Gamma Knife stereotactic radiosurgical treatment of idiopathic trigeminal neuralgia: long-term outcome and complications

KOSTAS N. FOUNTAS, M.D., PH.D.,1 JOSEPH R. SMITH, M.D.,1 GREGORY P. LEE, PH.D.,2 PATRICK D. JENKINS, P.A.-C.,1 REBECCA R. CANTRELL, PH.D.,3 AND W. CHRIS SHEILS, M.D.4

Departments of 1Neurosurgery, 2Neurology and Neuropsychology, 4Radiation Oncology, and 3Southeast Gamma Knife Center, Medical College of Georgia, Augusta, Georgia

Object. Stereotactic radiosurgery (SRS) with the Gamma Knife (GK) is a rapidly emerging surgical modality in the management of medically refractory idiopathic trigeminal neuralgia (TN). The current study examines the long-term outcome in patients with drug-resistant idiopathic TN who underwent GK surgery at the authors’ institution.

Methods. One hundred and six consecutive patients (38 men and 68 women) with proven medically refractory idiopathic TN were included in this retrospective study. Their ages were 41–82 years (mean 72.3 years). All patients underwent SRS with prescribed maximal radiation doses ranging from 70 to 85 Gy. Isocenters 1–3 were used and plugging was used selectively. The follow-up period was 12–72 months (mean 34.3 months). The patients were divided into 2 groups according to their history of previous surgery.

Results. The initial response rate in patients with no history of previous surgery was 92.9%; in those who had undergone previous surgery, the initial response rate was 85.7%. At the end of the 1st posttreatment year, an excellent outcome was achieved in 82.5% of patients who had not had previous surgery, and in 69.4% of those who had. The respective outcome rates for the 2nd posttreatment year were 78 and 63.5%, respectively. The most common complication was the development of persistent paresthesia, which occurred in 15.8% of patients with no previous surgery and 16.3% of those with previous surgery.

Conclusions. Stereotactic radiosurgery with the GK is a safe and effective treatment option for patients with medically refractory idiopathic TN. (DOI: 10.3171/FOC-07/12/E8)

KEY WORDS • complication • Gamma Knife • outcome • stereotactic radiosurgery • trigeminal neuralgia

Idiopathic TN is the most common cranial neuropathy, with an incidence rate estimated at approximately 3–5 cases per year per 100,000 persons, which translates to 15,000 new cases each year in the United States alone. It is well-known that the incidence of idiopathic TN increases with age, and that women are more commonly affected. Medical therapy is considered the first line of treatment. Numerous medications have been introduced for the amelioration of the disabling facial pain in these patients, and have had variable success. Approximately 25% of patients with idiopathic TN, however, will eventually have to undergo a surgical procedure either because of progressive failure of the medical regimen or due to the development of tachyphylaxis and/or serious side effects.

Approximately 8000 patients receive surgical treatment for idiopathic TN each year in the US. Several surgical options are available for patients with medically refractory TN. The most commonly used surgical procedures for these patients include microvascular decompression, percutaneous radiofrequency rhizotomy, percutaneous balloon microcompression, percutaneous glycerol rhizolysis, posterior fossa trigeminal rhizotomy, and SRS. The existence of multiple surgical options indicates that none of these treatments are truly ideal. In fact, the selection of the most appropriate surgical approach remains controversial and should be individualized for each patient.

Stereotactic radiosurgery with GKS is an established treatment option for medically refractory idiopathic TN. Indeed, an exponentially increasing number of clinical studies have recently appeared in the literature, reporting on the outcomes in patients undergoing GKS. However, the results vary significantly among different studies; this variation, in combination with the ill-defined outcome criteria and nonstandardized reporting of outcome of nonhomogeneous clinical series (patients with or without previous surgeries and patients with idiopathic or sec-
ondary TN), make the interpretation of the reported outcome rates quite confusing.

In the present study we present the following: the initial response rate; the short-, intermediate-, and long-term pain outcome of patients with pharmacoresistant idiopathic TN treated at our institution with GKS; and a review of the pertinent literature.

Clinical Material and Methods

Study Design

This retrospective study included a 7-year period between January 2000 and June 2006. The patients’ hospital charts, procedural notes, and outpatient clinic charts were carefully reviewed. Analysis of our data was performed according to the current Health Insurance Portability and Accountability Act guidelines.

Patient Population

One hundred and six consecutive patients (38 men and 68 women) with an established diagnosis of typical idiopathic TN (as described by the International Association for the Study of Pain) were included in our study. They ranged in age from 41 to 82 years, with a mean age (± standard deviation) of 72.3 ± 0.3 years. All included patients had medically refractory TN, and had been treated with various pain medications for at least 2 years prior to SRS treatment. The preoperative workup in these patients included detailed neurological examination with emphasis on trigeminal nerve examination; basic laboratory studies and examinations including a complete blood cell count, clotting studies, basic biochemical tests, electrocardiography, and chest x-ray films; and brain MR imaging in a 1.5-T machine.

The decision to use GKS was based on the following criteria: 1) patient age; 2) the absence of vascular compression of the involved trigeminal nerve on the MR images; 3) the patient’s general medical condition; 4) the failure of previous surgical procedures; and 5) the patient’s willingness to undergo a minimally invasive procedure.

We divided our patients into 2 different groups according to their history of previous surgical treatment, and separately assessed the initial response rates and the short-, intermediate-, and long-term outcome and complication rates in these groups.

Stereotactic Radiosurgical Procedure

Written consent was obtained in all cases. The majority of our procedures (105 of 106 patients [99.1%]) were performed on an outpatient basis, while 1 patient (0.9%) had to stay for overnight observation due to a hypertensive episode, consistent with the patient’s medical history.

We used the Leksell Gamma Plan Model B unit (Elekta Instruments) in this study. A Leksell titanium stereotactic frame (Elekta AB Instruments) was applied with the patient under sedation and with local anesthesia induced. Volumetric acquisition brain MR imaging and a head CT scan were obtained, while visual anatomic point-to-point matching was performed between the CT and MR studies to rule out any magnetic field–generated image distortion (unfortunately, automatic image fusion cannot be performed in our GK unit). Although the exact incidence of MR image distortion is not known, the potential disastrous complic-
tions associated with such miscalculation has forced us routinely to perform both studies in our cases. In the present study, there was only 1 case in which we had to repeat the MR imaging and surgical planning because there was a larger than 10-mm discrepancy between anatomical landmarks on MR imaging and CT. The planning of the procedure and the actual treatment were performed by a team including a physicist, a radiation oncologist, and a neurosurgeon (Fig. 1).

The trigeminal nerve dorsal root entry zone was targeted in all of our cases. The maximum dose used in our series was 85 Gy (prescribed dose range 70–85 Gy, median dose 80 Gy) with the 30% isodose adjacent to the root entry zone (Table 1). In 68 cases, we used plugging to maximize conformity (equal distribution of the prescribed radiation dose to the entire cross-section of the nerve root) and at the same time to minimize the delivered dose to the adjacent pontine surface. The criterion for the employment of plugging was solely the trigeminal nerve root morphology. The 4-mm collimator was used in all our cases. The mean number of isocenters in our series was 1.0 (range 1–3, median 1). The number of isocenters used was not associated with previous treatment but rather to the morphological characteristics of the trigeminal nerve root. Again, our goal was to accomplish equal coverage of the entire cross-section of the nerve root. One patient (0.9%) underwent 2-isocenter treatment, and 1 (0.9%) underwent 3-isocenter treatment.

Follow-Up Evaluation

The follow-up period ranged from 12 to 72 months (mean follow-up time 34.3 months, median 36 months). Clinical assessment was performed via detailed clinical evaluations every 6 months for the first 3 postoperative years and every 12 months thereafter.

We used the following outcome criteria in the present study. Initial response was defined as the early decrease in pain severity and/or frequency, which was observed within the first 12 posttreatment weeks. Complete relief of pain, with or without continuation of the preoperative pain medications was considered excellent outcome. Decrease of the severity and/or frequency of preoperative pain > 90% was considered a good outcome, while pain severity and/or pain frequency decrease of 10–90% was considered fair outcome. A < 10% decrease in pain severity and/or frequency was considered a poor outcome.

Results

Pain Distribution

In regard to the anatomic localization of trigeminal pain in our cohort, our results are demonstrated in Fig. 2. In 37 (34.9%) of 106 patients, the pain was of V3 distribution. Sixty-three patients (59.4%) suffered facial pain on the left side, and 43 patients (40.6%) had pain on the right side.

Previous Surgical Procedures

Concerning previous surgical treatment, 49 patients (46.2%) had undergone at least 1 previous surgical procedure for TN, and the remaining 57 patients (53.8%) had not. In the group of patients who had undergone previous surgical procedures, 2 patients had undergone 4 procedures, 5 patients had had 3, 13 patients had undergone 2, and 29 patients had undergone 1 previous surgical intervention for...
TN. More specifically, 26 of the previously performed procedures were percutaneous radiofrequency rhizotomies, 19 were GKS, 17 were microvascular decompressions, 5 were peripheral alcohol injections, 4 were posterior fossa surgical rhizotomies, 4 were glycerol rhizotomies, 2 were peripheral trigeminal branch surgical neurectomies, and 1 was a balloon compression procedure.

Initial Response to Treatment

The initial response rate in the 57 patients with no previous surgeries was 92.9% (53 patients), while the rate was 85.7% (42 of 49 patients) in the group of patients who had undergone surgery previously. The overall initial response rate in our cohort was 89.6% (95 of 106 patients), while 10.4% (11 of 106 patients) failed to respond to SRS.

The observed difference in initial response rates between patients with and without previous surgical procedures did not reach statistical significance ($\chi^2 = 1.485, p = 0.13$). The majority of our patients who had not undergone previous surgery for TN showed some response within the first 4 weeks posttreatment (50 of 53 patients), while a limited number of patients (3 of 53) responded to treatment after a longer period (pain improvement within 5–12 weeks after treatment). In contrast, only 20 of 42 patients who had undergone previous surgeries responded to GKS within the first 4 weeks, while 22 demonstrated a late response (5–12 weeks posttreatment).

Long-Term Pain Outcome

At 1 year after SRS, follow-up data were available for all participants. Data were available for 91 patients after 2 years, 78 after 3 years, 59 after 4 years, 35 after 5 years, and 23 patients at 6 years after SRS. The observed excellent outcome rates for both groups of patients (with and without previous surgeries) are demonstrated in Fig. 3. The overall excellent rates for the 1st, 2nd, 3rd, 4th, and 5th posttreatment years were 76.4, 71.4, 67.9, 66.1, and 60%, respectively.

The observed excellent and good outcome rates were higher for patients who had not undergone previous surgery for TN compared with those who had. However, this trend did not reach statistical significance at any of the follow-up points ($\chi^2 = 3.87, p = 0.27$ for posttreatment Year 1; $\chi^2 = 2.99, p = 0.39$ for Year 2; $\chi^2 = 2.35, p = 0.50$ for Year 3; $\chi^2 = 0.99, p = 0.80$ for Year 4; $\chi^2 = 1.66, p = 0.64$ for Year 5; and $\chi^2 = 2.27, p = 0.51$ for Year 6). Likewise, statistical analysis of our current clinical data with the chi-square and nonparametric Kolmogorov–Smirnov tests demonstrated no statistically significant difference in outcome rates between patients treated with different radiation doses ($p = 0.56$). Similarly, the usage of 1, 2, or 3 radiation isocenters resulted in no statistically significant difference in outcome rates ($p = 0.81$). In addition, the use of plugging in the treatment plan resulted in no statistically significant difference in the outcome rates ($p = 0.38$).

Complication Rates

There were no intraoperative or early postoperative complications in our series. In 1 patient with a known history of poorly controlled chronic arterial hypertension, however, there was an episode of severe arterial hypertension that was medically managed with no further consequences. The most commonly observed procedure-related delayed complication in the present study was persistent facial numbness, which arose in 17 (16.0%) of 106 patients. More specifically, the incidence of persistent facial numbness among patients with no previous surgery was 15.8% (9 of 57 patients), while the rate among patients with previous surgery was 26.3% (11 of 42 patients). The incidence of persistent facial numbness among patients with previous surgery was 26.3% (11 of 42 patients).

### Table 2

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>PostTx Year 1 Outcome (%)</th>
<th>PostTx Year 2 Outcome (%)</th>
<th>PostTx Year 3 Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Excellent</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Kondziolka et al., 1996</td>
<td>51</td>
<td>37†</td>
<td>41†</td>
<td>—</td>
</tr>
<tr>
<td>Kondziolka et al., 1998</td>
<td>23</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nicol et al., 2000</td>
<td>42</td>
<td>73.8†</td>
<td>21.4†</td>
<td>—</td>
</tr>
<tr>
<td>Maesawa et al., 2001</td>
<td>220</td>
<td>75.8†</td>
<td>21.4†</td>
<td>71.3†</td>
</tr>
<tr>
<td>Pollock et al., 2002</td>
<td>117</td>
<td>67†</td>
<td>51†</td>
<td>60†</td>
</tr>
<tr>
<td>Peit et al., 2003</td>
<td>112</td>
<td>70†</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Massager et al., 2004</td>
<td>47</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Shaya et al., 2004</td>
<td>40</td>
<td>40†</td>
<td>30†</td>
<td>—</td>
</tr>
<tr>
<td>Dzynma et al., 2005</td>
<td>73</td>
<td>52.7†</td>
<td>25.7‡</td>
<td>33†</td>
</tr>
<tr>
<td>Jawahar et al., 2005</td>
<td>81</td>
<td>42.3†</td>
<td>26.9†</td>
<td>—</td>
</tr>
<tr>
<td>Sheehan et al., 2005</td>
<td>151</td>
<td>47</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>Two et al., 2005</td>
<td>38</td>
<td>—</td>
<td>—</td>
<td>16†</td>
</tr>
<tr>
<td>Fountas et al., 2006</td>
<td>77</td>
<td>80.8‡</td>
<td>7.7‡</td>
<td>69.2‡</td>
</tr>
<tr>
<td>Massager et al., 2007</td>
<td>358</td>
<td>—</td>
<td>—</td>
<td>74†</td>
</tr>
<tr>
<td>Present study</td>
<td>106</td>
<td>82.5‡</td>
<td>8.8‡</td>
<td>78§</td>
</tr>
</tbody>
</table>

‡ Indicates percentage of patients with previous surgery.
§ Information on previous surgery status not available.

* Percentages straddling the “Good” and “Excellent” columns are combined good and excellent values. Abbreviations: Tx = treatment; — = not available.
surgery was 16.3% (8 of 49 patients). The difference in the occurrence of posttreatment facial numbness between patients with and without previous surgery was not statistically significant ($\chi^2 = 0.46, p = 0.73$). Interestingly, posttreatment facial numbness developed within the 1st year posttreatment in patients of both groups. Moreover, the posttreatment incidence of facial numbness was almost equally distributed among patients receiving 70 Gy, 75 Gy, 80 Gy, and 85 Gy maximal radiation doses ($\chi^2 = 0.93, p = 0.53$).

Additionally, there were 4 cases (3.8%) in which facial tingling and numbness developed after SRS. Two of these patients had undergone previous surgery and 2 had not. In 2 other cases (1.9%), isolated facial tingling developed postoperatively in patients who had not undergone previous surgery. There were no cases of mastication muscle deficit or corneal reflex loss and no cases of clinically symptomatic postradiation edema. In the 29 patients in whom brain MR imaging studies were obtained at follow-up there was no evidence of radiation-induced necrosis in either the pontine or brainstem. However, contrast enhancement of the treated trigeminal nerve root entry zone was noted in 23 (79.3%) of these 29 patients. All MR imaging studies were obtained at least 4 months after GKS.

**Discussion**

Stereotactic radiosurgery is the least invasive surgical modality used in the management of patients with medically refractory TN. Its use has exponentially increased during the last decade.\(^1\,\,6\,\,8\,\,10\,\,15\,\,17\,\,19\,\,28\) Comparison of GKS with the other neuroablative or decompressive surgical modalities has been addressed in previous studies.\(^6\,\,16\) Numerous authors have reported on SRS with the GK, and outcome and complication rates have been variable.\(^1\,\,6\,\,8\,\,10\,\,15\,\,17\,\,19\,\,28\) The observed variation in success rates in the literature may be explained by the subjectivity of assessing pain (which is the most important outcome parameter in these studies), the multifactorial causes of TN (idiopathic or secondary to a pathological entity), the significantly varying stereotactic radiosurgical treatment protocols (different anatomical targets and different radiation doses), and the usage of ill-defined and widely variable outcome assessment criteria.

In the present study, we attempted to make our series more homogeneous by including only patients suffering idiopathic TN and excluding any secondary TN cases. We also divided our participants in 2 groups based on patient history of previous surgery for TN, and evaluated their outcome and their complication rates separately. We compared our results with those of previously published studies of SRS with the GK, including those that included only patients with idiopathic TN. We emphasize, however, that comparison between the various studies cannot be accurate because in the majority of cases the authors do not describe the pain measurement methodology used.\(^8\) In addition, utilization of inconsistent and significantly varying outcome criteria further complicates any meaningful comparisons between the studies.\(^16\)

The initial response rates in our patients are comparable to those reported in the majority of previous studies of GKS.\(^1\,\,6\,\,12\,\,15\,\,16\,\,20\,\,28\) The effect of the latency period after SRS in our study is comparable with the findings in previously reported series.\(^8\,\,17\,\,22\,\,23\,\,29\,\,31\) Interestingly, patients with previous surgery seem to be more frequently late responders to GKS than patients with no history of previous surgery. Our excellent and good outcome rates are comparable to those reported in previously published studies.\(^5\,\,8\,\,17\,\,19\,\,23\) The observed excellent and good outcome rates in our patients as well as those of other large studies published in the last decade are summarized in Table 2.

Patients without a history of surgery for TN responded better to SRS treatment and had consistently higher excellent and good outcome rates than the patients who had undergone previous surgery. Although the observed differences in outcome did not reach levels of statistical significance in our study, a history of previous surgery has been previously identified as a negative prognostic factor.\(^1\,\,8\,\,17\,\,23\,\,24\,\,31\) Meticulous analysis of our pain outcome data revealed that the difference in the observed excellent outcome rates between patients who had and had not undergone previous surgeries became more profound as the time progressed, reaching a maximum at posttreatment Year 6. This finding may indicate that patients with no previous surgeries not only respond better to SRS treatment but maintain their excellent or good response longer than patients with a history of previous surgery; this parameter should be seriously considered in the surgical planning for SRS. Régis and colleagues\(^24\,\,25\) and Massager et al.\(^19\) have suggested that using a higher radiation dose and targeting the distal portion of the trigeminal root immediately posterior to the gasserian ganglion may improve outcome in patients with idiopathic TN who have had multiple previous surgeries.

The optimal radiation dose in SRS treatment of TN remains a controversial issue. We prescribed radiation doses of 70–85 Gy in the present study. Statistical analysis of our outcome data demonstrated that none of the radiosurgical technique parameters (radiation dose, number of isocenters, and use of plugging or not) was correlated to the patients’ outcome. Significant variation exists in the prescribed radiation doses in previously published series.\(^1\,\,3\,\,13\,\,17\,\,28\,\,29\) It must be emphasized that the actual delivered dose might be different from the prescribed maximal dose from one GK unit to another due to variations in the output factor for the 4-mm collimator, 0.8–0.85, depending on the institution and medical physics techniques used to measure the output factor.\(^9\) In addition, several other parameters such as advanced patient age, the presence of concomitant vasculopathy, systemic diseases such as multiple sclerosis, a small trigeminal cistern, and/or a history of previous radiosurgical treatments may lead to the use of a lower radiation dose.\(^4\) Massager et al.\(^20\) have emphasized the fact that the radiobiological effect of GKS may be related to the energy delivered to the trigeminal nerve root volume, rather than the maximal radiation dose delivered. These authors found that a 90-Gy dose can be used when targeting anteriorly to the retrogasserian part of the trigeminal nerve, while they recommended not using beam channel blocking when possible.

Posttreatment facial numbness was the most common procedure-related complication in our current series. It occurred in 15.8% of our patients with no previous surgery and in 16.3% of patients with previous surgery, while its overall incidence rate was 16.0%. Similarly, Shaya et al.\(^28\) reported the development of persistent facial numbness in
17.5% of their cases. However, other clinical investigators have reported lower incidence rates of posttreatment facial numbness. The development of numbness was slightly higher in the group of patients with previous surgery in our study. However, this difference was not statistically significant. The history of multiple previous surgical procedures can theoretically make the trigeminal nerve more vulnerable and consequently predispose for posttreatment facial numbness. It has been postulated that increased radiation dose may increase the risk of postoperative facial numbness. In a recent study, Massager and colleagues, demonstrated that the incidence of trigeminal nerve dysfunction is significantly related to the prescription dose and the usage of shielding. Interestingly, Massager et al., in another series, reported only 4% posttreatment incidence of facial numbness in a cohort of patients treated with 90-Gy maximal prescription dose. The incidence of facial numbness in their study is significantly lower than that observed in ours, although our maximal radiation doses were lower than theirs. It is apparent that post-SRS facial numbness is associated not only with the prescribed maximal radiation dose, but also with other parameters such as the actual delivered radiation dose, the exact anatomic location of the target, a history of previous surgery for TN, and the presence of concomitant vasculopathy or other systemic diseases. A better understanding of the radiobiology of the trigeminal nerve will help to minimize the occurrence of post-SRS numbness and trigeminal nerve dysfunction in general and to maximize the efficacy of GKS.

The development of tingling after SRS with or without associated facial numbness was the other complication that occurred in our patients. Its incidence was almost equal between patients without and with previous surgery. No association could be established between the development of posttreatment tingling and the prescribed radiation dose, the number of isocenters used, or the use of plugging. No cases of clinically symptomatic radiation-induced edema or necrosis were noted in our cohort. Furthermore, no evidence of pontine or brainstem radiation necrosis was found on MR imaging. Imaging enhancement of the involved trigeminal nerve root entry zone was observed in 79.3% of the patients in whom imaging studies were obtained. This finding is in agreement with the findings of Massager et al., who reported focal enhancement in 83% of their cases. In contrast, Gorgulho et al. reported trigeminal nerve enhancement on posttreatment MR images in only 56.7% of their patients. Interestingly, they found pons enhancement in 10.8% of their patients and concluded that posttreatment pontine enhancement seemed to be a positive prognostic factor for pain relief without a higher incidence of complications.

Conclusions

The observed excellent and good long-term outcome rates in our study supports the use of GKS as a valid surgical treatment option for patients with medically intractable idiopathic TN. Patients who have not had previous surgery to the trigeminal nerve seem to respond to SRS treatment earlier and better than patients who have. In addition, a higher proportion of patients with no previous surgery maintain their excellent or good pain outcome throughout follow-up. Although the prescribed maximal radiation dose, the number of the isocenters used, and the use of plugging, were not associated with the overall outcome in our series, the issue of the ideal dose and the ideal location of the anatomic target remain to be defined. A better understanding of the radiobiology of the trigeminal nerve root entry zone may help to maximize the efficacy and minimize the complication rates of GKS. Finally, the development of a universally accepted outcome classification system seems imperative for the meaningful and accurate clinical interpretation of the results reported by different centers worldwide.

References

2. Brismar R: Gamma knife surgery with a dose of 75 to 76.8 Gray for trigeminal neuralgia. J Neurosurg 100:848–854, 2004
Outcome after GKS for idiopathic TN


Address correspondence to: Kostas N. Fountas, M.D., Ph.D., Lambrou Katsoni Street, Terpsithea-Larisa, 41500 Greece. email: knfountasmd@excite.com.