NHS England

Evidence Review:

Stereotactic Radiosurgery (SRS) for adults with Parkinson's tremor and Familial Essential Tremor

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1. Introduction

The basic principle of stereotactic radiosurgery (SRS) is the elimination of a functional disorder, or destruction of abnormal tissues, by administration of a strong and highly focused dose of radiation. The procedure allows radiation to be limited to the targeted area and thus helps spare the surrounding tissues as much as possible.

SRS is routinely used in the treatment of a number of different brain and central nervous system pathologies as defined by a number of clinical commissioning pathways. Here, we consider the use of SRS as the final treatment option for patients with drug resistant tremor associated with Parkinson's disease and familial essential tremor (FET).

2. Summary of results

We conclude there is low level evidence (level 3) to support the use of stereotactic radiosurgery in the treatment for movement disorders. In conclusion there is insufficient evidence for efficacy, safety, impact on quality of life and cost effectiveness.

To date there has been no randomised trial comparing stereotactic radiosurgery with any other treatment modality such as deep brain stimulating and/or radiofrequency ablation. Stereotactic radiosurgery has been reserved for patients with intractable tremor, where more invasive surgical therapies are contraindicated.

Two recent prospective studies (level 3) have reported a significant improvement in activities of daily living (ADL). Witjas et al (2015) reported a 72.2% improvement (0-100%) in ADL and Ohye et al (2012) reported 81.1% patients rating a tremor score as 'excellent' or 'good' post stereotactic radiosurgery. The largest case series (level 3) within the last five years by Kooshkabadhi et al, 2013 (n=88) showed at least 81% improvement in at least one of the three tremor scores.

These two prospective studies have also evaluated the size of the thalamic lesion pre and post radiation with brain MRI scans, with an overall expected lesion response in the majority of patients. However, authors have noted the thalamic site can fluctuate and warrants further investigation. Witjas et al (2015), described one patient (n=50) with an extensive thalamic response that spontaneously resolved.

The results of these three cases series are consistent with a recent systematic review by Campbell et al, 2015 (level -2). The review evaluated 29 papers of which were primarily case reports and patient case series. Sixteen studies evaluated tremor scores pre and post stereotactic radiosurgery, patient numbers in the studies varied from 172 to 8. All studies except one study showed an improvement in tremor score, range of improvement from 50-100%. Overall the systematic review concluded approximately 80% of patients with intractable tremor had some clinical benefit following the procedure. The review identified the largest case series, conducted by Young et al 2010 (n=172) which showed an improvement in both drawing and writing scores ($P<0.001$), at 6 month follow-up.

The three recent cases series (Witjas et al (2015), Ohye et al (2012) and Kooshkabadhi (2013)) describe at least one patient developing transient contralateral weakness following SRS therapy, which resolved spontaneously. No other significant side effects were reported. In the systematic review (Campbell et al, 2015) complication rate reported varied between 0% -16 %, predominately motor symptoms. In the review, one group reported a thalamic haemorrhage at treatment site, although the patient was on anticoagulant treatment. In addition three groups in the review reported patient deaths attributed to the therapy. One patient developed aspiration pneumonia secondary to dysphagia, one died of radiation necrosis (bilateral lesions), one died of haemorrhagic stroke at site of lesion 7.5 years after procedure. One group described a correlation between lesion seize and dose in Gy. The authors concluded on the basis of the systematic review unilateral gamma knife thalamotomy using doses from 130-150 Gy is well tolerated and safe. However to date there has not been a long term follow-up study and requires further investigation.

We found no specific evidence relating to the model of care post-SRS that may impact on the long term duration of response, for example input from other specialities such as occupational health, physiotherapy.

3. Research questions

What is the cost of SRS for movement disorders and comparisons with other treatment modalities?
What is the clinical effectiveness of SRS for movement disorders and comparisons with other treatment modalities?
In relation to duration of response, what is the evidence for the most effective model of care to support long term improvement / maintenance of efficacy?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix 1

Grade	Study design and			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
2-	Systematic review	0	Unilateral GKT dose varied 120-200Gy	Clinical effectiveness of the intervention	Assess safety and efficacy of gamma knife thalamotomy in treatment of intractable tremor in patients who are not candidates for deep brain stimulation	16 studies (patients varied from 8-172) evaluated the tremor score pre and post intervention, with all showing improvement except one study by Lim et al (n=18). Response varied from 50-100%. Largest case series by Young et al, 2000 n=172 showed 81% improvement in FTM scale. Follow up in this cohort was at least 6 months with improvement in drawing (3.3 to 1.6) and writing (3.1 to 1.3) scores P<0.0001. Review concluded approximately 80% of patients expect to receive some clinical benefit.	Effect of treatment on activities of daily living and quality of life	Evaluated findings from Ohye et al study as discussed above	Campbell, Allison M.; Glover, Janis; Chiang, Veronica L. S.; Gerrard, Jason; Yu, James B.. Gamma knife stereotactic radiosurgical thalamotomy for intractable tremor: a systematic review of the literature. Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology. 2015	Rate of complication varied from 0%-16%. The largest series (Young et al n=172), complication rate of 8.4%, included contralateral sensory loss and contralateral motor impairments, ranging from mild to significant. 6/14 patients with motor complications did not resolve. Across all studies the most common adverse events reported were motor problems from mild weakness to hemiparesis and dysphagia. One group reported a thalamic haemorrhage at treatment site, at 14 month follow up (patient was on warfarin). 3 groups reported patient deaths attributed to the therapy, one patient developed aspiration pneumonia secondary to dysphagia, one died of radiation necrosis (bilateral lesions) and one died of haemorrhagic stroke at site of lesion 7.5 years after procedure.	Yes	Population: Patients with intractable tremor: ET, PD, MS and stroke Following a review of studies, the authors concluded that gamma knife thalamotomy for intractable tremor provided clinical benefit to approximately 80% of patients. Identified study that directly correlated lesion size and dose. Identified across all studies patients with adverse outcomes were found to have lesions sizes larger than expected. Identified no randomised control trials. Limitations of review, treatment in largely an elderly patient cohort with contraindications to invasive surgery. All major studies have been conducted at large neurology and functional neurosurgery departments with access to multi-disciplinary staff. The authors conclude on the basis of the systematic review of literature unilateral gamma knife thalamotomy using doses from 130 to 150Gy appears to be well tolerated and safe. The systematic review is downgraded in view of review of literature (lack of meta-analysis) which is predominately case reports and retrospective case series. The lack of blinded observers, variable follow up period increased the bias in these collective studies.
3	Single study	50pts , M:32 ET=36, PD=14	Unilateral GKT, dose of 130Gy targeted at the ventral intermediate nucleus (thalamic lesion)	Clinical effectiveness of the intervention	To assess improvement in global tremor severity. i) blinded video assessment of upper limb tremor score, ii) un-blinded tremor severity the following parameters: (a) Global tremor severity of three tremor components; rest, postural and intention, using the Fahn-Tolosa-Mann Tremor Scale (b) Washington Heights Inwood Genetic study of essential tremor rating score (0 = no tremor, 4 = severe tremor). (c) Assessment of activities of daily living (ADL) using self-designed questionnaire (25 items, score 1 = activities without difficulty, 4 = activities with severe difficulty). (d) Testing of cognitive function which was assessed using Mattis Dementia Rating Scale and Verbal fluency test. Five patients were unable to complete full neuropsychological testing.	i) Independent movement disorders neurologist assessed tremor on video (single blinded assessment). Blinded assessment with improvement in upper limb tremor score by 54.2%% (36.2-79.2%, P<0.0001 at 12 months). ii) Un-blinded assessment improvement of total tremor score by 63.4% (38.3-90.6%, P<0.001). iii) ADL mean improvement at 12 month by 72.2% (0-100%). iv) No change in cognitive function.	MRI evaluations of thalamic region pre and post treatment	38/50 patients had normal neuroimaging response with hyper-intensive limited signal changes and central ring shaped enhancement. 11/50 patients had absence of visible lesion or v.min alterations. 1 patient had extensive response with oedema that resolved spontaneously.	Witjas, Tatiana; Carron, Romain; Krack, Paul; Eusebio, Alexandre; Vaugoyeau, Marianne; Hariz, Marwan; Azulay, Jean Philippe; Régis, Jean. A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology. 2015	One patient developed transient contralateral hemiparesis at 12 months that resolved within 3 weeks.	Yes	Population: PD/ET patients with severe tremor Single blinded prospective study. No control group, although bias is reduced on assessment with single blinded assessment, a lack of comparative group, grade evidence as 3. However patients in this cohort had a mean age of 75, and other available therapies such as DBS (deep brain stimulation) conducted on younger patients with potentially fewer co-morbidities as is a more invasive procedure then GKT.

3	Single study	86 patients (88 procedures) mean age 71, M: 51 F: 35. Essential tremor n=48 (mean age 45), Parkinson's disease (PD) n=27 (mean age 76). Multiple sclerosis n=11 (mean age 45).	GKT - gamma knife thalamotomy MRI used to localise site and conducted pre and post procedure. Maximum dose of Gamma knife technology used 140Gy.	Clinical effectiveness of the intervention	Improvement in Tremor measured on i) FTM tremor score ii) Writing score iii) Ability to drink from a cup. Scores conducted pre and post intervention.	Overall in all patient group improvement in mean tremor score pre-treatment 3.28+/-0.79 to 1.81+/- 1.15 (P<0.001), writing score 2.78+/-0.82 to 1.62+/- 1.04 (P<0.0001) drinking Score 3.14+/-0.78 to 1.80 +/-1.15 (P<0.0001) In ET group all scores significant P<0.0001. tremor score 3.31 to 1.8, writing score 2.7 to 1.4 water drinking score, 3.1 to 1.7 and in PD group Writing score 2.4 to1.3, Tremor score 3.0 to 1.5 and water score 2.9 to 1.5. In total 70pts (81%) had at least one improvement in their scores following GKT tx. 66% (57) had improvement in all 3 scores, 13% (11pt) in 2 scores and 2% (2pts) in one score. For any indication, clinical benefit of radiosurgery occurred at average of 2 months (1 week – 8 months). 19%, 16 patients failed to respond.	0	0	Kooshkabadi, Ali; Lunsford, L. Dade; Tonetti, Daniel; Flickinger, John C.; Kondziolka, Douglas. Gamma Knife thalamotomy for tremor in the magnetic resonance imaging era. Journal of Neurosurgery. 2013	2 patients developed temporary contralateral hemiparesis 6 months post GKT, 1 patient noted dysphagia at 8 months, and 1 patient reported facial sensory loss.	Yes	Population: Patients with significant limitations in activities of daily living, tremor intractable to medical treatment. In total 3 groups; ET- essential tremor, PD- Parkinson's disease, MS-multiple sclerosis. Variability in outcome measures as not all patients were followed up at the treatment centre, follow up via telephone where possible. No control arm to the study
3	Multi-study	72 patients, M: 38, F: 34, ET=13, PD=59	GKT used a single dose of 130Gy. MRI to localise thalamic site	Clinical effectiveness of the intervention	To assess improvement in tremor (i) clinical neurological examination (ii) unified Parkinson's disease rating scale (UPDRS) (iii) EMG - Electromyography (iv) video recording. Overall patients response as 'Excellent improvement' (no tremor +/- muscular rigidity), 'Good' > 50% improvement, 'No change' <50% improvement, 'worse' deterioration.	At 24 months 53 patients completed follow up, 81.8% (43/53) patients categorised as excellent or good, 15.1% (8/53) no change and 3.8% (2/53) deteriorated. At 24 months on the UPDRS III score 58.% of PD patients and 60% of ET patients scored zero (no tremor) and 79.25 P<1. Significant improvement in UPDRS II (activities of daily living) and UPDRS III (motor examination) score at 24 months P<0.05. UPDRS II 7.49+/-5.51 to 4.65+/-3.73 and in UPDRS III 14.45+/-10.12 to 8.81+/-8.66. No reduction for mentation, behaviour and mood (UPDRS I) and no significant increase in exacerbations or complications (UPDRS IV), change in symptoms observed ~ 3 months post treatment. GKT had no impact on regular medication doses post intervention at 24 months (regular medication). Of the 41 patients tested for EMG, 56.9% had tremor decrease post treatment. Also 11/17pts who had video recording exhibited a good or excellent response.	MRI evaluations of thalamic region pre and post treatment.	Thalamic lesion size fluctuated. 65.6% converged to a spherical shape, 23% sphere with streaking and 10.9% to extended high signal zone.	Ohye, Chihiro; Higuchi, Yoshinori; Shibazaki, Toru; Hashimoto, Takao; Koyama, Toru; Hirai, Tatsuo; Matsuda, Shinji; Serizawa, Toru; Hori, Tomokatsu; Hayashi, Motohiro; Ochiai, Taku; Samura, Hirofumi; Yamashiro, Katsumi. Gamma knife thalamotomy for Parkinson's disease and essential tremor: a prospective multicentre study. Neurosurgery. 2012	No severe complications. 1 patient did develop transient weakness.	Yes	Population: Patients with refractory tremor of PD or ET aetiology Multicentre prospective study, no control group. Low grade evidence.
3	Single study	2 patients	Unilateral radiosurgery and contralateral DBS	Clinical effectiveness of the intervention	Tremor	Bilateral tremor resolved	0	0	Franzini, Angelo; Marchetti, Marcello; Brait, Lorenzo; Milanesi, Ida; Messina, Giuseppe; Forapani, Elisabetta; Broggi, Giovanni; Fariselli, Laura. Deep brain stimulation and frameless stereotactic radiosurgery in the treatment of bilateral parkinsonian tremor: target selection and case report of two patients. Acta Neurochir (Wien). 2011	Nil reported	Yes	Case report of severe bilateral upper limb parkinsonia tremor associated with significant bias. In both patients, deep brain stimulation was performed on the contralateral side and radiosurgery on the unilateral side, the potential confounding effect remains uncertain.

Appendix 2

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Not applicable
Updated search terms - Population	
Updated search terms - Intervention	• Stereotactic radiosurgery • Cyberknife • Gamma Knife • LINAC • Linear accelerator radiosurgery • radiosurgery
Updated search terms - Comparator	• Deep brain stimulation • thalamotomy • neurostimulation • neuro-stimulation • neuro stimulation • lesional surgery
Updated search terms - Outcome	Not applicable

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, the following are included: 1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reach 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc) that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 5. Expert opinion
	Specific inclusion criteria
	Published within the last 10 years
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site
	Specific exclusion criteria
	None