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Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study

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OBJECTIVE Gamma Knife surgery (GKS) is one of the surgical alternatives for the treatment of drug-resistant trigeminal neuralgia (TN). This study aims to evaluate the safety and efficacy of GKS in a large population of patients with TN with very long-term clinical follow-up.

METHODS Between July 1992 and November 2010, 737 patients presenting with TN were treated using GKS. Data were collected prospectively and were further retrospectively evaluated at Timone University Hospital. The frequency and severity of pain, as well as trigeminal nerve function, were evaluated before GKS and regularly thereafter. Radiosurgery using the Gamma Knife (model B, C, 4C, or Perfexion) was performed with the help of both MR and CT targeting. A single 4-mm isocenter was positioned in the cisternal portion of the trigeminal nerve at a median distance of 7.6 mm (range 4–14 mm) anterior to the emergence of the nerve (retrogasserian target). A median maximum dose of 85 Gy (range 70–90 Gy) was prescribed.

RESULTS The safety and efficacy are reported for 497 patients with medically refractory classical TN who were never previously treated by GKS and had a follow-up of at least 1 year. The median age in this series was 68.3 years (range 28.1–93.2 years). The median follow-up period was 43.8 months (range 12–174.4 months). Overall, 456 patients (91.75%) were initially pain free in a median time of 10 days (range 1–180 days). Their actuarial probabilities of remaining pain free without medication at 3, 5, 7, and 10 years were 71.8%, 64.9%, 59.7%, and 45.3%, respectively. One hundred fifty-seven patients (34.4%) who were initially pain free experienced at least 1 recurrence, with a median delay of onset of 24 months (range 0.6–150.1 months). However, the actuarial rate of maintaining pain relief without further surgery was 67.8% at 10 years. The hypesthesia actuarial rate at 5 years was 20.4% and at 7 years reached 21.1%, but remained stable until 14 years with a median delay of onset of 12 months (range 1–65 months). Very bothersome facial hypesthesia was reported in only 3 patients (0.6%).

CONCLUSIONS Retrogasserian GKS proved to be safe and effective in the long term and in a very large number of patients. Even if the probability of long-lasting effects may be modest compared with microvascular decompression, the rarity of complications prompts discussion of using GKS as the pragmatic surgical first- or second-intention alternative for classical TN. However, a randomized trial, or at least a case-matched control study, would be required to compare with microvascular decompression.

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KEY WORDS trigeminal neuralgia; Gamma Knife radiosurgery; safety; efficacy; stereotactic radiosurgery; pain

ABBREVIATIONS BNI = Barrow Neurological Institute; CTN = classical trigeminal neuralgia; GKS = Gamma Knife surgery; MVD = microvascular decompression; TN = trigeminal neuralgia.

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Trigeminal neuralgia (TN), also known as "tic douloureux," is a serious health problem with a prevalence of 12.6 per 100,000 people.[44] Patients typically describe a severe and sudden pain in the face like an electric shock. While the etiology remains unclear, there is growing evidence supporting the fact that in most patients one of the main causal factors resides in the compression of the trigeminal nerve root, close to its entry into the pons by an aberrant arterial or venous loop.[19]

According to the most recent classification of the International Headache Society,[10] classical trigeminal neuralgia (CTN) must be distinguished from symptomatic TN. CTN includes all cases without an established etiology, i.e., the idiopathic cases, as well as cases with potential vascular compression of cranial nerve V.[10] Drug therapy is the first line of treatment and offers adequate pain relief in many patients.[41] Carbamazepine (highest level of evidence) and oxcarbazepine (best tolerance) are the most commonly prescribed drugs for the treatment of TN.[5] A minority of patients have hypersensitivity reactions, with some forms being associated with substantial morbidity and mortality. In Northern Europeans, the *HLA-A*3101* allele is associated with carbamazepine-induced hypersensitivity reactions.[20] Patients who do not respond to medical therapy or have intolerable adverse effects are suitable candidates for surgery.[41] Surgical treatments include microvascular decompression (MVD), percutaneous ablative procedures that produce a partial lesion of the nerve (thermocoagulation, microcompression, and glycerol injection), and radiosurgery.[21] MVD tackles the presumed cause by separating the offensive vessel loop from the trigeminal nerve and is currently considered as the gold-standard surgical treatment for drug-resistant TN.[1]

Radiosurgery is a minimally invasive neurosurgical approach. The concept of radiosurgery was first introduced by Lars Leksell in 1951 when he treated a patient suffering from essential TN using a prototype guiding device linked to a dental x-ray machine.[16] Later, Leksell conceived the Gamma Knife, a tool dedicated to radiosurgery that uses multiple focusing beams from cobalt-60 sources.[15] Several retrospective studies[6,13] and a few prospective studies[32] have reported good short-term and midterm safety and efficacy of Gamma Knife surgery (GKS) for TN. GKS is known to be the least invasive neurosurgical approach for medically refractory TN.[5,9] However, the long-term outcomes have not been well documented.[6,13,43]

Methods

Type of Study

The study was designed as an open, self-controlled, noncomparative study.[30] A case report form was created and was completed prospectively when the first patient was treated at Timone University Hospital. Clinical examinations and MRI were performed (the later to exclude secondary cases). Data were retrospectively analyzed. Permission from the ethics committee was obtained for this historical cohort study.

Patients

From July 1992 through November 2010, 737 patients presenting with intractable TN were prospectively selected and treated with radiosurgery at Timone University Hospital in Marseille, France. A total of 497 patients had more than 1 year of follow-up. We excluded from our final analysis patients with TN secondary to multiple sclerosis,[37] megadolichobasilar artery compression,[39] or a second GKS treatment,[40] which are reputed to have more variable responses to radiosurgery and were beyond the scope of this study.

Basic Demographic Data

The median patient age was 68.3 years (range 28.1–93.2 years); 225 patients (45.3%) were men and 272 (54.7%) were women. Pain was on the right side in 267 patients (53.7%) and on the left side in 230 patients (46.3%). Only 19 patients (3.8%) had bilateral pain, but never simultaneously. Pain was predominantly distributed in the V2 territory of the trigeminal nerve (29.4%), followed by V2 and V3 (24.5%), V3 (19.5%), V1 and V2 (13.9%), V1, V2, and V3 (6.8%), V1 (5.4%), and V1 and V3 (0.02%) territories (Table 1). All patients presented with typical pain according to further described criteria (i.e., TN1; please see *Diagnostic Criteria Using the International Headache Society Definitions*). The median time between pain onset and radiosurgery treatment was 68.3 months (range 6–531 months). Preoperative MRI revealed the presence of a vascular compression in 278 cases (55.9%). Twenty-six patients (5.2%) died but were not excluded from the study because they had at least 1 year of follow-up, as did the other patients enrolled in the study.

Details of Previous Treatments

One hundred seventy-three (34.8%) patients had prior surgical procedures, of which 102 (20.5%) patients had only 1 previous intervention, 41 (8.2%) patients had 2 previous surgeries, and 30 (6%) had 3 or more previous surgeries.

Previous surgeries consisted of radiofrequency ablation in 99 (19.9%) patients, balloon microcompression in 64 (12.9%) patients, MVD in 45 (9.1%) patients, and glycerol rhizotomy in 6 (1.2%) patients.

Before GKS, 107 (21.5%) patients had sensory disturbance in relation to a previous surgical procedure, which consisted of slight hypesthesia in 99 (19.9%) and severe hypesthesia in 8 (1.6%) patients. GKS was the first surgical procedure in 324 patients (65.2%). All patients had drug-resistant TN or major intolerance to all therapies. Two hundred sixty-three patients (52.9%) reported substantial side effects to drug therapy at the time of radiosurgery.

Diagnostic Criteria Using the International Headache Society Definition

All patients fulfilled the criteria of the International Headache Society.[10] Evaluation of the type of TN was made according to the classifications proposed by Eller et al.[7] and comprised idiopathic TN1 and TN2. TN1 is described as typically sharp, shooting, electrical shock like, with pain-free intervals between attacks that is present for more than 50% of the time; TN2 is described as an ach-

TABLE 1. Clinical preoperative and demographic data

Variable	Value*
Sex	
Male	225 (45.3)
Female	272 (54.7)
Median age (yrs) (range)	68.3 (28.1–93.2)
Median duration of follow-up (mos) (range)	43.8 (12–174.4)
Side of pain	
Right	267 (53.7)
Left	230 (46.3)
Pain distribution	
V2	146 (29.4)
V2 & V3	122 (24.5)
V3	97 (19.5)
V1 & V2	69 (13.9)
V1 & V2 & V3	34 (6.8)
V1	27 (5.4)
V1 & V3	1 (0.02)
Preop MRI vascular conflict (other than megadolichobasilar compression)	278 (55.9)
No prior surgery	324 (65.2)
Prior surgery	173 (34.8)
1	102 (20.5)
2	41 (8.2)
≥3	30 (6)
Type of prior surgery	
Radiofrequency lesion	99 (19.9)
Balloon microcompression	64 (12.9)
Microvascular decompression	45 (9.1)
Glycerol rhizotomy	6 (1.2)
Side effects from prior surgery	107 (21.5)
Facial sensitivity before GKS	
Normal	393 (79.1)
Slight hypesthesia	96 (19.3)
Severe hypesthesia	8 (1.6)
Anesthesia	1 (0.02)

* Values indicate the number of patients (%) unless otherwise indicated.

ing, throbbing, or burning pain that is present for more than 50% of the time and is constant in nature (constant background pain being the most significant attribute). Only patients fulfilling the criteria for the TN1 type were included. The preoperative MRI protocol included 3D T1-weighted images, with and without contrast, and T2 CISS (constructive interference in steady state) without contrast.

Brief Description of the Operative Technique

All patients underwent GKS. After application of the Leksell model G stereotactic frame (Elekta Instruments AB) under local anesthesia, all patients underwent stereotactic MRI and CT for target definition. The MRI sequences used to identify the trigeminal nerve were T2-type semi-millimetric CISS (Siemens) without contrast and contrast-enhanced T1-weighted images. Bone CT routinely supplements the neuroradiological investigation to correct any distortion errors on the MRI images.[32,38]

Between July 1992 and November 2010, models B, C, 4C, or Prefexion of the Gamma Knife were successively used (Elekta Instruments AB).

A single 4-mm isocenter was used in all patients and positioned in the anterior cisternal portion of the trigeminal nerve at a median distance of 7.6 mm (range 4–14 mm) anterior to the emergence of the nerve (retrogasserian target). This target has been classically used in our center since the beginning of GKS treatments for TN, as detailed in previous studies.[29,30,32,33]

The median value of the maximum dose delivered was 85 Gy (70–90 Gy). Furthermore, we initially give a dose of 90 Gy at the 100% isodose. Beam channel blocking is used depending on the maximal dose received by 10 mm^3 of the brainstem. If this dose is more than 15 Gy, we diminish the dose, and then if still necessary we start beam channel blocking to make it possible for us to avoid the so-called "Flickinger effect" (increasing the mean dose to the nerve also increases toxicity).[8] All interventions were performed by the senior neurosurgeon (J.R.).

Follow-Up Monitoring

Initial follow-up was based on clinical evaluations performed at regular intervals of 3 months, 6 months, and 1 year after the treatment and on a yearly basis thereafter. All patients were seen in person for the proper evaluation of safety and efficacy, including facial sensory testing, corneal reflex, and jaw motility. For long-term follow-up updates, telephone interviews were considered acceptable for patients unable to visit us either because of distance or general health-related conditions.

The patients and referring doctor were instructed to continue the medication unchanged for at least 1 month, and then were instructed to diminish the drug doses progressively in cases of pain freedom. Every clinical evaluation made by our medical team during the follow-up course was prospectively noted in the database so that we had continuous and prospective up-to-date information. The 15 types of essential data, as considered by Zakrzewska and Thomas[48] for articles reporting the outcomes of the surgical treatment for TN, were followed and are presented hereafter. At our center, systematic MR follow-up has never been part of our protocol.

Explicit Definitions of Outcome Measures

Outcome measures included initial pain freedom, onset of the sensory disturbance, recurrence, and recurrence without further surgery. Efficacy is reported according to the Barrow Neurological Institute (BNI) scale (Class I, no trigeminal pain and no medication; Class II, occasional pain not requiring medication; Class IIIa, no pain but continued medication; Class IIIb, controlled with medication; Class IV, some pain but not adequately controlled with medication; Class V, severe pain and no pain relief). A successfully treated patient was pain free without medication (BNI Class I).

The degree of hypesthesia is reported using the BNI fa-

cial hypesthesia scale (Class I, no facial numbness; Class II, mild facial numbness and not bothersome; Class III, facial numbness and somewhat bothersome; Class IV, facial numbness and very bothersome).[34] The corneal reflex was assessed in all patients. Additionally, the appearance of dysesthesias, allodynias, paresthesias, anesthesia dolorosa, masseteric weakness, neurological complications outside of the trigeminal nerve territory, systemic complications, and death were carefully noted.

Recurrence was defined as change from Class I to a lower outcome class. Thus, the situation of a patient who had been pain free without medication (Class I) and who then restarted taking specific drugs but who remained pain free on medication (Class II) was considered as a recurrence.

The latency intervals to becoming pain free or developing recurrence or a sensory disturbance, the dates of medication changes, and the dates of further surgical procedures were also carefully monitored.

Definition of Minor and Major Recurrence

A minor recurrence was defined as one that was well tolerated by the patient (lower pain frequency and intensity) that did not require a new surgical therapy. A major recurrence was defined as requiring a further surgical procedure. We use the term "initial efficacy" when a patient is pain free with or without medication in the first 6 months after the radiosurgery and has no recurrence in the year that follows the procedure.

The probability of maintaining pain relief with further surgery will be separately reported in our clinical study.

Patient Satisfaction

Patient satisfaction was evaluated at the last follow-up through a simple questionnaire. The items proposed as an answer in our semistructured questionnaire included: "No regret, I would have radiosurgery again with no hesitation;" "No opinion;" and "I regret performing radiosurgery (and would not do it again)."

Statistical Analysis

All statistical analyses were performed using R software (version 2.12.0, R Foundation for Statistical Computing). The survival R package was used for the survival analysis. For the evaluation of outcomes such as pain free, hypesthesia, and recurrence, the time-to-event was estimated using the Kaplan-Meier method. Bivariate analysis was then performed to identify the predictive factors among the collected variables. For qualitative variables, Kaplan-Meier curves were used to graphically represent survival among the different groups and compared using the univariate log-rank test. For all variables, the effects were estimated and tested by fitting univariate Cox proportional hazards regression models. The proportionality of the hazards was assessed graphically by log cumulative hazard plots. For qualitative variables, the chi-square test was performed when valid; otherwise the exact Fischer test was used. For quantitative variables, the Mann-Whitney test was performed given the number of patients. All tests were 2-sided, and p values < 0.05 were judged to be significant.

Results

Details of Follow-Up Period

The median follow-up period was 43.8 months (range 12–174.4 months).

Initial Rate of Pain Freedom Response

Four hundred fifty-six patients (91.75%) were initially pain free in a median time of 10 days (range 1–180 days). The initially pain-free actuarial rates at 0.5, 1, 2, 3, 4, 5, and 6 months were 53.52%, 73%, 83.5%, 88.1%, 88.9%, 89.5%, and 91.75%, respectively (Fig. 1; with the flat part of the curve being practically reached at 6 months).

The following characteristics showed a negative and statistically significant difference: previous surgical intervention ($p = 0.005$, HR 0.24, and 95% CI 0.09–0.65), only 1 previous surgical intervention ($p = 0.009$, HR 0.16, and 95% CI 0.04–0.64), and a previous history of MVD ($p = 0.01$, HR 0.64).

Differences in age ($p = 0.172$), time elapsed until treatment onset ($p = 0.731$), and the sides of pain ($p = 0.4$) were not statistically significant.

Postoperative Sensory Assessment: Details of Other Postoperative Complications

No patient experienced an early complication after GKS. Seventy-two patients (21.1% actuarial rate) later developed sensory dysfunction such as paresthesias or objective facial sensory loss, which occurred especially during the first 5 years after GKS. The time of onset of hypesthesia occurred at a median of 12 months (range 1–65). Patients had either mild hypesthesia in 49 (8.3%) cases or severe in 23 (4.6%) cases. We also assessed hypesthesia using the BNI facial hypesthesia scale: mild facial numbness in 61 (12.3%) patients; facial numbness that

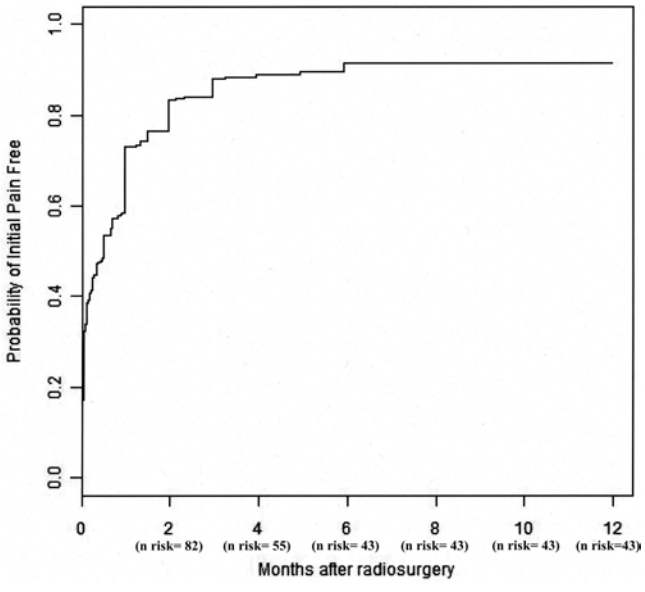

FIG. 1. Probability of an initial pain-free onset depending on the time since GKS. The probability of being initially pain free reaches a plateau at 6 months (with a rate of freedom from pain of 91.75%). The initial pain-free actuarial rates at 0.5, 1, 2, 3, 4, 5, and 6 months were 53.52%, 73%, 83.5%, 88.1%, 88.9%, 89.5%, and 91.75%, respectively.

was somewhat bothersome in 8 (1.6%) patients; and facial numbness that was very bothersome in 3 (0.6%) patients.

The 3 patients with very bothersome hypesthesia said that their quality of life was worse and that this dysfunction was not a good tradeoff, whereas the majority of the patients who developed numbness after GKS (69 of 72 patients; 95.8%) considered that their quality of life improved after GKS and that the sensory dysfunction was a good tradeoff for pain relief.

The hypesthesia actuarial rates at 0.5, 1, 2, 3, 5, and 7 years were 6.4%, 10.2%, 16.8%, 18.3%, 20.4%, and 21.1%, respectively, and remained stable for 14 years (Fig. 2). No patients developed a trigeminal motor deficit after GKS or other cranial nerve deficits. There were 0 cases of anesthesia dolorosa or dry-eye syndrome.

Management and Results of Recurrent Pain

One hundred fifty-seven (34.4%) of the patients who were initially pain free (456 patients) experienced at least 1 recurrence after GKS. The median time to recurrent pain was 24 months (range 0.6–150.1 months). Because of recurrent medically refractory pain, 112 (22.5%) patients required further surgeries. Eighty-five (17.1%) patients required only 1 further surgery, 21 (4.2%) required 2 further surgeries, and 6 (1.6%) required 3 or more surgeries.

In our unit, the most common intervention after failed GKS was balloon microcompression, which was performed in 61 (12.3%) patients, followed by thermocoagulation in 29 (5.8%) patients, MVD in 21 (4.2%) patients, and glycerol rhizotomy in 1 (0.02%) patient (Table 2).

Usually, in our clinic, if a first-intention MVD treatment was proposed but declined by the patient in the absence of efficacious GKS, it is usually proposed again and frequently accepted by the patient.

The actuarial probabilities of maintaining pain relief without medication at 0.5, 1, 2, 3, 5, 7, 10, 12, and 14 years were 93.4%, 85.9%, 78.6%, 71.8%, 64.9%, 59.7%, 45.3%, 40.7%, and 33.9%, respectively (see Fig. 3). Having three or more previous surgeries was a factor associated with decreased long-term efficacy ($p = 0.0163$; HR 1.98; 95% CI 1.13–3.47) in comparison with patients having undergone fewer than 2 prior surgeries. Post-GKS hypesthesia onset was associated with a higher probability of maintaining pain relief ($p = 0.0003$; HR 0.27; 95% CI 0.13–0.56).

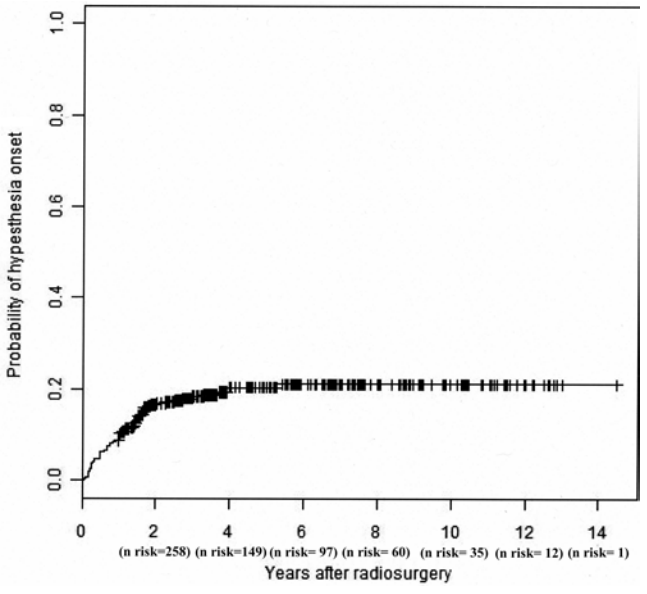

FIG. 2. Actuarial probability of having new-onset hypesthesia depending on the time since GKS. The hypesthesia actuarial rates at 0.5, 1, 2, 3, 5, and 7 years were 6.4%, 10.2%, 16.8%, 18.3%, 20.4%, and 21.1%, respectively, and remained stable for 14 years.

TABLE 2. Postoperative assessment

Variable	Value*
Initially pain free	456 (91.75)
Post-GKS sensory dysfunction	72 (14.5)
Mild	49 (9.8)
Severe	23 (4.6)
BNI facial hypesthesia scale	
No facial numbness	425 (85.5)
Mild facial numbness	61 (12.3)
Facial numbness, somewhat bothersome	8 (1.6)
Facial numbness, very bothersome	3 (0.6)
Recurrence of pain	157 (34.4)
Median time to pain recurrence in mos (range)	24 (0.6–150.1)
Additional treatment after GKS	112 (22.5)
No. of treatments	
1	85 (17.1)
2	21 (4.2)
≥3	6 (1.2)
Type of treatment	
Balloon microcompression	61 (12.3)
Radiofrequency lesion	29 (5.8)
Microvascular decompression	21 (4.2)
Glycerol rhizotomy	1 (0.02)

* Values indicate the number of patients (%) unless otherwise indicated.

Probability of Maintaining Pain Relief Without Further Surgery

The actuarial probabilities of maintaining pain relief without further surgery at 0.5, 1, 2, 3, 5, 7, and 10 years were 96.1%, 92.1%, 88.1%, 84.2%, 79.7%, 75.4%, and 67.8%, respectively, and remained stable through 14 years (Fig. 4). We found statistically significant data for 3 or more previous surgeries ($p = 0.007$; HR 2.64; 95% CI 1.3–5.37) and the presence of post-GKS hypesthesia ($p = 0.006$; HR 0.06; 95% CI 0.01–0.46).

Postoperative Patient Satisfaction

The vast majority of patients (93.8%) expressed a high level of satisfaction, did not regret undergoing GKS, and would undergo the procedure again. A minority of the patients had no opinion (4.6%), and 2.3% would not undergo the procedure again.

Discussion

There are several neurosurgical therapeutic options for

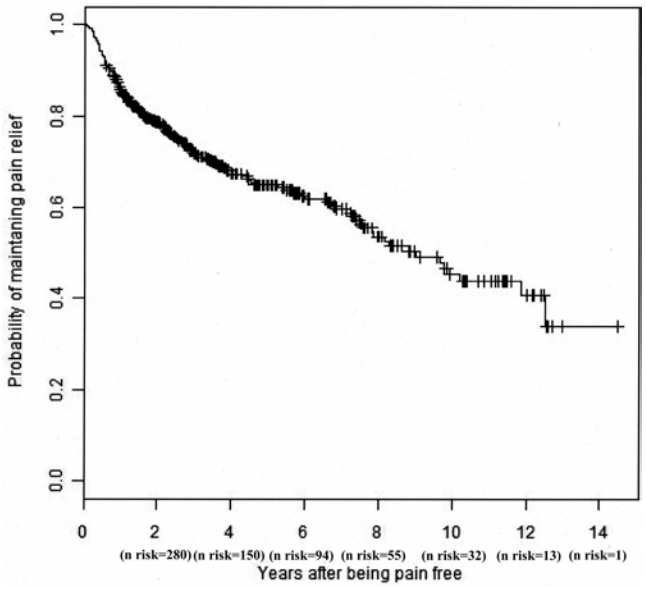

FIG. 3. Actuarial probability of maintaining pain relief without medication. The actuarial probabilities of maintaining pain relief at 0.5, 1, 2, 3, 5, 7, 10, 12, and 14 years were 93.4%, 85.9%, 78.6%, 71.8%, 64.9%, 59.7%, 45.3%, 40.7%, and 33.9%, respectively.

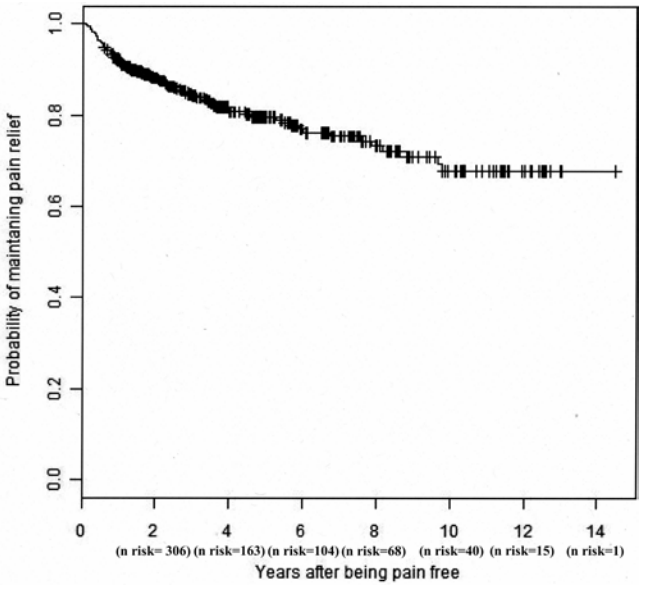

FIG. 4. Actuarial probability of maintaining pain relief without new surgery depending on the time since pain cessation. The actuarial probabilities of maintaining pain relief without further surgery at 0.5, 1, 2, 3, 5, 7, and 10 years were 96.1%, 92.1%, 88.1%, 84.2%, 79.7%, 75.4%, and 67.8%, respectively, and remained stable for 14 years.

drug-resistant CTN. Radiosurgery was first used for TN treatment in the 1960s by Lars Leksell.[16] Its safety and efficacy started to be evaluated in the early 1990s, including by our team.[28,31] A cornerstone paper was the multicentric study of Kondziolka et al., which appeared in 1996[12] and generated a profound paradigm shift in radiosurgical practice.[33] The reappraisal of radiosurgery for TN in the 1990s was made possible by the development of high-resolution MRI, which enabled the proper visualization of the cisternal portion of cranial nerve V.[30,33] Radiosurgery is currently regarded as the least invasive neurosurgical approach for TN.[5,9,44] A trigeminal nerve deficit usually appears within the first 2 years after radiosurgery, but has also been reported as late as 5 years after treatment.[13] The only side effect reported in our long-term study is trigeminal nerve sensory disturbance. Only 21.5% of the patients reported this side effect, and the vast majority did not consider it as bothersome or disabling. The mechanisms of action of radiosurgery for TN are not known. Several authors have reported a higher rate of pain relief in patients experiencing hypesthesia.[25] However, contrary to the percutaneous techniques, it is noteworthy to point out that the majority of the patients experiencing long-term pain freedom in our study did not report hypesthesia. Consequently, we do not consider hypesthesia necessary for the efficacy of radiosurgery. In the meta-analysis by Gronseth et al.,[9] the rate of hypesthesia reported after radiosurgery is similar to the rate of hypesthesia after MVD and much lower than the rate of hypesthesia reported after percutaneous ablative procedures. This observation suggests that radiosurgery may involve a mechanism of action that is more subtle than a purely destructive one.

The technical nuances of GKS have a major impact on the clinical outcome of radiosurgery for TN.[33] Pain control increases according to the dose prescription, but a larger volume of nerve treated has been reported to dramatically increase the toxicity (i.e., the risk of bothersome hypesthesia) without increasing the rate of pain relief.[8] Also, a target placed close to the brainstem at the level of the root entry zone[26] seems to be associated with a higher risk of numbness and higher risk of bothersome hypesthesia. This fact is confirmed by the recent paper by Sheehan et al.[42] who found more numbness in a group of patients where the target used was the so-called dorsal root entry zone in comparison with the more anterior cisternal target that the authors used later on in their series. The major impact of these technical nuances may explain the large variability in the safety and efficacy reported in the literature. Of note, the remarkable high response rate in our series (initial pain freedom rate of 91.3% at 6 months) and low hypesthesia rate on a long-term basis are likely due to the use of a high maximum prescription dose (median 85 Gy) and use of the "anterior retrogasserian target."

There are only 3 studies reporting long-term outcome after GKS.[6,13,43] Dhople et al.[6] described the outcomes for 102 patients, with a median follow-up of 5.6 years (range 13–115 months). The target was the dorsal root entry zone with a median maximal dose of 75 Gy (range 70–80 Gy). Regarding the classical outcomes, the initial pain freedom rate was 81%, bothersome hypesthesia rate was 6% (the global rate not reported), and the probabilities of maintaining pain relief at 3, 5, and 7 years were 41%, 34%, and 22%, respectively.

Kondziolka et al.[13] reported the outcomes for 503 patients, of whom 107 had more than 5 years of follow-up. The target was placed at "3–8 mm anterior from the junction of the trigeminal nerve and pons." The maximal dose delivered was 80 Gy. Regarding the classical outcomes: the initial pain freedom rate was 89%; sensory dysfunction

appeared in 10.5% of patients with 1 case of deafferentation pain (in a patient who already had decreased facial sensation after previous MVD); and the probabilities of maintaining pain relief at 3, 5, and 10 years were 71%, 46%, and 30%, respectively.

Young et al.[43] reported outcomes for 315 patients with a mean duration of follow-up of 68.9 ± 41.8 months. The target was placed "on the trigeminal nerve, with the 20% isodose line tangential to the pontine surface." All patients were treated with a maximal dose of 90 Gy. Regarding the classical outcomes, initial pain-freedom rate was found in 85.6% of cases, and hypesthesia was found in 32.9% (and very bothersome in 4.5%) of cases. Furthermore, dry-eye syndrome was encountered in 22.4% and jaw weakness in 11.2% of patients.

The gold-standard neurosurgical procedure is MVD. Although no prospective randomized trial exists, MVD seems to be the approach that provides the highest chance of maintaining long-term pain relief.[17,27] MVD is not expected to damage the nerve, but presumably acts by alleviating the pathophysiological cause of TN, namely, compression of the trigeminal nerve by a vascular loop. MVD carries a small but definite risk of major, including fatal, complications. In 1996, Barker et al.[1] reported the retrospective evaluation of a large cohort of 1155 patients treated with MVD and followed up for at least 1 year (median follow-up 6.2 years). Thirty percent of the patients experienced recurrence of pain. Due to severe recurrence, 11% of patients underwent a second operation. The major complications reported by the authors included 2 postoperative deaths (0.2%), 1 brainstem infarction (0.1%), 4 intracerebral hematomas, 4 cerebellar edemas, 2 cases of hydrocephalus, 12 cases of facial palsy (2 permanent), 15 cases of extraocular muscle palsy (2 permanent), 16 cases of ipsilateral hearing loss, 22 cases of severe facial numbness, 20 cases of CSF leakage, 4 cases of pseudomeningocele, 5 cases of bacterial meningitis, 225 cases of chemical meningitis, 2 cases of pneumonia, and 1 case each of septicemia, myocardial infarction, transverse sinus thrombosis, pulmonary embolus, and permanent contralateral hearing loss.[1] Few other reports[2,24,47,48] used independent outcome assessments after MVD.[5] These case series confirm the results of Barker et al., with a 75% chance of maintaining pain relief at 3 years and a risk of operative mortality of 0.2% (rising to 0.5% in other reports).[1] Major problems such as CSF leakage, infarcts, or hematomas are reported in 4% of the patients, and aseptic meningitis in 11%; diplopia due to injury to cranial nerves IV and VI (most frequently transient) and facial palsy are rare.[2,47] Ipsilateral hearing loss is a major long-term complication that has been reported in as many as 10% of patients.[2,47] Sensory loss is observed in 7% of patients.

Percutaneous techniques (thermocoagulation, balloon microcompression, and glycerol injection) share an ablative mechanism of action. All of these procedures require brief general anesthesia, the penetration of a probe through the foramen ovale under fluoroscopic control or navigation, and a physical action (thermal, mechanical, or chemical) on the fibers of cranial nerve V at the level of the gasserian ganglion. Generating a certain level of hypesthesia is classically necessary for the complete and prolonged efficacy of these techniques. Thus, all these percutaneous techniques are associated with a high rate of more or less disabling trigeminal nerve dysfunction. In the main series of the literature (see Lopez et al.[18]), the 3-year actuarial rate of complete pain relief has been reported as 58% to 64% for radiofrequency thermocoagulation,[18,45] 53% to 54% for glycerol rhizolysis,[23,36] and 69% for balloon microcompression.[3] Masticatory weakness has been reported in 12% of patients after thermocoagulation[14,18,45] and in 3% after glycerol rhizolysis.[23,35,36] Troublesome dysesthesia has been reported in 4% of patients after thermocoagulation,[11,14,45] in 8.5% after glycerol rhizolysis,[4,23] and in 10% after balloon microcompression.[22] Anesthesia dolorosa has been reported in 1.5% of patients after thermocoagulation,[11,14,45] 2.5% after glycerol rhizolysis[23,35,36] and has not been reported after balloon microcompression.[22] Keratitis is observed was 1.5% of patients after thermocoagulation[11,14,45] and 2% after glycerol rhizolysis[23,35,36] but was not reported after balloon microcompression.[22] It is important to note that with all these neurosurgical procedures, postoperative morbidity is lower in high-volume units.

Very few Level I evidence papers concerning the evaluation of the different surgical techniques for the treatment of TN are available.[44] The quality of reporting evaluations of surgical treatments for TN rarely follow the recommendations published in 2003 by Zakrzewska and Lopez.[46]

Conclusions

The present study is unique due to the fact that the data were collected in a prospective fashion, the cohort is very large, and a long-term follow-up was conducted; however, this study is still limited by the absence of randomization. This series represents, to date, the study with the largest case series available and has the advantage of a very long-term follow-up. Additionally, this study brings to light the fact that the percentage of bothersome hypesthesia is low (0.3%) using a range of doses between 70 and 90 Gy with the retrogasserian target. This study provides reasonable long-term evidence of the very high safety and efficacy of GKS in CTN. Radiosurgery is a rational first-line neurosurgical option for TN. The spectrum of complications clearly differs between different neurosurgical options and must be taken into account during the decision-making process. The rarity of the complications and the important probability of long-lasting effects prompt us to regard GKS as a pragmatic surgical first- and/or second-intention alternative for CTN. However, MVD remains as the reference technique, and further prospective randomized studies are still needed to compare the long-term efficacy of radiosurgery with MVD. We expect these studies to clarify the potential role of each approach. Neurosurgical techniques offer the highest chance of improving quality of life in patients with medically refractory TN. However, surgery is not indicated for all these patients; they should be informed about the full range of choices, and they must integrate the benefits and risks of each alternative in the decision-making process. The centers able to provide patients with all these techniques are better placed to contribute to these clarifications.

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Conception and design: Régis, Tuleasca, Levivier. Acquisition of data: Régis, Tuleasca, Donnet. Analysis and interpretation of data: Régis, Tuleasca, Levivier. Drafting the article: Régis, Tuleasca, Levivier. Critically revising the article: Régis, Tuleasca, Resseguier, Carron, Donnet, Levivier. Reviewed submitted version of manuscript: Régis, Tuleasca, Resseguier, Carron, Donnet, Levivier. Approved the final version of the manuscript on behalf of all authors: Régis. Statistical analysis: Resseguier, Gaudart. Administrative/technical/material support: Régis, Donnet, Gaudart, Levivier. Study supervision: Régis, Gaudart, Levivier.

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