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Radiosurgery for epilepsy: clinical experience and potential antiepileptic mechanisms

Mark Quigg, MD, MS, FANA¹, John Rolston, MD, PhD², and Nicholas M. Barbaro, MD^{2,3}

¹Dept Neurology, University of Virginia, Charlottesville, VA, USA

²Dept Neurological Surgery, University of California at San Francisco, San Francisco, CA, USA

³Dept Neurology, University of California at San Francisco, San Francisco, CA, USA

Summary

Stereotactic radiosurgery, well established in the noninvasive treatment of focal lesions that are otherwise difficult to access through open surgery, is an emerging technology in the treatment of focal epileptic lesions. Recent studies suggest that seizures from hypothalamic hamartomas and mesial temporal lobe epilepsy remit at clinically significant rates with radiosurgery, but large variations among different studies have raised questions about appropriate treatment protocols and mechanisms. Proposed anticonvulsant mechanisms include neuromodulatory effects or ischemic necrosis of epileptic tissue. An ongoing trial that directly compares efficacy, morbidities, and cost of radiosurgery versus open surgery for mesial temporal lobe epilepsy is underway.

Keywords

radiosurgery; mesial temporal lobe epilepsy; epilepsy surgery; Gamma Knife; partial seizure

Introduction

The devices available for stereotactic radiosurgery (RS) share the common feature of focusing ionizing radiation to small targets deep within brain tissue, sparing damage to surrounding tissue. This ability has been used to treat difficult-to-access lesions such as deep tumors and arteriovenous malformations. In fact, the efficacy of RS in treating epilepsy associated with these lesions was the main factor leading to its use in recent trials of mesial temporal lobe epilepsy (MTLE). That RS is an outpatient procedure that does not require general anesthesia or postoperative intensive care is additionally attractive.

We review the devices of RS, discuss briefly the antiepileptic effects in treatment of epileptogenic mass lesions, and update its status in treatment of MTLE. Because the results in MTLE vary considerably, we also discuss available animal model and clinical data to investigate anticonvulsant mechanisms of the radiosurgical lesion.

Corresponding Author: Mark Quigg, MD, MSc, FANA, Box 800394, HSC, Department of Neurology, University of Virginia, Charlottesville, VA 22908, Ph: 434.924.5312, Fx: 434.982.1762, quigg@virginia.edu.

Disclosures

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

RS Devices

Several sources of focal ionizing radiation are in clinical use.

Proton beam accelerator

A proton beam accelerator strips protons of their electrons and aims them at a target. An advantage of the proton beam accelerator is that protons, having mass, scatter less when entering tissue. Furthermore, the most intense radiation concentrates at the end of the proton's trajectory, a phenomenon known as the Bragg peak (Haffty and Wilson 2009). Despite these advantages, the limited availability of proton beam accelerators, their high costs (Mehta 1995), and relative difficulties in constructing complexly shaped targets limit widespread use.

Photon/linear accelerators

The other carriers of ionizing radiation, photons, are easier to generate. The tradeoff is that photons, being massless, tend to scatter more readily than protons and are therefore more complicated to aim (Haffty & Wilson 2009, Khan 2010, Mehta 1995). Rather than the aiming of a single proton beam, photons are best aimed by concentrating multiple weak sources to a single intense focus point. The Novalis Tx (Varian Medical Systems, Palo Alto, CA) and CyberKnife (Accuray, Inc.; Sunnyvale, California, USA) are linear accelerators that are steered about to direct many single beams at a common aiming point. The Gamma Knife (GK) (Elekta AB; Stockholm, Sweden) consists of ~200 separate radioactive cobalt-60 sources housed inside a hemispheric chamber and focused to a single target. The target, in turn, is determined and maintained with the patient installed into a stereotactic frame. Except where noted, the studies cited below used GK radiosurgery.

RS of lesional epilepsies

The anticonvulsant effects of RS were first observed in treatment of CNS tumors and vascular lesions (Gerszten, et al. 1996, Heikkinen, et al. 1989, Kurita, et al. 1998, Schauble, et al. 2004, Schrottner, et al. 1998, Steiner, et al. 1992). In these cases, however, successful treatment of seizures is difficult to distinguish from successful treatment of the underlying lesions. Seizure remission rates in RS of arteriovenous malformation range from 55–80%. Although the usefulness of RS in treatment of cavernous malformation is controversial (mainly from high rates of hemorrhage in some series (Steiner, et al. 2010)), RS causes remission of seizures in 25–64% of patients with cavernous malformation (Kim, et al. 2011, Régis, et al. 2000b).

RS has been used to treat epileptogenic hypothalamic hamartomas (HH) given difficulties with access in open surgery. However, while most patients experience a reduction in seizure frequency, seizure freedom is found in only ~30% of cases when pooled across multiple studies (Frazier, et al. 2009, Régis, et al. 2000a). Although no studies exist for HH surgery that are randomized by treatment method, retrospective case series suggest that other surgical methods besides RS may have better outcomes in terms of seizure remission. For example, transcallosal resection has a seizure remission rate of 54% (Ng, et al. 2006). Transventricular endoscopic resection also has similar rates of success (Ng and Rekate 2007, Shim, et al. 2008). These invasive techniques, however, may not be able to be used depending on the characteristics and location of the HH.

Use in MTLE

Seizure Remission

The first use of focal radiation to treat “lesionless” epilepsy in a systematic fashion was reported by Talairach (Talairach, et al. 1974) who treated 44 patients between 1959–1973 with the use of implanted yttrium⁹⁰. Although ~5 year outcomes of 75% seizure remission were reported, early attempts with other forms of RS were not encouraging (Barcia, et al. 1994, Linquist, et al. 1991).

Régis et al. resurrected the GK technique for treatment of MTLE in 1995 (Régis, et al. 1995), and then conducted a subsequent trial of 7 MTLE patients (Régis, et al. 1999). In this series, a target comprising the parahippocampal gyrus, head and anterior body of the hippocampus, and amygdala, comprising a ~6.5ml 50% isodose volume, was treated with 25 Gy.

A variety of single-center case reports and case series followed (Cmelak, et al. 2001, Hoggard, et al. 2008, Kawai, et al. 2001, Prayson and Yoder 2007, Srikijvilaikul, et al. 2004). With one exception (Hoggard, et al. 2008), these series used doses smaller than 25Gy, and rates of seizure remission were low or nil.

Two larger, prospective, multicenter trials followed, one European (Régis, et al. 2004) and one US (Barbaro, et al. 2009). The European trial demonstrated a 2 year postoperative seizure remission rate of 62% with the use of a treatment protocol identical to the group’s earlier studies. Barbaro et al. in the US Multicenter Pilot Study randomized 30 patients to a high (24 Gy, n = 13) or low dose (20 Gy, n = 17) delivered to the target as specified by Régis et al (Régis, et al. 2004) with the added specification that 50% isodose volumes were restricted to 5.5–7.0 ml attained with 2–6 isodoses. Ten patients in each group were seizure free at 36 months of follow-up, resulting in a remission rate of 77% in the high dose and 59% in the low dose group.

Vojtěch et al. released a retrospective analysis of 14 patients with markedly different results (Vojtěch, et al. 2009). Initial doses were identical to that reported by Régis, and in fact, 6 of the patients overlap with the European multicenter trial (Régis, et al. 2004). Doses decreased with accumulated experience; of the 14 patients in the report, the last 6 were treated with 18 Gy because of clinically significant “prominent radiosurgical responses” associated with 25 Gy. None of the 14 patients were seizure free after 39 months.

Finally, seizure remission rates were reported for a 15 patients with follow-up durations >5 years (Bartolomei, et al. 2008). Nine of 15 (60%) remained seizure free.

Secondary outcomes

Neurocognitive and psychological outcomes have been measured at different points of the post-surgical follow-up period. McDonald et al evaluated three patients treated on the language dominant side during the period of development of the radiosurgical lesion and found a significant impairment in at least one measure of verbal memory with sparing of IQ, visual memory, and language (McDonald, et al. 2004). Measurements of cognitive function at 12 postoperatively (again corresponding to the period of maximum radiosurgical edema (Chang, et al. 2010)) found that verbal memory have no consistent impairments, but that tests of cognitive processing speed demonstrate trends of worsening in a dose-dependent fashion (Quigg, et al. 2011); impairment, however, is not reliably proportional to the volume of edema (Chang, et al. 2010).

At 24 months postoperatively (when edema resolves in most patients, leaving atrophic residual tissue (Chang, et al. 2010)), Régis et al. in the European multicenter trial noted no significant cognitive deficits (Régis, et al. 2004). In fact, 20% experienced some degree of cognitive improvement, and only one patient a decline to a degree under that considered significant for that trial. Similar findings were seen in the US Multicenter Pilot Study (Barbaro, et al. 2009, Quigg, et al. 2011), Impairment occurred in one measure of verbal memory (Wechsler Memory Scale or the California Verbal Learning Test) in 25% of patients treated on the language-dominant side when testing was measured in terms of relative change indices (significant score changes beyond that expected from test-retest variability). Conversely, 16% of language dominant RS patients experienced improvements in the same measures. These proportions compare favorably against findings after open anterior temporal lobectomy (Stroup, et al. 2003). Comparison of mean scores obtained from patients at 24 months after RS, using the tests of verbal memory above, as well as the Boston Naming Test, Trail Making Test, and Beck Depression Inventory, revealed no overall neuropsychological changes in the patients between their preoperative baseline and post-treatment states. Importantly, quality of life scores were significantly improved in those patients attaining seizure freedom. The long-term follow-up study reported by Bartolomei et al (Bartolomei, et al. 2008) shows that neuropsychological results are stable (although the exact timing of testing in relationship to follow-up course was not reported).

Safety and development of the RS lesion

Since RS is a surgical technique, some side effects of RS are similar to those of standard surgery. For example, typical “temporal lobe” homonymous visual field defects as seen after anterior temporal lobectomy (Engel, et al. 1993) occur in 43% (Régis, et al. 2004) – 50% of patients (Barbaro, et al. 2009). Although verbal memory impairments are seen after dominant hemisphere surgery either by RS or open surgery, the focused nature of RS targeting induces a “superselective” lesion, analogous to the putative advantages of selective amygdalohippocampectomy over anterior temporal lobectomy (Clusmann, et al. 2002, Helmstaedter, et al. 2003, Jones-Gotman, et al. 1997, Wyler, et al. 1995). Formal comparison is pending a randomized study (see below).

Some side effects, especially during development of the radiosurgical lesion, are unique to RS. The time course of the RS lesion and associated symptoms has been well documented (Régis, et al. 2004). Most studies find a dramatic increase in the number of auras, starting ~6–8 months and peaking between 9–12 months after RS. In studies with higher doses and greater proportions of seizure remission (Régis, et al. 2004), the number of complex partial seizures simultaneously drops with the increase in auras; often, subjects have no complex partial seizures from the time they notice the increase in auras. Barbaro et al (Barbaro, et al. 2009) documented a dose-dependent pattern of earlier onset of remission of complex partial seizures and reduced aura production with higher doses. Vojtěch et al (Vojtěch, et al. 2009) described an exacerbation of both auras and complex partial seizures, with complex partial seizures during peak event expression predominating in high dose protocols and auras in low dose protocols.

New-onset headaches (occurring in 14% (Régis, et al. 2004) to 70% of patients (Barbaro, et al. 2009)) do not have predictable timing and can precede or follow changes in aura and seizure frequencies or MRI. In contrast, the time course of MRI changes is predictable (with the limitation that no study thus far has systematically obtained MRI from all patients at fixed intervals shorter than one year postoperatively; interim neuroimaging is obtained to evaluate patient complaints). The most striking effects are the development of a dose-dependent T2 hyperintensity, contrast enhancement, and vasogenic edema with mass effect beginning 9 months postoperatively and peaking at 12 months. These changes correspond to declines in complex partial seizures and to transient increases in the number of auras

(Chang, et al. 2010). At 24 months, the mass effects resolve to mild atrophy of the mesial temporal lobe.

Serious adverse events have also been reported with the use of RS for MTLE (Barbaro, et al. 2009, Prayson & Yoder 2007, Srikijvilaikul, et al. 2004). One death reported by Prayson et al occurred two weeks post-radiation, due to “persistent seizure complications.” Because radiographic changes occur on the order of months, rather than days, it is unlikely that RS contributed to this patient’s outcome. An autopsy showing mesial temporal sclerosis, but no radiation-induced pathology, supports this interpretation (Prayson & Yoder 2007). Additional mortality was reported by Srikijvilaikul et al., who described one death at 1 month and another at 1 year following RS (Srikijvilaikul, et al. 2004). Both were attributed to complications of seizures, consistent with sudden unexplained death in epilepsy (SUDEP). A protocol-defined severe event was reported by Barbaro et al (Barbaro, et al. 2009). Between 12–15 months after RS at 24Gy, one patient exhibited signs of increasing intracranial pressure (headaches, visual changes, and papilledema). Anterior temporal lobectomy was performed at 15 months leading to seizure freedom and resolution of symptoms.

While side effects and adverse events of RS are clearly important, they should be viewed in the light of the complications occurring with open surgery. For example, mortality and visual field changes have been reported in open surgery (Engel, et al. 1993). Complications of open surgery include permanent hemiparesis (2%), bleeding requiring transfusion (2.3%), and infection (0.8%) (Engel 1993; McClelland 2011). These side effects have, as of yet, not been observed in RS.

Controversies in radiosurgical treatment protocols and mechanisms

Trials of RS for MTLE show a wide variation of clinical efficacies; therefore, differences in protocols and potential mechanisms require examination.

Target

All studies of MTLE cited above, despite minor variations in description, target essentially the same anatomy: the amygdala, anterior hippocampus, and the parahippocampal gyrus, regions corresponding to anatomical structures found most important in seizure remission following standard surgery (Seigel, et al. 1990). However, those patients with “epileptogenic zones” that extend beyond those traditionally attributed to MTLE may not be good RS candidates; long term seizure remission is less likely in these cases because of the highly restricted field of RS (Rheims, et al. 2008).

Isodose centers

No data is available in determining the number of isodose centers (“shots”) that are optimal to distribute and shape the radiation dose within a particular isodose volume for MTLE. Based on Régis’ preliminary studies (Régis, et al. 1995) (all of which were limited to 2 shots), Barbaro et al specified a range of 2–6 shots in the US Multicenter Pilot Study. In general, neurosurgeons recommend “conformal” RS with multiple isodose centers to tailor dose to anatomy and to protect bystander tissue (such as the brainstem and optic nerve in the case of RS of MTLE).

Volume

When reported, the 50% isodose volumes (the volume into which 50% of the total radiation dose is delivered) typically range in the 6.0–8.5ml range. Régis et al in preliminary studies (Figure 1) determined that there was a narrow window of ineffective anticonvulsant effect

versus excessive toxicity in terms of volume of maximum radiation edema at 12 months postoperatively. On this basis, Barbaro et al specified treatment volumes limited to 5.5–7.5ml in their studies (Barbaro, et al. 2009).

Dose

Of the various parameters, dose appears to be best correlated to outcome (Figure 2), and is the only variable rigorously studied; in the US Multicenter Pilot Study, the group randomized to 24Gy had a higher proportion seizure remission than those to 20Gy (a finding tempered by lack of statistical power) (Barbaro, et al. 2009). As Figure 2 suggests, 20Gy appears to serve as a threshold at or over which seizure remission occurs.

Mechanisms

Radiation dose stands at the center of the controversy of mechanisms of the anticonvulsant effects of RS. Fundamental to RS is ionization - the stripping of electrons resulting in the alteration of chemical bonds or the production of free radicals (Haffty and Wilson 2009, Khan 2010). Susceptibility to ionizing radiation is proportional to DNA synthesis. Differentiated neurons are relatively radio-resistant; actively proliferating tissue, like vasculature, is radiosensitive. Furthermore, although animal models of epilepsy – usually rats - are helpful in evaluating mechanisms of anticonvulsant effects of radiation, rat brains are remarkably radio-resistant and “scaling up” directly to humans to predict anticonvulsant dosing is not applicable.

Studies with rat models of limbic epilepsy that followed the first reports of RS for MTLE emphasize that destruction of the epileptic focus is not necessary for an anticonvulsant effect. For example, a dose-dependent reduction in spontaneous seizures was shown in kainic-acid treated epileptic rats (Maesawa, et al. 1999, Maesawa, et al. 2000) and in electrical-stimulation epileptic rats (Chen, et al. 2001) despite the lack of evidence of gross neuronal injury. Cognitive functions were spared; for example, water maze performance was unimpaired after treatment (Maesawa, et al. 1999, Maesawa, et al. 2000).

These nondestructive “neuromodulatory effects” (Régis, et al. 2002, Régis, et al.) were further evaluated with RS of normal rats. A 50 Gy isodose induced different amplitudes and timing of changes in neuronal enzymes, raising the possibility that different neuronal systems vary in susceptibility to radiation (Régis, et al. 1996). Tsuchitani et al (Tsuchitani, et al. 2003) report in an abstract that hippocampi of normal rats were treated with 40 Gy. Whereas the numbers of nonspecific neurons of the hippocampus remained unchanged, both calbindin-staining interneurons (excitatory) and GAD-staining interneurons (inhibitory) were substantially decreased. Physiologic changes resulting from these selective interneuronal losses were not measured.

Kindling experiments demonstrate that RS may have different effects depending on whether normal or kindled circuitry is involved (Jenrow, et al. 2006). Three groups of rats were treated with hippocampal RS at different time points of an electrical stimulation kindling protocol to observe which experienced the most severe seizures. Relative to controls, the occurrence of stage 6 seizures is significantly increased by irradiation before kindling, but is unaffected by irradiation at kindling stage 3, and significantly is reduced by irradiation at kindling stage 5. Thus, epileptic tissue exposed to radiation may undergo different changes than normal tissue, or, perhaps more likely, lack processes of plasticity and repair enjoyed by normal tissue. Other experiments with the use of more widespread radiation doses (analogous to traditional fractionated radiotherapy) support the hypothesis of alterations in neurogenesis and plasticity in irradiated tissue. For example, Tan et al demonstrated that low doses of brain irradiation (0.5–6Gy) in normal rats induce an 80% decrement in neuronal

precursor cells in the dentate gyrus. Whereas lower doses allow a compensatory proliferation of neuronal precursors during recovery, higher doses completely block compensatory proliferation (Tan, et al. 2011).

Neuromodulatory effects, however, may not be entirely beneficial, as demonstrated by proconvulsant effects outlined in above animal experiments (Jenrow, et al. 2006). This point is emphasized by results of low-dose human protocols - perhaps designed to emulate nondestructive doses in animal models - in which paradoxical exacerbation in auras or sometimes complex partial seizures are seen in parallel with development of the RS lesion (Chang, et al. 2010, Vojtěch, et al. 2009). In contrast, neuromodulatory effects may account for findings of a case series of treatment of temporal lobe epilepsy (hippocampal sclerosis not specified) with fractionated stereotactic RS (Grabenbauer, et al. 2002) (as opposed to single-dose schemes discussed so far). In this protocol, doses of 21 Gy (7×3 Gy, 6 patients) or 30 Gy (15×2 Gy, 6 patients) were administered and follow-up performed for 24 months. Although no patients achieved seizure remission, seizure reduction occurred at mean 46% with no patients experiencing seizure exacerbation. A limitation is that postoperative imaging was not reported.

In contrast to neuromodulatory mechanisms, other findings in both animal models and human epilepsy suggest that gross structural changes in the target zone, more akin to the use of RS as a destructive surgical tool, better account for the anticonvulsant effects seen in more successful protocols. MRI and mass spectroscopy (Chang, et al. 2010) data from the US Multicenter Pilot Study (Barbaro, et al. 2009) show that the volume of contrast enhancement and T2 hyperintensity seen on MRIs obtained 12 months after RS correlate strongly with outcome (Figure 3). No patients with T2-weighted volumes of edema < 200 ml at 12 months went on to experience seizure remission between 24–36 months (Chang, et al. 2010). Furthermore, magnetic resonance spectroscopy (MRS) within RS target zone show evidence of frank ischemia; one year after RS, lactate (evidence of anaerobic metabolism) appears, and choline, creatine, and NAA levels (evidence of normal neuronal activity) are largely absent (Chang, et al. 2010). Similar findings of decreased markers of neuronal activity were observed with MRS > 1 year after RS in a trial of 6 patients (without seizure responses results reported) (Hajek, et al. 2003).

Although animal models of epilepsy cited above do not demonstrate necrosis of tissue, one possible confounder may be an insufficient duration of observation following irradiation. Hippocampi irradiated > 50 Gy in normal rats and followed for > 6 m (longer than durations of Maesawa (Maesawa, et al. 1999, Maesawa, et al. 2000) or Chen (Chen, et al. 2001)) show evidence of neuronal destruction (Liscak, et al. 2002).

Analogous to findings of ischemia via MRS in humans, irradiation can cause ischemic changes by affecting vasculature as seen in animal models. Kamiryo et al (Kamiryo, et al. 2001) showed that rat brains treated with RS at 75 Gy and examined 3 months later have, through the method of vascular casting, a markedly decreased vascular density. Electron microscopy demonstrates thickening of the vascular basement membrane. These vascular changes precede development of necrosis within the radiosurgical target.

Supporting data from treated human tissue (as opposed to MRS data) is difficult to interpret because tissue may be obtained from failed rather than successful RS. For example, patients who underwent open surgery after failed RS demonstrated hippocampal sclerosis and “radiational changes” in operative samples (Srikijvilaikul, et al. 2004). In the US Multicenter Pilot Study, the patient who underwent anterior temporal lobectomy for steroid-dependent symptoms (and who was seizure-free for ~ 3 months before open surgery) was found to have hippocampal sclerosis as well as evidence of chronic infarcts with prominent

hyalinization, thickening, and closure of small vessels (Figure 4). Therefore, limited data from human histopathology show, in the RS target in a patient with decreased seizure frequency, ischemic changes arising from radiation-induced damage to vasculature.

Clinical data suggests that the two mechanisms discussed above – neuromodulation and neuronal destruction – may not mutually exclusive. For example, patients in the US Multicenter Pilot Study were asked to describe the symptoms of their typical auras, which in turn were classified as originating from “mesial” or “nonmesial” structures as validated by previous studies of auras recorded with intracranial monitoring (Bancaud, et al. 1994, Binder, et al. 2009, Fried, et al. 1995, Maillard, et al. 2004, Palmini and Gloor 1992, Penfield & Perot 1963, Vignal, et al. 2007) (Figure 5). At baseline, 76% of patients had auras, with 69% consisting of “mesial” symptoms. During the peak RS effect at 12 months, corresponding to development of ischemia within the target zone and surrounding edema, mesial auras increased in relative proportion (79%) of all aura types. After resolution of the RS lesion and simultaneous decrease in complex partial seizures, the number of patients with auras decreased to 54% with the proportion attributable to mesial auras decreased to 30%. The inversion of proportion with mesial versus nonmesial auras along with the decrease in complex partial seizures suggests that successful RS of the limbic system for MTLE causes an heterogeneous lesion: a core within the RS target that includes destructive ischemia, and a penumbra of tissue exposed to less intense radiation that may include a time-dependent expression of neuromodulatory proconvulsant and anticonvulsant effects. The “cockade” theory (after the concentric rosettes once fastened upon military hats), originally proposed by Régis (Regis, et al. 2010) may be further characterized in ongoing trials of RS.

Conclusions

In summary, clinical trials of RS for MTLE show mixed results. Protocols that depend on higher doses of RS result in seizure remission rates within ranges reported for standard open surgery. Certain patients may be attracted to the noninvasive alternative of RS, and others dissuaded by the delay in anticonvulsant effect. An ongoing NIH-funded, multicenter trial, the ROSE Trial (Radiosurgery or Open Surgery for Epilepsy), randomizes patients to either technique and will compare seizure remission, cognitive outcomes, and cost. Not only will final outcomes (determined during the course of the last year of the three year follow-up period) be measured, but serial, interim measures in patient safety, quality of life, mood, and health care utilization will be compared between the two groups to guide physicians to direct patients between traditional and RS techniques matched to patient characteristics.

Outside of the ROSE Trial, other important questions remain to be answered. We do not know what role RS can play in lesionless, extratemporal lobe epilepsy. Also unknown is the possibility of supplementing standard surgery with RS, as in the case of treating “failed” open temporal lobectomy (Ansche and Romanelli 2008). Use of RS in either group of patients presupposes that adequate localization of epileptic foci can be undertaken without significant use of intracranial electrodes, since the advantages of so-called “noninvasive” RS diminish with the need for invasive localization. Design of protocols will require identification of a suitably homogeneous group of patients with appropriate localization protocols.

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Figure 1.

Effect of 50% isodose volume of a 24Gy dose in early trials of radiosurgery for mesial temporal lobe epilepsy (Régis, personal correspondence). Responses are reported in an edema-severity scale (Hayashi, et al. 2002) with the highest number designating mass effect with midline shift. A relatively narrow window of efficacy and toxicity appears between 5.5–7.5ml and was the basis for treatment volume restrictions in the US Multicenter Pilot Study (Barbaro, et al. 2009).

Figure 2.

Dose-response curve of treatment of human mesial temporal lobe epilepsy with radiosurgery with response = percent “seizure-free” (typically Engels outcome 1B or better) as defined by each trial. Each point designates the total number of patients in each trial paired with a letter designating first author of each report. Studies with more than one dose are shown divided among doses. 2 studies (Régis, et al. 2004, Vojtěch, et al. 2009) list 6 overlapping patients, but are shown independently here. A = Régis 1999 (Régis, et al. 1999); B = Kawai 2001 (Kawai, et al. 2001); C = Cmelek 2001 (Cmelak, et al. 2001); D = Srijvilaikul (Srikijvilaikul, et al. 2004); E = Régis 2004 (Régis, et al. 2004); F = Prayson 2007 (Prayson and Yoder 2007); G = Hoggard 2008 (Hoggard, et al. 2008); H = Barbaro (Barbaro, et al. 2009); J = Vojteck (Vojtěch, et al. 2009). Orange = prospective multicenter, yellow = single center case series.

Figure 3.

From the US Multicenter Pilot Trial (Barbaro, et al. 2009), MRI changes at 12 months after radiosurgery—specifically the volume of T2-weighted edema—predicted subsequent seizure remission between months 24–36. No patient with edema volumes < 200cc had seizure remission. These findings may help triage patients for subsequent standard open surgery if noninvasive RS is insufficient (Chang, et al. 2010).

Figure 4. 10× (A) and 20× (B) views of hippocampal sections after anterior temporal lobectomy performed on a patient with MTLE. Surgery was performed 15 months after radiosurgery with 24Gy because of persisting headaches and visual changes. The patient was seizure-free for 3 months before surgery. Evidence of diffuse vascular hyalinization and inflammation, leading to small infarcts and astrocytic reaction, predominate. Some changes attributable to acute ischemia during surgery are present as well. * = regions of chronic infarct. V = hyalinized vessels. Arrows = reactive astrocytes. / = acute ischemic changes associated with surgery. mo = molecular layer. Gr = granule cells. Bars = 100µm.

Figure 5.

Proportion of patients with auras with symptoms attributable to mesial localization (orange) vs nonmesial localization (blue) during baseline, 12m, and 36m after radiosurgery in the US Multicenter Pilot Trial (Barbaro, et al. 2009). P-values from McNemar's test. The proportion of auras of mesial onset declined significantly during the course of the trial. Epig = epigastric; o-g = olfactory-gustatory; exp = experiential; sens = sensory; vis = visual.