T rigeminal neuralgia is a well-known pain syndrome characterized by short and intense attacks of pain in the somatosensory distribution of the trigeminal nerve. Most patients have idiopathic TN. Secondary TN accounts for a minority of cases, and can be caused by compression of the nerve by a space-occupying lesion or by demyelization of the REZ, which is usually due to MS. Management of TN is initially pharmacological and involves a regimen of anticonvulsant or antidepressant drugs. If the medical treatment is unsuccessful or produces too many side effects, invasive treatment can be performed. The most widely used surgical treatments are MVD and percutaneous rhizotomy using RF-induced heat, glycerol, or balloon microcompression. These techniques have been used for many years, and literature reviews on their efficacy and side effects are available. More recently, GKS has been used for the treatment of TN. Numerous reports have demonstrated the initial effectiveness of radiosurgical procedures in the treatment of TN.

Clinical article

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Object. The success rates and side effects of Gamma Knife surgery (GKS) in patients with trigeminal neuralgia (TN) are not fully clear. A comparison of data across previous reports is hampered by differences in treatment protocols, lengths of follow-up, and outcome criteria. The purpose of this paper is to contribute to knowledge of the efficacy of GKS in TN by reviewing data in a large group of patients with this disorder, who were treated with a uniform treatment protocol and evaluated using a well-established pain scale and Kaplan-Meier analysis.

Methods. The authors reviewed 450 treatments in 365 patients with medically refractory TN who were treated between June 2002 and October 2009 at the Gamma Knife Center Tilburg. In all patients 80 Gy was prescribed, with a single 4-mm isocenter located at the root entry zone (REZ). In 79 patients repeated GKS was performed using a uniform dose of 80 Gy, which was delivered in a highly standardized manner, to a spot anterior to the position of the first treatment. Follow-up was obtained by reviewing the patients' medical records and conducting telephone interviews. Outcome was assessed using the Barrow Neurological Institute (BNI) pain scale and the BNI facial numbness scale.

Results. The median follow-up period was 28 months. In the idiopathic TN group, rates of adequate pain relief, defined as BNI Pain Scores I–IIIB, were 75%, 60%, and 58% at 1, 3, and 5 years, respectively. In the multiple sclerosis (MS)–related TN group the rates of adequate pain relief were 56%, 30%, and 20% at 1, 3, and 5 years, respectively. Repeated GKS was as successful as the first. An analysis of our treatment strategy of repeated GKS showed rates of adequate pain relief of 75% at 5 years in the idiopathic TN and 46% in the MS-related TN group. Somewhat bothersome numbness was reported by 6% of patients after the first treatment and by 24% after repeated GKS. Very bothersome numbness was reported in 0.5% after the first GKS and in 2% after the second treatment.

Conclusions. In this study the authors analyzed outcomes of GKS in a large cohort of patients with TN; uniform treatment consisted of 80 Gy delivered to the REZ. The initial and long-term outcomes of pain relief and sensory dysfunction are comparable to recently published results at other institutions, where similar outcome criteria were used. These data should prove helpful to assist patients and clinicians in their TN management decisions.

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of TN.1,3–5,7,10–12,15–20,22–25,27–30,32,33,35,36 However, data on the long-term efficacy of GKS are limited.6,18,19,29 Moreover, a direct comparison of the various published reports is hampered by differences in outcome parameters, treatment protocols, and lengths of follow-up. Some reports only list the percentage of patients who remain pain free at the last follow-up, whereas for a correct analysis of the efficacy of a treatment, Kaplan-Meier analysis must be performed. The purpose of this report is to contribute to our knowledge of the efficacy and side effects of GKS for TN by reviewing a large group of patients, who were treated with a uniform treatment protocol and evaluated using a well-established pain scale and Kaplan-Meier analysis.

Methods

Patient Characteristics

Between June 2002 and October 2009, 365 patients were treated for TN at the Gamma Knife Center Tilburg. The total number of GKSs performed during this period was 450. In 79 patients a second GKS was performed on the same side, and in 6 patients bilateral pain was treated. Repeated GKS was offered to patients who initially experienced significant pain relief but subsequently had pain recurrence. The majority of patients (285 patients [78%]) had idiopathic TN; 31 (8%) had TN due to MS; 26 (7%) had atypical pain; 14 (4%) had tumor-related TN (12 meningiomas, 1 acoustic neuroma, and 1 pituitary adenoma); and 9 (2%) had TN due to unusual causes such as brainstem infarction, cluster headache, and postherpetic pain. The small group of patients, whose TN was due to an unusual cause, were excluded from analysis in this study. Typical pain was defined as short attacks of intense, stabbing pain in the distribution of the trigeminal nerve in response to inextremities. Atypical pain was defined as the pain was burning or aching, and present more than 50% of the time.9 This group was deemed to have a separate diagnosis and is reported as such. There was a slight right-sided predominance of pain (53% of patients). Pain was bilateral in 2 (1%) of the patients with idiopathic TN and in 4 (13%) of the patients with MS-related TN. The mean age of the study population was 65 ± 13 years (range 27–91 years) and the male/female ratio was 45%/55%. In 169 patients (46%) invasive treatment had been performed prior to GKS. Of these patients, 138 had been treated with one or more percutaneous RF lesions (range 1–8 lesions), 15 patients with both RF lesions and MVD, 11 patients with MVD, and 5 patients with a combination of peripheral neuroma and an ablative procedure.

Radiosurgical Technique

The Gamma Knife 4C unit (Elekta AB) was used in patients treated before November 2008. Treatments thereafter were performed using the Gamma Knife Perfexion unit. Treatment planning was done by a team consisting of a neurosurgeon, a radiation oncologist, and a medical physicist. After local anesthesia had been obtained, the patient’s head was fitted with the Leksell stereotactic frame. A T2-weighted turbo spin echo sequence was used with a 512 × 512 matrix size and a slice thickness of 0.7 mm. A 4-mm single shot was centered on the proximal part of the trigeminal nerve, with the 40% isodose line touching the surface of the brainstem. The prescription dose was 80 Gy to the 100% isodose line. In patients who experienced recurrent TN after a first successful treatment, a second GKS was offered. In these cases the 4-mm shot was centered anteriorly, on the intracisternal portion of the trigeminal nerve. The exact position was determined by placing the 50% isodose of the shot so that it touched the 50% isodose of the shot of the first treatment. With the use of this treatment protocol, the cumulative dose of the two treatments did not exceed 80 Gy at any point along the nerve.

Outcome Assessment and Analysis

The effect on pain was assessed using the BNI pain scale, a self-reported index on pain control and medication usage.30 Data were obtained by reviewing the patients’ medical records or conducting telephone interviews. Treatment failure was defined as a reported pain level that was categorized as BNI Pain Score IV or V, which coincided in 90% of cases with the patients’ choice to subsequently undergo an invasive surgical procedure or repeated GKS. If patients did not experience any pain relief after GKS the time of failure was set at 0 months.

Numbness was evaluated using the BNI facial numbness score.30 Symptoms of dry eye or mastication weakness were not routinely assessed.

Statistical analysis was performed using SPSS software, version 16.0 (SPSS, Inc.). Freedom from pain recurrence was assessed using a Kaplan-Meier survival analysis. The log-rank test was used to compare the Kaplan-Meier data. Multivariate analysis was performed using factors that had been deemed significant in the log-rank test by using the Cox proportional hazards regression analysis. Differences in numbness scores were analyzed with the use of the chi-square test. A probability value of less than 0.05 (2-tailed) was considered significant.

Results

Follow-up was incomplete in 31 patients (8%): 15 patients (4%) were lost to follow-up and 16 patients (4%) died. The median follow-up for the study population was 28 months with a wide range of 3–85 months. A minimum follow-up of 5 years was available in 46 patients.

Pain Relief

The time of the first noticeable effect was stated in the medical records of 99 patients who experienced pain reduction after GKS. The median time to relief was 20 days (range 1 day–5 months).

Figure 1 shows the Kaplan-Meier analysis in patients with idiopathic TN, tumor-induced TN, MS-related TN, and atypical pain. Initial response-to-treatment rates were high, with the exception of the atypical pain group. The probability of achieving long-term pain relief was significantly worse in patients with MS and in patients with
atypical pain than it was in patients with idiopathic TN (p < 0.01). The 1-, 3-, and 5-year freedom-from-failure rates (BNI Pain Scores I–IIIB, “adequate pain relief”) in the idiopathic TN group were 75%, 60%, and 58%, respectively. In the MS-related TN group, these numbers were 56%, 30%, and 20%, respectively. There was no statistically significant difference between the tumor-related TN group and the idiopathic TN group, but the former group was too small to draw conclusions.

Figure 2 shows the Kaplan-Meier analysis in patients in the idiopathic TN group stratified by a history of prior invasive treatment. Patients who had earlier undergone invasive treatment were significantly less likely to maintain pain relief (p < 0.001). Among patients with idiopathic TN, the 5-year rate of adequate pain relief in patients who had a history of invasive treatment was 47%; the rate in patients who had not undergone invasive treatment was 70%.

We compared the efficacy of the first and second treatments in patients in the idiopathic TN group (Fig. 3). The efficacy of the first and repeated GKSs was comparable, as seen in the Kaplan-Meier plot (not significant, log-rank test).

In the multivariate analysis, the presence of prior invasive treatment and atypical pain were factors associated with earlier pain recurrence (p < 0.01). The presence of MS failed to reach significance (p = 0.1).

We analyzed the combined results of the first and, when applicable, the second treatment in the idiopathic TN group. The Kaplan-Meier plot in Fig. 4 depicts the results of our management strategy of performing a second GKS if the first treatment resulted in significant pain reduction but only temporarily. Repeated GKS was performed in 17% of patients with idiopathic TN. The 5-year freedom-from-recurrence rate in our management plot was 75%. In the MS-related TN group 35% of patients were treated again, resulting in a 46% freedom-from-recurrence rate at 5 years.

Of the patients who experienced pain relief after one treatment, the majority (56%) were pain free without medication (BNI Pain Score I). Occasional pain without medication (BNI Pain Score II) was reported in 14% and pain free with medication (BNI Pain Score IIIA) in 14%. A BNI pain score of IIIB was reported in 12% of these patients. Figure 5 shows the pain scores in patients who
experienced adequate pain relief (BNI Pain Scores I–IIIB) clustered per year after GKS; the distribution of pain scores at longer follow-up examinations is also given for a comparison. A relatively large number of patients had a BNI pain score of IIIA (no pain with medication) during the 1st year compared with longer follow-up times. This reflects the fact that we recommended that patients taper off their medications when they became pain free, which was usually in the first months after treatment. This led to a relatively high proportion of patients who were pain free but still used medication (BNI Pain Score IIIA) in the 1st year. The distribution of pain scores remained stable in the following years. The percentage of patients treated for idiopathic TN with an excellent outcome (BNI Pain Score I) at 5 years was 32%.

**Numbness Assessment**

The self-reported numbness scores after first and repeated GKS for TN are presented in Fig. 6. A not bothersome numbness (BNI Facial Numbness Score II) was reported by 29% of patients, a somewhat bothersome numbness (BNI Facial Numbness Score III) by 6%, and very bothersome numbness (BNI Facial Numbness Score IV) by 0.5% of patients after a single GKS. After a second GKS, BNI Facial Numbness Scores II, III, and IV were reported in 30%, 24%, and 2% of patients, respectively (p < 0.01, chi-square test). After stratifying for idiopathic TN and MS-related TN, no statistically significant differences were found in the numbness scores. In the MS-related TN group 32% of patients experienced not bothersome numbness (BNI Facial Numbness Score II), and 5% reported somewhat bothersome numbness (BNI Facial Numbness Score III). We observed one case of anesthesia dolorosa (0.3%). This patient had been treated 3 times prior to GKS with glycerol rhizotomy followed by MVD, which resulted initially in a complete facial numbness that later partly recovered to sensory loss of the third branch of the trigeminal nerve. Subsequent treatment by neuromodulation of the motor cortex was successful.

To evaluate the evolution of new numbness as time passed after GKS, BNI numbness scores after the first treatment were clustered per year. The distribution graph of the BNI numbness scores is shown in Fig. 7. These data suggest a delayed occurrence of numbness, which can develop even after several years.

We could not demonstrate a significant difference in the distribution of numbness scores in patients with and

![Fig. 4. Kaplan-Meier plots depicting the probability of maintaining adequate pain relief (BNI Pain Scores I–IIIB) in patients with idiopathic TN by using our management strategy of offering repeated GKS when patients experienced pain recurrence after initial relief.](image1)

![Fig. 5. Bar graph showing BNI pain scores (shown in Arabic numerals) at increasing follow-up times post-GKS in patients who maintained adequate pain relief (BNI Pain Scores I–IIIB).](image2)

![Fig. 6. Bar graph showing BNI Facial Numbness Scores I–IV (shown in Arabic numerals) after a single GKS (left bar) and repeated treatment (right bar). The difference between the first and second treatments is highly significant (p < 0.001).](image3)
without a history of invasive treatment. The percentages of bothersome numbness after one GKS were 6% and 9%, respectively, in patients with and without prior invasive treatment. Furthermore, no correlation was found between pain scores and facial numbness scores.

**Discussion**

Throughout the past 15 years GKS increasingly has been used in the treatment of refractory TN. However, its role as it compares with other treatment modalities such as MVD and percutaneous ablative procedures remains unclear. No results of randomized trials comparing GKS with other widely used invasive procedures have been made available. Data covering rates of initial and long-term pain relief and treatment side effects should be well established, for each treatment modality, to assist patients and clinicians in health management decisions. For MVD and percutaneous ablative techniques, which have been used for many years, several extensive reviews are already available. Pain relief after MVD is clearly superior to that achieved using other treatment modalities, with pain free without medication (BNI Pain Score I) rates at 10 years postsurgery of approximately 70%. Side effects, such as deafness, facial palsy, trigeminal nerve dysfunction, infection, cerebellar infarction, and even death, occur rarely in experienced hands. According to a meta-analysis of percutaneous ablative techniques, approximately 50% of patients are expected to be pain free with or without medication (BNI Pain Scores I–IIIA) at 5 years, but results in individual reports are quite variable. Side effects are highest for RF lesioning according to the same meta-analysis and consist mainly of trigeminal dysfunction with corneal numbness (10%), masticatory weakness (12%), keratitis (1%), anesthesia dolorosa (2%), and troublesome dysesthesia (4%). Complications such as meningitis, vascular injury, and cranial nerve deficits have been reported but are rare (< 1%).

Gamma Knife surgery is a relatively new treatment and issues concerning long-term outcomes are not fully clarified. Recently, several centers reported long-term results of GKS for TN. A comparison of reported results, however, is troublesome because of differences in treatment protocols, outcome criteria, data analysis, and length of follow-up. In the present study we have attempted to contribute to the present knowledge of GKS for TN by reviewing a large group of patients with TN who were treated by GKS using a uniform treatment protocol and evaluated using a widely applied outcome scale and Kaplan-Meier analysis.

**Pain Relief in Patients with Idiopathic TN**

Data in the present study can be compared with those of other recently published reports in which the same outcome criteria were used in large patient populations and a sufficient follow-up was available. Treatment protocols, however, were not uniform across these studies and also varied between different institutions. The protocols that are the most comparable to that of the present study are shown in Table 1. Kondziolka et al. used a median prescription dose of 80 Gy to the REZ, with the 20% isodose line touching the brainstem, and Little et al. used a prescription dose of 80 Gy to the REZ in 69% of their cases, with the 50% isodose line at the surface of the brainstem. In the present study all patients were treated by delivery of 80 Gy to the REZ, with the 40% isodose line touching the brainstem. In the studies conducted by Kondziolka et al., Little et al., and in the present study, the percentages of patients who had undergone prior invasive treatment (a well-known prognostic variable) were 43%, 37%, and 46%, respectively. Kaplan-Meier survival plots predicted adequate pain relief (BNI Pain Scores I–IIIB) at 5 years in 46%, 63%, and 58% of patients with idiopathic TN in the present study. Adequate pain relief at 1 year was reported in 80% of patients by Kondziolka et al. and in 75% of patients with idiopathic TN in the present study. In another recently published series, Dhople et al. reported 5-year adequate pain relief (BNI Pain Scores I–IIIB) rates of 34%. However, a lower median prescription dose of 75 Gy to the REZ was used, which makes that series somewhat less comparable. Finally, Riesenburger et al. treated 53 patients with a median of 80 Gy directed to the REZ and reported 58% adequate pain relief at a median follow-up of 48 months. In patients with idiopathic TN, excellent outcome, defined as pain free without medication, has been reported in 29%–32%. In our series 32% of patients with a follow-up longer than 5 years reported an excellent outcome (BNI Pain Score I).

The aforementioned studies (Table 1) and this study focused on large patient cohorts with long follow-ups and Kaplan-Meier analyses based on the same outcome definitions. The reported outcomes are comparable. Therefore, we feel that these numbers—adequate pain relief (BNI Pain Scores I–IIIB) at 5 years in 34%–63% of patients and complete pain relief without medication (BNI Pain Score I) in approximately 30% of patients—are the best.
estimates presently available for patients with idiopathic TN who were treated by delivery of 80 Gy to the REZ using a single 4-mm shot.

Our data show that the second GKS was as successful as the first, albeit at the expense of more sensory disturbances. Dvorak et al. reviewed the results of other groups who reported limited experience with repeated GKS. Kaplan-Meier analyses were lacking, and a highly variable dose prescription and patient selection were used. Overall, there appears to be a dose-response relationship between the cumulative dose for both pain relief and side effects. Repeated GKS in our patients with an initial favorable response resulted in a 5-year adequate pain relief in 75% of patients, with somewhat bothersome numbness in 24% of patients and very bothersome numbness in 2% of patients. Despite the relatively high rates of numbness, patients frequently reported high satisfaction rates when they experienced pain relief. In our opinion, this treatment regimen is justified in patients with debilitating pain recurrence, who, in our experience, are happy to trade their pain for an increased chance to develop numbness.

Pain Relief in MS-Related TN

In patients with MS-related TN, GKS seems to be a less effective treatment, similar to MVD and percutaneous ablative techniques. In the majority of published studies on the efficacy of GKS for MS-related TN, very few patients were included and follow-up was limited. The largest published series on GKS in patients with MS was reported by Zorro et al., who reviewed outcomes using the BNI pain scoring system in 37 patients with a median follow-up of 56 months. Our study included 31 patients with MS-related TN with a modest median follow-up of 16 months. Zorro et al. prescribed a median dose of 80 Gy (range 70–90 Gy), whereas we prescribed a uniform dose of 80 Gy. The 5-year adequate pain relief (BNI Pain Scores I–IIIB) in the Kaplan-Meier analysis after a single GKS was 54% in the study conducted by Zorro et al.; the percentage in the present study was 20%. Our results showed a highly significant difference in pain relief when we compared patients with MS-related TN and patients with idiopathic TN in the univariate analysis, but this difference failed to reach significance in the multivariate analysis. A possible explanation for these deviating results is the limited statistical power imposed by the small number of patients in the MS-related TN group.

To achieve pain relief in patients with MS-related TN, more treatments are required than for patients with idiopathic TN. We retreated 11 (35%) of 31 patients, as opposed to 17% in the idiopathic TN group. The Kaplan-Meier analysis of this management strategy showed a 56% chance of adequate pain relief at 5 years. This shows that GKS followed by a second procedure when pain recurs leads to reasonable results in patients with MS-related TN, within the context of other treatment modalities.

In our opinion GKS is a valid treatment option for MS-related TN because of its minimally invasive nature.

Decreased Facial Sensation

A mild form of numbness, which was not bothersome to the patients, was reported in 36% of patients treated by Riesenburger et al., 17% treated by Little et al., and 29% treated by us in the present study. Dhople et al. reported bothersome numbness in 6% of their patients, whereas Riesenburger et al. did not observe bothersome numbness in their patients. In our series 6% of patients reported somewhat bothersome numbness (BNI Facial Numbness Score III) after the first GKS. Kondziolka et al. reported on 53 patients (10.5%) with new sensory dysfunction. In an attempt to evaluate whether this was bothersome, 40 patients were contacted, 16 of whom reported bothersome numbness, corresponding to an estimated 4% in their series. In contrast to these relatively low rates of bothersome numbness, data are reported by Little et al., who identified bothersome numbness in 17% of their patients. In conclusion, the rate of new bothersome numbness, based on recently published large series, including ours, is estimated to be 0%–17%, with the majority of the reports showing rates of 6% or less.

We encountered one case (0.3% of patients) of anesthesia dolorosa. To our knowledge, only one other case of anesthesia dolorosa after GKS in TN has been reported in the literature by the Pittsburgh group, accounting for 0.2% in their series. Interestingly, both patients had decreased facial sensation after prior MVD.

There is evidence that the development of new numbness correlates with pain relief. Correlation of pain and numbness scores in our data could not confirm this finding. This controversial finding is possibly explained by the uniformity of the treatment protocol. Studies finding a correlation used a range of prescription doses, with a lower dose possibly leading to both less pain relief and fewer sensory deficits and a higher dose leading to better pain relief with more sensory deficits, whereas in our study only one prescription dose was used.

Our data showed that the occurrence of new numb-
ness slowly evolves for several years after treatment. To make an accurate comparison of different reported rates of facial numbness after GKS, not only do dose prescription and outcome criteria have to be taken into account, but also the length of follow-up, preferably using Kaplan-Meier analysis.

Conclusions

To determine the role of GKS in the treatment of TN, an assessment of the initial and long-term effects of the procedure and its side effects is of vital importance. Therefore, Kaplan-Meier analysis with long-term follow-up of large patient cohorts treated with uniform protocols and evaluated with the same outcome measures are necessary. At present, such data are limited. This study was conducted to improve our present knowledge. Based on data currently available in the literature and data from the present study, adequate pain relief after GKS with 80 Gy to the REZ is estimated to be between 75% and 80% at 1 year and between 46% and 63% at 5 years. One-third of patients will experience excellent outcome at 5 years. Newly acquired bothersome sensory defects have been reported in 0%–17%.

Repeated GKS can be easily applied because of its noninvasive nature and limited additive morbidity. Therefore, future data should also reflect the results of the combined effects of primary and repeated GKS, especially because repeated GKS is currently used with a highly variable dose prescription and patient selection. Using our treatment strategy of repeated GKS, at 5 years post-GKS adequate pain relief was obtained in 75% of patients with idiopathic TN and 56% of patients with MS-related TN, at the expense of increased facial sensory deficits that were not classified as bothersome by the majority of the patients. These numbers should be helpful to assist patients and clinicians in their TN management decisions. In our clinic MVD, RF lesioning, and GKS are available. As our experience with GKS has increased over the past years, we have adapted our strategy and currently recommend GKS in the majority of patients who refuse or are unable to undergo MVD.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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