Case study

Gamma Knife® radiosurgery for medically intractable epilepsy

Case

Medically intractable epilepsy

Author:

Professor Dr. R. Martinez, Head of Functional Neurosurgery and Radiosurgery, Ruber International Hospital, Madrid, Spain

Overview

Epilepsy is a chronic neurological disorder that affects around 50 million people globally[1] and is characterized by recurrent seizures. Up to 70% of cases are controlled with antiseizure medications but around 30% have medically intractable epilepsy.[1] For these patients, their condition can lead to a poor quality of life and difficulties in undertaking normal daily activities.[2]

Surgical techniques, including stereotactic radiosurgery (SRS), may be used to improve seizure control and quality of life for medically intractable epilepsy patients.[3] Among the known causes for epilepsy that are responsive to surgical intervention are mesial temporal lobe epilepsy (MTLE)[4-7] and hypothalamic hamartomas (HHs).[4,8,9] In addition, for some patients suffering from complex epilepsies, palliative procedures such as callosotomy can be applied.[10]

Leksell Gamma Knife® (LGK) SRS, targeting the medial temporal lobe, is a minimally invasive treatment option for MTLE patients contraindicated for, or reluctant to undergo, open surgery,[11] offering improved quality of life and protection of cognitive function.[4,12] In addition, LGK SRS targeting the HH lesion is an established, safe and effective treatment for medically intractable epilepsy associated with small HHs.[9,13-15] It has also been used to treat cases of extra-temporal epilepsy and for palliative procedures, such as anterior corpus callosotomy.[10,16]

At the Functional Neurosurgery and Radiosurgery Unit at Ruber International Hospital, we have treated 65 medically intractable epilepsy patients using LGK SRS since 1998. Patients with temporal or extratemporal epilepsy (60% male, 40% female) ranged from 25-36 years old (median 27 years). Patients with HH (55% female, 45% male) ranged from 1.5-45 years old (median 18 years). These patients experienced daily, very disabling epileptic seizures that did not respond to medication. Most had an epileptic history of at least 7 years, except for severe cases of HH in childhood where we acted immediately due to the severity of the condition. Around 75% of patients could not lead an active life due to their condition. In addition to epileptic seizures, major symptoms prior to LGK SRS included cognitive impairment and aggression. Our experience of treating epileptic patients with callosotomy is more limited. We have performed this procedure in five patients aged between 16 and 25 years. In all cases, LGK SRS was selected due to potential surgical risk, including post-surgery neurological deficit, and according to patient choice. The patient tolerated the procedure well. Unfortunately, however, there was no effect on her tremor.

Adoption of new imaging modalities

More recently new imaging modalities were added to our DBS and lesioning procedures, including FGATIR MRI.[2] This sequence provides excellent delineation of grey and white matter, allowing better visualization of the thalamus contours and the rubro-thalamic connections.[4] Note that during these invasive procedures, the awake patient is monitored to maximize tremor control and minimize unwanted side effects. In our experience, in concordance with the literature, these new landmarks are beneficial in determining the optimal target for tremor control (figure 2).

Second Gamma Knife procedure (January 2023)

Following these new imaging developments, it was decided to review the essential tremor case first treated in January 2021. 3T FGATIR MRI images were obtained, which allowed visualization of the nucleus ruber and rubral wing (figure 3). The latter is a hypointense white matter tract in the thalamus that contains the dentato-rubro-thalamic tract (DRT), which is considered a potential target in DBS for the treatment of tremor[2].

Coregistration of the frameless 3T FGATIR MRI scan to the frame-based stereotactic 1.5 T planning MRI scan in GammaPlan revealed that the initial shot was located slightly above the DRT (figure 3). It was decided to perform a second Gamma Knife procedure, with the new 4 mm shot located more inferiorly and medially to better target the DRT. The patient was immobilized as before.

The treatment was planned in Leksell GammaPlan® version 11.3.2 and was delivered using Gamma Knife® Icon™. A dose of 32.5 Gy was prescribed on the 50% isodose line (see Figure 3). The distance between both isocenters was 2.6 mm. The prescription dose was lowered to limit dose in the region that overlapped the original treatment.

Ten days after the second Gamma Knife treatment the tremor had almost completely disappeared and the patient's right hand was fully functional again. A recent follow-up confirmed that tremor control has now persisted for eight months.

Radiosurgical Protocol

Our inclusion criteria for this study are as follows:

- A confirmed diagnosis of MTLE, extratemporal epilepsy or HH based on high-resolution MRI findings.
- Refractory epilepsy that failed to respond to standard anti-epileptic drugs.
- Availability of longitudinal clinical and radiological follow-up data.

Prior to 2022, patients were fitted with the Leksell G type stereotactic frame and, since 2022, they have been immobilized using the Leksell Vantage™ frame. Patients under 12 years of age, and those with significant behavioral problems, are treated under general anesthesia. Otherwise, light sedation and control of epileptic seizures have been sufficient to deliver treatments without problems.

Pre-treatment imaging includes high-resolution T1- and T2-weighted MRI with 1–1.5 mm slices of the whole brain, incorporating contrast enhancement with the T1 series. Planning is carried out using Leksell GammaPlan® treatment planning software.

The radiosurgery is performed using the Leksell Gamma Knife, (Gamma Knife versions B and C prior to 2007, Gamma Knife Perfexion from 2007-2017, and Gamma Knife Icon since 2017).

For HHs, the treatment plan aims to encompass the entire lesion, with a median marginal dose of 16–20 Gy delivered to the 50% isodose line (figures 1 and 2). For MTLE, the target volume includes the hippocampus, amygdala, and parahippocampal gyrus, with a prescription dose of between 24–25 Gy at 50% isodose (figures 3 and 4). For extratemporal epilepsy, the target is determined by prior stereoelectroencephalography (SEEG) and planning is adapted in GammaPlan using MRI under stereotaxic conditions (figure 5). The target volume includes the cortex of the epileptic focus with the same dose and isodose parameters applied in MTLE.

Risk areas at the target periphery include the brainstem, optic pathway and hypothalamus. The maximum dose to these structures is kept to less than 10 Gy.

In callosotomy procedures, we target specific regions of the corpus callosum to disrupt interhemispheric seizure propagation, especially in the anterior (figure 6). The maximum dose applied is 120 Gy, with a coverage dose of 60 Gy at the 50% isodose. The volume of peripheral brain tissue that receives more than 10 Gy has always been less than 3 cm³.

These Gamma Knife treatments last between 1-3 hours. Afterwards, patients remain under observation for 4 hours before they are discharged. They do not require additional medication and must remain on anti-epileptic treatment. Patients tolerate the treatment extremely well with no immediate side effects. Follow-up consists of consultations and MRI scans every six months for the first 3 years, and then annually for at least another 5 years.

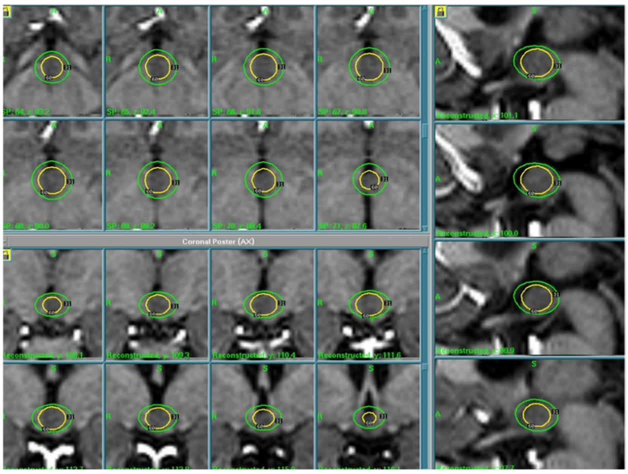

Figure 1.
Treatment plan for HH case example 1. The HH is included within the prescription isodose (yellow line) and the peripheral optic pathway is located outside the 10 Gy isodose (green line).

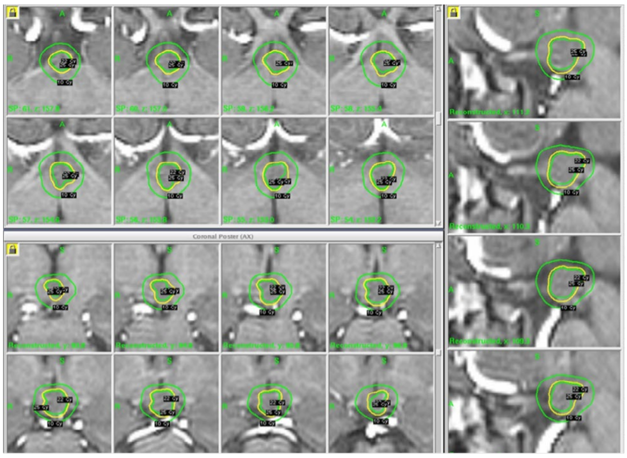

Figure 2.
Treatment plan for HH case example 2. The HH is covered by the 20 Gy prescription isodose (yellow line), inside which is shown the 22 Gy isodose (internal green line). The optic pathway and the hypothalamic fornix are exposed to less than 10 Gy (external green line).

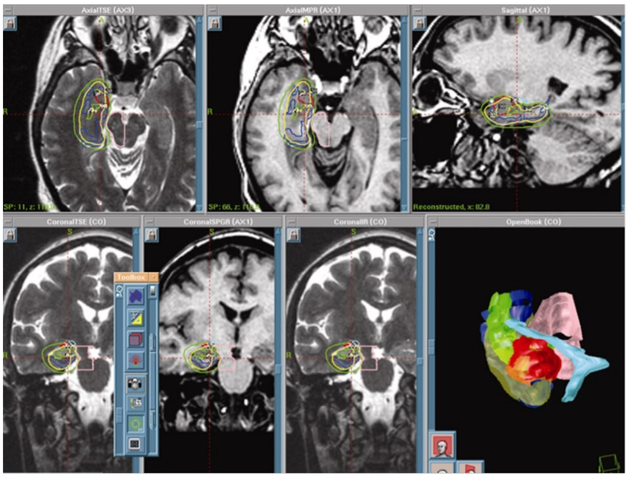

Figure 3.
Treatment plan for MTLE case example 1. Dose planning includes the medial part of the temporal lobe and the amygdala. The yellow line represents the 24 Gy prescription isodose. The peripheral green line corresponds to the 10 Gy isodose.

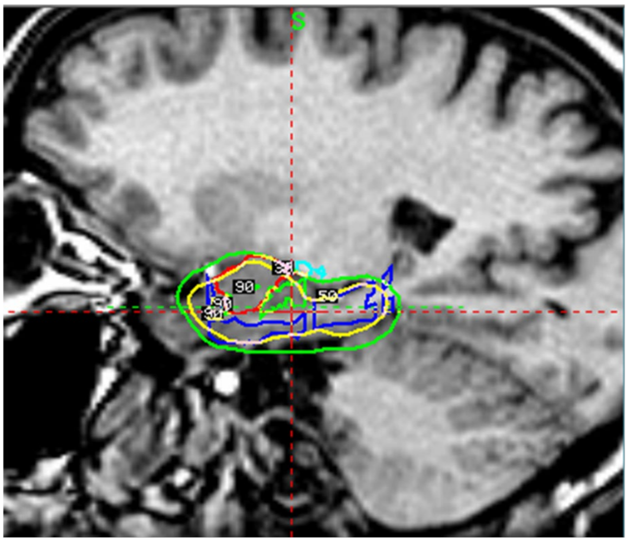

Figure 4.
Treatment plan for MTLE case example 1. Sagittal view: the yellow line represents the 24 Gy prescription isodose, while the outer green line represents the 10 Gy isodose.

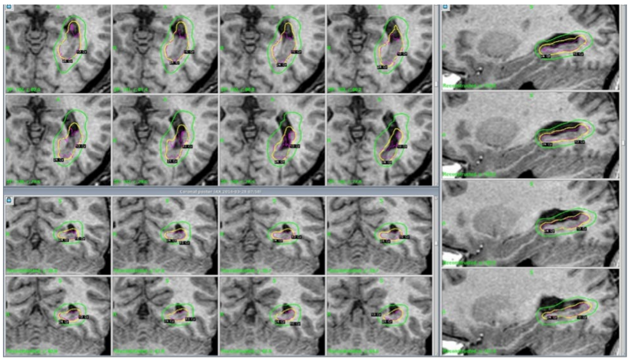

Figure 5.
Treatment plan for extratemporal epilepsy case example [1]. The epileptic focus located in the left occipital lobe is treated with 20 Gy at the 50% isodose (yellow isodose line) and the optic pathway is exposed to less than 10 Gy (green isodose line).

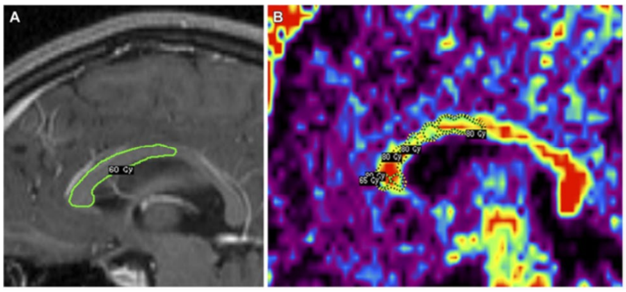

Figure 6.
Callosotomy case example 1: Blockade of the anterior part of the corpus callosum with a coverage dose of 60 Gy at the 50% isodose. (Figure published with permission of Prof Regis).

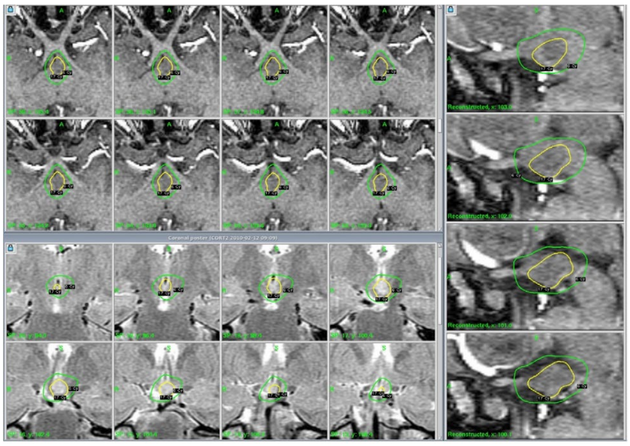

Figure 7.
Treatment plan for HH case example 2. This is retreatment of the case in figure 2, showing a 40% reduction in volume. The coverage isodose (yellow line) is now 18 Gy and the optic pathway and hypothalamic fornix are exposed to less than 8 Gy.

Results

The overall response for the treatment of medically intractable epilepsy using LGK SRS at our institution is 70% (to Engel I or II* with or without mediation) in cases of HH, MTLE and extratemporal epilepsy.

After LGK callosotomy, drop attacks have been controlled in four out of five patients treated. General seizures have decreased in severity and frequency in all callosotomy patients, but they remain at Engel III.

In all cases, there were no permanent side effects, although transitory depression was experienced in two cases of MTLE.

LGK SRS has a significant impact on patient quality of life, which improved, on average, by 70% on quality-of-life measurement scales (EQ-5D health states17). At least 70% of cases are able to work normally and, in cases of HH, 90% have improved with respect to behavior and cognitive deficit.

In 50% of HH cases, we observed a reduction in the HH volume (figure 7). 30% of cases were treated again due to exacerbation of the crises. These patients improved again after the second treatment.

In cases of MTLE, the effects of LGK SRS increased over time, reaching its full effect 12 months post-radiosurgery. All cases showed some degree of long-term mesial temporal atrophy after treatment (figure 8).

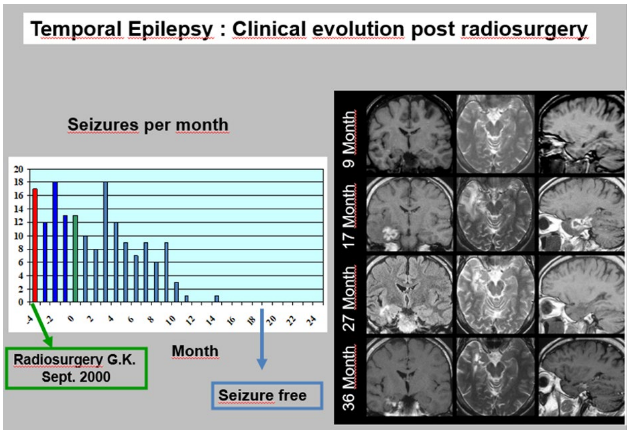

Figure 8.
Clinical evolution post LGK SRS in MTLE cases. Maximum effect was reached 16 months post-radiosurgery (left). MRI scans at 17 and 27 months show contrast enhancement in the right temporal lobe along with edema that disappeared in the MRI performed at 36 months.

Discussion

Radiosurgery, particularly LGK SRS, has emerged as a minimally invasive alternative for treating certain forms of drug-resistant epilepsy. The reviewed literature evaluates its safety, efficacy, and broader impact on patient outcomes across different types of epilepsy, including corpus callosotomy for refractory seizures, HHs, and focal epilepsies.18-22 Radiosurgery impacts the epileptogenic zone by inducing delayed necrosis and neuromodulation[19], gradually reducing seizure activity over months.

Systematic review of radiosurgery in epilepsy applications demonstrates the use of radiosurgery to treat MTLE,[5-7,12] extratemporal epilepsy,[16] HH13-15 and for callosotomy.[10]

HH-related epilepsy often presents as gelastic seizures, which may progress to catastrophic epileptic encephalopathy. Radiosurgery offers a non-invasive alternative to traditional resective surgery. In a prospective trial involving 48 patients, 68.8% achieved Engel Class I/II outcomes, indicating seizure freedom or substantial improvement. Psychiatric comorbidities improved or resolved in 84% of cases. No permanent neurological deficits were reported.[13-15]

Gamma Knife Corpus Callosotomy (GK-CC) is primarily used for patients with intractable epilepsy characterized by severe drop attacks (DAs) and generalized seizures. In a cohort of 19 patients[10], 68% experienced significant seizure reduction and 16% achieved complete seizure freedom.

Transient side effects were mild and no major long-term complications were reported. GK-CC demonstrates comparable efficacy to traditional surgical callosotomy[2,10] while minimizing risks such as infection, disconnection syndrome, and cerebrospinal fluid leakage.

Level 2 evidence supports radiosurgery in MTLE and HH.[18] In other cases, palliative radiosurgery, such as callosotomy, shows promise in reducing seizure burden in inoperable or high-risk cases.

Challenges associated with radiosurgery include delayed therapeutic effects (several months) and the absence of randomized controlled trials limit the establishment of definitive guidelines.[12,15,18,19] However, the advantages of radiosurgery over surgery are that it offers reduced risk of permanent deficits and favorable neuropsychological outcomes compared to resective procedures.[3,6] Although radiosurgery avoids many risks associated with open procedures, including infection, significant neurological deficits, and prolonged recovery, it requires precise imaging and planning to target the epileptogenic zone effectively[6,7].

Looking ahead, randomized trials comparing radiosurgery with conventional surgical techniques are necessary to solidify its role in epilepsy management[18]. In addition, technological advances, such as improved imaging and targeting methodologies, may further enhance outcomes.

Conclusions

LGK SRS allows us to deliver an extremely precise and accurate radiation dose to epileptic targets within the brain, while sparing the surrounding healthy tissue and critical structures. In our experience, this is a safe and effective treatment option for medically intractable epilepsy, providing a treatment response rate in line with published evidence.4,5,7,10,12,14,18-22

Radiosurgery represents a valuable option for managing specific epilepsy subtypes, particularly for patients unsuitable for traditional surgery. Its safety profile and efficacy justify its inclusion in comprehensive epilepsy treatment strategies.

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*According to the Engel Classification Scale for epilepsy surgery outcomes, as follows:

- Class I: Free of disabling seizures
- Class II: Rare disabling seizures, less than 3 seizure days per year
- Class III: Worthwhile improvement, or greater than 80% reduction in seizure frequency
- Class IV: No worthwhile improvement, or less than 80% reduction in seizure frequency

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