

## Original Article

# Salvage Gamma Knife Radiosurgery after failed management of bilateral trigeminal neuralgia

Ami B. Raval, Jennifer Salluzzo<sup>1</sup>, Tomas Dvorak<sup>2</sup>, Lori Lyn Price<sup>3</sup>, John E. Mignano<sup>4</sup>, Julian K. Wu<sup>5</sup>

Department of Neurosurgery, Healthcare Associates in Medicine, Staten Island, NY 10304, <sup>1</sup>Department of General Surgery, Hospital of St. Raphael, New Haven, CT 06510, <sup>2</sup>Department of Radiation Oncology, MD Anderson Cancer Center, Orlando, FL 32806, <sup>3</sup>BioStatistics Research Center, Institute of Clinical Research and Health Policy Studies, <sup>4</sup>Departments of Radiation Oncology, <sup>5</sup>Neurosurgery, Boston Gamma Knife Center, Tufts Medical Center, Tufts University School of Medicine, Boston, MA 02111, USA

E-mail: \*Ami Raval - Araval1218@yahoo.com; Jennifer Salluzzo - Jennifer.salluzzo@gmail.com; Tomas Dvorak - td39@columbia.edu; Lori Lyn Price - lprice1@tuftsmedicalcenter.org; John Mignano - Jmignano@tuftsmedicalcenter.org; Julian Wu - jwu3@tuftsmedicalcenter.org  
\*Corresponding Author

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## Abstract

**Background:** The incidence of bilateral trigeminal neuralgia (TN) is 1-6% of total number of TN cases. Gamma Knife Radiosurgery (GKRS) is effective in treating unilateral TN; however, outcomes of bilateral TN treated by GKRS have not been well evaluated. The purpose of this study is to evaluate the long-term GKRS outcomes of bilateral TN at our institution and compare with our published treatment outcomes of unilateral TN.

**Methods:** Between 2000 and 2006, eight patients with bilateral TN were treated with GKRS. Data available on seven patients were collected. Facial pain outcomes were defined using the Barrow Neurological Institute pain intensity scale. Outcomes and toxicities were compared to published outcomes of unilateral TN patients treated with GKRS at our institution.

**Results:** The incidence of bilateral TN in our series is 2.3%. Treatment outcomes were excellent in 5/14, good in 1/14, and poor in 8/14. Median follow-up time was 58 months. Median time-to-failure was 38 months. Pain control rate was 80% at 12 months and 65% at 36 months. Bothersome side effects were seen in 4/14 nerves treated. Compared with our long-term unilateral TN cohort, there was no statistically significant difference in outcome, time-to-failure, or rate of toxicity.

**Conclusion:** Bilateral TN is rare, and effective treatment is crucial to improve the quality of life of those afflicted. Salvage GKRS is a reasonable treatment modality for individuals with bilateral TN.

**Key Words:** Bilateral, Gamma Knife surgery, stereotactic radiosurgery, trigeminal neuralgia

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## INTRODUCTION

Trigeminal neuralgia (TN) is a debilitating disorder characterized by lancinating facial pain confined to the

somatosensory distribution of the trigeminal nerve. Approximately 95% of cases have V2, or V3 division, primarily affected, with V1 being involved in less than 3% of cases. Typical TN pain is characterized by:

(1) Intermittent nature of lancinating facial pain, with freedom from pain between attacks; (2) paroxysmal pain usually lasting several seconds to minutes; (3) the ability of the pain to be provoked by triggering factors; and (4) anesthesia of the trigger area can relieve pain. Neurological examination is always normal.<sup>[5]</sup>

Typical TN is classically defined as a unilateral disease. However, bilateral facial pain with features of TN has been cited with an incidence of 1-6% in the larger series.<sup>[2,7]</sup> Diseases associated with developing bilateral TN include multiple sclerosis (MS), Paget's disease, and tabes dorsalis.<sup>[9,17,21]</sup>

The first-line treatment options for unilateral typical TN include medications such as anticonvulsants and antidepressants. When these fail, more invasive treatments are utilized such as microvascular decompression and percutaneous radiofrequency electrocoagulation (RFE). More recently, Gamma Knife Radiosurgery (GKRS) has been used for the treatment of TN with promising results.<sup>[3,4,6,10,11,13-15,18,19,22,25]</sup>

There is no single or standard method of treating bilateral TN. There are numerous reports on the efficacy of treating bilateral TN with microvascular decompression (MVD) or percutaneous RFE with varying results.<sup>[23]</sup> The purpose of this investigation was to examine our institutional cases of bilateral TN treated with GKRS.

## MATERIALS AND METHODS

### Patient population

From 2002 to 2006, 354 patients were treated with GKRS for TN. Of these, eight patients had bilateral TN and

were treated with bilateral GKRS at our institution. One patient was lost to follow-up. Data on the remaining seven patients were collected from their medical records as well as by a follow-up phone survey.

The mean age of the study population at initial GKRS procedure was 62 years, and the male to female ratio was 2:5. Two patients also had an underlying history of MS. Of the seven patients, four presented initially with right-sided TN. Four of the seven patients had undergone procedures other than GKRS for management of their TN. Two patients underwent RFE, one patient underwent MVD, and the other patient underwent both RFE and MVD [Table 1].

### Selection criteria

Patients with symptoms characteristic of typical TN were treated. All patients underwent separate treatments for their bilateral TN. Typically, the onset on one side preceded the onset on the contralateral side. Therefore, the decision of which side to treat with the first treatment was made based on the side in which the symptoms initially started, or if the patient had simultaneous bilateral TN symptoms, the side in which the symptoms were more severe was treated first. All patients were treated with medication prior to GKRS. Only patients who were refractory to medical management or were unable to tolerate the side effects of medications were considered for GKRS. Patients with atypical facial pain symptoms or with TN secondary to mass lesions were excluded from this study.

### Radiosurgical technique

All treatments were performed on an outpatient basis. After written consent was obtained from the patients,

**Table 1: Summary of patient treatment data**

Sex	Side	Age at Tx	Dose (Gy)	Time-to-failure (months)	Follow-up time (months)	Time between treating the sides (months)	Previous procedures	Multiple sclerosis?	Bothersome side effects?
Male	Right	54	80		59	8		Yes	No
	Left	55	80	15			Left RFA		No
	Left	56	45	14					
Male	Right	68	85	43	43	5	Right RFA	No	No
	Left	68	80					No	No
Female	Right	59	80		90	9		No	No
	Left	58	80	75			Hx of left MVD		Dysesthesias
Female	Right	58	80	1	76	2	Right RFA + MVD	Yes	Masseter weakness, dysesthesia
	Left	58	80	7					Masseter weakness
Female	Right	81	83		72	22		No	No
	Left	79	80					No	No
Female	Right	45	80	13	55	1		No	No
	Left	45	80	56.5					Dysesthesia
Female	Right	72	80	11	71	48		No	No
	Right	74	45						No
	Left	76	85	24					No
	Left	78	45						No

RFA: Radiofrequency ablation, MVD: Microvascular decompression

0.5-1 mg of Lorazepam was given orally. A Leksell Model G stereotactic frame was applied after injection of local anesthesia with 0.25% Bupivacaine with epinephrine 1:200,000 subcutaneously to the pin sites. Volumetric 1-mm slice thickness contrast-enhanced T1- and T2-weighted magnetic resonance imaging was performed with a 1.5 T magnetic resonance image scanner. The trigeminal nerve was localized in axial, coronal, and sagittal planes. Targets were determined and treatment planning was performed by a team consisting of a neurosurgeon, a radiation oncologist, and a physicist. Patients who have not had prior GKRS were treated with doses between 80 and 85 Gy prescribed to the maximum dose, with a median treatment dose of 80.9 Gy, delivered to a single isocenter by using a 4-mm collimator. The isocenter was placed along the trigeminal nerve, typically in the prepontine cistern or near its entrance into Meckel's cave, such that the 20 Gy or less isodose line was tangential to the brainstem surface. Collimator plug patterns were utilized when necessary to ensure that the brainstem did not exceed a tolerable maximum dose of 20 Gy.

Ipsilateral repeated GKRS was offered, but only to patients who initially experienced significant pain relief with the first GKRS procedure for more than 6 months, but then had recurrence of pain. During the time of this study, the repeat GKRS dose utilized was 45 Gy prescribed to the maximum dose, which was delivered to a single isocenter by using a 4-mm collimator. No attempt was made to replicate isocenter placement from the initial GKRS treatment.

### Follow-up and statistical analysis

Data were collected by detailed clinical evaluations obtained from medical records, as well as telephone follow-up survey. Each treated side was assessed separately and the outcome results were based on the total number of sides treated ( $n = 14$ ).

Initial response rate was defined as improvement of pain symptoms within the first 6 months of treatment. Overall, facial pain outcomes were defined using the Barrow Neurological Institute Pain Intensity Scale as follows: Class I: No pain, no medications; Class II: Occasional pain, no medications; Class IIIa: No pain, medication controlled; Class IIIb: Pain, medication controlled; Class IV: Pain, not medication controlled; and Class V: No pain relief. Excellent outcome was defined as groups I and II (no pain), good outcome as groups IIIa and b (some pain adequately controlled with medication), and poor outcome as groups IV and V (pain, not adequately controlled). Both excellent (I and II) and good (IIIa and b) outcomes were considered effective treatments of TN with GKRS. Treatment failure was defined as pain outcomes of IV and V on follow-up.

Data on toxicity were also collected and subjectively defined by the patient as none, mild, or bothersome. Toxicity was defined as paresthesias, dysesthesias, altered/loss of taste, bite weakness, numbness, or loss of corneal sensation.

Outcomes and toxicities were compared to historical outcomes of unilateral treatment of TN patients ( $n = 53$ ) treated with GKRS at Tufts Medical Center during 1999-2002.<sup>[19]</sup> The Chi-square test was used to test for differences in toxicity rates. The Kaplan–Meier method was used to estimate time until trigeminal pain recurrence for each group. The log-rank test was used to compare pain-free duration between groups. Left and right sides on the same patients were treated as independent measures, i.e. 14 sides in total were analyzed. Each side treated with GKRS was considered individually with respect to follow-up and outcome. Long-term results for each side treated included sides that underwent repeated treatment with GKRS.

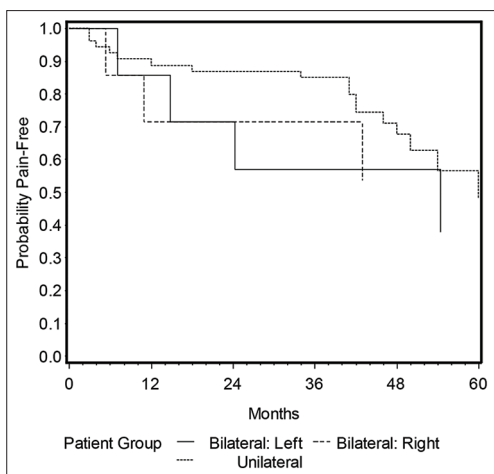
## RESULTS

The rate of bilateral TN was 2.3%. Follow-up ranged from 22 to 89 months. Median follow-up time was 58 months. In our study, the average time for development of contralateral symptoms was approximately 13 months.

Initial response rate to GKRS was seen in 13/14 nerves treated. Outcomes were excellent in 5/14 nerves, good in 1/14, and poor in 8/14 of nerves treated in this patient cohort. Our latest follow-up time ranged from 22 to 89 months, with a median follow-up time of 58 months. Overall median time-to-failure was 54 months. Excellent outcome on the left side was seen in two patients and median time-to-failure was 54 months. Excellent outcome on the right side was noted in four of the seven patients. As in less than 50% of the patients the treatment for right-sided TN failed, we could not calculate a median time-to-failure. There was no statistically significant difference in treatment outcomes between the left and right sides (log-rank  $P = 0.48$ ), although the sample size was small [Figure 1]. At the last follow-up, only 2/7 patients were still taking medications, one on carbamazepine only and the other on carbamazepine with Baclofen. They reported adequate pain relief with these medications. Follow-up in these patients was 72 months and 43 months, respectively.

### Pain control rate

Using the Kaplan–Meier product limit method, our analysis of GKRS for bilateral TN demonstrated a pain control rate of 80% at 12 months and 65% at 36 months [Figure 2]. Compared with our long-term unilateral TN cohort, there was no statistically significant difference in outcome or time-to-failure (log-rank  $P = 0.63$ ) [Figure 2]; there was also no statistically significant difference in the rate of toxicity ( $P = 0.63$ ).<sup>[19]</sup>



**Figure 1: Kaplan–Meier plot of bilateral TN patient outcomes by side and unilateral TN patient outcomes as time-to-failure in months**

### Repeat GKRS treatment

There were three repeat GKRS treatments for two patients who experienced recurrence of symptoms after initially obtaining relief following GKRS. The repeat dose was 45 Gy to the previously treated side. The first patient had one side retreated, while the other had recurrence of symptoms at both sides and, therefore, had both sides retreated.

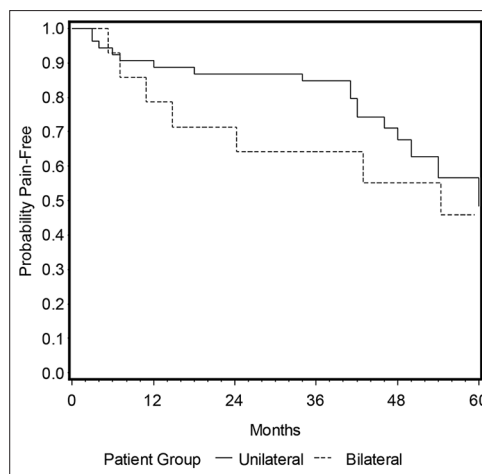
### Toxicity

Of the total number of sides treated ( $n = 14$ ), six sides had some symptoms of toxicity; there was no statistically significant difference with respect to side ( $P = 1.00$ ). Bothersome side effects were reported in 4/14 nerves treated. Of the four treatments that resulted in bothersome side effects, two were in a patient with MS and one was in a patient who had undergone MVD prior to the GKRS.

## DISCUSSION

There are a few studies in the literature describing treatment for bilateral TN, but to our knowledge, there is no study to date that has examined the long-term efficacy of GKRS in the treatment of patients with bilateral TN. Brisman's study evaluated whether RFE with or without glycerol denervation benefited patients with bilateral TN.<sup>[2]</sup> In a cohort of 32 patients, he demonstrated that RFE for bilateral TN showed a high initial pain relief rate, with pain recurrence in 28% of patients over an interval of 1-72 months. Postoperative complications included dysesthesias in approximately 10% of patients, keratitis in 10%, and cranial palsies in 3% of patients.

More recently, Bozkurt *et al.* published one of the largest series of patients treated for bilateral TN with radiofrequency rhizotomy.<sup>[1]</sup> In their cohort of 89 patients with bilateral TN, 54 underwent treatment for both sides



**Figure 2: Kaplan–Meier plot of combined bilateral TN patient outcomes and unilateral TN patient outcomes as time-to-failure in months**

with a total of 146 radiofrequency rhizotomy procedures performed for both sides. While all the patients had bilateral TN, some were treated medically and responded, and therefore, did not undergo a rhizotomy on that side. Initial success was noted in 86 of the 89 patients (96.6%) after the first rhizotomy; however, this included patients who underwent rhizotomy treatment for only one side. Early recurrence of pain within 6 months was observed in 12.3% of patients, while late recurrence defined as greater than 6 months occurred in 28% of patients during an average follow-up period of  $101.71 \pm 77.7$  months. Complications from the procedure which included diminished or absent corneal reflex, masseter paresis, or painful dysesthesias occurred in 17 of the 89 patients treated (19%).

Pollack *et al.* described their 14-year experience with MVD for treatment of bilateral TN.<sup>[17]</sup> They studied a total of 32 patients, of whom 10 patients underwent bilateral MVDs with recurrence-free rates after one operation per treated side being 100% and 78% at 1 and 5 years, respectively. Second unilateral MVD surgeries were performed in two patients and with these procedures included, symptom control rates were 100% and 92% at 1 and 5 years after surgery, respectively. The long-term results of bilateral TN patients in the study of Pollack *et al.* included those of patients who had undergone bilateral but also unilateral MVD despite having bilateral symptoms. In contrast, all of our patients with bilateral TN were treated with bilateral GKRS.

Using the Kaplan–Meier product limit method, our analysis of GKRS for bilateral TN demonstrated a pain control rate of 80% at 12 months and 65% at 36 months [Figure 2]. The long-term outcomes were calculated to be excellent in 5, good in 1, and poor in remaining 8 of the 14 sides treated in our bilateral TN patients. This relatively low rate of excellent and good

outcomes can be explained by our median follow-up time of 58 months, which includes patients who had follow-up ranging up to 89 months. As these patients are followed for a longer period of time, more recurrences of pain are seen. While the success rate is not as high as rates obtained with other techniques, GKRS should be considered for treatment of bilateral TN when other treatment modalities have failed.

The longer the patients with unilateral TN are followed, the more likely it is that they may develop contralateral symptoms.<sup>[2]</sup> Peet and Schneider reported an increase in the incidence of bilaterality from 2.7 to 5.9% over a 10-year follow-up period.<sup>[16]</sup> Pain occurrence on the contralateral side of the face accompanying the initial unilateral symptoms was observed at an average of  $124.7 \pm 87.13$  months in Bozkurt *et al.*'s study.<sup>[1]</sup> In our study, the average time for development of contralateral symptoms was much shorter, which was approximately 13 months.

### Repeated GKRS for bilateral TN

We had two patients who had repeated GKRS for recurrent symptoms. Both patients received 80 Gy for the first treatment. The first patient had a history of MS and initially had received treatment for right-sided TN. At the latest follow-up of 4 years and 11 months, the patient remained symptom-free on the right side. Contralateral left-sided TN symptoms were treated approximately 8 months after the first treatment to the right side. Time to treatment failure on the left was 14 months, at which time he was retreated at a dose of 45 Gy. Unfortunately, his left-sided symptoms recurred approximately 2 months after his second treatment, and since then, he has also undergone RFE, without any symptomatic relief. Therefore, while his right-sided symptoms were considered treated effectively, his left-sided TN was considered a treatment failure. The second patient was treated with 80 Gy to her right nerve and symptoms recurred approximately 10 months thereafter. She subsequently underwent a retreatment with 45 Gy on the right side, and at a follow-up of 71 months, she has remained symptom-free on her retreated right side. She has also remained pain-free on the contralateral left side which she was treated for 4 years after her initial treatment of her right side. Therefore, repeat GKRS should be offered to patients who experienced initial pain relief, as it may provide durable long-term symptom relief.

Repeated GKRS in patients with unilateral TN who had recurrent symptoms gave adequate pain relief in 75% of patients, albeit with some bothersome numbness in 24% and severely bothersome numbness in 2% of patients.<sup>[24]</sup> Dvorak *et al.*'s study reviewing second GKRS results suggested a dose-response relationship between the cumulative dose received and

the side effects.<sup>[5]</sup> In addition, patients treated with a higher dose may experience higher rates of trigeminal nerve dysfunction.<sup>[4]</sup> In our cohort, all the patients with bothersome dysesthesias underwent only one GKRS treatment at a dose of 80 Gy. Thus, in this small cohort, radiation dose was not correlated with post-treatment dysesthesias.

### History of prior surgical procedure

Multiple studies have also shown that a history of prior invasive surgical procedure predicts a worse outcome after GKRS.<sup>[4,6]</sup> Four of the seven patients treated in our cohort with GKRS also had other treatments for their TN [Table 1]. The median pain-free time for this group was 28.82 months. All these patients had pain returning on the side treated with other procedures. There was no statistically significant difference ( $P = 0.14$ ) between patients who were treated with other procedures in addition to GKRS and patients treated only with GKRS. Given this, we believe that GKRS may still provide some benefit to patients with bilateral TN who had previously been treated with other modalities.

### MS associated bilateral TN

TN associated with MS has been reported to occur at a younger age and to carry a higher likelihood of bilaterality.<sup>[8,9,20,21]</sup> Kondziolka *et al.*'s series evaluating MS-TN patients treated with GKRS commented that "poorer results" were found with MS-TN patients.<sup>[11,12]</sup> In addition, Brisman observed that there was a tendency for MS-TN patients in whom no prior procedure had been performed to benefit more often than those who have had a previous procedure.<sup>[3]</sup> Our cohort had two patients with MS who presented with typical symptoms of TN. Both these patients had undergone other surgical procedures prior to GKRS for their MS-TN. These patients had recurrence of pain on both sides, with an earlier time to pain recurrence on the side previously treated with other procedures. This emphasizes that having MS with bilateral TN symptoms poses a difficult treatment challenge.

### CONCLUSION

Though rare, effective treatment for bilateral TN is crucial to improve the quality of life of those afflicted. While there are multiple treatment options available for TN patients, it is the physician's responsibility, along with that of the patient to select a treatment method that considers the patient's age, comorbidities such as history of MS, and prior procedures. Our study and review of the literature on treatment of bilateral TN suggests that GKRS is the least invasive treatment with low risk of side effects and, therefore, should be considered as a salvage treatment option for patients with bilateral TN in whom other options may have failed.



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