Seeking New Paradigms in Epilepsy: Stereotactic Radiosurgery

Jean Régis, MD, Romain Carron, MD, Fabrice Bartolomei, PhD, and Patrick Chauvel, PhD

Radiosurgery is a neurosurgical approach consisting of the delivery of a high energy confined to a small, sharply limited target with stereotactic accuracy in a single session either to create a lesion or to induce a desired biological effect.[1,2] Since the first attempt by the pioneers in Stockholm, the practice of radiosurgery has changed dramatically. Nowadays, in the vast majority of the indications, Gamma Knife (GK) radiosurgery entails the use of nondestructive low dose to induce subtle biological effects like apoptosis in tumors or endothelial proliferation in arteriovenous malformations (AVMs).

THE DIFFERENTIAL EFFECT CONCEPT

This is the classic clinical observation that in 85% of the AVMs associated with a drug-resistant or medically intractable epilepsy, radiosurgery is followed by seizure cessation or a dramatic improvement of epilepsy occurs long before the occlusion of the AVM itself (Figure 1). Moreover, when the AVM is located in a highly functional area, the seizure cessation is obtained without clinical deficit. This observation led us to put forth the concept of clinical differential effect in 1992: Radiosurgery can induce a functional effect such as rendering the cortex surrounding the AVM no longer epileptic without destroying the underlying function, thanks to its capacity to alter some systems specifically while sparing others. The first proof of concept came from the demonstration of the existence of such an effect at the biochemical level in the striatum of rats.[3] With the help of an original rat frame,[4] a group of rats received a single isocenter of 4 mm in the left striatum with a maximum dose of 50 Gy using the GK (Figure 2). Biochemical analyses demonstrated no change in the level of the glutamate decarboxylase but a significant decrease in the choline acetyltransferase level, indicating an injury of the catecholaminergic system with concomitant sparing of the GABAergic system. Similarly, GABA was unchanged despite a major decrease in the amino excitatory acids (glutamate and aspartate). This experimental demonstration led us to consider radiosurgery as a neuromodulation therapy[1-3] and encouraged us to organize several prospective clinical trials.[5-9] More recently, the demonstration of the existence of a differential effect at the cellular level came from the

Charlottesville group.[10] In epileptic rats irradiated with 40 Gy in the temporal lobe with the GK, immunohistochemical study suggested that at least 1 subtype of hippocampal interneurons was selectively vulnerable to GK radiosurgery. Neuronal cells appear to have undergone a phenotypic shift with respect to calbindin and glutamate decarboxylase-67 expression. There is now a growing body of evidence in favor of a neuromodulatory effect of radiosurgery.[1,2,11]

A series of successive clinical trials has been carried out in Marseille to evaluate GK surgery in epilepsy. In 1993, we organized a phase II prospective trial in 4 mesial temporal lobe epilepsy (MTLE) patients with a goal of dose ranging and toxicity evaluation.[7,9] In 1995, the good safety and impressive efficacy in the patient receiving the 24-Gy dosage led us to organize a phase III prospective single-center study in 4 MTLE patients (24 Gy, 7-8 cm³) to evaluate the reproducibility of the efficacy.[5] In 1996, we organized a prospective multicentric European study (21 MTLE patients), confirming the reproducibility of the safety efficacy.[8] In 1998, a dose de-escalation study (24, 20, 18 Gy) showed that the efficacy decreased dramatically when the marginal doses were < 24 Gy.[6] Finally, the neurologists from our team performed a long-term evaluation (> 5-year follow-up) of the first 15 consecutive patients treated according our standard protocol.[12] This study confirmed the good safety and efficacy of GK surgery in this group of patients over the long term with a rate of 60% of Engel I at a mean follow-up of 8 years,[12-16] comparing well with the safety and efficacy of open surgery over the long term. More recently, a multicenter prospective trial in the United States confirmed all our findings.[17] Radiosurgery has been the current practice for selected pure MTLE in our group ever since.[18]

There are convincing arguments for such an investigation of the potential role of radiosurgery in epilepsy surgery. We know the following:

1. The safety and efficacy of radiosurgery for the treatment of numerous small, deep-seated intracerebral tumors or malformations have been well documented since the 1950s.
2. Radiosurgical treatment of small corticosubcortical lesions associated with epilepsy is known to be associated with seizure cessation in a high percentage of cases (58%-80% in AVMs) long before the expected occlusion of the lesion
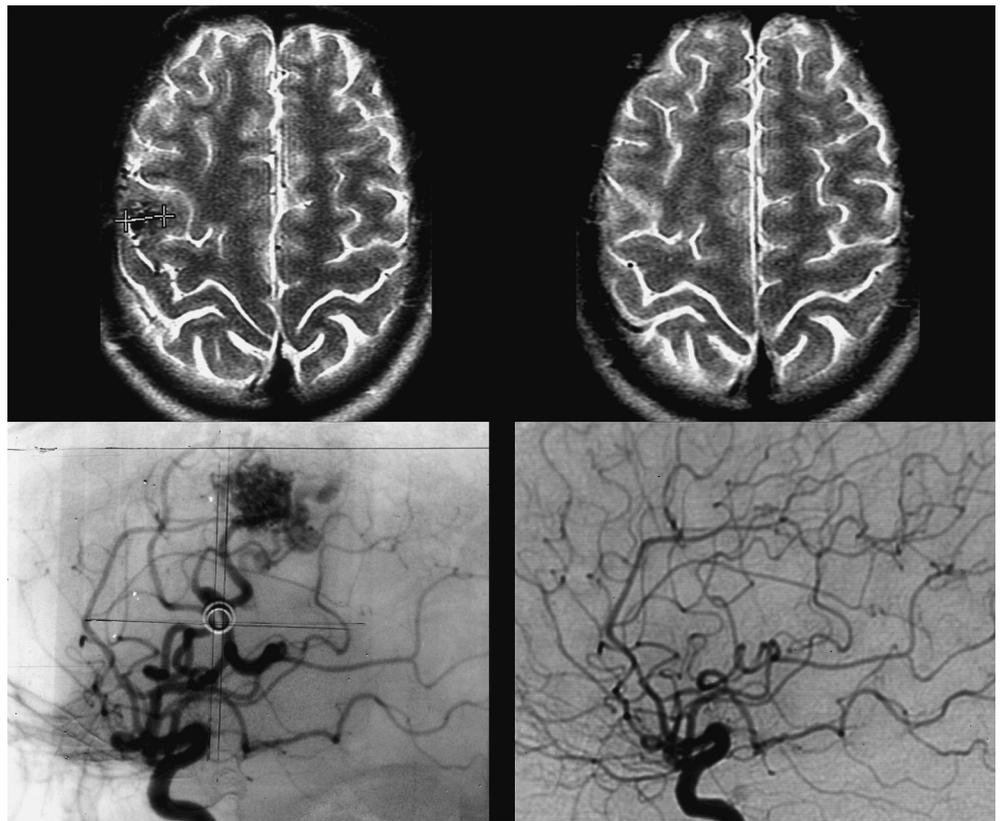
FIGURE 1. A precentral arteriovenous malformation (AVM) discovered in the context of somatomotor seizures with a Bravais-jacksonian walk was treated by radiosurgery in April 1994. Some months after radiosurgery, far before AVM occlusion, seizure cessation was observed, without any neurological deficit and especially no pyramidal motor deficit. Radiosurgery, creating AVM thrombosis and making the cortex surrounding the AVM no longer epileptic, has achieved 2 specific desired biological effects while preserving the underlying function. This is a clinical example of the differential effect of Gamma Knife surgery.

and sometimes even despite failing to cure the vascular malformation itself.

3. Radiotherapeutic treatment of epilepsies with or without space-occupying lesions can lead to a reduction in seizure frequency and/or severity.

4. Experimental models of epilepsies treated with radiation therapy have demonstrated a dose-dependent positive effect of radiation on the frequency and severity of the seizures and on the extent of discharge propagation.
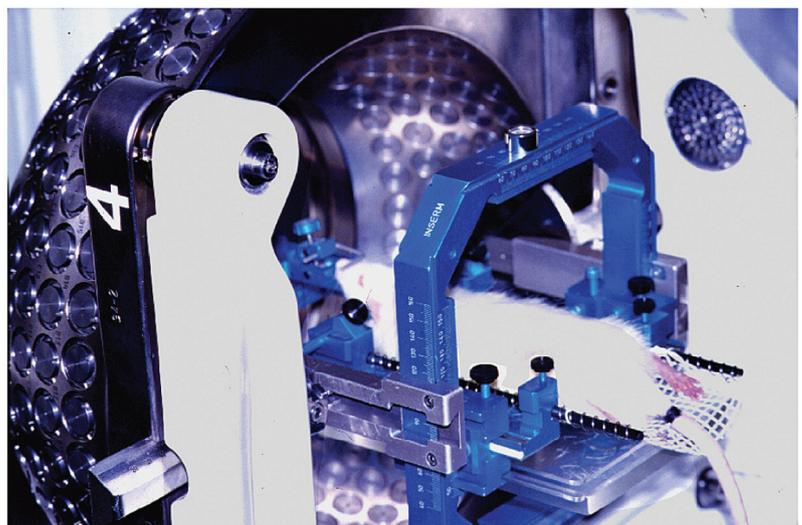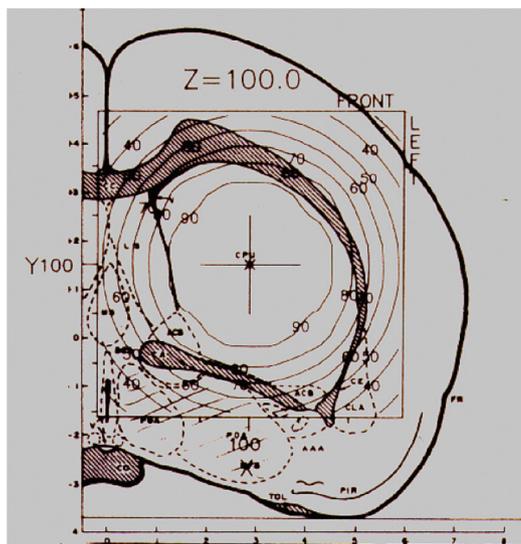

FIGURE 2. Biochemical demonstration of the existence of a differential effect of radiosurgery. With the use of an original stereotactic frame for rats, the striatum was targeted with a single shot of 4 mm and 50 Gy at the maximum point. Choline acetyltransferase, but not glutamate decarboxylase, was dramatically reduced; similarly, the amino excitatory acids, but not GABA, were dramatically cut down. Reprinted from Régis et al[3] with permission.

FIGURE 3. Typical planning of a Gamma Knife surgery for a MTLE on the dominant side in a patient with a high level of functioning. This patient presented with a series of risk factors for a post-operative verbal memory decline in case of microsurgical resection: Dominant-side MTLE with no atrophy or hippocampal sclerosis, few preoperative neuropsychological deficit in patient with a high level of functioning. Additionally, a Wada test predicted a severe verbal memory deficit in case of amygdalohippocampectomy, and the patient was contraindicated for a microsurgery. In October 2003, the patient was treated with a dose of 24 Gy at the 50% isodose line according to our standard protocol. Seizure cessation occurred 1 year after the radiosurgical intervention with no side effects. At 2 years, the neuropsychological testing was improved, especially the verbal memory items (before drug reduction).
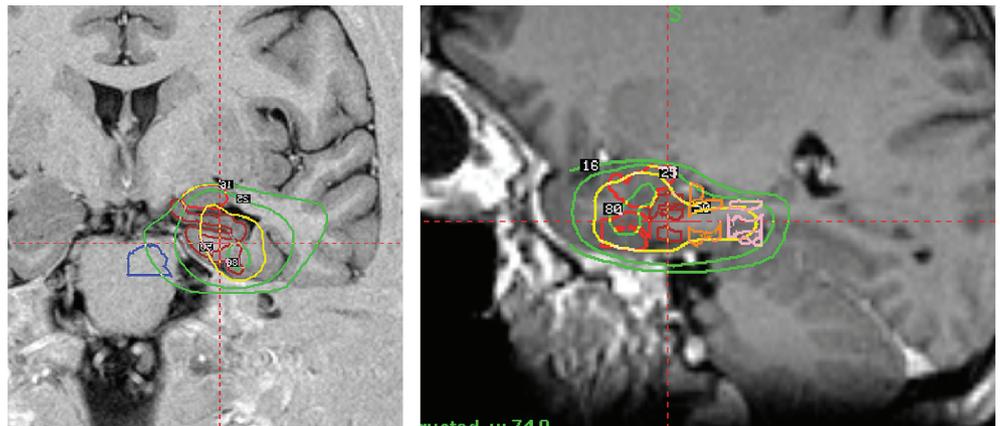
Different kinds of radiation to treat epilepsies have already been proposed. Lars Leksell conceived GK radiosurgery as a tool for functional neurosurgery.[19,20] Accordingly, he used GK in movement disorders, trigeminal neuralgia, and other pain syndromes but not for epilepsy surgery.[21] The first radiosurgical treatments for epilepsy surgery were performed by Talairach in the 1950s.[22] Talairach was another pioneering expert in stereotaxis. Unlike Leksell, he had specific involvement in epilepsy surgery and led one of the first large comprehensive programs for epilepsy surgery. As early as 1974, he reported the use of radioactive yttrium implants in patients with MTLE without space-occupying lesions and showed a high rate of seizure control in patients with epilepsies confined to the mesial structures of the temporal lobe.[22] In 1980, Elooma,[23] apparently unaware of the pioneer work of Talairach, promoted the idea of focal irradiation for the treatment of temporal lobe epilepsy based on the preliminary reports of Tracy,[23a] Von Wieser,[24] and Baudouin et al.[15] Furthermore, clinical experience with the use of GK- and linear accelerator–based radiosurgery in AVMs and corticosubcortical tumors (mostly metastases and low-grade glial tumors) revealed an antiepileptic effect of radiosurgery in the absence of a necrotizing effect.[25-27] A series of experimental studies in small animals confirmed this effect[28,29] and emphasized its relationship to the dose delivered.[30-33] Barcia Salorio et al[34] and later Lindquist et al[35-37] reported small and heterogenous groups of patients treated with the aim of seizure cessation; however, results were poor. Unfortunately, these data were never published in peer-reviewed articles, and precise data are unavailable.

In the Department of Stereotactic and Functional Surgery in Marseille, the 2 major fields of expertise are epilepsy surgery and radiosurgery. This context has therefore facilitated the investigation and development of a potential role for GK radiosurgery in the treatment of intractable epilepsy. The first attempt to treat an MTLE was made in Marseille in March 1993.[7] Since then, 217 cases of epilepsy surgery with GK radiosurgery have been performed.

Among 11 066 GK surgery procedures accomplished in our neurosurgical unit within a 20-year period (between July 1992 and December 2012), only 217 were proposed in patients referred for epilepsy surgery (roughly 10 patients per year). During the same period, we performed 759 nonradiosurgical neurosurgical operations for epilepsy surgery. The philosophy of our team is to define the niche of patients in whom the safety-to-efficacy ratio makes it advantageous or in whom it at least compares favorably with open neurosurgery.[38] Obviously, this represents a small subset of patients in our present experience (23%). However, a portion of the

FIGURE 4. Clinical results of the radiosurgical treatment of a left mesial temporal lobe epilepsy performed on December 17, 1997. Nine years after the radiosurgical intervention performed on the dominant side of a right-handed patient, the neuropsychological performances were dramatically improved, particularly on the verbal memory items (> 2 standard deviation).
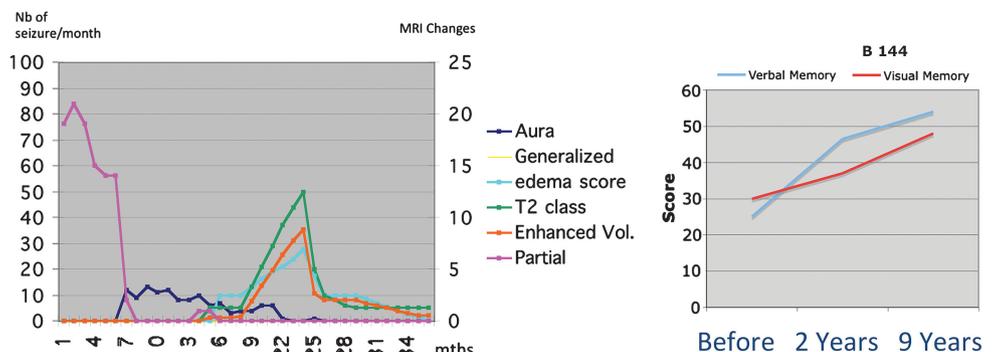
FIGURE 5. Anterior corpus callosotomy with the Gamma Knife in an 18-year-old patient with a severe drug-resistant bifrontal epilepsy since 5 years of age with frequent falls. After a stereo-electroencephalographic investigation demonstrating the bifrontal extent of the epileptogenic zone, a corpus callosotomy was decided. Left, the planning of the Gamma Knife surgery (80 Gy at the 50% isodose line). The main benefit of this callosotomy was to reduce the frequency of seizures with falls. Right, 1 year after radiosurgery, no deficit was observed, and the tractography demonstrated the section of the corpus callosum fibers.
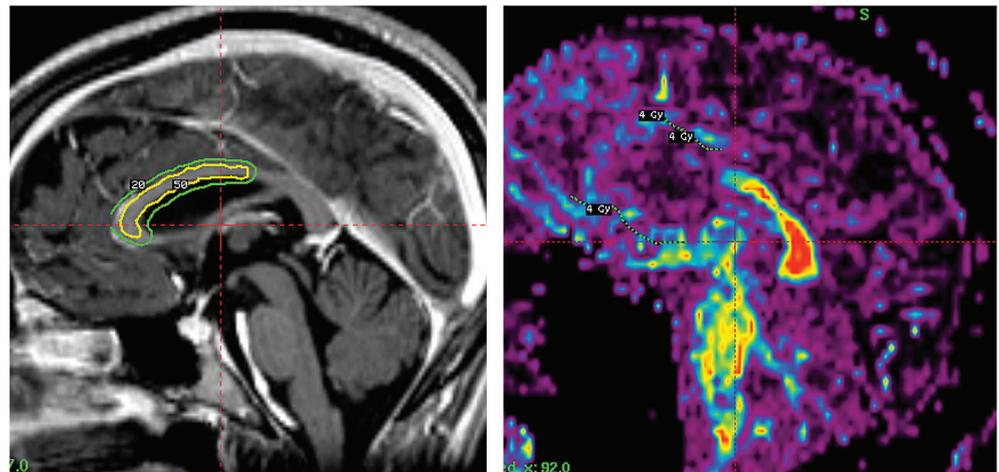
patients we now treat by GK surgery are directly referred to us for this specific procedure. The actual percentage of patients coming from our own clinical program of investigation for epilepsy and operated on by GK surgery is only 14.6%.

HYPOTHALAMIC HAMARTOMAS

Hypothalamic hamartomas (HHs) may be asymptomatic, associated with precocious puberty or with neurological disorders (including epilepsy, behavior disturbances, and cognitive impairment), or both. The seizures usually begin early in life and are often particularly drug resistant from the outset. The evolution is unfavorable in most patients because of behavioral symptoms (particularly aggressive behavior) and mental decline, which occur as a direct consequence of the seizures,[39] in the setting of an epileptic encephalopathy. Interestingly, in our experience, reversal of this encephalopathy

FIGURE 6. The activity of radiosurgery for epilepsy is reserved for highly selected patients, but this activity is sustained over years. Hypothalamic hamartomas (HHs) and mesial temporal lobe epilepsy (MTLE) are the 2 major indications. Epi, epilepsy; TN, trigeminal neuralgia; VIN, ventral intermediate nucleus radiosurgery for tremor.

after radiosurgery seems to start even before complete cessation of the seizures and seems to be correlated to the improvement in background electroencephalograph activity. These continuous discharges might lead to the disorganization of several systems, including the limbic system. Their disappearance may well account for the improvement seen in attention, memory, cognitive performance, and impulsive behavior. Thus, the goal of radiosurgery is the reversal of the epileptic encephalopathy rather than seizure cessation stricto sensu. Consequently, we consider it essential to operate on these young patients as early as possible, whatever the surgical approach (resection or radiosurgery).

The intrinsic epileptogenicity of HHs has been demonstrated,[40,41] even though the mechanisms of the epilepsy associated with HHs are still debatable. The boundary of the target zone of treatment is that of the lesion visualized on magnetic resonance (MR) imaging. This contrasts greatly with cases of MTLE in which there is no such clear delineation of an epileptogenic zone.

We retrospectively analyzed radiosurgery in a series of 10 patients collected from centers around the world.[42] The very good safety-to-efficacy ratio (all improved, 50% cured, and no adverse effects except 1 case of poikilothermia) led us to organize a prospective multicenter trial. Our trial of 64 prospectively evaluated patients is unique with regard to the number of patients and the strict methodology. We have published a preliminary report of this study,[43-45] and the final evaluation is in progress. These 64 patients operated on between 1999 and 2007 have all been followed up for > 3 years (36-107 months). According to our policy, the patient and the family are offered a second radiosurgery in case of partial benefit when the lesion is anatomically small and well defined. Because of the significant but partial efficacy, 25 patients (62.5%) were treated twice. The preoperative cognitive functions, behavioral disturbance, seizure severity, and anatomic type were characterized.[46,47] The goal of the preoperative workup was to adequately select the candidates for inclusion and to evaluate
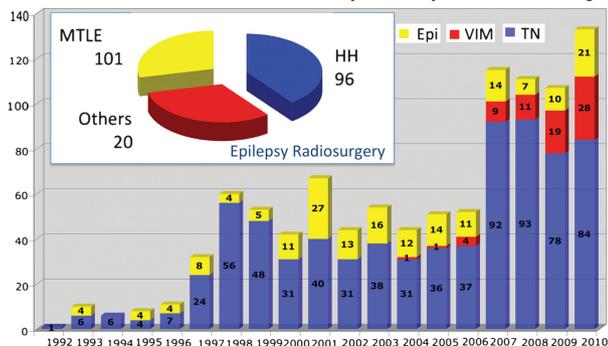
the baseline neurological and endocrinological functions. All radiosurgical procedures were carried out with a model B, C, 4C, or Perfexion GK (Elekta Instrument, Stockholm). We consistently elaborated multi-isocentric complex dose planning of high conformity and selectivity. We used low peripheral doses because of the close relationship with optic pathways and hypothalamus (median, 17 Gy; range, 13-26 Gy). The lesions treated are generally small (median, 9.5 mm; range, 5-26). We pay special attention to the dose delivered to the mammillary body and fornix, and we always try to tailor the dose plan for each patient on the basis of the use of a single run of shots with the 4-mm collimator. Patients were evaluated with respect to seizures, cognition, behavior, and endocrine status 6, 12, 18, 24, and 36 months after radiosurgery and then every year. Results demonstrate that in 65% of these patients, an Engel I or II is achieved. An Engel III is observed in 20% of the patients. The frequency of seizures before radiosurgery was 92 seizures per month (mean, 427 ± 1009; minimum, 3.3) and dropped to 6 seizures per month afterward (mean, 34.6 ± 78; minimum, 0; maximum, 425). In the majority of these patients, a dramatic behavioral and cognitive improvement was observed. Psychiatric and cognitive comorbidity was cured in 28%, improved in 56%, and stable in 8% of the patients. Globally, a very good result was obtained in 60% of the patients. A microsurgical approach was performed in 6 patients (9.3%) with quite large HHs and poor efficacy of radiosurgery. Microsurgery was performed in 6 patients (17%), (33%) and (50%). After this microsurgical approach, 1 patient was cured (Engel I), 2 were improved (Engel III), and 3 were not improved (Engel IV). No permanent or even transient neurological deficits were seen.

A transient increase of seizure was observed in 7 patients (17.5%). Transient nondisabling poikilothermia was observed in 3 cases.

Topographic classification of the lesion based on a good high-resolution MR imaging is a key feature of the decision-making process.[43] Previous classifications were based on anatomic[48-50] or surgical[51] criteria. These classifications do not describe the large diversity of these lesions and ignore their therapeutical consequences. As underlined by Palmini and coworkers,[52] the exact location of the lesion in relation to the interpeduncular fossa and the walls of the third ventricle correlates with the extent of excision, seizure control, and complication rate. On this basis, we classify the HHs according to their topography using our own classification.[43,44] In our experience, this classification correlates well with the clinical semiology and severity and is especially useful in the selection of the surgical strategy.

Type I (small HHs located inside the hypothalamus extending more or less into the third ventricle) are certainly the best candidates for GK surgery. In this population, the risk of microsurgical removal is likely to be high.

In type II (the lesion is small and mainly in the third ventricle), radiosurgery may be the safer alternative. Although the endoscopic and transcallosal interforniceal approaches have been attempted, the risks of short-term memory worsening, endocrinological disturbances (hyperphagia with obesity, low

thyroxine, sodium metabolism disturbance), and thalamic or thalamocapsular infarcts have been reported by the most enthusiastic and skillful neurosurgeons. However, for very severe repeated status epilepticus, we propose as a salvage surgery either a transcallosal interforniceal approach or an endoscopic approach (depending on the width of third ventricle). In emergency situations, if the lesion is small and the third ventricle is wide, the endoscopic approach is chosen.

In type III (lesion located essentially in the floor), the extremely close relationship between the mammillary body, the fornix, and the lesion clearly leads us to prefer GK surgery. We speculate that sessile HHs (type IV) always have more or less an "extension" in the hypothalamus close to the mammillary body. Thus, when a lesion is classified as a type II, the lesion appears on the MR as located mainly in the third ventricle but is likely to have a "root" in the hypothalamus. The same assumption is made for type III.

In type IV (the lesion sessile in the cistern), a disconnection can be discussed (pterional approach with or without orbitozygomatic osteotomy). However, if the lesion is small, GK surgery can be recommended because of its safety and its capability to reach at the same time the small component located within the hypothalamus itself, frequently visible on the high-resolution MR. In the Delalande and Fohlen[16] experience, only 2 patients among 14 were seizure free after a single disconnection through a pterional approach. Consequently, we use this approach for lesions too large for GK surgery as a first step of a staged approach.

In most circumstances, the patient is improved but not seizure free after the first microsurgical step, and GK surgery is scheduled at 3 months as a second step.

Type V (pediculate) is rarely epileptogenic and can easily be cured by radiosurgery or disconnection through a pterional approach. In case of severe epilepsy, the second therapeutic modality allows faster cessation of seizures. However, a distant extension of the HH into the hypothalamus close to the mammillary bodies must be cautiously looked for on high-resolution MR. Its visualization will prompt us to consider GK surgery to treat both parts of the lesion, especially in cases when the cisternal component is small.

Type VI (giant) does not represent a good indication for first intention radiosurgery because, in nearly all cases, a combination of several therapeutic modalities should be used. Even if GK surgery does not seem to be suitable when the lesion is large, "radiosurgical" disconnection has been envisaged (radiosurgery targeting only the superior part in the hypothalamus and/or the third ventricle, leaving untreated all the lesion lower than the floor) but has been systematically disappointing. In our opinion, this strategy may cause loss of precious time for the child to be treated effectively. Consequently, we do not advocate this strategy. When microsurgical resection has left a small remnant in the third ventricle and active epilepsy, reoperation can be envisaged by GK surgery.

Two major questions remain. First, we know that complete treatment or resection of the lesion is not always mandatory,[53-55] but we do not know how to predict in an individual patient the amount (and mapping) of the HH that

must be treated to obtain a complete antiepileptic effect. Second, we know that these patients frequently present with an electroclinical semiology, suggesting involvement of the temporal or frontal lobe that can mimic a secondary epileptogenesis phenomenon.[41,56] In our experience, some of these patients can be cured completely by the isolated treatment of the HH, whereas a partial result is obtained in others with residual seizures despite significant overall psychiatric and cognitive improvement. In this second group, it is tempting to propose that such a secondary epileptogenic area accounts for the partial failure.

Our initial results indicate that GK surgery is as effective as and much safer than microsurgical resection.[57] GK surgery also avoids the vascular risk related to radiofrequency lesioning or stimulation. The disadvantage of radiosurgery lies in its delayed action. Longer follow-up is mandatory for proper evaluation of the role of GK surgery. Results are faster and more complete in patients with smaller lesions inside the third ventricle (stage II). The early effect on subclinical electroencephalographic discharges appears to play a major role in the dramatic benefit concerning at once the sleep quality, behavior, and cognitive developmental functions. GK surgery can safely lead to the reversal of the epileptic encephalopathy.[42,44,45,58]

Considering the very poor clinical prognosis of this condition and the invasiveness of microsurgical resection, GK can now be regarded as the first-line option for small to middle-sized HHs associated with epilepsy because it can lead to dramatic improvements in the future of these young patients. The role of secondary epileptogenesis of widespread cortical dysgenesis in these patients needs to be better evaluated and understood to optimize patient selection and to define the best treatment period.

MESIAL TEMPORAL LOBE EPILEPSY

The first GK surgery operations for MTLE were performed in Marseille in March 1993. Because no similar experience in the literature was available at that time, we were obliged to base our technical choices on hypothesis and experience in radiosurgery for other pathological conditions. Four patients were treated with different technical strategies (dose, volume, target definition). The impressive delayed radiological changes observed some months after radiosurgery[59] drove us to stop for a while and follow up these first 4 patients. As a result of the clinical safety of the procedure in these patients and the gradual disappearance of the acute MR changes after some months, we treated several new series of patients under strict prospective controlled trial conditions (with ethical committee approval). The treatment for the next 16 patients was based on that of the first patient who had a successful outcome (as opposed to the 3 others who had partial or no effect).

This "classic planning" was based on the use of two 18-mm shots covering a volume of about 7 cm³ at the 50% isodose (24 Gy) and has turned out to produce a high rate of seizure cessation.[60,61] For epileptological and safety reasons, the targeting was very much centered on the parahippocampal

cortex and spared a significant part of the amygdaloidal complex and hippocampus. The refinement of the GK surgery technique and the need to find a dose that would create more limited MR alterations during the acute phase led us to reduce the dose from 24 to 20 and 18 Gy at the margin. However, this caused a significant decrease in the rate of seizure cessation. We have reviewed the long-term follow-up of our first 15 patients operated on by state-of-the-art GK surgery for MTLE (24 Gy) (Figure 3).[6] The mean follow-up was 8 years, and at the last follow-up, 73% were seizure free. These long-term results compare favorably with microsurgical results. No permanent neurological deficit was reported except a visual field deficit in 9 patients.[12] After microsurgery for MTLE on the dominant side, a verbal memory deficit is classically observed in 30% to 50% of the patients.[62,63] It is of special importance to note that none of our patients has harbored any neuropsychological worsening (using the evaluation published by Clusmann et al[13]) and especially no verbal memory decline (Figure 4).[5,6,8,12] This finding from our 4 prospective trials has been confirmed by a US prospective trial.[64]

The timetable of events after radiosurgery and the follow-up is quite standardized. Patients are informed that the main drawback of radiosurgery lies in its delayed efficacy. Typically, the frequency of the seizures is not modified significantly for the first few months. Thereafter, there is a rapid and significant increase in auras for some days or weeks before the seizures eventually disappear. Usually. the peak in seizure cessation is observed around the 8th to 18th month with a clear variability in the delay in onset. In 1 patient, this occurred 26 months after GK radiosurgery. We usually consider a delay of 2 years as the minimum for postradiosurgery follow-up. In the absence of initial radiological changes or clinical benefit, the recommendation is to wait for the onset of the MR imaging changes and their subsequent disappearance. All our patients had the same pattern of MR changes regardless of the margin dose (18-24 Gy) and treatment volume (5-8.5 cm³). However, the degree of these changes and their delay of onset varied according to the dose delivered to the margin, the volume treated, and the individual patient. To allow an optimal evaluation, we recommend that subsequent microsurgery not be considered before the third year after radiosurgery. Similarly, we believe that a patient who undergoes a cortectomy before the onset of the MR changes has occurred cannot be assumed to have failed radiosurgical treatment. Of course, before consideration of any further surgery, the reason for the failure needs to be addressed. After a review of the medical records of patients treated with radiosurgery for MTLE, it was sometimes possible to identify likely causes of failure, such as the following:

1. Poor patient selection (eg, patients with epilepsy involving more than the MTL structures)
2. Patients with a diagnosis of treatment failure (< 3 years) who had been operated on too soon after radiosurgery[65]
3. Targeting of the amygdala and hippocampus (which in our opinion is not the optimal target in terms of safety and efficacy) instead of the parahippocampal cortex[66]
4. Insufficient dose[65-67]

Our current strategy of treatment is based on our first series of MTLE patients who were strictly selected and treated systematically with a very simple but very reproducible dose planning strategy.[5,7] Identifying putative improvements in the methodology requires a systematic analysis of the influence of the technical data from our experience and from the literature on the outcome of those patients.

THE "TECHNICAL" QUESTIONS

The Dose Issue

The first targets used in functional GK radiosurgery (capsulotomy, thalamotomy of ventral intermediate nucleus., or the centromedianum, pallidotomy) were treated with a high dose (300-150 Gy) delivered in very small volumes (3-5 mm in diameter).[21] The goal was to destroy a predefined, very small anatomic structure with stereotactic precision. Quite a significant variability in the delay and amplitude of the MR changes has been reported with a fixed dose regimens.[41,68] Barcia Salorio et al[13] have presented several times a small and heterogeneous group of patients treated with different kinds of devices and dose regimens. Apparently, some of those patients had no expanding lesion and were treated with very large volumes and very low doses (about 10 Gy). On the basis of this experience, several teams have made the assumption that very low doses, as low as 10 to 20 Gy at the margin, should be as effective as the 24-Gy protocol (at the margin) that we used for our first series of patients with MTLE.[5] A cautious examination of the last proceeding of Barcia Salorio et al[34] shows that individual information on the dose at the margin, the volume, and the topography of the epileptogenic zone is not provided. Moreover, among the 11 patients reported, the actual rate of seizure cessation is apparently only 36% (4 of 11), which is much lower than what would be expected with resection in MTLE. In a heterogeneous group of 176 patients, Yang et al[67] confirmed that only a very low rate of seizure control is achieved when low doses (9-13 Gy at the margin) are used.

The experience with the radiosurgical treatment of HHs indicates that 18 Gy at the margin appears to be a threshold in terms of probability of seizure cessation.[42] In this group of patients (36 cases), only 1 patient showed MR changes. The majority of the AVM cases with worsening of the epilepsy were treated with a range of doses between 15 and 18 Gy. Similarly, poor results have been reported by Cmelak et al[65] in 1 MTLE patient treated with linear accelerator–based radiosurgery, with 15 Gy at the 60% isodose line, who underwent surgical resection 1 year later. In this case, the authors first observed a slight improvement followed by an obvious worsening. A recent de-escalation study has allowed us to demonstrate poorer results in patients receiving doses of 18 or 20 Gy compared with 24 Gy at the margin.[61,69] As a result of the rate of seizure cessation achievable by conventional resection, a radiosurgical strategy associated with a much lower rate of seizure cessation appears unacceptable. Fractionated stereotactically guided radiotherapy has been demonstrated to fail systematically in controlling seizures. Among 12 patients treated by Grabenbauer and colleagues,[60,70] none

has achieved seizure cessation; only seizure reduction was obtained in this series.

Experimental studies on small animals have demonstrated the antiepileptic effect of radiosurgery,[30,32,71] the dose dependence of this effect,[30-32,72] and the possibility of obtaining clear antiepileptic effect without macroscopic necrosis.[31] Of course, the rodent models of epilepsy are far from being good models of human MTLE. However, taking into account the huge difference in volume of the target, it is intriguing to notice that according to our clinical experience in humans, a similar maximum dose range of 40 to 50 Gy is currently providing the optimal safety-to-efficacy ratio.

The Target Definition

When the target is a lesion that can be precisely depicted with optimal imaging sequences, the question of the selection of the marginal dose is quite easily addressed by correlating safety-efficacy and individual outcome to the marginal dose. This can be refined with stratification according to volume, location, age, etc. However, in patients presenting with MTLE, this process is invalid for 2 reasons. First, there is no consensus regarding the extent of MTL resection required. Second, the concept of MTLE syndrome with a stable extent of the epileptogenic zone and surgical target is increasingly a topic of debate.[14,73]

Volume (in association with marginal dose) is well known to be a major determinant of the tissue effect, as shown in integrated risk/dose volume formulas.[74] In our first series of patients, this marginal isodose volume (or prescription isodose volume) was approximately 7 cm³ (range, 5-8.5 cm³).

An attempt to correlate dose/volume and the effect on seizures and on the MR changes (as evaluated by volume of the contrast enhancement ring, extent of the high T2 signal, and the importance of the mass effect) has been published recently.[61] In this study, we found, not surprisingly, that the higher the dose and volume were, the higher the risk was of having more severe MR changes, but also the higher the chance was of achieving seizure cessation. However, these data have limited value. Hence, more precise identification of those structures of the MTL that need to be "covered" by the radiosurgical treatment may allow more selective, but just as efficacious, dose planning strategies despite smaller prescription isodose volumes.

Growing evidence supports the organization of the epileptogenic zone into networks, meaning that several different and possibly distant structures fire simultaneously at the onset of the electroclinical seizure. This kind of organization explains why the risk of failure is so high when a simple topectomy (without preoperative investigations) in severe drug-resistant epilepsies is associated with a benign lesion.[75] This has also been reported in MTLE.[14,73] Certain nuclei of the amygdaloidal complex, head, body, tail of the hippocampus, perirhinal cortex, entorhinal cortex, and parahippocampal cortex may be associated with the genesis of the seizures. The role of the entorhinal cortex in epilepsy is supported by experimental studies in animals.[59,76] The entorhinal cortex is considered to be the amplifier of the

"amygdalohippocampal epileptic system." The pattern of the associated structures, including that of the structure playing the leader role, can vary significantly from patient to patient.[14,73] A subgroup of patients have clonic discharges and involvement of the entorhinal cortex, amygdala, and head of the hippocampus, with a clear leader role of the entorhinal cortex. Wieser et al[77] analyzed the postoperative MR images of patients operated on by Yasargil (amygdalo-hippocampectomy) and were able to correlate the quality of the resection of each substructure of the MTL area and the outcome with respect to seizures.[77] Only the quality of the removal of the anterior parahippocampal cortex was strongly correlated with a higher chance of seizure cessation. We tried to perform a similar study in patients treated with GK radiosurgery.[61] We defined and manually drew the limits of subregions on the stereotactic images of all these patients. The amygdala, head, body, and tail of the hippocampus were first delineated. The white matter, parahippocampal cortex, and cortex of the anterior wall of the collateral fissure were then drawn separately and divided into 4 sectors in the rostrocaudal axis corresponding to the amygdala, head, body, and tail of the hippocampus.[61]

PATIENT SELECTION

Whang and Kwon[78] (without having performed specific preoperative epileptological workup beforehand) treated patients with epilepsy associated with slowly growing lesions and observed seizure cessation in only 38% (12 of 31) of the patients. This kind of observation emphasizes the importance of preoperative definition of the extent of the epileptic zone and of its relationship with the lesion.[75,79] In our institution, the philosophy is to tailor the investigations for each individual case. In some patients, electroclinical data, structural and functional imaging, and neuropsychological examination are sufficiently concordant for surgery of the temporal lobe to be proposed without depth electrode recordings. In other cases, the level of evidence for MTLE is deemed insufficient, and a stereoelectroencephalographic study is performed. The strategy of stereoelectroencephalographic implantation is based on the primary hypothesis (mesial epileptogenic zone) and alternative hypotheses (early involvement of the temporal pole, lateral cortex, basal cortex, insular cortex, or other cortical areas). The goal of these studies is to record the patient's habitual seizures to establish the temporospatial pattern of involvement of the cortical structures during these seizures. In these patients, the high resolution of depth electrode recording clearly allows fine tailoring of surgical resection, according to the precise temporospatial course of the seizures.

The main limitation of radiosurgery is the size of the target (prescription isodose volume). The radiosurgical treatment of MTLE is certainly the most selective surgical therapy for this group of patients. The requirement for precision and accuracy in the definition of the epileptogenic zone is consequently higher. Furthermore, if depth electrode investigation enables demonstration of a particular subtype of MTLE, this can lead to tailoring of the treatment volume and frequently allows the volume to be reduced.

THE POTENTIAL CONCERNS

The risk of long-term complications must always be scrutinized cautiously in functional neurosurgery. Radiotherapy is most frequently used in the brain for short-term life-threatening pathologies. The use of radiotherapy in young patients with benign disease such as pituitary adenomas or craniopharyngioma has been associated with a significant rate of cognitive decline[80,81] and tumor genesis,[82] including some carcinogenesis.[83] If the risk of radiation-induced tumor were similar with radiosurgery, we should by now have observed numerous cases. However, such reported cases[84-86] are extremely rare and frequently fail to meet the classic criteria by which tumors are deemed to be radiation induced.[16] In fact, if this risk exists, it is likely to be about 1 in 10 000, which is far lower than the mortality risk associated with temporal lobectomy.[68,87-90]

Epilepsy is a life-threatening condition. The risk of sudden unexplained death in epileptic patients is well known.[91,92] This risk is higher in patients treated with > 2 antiepileptic drugs with an IQ < 70 (as independent factors). Because seizure cessation after surgery reduces the mortality risk to that of the general population,[92] microsurgical resection of the epileptogenic zone may confer better benefit in terms of the possibility of immediate seizure cessation and therefore reduced mortality risk compared with the more delayed benefits of radiosurgical treatment. Our patients are systematically informed about this disadvantage of radiosurgery.

WHAT ARE THE CURRENT INDICATIONS?

We still consider the use of radiosurgery for MTLE to be experimental. 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. Potential sparing of memory function is still a matter of debate and needs to be established with comparative studies. There is also a need for further demonstration of long-term efficacy and safety of radiosurgery. Worldwide, microsurgical cortectomies for MTLE have proven to be very satisfactory owing to the rarity of surgical complications and a high rate of seizure freedom. In our experience, the most important selection parameters are the demonstration of the purely mesial location of the epileptogenic zone and the clear understanding by the patient of the advantages, disadvantages, and limitations. One other very good indication in our experience is proven MTLE but previous failure of microsurgery, supposedly resulting from insufficient posterior extent of the resection. The best candidates are young patients with mid-severity epilepsy (working, socially well adjusted), a high level of functioning (able to understand clearly the limits and constraints of radiosurgery), a very high risk of memory deficit with microsurgery (MTLE on the dominant side with little or no atrophy, few deficits of the verbal memory preoperatively), and potentially huge social and professional consequences in case of postoperative memory deficit.[2,18,93]

CONCLUSIONS

The field of epilepsy surgery is a new and promising one for radiosurgery. However, the determination of the extent of the epileptogenic zone requires specific expertise, which is crucial for achieving a reasonable rate of seizure cessation. In addition, the huge impact of fine technical details on the efficacy and possible toxicity of the procedure means that, at present, its use for these indications remains under evaluation, and further prospective study is absolutely required. It is difficult to know whether we really are at the dawning of broader indications for the use of radiosurgery; in the upcoming years, our ability to identify the correct technical strategies should determine whether this is so.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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