissues. Technological advances in past decades have been instrumental in accomplishing this goal. These come in the form of high-resolution imaging and more powerful treatment planning software, allowing precise mapping of the 50% isodose line to the VIM nucleus.

At the cellular level, GKT eradicates neurons with abnormal electrophysiological properties through apoptosis initiated by radiation-induced DNA damage. Thus, neurons constituting the VIM nucleus are no longer able to fire and divide, ultimately increasing the tremor control of afflicted patients. Double-stranded DNA breaks in specific neurons are the intended outcome of ionizing radiation because single-stranded DNA breaks are more likely to be repaired by cellular enzymes [13]. Nervous tissue reactions and edema following brain radiosurgery likely occur 3 to 10 months following the procedure and are classified as sub-acute tissue reactions [1]. Acute tissue reactions, occurring 12-48 hours following GKT, are not frequently observed because the effects of radiosurgery take time to manifest clinical symptoms [1].

Selecting a dose is another important aspect to treatment planning. In the large GKT analysis conducted by Duma et al. [7], 22 thalamotomies were performed using a mean maximum dose of 120 Gy and 22 thalamotomies were performed using a mean maximum dose of 160 Gy. The authors reported that the 160 Gy dose group exhibited statistically superior ($P < 0.04$) complete, excellent, and good tremor improvement when compared to the 120 Gy dose group. No procedure-related complications were related to dose selection. Ohye et al. [14] has reported positive outcomes when using a relatively mild dose of 130 Gy. At Gamma Knife of Spokane, we prescribe a maximum dose of 140 Gy, with 70 Gy administered to the 50% isodose line using a 4-mm GK collimator [1]. In our experience with GKT, we feel that the 140 Gy maximum dose provides patients with significant tremor reduction while limiting treatment-associated toxicities to surrounding neurological tissue.

The challenges associated with GKT are the time interval between radiosurgery and clinical effect and the variability of the thalamic reaction and inability to predict the potential complications for specific patients following the procedure. In the 31 patients treated with GKT by Ohye et al. [14], tremor reduction began approximately one year following treatment. This delay in treatment effect may not be acceptable for some patients. In addition, the authors observed two different types of lesions: one of a simple oval shape and one of a complex irregular shape. The authors did not report a correlation between tissue reaction and tremor outcome. However, in some patients the lesion may extend into the internal capsule or medial thalamic region, ultimately causing a variety of possible delayed-onset complications months after the procedure that cannot be anticipated. We previously reported a case where a 65 year old female patient experienced complete tremor relief approximately eight months following a left VIM nucleus GKT [1]. However, at the one year follow-up appointment, the patient experienced dysarthria, balance problems, and numbness in the first three fingers of her right hand. The patient then underwent steroid therapy and reported dramatic improvements in her procedure-related complications.

Conclusion

GKT is an effective treatment modality for patients diagnosed with tremors, with improvement rates ranging from 80 to 100%. In addition, due to the minimally-invasive nature of GKT, this procedure comes with a different, and in many cases, preferable risk profile when compared to neurosurgery. We suggest that GKT be presented as a viable treatment option to tremor patients who are poor candidates for neurosurgery and to patients who prefer a minimally-invasive treatment alternative. Further clinical outcome studies treating larger numbers of patients are needed to assess the long-term efficacy of GKT for specific subsets of tremor patients.

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