



## Review article

# Radiosurgery for epilepsy: Systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline



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## ABSTRACT

**Background:** While there are many reports of radiosurgery for treatment of drug-resistant epilepsy, a literature review is lacking.

**Objective:** The aim of this systematic review is to summarize current literature on the use of stereotactic radiosurgery (RS) for treatment of epilepsy.

**Methods:** Literature search was performed using various combinations of the search terms “radiosurgery”, “stereotactic radiosurgery”, “Gamma Knife”, “epilepsy” and “seizure”, from 1990 until October 2015. Level of evidence was assessed according to the PRISMA guidelines.

**Results:** Fifty-five articles fulfilled inclusion criteria. Level 2 evidence (prospective studies) was available for the clinical indications of mesial temporal lobe epilepsy (MTLE) and hypothalamic hamartoma (HH) treated by Gamma Knife (GK) RS. For remaining indications including corpus callosotomy as palliative treatment, epilepsy related to cavernous malformation and extra-temporal epilepsy, only Level 4 data was available (case report, prospective observational study, or retrospective case series). No Level 1 evidence was available.

**Conclusion:** Based on level 2 evidence, RS is an efficacious treatment to control seizures in MTLE, possibly resulting in superior neuropsychological outcomes and quality of life metrics in selected subjects compared to microsurgery. RS has a better risk-benefit ratio for small hypothalamic hamartomas compared to surgical methods. Delayed therapeutic effect resulting in ongoing seizures is associated with morbidity and mortality risk. Lack of level 1 evidence precludes the formation of guidelines at present.

## 1. Introduction

Developed under the auspices of the International Stereotactic Radiosurgery Society (ISRS) Guideline Committee, the aim of this systematic review was to summarize current literature specific to radiosurgery (RS) for treatment of epilepsy. RS remains a debated

therapeutic domain despite nearly two decades of treatment. Comparison to conventional microsurgery is a challenge since, despite many published case reports and case series, there remain a relative paucity of robust data in the form of prospective controlled trials (Mindermann, 2015; Spencer, 2008). The vast majority of existing data are based on Gamma Knife (GK) with fewer reports of linear accelerator

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(LINAC) methods. As a result, the present systematic review summarizes predominantly GK-based RS for epilepsy. Because of lack of data, it is not yet possible to compare efficacy and safety profiles of different RS methods for different indications.

The first observations of a positive effect of RS on seizure control came from studies of radiosurgical treatment of cerebral tumors (Schrottner et al., 1998) and cerebrovascular malformations (Heikkinen et al., 1989), and in the 1990's this method was subsequently pioneered as an alternative to conventional microsurgery in patients with mesial temporal lobe epilepsy (MTLE) (Régis et al., 1995). Similar to conventional epilepsy microsurgery, the main indication for RS in epilepsy is in patients with pharmacoresistant focal epilepsy; that is, patients in whom the epileptogenic zone can be reasonably accurately defined and surgically treated without undue functional risk; whose seizures remain incompletely controlled by anti-epileptic drugs (AED); and in whom risk and/or handicap of ongoing epilepsy outweigh risks of surgery. The majority of reported cases of focal epilepsy in which RS is used with curative intent are patients with MTLE (Barbaro et al., 2009; Chang et al., 2010; Régis et al., 2004b), followed by epilepsy related to hypothalamic hamartoma (Abla et al., 2010; Bourgeois et al., 2013; Mathieu et al., 2006; gis et al., 2000a, 2004a; gis et al., 2000a, 2004a; Selch et al., 2005) and a small number of extra-temporal epilepsy cases (Irislimane et al., 2013; McGonigal et al., 2014). In some patients with widespread/bilateral refractory epilepsy, RS is a palliative rather than curative procedure, the aim being to cause a lesion that reduces seizure propagation, for example anterior corpus callosotomy (Feichtinger et al., 2006). In addition, RS may be offered to some patients whose epilepsy is inoperable by conventional means because of high risk of complication (McGonigal et al., 2014). Finally, RS may be offered after failed epilepsy surgery (Lee et al., 2015).

A targeted dose of RS delivered within a restricted volume of the EZ aims to alter epileptogenic cerebral tissue to yield a reduction in seizures. The effects are typically delayed by many months while radiation produces destructive changes within the brain tissue. The mechanism of action of RS in treating epilepsy is not yet fully elucidated but is thought to involve both ischemic necrotic and neuromodulatory effects (Quigg et al., 2012; Régis et al., 2010). Efficacy of RS has been shown to depend on many factors, in particular delineation of the EZ. Target planning is a major challenge in patients and typically dependent on both clinical and neurophysiological data (McGonigal et al., 2014; Rheims et al., 2008) rather than radiological data alone. This aspect clearly differs from non-functional RS indications such as tumours (Régis et al., 2004b).

For the present review, we summarize reports relating to epilepsy as the primary indication for RS, taking into account patient selection, intervention, comparison with conventional microsurgery and outcome. RS in the curative treatment of arteriovenous malformations and cerebral tumours is not included, since the main indication for treatment is usually lesional. Due to study heterogeneity, guidelines are based upon systematic review of the literature rather than meta-analysis.

## 2. Methods

Systematic review of the literature was undertaken according to methodological standards outlined in the PRISMA statement (Moher et al., 2009). Using the search engines Pubmed, Web of Science, Google Scholar and Scopus, articles in English or French were independently searched by two researchers using the following search terms: “epilepsy AND radiosurgery” and “epilepsy AND Gamma Knife”, “epilepsy AND linear accelerator” as well as their derivations, as keywords or text words.

Search was performed for all available articles from January 1990 to October 2015. Relevant items were included if epilepsy was the primary indication for RS. Articles were excluded if they dealt with RS treatment of intracerebral lesions that did not primarily aim at treating

refractory epilepsy. Additional articles were identified from the bibliographies of articles found in the primary search.

Articles were classed according to level of evidence (Wright et al., 2007) as follows:

Level 1: Randomized controlled trial;

Level 2: Prospective studies without randomization, with pre-defined inclusion criteria and outcome measures;

Level 3: Observational studies with control groups (cohort and case-control);

Level 4: Observational studies without control groups (cross-sectional and case-series).

Highest levels of evidence are given most weight when summarizing data.

## 3. Results

Initial search yielded 695 results. After eliminating articles that did not meet inclusion criteria, 55 articles were selected. No Level 1 evidence was available. Two prospective trials (level 2 evidence) have been performed on RS specific to MTLE and two prospective trials with predefined inclusion criteria specific to HH. The remaining articles were uncontrolled prospective observational studies, retrospective case series or case reports, all Level 4 evidence. Results from Level 2 studies (prospective trials) were preferentially taken into account for the purposes of the present article. We also present Level 4 retrospective case series where relevant. Since most articles focus on epilepsy treatment in a specific patient group or pathology, the results will be divided into clinical categories as follows:

1. Mesial temporal lobe epilepsy (MTLE)
2. Extra-temporal partial epilepsy
3. Corpus callosotomy
4. Epilepsy associated with hypothalamic hamartoma (HH)
5. Epilepsy associated with cavernous malformations

### 3.1. RS in the treatment of MTLE

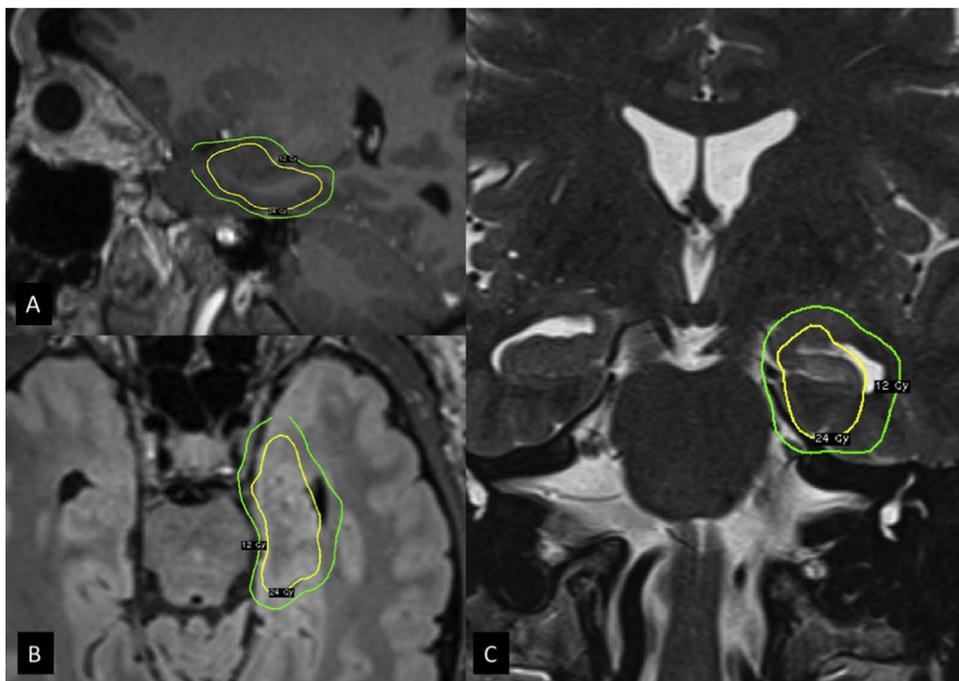
This represents the clinical indication for GK with the largest amount of good quality data, with over 225 patients reported. Two prospective studies (Level 2 evidence) have been published, one European (Régis and colleagues (Régis et al., 2004b) in 2004) and one North American (Barbaro and colleagues (Barbaro et al., 2009) in 2009).

#### 3.1.1. Patient and target selection for GK in MTLE

In their pioneering prospective trial in 2004, (Régis et al. (2004b) described 21 patients aged between 18 and 45 years, recruited from 3 European centers. All had been selected for mesial temporal lobectomy for intractable epilepsy and were offered GK as an alternative treatment. Seizure frequency was measured using patient diaries before and after GK. Thorough assessment by expert teams, including stereo-electroencephalography (SEEG) or foramen ovale recording prior to patient selection, ensured very high level of diagnostic confidence in establishing epilepsy syndrome and lateralization (Wada testing of language function). Visible hippocampal atrophy on MRI was an inclusion criterion. MTLE was left sided in 13/21 patients.

The North American prospective study published by Barbaro and colleagues in 2009 reported 30 adult patients recruited from 7 centers in the US, again chosen from patients with similar robust diagnostic criteria of MTLE (of which half were left-sided), eligible for anterior temporal lobectomy.

In Régis et al. a prescription dose of 24 Gy was used in all subjects, corresponding to the 50% isodose curve, being as homogeneous as possible in terms of dose volume and anatomical location: anterior part of parahippocampal region; entorhinal area adjacent to the collateral sulcus, and the rhinal sulcus; the head of the hippocampus; the anterior



**Fig. 1.** Dose-planning of a left (dominant side) mesial temporal lobe epilepsy. The planning is displayed on the sagittal (A), axial (B) and coronal (C) views. Note on the coronal view (C) the hippocampal sclerosis. The marginal isodose line (24 Gy at the 50%) is covering the anterior parahippocampal Gyrus and the collateral fissure plus part of the hippocampus and amygdaloid complex. The planning is shaped such a way that the 12 Gy isodose line spares the mesencephalon and optic tract.

part of the hippocampal body; and the amygdalofugal part of the amygdaloid complex (see Fig. 1) were targeted (Régis et al., 2004a). Barbaro et al. (2009) randomly allocated to treatment with either 20 Gy or 24 Gy using the same volume and anatomical location (and like Régis et al.'s study, containing a 50% isodose), comprising the amygdala, anterior 2 cm of hippocampus and parahippocampal gyrus. The maximum dose allowed to nearby brainstem was 10 Gy and to optic nerves 8 Gy in both studies.

**3.1.2. Seizure freedom and neuropsychological outcome in MTL**

Results are summarized in Table 1. In Régis et al. (2004b), 13/20 (65%) patients with at least 2-year follow-up became seizure free and

all 20 had significant reduction in seizure frequency. Improvement was preceded by a period of increased seizures at around 9–12 months post-GK, generally auras. Quality of life measures improved and neuropsychological tests were stable at 2-year follow-up; however detailed testing of verbal memory was not included (Tables 1 and 2).

In the study by Barbaro et al. (2009), similar reduction in seizure frequency preceded by increased auras were seen in both low dose and high dose groups, with follow-up data available at 36 months. A greater proportion (75%) of patients treated with 24 Gy became seizure-free and at an earlier time-point, than those treated with 20 Gy (60% seizure free), though not statistically significant. In 26 patients who underwent complete neuropsychological testing for the full study period, no

**Table 1**  
MTLE outcomes in prospective or retrospective studies with > 4 adult patients included and adequate outcome data reported.

Author, year	Study design and evidence level	Modality/case number	Marginal dose (Gy)	Treatment volume (mm3)	Minimum follow up (months)	Seizure free outcome (Engel class I), number of patients (%)	Neuropsychology outcome
Régis et al, 2004	Prospective observational; level 2	GK, 21	24	5.500-9.000	24	13/20 (65)	No deterioration any patient
Barbaro et al, 2009	Prospective observational; randomized low dose/ high dose; level 2	GK, 30	20 or 24	5.500-7.500	36	20/30 (67)	Verbal memory impairment 4/26 (15%); 0 declined on >1 measure. Verbal memory improvements in 3/26 (12%).
Srikijvilakul et al, 2004	Retrospective; level 4	GK, 5	20	7320	18	0	Stability at 6 month follow-up at group level
Bartolomei et al, 2005	Retrospective; level 4	GK, 15	24	5500-9000	60	9/15 (60)	
Hoggard et al, 2008	Retrospective	GK, 8	25	5500- 6900	24	3/8 (38)	Stability all patients
Rheims et al, 2008	Retrospective; level 4	GK, 15	21.1+/-2.6	6960-12500	31	1/15 (6.6)	Not specified
Liang et al; 2010	Retrospective; level 4	LINAC, 7	12Gy at 85 isodose line	38250-45270	24	0	Stability all patients
Usami et al, 2012	Retrospective; level 4	GK, 7	18 or 25	7800-12300	16	2/7 (28.5) (both treated with 25Gy)	Not specified
Vojtech et al, 2015	Retrospective; level 4	GK, 14	18 or 21-24	5200-7700	175	1/14 (7.1)	Not specified

GK = gamma knife; LINAC = linear accelerator. Shaded lines = prospective studies (level 2 evidence). Unshaded lines = retrospective studies (level 4 evidence).

**Table 2**

Adverse effects of radiosurgery in MTLE treatment. Studies are shown here that include at least 4 adult patients with MTLE and adequate data on clinical adverse events related to RS.

Authors	Year	Grade of evidence	Method	Isodose range	N° of patients treated	Severe or unexpected adverse effects	Mild-moderate adverse effects	Neuropsychology outcome	Comments
Régis et al <sup>1</sup>	2004	2	GK	Marginal dose of 23-25 Gy to the 50% isodose line	21	None	Visual field defects in 9/20: 8 quadrantanopia, 1 hemianopia (optic tract damage)	QoL measures improved and neuropsychological tests stable at 24 months	1 death considered unrelated to GK (myocardial infarction)
Barbaro et al <sup>2</sup>	2009	2	GK	Marginal dose of 20-24 Gy to the 50% isodose line	30	1 symptomatic brain edema requiring steroids and eventually temporal lobectomy	Quadrantanopia in 62.5%  17/30 received steroids for headaches +/- radiological change of edema	No patient deteriorated on >1 measure at 12 and 24 months; 25% (3/12) improved verbal memory after dominant hemisphere GK	No dose effect on adverse events
Srikijvilaikul et al <sup>3</sup>	2004	4	GK	Marginal dose of 20 Gy to the 50% isodose line	5	2 deaths related to ongoing seizures (1 SUDEP, one drowning).	Headaches requiring steroids in 1 patient	No change at group level pre- and 6 months post-GK.	Short follow-up does not allow meaningful assessment of neuropsychological outcome
Hoggard et al <sup>4</sup>	2008	4	GK	Marginal dose of 25 Gy to the 50% isodose line	8	No	2 patients increased intracranial pressure with dysphasia requiring steroids; seizure worsening including SE in 1; development of new drop attacks in 1; change in seizure pattern with clustering	Results stable pre- and post- GK in all	
Rheims et al <sup>5</sup>	2008	4	GK	Marginal dose of 18-24 Gy to the 50% isodose line	15 of which 10 had "pure" MTLE	None	Headaches requiring steroids in 4 patients; 2 asymptomatic quadrantanopias	Not reported	Case mix heterogeneous; non MTLE cases
Liang et al <sup>6</sup>	2010	4	LINAC	Total marginal dose of 12Gy at the 85% isodose line	7	1 dysphasia 9 months post-LINAC without MRI change; 1 seizure worsening and ataxia without MRI change	2 asymptomatic visual field defects	No statistical analysis provided	Not specified
Usami <sup>8</sup> et al	2012	4	GK	Marginal dose of 18-25 Gy to the 50% isodose line	7	1 death by drowning seizure 12 months post-GK;	N/A	Not specified	Not specified
						2/7 had symptomatic radionecrosis requiring late lobectomy (5 and 10 years post-GK)			
Kawamura et al <sup>9</sup>	2012	4	GK	Marginal dose of 20-25 Gy to the 50% isodose line	4	One death by drowning seizure 7 months post-GK.			
						One patient developed cognitive impairment, aphasia and right hemiparesis 12 months post-GK due to cerebral edema, requiring IV steroids, with subsequent full recovery.			
						One patient developed severe headache, visual change with quadrant hemianopia, and frequent partial seizures 5 years after GK, with radiologic signs of radionecrosis; temporal lobectomy performed			
						One case had cognitive impairment and hemiparesis associated with intracerebral cyst 10 years post-GK; complete recovery after resection of lesion			

Abbreviations: GK = gamma knife; LINAC = linear accelerator; N/A = not applicable; QoL = quality of life; SE = status epilepticus; SUDEP = sudden unexpected death in epilepsy. Shaded lines = prospective studies (level 2 evidence). Unshaded lines = retrospective studies (level 4 evidence).

1. Régis et al. (2004b).
2. Barbaro et al. (2009).
3. Hensley-Judge et al. (2013).
4. Srikijvilaikul et al. (2004).
5. Hoggard et al. (2008).
6. Rheims et al. (2008).
7. Liang et al. (2010).
8. Usami et al. (2012).
9. Kawamura et al. (2012).

patient deteriorated on more than one measure and 25% (3/12) had improved verbal memory after dominant hemisphere GK. Neuropsychological testing of the same cohort at 36 months reported no decline in verbal memory in patients treated on the dominant side (Quigg et al., 2011).

Longer term outcome in a European cohort, overlapping with but not the same as the series from Régis et al. (2004, 2004b) Régis et al., 2004b Régis et al. (2004, 2004b), found 9/15 (60%) seizure-free (Engels class 1A or 1B) after a mean follow-up of 8 years (Bartolomei et al., 2008). Rheims et al. (Level 4) (Rheims et al., 2008) reported comparable outcomes in pure MTLE but poorer outcomes in patients whose epilepsy extended beyond mesial temporal structures as defined by SEEG, with 4/5 showing no benefit from RS. Vojtech and colleagues (Vojtech et al., 2015), reporting on a cohort initially published in 2009

(Vojtech et al., 2009) (level 4 data), described extremely poor short and long-term results (up to 16 years) with 0/14 patients becoming seizure free.

### 3.1.3. Radiologic and histopathologic effects in MTLE

In Régis et al. (2004b) (Level 2 evidence), radiologic effects occurred in all after a median delay of 11.5 months. In Barbaro et al. (2009) (Level 2 evidence), despite the homogeneity of GK dose planning for each group, radiologic responses varied widely from minimal change to significant brain edema. Vojtech and colleagues (Vojtech et al., 2015) on the other hand (Level 4 evidence) indicated marked radionecrosis in all 14 treated patients, and gliosis, pseudocysts and/or microbleeds in some. Contrast enhancement was found to persist as long as 16 years post-GK, even showing signs of progression in some

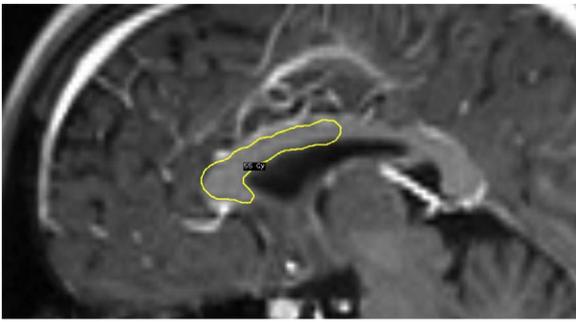


Fig. 2. Dose-planning of a callosotomy. The sagittal view is showing that the 50% isodose line (55 Gy) covers more than the anterior half of the corpus callosum.

patients. A British study reported on outcome and radiological findings in 8 patients including serial MR diffusion-weighted imaging and spectroscopy in some (Hoggard et al., 2008). The patients with the most florid radiological signs of edema tended to become symptomatic (dysphasia, transient seizure worsening including one case of status epilepticus) and to ultimately have better seizure outcome. This pattern of diffusion-weighted MR changes was considered indicative of increased extracellular fluid and vasogenic edema, rather than intracellular fluid and cytotoxic edema as previously suggested.

Histopathological studies of temporal lobe in patients subsequently operated because of poor outcome have shown various radiation effects in treated brain structures, including chronic perivascular inflammation, vascular necrosis, foci of edema with necrosis, microglial proliferation, reactive gliosis and neuronal loss (Rheims et al., 2011; Srikijvilaikul et al., 2004; Vojtech et al., 2015).

### 3.1.4. Adverse effects in MTL

It should be remembered that higher numbers of isocenters and lower dose-volume ratios are generally associated with fewer adverse effects, and because of evolving GK methodology, prevalence and type of adverse effects in the earliest series are not necessarily comparable to recent reports. Results are summarized in Table 2.

Régis et al. (2004b) (Level 2 evidence) reported no major adverse effects in MTL; one patient was reported as having died of myocardial infarction, a complication supposed unrelated to RS. Visual field defect occurred in 9/20, of which 1 was a hemianopia likely due to optic tract damage; the rest were predictable quadrantanopias. In Barbaro et al., (2009) (Level 2 evidence), one patient in the high dose group developed severe cerebral edema. No statistical difference in adverse events occurred between low and high dose groups; overall 63% were given steroids, and 50% had visual field deficits, similar to Régis et al., (2004a). Another report Hensley-Judge et al. (2013) found 62.5% prevalence of superior quadrantanopia, comparable to anterior temporal lobectomy.

From retrospective case series, reported adverse effects include injury or death due to seizures (accidents or sudden unexpected death in epilepsy (SUDEP) (Srikijvilaikul et al., 2004)) while awaiting therapeutic effect of RS, and late complications of radionecrosis (Chen et al., 2014; Usami et al., 2012; Vojtech et al., 2009). Low dose LINAC radiosurgery in 7 patients was associated with significant side effects as well as poor seizure outcome, with 2/7 patients suffering permanent neurological complications (Liang et al., 2010).

### 3.2. RS in the treatment of extratemporal epilepsy

Two very small case series using GK RS (Level 4 evidence) described improved seizure frequency and severity in 2/4 patients with paracentral epilepsy (McGonigal et al., 2014) and 2/3 patients with insular epilepsy (Irislimane et al., 2013). In particular no motor deficit occurred in patients treated for motor cortex epilepsy (McGonigal et al., 2014). The dose prescribed was 24 Gy to a median volume of 2.34 cm<sup>3</sup>,

representing a similar dose but smaller volume than patients treated for MTL. Irislimane and colleagues (Irislimane et al., 2013) also observed lack of MRI change post-GK and no significant adverse effects in their study of insular epilepsy treated by slightly lower doses (20 Gy) in a median volume of 3.0 cm<sup>3</sup>. This is clearly in contrast to GK-treated MTL, in which radiological changes are almost always seen, the appearance of which indeed heralds the therapeutic effect; absence of radiologic change in the presence of therapeutic benefit might evoke a neuromodulatory mechanism (McGonigal et al., 2014).

Another small study reported LINAC radiosurgery in 3 patients to treat inoperable dominant hemisphere epilepsy associated with periventricular heterotopia (Wu et al., 2013). Seizure reduction or freedom was obtained in all three patients, albeit with a phase of significant cerebral edema in 2/3 requiring steroids.

### 3.3. RS corpus callosotomy for refractory bilateral epilepsy

In RS anterior corpus callosotomy, high doses of radiation (55–170Gy (Bodaghabadi et al., 2011; Celis et al., 2007; Eder et al., 2006; Pendl et al., 1999)) within a relatively small volume produce focal destruction of callosal fibers (Fig. 2). There is thus a much higher dose-volume ratio in RS corpus callosotomy than in MTL. A total of ~19 children and adult cases have been described in the literature. Reports have described anterior (Bodaghabadi et al., 2011; Eder et al., 2006; Feichtinger et al., 2006; Pendl et al., 1999) and, less commonly, posterior (Eder et al., 2006; Smyth et al., 2007) callosotomy in adults and children, often in Lennox Gastaut syndrome with drop attacks. While nearly all have used GK, a single case study showed similar outcome using LINAC (Celis et al., 2007). Although no seizure freedom has been reported, significant improvement in disabling seizures (generalized tonic-clonic seizures (GTCS) and/or drop attacks) has been described across all published studies, with no serious adverse effects so far indicated. Seizure types other than drop attacks and GTCS responded less well in the largest single series (8 patients) (Feichtinger et al., 2006). Improvement in seizure control occurs earlier than in GK-treated MTL, with median delay of around 3 months (Pendl et al., 1999). Focal radionecrosis followed by atrophy in the corpus callosum has been shown on MRI, and diffusion tensor imaging in a single subject (Moreno-Jimenez et al., 2012) suggests that GK produces axonal degeneration of callosal fibers.

### 3.4. RS for epilepsy associated with hypothalamic hamartoma (HH)

Treatment of epilepsy associated with hypothalamic hamartoma by RS was first described in a case report of an adult patient in 1988<sup>4</sup>. A multi-center retrospective study of GK RS by Régis and colleagues (Régis et al., 2000a) in 2000 showed promising results in 10 patients, with 4/10 becoming seizure free and 3/10 showing significant improvement, without persistent adverse effects. This paved the way to a prospective study (Level 2 evidence) by Régis and colleagues (Régis et al., 2004a, 2006, 2007) in Marseille, from 1999 onwards, which has to date recruited over 60 patients; long-term data is available in 48 patients (Régis et al., in press (Régis et al., 2016)). An ongoing prospective observational GK study (Level 2 data) by Mathieu and colleagues (Bourgeois et al., 2013; Mathieu et al., 2010) has to date reported 12 patients. Results are summarized in Table 3, which highlights the small number of studies with adequate follow-up data.

#### 3.4.1. Patient selection for RS in epilepsy associated with HH

Patients with HH typically show intractable epilepsy often with gelastic seizures, and associated learning disability, behavioral problems and/or neuroendocrine dysfunction. Prospective trials with GK showed an effect of lesion size and topological classification, whereby small intrahypothalamic hamartomas had the best outcome (Jean et al., 2017). Although various means of classifying HH exist (Kerrigan et al., 2013), Régis and colleagues proposed a classification of HH into 5

**Table 3**

Hypothalamic hamartoma outcomes in prospective or retrospective studies with &gt; 4 adult patients included and at least 2 years' follow-up data provided.

Author, year	Modality/ case number/ age range (median)	Diameter of HH (mm)	Marginal dose (Gy) range and median	Treatment volume (mm <sup>3</sup> ) range and median	Minimum follow up (months)	Adverse effects	Satisfactory seizure outcome due to RT (Engel class I or II), number of patients (%)	Neurocognitive outcome	Psychosocial outcome
Régis et al. 2006 <sup>1</sup> ; Régis et al. 2007 <sup>2</sup>	GK; n=57 treated in total; 3 year follow up data available for 48; age 3-50 years (median 16.5)		14-25 (17)	28–1600 (398)	36	No major adverse effects. Transient poikilothermia 3/57 (6%). No major endocrinological effect; 1 case of thyroid dysfunction detected 3 years post-GK	33/48 (68.8)	Evaluation before and 3 years after available in 39 patients; no decline at group level	NB from Régis et al. 2016 (in press): Of 45 patients with psychiatric morbidity: complete resolution in 15/45 (33%), improved in 23/45 (51%), stable in 6 (14%); continued deterioration in 1/45 (2%)
Mathieu et al. 2010 <sup>3</sup> ; Bourgeois et al. 2013 <sup>4</sup>	GK; n=7 with adequate follow-up; age range 12-57 years		14-20	300-1000	24	No serious adverse effects. 3 transient psychiatric disturbances	6/7 (86%)	3/4 improved and 1/4 stable	Improved QoLIE-89 (n.s.)
Régis et al. 2000a <sup>5</sup>	GK; n=7 with adequate follow-up; age range 1-32 years (mean 14)	Aug-22	Dec-20	134-2674.8 mm <sup>3</sup> (646.7)	24	No serious adverse events. 1 case non-disabling poikilothermia	5/7 (72%)	Not specified	Not reported in detail
Abla et al. 2010 <sup>6</sup>	GK; 8 with adequate follow-up; age range 5.7-29.3 years (median 15.1)		16-20 (median 18)	169-3000 mm <sup>3</sup> (mean 695)		Transient side effects: 1 poikilothermia, 1 increased depression; 2 weight gain/increased appetite; 1 anxiety	3/8 (37.5%)	No adverse effects on cognition; formal testing not reported	QoL considered improved in 9/10 patients

HH = hypothalamic hamartoma; GK = gamma knife; LINAC = linear accelerator; QoL = quality of life. Shaded lines = prospective studies (level 2 evidence). Unshaded lines = retrospective studies (level 4 evidence).

1. Régis et al. (2006).
2. Régis et al. (2007).
3. Mathieu et al. (2010).
4. Bourgeois et al. (2013).
5. Régis et al. (2000a).
6. Abla et al. (2010).

categories according to anatomical features and size (Régis et al., 2006) and used this in analyzing the results of their prospective trial, as did the Quebec group in their prospective observational study (Mathieu et al., 2010). These studies agree that Régis classification types I–III HH, especially type I HH (small hamartomas located within the hypothalamus and extending more or less into the third ventricle) are associated with best results. While Mathieu et al. suggested that good epilepsy outcome in smaller HH may be due to treatment of the whole lesion (Mathieu et al., 2010), the study by Régis and colleagues observed seizure free outcome in 2 patients who had only partial coverage of the lesion (Régis et al., 2000a). This is in keeping with findings from HH surgery, whereby marked seizure improvement is not inevitably related to complete resection (Harvey et al., 2003).

#### 3.4.2. RS intervention protocol in epilepsy associated with HH

Level 4 trials indicate a possible effect of dose in HH: GK doses > 17 Gy were used in all patients who became seizure-free, whereas doses of < 13 Gy were never associated with seizure freedom (Régis et al., 2000a). Outcome according to dose was however not specifically reported in their prospective study results (gis et al., 2006, 2007; Régis et al., 2006, 2007). Mathieu and colleagues (Mathieu et al., 2010) (Level 2 data) reported that 4/6 patients with smaller (Régis grade I–III) HH treated with 14–20 Gy became seizure free. Multi-isocentric dose planning (Fig. 3) is often required for optimal coverage of the lesion, with a range of 2–36 isocenters (median 9) reported by Régis et al (Régis et al., 2006).

#### 3.4.3. Comparison with surgery for epilepsy associated with HH

Various surgical approaches for HH have been proposed (for review see Mittal et al. (Mittal et al., 2013) 2013). Available data from Level 2 prospective trials indicate comparable or better results using GK, at least for smaller HH, with markedly reduced rate of adverse effects. A single small retrospective study of LINAC-treated patients with HH (Selch et al., 2005) found similar results to those reported with GK.

#### 3.4.4. Outcome after RS in epilepsy associated with HH

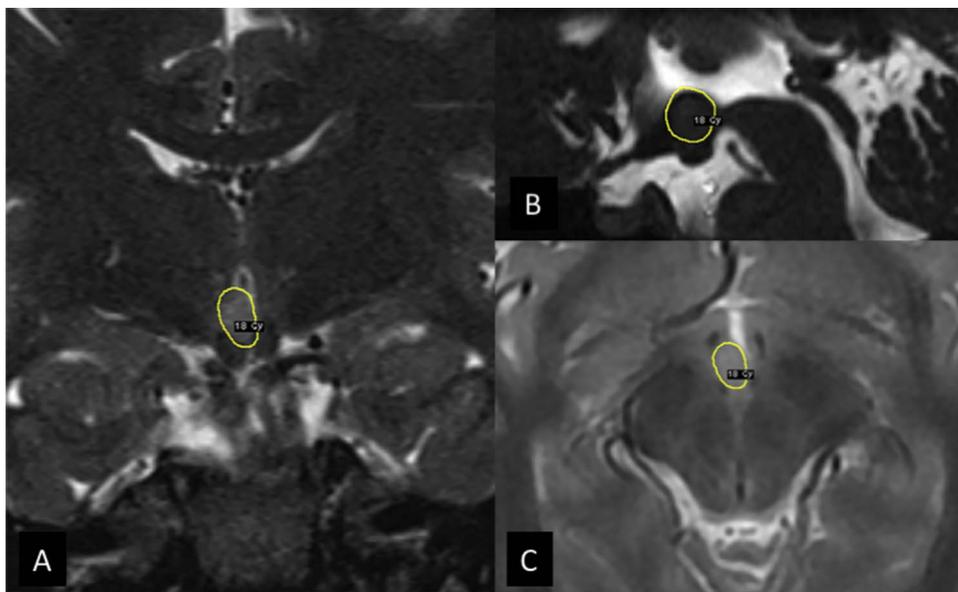
Improvement in seizure control (seizure free or only rare gelastic seizures) was reported in 60% of patients in the French prospective trial (Level 2) (Régis et al., 2006) and 66% in the smaller Canadian prospective observational study (Level 2) (Mathieu et al., 2010). The Canadian study found poor results in all cases of attempted radiosurgical disconnection of the HH in patients with large (Régis grade IV–VI)

lesions (Mathieu et al., 2010). Improvements not only in seizure control but also in behavior and sleep pattern have been frequently observed (Régis et al., 2007). Positive effect on behavior tended to occur early, in the first weeks following GK, and continued to improve during a 2–6 month period post-GK, despite persistent seizures at this time (Régis et al., 2007). Interestingly this period corresponds to improved sleep patterns and EEG normalization (Régis et al., 2007). Reduction in seizures was typically observed at a later phase, sometimes preceded by a seizure “peak” as described for GK treatment of MTLE (Barbaro et al., 2009; Bartolomei et al., 2008), followed by disappearance of seizures and stabilization of the clinical picture. Longer term experience highlights the need to allow at least 3 years follow up for adequate evaluation of seizure outcome (Régis et al., 2006) and even longer for assessment of cognition and behavior (Mathieu et al., 2010). Good seizure control (Engels Class I or Class II) was seen in 68.8% at > 3 years follow up in the prospective cohort (Régis et al., 2016). Studies agree on the tendency for neurobehavioral improvement after GK for HH, which seems not entirely dependent upon seizure outcome (Régis et al., 2013); neuropsychological function and quality of life measures are encouraging (Bourgeois et al., 2013; Régis et al., 2016). No major adverse events have been reported (Mathieu et al., 2010; Régis et al., 2007); rare cases of poikilothermia (gis et al., 2004a, 2007; Régis et al., 2004a, 2007) and transient worsening of seizures have been described (Régis et al., 2007) but no endocrine disturbance (Régis et al., 2007).

#### 3.5. RS for epilepsy associated with cavernous malformations

Many case series of cavernous malformations are heterogeneous, including patients presenting with hemorrhage, others with seizures, and some with both, associated with supratentorial or infratentorial cavernomas. It is therefore difficult to extract data that specifically deal with RS treatment of cavernoma-related pharmacoresistant epilepsy (see Table 3).

Régis and colleagues performed a multicenter retrospective study (Level 4) (Bartolomei et al., 1999; Régis et al., 2000b) and reported 49 patients with cavernoma and intractable epilepsy, of which 35% had involvement of functional cortex that precluded microsurgery. Over half were seizure free at last follow-up after GK and 3/4 of all patients had significant improvement in seizure control. A later case series retrospectively compared non-matched cases treated with either microsurgery or radiosurgery for supratentorial cavernous malformations (Shih and Pan, 2005), in which 16 patients presented with seizures and



**Fig. 3.** Dose-planning for a hypothalamic hamartoma. The lesion is a type II hamartoma mainly located in the third ventricle lateralized on the right side. The reference marginal isodose line (18 Gy at the 50% isodose) is displayed in coronal (A), sagittal (B) and axial (C) views. On the T2 weighted coronal view (A) the close relationship of the hamartoma with the right mammillary body is well illustrated. On the sagittal T2 weighted imaging the antero-posterior location of the hamartoma right in front of mammillary body and inserted on the hypothalamus at the level of its posterior third (mammillary part of the hypothalamus). On the axial T2 weighted images the HH is located posterior to the fornix and anterior to the mammillo-thalamic tract.

were treated by RS. Only 4/16 patients (25%) became seizure free after RS, compared to 11/14 (79%) seizure free following microsurgery (Shih and Pan, 2005); however, mean dose at the periphery was relatively low at 13.3 Gy compared to 19.2 Gy in Régis et al. (Régis et al., 2006).

#### 4. Discussion

Current literature on RS for epilepsy includes, at best, prospective but non-randomized studies in MTLE and HH (Level 2 evidence). Results of the multicenter randomized prospective trial on MTLE (RS vs. Open Surgery for Epilepsy, ROSE) were awaited at time of review. For all other reported indications of RS, only Level 4 data are available. The lack of methodologically robust studies should be taken into account when interpreting diverse opinions on the role of RS in epilepsy (Mindermann, 2015; Quigg et al., 2012; Régis et al., 2012; Spencer, 2008).

##### 4.1. Risk-benefit ratio of RS in different epileptological indications

Concerning GK for MTLE, available data from 2 prospective multicenter studies indicate that 60–75% of patients achieve seizure freedom at long-term follow-up, thus broadly comparable to microsurgery. Anterior temporal lobectomy for MTLE is well-established (Wiebe et al., 2001), effective (Sperling et al., 1996) and safe (Behrens et al., 1997; Rydenhag and Hans, 2001), with seizure freedom in 70–75% of patients in the short (Sperling et al., 1996) and long term (McIntosh et al., 2004). Minor morbidity with microsurgery is estimated at around 8–9% and major morbidity at around 2–3% (Rydenhag and Hans, 2001), including hemiparesis, language disturbance and memory dysfunction. Prospective studies of GK have shown lower rates of major adverse effects than microsurgery in treating MTLE. On the other hand, the delay incurred in seizure improvement by choosing RS over anterior lobectomy may itself be the cause of major morbidity and mortality due to ongoing seizures (Srikijvilaiikul et al., 2004) and estimating risk-benefit ratio for a given patient must take account of both aspects.

The main relevance of RS in MTLE, due to the very focal and “super-selective” nature of the target (Quigg et al., 2012), may be in preserving neurocognitive function especially when epilepsy involves the language-dominant side. Neuropsychological, psychiatric and psychosocial function are extremely important outcome measures in epilepsy surgery (Derry et al., 2000; Glosser et al., 2000; Markand et al., 2000), and are intricately related to localization of the epileptogenic zone, seizure severity and seizure frequency (Spencer and Huh, 2008) as well as

environmental and genetic factors. Studies of GK in MTLE show low prevalence of decline in verbal memory, comparing favorably to temporal lobectomy on the language dominant hemisphere side, in which decline occurs with variable prevalence of up to 60% (Baxendale et al., 2006; Meador, 2002; Spencer and Huh, 2008; Stroup et al., 2003). Clarifying this important issue, as well as psychiatric and quality of life outcomes will be addressed by the ROSE trial (Mindermann, 2015).

The other indication of RS for epilepsy with Level 2 data is hypothalamic hamartoma. There appears to be convincing evidence of at least equivalent efficacy and superior tolerance of GK in treating epilepsy related to HH, for certain anatomical subtypes of HH, with improved seizure control and neurobehavioral status. The risk-benefit ratio of GK appears favorable when topological classification indicates localization within the hypothalamus and/or third ventricle, without extending below the floor of the third ventricle (Régis grade I–III (Régis et al., 2006)). On the other hand, large HH tend to be much less successfully treated by GK and conventional surgery is indicated as first line treatment in these patients. Freedom from disabling seizures such as drop attacks is a very important outcome parameter even if full control of seizures is not achieved. Since neurobehavioral and cognitive dysfunction associated with epilepsy are often just as (or even more) disabling than seizures (Kerrigan et al., 2005), the cognitive, psychiatric and behavioral outcomes are key measures of surgical success in this patient population.

For remaining epileptological indications (extra-temporal refractory focal epilepsy, anterior callosotomy, and cavernous malformation), current lack of high-level evidence precludes proposal of guidelines. At best, data indicate that RS may have advantages over conventional surgery for selected patients with these indications, which require further study.

A concern with RS in general is the risk of inducing radiation damage that may contribute to tumor genesis. According to current data reflecting 30 years of RS use, no case of tumor has been observed in association with RS treatment of epilepsy (Régis et al., 2006).

##### 4.2. Methodological issues to consider when assessing RS outcome

The nature of RS, in terms of its mechanism of action and clinical effect, is fundamentally different from all other epilepsy treatments (Liscak et al., 2002; Quigg et al., 2012; Régis et al., 2010). Practice of radiosurgery has evolved over time according to technical advances and clinical experience. The learning curve in the practice of RS for epilepsy, as well as improvements in the precision of neuroimaging

guidance, have thus produced a gradual shift in dose planning methodology, increased conformity and lower dose-volume ratio being used. Technical evolution is likely one explanation for the relatively lower number of adverse effects reported in the last decade compared to in the earliest period of GK use; for example, requirement for steroid use in treating radiation-induced edema has reduced over time in most experienced centers. Another issue specific to RS for epilepsy is outcome assessment. The main desired endpoint of epilepsy surgery is improved seizure control, classically assessed according to seizure frequency (Engel, 1993; Wieser et al., 2001a) and to a lesser degree, seizure severity (for example aura alone versus seizure with loss of consciousness) (Engel, 1993). Surgery aims to achieve seizure freedom, with or (ideally) without continuation of AED therapy. The question of how best to measure surgical outcome raises specific issues for RS in epilepsy, since not only seizure frequency, but seizure severity or specific aspects of clinical expression may be altered (e.g. avoidance of loss of consciousness or falls), eventually leading to an overall positive impact for the patient even if seizure freedom is not achieved. Such qualitative aspects of seizure outcome are poorly reflected in conventional surgical outcome scales (Engel, 1993; Wieser et al., 2001b).

## 5. Conclusions

Formal guidelines cannot yet be issued (see Supplementary Material for ISRS recommendations) since, to date, non-randomized prospective trials of GK in MTLE and HH represent the highest quality (Level 2) data available, with results being awaited from an ongoing randomized prospective study in MTLE. However, these studies indicate that GK can produce at least comparable rates of seizure freedom or seizure improvement for pure MTLE and selected HH compared to conventional surgery. There is no overall increase in the burden of adverse effects, despite the well-recognized disadvantage of delayed therapeutic effect and theoretical risk of radiation-induced damage to surrounding neural tissue with GK. There are preliminary indications that GK may provide advantages in neuropsychological outcome for treating dominant hemisphere MTLE. There appears to be a clear benefit-risk ratio in favour of RS for small HH. Further data is needed to evaluate the use of RS in anterior callosotomy, epilepsy related to cavernous malformation and extra-temporal focal epilepsies.

## Disclaimer

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

## Disclosure

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eplepsyres.2017.08.016>.

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