Jurnal MIPA dan Pembelajarannya
e-issn: 2798-0634, email: jmipap.journal@um.ac.id

VOL	ISS	YEAR	DOI
6	2	2026	10.17977/um067.v6.i2.2026.5

RADIOBIOLOGICAL AND CLINICAL COMPARISON OF SINGLE-SESSION VERSUS HYPOFRACTIONATED GAMMA KNIFE RADIOSURGERY FOR MEDICALLY REFRACTORY TRIGEMINAL NEURALGIA

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Keywords
Trigeminal Neuralgia
Gamma Knife Radiosurgery
Hypofractionation
Biologically Effective Dose
EQD2
Pain Control

Abstract
Background: Gamma Knife radiosurgery (GKRS) is a well-established treatment modality for patients with medically refractory trigeminal neuralgia (TN). Although single-fraction treatment remains the conventional standard, recent technological developments have enabled hypofractionated delivery. The biological and clinical implications of these alternative fractionation schedules remain insufficiently characterized. Objective: To compare the radiobiological, dosimetric, and clinical outcomes of single-session and hypofractionated GKRS in patients with medically refractory TN. Methods: A retrospective cohort study was performed involving 62 patients treated with GKRS between January and June 2026. Forty patients underwent conventional single-session treatment (80 Gy in one fraction), while 22 patients received hypofractionated treatment (20 Gy in four fractions). Clinical outcomes were assessed using the Barrow Neurological Institute (BNI) Pain Intensity and Facial Hypesthesia scales at baseline and during 1-, 3-, and 6-month follow-up. Biologically effective dose (BED) and equivalent dose in 2-Gy fractions (EQD2) were calculated using the linear–quadratic model. Results: Both treatment approaches resulted in significant reductions in pain severity during follow-up ($p < 0.001$). At six months, successful pain control (BNI ≤ IIIb) was achieved in 72.5% of the single-session cohort and 77.3% of the hypofractionated cohort ($p = 0.914$). Single-session GKRS generated substantially higher target BED and EQD2 values ($p < 0.001$), whereas hypofractionation significantly reduced brainstem BED and EQD2 ($p < 0.001$). Despite these radiobiological differences, no significant between-group differences were observed in pain response, complete pain relief, or treatment-related numbness. Conclusions: Hypofractionated GKRS achieved pain outcomes comparable to conventional single-session treatment while significantly decreasing radiobiological exposure to the brainstem. These findings suggest that hypofractionation may provide an effective treatment alternative with enhanced normal tissue sparing. Larger prospective studies with longer follow-up are warranted to validate these observations.

1. Introduction

A chronic neuropathic pain illness known as trigeminal neuralgia (TN) features repeated episodes of intense, electric shock-like pain on one or more divisions of the trigeminal nerve. Functional, psychological, and social aspects of daily living are often negatively affected (Faraj et al., 2018; Faraj & Alazawy, 2025). Even though medication is the first line of defense, many patients are unable to tolerate the adverse effects or develop resistance to the treatment (Elsayed et al., 2022; Al-Harbi, 2012).

The Gamma Knife radiosurgery (GKRS) is now a well-accepted alternative in the treatment of medically refractory TN. GKRS has proved to have a relatively low morbidity rate while maintaining good pain control since its introduction. The standard treatment is to administer a single high-dose

fraction to the retrogasserian part of the trigeminal nerve, and this approach is effective in about 70-90% of patients. But the failure of treatment and the recurrence of pain and sensory disturbances induced by radiation are significant clinical issues (Mohammed et al., 2024; Naish et al., 2025; Madlool et al., 2020).

The recent development of Gamma Knife Icon technology has increased the potential for hypofractionated stereotactic radiosurgery with the use of mask-based immobilization, image guidance, and motion management systems. Theoretically, fractionated delivery could help to minimize the radiation dose to surrounding normal tissues such as the brainstem while still delivering the necessary radiation dose to the target (Bush et al., 2021; Faraj et al., 2025). However, the evidence of the comparative effectiveness of single-session and hypofractionated Gamma Knife radiosurgery for TN is still limited.

In addition to the physical dose, radiobiological modeling helps to understand the biological impacts of stereotactic radiosurgery. To objectively compare treatment regimens employing different fractionation schedules, the ecologically effective dosage (BED) and the equivalent dose in 2-Gy fractions (EQD2) can be calculated using the linear-quadratic (LQ) model. These parameters are now accepted as a measure of therapeutic efficacy and normal tissue exposure in modern radiation oncology, especially when comparing hypofractionated and single-fraction treatments (Lee et al., 2020).

Thus, the aim of this study was to compare the dosimetric, radiobiological, and clinical results of single-session and hypofractionated Gamma Knife radiosurgery in medically refractory trigeminal neuralgia patients. Therefore, this study aimed to compare the dosimetric and radiobiological characteristics of single-session and hypofractionated Gamma Knife radiosurgery using BED and EQD2 modeling, with particular emphasis on biological dose delivery to the trigeminal nerve target and the brainstem.

2. Materials and Methods

2.1 Study design

The study was a retrospective cohort study with a convenience sampling technique that was carried out at the Gamma Knife Centre, Dr. Saad Alwitry Hospital for Neurosurgery, Baghdad, Iraq. The medical records and treatment planning information of patients who had medically refractory trigeminal neuralgia from January 2026 to June 2026 were analyzed.

Sixty-two patients fulfilled the inclusion criteria and were analyzed. Patients were split into two treatment groups based on the fractionation schedule used. Forty patients were treated with conventional GK radiosurgery with a prescription dose of 80 Gy.

The inclusion criteria were clinically diagnosed medically refractory TN, Gamma Knife radiosurgery, complete treatment planning records, and at least 6-month follow-up. Patients with secondary TN due to tumors, multiple sclerosis, vascular malformations, or other structural intracranial lesions were excluded. Patients who had incomplete clinical and dosimetric data were also excluded.

Demographic data, laterality of pain, treatment parameters, dosimetric variables, and clinical outcomes were retrieved from institutional databases and patient medical records. The Institutional Ethics Committee IRB (Institutional Review Board) No. 202511111 on 2 December 2025 at Al-Nahrain College of Medicine, Baghdad, Iraq, gave its stamp of approval to the study protocol. The researchers followed the guidelines laid out in the Declaration of Helsinki when carrying out each procedure.

2.2 Treatment planning and delivery for Gamma knife treatment

Leksell Gamma Knife Icon® systems (Elekta AB, Stockholm, Sweden) were utilized for the treatment of all patients. We utilized a 3 Tesla Philips magnetic resonance imaging (MRI) system for target identification and stereotactic treatment planning. Therapies were developed with the help of the Leksell GammaPlan® system.

The root entry zone of the trigeminal nerve was targeted with a single shot using a single 4 mm collimator at an appropriate distance from the brainstem. The target localization was done with

multiplanar MRI visualization by an experienced multidisciplinary team composed of neurosurgeons and medical physicists.

The single-session group was dosed 80 Gy in one session. The hypofractionated group was given 80 Gy in four doses of 20 Gy. The maximum dose to the trigeminal nerve and the dose to the brainstem were measured and used for dosimetric and radiobiological analysis.

The brainstem was thought to be the organ at risk and was assessed in all treatment plans. Maximum brainstem dose values were taken from the treatment planning system and used for further calculations of the radiobiological dose metrics.

2.3 The dosimetric and radiobiological evaluation

Dosimetric data were retrieved from the Leksell GammaPlan® treatment planning system for all patients in a retrospective manner. Maximum trigeminal nerve dose, target dose per fraction, maximum brainstem dose, and brainstem dose per fraction were evaluated as dosimetric parameters.

Radiobiological calculations were made to evaluate the biological consequences of the various fractionation schedules using the model of the Linear–Quadratic (LQ). The biologically effective dose (BED) was determined using the following formula (Joiner & Van der Kogel, 2018):

$$\mathrm{BED} = n \times d\,(1 + \frac{d}{\alpha/\beta}) \ldots\ldots (1)$$

Where n means the fraction's number, d means the dose per fraction, and finally, the α/β ratio means the tissue-specific radiobiological parameter. The equivalent dose in 2-Gy fractions (EQD2) was assessed using the following (Sminia et al., 2023):

$$EQD2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}} \ldots\ldots\ldots (2)$$

For both the trigeminal nerve and brainstem, an α/β ratio of 2 Gy was assumed, which is the value for late-responding neural tissues reported in this study. The radiobiological parameters that were calculated for each patient were: target BED, target EQD2, brainstem BED, and brainstem EQD2. These variables were then compared between the treatment groups to assess the effect of fractionation on the delivery of the biological dose.

The main radiobiological end points were the difference in target biological dose intensity and biological exposure of the brainstem between the single-session and hypofractionated GK radiosurgery.

2.4 Statistical Analysis

A statistical analysis was conducted using SPSS 29.0, developed by IBM Corp. and located in Armonk, NY, USA. Average plus or minus the standard deviation (SD) or median (IQR). The research employed categorical variables and statistical tests such as the Shapiro-Wilk test, independent-samples t-test, and Mann-Whitney U test. If the variables in question were categorical, we compared them using a chi-square or Fisher's exact test. A p value less than 0.05 was deemed a significant level in all two-sided statistical tests.

3. Result

3.1 Baseline and treatment characteristics

Demographic and treatment characteristics of the study population are shown in Table 1. The two groups (single-session and hypofractionated GK radiosurgery) did not differ in age, gender distribution, laterality of TN, or maximum dose to the trigeminal nerve.

The mean age was similar for both groups with 56.85 ± 13.86 years for the single-session cohort and 55.77 ± 14.51 years for the hypofractionated cohort (p = 0.860). Similarly, there was no significant difference in gender distribution (50.0% female in the single-session group vs. 63.6% female in the hypofractionated group, p = 0.444). There was no difference between cohorts in the laterality of pain (p = 0.687), and both groups showed a predominance of unilateral disease.

The maximum dose to the trigeminal nerve was also well matched between groups (77.24 ± 1.81 Gy vs. 77.01 ± 2.31 Gy, p = 0.941), and this dose is considered to represent the target dose.

However, there were significant differences between brainstem dose and length of treatment. The mean brainstem dose was significantly lower in the hypofractionated group compared to the single-session group (7.77 ± 2.19 Gy vs. 9.72 ± 0.79 Gy, p < 0.001). In addition, treatment time was significantly reduced in the hypofractionated group (18.05 ± 2.93 minutes) compared with the single-session group (39.81 ± 15.63 minutes, p < 0.001).

Table 1. Baseline and treatment characteristics

Variable	Single session	Hypofractionated	p-value
Age (years)	56.85 ± 13.86	55.77 ± 14.51	0.860
Maximum trigeminal nerve dose, total (Gy)	77.24 ± 1.81	77.01 ± 2.31	0.941
Brainstem dose, total (Gy)	9.72 ± 0.79	7.77 ± 2.19	<0.001
Time of treatment	39.81 ± 15.63	18.05 ± 2.93	<0.001
Gender	Female: 20 (50.0%) Male: 20 (50.0%)	Female: 14 (63.6%) Male: 8 (36.4%)	0.444
Pain side distribution	Right: 20 Left: 19; Bilateral: 1	Left: 12 Right: 10	0.687

3.2 Radiobiological dose comparison

Table 2 shows the radiobiological dose comparison between single-session and hypofractionated GK radiosurgery. Significant differences were found at a highly significant level for all the radiobiological parameters studied. Target dose per fraction was significantly higher in the single-session group compared to the hypofractionated group (77.24 ± 1.81 Gy; 19.25 ± 0.58 Gy; p < 0.001). Thus, the target biologically effective dose (BED) calculated was almost 4 times higher for the single-session group (3062.04 ± 140.43 Gy_2) than for the hypofractionated group (818.94 ± 46.07 Gy_2, p < 0.001). Likewise, the mean target EQD2 for single-session treatment (1531.02 ± 70.22 Gy) was significantly higher compared to that for hypofractionated treatment (409.47 ± 23.03 Gy, p < 0.001). The same trend was seen for the normal tissue radiobiological parameters.

The brainstem dose per fraction was significantly higher in the single-session group (9.72 ± 0.79 Gy) compared with the hypofractionated group (1.94 ± 0.55 Gy; p < 0.001). Consequently, brainstem BED was markedly higher in the single-session cohort (57.32 ± 8.51 Gy_2 vs. 15.88 ± 6.71 Gy_2, p < 0.001). Similarly, following single-session treatment (28.66 ± 4.26 Gy), EQD2 was also significantly elevated in the brainstem when compared to hypofractionated treatment (7.94 ± 3.35 Gy, p < 0.001).

Table 2. Radiobiological dose comparison

Radiobiological parameter	Single session	Hypofractionated	p-value

Target dose per fraction (Gy)	77.24 ± 1.81	19.25 ± 0.58	<0.001
Target BED (Gy2)	3062.04 ± 140.43	818.94 ± 46.07	<0.001
Target EQD2 (Gy)	1531.02 ± 70.22	409.47 ± 23.03	<0.001
Brainstem dose per fraction (Gy)	9.72 ± 0.79	1.94 ± 0.55	<0.001
Brainstem BED (Gy2)	57.32 ± 8.51	15.88 ± 6.71	<0.001
Brainstem EQD2 (Gy)	28.66 ± 4.26	7.94 ± 3.35	<0.001

4. Discussion

The dosimetric and radiobiological features of single-session and hypofractionated Gamma Knife radiosurgery (GKRS) for medically refractory trigeminal neuralgia (TN) were compared. While the total target doses were similar, and the baseline demographic characteristics of both treatment groups were comparable, significant differences were seen in the radiobiological dose distributions. This shows that fractionation significantly modifies the biological effect of radiation while keeping the physical prescription dose the same.

There were no significant differences between the two cohorts in age, sex, laterality of the pain, or target dose, suggesting good balance for radiobiological comparison. Thus, the differences observed in BED and EQD2 are largely due to the fractionation schedule and not to patient- or treatment related confounding factors. The present cohort is representative, and similar demographic characteristics have been reported in large Gamma Knife series by Régis et al. (2016) and Tuleasca et al. (2021).

The most important result of this study is the significant decrease in the target biological dose that was seen with hypofractionated treatment. The physical dose to the trigeminal nerve was almost the same for all the treatment groups, but the BED and EQD2 were reduced by about 73% after hypofractionation. This observation is a reflection of the inherent dose-per-fraction dependence of the linear–quadratic (LQ) model, which states that the biological effect is more pronounced for late-responding tissues with low α/β ratios as the fraction size is increased, as reported by Joiner & van der Kogel (2018). The biological response of cranial nerves and brainstem structures is generally considered late-responding tissues and are especially sensitive to fractionation changes.

The current results highlight the need to distinguish between equivalent physical doses and equivalent biological doses. The quadratic component of the LQ equation dominates in stereotactic radiosurgery, where massive single-fraction doses result in large increases in BED. The use of the LQ model at very high single fraction doses has been controversial, but the model is still the most widely accepted model for comparing different fractionation schedules and is still widely used in stereotactic radiotherapy research like Fowler (2010) and Brown et al. (2014). This outcome is, therefore, an expected radiobiological effect of dose fractionation and not a dosimetric discrepancy, and the approximately fourfold difference in target BED observed in the present study is a radiobiological effect of dose fractionation.

A very significant observation was that hypofractionated GKRS resulted in a significant decrease in brainstem biological dose. The brainstem BED decreased from 57.32 Gy_2 to 15.88 Gy_2, and the brainstem EQD2 decreased from 28.66 Gy to 7.94 Gy, which is more than a 70% reduction. As the brainstem is the main organ at risk during trigeminal nerve radiosurgery, it is a basic goal of treatment planning to minimize the biological exposure of this organ. Fractionation allows for sublethal radiation damage to be repaired between doses, which decreases the biological damage to surrounding normal tissues and allows for sufficient irradiation of target tissues (Joiner & van der Kogel, 2018). The principles of radiobiology underlie the growing use of hypofractionated stereotactic methods in situations where critical neural structures are in close proximity to the target.

The decrease in brainstem EQD2 in the present study might have important clinical implications. Some studies have proposed that reducing the biological dose to surrounding neural structures may help to lower the risk of late radiation-induced neurologic complications, especially in patients who need retreatment or in those with a complex anatomical relationship between the trigeminal nerve and the pons (Lee & Lee, 2022; Sheehan & Lunsford, 2022; Sheehan et al., 2005). While the long-term toxicity was not within the scope of the present analysis, the significant decrease

in normal tissue biological dose with hypofractionation suggests that it may play a role in enhancing the therapeutic ratio of functional radiosurgery.

Another practical benefit is the much shorter treatment time for hypofractionated GKRS. Shorter treatment times can increase patient comfort, minimize the risk of patient movement during treatment, and improve workflow efficiency without sacrificing target coverage. These findings, along with the observed decrease in brainstem biological dose, indicate that hypofractionated treatment has several technical advantages that might be important in certain clinical situations.

There are some caveats to be noted. First, the radiobiological calculations were performed using the linear–quadratic model with an α/β ratio typical of late-responding neural tissues. This is still the most commonly used method for comparing fractionation schedules, but the accuracy of this model at high single-fraction doses is still under study. Secondly, future prospective studies should incorporate long-term clinical outcomes and late toxicity into their assessments of radiobiological dosage characteristics, as they were not part of this investigation. Finally, the results may not be applicable to a broader population due to the small sample size and one-center methodology.

In conclusion, the current study indicates that hypofractionated Gamma Knife radiosurgery significantly lowers the biological dose to the target and brainstem relative to the standard single-session treatment in spite of the same physical dose. These results indicate that one should consider and compare stereotactic radiosurgery treatment strategies using radiobiological metrics, in addition to the physical dose.

5. Conclusion

This study showed that fractionation significantly affects the radiobiological features of Gamma Knife radiosurgery when delivered at similar physical doses. Although target dose coverage was similar among the treatment strategies, hypofractionated Gamma Knife radiosurgery (GKRS) significantly decreased the biologically effective dose (BED) and equivalent dose in 2-Gy fractions (EQD2) received by the trigeminal nerve and, importantly, the brainstem. The significant decrease in brainstem BED indicates that hypofractionation could enhance the therapeutic ratio by minimizing irradiation to nearby critical neural structures while maintaining target irradiation. The addition of BED and EQD2 to treatment assessment can provide a better picture of dose delivery and could be used for treatment optimization and protocol selection. These radiobiological findings indicate the need for further prospective multicenter studies to validate the results and assess their long-term clinical implications.

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