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Long-Term Efficacy of Gamma Knife Radiosurgery on Pain Control in Trigeminal Neuralgia

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ABSTRACT

AIM: To investigate the efficacy of Gamma Knife radiosurgery (GKRS) in patients with Burchiel type 1 and 2 trigeminal neuralgia (TN).

MATERIAL and METHODS: A retrospective analysis of prospectively collected data of 163 patients who underwent GKRS between December 2006 and December 2021 was performed. The median follow-up was 37 (range, 6–168) months. The target was the cisternal portion of the trigeminal nerve, and the median prescribed dose was 85 (range, 75–90) Gy. Pain severity was evaluated using the Barrow Neurological Institute (BNI) pain intensity score. All patients had BNI IV or V before GKRS. BNI IIIb or better was defined as adequate pain relief. Logistic regression analysis was conducted to determine the prognostic significance of different pretreatment and treatment variables.

RESULTS: The initial pain relief rate was 85%, with a median period of 25 (range, 1–90) days. At the final follow-up, 62.5% of patients had adequate pain relief. BNI I was achieved in 8% of patients within the first 24 h after GKRS; this rate was 22% at the final follow-up. The pain-free interval was significantly shorter in the 75 Gy group than in the 90 Gy group (p=0.04). The predicted adequate pain relief rates at the 3rd and 6th month and 1st, 3rd, 5th, and 7th year were 84%, 79%, 76%, 67%, 59%, and 55%, respectively. The complication rate was 8%, with disturbing facial sensorial dysfunction in four patients, decreased corneal reflex in three patients, and masseter dysfunction in six patients. Univariate and multivariate logistic regression analyses revealed Burchiel type 1 TN (p=0.001) and male gender (p=0.037) as predictors of increased initial pain relief rate and shorter time to initial pain relief day, respectively.

CONCLUSION: Appropriate patient selection is the key to successful TN treatment. GKRS can be recommended, especially for patients with Burchiel type 1 TN, with low complication rates and effective long-term pain relief.

KEYWORDS: Barrow Neurological Institute (BNI) pain intensity score, Burchiel classification, Gamma Knife radiosurgery, Pain, Trigeminal neuralgia

ABBREVIATIONS: BNI: Barrow Neurological Institute, **GKRS:** Gamma Knife radiosurgery, **REZ:** Root entry zone, **TN:** Trigeminal neuralgia

INTRODUCTION

Trigeminal neuralgia (TN) is the most common type of facial neuralgia diagnosed completely using clinical findings. It has a sudden onset, can last from seconds to minutes, progresses with paroxysmal attacks, and does not have neurological deficits with spontaneous recovery periods and trigger zones classically (7). Different classifications are used for TN. Burchiel classification is most commonly used in neurosurgery practice (4), which consists of briefly type 1

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indicating >50% episodic pain and type 2 indicating >50% constant pain. Surgical and interventional procedures are applied in severe, intolerable, and drug-resistant cases of TN. The first use of radiosurgery (SRS) in TN treatment dates back to the 1950s (11), and since then, several centers have reported the efficacy and safety of Gamma Knife radiosurgery (GKRS) (10,12,19,21,25). Today, GKRS is applied for patients with drug-resistant TN. Burchiel type 1 is the most common type of TN for which GKRS is used (14).

In this study, we conducted a retrospective analysis of prospectively accumulated data of 163 patients who underwent GKRS.

MATERIAL and METHODS

Ethical Statement

This retrospective study of prospectively managed data was authorized by the Institutional Review Board of Koc University Hospital (2022.021.IRB.016) and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from the participants.

Study Cohort

Between December 2006 and December 2021, 228 GKRS procedures were performed for patients with intractable TN in our GKRS unit. Data were collected prospectively and analyzed retrospectively. Patients with TN with multiple sclerosis (n=14), tumor (n=9), and herpes simplex virus infection (n=1) who were deceased independently of TN etiology and 15 repeat GKRS procedures were excluded from the study. Follow-up was performed at the 3rd and 6th month and 1st, 3rd, 5th, and 7th year, respectively.

A total of 163 patients with Burchiel type 1 (90.2%) and type 2 (9.8%) TN were included in this study. Table I shows the patients' characteristics. Briefly, the median symptom duration before GKRS was 6 years (range, 0.5–40 years), 56.3% of symptoms were on the right side, and 63.4% of patients were women. The median age was 64.5 years (range, 24–84 years), and 69% of patients were aged <70 years. There were 83 patients (50.9%) with a previous history of surgery for TN. Sensory dysfunction was present in 16.1% of patients before GKRS.

GKRS Technique

GKRS was performed using Leksell Gamma Knife® model 4C (2006–2012), Perfexion™ (2012–2016), and Icon™ (2017–2022) (Elekta Instrument AB, Stockholm, Sweden). Gradient Echo and postcontrast 1-mm thin-slice axial MR images were obtained before or after applying a Leksell stereotactic frame, based on the available Gamma Knife® model. A single 4-mm isocenter was typically placed along the symptomatic trigeminal nerve at the root entry zone (REZ), defined as the area of the trigeminal nerve from its entrance into the pons to 7 mm peripherally. The median maximum dose was 85 Gy (range, 75–90 Gy), and the median margin dose was 42.5 Gy (range, 37.5–45 Gy) delivered at the 50% isodose line.

Treatment Response

Treatment results were evaluated according to the patient's pain status at follow-up visits and telephone surveys. The latest pain status of all patients was evaluated by telephone survey. The Barrow Neurological Institute (BNI) pain intensity score was used for evaluating pain relief. Briefly, the BNI scale is as follows: BNI I, complete pain relief without medication; BNI II, has little pain but does not require medication; BNI

Table I: General Patient Characteristics

Parameters	Values
Age, median, (year)	64.5
Sex, n (%)	
Male	60 (37)
Female	103 (63)
Side of pain, n (%)	
Right	92 (56)
Left	71 (44)
Type of pain, n (%)	
Burchiel type 1	147 (90)
Burchiel type 2	16 (10)
Pain distribution, n (%)	
V1	2 (1)
V2	55 (34)
V3	36 (22)
V1-2	14 (9)
V2-3	47 (29)
V1-2-3	9 (5)
Median length of disease, (months)	72
Previous surgery, n (%)	83 (51)
1	43 (27)
2	19 (12)
>3	20 (13)
Procedure type, n (%)	
Radiofrequency ablation	50 (60)
Balloon compression	3 (4)
Microvascular decompression	23 (26)
Glycerol rhizotomy	15 (11)
Preexisting sensory dysfunction, n (%)	
Yes	26 (16.1)
No	137 (83.9)

IIIa, no pain, continued medication; BNI IIIb, pain can be controlled with medication; BNI IV, pain relief is available, but not controlled with medication; BNI V, has severe pain, no improvement. The parameters evaluated in this study were initial pain relief to pain, initial treatment failure, pain-free interval, partial recurrence time, total recurrence time, and the need for further surgery. All patients initially presented with BNI IV–V TGN. We categorized the treatment outcomes as complete (BNI I), significant (BNI I–IIIa), adequate (BNI I–IIIb), and poor (BNI IV–V) pain relief as defined by Kondziolka et al. (10).

Partial recurrence was defined as a final BNI I–IIIb score that does not require a new surgical procedure. Total recurrence was defined for those with BNI IV–V and requiring additional surgical intervention. The date of total recurrence was considered as the time when the pain became BNI IV–V, based on medical records or telephone interviews. Patients who showed no significant improvement in pain in the first 6 months after GKRS and whose pain improved but then recurred as BNI IV–V were considered as treatment failure.

All patients were examined in detail before GKRS, and existing sensory problems were recorded. In the follow-up, detailed neurological examinations, primarily corneal reflex, chewing functions, and facial sensory tests, were performed. The presence of any impairment in these findings was considered as a complication. Patients with suspected deficits in telephone surveys were invited for examination.

RESULTS

The follow-up period ranged from 6 to 168 months, and the median follow-up period was 37 months.

Initial Pain Results

In 85% of patients (n=138), initial pain relief (BNI I–IIIb) was observed within 1–90 days (median = 25 days). A total of 25 patients (15%) did not benefit from GKRS (BNI IV–V). Pain relief started in 11% of patients in the first 24 h, and pain relief was achieved between the 15th and 30th day in 51% of patients. Complete pain relief was observed in 12.5% of patients in the 3rd month, whereas adequate pain relief was observed in 85%. The initial pain relief rate was statistically significantly different between patients with Burchiel type 1 and 2 (p=0.001) TN. The rate of pain relief in patients with Burchiel type 1 TN was 89.1% (n=131) and 45.5% (n=7) in those with type 2 TN. Another statistically significant difference was observed between the initial pain relief day in patients according to gender (p=0.037), where it was shorter in men.

No significant difference was observed between patients' age, gender, Burchiel type, time to treatment, presence of pretreatment procedure, applied dose, initial pain relief day, and last pain status (p=0.025).

Long-Term Pain Results

A total of 138 patients benefited from GKRS at baseline. In the final follow-up, 102 patients (62.5%) achieved adequate pain relief, and 36 patients had total recurrence with BNI scores IV–V. Partial recurrence occurred in 52 of 102 patients whose pain scores switched from BNI I, BNI II, and BNI IIIa to the next form and did not require any additional surgical intervention. The median pain-free interval was 35 months. A statistically significant difference was observed between the pain-free duration of patients according to the dose (p=0.002). The pain-free interval of patients treated with 75 Gy was significantly shorter than that of patients treated with 90 Gy (p=0.040). Univariate and multivariate analyses revealed no statistically significant differences in age, gender, Burchiel type, pain distribution, disease duration, previous surgery, and initial pain relief day in patients according to the incidence of recurrence (p>0.05). A total of 46 additional procedures were performed in 36 patients, of which 48% (n=22) were GKRS. The other applied procedures were microvascular decompression (MVD) (n=8) and radiofrequency (RF) ablation (n=16). In total, 20 patients experienced new facial sensory deficits, of whom 4 had disturbing symptoms. No statistically significant relationship was found between the applied radiation dose and facial sensory disturbance. Six patients had masseter dysfunction, and three patients had decreased corneal reflex. The overall complication rate was 8% (n=13) (Table II).

After the initial response, we used the Kaplan–Meier method to analyze the pain-free interval (Figure 1). The predicted adequate pain relief rates in the 3rd and 6th month and 1st, 3rd, 5th, and 7th year were 84%, 79%, 76%, 67%, 59%, and 55%, respectively (Figure 2). Regarding the recurrence of cases, age, gender, type of pain, pain distribution, time to treatment, pretreatment procedure, initial pain relief day, and isodose values showed no statistically significant difference. The predicted complete pain relief without medication was 12.5% at 3 months, 19.6% at 6 months, 28.5% at 1 year, 22.3% at 3 years, 14.2% at 5 years, and 7.1% at 7 years. The possibility for significant pain relief was 63.4%, 63.4%,

Table II: Patient Outcomes After GKRS

Outcomes	Values
Initial pain response (BNI I–IIIb)	85%
Initial pain response (day)	
Median	25
Mean	27.4 ± 22.4
Initial treatment failure (BNI IV–V), n (%)	25 (15)
Total recurrence, n (%)	36 (26)
Complication, n (%)	13 (8)
Severe sensorial dysfunction	4 (2.5)
Decreased corneal reflex	3 (1.8)
Masseter dysfunction	6 (3.7)
New-onset sensory dysfunction, n (%)	20 (12.2)
Mild	16 (9.8)
Severe	4 (2.4)

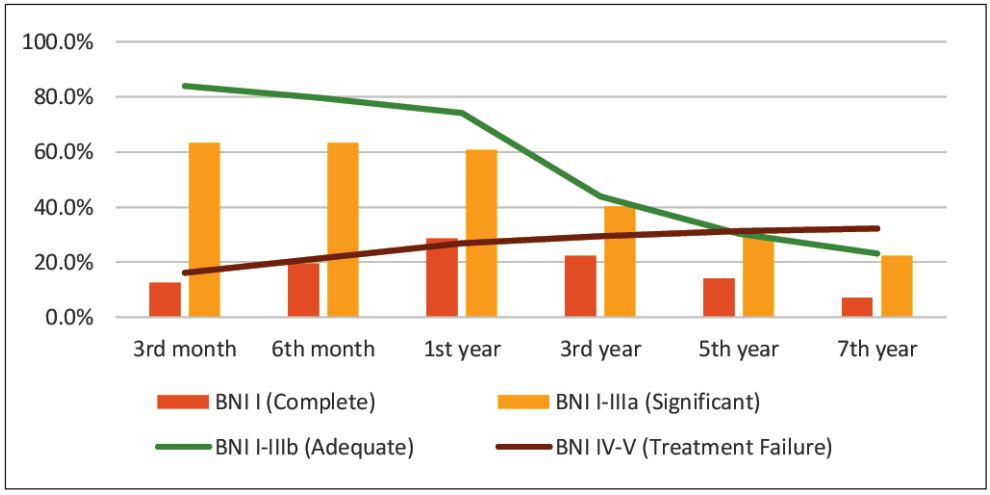

Figure 1: Clinical results after GKRS in trigeminal neuralgia.

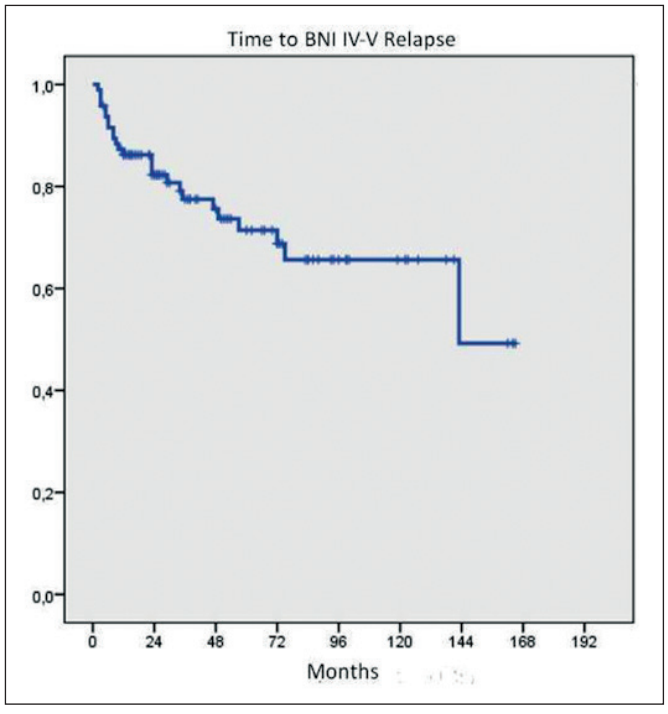

Figure 2: Kaplan–Meier curve; from the time of GKRS until achieving BNI IV–V.

60.7%, 40.2%, 29.5%, and 22.3% in the 3rd and 6th month and 1st, 3rd, 5th, and 7th year, respectively. At the final follow-up, 22% of patients showed complete improvement, whereas 62.5% had adequate pain relief.

DISCUSSION

Surgical methods are important treatment options that increase the quality of life in patients with drug-resistant TN. MVD is the only procedure with the most prolonged known pain control (1,3). Although percutaneous procedures provide reasonable pain control of up to 90%, posttreatment efficacy declines after the first year (6). These interventions may not be suitable for all patients, and GKRS should be considered in these groups. No randomized controlled comparative study of GKRS with other methods has been reported in the literature. A few studies have compared pain relief rates with GKRS, MVD, and percutaneous interventions (2,8,20). Although pain relief is similar for rhizotomy and GKRS, rhizotomy acts faster, and the rate of side effects is higher than that for GKRS (8). MVD provides a longer duration of pain relief than GKRS (2,20) and may have serious side effects such as hearing loss, cerebrospinal fluid leak, hemorrhage, lower cranial nerve palsy, and infection (1,27).

Target, Dose, and Complications

Regarding TN treatment, data on the target and applied radiation dose of GKRS are still unclear. The first target used for GKRS was the gasserian ganglion by Leksell (11). Subsequent studies targeted the trigeminal REZ and retrogasserian area. The generally recommended dose is 60–90 Gy, and the most commonly used target is the cisternal portion of the nerve (25). The dose is decided according to the target, and ≥80 Gy is often preferred (9,17,24). Furthermore, studies have reported an increasing frequency of complications with doses >90 Gy (10,21). A median dose of 85 Gy was prescribed to the cisternal area in our study, and the complication rate was 8%. New-onset numbness was observed in 12.2% of patients (and only four were troublesome). Trigeminal nerve sensory dysfunction is the most common side effect, which subsides over time and several patients ignore it. Anesthesia dolorosa, dry eye syndrome, hearing problems, and masseter dysfunction are less common side effects (25). In the efficacy analysis between doses, the administered dose showed no statistical significance in treatment efficacy, and there was no significant difference between the doses for the development of sensory dysfunction in our study.

Pain Control

Tuleasca et al. systematically compiled 45 studies on GKRS treatment in patients with TN and reported a mean of 15 days and a median latency period of 78 days for time to pain relief (25). In our study, the initial pain relief day was a median of

25 days (range, 1–90 days) and a mean of 27.43 ± 22.44 days. In parallel with the literature, the expected initial pain relief time after GKRS was within 1 month. In the largest series published to date, 89% of 503 patients responded to treatment in the 1st month, and the median time for complete pain relief was reported as 5 months (10,25). In the review of Wolf and Kondziolka (26) published in 2016, they emphasized that according to four large long-term studies (10,13,15,21), adequate improvement (BNI I–IIIb) was observed in 46%–65% of patients with Burchiel type 1 TN in the 5th year after GKRS.

Regis et al. examined the pain-free rate without the need for surgical treatment (22). During a median follow-up of 118.4 months (range, 84.2–174.4 months), the pain-free rate without the need for surgery (BNI I–IIIb) was reported as 83.6%, 80.3%, 75.4%, 67.7%, and 67.7% in the 3rd, 5th, 7th, 10th, 12th years, respectively. They further observed that 45.9% of patients with pain relief at baseline had recurrences, and only 32.3% were considered as major recurrences and required a new surgical procedure. In our study, the rate of adequate pain relief rates at 0.5, 1, 3, 5, and 7 years after a median follow-up of 37 months were 79%, 76%, 67%, 59%, and 55%, respectively. The total recurrence rate was 26% (n=36), and 48% of patients in this group underwent repeat GKRS.

In another long-term study, initial pain relief was achieved in 94% of patients with classical TN; 27% of them had the initial pain relief within the first 24 h. The painless group with or without medication (BNI I–IIIb) comprised 82% in the 7th year (16). In our study, pain response was observed in 11% of patients (n=15) in the first 24 h. The literature reports recurrence rates of 0%–52.2% (mean 24.6%, median 23%) (25). Such different results are due to the technical differences in the studies, and in most studies conducted, patient characteristics and treatments were evaluated in heterogeneous groups (18). According to the multivariate analysis of Marshall et al., numbness after GKRS is an important preliminary finding for the effectiveness of GKRS (15). There are clinical studies in which GKRS is statistically more effective in patients who did not receive interventional treatment before radiosurgery, and there are also those who state that it is insignificant, as in our study (5).

According to Burchiel's pain type, the effectiveness of GKRS, the duration of response to pain, and the time spent without pain were analyzed in previous studies. A higher pain recurrence rate in Type 2 TN patients was found to be statistically significant (13,15,23). In our study, the response rate to treatment was 89% in the Burchiel type 1 and 45.5% in type 2.

CONCLUSION

GKRS is currently the only minimally invasive treatment for patients with Burchiel type 1 and 2 TN. This procedure can be applied with a low complication risk in patient groups diagnosed with Burchiel type 1 and 2 TN and who can tolerate the time required for pain recovery. We intend to emphasize that treatment methods should be applied according to the TN type, especially in the treatment choices of patients with TN. GKRS should also be mentioned when discussing TN treatment options with patients. In the future, it is necessary to conduct studies in which patient characteristics and applied treatment methods show a homogeneous distribution.

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AUTHORSHIP CONTRIBUTION

Study conception and design: GO, YS, SP
Data collection: GO, YS, SP
Analysis and interpretation of results: GO, YS
Draft manuscript preparation: GO, YS
Critical revision of the article: YS, SP
Other (study supervision, fundings, materials, etc...): SP
All authors (GO, YS, SP) reviewed the results and approved the final version of the manuscript.

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