Check for updates

# Gamma Knife Radiosurgery for Trigeminal Neuralgia: Role of Trigeminal Length and Pontotrigeminal Angle on Target Definition and on Clinical Effects

*Lina Raffaella Barzaghi*[1], *Luigi Albano*[1,3], *Claudia Scudieri*[1], *Carmen Rosaria Gigliotti*[2], *Francesco Nadin*[1], *Antonella del Vecchio*[2], *Pietro Mortini*[1]

■ OBJECTIVE: **Gamma Knife radiosurgery (GKRS) is a well-defined treatment for trigeminal neuralgia. The aim of this study was to determine how the GKRS planning might change on the basis of the patient's own anatomy and how to best choose the target location.**

■ METHODS: **Trigeminal cisternal length, pontotrigeminal angle, and distance between middle of the shot and emergence were evaluated in 112 consecutive GKRS plans for trigeminal neuralgia. Correlations with pain outcomes and facial hypoesthesia were analyzed.**

■ RESULTS: **The mean angle was 29° ± 4.4° and 37° ± 0.9°, respectively, in patients developing and not developing severe hypoesthesia ($P = 0.045$), despite no significant difference on brainstem dose (11.9 ± 0.8 and 10.5 ± 0.3 Gy; $P = 0.22$). The length of the nerve was not relevant on clinical outcomes but the shot-emergence distance (mean 8.1 ± 0.2 mm) depended on both trigeminal length and angle ($P = 0.01$). At constant prescription dose, 6-month cumulative rates of pain relief and control without therapy were 52.9% when the shot-emergence distance was ≤8 mm, whereas 25% when this distance was >8 mm ($P = 0.017$). The maintenance of good pain control was more long lasting in the first group (49.5 ± 6.6 vs. 25.4 ± 5 months; $P = 0.006$) with a 5-year cumulative rate of 70% and 26%, respectively ($P < 0.001$).**

■ CONCLUSIONS: **The pontotrigeminal angle and the shot-emergence distance should be considered during GKRS planning: the first as a potential risk factor for hypoesthesia, and the second should not exceed 8 mm.**

## INTRODUCTION

Trigeminal neuralgia (TN), as stated by the International Headache Society, is the most common among "painful cranial neuropathies and other facial pains."[1] Medical treatment is the first therapeutic choice, whereas surgery and radiosurgery are indicated in the presence of drug side effects or therapy failure.[2,3]

Gamma Knife radiosurgery (GKRS) is an effective and safe treatment for classic TN.[4-12] The goal is to obtain the most effective and long lasting pain control with the lowest facial bothersome hypoesthesia risk, considering the following 3 variables: 1) the prescription dose; 2) the dose-volume histogram (DVH) of the brainstem; and 3) the isocenter location. The range of the dose varies from 70 Gy (minimal effective dose) to 90 Gy. The best pain control seems, in fact, to occur when higher doses are adopted, but beyond 90 Gy the efficacy rate remains similar with an increased complication rate.[4,5,8,13,14] The dose administered to the brainstem is related to the risk of trigeminal nerve dysfunction and is not well defined in current literature.[8,15,16] Many authors reported that 10 $mm^3$ of the

**Key words**
- Gamma Knife radiosurgery
- Pontotrigeminal angle
- Retrogasserian target
- Root entry zone
- Trigeminal nerve length
- Trigeminal neuralgia

**Abbreviations and Acronyms**
**BNI**: Barrow National Institute
**CI**: Confidence intervals
**Dmax**: Maximal prescription dose
**DVH**: Dose-volume histogram
**GKRS**: Gamma Knife radiosurgery
**MRI**: Magnetic resonance imaging
**MVD**: Microvascular decompression
**REZ**: Root entry zone
**TN**: Trigeminal neuralgia

*From the Departments of [1]Neurosurgery and Gamma Knife Radiosurgery; [2]Medical Physics; and [3]Neuroimaging Research Unit, Institute of Experimental Neurology, IRCCS San Raffaele Scientific Institute and Vita-Salute University, Milan, Italy*

*To whom correspondence should be addressed: Lina Raffaella Barzaghi, M.D. [E-mail: barzaghi.linaraffaella@hsr.it]*

*Citation: World Neurosurg. (2020) 142:e140-e150.*
*https://doi.org/10.1016/j.wneu.2020.06.147*

*Journal homepage: www.journals.elsevier.com/world-neurosurgery*

*Available online: www.sciencedirect.com*

brainstem should receive a maximum dose of 12 Gy[16] or 15 Gy[6]; conversely, other authors placed the isocenter so that the brainstem surface was irradiated at the 20%–30% isodose line or less.[11,17,18] Finally, there are 2 main strategies for the isocenter placement along the fifth nerve: the root entry zone (REZ), or posterior target, and the retrogasserian target, which is the anterior cisternal portion of the nerve.[4,5,19,20]

The fifth nerve length and its proximity to the pons are very heterogeneous among patients. In this study we investigated how the trigeminal length and the angle between pons and nerve influences the GKRS planning. We also analyzed the position of the shot to see if this and the earlier mentioned anatomic variables could be predictive factors for pain relief and trigeminal dysfunction.

## METHODS

### Study Design

The study follows a retrospective observational cohort design and the principles outlined in the Declaration of Helsinki. Informed consent to GKRS treatment, data collection, and publication was signed by all patients and approved by the institutional review board.

### Patient Selection

Patients with TN, who consecutively underwent GKRS from 2009–2018 at our institute, were considered for enrollment in the study (n = 244). Indications for radiosurgery were pharmaco-resistant TN, intolerance to painkillers, and patient's preference when microvascular decompression (MVD) was proposed. Inclusion criteria encompassed 1) diagnosis of classic TN based on International Classification of Headache Disorders[1]; 2) availability of a minimum follow-up after GKRS equal to 12 months; 3) magnetic resonance imaging (MRI)-based planning; and 4) no previous radiosurgery.

### GKRS Technique

Patients underwent placement of the Leksell stereotactic head frame (model G, Elekta Instruments AB, Stockholm, Sweden). The following MRI sequences were carried out on the MRI machine (Philips Achieva, 1.5 Tesla, Eindhoven, The Netherlands) to identify the trigeminal nerve: (i) 3-dimensional axial T2-weigheted turbo spin-echo (repetition time = 1500 ms, echo time = 250 ms, flip angle = 90°, slice thickness = 1.0 mm, voxel size 1.0 x 1.0 x 1.0 mm, matrix size = 256 x 256); (ii) 3-dimensional axial gadolinium-enhanced T1-weighted (repetition time = 30 ms, echo time = 4605 ms, flip angle = 25°, slice thickness = 1.0 mm, voxel size 1.0 x 1.0 x 1.0 mm, matrix size = 256 x 256).

Treatment plans were performed using the Leksell Gamma Knife Perfexion model (Elekta Instruments AB): one single shot was placed on the retrogasserian portion of the trigeminal nerve, with a maximal prescription dose (Dmax) of 90 Gy via a 4-mm collimator. The 12-Gy isodose was then plotted and DVH of the brainstem analyzed to define the volume receiving 12 Gy, accepting a maximal dose to 10 $mm^3$ of the brainstem equal to 12 Gy or less. The prescription dose and the shot location were therefore adjusted according to brainstem proximity both by decreasing the Dmax or moving a little bit anteriorly to the

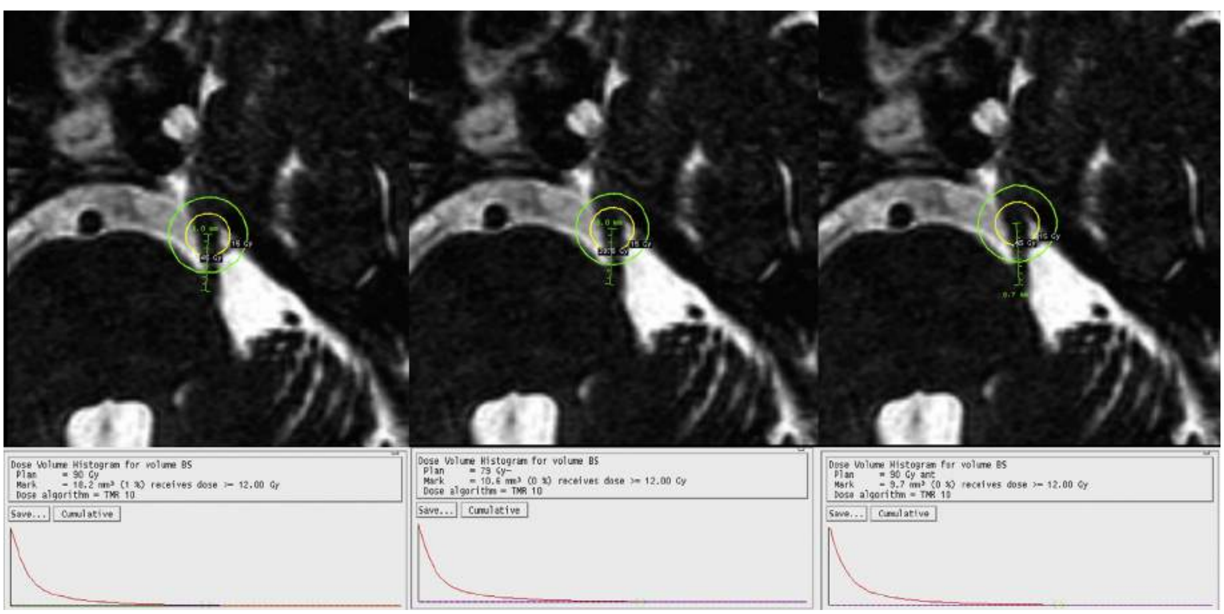


**Figure 1.** Examples of different strategies applicable on Gamma Knife planning. In this case, presenting a long nerve, using a prescription dose of 90 Gy (100%), the maximal dose to 10 $mm^3$ of the brainstem exceeds 12 Gy (constrain accepted in this study). Maintaining the same accepted maximal dose to brainstem, we can prescribe 90 Gy placing the middle of the shot 8.7 mm away from the brainstem emergence or we can reduce the dose (79 Gy) without changing the distance (8 mm).

isocenter, along the cisternal portion of the trigeminal nerve, as shown in **Figures 1** and **2**. Sector-blocked treatments were used when certain anatomic conditions occurred and only following a reduction of the prescription dose. Generally they were adopted, according to neurosurgeon's personal experience, if all other strategies to decrease the brainstem irradiation were insufficient. The Dmax to the nerve was maintained between 70 and 90 Gy.

## Data Collection and Outcome Evaluations

Clinical evaluation was obtained at baseline, 3, and 6 months after GKRS and then yearly or when clinically indicated. Outcome evaluation was performed using both data stored in the institutional database and the last available follow-up questionnaire by assessing the level of facial pain before GKRS and the degree of pain relief according to BNI (Barrow National Institute) pain intensity scale, time interval between treatment and pain relief, use of medication before and after treatment, and degree of facial hypoesthesia (if any) according to BNI facial numbness scores. Initial pain outcomes were evaluated at 6 months and were divided into a binary scale with BNI I—IIIb falling under "good pain control with or without medication" and scores IV—V falling under "poor pain relief or failure." To define the pain relief without medication, a second binary scale was made: BNI I—II and BNI III—V. At the last follow-up, among successfully treated patients, maintenance of good pain control with or without medication were calculated, defining a recurrence as any change from the best class after GKRS to a lower outcome class (minor recurrence) or pain requiring new GKRS or surgical treatment (major recurrence).

## MRI Measurements

Stereotactic MRI sequences were retrospectively reviewed on the Gamma Plan software (Elekta Instruments AB) by 2 neurosurgeons; they drew a first line along the trigeminal nerve from the brainstem to the trigeminal incisura on the petrous bone to measure its cisternal length. To define the angle between the nerve and the brainstem they traced a second line, tangent to the pons through the point where the trigeminal nerve arises from the brainstem. A right-angled triangle (**Figure 3**) was drawn to calculate the $\alpha$-angle, between the nerve (*hypotenuse*) and the

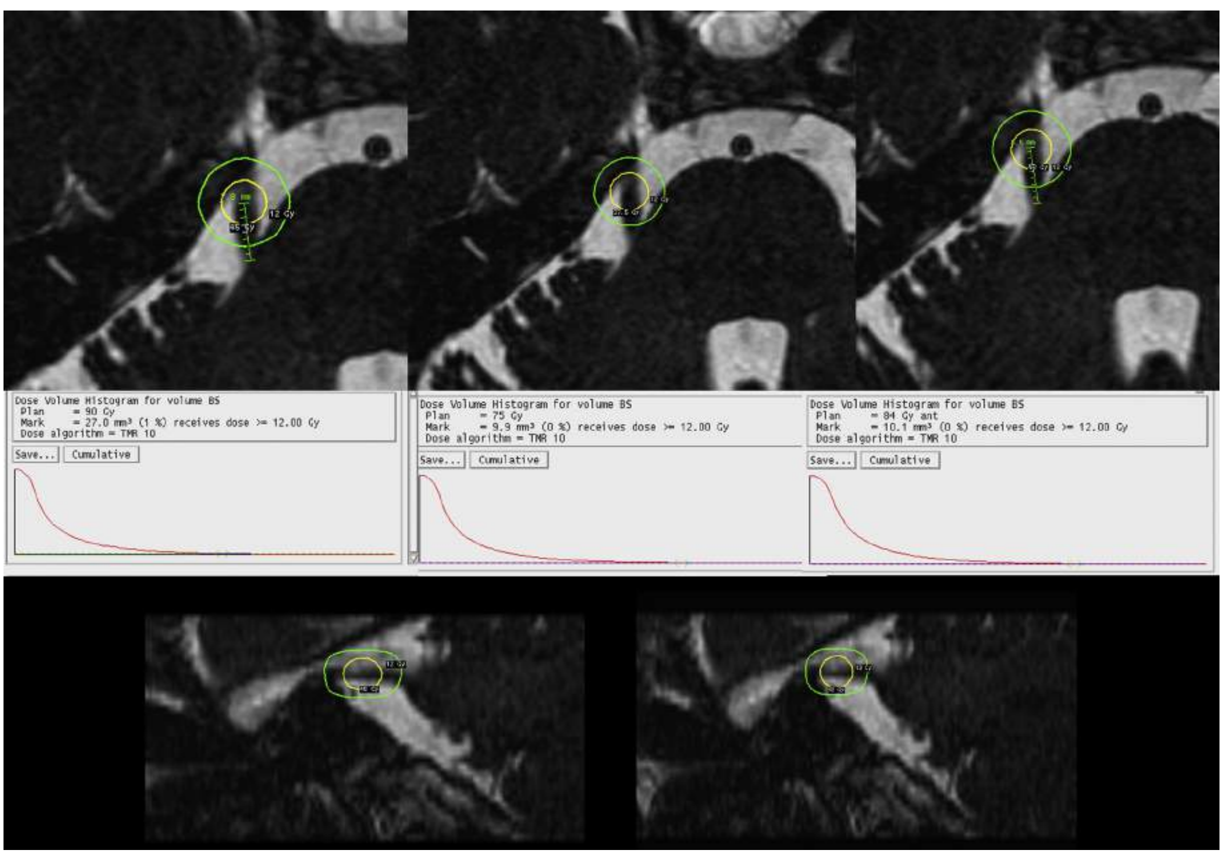


**Figure 2.** Examples of Gamma Knife planning. Using a prescription dose of 90 Gy at 7.8 mm of distance between middle of the shot and trigeminal emergence from the brainstem, the maximal dose to 10 $mm^3$ of the brainstem exceeds 12 Gy, the limit adopted in this study (upper and lower rows, figures on the left). It is possible to decrease the dose (75 Gy) without changing the isocenter position (7.8 mm from the brainstem, upper row figure on the middle, lower row figure on the left). It is also possible to move the shot anteriorly, using a higher prescription dose (84 Gy). The shot pons distance is 8.5 mm in this latter plan (upper and lower row figures on the right).

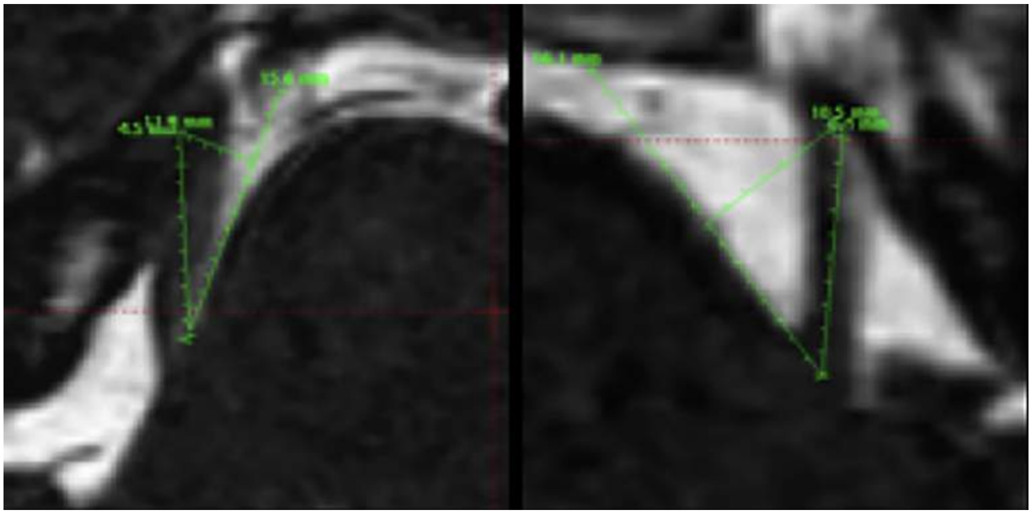

**Figure 3.** A right-angled triangle was drawn between the line passing through the major axes of trigeminal nerve and the line tangent to the pons through the point where the trigeminal nerve arises from the brainstem. A third line, from the trigeminal incisura and perpendicular to the brainstem tangent line, was traced using the "line 90°" function. *Cathetus*$_b$ = segment from trigeminal emergence to the intersection point between tangent line and its perpendicular line; *cathetus*$_a$ = segment from trigeminal incisura to intersection point on tangent line; *hypotenuse* = distance between trigeminal emergence and incisura (trigeminal length). The angle $\alpha$, between hypotenuse and cathetus$_b$, was calculated.

brainstem (*cathetus*$_b$), first through the trigonometric function $sin\alpha = chatetus_a/hypotenuse$ and subsequently as a result of $sin^{-1}$. Finally, the distance between the middle of the isocenter and the brainstem emergence of the trigeminal nerve was measured.

### Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics package (SPSS Statistics for Macintosh, Version 20, IBM Corporation, Armonk, New York, USA).

Continuous data were expressed as mean ± standard error and categorical variables as frequencies/percentages. Interrater reliability testing was assessed by repetition of drawing and measures in all subjects by a second rater. Cohen's $\kappa$ coefficient was calculated.

The Student *t*-test was used to compare continuous variables, and the Spearman rank test to perform the bivariate analysis of independent variables. For the outcomes evaluation, such as pain relief and recurrence, the time-to-event was estimated using the Kaplan-Meier method with the log-rank test.

A probability value <0.05 was considered indicative of statistical significance, and 95% confidence intervals (CI) were reported.

## RESULTS

### General Results, Initial Pain Outcome, and Long-Term Maintenance

Overall, 112 patients met the inclusion criteria; the mean follow-up was 61.1 ± 3.5 months (12–126 months, median 58).

Tables 1 and 2 report clinical characteristics, GKRS data, and MRI measurements. Interrater reliability for trigeminal length ($\kappa$ = 0.72), cathetus$_a$ ($\kappa$ = 0.78), and distance between isocenter and emergence ($\kappa$ = 0.76) were good.

The cumulative initial pain relief and control without therapy at 6 months was 34.2% (95% CI, 25.2%–43.2%), and the good pain control with and without therapy 89.3% (95% CI, 83.9%–95.1%). The cumulative pain minor and major recurrence free rates at 5 years were 49.3% (95% CI, 42.7%–55.3%) and 64.9% (95% CI, 58.9%–70.9%). Initial BNI I–II was a positive prognostic factor for long-term pain control, as shown in Kaplan-Meier analysis (P = 0.017 and 0.019; Figure 4). Trigeminal length and pontotrigeminal angle did not influence initial (6 months BNI I–II cumulative rate: P = 0.93 and P = 0.76; 6 months BNI I–IIIa cumulative rate: P = 0.85 and P = 0.92) or long-term pain outcomes (cumulative free rate of pain minor recurrence: P = 0.18 and P = 0.83; cumulative free rate of pain major recurrence: P = 0.10 and P = 0.96).

### Hypoesthesia

New occurrence of light hypoesthesia (BNI II) occurred during the follow-up in 9 patients among 103 with normal trigeminal function before GKRS (8.7%). Severe hypoesthesia (BNI III–IV), as a new occurrence or worsening, was recorded in 6 out of 112 patients (5.3%; Table 3). The mean $\alpha$-angle was 29° ± 4.4° in patients who developed severe hypoesthesia, and narrower compared with patients without trigeminal dysfunction (37° ± 0.9°; P = 0.045), whereas the trigeminal length was not significantly different (11.25 ± 0. mm and 11.2 ± 0.2 mm, P = 0.96). The maximal dose to 10 mm$^3$ of the brainstem was slightly higher in patients with severe hypoesthesia after GKRS (11.9 ± 0.8 Gy), compared with patients without (10.5 ± 0.3 Gy), but this difference was not significant (P = 0.22). The influence of beam channels

**Table 1.** Characteristics of 112 Patients with Trigeminal Neuralgia Treated by Gamma Knife Radiosurgery

| Female Sex (n, %) | 74 | 66.1% |
|---|---|---|
| Age (mean ± SE, range) | 63.9 ± 1.1 yrs | 28–92 yrs |
| Side (n, %) | | |
| Left | 53 | 47.3% |
| Right | 53 | 47.3% |
| Bilateral | 6 | 5.4% |
| Trigeminal branch involved (n, %) | | |
| V2, V3 | 40 | 35.7% |
| V3 | 22 | 19.6% |
| V1-V2 | 20 | 17.9% |
| 1-V2-V3 | 17 | 15.2% |
| V2 | 11 | 9.8% |
| V1 | 2 | 1.8% |
| Prior surgery | | |
| No | 92 | 82.1% |
| Yes (MVD or percutaneous procedures) | 14 | 17.9% |
| Trigeminal dysfunction before GKRS | | |
| No | 103 | 92% |
| Yes | | 8% |
| BNI facial numbness 2 | 8 | |
| BNI facial numbness 3 | 1 | |
| BNI facial numbness 4 | 0 | |

SE, standard error; MDV, microvascular decompression; GKRS, Gamma Knife radiosurgery; BNI, Barrow National Institute.

**Table 2.** Dose and Magnetic Resonance Imaging Measurements in 112 Patients with Trigeminal Neuralgia Treated by Gamma Knife Radiosurgery

| Maximum dose | n | % | |
|---|---|---|---|
| 70–79 Gy | 26 | 23.2% | / |
| 80 Gy | 70 | 62.5% | / |
| 81–90 Gy | 16 | 14.3% | / |
| Plug (n, %) | | | / |
| No | 99 | 88.4% | |
| Yes | 13 | 11.6% | |
| | mean ± SE | Range | Median |
| Maximum dose | 79.2 ± 0.5 Gy | 70–90 Gy | 80 Gy |
| Trigeminal nerve length | 11.2 ± 0.2 mm | 6.9–17 mm | 11 mm |
| Distance middle of isocenter–brainstem | 8.1 ± 0.2 mm | 4–12.7 mm | 7.9 mm |
| Angle $\alpha$* | 36.5° ± 0.9° | 16.3°–58.1° | 36.2° |
| Dose to 10 $mm^3$ of brainstem | 10.6 ± 0.3 Gy | 3.9–23.8 Gy | 10.5 Gy |

SE, standard error.
*Angle $\alpha$, angle between the brainstem and the trigeminal nerve. Explanation in the text (Methods).

blocking on hypoesthesia was tested, even if used in only 13 cases: severe hypoesthesia occurred only in the group without block (6/99, 6.1% vs. 0/13, 0%; P = 0.362) and new hypoesthesia in 12 of 92 patients without block (13%) and in only 1 of 11 patients with sectors blocked (9.1%; P = 0.71).

### Influence of Trigeminal Length and Pontotrigeminal Angle in GKRS Planning

The prescription dose was correlated, as expected, with the length of the nerve (P = 0.05) but not with the amplitude of $\alpha$-angle (P = 0.3). The dose to 10 $mm^3$ of the brainstem was inversely related with both the trigeminal length (P = 0.01) and the angle measurement (P = 0.01), as shown in Figure 5, whereas the shot-emergence distance was correlated with the nerve length and inversely related with the amplitude of pontotrigeminal angle (P = 0.01).

### Influence of the Shot-Pons Distance on Pain Outcomes and Hypoesthesia

In our analysis, both the trigeminal length and the angle drove the final shot placement along the nerve. Thus to investigate if the isocenter location may change pain outcomes we must consider a constant prescription dose; therefore we performed this analysis only in patients treated with 80 Gy without sectors blocked. In this selected population, cumulative rates of initial pain relief and control without therapy (BNI I and II) were higher when the shot-pons distance was ≤8 mm compared with a distance >8 mm (P = 0.017), as shown in Figure 6. The delay of pain recurrence was longer in the group with shot-pons distance ≤8 mm, in mean 49.5 ± 6.6 compared with 25.4 ± 5 months in the group with distance >8 mm (P = 0.006), as shown in Figure 6 also by Kaplan-Meier analyses for pain minor (P < 0.001) and major recurrence (P < 0.001).

To better interpret our results, we divided our general population successfully treated into 2 groups: patients with shot placed 8 mm from the brainstem or less and Dmax equal to 80 Gy or less (group A: shot near, lower dose) and patients with shot placed >8 mm from the brainstem and Dmax equal to 80 Gy or more (group B: shot far, higher dose). In this analysis, we test the role of the isocenter position on GKRS efficacy also considering the possibility of adopting higher doses when the shot was more distant from the pons. As shown in Figure 6, cumulative pain relief and control without therapy occurred more frequently in group A compared with group B, but the difference was not significant (P = 0.21). Conversely, cumulative free rates of pain minor and major recurrence were better in group A compared with B (P = 0.001 and P = 0.005).

Finally, the shot-pons distance was in mean 7.9 ± 0.6 mm in patients who developed severe hypoesthesia, and 8.1 ± 0.2 mm in patient without trigeminal dysfunction (P = 0.78); analyzing cases treaded with the same dose (80 Gy) without sectors blocked

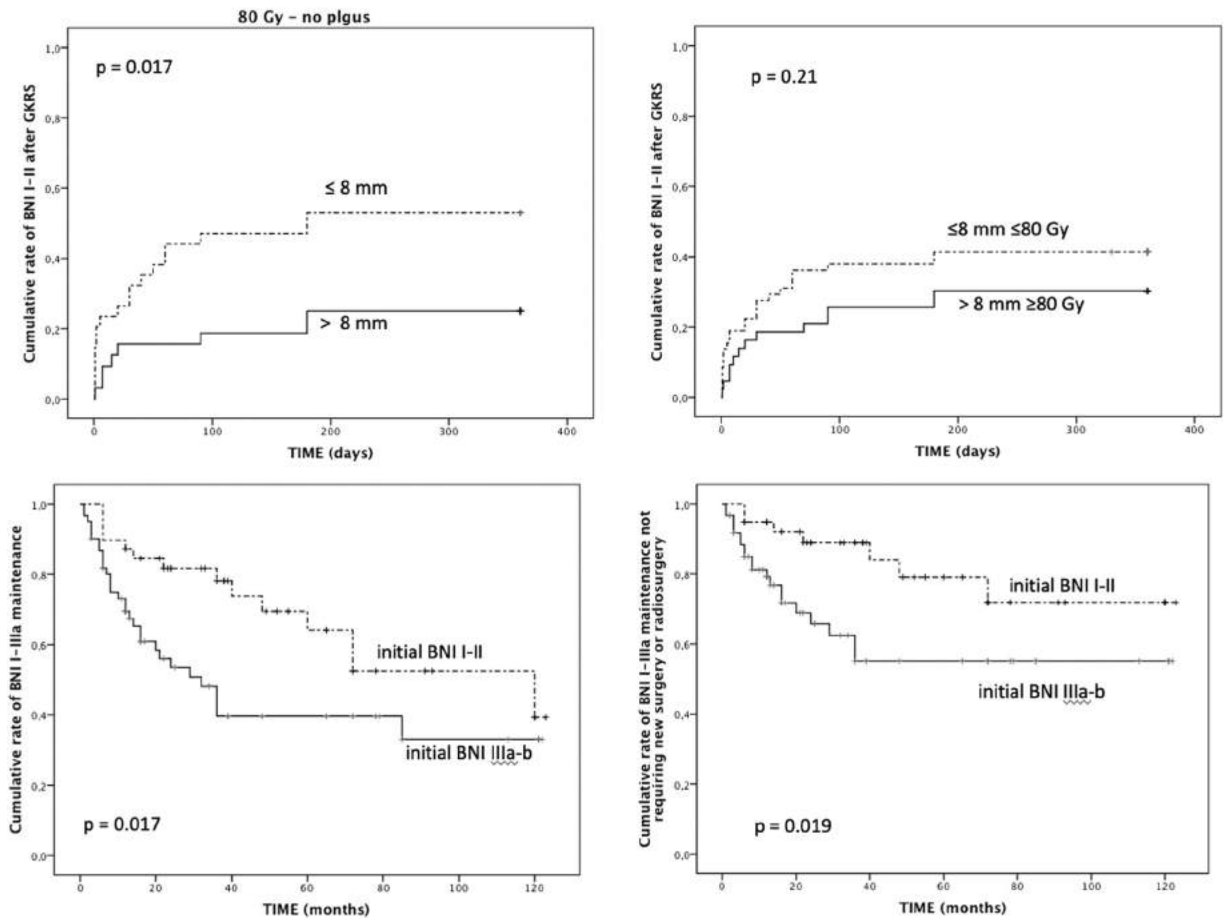


**Figure 4.** Kaplan-Meier analyses. General population was stratified according to initial pain response: cumulative maintenance of initial pain control with or without therapy 5 years after Gamma Knife radiosurgery (GKRS) was 51.1% (95% confidence interval [CI], 28.9%–73.3%) when BNI (Barrow National Institute) I–II was achieved after GKRS, better than in BNI IIIa and IIIb post-GKRS grades (38.9%; 95% CI, 23.9%–53.9%; $P = 0.017$). The cumulative rate of pain control not requiring new surgery or radiosurgery at 5 years was 70.4% (95% CI, 68.3%–72.5%) when BNI I–II was achieved, and 54.7% (95% CI, 38.3%–71.1%; $P = 0.019$) when BNI III was obtained after GKRS.

results were similar that those in all population (7.8 ± 0.7 mm vs. 8.2 ± 0.2 mm; P = 0.57).

## DISCUSSION

When Lars Leksell introduced the use of GKRS for the treatment of TN, the initial idea was to cause a lesion in the Gasser's ganglion, similarly to percutaneous rhizotomy. Rand et al.,[21] in 1993, proposed the retrogasserian portion of the fifth nerve as a target for GKRS. Lindquist et al.[22] first and then Kondziolka et al.[4] in a successive multicentric study published in 2006, adopted the REZ as the preferred target for GKRS, advocating that the oligodendrocytes within the compact union of fibers near the trigeminal emergence have an increased sensibility to irradiation compared with Schwann cells.[22] Moreover, in the MRI era, the nerve can be clearly identified as it traverses the cerebrospinal fluid, and therefore the REZ may be indirectly localized by considering the segment of the trigeminal nerve adjacent to the brainstem and located 0–3 mm away from the pons.[23] The retrogasserian target continues to be used and some neurosurgeons are in favor of this isocenter position because the long-term pain control is higher when this anterior target is used.[5,7,8,19] Moreover, bothersome hypoesthesia rate is lower when the anterior target is adopted rather than the posterior, and dry eye syndrome or keratitis are seen almost exclusively adopting the REZ target.[8,20]

Recent International Stereotactic Radiosurgery Society recommendations suggest that the optimal position of the shot is 0–8 mm anterior to the trigeminal emergence from the pons, in accordance to a previous prospective randomized trial published by Regis et al.[5,8] This study demonstrated that, when the retrogasserian target was adopted, the distance between the shot and trigeminal emergence was significantly inferior in patients successfully treated (7.5 mm) compared with those with

**Table 3.** Outcomes of 112 Patients with Trigeminal Neuralgia Treated by Gamma Knife Radiosurgery

| BNI 6 Months after GKRS | n | % | % | |
|---|---|---|---|---|
| BNI I | 18 | 16.1% | | |
| BNI II | 20 | 17.9% | 33.9% | IPR w/o m |
| BNI IIIa | 57 | 50.9% | 84.8% | IPR w w/o m |
| BNI IIIb | 5 | 4.5% | 89.3% | IgPC w w/o m |
| BNI IV | 10 | 8.9% | 10.7% | Failure |
| BNI V | 2 | 1.8% | | |
| Delay of pain control/relief Mean ± SE, range, median | | 35.4 ± 5.2 days | 1–180 days | 10 days |
| Minor pain recurrence n, % | | 45/100 | 45% | |
| Major pain recurrence n, % | | 27/100 | 27% | |
| Time of minor recurrence mean ± SE, range, median | | 22.3 ± 3.8 months | 1–120 months | 12 months |
| Time of major recurrence mean ± SE, range, median | | 17 ± 3.3 months | 1–72 months | 12 months |
| Trigeminal dysfunction after GKRS n, % | | | | Severe |
| BNI II | | 9/103 normal | 8.7% | |
| BNI III | | 5/112 | | 4.5% |
| BNI IV | | 1/112 | | 0.9% |

BNI, Barrow National Institute; GKRS, Gamma Knife radiosurgery; IPR, initial pain relief; w m, with medication; w/o m, without medication; IgPC, initial good pain control; SE, standard error.

treatment failure (8.4 mm; $P = 0.014$).[5] However, reliable data regarding the optimal distance between shot and brainstem, absolute or relative to the trigeminal nerve length, are not well represented in the literature. Longer cisternal fifth nerve extension predicts decreased efficacy of GKRS in the article by Marshall et al.,[15] but other authors did not demonstrate this association when they considered the absolute measures, as well as the ratio between nerve and targeting length.[5,15,24-27]

The aim of this study was first to investigate the anatomy of this region, considering not only the nerve as previously done (length, volume, shot-emergence distance, or ratio) but also its orientation with respect to the brainstem. In fact, the trigeminal nerve may be short or long and the angle between the nerve and the brainstem more or less wide. Our results demonstrated a mean length of trigeminal nerve equal to 11.2 ± 0.2 mm (range, 6.9–17 mm) and a mean amplitude of the angle between pons and nerve of 36.5° ± 0.9° (range, 16.3°–58.1°). A previous anatomic study performed on 3 Tesla MRI reported a similar mean cisternal length of the trigeminal nerve (9.7 ± 1.7 mm in women and 10.3 ±1.8 mm in men).[28] The angle between the nerve and pons was recently calculated in a population of patients with TN and it was 42.4° ± 8.7°.[29] In our experience, the absolute length of the trigeminal nerve did not influence pain outcomes either with regard to posttreatment facial hypoesthesia. Conversely, Hung et al.[25] described a correlation between radiation-induced facial hypoesthesia and both the trigeminal length (>11 mm) and the targeting ratio (<36%), but not with the absolute targeting distance. The angle between pons and nerve was not related with the pain outcome, but it seemed important to determine the severe hypoesthesia risk after GKRS. Bothersome hypoesthesia occurred when pontotrigeminal angle was narrower (approximately <30°) despite similar brainstem dose. A possible explanation of this result is that trigeminal dysfunction depends not only on the dose to the brainstem, which is very low in our series despite a non-negligible incidence of severe hypoesthesia, but also on the region covered by radiation (i.e., nuclei of trigeminal nerve, dorsal and ventral trigeminothalamic tract, spinotrigeminal tract, proximal pontine segment of trigeminal nerve or Gasser's ganglion). This meaningful angle might play an important role, and further studies including advanced MRI may contribute to fully appreciating its relevance.

The second aim of this study was to understand if the patient's anatomy influenced the GKRS planning strategy and how. In our retrospective analysis, longer nerves were related with higher prescription doses, lower brainstem doses, and longer shot-emergence distances; wider pons-trigeminal nerve angles were related with lower brainstem doses and shorter shot-emergence distances. These results reflect 3 different hypotheses that may be considered during GKRS planning: according to the DVH of the brainstem and accepted constrain, we can decrease the prescription dose, move the shot anteriorly, or use a sector-blocked treatment. Usually beam channels block are adopted as the last option, and as previously reported, never with a prescription dose equal to 90 Gy.[6,8,14,30] Consequently, a long nerve and a wide angle seem favorable anatomic conditions for GKRS planning.

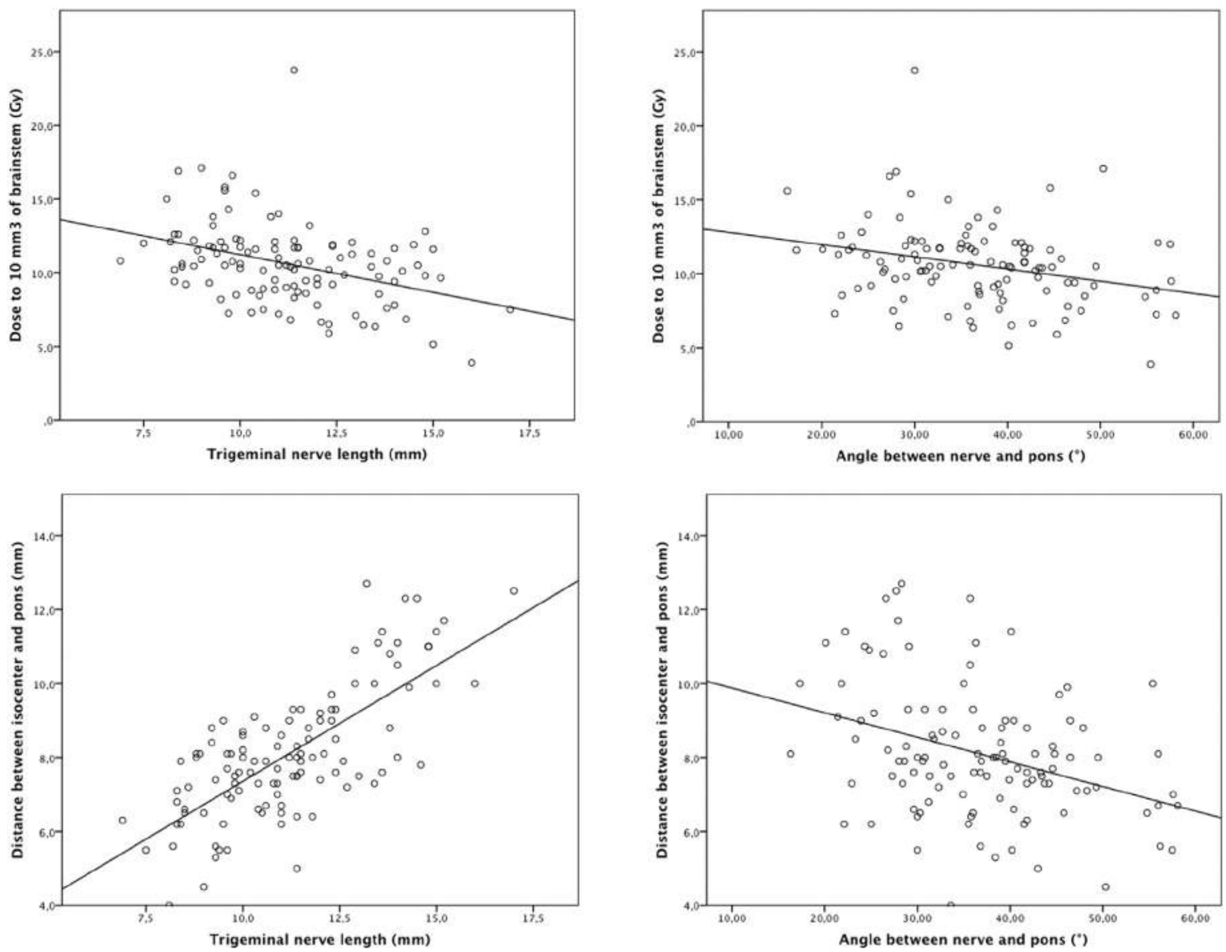


**Figure 5.** Upper row: scatter plots demonstrating relation between the maximal dose to 10 $mm^3$ of the brainstem and the trigeminal length ($P = 0.01$) or the pontotrigeminal angle amplitude (α-angle; $P = 0.01$). Lower row: scatter plots demonstrating relation between the distance shot-pons and the trigeminal length ($P = 0.01$) or the pontotrigeminal angle amplitude ($P = 0.01$).

As demonstrated in our study, the final isocenter position depends on both the trigeminal length (direct relation) and the pontotrigeminal angle (inverse relation), but are there some constraints or further recommendations? To investigate the optimal shot location we restricted our analysis to patients treated with a constant dose and without sectors block: we can confirm that the isocenter placed 8 mm or less from the emergence of the nerve was associated with higher initial pain relief and control without therapy and longer maintenance of satisfactory pain control. A more complex question to answer is: What is more important, the prescription dose or the shot location? Considering both the shot distance and the dose in each patient, we repeated the analysis also including different prescription doses: long-term results were better in the group with shot distance ≤8 mm from the pons and Dmax equal to 80 Gy or less compared with the group with shot distance >8 mm and Dmax equal to 80 Gy or more. We can therefore conclude that, in a very long nerve, the shot should be not moved anteriorly >8 mm, even if doing so the dose may be 90 Gy. It is preferable to slightly decrease the doses without changing the isocenter position (**Figure 1**).

### Interpretation and Generalizability

Our study and recent literature evidence suggest that targeting of the trigeminal nerve should not be necessarily based on a more anterior or posterior location, but should depend on patient's anatomy.[8,26,31] Prescribing 90 Gy at 100% through a 4-mm collimator, the shot could be moved along the nerve until the maximal dose to 10 $mm^3$ of the brainstem is 15 Gy or less[6] and the distance between the middle of the shot and the pons does not exceed 8 mm, as already demonstrated. When this distance is not sufficient to reduce the brainstem irradiation, the prescription dose must be reduced, and the use of sectors blocking could be considered. A recent article describes that patients with a smaller volume of nerve (<35% of the total nerve volume) that received a high dose (≥80% isodose) were less likely to experience TN recurrence.[26] Thus the prescription dose and

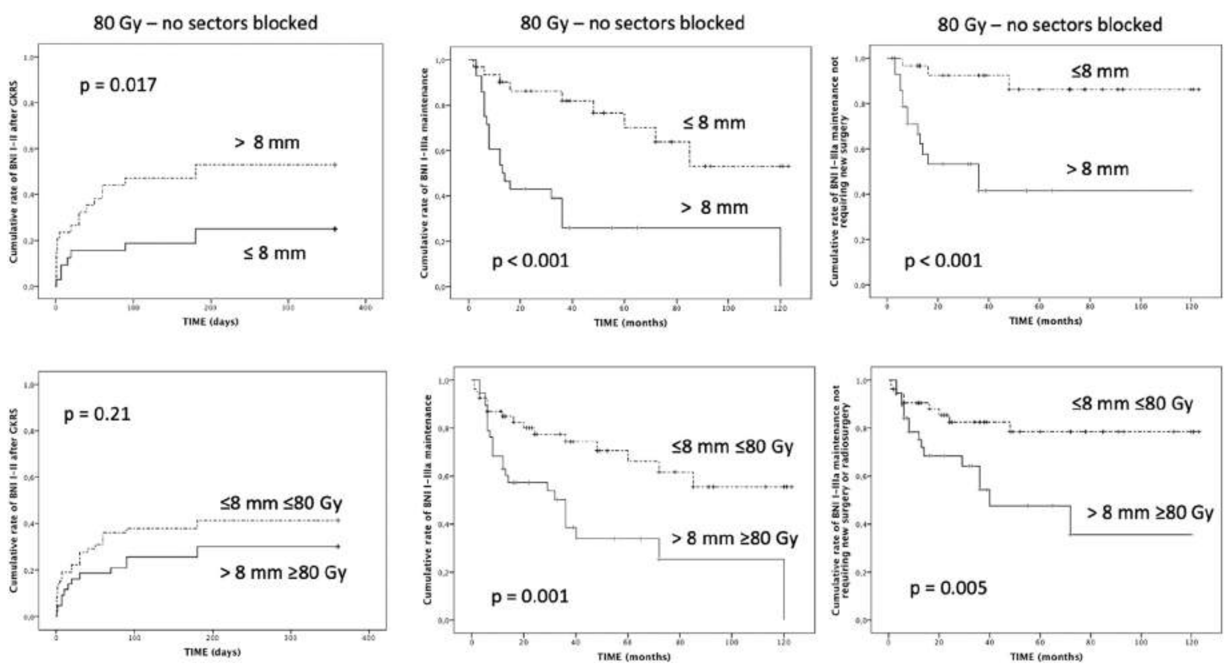


**Figure 6.** Kaplan-Meier analyses. Upper row, patients treated at constant prescription dose (80 Gy, 100%) without sectors blocking: on the left cumulative rates of initial pain relief and control without therapy at 6 months were 52.9% (95% confidence interval [CI], 35.7%−70.1%) when the shot-pons distance was ≤8 mm, and 25% (95% CI, 10.6%−39.4%) when the distance was >8 mm ($P = 0.017$); on the middle cumulative maintenance of initial good pain control with or without therapy at 5 years was 70% (95% CI, 50%−90%) when the shot-pons distance was ≤8 mm, and 26% (95% CI, 8.8%−43.2%) when the distance was >8 mm ($P < 0.001$); on the right cumulative rate of pain control not requiring new surgery or radiosurgery at 5 years was 86.2% (95% CI, 70.8%−100%) when the shot-pons distance was ≤8 mm, and 41.8% (95% CI, 20.4%−62.8%; $P < 0.001$) when the distance was >8 mm. Lower row, general population was divided into 2 groups: group A = shot near, lower dose; and group B = shot far, higher dose. On the left cumulative rates of pain relief and control without therapy at 6 months were 41.4% (95% CI, 28.4−5.4) in group A, and 31% (95% CI, 17%−45%) in group B ($P = 0.21$); on the middle cumulative maintenance of initial good pain control with or without therapy at 5 years was 66.2% (95% CI, 50.2%−82.2%) in group A, and 33.8% (95% CI, 16%−51.6%) in group B ($P = 0.001$); on the right cumulative rate of pain control not requiring new surgery or radiosurgery at 5 years was 78.5% (95% CI, 64.9%−92.1%) in group A, and 47.6% (95% CI, 26.4%−68.8%) in group B ($P = 0.005$).

beam channels block could be optimized based on the volume of the nerve or considering the integral dose, as previously reported.[30,31] Moreover, a narrow pontotrigeminal angle is a risk factor for severe hypoesthesia and should be pondered on the selection of the prescription dose to the nerve or using sectors block.

## Study Limitations

Limitations of this study include its retrospective and single-center design, exposing our analysis to bias errors. Probably adopting 12 Gy as a limit to brainstem maximal dose, our philosophy tended to target the nerve distally and not always on the optimal way; so we did not test any virtually position along the nerve but only the cisternal distal part. We chose to test the 8 mm distance not only because this was our mean value but also because it was the value suggested in the literature, but not statistically demonstrated, as the major distance of the isocenter from the pons. We analyzed the shot-emergence distance as a continued value (data not shown) and as a categorical variable with similar results but we were unable to test lower value (i.e., 3−4 mm) as a cutoff of shot-emergence distance because cases treated on the emergence proximity (very short nerves) were infrequent. Notably, our aim was not to compare REZ and retrogasserian target, but to define using the last-one how to best plan GKRS choosing between moving a few millimeters anteriorly to the isocenter or decreasing the dose without increasing the distance >8 mm.

One more potential limitation of using MRI-based morphologic parameters may be a prior MVD surgery, which can change the anatomy of this region because of the materials adopted during surgery and postoperative scar. However, we did not experience any difficulty: first, because only 14 patients were treated by a surgical procedure before radiosurgery; and second, because the main issue after MVD could be to overestimate the volume of the trigeminal nerve due to interposed scar tissue but not to draw the longitudinal axis of the nerve between the emergence from the pons and the Meckel cave.

Finally, we did not show in this article an analysis of further variables, such as integral dose or cisternal trigeminal volume, and clinical outcomes because major groups, expert on GKRS, published these data previously. Thus we focused our analysis on anatomic characteristics, especially the pontotrigeminal angle never analyzed. Prospective studies and advanced MRI investigations will be needed to better characterize the virtues and limitations of this measure in a single patient.

## CONCLUSIONS

BNI III—IV hypoesthesia after GKRS was associated with a narrow angle between pons and nerve, whereas trigeminal length did not directly influence any outcomes. However, both the trigeminal length and the pontotrigeminal angle drove the targeting in GKRS for TN: the shot placed 8 mm or less from the brainstem at the constant dose of 80 Gy was predictive for a better initial pain relief and control without therapy and a lower cumulative risk of any pain recurrence. The isocenter position seems more important than a prescription dose >80 Gy on long-term pain control.

## CRediT AUTHORSHIP CONTRIBUTION STATEMENT

**Lina Raffaella Barzaghi:** Conceptualization, Methodology, Software, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Luigi Albano:** Methodology, Software, Validation, Data curation, Writing - review & editing. **Claudia Scudieri:** Data curation. **Carmen Rosaria Gigliotti:** Software, Validation, Data curation. **Francesco Nadin:** Data curation. **Antonella del Vecchio:** Supervision. **Pietro Mortini:** Supervision.

## ACKNOWLEDGMENTS

The authors are grateful to all the staff, past and present, of the Gamma Knife Unit: Stefania Acerno, M.D., Nicola Boari, M.D., Camillo Ferrari da Passano, M.D., Lorenzo Gioia, M.D., Micol Valle, M.D., Piero Picozzi, M.D., Alberto Franzin, M.D., Lucia Perna, M.S., Paola Mangili, M.S., Patrizia Signorotto, M.S., Angelo Bolognesi, M.D., Mrs. Gloria Montanini, and Mrs. Denise O'Toole.

## REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
2. Wiffen PJ, McQuay HJ, Moore RA. Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev*. 2005:CD005451.
3. Jorns TP, Zakrzewska JM. Evidence-based approach to the medical management of trigeminal neuralgia. *Br J Neurosurg*. 2007;21:253-261.
4. Kondziolka D, Lunsford LD, Flickinger JC, et al. Stereotactic radiosurgery for trigeminal neuralgia: a multiinstitutional study using the gamma unit. *J Neurosurg*. 1996;84:940-945.
5. Regis J, Metellus P, Hayashi M, Roussel P, Donnet A, Bille-Turc F. Prospective controlled trial of Gamma Knife surgery for essential trigeminal neuralgia. *J Neurosurg*. 2006;104:913-924.
6. Regis J, Tuleasca C, Resseguier N, et al. Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. *J Neurosurg*. 2016;124:1079-1087.
7. Regis J, Tuleasca C, Resseguier N, et al. The very long-term outcome of radiosurgery for classical trigeminal neuralgia. *Stereotact Funct Neurosurg*. 2016;94:24-32.
8. Tuleasca C, Regis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: a systematic review. *J Neurosurg*. 2018;130:733-757.
9. Little AS, Shetter AG, Shetter ME, Bay C, Rogers CL. Long-term pain response and quality of life in patients with typical trigeminal neuralgia treated with gamma knife stereotactic radiosurgery. *Neurosurgery*. 2008;63:915-923 [discussion: 923-914].
10. 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;111:351-358.
11. Kondziolka D, Zorro O, Lobato-Polo J, et al. Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. *J Neurosurg*. 2010;112:758-765.
12. 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;47:1013-1019.
13. Pollock BE, Phuong LK, Gorman DA, Foote RL, Stafford SL. Stereotactic radiosurgery for idiopathic trigeminal neuralgia. *J Neurosurg*. 2002;97:347-353.
14. Flickinger JC, Pollock BE, Kondziolka D, et al. Does increased nerve length within the treatment volume improve trigeminal neuralgia radiosurgery? A prospective double-blind, randomized study. *Int J Radiat Oncol Biol Phys*. 2001;51:449-454.
15. Marshall K, Chan MD, McCoy TP, et al. Predictive variables for the successful treatment of trigeminal neuralgia with gamma knife radiosurgery. *Neurosurgery*. 2012;70:566-572 [discussion: 572-563].
16. Massager N, Lorenzoni J, Devriendt D, Desmedt F, Brotchi J, Levivier M. Gamma Knife surgery for idiopathic trigeminal neuralgia performed using a far-anterior cisternal target and a high dose of radiation. *J Neurosurg*. 2004;100:597-605.
17. Nicol B, Regine WF, Courtney C, Meigooni A, Sanders M, Young B. Gamma Knife radiosurgery using 90 Gy for trigeminal neuralgia. *J Neurosurg*. 2000;93(suppl 3):152-154.
18. Hasegawa T, Kato T, Iizuka H, Kida Y. Long-term results for trigeminal schwannomas treated with Gamma Knife surgery. *Int J Radiat Oncol Biol Phys*. 2013;87:1115-1121.
19. Park SH, Hwang SK, Kang DH, Park J, Hwang JH, Sung JK. The retrogasserian zone versus dorsal root entry zone: comparison of two targeting techniques of Gamma Knife radiosurgery for trigeminal neuralgia. *Acta Neurochir (Wien)*. 2010;152:1165-1170.
20. Xu Z, Schlesinger D, Moldovan K, et al. Impact of target location on the response of trigeminal neuralgia to stereotactic radiosurgery. *J Neurosurg*. 2014;120:716-724.
21. Rand RW, Jacques DB, Melbye RW, Copcutt BG, Levenick MN, Fisher MR. Leksell Gamma Knife treatment of tic douloureux. *Stereotact Funct Neurosurg*. 1993;61(suppl 1):93-102.
22. Alexander, E, III, Loeffler, J.S. Lunsford L.D. (eds). Vol 1. Stereotactic Radiosurgery. McGraw-Hill. New York: History of Radiosurgery;1993.
23. Maesawa S, Salame C, Flickinger JC, Pirris S, Kondziolka D, Lunsford LD. Clinical outcomes after stereotactic radiosurgery for idiopathic trigeminal neuralgia. *J Neurosurg*. 2001;94:14-20.
24. Baschnagel AM, Cartier JL, Dreyer J, et al. Trigeminal neuralgia pain relief after Gamma Knife stereotactic radiosurgery. *Clin Neurol Neurosurg*. 2014;117:107-111.
25. 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.
26. 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*. 2018;128:891-896.
27. Sharim J, Lo WL, Kim W, et al. Radiosurgical target distance from the root entry zone in the

treatment of trigeminal neuralgia. *Pract Radiat Oncol*. 2017;7:221-227.

28. Kakizawa Y, Seguchi T, Kodama K, et al. Anatomical study of the trigeminal and facial cranial nerves with the aid of 3.0-tesla magnetic resonance imaging. *J Neurosurg*. 2008;108:483-490.

29. Cheng J, Meng J, Liu W, Zhang H, Lei D, Hui X. Nerve atrophy and a small trigeminal pontine angle in primary trigeminal neuralgia: a morphometric magnetic resonance imaging study. *World Neurosurg*. 2017;104:575-580.

30. Massanger N, Murata N, Tamura M, et al. Influence of nerve radiation dose in the incidence of trigeminal dysfunction after trigeminal neuralgia radiosurgery. *Neurosurgery*. 2007;60:681-688.

31. Mousavi SH, Niranjan A, Akpinar B, et al. A proposed plan for personalized radiosurgery in patients with trigeminal neuralgia. *J Neurosurg*. 2018;128:452-459.

*Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

*Received 12 March 2020; accepted 18 June 2020*

*Citation: World Neurosurg. (2020) 142:e140-e150.*
*https://doi.org/10.1016/j.wneu.2020.06.147*

*Journal homepage:* ***www.journals.elsevier.com/world-neurosurgery***

*Available online:* ***www.sciencedirect.com***