Gamma Knife Radiosurgery for Multiple Sclerosis-Associated Trigeminal Neuralgia

**BACKGROUND:** Trigeminal neuralgia in the setting of multiple sclerosis (MS-TN) is a challenging condition to manage that is commonly treated with Gamma Knife radiosurgery (GKRS; Elekta AB). However, data regarding the efficacy of this treatment are somewhat limited, particularly for repeat GKRS.

**OBJECTIVE:** To report outcomes of GKRS for MS-TN from a cohort study.

**METHODS:** Retrospective review of our GKRS database identified 77 cases of unilateral MS-TN (UMSTN) in 74 patients treated with GKRS between 2001 and 2016, with 37 cases undergoing repeat GKRS. Background medical history, treatment outcomes and complications, and dosimetric data were obtained by retrospective chart reviews and telephone interviews.

**RESULTS:** Eighty-two percent of UMSTN cases achieved Barrow Neurological Institute (BNI) IIIb or better pain relief following initial GKRS for a median duration of 1.1 yr. Estimated rates of pain relief at 1, 3, and 5 yr were 51, 39, and 29% respectively. Eighty-eight percent achieved BNI IIIb or better pain relief after repeat GKRS for a median duration of 4.0 yr. Estimated rates of pain relief at 1 and 3 yr were 70 and 54%, respectively. Median doses for initial and repeat GKRS were 85 and 80 Gy to the 100% isodose line, respectively. Those with MS-TN had a shorter duration of BNI IIIb or better pain relief after initial (4.6 vs 1.1 yr), but not repeat GKRS (3.8 vs 4.0 yr) compared to a historical cohort from our institution.

**CONCLUSION:** GKRS is an effective, well-tolerated treatment for patients with MS-TN. More durable relief is often achieved with repeat GKRS.

**KEY WORDS:** Gamma Knife, Multiple sclerosis, Radiosurgery, Trigeminal neuralgia

**ABBREVIATIONS: BNI, Barrow Neurological Institute; CI, confidence interval; CT, computed tomography; EMR, electronic medical record; GKRS, Gamma Knife radiosurgery; HR, hazard ratio; IDL, isodose line; IQR, interquartile range; I-TN, idiopathic trigeminal neuralgia; MS, multiple sclerosis; REZ, root entry zone; SRS, stereotactic radiosurgery; TN, trigeminal neuralgia; UMSTN, unilateral MS-TN**

idiopathic trigeminal neuralgia (I-TN) is a facial pain syndrome classically described as unilateral, severe, electric, or lancinating pain in areas innervated by one or more trigeminal nerve divisions, caused by vascular compression of the trigeminal nerve root entry zone (REZ). There are variants of the syndrome where the pain is thought to be due to a different etiology, such as TN caused by multiple sclerosis (MS-TN). In MS-TN, the pain is thought to be caused by demyelinating plaques in the region of the trigeminal nerve REZ. MS-TN is a challenging condition to manage and is frequently resistant to medical or surgical intervention.
study aims to report the outcomes of MS-TN patients treated with GKRS at our institution.

METHODS

Patient Population

A retrospective review of our GKRS database was performed to identify patients with MS-TN treated with GKRS between 2001 and 2016. All patients with a history of MS and TN treated with at least one GKRS procedure at our institution were included. The number of eligible patients determined the study size. This study conforms to STROBE reporting criteria. Seventy-seven cases of unilateral MS-TN (UMSTN) in 74 patients were treated with GKRS at our institution between 2001 and 2016, 37 of which received more than one treatment. Thirty-five initial and 22 repeat GKRS have been previously reported.8,10 Three patients received GKRS to both trigeminal nerves. Background medical history, treatment outcomes and complications, and dosimetric data were obtained by retrospective review of the electronic medical record (EMR). Patient demographics and relevant past medical history are summarized in Table 1. Institutional review board approval, including a waiver of informed consent, was obtained for this study.

Radiosurgical Technique and Dosimetry

The radiosurgical technique used has been previously described.8 On the day of GKRS, a Leksell Model G stereotactic headframe (Elekta AB) was placed by a neurosurgeon. A high-resolution magnetic resonance image of the brain or noncontrasted computed tomography (CT) was obtained. Treatment plans were generated using Leksell GammaPlan software (Elekta AB). Early in the study, the shot for initial GKRS was placed proximally so that the 50% isodose line (IDL) was tangential to the pons surface. Later in the study, it was placed more distally in order to reduce the risk of facial numbness.16 At repeat GKRS, the shot was placed more distally in order to place the 50% isodose line tangential to the pons surface. Later in the study, it was placed more distally in order to reduce the risk of facial numbness.16 At repeat GKRS, the shot was placed in the opposite location, and the dose slightly reduced to decrease toxicity.8,9,17,18 Patients with MS-TN were treated with the same institutional dose guidelines as patients with I-TN. CT-only planning was done using direct visualization of the nerve or by placing the shot several millimeters proximal to the impression of the nerve on the petrous bone.8,19 Dosimetric data were obtained from the treatment planning software. Prescription dose as well as dose and distance to the REZ, pons surface, and the petrous dura were recorded as shown in Figure 1.9 REZ dose was defined as the point dose at the midpoint of the nerve entering the pons. Dose to the pons was defined as the maximal point dose to the pons surface. Dose to the petrous dura was defined as the maximal point dose to the midpoint of the nerve where it intersects the petrous dura. Twelve initial and 3 repeat GKRS plans could not be retrieved from older storage media. In these cases, data were obtained from prior databases and the EMR when possible.

Follow-up Procedures

After GKRS, patients were instructed to begin tapering their medications once their pain had resolved and scheduled for a follow-up appointment 3 to 6 mo after treatment. If they had achieved pain control at that time, they were instructed to return as needed. Long-term follow-up data, including data regarding time to pain relief, durability and toxicity of treatment, and any remaining data that were not available in the EMR were obtained by standardized telephone interview conducted by a single physician in January 2017. An attempt to contact all patients except those listed as deceased in the EMR was made.

Treatment Outcomes

Treatment outcomes were evaluated using the Barrow Neurological Institute (BNI) pain scale.20 A BNI IIIb or better response was considered a successful treatment. Complete failure was defined as BNI IV or IV pain. Partial treatment failure was defined as patients who relapsed from BNI I to BNI II-IIIb without reaching BNI IV-V. Patients who never achieved pain relief were defined as having a pain relief duration of 0.

Statistical Analysis

Patient and treatment characteristics were summarized with descriptive statistics. Median and interquartile range (IQR) and frequency and relative frequency were used for continuous and categorical variables, respectively. Time-to-event outcomes beginning at the date of GKRS were estimated using the Kaplan–Meier method, and stratified outcomes were compared with the log-rank test. Patients were
FIGURE 1. Axial T1 MRI showing an initial GKRS plan with the shot placed distally so that the 20% IDL (circle) was tangential to the pons surface, and the center of the shot at the crosshairs. A, The petrous dura was defined as the dose to the midpoint of the nerve as it intersected the petrous dura surface. B, The pons dose was defined as the maximal point dose to the pons surface. C, The REZ was defined as the midpoint of the nerve intersection with the brainstem. The distances from the isocenter to the petrous dura, pons, and REZ were measured at 4.2, 4.9, and 9.2 mm, respectively.

censored at their last follow-up. Univariate Cox proportional hazards methods were used to estimate the hazard ratios (HR) associated with patient and treatment-related variables for time-to-event outcomes. Logistic regression models were created for variables of interest for BNI IIIb failure after initial GKRS. The aforementioned methods were applied to both initial GKRS and the subgroup of patients receiving repeat GKRS. P values of ≤ .05 were considered statistically significant. Patients with partially missing data were only included in analyses of variables where no data were missing. R version 3.3.2 software (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

RESULTS

Outcome Data

Detailed outcome and toxicity data for initial and repeat GKRS are shown in Tables 2 and 3 respectively.

Initial GKRS

Seventy four of 77 cases of UMSTN had sufficient follow-up to determine BNI pain score outcomes. Three patients had both nerves treated sequentially. Sixty one out of 74 cases (82%) of UMSTN achieved BNI IIIb or better pain relief following initial GKRS, with 18 cases (24%) achieving BNI I pain relief. Median time to BNI IIIb pain relief was 4.5 wk. At a median follow-up of 2.5 yr (IQR 0.8-5.9 yr), the estimated median duration of BNI IIIb or better pain relief after initial GKRS was 1.1 yr (95%

TABLE 2. Outcomes and Toxicity of Initial GKRS

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<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Median (IQR)/%</th>
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<td>BNI prior to GKRS</td>
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<tr>
<td>IV</td>
<td>25</td>
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<td>V</td>
<td>52</td>
<td>67.5</td>
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<tr>
<td>BNI after GKRS</td>
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<td></td>
</tr>
<tr>
<td>I</td>
<td>18</td>
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<tr>
<td>II</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td>IIIa</td>
<td>18</td>
<td>24.3</td>
</tr>
<tr>
<td>IIIb</td>
<td>23</td>
<td>31.1</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>1.4</td>
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<td>Time to BNI I response (weeks)</td>
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<tr>
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<td>8</td>
<td>3</td>
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<tr>
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<td>0</td>
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<tr>
<td>Corneal dryness</td>
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<td>4.1</td>
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</tr>
</tbody>
</table>

BNI = Barrow Neurological Institute; GKRS = Gamma Knife radiosurgery; IQR = interquartile range; N = number.

TABLE 3. Outcomes and Toxicity of Repeat GKRS

<table>
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<tr>
<th>Variable</th>
<th>n</th>
<th>Median (IQR)/%</th>
</tr>
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<tbody>
<tr>
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<tr>
<td>II</td>
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<td>IIIa</td>
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<td>V</td>
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<td>Time to BNI IIIb response (weeks)</td>
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<tr>
<td>Time to BNI I response (weeks)</td>
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<td>4 (4-8)</td>
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<table>
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<th>Total</th>
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<th>78.8</th>
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<tr>
<td>Unable to determine severity</td>
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<tr>
<td>Anesthesiadolorosa</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Corneal dryness</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

BNI = Barrow Neurological Institute; GKRS = Gamma Knife radiosurgery; IQR = interquartile range; N = number.

Estimated rates of pain relief at 1, 3, and 5 yr were 51, 39, and 29%, respectively. Figure 2A illustrates the Kaplan–Meier curve for BNI IIIb or better pain relief following initial GKRS. At last follow-up, 50 of 74 (68%) of cases had experienced BNI IIIb failure.
The most common complication of initial GKRS was facial numbness, which was seen in 19 cases (26.3%), including 3 cases (4.1%) of bothersome numbness. Three cases (4.2%) developed ipsilateral corneal anesthesia, although none experienced vision loss. No patients experienced anesthesia dolorosa.

**Repeat GKRS**

Thirty-seven cases of UMSTN were treated with repeat GKRS after initial GKRS failure at a median interval of 1.26 yr. Thirty-one of the 37 (84%) treated with repeat GKRS had a successful initial GKRS. Of 34 patients with sufficient follow-up to determine pain outcomes, 30 (88%) achieved BNI IIIb or better pain relief, with 12 (35%) achieving BNI I following repeat GKRS. Median time to BNI IIIb pain relief was 4.5 wk. At a median follow-up of 2.3 yr (IQR 1.1-3.3 yr) from repeat GKRS, the median duration of BNI IIIb or better pain relief after repeat GKRS was 4.0 yr (95% CI 1.9 yr—not calculated). Estimated rates of pain relief at 1 and 3 yr were 70 and 54%, respectively. At last follow-up, 15 of 34 (44%) cases had experienced BNI IIIb failure. Figure 2B illustrates the Kaplan–Meier curve for BNI IIIb or better pain relief after repeat GKRS. There was a trend towards longer durability of pain relief for repeat vs initial GKRS, \( P = .09 \), as shown in Figure 3.

As with initial GKRS, the most common complication experienced was facial numbness, which was seen in 26 cases (78.8%). However, in only one case (2.9%) was the numbness reported as bothersome. Three (8.6%) cases developed new ipsilateral corneal anesthesia. No patients developed anesthesia dolorosa or vision loss.

**Comparison to Historical Controls**

The current series was compared to a large cohort of patients with unilateral I-TN from our institution.8,21 Patients with I-TN had a longer median duration of BNI IIIb or better pain relief after initial GKRS when compared to those with MS-TN (4.6 vs 1.1 yr, \( P < .001 \)), but not after repeat GKRS (3.8 vs 4.0 yr, \( P = .93 \)). Figures 4A and 4B show the Kaplan–Meier curves comparing BNI IIIb pain relief for initial and repeat GKRS in typical TN and MS-TN.

**Dosimetric Data**

The median doses for initial and repeat GKRS were 85 Gy (IQR 85-90) and 80 Gy (IQR 80-80), respectively. The median cumulative dose for cases who received 2 GKRS was 170 Gy (IQR 165-170). Detailed dosimetric data were available for 65 initial GKRS and 30 repeat GKRS plans and are summarized in Table 4.
FIGURE 4. Comparison of GKRS for MS-TN to a large cohort of classical TN treated at our institution. A. Patients with MS-TN (solid line) than those with classical TN (dashed line) had a shorter duration of pain relief after initial GKRS, 1.1 vs 4.6 yr, \( P < .001 \). B. There was no statistically significant difference in durability of pain relief after repeat GKRS between the 2 populations.

Predictors of Pain Relief

No statistically significant predictive factors of duration of pain relief after initial GKRS were identified. Multiple predictors for durability of pain relief after repeat GKRS were identified. Patients with nonclassical symptoms were more likely to have a shorter duration of relief (HR 10.51, \( P = .03 \)). Cases with a higher dose to the pons (HR 1.05, \( P = .03 \)), and REZ (HR 1.05, \( P = .02 \)) were also more likely to have a shorter duration of pain relief. The presence of MS plaques in the ipsilateral pons did not predict for treatment failure after initial (HR 1.44, \( P = .35 \)) or repeat GKRS (HR 1.42, \( P = .68 \)). A successful initial GKRS did not predict for repeat GKRS failure (HR 1.06, \( P = .935 \)).

PredictorsofFacialNumbness

A logistic regression model identified the cumulative dose (\( \beta = .02, P < .01 \)) and the cumulative dose to the pons (\( \beta = .03, P = .02 \)), and petrous dura (\( \beta = .02, P = .03 \)) as predictive of the presence of facial numbness after repeat GKRS. A linear regression identified the cumulative dose delivered as the sole predictor of facial numbness after repeat GKRS (\( \beta = .02, P = .03 \)).

DISCUSSION

Key Results

We report a large, single institution series of MS-TN treated with GKRS, including the largest series of MS-TN patients treated with repeat GKRS reported to date. GKRS for MS-TN is effective and well tolerated, with 82% of cases having a successful initial procedure, and similar success with repeat GKRS after treatment failure. Repeat GKRS had a trend towards longer duration of pain relief, with durability similar to that of repeat GKRS for I-TN.

Initial GKRS

Our results show that GKRS is an effective treatment option for MS-TN, with 82% of patients experiencing pain relief from their
initial GKRS. Durability of pain relief was limited, with a median duration of 1.1 yr, which is significantly less than that for a large cohort of patients with classical TN treated at our institution. The shorter durability of pain relief after GKRS for MS-TN than patients with I-TN has been noted before, including a recently reported large multicenter retrospective series.14 While GKRS was well tolerated overall, the complication rates were on the higher end of the reported range. This could be at least partially explained by the higher doses used and the anterior targeting of shots early in the study.16 This limited durability of pain relief frequently leads to further interventions, including GKRS.

**Repeat GKRS**

Repeat GKRS for MS-TN in the setting of treatment failure or lack of response is a reasonable option, with 88% of cases having a successful GKRS, with a median pain relief duration of 4.0 yr. This result is similar to the durability of pain relief for a large cohort of patients treated with repeat GKRS for I-TN at our institution.8 Previous reports of repeat GKRS for I-TN have noted similar or improved results with repeat GKRS compared with initial GKRS, which is consistent with this series.8,9,22 Higher cumulative doses have been associated with improved pain control in the setting of repeat GKRS, and the relatively high dose used for repeat GKRS may have contributed to the high rates of successful repeat GKRS.23

Repeat GKRS was associated with very high overall rates of facial numbness in this series without an increase in the rates of bothersome numbness or serious complications such as anesthesia dolorosa, which are similar to those reported in the literature for repeat GKRS for I-TN.8,9,18 Patients with MS treated with GKRS for various indications have been reported to have higher toxicity rates than patients without MS.24 A trend in increasing numbness with increasing cumulative dose after repeat GKRS for I-TN has also been reported, which was also seen in this series.23 The relatively high doses and anterior targeting of shots may have contributed to the high rates of facial numbness.

**Predictors of Response and Numbness**

As with I-TN, patients with symptoms consistent with classical TN were more likely to have long-term relief following repeat GKRS than those with nonclassical symptoms.21 As with our previous report, we did not find a relationship between facial numbness and pain response.10 This differs from I-TN, where a relationship between postprocedure facial numbness and pain response has been reported in multiple large series in both the initial and repeat setting.7,9,21,23

Multiple dosimetric factors were found to be predictive of pain relapse and facial numbness after repeat GKRS. In this series a higher dose to the pons and REZ at repeat GKRS were associated with a higher risk of relapse, while in I-TN the opposite relationship would be expected. Higher cumulative total dose, dose to the pons, and dose to the petrous dura were associated with a higher risk of facial numbness after repeat GKRS, as has previously been shown in I-TN.25

There may be an ideal dose range for GKRS for I-TN, with doses above the ideal range resulting in decreased efficacy and increased toxicity, and doses below the ideal range not yielding effective pain relief.26 MS-TN may be similar but with different dose–response levels. The dose threshold needed for effective, durable treatment may be higher than for I-TN, explaining the poor duration of pain relief with initial GKRS, but cumulative doses for 2 GKRS in a short interval may begin to exceed the dose tolerance of the nerve, leading to increasing risk of pain relapse and toxicity.

Biopsies of trigeminal nerves in patients with MS-TN have shown demyelination in the CNS portion of the trigeminal nerve in the absence of vascular compression with different features than nerves with TN due to vascular compression, including evidence of ongoing demyelinating activity.27,28 High doses of radiation to an area with ongoing autoimmune demyelination could potentially trigger further autoimmune damage to the trigeminal system, leading to increased toxicity and failure rates, similar to patients treated for malignant tumors with a combination of radiation and immunotherapy.32 Severe toxicity, including MS flares, has previously been reported in patients with MS who undergo both stereotactic radiosurgery (SRS) and external beam radiation to the brain.24,28,31

Additionally, some patients with MS-TN likely have thalamic or cortically mediated pain. Axonal degeneration in the trigeminal nerve has been reported after SRS doses of 80 Gy in a primate model, which was the median dose delivered for repeat GKRS in this series.33 In cases where the pain is caused by more central lesions, this could lead to a new or worsening deafferentiation pain component.

**Limitations**

While this is one of the largest series reported to date on GKRS for MS-TN, it is still limited by the overall low numbers, which make it difficult to elucidate predictive factors for successful treatment. The median follow-up in this series is relatively short, particularly in comparison to the median duration of pain relief after repeat GKRS. Additionally, this series is limited by its single institution retrospective nature, which introduces selection bias into the treated population. There is also the possibility of recall bias by the patient, particularly with long intervals between GKRS and the telephone interview. This recall bias and the heterogeneity of timing of the interview may have affected the reported efficacy and toxicity rates. This is compounded by the fact that not all patients were able to present for examination by a physician posttreatment. Finally, there is the possibility of interviewer bias when conducting the telephone interview. An attempt to limit this was made by having one author who was not involved in treatment planning conduct all telephone interviews (CAH).

**Generalizability**

While this report has the limitations of a single institution retrospective series, it is one of the largest reported to date. The trend towards improved pain control with repeat GKRS
can be useful in counseling patients after treatment failure. The improved control in those with classical TN symptoms can be used to improve patient selection for repeat GKRS.

CONCLUSION

GKRS is an effective treatment modality for patients with MS-TN, but the durability of pain relief is limited compared to patients with I-TN. Repeat GKRS can be performed if necessary, with results similar to repeat GKRS for I-TN. An increase in facial numbness rates is seen after repeat GKRS without an associated increase in the rates of bothersome numbness or other severe complications. Patients with classical TN symptoms are more likely to have a longer duration of pain relief following repeat GKRS. The ideal dose and targeting of the shot along the trigeminal nerve are unclear in MS-TN and may be different than for patients with I-TN, warranting further study.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

REFERENCES