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Stereotactic Radiotherapy in the Management of Epilepsy

MS Mat Samuji* and Frederik Vernimmen

Department of Radiation Oncology, Cork University Hospital, Wilton, Cork, Ireland

Abstract

Although the main stay of epileptic therapy is pharmacological certain forms of epilepsy such as temporal lobe epilepsy and epilepsy associated with benign diseases of the brain can also be successfully managed surgically. A neurosurgical procedure has the advantage of an immediate therapeutic result. When surgery is not possible, therapeutic irradiation is an option, but there is always a latent time between the radiation and the improvement in the epilepsy. This radiation is under the form of photon radiation produced by Cobalt sources in a Gamma knife® or by Linear accelerators. Special beam collimation techniques produce a sharp beam allowing for a high dose to be delivered to the target without side effects on the normal surrounding brain. The desired therapeutic effect comes from the late radiation effects, and hence is not immediate. The absorption in tissue of photon radiation is such that there is always an exit dose, and this contributes to radiation side effects on normal tissue. Particle radiation beams such as a proton beam have a dose absorption advantage over photons because there is a lower entry dose and no exit dose. This has the potential to treat the brain with a lower risk of side effects, and a lower integral dose. Presently radiation dose selection is aimed at causing tissue destruction in the target volume. Dose schedules that do not cause tissue necrosis but have a neurophysiologic therapeutic effect are presently under investigation.

New irradiation technologies such as micro photon beams using synchrotron radiation and mini proton beams are been studied especially for their potential in epilepsy therapy. These technologies could greatly improve the therapeutic ratio as they cause no damage to brain tissue. If proven to have a therapeutic effect these new developments would expand the role of radiation in managing epilepsy.

Keywords: Epilepsy; Radiosurgery; Proton therapy; Micro radiation beam

Abbreviations: Micrometers: µm; Gray: Gy; Mega Volts: MV; Stereotactic radiosurgery: SRS; Hypo Fractionated Stereotactic Radiotherapy: HSRT; Hypothalamic hamartoma: HH; Arterio Venous Malformations: AVM; Temporal lobe epilepsy: TLE; Central Nervous System: CNS; Tumour control probability: TCP; Normal tissue complication probability: NTCP; Micro beams: MRT; Mini beam radiation therapies: MBRT; Magnetic Resonance Imaging: MRI

Introduction

By reviewing the literature the authors present the current options for radiotherapy of certain forms of epilepsy. In addition, new radiotherapeutic technological developments are discussed which could expand the role of radiotherapy in managing epilepsy. From a radiotherapy point of view and excluding malignancies two categories of epilepsy can be considered for treatment. One is epilepsy caused by the presence of a benign lesion of the brain such as an arteriovenous malformation, a cavernous haemangioma or a hamartoma of the hypothalamus. For this lesional epilepsy the main aim of radiation therapy is to treat the primary condition with the beneficial effects on epilepsy control being a secondarily objective.

Radiation is also used for non-lesional epilepsy, mainly temporal lobe epilepsy. Here the aim is to cause histopathological necrosis in a small volume of brain harbouring the epileptogenic center.

Irradiation is the deposition of energy (dose) in the target by various radiation modalities using a variety of irradiation techniques. This dose is expressed in units of Gy, and the beam energy used to deliver the dose is expressed as MV. It is the absorption of this energy by the cell structures that causes the individual cell damage resulting in therapeutic effect. Radiation total dose/fractionation schedules used vary. When the total dose is delivered in 1 single session (fraction), this is defined as stereotactic radiosurgery (SRS). Using a small number of fractions (3-7) is called hypofractionated radiotherapy which is commonly applied under stereotactic conditions and hence is called Hypo Fractionated Stereotactic Radiotherapy (HSRT).

The vast majority of treatments are with SRS. In terms of beam delivery a number of machines exist. With the Gamma Knife® multiple narrow static beams, each produced by an individual Cobalt source are directed to a fixed single spot or isocenter. This small area of convergence can be placed in multiple locations within the target volume by moving the patient's head around with small movements of the head fixation mechanism (Figure 1).

A proton beam is produced by a cyclotron or a synchrotron and has particular physical characteristics (the Bragg peak) which make it theoretically a better radiation modality in and around sensitive structures such as the brain as there is a lower entry dose proximal to the target with no dose distal to the target (Figure 2).

Treatment of Lesional Epilepsy

Hamartomas are benign overgrowths of normal appearing tissue comprised of glia, neurons, and fibre bundles. Hypothalamic located hamartomas are of particular interest in terms of the topic under discussion. They are rare lesions with a prevalence of 1-2 in 100,000 people [1]. Based on the anatomic relationship between the hamartoma and the hypothalamus, they can be divided into pedunculated and sessile subtypes. The pedunculated lesions do not arise within the hypothalamus but attach with a narrow base and project outside the

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***Corresponding author:** Mohd. Syafawi Mat Samuji, Department of Radiation Oncology, Cork University Hospital, Wilton, Cork, Ireland, Tel: 00-353-863522357, Fax: 00-353-21-4921346, E-mail: mohd.samuji@hse.ie

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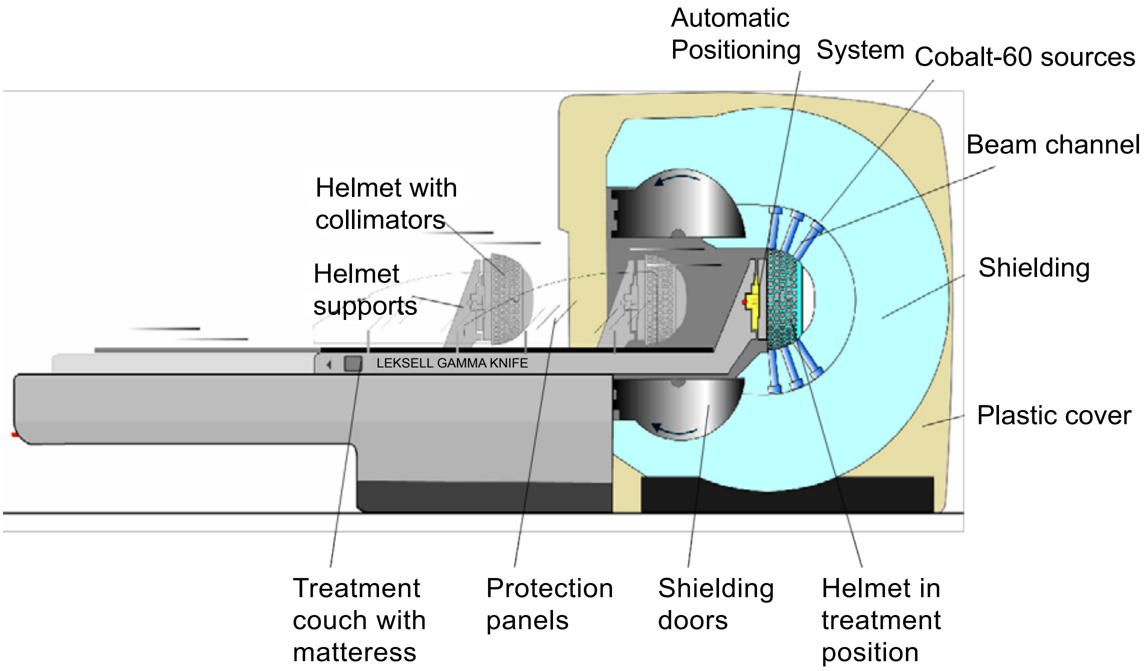

Figure 1: Schematic diagram of a Gamma Knife

Diagram shows the patient couch with head collimator helmet containing the beam collimation inserts for the 201 individual Cobalt sources (not all shown), all directed at a fixed point in space within the Gamma Knife.

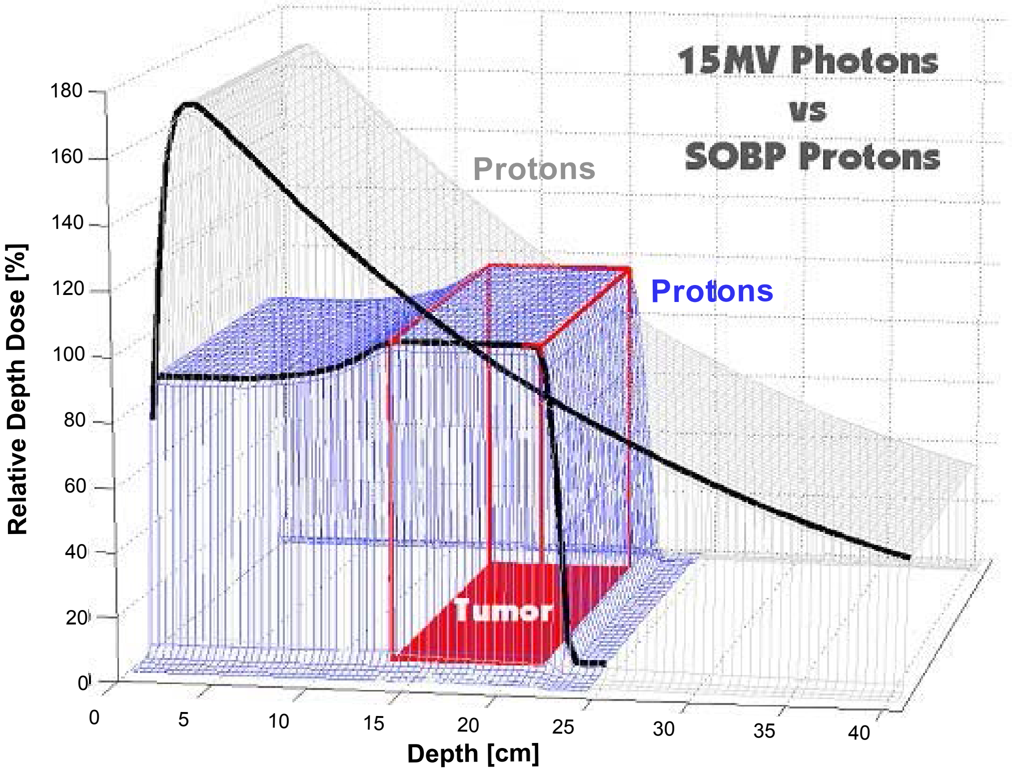

Figure 2: Proton beam dose absorption

Diagram shows the relative differences in dose absorption along the depth central axis of a proton beam compared to a photon beam. The lower entry dose and absence of exit dose are demonstrated.

ventricle. This location more likely present with precocious puberty. The sessile lesions lie within the hypothalamus itself and often cause seizures and variable degrees of mental retardation and aggressive behaviour, particularly if the seizures are not well controlled. Seizures consist of gelastic attacks, which can evolve into drop attacks, tonic, tonic–clonic, and secondarily generalized seizures [1].

Surgical resection of hypothalamic hamartomas has been reported to improve control of gelastic seizure activity, but is associated with complications, such as motor, visual, and hypothalamic deficits [2-5]. Surgical techniques such as transcallosal, a pterional approach, and endoscopic resection results in 15 % to 54 % freedom of seizures varying on the technique [6].

Radiosurgery by nature of its non invasiveness has an advantage over open surgery. However, although most patients experience a reduction of seizure frequency, seizure freedom is found in around 30 % of cases [7, 8]. No studies randomized by treatment method exist. Mathieu [9] undertook a prospective observational study of the outcomes of 9 patients who underwent radiosurgery for HH. Epilepsy began in infancy in all cases and was refractory to standard antiepileptic drugs. The patients received an average of 2 antiepileptic drugs before undergoing radiosurgery. Post SRS seizure status was assessed every 3 months and reported using the Engel Classification. Quality of life evaluation was performed annually using a standardized questionnaire, and neuropsychological evaluation was performed after 2 years. Using the Régis Classification, 6 patients had smaller hamartomas (Grade I-III) and underwent treatment of the entire lesion, using a margin dose of 14-20 Gy. Treatment volume ranged from 0.3 to 1.0 ml. Three patients had larger lesions (Grade IV-VI) for which a radiosurgical disconnection was attempted, targeting the area of attachment to the hypothalamus. For those patients, the margin dose was 15 or 16 Gy, with treatment volume ranging from 0.8 to 1.8 ml. Disconnection led to no improvement in epilepsy (Engel Class IV). Four patients in whom the entire lesion was treated are now seizure free (Engel Class I), with another having only rare seizures (Engel Class II). Quality of life and verbal memory were improved in those patients with more than 3 years of follow-up. No adverse event occurred after radiosurgery. Abla [10] followed 10 patients for a mean follow-up of 43 months (range 18-81 months). The mean SRS dose directed to the 50% isodose line was 18 Gy (range 16-20 Gy). Of the 10 patients, 6 are seizure free (2 after they underwent additional surgery), 1 has a 50%-90% reduction in seizure frequency, 2 have a 50% reduction in seizure frequency, and 1 has observed no change in seizure frequency. Overall quality of life, based on data obtained from follow-up telephone conversations and/or surveys, improved in 9 patients and this was due to improvements in seizure control. Short-term memory loss was noted in 3 patients, and 5 patients experienced behavioural symptoms. Incidences of radiation morbidity were all temporary and included poikilothermia (1 patient), increased depression (1 patient), weight gain/increased appetite (2 patients), and anxiety (1 patient) after SRS.

Cerebral AVM's occurs universally in 1.1 per 100000 people. They are the cause of serious neurological morbidity or even death when they bleed [11]. Apart from a haemorrhage the second most common presentation is with seizures, which occur in 20% - 31% of cases [11-13]. Seizures can be either focal or generalized. The present treatment options for AVM's are surgery, embolization and radiation either on their own or in combination. Advances in neuroimaging and in microsurgical techniques permits surgery with complete resection for many AVMs with a low morbidity rate, and this is the preferred treatment when possible. However some AVMs cannot be resected because of location in or close to critical brain structures or because of contraindications for anaesthesia [14]. SRS is appropriate for patients harbouring small AVMs, especially when located in eloquent areas. Lesions most effectively treated have volumes < 10 cm^3 or a maximum diameter of < 3 cm [11]. The primary aim of SRS is to achieve complete obliteration which relies on the late radiation effects on the AVM tissues. The radiation dose selection is determined by parameters know to achieve obliteration, and falls within the 18-25 Gy range. Long term outcomes for linac radiosurgery have recently reported. Obliteration rates increased with longer follow up and at 3, 5, 10 and 15 years were 46.9 %, 61.3%, 74.2% and 90.3% respectively [15]. The post procedural actuarial symptomatic radiation injury rates, after a single radiation surgery session, at 5, 10, and 15 years were 12.3%, 16.8%, and 19.1%, respectively [15]. Improvement or cure from the epilepsy is a desirable additional therapeutic effect. The results in terms of Engel class I outcomes depend on a number of factors such as anatomical location, size, and age of patient but is in the order of 53% -66% [16,17]. However the median time to seizure free status is in the order of 20 months, again reflecting the late radiation effects on tissue [16]. For those patients who over time achieve complete obliteration seizure control can be as high as 85% [18]. Yang et al. [19] studied 161 patients treated with SRS with a mean follow up of 89.8 months. Of those patients with a history of seizures prior to SRS, 76.7 % became seizure free (Engel scoring). For those patients that achieved complete AVM obliteration this increased to 96.7%.

Immediate post radiosurgery effects are rare as the brain is a late responding type of tissue. Symptomatic image changes are found in 10% of patients. These changes are mainly white matter signal changes on T2 MRI imaging. These resolve in about half of the patients over time. Permanent changes as a result of radiation necrosis occur in 2 % of patients [11]. The dose-volume parameters are the most important factors in developing delayed reactions with patients receiving < 20 Gy fairing better then patients receiving more than 20 Gy [14].

Cavernous haemangiomas, also called cavernomas have a 4% risk of a first seizure within 5 years after discovery. Contrary to AVM's this risk is not affected by a haemorrhage. Features associated with the occurrence of epilepsy are lesion multiplicity and cortical location [20]. Because SRS rarely produces radiological obliteration, and because the only way to verify therapeutic effect is by long term clinical follow up its use remains somewhat controversial. Radiosurgery is advocated in unresectable patients who have repeatedly symptomatic bleeds in order to reduce the future bleeding risk. Liscak [21] using a median dose of 16 Gy reported a reduction in the bleeding risk from 2% before SRS to 0.5% after a 2 year latent interval. Epilepsy when present improved in 45% of cases. Leveque et al. [22] reported 53% of patients to be seizure free after a mean marginal dose of 19.17 Gy. Twenty % of patients had a significant decrease in the number of seizures, with the remaining 26% showing little or no improvement. Both microsurgery and radiosurgery are reported to be equally good in terms of epileptic control [23], but microsurgery is the preferred treatment as there is no latent time and is a better option to deal with the bleeding risk. [24-26]. The risk of temporary and permanent morbidity caused by radiosurgery was 14.6 and 0.9%, respectively [21].

Treatment of Non-Lesional Epilepsy

TLE is the most common of the localization-related epilepsies. Most cases of TLE can be further localized to the mesial temporal lobe (hippocampus, amygdala, and parahippocampal gyrus). Ictal onset in mesial temporal lobe structures can produce a seizure aura, such as an olfactory hallucination, an epigastric sensation, or psychic symptoms.

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Progression of the seizure is often associated with loss of awareness and motor automatisms. Mesiotemporal sclerosis is the most frequent underlying cause of mesial TLE (81%) [27]. CNS infection, head trauma, and perinatal injury are other causes [28,29].

Surgery is commonly performed in drug resistant TLE epilepsy and is an effective treatment modality [30].

Radiosurgery has been explored as an alternative to open surgery. Regis, et al were the first to use the Leksell Gamma Knife on a small number of patients and showed amelioration of seizures with minimal morbidity and mortality [31,32]. Their approach resulted in 6 of the 7 patients being seizure-free (Engel class I) at a mean follow-up of 34 months (22–61 months). The only noted side-effects were transient headaches and a homonymous superior quadrantanopia in a single patient. The radiation target was the parahippocampal gyrus, head and anterior body of the hippocampus, and amygdala, comprising a volume of 6.5 cm^3, and treated with 25 Gy. Subsequently a variety of single-center case reports and case series followed [33-37].

Two prospective multicenter trials followed. The European trial demonstrated a 2-year post SRS seizure remission rate of 62% [38]. The U.S. trial [39] randomized 30 patients to a high (24 Gy, n = 13) or low dose (20 Gy, n =17) delivered to the target as specified by European trial with the added constraint that the target volumes were restricted to 5.5–7.0 cm^3. Ten patients in each group were seizure free at 36 months resulting in a remission rate of 77% and 59% respectively.

Side effects of SRS to the temporal lobe can be divided into acute and delayed. The acute side effects include headache, nausea, depression and visual field deficits. Incidence of new onset headaches varies from 14% to 70%, and visual field deficits occurred in 43% to 50% of patients [38,39]. Memory impairment can occur after radiosurgery and an incidence of 12% has been reported [39]. Serious delayed complications include radiation necrosis [40,41], second malignancy [42], cyst formation and cognitive impairment [43].

New Developments

Technological

The therapeutic beneficial end result of radiation is a balance between TCP versus NTCP. This ratio can be improved by a “sharpening of the beam”. One way to achieve this is by the use of micro beams and mini beam radiation therapies with beam widths ranging from 25 to 100 µm (MRT) or 500 to 700 µm (MBRT) [44]. In comparison the diameter of human hair varies from 17 to 180 µm .These beam dimensions are a fraction of the size of beams used in routine SRS practice (smallest= 4mmØ). Such very small beams can be produced by synchrotron radiation. Synchrotron radiation is a product of accelerating particles (protons & electrons) to a very high energy and bending their trajectory in a magnetic field as is happening in a synchrotron, hence its name. Synchrotron radiation is of an intensity in the order of a billion times greater than conventional x-rays, has extremely small beam dimensions in the order of a few microns, has very low divergence, and is tunable to a desired energy [45-47]. The same approach of using very small beams has been investigated with proton beams for the specific purpose of treating benign brain conditions such as epilepsy [44].

These tiny individual beams transverse the brain tissue without causing damage but a therapeutic radiation effect can be achieved by focussing a number of different individual beams on a specific target. This combined with the improvements in neuro MRI imaging whereby tracts can be visualized offers the potential to very selectively interrupt signal pathways, or to target an epileptogenic centre.

Radiobiological

Although radiosurgery has been shown to reduce seizures in various forms of medically intractable epilepsies, the mechanism by which this abatement occurs is unclear, although several possible mechanisms have been proposed.

Destruction of the epileptic focus and its pathway of spread by necrotizing radiosurgical doses or, alternatively, suppression of the epileptic activity by a neuromodulatory effect at non-necrotizing doses have been postulated as the basis of the anti-epileptic effect [48,49].

Most of the radiation treatments for epilepsy have been with SRS due to technical factors mainly related to patient’s head immobilization and targeting systems. It is not clear if a single radiation dose is necessarily the best way from a radiobiological point of view to achieve the therapeutic goal. Traditionally in order to achieve the desired therapeutic effect the radiosurgery doses have been “destructive”, in the sense that a small volume of brain tissue is completely destroyed with all the classical histopathological features of brain radio necrosis Radiation necrosis is caused by vascular endothelial cell damage, resulting in fibrinoid necrosis of small arterial vessels. Occlusion of these vessels results in focal coagulative necrosis and demyelination of the overlying brain parenchyma [50,51]. There is growing interest in the concept that the same therapeutic effect might also be achieved by lower doses of radiation. Such doses would not induce necrosis but have a rather neuromodulatory effect resulting in the same therapeutic result but at a lower risk of side effects. As glial cells are more radiosensitive than neurons, Barcia-Salorio proposed low-dose radiosurgery may reduce glial scar formation, allowing increased dendritic sprouting, improved cortical reorganization, and, consequently, fewer seizures [52]. Monnier and Krupp reported that low-dose radiation (10 Gy) diminished cortical activity [53].

Studies are underway to investigate these threshold doses to achieve such neuromodulation [54,55] .Nothing is known about the value of fractionation for control of the non lesional epilepsy. For radiosurgery of lesional epilepsy hypofractionation has been used to improve the therapeutic ratio [56,57]. With the development of non-rigid, fast and accurate robotic patient immobilization systems hypofractionation is becoming more and more feasible.

The Future

Lesional epilepsy

In this category of patients the radiation dose/volume parameters and irradiation techniques will remain being determined by the therapeutic aims for the primary disease. However independently of this the potential exists to treat the associated epilepsy by the use of micro beam technology to disrupt tracts along which the epileptic wave propagates. The therapeutic results for the epilepsy would be immediate, whilst awaiting the latent therapeutic effects on the lesion itself.

Non-lesional epilepsy

The presently available radiation techniques allow for the accurate dose delivery to a small but still macroscopic volume of brain tissue in the order of a couple of cm^3. Radiation dose selection constitutes very likely “overkill”. The first step in improving the therapeutic ratio is the use of lower radiation doses to similar volumes using present irradiation techniques in order to avoid tissue destruction but still obtain the desired therapeutic effect. Once it is established that lower doses are equally effective, the use of proton beams in their present form for radiosurgical use [58] would further enhance the therapeutic ratio based on their lower integral dose and lower risk of radiation side-effects.

Synchrotron micro beams, already available, are presently researched for their potential in epileptic therapy based on their ability to do damage to microscopic volumes without brain tissue side effects providing an even better therapeutic ratio. This damage could be either directed at the epileptogenic center, tracts propagating the epileptic wave, or both. Proton mini beams have the theoretical potential to improve the results even more as they are sharper than synchrotron micro beams.

Conclusion

Stereotactic radiotherapy has presently a limited role in the management of epilepsy. Based on new technologies of delivering radiation combined with a better understanding of the radiobiology, this role could be expanded. Further research is required to establish the role of radiotherapy in the overall armentarium of epilepsy therapy.

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