

Original Article

Gamma knife radiosurgery for typical trigeminal neuralgia: An institutional review of 108 patients

Ameer L. Elaimy^{1,2}, Andrew F. Lamm^{1,2}, John J. Demakas¹, Alexander R. Mackay¹, Wayne T. Lamoreaux², Robert K. Fairbanks², Robert D. Pfeffer³, Barton S. Cooke^{1,2}, Benjamin J. Peressini⁴, Christopher M. Lee²

¹Department of Neurosurgery, Gamma Knife of Spokane, Spokane, WA, ²Department of Radiation Oncology, Gamma Knife of Spokane and Cancer Care Northwest, Spokane, Washington, ³Department of Radiation Oncology, Rockwood Health System, Spokane, WA, ⁴DataWorks Northwest, Coeur d'Alene, Idaho, USA

E-mail: Ameer L. Elaimy - aelaimy@hotmail.com; Andrew F. Lamm - alamm@carroll.edu; John J. Demakas - jdemakas@me.com; Alexander R. Mackay - gkspokane@armackay.net; Wayne T. Lamoreaux - wayne.lamoreaux@ccnw.net; Robert K. Fairbanks - robert.fairbanks@ccnw.net; Robert D. Pfeffer - rpfeffer@gmail.com; Barton S. Cooke - bo@gkspokane.com; Benjamin J. Peressini - benperessini@dataworksnnw.com;

*Christopher M. Lee - lee@ccnw.net

*Corresponding author

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Abstract

Background: In this study, we present the previously unreported pain relief outcomes of 108 patients treated at Gamma Knife of Spokane for typical trigeminal neuralgia (TN) between 2002 and 2011.

Methods: Pain relief outcomes were measured using the Barrow Neurological Institute (BNI) pain intensity scale. In addition, the effects gender, age at treatment, pain laterality, previous surgical treatment, repeat Gamma Knife radiosurgery (GKRS), and maximum radiosurgery dose have on patient pain relief outcomes were retrospectively analyzed. Statistical analysis was performed using Andersen 95% confidence intervals, approximate confidence intervals for log hazard ratios, and multivariate Cox proportional hazard models.

Results: All 108 patients included in this study were grouped into BNI class IV or V prior to GKRS. The median clinical follow-up time was determined to be 15 months. Following the first GKRS procedure, 71% of patients were grouped into BNI class I-IIIb (I = 31%; II = 3%; IIIa = 19%; IIIb = 18%) and the median duration of pain relief for those patients was determined to be 11.8 months. New facial numbness was reported in 19% of patients and new facial paresthesias were reported in 7% of patients after the first GKRS procedure. A total of 19 repeat procedures were performed on the 108 patients included in this study. Following the second GKRS procedure, 73% of patients were grouped into BNI class I-IIIb (I = 44%; II = 6%; IIIa = 17%, IIIb = 6%) and the median duration of pain relief for those patients was determined to be 4.9 months. For repeat procedures, new facial numbness was reported in 22% of patients and new facial paresthesias were reported in 6% of patients.

Conclusions: GKRS is a safe and effective management approach for patients diagnosed with typical TN. However, further studies and supporting research is needed on the effects previous surgical treatment, number of radiosurgery procedures, and maximum radiosurgery dose have on GKRS clinical outcomes.

Key Words: Barrow Neurological Institute pain intensity scale, gamma knife radiosurgery, trigeminal neuralgia

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INTRODUCTION

Trigeminal neuralgia (TN) is a disorder of cranial nerve (CN) V that affects approximately 4.3 per 100,000 persons per year.^[8] The International Association for the Study of Pain describes TN as intense, sudden, usually unilateral, shock-like or lancinating episodes of pain in one or more of the three divisions of the trigeminal nerve.^[2] Patients who suffer from TN most commonly experience severe facial pain while brushing teeth, chewing, talking, combing hair, and touching the face. While evidence suggests that the majority of TN cases are the consequence of focal compression of the entry zone of the root of the trigeminal nerve,^[12] patients may also experience trigeminal-related facial pain secondary to a brain tumor or multiple sclerosis (MS).^[1]

With >15,000 patients diagnosed with TN per year, finding optimal courses of treatment in select patient subsets is imperative for clinicians.^[3] Medication in the form of anticonvulsants and antidepressants is the first line of treatment in achieving facial pain control. However, many patients become resistant or experience bothersome side-effects from the pharmaceuticals, which include memory deficits, nausea, insomnia, confusion, sedation, and neuropathy.^[3] For patients where medication has failed, neurosurgical intervention is often the next facial pain management approach. The surgical modalities for TN treatment include craniotomy with microvascular decompression (MVD) or other surgical techniques that have the ability to destroy or block specific parts of the trigeminal ganglion or root.^[2,12] Although neurosurgery has proven to be effective in achieving facial pain control, it is contraindicated for a fraction of patients and is known to come with many potential complications due to its invasive nature.

Beginning in the 1950s, Professor Lars Leksell used radiosurgical techniques to perform gangliotomies targeted at the gasserian ganglion.^[11] In recent years, stereotactic radiosurgery using the Gamma Knife has emerged as a popular primary and repeat treatment modality for patients with medically^[10] and surgically^[7] refractory TN. The efficacy of Gamma Knife radiosurgery (GKRS) is associated with the sub-millimeter precision of its image-guided target. Unlike the surgical alternatives, GKRS can be offered to virtually every patient, is performed on an outpatient basis, and is the most minimally invasive neurosurgical procedure for patients who suffer from TN. In addition to the relatively low incidence of procedure-related complications, GKRS is an attractive management approach for medication intolerable patients who are contraindicated from neurosurgery and for patients who prefer the minimally invasive of radiosurgery. In various published reports analyzing the efficacy of GKRS for TN, 59-94% of patients experienced some level of facial pain

relief.^[5] However, questions remain regarding the duration of facial pain relief, as well as the effects previous surgical treatment, number of GKRS procedures, and maximum radiosurgery dose have on patient clinical outcomes. For this reason, we retrospectively report on our experience with the 108 patients with a diagnosis of typical TN treated with GKRS at our institution.

MATERIALS AND METHODS

Patient population

Between 2002 and 2011, 143 patients with medically refractory TN were treated at Gamma Knife of Spokane (Deaconess Hospital, Spokane, WA). Of the 143 patients, 23 were excluded from this study due to a diagnosis of atypical TN (continuous burning pain confined to the trigeminal nerve). An additional 12 patients with typical TN were lost during follow-up, which leaves 108 patients in the present retrospective analysis.

After obtaining approval from institutional review board (IRB) Spokane (IRB 1554) and the University of Washington Human Subjects Division (Human Subjects Application 36306), the following pretreatment factors were recorded from the patient's medical records: Gender, age at first GKRS treatment, age at repeat GKRS treatment (if applicable), history of MS, pain laterality, original pain distribution, and previous surgical treatment. Table 1 shows the patient population baseline characteristics and radiosurgery dose selection grouped by number of GKRS procedures. The median patient age at the first GKRS procedure was determined to be 67 years (22-94) and the median patient age at repeat GKRS procedures was determined to be 72 years (48-91). Eight patients (7.4%) had a history of MS. A majority of the patients were female and patients experienced facial pain more commonly on the right side. Before the first GKRS procedure, 12 patients (11%) had undergone prior MVD or percutaneous procedures. The decision to proceed with GKRS was based on pharmacological failure, pain recurrence following surgical treatment, patient preference, and at the recommendation of the treating physician.

Gamma knife radiosurgery technique

All patients were treated using the Model C Leksell ⁶⁰Co Gamma Knife. Before the GKRS procedure, a local anesthetic was applied to the patient's head to facilitate pain-free placement of the stereotactic head frame. Gadolinium enhanced magnetic resonance imaging of the head within the coordinate frame was performed to allow a neurosurgeon, radiation oncologist, and medical physicist to concurrently plan the radiosurgery treatment. In the majority of patients, the dorsal root entry zone of CN V was the radiosurgical target where a single 4-mm isocenter was

Table 1: Patient population baseline characteristics and maximum radiosurgery dose grouped by trigeminal neuralgia treatment episode

Patient characteristic	Treatment order			
	First n (%)	Second n (%)	Third n (%)	All n (%)
Gender				
Female	69 (64)	10 (56)	0 (0)	79 (62)
Male	39 (36)	8 (44)	1 (100)	48 (38)
Total	108 (100)	18 (100)	1 (100)	127 (100)
Age group				
20-39	4 (4)	0 (0)	0 (0)	4 (3)
40-59	27 (25)	4 (22)	0 (0)	31 (24)
60-79	56 (52)	10 (56)	1 (100)	67 (53)
80+	21 (19)	4 (22)	0 (0)	25 (20)
Total	108 (100)	18 (100)	1 (100)	127 (100)
History of multiple sclerosis				
Yes	8 (7)	2 (11)	0 (0)	10 (8)
No	99 (92)	16 (89)	1 (100)	116 (91)
Unknown	1 (1)	0 (0)	0 (0)	1 (1)
Total	108 (100)	18 (100)	1 (100)	127 (100)
Pain laterality				
Left	40 (37)	8 (44)	1 (100)	49 (39)
Right	68 (63)	10 (56)	0 (0)	78 (61)
Total	108 (100)	18 (100)	1 (100)	127 (100)
Original pain distribution				
All	26 (24)	3 (17)	1 (100)	30 (24)
V1	8 (7)	1 (6)	0 (0)	9 (7)
V1-V2	16 (15)	2 (11)	0 (0)	18 (14)
V2	14 (13)	3 (17)	0 (0)	17 (13)
V2-V3	24 (22)	4 (22)	0 (0)	28 (22)
V3	20 (19)	5 (28)	0 (0)	25 (20)
Total	108 (100)	18 (100)	1 (100)	127 (100)
Previous surgical treatment				
Yes	12 (11)	4 (22)	0 (0)	16 (13)
No	96 (89)	14 (78)	1 (100)	111 (87)
Total	108 (100)	18 (100)	1 (100)	127 (100)
Radiation dose maximum				
<84	12 (11)	15 (83)	1 (100)	28 (22)
84	27 (25)	2 (11)	0 (0)	29 (23)
86	41 (38)	1 (6)	0 (0)	42 (33)
>86	28 (26)	0 (0)	0 (0)	28 (22)
Total	108 (100)	18 (100)	1 (100)	127 (100)

placed. However, a 4-mm isocenter was placed at the retrogasserian zone of CN V if the prepontine cistern was determined to be too shallow. This decision is based on an effort to avoid including the brainstem in the 4-mm target. For patients who underwent multiple GKRS procedures, the 4-mm isocenter was placed directly anterior to the first target. The median

maximum GKRS dose delivered to the 50% isodose line was 86 Gy (70-90) for the first treatment and 60 Gy (40-86) for repeat treatments.

Statistical analysis

Treatment episodes were categorically grouped by gender (male, female), age at treatment (20-39, 40-59, 60-79, and ≥ 80), pain laterality (left, right), original pain distribution (V1, V1-V2, V2, V2-V3, V3), previous surgical treatment (yes, no), maximum GKRS dose in Gy (<84, 84, 86, >86), and number of GKRS procedures (first, repeat). For patients who underwent multiple GKRS procedures, each treatment and its subsequent outcome was considered a separate data point. As a result, 127 GKRS procedures were performed on the 108 patients included in this study. Patient age at treatment and maximum GKRS dose were considered continuous variables in multivariate hazard ratio analysis.

Every patient in this study was grouped into class IV or V of the Barrow Neurological Institute (BNI) pain intensity scale prior to GKRS.^[15] The BNI pain intensity scale was also used as a measurement of response to GKRS following both initial and repeat treatments.^[15] Patients were grouped into BNI class I if they experienced complete facial pain relief and did not require medication. Patients were grouped into BNI class II if they experienced a significant reduction in facial pain and did not require medication. Patients were grouped into BNI class IIIa if they experienced complete facial pain relief with the use of medication. Patients were grouped into BNI class IIIb if they experienced persistent facial pain that could be adequately managed with medication. Patients were grouped into BNI class IV if they experienced persistent facial pain that could not be adequately managed with medication. Patients were grouped into BNI class V if they did not experience a reduction in facial pain.

We also constructed Andersen 95% confidence intervals for the median time of pain relief for the gender groups, age at GKRS groups, pain laterality groups, previous surgical treatment groups, number of GKRS procedures groups, and maximum radiosurgery dose groups. Exact conditional maximum likelihood estimates were used to calculate the hazard ratio of each group and Fisher 95% confidence intervals were constructed for statistical significance testing between the hazard ratios of each group. Finally, the Cox proportional hazard model was used in a multivariate analysis of the gender groups, age at GKRS groups, pain laterality groups, previous surgical treatment groups, number of GKRS procedures groups, and maximum radiosurgery dose groups. All statistical analyses used StatsDirect Version 2.5.7 (StatsDirect Ltd., Altrincham, UK) and SigmaPlot Version 11.0 (SYSTAT Software, Inc., San Jose, CA). Statistical Significance was set at a $P < 0.05$.

RESULTS

Pain relief outcomes

We performed a total of 127 GKRS procedures on 108 patients with a diagnosis of typical TN between 2002 and 2011. Specifically, 108 patients underwent at least one GKRS procedure, 18 patients underwent at least two GKRS procedures, and one patient underwent three GKRS procedures for a total of 19 repeat treatments. The median clinical follow-up time was determined to be 15 months (0-113). Following the first GKRS procedure, 71% of patients were grouped into BNI class I-IIIb (I = 31%; II = 3%; IIIa = 19%; IIIb = 18%) and the median duration of pain relief for those patients was determined to be 11.8 months. Figure 1 illustrates the time period (in months) in which facial pain recurred for patients grouped into BNI class I-IIIb following the first GKRS procedure. Specifically, 75% of patients experienced pain relief 3.5 months following GKRS, 50% of patients experienced facial pain relief 11.7 months following GKRS, and 25% of patients experienced facial pain relief 22.3 months following GKRS. Following the second GKRS procedure, 73% of patients were grouped into BNI class I-IIIb (I = 44%; II = 6%; IIIa = 17%, IIIb = 6%) and the median duration of pain relief for those patients was determined to be 4.9 months. Figure 2 illustrates the time period (in months) in which facial pain recurred for patients grouped into BNI class I-IIIb following repeat GKRS procedures. Specifically, 75% of patients experienced facial pain relief 1.8 months following repeat GKRS, 50% of patients experienced facial pain relief 4.6 months following repeat GKRS, and 25% of patients experienced facial pain relief 65.7 months following repeat GKRS. Table 2 shows the distribution of TN treatment episodes by BNI class.^[15]

An initial statistical analysis was performed using univariate hazard ratio confidence intervals. Within

each treatment category, a reference group was selected (gender = female, age ≤ 60 years, pain laterality = right, previous surgical treatment = no, number GKRS procedures = one, maximum GKRS dose ≤ 84 Gy) and was tested against the other group's hazard ratios. Univariate hazard ratio analysis of age groups indicated that patients < 60 years of age experienced superior levels of facial pain relief when compared with patients ≥ 60 years of age ($P = 0.038$). Univariate hazard ratio analysis of gender groups, pain laterality groups, previous surgical treatment groups, number of GKRS procedures groups, and maximum radiosurgery dose groups did not yield any statistically significant results.

Further statistical analysis was conducted using multivariate Cox regression analysis with hazard ratio estimates and confidence intervals. The multivariate analysis utilized the same reference groups as the univariate analysis. However, patient age at treatment and maximum radiosurgery dose were considered continuous variables. It was found on multivariate hazard ratio analysis that gender ($P = 0.210$), age at

Table 2: Distribution of trigeminal neuralgia treatment episodes by Barrow Neurological Institute class

Pain relief measure	Treatment order			
	First <i>n</i> (%)	Second <i>n</i> (%)	Third <i>n</i> (%)	All <i>n</i> (%)
Barrow neurological institute class				
I	33 (31)	8 (44)	0 (0)	41 (32)
II	3 (3)	1 (6)	0 (0)	4 (3)
IIIa	21 (19)	3 (17)	0 (0)	24 (19)
IIIb	19 (18)	1 (6)	0 (0)	20 (16)
IV	2 (2)	0 (0)	0 (0)	2 (2)
V	30 (28)	5 (28)	1 (100)	36 (28)
Total	108 (100)	18 (100)	1 (100)	127 (100)

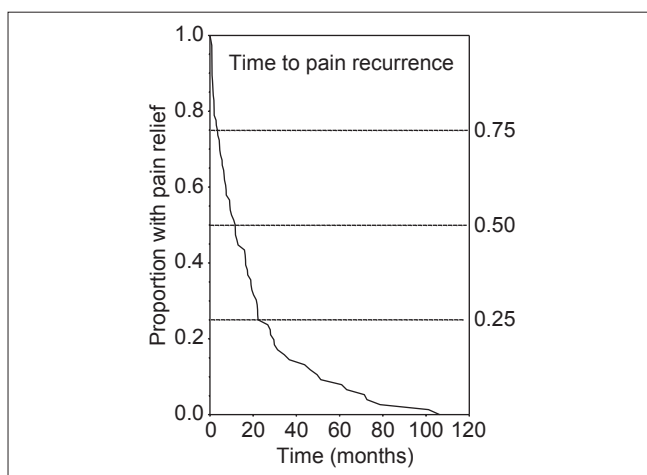


Figure 1: Time period (in months) in which facial pain recurred for patients grouped into BNI class I-IIIb following the first GKRS procedure

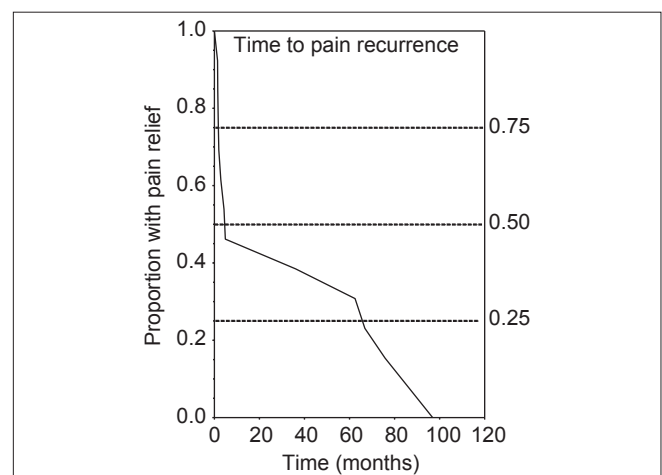


Figure 2: Time period (in months) in which facial pain recurred for patients grouped into BNI class I-IIIb following repeat GKRS procedures

treatment ($P = 0.343$), pain laterality ($P = 0.375$), previous surgical treatment ($P = 0.196$), number of GKRS procedures ($P = 0.374$), and maximum radiosurgery dose ($P = 0.533$) did not statistically impact facial pain relief.

Procedure-related complications

Of the 12 patients who underwent previous surgical treatment, 6 (50%) reported facial numbness prior to GKRS and 1 (8%) reported facial paresthesias prior to GKRS. Following the first GKRS procedure, new facial numbness was reported in 20 patients (19%) and new facial paresthesias were reported in 8 patients (7%). Of the 18 patients who underwent repeat GKRS procedures (19 treatments), 3 (17%) had already experienced facial numbness as a result of the first GKRS procedure. Following repeat GKRS procedures, new facial numbness was reported in four patients (22%) and new facial paresthesias were reported in one patient (6%). No other complications were observed in the 108 patients included in this study.

DISCUSSION

Because the difficulty of radiosurgical targeting of the trigeminal nerve virtually disappeared with the advent of magnetic resonance imaging, GKRS has emerged as an effective and minimally invasive treatment modality for patients with medically refractory TN. In addition, many physicians have grown to recognize GKRS as the primary management approach for patients who are thought to be poor surgical candidates due to comorbidities or advanced age. Although several retrospective and some prospective studies have been published analyzing the efficacy of GKRS in the management of TN-related facial pain, questions remain regarding treating patients in specific clinical scenarios and their subsequent outcomes.^[5] Our comprehensive analysis evaluates the time in which facial pain recurs, as well as the effects patient population baseline characteristics have on GKRS clinical outcomes.

The BNI pain intensity scale is a commonly used entity to assess the efficacy of radiosurgical treatment for patients with TN.^[15] In our analysis, 76 patients (71%) were grouped into BNI class I-IIIb following their first GKRS procedure. In addition, 75% of patients grouped into BNI class I-IIIb following their first GKRS procedure experienced pain relief 3.5 months following treatment. The latency between treatment and effect should be discussed with patients who are candidates for both GKRS and neurosurgery. This is due to the more rapid effect of pain relief that the neurosurgical options could provide. In a previous article, we reviewed the body of world literature from 2006 to 2011 analyzing GKRS for TN treatment and identified 13 studies where the BNI pain intensity scale was used to assess single-treatment GKRS.^[5] In these published reports,

patients grouped into BNI class I-IIIb ranged from 59% to 94%.^[5] A major limitation of retrospective reviews is the variable demographic information and ability to tolerate treatment of the studied patient population. However, this cumulative evidence suggests that GKRS provides TN patients with increased levels of facial pain control and should be presented as a viable treatment option to all TN patients, especially those who would be better-served by a minimally invasive modality.

Many clinicians take into account the surgical history of TN patients when recommending GKRS. In our analysis, previous surgical history did not significantly impact pain relief. Fountas *et al.*^[6] compared the outcomes of 106 patients with idiopathic TN based on whether or not they had undergone previous surgical or radiosurgical procedures. The authors reported that the patient group without a history of previous surgical or radiosurgical procedures exhibited superior pain relief outcomes, with 1- and 2-year complete pain relief rates of 82.5% and 78%, respectively. The 1- and 2-year complete pain relief of the patients who had previously undergone neurosurgical or radiosurgical procedures was determined to be 65.4% and 63.5%, respectively. Little *et al.*^[13] found a statistically significant correlation between GKRS failure in patients with a history of MVD. We feel that additional clinical outcome studies are needed that contain more strict criteria for the patient population than has been previously reported to ultimately assess the durability of pain relief in patients who undergo GKRS for TN after experiencing facial pain recurrence following neurosurgery.

At our institution, patients who underwent one GKRS procedure did not statistically differ in term of facial pain relief when compared with patients who underwent more than one GKRS procedure. Similar to our results, Verheul *et al.*^[16] concluded that patients treated with repeat GKRS exhibit similar facial pain control rates when compared with patients treated a single time with GKRS in their analysis of 365 patients. In addition, Park *et al.*^[14] did not find differences in the time to initial response, time to pain recurrence, and overall pain relief when comparing patients treated with one versus multiple GKRS procedures. As in our study, the authors reported that patients treated more than once with GKRS are more likely to experience facial numbness and other facial sensory changes following the procedure. We suggest that patients be educated on the increased likelihood of experiencing procedure-related complications before proceeding with repeat GKRS.

Defining the optimal maximum GKRS dose that can be delivered safely to select patient subsets is an area of controversy in the radiosurgical management of TN. In our study, maximum GKRS dose did not impact facial pain relief when treated as a continuous variable in multivariate hazard ratio analysis. Kim *et al.*^[9] compared the outcomes of 66 TN patients treated with a maximum GKRS dose of 80 Gy

with 44 patients treated with a maximum GKRS dose of 85 Gy. Although the two studied groups did not statistically differ in terms of facial pain relief and radiation-induced complications, the authors reported that the patients in the 85 Gy group experienced a more rapid response to treatment when compared with the patients in the 80 Gy group. Dvorak *et al.*^[4] analyzed initial (median = 85 Gy) and retreatment (median = 45 Gy) GKRS doses in 28 patients diagnosed with TN. The authors did not report any facial pain control and patient morbidity predictors in their analysis. However, they did compare their study outcomes with seven published retreatment reports and found that successful levels of pain control (>50%) were correlated with cumulative maximum radiosurgery doses >130 Gy, as well as new trigeminal nerve dysfunction (>20%).

CONCLUSIONS

GKRS is an effective treatment modality for patients diagnosed with typical TN that provides patients with a significant duration of facial pain relief when used as a primary or repeat management approach. Although our retrospective analysis did not find previous surgical treatment, number of radiosurgery procedures, and maximum radiosurgery dose to statistically impact facial pain relief, further clinical studies and supporting research is needed to assess the durability of GKRS for specific patient subsets.

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