SRS for Trigeminal Neuralgia

I. Introduction:

This white paper will focus on trigeminal neuralgia (TN) - with sections one though five (**I-V**) comprising a general review of trigeminal neuralgia from eMedicine.com, more information can be found at http://emedicine.medscape.com/article/1145144-overview and http://emedicine.medscape.com/article/248933-overview. Section six (**VI**) will provide an overview of imaging associated with TN. Section seven (**VII**) will provide a literature review on stereotactic radiosurgery for TN and section eight (**VIII**) (Society Members Only) will provide clinical indications and treatment guidelines on stereotactic radiosurgery for TN.

II. Definition and incidence:

Idiopathic TN is the most common type of facial pain neuralgia. The pain typically occurs in the distribution of one of the branches of the trigeminal nerve (cranial nerve V), usually on one side. Rarely, it can affect both sides, although simultaneous bilateral trigeminal neuralgia is uncommon. It involves both the mandibular and maxillary divisions of the trigeminal nerve in 35% of affected patients. Isolated involvement of the ophthalmic division is much less common (2.8% of TN cases).

According to Penman in 1968, the prevalence of TN is approximately 107 men and 200 women per 1 million people.[1] Mauskop states that approximately 40,000 patients in the United States have this condition at any particular time.[2] The incidence is 4-5 cases per 100,000. The disease begins after age 40 in 90% of patients and is slightly more common in women. Rushton and Olafson found that approximately 1% of patients with multiple sclerosis (MS) develop TN,[3] whereas Jensen et al stated that 2% of patients with TN have MS.[4]

A lack of clear definitions for facial pain has hampered the understanding of trigeminal neuralgia. The condition has no clear natural history, and no long-term follow-up study of the progression of the disorder has ever been published. In an attempt to rationalize the language of facial pain, recently, a new classification scheme that divides facial pain into several distinct categories was introduced:[5]

- Trigeminal neuralgia type 1 (TN1): This is the classic form of trigeminal neuralgia in which episodic lancinating pain predominates. (also known as "Typical TN").
- Trigeminal neuralgia type 2 (TN2): This is the atypical form of trigeminal neuralgia in which more constant pains (aching, throbbing, burning) predominate. (also known as "Atypical TN").
- Trigeminal neuropathic pain (TNP): This is pain that results from incidental or accidental injury to the trigeminal nerve or the brain pathways of the trigeminal system.
- Trigeminal deafferentation pain (TDP): This is pain that results from intentional injury to the system in an attempt to treat trigeminal neuralgia. Numbness of the

face is a constant part of this syndrome, which has also been referred to as anesthesia dolorosa or one of its variants.

- Symptomatic trigeminal neuralgia (STN): This is trigeminal neuralgia associated with multiple sclerosis (MS).
- Postherpetic neuralgia (PHN): This is chronic facial pain that results from an outbreak of herpes zoster (shingles), usually in the ophthalmic division (V1) of the trigeminal nerve on the face and usually in elderly patients.
- Geniculate neuralgia (GeN): This is typified by episodic lancinating pain felt deep in the ear.
- Glossopharyngeal neuralgia (GPN): This is typified by pain in the tonsillar area or throat, usually triggered by talking or swallowing.

III. Differential diagnosis:

TN presents with multiple episodes of severe and spontaneous pain that usually lasts seconds to minutes. The pain is often described as shooting, lancinating, shocklike, or stabbing. The episodes frequently are triggered by painless sensory stimulation to perioral trigger zones, eg, a patch of facial skin, mucosa, or teeth innervated by the ipsilateral trigeminal nerve. Triggers include touch, certain head movements, talking, chewing, swallowing, shaving, brushing teeth, or even a cold draft. The most commonly affected dermatomal zones are innervated by the second and third branches of the trigeminal nerve.

The episodes may be repetitive, recurring, and remitting randomly. Pain-free intervals, which might last for years early in the course of TN, typically grow shorter as the disease progresses. During episodes of pain, some many patients have difficulty talking, eating, and maintaining facial hygiene out of fear of triggering the pain.

Standard bedside neurological examination findings are normal in TN. Patients may refuse examinations of the face, fearing the triggering of pain. Male patients may present with an area of the face, the trigger zone, that is unshaven and unkempt. The finding of significant numbness in the trigeminal distribution of TN suggests secondary TN and more extensive damage to the trigeminal nerve.

Most of the following conditions are not easily confused with TN:

- Trigeminal neuropathy: Sensory loss is usually prominent; constant burning pain is common.
- Herpetic and postherpetic neuralgia (PHN): This condition usually affects the first branch of the trigeminal nerve. The diagnosis of PHN usually requires the outbreak of shingles (herpes zoster) in the forehead or eye. Acute herpetic neuralgia is the norm in shingles, but pain that persists after the lesions have healed is PHN. The risk of PHN development is directly related to patient age.

- Neoplasms: These may present as a compressing mass or neoplastic cell infiltration of the trigeminal nerve. Pain is usually more constant than in TN1, and facial numbness is more common.
- Granulomatous inflammation (eg, tuberculosis, sarcoidosis, Behçet syndrome, collagen vascular diseases): These and other vasculitides may affect the trigeminal nerve and simulate TN.

Other conditions that may mimic TN include odontogenic pain, geniculate neuralgia, glossopharyngeal neuralgia, temporomandibular disorders, cluster headache, hemicrania, and SUNCT (short-lasting, unilateral neuralgia from headache attacks with conjunctival injection and tearing) syndrome.

The diagnosis of facial pain is almost entirely based on the patient's history. In most cases of facial pain, no specific laboratory tests are needed. A blood count and liver function tests are required if medications are contemplated, specifically with carbamazepine. Oxycarbazine can cause hyponatremia, so the serum sodium should be tested after institution of therapy. Brain imaging, particularly MRI using heavily T2 weighted (FIESTA) sequences, is critical to exclude a neoplastic cause of TN.

Although rarely indicated, appropriate blood work for rheumatic diseases, such as scleroderma (trigeminal neuropathy is reported in up to 5% of patients with this collagen vascular disease) and systemic lupus erythematosus, should be undertaken in patients with atypical features of facial pain and a systemic presentation of collagen vascular disease. Appropriate blood work includes a sedimentation rate, antinuclear antibody titer, double-stranded DNA, anti-Sm antibody, lupus erythematosus cell preparation, and complete blood count to look for hematological abnormalities (eg, hemolytic anemia, leukopenia, thrombocytopenia). Particularly in the case of scleroderma, creatinine kinase and aldolase levels may be elevated with muscle involvement. Antibody titers to SCL-86 and SCL-70 may also be present.

IV. Pathophysiology

The etiology of most cases of TN is chronic vascular compression and injury to the trigeminal nerve at its entrance into the brainstem (pons). In one study, 64% of the compressing vessels were identified as an artery, most commonly the superior cerebellar (81%). Venous compression was identified in 36% of cases.[6]

Vascular compression of the trigeminal nerve appears to cause demyelination and remyelination of the nerve with persisting abnormalities of myelination (dysmyelination). The most common theoretical explanation for TN proposes that high-frequency ectopic impulses are either generated from or augmented by areas of dysmyelination[7]. These abnormal discharges may ignite a chain reaction of neuronal depolarization in the trigeminal ganglion[8]. The subsequent cascade of neuronal activity is progated centrally into the trigeminal nucleus and is then perceived by the patient as an overwhelming burst of pain.

Although most cases of TN are caused by vascular compression, other structural disease is present in secondary TN, which can produce either typical or atypical pain. For example, a mass such as a meningioma may displace and damage the nerve, resulting in pain. Alternatively, inflammation secondary to multiple processes may be due to the underlying lesion.

In MS, lesions in the pons at the root entry zone (REZ) of the trigeminal fibers have been demonstrated. This is one form of "symptomatic" trigeminal neuralgia related to visible pathology.

V. Treatment options:

Treatment options for TN include medicines, surgery, and complementary approaches. Since most patients incur TN when older than 60 years, medical management is the logical initial therapy. Medical therapy alone is adequate treatment for 75% of patients. According to Dalessio et al, medications work by interrupting the temporal summation of afferent impulses that precipitate the attack[9]. Once a patient experiences breakthrough pain on a single agent, a second and even a third additional medication may be required to restore relief. Medical therapy often is sufficient and effective, allowing surgical consideration only if pharmacologic treatment fails. Because this disorder may remit spontaneously after 6-12 months, patients may elect to discontinue their medication in the first year following the diagnosis. Most must restart medication in the future.

Anticonvulsant medicines—used to block nerve firing—are generally effective in treating TN. These drugs include carbamazepine, oxcarbazepine, topiramate, clonazepam, phenytoin, lamotrigin, and valproic acid. Gabapentin or baclofen can be used as a second drug to treat TN and may be given in combination with other anticonvulsants.

Tricyclic antidepressants such as amitriptyline or nortriptyline are used to treat pain described as constant, burning, or aching. Typical analgesics and opioids are not usually helpful in treating the sharp, recurring pain caused by TN. If medication fails to relieve pain or produces intolerable side effects such as excess fatigue, surgical treatment may be recommended.

The most effective medication for the treatment of trigeminal neuralgia (TN) is carbamazepine. It acts by inhibiting the neuronal sodium channel activity, thereby reducing the excitability of neurons. The effective dose ranges from 600-1200 mg/d, with serum concentrations between 40-100 mcg/mL. However, many adverse CNS effects (eg, vertigo, sedation, ataxia, diplopia) are associated with carbamazepine, which may make it difficult to use in elderly patients. The dose may be tapered once pain is controlled, since remission may occur. A complete blood count (CBC) must be obtained during the first few weeks of therapy and yearly thereafter. Agranulocytosis and aplastic anemia are extremely rare adverse effects, but suppression of the WBC count is not uncommon. This mild suppression of the WBC count does not warrant discontinuation of carbamazepine therapy. Hepatic function should also be monitored. Up to 70% of patients receive complete or acceptable partial relief, at least temporarily. Oxycarbazine is a newer agent

that may have fewer side effects, but it can cause hyponatremia, which should be monitored with serial serum sodium measurements in the first few weeks of therapy.

Gabapentin, lamotrigine topiramate, and several other newer anticonvulsants are being used to treat TN. Further outcome studies on their use in the treatment of TN are needed. Gabapentin has demonstrated effectiveness, especially in patients with MS. In 1997, Sist et al reported 2 patients with TN responsive to gabapentin.[10] In 1998, Khan reported complete relief of secondary TN in 6 of 7 patients with MS receiving gabapentin doses from 900-2400 mg/d.[11] In a similar, uncontrolled, small study of patients with MS, Solaro et al reported that 5 of 6 individuals found complete and sustained relief with gabapentin.[12] Lamotrigine, another new antiseizure medication, was reported by Lunardi et al to provide impressive and sustained relief of TN in one small, open-label, prospective study.[13] To date, the efficacy of gabapentin and lamotrigine versus placebo or their efficacy in patients whose pain is refractory to carbamazepine has not been established. As stated by Carrazana and Schachter, of these 2 new agents, gabapentin has advantages, which include faster titration, no known drug interactions, and no known idiosyncratic skin reaction.[14]

Phenytoin, although not approved by the FDA for idiopathic TN and believed to be less effective than carbamazepine, probably is effective for some patients with this disorder according to Loeser[15]. It has the same mechanism of action as carbamazepine and poses a similar risk panel, except for the risk of aplastic anemia. Of those who fail to attain relief with carbamazepine alone, an additional 8-20% of patients may respond adequately if phenytoin is added to the treatment regimen. According to one small study by Braham, phenytoin produced complete relief of pain in 30-40% of 43 patients and partial relief in an additional 30-40% at 300-600 mg/d. Blom et al stated that doses of 300 mg/d were less effective, although doses of 400-600 mg caused more adverse effects.[16] No correlation has been found between blood levels of phenytoin and therapeutic effect. Loeser recommends that the dose can be increased until relief is obtained or undesirable adverse effects appear (eg, dizziness, ataxia, diplopia, nystagmus, nausea.[15] Raskin reports relief of intolerable pain with 250 mg of intravenous phenytoin over 5 minutes, allowing relief for hours to 3 days, sufficient for an adequate history and re-examination.[17]

Other anticonvulsant agents possibly useful in the treatment of this disorder include sodium valproate and clonazepam. According to Zakrzewska et al, their therapeutic efficacy has not been confirmed by formal studies.[18] In 2006, He et al reported that the evidence from randomized controlled trials was insufficient to show significant benefit from non-antiepileptic drugs in trigeminal neuralgia.[19]

Baclofen may be effective in patients with TN. Commonly, baclofen is added to anticonvulsants when breakthrough symptoms occur. In 1980, Fromm et al demonstrated baclofen to be useful in a small, uncontrolled study.[20] Of the 14 patients with idiopathic TN resistant to carbamazepine, 10 found relief with 60-80 mg/d of baclofen. The starting dosage is 10 mg/d, which can be increased, if needed, to 60-80 mg/d administered 3-4 times per day (it has a short half-life of 3-4 h).[20] According to Parekh et al and Raskin,

the dose of carbamazepine then may be reduced to 500 mg/d to maintain a putative synergistic effect.17, [21] In 1987, Fromm et al suggested that L-baclofen represents a significant improvement over racemic baclofen in the treatment of TN.[22]

Surgical treatment is indicated for patients whose TN is intractable despite medical therapy, in those who are intolerant to the adverse effects of the medications, and in those in whom previous procedures failed. In some studies, more than 50% of patients with TN eventually had some kind of surgical procedure. Experience would indicate that medical management eventually fails in most patients with TN, and those patients undergo surgery.

Several neurosurgical procedures are available to treat TN. The choice among the various types depends on the patient's preference, physical well-being, previous surgeries, presence of multiple sclerosis, and area of trigeminal nerve involvement (particularly when the upper/ophthalmic branch is involved). Some procedures are done on an outpatient basis, while others may involve a more complex operation that is performed under general anesthesia. Some degree of facial numbness is expected after most of these procedures, and TN might return despite the procedure's initial success. Depending on the procedure, other surgical risks include hearing loss, balance problems, infection, and stroke.

Percutaneous procedures for TN can usually be performed on an outpatient basis under local or brief general anesthesia at acceptable or minimal risk of morbidity. For these reasons, they commonly are performed in debilitated persons or those older than 65 years.

Zakrzweska and Thomas described 3 types of minimally invasive procedures, percutaneous radiofrequency (RF) rhizotomy, percutaneous glycerol rhizotomy, and percutaneous balloon microcompression.[23] A rhizotomy is a procedure in which select nerve fibers are destroyed to block pain. A rhizotomy for TN causes some degree of permanent sensory loss and facial numbness. Several forms of rhizotomy are available to treat TN. In each procedure, the surgeon introduces a trocar or needle lateral to the corner of the mouth and, under fluoroscopic guidance, into the ipsilateral foramen ovale to allow a direct approach to the gasserian ganglion and its three roots.

RF rhizotomy is an outpatient procedure performed by placing a needle into the gasserian ganglion, through which an electrical current passes, heating the probe and producing a thermal lesion in the ganglion. The reported rate of pain recurrence is the lowest compared with other percutaneous procedures, with the average patient experiencing 3 years of excellent pain relief.[24] Complications of RF rhizotomy depend on the amount of numbness created by the lesion. Dysesthesia has been reported in up to 5-25% of patients, corneal numbness in up to 15%, and masseter weakness in about 4%. These complications are markedly reduced if the numbness produced by the procedure is limited. Some of these complications may be reversible. To avoid ophthalmic complications, some experts do not recommend this approach when the ophthalmic division is involved.[25] This procedure appears to be affected by the highest recurrence rate .[26] [27]

With percutaneous balloon microcompression, the operator inserts a balloon catheter through the foramen ovale into the region of the ganglion and inflates it for 1 to 10 minutes. Studies with percutaneous balloon microcompression have shown that this procedure carries about the same complications and average pain-free outcome as with glycerol rhizotomy (~2 y).[28 29] As related by Meglio and Cioni, some surgeons report excellent results with percutaneous balloon microcompression, which are comparable to those with RF rhizotomy.[30]

Microvascular decompression (MVD) is the most invasive of all surgeries for TN, but it also offers the lowest probability that pain will return. A neurectomy, which involves cutting part of the nerve, may be performed during MVD if no vessel is found to be pressing on the trigeminal nerve. Neurectomies may also be performed by cutting branches of the trigeminal nerve in the face. When done during MVD, a neurectomy will cause permanent numbness in the area of the face that is supplied by the nerve or nerve branch that is cut. However, when the operation is performed in the face, the nerve may grow back and in time sensation may return. Peripheral neurectomy, although safe and effective, is rarely used but may be of value in patients who have TN and a limited life span.[31]

MVD is usually indicated for patients younger than 70 years who are at lower risk for complications during general anesthesia, although healthy older patients may tolerate the procedure well. MVD is commonly is performed in younger, healthier patients, especially those with pain isolated to the ophthalmic division or in all 3 divisions of the trigeminal nerve and in those with secondary TN. MVD is now the most common surgery performed for TN and is the classic and most effective surgical procedure. It involves a posterior fossa craniotomy and dissection of vascular elements that compress the trigeminal nerve in the subarachnoid space. Surgeons perform the operation under general anesthesia, incising the skin behind the ear and performing a 3-cm craniectomy. After retracting the dura to expose the trigeminal nerve, they identify an arterial loop compressing the nerve as it enters the pons. They then pad the vascular structure with Teflon felt. The effectiveness of MVD is based on the hypothesis that compression from vessels in the vicinity of the trigeminal nerve leads to abnormal nerve activity.

Patients spend 4-10 days in the hospital and another week convalescing at home. Thus, recovery is more prolonged than with percutaneous procedures. Effectiveness of surgical procedures in TN has been studied. Burchiel reports that 90% of patients are pain free.[32] For the MVD, 15 years of relief is typical.

Mortality for MVD approaches 0.5%. Serious morbidity includes dizziness, temporary facial palsy, cerebrospinal fluid leaks, meningitis, cerebellar stroke, and hearing loss, which may occur in 1-5% of cases. Morbidity associated with trigeminal nerve decompression stems from hemorrhage, infection, and possible damage to the brainstem around the area of decompression. Adverse effects of surgery include corneal anesthesia, facial numbness outside of the trigger zone, new facial pain, facial dysesthesias, and intracranial hemorrhage (rare). Anesthesia dolorosa (TN pain associated with dense

hypesthesia) is usually a result of surgical treatment and is difficult to treat. In a 1999 study, cerebellar injuries and hearing loss occurred in less than 1% of the patients, and CSF leakage occurred in 1.85%.[33] As expected, these complication rates were inversely proportional to the total number of procedures performed. In centers where MVD is frequently performed, complications include facial dysesthesia (0.3%), facial numbness (0.15%), cerebellar injuries and hearing loss (<1%), and CSF leakage (<2%).

Relatively poor outcomes studies have been performed thus far on procedures for TN. The chance of success is seemingly less likely the longer the duration of symptoms. Of all the procedures, MVD carries the lowest rate of facial dysesthesia at 0.3%. Facial numbness caused by MVD is not common (0.15%) compared with that caused by the percutaneous procedures; in addition, MVD is the procedure of choice in younger patients who desire no sensory deficit. MVD is also the most likely treatment to provide sustained postoperative pain relief.

One study found that 70% of patients had excellent results (defined as a cure or significant pain relief) 10 years after the procedure, with a recurrence rate of less than 1%.[34] Possible reasons for failure include new vascular compression from scarred implants or other sources, but these are rarely identified during posterior fossa re-exploration for failed MVD. After an initial 10% risk of recurrence of TN within one year after MVD, the risk of pain recurrence is about 3.5% every succeeding year.[35] The reasons for this recurrence are not clear.

VI. Imaging associated with trigeminal neuralgia

The initial challenge with imaging studies associated with trigeminal neuralgia and SRS is to meticulously define the retrogasserian sensory root of cranial nerve fine (CN V) in the prepontine cistern. Imaging the nerve was originally done with CT contrast enhanced cisternography alone. However, after detailed comparison studies, and now several years of experience, thin section MRI scanning using a thin slice FIESTA (heavily T-2 weighted) sequence has largely replaced cisternography at Universities such as Stanford for identifying the trigeminal nerve target. Multiplan image fusion is utilized to develop a composite data set for final target definition.

In the occasional patient in whom MR imaging is not possible, most commonly because of a pacemaker, CT cisternography is still performed. In such patients the procedure begins with a lumbar puncture and the instillation of 5 to 8 cc of iodinated contrast (IsoView 300M) into the lumbar subarachnoid space. The patient is kept in a prone trendelenberg position for 10 to 20 minutes allowing contrast to traverse the foramen magnum. Ideally, but not necessarily, this can be monitored under fluoroscopy. Subsequent to the dye equilibrating throughout the intracranial cisterns, the patient is expeditiously imaged with thin slice high resolution CT through the entire head as is typically done for any other routine intracranial SRS case.

Defining the optimal target is generally the biggest technical challenge confronting the novice who embarks upon the initial treatment of patients with TN. Even with ideal MR

imaging the anatomy can be far from ideal in some patients. However, with experience it should be possible to delineate the prepontine trigeminal nerve (i.e. retrogasserian sensory root) in all patients. A few important tricks for this include:

1) Identify the opposite trigeminal nerve with the understanding that anatomy tends to be symmetric.
2) Find the trigeminal eminence where the dorsal root merges with the lateral pons.
3) Find Meckel's cave in every patient by virtue of its characteristic notch on CT, and on MRI, the splaying of the three trigeminal divisions.
4) Once the nerve has been identified at the brainstem and within Meckel's cave, it is a fairly safe bet to conclude that the trigeminal sensory root will travel from one to the other.
5) It is important to reference the reconstructed coronal and sagittal images throughout the entire process of target definition as well as the axial slices.
6) Generally speaking the target volume will be encompassed by 2 to 3, two mm thick MR slices

The most common mistakes include:

1) Mistaking adjacent blood vessels for CN V itself; these are often the offending vessel responsible for producing the disorder in the first place. Note that vessels can be traced from slice to slice, and will enhance on CT, which is a good reason to use contrast for CT scanning.
2) In previously operated (MVD) patients, the delineation of the intracisternal nerve segment can be quite challenging; in such cases the teflon pledget distorts the normal anatomy and the mass itself often obscures the nerve. Such cases require extra diligence.

It is critical to realize that the process of delineating the trigeminal nerve is never a simple process. In fact, many novices can badly misplace the target resulting in either an ineffectual or dangerous SRS procedure. However, credible target definition is almost always possible utilizing contemporary imaging techniques. (Please note this section is an excerpt from Dr. John Adler's Stanford University Trigeminal Neuralgia Guidelines.)

VII. Literature review on stereotactic radiosurgery for trigeminal neuralgia

This section reviews the literature pertaining to the treatment of TN with stereotactic radiosurgery (SRS); this procedure is often referred to as a rhizotomy being conceptually comparable to other methods for lesioning nerves that involve either thermal or mechanical energy. Many patients with TN are poor candidates for craniotomy and microvascular decompression (MVD) due to advanced age or the presence of medical comorbidities. Among this high risk patient population SRS is the least invasive treatment for TN. Moreover it can sometimes be a reasonable option when TN pain is refractory to prior surgical procedures. SRS is also a good alternative for most patients with medically refractory TN, especially those who do not want to accept the greater surgical risk of an MVD for a greater chance of pain relief. Both cobalt and linear accelerator-based radiosurgery has been advocated as a logical non-invasive alternative to MVD or other percutaneous surgeries.[36]

SRS uses computerized imaging to target tightly focused beams of high dose radiation to the site where the trigeminal nerve exits the brainstem. Such a localized radiation injury typically disrupts the transmission of pain signals to the brain. Frame-based SRS (either cobalt or linear accelerator-based) has been established as an effective treatment modality for TN. More recently image guided "frameless SRS" has been demonstrated to achieve comparable outcomes when treating TN. Using noninvasive head immobilization and x-ray image to image correlation, frameless SRS dynamically and accurately tracks skull position and orientation during treatment and has the ability to deliver nonisocentric, homogeneous conformal irradiation to an extended length of the trigeminal nerve. Frame-based SRS is usually administered to the retrogasserian sensory root as a single maximum dose of 70 to 90 Gy. Contemporary studies indicate that the average pain-free outcome after SRS is about the same as for radiofrequency (RF) rhizotomy, or around 3 years.[37] [38]

The majority of data on SRS for TN has been published using frame-based techniques. The first use of SRS for TN in 1953 is credited to Leksell, who utilized this approach in 2 patients with good initial success; this data was not published until 1971.[39] However, considerable progress with radiosurgical lesioning of the TN required the development of modern computerized imaging and especially when, in the 1990's, surgeons learned to target the trigeminal nerve with stereotactic MRI.

In 1996 Kondziolka et al[40] reported the results from a multi-institutional study that used frame-based SRS to treat intractable TN. Fifty patients at 5 institutions underwent frame-based SRS using a single 4-mm isocenter targeted at the trigeminal nerve root entry zone; thirty-two patients had undergone prior surgery, and the mean number of such procedures was 2.8 (range 1 to 7). The radiosurgical dose in the Kondziolka study varied from 60 to 90 Gy. After a median follow-up of 18 months (range 11 to 36 months), twenty-nine patients (58%) responded with excellent pain control, 18 (36%) obtained good pain relief, while three (6%) patients were deemed SRS failures. Of note, the median time to pain relief was 1 month (range 1 day to 6.7 months). Nevertheless, at 2 years, only 54% of patients were pain free and 88% had 50% to100% relief. The 1996 Kondziolka study concluded that a maximum dose of 70 Gy or greater was associated with a significantly greater chance of complete pain relief (72% vs. 9%, $p = 0.0003$). Three patients (6%) developed increased facial paresthesia after treatment, which resolved totally in one case and improved in another. The authors concluded that the proximal trigeminal nerve and root entry zone, which is generally well defined on T-2 weighted magnetic resonance imaging, was the most appropriate anatomical target for radiosurgery.

In a 1998 Kondziolka, et al[41] published another study in which 106 subjects were treated with frame-based SRS, all of whom had medically or surgically refractory TN. Once again a single 4-mm isocenter of radiation was focused on the proximal trigeminal nerve just anterior to the pons and using a dose of 70 to 90 Gy. After SRS, 64 patients (60%) became free of pain and required no medical therapy, 18 (17%) had a 50% to 90% reduction in pain severity or frequency, and 9 (9%) had slight improvement. After a median follow-up of 18 months, 60% of patients were pain free, 17% were moderately improved, and 23% were not meaningfully improved. The author concluded that this

technique was associated with a low risk (10%) of facial paresthesias or sensory loss, yet offered a high rate (86%) of significant, albeit initial, pain relief. Once again it was advocated to keep the target volume 2 to 3 mm anterior to the root entry zone so as to minimize radiation exposure of the brainstem.

At the turn of the century, the optimal dose and target for SRS of TN still remained relatively undefined. Experimental studies in primate models demonstrated focal axonal degeneration of the trigeminal nerve at a dose of 80 Gy and partial nerve necrosis at higher doses (100 Gy).[42] A study by Regis et al[43] advocated a maximum dose of 90 Gy coupled with a more anterior (closer to retrogasserian portion of the nerve) radiosurgery target for TN. This was a series of 57 patients treated with a maximum dose of 75 to 90 Gy with 87% of patients initially pain-free.

In 2001 Flickenger et al[44] reported on a randomized, prospective blinded trial of frame-based SRS in which patients with TN were divided into two treatment arms; patients in one arm of the study were treated with one isocenter (mean nerve length 5.4 ± 0.4 mm), and in the second arm the patients were treated with two isocenters (mean nerve length 8.7 ± 1.1 mm). No benefit in terms of pain was found in the patients with two isocenter radiosurgery, but there was a higher rate of facial sensory loss. The authors found a higher complication rate (although not statistically significant) in the two-isocenter arm without a corresponding increase in response rates. Reports from Pollock et al[45] in 2001 using frame-based SRS found a higher rate of sensory loss at 90 Gy, even with the more traditional posterior nerve target. The authors reported a 54% rate of permanent trigeminal nerve dysfunction in patients treated with SRS at the maximum dose of 90 Gy, compared with previous reports of a 10% rate of trigeminal nerve dysfunction at doses closer to 80 Gy.

Hypesthesia is the most common complication reported after radiosurgery for TN and as mentioned earlier, higher treatment doses have been linked to higher complication rates in the published literature[46]. Numbness or paresthesia has been reported to occur in 6 to 54% of patients after treatment with SRS. Bothersome dysesthesias have been reported in 32% of cases, and 8% of patients with TN who were treated with a 90 Gy maximum dose experienced corneal numbness.[46]

In 2003, Romanelli, et al[46] reported on a frameless SRS system that delivers nonisocentric, conformal and homogeneous radiation doses to the trigeminal nerve. Ten patients with TN were treated, the first five patients with a mean prescribed dose of 64.3 Gy delivered at the 80% isodose line with a 70% short-term response rate. All five patients reported excellent initial pain relief, with a median latency to pain relief of only 24 hours (range 24 to 78 hours). In one patient, however, severe dysesthesias developed. The dose was then decreased to 60 to 64 Gy delivered at the 80% isodose line in the remaining five patients and the latency of pain relief increased to 2 months.

In 2008 Villavicencio et al[47] reported preliminary multicenter experience treating TN with frameless nonisocentric SRS. A total of 95 patients were treated between May 2002 and October 2005 and radiosurgical dose and volume parameters were retrospectively

analyzed. Optimal treatment parameters were identified for 64 out of 95 patients (67%) who had excellent, sustained pain relief with no complications, including severe or moderate hypesthesia. The median time to pain relief was 14 days (range 0.3 to 180 days). Post-treatment numbness occurred in 45 (47%) of the patients treated and the overall rate of complications was 18%. Higher radiation doses and treatment of longer segments of the nerve led to both better pain relief and a higher incidence of hypesthesia; the presence of post-treatment numbness was predictive of better pain relief. At the mean follow-up time of 2 years, 47 of the 95 patients (50%) had sustained pain relief, all of whom were completely off pain medications. In general this study suggest that the optimal radiosurgical treatment parameters for treatment of idiopathic TN is a median maximal dose of 78 Gy (range, 70 to 85.4 Gy) and a median length of the nerve treated of 6 mm (range, 5 to 12 mm).

In 2009, Adler et al[48] published a single-institution prospective study, evaluating clinical outcomes in a group of 46 intractable idiopathic TN patients who underwent SRS with a nonisocentric frameless system between January 2005 and June 2007. During a single SRS session, a 6-mm segment of the affected nerve was treated with a mean marginal prescription dose of 58.3 Gy and a mean maximal dose of 73.5 Gy. Symptoms disappeared completely in 39 patients (85%) after a mean latency period of 5.2 weeks, with most pain relief beginning within the first week. After a mean follow-up period of 14.7 months, patient-reported outcomes were excellent in 33 patients (72%), good in 11 patients (24%), and poor or no improvement in 2 patients (4%). TN recurred in a single patient after a pain-free interval of 7 months, however all symptoms abated after a second SRS procedure. Significant facial numbness was reported in 7 patients (15%). The authors concluded that optimized nonisocentric frameless SRS treatment of TN resulted in high rates of pain relief and a more acceptable incidence of facial numbness than reported previously.

In 2009 Dvorak et al[49] published on the success of retreatment with frame-based SRS. Between December 2003 and January 2006, 28 patients were treated with repeat frame-based SRS and comparison was made with other reported series. All patients had been initially treated with SRS at the same institution, and only those with significant pain improvement were offered retreatment. The maximum dose was prescribed using a single 4-mm isocenter with the initial median dose of 80 Gy, median retreatment dose of 45 Gy, and median cumulative dose of 125 Gy. The median clinical follow-up after the second SRS was 19.7 months. Clinical outcomes were compared with 8 previously reported retreatment series (including 1 abstract), both for rate of pain control and for rate of complications. Outcomes after the second SRS were excellent in 29% (8 patients), good in 32% (9), and poor in 39% (11). Four patients (14%) experienced no improvement after repeat SRS. Eight patients (29%) experienced new trigeminal nerve dysfunction, including numbness (11%), paresthesia (14%), dysesthesia (4%), taste alteration (11%), and bite weakness (4%). Seven published peer-reviewed retreatment series and the authors' data (total 215 patients) were analyzed and univariate analysis failed to reveal any significant predictors of pain control or complications. However, there was a cumulative dose-response relationship for both pain control ($p = 0.04$) and new trigeminal dysfunction ($p = 0.08$) and successful pain control was strongly correlated

with development of new dysfunction (p = 0.02). A cumulative dose > 130 Gy was more likely to result in successful (> 50%) pain control, but was also more likely (> 20%) to result in development of new nerve dysfunction.

In a large series in 2009, Dhople et al[50] reported on 112 patients treated with frame-based SRS between June 1996 and July 2001. Of these, 67% had no invasive operations for TN prior to SRS, 13% had 1, 4% had 2, and 16% had 3 or more. The median prescribed dose was 75 Gy (range 70 to 80 Gy) and was delivered to the 50% isodose line of the involved trigeminal nerve root entry zone. The median follow-up was 5.6 years (range 13 to 115 months), after SRS, 64% reported of patients reported an excellent outcome, 5% had no pain but were still on medication, 12% had reported a fair outcome, and 19% reported a poor outcome. The median time to response after SRS was 2 weeks (range 0 to12 weeks) and the median response duration was 32 months (range 0 to 112 months). New bothersome facial numbness was reported in 6% of cases. The authors concluded that although frame-based SRS achieves excellent rates of initial pain relief, a steady rate of late failure, particularly among patients who had undergone prior invasive surgical treatment was evident.

Recently, Riesenberger et al[51] published a study where the authors examined outcomes in a series of patients with TN who underwent a single frame-based radiosurgical treatment followed for a minimum of 36 months. Fifty-three consecutive patients with typical, intractable TN received a median maximum radiation dose of 80 Gy applied with a single 4-mm isocenter to the affected trigeminal nerve. A good treatment outcome was achieved in 31 (58.5%) patients for whom the mean follow-up period was 48 months (range 36 to 66 months) and statistical analysis showed no difference in outcomes between patients previously treated with MVD or rhizotomy compared with patients with no previous surgical treatments. However, 36% of patients reported some degree of post-treatment facial numbness.

In 2010 Kondziolka et al[52] retrospectively reviewed outcomes in 503 medically refractory patients with TN who underwent frame-based SRS. The median patient age was 72 years (range 26 to 95 years) and prior surgery had failed in 205 patients (43%). SRS was typically performed using MR image guidance, a single 4-mm isocenter, and a maximum dose of 80 Gy. Patients were evaluated for up to 16 years after treatment and 107 patients had more than 5 years of follow-up. Eighty-nine percent of patients achieved initial pain relief , with or without medications and a faster initial pain response was seen in patients with TN without additional symptoms or prior surgery or with a pain duration of < or = 3 years. One hundred ninety-three (43%) of 450 patients who achieved initial pain relief reported some recurrent pain 3 to 144 months after initial relief. Factors associated with earlier pain recurrence were additional symptoms and more than 3 prior failed surgical procedures. Fifty-three patients (10.5%) developed new or increased subjective facial paresthesias or numbness and 1 developed differentiation pain. The authors concluded that patients who developed sensory loss had better long-term pain control (78% at 5 years).

Patients with atypical TN have unilateral pain that is constant or near constant and is described as dull, aching, or burning. Most studies of SRS are in patients with typical TN. In 2007 Patil et al[53] reported on a study of the treatment of atypical TN with frameless SRS where a 6 to 8 mm segment of the trigeminal nerve was targeted in a single radiosurgical dose. A total of 7 patients were treated with a median maximum dose of 78 Gy and a median marginal dose of 64 Gy and the proximal 3 mm of the nerve at the brainstem was excluded. Over a median follow-up period of 20 months, four patients had complete pain relief with no recurrence, 2 had minimal pain relief with some decrease in the intensity of their pain, and 1 patient experienced no pain relief and pain relief was reported within 1 week of treatment in 4 patients and at 4 months in 2 patients. Complications after SRS included bothersome numbness in 3 patients and significant dysesthesias in 1 patient. The authors concluded that compared with patients with classic TN, patients with atypical TN have an overall lower rate of pain relief.

Dhople et al[54] also reported on the efficacy and quality of life (QOL) outcomes associated with treating atypical TN with frame-based SRS between September 1996 and September 2004. Thirty-five patients presented with either atypical TN (57%); or with classic TN that then progressed to atypical TN. The median prescription dose was 75 Gy (range, 70 to 80 Gy) and was delivered to trigeminal nerve root entry zone. Treatment efficacy and QOL improvements were assessed with a standardized questionnaire after a median follow-up of 29 months (range, 3 to 74 months), and 72% of patients reported excellent/good outcomes, with mean time to relief of 5.8 weeks (range, 0 to 24 weeks) and mean duration of relief of 62 weeks (range, 1 to 163 weeks). There was a trend toward longer time to relief ($p = 0.059$), and shorter duration of relief ($p = 0.067$) in patients with atypical TN compared to those with classic TN. The authors concluded that the rate of pain relief for atypical TN was similar to the rate achieved from frame-based radiosurgical treatment of classical TN.

VIII. Clinical indications and treatment guidelines on stereotactic radiosurgery for the trigeminal neuralgia

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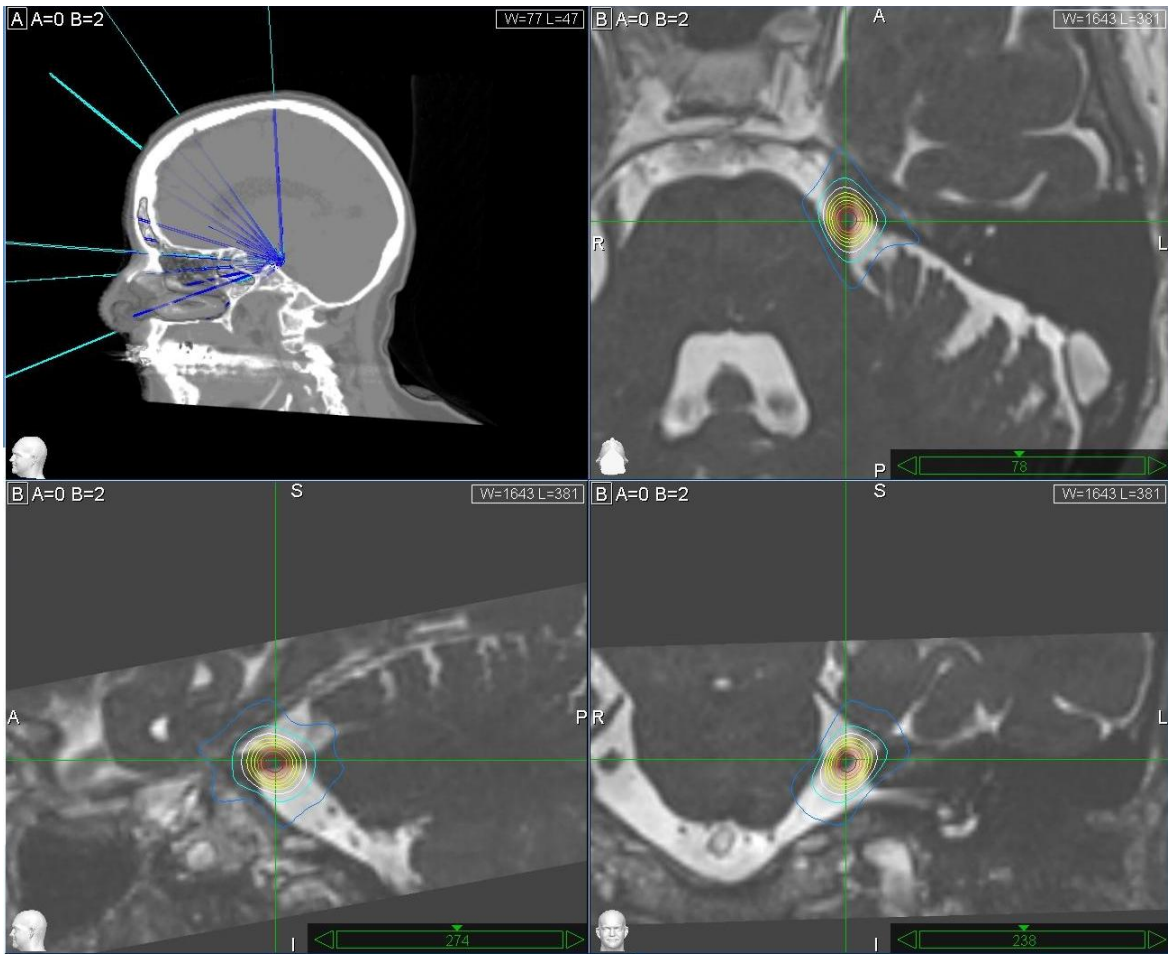

Figure 1: Example of an optimized treatment plan for trigeminal neuralgia (TN), the target is the retrogasserian segment of the trigeminal nerve running within the cysternal space, note the steep dose gradient to the brain stem.

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