Evolving paradigm in drug resistant epilepsy radiosurgery -
Techniques, indications and outcomes

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Abstract

Drug resistant epilepsy is one of the most common chronic neurologic disorders. These patients are at increased risk for serious morbidity and mortality, including cognitive disorders, poor academic performance, unemployment, depression, physical trauma, and sudden death in epilepsy. The goals of treatment for individuals with drug-resistant epilepsy are to render the patient seizure free, avoid treatment-related adverse effects, and allow the individual to become a participating and productive member of society. Focal cortical resection is a consideration in patients with drug-resistant focal epilepsy if the seizures emanate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction. Concerns regarding surgical morbidity especially on the cognitive function, visual field deficits limiting to superior quadrant, psychiatric problems have generated enthusiasm for more minimally invasive interventions like Stereotactic Radiosurgery (SRS), Laser Interstitial thermal therapy (LIIT), Radiofrequency thermocoagulation & Focussed ultrasound. Authors in this article discussed the technique, indications and complications of SRS for drug resistant epilepsy.

Key Words: cavernoma, corpus callosotomy, cyberknife, drug resistant epilepsy, gammaknife, hypothalamic hamartoma, mesial temporal sclerosis, radiosurgery

Introduction

Epilepsy is one of the most common chronic neurologic disorders. International League Against Epilepsy (ILAE) defined drug-resistant epilepsy, estimated between 20-40%, as the failure of adequate trials of two tolerated, appropriately chosen and administered antiseizure medications (whether as monotherapy or in combination) to achieve seizure freedom. Such patients are at increased risk for serious morbidity and mortality, including cognitive disorders, poor academic performance, unemployment, depression, physical trauma, and sudden death in epilepsy. The goals of treatment for individuals with drug-resistant epilepsy are to render the patient seizure free, avoid treatment-related adverse effects, and allow the individual to become a participating and productive member of society. Focal cortical resection is a consideration in patients with drug-resistant focal epilepsy if the seizures emanate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction. Success of any Epilepsy surgery depends on the robust localisation of epileptogenic focus which includes functional or metabolic imaging and intracranial EEG monitoring, underlying surgical pathology and seizure type. Concerns regarding surgical morbidity especially on the cognitive function, visual field deficits limiting to superior quadrant, psychiatric problems have generated enthusiasm for more minimally invasive interventions like Stereotactic Radiosurgery (SRS), Laser Interstitial thermal therapy (LIIT), Radiofrequency thermocoagulation & Focussed ultrasound.1 Radiosurgery is least invasive of all the available options. The demonstrated advantages of radiosurgery are the comfort of the procedure, the absence of general anesthesia, the absence of surgical complications and mortality, the very short hospital stay, and the immediate return to the previous level of functioning and employment.

Epilepsy Radiosurgery - Basic Principles

Radiosurgery involves delivery of High energy X rays or gamma rays in a small sharply limited target in a single...
session with stereotactic accuracy for a lesional or non-lesional effect.

1. Basic Principles of Radiosurgery Machines
The mechanical accuracy of the radiation delivery system and steepness of the dose gradient are the key factors of a radiosurgery system.

- The average mechanical accuracies of the modern radiosurgery machines are less than a millimetre.
- Besides accuracy the thickness and resolution of the stereotactic images are equally important in evaluating the accuracy of the whole radiosurgery procedure.
- Target conformity and the radiation dose gradient properties of each machine is very difficult to compare the outputs because the treatment plan depends on the target shape, target size, the planning personnel, the time spent on planning, and the techniques used. Gamma Knife users usually prescribe the irradiation dose on isodose lines of about 50% of the maximum dose, whereas users of the other machines use isodose lines of between 70 and 90%.
- Frameless radiosurgery is a thoroughly non-invasive treatment offering submillimetric accuracy. Furthermore, the absence of a stereotactic frame opens up a wide space for additional beam trajectories, thus enhancing the beam access to skull base or deep brain lesions. An additional degree of radioprotection is provided by the ability to hypofractionate the treatments if needed.

2. Mechanism of Action in Epilepsy: Differential Effect Concept Producing Neuromodulation

- Clinical Level: Deep seated AVM’s with DRE post SRS show immediate seizure cessation before the nidus obliteration. Radiosurgery induces a functional effect such as rendering the cortex surrounding the AVM no longer epileptic without destroying the underlying function
- At Cellular level: In rat experiments, Injury of the catecholaminergic system with concomitant sparing of the GABAergic systems & Neuronal cells appear to have undergone a phenotypic shift with respect to calbindin and glutamate decarboxylase-67 expression. The lack of target necrosis as shown by follow-up MRs points toward a neuromodulatory effect induced either by gliosis, down-regulation of firing neurons and reduced vascular supply.

3. Epileptogenic Substrate Localisation Tools
The goal of presurgical evaluation for epilepsy surgery is to lateralize and localize the seizure focus accurately; this includes phase I and phase II evaluation:

- **Phase I evaluation** includes the use of non-invasive modalities to determine where the seizure starts; this includes techniques such as video-EEG, MEG, 3 tesla MRI (T1,T2 & FLAIR), Functional Neuroimaging using - interictal PET, ictal SPECT/ SISCOM, and neuropsychological assessment.
- **Phase II evaluation** includes the use of surgically placed electrodes directly over the brain parenchyma to determine where exactly the seizure is originating. This phase involves the use of invasive techniques such as placement of subdural grids/stripes and/or depth electrode placement for electrocorticography (ECoG) and stereo-electroencephalography (SEEG).

4. Evaluating Efficacy of Interventions
Engel Epilepsy Surgery Outcome Scale, which has become the de facto standard when reporting results in the medical literature

| Class 1 Free of Disabling Siezures | Class II Rare Disabling Siezures |
|-----------------------------------|---------------------------------|
| A  | Initially seizure free, rare siezures now |
| B  | Rare disabling siezures |
| C  | Rare siezures for the last 2 yrs |
| D  | Nocturnal siezures for last 2 yrs |

| Features                  | Gamma Knife (Fig 1) | Cyberknife (Fig 2) | X-Knife / Linac Knife |
|---------------------------|---------------------|--------------------|-----------------------|
| Fixation                  | Fixed Frame Based   | Frameless – Double reinforced stereotactic mask |
| Radiation Source          | Co-60               | Linac mounted on robotic manipulator |
| Planning System           | TPS based           | Linear Accelerators |
| Focussing Methods         | Multiple Sources    | Multiple pencil beams |
| Planning System           | Advanced Monte-carlo algorithms |
| Maximum Dose Rate         | 2.5 - 3.5gy/ mt.    | 1000 mu/mt.        |
|                          |                     | 1200-2000 mu/mt.   |
| Collimator                | 4mm,8mm,16mm        | Cone: 5-60mm & Iris MicroMLC |
|                          |                     | Cones 5-20mm       |
| Target Tracking           | Not available       | Realtime X-Ray & Optical tracking |
|                          |                     | Offline X – Ray Tracking |
| Avg. Mechanical Accuracy  | ~ 0.3mm             | ~ 0.3mm            |
| Overall System Accuracy   | ~ 1mm               | ~ 1mm              |
5. Indications for Epilepsy Radiosurgery

A) Radiosurgery in Mesial Temporal Lobe Epilepsy

Patients typically experience focal dyscognitive seizures, (complex partial seizures) with or without aura or tonic-clonic seizures. The most common pathologic substrate associated with temporal lobe epilepsy is hippocampal sclerosis (mesial temporal sclerosis), which is characterized by selected focal neuronal loss and gliosis in the hippocampus, predominantly affecting CA1, CA3, and the dentate granule cell layer. Hippocampal sclerosis is the most commonly encountered histopathologic diagnosis at the time of epilepsy surgery in adults.

- **Patient Selection:** SRS is not for all MTLE. Indications include
  - Young Patients with High level of functioning // Socially adapted // Working
  - Concerned by the risks of MS & the stop of work // No atrophy // Dominant side
  - Few neuropsychological deficit before Surgery // WADA Failure
- **Target Location for Amygdalohippocampectomy:**
  - Anterior part of parahippocampal region; entorhinal area adjacent to the collateral sulcus, and the rhinal sulcus; the head of the hippocampus; the anterior part of the hippocampal body; and the amygdalofugal part of the amygdaloid complex (Fig 3).
- **Doses:** Marginal dose – 24gy. maximum dose allowed to nearby brainstem was 10 Gy and to optic nerves 8 Gy.
- **Efficacy:** Radiosurgery in properly selected patients provide favourable efficacy (nearly 65-70% Engel class I response) comparable to surgical series and superior neuropsychological outcomes (Verbal & spatial memory) and quality of life metrics compared to microsurgery. As Left temporal lobe resections can result in decrements in verbal memory, while spatial memory and learning may be affected by right-sided surgery.
- **Side-Effects:** Acute - Headache, nausea, vomiting. Long term – Radionecrosis, for higher doses
- **Response Timeline:**
  - Delayed onset of MRI changes and the excellent initial resolution is a good predictor of the seizure cessation.
  - Average latency before reducing or stopping seizures is at least 6-9 months.
  - Nearly all patients experience transient exacerbations in auras before seizures decrease or remit. The most dramatic drop in seizure rate occurs between 12 and 18 months, coinciding with the development and resolution of maximal changes on magnetic resonance images.
• Long term MR lesioning not mandatory for seizure cessation.

**B) Radiosurgery in Hypothalamic Hamartomas**

HH are developmental epileptogenic malformations that grow inside the hypothalamus (sessile or intrahypothalamic) or mostly within the third ventricle (pedunculated or parahypothalamic) & variably associated with central precocious puberty and gelastic (laughing or crying) seizures.\(^{3}\)

Classified as sessile or pedunculated lesions, depending on the width of their attachment to the tuber cinereum and the pattern of growth which can be, respectively, contained inside the hypothalamic parenchyma or mainly expanding toward the ventricular or interpeduncular space. Sessile hamartomas can be further divided into Type I (midline), II (lateral), III (intraventricular), and IV (giant). The size of Types I, II, and III lesions is ≤ 20 mm, whereas Type IV is > 20 mm. Associated seizures could be gelastic seizures, generalized tonic or tonic-clonic seizures, drop attacks, and partial seizures and appears to be crucially affected by the HH location and its relation to hypothalamic structures. Large lesions with pituitary stalk compression result in precocious puberty. Small unilateral intrahypothalamic lesions (Valdueza Types I and II) can be associated with severe seizures that lead to behavioral and cognitive deterioration. Severe, medically refractory seizures are common with HH that are broadly attached to the mamillary bodies, with thalamocortical spreading of the epileptic activity through the mammillothalamic tract. GABAergic inhibitory neurons exhibiting an intrinsic “pacemaker-like” behavior. The degree of seizure control is linked to the extent of the surgical intervention. Incomplete resection, disconnection, or ablation of the HH can be associated with incomplete seizure control, whereas freedom from seizures may be induced by a more aggressive approach. Surgical approaches include microsurgical resection, endoscopic resection or disconnection, radiofrequency lesioning, and interstitial brachytherapy.

Resective surgery is an excellent option for large pedunculated HH; the lesser the hypothalamic attachment, the lower is the chance to develop metabolic complication. Direct surgical approaches to these lesions pose significant risks due to neuro-metabolic injury. SRS is emerging modality which provides excellent seizure outcomes and no long lasting complications.

• **Target:** Increased T2 signal without contrast enhancement lesion (Fig 4).
• **Dose:** Marginal dose – 18gy/1 fr. or 30gy / 5fr.
• **Efficacy:** In most patients Engel Class I or II outcomes are seen after radiosurgery. Early treatment associated with favourable outcomes.
• **Side-effects:** Nil. No serious permanent complications, such as metabolic disorders, hemiparesis, cranial nerve deficits, or short-term memory deficits, have been reported after radiosurgery for HH

**Response Timeline:** Temporary worsening of seizures can be seen as early as 2 months correlating radiologically with pseudoprogression after the procedure, followed by progressive resolution; this outcome is associated with the delivery of high Doses (>16gy).

**C) RS for Epilepsy Associated with Cavernous Malformations**

Stereotactic radiosurgery (SRS) role is controversial due to following reasons

• Because of the absence of neuroimaging criteria to gauge their successful obliteration.

• Latency period for decreased risk of haemorrhage appears to occur at 2 years after SRS. Hence, difficult to discern whether this reflects true therapeutic benefit versus the natural history of decreased haemorrhage rates after initial “clustering” of haemorrhage events.

• Because arteriopathy is not an aetiology of CCM there is no explanation on biological basis.

• Increased incidence of radiation-induced complication by poor radiological localization and the dose planning software available initially.

• **Patient Selection:** Cavernoma presenting with seizures arising from eloquent cortex surrounding the lesion, correlated electro-clinically (Fig 5).

• **Dose:** Margin dose 14gy.

![Figure 4: Intrahypothalamic hamartoma CK Radiosurgery](image)
**Efficacy:** Engel class 1 response in 55%, Class-2 response in 25%. Mesiotemporal region CM: poor outcome while central and lateral temporal region CM have a excellent outcomes.

**D) RS Corpus Callosotomy for Refractory Bilateral Epilepsy**

- **Patient Selection:** remains a palliative procedure and does not achieve a cure.
- **Primary Procedure:** Patients with medically intractable epilepsy with multifocal origins of epileptic activity especially the atonic siezures, who are not candidates or willing for focal resection.
- **Adjuvant Procedure:** In patients with failed or insufficiently effective earlier treatment with – earlier partial / first stage callostomy, lesionectomy, Vagal nerve stimulation or DBS.
- **Target:** Anterior Callosotomy - genu, rostrum, and the anterior half of the body of the corpus callosum. on injury to surrounding structures (Fig 6).
- If the patient seldom achieves satisfactory improvement in the seizure outcome, and second or third stepwise callosotomy might be needed extending the lesioning posteriorly.
- **Dose:** 65gy at 50%
- **Efficacy:** RS CC is disconnection procedure, which prevents epileptic discharges from propagating between 2 cerebral hemispheres. Patients with normal MRI findings and lateralized electroencephalography showed the best seizure control compared with patients with abnormal MRI findings and nonlateralized electroencephalography. Reduces the frequency and severity of drop attacks (DAs), atomic seizures of several generalized epilepsies, including Lennox-Gastaut syndrome (LGS), generalized tonic-clonic seizures (GTCS), and tonic seizures. Similar to microsurgical callosotomy, Drop Attacks closely followed by GTCS respond best to radiosurgical callosotomy. Absence, myoclonic, and CPS practically remain unaffected by radiosurgical callosotomy.
- **Side-effects:** Symptomatic edema (25% cases) causing headache and nausea (without vomiting), and transient neurologic deficit.

**Conclusions**

In the presence of choices when none is the gold standard, Radiosurgery needs to prove a better risk/benefit profile than its competitors. The reasons for this limitation are multifactorial pathophysiology, prevailing pessimism, and a skeptical attitude toward functional radiosurgery, especially for ablative radiosurgery. Further evaluation in randomized controlled trials and prospective registries is needed to define a better level of evidence.

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