Narrative review

Refractory Trigeminal Neuralgia Recurrence in Patients Treated with Stereotactic Radiosurgery

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Abstract
Trigeminal neuralgia is a craniofacial neuropathic disorder that follows one or more of the branches of cranial nerve V, causing paroxysmal attacks of high intensity that roduce disability and is more prevalent in women. The first line of treatment is pharmacological to relieve symptoms and avoid recurrences and complications. However, it has a high rate of refractoriness, so other non-invasive procedures, such as stereotactic radiosurgery, have been developed. This treatment offers relief of symptoms for a longer period, allowing the patient to score between the I-III range on the Barrow Neurological Institute score; however, it can also recur. To determine the recurrence of refractory trigeminal neuralgia in patients treated with stereotactic radiosurgery, a narrative review of original scientific journal articles in English and Spanish, published from 2019 to 2024, was performed. Nevertheless, the safety and efficacy of radiosurgery allow multiple treatments to be performed without serious complications, with a low incidence of hypoesthesia and a low prevalence of aneurysms.

Keywords
Trigeminal Neuralgia, Radiosurgery, Hypesthesia, Treatment Outcome, Efficacy, Recurrence.

Resumen
La neuralgia del trigémino es un trastorno neuropático craneofacial que sigue una o más de las ramas del nervio craneal V y ocasiona ataques paroxísticos de alta intensidad, produce discapacidad y es más prevalente en el sexo femenino. El tratamiento de primera línea es el farmacológico, con el objetivo de aliviar los síntomas, evitar recidivas y complicaciones. Sin embargo, presenta un alto índice de refractariedad, por lo que se han desarrollado otros procedimientos no invasivos como la radiocirugía estereotáctica. Este tratamiento ofrece un alivio de los síntomas durante un periodo más prolongado que permite al paciente puntuar entre el rango I-III en la escala del Instituto Neurológico Barrow; sin embargo, también puede reaparecer. Con el objetivo de determinar la recurrencia de neuralgia del trigémino refractaria en pacientes tratados con radiocirugía estereotáctica, se realizó una revisión narrativa de artículos originales de revistas científicas en inglés y español, publicados de 2019 a 2024. La recurrencia posterior a la radiocirugía puede estar determinada por características propias de la enfermedad, así como por el plan de tratamiento. A pesar de ello, debido a la seguridad y eficacia que ofrece, es posible realizar múltiples intervenciones sin presentar complicaciones graves y obteniendo baja incidencia de casos de hipoestesia y una escasa prevalencia de aneurismas.

Palabras clave
Neuralgia del Trigémino, Radiocirugia, Hipoestesia, Eficacia, Recurrencia.

Recurrencia de la neuralgia del trigémino refractaria en pacientes tratados con radiocirugía estereotáctica

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Introduction

Trigeminal neuralgia (TN) is a neuropathic craniofacial pain characterized by unilateral paroxysmal attacks of high intensity in the distribution of the three branches of the trigeminal nerve.[i] The prevalence is less than 0.1 %, with an annual incidence of four to 13 cases per 100,000 people, increasing with age (> 50 years). In addition, it has been observed to affect more women than men, with a ratio of 1:1.5 to 1:1.7.[ii]

Chronic pain debilitates and negatively impacts the quality of life, generating disability in daily activities, such as drinking and eating.[iii] Commonly, cases of idiopathic trigeminal neuralgia and those associated with concomitant chronic pain are reported more in women, increasing the complexity of its management.[iv] Because of this, the development of depression and anxiety disorders is higher, along with an intolerance to first-line pharmacotherapy.[v] In addition, patients with TN have a 4.4 times higher risk of developing dementia, making conventional treatment even more complex and less effective.[vi]

In patients in whom pharmacological treatment was unsuccessful, 40 % of the patients present detachment to treatment due to interactions and adverse effects of first-line drugs after one year[vii], so alternative treatments such as stereotactic radiosurgery (SR), microvascular decompression, balloon compression, among others[viii] are recommended, with prior imaging studies such as magnetic resonance imaging (MRI). However, 31% of patients treated with SR have a recurrence of symptoms within a mean time of eight months.[ix]

The high degree of recurrence of trigeminal neuralgia presents a challenge for innovation in different treatments, such as radiotherapeutics,[ii] to achieve success in relieving symptoms as well as avoiding relapses. SR is an effective treatment method for the benefit of patients who do not respond adequately to first-line drugs.[x]

SR is a type of radiotherapy that uses 3D imaging to focus radiation beams on a specific area of the brain. In current use, it proves to be an alternative for TN patients who do not respond to other invasive surgical procedures or who are not candidates due to age and other comorbidities.[xi] An initial pain relief rate of 85% and 55% at 7 years has been observed.[xii] It is considered a method with a low risk of complications, as it is a non-invasive procedure, performed under local anesthesia and safe for repeated use.[xiii]

An information search was performed through HINARI, PubMed, *Web of Science* and LILACS databases. Articles published from 2019 to 2024, in Spanish and English, in primary and secondary sources were selected. The boolean operators "Trigeminal neuralgia AND treatment OR quality of life", "Stereotactic radiosurgery AND trigeminal neuralgia", "Stereotactic radiosurgery AND trigeminal neuralgia AND efficacy OR recurrence" were used in the search strategy, "Stereotactic radiosurgery AND Trigeminal neuralgia AND aneurysm OR hypoesthesia" and articles were selected according to validity criteria, with the aim of describing the recurrence ofrefractory trigeminal neuralgia in patients treated with stereotactic radiosurgery.

Discussion

Refractory trigeminal neuralgia and its treatment

TN is a condition characterized by chronic pain affecting the trigeminal nerve, esponsible for facial sensitivity. This disease is divided into classic TN, also known as primary TN, which is characterized by unilateral recurrent paroxysmal episodes of pain, describped as electric shocks or stabbing, and may also present with continuous pain; secondary TN caused by identifiable underlying conditions such as multiple sclerosis, tumors, or injuries; and atypical TN, which includes any neuralgia that does not meet the characteristics of classic TN.[xiv]

This medical condition is commonly associated with neurovascular compression or irritation of the nerve root near the point of entry into the pons. The superior cerebellar artery is the most common cause of compression, but the anterior inferior cerebellar artery, basilar artery, and pontine veins are also involved. Likewise, TN can be secondary to pathologies such as multiple sclerosis, autoimmune diseases, compression by tumors, or vascular malformations.[xv]

Various theories have been postulated on the pathophysiology of TN, the most widely accepted being the one presented by Fromm *et al.*, known as the "epileptogenic theory", which mentions that chronic irritation of the trigeminal nerve endings generates a change in the inhibition systems in the sensitive nuclei of the nerve, thus resulting in an increase in their activity due to the appearance of action potentials of ectopic stimuli. Due to the increase in this activity and the decrease in the function of the inhibition mechanisms, paroxysmal discharges of the interneurons are generated in response to the different stimuli that result in painful crises.[xvi]

Part of the clinical criteria used to make the diagnosis are recurrent, paroxysmal and unilateral facial pain, which follows the path of some branch of the trigeminal nerve; it can be a pain that lasts from seconds to two minutes, of strong intensity and that provokes a sensation of an electric shock or is stabbing. In addition, an episode can be triggered by innocuous stimuli such as chewing or brushing teeth, among others. However, any other cause must always be excluded.[xvii]

Conventional treatment seeks to relieve pain as well as improve the patient's quality of life. There are multiple options, but the first line of treatment is drugs such as carbamazepines, gabapentin, and pregabalin.[xviii]

In a study conducted by Zhong *et al.*, it was observed that first-line drug treatment has a 15 % probability of being refractory, requiring the use of second-line treatments. Among these treatments are surgical interventions such as vascular decompression, percutaneous procedures and Gamma Knife® radiosurgery (GKRS). Microvascular decompression (MVD) is the treatment of choice, as it provides relief after relocation of the vessel compressing the nerve or by placing a barrier between the two structures.[xix]

Radiosurgery is a less invasive procedure, which consists of irradiating the nerve root, thereby causing an interruption in the pain signals traveling to the brain.[xx] On the other hand, there are less common treatments such as glycerol injections, nerve blocking through anesthetic or steroid injections, Botox injections in the affected areas, and lifestyle changes.[xxi,xxii]

Efficacy of Stereotactic Radiosurgery in Trigeminal Neuralgia

SR is a type of radiation therapy used in the treatment of malignant and benign brain pathologies, such as TN. SR uses multiple highly conformal radiation beams that converge on a specific, radiographically delimited treatment volume through gamma-ray devices or linear accelerators, generating tissue ablation. Because of its high precision, the surrounding normal brain tissue receives low radiation doses due to rapid energy dissipation, which decreases its toxicity.[xxiii]

SR in TN aims to reduce pain intensity according to the Barrow Neurological Institute (BNI) scale (Table 1) and its refractoriness without producing high toxicity.[xxiv] No consensus has been reached on the optimal dose for long-term pain relief; however, it has been observed that the higher the dose, up to 90 Gy, the greater the pain control, without increasing hypoesthesia.[xxv] Boling *et al.*, conducted a comparative analysis of 80 Gy and 85 Gy doses, finding that the latter resulted in prolonged pain relief without an increase in adverse effects.[xix]

Among the equipment used is the Gamma Knife® (GKRS), which has shown effective initial pain relief in 91.75 % of patients, and recurrences in 34.4 % of them.[xxvi] Dinh *et al.*, evaluated its efficacy in refractory primary TN and their results indicate that, within three months, 84.4 % of patients had pain relief and 78.8 % were pain-free without the use of medication. However, the recurrence rate was 14.3 %.[xxvii] Similar data were obtained in a study by Bal *et al.*, using Cyberknife® (CKRS), in which 80 % of patients obtained pain relief.[xxviii]

It has been observed that the pain relief produced by SR is maintained in the long term with a BNI-I to BNI-III.[xxix] In the first series performed in Latin America, Constanzo *et al.*, reported that patients who had pain improvement reached a BNI I-IIIa in an average of 3.86 months and maintained it for an average of 14.4 months.[xxx] In addition, short-term pain relief has also been observed. Perez *et al.*, reported that patients treated with CKRS obtained early pain relief, within seven days post-treatment, obtaining maximum relief after 30 days.[xxxi]

However, pain relief progressively decreases, presenting recurrences (Table 2). These are defined as a BNI of IV/V in patients who had initial pain relief with BNI of I-III.[xxxii] It has been found that despite having initial relief in 83 % of patients, 40 % of them present recurrence.[xxxiii] For this reason, an attempt has been made to elucidate factors associated with recurrence, among which are the characteristics of the disease and the treatment (Table 3).

Barzaghi *et al.*, evaluated factors affecting the duration of SR effect in 112 patients with classic TN. They found that a radiation dose lower than 80 Gy, a calibrated dose rate lower than 2.5 Gy/min, and a distance between the isocenter and trigeminal nerve emergence greater than 8 mm were related to a shorter duration of pain relief.[xxxiv]

Recurrences have also been reported in patients with secondary TN. Leduc *et al.*, compared the efficacy of radiosurgery in TN secondary to multiple sclerosis versus classic/idiopathic, finding that pain relief lasts less in the former group. In patients who had an initial response with BNI of IIIa or less, 78 % with secondary TN recurred within 29 months, compared to 52 % of the control group who had recurrence within 75 months.[xxxv]

Regarding the efficacy of SR in TN secondary to tumors, irradiation of different targets has been evaluated. Franzini *et al.*, treated only the trigeminal nerve with GKRS and found that all six patients achieved a BNI less than or equal to IIIb in an average period of 3.4 months and only one presented recurrence at 64 months. In addition, they concluded that prospective studies with a larger sample still need to be performed to demonstrate the time of efficacy and recurrence.[xxxvi]

Nevertheless, irradiating the tumor alone does not provide complete pain relief and recurrences are observed with BNI-V.[xxxvii] Hall *et al.*, calculated the rate of change of BNI over time (ΔBNI). They found that depen-

Table 1. Barrow Neurological Institute pain intensity score for trigeminal neuralgia.

Score**	Description
I	No trigeminal pain, no medication
II	Occasional pain, no medication required
III	Some pain, adequately controlled with medication
IIIa	No pain, continued medication
IIIb	Persistent pain, controlled with medication
IV	Some pain, not adequately controlled with medication
V	Severe pain, no pain relief

** BNI values I-III are considered good outcomes and BNI IV-V poor response to treatment.

Source: Cordero Tous N, Cruz Sabido J de la, Román Cutillas AM, Saura Rojas EJ, Jorques Infante AM, Olivares Granados G. Outcome of radiosurgery treatment with a linear accelerator in patients with trigeminal neuralgia. Neurologia. 2017;32(3):166-174. DOI: 10.1016/j.nrl.2015.10.003

Table 2. Effectiveness of radiosurgery in trigeminal neuralgia according to BNI and recurrence

Author	BNI pre-SR*	Dose	BNI post-tx**	Time to relief	Recurrence
Rogers C, et al[xxiv].	IV	35-40 Gy+	BNI of I in 19 (35 %), II in 3 (6 %), III in 26 (48 %), and IV in 4 (7 %), V in 2 (4 %)	15 days, 31 % en ≤ 24 h)	36 % in 2.5 years
Régis J, et al[xxvi]	V	70-90	BNI of I= 85.5 %, BNI of II=12.3 %, BNI of III=1.6 % and BNI of IV=0.3 %.	10 days (1-180)	34.4 % in 24 months
Dinh HK, et al[xxvii].	IV-V	50-84	NIB of I-III=84.8 %	6 months	14.3 %
Shrivastava A, et al[xxxii].	IV-V	80	NIB of I= 38/78, NIB of II=4/78, NIB of III=36/78	15 days	28 patients in 17 months
Ali S, et al[xxxiii].	IV-V	70-90	NIB of I-III=83 %	3months	40 % in 2-3 years

BNI= Barrow Neurological Institute Pain Intensity Scale, Gy+= Grays.
BNI pre-tx* Barrow Neurological Institute pre-tx pain intensity scale, Gy+= Grays.
BNI post-tx** Barrow Neurological Institute pain intensity scale post treatment.

Table 3. Factors associated with recurrence of Trigeminal Neuralgia after Radiosurgery

Author	Dose	Target	Distance between isocenter and root entry zone	Nerve volume within 50 % isodose	Beam size	BNI post-SR*	Outcomes
Barzaghi LR, *et al.*[xxxiv]	70-90	RGZ**	8.1 ± 0.2 mm	22.5 ± 1,1 mm^3	-	BNI of I-IIIb= 89.3 % in 35.3 ± 5.2 days	Less long-term pain relief was associated with isocentre-REZ distance ≤ 8 mm = < 0.001), dose < 80 Gy (p= 0.038), dose calibration rate < 2.5 Gy/min (p = 0.018).
Wolf A, *et al.*[xxxix]	80-90	DREZ++	4.9 mm	<35 % o > 35 %	4 mm	BNI of I-IIIb= 89.1 % in 1.9 months	The presence of MS+ was associated with worse outcomes, only 61 % maintained relief for one year.
Conti A, *et al*[l]	70-75	DREZ	-	23.8-29 mm^3	5-6 mm	BNI of I-III= 96.8 % in 6 months	A low isodose (< 1.4 mJ) and nerve volume < 30 is associated with higher recurrence, as is having MS.
Ortholan C, *et al.*[xl]	90	DREZ	-	-	5-6 mm	BNI of I-IIIa= 91.5% in 3.3 months	Recurrence rate at 12 months was higher in patients with 5 mm shot with Dmax to the brainstem < 25 Gy (26.4 %).

Author	Dose	Target	Distance between isocenter and root entry zone	Nerve volume within 50 % isodose	Beam size	BNI post-SR*	Outcomes
Park H, *et al*[xlii]	80-85	DREZ y RGZ	-	2.7± 0.8 (isodose 50 %) x10^2 cm^3	-	BNI of I-IIIb= 92.8 % in one and a half months	Disease duration > 3 years and insufficient inclusion of nerve compression sites in the target are correlated to worse long-term outcomes.
Lovo E, *et al*[xliii]	80-96	RGZ y DREZ	DREZ= <4 mm/ RGZ => 8 mm	RGZ=32.7/ DREZ= 30.6 mm^3	4 mm	BNI de I-IIIb= 65.6 % (distal) y 52.9 % (proximal)	Recurrence of 21.9% in 120 days in distal group and 60 days in proximal group.

BNI post-SR*: Barrow Neurological Institute's Post-Radiosurgery Pain Intensity Scale.
EM+ = Multiple Sclerosis.
BNI= Barrow Neurological Institute Pain Intensity Scale.
RGZ**: Retrograsserian Zone.
DREZ++= dorsal root entry zone.

ding on the target irradiated changes the proportion of patients with pain recurrence, showing higher recurrence when irradiating only to the tumor. On the other hand, pain relief improves when irradiating both targets, the trigeminal nerve and the tumor.[xxxviii]

In addition to the type of neuralgia, differences in recurrence have also been observed according to the treatment plan, including dose, target, and size of the irradiated volume.[xxxix] Conti *et al.*, analyzed these characteristics by irradiating the full diameter of the nerve 5-6 mm from the cisternal portion of the nerve, with a dose of 60Gy prescribed at 80 % isodose. Their results indicate that treating a small nerve volume (< 30 mm^3), a low integral dose (< 1.4 mJ), and the presence of multiple sclerosis are indicators of recurrence.[xl]

Following these results, Ortholan *et al.*, performed a prospective study comparing different shot sizes. Patients received 5 mm D_{max} < 25 Gy (group 1), 6 mm D_{max} < 25 Gy (group 2), or 6 mm with D_{max} > 25 Gy (group 3), and obtained recurrence rates of 26.4 %, 16.5 %, and 5 %, respectively. These results indicate that irradiating a larger nerve volume with a higher dose decreases recurrence.[xl]

With respect to the target, it has been investigated which part of the nerve responds best to SR, either proximal or distal to the emergence of the brainstem nerve root (BSN).[xli] In the REZ, peripheral myelin transitions to central myelin, being more sensitive to chronic compression by surrounding blood vessels, resulting in axonal demyelination. Park *et al.*, analyzed the relationship between the nerve vascular compression zone and the SR target, and found that targeting the nerve in the actual vascular compression zone improves SR results.[xlii]

Similar results were obtained by Hopkins *et al.*, who found that distal targeting is associated with higher rates of pain relief.[xli] Likewise, Lovo *et al.*, observed that targeting the retrogasserian area is more effective in pain relief. The distal group exhibited recurrence in 21.9 % of patients, while the proximal group demonstrated recurrence in 29.4 % of patients. These rates were observed after 120 days and 60 days, respectively.[xliii]

Reintervention with SR has been evaluated in patients who present recurrences after the first radiosurgery, specifically in those who initially had a good response.[xliv] Guillemete *et al.*, observed that the efficacy and safety of a second intervention with Cyberknife® is similar to the first treatment. After the second intervention, adequate initial pain relief was obtained in 87.9 %, in the long term in 92.1 %, 74.0 %, 58.2 %, and 58.2 % at 6, 12, 24, and 36 months respectively. In addition, they analyzed possible predictors of the efficacy of the second treatment and found that the presence of hypoesthesia or its aggravation after the first SR is a predictive factor of a better outcome for second treatment.[xlv]

A comparison has been made between the performance of MVD and that of SR in patients with post-SR recurrence of primary trigeminal neuralgia. Raygor *et al.*, found that patients who presented with sensory disturbances obtained pain relief for a longer time, the same as in the first SR. However, they reported that MVD had better results, with a percentage of pain relief of 86 % and 75 % in the first and fifth year of follow-up compared to 73 % and 27 % respectively in the

SR group. On the other hand, two patients treated with MVD presented complications: one of them presented cerebrospinal fluid leakage and required a new intervention, while the other one presented postoperative hyperacusis.[xlvi]

Hypoesthesia and aneurysm in patients with trigeminal neuralgia after stereotactic radiosurgery

Among the most frequent complications associated with the use of SR in TN is hypoesthesia. Romanelli *et al.*, demonstrated that, out of a total of 343 patients, numbness was found in 6.1% after 36 months post-intervention that was bothersome or disabling; another 48 patients presented other non-disabling sensory affectations.[xlvii]

The presence of hypoesthesia in patients after radiosurgery is associated with multiple reinterventions. Helis *et al.*, demonstrated that 19 cases of 77 participants presented facial hypoesthesia after the first intervention; among these cases, three patients reported the sensation of numbness as bothersome. In the same study, with a sample of 34 patients who underwent a second radiosurgery, 26 developed hypoesthesia, only one patient described this sensation as bothersome.[xlviii]

Another study by Helis *et al.*, showed that, after the third radiosurgery, the most frequent complication was hypoesthesia; in addition, ten patients presented facial alteration out of a total of 22 persons. Likewise, 18 patients reported clinical improvement associated with TN during a mean time of 3.8 years after the last intervention. No predictors for recurrence after a third intervention could be detected due to the low number of participants in the study.[xlix]

Guillemette *et al.*, found that the recurrence of neuralgia after treatment with SR was in 53 cases, 24 of which were associated with neuralgia due to multiple sclerosis and 27 of idiopathic cause. Similarly, the study showed adequate pain relief of 77% at one year, 62% at three years and 50% at five years.[l]

The number of interventions for refractory TN shows a prolongation in pain relief between surgical procedures. A third intervention with SR reduces TN symptomatology by 93%. However, the time to recurrence was compared between the three interventions with SR, and no predictors were obtained for the recurrence of pain at one-year post-surgery (p= 0.84).[li] Likewise, Tempel *et al.*, found no statistically significant evidence between the time of the three interventions and the recurrence of neuralgia episodes.

Multiple SR interventions indicate that the most common complications are facial sensory dysfunction after each procedure. Tempel *et al.*, also reported that 17.6% of patients had hypoesthesia after the first procedure, 11% after the second SR, and 0% reported sensory complications after the third SR.[lii]

Paresthesia in post-surgical patients is usually associated with the exact location of the nerve where the radiation is performed. Lovo *et al.*, demonstrate that there is a higher incidence of paresthesia if the target of therapy is located at the dorsal root entry zone compared to Gasser's ganglion.[liii] Gorgulho *et al.*, mention that high doses of radiation at the entry zone of the trigeminal nerve may present this same complication.[liii]

The presence of an aneurysm is observed as a complication after the use of GKRS, the etiology of which is unknown. However, it is thought that endothelial injury activates the coagulation cascade and fibrin deposition, in addition to inducing oxidative stress. Arteries close to the trigeminal nerve, such as the superior cerebellar artery that runs adjacent to the nerve, and the anteroinferior cerebellar artery, that receive significant radiation, are the most affected.[liv]

Aneurysm formation due to the use of GKRS is not only associated with TN therapy but also with vascular malformations or tumors.[lv] The formation of aneurysms associated with TN is slightly reported; however, it is important because it is a lethal complication for patients if it is not detected promptly. Eleven cases of aneurysm post-SR with GK have been reported, of which two cases were operated on once due to TN and presented rupture of the aneurysm at nine and 13 years, respectively, post GKRS.[lvi]

The use of SR for TN remains the safest surgical option for refractory patients who are unsuitable for MVD or other interventions; therefore, Chung *et al.*, conclude that a 10-year follow-up of patients after RC intervention is pertinent. Similarly, early intervention is important to avoid rupture.[liv]

Conclusion

SR generates post-treatment symptom relief for a longer period of time, with a low risk of adverse effects. Likewise, it is considered an alternative to improve recurrence in older patients with comorbidities who cannot undergo invasive treatments.

Regarding SR safety and recurrence, the number of interventions performed has a positive influence on TN symptomatology, increasing the time in which recurrence occurs. The most common adverse effect is hypoesthesia, which is associated with a greater number of interventions, although it has not been described as disabling. On the other hand, the incidence of aneurysm development within the first nine years is very low.

The literature recommends using adequate doses, irradiate a larger nerve volume, and target the retrogasserian area to reduce recurrence in TN. However, more prospective studies, with larger numbers of patients, are required to verify safety and efficacy.

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