

Trigeminal Neuralgia

Impact of radiosurgery on the surgical treatment of trigeminal neuralgia

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Abstract

Background: The history of the development of current available techniques to treat TN was reviewed.

Methods: The largest peer-reviewed publications on the surgical treatment of refractory TN were analyzed, considering the pros and cons of each technique. Results of modern peer-reviewed radiosurgery series were presented, taking into consideration the approach of each research article. Radiation doses and targets for radiosurgery were discussed to maximize the understanding of this technique.

Results: It is concluded that radiosurgery is the least invasive modality with the fewest side effects, although, to match the results of the competing techniques, a substantial number of patients still need some medication intake.

Conclusion: Further studies determining the ideal target and radiation dose may bring radiosurgery results to the level of the ones achieved with microvascular decompression, currently considered the gold-standard method.

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Keywords:

Trigeminal neuralgia; Tic douloureux; Facial pain; Radiosurgery; Trigeminal nerve; Brain stem; Gasserian ganglion

1. Introduction

Trigeminal neuralgia was recognized as a unique medical condition since the time of the Greeks [51], but despite all attempts throughout history, no ideal therapeutic option has emerged to treat refractory TN. Anticonvulsants are the choice for initial management of trigeminal pain. However, about 25% of the patients do not respond to anticonvulsants [14]. Among those who experience benefit from the medication, an additional number of patients develop intolerance to medication due to side effects [65].

Abbreviations: BC, balloon compression; CISS, constructive interference in steady state; GG, gasserian ganglion; GR, glycerol rhizolysis; IDL, isodoseline; MVD, microvascular decompression; REZ, root entry zone; RFR, radiofrequency rhizolysis; SRS, stereotactic radiosurgery; TN, trigeminal neuralgia; V1, V2, V3, first, second, and third branches of the trigeminal nerve, respectively.

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2. Historical background of surgical treatment of TN

Trigeminal neuralgia has baffled surgeons since the 18th century. Peripheral section of trigeminal nerve branches was practiced at that time in France [6]. It fell out of favor for interventions to the GG because of its inconsistent success. Initially approached extracranially through the pterygoid fossa [52,61,69], it was not until 1891 that surgeons had the “audacity” to open the skull to treat trigeminal pain. Hartley [22,69], in the United States, and Krause [33], in Germany, started removing the ganglion extradurally through the temporal fossa. Poor visualization and hemostasis led to the unacceptable mortality of 24% [61,68]. In 1905, Cushing reported 332 extradural ganglionectomies with only 2 fatalities. Later on, Sweet [61] summarized well when he wrote about Cushing’s surgical skillfulness: “Cushing’s skills led to the persistence in using an unnecessarily extensive operation for trigeminal neuralgia.” Concomitantly to Hartley’s and Krause’s study, Horsley et al [24] attempted the retrogasserian selective rootlet section intradurally. The unfortunate death of the patient brought in favor extradural retrogasserian neurotomy, widely popularized by Frazier [70] in the earlier

Table 1
Summary of the most extensive series results at long-term follow-up on the surgical treatment of TN

Authors	Technique	No. of patients	Pain relief at follow-up (%)	Recurrence (%)	Follow-up (y)
Barker et al [1]	MVD	1155	70 ^a	30	10
Broggi et al [4]	MVD	148	75 ^a	15.3	3.2
Broggi et al [5]	RFR	1000	76.9 ^a	18.1	9.3
Kanpolat et al [29]	RFR	1600	57.7 ^a	25.1	5
Skirving and Dan [56]	BC	496	68 ^a	32	10.7
Saini [54]	GR	469	17.4 ^a	82.6	5
Slettebo et al [57]	GR	60	50 ^a	43	4
Maesawa et al [38]	SRS	220	56.6 ^b	13.6	3
Pollock et al	SRS	117	55 ^a	32	3
Smith et al [58]	SRS	60	45.2 ^a	25.6	3

^a Pain free and medication free.

^b Pain free with and without medication.

1900s. Thousands of patients were submitted to this procedure until the critical review of the surgical side effects some decades later [42]. Although in 1925 Dandy noticed vascular compression of the rootlets at the REZ, intracranial surgery was felt to be a too aggressive treatment of the disease [10,61].

Minimally invasive approaches to TN paralleled the surgical efforts that culminated with the elegant MVD, established by Janetta [25]. Alcohol rhizolysis was tried with different routes and finally settled through the foramen ovale [67]. Up to 5000 patients were reported to be treated in the early decades of the 20th century by this approach [21].

The access of the GG through the foramen ovale led to the development of percutaneous treatments. Electrocauterization of the ganglion, started in 1931 with Kirschner [61], evolved to selective radiofrequency rhizotomy with the efforts of Sweet [64]. Glycerol injection was discovered surreptitiously by Leksell and coworkers [20] while applying radiosurgery to the trigeminal ganglion. Percutaneous compression by inflating a balloon was later described and continues to be favored in many centers [40].

The immediate, greater than 90% success observed with multiple surgical modalities for TN is similar, including MVD [1,4], RFR [5,29,66], BC [7,56], GR [8,26,53,54,57,71], and SRS [31,38,46,48,50,58]. Table 1 discloses the largest peer-reviewed publications describing all different treatment modalities. The publications were selected based on long follow-up, precise description of pain relief (complete/significant/medication use), and recurrence rate according to Kaplan-Meier analysis. The recurrence rate is similar among the different techniques, except for GR, which is higher [37]. Microvascular decompression is the only approach that interferes in the believed pathophysiology of the pain, therefore leading to less sensory deficits than the ablative techniques. The potential for high morbimortality of

MVD makes the choice of ablative techniques enticing, especially for the elderly and surgically unfit, which compose a considerable amount of the TN population. Among all ablative techniques, RFR seems to be the most effective because it presents the highest percentage of pain relief over time. However, it also presents the highest complication rate [37]. SRS emerges as the least invasive technique with remarkable results, making this modality extremely attractive to patients, even those suitable for MVD.

3. The early radiosurgery period

Stereotactic radiosurgery initiated by Lars Leksell [20] was actually first used in humans to treat TN. A focused dose of radiation was delivered concentrically to the trigeminal ganglion with an X-ray tube attached to a stereotactic arc-centered device. The patient experienced long-lasting pain relief [34]. The initial 2 patients had follow-up for up to 17 years. Difficult visualization of the ganglion on plain X-rays and the use of a solution of glycerol and tantalum to demonstrate the trigeminal complex in the Meckel's cave led to the unexpected finding of the toxic effect of glycerol to the trigeminal branches [19,20]. The exciting new finding led Leksell and coworkers to lose interest in radiosurgery for treatment of TN for more than one decade.

The less than complete success rate associated with the complications achieved with the other approaches created the opportunity to revisit radiosurgery as an option in the mid 1980s.

Continuous imaging development allowed detailed visualization of the entire trigeminal pathway, from the 3 branches inside Meckel's cave until the REZ at the pons (Fig. 1). The GG used to be the only reliable target for radiosurgery,

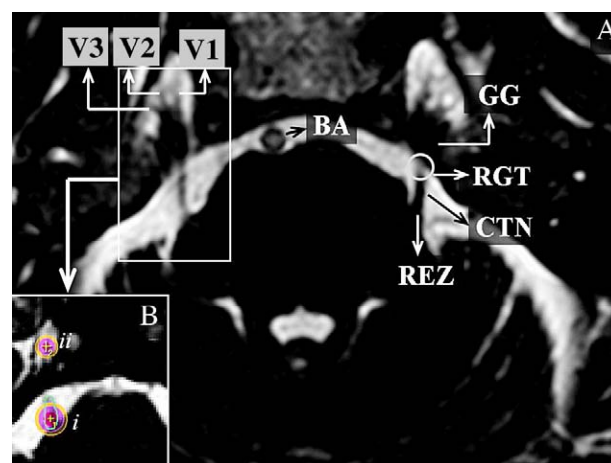


Fig. 1. A: MRI-CISS axial image representing possible radiosurgery targets for TN: trigeminal root entry zone (REZ), cysternal portion of the trigeminal nerve (CTN), retrogasserian target (RGT) and V1, V2, and V3 branches of the trigeminal nerve. B: Radiosurgery plans illustrating some targets for the treatment of TN. 1) Plan example using a 5-mm collimator at the REZ. 2) Plan example showing the possible selective radiosurgery toward each trigeminal branch inside Meckel's cave with the use of a 3-mm collimator.

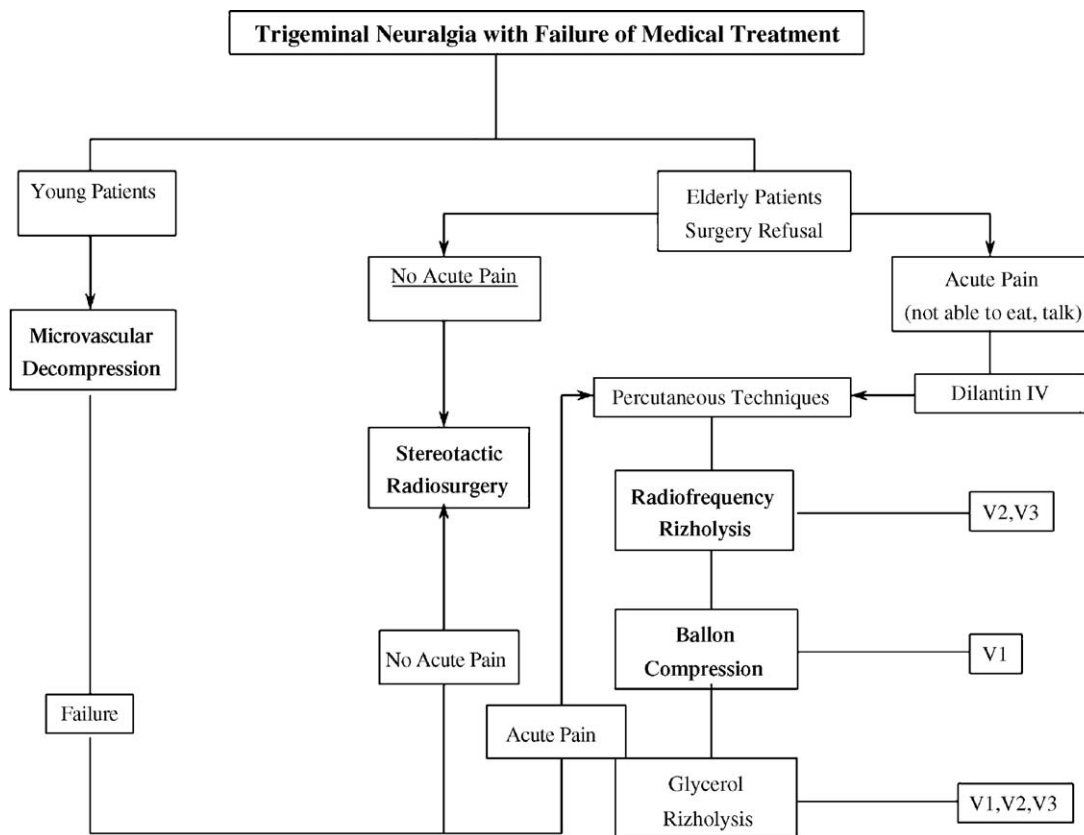


Fig. 2. Flow chart of the current practice of surgery for TN at UCLA. Young patients are recommended to have MVD. Elderly patients with pain partially controlled with medication or patients who refuse surgery are offered SRS. Elderly patients in TN crisis and noncooperative are offered BC, whereas cooperative patients are offered radiofrequency (RF) ablation or glycerol injection. Failures of MVD are considered for SRS or for percutaneous procedure if in acute crisis. The selection of which percutaneous technique to use varies according to the preference of the neurosurgeon.

whereas plain X-ray was the sole image technique available. In the 1990s, thin-cut magnetic resonance imaging (MRI) and use of special sequences made it possible for radiosurgery to be the only minimally invasive technique modifying the trigeminal pathway at the same site modern microsurgery does. The delayed effect of radiosurgery leads to a case-by-case analysis when indicating surgery for refractory TN (Fig. 2).

Recently, several authors reported their results of SRS for TN [2,16,23,31,38,39,41,43-47,50,55,58,72] (Table 2). There are, however, disagreements on the SRS approach, centering mostly on the dose applied and the location of the target in the trigeminal complex (Fig. 1).

4. Target definition in radiosurgery

Most authors reporting on radiosurgery for TN define the isocenter position based on the IDL touching the brain stem surface in an attempt to limit the radiation dose delivered to this structure. Kondziolka et al [31,32] defined the isocenter position by the 30% IDL touching the pons. Pollock et al [45] described the 20% as the median IDL at the brain stem surface when delivering 90 Gy and the 40% IDL when delivering 70 Gy. Nicol et al [41] and Hasegawa et al [23]

also chose the 20% IDL tangential to the pons surface. In the University of California at Los Angeles (UCLA) experience [16,58], similar to that of Petit et al [43], the isocenter is placed with the 50% IDL adjacent to the region where the trigeminal nerve enters the brain stem (REZ). In general, better pain relief and more sensory complications are reported with higher doses to the trigeminal REZ.

Other groups propose to place the isocenter even further away from the REZ, juxtaposterior to the GG [39,47]. The results were very encouraging, with 84.9% of the patients presenting significant pain improvement initially, 3.92% presenting numbness, and 13.3% with recurrence at a median follow-up of 55 months. The maximum dose was lower than the doses commonly reported (range, 8-45 Gy). Massager et al [39] treated essential TN patients by delivering 90 Gy and by using the same isocenter positioning described by Regis et al [47], with mild variations from the original protocol. Pain improvement was observed in 71% of the cases at 42 months follow-up. Numbness was reported by 38.3% of the patients, and was bothersome in 4.25%.

Authors targeting the nerve itself argue against bringing the isocenter closer to the REZ, avoiding the delivery of a high radiation dose to the brain stem. However, many

Table 2
Summary of radiosurgery results for TN

Authors	No. of patients	Dose (Gy)	Initial pain relief (%)	Recurrence (%)	Numbness (%)	Follow-up (mo)
Kondziolka et al [31]	50	60-90	94	6	6	18 ^a
Young et al [72]	110	70-80	95.5	34	2.7	19.8 ^a
Rogers et al [50]	54	70-80	96	21	14	12 ^b
Nicol et al [41]	42	90	95.2	4.8	16.7	14 ^b
Pollock et al [45]	68	70	86	26	15	14.4 ^a
Regis et al [47]	53	8-45	92.1	13.3	4	55 ^b
Maesawa et al [38]	220	60-90	82.3	13.6	10.2	24 ^b
Smith et al [58]	60	70-90	95.5 ^c 79 ^d	25.6	25	23 ^a
Petit et al [43]	112	70-80	77	29	7.3	30 ^b
Massager et al [39]	47	90	83	8	38.3	16 ^a

^a Mean follow-up.

^b Median follow-up.

^c Patients not submitted to prior procedures.

^d Patients submitted to prior procedure.

publications [3,39] showed a consistent correlation between pain relief and closeness to the REZ, although accompanied by increased numbness. Pollock et al [45] published a dose comparative study of 70 vs 90 Gy to the trigeminal nerve. The isocenter was placed in a manner that the dose to the REZ was similar between the 2 groups; therefore, only the trigeminal nerves received different doses. No better pain relief was observed in the high-dose group; however, a higher incidence of numbness occurred. A study comparing 1 vs 2 isocenters targeted at the trigeminal nerve showed higher incidence of sensory deficits but no better pain outcome [15]. In summary, neither a larger nerve extension nor a higher radiation dose to the nerve convincingly showed an impact on pain relief, but it did lead to more numbness.

The Pollock et al [45,46] and Brisman and Mooij [3] findings taken together with recent studies at UCLA showing a highly significant correlation between enhancement of the REZ and pain relief suggest that the magnitude of the dose delivered to the REZ (Gorgulho et al, in press), is more important than the absolute dose delivered to the nerve itself (Fig. 3).

5. Dose definition in radiosurgery

When treating TN with SRS, the prescribed radiation dose is the maximal dose; therefore, when discussing delivered dose it means both maximal and prescribed doses. Kondziolka et al [31] found a significant improvement in pain control, without an increased rate of sensory deficits, when a minimal dose of 70 Gy was prescribed. Brisman's

series [2] disclosed 57.7% of patients having 50% or more pain relief when a 4-mm collimator was used to deliver 75 Gy. The isocenter position was defined by the 40% to 50% IDL touching the pons. Dysesthesias were reported in 3.2% of the cases. Nicol et al [41] delivered 90 Gy, also with a 4-mm collimator and the 20% IDL touching the brain stem. At mean follow up of 14 months, 50% or more pain relief was reported in 95.2% of the patients and 74% were pain free and medication free. Numbness, however, was reported in 16.7% in comparison with the 3.2% noticed by Brisman and Mooij [3]. Petit et al [43] delivered 70 to 80 Gy as the maximal dose to the REZ and obtained 70% excellent and good outcomes at 1-year follow-up. Comparison of the results among the different series, with either low or high dose, suggests that higher dose at the REZ leads to better pain relief, although more sensory compromise should be expected.

The precise dose that will achieve better results and less recurrence within acceptable rates of sensory complications is still to be defined. The ideal dose appears to be somewhere between 70 and 90 Gy because pain control was significantly poorer when less than 70 Gy [31] was delivered to patients, and 100 Gy caused nerve necrosis in baboons [30]. The definition of where to place the isocenter also impacts the final decision of the dose prescription. UCLA studies support the prescription of 90 Gy because of the lack of bothersome dysesthesia and other major complications [18,58] (Table 2).

6. Radiosurgery indications and modern technique

Radiosurgery was classically indicated for patients who failed previous treatments or were not suitable to undergo anesthesia due to their fragile medical status. Currently, at UCLA, radiosurgery is offered for patients with TN based on the flow chart presented in Fig. 2. MVD remains the

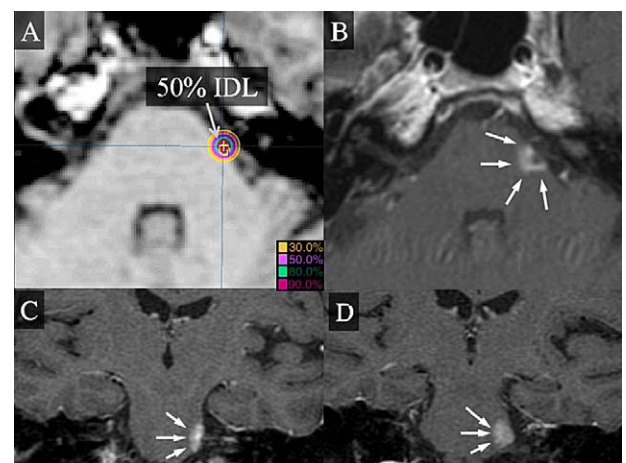


Fig. 3. Enhancement at the pons after the delivery of 90 Gy targeting at REZ. A: Radiosurgery plan using a 5-mm collimator. B: Enhancement at axial cuts 10 months after radiosurgery (90 Gy). C and D: Brainstem enhancement shown at coronal slices.

gold-standard treatment for patients suitable for the procedure. However, the minimally invasive nature of radiosurgery seems more attractive for an increasing number of patients seeking first-time surgical relief of the pain. Moreover, our own data [58] and that of others [36,38,43,46,58] showed that patients receiving SRS as first surgical approach achieved better pain relief than those who had previous procedures. The explanation for this observation can go in 2 directions: either radiation works better in an intact nerve or patients having radiosurgery after a failure define a more “resistant” population to any treatment.

Our previous studies stress the importance of precise radiation delivery, exquisite imaging and the use of a small-diameter collimator when treating TN [13,16,18,58]. Especially, units using linear acceleration-based radiosurgery need to have a strict quality control of their instrumentation and use collimators smaller than 8 mm in diameter. The falloff of the dose with large collimators deems their use risky for the treatment of TN [59,60]. When considering dedicated linear acceleration devices, the precision is as reliable as the gamma knife precision [11]. Accuracy remains an important aspect of the radiosurgery process because the target has a diameter of 3 mm and it is targeted by a 3- to 5-mm collimator [9]. Therefore, every single detail counts to improve precision. Minimal inaccuracy can lead to complete failure in reaching the target and in radiation being delivered to the cerebral spinal fluid in the pre-pontine cistern.

High-resolution imaging, including 1-mm MRI slices throughout the trigeminal nerve entry zone, multi-MRI sequencing, and multi-image fusion much improves the accuracy of the stereotactic technique [9,12,27,59,60]. Moreover, visualization of the trigeminal nerve and the encroaching vasculature in the REZ is hampered when thin slices and high-resolution imaging are not performed, ultimately compromising the quality of the most important portion of the radiosurgery procedure, that is, targeting. Recently, we have reported on the importance of special MRI sequencing [9] to improve the stereotactic targeting [11,12]. This remarkable improvement in imaging resolution and improvement in radiosurgery technique most likely will allow the placement of isocenter selectively in the branches of trigeminal nerve in the Meckel’s cave (Fig. 1B).

Radiosurgery for TN emerges as the least invasive technique, which leads to initial pain relief in more than 90% of the patients and complete absence of pain in approximately 75% of the cases. Recurrence rate ranges from 10% to 35% (Table 2). Recurrence has also been reported as more frequent in patients submitted to prior procedures [46,58]. Both recurrence and pain outcome have been reported associated with factors such as radiation dose, isocenter placement (closeness to the brain stem and volume of brain stem receiving a certain dose of radiation), occurrence of numbness, and trigeminal pain etiology.

The main criticism of SRS for TN is the absence of long-term follow-up studies in a substantial number of patients,

as opposed to publications describing the outcomes for the competing techniques. Despite the lack of long-term results, radiosurgery series are very consistent toward pain relief and complications. Radiation-related effects may be acute, acute delayed, and delayed. The current mean follow-up reached in radiosurgery literature allows conclusions regarding the first 2 types of complications.

The most frequently reported complication of radiosurgery is facial numbness [39,41,58], which is bothersome in a minority of the cases (4–12%) [43,46,47,58]. Numbness incidence varies broadly in the literature (Table 2). Data suggest a correlation between the radiation dose and the distance between the isocenter and brain stem [3,18,45]. Moreover, numbness is also a subjective symptom. Follow-up information is frequently collected by telephone conversation or post-mailed questionnaire. Numbness perception and impact may vary significantly among individuals. There is no standard protocol to evaluate decreased facial sensation, which causes the comparison within the series to be somewhat imprecise. All these factors seem to bias the final reported numbness incidence. Bothersome paresthesias, anesthesia dolorosa, masseter weakness, keratitis, balance problems, decreased hearing, facial paresis, meningitis, and subarachnoid hemorrhage are by far more common among the other techniques [1,5,7,17,28,29,35,49,54,57,62,63,66]. Radiosurgery series are very consistent and homogeneous toward major complications. Although radiosurgery results do not appear to be better compared to other minimally invasive techniques, no other technique presented such low complication rates. No mortality due to SRS has been described. Mortality, although at very low rates, has been described with all the other techniques.

7. Conclusions

The current state of the art of radiosurgery practice makes it one of the most effective and safe surgical options for the treatment of refractory TN. Further studies on long-term follow up, targeting location based on exquisite imaging and precision of radiation delivery, coupled with better understanding of the radiation biologic effect on the REZ of the trigeminal nerve, may improve pain control and decrease the sensory side effects.

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