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Stereotactic radiosurgery for movement disorders

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Abstract

Initially designed for the treatment of functional brain targets, stereotactic radiosurgery (SRS) has achieved an important role in the management of a wide range of neurosurgical pathologies. The interest in the application of the technique for the treatment of pain, and psychiatric and movement disorders has returned in the beginning of the 1990s, stimulated by the advances in neuroimaging, computerized dosimetry, treatment planning software systems, and the outstanding results of radiosurgery in other brain diseases. Since SRS is a neuroimaging-guided procedure, without the possibility of neurophysiological confirmation of the target, deep brain stimulation (DBS) and radiofrequency procedures are considered the best treatment options for movement-related disorders. Therefore, SRS is an option for patients who are not suitable for an open neurosurgical procedure. SRS thalamotomy provided results in tremor control, comparable to radiofrequency and DBS. The occurrence of unpredictable larger lesions than expected with permanent neurological deficits is a limitation of the procedure. Improvements in SRS technique with dose reduction, use of a single isocenter, and smaller collimators were made to reduce the incidence of this serious complication. Pallidotomies performed with radiosurgery did not achieve the same good results. Even though the development of DBS has supplanted lesioning as the first alternative in movement disorder surgery; SRS might still be the only treatment option for selected patients.

Key Words: Movement disorders, pallidotomy, stereotactic radiosurgery, thalamotomy

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INTRODUCTION

Stereotactic radiosurgery (SRS) was developed with the aim of creating a minimally invasive technique capable of precisely generating a focal lesion in the brain. In his first procedure, Lars Leksell used an orthovoltage X-ray source adapted to his arc-centered stereotactic frame to treat a trigeminal neuralgia patient.[28] At that point, his main goal was to develop a device to treat functional disorders of the brain, including intractable pain, movement disorders, and epilepsy. Although Leksell and his group described the utility of SRS in functional diseases,[27,49] the technique has advanced and proved its invaluable utility in the treatment of other major neurosurgical pathologies including arteriovenous malformations, metastases, and malignant and benign tumors of the brain and skull base.[3,14,24,46]

Many decades after the development of SRS, the interest for functional radiosurgery returned in the beginning of the last decade.[30,43] Encouraged by the advances in imaging and computerized software systems dedicated to radiosurgery planning, its applications to chronic pain syndromes, especially trigeminal neuralgia, as well as psychiatric and movement disorders have been used in many medical centers around the world.[2,7,8,12,16,17,23,36,42,45,53,54] The application of SRS for movement disorders was also stimulated by the good results obtained with radiofrequency lesioning.[5,19,20,21,26,31,32,51]

The safe and effective dose to be used for functional radiosurgery was not initially known. Previous reports disclosed that doses of 180–200 Gy were capable of creating a focal lesion in the brain for the treatment of chronic pain.[27,49,50] The initial high doses are currently being reduced, with a tendency toward fewer complications. Collimator size and number of isocenters have also been a matter of concern since the use of multiple isocenters and large-size collimators was related to an increase in the complication rate.[6,15,25,34,56] The literature related to SRS performed to treat movement disorders was developed using the gamma unit. In spite of the fact that there is no report on the utilization of the linear accelerator (Linac) technique for the treatment of movement disorders, the application of a dedicated Linac to perform accurate lesions in the thalamus for the treatment of pain has been described.[18] Another study demonstrated the precision of a 3-mm Linac collimator used to generate lesions restricted to the subthalamic nucleus (STN) and substantia nigra of the vervet monkey.[4] Other reports have demonstrated the capability of dedicated Linacs to reach the necessary precision to treat small functional targets, including its clinical application for the treatment of trigeminal neuralgia.[45,47] This article represents a broad review of the usefulness of SRS for the treatment of movement disorders, with regard to its indications, techniques, applications, and complications.

INDICATIONS AND PATIENT SELECTION

The indications of SRS for the management of movement disorders are essentially the same as those of the usual stereotactic open surgery. These include patients with advanced Parkinson's disease (PD), essential tremor (ET), and tremor related to other medical conditions such as multiple sclerosis and trauma not controlled with the best medical therapy.[2,5,7,12,16,19,21,26,36,42,43,57]

Since neurophysiology-guided radiofrequency stereotactic surgery or deep brain stimulation (DBS) offers advantages over SRS, this procedure is reserved for a small subset of patients. These patients have conditions that may turn them into unacceptable candidates for invasive stereotactic neurosurgical intervention, including very elderly patients, high-risk surgical patients suffering from severe cardiac or pulmonary pathology, and those using anticoagulants. In these cases, SRS can be the only available treatment option. There are also patients who may choose SRS to avoid an invasive surgical procedure.[7,11,16,36,42,43,56]

Invasive stereotactic surgery, including both radiofrequency lesioning and DBS, may be associated with significant morbidity and possible mortality. These procedures carry an inherent risk of intracerebral hemorrhage, infection, seizures, brain displacement, tension pneumocephalus, and direct injury from probe placement, among others.[1,48,51,56]

SRS is a less invasive procedure that does not involve opening of the cranium or incisions and there is no risk of hemorrhage or meningitis from operative infection. The postoperative patient care is simpler and patients return earlier to their regular activities with a reduction in hospitalization time. The disadvantages of the technique include uncertain target determination due to the impossibility of confirming the lesion site intraoperatively with physiologic testing, relying exclusively on anatomical targeting. Moreover, a mean delay of 6 months for clinical improvement is mandatory after SRS.[7,12,16,36,42,43,56]

THALAMOTOMY

Radiosurgical thalamotomy for pain was one of the first performed functional radiosurgery procedures.[27] Its application targeting the nucleus ventralis intermedius (VIM) has been performed by several authors in the treatment of tremor in patients with PD, ET, and tremor related to multiple sclerosis, trauma, or other causes. The reported results and complications with SRS thalamotomy are comparable to those achieved using other methods [Table 1].[7,9,11,16,36,37,43,53]

Regarding the ideal target for SRS thalamotomy, Ohye *et al.*[36] initially described an intentional displacement of at least 2 mm more medially and anteriorly from the actual target to avoid possible damage to the internal capsule and the sensory nucleus of the thalamus. The knowledge that the high-signal zone surrounding a thalamic lesion is functionally almost intact has changed the placement of the lesion at the real target instead of shifting away to avoid capsular and sensory nucleus involvement.[38] Moreover, a more conservative approach was recommended using 130 Gy and preventing the 10–15% isodose line from extending into these structures. Another important clue is the concept that each thalamic nucleus is represented more constantly by the percentage of thalamic length than by the distance from posterior commissure. Therefore, the regular coordinates for thalamotomy can be adjusted for the VIM nucleus to be at a length of 45% from the anterior tip of the thalamus in the horizontal plane.[35]

Table 1: Literature review of radiosurgery thalamotomy for movement disorders

Authors and year	Pathology	Patients	Lesions	FU (months)	Good (%)	Mild	Failed	Complications (%)	Excellent (%)
Pan *et al.*, 1996[42]	PD	6	6	4.5 (2–9)	3 (50)	3 (50)	–	–	1(16.6)
Duma *et al.*, 1998[7]	PD	34	38	28 (6–58)	3 (50)	11 (29)	4 (10.5)	4 (10.5)	No
Young *et al.*, 2000[52]	PD	102	102	47 (11–93)	78 (76.5)	12 (11.8)	–	12(11.8)	2(1.9)
Young *et al.*, 2000[52]	ET	51	51	26 (NR)	47 (92.1)	–	–	4(7.8)	1(1.9)
Ohye *et al.*, 2002[40]	PD and ET	30 #	30	30 (24–96)	24 (80)	–	–	6(20)	No
Duma *et al.*, 2007[6]	PD and ET	42	46	30 (6–90)	25 (54)	13 (28)	4 (8.6)	4(8.6)	1(2.3)
Kondziolka *et al.*, 2008[25]	ET	27#	27	36 (4–96)	18 (66.6)	6 (22.2)	–	3(11.1)	2(7.4)
Ohye *et al.*, 2009[36]	PD and ET	85	NR	*	80 &	NR	4 (4.7)	NR	
Young *et al.*, 2010[54]	ET	161	203	56 ± 31	2 (14.2)	81 &	NR	NR	14(6.9)
Lim *et al.*, 2010[29]	PD and ET	14#	14	19.2 (7–30)	Serious: 1(6)	NR	NR	NR	3(21.4)
Elaimi, 2010[9]	ET	1	1	72	1 (100)	1 @			

PD: Parkinson's disease, ET: Essential tremor, NR: Not reported, FU: Median and range follow-up, *Over a 17-year interval (median follow-up and range not reported), #Patients available for follow-up, and Excellent and good, @Transient

Pan *et al.*[42] described the treatment of eight patients with PD with SRS thalamotomy. Follow-up was available in six patients. Tremor disappeared in three and improved in the other three. There was one case of contralateral limb weakness, which appeared 3 months after treatment.

Duma *et al.*[6] presented a series of 42 patients submitted to 46 lesions for the treatment of PD and ET. No change in tremor was observed in 4 (8.6%) patients, mild improvement in 4 (8.6%), good improvement (more than 50%) in 13 (28%), excellent improvement in 13 (28%), and complete elimination was observed in 12 (26%) patients. Clinical and radiological follow-up ranged from 6 to 90 months (median 30 months). The median time of improvement onset was 2 months (range: 1 week to 8 months). Independent neurologist evaluation scores of patient's response to treatment were obtained at regular clinical follow-up intervals. Complications were observed in 1 (2.3%) patient who was submitted to bilateral lesions and suffered a mild acute dysarthria 1 week after treatment.

A comparison study was conducted between a subgroup of patients in whom "low-dose" lesions (mean 120 Gy) and those in whom "high-dose" lesions were made (mean 160 Gy) for purposes of dose–response information.[7] There was better tremor reduction in the high-dose group (78% mean improvement) than in the low-dose group (56% mean improvement) ($P = 0.04$). There were no neurological complications.

Young *et al.*[52] reported the results of 102 PD patients who underwent SRS thalamotomy for the treatment of tremor. After a median follow-up of 47 months (range: 11–93 months), 78 (76.5%) were completely tremor free, 12 (11.8%) were nearly free, and 12 (11.8%) had failed the treatment. Blinded assessments of Unified Parkinson's Disease Rating Scale (UPDRS) tremor scores showed statistically significant improvements in overall tremor, action tremor, and tremor at rest. Statistically significant improvements were also seen in rigidity and maintained at 4-year follow-up evaluation. The study also included 52 patients with ET and 4 with other forms of tremor (following stroke, cerebral trauma, or encephalitis) in a total of 158 patients. In the whole group, one transient (0.66%) and two permanent complications (1.3%) were reported. In all three of these patients, the side effects were due to lesions that became larger than expected, and not because of targeting errors.

The largest series of SRS thalamotomy for ET[55] presented the results of 161 patients, who underwent a total of 203 thalamotomies (119 unilateral and 42 bilateral). The vast majority of the patients were treated with 140 Gy, varying from 140 to 150 Gy, using a single isocenter and the 4-mm collimator. A statistically significant decrease in tremor scores for both writing and drawing was observed after a mean postoperative follow-up duration of 56 ± 31 months. Overall, 81% of patients showed improvements in drawing and 77% showed improvement in writing

scores. There were 14 patients who suffered neurological side effects that were temporary (6) or permanent (8), which accounted for 6.9% of the 203 treatments. As in other series in the literature, there was a clear-cut correlation between lesion volume and complications. The mean lesion volume for the 157 procedures in which no complications were identified was 188 ± 224 mm^3, and for the 14 procedures following which complications were identified, the mean lesion volume was 871 ± 742 mm^3 ($P < 0.001$).

Ohye *et al.*[40] presented a series of 53 patients submitted to radiosurgery thalamotomy. The reported results were based on 30 patients with at least 2 years of follow-up (median 30 months, range: 2–8 years) after treatment. Clinical outcome was satisfactory in 24 (80%) patients with a reduction of the tremor to less than 25% of the preoperative state. Treatment failure was observed in 6 (20%) patients, after one (two patients) or two (four patients) procedures. There were no reported complications.

Kondziolka *et al.*[25] reported a series of 31 patients harboring ET submitted to SRS thalamotomy with a mean follow-up of 36 months (range: 4–96 months). Patients were treated with a single 4-mm collimator with a dose of 130–140 Gy. Of the 27 evaluable patients, 18 (66.6%) showed improvement in both action tremor and writing scores, 6 (22.2%) only in action tremor, and 3 (11.1%) in neither tremor nor writing. The authors used the Fahn–Tolosa–Marin Clinical Tremor Rating Scale[10] to assess pre- and postoperative tremor, showing that scores for both tremor and writing were found to be statistically significant. The typical response time was 1–4 months, although three patients had significant tremor improvement within 2 days. Two complications (7.4%) were reported in the study. One patient presented with transient mild right hemiparesis and dysphagia. Another patient suffered a mild right hemiparesis and speech impairment months after SRS. In one case, a magnetic resonance imaging (MRI) follow-up study showed a larger than expected volume of contrast enhancement, which resolved over the next 18 months.

The results of SRS thalamotomy were considered as good as those published on radiofrequency thalamotomy or DBS with regard to efficacy and incidence of complications.[7,25,39,52] Essentially, 85–90% of patients showed significant improvements in tremor in short-term follow-up studies. These results have changed the use of the open lesioning technique in favor of SRS thalamotomy in some centers.[7,25,36,56]

On the other hand, the results of a prospective study to evaluate clinical outcomes after SRS thalamotomy for disabling tremor,[29] with blinded independent neurological evaluations, reported no marked improvement of resting, postural, and action tremor after treatment. The authors described the results of 14 patients (11 with ET and 3 with PD) treated with a dose of 130–140 Gy with a single 4-mm collimator, after a mean follow-up of 19.2 months (range: 7–30 months). The Fahn–Tolosa–Marin Tremor Rating Scale activities of daily living scores improved significantly after SRS. However, the degree of this improvement appeared to be modest and less than what is typically observed with neuromodulation. There was no significant improvement in other items (resting tremor, postural tremor, action tremor, drawing, pouring water, head tremor). Handwriting and UPDRS activities of daily living scores also tended to improve. Marked and sustained improvement of tremor was observed in only two patients (with ET). Three patients developed delayed neurological adverse events, which were mild in two patients and serious in one. Because of lack of tremor suppression from SRS, two patients subsequently underwent open surgery.

Complications of SRS for the treatment of movement disorders have been described in eight patients by Okun *et al.*[41] These included lesions that were off target, death secondary to dysphagia, and aspiration pneumonia, hemiplegia, visual field deficits, aphasia, and pseudobulbar laughter. Siderowf *et al.*[44] also described the occurrence of complex involuntary movements after gamma knife thalamotomy for ET.

The Quality Standards Subcommittee of the American Academy of Neurology[59] stated disadvantages of SRS, including dependence on anatomical imaging, delay of weeks to months for clinical results to occur, and risk of delayed progressive neurological deficits. Although the overwhelming majority of post-radiosurgery MRI studies depict a lesion in exactly the planned location with the expected appearance, they concluded that there is insufficient evidence to make recommendations regarding the use of SRS in the treatment of ET. The advantage of SRS is that tremor relief can be provided to patients (particularly the elderly) who would not be good candidates for DBS.

PALLIDOTOMY

The feasibility and results demonstrated with SRS thalamotomy associated with the previously reported long-term outcomes with radiofrequency pallidotomy[20] made the globus pallidus internus (GPi) the next natural target to radiosurgery [Table 2].

Radiosurgical pallidotomy was first reported by Rand,[43] who used the technique in eight patients with doses between 140 and 165 Gy. Significant improvement of contralateral rigidity, bradykinesia, and dyskinesias was observed in 4 (25%) patients. Positive results without a major impact in quality of life were observed in 2 (25%) patients and there was no change in the course of the disease in the other 2 (25%) patients.

Table 2: Literature review of radiosurgery pallidotomy for movement disorders

Authors and year	N	Lesions	Dose (Gy)	FU (months)	Excellent (%)	Good (%)	Fair (%)	Poor (%)	Complications (%)
Rand *et al*., 1993[43]	8	8	140–165	NR	2 (25)	4 (50)	–	2 (25)	No
Friedman *et al*., 1996[12]	4	4	180	12	–	1 (25)	–	3 (75)	1 (25)
Bonnen *et al*., 1997[2]	1	1	140	NR	–	–	1 (100)	–	1 (100)
Young *et al*., 1998[57]	29	34	120–140	20.6 (6–48)	65.5–86.6#*	–	–	1 (3.4)	
Duma *et al*., 2007[6]	18	160 (90-165)	8 (6–40)	–	6 (33)	3 (17)	9 (50)	9 (50)	

NR: Not reported, FU: Median and range follow-up, #Excellent and good, *Depending on the symptom: Bradykinesia or dyskinesia

Friedman *et al*.[12] described four cases of PD who underwent unilateral pallidotomy using a 4-mm collimator and a dose of 180 Gy. No patient improved in a significant manner within the follow-up interval of 18 months. One patient developed a stroke related to radiation vasculopathy with severe radiation changes in the blood vessels adjacent to the radiosurgical lesion.

Bonnen *et al*.,[2] in a single case report, described a permanent contralateral homonymous hemianopsia and transient hemiparesis in a patient treated with SRS pallidotomy. The resulting lesion was greater than expected.

A comparative study with 51 patients with PD who underwent pallidotomy was reported by Young *et al*.[58] Patients were divided into two groups: 29 were treated with radiosurgery and submitted to 34 lesions, while 22 were treated with radiofrequency and submitted to 25 lesions. The median follow-up in this series was 20.6 months (range: 6–48 months). The evaluations of motor performance and postoperative assessments were obtained by blinded observers who had no role in or knowledge of the treatment course of these patients. The applied dose in the radiosurgery group was 120–140 Gy with a 4-mm collimator. In this study, improvement in dyskinesias was observed in 86.6% and 83.3%, and in bradykinesia and rigidity in 65.5% and 63.6% in the SRS and radiofrequency group, respectively.

One patient in the radiosurgery group (3.4%) presented with contralateral homonymous hemianopsia secondary to a lesion larger than expected (volume 950 mm^3) at 9 months postoperatively. Two other patients developed larger lesions (520 mm^3 and 700 mm^3, respectively) but those were not associated with any clinical side effects. Thus, 1 of 29 patients (3.4%) and 1 of 34 lesions (2.9%) were associated with a clinical complication. According to the author, the results were equally as good as those obtained in the radiofrequency pallidotomies when electrophysiological localization was used.

As mentioned earlier for thalamotomies, the drawbacks of radiosurgical pallidotomy concern the latency between the procedure and the clinical benefit (2–3 months minimum) and the possibility that the lesion produced by radiosurgery will continue to enlarge on a delayed basis and involve adjacent normal structures.

Duma *et al*.[6] reported a series of 18 patients with PD who underwent stereotactic SRS pallidotomy. Fifteen patients were treated using a single and three were treated using two 4-mm collimators with a median maximum prescription dose of 160 Gy (range: 90–165 Gy). Patients were submitted to independent neurologist evaluations and UPDRS[33] scoring of patient response to treatment at regular clinical follow-up intervals. The reported results were as not as good as expected. Over a median average follow-up of 8 months (range: 6–40 months), only 6 (33%) patients showed transient improvement in rigidity and dyskinesia. Three (17%) patients were unchanged and 9 (50%) were worsened by the treatment. Of the six patients with improvement, two exhibited visual field deficits. Overall, 4 (22%) had visual field deficit, 3 (16%) had speech or swallowing difficulties, 3 (16%) had worsening of their gait, and 1 (5%) had numbness in the contralateral hemibody. Nine patients (50%) had one or more complications related to the treatment, which were unresponsive to steroid treatment and considered to be permanent.

The explanation of the high complication rate in this series was related to the variability and unpredictability of the lesion size when the GPi served as the target. The differences in outcome comparing VIM and GPi led the authors to believe that there is a difference in sensitivity to radiation between these two nuclei, probably representing anatomical susceptibility to very small venous or arterial infarctions in the area of the GPi, caused by the tapering end artery distribution of the lenticulostriate supply.[13,15]

For the same dose at similar follow-up intervals (160 Gy maximum dose at 8-month follow-up), lesion sizes varied from 6 to 30 mm on T1-weighted MRI sequences with gadolinium enhancement. Follow-up MRI imaging at 1 year revealed accurately placed lesions, but with variable and unpredicted sizes. Over time, lesions tended to decrease slightly, but in general were consistent throughout the course of follow-up.[8]

The number of centers that have been performing

radiosurgery pallidotomies compared to those performing thalamotomies reflects the lack of reliability of the procedure and that other therapeutic options are superior to SRS targeting the GPi. The majority of the institutions have abandoned the procedure due to an unacceptable complication rate.

SUBTHALAMOTOMY

The STN is the main target for DBS for the treatment of PD. The only report of radiosurgery subthalamotomy in the literature described the case of an old patient previously submitted to a radiofrequency pallidotomy who underwent a contralateral radiosurgery lesion of the STN. After 3.5 years of follow-up, the STN lesion was stable and well placed and the patient experienced reduction in dyskinesias and improvement in tremor and rigidity.[22]

CONCLUSIONS

Advances in stereotactic techniques associated with improvements in MRI targeting, planning software, and a better knowledge of SRS parameters brought the technique to a precision capable of performing focal and precise lesions in the basal ganglia for the treatment of movement disorders.

Using modern functional SRS parameters, radiosurgery thalamotomy has become a safe and useful procedure for patients who are not suitable for an open surgical procedure. The reported results and complications of SRS are comparable to those of thalamic lesions generated by neurophysiologically guided radiofrequency procedures.

Complications were always related to the variability of lesion volumes using the same radiosurgical parameters rather than to the stereotactic target precision. The factors related to this unpredictable thalamic reaction to high single-dose radiation are still unknown.

Similar results and safety were not achieved with pallidal radiosurgery lesions. The results of radiosurgery pallidotomy are not homogeneous in the literature. Many reports disclosed an unacceptably high complication rate. Although just a few centers reported their results, the majority of them were not satisfactory, leading them to abandon the procedure.

Further studies are necessary to establish the role of SRS targeting the STN, since its small size and complex anatomical relationships make this nuclei less suitable for the procedure.

Even though the development of DBS, with its possibility of reversibility and fine adjustments of stimulating parameters, has supplanted lesioning as the first alternative in movement disorder surgery; SRS might still be the only treatment option for selected patients.

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