Radiosurgical Management of Trigeminal Neuralgia

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KEYWORDS

• Trigeminal neuralgia • Stereotactic radiosurgery • Facial pain

KEY POINTS

- Stereotactic radiosurgery represents a safe and effective noninvasive treatment option for patients with trigeminal neuralgia.
- The major limitation of radiosurgery as compared with microvascular decompression is the limited durability of pain relief.
- Optimal populations for radiosurgery include patients older than 70 years, patients with multiple sclerosis, and patients with significant medical comorbidities.

INTRODUCTION

Trigeminal neuralgia, also known as *tic douloureux*, is a severe paroxysmal facial pain located within the trigeminal distribution on the face. This condition has been described as a "suicide disease" because of the severe intensity of the pain. Approximately 45 000 people in the United States have been diagnosed with trigeminal neuralgia.

Classification and Cause

Trigeminal neuralgia is one of several different types of facial pain that can have similar characteristics. The most widely accepted classification scheme for facial pain was published by Burchiel.[1] The Burchiel classification is summarized in **Table 1**. Classic idiopathic trigeminal neuralgia is known as type I trigeminal neuralgia in the Burchiel classification. It is defined as pain that is episodic at least 50% of the time. It is located within any of the 3 divisions of the trigeminal nerve. It is also commonly described as sharp, stabbing, or electrical shocklike in quality. The intensity of the pain has been described using the Barrow Neurologic Institute (BNI) pain scale. This scale is commonly used in the scientific literature to describe pain before and after an intervention and to compare results between multiple series. The BNI scale is summarized in **Table 2**.

The pathophysiology of type I trigeminal neuralgia has been explained by what has become known as the *vascular hypothesis*. This hypothesis posits that the episodic pain syndrome of trigeminal neuralgia is caused by compression of the trigeminal nerve by a blood vessel.[2] The most common offending vessel is the superior cerebellar artery. It is also thought that the brain settles within the cranial vault with age and, thus, creates a greater likelihood for such an interaction between blood vessel and trigeminal nerve in the more elderly population.

Other causes that can produce pain syndromes similar to idiopathic trigeminal neuralgia include multiple sclerosis, tumors of the skull base (eg, meningioma, acoustic neuroma, metastatic disease), Charcot-Marie-Tooth disease, Lyme disease, herpes zoster, traumatic nerve injury, and

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Neurosurg Clin N Am 24 (2013) 613–621
http://dx.doi.org/10.1016/j.nec.2013.05.001
1042-3680/13/$ – see front matter

Table 1
Burchiel classification scheme for facial pain

Diagnosis	Clinical History
Type I trigeminal neuralgia	>50% episodic pain
Type II trigeminal neuralgia	<50% episodic pain
Trigeminal neuropathic pain	Caused by unintentional trauma (eg, tooth extraction)
Trigeminal deafferentation pain	Caused by intentional trauma (eg, rhizotomy)
Symptomatic trigeminal neuralgia	Multiple sclerosis
Postherpetic neuralgia	Herpes zoster outbreak in trigeminal distribution
Atypical facial pain	Somatoform pain

somatoform pain disorders. The importance of the various causes of facial pain with regard to the use of stereotactic radiosurgery (SRS) is the fact that radiosurgical management has a high rate of response for type I pain but an inferior response rate for some of the other causes. The risk of SRS-related toxicity, although low, is another reason to differentiate between the various causes of facial pain. Patients with herpetic neuralgia and neuropathic pain from traumatic nerve injury are unlikely to respond to radiosurgery.

THERAPEUTIC OPTIONS

Several treatment options have evolved over time, including the use of antiepileptic medications, microvascular decompression (MVD) surgery, percutaneous rhizotomy, and SRS. The treatment option used for each individual case depends on factors such as patients' age, medical comorbidities, and prior treatment options that have either succeeded or failed. A proposed management algorithm is depicted in **Fig. 1**.

Table 2
BNI pain intensity scale

Pain Score	Definition
I	No trigeminal pain, no medication
II	Occasional pain, not requiring medication
III	Some pain, adequately controlled with medication
IV	Some pain, not adequately controlled with medication
V	Severe pain, no pain relief

Medical Management

The first-line therapeutic option for newly diagnosed trigeminal neuralgia is medical management. In general, antiepileptics are the most common type of medication used for trigeminal neuralgia, though tricyclic antidepressants, benzodiazepines, and narcotics have all been used. The single most effective medication for trigeminal neuralgia is carbamazepine (Tegretol). Other medications that have reported responses include phenytoin (Dilantin), baclofen (Gablofen), oxcarbazepine (Trileptal), gabapentin (Neurontin), and lamotrigine (Lamictal). Patients who have an initial response to medical management can undergo a trial of withdrawal of medications over time as the pain may undergo remission. It is not uncommon, however, for patients to become refractory to medical management over time, and these patients will commonly require surgical or ablative management. Furthermore, some of the antiepileptics will commonly have associated toxicities, such as sedation, cognitive changes, and ataxia. Carbamazepine, in particular, can have a high rate of such toxicities. Oxcarbazepine and gabapentin may have lower rates of toxicity. A common indication for surgical or radiosurgical intervention is when patients experience medication-related toxicity from antiepileptics that start to affect their quality of life.

MVD

MVD is a surgical technique involving a craniotomy and decompression of the trigeminal nerve from the offending blood vessel. Intraoperative insertion of an inert implant (generally Teflon, DuPont, Wilmington, DE) allows for the prevention of recurrent vascular compression. The chief advantage of MVD is the fact that the pain relief is durable and likely curative. In general, 70% of patients treated with MVD continue to be pain free 20 years after the operation.[3] Operative morbidity and mortality is generally quite low but increases after 70 years of age, which is the age that noninvasive alternatives may have a greater therapeutic ratio.[4]

SRS

SRS represents a noninvasive treatment option for trigeminal neuralgia, with its main advantage being its noninvasiveness and low morbidity rate. Most of the data that exist for radiosurgical management of trigeminal neuralgia is using the Gamma Knife

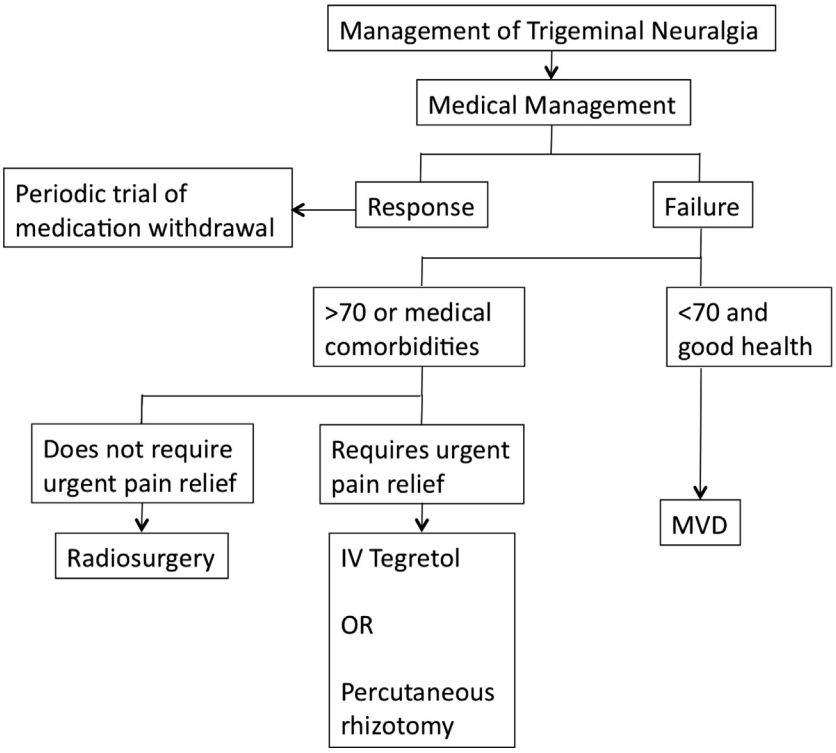

Fig. 1. Management algorithm for trigeminal neuralgia.

(Elekta, Stockholm, Sweden), although there is an emerging literature for linear accelerator approaches. The major disadvantage of SRS is the limitation in the durability of the pain response. Most series have shown that the median duration of radiosurgical response to be on the order of 5 years. Although SRS can be repeated, for younger patients, even a second application of SRS may not remain effective throughout their lifespan. Elderly patients and those with surgical contraindications, such as severe cerebrovascular or cardiovascular disease or bleeding diatheses, may also be best treated with a radiosurgical approach.

Percutaneous Rhizotomy

Percutaneous ablative techniques have also shown success in the treatment of trigeminal neuralgia. These techniques include radiofrequency rhizotomy, glycerol rhizotomy, and balloon rhizotomy. The chief advantage of percutaneous ablative techniques is that pain relief is immediate and that they often do not require general anesthesia. Comparison of the percutaneous procedures has suggested that they likely have very similar response rates and durability of response. However, the likelihood of persistent hypesthesia may be higher than what is seen with MVD or a radiosurgical approach. The durability of response for percutaneous techniques is limited and similar to results with SRS.

OUTCOMES AFTER TRIGEMINAL NEURALGIA RADIOSURGERY

Because most of the data for radiosurgical outcomes have come using the Gamma Knife unit, for the purpose of this review, the following radiosurgical outcomes will refer specifically to Gamma Knife radiosurgery (GKRS) results, with the exception of the section specifically dedicated to linear accelerator approaches.

Prospective Studies

There are few prospective studies for the use of SRS in the treatment of trigeminal neuralgia.[5–7] The first such study was a prospective study performed by a group from Marseille, France and was a quality-of-life assessment showing improvement in all quality-of-life parameters and finding that 58 of 83 (70%) responders were able to come off of medications.[5] A second prospective study conducted at the Mayo Clinic looked at the cost-effectiveness of SRS versus MVD as a definitive treatment option for trigeminal neuralgia.[6] In this study, MVD was more expensive in the near

term; but for patients with longer life expectancies, it seemed to be the more cost-effective treatment option. The University of Pittsburgh conducted a randomized prospective study of 87 patients in which patients were randomized to 1 versus 2 isocenters.[7] The rationale for such a study was to determine whether an increased length of nerve treated resulted in any difference in either efficacy or toxicity of radiosurgical treatment. Although there was no change detected in efficacy, the incidence of complications correlated with the nerve length irradiated (more facial numbness with 2 isocenters vs 1 isocenter).

Response Rate and Durability of Pain Response

Several large retrospective series have also been reported for trigeminal neuralgia after definitive SRS.[8–18] The results of the largest series of GKRS for the treatment of trigeminal neuralgia are summarized in **Table 3**. The series that have been reported have been shown quite similar results regarding pain response. In a series from Wake Forest, Marshall and colleagues[14] reported a cohort of more than 400 patients with trigeminal neuralgia and reported an 86% initial response to pain within 3 months.

Among the greater concerns for treatment with SRS is the increasing possibility of pain relapse with increasing time after treatment. Riesenburger and colleagues[17] reported that pain relapse after SRS is a time-dependent phenomenon. Marshall and colleagues[14] reported a median durability of 4.9 years for patients with type I trigeminal neuralgia. Lucas and colleagues[12] have recently reported that the initial successful response and ability to discontinue medications was the dominant factor predicting durable pain relief after SRS.

Factors that Affect Response

Several factors have been identified that affect the likelihood of treatment success for SRS in the treatment of trigeminal neuralgia. The development of posttreatment numbness has been identified as a major factor that predicts the success of treatment in multiple series.[11,14,16] Prior surgery for trigeminal neuralgia[13] and particularly radiofrequency ablation of the nerve[14] seems to decrease the likelihood of treatment response. Regis and colleagues[5] showed a sequential decrease in response with every previous procedure performed. Having magnetic resonance imaging (MRI) evidence of contact between a blood vessel and the trigeminal nerve seems to predict a better response after SRS.[19] The dose rate of the Gamma Knife sources does not seem to affect the response rate.[20]

Radiosurgical Dosing

Doses delivered for SRS generally range between 70 and 90 Gy prescribed to the isocenter. There has been one series whereby patients were treated in the repeat setting and pain responses were seen at doses as low as 45 Gy prescribed to the isocenter.[21] Pollock and colleagues[22] reported results from the Mayo Clinic in which patients were treated with either 70 or 90 Gy. Patients in the 90-Gy cohort experienced a greater degree of pain relief but also had a greater degree of numbness. The mechanism of pain relief is thought to be focal axonal degeneration of the trigeminal nerve that affects pain fibers proportionately more than sensory fibers.[10] At higher doses, necrosis is seen more commonly and may contribute to the response to SRS.[23] The upper limit of the acceptable dose range seems to be 90 Gy because several large publications have used this dose and found it to be safe.[5,15,24]

Table 3
Selected large series of Gamma Knife radiosurgery for trigeminal neuralgia

Institution	Number	Median Dose (Gy)	Response Rate (%)	Any Toxicity (%)
Pittsburgh	503	80	89	11
Marseille	497	85	91	14
Wake Forest	448	90	86	44
Columbia	293	75	76	5
University of Virginia	136	80	90	19
Mayo	117	90	85	37
Maryland	112	75	81	6[a]
Brussels	109	90	82	38[b]

[a] Series reported bothersome numbness only.
[b] Beam channel blocking was used in this series.
Data from Refs.[5,8,10,14,16–18,38]

Type II Trigeminal Neuralgia

Several reports have demonstrated a decreased response rate and durability of response in patients with type II trigeminal neuralgia when treated with surgical or radiosurgical modalities. Tyler-Kabara and colleagues[25] showed that, in series of 2264 patients with trigeminal neuralgia, those with type II pain had a greater risk of relapsing over time as compared with patients with type I pain. There have been much more limited series assessing the outcomes of patients with non–type I trigeminal neuralgia after SRS. This population has been difficult to assess because of the heterogeneity of the population in general and the nonstandardized classification systems used by various institutions. Dhople and colleagues[9] published a series of 35 patients with atypical trigeminal neuralgia from the University of Maryland. In this series, the investigators encompassed patients with type II pain (continuous) as well as patients with burning as opposed to lancinating pain. There was a trend toward longer time before pain relief and shorter duration of pain relief in patients with atypical trigeminal neuralgia in this series.

A series from Wake Forest University compared outcomes of patients with type I and type II trigeminal neuralgia.[14] In this series, there were 61 patients with type II trigeminal neuralgia and 32 patients with atypical facial pain. Patients with type II trigeminal neuralgia and atypical facial pain both had decreased initial response rates after SRS as well as a decreased durability of pain relief. Median durability of pain relief was 4.9 years for type I, 1.7 years for type II, and 0.7 years for atypical facial pain.

MS-Related Trigeminal Neuralgia

Multiple sclerosis (MS)-related, also called *symptomatic*, trigeminal neuralgia comprises approximately 1% of patients with trigeminal neuralgialike symptoms. The most important distinction in this population with regard to therapeutic options is the difference in pathophysiology of the pain. MS-related trigeminal neuralgia is caused by a demyelinating process within the trigeminal neuronal pathway. Microvascular decompression is not considered an adequate treatment option because it does not address the pathophysiology of the disease. Medical management is considered to be the first-line therapy like it is for idiopathic trigeminal neuralgia. Surgical options, such as glycerol rhizotomy and SRS, have also been reported. Because of the relative rarity of symptomatic trigeminal neuralgia, available published evidence is limited to small single-institution retrospective series. In one such study published by the University of Pittsburgh, 37 patients were treated with GKRS using a dose range between 70 and 90 Gy.[26] The investigators reported that 36 of 37 patients reported BNI I-IIIb pain at some point in their course, with 23 patients experiencing a BNI I pain score. Five percent of patients experienced a new-onset paresthesia in this series.

Bilateral Trigeminal Neuralgia

Bilateral trigeminal neuralgia is a complicated clinical entity that represents approximately 2% of patients with trigeminal neuralgia. The cause of bilateral trigeminal neuralgia is commonly related to either Charcot-Marie-Tooth disease or multiple sclerosis.[27] It has been shown that patients with bilateral trigeminal neuralgia are less likely to have blood vessel compression on MRI[19] and, thus, likely that a proportion of these patients have pain that is not caused by vascular compression. The clinical complexity of the bilateral pain is related to the possibility of bilateral trigeminal nerve dysfunction that can result from an ablative treatment. The efficacy of MVD is in question given the difference in pathophysiology of the patients with bilateral pain. SRS for bilateral trigeminal neuralgia has been reported in an 8-patient series by Tufts Medical Center without significant toxicity.[28] However, long-term efficacy remains to be reported. One approach to avoid bilateral trigeminal nerve dysfunction has been to treat the more symptomatic side first, then follow patients for 6 to 12 months to assess for efficacy and toxicity before deciding on the management of the other side.

Repeat Radiosurgery

Because the median durability of pain relief after SRS is on the order of 5 years, more than half of patients receiving primary SRS will have a recurrence of trigeminal neuralgia pain at some point in their lifetime. In this scenario, a second application of SRS is a reasonable treatment option. Several institutions have now reported on the efficacy of repeat SRS and found that the response rate and durability of a second response are similar to what is seen with the first application.[21,29–35] Select results of repeat radiosurgical series are presented in **Table 4**.

Patient selection is an important issue in patients who are considered for a second radiosurgical procedure. A detailed history is necessary to rule out the possibility that the pain patients are experiencing is truly a recurrence of trigeminal neuralgia as opposed to a consequence of previous SRS, such as deafferentation pain. A common

Table 4
Repeat radiosurgery series for relapsed trigeminal neuralgia

Institution	Number	Median Retreatment Dose (Gy)	Response Rate (%)	Any Toxicity (%)
Mayo	19	76	95	21
Columbia	45	40	62	13
Wake Forest	37	84	84	57
Tufts	27	45	86	29
Medical University of Graz	22	74	100	74
Pittsburgh	119	70	87	21
Maryland	18	70	78	11
Tangdu Hospital (China)	34	71	97	12

Data from Refs.[21,29–35]

practice is to select patients who had a good pain outcome after their initial SRS.

Linear Accelerator-Based Approaches

Linear accelerator-based approaches for trigeminal neuralgia are used less than Gamma Knife SRS for several reasons, including the difficulty in accurately characterizing the output factor for a 4-mm collimator, the instability associated with a linear accelerator gantry, and the fact that inaccuracies are cumulative. The potential inaccuracy for a linear accelerator treatment of trigeminal neuralgia has been estimated to be as great as 30%. For sufficient treatment of trigeminal neuralgia on a linear accelerator using a 4-mm collimator, a root mean square value of all errors likely needs to be less than 1 mm.[36]

The largest series of linear accelerator-based SRS was published by a group from the University of California, Los Angeles.[24] In this series of 179 patients, the investigators demonstrated a response rate and durability of treatment similar to that seen with Gamma Knife series. A median dose of 90 Gy (range, 70–90 Gy) with the 30% isodose line tangential to the pons was used in this series.

RADIOSURGICAL TARGETING FOR TRIGEMINAL NEURALGIA

The technical goal of trigeminal neuralgia SRS is to place a radiosurgical 4-mm isocenter onto the trigeminal nerve as it runs through the prepontine cistern. The rationale for placing the isocenter within the prepontine cistern is that the nerve can be well visualized on MRI in this area and that the nerve is also surrounded by cerebrospinal fluid, allowing for the precise targeting and sharp dose falloff beyond the nerve, minimizing the risk of damage to surrounding structures, such as the brainstem and temporal lobe.

There are several hypotheses on the target of radiation effect when trigeminal neuralgia is treated with SRS. The putative target of radiation damage is important because of the implications it has on the ideal isocenter location. Kondziolka and colleagues[10] have published that the dorsal root entry zone is more radiosensitive than more distal portions of the nerve because of the transition between more radiosensitive oligodendrocytes and more resistant Schwann cells. This finding was supported from data from Columbia University, which demonstrated improved pain outcomes in patients with greater volumes of brainstem receiving a dose of 15 Gy.[37] A strategy for targeting the dorsal root entry zone places the isocenter such that the 50% isodose line is tangential to the brainstem. However, data from multiple other series have reported equivalent pain relief while targeting a more distal portion of the nerve, such as the pars triangularis.[5]

Current targeting strategies include targeting the pars triangularis and using the 20% isodose line to determine the isocenter location (**Fig. 2**). The rationale for targeting the pars triangularis is that it is a relatively distal portion of the nerve but would allow targeting of the entire nerve circumference before it diverges into multiple branches. Other series have placed the 20% isodose line such that it is tangential to the brainstem surface. The rationale for this approach is to constrain the brainstem surface to less than 20 Gy because this dose has been implicated in treatment-related numbness. With this approach, it is common that most of the high-dose region is within the pars triangularis.

Another controversy regarding the targeting and delivery of SRS for trigeminal neuralgia involves

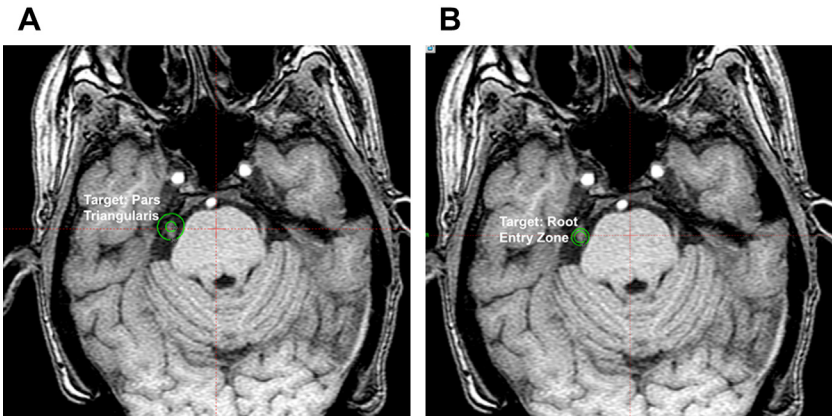

Fig. 2. Targeting strategies for trigeminal neuralgia radiosurgery. (*A*) Gamma Knife plan in which the target is the pars triangularis. In this plan, the 20% isodose line is tangential to the brain stem. (*B*) Gamma Knife plan in which the target is the dorsal root entry zone. In this plan, the 50% isodose line is tangential to the brainstem.

the question of collimator plugging. Plugging blocks a portion of the collimator to shape the beam to incorporate a greater length of nerve and to decrease the amount of brainstem exposure. A study from Brussels showed that the addition of plugging, although it modestly improved the response to the Gamma Knife, caused a greater degree of bothersome numbness.[38] The investigators concluded that plugging should be avoided.

There exists a population of patients with trigeminal neuralgia who are candidates for radiosurgical management but have contraindications to MRI, such as pacemaker placement, ferromagnetic implant, or shrapnel exposure. In such patients, computed tomography–based treatment planning has been reported in which the targeting of the nerve is done based on anatomic landmarks, such as the trigeminal impression on the temporal bone.[39,40] Further follow-up is likely necessary to ensure that this population does not have a higher rate of late toxicity or late pain recurrence.

RADIOSURGICAL COMPLICATIONS

Trigeminal nerve dysfunction is the major possible toxicity in patients who have received SRS for trigeminal neuralgia. The mechanism for such radiosurgical toxicity is damage to the sensory fibers within the trigeminal nerve. There have been several series that have reported higher rates of numbness in patients who have received higher doses and those who have a greater length of nerve treated. There has also been an association between patients who experience postradiosurgical numbness and the durability of radiosurgical treatment response.[11,14,16] Other series have suggested that excellent pain relief responses can be achieved in the absence of trigeminal nerve dysfunction.[5,15] Recent data from the University of Pittsburgh suggest that patients receiving gabapentin may have a lesser risk of GKRS-induced numbness.[41] More severe toxicities that occur following SRS include corneal anesthesia and anesthesia dolorosa. The likelihood of more severe toxicity is rare, with anesthesia dolorosa rates reported to be less than 1%.

SUMMARY

SRS represents a safe and effective noninvasive treatment option for trigeminal neuralgia. The major limitation of SRS lies in its limited durability as compared with MVD. Patients older than 70 years with multiple sclerosis or significant medical comorbidities represent populations that may be best suited for SRS. Patients are generally best managed by a multidisciplinary team to determine which treatment option is optimal for each patient.

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