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Advanced Gamma Knife Treatment Planning of Epilepsy

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1. Introduction

1.1 Background

Epilepsy is not a single disease, but a broad group of conditions characterized by recurrent seizures resulting from the abnormal firing of cerebral neurons (1). Both medical and surgical treatments have been available for over a century, but there has been recent interest in radiosurgery as an alternative to open surgery for patients with medically intractable epilepsy.

Mesial temporal lobe epilepsy (MTLE) specifically consists of atrophy and gliosis within the limbic system and is the most frequent cause of medically intractable epilepsy in adults (2). Currently, the standard treatment for epilepsy is the use of anticonvulsants. Medically intractable cases may be treated with temporal lobectomy, consisting of removal of parts of the superior temporal gyrus, temporal portion of the amygdala, and the hippocampus.

Other causes of epilepsy include hypothalamic hamartomas (HH) and vascular malformations. Hypothalamic hamartomas are benign lesions composed of varying amounts of glia, neurons, and myelinated fibers. These tumors are often associated with gelastic seizures, precocious puberty, and behavioral problems (3) and often do not respond well to anticonvulsant therapy. As a result, surgical resection and stereotactic radiofrequency thermocoagulation have been used to treat HH (4). Epilepsy is also a symptom of cerebral vascular malformations. In particular, patients with cavernous malformations (CM) frequently present with drug-resistant epilepsy (5).

Given the toxicity of open surgery and poor quality of life for patients with medically intractable epilepsy, stereotactic radiosurgery (SRS) with the Gamma Knife has been proposed as a viable alternative to open surgery for treating these patients. Preliminary data have shown that Gamma Knife radiosurgery is highly promising in terms of safety and efficacy for the treatment of MTLE (6-8). Potential advantages of Gamma Knife radiosurgery include lower morbidity and lower cost with equal effectiveness. One potential disadvantage of radiosurgery is the latency of response, which may be up to two years (9). Although much of the data are promising, the results of Vojtěch et al suggest that more study is needed (10). Based on these data, an international clinical trial is currently being conducted for determining the role of radiosurgery for managing MTLE.

1.2 Radiosurgery for MTLE

Because radiosurgery for MTLE is still an experimental procedure, a multi-center Phase III clinical trial known as the ROSE trial (Radiosurgery or Open Surgery for Epilepsy) was initiated in 2009 to investigate the use of Gamma Knife radiosurgery as an alternative to open surgery for the treatment of medically intractable mesial temporal lobe epilepsy (11, 12). The primary objective of this study is to demonstrate the equivalence of radiosurgery with temporal lobectomy in terms of freedom from seizures. Other endpoints include quality of life, neuropsychological outcomes, and cost-effectiveness.

Due to the location of the target volume and proximity of critical structures, Gamma Knife radiosurgery for mesial temporal lobe epilepsy (MTLE) is technically challenging. In this chapter we will discuss the methods used for planning Gamma Knife radiosurgery treatments for epilepsy, the equipment used for delivering these treatments, and challenges specific to the treatment of MTLE and other causes of epilepsy.

Similar to the traditional surgical approach to treatment of MTLE with temporal lobectomy, the proposed radiosurgical treatment target is comprised of the amygdala, anterior 2 cm of the hippocampus, and the parahippocampal gyrus. Images of a representative target volume are shown in FIG. 1. The current target prescription dose is 24 Gy, which is based on the results of an earlier study in which lower doses were shown to result in reduced efficacy (13). The total irradiated volume is maintained to be less than 7.5 mL in order to minimize late radiation sequelae such as festering radiation necrosis.

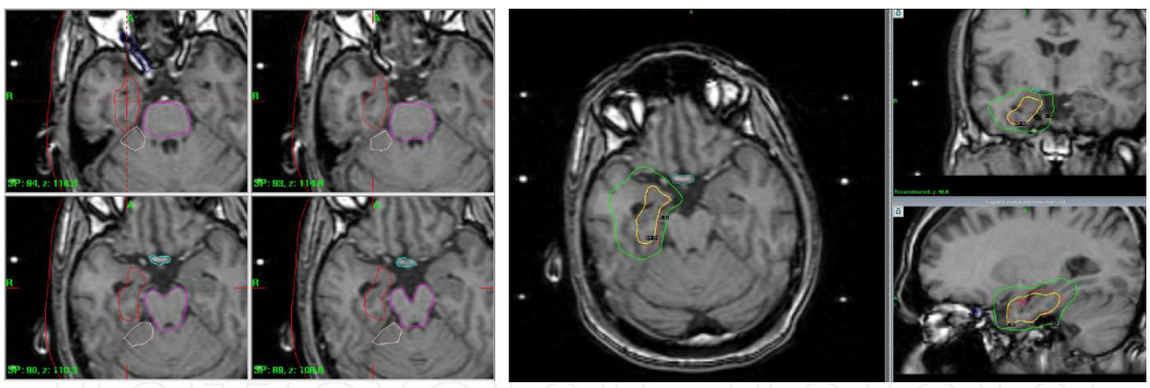


Fig. 1. (left) MR image showing target volume (red), brainstem (pink), and optical chiasm (blue). The target volume consists of the amygdala, anterior hippocampus, and parahippocampal gyrus. (right) A typical dose distribution is shown with the prescription (24 Gy) isodose line shown in yellow and the 8 Gy isodose line in green.

1.3 Radiosurgery for hypothalamic harmatomas and cavernous malformations

Studies have demonstrated that the use of stereotactic radiosurgery for treatment of epilepsy associated with hypothalamic hamartomas is safe and effective (14-22). In 2000, Régis *et al* reported the results of a multi-center study that involved ten patients treated at seven sites with Gamma Knife SRS (15). The median follow-up was 28 months and the results demonstrated a clear relationship between dose and efficacy and the authors recommended a margin dose of 18 Gy or more. Selch *et al* described the use of linac based SRS for the treatment

of HH (18). A good summary of the various treatment options for HH including SRS has been published by Régis *et al* (20). This report also includes the results of a prospective study of Gamma Knife SRS for hypothalamic hamartomas. At the time of publication, the authors had sufficient (3 years) follow-up to report results for 27 patients and found that a very good result was obtained in 60% of the patients.

Data have also been published regarding the use of radiosurgery for treatment of epilepsy associated with cavernous malformations (23-28). In 1999, Bartolomei *et al* reported the results of a retrospective study to evaluate the feasibility of using radiosurgery to treat epilepsy associated with cavernous malformations (23, 29). Data from forty nine patients were included in this study, with over 70% either seizure-free or with a significant reduction

Study	Year	No. of Patients	Findings
Hypothalamic Hamartomas			
Régis *et al* (15)	2000	10	40% patients were seizure free.
Unger *et al* (16)	2002	4	No patients seizure free
Barajas *et al* (17)	2005	3	No patients seizure free
Selch *et al* (18)	2005	3	67% seizure free
Matthieu *et al* (19)	2006	4	75% of patients showed improvement
Régis *et al* (20)	2006	27	Very good result in 60% of patients.
Abla *et al* (21)	2010	10	40% were seizure free after SRS.
Mathieu *et al* (22)	2010	9	4/6 patients with smaller tumors seizure free. 0/3 with larger tumors seizure free.
Cavernous Malformations			
Bartolomei *et al* (23)	1999	49	53% of patients seizure free.
Kim *et al* (24)	2005	12	75% of patients seizure free
Liscák *et al* (25)	2005	44	45% improved after radiosurgery
Liu *et al* (26)	2005	28	53% reported good seizure control
Shih and Pan (27)	2005	16	25% remained seizure free.
Hsu *et al* (28)	2007	14	64% seizure free. Linac based radiosurgery.
Mesial Temporal Lobe Epilepsy			
Régis *et al* (7)	1999	7	83% of patients were seizure free.
Régis *et al* (6)	2004	20	65% were seizure free.
Vojtech *et al* (10)	2009	14	18, 20, or 25 Gy. No seizure control achieved.
Quigg *et al* (8)	2011	26	Patients received 20 or 24 Gy. No neuropsychological changes from baseline at 24 months.

Table 1. Published Studies for Radiosurgical Treatment of Epilepsy Due to Various Causes.

in the number of seizures. Shih and Pan reported on 46 patients treated with surgery or radiosurgery for supratentorial cavernous malformations (27). Of this group, 24 of 46 patients presented with seizures. The results suggested that patients undergoing craniotomy had better bleeding and seizure control than those receiving Gamma Knife radiosurgery.

A brief summary of the literature regarding radiosurgical treatment of epilepsy due to various causes can be found in TABLE 1. We also refer the reader to the literature reviews on this topic by Quigg and Barbaro (2) and Romanelli *et al* (30).

2. Methods and techniques

2.1 Mesial temporal lobe epilepsy

The dosimetric criteria for the ROSE trial included: 1) prescription dose of 24 Gy to the 50% isodose line (*i.e.*, maximum dose of 48 Gy), 2) total volume receiving 24 Gy (V-24 Gy) within the range of 5.5-7.5 cm^3, 3) maximum brainstem dose of 10 Gy, and 4) maximum dose of 8 Gy to the optical apparatus.

2.2 Hypothalamic hamartomas

Planning for hypothalamic hamartomas is challenging due to the proximity of the brainstem and the optical apparatus (FIG. 2). However, compared to MTLE, planning for HH is less challenging due to lower doses and smaller target volumes for hypothalamic hamartomas. In our institution, target doses range from 15-18 Gy. Target volumes have ranged from 0.3 to 2.1 cm^3, with a mean volume of 0.81 cm^3 (N=4).

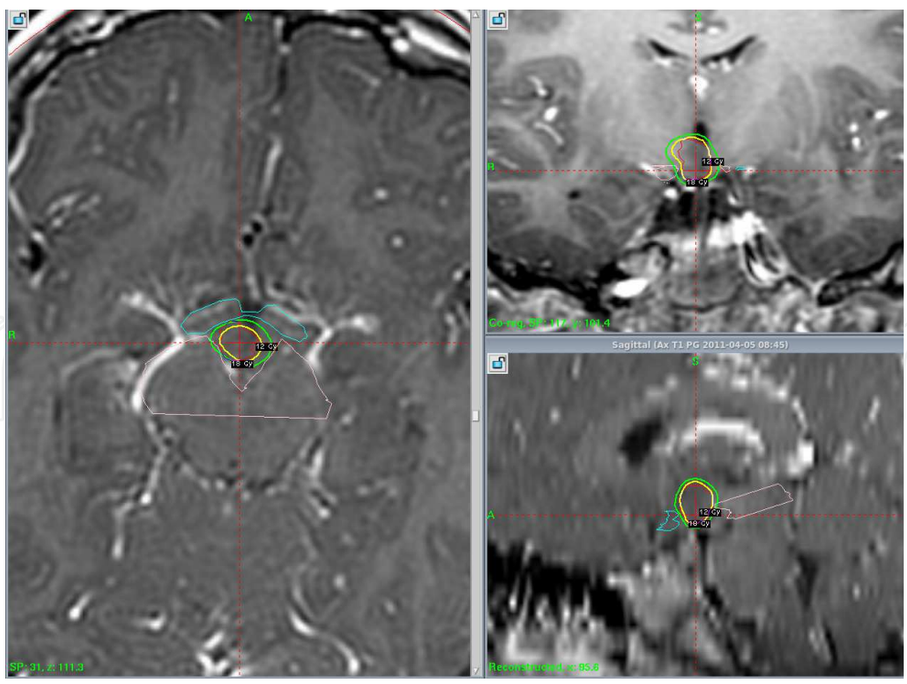


Fig. 2. Radiosurgery treatment for hypothalamic hamartoma. Note the proximity of the brainstem and the optical chiasm to the target volume. The prescription isodose line is shown in yellow and the 12 Gy isodose line in green.

2.3 Benchmarking treatment planning practices

Due to the critical location of these lesions, special radiosurgical treatment planning techniques are applied to minimize the dose to the surrounding normal brain and functional structures. In order to achieve optimal dose fall-off outside of the target, it is preferable to use small collimators (i.e., 4-mm diameter) for treating such lesions. Selective blocking of individual beamlets is a must for enhancing the dose gradient toward a nearby critical structure. However, selective blocking and planning techniques are known to vary significantly among different Gamma Knife models and individual users. To benchmark such differences, a pre-clinical trial quality assurance procedure was developed. The results of such a study are summarized in the following section.

3. Comparison among present gamma knife models for treating MTLE

There are multiple models of the Leksell Gamma Knife currently in use. The newest is the Perfexion model introduced in 2006 (5-7). The Perfexion uses 192 Cobalt-60 sources (versus 201 Cobalt-60 sources of prior Gamma Knife models) focused on a single point, the isocenter. The sources are arranged and divided conically into 8 sectors each containing 24 sources. The sources can be collimated to form circular beams with a 4-mm, 8-mm, or 16-mm diameter respectively or blocked entirely, with each sector being independently controlled, which is fundamentally different from previous models.

By contrast, the previous model Gamma Knife (Model 4C) uses 201 Cobalt-60 sources. The sources are collimated to form circular beams with 4 mm, 8 mm, 14 mm, or 18 mm diameters. The collimator size is selected by switching helmets. All beams have the same diameter, but individual beams can be blocked by "plugging" the helmets. However, switching helmets and changing plugging patterns can be time consuming, so in reality only a limited number of plugging patterns are used. Despite these differences, the mechanical accuracy of all Gamma Knife models has been consistently maintained to be better than 0.4 mm. As a result, Gamma Knife has so far been the only radiosurgical modality reported for managing intractable mesial temporal lobe epilepsy.

As part of the physics review process for the ROSE trial, each center was required to submit a treatment plan based on a sample data set for the purpose of quality assurance. Image data for this sample patient were transferred to participating institutions. The target volume was then delineated and a treatment plan was created to satisfy the previously described dosimetric constraints. The plans were then transferred to the review center for a centralized review by the trial director. Plans that did not satisfy the dosimetric constraints were revised and resubmitted. Plans were submitted for the Gamma Knife Perfexion and C/4C models, depending on the device used at the individual centers. These data were analyzed to look for potential differences between the Perfexion and C/4C models.

A total of 13 plans from 8 institutions satisfied the dosimetric constraints and were included in the data analysis. This included seven plans for the Model 4/4C and six plans for the Perfexion. Details of the individual plans are shown in TABLE 2.

Parameters studied included beam-on time, number of shots, volume receiving 24 Gy (V-24Gy), minimum dose to the delineated target, and the gradient index. Beam-on time was

Plan	Institution	Machine	V-24Gy (cm^3)	Minimum dose (Gy)	Beam-on Time (min)	No. of Shots	Gradient Index
1	1	4C	5.6	6.7	128	17	3.16
2	2	4C	5.7	7.2	209	37	2.90
3	2	4C	5.6	6.0	209	26	2.95
4	3	4C	5.5	6.9	228	20	3.47
5	4	4C	6.2	3.2	180	22	2.86
6	4	4C	5.5	3.8	138	17	3.09
7	5	4C	6.2	9.9	51	4	2.71
All 4C		**4C**	**5.8±0.3**	**6.2±2.2**	**163±62**	**20.4±10.0**	**3.0±0.2**
8	2	Pfxn	6.7	7.1	197	23	3.02
9	6	Pfxn	7.5	5.2	158	17	2.93
10	7	Pfxn	5.6	6.4	120	17	3.02
11	2	Pfxn	5.5	7.0	246	26	2.96
12	8	Pfxn	7.5	7.2	123	19	2.87
13	8	Pfxn	7.4	8.7	88	12	2.95
All Pfxn		**Pfxn**	**6.7±0.9**	**6.9±1.1**	**155±58**	**19.0±4.9**	**3.0±0.1**

Table 2. Summary of Treatment Planning Results of a Single MLTE Case by 8 Individual Institutions.

calculated assuming a dose rate of 3.0 Gy/minute. The gradient index was defined as the volume receiving the prescription dose (24 Gy) divided by the volume receiving half the prescription dose (12 Gy).(31) The Wilcoxon rank-sum test was employed to check for statistical significance.

The average 24-Gy volume was larger for Perfexion plans as compared with Model 4/4C plans, suggesting more aggressive targeting of the treatment area while satisfying normal tissue constraints due to the added flexibility of the Perfexion. Plans created for the Perfexion tended to have a higher minimum dose to the target volume (FIG. 3), which is consistent with the above result. In addition, the results showed that the plans for the Perfexion tended to have shorter beam-on times (155±58 vs. 163±62**)** and used fewer shots (19±5 vs. 20±10). However the differences were not statistically significant due to the small sample size (FIG. 4). In particular, Plan 7 (for the 4C) used only four shots and had an extremely short beam-on time. After excluding Plan 7, the beam-on time and number of shots for the Model 4C increase to 182±41 minutes and 23±8 shots, respectively. The mean gradient index was 3.0 for both the Perfexion and the Model 4C.

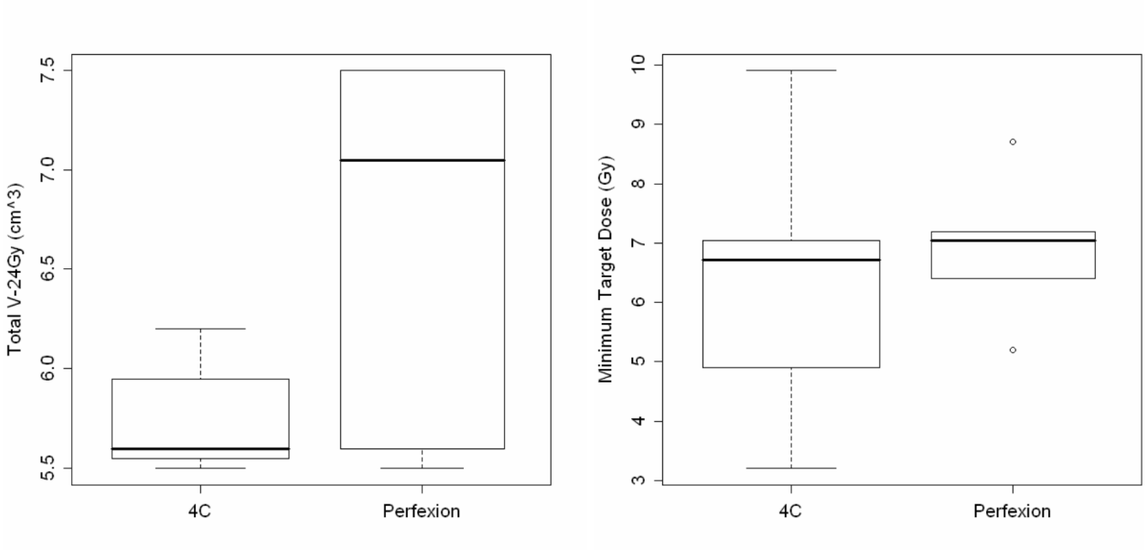


Fig. 3. Boxplots showing the total volume receiving the prescription dose and the minimum dose received by the target. Differences were not statistically significant, although the results suggest that plans generated for the Perfexion provide better target coverage.

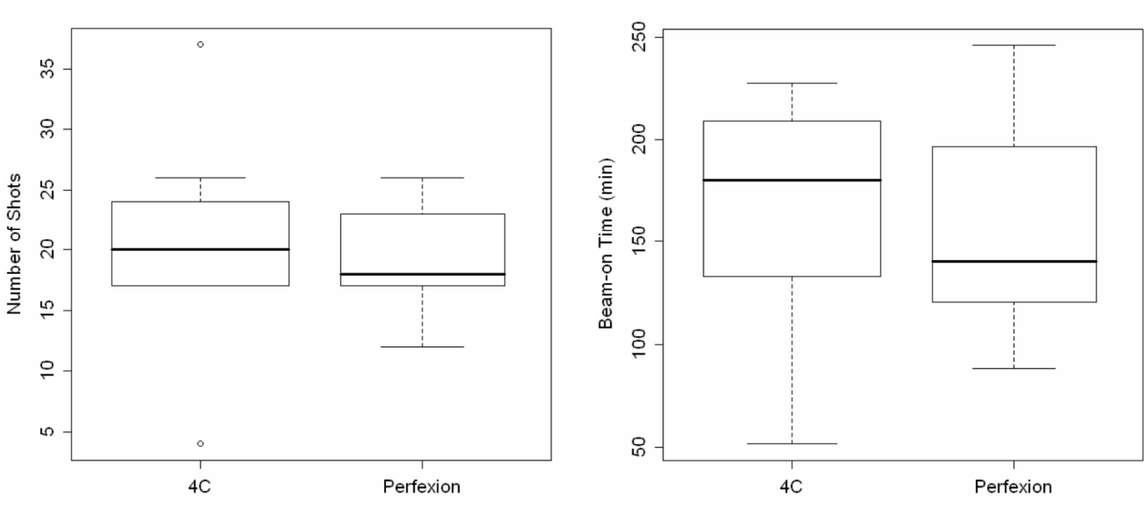


Fig. 4. Comparison of the number of shots and beam-on time of treatment plans for the Gamma Knife Perfexion and Model 4C. Due to high variability in the results, differences are not statistically significant. However, the mean number of shots and mean beam-on time are lower for the Perfexion.

4. Summary

Gamma Knife radiosurgery is being actively investigated as an alternative to open surgery for the treatment of MTLE and other forms of medically intractable epilepsy. Despite notable efficiency and practice differences between the various Gamma Knife models, consistent treatment planning practices and dosimetric parameters are demonstrated for a multi-institutional international trial setting. The final clinical results of such a trial for treating MTLE are forthcoming.

5. References

[1] Engle JJ, Pedley TA. Introduction: What is Epilepsy? In: Engle JJP, Timothy A, ed. Epilepsy: A comprehensive textbook. Philadelphia: Lippincott-Raven Publishers; 1997:1-7.

[2] Quigg M, Barbaro NM. Stereotactic Radiosurgery for Treatment of Epilepsy. *Arch Neurol* 2008; 65:177-83.

[3] Kuzniecky R, Guthrie B, Mountz J, *et al.* Intrinsic epileptogenesis of hypothalamic hamartomas in gelastic epilepsy. *Annals of Neurology* 1997; 42:60-7.

[4] Harvey AS, Freeman JL. Newer operative and stereotactic techniques and their application to hypothalamic hamartoma. In: Wylie EG, Ajay, Lachhwani DK, eds. The treatment of epilepsy:principles and practice 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:1169-74.

[5] Casazza M, Broggi G, Franzini A, *et al.* Supratentorial Cavernous Angiomas and Epileptic Seizures: Preoperative Course and Postoperative Outcome. *Neurosurgery* 1996; 39:26-34.

[6] Régis J, Rey M, Bartolomei F, *et al.* Gamma Knife Surgery in Mesial Temporal Lobe Epilepsy: A Prospective Multicenter Study. *Epilepsia* 2004; 45:504-15.

[7] Régis J, Bartolomei F, Rey M, *et al.* Gamma Knife Surgery for Mesial Temporal Lobe Epilepsy. *Epilepsia* 1999; 40:1551-6.

[8] Quigg M, Broshek DK, Barbaro NM, *et al.* Neuropsychological outcomes after Gamma Knife radiosurgery for mesial temporal lobe epilepsy: A prospective multicenter study. *Epilepsia* 2011; 52:909-16.

[9] Régis J, Bartolomei F, Rey M, *et al.* Gamma knife surgery for mesial temporal lobe epilepsy. *Journal of Neurosurgery* 2000; 93:141-6.

[10] Vojtěch Z, Vladyka V, Kalina M, *et al.* The use of radiosurgery for the treatment of mesial temporal lobe epilepsy and long-term results. *Epilepsia* 2009; 50:2061-71.

[11] Barbaro NM, Quigg M. Epilepsy - radiosurgery for epilepsy. *Rev Neurol Dis* 2009; 6:39.

[12] Barbaro NM, Quigg M, Broshek DK, *et al.* A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. *Ann Neurol* 2009; 65:167-75.

[13] Bartolomei F, Hayashi M, Tamura M, *et al.* Long-term efficacy of gamma knife radiosurgery in mesial temporal lobe epilepsy. *Neurology* 2008; 70:1658-63.

[14] Arita K, Kurisu K, Iida K, *et al.* Subsidence of seizure induced by stereotactic radiation in a patient with a hypothalamic hamartoma. *Journal of Neurosurgery* 1998; 89:645-8.

[15] Régis J, Bartolomei F, de Toffol B, *et al.* Gamma Knife Surgery for Epilepsy Related to Hypothalamic Hamartomas. *Neurosurgery* 2000; 47:1343-52.

[16] Unger F, Schröttner O, Feichtinger M, *et al.* Stereotactic radiosurgery for hypothalamic hamartomas. *Acta Neurochir Suppl* 2002; 84:57-63.

[17] Barajas MA, G. Ramírez-Guzmán M, Rodríguez-Vázquez C, *et al.* Gamma knife surgery for hypothalamic hamartomas accompanied by medically intractable epilepsy and precocious puberty: experience in Mexico. *Special Supplements* 2005; 102:53-5.

[18] Selch MT, Gorgulho A, Mattozo C, *et al.* Linear Accelerator Stereotactic Radiosurgery for the Treatment of Gelastic Seizures due to Hypothalamic Hamartoma. *Minim Invasive Neurosurg* 2005; 48:310,4.

[19] Mathieu D, Kondziolka D, Niranjan A, *et al.* Gamma Knife Radiosurgery for Refractory Epilepsy Caused by Hypothalamic Hamartomas. *Stereotactic and Functional Neurosurgery* 2006; 84:82-7.

[20] Régis J, Scavarda D, Tamura M, *et al.* Epilepsy related to hypothalamic hamartomas: surgical management with special reference to gamma knife surgery. *Child's Nervous System* 2006; 22:881-95-95.

[21] Abla AA, Shetter AG, Chang SW, *et al.* Gamma Knife surgery for hypothalamic hamartomas and epilepsy: patient selection and outcomes. *Special Supplements* 2010; 113:207-14.

[22] Mathieu D, Deacon C, Pinard C-A, *et al.* Gamma Knife surgery for hypothalamic hamartomas causing refractory epilepsy: preliminary results from a prospective observational study. *Special Supplements* 2010; 113:215-21.

[23] Bartolomei F, Régis J, Kida Y, *et al.* Gamma Knife radiosurgery for epilepsy associated with cavernous hemangionmas: a retrospective study of 49 cases. *Stereotactic and Functional Neurosurgery* 1998; 72:22-8.

[24] Kim MS, Pyo SY, Jeong YG, *et al.* Gamma knife surgery for intracranial cavernous hemangioma. *Special Supplements* 2005; 102:102-6.

[25] Liscák R, Vladyka V, Simonová G, *et al.* Gamma knife surgery of brain cavernous hemangiomas. *Special Supplements* 2005; 102:207-13.

[26] Liu K-D, Chung W-Y, Wu H-M, *et al.* Gamma knife surgery for cavernous hemangiomas: an analysis of 125 patients. *Special Supplements* 2005; 102:81-6.

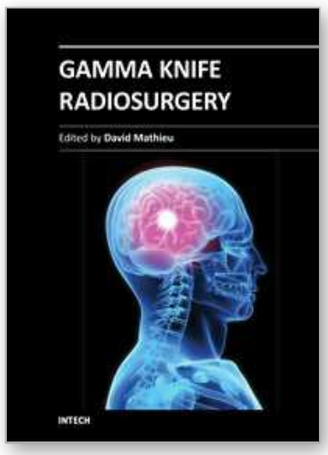
[27] Shih Y-H, Pan DH-C. Management of supratentorial cavernous malformations: craniotomy versus gammaknife radiosurgery. *Clinical Neurology and Neurosurgery* 2005; 107:108-12.

[28] Hsu PW, Chang CN, Tseng CK, *et al.* Treatment of Epileptogenic Cavernomas: Surgery versus Radiosurgery. *Cerebrovascular Diseases* 2007; 24:116-20.

[29] Régis J, Bartolomei F, Kida Y, *et al.* Radiosurgery for Epilepsy Associated with Cavernous Malformation: Retrospective Study in 49 Patients. *Neurosurgery* 2000; 47:1091-7.

[30] Romanelli P, Muacevic A, Striano S. Radiosurgery for hypothalamic hamartomas. *Neurosurgical Focus* 2008; 24:E9.

[31] Paddick I, Lippitz B. A simple dose gradient measurement tool to complement the conformity index. *J Neurosurg* 2006; 105 Suppl:194-201.



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