Stereotactic radiosurgery for functional disorders

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When Lars Leksell presented SRS in 1951, his original intention was to use the technique for the treatment of functional disorders such as PD, psychiatric conditions, and chronic pain syndromes. He developed the first Gamma Knife in 1967 and originally used slit-shaped collimators to make discoid-shaped lesions in the brain with stereotactic guidance and high precision using focused γ-radiation in a noninvasive fashion. The second Gamma Knife model, produced in 1975, had circular collimators as we know them today—producing spherical lesions—and in 1988 the Gamma Knife took on the design and source geometry that has more or less remained unchanged since. With the reports by Solberg et al. in 1998, linear accelerators were introduced as tools for making lesions with small collimator apertures for the treatment of functional disorders, first in an animal model and later in humans.

The purpose of the present study is to provide an overview of the current literature on SRS in the treatment of movement disorders, epilepsy, chronic pain syndromes (including TN), and psychiatric disorders. A search of the online database of the National Library of Medicine was conducted using the following search term combinations: radiosurgery OR Gamma Knife; tremor; Parkinson disease; thalamotomy; pallidotomy; pain; trigeminal neuralgia; epilepsy; and psychiatric disease. We selected articles pertinent to this report and added historical papers. Publications were categorized into 4 groups: movement disorders, pain, epilepsy, and psychiatric disease. Our experience and that of authors from numerous treatment centers is discussed in a critical manner. We have also included personal experiences and unpublished data when appropriate.
Movement Disorders

Treatment of Tremors

Radiosurgical treatment of tremor has been performed successfully for more than 25 years by directing a 4-mm-collimator shot into the posterior ventrolateral thalamus close to the internal capsule (Fig. 1). The authors of several studies have reported success rates in tremor control in patients with PD, essential tremor, and tremor related to multiple sclerosis or other causes that are comparable to those achieved using other methods. Complications are usually rare, mild, and temporary, although unusual complications and severe, permanent complications have also been reported. The most common applications of SRS in the treatment of movement disorders are summarized in Table 1.

The first reports of using GKS in the treatment of tremor were published in the early 1990s, when Rand et al. in the United States, Lindquist and colleagues in Europe, and Ohye et al. in Japan described their experiences. The positive findings of these groups have since been duplicated at numerous treatment centers around the world. The most comprehensive series was published by Young and associates, who reported on long-term follow-up of up to 8 years in 102 patients with tremor related to PD, 52 patients with essential tremor, and 4 patients with tremor as a result of stroke, encephalitis, or head injury. Treatment was performed with the Gamma Knife using a 4-mm collimator and a maximum radiation dose of 120–160 Gy. Of special note is the fact that blinded pre- and postoperative rating was performed by a team of independent evaluators skilled in evaluating movement disorders. The severity of PD was scored using a validated rating scale (Unified PD Rating Scale) to assess tremor and rigidity. In 88% of patients with parkinsonian tremor and 88% of patients with essential tremor, there was long-term relief of symptoms after GKS, which was statistically significantly improved over baseline status. In 50% of patients with other tremors there was improvement, and complications were noted in 3 of 158 patients (1.9%; 1 patient with transient and 2 with mild permanent complications).

Sato and associates addressed the question of optimal target selection by comparing the radiosurgical target with the target used for stereotactic radiofrequency coagulation. Because the center of the radiosurgical treatment plan is positioned in such a way that the internal capsule laterally and the ventralis-caudalis sensory nucleus of the thalamus posteriorly do not suffer radiation damage, this radiosurgical target is typically located 1–2 mm more medial and anterior than the “real” target. In their study, Sato et al. describe 4 patients who underwent radiosurgical treatment planning followed by radiofrequency lesioning of the Vim for the treatment of tremor. Electrophysiological recording demonstrated that the tremor-synchronous cells with rhythmic discharge typically found in the Vim region were indeed present within the radiosurgical target. The authors concluded that current planning strategies for Vim radiosurgical thalamotomy were adequate. The issue of extent of necrosis after radiosurgical creation of a lesion was addressed by the same authors in a different publication. Specifically, the area of the blood–brain barrier disruption, seen on contrast-enhanced MR images as a ring of enhancement, was the target of their research. Two patients with tremor in whom previous GKS had failed underwent open stereotactic thalamotomy with neurophysiological recording. The authors found that the area corresponding to the ring enhancement seen on MR images was active neural tissue with viable tremor cells and not, as may be assumed, necrotic tissue.

Treatment of PD

Radiosurgical pallidotomy has been tried in several institutions but abandoned due to an unacceptable complication rate in most cases. Our own results in 4 patients indicate that the success rate is significantly lower than would be expected with other forms of treatment, such as deep brain stimulation therapy. A postmortem analysis in 1 of our pa-
TABLE 1

Parameters of radiosurgery for movement disorders*  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Movement Disorder</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PD</td>
<td>Tremor</td>
<td>Dystonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>max. dose (Gy)</td>
<td>GPI</td>
<td>Vim</td>
<td>Vim or GPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td>120–180</td>
<td>120–180</td>
<td>160</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% improved</td>
<td>up to 50–85%</td>
<td>up to 88%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% w/ complications</td>
<td>up to 60%</td>
<td>up to 90%</td>
<td>limited frequency</td>
<td>rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>some severe</td>
<td>&amp; severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Table is a summary of the results obtained in a number of studies on radiosurgery for functional disorders. 

Abbreviation: GPI = globus pallidum internus.


tients with PD who died 30 months after GKS pallidotomy, presumably of unrelated causes, also raises concerns over optimal lesion location, potential injury to the optic tract, and the risk of postradiosurgical vascular changes possibly resulting in a basal ganglia stroke. The authors of other studies also strongly advise against the generalized use of radiosurgery for the treatment of PD.

Radiosurgical pallidotomy was first reported on by Rand et al., 30 who used the technique in 8 patients, 4 of whom had significant relief of contralateral rigidity. There were no reports of significant side effects. A less encouraging result was obtained by Friedman et al., 42 who reported on 4 patients with PD treated with unilateral pallidotomy using a maximum dose of 180 Gy. Only 1 patient had reduced dyskinesia afterwards but also experienced temporary dementia and psychosis. The authors questioned the feasibility of performing radiosurgical pallidotomies.

A more positive experience is reported by Young and coworkers 22 who treated 2 groups of patients: 29 patients with radiosurgical pallidotomy and 22 with radiofrequency lesioning in the posteroventral pallidum internum. After a mean follow-up period of 20.6 months, more than 80% of patients in both groups had significant improvement in dyskinesia, and two thirds of patients had improvements in bradykinesia or rigidity. In 27.7% of patients in the radiofrequency lesioning group there was transient postoperative confusion. Only 1 patient in the GKS group (3.4%) had a complication in the form of a homonymous hemianopsia 9 months after treatment.

Duma 34 cautions that radiosurgical pallidotomy may be associated with an unacceptably high risk of complications. In his experience, the combination of poor outcome and high risk have led him to abandon this radiosurgical modality altogether. This concern is shared by Okun and colleagues 37 who reported on a study of 8 patients (who underwent 5 thalamotomies and 3 pallidotomies) with significant complications as a result of radiosurgical lesioning, including hemiparesis, hemianopsia, and pseudobulbar laughter. The authors questioned whether the overall risks of radiosurgical lesioning for PD had been underestimated and strongly recommended that this modality should be offered only with great reservation for the treatment of PD.

Treatment of Dystonia

For other movement disorders, the worldwide experience in treatment with SRS is limited. An initial case report from 1995 29 in which a patient with hemidystonia was treated with a radiosurgical pallidotomy was followed by the report of 2 cases, 48 and in an additional report in 2002 46 of patients treated with a lesion to the anterior ventrolateral thalamus. All patients were reported to have significant improvements, observable 2–3 months after treatment. A homonymous hemianopsia developed in the patient undergoing radiosurgical pallidotomy; treatment-related side effects in the other patients were not reported. Successful radiosurgical treatment of dystonia has been reported with the posteroventral pallidum or the ventral thalamus as the target, and there has also been a report of successful radiosurgical subthalamotomy 33 with long-term follow-up.

Pain

The most common applications of SRS for the treatment of pain are summarized in Table 2.

Trigeminal Neuralgia and Other Neuralgias

By far the most common indication for functional SRS is TN. Extensive wordwide research has been conducted regarding underlying pathophysiological mechanisms of pain relief, clinical outcomes, and comparative technologies. Because of the nonexistent procedure-related mortality rate, the low risk of significant complications, and its ability to provide pain control for tic doloreux, SRS for TN has certainly become one of the most important options when recommending treatment modalities to patients. Other forms of pain treatment with SRS have been described mostly in anecdotal form and are much less researched. We continue to rely mostly on clinical experience of some surgical centers when recommending SRS for certain chronic pain disorders. When it comes to treatment of pain related to a malignant growth, there is increasing evidence that SRS applied to the pituitary stalk region is an effective approach for patients with pain from metastatic cancer. 21 The same approach has also been tried in patients with poststrokethalamic pain syndrome; however, a much lower rate of success and a higher rate of complications was found.

Radiosurgical treatment for TN has been subject to
Both patients were reported to be pain free 1 and 5 months after radiosurgery to the Trepost (70–90 Gy) as described with GKS, the authors achieved sustained pain relief of 88% of patients, with a mean follow-up period of 23 months. The only reported complication was postprocedure numbness in 25%. Although there is no study comparing linear accelerator SRS to GKS in terms of outcomes or side effects, Ma et al. attempted model dose falloff and error tolerances when planning radiosurgical procedures for TN. The authors found no significant differences between the 2 modalities, provided that a high number of arcs is used (≥7), and a small interarc error is guaranteed; however, they caution about increased treatment time for multicompartment plans.

The question of whether the TREZ undergoes any kind of permanent change as a result of radiosurgery is addressed in a publication by Shetter and coauthors. They report on 6 patients who were treated with radiosurgery with 80–135 Gy in 1 or 2 sessions. Patients had persistent or recurrent facial pain and elected to undergo MVD surgery. The authors indicate that there were no abnormal findings around the nerve entry zone that were attributable to previous radiosurgery and therefore conclude that previous radiosurgery does not preclude patients from MVD in case of pain recurrence.

Stieber et al. describe the only reported—and successful—treatment of glossopharyngeal neuralgia in a patient who refused MVD surgery. A maximum dose of 80 Gy was delivered to the nerve at the entry into the osseous canal of the jugular foramen using a single 4-mm-collimator shot. The patient experienced gradual pain relief starting 6 weeks after treatment and was pain free without medication 3 months after treatment. She had partial recurrence of pain 6 months after treatment but did not require further medical or surgical therapy. No complications were reported.

Pollock and Kondziolka describe the successful application of a single 8-mm-collimator shot to the sphenopatavailable gland in a patient with sphenopalatine neuralgia. A maximum dose of 80 Gy was delivered, and the patient initially improved but then had recurrence of her pain that required a second treatment with the same treatment parameters. Six months after the second treatment, she was pain free and her vasomotor symptoms (nasal discharge, injected eye) also improved.

### Chronic Pain and Thalamic Pain Syndrome

After Steiner and Leksell reported initial successes in patients with chronic pain by making radiosurgical lesions in the thalamus, it took almost 2 decades before the treatment was investigated on a larger scale. Encouraged by some positive results, Young treated 41 patients with chronic pain related to structural spinal disorders or spinal cord injury, postherpetic neuralgia, stroke, and thalamic pain syndrome, or anesthesia dolorosa of the face. The treatment target was the medial thalamus, including the

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**TABLE 3**

Radiosurgery for epilepsy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MTLLE</th>
<th>Hypothalamic Hamartoma</th>
<th>DA–GTCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>target</td>
<td>amygdala, hippocampus</td>
<td>hypothalamic lesion</td>
<td>corpus callosum</td>
</tr>
<tr>
<td>max. dose</td>
<td>48–50</td>
<td>50</td>
<td>100–140</td>
</tr>
<tr>
<td>outcome</td>
<td>% improved</td>
<td>65</td>
<td>70–90</td>
</tr>
<tr>
<td></td>
<td>% w/ complications</td>
<td>45, mild</td>
<td>rare</td>
</tr>
</tbody>
</table>

* Table is a summary of the results obtained in a number of studies on radiosurgery for epilepsy. Abbreviations: DA = drop attack; GTCS = generalized tonic-clonic seizures; MTLLE = mesial temporal lobe epilepsy.

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extensive research. Both GKS and linear accelerator radiosurgery have been successfully applied to treat tic dolores refractory to medication after failed attempts at MVD, and ablative procedures such as transcutaneous peripheral neurotomy or glycerol injection.

Leksell began treating patients with TN in 1953, although his first report of 2 patients was not available until 1971. Both patients were reported to be pain free 1 and 5 months after radiosurgery to the trigeminal nerve. Hakan

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intralaminar nuclei, the lateral portions of the medial-dorsal nucleus, the centromedian nucleus, and the parafascicular nucleus. The 4-mm collimator was used to deliver 140–180 Gy in 1, 2, or 3 isocenters. Although two thirds of patients reported a reduction in their pain of 50% or more, the treatment was associated with significant side effects, including 1 death (personal communication). In another report, these unpredictable lesion sizes were studied and found to be typically seen when more than 1 isocenter was applied or when doses of more than 160 Gy were used.

Radiosurgical treatment of the pituitary stalk for post-stroke thalamic pain syndrome was recently described. In this study, 24 patients underwent GKS of the pituitary gland and stalk with a dose of 140–180 Gy. In 71% of patients, significant pain relief started as soon as 48 hours after treatment. However, after a follow-up period of 12–48 months, only 21% of patients had lasting pain relief. Ten patients (42%) also had reported side effects, which were usually related to hormone imbalance.

**Cancer-Related Pain Syndrome**

Leksell used radiosurgery early on to treat pain related to malignant tumors with the medial thalamus as the target. Since his initial reports, there have been few studies on using the same technique for cancer-related pain. Frighetto et al. in 2004 described their experience of using a linear accelerator with a 5-mm collimator to create a lesion in the medial thalamus of 3 patients, 1 of whom had metastatic cancer. All patients, including the patient with cancer, who died 2 weeks after treatment, had substantial pain relief and were able to reduce their medications.

Backlund and coworkers used Gamma Knife hypophysectomy in the treatment of 8 patients suffering from severe pain from advanced-stage breast cancer and achieved excellent pain relief in all patients. A somewhat different approach—originally reported by Lisák and Vladyka—is described in a multicenter prospective protocol of pituitary gland and stalk ablation with GKS in patients with pain related to bone metastases. One of the inclusion criteria was that the pain had to be responsive to morphine. The authors reported on 9 patients who were treated with either a single 8-mm-collimator shot or a 2-isocenter delivery of the 4-mm-collimator. A maximum dose of 160 Gy was delivered, and the radiation exposure of the optic structures was limited to 8 Gy or less. After a follow-up of 1–24 months, all 9 patients experienced significant pain relief without any reported side effects.

**Cluster Headaches**

In 1998, Ford et al. published the first report of successful treatment of cluster headaches by GKS. Of 6 patients treated with a 70-Gy maximum dose to the TREZ, 4 had excellent pain relief for a follow-up period of 8–14 months. No side effects were reported. A few years later, a prospective study was begun, which was just recently completed and published. Of the 10 patients treated in this study, only 3 had complete or almost complete relief of symptoms. Due to the high incidence of side effects (9 of 10 patients) with trigeminal parasthesia, hypesthesia, or deafferentation pain, the authors do not recommend treatment of cluster headaches with trigeminal radiosurgery. McClelland et al. confirmed the negative findings.

Targeting the sphenopalatine ganglion instead of the TREZ could be a promising solution and is being investigated.

**Epilepsy**

The most common applications of SRS for the treatment of epilepsy are summarized in Table 3.

**Mesial Temporal Lobe Epilepsy**

Mesial temporal lobe epilepsy and its treatment with SRS is one of the areas in radiosurgery with extensive evidentiary support. After first reports in humans a French group conducted basic laboratory tests to gain further insight into the mechanisms underlying radiosurgical anti-epileptogenesis. Rats received doses of 100 Gy to the striatum, resulting in a differential effect on different enzymes (glutamate decarboxylase and choline acetyltransferase) and secondarily between excitatory amino acids and non-excitatory amino acids, particularly γ-aminobutyric acid. Another animal study examined a kainic-acid rat model of epilepsy and the effect of varying doses of radiation. The authors were able to establish a clear relationship between increasing radiosurgical dose and decreasing seizure frequency measured by electroencephalography. A dose in the 40–60 Gy range was found sufficient to provide good seizure control without causing brain tissue necrosis and was therefore deemed appropriate for human use.

In 1985, Barcia-Salorio and colleagues reported on 6 patients treated with a cobalt unit using a 10-mm collimator. The epileptic foci in these patients received an estimated dose of 10 Gy. In 1994, the same group reported a long-term analysis using doses between 10–20 Gy. Five of 11 patients had complete cessation of seizures and another 5 were improved starting 3–12 months after treatment. Further experience was then reported from Sweden by Hellstrand et al., with more advanced techniques of localizing the epileptic focus, including magnetoencephalography and the use of GKS. In 1993, Régis and associates performed the first selective radiosurgical amygdalohippocampectomies for mesial temporal epilepsy. The 2 patients in their study both received a dose of 25 Gy to the 50% isodose and were seizure free within 1 year. Postoperative MR imaging studies in these patients revealed contrast enhancement corresponding to the 50% isodose. The same researchers then initiated a multicenter study, which was conducted at 3 European centers. Twenty patients underwent radiosurgery with 24–25 Gy delivered to the mesial temporal lobe for intractable mesial temporal lobe epilepsy. After a follow-up period of 2 years, 65% of these patients were seizure free, however, it took about 12 months surgery for the seizure frequency to begin to drop significantly. The authors also commented on the fact that all of their patients experienced a transient increase in seizures, mostly auras, before the number of seizures started to diminish. Nine patients (45%) were reported to have visual field defects, which, according to the authors, compares favorably with the results of microsurgical selective amygdalohippocampectomy or anterior temporal lobectomy, in which > 70% of patients have postoperative visual field deficits. Other transient complications included headache, nausea, vomiting, depression, and dizziness.
Hypothalamic Hamartomas, Gelastic Seizures

In 1998, Arita et al. reported the first case of a patient with a hypothalamic hamartoma suffering from gelastic and tonic-clonic seizures to be treated with SRS. The patient became seizure free with a follow up of almost 2 years. The reported MRI findings indicate a complete disappearance of the hypothalamic changes. As a result of this report, a multicenter retrospective study was conducted including 10 patients in 7 international centers. All patients reported improvement of their seizures, with 4 being seizure-free after a follow-up period of 12–71 months. The authors advocate a dose to the margin of the lesion of 17 Gy. These findings have since been confirmed using linear accelerator radiosurgery.

Corpus Callosotomy

Another fairly novel way of using radiosurgery in the treatment of epilepsy was first described in 1999 by Pendell et al., who described the treatment of 2 patients with long-standing Lennox–Gastaut syndrome and 1 patient with tonic-clonic and absence seizures with a corpus callosotomy of the anterior third of the corpus callosum. After a mean follow-up period of 36 months, all patients had improvement in their seizures. Encouraged by these results, the same group later published a report on 8 patients undergoing either anterior callosotomy (6 patients) or posterior callosotomy (2 patients) after previous surgical callosotomy. The patients were followed up for a minimum of 1 year (range 1–12 years). Drop-attack seizures were abolished in 3 patients, and 3 more patients had a 40–60% improvement of drop attacks. Generalized tonic-clonic seizures were abolished in 2 patients, and 2 other patients had a 50–60% improvement. Other seizure types did not respond as well to treatment, with a 20–70% reduction seen in 3 patients. There were only minor transient side effects in 2 patients, and mild changes on MR imaging were noted in only 25% of patients. The favorable results have since been confirmed and repeated with the use of a linear accelerator and have also been reported in children.

Psychiatric Disease

The first radiosurgical treatments of psychiatric disease were performed by Leksell in 1953 with a 300-kV x-ray device. Seven patients with OCD were treated by placing radiosurgical lesions into the anterior limb of the internal capsule. After 7 years’ follow-up, 5 patients reported long-term benefits. Further treatments were performed at the Karolinska Institute in Stockholm starting in 1988, first by using the 8-mm collimator and later—because of excessive lesion sizes—with the 4-mm collimator. Long-term follow-up 17 years after treatment of OCD with bilateral radiosurgical anterior capsulotomy at maximum doses of 120–180 Gy has been reported. In 27 of 28 targets, the volume of necrosis was measured on MR images to be 100 mm³ or less, and a radiation dose of at least 110 Gy reliably produced a lesioning effect.

Our institution has been involved in the neurosurgical treatment for psychiatric disease for the past 2 decades. Radiosurgery as a possible tool to treat OCD was introduced in the 1990s, encouraged by some positive reports from the Karolinska Institute. Because there are significant ethical concerns and organizational issues associated with the treatment of such patients, we have offered this treatment exclusively to an extremely treatment-refractory group of patients who were selected by a team of psychiatrists as part of a strict research protocol. At our own institution we continue to provide radiosurgical treatment for OCD to a small group of very treatment-resistant patients as part of an ongoing open-label research study. Our current treatment protocol calls for 2-isocenter shots with the 4-mm collimator to each side with a maximum dose of 180 Gy per shot (2 lesions on each side are created). With this treatment method we have achieved long-term and significant reduction of OCD symptoms in roughly two thirds of our patients. Preliminary findings are encouraging but longer follow-up is needed.

Conclusions

There is sufficient evidence in the literature to support the use of radiosurgery in the treatment of certain functional disorders. Stereotactic radiosurgery has become a standard neurosurgical tool for the treatment of TN because of favorable results and very limited risk of complications. Radiosurgical treatment of some other pain syndromes is promising with certain techniques (SRS to the pituitary stalk), while other techniques (such as medial thalamotomy) are no longer recommended. Certain types of epilepsy appear to respond well to SRS with acceptable risks. The supportive evidence on the treatment of hypothalamic hamartomas with SRS continues to accumulate. Although some procedures for the treatment of movement disorders are associated with high risks (radiosurgical pallidotomy, for example) it is feasible to offer radiosurgical thalamotomy to patients with tremor, especially in situations where open stereotactic approaches for lesioning or deep brain stimulation therapy are not possible or are too risky. The widespread use of radiosurgery in the treatment of psychiatric disorders is strongly discouraged unless performed within the confines of a research protocol and accompanied by the strong support of a dedicated psychiatry team.

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Functional stereotactic radiosurgery

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