Long-term efficacy of gamma knife radiosurgery in mesial temporal lobe epilepsy

ABSTRACT

Background: Gamma knife (GK) radiosurgery has been proposed as an alternative to classic microsurgery in mesial temporal lobe epilepsy (MTLE). Short-term follow-up studies have reported encouraging results, but long-term efficacy is not known.

Objective: To report the efficacy and tolerance of GK radiosurgery in MTLE after a follow-up > 5 years.

Methods: Patients with a follow-up > 5 years presenting with MTLE and treated with a marginal dose of 24 Gy were included in the study.

Results: Fifteen patients were included. Eight were treated on the left side, and 7 were treated on the right. The mean follow-up was 8 years (range 6–10 years). At the last follow-up, 9 of 16 patients (60%) were considered seizure free (Engel Class I) (4/16 in Class IA, 5/16 in Class IB). Seizure cessation occurred with a mean delay of 12 months (± 3) after GK radiosurgery, often preceded by a period of increasing aura or seizure occurrence (6/15 patients). The mean delay of appearance of the first neuroradiologic changes was 12 months (± 4). Nine patients (60%) experienced mild headache and were placed on corticosteroid treatment for a short period. All patients who were initially seizure free experienced a relapse of isolated aura (10/15, 66%) or complex partial seizures (10/15, 66%) during antiepileptic drug tapering. Restoration of treatment resulted in good control of seizures.

Conclusion: Gamma knife radiosurgery is an effective and safe treatment for mesial temporal lobe epilepsy. Results are maintained over time with no additional side effects. Long-term results compare well with those of conventional surgery. Neurology® 2008;70:1658–1663

GLOSSARY

AED = antiepileptic drug; ATL = anterior temporal lobectomy; FS = febrile seizures; GK = gamma knife; MR = magnetic resonance; MTLE = mesial temporal lobe epilepsy; MTLE-HS = mesial temporal lobe epilepsy associated with hippocampal sclerosis; NA = not available; NI = not improved; SF = seizure free; SGTCS = preoperative secondary generalized tonic-clonic seizures; SUDEP = sudden unexpected death in epilepsy; WMS = Wechsler Memory Scale; Ve = verbal category; Vi = visual category.

Mesial temporal lobe epilepsy (MTLE) is a frequent condition, often drug resistant and potentially remediable by surgery. Where this is the case, the mean rate of surgical success after anterior temporal lobectomy is approximately 70% at 1 year after surgery, ranging from 64% to 85%.

However, it is generally accepted that the rate of success decreases with longer follow-up, according to studies that have been interested in the long-term prognosis after anterior temporal lobectomy or amygdalohippocampectomy.

Gamma knife (GK) radiosurgery, targeting the mesial temporal lobe structures, has been proposed as an alternative to open cranial surgery in patients with MTLE associated with hippocampal sclerosis (MTLE-HS) in our group since 1993. The main objec-
The use of this method was to reduce invasiveness and to limit the morbidity of the surgical procedure. Pilot studies from our group using GK surgery for MTLE have shown encouraging results for feasibility, efficacy, and tolerance of the procedure after short- and medium-term follow-up.

A recent prospective European study has confirmed the efficacy of this procedure in improving seizure control as well as a favorable effect on quality-of-life scales. This study also suggested that GK may have a favorable (or at least not deleterious) effect on memory, but this effect is still to be fully demonstrated and remains controversial. A deescalation dose study demonstrated a dramatic reduction of efficacy when doses lower than 24 Gy (marginal) were used.

In the present article, we report the long-term effect of GK both in terms of efficacy and tolerance in patients with MTLE-HS. We report the results obtained in patients treated in our center using modern protocols of currently accepted dose (marginal dose of 24 Gy) and with follow-up ≥ 5 years.

**METHODS**

**Population.** Patients were selected from our current cohort of patients who underwent GK for mesial TLE on the basis of 1) a minimum follow-up of at least 5 years and 2) an optimal GK protocol using a marginal dose of 24 Gy.

We included in the final evaluation only patients for whom a recent clinical assessment (2006) was available. Indeed, patients were systematically and independently seen for clinical evaluation by two of the investigators (F.B. [or C.F. for the two patients from Lyon] and J.R.) during the last 6 months preceding the analysis of the series. Complementary data were also obtained if necessary by follow-up telephone call.

To date, 49 patients with MTLE have benefited from GK in our center (Marseille). No patients underwent operation before the minimal delay for the efficacy estimation of the method (i.e., 2 years). Of the 49 patients, 37 were treated more than 5 years ago. Twenty of these patients were treated using the optimal protocol with a marginal dose at 24 Gy, and 17 were treated with lower doses. Among the 20 patients treated at 24 Gy, 1 patient died 6 months after GK (considered to be a case of sudden unexpected death in epilepsy [SUDEP]). In 2 cases, the GK was considered “palliative,” performed in one case for bitemporal lobe epilepsy and in the other case after the failure of microsurgery, targeting a remnant posterior hippocampus. These patients were not included in the final evaluation. Two patients did not answer our invitation to clinic review or telephone call. These two patients were in Engel Class I at 3 years after GK. These 2 subjects were not included.

Finally, 15 patients were studied in the present article. All had drug-resistant epilepsies and benefited from a comprehensive presurgical evaluation such as that performed for a classic surgical approach including neurologistic examination, neuropsychological testing, video-EEG recordings of seizures, and MRI. For all patients, clinical data, EEG and video-EEG recordings converged to demonstrate features highly suggestive of unilateral mesial temporal lobe seizures. MRI presurgical scan with coronal slices showed moderate to marked focal atrophy of the hippocampus ipsilateral to the epileptogenic temporal lobe. Some had foramen ovale recordings (9 patients) to prove the origin of seizure in the mesial part of the temporal lobe.

All patients gave their informed consent before receiving GK treatment. The study was approved by the Ethics Committee (Comité Consultatif De Protection Des Personnes Dans La Recherche Biomedicale Marseille).

**GK procedure.** The Leksell stereotactic frame was fitted to the patient’s head, with local anesthesia being used. The frame was secured to the head with an angle to the horizontal plane where the front part of the frame was shifted downward, so that the frame-base plane aligned with the estimated ventricular temporal horn of the temporal lobe. After the frame had been fixed to the skull, stereotactic MRI and CT were performed. The MRI machine was calibrated before examination and the images verified by comparison against the CT images for each patient to detect and correct magnetic-distortion errors. The MRI study included a T1-weighted volumetric (three-dimensional) acquisition, a coronal T2-weighted acquisition with a long second echo, and a T2 relaxation mapping through the hippocampal body.

The aim was to cover the same anatomic loci in the mesial temporal lobe of each patient, by using as similar intra-individual doses and dose limits as possible. The target included 1) the anterior part of the parahippocampal region, the entorhinal area adjacent to the collateral sulcus, and the rhinal sulcus; 2) the head of the hippocampus; 3) the anterior part of the hippocampal body; and 4) the amygdalofugal part of the amygdaloid complex.

Two separate exposures with the 18-mm collimator were placed in the mesial temporal region of each patient, one anterior and one posterior. The total volume of the 50% isodose target area was within the range of 5,500 to 9,000 mm. The marginal dose was 24 ± 1 Gy, corresponding to the 50% isodose curve. The radiation dose to the brainstem was reduced to a minimum volume within the 25% isodose curve, as determined by the investigator, and the auditory nerve and chiasm never received a dose of >8 Gy. These safety thresholds were prioritized over the quality of the coverage of the target. Selective plugging of radiation sources was performed to decrease the radiation to the optic tract and to the brainstem. The frame was removed immediately after the second exposure, completing the treatment. The patient went back to the ward for observation. All of the patients were discharged the day after the operation.

**Follow-up after GK.** Patients were regularly seen by investigators every 6 months during the first 3 years of follow-up. Patients were asked to maintain a diary of dates and details of seizures at least during the 3 years after GK. Sei-
The outcome was classified according to a modified version of the Engel classification. For this evaluation, the “final” surgical outcome was assessed during the last 6 months preceding the analysis of data. A minimum of 2 years of stable status was considered for final outcome classification.

Antiepileptic drugs (AEDs) were initially continued, and an attempt to gradually decrease their dosage and number was made in patients with good results after 2 years (Engel Class I).

Brain MRI was performed at 6 months and every year after GK (figure). The amplitude of the magnetic resonance (MR) changes was initially evaluated systematically on each MR control, according to a previously described method by using three different criteria. The first is the volume of the contrast enhancement on three-dimensional T1-weighted images. The two others are scaling of the mass effect (edema score) and the extent of the high-intensity signal (HIS score) on the T2 sequence. Other tests were performed during follow-up evaluation, including visual-field and acuity tests, EEG, and neuropsychological tests (comprising the Wechsler Memory Scale).

RESULTS Long-term GK efficacy. The 15 patients included 9 men and 8 women with a mean age of 35 years (range 22–46 years) at the time of the GK procedure. Eight were treated on the left side, and 7 were treated on the right. The main characteristics of the population are indicated in table 1. The mean follow-up was 8 years (range 6–10 years).

At the last follow-up, 9 of 16 patients (60%) were considered seizure free (Engel Class I; 4/16 in Class IA, 5/16 in Class IB). Three patients were in Class II, 2 were in Class III, and 1 was in Class IV. One patient who was in Class III after GK treatment subsequently underwent standard anterior

In this case, prominent changes are seen at 17 months: inside the target volume is a heterogeneous T1 signal hypointensity and a contrast enhancement ring corresponding to the periphery of the target region. A gradual disappearance of signs over time was observed. Last MRI shows a residual necrotic cavity in the target volume.

Table 1 Main clinical characteristics of patients included in the present study

| Patient no./ | History of | Age at | Epilepsy | Date | Follow-up | Engel | Professional | Driving | Marital | Memory outcome
| sex/age at | FS | GK, y | duration, y | GK/side | y | class | status | status | status | (WMS) |
| seizure | onset, y | | | | | | | | |
| 1/F/27 | Yes | 36 | 9 | No | 1995/L | IB | Unchanged | Unchanged | Unchanged | NA |
| 2/M/16 | Yes | 35 | 19 | No | 1995/L | IB | Better | Unchanged | Stabile |
| 3/F/2 | Yes | 38 | 36 | Rare | 1996/L | 9 | IB | Unchanged | Stabile |
| 4/F/5 | No | 45 | 40 | No | 1996/R | 10 | IB | Better | Stable |
| 5/M/7 | Yes | 36 | 29 | Rare | 1996/R | 10 | IA | Better | Unchanged | Improved (Ve) |
| 6/F/12 | Yes | 34 | 22 | Rare | 1996/R | 10 | IA | Better | Unchanged | NA |
| 7/F/17 | Yes | 46 | 29 | No | 1997/R | 8 | IIIA | Worse | Unchanged | NA |
| 8/F/4 | Yes | 30 | 26 | Rare | 1997/L | 8 | IB | Better | Unchanged | Stabile |
| 9/M/10 | Yes | 43 | 33 | Frequent | 1997/R | 9 | IA | Better | Improved (Ve) |
| 10/F/4 | Yes | 33 | 29 | Rare | 1997/L | 7 | IIIA | Unchanged | Improved (Ve and Vi) |
| 11/M/1 | Yes | 22 | 21 | Rare | 1997/R | 7 | IV | Unchanged | Improved (Ve) |
| 12/F/5 | No | 45 | 40 | Rare | 1998/L | 6 | IIB | Better | Improved (Ve and Vi) |
| 13/M/7 | Yes | 30 | 23 | Rare | 1998/R | 7 | IIB | Better | Stabile |
| 14/F/25 | Yes | 32 | 7 | Rare | 1998/R | 7 | IIA | Worse | NA |
| 15/M/12 | Yes | 32 | 20 | Frequent | 1998/R | 8 | IA | Better | NA |

Neuropsychological evaluation used the Wechsler Memory Scale (WMS), and the conclusion of the neuropsychologist at the last follow-up period is summarized as either stable or improved. No preoperative or postoperative data are available for some patients (NA = not available).

FS = febrile seizures; GK = gamma knife; SGTCS = preoperative secondary generalized tonic-clonic seizures; Ve = verbal category; Vi = visual category.
temporal lobectomy and has been seizure free since the surgery.

Table 2 depicts the results obtained during follow-up after GK treatment. It seems that no patient improved during the first 6 months, and that most of the patients who were seizure free at the end of follow-up were already seizure free during the period of 2 to 3 years. It seems therefore that an excellent initial response has a good prognostic value for final outcome. In contrast, patients who were not initially responding or only partially improved did not subsequently show a favorable outcome.

As previously reported, seizure cessation occurred with a mean delay of 12 months (±3) after GK, often preceded by a period of increasing aura or seizure occurrence (6/15 patients). All patients showed neuroradiologic changes. These have been reported in detail elsewhere. They mainly consisted of the delayed appearance of a marked region of edema and signal changes with the treated temporal lobe. The mean delay of appearance of the first neuroradiologic changes was 12 months (±4). During the onset period of these radiologic changes, nine patients (60%) experienced mild headache and were placed on corticosteroid treatment for a short period.

**Antiepileptic drugs after GK.** All patients at the last follow-up were on medication, although there was a mean reduction in AED use across the group compared with the pre-GK period (2.2 before and 1.4 after GK; \( p = 0.01 \), Wilcoxon rank test).

All patients who were initially seizure free experienced a relapse of isolated aura (10/15, 66%) or complex partial seizures (10/15, 66%) during AED tapering. All patients benefited from reincrease or restoration of treatment, and this led to a good control of seizures in all of these cases. In table 2, the period in which such a seizure or aura reoccurrence was triggered by a decrease of medication in responder patients is indicated.

**Long-term side effects.** Long-term side effects mainly consisted in changes in visual fields, including an hemianopsia in 1 patient (6%) and an asymptomatic quadrantanopsia in 8 of 15 patients (53%).

No patient reported any aggravation of memory problems, but pre- and post-GK neuropsychological testing was not available for all of the patients included (table 1). Consequently, neuropsychological effect will not be extensively studied and discussed in this report. However, it deserves to be mentioned that for patients with pre- and post-GK testing, no worsening of memory scales was observed.

Favorable psychosocial outcome (table 1) regarding driving, working, and marital status was mainly observed in patients with favorable seizure outcome.

One patient had an asymptomatic post-GK cyst in the right temporal lobe detected on the 2-year follow-up MRI, the size of which has remained stable since.

**DISCUSSION** The main result of this study is that successful outcome obtained after GK may be maintained after several years of follow-up. Overall results after a mean follow-up of 8 years show that 60% of patients are in Engel Class I. Approximately half of these have rare residual auras. These preliminary results compare well with long-term results after open skull surgery performed in the overall group of patients with TLE and MTLE-HS. However, definitive conclusion about the efficacy of GK in this indication will require a larger population study and a direct comparison with classic surgery.
There have been few prognostic studies within the subgroup of patients with MTLE-HS.\textsuperscript{20-25} In one study, after a median follow-up of 63 months, the probability of achieving at least a 1-year period of continuous seizure freedom was 67\%.\textsuperscript{21} In another study, the prognosis after anterior temporal lobectomy for MTLE-HS was assessed after 3 to 4 years of follow-up. In this group, 70.6\% were seizure free during the third and fourth postoperative years.\textsuperscript{25} In a third study, with a mean follow-up at approximately 3 years, 61.8\% of patients were seizure free (Class I), 30.5\% in Class II and 7.7\% in Class III.\textsuperscript{22}

Even if the result must be confirmed on a larger series, our current experience indicates that, in patients who become seizure free after the expected delay following GK treatment, no late relapse occurs provided that patients maintain a sufficient AED therapy. Indeed, AED diminution or cessation was always associated with a relapse of seizures or increase in auras in our series.

This is probably one other difference with classic surgery because, in several series, approximately half of the patients no longer have AED after surgery.\textsuperscript{26} After anterior temporal lobectomy, approximately one-third of patients have a relapse, and approximately one-third of these relapses are related to AED reduction or cessation.\textsuperscript{26,27}

As for classic surgery, a proportion of patients are not (or insufficiently) improved after GK. The reasons for these failures are not well understood. In the cases of MTLE-HS, several series have found a relationship between prognosis and some indirect factors: age at seizure onset, epilepsy duration, localized EEG activities, and secondary generalization.\textsuperscript{21,23} However, the real reasons for these failures are probably related to the extension of the epileptogenic zone beyond the limits of the surgery or radiosurgery.

In the particular case of GK, the target is limited to the entorhinal cortex, a part of the amygdala and of the hippocampal head.\textsuperscript{8,9} Even if the entorhinal cortex and the anterior hippocampus are key structures for the genesis of MTLE,\textsuperscript{28} other regions of the temporal lobe may be particularly epileptogenic in patients with MTLE and a potential source of seizure. These regions include the posterior hippocampal/parahippocampal region,\textsuperscript{29} the temporal pole,\textsuperscript{30} or the temporal neocortex.\textsuperscript{31} Epileptogenesis in these sites may explain the failure of a proportion of patients treated with GK.

Regarding side effects, our results indicate that the long-term tolerance is excellent. No additional side effect or unexpected event was observed during the period of follow-up. One patient had an asymptomatic post-GK cyst in the medial temporal lobe. Such delayed cyst formation has been reported in series of arteriovenous malformation;\textsuperscript{32} these are usually asymptomatic, but in some patients clinical symptoms have justified ablation or drainage.\textsuperscript{32,33}

One patient in our series died of SUDEP during the first year after GK, a “silent” period in which no therapeutic effect is detectable. The risk of SUDEP is increased in young patients with drug-resistant epilepsy.\textsuperscript{14,35} Occurrence of SUDEP in patients treated with GK has been previously reported in a short series from the Cleveland Clinic,\textsuperscript{36} and is related to the delayed efficacy of GK. This certainly constitutes a disadvantage of GK in this population.

The patients who are potentially candidates for this treatment must be informed about the advantages and disadvantages of the methods. The main advantage is the very low morbidity of the method, being less aggressive than surgery. The main disadvantage is the delay of seizure remission, often preceded by a period of increasing seizure frequency. Patients must be also warned that a long-lasting AED treatment must be maintained (generally at a lower dose) after the procedure.

\section*{Acknowledgment}
The authors thank Dr. Aileen McGonigal for review of the English version of this article and for helpful comments.

\textit{Received March 13, 2007. Accepted in final form August 21, 2007.}

\section*{References}