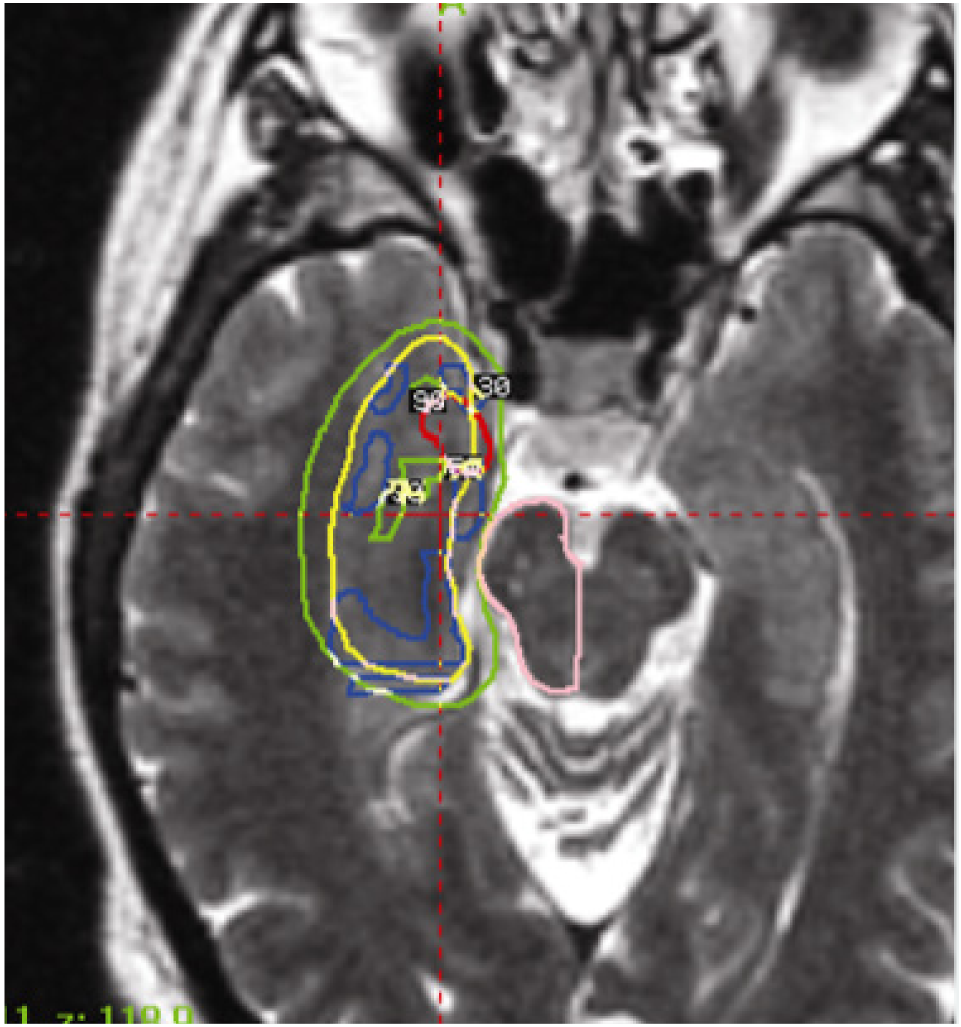
Elekta

Leksell Gamma Knife® radiosurgery for medically intractable epilepsy

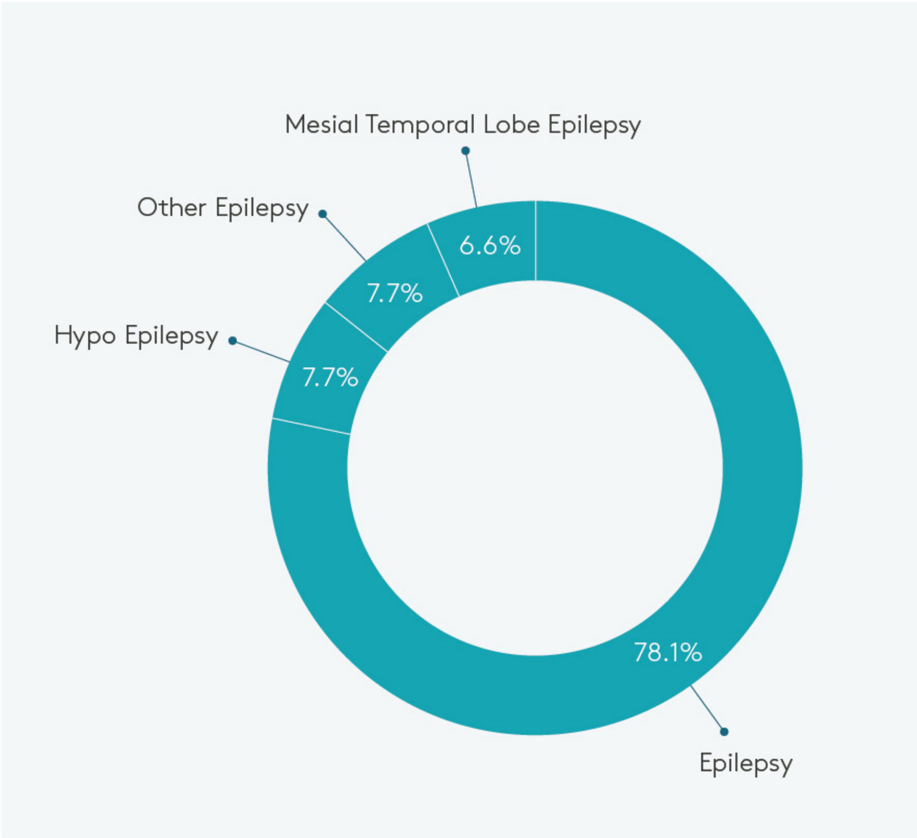


The global burden of epilepsy

Epilepsy is one of the most common neurological diseases globally, affecting around 50 million people worldwide and with an estimated 5 million cases diagnosed each year.[1] It is a chronic neurological disorder characterized by recurrent epileptic seizures. There are multiple underlying causes of epilepsy but in 50% of cases the cause is unknown.[1] Up to 70% of cases are controlled with antiseizure medications[1], leaving approximately 30% with medically intractable epilepsy.

Such patients are predisposed to a poor quality of life and difficulties with normal daily activities.[2] For these cases of drug-resistant epilepsy, surgery may improve seizure control and quality of life.[3] Several surgical methods are available for the treatment of intractable epilepsy, including resection, radiosurgery, neuromodulation and disconnection techniques, with a growing trend towards minimally invasive procedures, such as stereoelectroencephalography (SEEG), radiofrequency thermocoagulation (RF-TC), magnetic resonance imaging (MRI)-guided laser interstitial thermal therapy (MRg-LiTT) and stereotactic radiosurgery (SRS).[3-6] Treatments are selected and individually tailored to achieve the best possible outcome for the patient.

The region of the brain where seizures are generated is known as the epileptogenic zone (EZ)[7-8] and is localized, where possible, through careful diagnostic evaluation. The extent to which this region can be identified and removed (or disconnected) without damaging surrounding healthy areas of the brain determines the results of epilepsy surgery.[8]



Medically intractable epilepsy

Among the known causes for medically intractable epilepsy that are responsive to surgical or radiosurgical intervention are mesial temporal lobe epilepsy (MTLE),[9-12] hypothalamic hamartomas (HHs)[9,13-14] and cerebral cavernous malformations (CCMs).[9,15-16]

Mesial temporal lobe epilepsy

MTLE is the most common cause of drug-resistant focal epilepsy, identified through clinical, neuroradiologic and electrophysiologic means.[12] MTLE is responsible for two-thirds of focal seizure disorders, with about 30% of cases resistant to medical therapy.[4] Surgical techniques, such as anterior temporal lobectomy (ATL), can lead to long-term seizure remission if the EZ can be defined and safely removed or disconnected.[11] Surgical cure rates of 65-90% have been reported for MTLE.[9,10,17,18] In addition, radiosurgery may be considered for this type of epilepsy, offering comparable seizure reduction rates (52-85%) with low morbidity.[9,19] Minimally invasive procedures for the treatment of intractable MTLE, such as MR-guided laser interstitial thermal therapy (MRgLITT) and SRS may have comparable rates of postoperative seizure freedom and reoperation.[4]

Hypothalmic hamartomas

HHs are rare benign congenital lesions of the hypothalmus consisting of glia, neurons and fiber bundles.[9,13,20] They are commonly associated with precocious puberty, developmental cognitive delay and gelastic epilepsy.[5,9,13,14] In severe cases, patients can develop various types of generalized seizures, including drop attacks.[6] Individuals with HHs often present in early childhood with intractable epilepsy,[6,13,21] requiring early surgical or radiosurgical intervention to eliminate or reduce seizures,[6] as well as to improve or prevent severe psychiatric and cognitive comorbidities.[13] The location of HHs close to areas of the brain important for cognitive function presents a recognized surgical challenge in the treatment of these lesions. Microsurgery carries a significant risk of morbidity, including impairment of short-term memory.[6,14] SRS is a non-invasive alternative approach for the treatment of small HHs.[6,9,14,19]

Cerebral cavernous malformations

CCMs are rare benign vascular lesions that occur in 0.4-0.8% of the population[22] and commonly manifest as recurring seizures.[9,15] Up to 40% of CCM patients develop medically intractable epilepsy.[15] Surgical removal of the CCM prevents seizures in 50-90% of cases but is associated with high morbidity, especially when the lesion is located in deep or eloquent regions of the brain.[15] SRS is an alternative treatment option that offers good seizure control for such patients.[9,15,16,22] In addition, for some cases of intractable epilepsy that is generalized from onset or when the EZ involves homotopic regions in both hemispheres of the brain, palliative surgery may be used to reduce the seizure burden.[3] For example, corpus callosotomy is a disconnection procedure, which prevents epileptic discharges from propagating between the cerebral hemispheres.[23] This invasive surgical procedure carries the risk of surgical and neurological complications.[2,24] Division of the corpus callosum by SRS provides a non-invasive alternative palliative intervention for patients suffering from frequent drop attacks caused by rapid interhemispheric generalization,[2,23] offering better neuropsychological.

SRS for medically intractable epilepsy

Although surgical resection and some palliative surgical procedures have a good success rate in the treatment of medically intractable epilepsy, they are invasive and carry the risks of surgical and neurological complications.[4,9,12,14,17,18,25-28]

Where surgery has failed, is contraindicated or declined,[29-31] SRS may be considered as a safe and effective, non-invasive alternative for the treatment of intractable epilepsy when the target can be accurately defined using clinical, neurophysiological and radiological data.[9,21,29-32] SRS delivers a targeted dose of radiation to the EZ with the aim of controlling seizures. Unlike other surgical techniques, the effects of SRS in the treatment of epilepsy may be delayed, with seizure frequency often decreasing over time[2] and reaching its full effect several months after treatment.[2,9,31]

The positive effect of SRS on epileptic seizure control was first observed over 30 years ago following radiosurgical treatment of cerebral tumors and vascular malformations.[31] In the 1990s, its use was pioneered as an alternative to conventional surgery for the treatment of medically intractable MTLE and, in the early 2000s, for the treatment of drug-resistant epilepsy associated with HHs.[31] Since then, it has also been used to treat cases of extra-temporal epilepsy and for palliative procedures, such as anterior corpus callosotomy.[31]

The mechanism of SRS in the treatment of epilepsy is yet to be fully understood but it is thought to involve both ischemic necrosis and neuromodulatory effects.[27,31] This potential non-lesional approach for the treatment of the EZ, even in highly functional areas of the brain, has sparked much interest in the role of SRS in epilepsy surgery.[27]

Gamma Knife radiosurgery for intractable epilepsy

Leksell Gamma Knife was designed by a leading neurosurgeon as a safe and effective alternative to surgery for functional neurosurgery. It allows neurosurgeons to deliver an extremely precise and accurate radiation dose to targets within the brain while sparing the surrounding healthy tissue and critical structures.[9]

The efficacy and safety of Gamma Knife radiosurgery for a wide range of brain indications is well documented, including for the treatment of AVMs, vestibular schwannomas, meningiomas and brain metastasis,[12] as well as for functional disorders, such as trigeminal neuralgia, essential tremor and medically intractable epilepsy.[26,31]

GKRS for MTLE

GKRS was first used to treat MTLE in 1993.[12,18,27] Since then, the evidence for GKRS in the treatment of intractable MTLE has grown, demonstrating the safety and efficacy of this approach with comparable seizure remission rates to conventional surgery (52-85%) and improved neuropsychological outcomes.[9,10,12,17,18,27,31,33-35] Studies describe a dose of 24 Gy to the 50% isodose targeting the medial temporal lobe, including the amygdala, anterior hippocampus and nearby cortex (parahippocampal gyrus)[9,18,35] (figure 1). A lower dose of 20 Gy produces a reduced rate of seizure remission with no significant safety benefit.[17]

GKRS is described as a minimally invasive alternative treatment pathway for MTLE patients contraindicated for or reluctant to undergo, open surgery,[18] offering improved quality of life and protection of cognitive function.[9,35] In particular, the memory-sparing benefit of GKRS observed for patients with dominant temporal lobe MTLE is considered a major benefit over conventional microsurgery.[17,18,27,31]

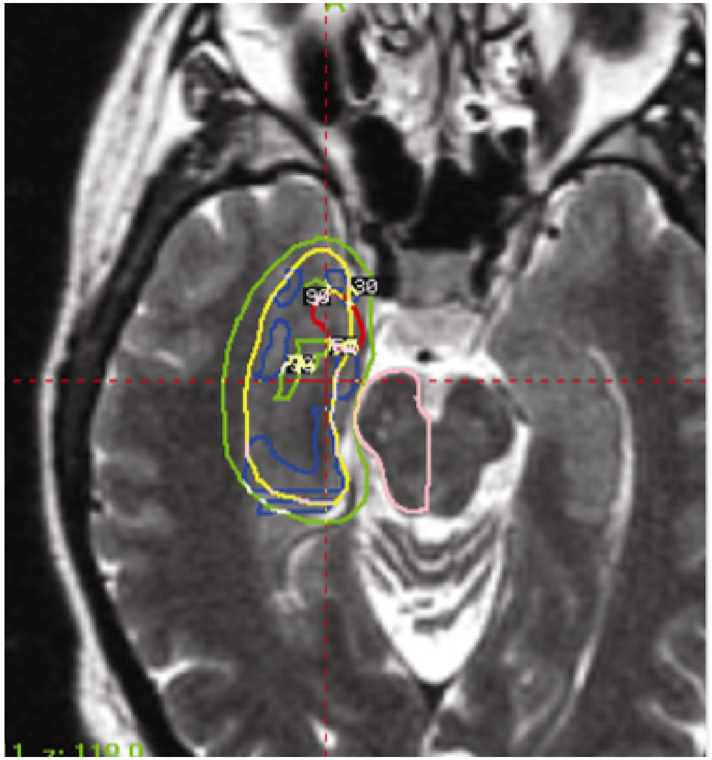


Figure 1.

Dose-planning of a mesial temporal lobe epilepsy displayed on an axial MRI image. Figure courtesy of Professor Roberto Martinez at Ruber Internacional Hospital in Madrid, Spain.

GKRS for HHs

GKRS is an established, safe and effective treatment for medically intractable epilepsy associated with small HHs.[5,6,14,26,36] It is used to alleviate seizures, as well as behavioural and cognitive abnormalities associated with these lesions,[6] offering comparable seizure control to conventional surgery[36] and an improved benefit to risk ratio.[6,21,28,31,37] A dramatic reduction of seizures (e.g. to Engel I or Engel II) has been reported in 60-65% of patients, in addition to behavioural and cognitive improvements.[6,21,27] Certain severe side effects associated with other surgical techniques, such as memory decline and endocrinologic complications, are absent following GKRS.[6,14,36]

Radiosurgery is the least invasive strategy for the treatment of intractable epilepsy associated with HH. Complications are very rare, and it avoids the vascular risks associated with microsurgery and thermocoagulation.[6,28] Given its favorable safety and efficacy profile, it has been suggested that GKRS may be considered as a first line treatment for epilepsy associated with small hypothalamic hamartomas.[13,14,36]

The GKRS target in this instance is the HH itself, which is identified and delineated by high resolution MRI27 (figure 2). An axial plane T1-weighted brain MRI (1.5-mm slice) with contrast has been used for HH localization with axial fast spin echo T2-weighted imaging (3-mm slice) to delineate the HH and adjacent critical structures, including the hypothalamus, the pituitary gland, and the optic apparatus.[13] Doses to the HH of 17 to 20 Gy have been described,[13,36] with doses to the optic apparatus and brainstem restricted to <8 Gy and <10 Gy, respectively.[13]

GKRS offers an alternative treatment for surgically inaccessible CCMs or for those located near eloquent areas of the brain.[38-39] It has been shown to improve quality of life[40] and provide good seizure control, with the majority of patients experiencing reduced seizures, and 43-53% becoming seizure free following treatment[9,16,40,41]. Low marginal doses of 9-19 Gy have been used, prescribed to 50-85% isodose.[38-41]

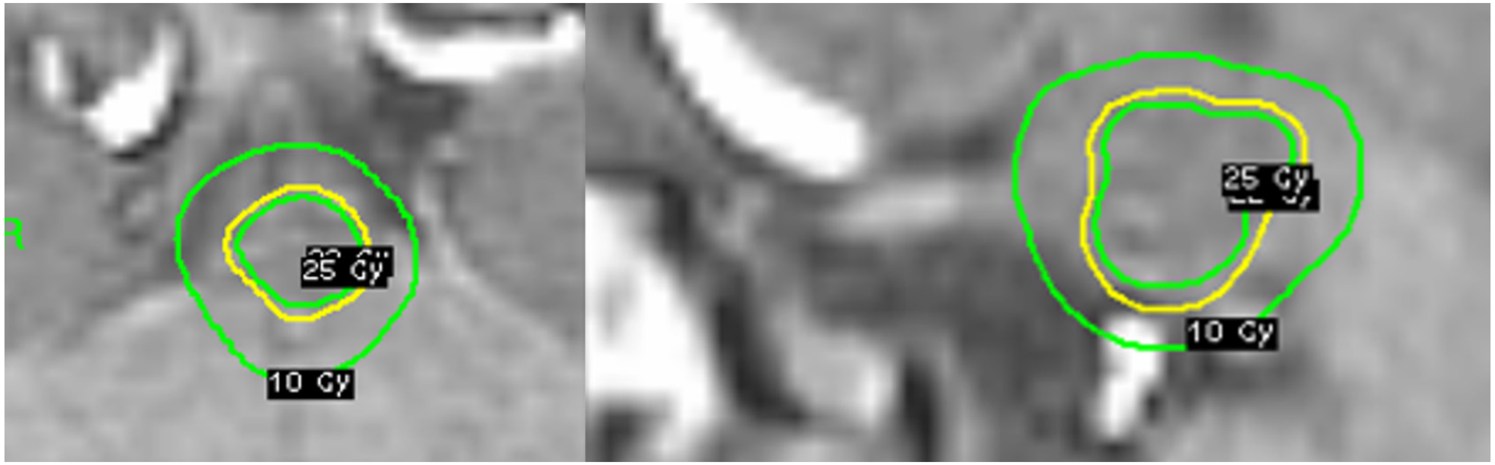


Figure 2.

Leksell Gamma Knife Dose planning for hypothalamic hamartoma illustrating an axial (left) MRI image and reconstructed (right) coronal MRI image. Figure courtesy of Professor Roberto Martinez at Ruber Internacional Hospital in Madrid, Spain

GKRS for corpus callosotomy

GKRS for corpus callosotomy was first described in 1999.[42] Since then, several cases of both anterior and posterior corpus callosotomies by SRS have been reported, resulting in improved seizure control with no acute side effects.[2]

The radiosurgical target for anterior corpus callosotomy is the genu, rostrum and anterior half of the corpus callosum, defined on axial, coronal and sagittal MRI sections[23]. Historically, the prescribed dose ranges from 55-85 Gy at 50% isodose, delivered to the target with the aim of creating a disconnection through lesioning or neuromodulation, while protecting surrounding structures.[23]

Gamma Knife provides a safe and effective, non-invasive alternative to corpus callosotomy by microsurgery for eligible patients with intractable epilepsy suffering from severe drop attacks, offering comparable efficacy without complications.[24,25]

Conclusions

The evidence for GKRS as a safe and effective treatment option for medically intractable epilepsy has gathered over the last three decades and continues to grow. This extremely precise technique provides patients with a viable alternative to open surgery, while its excellent dose fall off spares healthy tissue and reduces toxicity compared to other radiosurgical techniques.[43-52] For patients, GKRS is less invasive than open surgery, with fewer side effects and improved comfort.[12]

They can receive imaging and treatment on the same day in a convenient outpatient setting, without the trauma or recovery period associated with open surgery.

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