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LITERATURE REVIEW

Stereotactic radiosurgery for tremor: systematic review

International Stereotactic Radiosurgery Society practice guidelines

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OBJECTIVE The aim of this systematic review is to offer an objective summary of the published literature relating to stereotactic radiosurgery (SRS) for tremor and consensus guideline recommendations.

METHODS This systematic review was performed up to December 2016. Article selection was performed by searching the MEDLINE (PubMed) and EMBASE electronic bibliographic databases. The following key words were used: "radiosurgery" and "tremor" or "Parkinson's disease" or "multiple sclerosis" or "essential tremor" or "thalamotomy" or "pallidotomy." The search strategy was not limited by study design but only included key words in the English language, so at least the abstract had to be in English.

RESULTS A total of 34 full-text articles were included in the analysis. Three studies were prospective studies, 1 was a retrospective comparative study, and the remaining 30 were retrospective studies. The one retrospective comparative study evaluating deep brain stimulation (DBS), radiofrequency thermocoagulation (RFT), and SRS reported similar tremor control rates, more permanent complications after DBS and RFT, more recurrence after RFT, and a longer latency period to clinical response with SRS. Similar tremor reduction rates in most of the reports were observed with SRS thalamotomy (mean 88%). Clinical complications were rare and usually not permanent (range 0%–100%, mean 17%, median 2%). Follow-up in general was too short to confirm long-term results.

CONCLUSIONS SRS to the unilateral thalamic ventral intermediate nucleus, with a dose of 130–150 Gy, is a well-tolerated and effective treatment for reducing medically refractory tremor, and one that is recommended by the International Stereotactic Radiosurgery Society.

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KEY WORDS tremor; stereotactic radiosurgery; thalamotomy; systematic review

The most common movement disorder is tremor, either essential tremor (ET) or tremor arising in the course of other disorders, chiefly Parkinson's disease (PD). It tends to increase as the underlying disorder progresses and with age,[44] impairing performance and coordination of voluntary movements. Even mild cases affect the quality of a patient's personal and working life.[38,43,50,71]

Neurosurgery is the therapeutic option when initial pharmacological treatment fails or is contraindicated. The ventral intermediate nucleus (VIM) of the thalamus was

ABBREVIATIONS DBS = deep brain stimulation; ET = essential tremor; FTMRS = Fahn-Tolosa-Marin rating scale; GKRS = Gamma Knife radiosurgery; PD = Parkinson's disease; RFT = radiofrequency thermocoagulation; SRS = stereotactic radiosurgery; UPDRS = Unified Parkinson's Disease Rating Scale; VIM = ventral intermediate nucleus.

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identified early as the most suitable anatomical target site for controlling tremor.[35] Localizing the VIM was done indirectly by pneumoencephalography at first, subsequently by CT, and then by MRI.[46] Radiofrequency ablation of the VIM was one of the first procedures,[51] followed by deep brain stimulation (DBS) in 1967.[2,3,7,30,31,32,37]

Although stereotactic radiosurgery (SRS) was first developed for functional indications,[39] the application to movement disorders occurred only once advances in imaging technology allowed for precision targeting. At first, pallidotomy was performed and improved tremor severity in PD patients, but gave rise to additional complications,[11,22,25,36,40,85] and over time the VIM became the preferred target.[16]

SRS technologies vary in use as they pertain to tremor; however, most published experiences have been based on Gamma Knife radiosurgery (GKRS; Elekta AB). We have learned that it is a safe alternative to neurosurgery with improvement rates of 70%–80%, which are similar to those of radiofrequency thermocoagulation (RFT).[10,17,19,45,51,52,83,85,86,87] The disadvantages include the lack of an electrophysiological guide, delayed effectiveness such that clinical improvement can take months, and late complications that may arise and are irreversible.[72,83] Consequently, certain specialists reserve SRS for patients who are not candidates for surgery. The purpose of this systematic review was to identify and summarize the literature to provide consensus guidelines for practice as endorsed by the International Stereotactic Radiosurgery Society.

Methods

Article Selection

This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria. Article selection was performed by searching the MEDLINE (using PubMed) and EMBASE electronic bibliographic databases.[78] Further studies were identified by examining the reference lists of all included articles. The following key words were used: "radiosurgery" and "tremor" or "Parkinson's disease" or "multiple sclerosis" or "essential tremor" or "thalamotomy" or "pallidotomy." No date restrictions were imposed,[13] and only those articles written in the English language were reviewed. The search included published reports up to December 2016.

This query identified 642 papers that were assessed for relevance by 2 independent reviewers. In the first stage, titles and abstracts were screened. This resulted in a final selection of 49 papers, the full articles of which were reviewed in a second stage. The final selection was made using the following inclusion criteria: 1) case reports, patient series, and prospective and retrospective studies assessing SRS for the treatment of medically refractory tremor; and 2) studies that provided descriptions of treatment parameters, furnished clinical efficacy data (tremor monitoring, recurrence, quality of life), or provided data on clinical or radiological changes post-SRS. Exclusion criteria consisted of 1) animal studies, letters to the editor, expert opinions, and studies that did not describe any treatment parameters; 2) studies that only described the technology used without clinical outcomes; and 3) studies that did not include analyses of clinical efficacy or safety. The final selection included 34 studies, and the search strategy is summarized in Fig. 1.

Objectives

The primary objectives were to assess the efficacy of SRS in treating patients with intractable tremor and to evaluate the incidence and severity of adverse events after SRS. The secondary objectives were to determine the optimal dose prescription and target that achieves the best balance between tremor control and adverse effects, determine the impact of SRS on quality of life, and evaluate changes in MRI findings after SRS.

Results

The reviewed literature is summarized in Table 1. The mean patient age was 69 years, and 60% of patients were men. The mean history of tremor prior to SRS was 13 years (range 2–25 years). Several studies reported on few patients; 14 studies had fewer than 10 patients, and 6 had only a single patient. Only 10 publications reported on more than 50 patients, giving a maximum of 196 patients.[49]

Eight studies were classified as case reports; however, one of these reports comprised a series of 8 patients.[4,14,24,27,28,42,61,70] There were 3 prospective studies[41,55,79] and 2 comparative studies.[51,85] The remaining studies were single-institution series.[8,10,12,19,21,33,34,48,52,56–59,60,65,68,82,83,84] There were 2 meeting presentations published in a journal of abstracts.[18,49] The assessment methodology in 7 studies was based on independent neurological evaluation.

The first prospective study was a multicenter study by Ohye et al.[55] and included 72 tremor patients treated with a maximum dose of 130 Gy. Outcome was good or excellent in 81%, and no significant differences were observed between ET and PD patients. Assessment was based on the Unified Parkinson's Disease Rating Scale (UPDRS), and considerable score reductions for parts II and III were observed ($p < 0.05$). The median time to response was 6 months. A recurrence rate of 2.8% was observed after 12 tremor-free months.

Witjas et al.[79] also reported a prospective study. A single neurologist performed blinded evaluations of 50 patients with tremor (ET and PD) that was treated with 130 Gy. The evaluations were based on several measurement scales for tremor and quality of life. In addition, a blinded evaluation of video recordings was reported. The global improvement rate for tremor was 54.2% (improvement for all subscales), and improvement in quality of life was observed in 72.2% of treated patients ($p < 0.0001$), irrespective of etiology or tremor severity. However, Lim et al.[41] reported a prospective, single-blinded study of 14 patients treated with 130–140 Gy; the authors failed to observe any appreciable benefit in tremor control but did record a significant quality of life benefit.

Two comparative studies have been reported. The first, a single-blinded study by Young et al.,[85] compared 27 cases of GKRS thalamotomy with 11 control patients. The maximum dose ranged from 120 to 160 Gy, and the mean

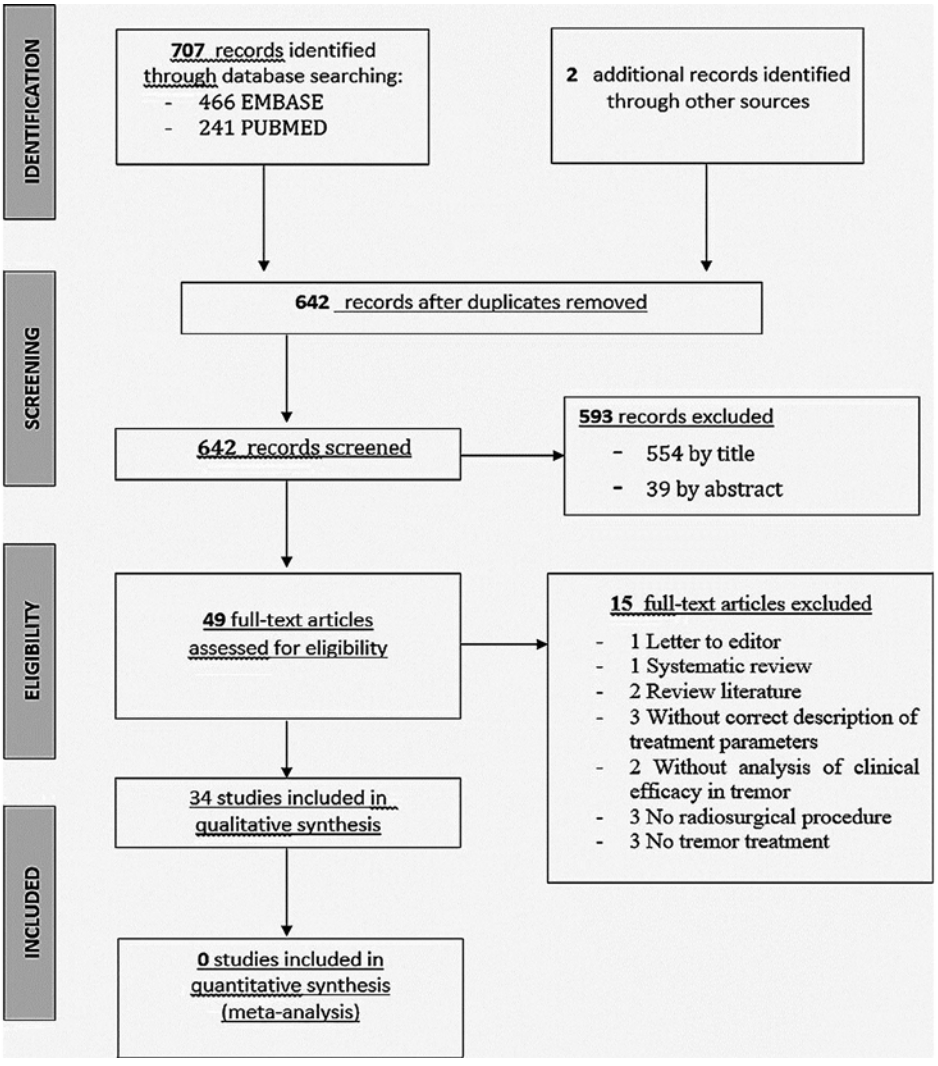

FIG. 1. Flow diagram showing the selection of studies for the systematic review of radiosurgical treatment of tremor.

follow-up was 22.2 months. UPDRS scores ($p = 0.05$) and the activities of daily living scale ($p = 0.008$) indicated an improvement in tremor outcomes in 88.9% of cases. Complete response was observed in 70.3% of the cohort. Niranjan et al.[51] compared thalamotomies performed using RFT, DBS, and GKRS in a retrospective comparative study. The study was limited by a small sample size within each cohort. Outcomes were similar in terms of tremor control, and side effects for GKRS tended to be transient. The time needed for response was longer for GKRS and immediate for RFT. However, RFT thalamotomy was associated with a high recurrence rate, and no conclusion as to superiority could be drawn.

Of the remaining studies, one of the largest series with a quantified assessment of tremor was reported by Young et al.[84] and subsequently expanded on in further reports by Frentress et al.[18] and Mojica et al.[49] The 161 ET patients were assessed by independent observers pre- and postprocedure using the Fahn-Tolosa-Marin rating scale (FTMRS). The dose was 140–150 Gy, and follow-up ranged from 6 to 60 months. Improvements were quantified for both drawing (81%) and writing (77%) and were highly significant ($p < 0.0001$).

Kooshkabadi et al.[34] reported on a large group of 86 patients treated with doses of 130–140 Gy, recording improvement in tremor in 81% ($p < 0.00001$). All 3 parameters measured by the FTMRS (writing, tremor, and drinking) improved in 66% of cases. Successive studies by Ohye et al.,[56,59,60] evaluating between 50 and 85 patients, also reported an improvement in tremor in 80.8% and a decrease in the UPDRS score of 58.9%.

There were 13 series with fewer than 50 cases, case reports excepted, with a mean tremor response of 86.82% and score (mainly UPDRS and FTMRS) improvements of 38.13%, although only 5 studies included quantification. Duma et al.[10] performed 42 thalamotomies in 38 patients, with improvement in 90% (disappearance of tremor in 24% and excellent response in 26%). They compared patients who received a mean dose of 160 Gy with patients who received 120 Gy and found a statistically significant association between improvement and high doses ($p < 0.04$).

TABLE 1. General characteristics of studies, patients, and treatment

Authors & Year	Study Type/ Blinded	No. of Pts	Level of Evidence	Pathology (ET/PD/other)	Age (yrs)	Target	Collimator Size (mm)	No. of Collimators	Dose in Gy*
Bonnen et al., 1997	CR/no	1	IV	0/1/0	68	GP	4	1	140
Cho et al., 2015	PS/no	7	IV	6/1/0	72.9	VIM	4	1	130
Duma et al., 1998[12]	PS/no	34	IV	0/34/0	73	VIM	4	1	130 (100–165)
Duma et al., 1999	PS/no	38	IV	0/38/0	72	VIM	4	1	130 (100–165)
Elaimy et al., 2010	CR/no	1	IV	1/0/0	65	VIM	4	1	140
Frentress et al., 2010	RS/yes	192	IV	74/118/0	NR	VIM	4	1	140
Friedman et al., 1999	PS/no	15	IV	12/3/0	69	VIM	4	1	120–140
Friehs et al., 1995	PS/no	3	IV	0/3/0	63.3	VOA/VOP	4	1	160
Hirato et al., 1995	CR/no	1	IV	0/1/0	71	VIM	4	1	150
Jawahar et al., 2004	CR/no	1	IV	1/0/0	80	VIM	4	1	130
Keep et al., 2002	CR/no	1	IV	0/1/0	73	STN	4	1	120
Kondziolka et al., 2008	PS/no	31	IV	31/0/0	77	VIM	4	1	130–140
Kooshkabadi et al., 2013	PS/no	86	IV	48/27/11	71	VIM	4	1	130–140
Lim et al., 2010	PpS/yes	14	IV	11/3/0	75	VIM	4	1	130–140
Lindquist et al., 1992	CR/no	2	IV	0/1/1	73	VL	8/4	1	180/200
Mathieu et al., 2007	PS/no	6	IV	0/0/6	46	VIM	4	1	130–150
Mojica et al., 2011	RS/yes	196	IV	76/120/0	NR	VIM	4	1	140
Niranjan et al., 1999	RS/no	12	IV	6/5/4	75	VIM	4	1	130–150
Niranjan et al., 2000	PS/no	11	IV	8/0/3	75	VIM	4	1	130–150
Ohye et al., 1996	PS/no	8	IV	1/6/1	61	VIM	4	1	140–150
Ohye et al., 2000	PS/no	31	IV	5/22/4	60	VIM	4	1	120–150
Ohye et al., 2002	PS/no	53	IV	11/35/7	NR	VIM	4	1	130
Ohye et al., 2005	PS/no	60	IV	0/60/0	NR	VIM	4	1	130
Ohye & Shibazaki, 2009	PS/no	85	IV	NR	NR	VIM	4	1	130–150
Ohye et al., 2012	PpS/no	72	IV	13/59/0	66.6	VIM	4	1	130
Okun et al., 2001	CR/no	8	IV	0/8/0	57.3	VIM/GP	4	1	100–200
Pan et al., 1996	PS/no	8	IV	0/8/0	59.3	VIM/VOA/VOP	4	2	160–180
Rand et al., 1993	PS/no	10	IV	3/7/0	69.3	VL	4	1	140–160
Rothstein, 2010	CR/no	1	IV	1/0/0	77	VIM	4	1	160
Witjas et al., 2015	PpS/yes	50	IV	36/14/0	74.5	VIM	4	1	130
Young, 1996	PS/no	5	IV	0/3/2	NR	VIM	4	1	140–160
Young et al., 1998	CC/yes	27	IV	8/16/3	73.3	VIM	4	1	120–160
Young et al., 2000	PS/yes	158	IV	52/102/4	69.8	VIM	4	1	120–160
Young et al., 2010	PS/yes	161	IV	161/0/0	72	VIM	4	1	141–152

CC = case-control study; CR = case report; GP = globus pallidus; NR = not reported; PpS = prospective study; PS = patient series; pt = patient; RS = retrospective study; STN = subthalamic nucleus; VL = ventral lateral nucleus; VOA = ventralis oralis anterior nucleus; VOP = ventralis oralis posterior nucleus.

* Reported as the mean, range, or mean (range).

Eight studies described clinical cases.[4,14,24,27,28,42,61,70] Okun et al.[61] described improvement of tremor in 87.5% of 8 patients. Only 2 clinical case studies quantified changes in the scores, reporting 67% and 100% improvement.[14,27]

It is mainly the VIM that is targeted for tremor, and, given the greater frequency of symptoms on the right side, 80% of the GKRS procedures reviewed involved left-sided thalamotomies. Target localization has been performed using MRI, employing T1-weighted and T2-weighted sequences with millimeter-thick slices (usually 1–2 mm; Fig. 2). Witjas et al.[79] used 0.5-mm slices and coregistration of the images with images that were previously obtained using tractography. The coordinates were located along the anterior commissure–posterior commissure line in nearly all series, shifted from the midpoint approximately 11 mm laterally, 7–8 mm posteriorly, and 2–4 mm above. Certain centers modify the target so that the 20%–30% isodose does not exceed the interior edge of the internal capsule.[8,33,34,51,57,58,65,68] The coordinates were corroborated by means of anatomical atlases in nearly all studies, in particular the atlas of Schaltenbrand and Wahren.[23] Young et al.[85] repeated their measurements and found errors ranging from 1 to 1.5 mm because of differences in location of commissures and other anatomical structures (SD: 0.5

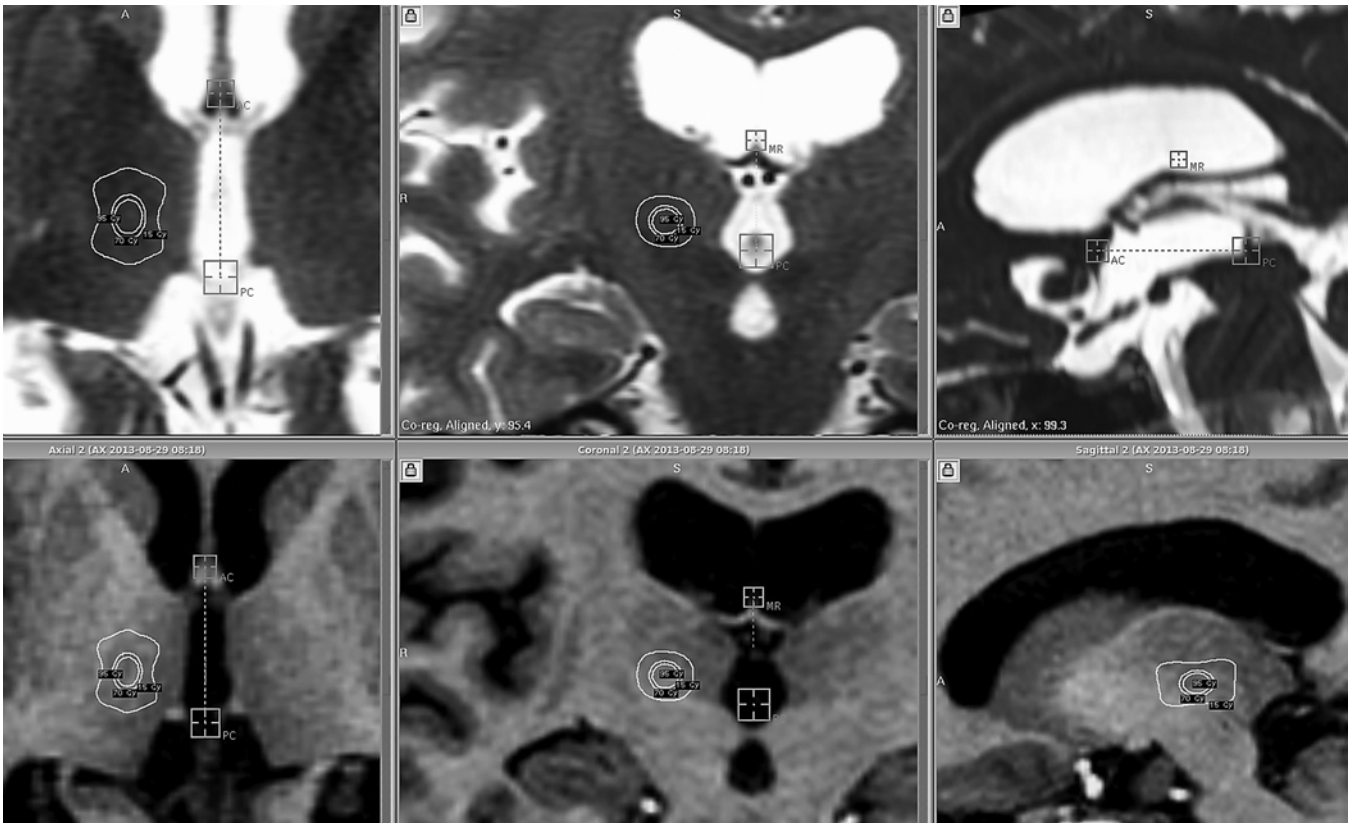

FIG. 2. MR images showing target localization of the VIM.

mm along the x-axis, 0.8 mm along the y-axis, and 1 mm along the z-axis).

The collimator size was 4 mm, except in one study that included a case treated with two 4-mm collimators[65] and another study that used 2 collimators on the same patient, one 4 mm and the other 8 mm.[42] The maximum prescribed dose used in most of the studies was 130–140 Gy, although the range was rather broad (100–200 Gy).

The mean improvement in tremor was 88%. Many studies did not specify the degree of improvement. Of those that did, tremor disappeared in 31% of cases and an excellent response was achieved in 22%, with a good response in 26% and a moderate response in 21%. The few articles that have quantified the impact on quality of life recorded a variation of 35.23% in the scores.[41,79,85] The mean time to response was 4.8 months, with a range from 3 weeks to 18 months. Few studies reported recurrence, with a tremor-free period of 10 months.[34,42,48,55,68] Table 2 lists the data relating to clinical response.

Twelve of the 34 studies reported no complications, and 2 studies failed to report complication rates. Complications were observed at approximately 4 months after treatment and tended to be transient with recovery after 9 months. Six studies[4,14,19,42,61,70] reported high complication rates (47%–100%) on account of the low number of patients per study. Only the report by Friedman et al.[19] had an assessable number of cases (n = 15), and the authors described 4 patients with severe edema that resolved completely in 1 patient after corticotherapy, improved significantly in 2 patients, and left a mild residual impairment in the remaining patient. The most severe complications were observed in patients previously treated by pallidotomy using RFT. The reports[34,55,84] with the largest number of patients, and hence the most representative studies, reported fewer complications (range 1.6%–16.7%). Witjas et al.[79] recorded a single case of transient hemiparesis 1 year after SRS that resolved in 1 month. Ohye et al.[55] reported a case of mild hemiparesis at 3 months post-SRS that resolved after 3 months. The most frequent complications were loss of strength or contralateral sensitivity, difficulty speaking, and dysphagia. In particular, there were 2 cases of thalamic hemorrhage, one at 14 months after GKRS[41] and another at 90 months.[70] Okun et al.[61] addressed the question of whether the dose they used, 200 Gy, might have been too high because they encountered several complications, including hemiparesis, pseudobulbar laughter, and dysphagia with death due to aspiration pneumonia. Another death resulting from thalamic hemorrhage in a patient treated with warfarin was recorded in 1 study 7 years after GKRS.[70] Table 3 lists the data on recurrence and complications.

There were few data on bilateral treatments.[10,12,21,34,58,59,61,83,84] Young et al.[84] included 42 patients with bilateral thalamotomy (at 20-month intervals) without complications. Okun et al.[61] reported 2 bilateral SRS thalamotomies, at 2- and 8-month time points, delivering 200 Gy/200 Gy in one patient and 200 Gy/150 Gy in the other. Both patients experienced complications and exhibited alterations extending to the internal capsule on MRI. In the second

TABLE 2. Clinical response

Authors & Year	No. of Pts	Dose (Gy)*	Follow-Up Mos (range)*	Tremor Rating Scale	% Tremor Improvement	Mos to Improvement (range)*	Quality of Life Improvement
Bonnen et al., 1997	1	140	36	None	100	NR	NR
Cho et al., 2015	7	130	7.3 (3–12)	FTMRS	85.7	4	NR
Duma et al., 1998[12]	34	130	28 (6–58)	UPDRS	89.5	2 (0.25–8)	NR
Duma et al., 1999	38	130	30 (6–72)	UPDRS	90.5	2 (0.25–8)	NR
Elaimy et al., 2010	1	140	72	UPDRS/FTMRS	100	0.5	NR
Frentress et al., 2010	192	140	84 (24–228)	UPDRS/CRST	83.3	NR	NR
Friedman et al., 1999	15	120–140	3–8	UTRS	100	1	NR
Friehs et al., 1995	3	160	NR (1–12)	UPDRS	100	0.75–1	NR
Hirato et al., 1995	1	150	6	None	100	3	NR
Jawahar et al., 2004	1	130	14	FTMRS	100	14	NR
Keep et al., 2002	1	120	42	None	100	1.25	NR
Kondziolka et al., 2008	31	130–140	36 (4–96)	FTMRS	88	NR	NR
Kooshkabadi et al., 2013	86	130–140	11.5 (1–152)	FTMRS	81	2 (0.25–8)	NR
Lim et al., 2010	14	130–140	19.2 (7–30)	UPDRS/FTMRS	21	7–24	11 of 14 pts (FTMRS ADL/ UPDRS part II)
Lindquist et al., 1992	2	180/200	24	None	100	4 (2–6)	NR
Mathieu et al., 2007	6	130–150	27.5 (5–46)	FTMRS	100	2.5 (2–3)	NR
Mojica et al., 2011	196	140	84 (24–228)	UPDRS/CRST	82.6	NR	NR
Niranjan et al., 1999	12	130–150	7 (3–24)	None	100	2 (1–6)	NR
Niranjan et al., 2000	11	130–150	6 (2–11)	FTMRS	100	0.5–3	NR
Ohye et al., 1996	8	140–150	12	None	100	3–15	NR
Ohye et al., 2000	31	120–150	12–72	None	87	12 (3–18)	NR
Ohye et al., 2002	53	130	24–96	None	80	12	NR
Ohye et al., 2005	60	130	3–24	UPDRS	82.5	3–15	NR
Ohye & Shibazaki, 2009	85	130–150	NR	UPDRS	80	6–12	NR
Ohye et al., 2012	72	130	24	UPDRS	81.8	3	NR
Okun et al., 2001	8	100–200	NR	None	87.5	2 (1–4)	NR
Pan et al., 1996	8	160–180	4.5 (2–9)	None	100	0.1	NR
Rand et al., 1993	10	140–160	NR	None	80	NR	NR
Rothstein, 2010	1	160	90	None	100	NR	NR
Witjas et al., 2015	50	130	12	FTMRS/WHIGET	54.2	1–12	72.2%
Young, 1996	5	140–160	6–19	NR	80	NR	NR
Young et al., 1998	27	120–160	22.2 (12–44)	UPDRS	88.9	2–3	20% improvement UPDRS part II
Young et al., 2000	158	120–160	52.5 (11–93)	UPDRS/FTMRS	88.6	NR	NR
Young et al., 2010	161	141–152	44 (6–60)	FTMRS	81	NR	NR

ADL = activities of daily living; CRST = Clinical Rating Scale for Tremor; WHIGET = Washington Heights-Inwood Genetic Study of ET tremor rating scale.
* Reported as the mean, range, or mean (range).

patient, a PET scan showed lowered metabolism in the region. On autopsy after death due to aspiration pneumonia, the target showed necrosis. However, the high doses appeared to be the source of the alterations. Duma et al.[10,12] reported on 4 patients who underwent bilateral treatment with a median radiation dose of 130 Gy, at 6-month time points, without complications.

Two types of thalamic lesions after SRS were described by Ohye et al.:[58] a clearly defined millimetric lesion with ring-shaped contrast uptake and, less often, a larger and diffuse lesion with substantial edema, with possible extension to the medial one-third of the internal capsule. A phenomenon of unclear origin consisting of band-like structures on the image, known as streaking, is often present and may also appear transiently after thermocoagulation but tends to be permanent after SRS.[55] The changes visible on the images appear at around 3–5 months and are unpredictable, not always being related to the dose, the response, or the onset of complications, and they do not always resolve over time. Changes on T1-weighted sequences seem to correlate better with the collimator and dose employed than the changes on FLAIR and T2-weighted sequences, which are more variable in size, appearance, and resolution. Figure 3 shows an example of MRI changes after

TABLE 3. Recurrence and complications

Authors & Year	No. of Pts	Dose (Gy)*	% Recurrence	No. of Adverse Events	Adverse Events Observed	Death	Cause of Death
Bonnen et al., 1997	1	140	0	1	Hemiparesis, hemianopa	0	NA
Cho et al., 2015	7	130	0	0	NA	0	NA
Duma et al., 1998[12]	34	130	0	0	NA	0	NA
Duma et al., 1999	38	130	5.2	1	Dysarthria	0	NA
Elaimy et al., 2010	1	140	0	1	Numbness	0	NA
Frentress et al., 2010	192	140	NR	3	Hemiparesis, dysphasia	NR	NR
Friedman et al., 1999	15	120–140	0	7	Transient slowed fine finger movements, action tremor, symptomatic edema	0	NA
Friehs et al., 1995	3	160	0	0	NA	0	NA
Hirato et al., 1995	1	150	0	0	NA	0	NA
Jawahar et al., 2004	1	130	0	0	NA	NR	NA
Keep et al., 2002	1	120	0	0	NA	NR	NA
Kondziolka et al., 2008	31	130–140	0	2	Hemiparesis & dysphagia, hemiparesis & speech impairment	2	Lung cancer
Kooshkabadi et al., 2013	86	130–140	6	4	Hemiparesis, dysphagia, facial numbness	0	NA
Lim et al., 2010	14	130–140	7	3	Thalamic hemorrhage, numbness	0	NA
Lindquist et al., 1992	2	180–200	50	1	Hemiparesis, dysphasia	0	NA
Mathieu et al., 2007	6	130–150	33.3	1	Hemiparesis	3	Complications of MS
Mojica et al., 2011	196	140	NR	5	Hemiparesis, speech difficulty	NR	NA
Niranjan et al., 1999	12	130–150	NR	1	Weakness & dysarthria	NR	NA
Niranjan et al., 2000	11	130–150	NR	1	Weakness of the contralateral arm & leg, dysarthria	NR	NA
Ohye et al., 1996	8	140–150	0	0	NA	2	CVA
Ohye et al., 2000	31	120–150	0	0	NA	0	NA
Ohye et al., 2002	53	130	0	NR	NA	0	NA
Ohye et al., 2005	60	130	0	NR	NA	0	NA
Ohye & Shibazaki, 2009	85	130–150	0	0	NA	0	NA
Ohye et al., 2012	72	130	2.8	1	Slight motor weakness	2	Other
Okun et al., 2001	8	100–200	0	5	Pseudobulbar laughter, hypophonia weakness & dysphagia, dysarthria, hemiparesis	1	Dysphagia/ aspiration
Pan et al., 1996	8	160–180	0	1	Contralateral weakness	0	NA
Rand et al., 1993	10	140–160	20	0	NA	0	NA
Rothstein, 2010	1	160	0	1	Weakness rt side & aphasia	1	Pneumonia
Witjas et al., 2015	50	130	0	1	Hemiparesis	0	NA
Young, 1996	5	140–160	0	0	NA	NR	NA
Young et al., 1998	27	120–160	NR	0	NA	NR	NA
Young et al., 2000	158	120–160	4	3	Weakness & dysphasia, balance problems, paresthesia	9	Unrelated
Young et al., 2010	161	141–152	NR	14	Sensory loss, hemiparesis, speech disturbances	31	Other

CVA = cerebrovascular accident; MS = multiple sclerosis; NA = not available.
* Reported as the mean or range.

GKRS thalamotomy. Friehs et al.[20] described a tendency toward smaller lesions in women. Duma et al.[10,12] found more signal changes on T2-weighted sequences in patients subjected to high doses. Friehs et al.[20] too observed this association and reported lesions larger than 2000 mm^3 in 3 patients who received doses greater than 160 Gy. Dose rate–related lesions have been described,[7,56] with lesions larger than 175 mm^3 recorded using MRI in patients treated after replenishing the ^{60}Co sources compared with 311 mm^3 in patients treated before replenishment ($p = 0.041$).[59] Major changes on T2-weighted and FLAIR sequences affecting the thalamus or internal capsule medially have been related to higher complication rates;[33,34,52,65,79,83] these complications may be serious[4,18,61,65] or they may also be asymptomatic.[24,57] Young et al.[84] reported a mean lesion size of 188 mm^3 on MRI after 157 GKRS procedures, with

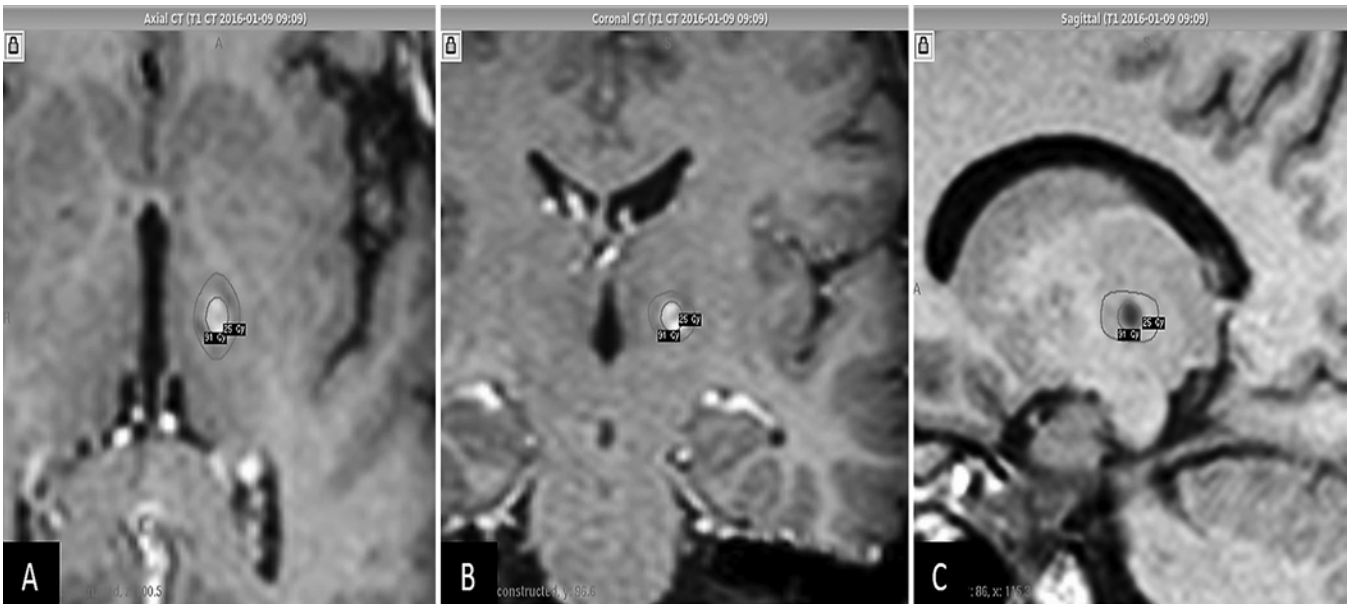

FIG. 3. MR images showing changes 1 year after GKRS thalamotomy (maximum dose 130 Gy). **A and B:** Axial (A) and coronal (B) Gd-enhanced T1-weighted images showing a millimetric lesion measuring a few millimeters that correlates with the 91-Gy isodose line. **C:** Sagittal T1-weighted image showing a low-signal region that coincides with the 91-Gy isodose line.

the size increasing to 871 mm^3 in patients with complications ($p < 0.001$). However, MRI can also show extensive effects without causing complications for patients.[57]

The likelihood of complications is related to the volume of brain parenchyma receiving a given dose. Several indices are used to estimate that volume, e.g., the gradient index.[62,63,76] Matrix size also appears to have an influence. Larger matrices may result in longer procedure times, longer exposure times, and higher total doses.[65] Using a single smaller collimator helps minimize the dose to peripheral tissue. Lindquist et al.[42] reported 2 patients who were treated with doses of 180 and 200 Gy, using an 8- and 4-mm collimator, respectively. The lower dose yielded greater response but also more complications and a larger lesion on MRI (800 mm^3 vs 120 mm^3).

Discussion

There are no randomized controlled studies comparing the use of SRS to treat tremor with other therapeutic options. Thus for this reason, the results obtained in this review are descriptive, like those in the recent review by Campbell et al.[7]

Considering studies with at least 10 patients, approximately 82% of patients experience clinical improvement after GKRS thalamotomy at doses between 130 and 150 Gy. Tremor response usually translates into enhanced quality of life. Few studies have reported quality of life changes using suitable scales.[41,79,85] These scales were designed to assess response to pharmacological treatment; hence, applying them to SRS, a unilateral procedure, may yield different results when contralateral clinical symptoms persist.[54]

The time to response varied from weeks to months (mean 4.8 months, median 2.5 months),[8,12,34,52,58,65] and the mean complication rate after GKRS thalamotomy was 17.4%. The complications may present months or years after SRS, and their severity is highly variable.[10,85] Edema after GKRS is a subacute reaction[67] and is usually completely or partially reversible. Siderowf et al.[72] reported a case of ET with serious complications after an SRS thalamotomy, but this study did not describe the technical details of treatment and hence has not been assessed with other publications.

Both RFT thalamotomy and DBS achieve control rates of 90%,[17,26,55] and the associated complications (hemorrhage, infections, convulsions, pneumocephalus, pulmonary embolism, late mechanical complications, death)[64,77,81] are different from those observed in SRS procedures. In the single comparative study,[52] the 13 patients treated with RFT thalamotomy improved, but tremor recurred in 50%. The 11 patients treated with DBS showed immediate improvement, with excellent sustained control in 9 patients. For the SRS patients, 12 of 15 exhibited good response after more than 6 months of follow-up, with 1 case of mild weakness in the contralateral limbs and dysarthria at 8 months following treatment that improved with corticosteroids. The authors concluded that efficacy was similar, the complication rate was higher for RFT and DBS, and the time to response was longer for GKRS. Another drawback of GKRS compared with DBS is the inability to confirm the location of the target using intraoperative monitoring. This makes correct anatomical identification essential, and nearly all studies use high-field MRI (at least 1.5 T) with thin slices on T2-weighted sequences and FLAIR studies, among others, in addition to T1-weighted sequences. MRI at higher field strengths (3 or 7 T) enhances VIM definition[9,15,74] but may also increase image distortion. Tractography can help identify adjacent traces to minimize

Level of evidence	Source of evidence
LEVEL I	Randomized controlled clinical trials. Randomized systematic reviews
LEVEL II	Cohort studies. Outcomes Research.
LEVEL III	Systematic review of case-control studies. Good quality cohort and case-control studies.
LEVEL IV	Case-series. Poor quality cohort and case-control studies.
LEVEL V	Expert opinion. Experimental studies.

FIG. 4. Levels of evidence summary based on details provided by the Oxford Centre for Evidence-Based Medicine (https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). The original levels of evidence were produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, and Martin Dawes beginning in November 1998. The latest update (March 2009) is by Jeremy Howick.

complications and, for this reason, should be integrated into SRS procedures.[47,66,80] Once the optimal target, i.e., the lateral portion of the VIM, has been determined using MRI, reconstructions based on computerized atlases can be associated. Once planning has been assessed and individual anatomical variability considered,[5] small shifts from the target may be made or blocking may be used to protect the internal capsule.[57]

The studies reviewed have used SRS in the form of a frame-based Gamma Knife system; hence, it is the only one assessed. There are other SRS technologies, for instance, the CyberKnife frameless image-guided robotic radiosurgery system (Accuray Inc.). Its utilization in functional disorders is practically limited to trigeminal neuralgia, but some articles have been published on its use for obsessive-compulsive disorder, dystonia, and neuropathic pain.[29,63,75] Fariselli et al.[15] described 2 patients treated for bilateral tremor, DBS on one side and CyberKnife SRS on the other, and achieved total control of tremor. However, the authors did not provide data on the dose delivered, response time, follow-up, or imaging findings. Hence, we cannot analyze that study and make recommendations. The Novalis system (Brainlab AG) is another important modality; however, its use specific to functional disorders is limited. Comparisons between GKRS and early dedicated linear accelerator SRS in such cases, requiring small collimators, have yielded controversial results.[1,73] At the present time, GKRS is broadly accepted as the procedure offering the greatest precision and accuracy while affording the possibility of safely using very small collimators and a large dose gradient, all indispensable attributes for functional treatments. GKRS thalamotomy should be performed with the support of a specialized multidisciplinary team capable of carrying out long-term follow-up and likewise capable of assessing the improvement both in the tremor and in the quality of life. This should be done blindly using validated scales both before and after treatment.

The doses used by the various authors were variable. It has been postulated that doses for functional treatments should be greater than 150 Gy to produce a lesion in the brain tissue.[42,65] Subsequently, lower doses were observed to be capable of altering function, and doses greater than 150 Gy were liable to elicit complications. The most recent studies have placed the optimal prescription dose at 130 Gy.[8,55]

There have been very few studies addressing the histological changes taking place at high doses. Okun et al.[61] described findings in a patient who died a few months after GKRS thalamotomy performed at 150 Gy and who had previously undergone an earlier procedure at 200 Gy. The region of the more recent treatment presented histological changes consistent with acute injury. Acute lesions coexisted with areas of organized injury (necrosis, gliosis, and inflammatory processes) in the region previously treated at the higher dose. Niranjan et al.[52] postulated the existence of a combination of tissue destruction and physiological alterations in the peripheral region of the thalamus and internal capsule, corresponding to an area receiving a not insignificant dose (14–70 Gy). A review of animal experiments described the region of the lesion after SRS as being highly contained and surrounded by normal brain parenchyma.[53] Applying microrecording, Ohye et al.[60] confirmed this finding in humans after GKRS thalamotomy. No neuronal activity was found at the center of the irradiated region, but there were neurons with normal activity immediately outside that region. Sustained neuronal activity may explain the occasional recurrence and the low complication rate. The necrotic lesion is very small but is ringed by vascular changes and gliosis, which some authors suggest may, thanks to a neuromodulatory mechanism, be responsible for the good long-term results achieved by both RFT thalamotomy and SRS.[52,69]

The results of this review should be evaluated with caution because of the impossibility of carrying out a quantitative study, and because the level of evidence of the selected articles was level IV (Fig. 4). Not all publications use the same scales, and most do not have the benefit of blinded evaluation design. Follow-up periods were highly variable. Although some articles reported good results for up to 6 or 7 years after SRS,[14,18,49,83] in general, follow-up tended to be short, which affects both the complication rate and the long-term response results.

Conclusions

Based on this systematic review of the literature, it can

TABLE 4. Recommendations for management of tremor

Level of Evidence	Recommendation
IV	SRS is recommended for patients w/ tremor for whom medical therapy has failed & who are not candidates for invasive surgery.
IV	SRS should be considered even for patients w/ tremor for whom medical therapy has failed even if they are candidates for invasive surgery since SRS appears to have a lower level of complications.
IV	GKRS has been performed w/ a single 4-mm collimator, single-fraction maximum dose of 130–150 Gy & the lesion made in the VIM located using advanced imaging modalities & stereotactic atlases.

be concluded that SRS thalamotomy is a method with suitable tremor control rates and is recommendable for patients for whom medical therapy has failed, offering patients different alternatives so that patients may play a role in treatment selection irrespective of whether they are candidates for invasive surgery (Table 4).

The procedure is safe and well tolerated as long as the following optimal conditions are fulfilled: 1) advanced imaging modalities are used; 2) a 4-mm collimator with GKRS (there is insufficient information on other systems) is used; 3) the maximum dose ranges from 130 to 150 Gy; and 4) the lesion is made in the VIM located based on available stereotactic atlases.

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Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods of care reasonably directed to obtain similar results. Physicians must make the ultimate judgment on the basis of characteristics and circumstances of each individual patient. Adherence to these guidelines will not ensure successful treatment in every situation. The authors of these guidelines and the International Stereotactic Radiosurgery Society assume no liability for the information, conclusions, or recommendations contained in this report.

Disclosures

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