Results of a third Gamma Knife radiosurgery for trigeminal neuralgia

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OBJECTIVE Gamma Knife radiosurgery (GKRS) is a commonly used procedure for medically refractory trigeminal neuralgia (TN), with repeat GKRS routinely done in cases of pain relapse. The results of a third GKRS in cases of further pain relapse have not been well described. In this study, the authors report the largest series of patients treated with a third GKRS for TN to date.

METHODS Retrospective review of institutional electronic medical records and a GKRS database was performed to identify patients who had been treated with a third GKRS at the authors' institution in the period from 2010 to 2018. Telephone interviews were used to collect long-term follow-up data. Pain outcomes were measured using the Barrow Neurological Institute (BNI) pain intensity scale, with a score $\leq$ IIIb indicating successful treatment.

RESULTS Twenty-two nerves in 21 patients had sufficient follow-up to determine BNI pain score outcomes. Eighteen of 22 cases had a successful third GKRS, with a median durability of pain relief of 3.88 years. There was no significant difference in the durability of pain relief after a third GKRS compared with those of institutional historical controls of prior series of first and second GKRS procedures. Ten cases had new or worsening facial numbness, with 1 case being bothersome. Four cases of toxicity other than facial numbness were reported, including 1 case of corneal abrasions and possible neurotrophic keratopathy. No cases of anesthesia dolorosa were reported. No factors predicting treatment success or the durability of pain relief were identified. Nonnumbness toxicity was more common in those with a proximally placed shot at the third GKRS.

CONCLUSIONS A third GKRS is an effective treatment option for TN patients who have pain relapse after repeat GKRS. Pain outcomes of a third GKRS are similar to those following a first or second GKRS. Toxicity is tolerable in patients with a distally placed shot at the third GKRS.

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KEYWORDS trigeminal neuralgia; Gamma Knife; stereotactic radiosurgery; repeat GKRS; third GKRS; pain

TRIGEMINAL neuralgia (TN) is a rare facial pain syndrome typically characterized by episodic, lancinating, severe pain in one or more distributions of the trigeminal nerve.¹ For patients who have pain refractory to medical therapy, Gamma Knife radiosurgery (GKRS) is a well-described noninvasive option with excellent pain relief rates and minimal toxicity. However, the durability of treatment is limited and pain frequently recurs.^{2–4} In such cases, repeat GKRS can be considered, offering similar efficacy but slightly increased rates of toxicity.^{5,6} Additional GKRS for multiply recurrent pain is not well described, with the literature limited to case reports and a

single retrospective series thus far.^{7–10} In the present retrospective review, we aim to report the outcomes of patients who underwent at least three GKRS procedures to a single trigeminal nerve for medically refractory TN.

Methods

Patient Population

Retrospective review of a single institutional electronic medical record (EMR) system and GKRS database was performed to identify patients who had undergone at least three GKRS procedures to a single trigeminal nerve in the

ABBREVIATIONS BNI = Barrow Neurological Institute; EMR = electronic medical record; GKRS = Gamma Knife radiosurgery; MS = multiple sclerosis; REZ = root entry zone; TN = trigeminal neuralgia.

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FIG. 1. Example of a physical dose composite plan of three GKRS procedures to the left trigeminal nerve with the pons (blue), trigeminal nerve (white), petrous dura (pink), and REZ (yellow) contoured. Figure is available in color online only.

period from 2010 to 2018. Twenty-four cases of unilateral TN in 23 patients treated with a third GKRS were identified. Demographic data, past medical history, treatment outcomes and toxicity, and dosimetric data were obtained from the EMRs and GKRS database. Symptoms consistent with Burchiel type 1 pain were termed “classic pain.”¹¹ All other patients were classified as having nonclassic pain. Patients with symptomatic TN per the Burchiel criteria were classified as having classic or nonclassic pain, depending on their symptoms.^{5,12,13} Telephone interviews were used to collect long-term follow-up data whenever possible. Multiple attempts to contact all patients were made unless the EMR listed them as deceased. Long-term follow-up and dosimetric data from prior databases were used if they could not be obtained otherwise. Institutional review board approval and a waiver of informed consent were obtained for this study.

radiosurgery Technique

On the day of the procedure, a Leksell model G head-frame was placed by a neurosurgeon. High-resolution noncontrast MRI of the brain was performed. A treatment plan was then generated using the Leksell GammaPlan treatment planning software (Elekta AB). A single shot using a 4-mm collimator was used for all treatments. Early in the study period, the shot was placed proximally on the nerve so that the 50% isodose line was tangential to the pons surface. Later in the study, the initial shot coordinate was placed more distally with the 20% isodose line tangential to the pons surface in an attempt to decrease toxicity based on new data.¹⁴ Institutional practice at the second GKRS was to place the shot in the location opposite the initial shot to minimize overlap.⁵ At the third

GKRS, the shot was placed to minimize overlap with prior shots as much as possible, but this was often limited by patient anatomy. Institutional practice for each subsequent GKRS was generally a decrease of 5 Gy from the prior GKRS dosing; for example, a patient who had received 85 Gy at the first GKRS was typically prescribed 80 Gy at the second GKRS and 75 Gy at the third GKRS.⁵ All doses were prescribed to the 100% isodose line.

radiosurgery Dosimetry

Prescription dose and dose to the surface of the pons, root entry zone (REZ), and petrous dura were obtained from the treatment planning system. Definitions of anatomical landmarks have been described elsewhere.³ In cases in which a treatment plan could not be accessed, available data from the EMR and prior databases were used. Six patients had at least one inaccessible treatment plan. For patients with all treatment plans available, composite plans of all treatment plans were generated using MIM version 6.9.3 (MIM Software Inc.). The trigeminal nerve, pons, REZ, and petrous dura were contoured, and the cumulative maximal and volumetric doses to these structures were calculated (Fig. 1). Integral dose to the trigeminal nerve within the 50% isodose line for each GKRS procedure was calculated using GammaPlan treatment planning software for all patients whose treatments were planned with same-day MRI, as previously described.¹⁵

Follow-Up

Patients were instructed to begin tapering off medical therapy for TN once their pain had resolved. They were scheduled for an initial follow-up appointment approxi-

TABLE 1. Summary of characteristics among 21 TN patients with 22 nerves treated with a third GKRS

Variable	Value
Median age at 3rd GKRS in yrs among 22 cases (IQR)	74.7 (65.1–81.3)
Sex, no. of cases (%)	
Male	10 (45.5)
Female	12 (54.5)
Side of 3rd GKRS, no. of cases (%)	
Rt	12 (54.5)
Lt	10 (45.5)
Bilat	1 (4.5)
Type of pain, no. of cases (%)	
Classic	21 (95.5)
Nonclassic	1 (4.5)
Bilat symptoms, no. of cases (%)	
Yes	3 (13.6)
No	19 (86.4)
History, no. of patients (%)	
MS	6 (28.6)
Family history of TN	2 (9.5)
Hypertension	13 (61.9)
Diabetes	4 (19.0)
Procedures prior to 1st GKRS, no. of cases (%)	
None	13 (59.1)
MVD	2 (9.1)
PTR	3 (13.6)
MVD & PTR	3 (13.6)
Nerve blocks/peripheral procedures	1 (4.5)
Procedures btwn 1st & 2nd GKRS, no. of cases (%)	
None	21 (95.5)
MVD	1 (4.5)
Median interval btwn 1st & 2nd GKRS in yrs among 22 cases (IQR)	1.6 (1.0–3.7)
Procedures btwn 2nd & 3rd GKRS, no. of cases (%)	
None	19 (86.4)
MVD	1 (4.5)
PTR	2 (9.1)
Median interval btwn 2nd & 3rd GKRS in yrs among 22 cases (IQR)	4.0 (2.7–5.8)
Smoking status, no. of patients (%)	
Never smoker	7 (33.3)
Former smoker	12 (57.1)
Current smoker	2 (9.5)

MVD = microvascular decompression; PTR = percutaneous trigeminal rhizotomy.

mately 3–6 months after GKRS, and if they had achieved acceptable pain control by the time of their first follow-up, they were then seen on an as-needed basis. No routine posttreatment neuroimaging was performed.

Treatment Outcomes

The Barrow Neurological Institute (BNI) pain intensity scale was used to measure pain outcomes for each individual nerve that had been treated with at least three GKRS procedures at our institution.¹⁶ Pain response was defined as a BNI score $\leq$ IIIB, as reported in multiple prior series

of GKRS for TN.^{2,3,10} Patients who never attained a pain response of a BNI score $\leq$ IIIB were counted as having a duration of relief of 0.

Statistical Analysis

Descriptive analyses were performed using count (frequency) and median (interquartile range) for categorical and continuous variables, respectively. Clinical characteristics of patients who had experienced pain relief, numbness, or other toxicity were compared to those of patients who had not by using the Fisher's exact and chi-square tests, as appropriate. Time to treatment failure was calculated as the duration from the date of GKRS to the date of pain worse than a BNI score IIIB (i.e., BNI score $>$ IIIB), estimated using the Kaplan-Meier method and compared across groups using the log-rank test. Patients with continued pain relief at the time of the last follow-up were censored at that point. Dosimetric factors were compared between patient groups that did or did not experience a given outcome (pain relief, numbness, or other toxicity) by using the Wilcoxon test. Univariable logistic regression models were performed to evaluate predictors of toxicity after a third GKRS. All statistical analyses were performed using R version 3.5 (R Foundation for Statistical Computing).

Results

Patient Population and Pain Response

Patient baseline characteristics are listed in Table 1. The median age at the time of the third GKRS was 74.7 years. Six patients had a history of multiple sclerosis (MS), 3 cases had bilateral symptoms, and 1 patient had nonclassic TN symptoms. The patient with nonclassic symptoms had been treated with a third GKRS given good responses to the first two GKRS procedures and our belief that the patient was at high risk for more invasive interventions because of medical comorbidities. Treatment outcomes for a third GKRS are summarized in Table 2. At a median follow-up of 3.33 years, 22 cases had sufficient follow-up data to determine pain outcomes. Of these cases, 18 attained pain relief with a BNI pain intensity score $\leq$ IIIB after the third GKRS, which was considered a treatment response. The median time to pain relief was 1 week (range 0–4.5 weeks) after treatment. The median time to treatment failure (BNI score $>$ IIIB) after the third GKRS was 3.88 years (95% CI 0.82–not reached; Fig. 2). The 1-, 3-, and 5-year rates of at least BNI score IIIB pain relief were 62.7%, 53.8%, and 40.3%, respectively. One patient was known to have died during the follow-up period; prior to death, this patient had experienced pain relapse after the third GKRS. There was no significant difference in the durability of pain relief (i.e., BNI score $\leq$ IIIB) between the first and the second (HR 1.05, 95% CI 0.77–1.43, $p = 0.77$) and the first and the third GKRS (HR 1.10, 95% CI 0.56–2.14, $p = 0.79$) when looking at historical controls of prior series of first and second GKRS procedures at our institution (Fig. 3).^{3,5} Three patients were treated with a fourth GKRS after pain relapse following the third GKRS.

Toxicity

Toxicity after a third GKRS is summarized in Table 2.

TABLE 2. Treatment outcomes and toxicity after a third GKRS

Variable	Value
BNI score prior to 3rd GKRS, no. of cases (%)	
IV	9 (40.9)
V	13 (59.1)
Best BNI score after 3rd GKRS, no. of cases (%)	
I	5 (22.7)
II	3 (13.6)
IIIa	4 (18.2)
IIIb	6 (27.3)
IV	0 (0)
V	4 (18.2)
BNI score at last FU, no. of cases (%)	
I	3 (13.6)
II–IIIb	9 (40.9)
IV–V	10 (45.5)
Median time to pain response in wks among 11 cases (IQR)	1 (0–4.5)
Facial numbness, no. of cases (%)	10 (45.5)
Mild	6 (27.3)
Bothersome	1 (4.5)
Unable to determine severity	3 (13.6)
Dry eye, no. of cases (%)	3 (13.6)
Corneal abrasion, no. of cases (%)	1 (4.5)

FU = follow-up.

Among the patients with no reported toxicity, the median follow-up was 1.97 years (IQR 0.83–5.68 years). After the third GKRS, 10 cases experienced new or worsening facial numbness. One case of bothersome facial numbness was noted; the patient in this case had received a maximal cumulative dose to the pons greater than the third quartile (125.35 Gy). No cases of anesthesia dolorosa were reported.

Four cases had ocular complications; 3 experienced mild dry or irritated eye, and 1 had corneal abrasions and possible neurotrophic keratopathy. The patient in the latter

FIG. 3. Kaplan-Meier curve showing time to treatment failure (BNI score > IIIb) after the third GKRS compared to those of historical cohorts of first and second GKRS procedures. There was no statistically significant difference between the three groups ($p = 0.96$).

case had had preexisting nonbothersome facial numbness after the second GKRS, which worsened after the third procedure. The doses for the first, second, and third GKRS were 90, 80, and 80 Gy, respectively. The first GKRS plan could not be retrieved from older storage media. The maximal dose to the pons at the second and third GKRS were 66.5 Gy and 50.4 Gy, respectively. Both of the cases with ocular complications and cumulative dosimetric plans had received maximal doses to the pons above the median, with one above the third quartile. All 3 patients who underwent a fourth GKRS experienced new toxicity.

Dosimetric and Treatment Data

Dosimetric data for the third GKRS were available for all 22 cases. Treatments for all patients were planned using MRI (19 cases) or CT and fused prior MRI (3 cases). Seven cases had a proximally placed shot (50% isodose line tangential to the pons) at the third GKRS, whereas the remainder had a shot placed distally on the trigeminal nerve. The median radiosurgical dose at the third GKRS was 75 Gy. The median integral dose at the third GKRS was 1.2 mJ. Composite plans were generated for 14 cases. The median maximal radiosurgical dose to the trigeminal nerve was 222.4 Gy, and the median maximal dose to the pons was 93.1 Gy. Detailed dosimetric information is shown in Table 3. Over the course of treatments, the median trigeminal nerve volume relative to baseline (prior to the first GKRS) was 0.6 (IQR 0.50–0.70).

Predictors of Pain Relief

Patient factors including MS, hypertension, diabetes, smoking status, or family history of TN were not associated with rates or durability of relief after a third GKRS. Additionally, pain relief or any numbness after a second GKRS was not associated with rates or durability of pain relief after a third GKRS. No dosimetric factors, including integral dose at the third GKRS and cumulative integral dose, were predictive of treatment efficacy.

FIG. 2. The 1-, 3-, and 5-year rates of pain relief (BNI score $\leq$ IIIb) were 62.7%, 53.8%, and 40.3%, respectively, with a median time to treatment failure (BNI score > IIIb) of 3.88 years.

TABLE 3. Dosimetric and treatment data

Variable	No. of Cases	Value
Median dose at 1st GKRS in Gy (IQR)	22	90 (85–90)
Median dose at 2nd GKRS in Gy (IQR)	22	80 (80–85)
Median dose at 3rd GKRS in Gy (IQR)	22	75 (75–80)
To pons	22	17.4 (13.8–28.9)
To REZ	22	9.5 (6.3–14.6)
To petrous dura	22	33.8 (21.1–52.3)
Median distance to landmarks at 3rd GKRS in mm (IQR)		
To pons	22	4.5 (3.7–5.3)
To REZ	22	6.2 (5.0–7.7)
To petrous dura	22	3.2 (2.4–4.1)
Median integral dose at 3rd GKRS in mJ (IQR)	19	1.2 (0.6–1.5)
Median cumulative integral dose after 3rd GKRS in mJ (IQR)	14	4.3 (3.9–5.5)
MRI or CT for treatment planning		
MRI	19	86.4%
CT only	0	0
CT & MRI	3	13.6%
Shot placement at 3rd GKRS		
Proximal (50% IDL tangential to pons)	7	31.8%
Distal (20% IDL tangential to pons)	15	68.2%
Median vol of trigeminal nerve in cm ³ (IQR)		
1st GKRS	14	0.1 (0.08–0.12)
2nd GKRS	14	0.09 (0.07–0.1)
3rd GKRS	14	0.06 (0.05–0.07)
Median composite doses in Gy (IQR)		
Max to trigeminal nerve	14	222.4 (200.8–232.3)
Max to pons surface	14	93.1 (73.9–115)
Max to REZ	14	80.5 (59.9–92.8)
Max to petrous dura	14	133.2 (100.9–165.6)
Median composite dose to volumes in cm ³ (IQR)		
Trigeminal nerve vol receiving 200 Gy	14	0.005 (0–0.01)
Trigeminal nerve vol receiving 160 Gy	14	0.02 (0.01–0.02)
Trigeminal nerve vol receiving 120 Gy	14	0.03 (0.02–0.05)
Trigeminal nerve vol receiving 85 Gy	14	0.04 (0.03–0.06)
Pons vol receiving 42.5 Gy	14	0.03 (0.01–0.05)
Pons vol receiving 17 Gy	14	0.29 (0.24–0.4)
Pons vol receiving 12 Gy	14	0.61 (0.53–0.77)

IDL = isodose line.

Predictors of Toxicity

No factors predictive of facial numbness after a third GKRS were identified. Toxicity other than facial numbness was associated with a proximally placed shot at the third GKRS: none of the 15 cases treated with a distal shot experienced nonnumbness toxicity as compared to 4 of 7 cases treated with a proximal shot ($p = 0.005$). Addition-

TABLE 4. Dosimetric predictors of toxicity other than facial numbness after a third GKRS

Variable at 3rd GKRS	No Toxicity (n = 18)	Toxicity (n = 4)	p Value
Dose to pons in Gy	16.85 (12.18–19.55)	41.55 (35.8–45.45)	0.006
Distance to pons in mm	4.6 (4.43–5.78)	2.85 (2.8–3.1)	0.004
Vol of nerve in cm ³	0.06 (0.06–0.08)	0.04 (0.03–0.04)	0.033
Max total dose to REZ in Gy	74.79 (55.21–84.80)	138.10 (121.51–154.70)	0.045

n = number of cases.

Values represent the median (IQR) unless indicated otherwise.

ally, the only patient who developed bothersome numbness had a proximally placed shot at the third GKRS. In addition to proximal shot placement, an increasing dose (in Gy) to the pons at the third GKRS, a decreasing distance from the isocenter to the pons surface at the third GKRS, a decreased trigeminal nerve volume at the third GKRS, and an increased cumulative dose to the REZ were associated with an increased risk of nonnumbness toxicity after a third GKRS (Table 4). Neither integral dose at the third GKRS nor cumulative integral dose was predictive of nonnumbness toxicity. The relationship between the dose to the pons at the third GKRS and the risk of nonnumbness toxicity (OR 1.02, 95% CI 1.08–1.75, $p = 0.04$) is shown in Fig. 4.

Discussion

GKRS for TN has been well described, as has repeat GKRS in cases of pain relapse or treatment failure.^{2,4–6} However, many patients experience pain relapse even after repeat GKRS, with approximately 50% of patients suffering pain relapse within 5 years of repeat GKRS.^{5,6} Treatment options for these patients are often limited. A third

FIG. 4. Relationship between dose to the pons at the third GKRS and the risk of toxicity other than facial numbness.

GKRS has been reported in one small retrospective series, as well as in cases reports.^{7–10} Here, we report the largest series to date of patients who have undergone a third GKRS for repeated treatment failure. Our results showed that a third GKRS is generally an effective treatment, with 18 of 22 cases attaining pain relief (i.e., BNI pain intensity score $\leq$ IIb). The efficacy of the treatment was also durable, with a median duration of pain relief of 3.88 years and a 5-year actuarial pain relief rate of 40.3%, findings similar to those previously reported.¹⁰ These results are promising considering the multiply recurrent nature of TN pain and the large proportion of patients with MS in this series, who are more likely to relapse. There was no statistically significant difference in the durability of a third GKRS as compared to those of first or second GKRS procedures, which were represented by large historical cohorts of patients treated at our institution. This is encouraging given the likely resistant nature of pain in the group of patients requiring a third GKRS.

A primary concern when offering a third GKRS for TN is the risk of severe toxicity. In this series, a third GKRS was generally well tolerated, with 10 (45.5%) of 22 cases experiencing new or worsening facial numbness, a rate similar to that for repeat GKRS for TN at our institution but higher than the rates reported for repeat GKRS in other series.^{5,6} A somewhat higher rate of sensory dysfunction is to be expected in the setting of multiple repeat procedures, so this rate is not unexpected. The relatively long duration of follow-up after the third GKRS among patients without any toxicity (median 1.97 years) makes it unlikely that further toxicity would develop with longer follow-up. Furthermore, while the rates of toxicity are high in this series, they do compare favorably to those in many series of percutaneous procedures, with reported dysesthesia and corneal anesthesia rates both reaching 20% in some series.¹⁷ In patients who have undergone multiple ablative procedures for TN, a third GKRS may ultimately be the least toxic option for those who are not candidates for microvascular decompression.

Multiple factors predicting nonnumbness toxicity were observed, including an increasing dose to the pons at the third GKRS, a decreasing distance from the isocenter to the pons surface at the third GKRS, and an increasing cumulative dose to the REZ. These three factors are likely related and indicative of the toxicity driven by damage to the proximal trigeminal nerve or the trigeminal nerve fibers as they travel through the pons.

One case of bothersome numbness was observed, and no cases of anesthesia dolorosa were reported. Ocular complications were seen in 4 cases. Three of the 4 cases were limited to mild dry eye, but 1 patient reported severe corneal abrasions and possible neurotrophic keratopathy. Cumulative dosimetric data could not be obtained for this patient because of an inaccessible initial GKRS plan; however, simple addition of the maximal doses to the pons at the second and third GKRS alone would have led to a maximal pons dose above the third quartile (116.9 vs 115 Gy). While the rate of dry eye is somewhat concerning, the relatively advanced age in our patient population (median age 74.7 years) may be a confounding factor, as the incidence of dry eye has been reported to increase with ad-

vancing age beyond 50 years, and 2 of the 4 cases of ocular complications occurred in patients older than 85 years at the time of the third GKRS.¹⁸

As previously mentioned, toxicity other than facial numbness was associated with an increasing dose to the pons at the third GKRS, more proximal shot placement at the third GKRS, and an increasing cumulative dose to the REZ at the third GKRS. An increase in toxicity with proximal shot placement and an increasing REZ dose has been previously reported in the setting of initial GKRS.^{3,14} Moreover, the only patient to experience bothersome numbness after the third GKRS had had a proximally placed shot, as well as a cumulative dose to the pons above the third quartile. While these data are hypothesis generating and will need validation in independent data sets, in cases of a third GKRS, we recommend placing the shot distally on the nerve and minimizing the dose to the pons as much as possible. In cases in which this can be done, the treatment is very well tolerated, with no cases of bothersome numbness or other toxicity reported.

An increased risk of toxicity other than facial numbness was also seen in patients with a smaller trigeminal nerve volume at the third GKRS. A primate study of GKRS to the trigeminal nerve has shown focal axonal degeneration at a dose of 80 Gy and nerve necrosis at a dose of 100 Gy.¹⁹ The extremely high cumulative doses in the present study likely led to at least some long-term axonal degeneration and necrosis, which could result in a decreased volume of the nerve. Having fewer functional axons at the time of radiosurgery would likely increase the risk of new or worsening symptoms with any further axonal loss, explaining the increased toxicity with decreased nerve volume. A similar relationship has not been noted in other studies investigating dose-volume relationships and outcomes of initial GKRS for TN; however, the doses delivered in these studies were substantially less than the cumulative dose received after a third GKRS and may not have reached a critical threshold of axonal loss to cause toxicity.^{15,20,21}

In cases of treatment failure after a third GKRS, we have offered a fourth GKRS in a very limited number of cases; only 3 patients in the present series underwent a fourth GKRS. All 3 of them had either MS or a family history of TN and were therefore believed to be poor candidates for microvascular decompression; they also declined or were not candidates for percutaneous ablation procedures. All 3 patients had maintained pain relief at the last follow-up with no severe toxicity; however, 2 of them had experienced new or worsening facial numbness, and all 3 experienced a new nonnumbness toxicity (2 with dry or irritated eye and 1 with dysequilibrium). While the data are extremely limited by the minimal numbers, we believe that a fourth GKRS can be considered in very select cases.

This series has several limitations. While it is the largest series to date on the subject, the total numbers are still very low, limiting the power to detect differences in subgroups and predictive factors. The single-institution, retrospective nature of the study carries an inherent selection bias, limiting the study's generalizability. The use of telephone interviews also introduces the possibility of interview bias, although we attempted to limit this by having all interviews conducted by a single physician who was

not involved in treatment planning. The long interval between GKRS and the telephone interview also introduces the possibility of recall bias. Finally, the patient population in this study is heterogeneous, including a substantial proportion of patients with MS and one with nonclassic pain, which further adds to the difficulty in generalizing the findings of the study.

Conclusions

GKRS is a well-established treatment modality for medically refractory TN, with repeat GKRS routinely performed if needed. However, the procedure's main limitation is the lack of durability of pain relief, with patients frequently experiencing pain relapse by 5 years after repeat GKRS. The use of a third GKRS in this situation is controversial. To our knowledge, this is the largest series of patients treated with a third GKRS for TN to date. A third GKRS for TN appears to be an effective treatment, particularly given the multiply recurrent nature of TN pain, with results similar to those seen in the initial and repeat GKRS setting. Toxicity rates in this series, particularly the high rates of apparent corneal toxicity, are concerning. However, no severe toxicity was noted among the patients with a distally placed shot. In well-selected patients, a third GKRS is a reasonable treatment option, with efficacy similar to that of an initial GKRS and acceptable toxicity with distal placement of the shot along the nerve to minimize the dose delivered to the brainstem.

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Author Contributions

Conception and design: Helis, Laxton, Chan. Acquisition of data: Helis, Jacobson, Lucas. Analysis and interpretation of data: Helis, Hughes, Lucas, Cramer, Tatter, Laxton, Chan. Drafting the article: Helis, Cramer, Tatter. Critically revising the article: Helis, Hughes, Munley, Bourland, Jacobson, Cramer, Tatter, Laxton, Chan. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Helis. Statistical analysis: Hughes. Study supervision: Chan.

Supplemental Information

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