The role of Gamma Knife radiosurgery in trigeminal neuralgia management and technical considerations

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Trigeminal neuralgia (TN) is a debilitating condition characterized by severe facial pain, often refractory to medical therapy. Gamma Knife radiosurgery (GKRS) has emerged as a valuable therapeutic option for patients with TN, offering effective pain relief while minimizing the risk of complications associated with traditional surgical approaches. This review provides a comprehensive overview of the role of GKRS in the treatment of TN, focusing on its efficacy, safety, and technical considerations. We discuss the underlying pathophysiology of TN, its diagnosis, and the rationale for using GKRS as a non-invasive treatment modality. Additionally, we explore the technical aspects and protocols employed in GKRS for TN, including target delineation, radiation dose selection, and treatment planning strategies. We also examine the outcomes of GKRS in terms of pain relief, recurrence rates, and complications, drawing from the latest evidence in the literature. By synthesizing current knowledge and clinical experience, this review aims to provide insights into the optimal use of GKRS in the management of TN and guide clinicians in decision-making and patient care.

KEY WORDS: Radiosurgery, Trigeminal neuralgia, Pain

INTRODUCTION

Trigeminal neuralgia (TN) is a neurological disorder characterized by sudden, unilateral electric shock-like pains in one or more divisions of the trigeminal territory. This condition can significantly impact mental health and severely impair patients’ lives [1]. According to the International Classification of Headache Disorders, TN can be classified into idiopathic, classical, and secondary types [2]. Idiopathic TN shows no significant abnormalities in diagnostic exams. Classical TN is identified when vascular compression of the trigeminal nerve root is visible on a magnetic resonance imaging (MRI) or observed during surgery. Secondary TN is linked to underlying diseases known to trigger TN, such as tumors or multiple sclerosis.

The primary treatment for TN involves pharmacological management with carbamazepine or oxcarbazepine [3]. However, these drugs often have limited efficacy over time and come with several side effects. In cases of classical TN, microvascular decompression (MVD) surgery can provide rapid symptom relief but carries...
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risks of serious complications, including brainstem infarction, hearing loss on the operated side, cerebrospinal fluid leakage, or facial numbness [4]. Percutaneous ablative techniques, which target the gasserian ganglion, are effective but pose a high risk of adverse effects like dysesthesias, corneal keratitis, or facial numbness [5].

Gamma Knife radiosurgery (GKRS) offers an alternative for cases of TN that do not respond to medication. This approach uses high-resolution MRI or computed tomography scans to accurately target the trigeminal nerve. Thanks to advancements in brain imaging and accumulated experience, the effectiveness of GKRS in treating TN has improved. However, debates and uncertainties remain regarding the best GKRS strategies. This article aims to summarize the existing literature on GKRS for intractable TN, focusing on treatment outcomes and strategies.

DIAGNOSIS

Accurate diagnosis of TN is crucial and involves detailed history and clinical examination. Mild sensory abnormalities on the affected side may be present, but abnormal neurological findings would require further evaluation for secondary TN. The typical clinical feature is sudden and brief pain lasting from a second to 2 minutes. This pain is often described as stabbing or electric shock-like, in the unilateral trigeminal area, more often in maxillary (V2) or mandibular (V3) divisions. Additionally, 14–50% of patients experience continuous pain in the same area [6-8]. The pain is triggered by innocuous mechanical stimuli in the affected trigeminal distribution, but spontaneous pain can also occur.

PATHOPHYSIOLOGY

Converging evidence suggests that neural pathology at the root entry zone (REZ) is responsible for TN pain [9-11]. The REZ is where the transition from peripheral to central myelination occurs, making it more susceptible to demyelination. It is established that demyelinated axons are hyperexcitable and generate ectopic impulses via ephaptic interactions among neurons. The voltage-gated sodium channel is considered to play an important role in the generation of ectopic activities in TN [12,13].

MECHANISM OF GAMMA KNIFE RADIOSURGERY

There is limited amount of histological data on the irradiated trigeminal nerve in human. A few case reports have shown histological changes consistent with fibrosis and axonal degeneration in the trigeminal nerve of TN patients who have undergone GKRS [14,15]. The effects of radiation are dose-dependent. In rhesus monkeys, doses of 80 Gy caused partial axonal degradation and 100 Gy caused necrosis. In human, histological changes were observed with a radiation dose of 70 Gy [15,16].

PAIN RELIEF AND complications of Gamma Knife Radiosurgery

The rate of pain relief without medication ranges from 44% to 83%, while with medication it ranges from 70% to 100% [17-23]. The median range for time to pain relief is 10 to 90 days, with a maximum interval of 180 days after GKRS [5]. Short-term pain relief rates ( < 1 year) with or without medication are higher than 75%, but long-term efficacy diminishes to approximately 50–60% at 5 years and 30–40% at 10 years or more [24-26]. The recurrence rate after GKRS ranges from 16.0% to 42.9% [18,20-22,24,26].

The most common complication of GKRS for TN is hypesthesia, with rates reported between 2.5% and 45%. However, the rate of bothersome hypesthesia (Barrow Neurological Institute [BNI] score III or IV) is lower, ranging from 0% to 17.0% [17-20,22-24]. Dry eye is another significant complication, occurring in up to 22.4% of cases [23,27,28]. Other complications include dysesthesia, paresthesia, and deafferentation pain.

TIMING OF SURGICAL INTERVENTION

There is limited data available to determine the timing for surgical intervention. A retrospective study of 121 patients who underwent GKRS found that early GKRS within 3 years from symptom onset resulted in faster pain relief and longer duration of adequate pain control [29]. The European Academy of Neurology guideline for TN recommends considering surgery when medical management with adequate doses fails to sufficiently control the pain [3].

TARGET (ISOCENTER) LOCATION

Anterior vs. posterior

The anterior targets include the gasserian ganglion or the cisternal segment of the trigeminal nerve (referred to as “retrogasserian,” an example shown in Fig. 1). The posterior target mainly focuses on the REZ, also known as the “Obersteiner-Redlich zone,” as it is more radiosensitive than other parts of the trigeminal nerve (Fig. 2). As REZ is a histological concept, its location is not fixed, but it is typically located within 3 mm from the nerve’s exit from the brainstem. Earlier studies have reported positive clinical outcomes from targeting the REZ. For example, Rand et al. [30] found that eight out of 12 patients with TN showed complete or partial symp-
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**Fig. 1.** A 4-mm isocenter was placed on the retrogasserian zone of the trigeminal nerve, with a prescription dose of 42.5 Gy at the 50% isodose line (yellow circles). The 10% isodose line (the outer green circles) did not cover the pons.

**Fig. 2.** A 4-mm isocenter was placed on the root exit zone of the trigeminal nerve, with a prescription dose of 42.5 Gy at the 50% isodose line (yellow circles). The 10% isodose line (the outer green circles) slightly covered the ventral side of the pons.
tomatic improvement without any complications. Nicol et al. [31] conducted a retrospective study on 42 patients with classical TN who received a maximum dose of 90 Gy at the REZ and reported complete pain relief in 73.8% of the patients, with facial paresthesia and dyseusia occurring in 16.7% and 9.5% of the patients, respectively. Some later studies have compared the effectiveness and safety of GKRS using these two targets. Matsuda et al. [32] analyzed 51 patients treated with GKRS at the posterior target and 49 patients treated with GKRS at the anterior target for medically intractable TN. They found that complete remission was not significantly different between the two groups, but the anterior target was associated with a higher complication rate [32]. It should be noted, however, that the anterior target received a higher prescription dose (88.5 ± 3.6 vs. 80 ± 0.0, p < 0.001) and was close to the plexus trigeminus.

In a few subsequent studies, the cisternal portion of the trigeminal nerve, as suggested by Régis et al. [26,33], was chosen as the anterior target. Park et al. [28] performed a retrospective study to compare the results of targeting the REZ and the retrogasserian zone (RGZ). Twenty-three patients (59.0%) received GKRS in the REZ, and 16 (41.0%) received GKRS in the RGZ with 80–90 Gy in the 100% isodose line. Treatment success, evaluated as the BNI pain score I–IIIb, was similar in the REZ group and the RGZ group (87.0% vs. 93.8%, respectively; p = 0.631). However, bothersome complications were observed in three patients (13.1%) in the RGZ group, while 0 (0%) were observed in the RGZ group (p = 0.255). The authors concluded that targeting the RGZ would yield comparable pain relief but with fewer bothersome complications.

Xu et al. [34] conducted a retrospective comparison of outcomes by targeting the REZ with different isodose lines overlapping the brainstem. They compared 36 patients in the proximal group, where the 50% isodose line overlapped the brainstem, with 63 patients in the distal group, where the 20% isodose line overlapped the brainstem. The results showed that GKRS with proximal targeting was associated with a longer duration of adequate pain relief (BNI pain score I–IIIb) and complete pain relief (BNI pain score I). However, newly developed or worsening facial numbness (BNI score II or III) was more frequent in the proximal group (53% vs. 15%, p = 0.015).

Jung et al. [35] evaluated the efficacy and side effects associated with GKS for TN with or without neurovascular compression. In this study, a single 4-mm isocenter was placed on the REZ, with a median distance of 3.2 mm (range, 2.4–5.3 mm) from the pons. The maximum prescription dose administered was 85 Gy (82.4–87.5 Gy). The authors observed that a trigeminal nerve deviated by neurovascular compression at the target coordinate was associated with a higher risk of facial hypesthesia when compared to a nondeviated trigeminal nerve.

Recent studies indicate that RGZ targeting is associated with a higher rate if treatment success (BNI score I–IIIb) and a comparable rate of complications compared to REZ targeting. However, achieving complete pain relief without pain (BNI score I) is more likely with REZ targeting [36,37]. The International Stereotactic Radiosurgery Society suggests an anterior target with level II evidence, as radiosurgery with an anterior target may achieve an outcome similar to that with a posterior target at a lower complication rate [5].

Ideal location

Massager et al. [19] evaluated the results of 47 patients who received GKRS for medically intractable TN over a mean follow-up period of 16 months. They positioned a single 4-mm isocenter in RGZ and used a maximum dose of 90 Gy, ensuring 10 mm³ or less of the brainstem received a dose of less than 12 Gy [19]. The actuarial curve showed that 71% of patients achieved pain relief greater than 90% at 42 months after GKRS, and two patients (4.3%) experienced bothersome facial numbness. The authors suggested placing the target approximately 5 to 8 mm anterior to the brainstem to optimize the result.

Similarly, in a prospective analysis of 100 patients treated with GKS to RGZ using a maximum dose of 85 Gy for essential TN, Régis et al. [21] suggested that the optimal location of the isocenter was 7.5 mm anterior to the brainstem. The authors found that the success rates were 72.7%, 84%, and 96.6% when the distance was more than 9 mm, between 9 and 7 mm, and less than 7 mm, respectively. However, the risk of hypesthesia also increased accordingly.

NUMBER OF ISOCENTERS AND LENGTH OF TREATED NERVE

Several studies have investigated the optimal number of isocenters and the length of the treated nerve in TN radiosurgery. In 2001, Flickinger et al. [38] conducted a randomized study comparing the outcomes of TN patients who received GKRS at a retrogasserian target using either one or two 4-mm isocenters. After a median follow-up of 26 months, they found that the rate of complete pain relief did not differ between the two groups. However, the group with two isocenters experienced more complications, such as facial numbness or paresthesia.

In a retrospective study by Pollock et al. [20], TN patients who received GKS at one isocenter (with a median length of nerve within the 50% isodose line of 5.9 mm) were compared to those who received GKRS at two isocenters (with a median length of
nerve within the 50% isodose line of 9.4 mm). The study found that a longer length of irradiated nerve was not statistically associated with achieving effective pain relief [20].

Alpert et al. [39] retrospectively analyzed 63 patients who underwent GKRS targeting the REZ, with either one (27 patients) or two (36 patients) 4-mm isocenters. The authors discovered that the patients treated with two isocenters received a higher dose (mean, 88.3 vs. 79.1 Gy; p < 0.001), and showed a greater improvement in BNI pain score (mean, 2.83 vs. 1.72; p = 0.003).

Based on the findings of these studies, using two isocenters or increasing the length of the irradiated nerve is likely to result in similar pain relief efficacy at an increased risk of radiation toxicity.

DOSE AND DOSE RATE

The majority of studies recommend a maximum dose of 70–90 Gy for maximal pain relief and minimal side effects. In 1996, Kondziolka et al. [17] published their institutional experience with 51 patients treated with GKRS for TN. The prescription dose ranged from 60–90 Gy, and a maximum dose over 70 Gy was significantly more likely to provide complete pain relief [17].

Pollock et al. [40] compared the effects of high-dose (90 Gy) radiation and low-dose (70 Gy) radiation in the treatment of 68 patients who underwent GKRS. They found that high-dose radiosurgery was associated with a higher rate of pain-free patients (61% vs. 41%, p = 0.017), but also a higher rate of permanent trigeminal nerve dysfunction (54% vs. 15%, p = 0.003) [40].

Longhi et al. [18] studied 160 patients with TN who were treated with GKRS as either the first nonmedical option or as an additional treatment after invasive procedures. They targeted the REZ with a maximum dose of 75–95 Gy, ensuring that the brainstem dose exposure did not exceed 15 Gy. Kaplan-Meier analysis revealed that a dose of 80–90 Gy was statistically associated with a pain-free outcome compared to a dose less than 80 Gy. Among the patients who experienced side effects, 70% had received a dose higher than 90 Gy.

In an animal study conducted by Zhao et al. [16], histological analysis of irradiated trigeminal nerves in five rhesus monkeys was performed. The researchers found that doses of 60–70 Gy had little effect, while a dose of 80 Gy could cause axonal degeneration and demyelination, and a dose of 100 Gy resulted in neural necrosis.

Cobalt-60, the radiation source used in GKRS, decays over time, with a half-life of 5.26 years. Prolonged treatment duration resulting from reduced dose rates can impact the biological effective dose by affecting the amount of sublethal radiation injury that is repaired during exposure. Studies investigating the effects of varying dose rates on GKRS outcomes for TN have yielded conflicting results. An early study by Balamucki et al. [41] examined 239 GKS cases in TN patients, and found no significant correlation between dose rate or treatment duration and the pain control. Similarly, Arai et al. [42] compared a low-dose rate group (1.21–2.05 Gy/min) and a high-dose rate group (2.06–3.75 Gy/min), and found no significant differences in pain control or trigeminal nerve complications. Conversely, Lee et al. [43] evaluated preoperative and postoperative pain in 133 TN patients treated with GKRS, and discovered that a higher dose rate (> 2 Gy/min) was associated with improved short-term pain relief and a lower long-term recurrence rate. Similarly, Yang et al. [44] reported that a decrease in dose rate of 1.5 Gy/min corresponded to a 31.8% decrease in overall pain severity improvement.

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There are conflicting results regarding the outcomes of radiosurgery for TN with neurovascular compression (NVC). Brismar et al. [45] analyzed the treatment outcomes of 181 patients who underwent GKRS based on the degree of NVC observed on MRI. They found that when there had been no previous surgical intervention, patients with NVC were more likely to experience 50% or better pain relief compared to patients without NVC (88% vs. 69%, p = 0.024). Another study also reported that patients with NVC were seven times more likely to achieve an adequate response [46].

However, Lorenzoni et al. [47] conducted a study involving 89 patients with TN and found that the presence of NVC was not associated with complete pain remission. In fact, they discovered that proximal NVC within 3 mm from the brainstem and compression of large vessels were associated with poor outcomes [47]. Sheehan et al. [22] performed a retrospective study involving 106 patients with TN who underwent GKRS, of which 63 patients (59.4%) had NVC observed on MRI. They found no significant difference in pain relief between patients with NVC and those without. In patients with NVC, they observed that higher radiation dose and closer proximity of the isocenter to the site of maximum vessel impingement were associated with pain relief after GKRS. Jung et al. [35] also reported that the presence of NVC was not a predictive factor for a favorable outcome, and they noted that side effects were more common when the trigeminal nerve was deviated by offending vessels if the radiosurgical target was the REZ. In summary, the presence of NVC does not necessarily indicate a poor outcome for GKRS in the treatment of TN.

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REPEAT GAMMA KNIFE RADIOSURGERY FOR RECURRENT TRIGEMINAL NEURALGIA

Repeat GKRS may be considered for recurrent TN when no alternative treatment options are feasible. It has been reported to have similar effectiveness to initial GKRS, with the main complication being new facial sensory dysfunction. Park et al. [48] conducted a study involving 119 patients with recurrent TN who underwent repeat GKRS. The median prescription dose for the repeat GKRS was 70 Gy (range, 50–90 Gy). Pain relief was maintained in 87.8% of patients at 1 year, 69.8% at 3 years, and 44.2% at 5 years, while facial sensory dysfunction was observed in 21% of patients at 18 months. Another study conducted by a Marseille group reported the long-term outcomes of nine cases of repeat GKRS for recurrent TN [49]. They used the RGZ target and delivered a median maximum dose of 90 Gy. The actuarial rate for pain control without medication at 6 months, 1 year, and 7 years were 100%, 75%, and 75%, respectively. The actuarial rates for new onset hypesthesia at the same time points were 33.3%, 50%, and 50%. The authors noted that although the effectiveness of pain control achieved by the second GKRS was comparable to that of the initial GKRS, the toxicity was significantly higher.

When performing repeat GKRS, certain factors should be taken into consideration. Effective pain control (BNI I–IIIb) following the first GKRS is a positive prognostic factor for repeat GKRS. However, even patients with no or minimal response to the first GKRS may still benefit from a repeat procedure [48,50,51]. The cumulative dose administered is strongly associated with the development of sensory dysfunction. Park et al. [48] reported that the cumulative lateral pons dose after repeat GKRS was higher in patients who experienced additional facial sensory dysfunction compared to those who did not (48.7 vs. 42.2 Gy, p = 0.034). They proposed a cutoff value of 44 Gy [48]. Some recommended values for a safe cumulative target dose range between 115 and 150 Gy [52-54].

CONCLUSION

GKRS is an effective tool for treating medically intractable TN, with high success rates and low complication rates. It provides a viable alternative to MVD surgery for patients with medical comorbidities or those who refuse invasive procedures. However, there are several areas that require further investigation. For example, the optimal location of GKRS targets and dose selection, particularly in recurrent cases, need to be studied to enhance effectiveness and minimize complications. Advanced imaging techniques and technical refinements based on long-term data accumulation are anticipated to broaden the role of GKRS for the treatment of TN in the future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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