CNS Spotlight

Trigeminal Nerve Atrophy Predicts Pain Recurrence After Gamma Knife Stereotactic Radiosurgery for Classical Trigeminal Neuralgia

Yong-Sin Hu, MD[*‡]
Cheng-Chia Lee, MD[‡§]
Wan-Yuo Guo, MD, PhD[*‡]
Chung-Jung Lin, MD[*‡]
Huai-Che Yang, MD[‡§]
Hsiu-Mei Wu, MD[*‡]
Kang-Du Liu, MD, MSc[‡§]
Wen-Yuh Chung, MD[‡§]

[*]Department of Radiology, Department of Neurosurgery, Taipei Veterans General Hospital, Taipei, Taiwan; [‡]School of Medicine, National Yang Ming University, Taipei, Taiwan; [§]Neurological Institute, Department of Neurosurgery, Taipei Veterans General Hospital, Taipei, Taiwan

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Correspondence:
Chung-Jung Lin, MD,
Department of Radiology,
Taipei Veterans General Hospital,
No. 201, Shipai Rd,
Sec. 2, Beitou District,
Taipei 112, Taiwan.
E-mail: bcjlin@gmail.com

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BACKGROUND: Trigeminal nerve atrophy and neurovascular compression (NVC) are frequently observed in classical trigeminal neuralgia (CTN).

OBJECTIVE: To determine whether nerve characteristics contribute to Gamma Knife (Elekta AB, Stockholm, Sweden) surgery (GKS) outcomes in unilateral CTN without previous surgery.

METHODS: From 2006 to 2012, 67 patients with unilateral CTN without previous surgery received GKS with a maximal dose of 90 Gy delivered to the trigeminal nerve juxta brainstem. Two evaluators, blinded to the side of pain, analyzed the magnetic resonance images before GKS to obtain the parameters, including nerve cross-sectional area (CSA), vessel type of NVC, and site of NVC along the nerve. Correlations of the parameters with pain relief (Barrow Neurological Institute [BNI] grades I-IIIb) and recurrence (BNI grades VI-V) were made by using Cox regression and Kaplan–Meier analyses.

RESULTS: The median CSA of the symptomatic nerves was significantly smaller than that of the asymptomatic nerves (4.95 vs 5.9 mm^2, $P < .001$). After adjustment for age and sex, larger nerve CSA was associated with lower initial pain relief (hazard ratio 0.81, $P = .03$) and lower pain recurrence after initial response (hazard ratio 0.58, $P = .02$). Patients with nerve atrophy (CSA of $\leq$ 4.4 mm^2 after receiver operating characteristic curve analysis) had a lower 5-yr probability of maintaining pain relief after initial response than those without nerve atrophy (65% vs 86%, $P = .04$).

CONCLUSION: Trigeminal nerve atrophy may predict pain recurrence in patients with initial post-GKS relief of CTN. Arterial and proximal NVC are not predictive of GKS outcomes. Future studies are required to determine optimal treatments for long-term pain relief in patients with CTN and trigeminal nerve atrophy.

KEY WORDS: Clinical outcome, Stereotactic radiosurgery, Trigeminal neuralgia, Trigeminal nerve atrophy, Neurovascular compression, Pain, magnetic resonance imaging

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Trigeminal neuralgia (TN) is a rare condition characterized by episodic electric-shock-like pain in the distribution of trigeminal nerve divisions and is triggered by innocuous stimuli.[1] The pathophysiology of classical trigeminal neuralgia (CTN) remains speculative and is considered to be associated with neurovascular compression (NVC).[2]

Surgical treatments may be indicated for patients with debilitating TN, which is refractory to medical therapy. Currently, the major categories of surgical treatments are microvascular decompression (MVD) and ablative procedures, such as Gamma Knife (Elekta AB, Stockholm, Sweden) surgery (GKS).[3] MVD is more cost-effective and has a lower rate of pain recurrence than GKS.[4,5] GKS is typically performed in patients with high anesthesia risks or a preference for less invasive management strategies. Although GKS achieves adequate pain relief in 75% to 89%

ABBREVIATIONS: 3-D, 3-dimensional; **BNI,** Barrow Neurological Institute; **CI,** confidence interval; **CSA,** cross-sectional area; **CTN,** classical trigeminal neuralgia; **GKS,** Gamma Knife surgery; **HR,** hazard ratio; **MR,** magnetic resonance; **MVD,** microvascular decompression; **NVC,** neurovascular compression; **TN,** trigeminal neuralgia

of patients with CTN at 1 yr, this rate drops to 46% to 58% after 5 yr.[6-8]

Because of the advancements in high-resolution magnetic resonance (MR) imaging techniques, trigeminal nerves can be evaluated noninvasively.[9,10] Studies have demonstrated that nerve characteristics, including NVC and trigeminal nerve atrophy, are more associated with symptomatic nerves than asymptomatic nerves.[11] Therefore, the influences of these nerve characteristics on treatment outcomes were investigated further. For example, some studies have revealed that NVC was associated with pain relief after GKS,[12,13] whereas other studies have not revealed such an association.[14,15] Moreover, studies have demonstrated trigeminal nerve atrophy to be associated with favorable MVD outcomes[16]; however, its influence on GKS outcomes remains relatively unknown. Therefore, the purpose of the present study was to determine whether nerve characteristics, including trigeminal nerve atrophy and NVC, contribute to the GKS outcomes of patients with unilateral CTN without previous surgery.

METHODS

Patients

A waiver of consent for the study protocol was approved by the local institutional review board. From 2006 to 2012, we selected eligible patients from 106 consecutive patients with TN who underwent GKS (Elekta AB) at our center. The indications for GKS were salient pain despite prior aggressive medical therapy or intolerance of adverse drug effects. After excluding patients with secondary TN (n = 6) and those with previous surgery (n = 33; MVD, n = 20; GKS, n = 8; and rhizotomy, n = 5; ≥2 surgeries, n = 1), we enrolled 67 patients (42 women and 25 men) with unilateral CTN in this study. The median symptom duration before GKS was 50 mo (range [R]: 2-252 mo), and the median age at the time of GKS was 64 yr (R: 22-90 yr; Table 1).

Imaging Examinations and Stereotactic Radiosurgery

All patients underwent MR imaging examinations using a 1.5-T MR scanner (Signa HDxt, General Electric Healthcare, Waukesha, Wisconsin) after a Leksell stereotactic frame was fixed to the patient's head. The routine gamma knife planning protocol included gadolinium-enhanced 3-dimensional (3-D) spoiled gradient-recalled (SPGR) imaging (repetition time, 9.3 ms; echo time, 4.2 ms [9.3/4.2]; flip angle, 15°; section thickness, 1 mm; matrix size, 256 × 256; and field of view, 260 × 260 mm) to delineate the trigeminal nerve and its relationship with the surrounding vasculature and brainstem. Stereotactic radiosurgery was performed using the Gamma Knife (Elekta AB) models B (from 2006 to 2007) and 4C (from 2007 to 2012). A single 4-mm isocenter was placed on the trigeminal nerve, typically located 4 mm anterior to the brainstem. The brainstem surface was irradiated at the 20% isodose line with the maximal dose of 18 Gy. The median maximal dose was 90 Gy (R: 83-90 Gy).

Trigeminal Nerve Cross-Sectional Area Measurements

To determine whether trigeminal nerve atrophy affects treatment outcomes, the trigeminal nerve cross-sectional area (CSA) was measured manually as described previously, with some modifications.[17] Axial 3-D SPGR-Gd images were transferred to a workstation (AW VolumeShare 5, General Electric Healthcare) for postprocessing and analysis. Two evaluators (a neuroradiologist and a radiology resident with 16 and 3 yr of experience in neuroimaging, respectively) independently analyzed the images while blinded to the side of pain and treatment outcomes. The CSA was measured at 5 mm from the nerve entry into the pons in a reformatted image plane perpendicular to the nerve course (Figure 1). If the trigeminal nerve was not clearly depicted as separate from the adjacent vasculature at 5 mm from its entry into the pons, the immediately adjacent image was used. The CSAs measured by each evaluator were averaged, and the CSA ratio was calculated as the CSA of the symptomatic nerve divided by that of the contralateral asymptomatic nerve to control for individual variations in nerve size.

TABLE 1. Clinical Characteristics of 67 Patients With Unilateral Classical Trigeminal Neuralgia who Underwent Gamma Knife Surgery[a]

Characteristic	Value (range)	
	Nerve CSA ≤ 4.4 mm² (n = 20)	Nerve CSA > 4.4 mm² (n = 47)
Male/female	7/13	18/29
Median age at the time of GKS, yr	64 (49-90)	63 (22-88)
Side of pain, right/left	14/6	30/17
Distribution of pain		
V1 only/V2 only/V3 only	0/3/4	1/14/8
V1 + V2	1	3
V2 + V3	8	16
V1 + V2 + V3	4	5
Median duration of symptoms before GKS, mo	60 (6-252)	48 (2-17)
Median follow-up, mo	27.5 (13-83)	38 (12-80)
Median time to initial response, mo	2 (1-18)	2 (1-18)
Median maximal dose, Gy	90 (83-90)	90 (85-90)

[a]GKS, Gamma Knife surgery (Elekta AB); CSA, cross-sectional area.

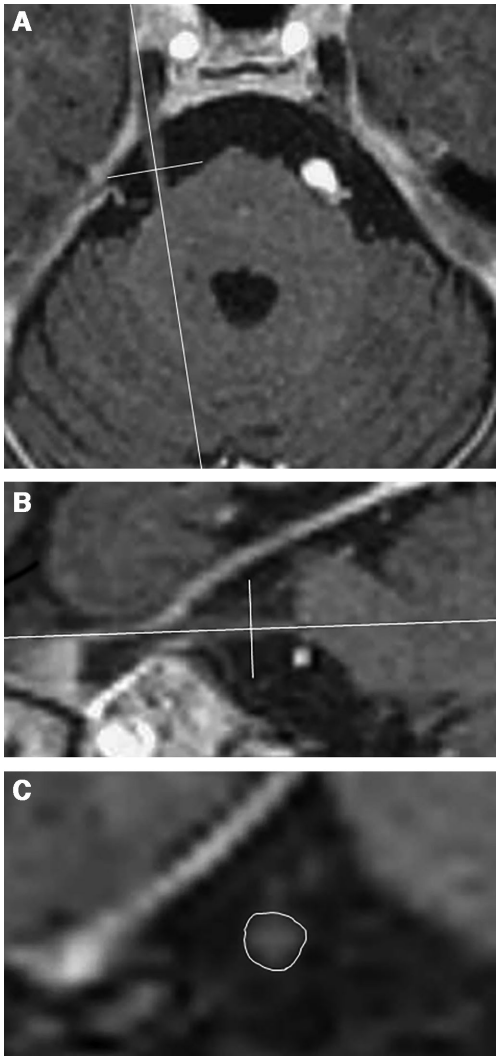

FIGURE 1. A, *Axial 3-D SPGR-Gd image showing the cisternal segment of the right trigeminal nerve. The trigeminal nerve CSA was measured at 5 mm from the nerve entry into the pons in an image plane perpendicular to the nerve course (white line,* **B***).* **C**, *The reformatted tangential cross-sectional view at 5 mm from the pons was magnified to facilitate CSA measurement.*

NVC Assessment

The evaluators analyzed the images to assess the presence, nature (artery or vein), and site of NVC along the trigeminal nerve by consensus reading. The presence of NVC was defined as a vessel in contact with the nerve, deviating the nerve from its presumed normal course, or deforming the nerve.[18] The cisternal segment of the nerve was divided into the proximal and distal halves to its entry into the pons. NVC at the proximal half was recorded, because the central myelin is more likely to fall on the proximal half and is considered vulnerable to symptomatic vascular compression.[9,11]

Clinical Follow-up and Outcome Evaluations

All patients were followed for at least 1 yr in 3- to 6-mo intervals after GKS. Patients' pre- and post-GKS clinical conditions were assessed by administering telephonic questionnaires, which addressed the patterns of facial pain before GKS, the degree of pain relief and facial numbness, medication use, and the time interval between GKS and initial pain relief. For patients with initial pain relief after GKS, the duration of pain relief was calculated as the time interval between initial pain relief and pain recurrence. The degree of pain relief and post-GKS facial numbness were scored using the Barrow Neurological Institute (BNI) pain intensity grades and BNI facial numbness scale, respectively.[19] BNI grades I to IIIb were defined as adequate pain relief, whereas BNI grade IV or V was defined as pain recurrence. To facilitate statistical analysis, BNI facial numbness scales II to IV were considered to indicate the presence of post-GKS facial numbness. Three technicians from our center's Gamma Knife Team who were not involved in patient management administered the telephonic questionnaires, to avoid selection bias between the surgeons and patients.

Statistical Analysis

Statistical analyses were conducted using SPSS for Windows (version 22; IBM Inc, Armonk, New York). The results are presented as medians (ranges) and numbers (percentages) for continuous and categorical variables, respectively. The interobserver reliability of the trigeminal nerve CSA calculation was assessed using intraclass correlation coefficients. The Mann–Whitney *U*-test or Wilcoxon signed-rank test was used, as appropriate, to compare the medians of continuous variables. Cox regression analyses and hazard ratios (HRs) were used to assess the times to initial pain relief and pain recurrence with respect to the nerve characteristics after adjustment for age and sex. Logistic regression analysis and odds ratios were used to assess the associations between facial numbness and nerve characteristics. To discriminate trigeminal nerves with pain recurrence, a cutoff CSA of the symptomatic nerve was determined through receiver operating characteristic curve analysis. The survival data of different groups were determined using the Kaplan–Meier method and were compared using the log-rank test. Statistical significance was set at a P value of $<.05$.

RESULTS

Outcomes of CTN after GKS

In total, 67 patients with unilateral CTN were followed for a median duration of 35 mo (R: 12-83 mo). Among these patients, 39 (58.2%) and 57 (85.1%) achieved complete (BNI grade I) and adequate (BNI grades I-IIIb) pain relief, respectively, after GKS (Elekta AB) at a median latency period of 2 mo (R: 1-67 mo; Table 2). Among the 57 patients, 12 (21.1%) experienced pain recurrence after a median duration of 30.8 mo (R: 3-82.9 mo).

Associations Between Nerve Characteristics and GKS Outcomes

The intraclass correlation coefficient for CSA measurement was 0.724 (confidence interval [CI], 0.612-0.804; $P < .001$) between the 2 evaluators. The median CSA of the symptomatic nerves (4.95 [R: 2.75-9.60] mm^2) was significantly ($P < .001$)

TABLE 2. Gamma Knife Surgery Outcomes of Patients with Unilateral Classical Trigeminal Neuralgia[a]

Treatment Outcome	Value
Initial pain response, BNI grade (%)	
I, no pain, no medication	39 (58.2)
II, occasional pain, no medication	1 (1.5)
IIIa, no pain, continue medication	5 (7.5)
IIIb, persistent pain, controlled with medication	12 (17.9)
IV, some pain, not controlled with medication	0 (0)
V, severe pain/no relief	10 (14.9)
Initial treatment failure (%)	10 (14.9)
Median time to initial response, mo (range)	2 (1-67)
Pain recurrence after initial pain relief (%)	12 (17.1)
Median time of pain recurrence, mo (range)	30.8 (3-82.9)
Post-GKS facial numbness, BNI scale (%)	
I, no numbness	31 (46.3)
II, mild numbness that is not bothersome	27 (40.3)
III, somewhat bothersome numbness	9 (13.4)
IV, very bothersome numbness	0 (0)

[a]GKS, Gamma Knife surgery (Elekta AB); BNI, Barrow Neurological Institute.

smaller than that of the asymptomatic nerves (5.90 [R: 2.65-10.05] mm^2). The median CSA ratio was 0.86 (R: 0.47-1.83). Table 3 presents the associations between the nerve characteristics and GKS outcomes, including initial adequate pain relief (BNI grades I-IIIb) and pain recurrence (BNI grade IV or V). After adjustment for age and sex, larger trigeminal nerve CSA was associated with lower initial pain relief (HR: 0.814, 95% CI: 0.674-0.982; $P = .03$) and lower pain recurrence after initial pain relief (HR: 0.581, 95% CI: 0.357-0.944; $P = .02$). The CSA ratio and NVC characteristics, including the presence of NVC as well as arterial and proximal NVC, were not predictive of GKS outcomes.

A CSA of 4.4 mm^2 was the most favorable discriminator between trigeminal nerves with and without pain recurrence. The median follow-up durations were 27.5 mo (R: 13-83) and 38 mo (R: 12-80) for patients with trigeminal nerve CSAs of $\leq$4.4 mm^2 (n = 20) and >4.4 mm^2 (n = 47), respectively. Kaplan–Meier analyses revealed that after GKS for all 67 patients, those with a trigeminal nerve CSA of $\leq$4.4 mm^2 were more likely to experience initial pain relief within 12 mo (Figure 2; log-rank test, $\chi^2 = 5.554$, $P = .01$). However, for the 57 patients who had initial pain relief after GKS, those with a trigeminal nerve CSA of $\leq$4.4 mm^2 were less likely to maintain pain relief at the 5-yr follow-up (Figure 3; log-rank test, $\chi^2 = 4.066$, $P = .04$). The estimated 5-yr probabilities of maintaining pain relief were 65% $\pm$ 10.7% and 86% $\pm$ 5.8% for patients with trigeminal nerve CSAs of $\leq$4.4 and >4.4 mm^2, respectively. In the 55 patients with at least 2 yr of follow-up, the adequate pain relief rates at the 2-yr follow-up were not significantly different (72% vs 84%, $P = .47$) between the patients with trigeminal nerve CSAs of $\leq$4.4 mm^2 (n = 18) and >4.4 mm^2 (n = 37).

Associations Between NVC Characteristics and Trigeminal Nerve CSAs

Although the trigeminal nerve CSA in patients with NVC (4.8 [R: 2.75-9.6] mm^2, n = 37) was not significantly ($P = .08$) smaller than that in patients without NVC (5.18 [R: 3.35-8.5] mm^2, n = 30), the statistical value indicated a trend. The trigeminal nerve CSA in patients with arterial NVC (4.78 [R: 2.75-8.35] mm^2, n = 30) was significantly smaller ($P = .03$) than that in patients without arterial NVC (5.2 [R: 3.25-9.6] mm^2, n = 37). Similarly, the trigeminal nerve CSA in patients with proximal NVC (4.73 [R: 2.75-9.6] mm^2, n = 26) was

TABLE 3. Cox Regression Analysis of Gamma Knife Surgery Outcomes and Nerve Characteristics[a,b]

Variable	Initial pain relief			Pain recurrence		
	n	HR (95% CI)	*P* Value	n	HR (95% CI)	*P* Value
CSA, mm^2	67	0.814 (0.674-0.982)	.03	57	0.581 (0.357-0.944)	.02
CSA ratio, %[c]	67	0.508 (0.208-1.242)	.13	57	0.184 (0.013-2.527)	.20
NVC presence			.13			.17
No	30	Ref.		22	Ref.	
Yes	37	0.516 (0.876-2.621)		35	0.448 (0.141-1.424)	
Arterial NVC			.10			.20
No	37	Ref.		28	Ref.	
Yes	30	1.546 (0.913-2.616)		29	0.455 (0.133-1.554)	
Proximal NVC			.52			.33
No	41	Ref.		33	Ref.	
Yes	26	1.202 (0.681-2.121)		24	0.508 (0.130-1.984)	

[a]HR, hazard ratio; CSA, cross-sectional area; NVC, neurovascular compression.
[b]With adjustment for age and sex.
[c]CSA ratio indicates symptomatic nerve CSA divided by contralateral asymptomatic nerve CSA.

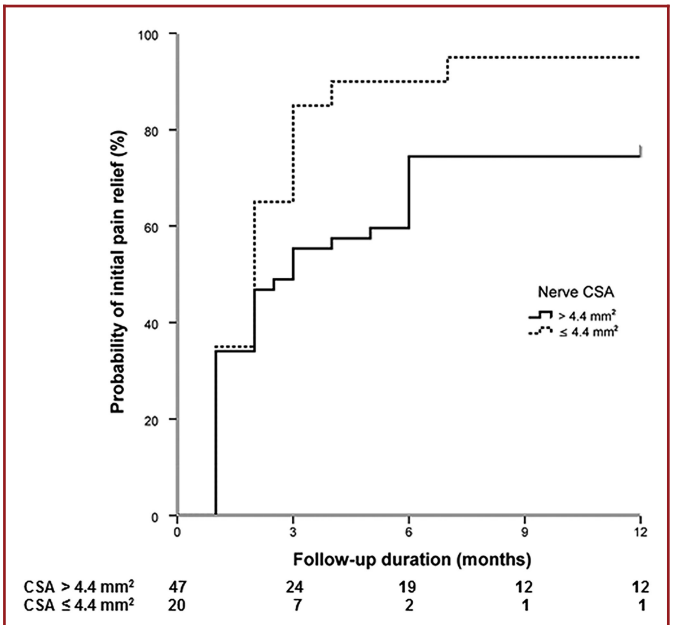

FIGURE 2. *Actuarial probability of initial adequate pain relief (BNI I-IIIb) within 12 mo after GKS (Elekta AB) for CTN, based on whether the trigeminal nerve CSA is more than 4.4 mm². The values below the x-axis represent the number of patients remaining in the analysis.*

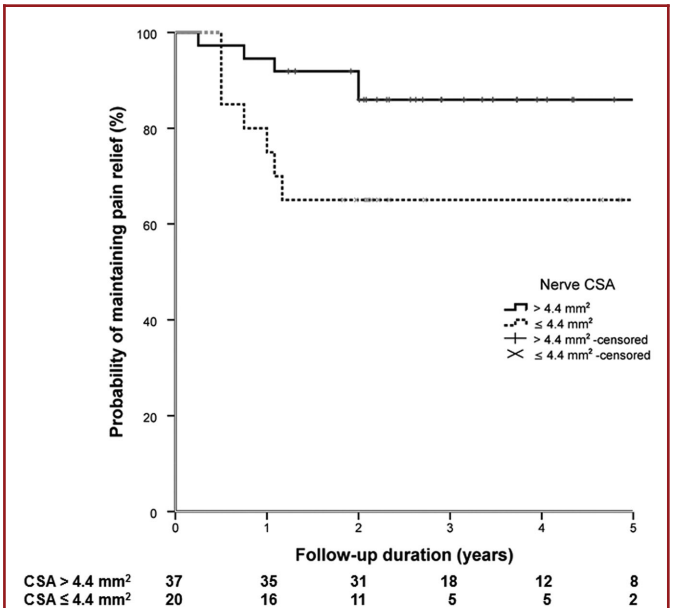

FIGURE 3. *Actuarial probability of maintaining pain relief (BNI I-IIIb) within 5 yr after GKS (Elekta AB) for CTN, based on whether the trigeminal nerve CSA is more than 4.4 mm². The values below the x-axis represent the number of patients remaining in the analysis.*

significantly smaller ($P = .04$) than that in patients without proximal NVC (5.2 [R: 2.75-9.6] mm², n = 41).

Post-GKS Facial Numbness

Among the 67 patients who underwent GKS, 36 (53.7%) exhibited new facial numbness (BNI scales II-III). No BNI scale IV or other complications, including mastication muscle weakness, decreased corneal sensation, hearing impairment, and anesthesia dolorosa were reported. The presence of post-GKS facial numbness was not associated with pain recurrence ($\chi^2 = 0.111$, $P = .73$). The logistic regression analysis results revealed no significant differences between the nerve characteristics and post-GKS facial numbness.

DISCUSSION

The findings of this study demonstrate that trigeminal nerve atrophy, defined by a CSA of ≤4.4 mm², was associated with post-GKS (Elekta AB) initial pain relief as well as subsequent pain recurrence in patients with CTN without previous surgery. Although NVC characteristics, including arterial and proximal NVC, were not predictive of GKS outcomes, these characteristics were associated with a smaller trigeminal nerve CSA. The present results may explain the phenomena in which some patients with CTN who undergo GKS are unable to maintain pain relief after 3 to 5 yr.

Trigeminal nerve atrophy and NVC are more frequently observed in the symptomatic nerves than in the asymptomatic nerves of patients with CTN.[11] Previous studies have investigated the associations between these nerve characteristics and the pathophysiology of CTN by analyzing the ultrastructure of trigeminal nerve root specimens obtained from patients with CTN.[20,21] The histopathology results revealed dysmyelination, demyelination, axonopathy, and axonal loss, resulting in the direct apposition of axons without an intervening myelin sheath. These structural changes may predispose to ephaptic transmission between adjacent axons and consequently lead to CTN symptoms.

Previous studies have used high-resolution MR imaging techniques to evaluate the atrophic changes of trigeminal nerves, either qualitatively by observing a smaller size of the symptomatic nerve than that of the contralateral asymptomatic nerve or quantitatively by measuring the nerve volume or CSA. In 2005, Kress et al[22] compared the trigeminal nerve volumes of the symptomatic and asymptomatic sides in 62 patients with TN and revealed that symptomatic side was significantly smaller than asymptomatic side with a mean volume difference of 28.9%. In 2006, Erbay et al[17] measured the trigeminal nerve CSA in 31 patients with TN and demonstrated that the symptomatic side had a significantly smaller mean CSA than the asymptomatic side (4.50 vs 6.28 mm², $P < .001$), which is compatible with our study results. Advanced MR imaging technique, namely diffusion tensor imaging, quantitatively measures the diffusivity

of trigeminal nerves to evaluate the integrity of axons, which shows lower fractional anisotrophy values in nerves with demyelination. Furthermore, studies have reported loss of trigeminal nerve volume and CSA to be strongly correlated with loss of fractional anisotrophy, and this finding supports the pathophysiologic association between trigeminal nerve atrophy and demyelination.[23,24]

The prognostication of trigeminal nerve atrophy on treatment outcomes has also been investigated. Leal et al[16] correlated the trigeminal nerve CSA variations and 2-yr clinical outcomes in 50 patients with TN who underwent MVD, and they revealed that patients with complete pain relief had significantly larger trigeminal nerve atrophic changes than those with partial pain relief or treatment failure. In 89 patients with TN, Lorenzoni et al[25] compared the GKS outcomes between patients with and without obvious trigeminal nerve atrophy and observed no association between trigeminal nerve atrophy and pain remission. Compared with our study, they qualitatively defined trigeminal nerve atrophy and used a different radiosurgery target at the distal portion of the trigeminal nerve root. Recently, Wolf et al[15] studied the influence of trigeminal nerve volume on 2-yr GKS outcomes in 58 patients with TN and reported that trigeminal nerve volume was not predictive of pain recurrence. However, more than half of their patients had undergone previous surgery before GKS, which may be a confounding factor, because prior invasive surgery can result in trigeminal nerve atrophy and is associated with less long-term pain relief after GKS.[25-29] By contrast, we selected a comparable number of patients with unilateral CTN without previous surgery who were followed for a longer duration after GKS. In addition, we quantified trigeminal nerve atrophy by measuring the proximal trigeminal nerve CSA, because trigeminal nerve volume can be confounded by individual variations in trigeminal nerve length.[30] The present results demonstrate that the 2-yr post-GKS adequate pain relief rates did not differ significantly between patients with and without trigeminal nerve atrophy; however, patients with a smaller trigeminal nerve CSA were more likely to experience post-GKS pain relief but less likely to maintain pain relief at follow-up. The underlying mechanism of this observation remains uncertain. In a primate study, GKS at 80 Gy caused focal axonal degeneration of trigeminal nerve and nerve necrosis was observed after GKS at 100 Gy.[31] These histology changes are related to GKS effect on TN. Furthermore, atrophic trigeminal nerves in patients with CTN were associated with axonal loss. We therefore postulate that atrophic trigeminal nerves may be more sensitive to radiation-induced electrical conduction block due to fewer axons, and they are thus more responsive to GKS initially. Nevertheless, later studies have shown that higher radiation energy delivered to the nerve volume is associated with higher pain relief and less pain recurrence.[15,32] Because the amount of energy delivered to the nerve may be determined by mean dose and target volume, atrophic trigeminal nerves may receive less radiation energy due to their smaller volume, and they are thus less likely to maintain the radiobiological effect of GKS.[33] By contrast, CSA ratio was not predictive of GKS outcomes. Among the 62 patients in our study, the CSA of 18 (26.9%) asymptomatic nerves were not larger than the median CSA (4.95 mm^2) of symptomatic nerves. This indicates that asymptomatic nerves are not unanimously larger than symptomatic nerves in patients with unilateral CTN.[17] Although we used CSA ratio to control for individual variations in nerve size, this approach may not be appropriate, because trigeminal nerve atrophy in asymptomatic side occurs in some patients with unilateral CTN.[16,17]

Because of the inconsistent results regarding the associations between NVC and GKS outcomes,[12-15,25,34] we further investigated the roles of arterial and proximal NVC and yielded similar findings of no association as demonstrated in previous studies.[14,15,25,34] Moreover, we observed arterial and proximal NVC to be associated with trigeminal nerve atrophy, which is consistent with the findings of previous studies.[16,23,35] Trigeminal nerve atrophy is also compatible with microstructural injury, namely demyelination and axonopathy, caused by pulsatile arterial compression at the trigeminal nerve segment proximal to the pons.[20,21,36] However, trigeminal nerve atrophy can be present without NVC.[37] Therefore, although arterial and proximal NVC can be attributed to trigeminal nerve damage, they may not necessarily affect the GKS outcomes of patients with CTN as trigeminal nerve atrophy does.

On the basis of the aforementioned findings, we propose a management strategy for patients with intractable CTN. For example, GKS may provide adequate long-term pain relief to patients without trigeminal nerve atrophy who prefer a less invasive treatment strategy. By contrast, patients with trigeminal nerve atrophy and NVC should undergo MVD if medically fit. Otherwise, a tailored radiosurgery, such as trigeminal nerve volume-based optimizing dosimetry or repeat GKS,[15,33,38] may be explored as a method to achieve a longer duration of pain relief. Finally, future studies might explore treatments strategies for achieving long-term pain relief in patients with CTN and trigeminal nerve atrophy.

Limitations

Our study has several limitations. First, the small sample size and retrospective design may limit the generalizability of the study results. Second, the pre- and post-GKS evaluations were mainly based on patients' subjective pain ratings rather than image signs or laboratory values, thus introducing a response bias. Third, our study results are hypothesis generating and need to be further validated given that other studies using different methods to define trigeminal nerve atrophy found conflicting results.[15,25] Finally, to measure the trigeminal nerve CSA, 1-mm-thick gadolinium-enhanced T1-weighted images were used to delineate the trigeminal nerves, which provided a low contrast between the trigeminal nerve and cerebrospinal fluid compared with that provided by T2-wighted images. In addition, the partial volume effects may have led to variable CSA measurements in this study.

CONCLUSION

The results of the present study demonstrate that in patients with unilateral CTN without previous surgery, the 2-yr post-GKS (Elekta AB) adequate pain relief rates between those with and without trigeminal nerve atrophy may be similar. However, patients with trigeminal nerve atrophy had a higher pain recurrence rate after initial pain relief than those without trigeminal nerve atrophy. Arterial and proximal NVC were determined to be associated with trigeminal nerve atrophy but were not predictive of GKS outcomes. These results may partly explain the lower effectiveness of GKS than that of MVD in long-term pain relief for TN. Future studies are required to develop optimal treatment strategies for patients with CTN and trigeminal nerve atrophy in order to improve their long-term outcomes.

Disclosures

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REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.
2. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *BMJ*. 2014;348(9):g474-g474.
3. Kotecha R, Miller JA, Modugula S, et al. Stereotactic radiosurgery for trigeminal neuralgia improves patient-reported quality of life and reduces depression. *Int J Radiat Oncol Biol Phys*. 2017;98(5):1078-1086.
4. Sivakanthan S, Van Gompel JJ, Alikhani P, van Loveren H, Chen R, Agazzi S. Surgical management of trigeminal neuralgia: use and cost-effectiveness from an analysis of the Medicare Claims Database. *Neurosurgery*. 2014;75(3):220-226; discussion 225-226.
5. Pollock BE, Schoeberl KA. Prospective comparison of posterior fossa exploration and stereotactic radiosurgery dorsal root entry zone target as primary surgery for patients with idiopathic trigeminal neuralgia. *Neurosurgery*. 2010;67(3):633-639; discussion 638-639.
6. Verheul JB, Hanssens PE, Lie ST, Leenstra S, Piersma H, Beute GN. Gamma Knife surgery for trigeminal neuralgia: a review of 450 consecutive cases. *J Neurosurg*. 2010;113 Suppl:160-167.
7. Douglas K, Oscar Z, Javier L-P, et al. Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. *J Neurosurg*. 2010;112(4):758-765.
8. Lucas JT, Jr, Nida AM, Isom S, et al. Predictive nomogram for the durability of pain relief from gamma knife radiation surgery in the treatment of trigeminal neuralgia. *Int J Radiat Oncol Biol Phys*. 2014;89(1):120-126.
9. Hughes MA, Frederickson AM, Branstetter BF, Zhu X, Sekula RF, Jr. MRI of the trigeminal nerve in patients with trigeminal neuralgia secondary to vascular compression. *Am J Roentgenol*. 2016;206(3):595-600.
10. Anderson VC, Berryhill PC, Sandquist MA, Ciaverella DP, Nesbit GM, Burchiel KJ. High-resolution three-dimensional magnetic resonance angiography and three-dimensional spoiled gradient-recalled imaging in the evaluation of neurovascular compression in patients with trigeminal neuralgia: a double-blind pilot study. *Neurosurgery*. 2006;58(4):666-673; discussion 666-673.
11. Antonini G, Di Pasquale A, Cruccu G, et al. Magnetic resonance imaging contribution for diagnosing symptomatic neurovascular contact in classical trigeminal neuralgia: a blinded case-control study and meta-analysis. *Pain*. 2014;155(8):1464-1471.
12. Brisman R, Khandji AG, Mooij RB. Trigeminal nerve-blood vessel relationship as revealed by high-resolution magnetic resonance imaging and its effect on pain relief after gamma knife radiosurgery for trigeminal neuralgia. *Neurosurgery*. 2002;50(6):1261-1266, discussion 1266-1267.
13. Erbay SH, Bhadelia RA, Riesenburger R, et al. Association between neurovascular contact on MRI and response to gamma knife radiosurgery in trigeminal neuralgia. *Neuroradiology*. 2006;48(1):26-30.
14. Sheehan JP, Ray DK, Monteith S, et al. Gamma Knife radiosurgery for trigeminal neuralgia: the impact of magnetic resonance imaging-detected vascular impingement of the affected nerve. *J Neurosurg*. 2010;113(1):53-58.
15. Wolf A, Tyburczy A, Ye JC, Fatterpekar G, Silverman JS, Kondziolka D. The relationship of dose to nerve volume in predicting pain recurrence after stereotactic radiosurgery in trigeminal neuralgia. *J Neurosurg*. 2017:128(3):1-6.
16. Leal PR, Barbier C, Hermier M, Souza MA, Cristino-Filho G, Sindou M. Atrophic changes in the trigeminal nerves of patients with trigeminal neuralgia due to neurovascular compression and their association with the severity of compression and clinical outcomes. *J Neurosurg*. 2014;120(6):1484-1495.
17. Erbay SH, Bhadelia RA, O'Callaghan M, et al. Nerve atrophy in severe trigeminal neuralgia: noninvasive confirmation at MR imaging–initial experience. *Radiology*. 2006;238(2):689-692.
18. Leal PR, Hermier M, Souza MA, Cristino-Filho G, Froment JC, Sindou M. Visualization of vascular compression of the trigeminal nerve with high-resolution 3T MRI: a prospective study comparing preoperative imaging analysis to surgical findings in 40 consecutive patients who underwent microvascular decompression for trigeminal neuralgia. *Neurosurgery*. 2011;69(1):15-26; discussion 26.
19. Rogers CL, Shetter AG, Fiedler JA, Smith KA, Han PP, Speiser BL. Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of The Barrow Neurological Institute. *Int J Radiat Oncol Biol Phys*. 2000;47(4):1013-1019.
20. Love S, Hilton DA, Coakham HB. Central demyelination of the Vth nerve root in trigeminal neuralgia associated with vascular compression. *Brain Pathol*. 1998;8(1):1-11; discussion 11-12.
21. Devor M, Govrin-Lippmann R, Rappaport ZH. Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. *J Neurosurg*. 2002;96(3):532-543.
22. Kress B, Schindler M, Rasche D, et al. MRI volumetry for the preoperative diagnosis of trigeminal neuralgia. *Eur Radiol*. 2005;15(7):1344-1348.
23. Leal PR, Roch JA, Hermier M, Souza MA, Cristino-Filho G, Sindou M. Structural abnormalities of the trigeminal root revealed by diffusion tensor imaging in patients with trigeminal neuralgia caused by neurovascular compression: a prospective, double-blind, controlled study. *Pain*. 2011;152(10):2357-2364.
24. Fujiwara S, Sasaki M, Wada T, et al. High-resolution diffusion tensor imaging for the detection of diffusion abnormalities in the trigeminal nerves of patients with trigeminal neuralgia caused by neurovascular compression. *J Neuroimaging*. 2011;21(2):e102-e108.
25. Lorenzoni JG, Massager N, David P, et al. Neurovascular compression anatomy and pain outcome in patients with classic trigeminal neuralgia treated by radiosurgery. *Neurosurgery*. 2008;62(2):368-376; discussion 375-376.
26. Sindou M, Leston J, Decullier E, Chapuis F. Microvascular decompression for primary trigeminal neuralgia: long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression. *J Neurosurg*. 2007;107(6):1144-1153.
27. Dhople AA, Adams JR, Maggio WW, Naqvi SA, Regine WF, Kwok Y. Long-term outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: implications of treatment and critical review of the literature. Clinical article. *J Neurosurg*. 2009;111(2):351-358.
28. Kondziolka D, Zorro O, Lobato-Polo J, et al. Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. *J Neurosurg*. 2010;112(4):758-765.
29. Kotecha R, Kotecha R, Modugula S, et al. Trigeminal neuralgia treated with stereotactic radiosurgery: the effect of dose escalation on pain control and treatment outcomes. *Int J Radiat Oncol Biol Phys*. 2016;96(1):142-148.
30. Hung YC, Lee CC, Liu KD, Chung WY, Pan DH, Yang HC. Radiosurgery target location and individual anatomical variation in trigeminal nerves. *J Neurosurg*. 2014;121 Suppl:203-209.
31. Kondziolka D, Lacomis D, Niranjan A, et al. Histological effects of trigeminal nerve radiosurgery in a primate model: implications for trigeminal neuralgia radiosurgery. *Neurosurgery*. 2000;46(4):971-976; discussion 976-977.
32. Massager N, Murata N, Tamura M, Devriendt D, Levivier M, Regis J. Influence of nerve radiation dose in the incidence of trigeminal dysfunction

after trigeminal neuralgia radiosurgery. *Neurosurgery*. 2007;60(4):681-688; discussion 687-688.
33. Mousavi SH, Niranjan A, Akpinar B, et al. A proposed plan for personalized radiosurgery in patients with trigeminal neuralgia. *J Neurosurg*. 2017;128(2):1-8.
34. Cheuk AV, Chin LS, Petit JH, Herman JM, Fang HB, Regine WF. Gamma knife surgery for trigeminal neuralgia: outcome, imaging, and brainstem correlates. *Int J Radiat Oncol Biol Phys*. 2004;60(2):537-541.
35. Lutz J, Thon N, Stahl R, et al. Microstructural alterations in trigeminal neuralgia determined by diffusion tensor imaging are independent of symptom duration, severity, and type of neurovascular conflict. *J Neurosurg*. 2016;124(3):823-830.
36. Hilton DA, Love S, Gradidge T, Coakham HB. Pathological findings associated with trigeminal neuralgia caused by vascular compression. *Neurosurgery*. 1994;35(2):299-303; discussion 303.
37. Miller JP, Acar F, Hamilton BE, Burchiel KJ. Radiographic evaluation of trigeminal neurovascular compression in patients with and without trigeminal neuralgia. *J Neurosurg*. 2009;110(4):627-632.
38. Aubuchon AC, Chan MD, Lovato JF, et al. Repeat gamma knife radiosurgery for trigeminal neuralgia. *Int J Radiat Oncol Biol Phys*. 2011;81(4):1059-1065.

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COMMENT

In this paper, the authors attempt to clarify what factors can predict whether a patient with trigeminal neuralgia will respond to stereotactic radiosurgery, which other papers have evaluated with varying results. Their results show that patients with lower trigeminal cross-sectional area have better initial response but less lasting result. This finding can be used to guide decision making for patients and surgeons, and will certainly stimulate further investigation that may help enlighten this topic further.

Brent D. Weinberg
Atlanta, Georgia

Four Dancers, Edgar Degas [Public domain], 1899, oil on canvas, National Gallery of Art, Washington, DC (http://artemisdreaming.tumblr.com/post/16224322270/four-dancers-1899-national-gallery-of-art, Public Domain, https://commons.wikimedia.org/w/index.php?curid=31397087)