Long-Term Results of Gamma Knife Radiosurgery for Trigeminal Neuralgia

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Daiki Sato, Motohiro Hayashi, Ayako Horiba, Shiro Horisawa, Takakazu Kawamata

OBJECTIVE: **Although the short- to medium-term efficacy of Gamma Knife therapy for drug-resistant essential trigeminal neuralgia has been reported, long-term evaluations are limited. We evaluated patient data obtained at least 10 years post-treatment and examined the significance of this treatment using new end points.**

METHODS: **Among 249 consecutive patients with essential trigeminal neuralgia who were treated with Gamma Knife radiosurgery (retrogasserian target/4-mm single isocenter/90 Gy at 100%) at our institution between January 2003 and October 2011, 103 patients who were followed up for at least 10 years (mean, 174 [120–219] months) after treatment and whose data were amenable to accurate evaluation, were included in this retrospective study. Herein, we used the Barrow Neurological Institute (BNI) pain intensity scale as a clinical evaluation method for pain and the BNI numbness scale to evaluate complications (namely facial dysesthesia).**

RESULTS: **The initial and final follow-up pain attack cessation (BNI pain intensity score I–IIIa) rate was 82.5% (85 of 103) and 58.2% (60 of 103), respectively. Furthermore, sensory impairment (BNI numbness score ≥ II) at the last follow-up was observed in 24.3% (25 of 103) of the cases, while very bothersome status (BNI numbness score IV) was observed in 2.9% of the cases.**

CONCLUSIONS: **Gamma Knife radiosurgery for essential trigeminal neuralgia showed good therapeutic effects during long-term follow-up. Serious complications of significant concern in the short- to mid-term follow-up, resolved spontaneously. Therefore, the indications for treatment should be expanded to include patients who strongly desire Gamma Knife therapy.**

INTRODUCTION

The annual incidence of trigeminal neuralgia is 4–5 cases per 100,000 individuals, and the condition is more common among women than men with a male-to-female ratio of 1:1.74.[1] The diagnostic criteria of trigeminal neuralgia include recurrent unilateral paroxysmal facial pain occurring in 1 or more areas innervated by the trigeminal nerve branch not extending beyond the trigeminal nerve region which lasts between 1 second and 2 minutes. Trigeminal neuralgia can be classified into the following 3 subtypes: classical, which occurs without any obvious cause other than neurovascular compression; secondary, which accompanies an underlying condition; and idiopathic, which does not show any specific anomaly on electrophysiological assessments or magnetic resonance imaging.[2]

Carbamazepine is the recommended first-line treatment for trigeminal neuralgia[3]; however, its effect gradually declines, with the initial response rate of 69% dropping to 22% after 5–16 years.[4] If drug therapy is inadequate, microvascular decompression should be considered for treating classical trigeminal neuralgia. Unfortunately, surgery under general anesthesia is not an option in many patients, including geriatric patients who frequently develop trigeminal neuralgia.[1] Stereotactic radiosurgery (Gamma Knife radiosurgery) should be considered in these cases and patients who do not wish to

Key words
- Gamma Knife
- Pain
- Paresthesia
- Radiosurgery
- Trigeminal neuralgia

Abbreviations and Acronyms
BNI-N: Barrow Neurological Institute numbness scale
BNI-P: Barrow Neurological Institute pain intensity scale

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undergo surgery, who have developed drug-resistance, or who have idiopathic trigeminal neuralgia.

Tuleasca et al.[5] conducted a systematic review of 65 studies on Gamma Knife radiosurgery treatment outcomes for 6461 patients in 2018. Of all the studies reviewed, 45 reported the use of Gamma Knife radiosurgery and listed the outcomes for 5687 patients. However, most of these reports described short-term outcomes, with mean and median follow-up periods of 7.1–92 months and 6.7–76 months, respectively; only a few studies have reported on long-term outcomes. Accordingly, the mean pain-free rate was 84.8% (66.6%–100%) with a recurrence rate of 24.6% (0%–52.2%) and a complication rate of 21.7% (0%–68.8%), including facial numbness.

Therefore, we included cases that were followed up for ≥10 years, which can be considered to be an adequate duration for evaluating the efficacy of a therapy. We considered the usefulness of the therapy while paying attention to new outcome measures that were closely related to paroxysmal pain with the greatest influence on the activities of daily living.

MATERIALS AND METHODS

Patients

Using medical records and telephonic interviews, we conducted a retrospective study of 249 consecutive patients who underwent Gamma Knife radiosurgery for trigeminal neuralgia at the Tokyo Women's Medical University Department of Neurosurgery or its affiliated hospitals between January 2003 and October 2011. We excluded cases where the patient was unavailable or the treatment details were unclear. Furthermore, for deceased patients, we interviewed the patients' relatives to determine disease history. Ultimately, we analyzed 103 cases that could be followed up for ≥10 years after treatment and for which accurate information could be collected. Patients who had died were scored on the basis of the patients' family's observations immediately before death. Those who died before 10 years had passed after treatment were excluded.

Treatment

Treatment was planned using the Gamma Plan software, which creates bone computed tomography–magnetic resonance imaging fusion images based on heavily T2-weighted 3-dimensional constructive interference in steady-state images from 0.5-mm-thick axial slices obtained using magnetic resonance imaging and 1.0-mm-thick slices obtained using computed tomography (bone images). All patients underwent a single exposure (maximum radiation dose, 90 Gy) using a 4-mm collimator targeted at the retrogasserian region (posterior to the gasserian ganglion; i.e., trigeminal notch on the petrous ridge) on the affected side. Specifically, the Y and Z axes for the 50% isodose line were set in an anteroinferior (6 to 9 o'clock) direction within the area around an isocenter that included the part of the petrous bone.

The 18 Gy (20% isodose) line from the brainstem was separated; if the prepontine cistern was narrow and the trigeminal nerve was too short, beam plugging was used to avoid higher irradiation to the brainstem.

Table 1. Barrow Neurological Institute Pain Intensity Score

Score	
I	No trigeminal pain, no medication
I	Occasional pain, not requiring medication
IIIa	No pain with medication
IIIb	Some pain, adequately controlled with medication
IV	Some pain, not adequately controlled with medication
V	Severe pain/no pain relief

Outcome Measures

We considered the maximum effect after treatment as the initial effect and investigated the changes in the effect after 10 years, recurrence during the follow-up period, and the presence of complications, including numbness. The Barrow Neurological Institute pain intensity (BNI-P) score which was used to assess pain intensity is detailed in Table 1. The Barrow Neurological Institute numbness scale (BNI-N) score was used to monitor numbness complications (Table 2). We also investigated cases that received additional therapy due to poor initial outcome (initial BNI-P V) and recurrent cases that received additional therapy.

RESULTS

Of the 103 patients, 71 women (68.9%) and 32 men (31.0%) with a mean age of 67 years (range, 29–88 years) years and a mean follow-up period of 174.9 months (range, 120–219 months) were included in this study (Table 3). Evaluation of the initial effect using BNI-P revealed that 85 of 103 (82.5%) cases reported adequate pain relief (BNI-P I–IIIa), and 71 of 103 (68.9%) cases reported no pain attacks without medication (BNI-P I) (Table 4). At the time of the final follow-up, these values had changed to 58.2% (60 of 103) and 37.8% (39 of 103), respectively (Table 4).

Among of the initial adequate pain relief (BNI-P I–IIIa) cases, 68.2% (58 of 85) retained the adequate pain relief status at the final follow-up (BNI-P I–IIIa), whereas 22.3% (19 of 85) of the patients showed complete recurrence and required additional therapy (BNI-P I–IIIa to V, Rec) (Figure 1).

Trigeminal sensory impairment (facial numbness) due to higher doses of irradiation was the most commonly observed complication at the final follow-up which accounted for 24.3% (25 of 103) of all cases (BNI-N ≥ II). Severe sensory impairment (BNI-N IV) accounted for 2.9% (3 of 103) of all cases (Table 5).

Table 2. Barrow Neurological Institute Facial Numbness Score

Score	
I	No facial numbness
II	Mild facial numbness, not bothersome
III	Facial numbness, somewhat bothersome
IV	Facial numbness, very bothersome

Table 3. Patient Characteristics

Variable	Value*
Sex	
Female	71 (68.9)
Male	32 (31.0)
Median treatment age in years (range)	67 (29–88)
Median duration of follow-up in months (range)	175 (120–219)
Target: Retrogasserian region	103 (100)
Dose 90 Gy	103 (100)
Isocenter Single	103 (100)

*Values indicate the number of patients (%) unless otherwise indicated.

In 25 patients with post-treatment complications, the maximum dose of irradiation to the brainstem (10 mm^3 volume dose) averaged 7.7 (4–13) Gy. As beam plugging was used in only 1 case, the differences between the beam plugged and unplugged cases was not evaluated.

DISCUSSION

Long-Term Treatment Results

In Gamma Knife radiosurgery for trigeminal neuralgia, the short-term treatment outcomes have demonstrated pain-free status in 66.6%–100% of the cases (mean, 84.8%; median, 85.6%), with 28.6%–100% (mean, 53.1%; median, 52%) of the patients becoming medication-free.[5] Among the 130 cases in our hospital where follow-up was possible for a minimum of 2 years, 112 (86%) cases were pain-free; of which, 86 (57.3%) cases achieved medication-free status.[6]

At 7 years, the following rates of sustained pain relief were reported in previous studies: 32%,[7] 22%,[8] and 59.7%.[9] We present 2 reports describing the findings of long-term follow-up investigations. Kondziolka et al.[10] reported sustained pain relief in 503 cases, stating that the rate of adequate pain relief (BNI-P I–IIIa) was 80%, 71%, 46%, and 30% after 1, 2, 5 and 10 years, respectively. At the time of the final evaluation, pain was controlled in 66% (330 of 503) of patients. As for the treatment method, most patients underwent 80-Gy irradiation with a single 4-mm isocenter targeted 3–8 mm anterior to the junction between the trigeminal nerve and the pons (the REZ target); however, some patients received a double dose and some received a dose of 60–90 Gy, indicating that the study did not use a standardized treatment protocol.[10] Moreover, the follow-up period varied from 3–156 months, indicating that there were short-term.

In another study, Regis et al.[9] investigated long-term pain relief in 497 cases. The median follow-up period was 43.8 (12–174.4) months, which was as varied as in the abovementioned study. The patients were treated with a single 4-mm isocenter and retrogasserian targeting with a median maximum dose of 85 Gy (range 70–90 Gy). The rates of pain relief without medication after 10, 12, and 14 years were 45.3%, 40.7%, and 33.9%, respectively. The efficacy of pain cessation was superior to Kondziolka's study.

Generally, the recurrence rate is reported to be 0%–52.2% (mean, 24.6%; median, 23%).[5] The recurrence rate in this study was 23.5%, which remained similar throughout our long-term follow-up. Many of the patients who underwent additional treatment for microvascular decompression showed good outcomes (Table 4). However, 2 cases failed to demonstrate an initial effect nor was improvement evident after additional treatment; this could be due to an error in the diagnosis of trigeminal neuralgia, low irradiation accuracy, or resistance to radiation.

Complications

According to a previous systematic review, the mean rates of developing sensory impairment were 21.7% (median 29%;

Table 4. BNI-P Scores at the Initial and Final Evaluations

BNI-P	Initial Evaluation n	Initial Evaluation %	Final Evaluation n	Final Evaluation %
I	71	68.9	39	37.8
II	3	2.9	8	7.7
IIIa	11	10.6	13	12.6
IIIb	9	8.7	11	10.6
IV	3	2.9	4	3.8
V	6	5.8	0	0
Others*	0	0	28	27.1
Total	103	100	103	100
Adequate pain-relief rate†	(71 + 3 + 11)/103	82.5	(39 + 8 + 13)/103	58.2

*Others: recurrence requiring additional treatment.
†Adequate pain-relief rate was calculated as follows: (I+II+IIIa)/Total.

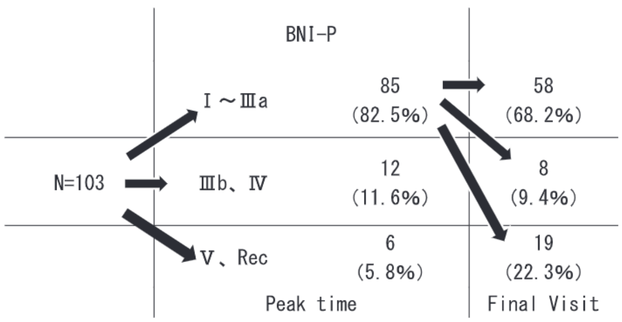

Figure 1. The changes in BNI-P.

0%–68.8%) for BNI-N II–IV and 17.3% for BNI-N IV (very bothersome).[5] We have already reported the investigation of the short-term outcomes. Sensory impairment developed in 23.0% of all cases; of which, 12.3% were categorized as BNI-N IV (very bothersome); this can hardly be considered an acceptable outcome from a patient's emotional point of view.[11] With at least 10-years follow-up period in this study, the sensory impairment of grade BNI-I II–IV showed an equivalent result of 24.2%. Surprisingly, the incidence of severely bothersome sensory impairment (BNI-N IV) decreased significantly to 2.9%. Regarding the sensory impairment in the 58 cases that maintained adequate pain relief for 10 years after initial treatment (**Figure 1**), 29.3% showed a grade of BNI-N II–IV and 1.7% (1 of 58) were classified as BNI-N IV (very bothersome) (**Table 5**). Cases with pain attack cessation experienced more sensory impairment than all other cases. Although the underlying reason for this finding is unclear, it indicates that severe sensory impairment can be alleviated over a long-term period. Therefore, sensory loss (anesthesia)—a rare complication—did not occur in cases that achieved and maintained a high level of therapeutic effect. However, we did not observe particularly fewer complications in cases where the effect is considered to be insufficient; thus, there is no correlation between the therapeutic effect and sensory loss complications.

At the final follow-up, the incidence of BNI-N II–IV complications was 24.3% (25 of 103). We tried to investigate the reason for the sensory impairment. Massager et al.[12] reported that the usage of beam plugging to prevent overexposure of the total radiation dose to the brain stem might cause a higher rate of sensory impairment, probably due to overexposure of the trigeminal nerve with a lower dose area. In our cases, there was only 1 case of plug-use in all cases who experienced complications. We calculated the maximum dose to the brain stem (at 10 mm^3 volume) for cases with complications, which averaged 7.7 (4–13) Gy. Since the tolerable dose of radiation to the brainstem is usually 14 Gy in SRS equivalent, the results of this study may suggest that the complications were not caused by overexposure of one dose to the brain stem but by trigeminal nerve irradiation itself.

Recent reports have indicated that the biological effective dose (BED) significantly correlates with clinical outcomes; it is not simply a matter of prescribed dose or irradiation location. Tuleasca et al.[13] reported the relationship between the physical dose and the incidence of hypoesthesia was not significant; the overall incidence was approximately 20%. However, a clear relationship was found between the BED and the incidence of hypoesthesia, with the incidence increasing from <5% after a BED of approximately 1800 $Gy_{2.47}$ to 42% after approximately 2600 $Gy_{2.47}$. Efficacy in terms of freedom from pain, was approximately 90%, irrespective of the BED (1550–2600 $Gy_{2.47}$) at 1 and 2 years. The data suggested that "pain-free" status developed more slowly at lower BED values. Yang et al. reported that BED was an independent predictor of the degree of

Table 5. BNI-N Results

BNI-N	Last evaluation* n	Last evaluation* %	Adequate Pain Relief n	Adequate Pain Relief %
I	50	48.5	41	70.6
II	14	13.6	10	17.2
III	8	7.8	6	10.3
IV	3	2.9	1	1.7
Others†	28	27.1	0	0
Total	103	100	58	100
Adequate pain-relief complication rate‡	-	-	(10 + 6 + 1)/58	29.3
Final complication rate§	(14 + 8 + 3)/103	24.3	-	-

*Last evaluation: final evaluation for non-recurrence cases and last evaluation just before additional treatment for recurrence cases.
†Others: recurrence requiring additional treatment.
‡Adequate pain relief complication rate = (II+III+IV)/Total.
§Final complication rate = (II+III+IV)/Total.

improvement in all 3 dimensions of pain severity (pain intensity, and interference with general and orofacial activities of daily living). A decrease in dose rate by 1.5 Gy/min corresponded to 31.8% less improvement in the overall severity of pain. Postradiosurgery incidence of facial numbness was increased for BEDs in the highest quartile. Treatment time is an independent predictor of pain outcomes, suggesting that prescription dose should be customized to ensure isoeffective treatments, while accounting for the possible increase in adverse effects at the highest BEDs.[14]

Although we have not been able to examine this issue to that extent, our experience has given us a similar sense of the complication rate before and after cobalt-60 (Co^{60}) source replacement; we agree that this is true not only for trigeminal neuralgia but also for tremor with ventral intermediate nucleus of the thalamus targeting. In the near future, we aim to review our treatment cases again using BED conversion and will consider BED as a criterion for determining the prescribed dose.

Recently, frameless stereotactic radiosurgery (ZAP-X; ZAP Surgical Systems, Inc., San Carlos, CA) has been gradually introduced worldwide. We expect that this treatment device will bring stable clinical outcomes for functional brain diseases in the future, since it is an X-ray—based device that ensures the most stable BED as a sustainable radiation source with a higher dose ratio.

Limitations

The study was a retrospective study which used telephonic interviews to obtain data. Deceased patients' outcomes were evaluated by interviewing their family members and cases with unclear information were excluded. This may have resulted in bias of our study.

CONCLUSIONS

Our findings regarding the effect of Gamma Knife radiosurgery for trigeminal neuralgia were similar to those previously reported for both the initial assessment and the final follow-up. However, post-treatment complications, which are related to the selection of the treatment method, such as severe sensory loss, can greatly affect the patient's activities of daily living and emotional status. The proportion of cases who developed such effects experienced a significant reduction thereof between the time immediately after treatment and the final follow-up. Although more research is needed through the use of follow-up surveys, we believe that Gamma Knife radiosurgery should be considered as the first-line therapy for geriatric patients and in inoperable cases rather than avoiding surgery due to concerns about complications.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Daiki Sato: Conceptualization, Data curation, Formal analysis, Investigation, Writing — original draft. **Motohiro Hayashi:** Conceptualization, Writing — review & editing. **Ayako Horiba:** Formal analysis, Investigation. **Shiro Horisawa:** Writing — review & editing. **Takakazu Kawamata:** Writing — review & editing.

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