Failure of low-dose radiosurgery to control temporal lobe epilepsy

Report of two cases


Department of Neurosurgery, Graduate School of Medicine, University of Tokyo; Department of Neurosurgery, Japanese Red Cross Hospital; and Department of Neuropathology, Tokyo Metropolitan Neurological Institute, Tokyo, Japan

Radiosurgical treatment of intractable epilepsy has emerged as a noninvasive alternative to resection. Although gamma knife surgery (GKS) reportedly is effective when the radiation dose is sufficient to cause a destructive reaction in the targeted medial temporal lobe, the optimal target area and dose distribution are largely unknown. Some investigators have suggested that focused irradiation from a nondestructive dose is also effective. In this article the authors report two cases of medial temporal lobe epilepsy in which the patients underwent GKS performed using a 50% marginal dose of 18 Gy covering the amygdala, hippocampal head and body, and parahippocampal gyrus. In both cases this procedure failed to control seizures. Both patients became seizure free after undergoing anterior temporal lobectomy 30 and 16 months, respectively, after radiosurgery.

KEY WORDS • epilepsy surgery • radiosurgery • temporal lobe epilepsy

Recen t advances in radiosurgery have prompted attempts to treat intractable epilepsy with focused irradiation of epileptogenic foci. Although a favorable outcome for selective radiosurgical amygdalohippocampectomy in intractable TLE was recently reported, the optimal target area and dose distribution, resultant histological change, and mechanism by which focused irradiation eliminates seizures are largely unknown. The radiosurgery resulted in a prominent tissue reaction within and around the targeted area, necessitating corticosteroid treatment. Other authors have reported clinical experiences and experimental findings in which irradiation from lower doses has had a beneficial effect on seizures without causing destructive changes in the irradiated brain. This is an attractive possibility because it may avoid potentially hazardous radiation effects and corticosteroid treatment and, furthermore, may preserve the remaining function of medial temporal structures. We began using GKS for intractable TLE in 1996. Our first two cases were treated using a low-dose protocol, but this proved to be ineffective. Additional surgical treatment completely eliminated seizures in both patients. In this report we present our experience with these two cases.

Clinical Material and Methods

Our protocol for using GKS for the treatment of intractable TLE was approved by the ethics committee of the University of Tokyo in August 1996. Candidates for treatment were selected because they gave informed consent and had received a diagnosis of unilateral medial TLE based on findings of a presurgical evaluation protocol that included video-EEG, MR imaging, ictal and interictal SPECT, interictal FDG-PET, and neuropsychological tests. The targeted area and dose were not strictly prescribed in the protocol.

We started with a marginal dose of 18 Gy to the 50% isodose line, which completely covered the amygdala, hippocampal head and body, and parahippocampal gyrus (Fig. 1). The rationale for choosing this low dose of radiation is presented in the Discussion. From a practical point of view, we began using the low-dose protocol because we

Abbreviations used in this paper: EEG = electroencephalography; FDG-PET = [18F]fluorodeoxyglucose–positron emission tomography; GKS = gamma knife surgery; MR = magnetic resonance; SPECT = single-photon emission computerized tomography; TLE = temporal lobe epilepsy.
believed it would more likely avoid irreversible neurological deficits. If the procedure proved to be unsuccessful, we planned to escalate to additional surgical treatment. We did not plan to repeat GKS because its effect on the adjacent critical structures, such as the optic tract and pons, is unpredictable.

Case Reports

Case 1

History. At the age of 2 years this patient experienced her first febrile convulsion, which was frequently repeated thereafter. A diagnosis of TLE was made when she was 6 years old. Various medication regimens prescribed at several hospitals failed to control her seizures. She was referred to us when she was 31 years of age, at which time she was suffering a few simple partial seizures per week and a few complex partial seizures per month. The seizures were ushered in by a strange sensation in which she felt unfamiliar with her surroundings, followed by a disturbance of consciousness accompanied by salivation and manual automatism.

Examination. An EEG study demonstrated interictal epileptiform discharges issuing from the patient’s right anterior temporal region. An MR imaging study revealed right hippocampal sclerosis. Hippocampal volumes were 2577 mm$^3$ on the right side and 3373 mm$^3$ on the left, and hippocampal T$_2$ relaxation times were 153.9 msec on the right side and 125.4 msec on the left. An FDG-PET study revealed interictal hypometabolism in the right medial temporal lobe. The patient’s intelligence and memory tests yielded normal results. Intracarotid artery amobarbital testing revealed language dominance on the left side. Video-EEG demonstrated that seizure initiation coincided with a fast rhythmic discharge from the right sphenoidal lead.

Radiosurgery and Post-GKS Course. The patient underwent GKS targeted to her right medial temporal lobe according to the aforementioned protocol. The calculated target volume receiving more than 18 Gy measured 6.2 cm$^3$ (Fig. 1 upper). The patient continued to have seizures with the same frequency after GKS. Magnetic resonance images obtained at 3, 7, and 30 months and SPECT scans obtained at 6 months after GKS revealed no morphological or blood-flow changes related to irradiation. Magnetic resonance studies obtained at 3 and 7 months post-GKS included T$_1$-weighted images with contrast enhancement and T$_2$-weighted images. Those obtained at 30 months post-GKS included routine T$_1$- and T$_2$-weighted images and fluid-attenuated inversion-recovery images, albeit without contrast enhancement. The patient’s memory scores at 7 months post-GKS remained normal.

Operation and Postoperative Course. After a 30-month observation period post-GKS, the patient underwent anterior temporal lobectomy because she could no longer tolerate the disabling seizures. The inferior two thirds of the amygdala, the anterior 2.5 cm of the hippocampus, and the anterior 5 cm of the basolateral temporal lobe were removed. The resection was tailored so that the superior temporal gyrus was preserved. The intraoperative findings were unremarkable. The patient has been free from seizures for 20 months postoperatively, and during this time her dosages of antiepileptic drugs were tapered.

Pathological Findings. Histological examination of the resected specimen revealed hippocampal sclerosis with typical neuronal loss most prominent in CA1 (Fig. 2 upper left). In addition, however, strikingly atypical findings were observed. There was a small necrotic focus, approximately 5 mm in diameter, which was localized within the medial aspect of the posterior portion of the hippocampal head and the anterior portion of the hippocampal body. Prominent vascular changes characterized by vessel-wall thickening and fibrinoid and hyalin degeneration were found within the necrotic focus (Fig. 2 upper center). Furthermore, reactive astrocytes and scattered remaining neurons, which appeared swollen with granular cytoplasm, were observed in CA1 (Fig. 2 upper right). Neurons in other areas of the hippocampus were comparatively preserved, but some of them had degenerated and contained vacuolar cytoplasm (Fig. 2 upper right).

Case 2

History. This 22-year-old man had experienced a febrile convulsion at the age of 6 months, and he had a 13-year history of medically intractable TLE. As an adult, he suffered a few seizures each week, which emerged as an epigastric aura followed by motion arrest, staring, and salivation; these symptoms were followed by manual automatism, mainly on the right side.

Examination. This patient’s intelligence was normal. Magnetic resonance imaging revealed typical hippocampal sclerosis; hippocampal volume was 1948 mm$^3$ on the right side and 2816 mm$^3$ on the left, and hippocampal T$_2$ relaxation times were 168 on the right side and 132.7 on the
The N-acetylaspartate/(creatine + choline) ratio of the medial temporal lobe measured using proton MR spectroscopy was 0.1 on the right side and 0.16 on the left. Interictal SPECT and FDG-PET scans demonstrated hypoperfusion and hypometabolism in the right medial temporal lobe. Scalp EEG and magnetoencephalography readings demonstrated interictal epileptiform discharges from the bilateral anteromedial temporal region. Intraoperative findings were unremarkable, other than scattered adhesion of the arachnoid membrane to the dura mater. This patient has been free from seizure for 31 months since surgery.

Operation and Postoperative Course. After a 16-month observation period, the patient underwent anterior temporal lobectomy. Approximately the inferior two thirds of the amygdala and the anterior 2.5 cm of the hippocampus and parahippocampal gyrus were resected, along with the anterior 4.5 cm of the lateral temporal lobe. Intraoperative findings were unremarkable, other than scattered adhesion of the arachnoid membrane to the dura mater. This patient has been free from seizure for 31 months since surgery. During this time his dosage of antiepileptic drugs has been tapered.

Pathological Findings. Histological examination of the resected specimen revealed typical hippocampal sclerosis (Fig. 2 lower left). Additionally, we observed reactive gemistocytic astrocytes and scattered degenerated neurons, similar to those found in the specimen in Case 1 (Fig. 2 lower center and right). Reactive astrocytes were also observed in the amygdala. No necrotic focus or vascular degeneration were observed in the specimen obtained in Case 2.

Discussion

Using GKS with our low-dose protocol did not eliminate seizures during the follow-up periods, which lasted 30 and 16 months, respectively, in the two cases. The results of the presurgical evaluations strongly indicated that these two patients had unilateral medial TLE. Following resection of the ipsilateral anteromedial temporal...
lobe, both patients stopped having seizures. Incorrect patient selection and incorrect targeting of irradiation, therefore, were unlikely reasons for the failure of GKS, although there remains a small possibility that both patients had the lateral neocortical type of TLE. Regis, et al., recently reported seven cases of TLE that were successfully treated by GKS. All patients became free from seizures after a mean delay of 10 months. Our observation periods were longer than this, but shorter than 3 years, at which time the full effect of GKS on the vascular system is achieved in the majority of cases. It is possible that, in our patients, the seizures would have decreased after longer follow-up periods; however, the patients could no longer tolerate their disabling seizures.

We observed no changes on MR images after low-dose GKS, in contrast with prominent MR imaging changes documented after higher dosage GKS. Unexpectedly, however, we observed clear histological reactions. In both cases the resected hippocampal tissue contained reactive astrocytosis and peculiar degenerated neurons. These findings are not usually observed in hippocampi of patients with TLE. Experimental GKS, in which the maximum dose was less than 70 Gy, produced no pathological changes in the rat brain within 90 days; however, there has been no previous report on long-term histological changes after GKS at lower doses in the human brain. In the present cases the reactive astrocytosis was most likely due to the effect of irradiation because it was a major pathological change found not only at the target site following experimental GKS, but also in surrounding regions. We observed a small necrotic focus in the medial region of the hippocampus in Case 1. This lesion was accompanied by prominent vascular degeneration, which was another major histopathological change observed post-GKS in rodent models.

Reviewing the dose planning (Fig. 1 upper), we found that the necrotic lesion in Case 1 was located within the 70% (that is, the 25.2-Gy) isodose line but was much smaller than the area surrounded by the line. There was no necrotic lesion in the hippocampus in Case 2. Therefore, the necrotizing threshold might have been approximately 36 Gy, which was the peak dose used in our protocol. Regis and colleagues used a 50% marginal dose of 25 Gy, and the calculated volume of their target was 6500 mm³. The 25-Gy isodose line included the hippocampal head, the anterior portion of the hippocampal body, the amygdalofugal portion of the amygdala, and the entorhinal area. According to their dose planning, the contour between the 50% and 70% isodose areas was very steep, so that the 70% (that is, 35-Gy) isodose line surrounded most of the aforementioned structures. Those medial temporal structures appeared amorphous and necrotic on MR images obtained 3 years post-GKS. Our experiences and those of Regis and colleagues indicate that a dose greater than approximately 35 Gy is necessary to necrotize the brain and that necrotizing most of the medial temporal structures is necessary to achieve seizure control.

The reason we found no posttreatment changes on MR images in our two cases is unknown. Coinciding with the cessation of seizures 10 months after GKS, Regis and colleagues observed a ringlike contrast enhancement in the medial temporal lobe and an increased T₂ signal of white matter in almost the whole temporal lobe. If contrast enhancement is closely associated with necrosis, the lesion in Case 1 would have been depicted on MR images. It is possible that we missed the changes on MR images because we did not perform these studies between 7 and 30 months post-GKS. Still, we did not observe a prominent increase in the T₂ signal of temporal white matter at 7 and 15 months post-GKS in Case 2. After we treated these two patients, we increased the 50% dose to 25 Gy and treated five additional patients for TLE. Although we are still conducting follow-up review in these five patients, we have observed changes on MR images that have a character and timing similar to the observations of Regis and colleagues.

One of the reasons we initially used a low radiation dose was the accumulated evidence that radiosurgical treatment of tumors and vascular malformations often results in concomitant control of epileptic seizures without significant damage to surrounding brain tissue (for a review, see Kitchen). The radiation dose delivered to brain tissue around the lesions was less than 20 Gy in those situations. After GKS we saw a decrease in seizure frequency much earlier than we observed morphological changes in the arteriovenous malformation. We also found that GKS targeted to cavernous angiomia seated in the medial temporal lobe eliminated seizures completely with no radiographic change in the angiomia itself. Nevertheless, a medial temporal location was recently reported to carry a higher risk of treatment failure in a retrospective study of GKS for epilepsy associated with cavernous angiomia.

Another reason we chose a low radiation dose arose from reports from two groups that 10 to 20 Gy of radiation eliminated seizures in nonlesional epilepsy. Barcia-Salorio and associates treated 11 patients with radiosurgery with a total dose of 10 to 20 Gy. They used a stereotactic system coupled to a conventional 60Co unit with a 10-mm collimator, and employed the cross-fire technique. Seven of their patients had TLE and one of them underwent bilateral irradiation. Four patients, including two with TLE, became completely seizure free, and three patients experienced seizure reduction greater than 80%. Heikkinen, et al., reported a case of TLE that was successfully treated with radiosurgery with a total dose equivalent to 10 Gy. Five fractions of 3 Gy each were given on successive days to a spherical volume 2 cm in diameter, which was centered at the hippocampal head, by using a 6-MeV linear accelerator with a stereotactic frame. Successfully treated patients in these reports experienced seizure reduction after a delay of 3 months to 1 year. Although no posttreatment changes were found on computerized tomography and MR images in the latter group, detailed information on dose planning, pre- and posttreatment MR imaging, and neuropsychological status were not available in either report.

It is difficult to draw any definite conclusion based on our limited experience with two cases of failed GKS. They suggest, however, that it might be a mistake in some cases to expect seizure cessation, at least during the early posttreatment period, as a result of GKS at doses that do not induce apparent radiological reaction or destruction of a large area of the medial temporal structures. To achieve seizure cessation by using GKS, it may be necessary to destroy the medial temporal structures completely, as in a resection. Unfortunately, we lack sufficient experimental
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and clinical information for further speculation. Clinical evidence of the efficacy of radiosurgical treatment for epilepsy is still limited. The animal studies reported thus far focus on rodents and felines, and the results of those studies are difficult to interpret because epilepsy models in these animals do not precisely represent human TLE.13 Much more information must be accumulated from clinical and experimental studies on radiosurgical treatment of epilepsy before initiating wider use of this procedure.

References

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Address reprint requests to: Kensuke Kawai, M.D., D.M.Sc., Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, 2-6-1 Musashidai, Fuchu-shi, Tokyo 183–0042, Japan. email: kenkawai-tky@umin.ac.jp.