Radiosurgery for trigeminal neuralgia: why, when and how?

Radiocirurgia para neuralgia do trigêmeo: porque, quando e como?

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ABSTRACT

Radiosurgery is a relatively novel technique in the armamentarium of TN treatment. Since 50% of the patients eventually require a surgical procedure to alleviate pain, the appropriate selection of patients to the different surgical techniques is a question of utmost relevance. The systematic literature reviews and the largest peer reviewed publications on the surgical treatment series of refractory trigeminal neuralgia are discussed considering the pros and cons of each surgical technique. Protocol variations and results of modern peer reviewed radiosurgery series are presented with focus on radiation doses and targets, aiming to maximize the understanding of the technique. Further well designed randomized trials focusing on the determination of the ideal target and radiation dose can optimize radiosurgery results, aiming to achieve the level of the results obtained with microvascular decompression, currently considered the gold-standard method.

Key-words: Trigeminal Neuralgia, radiosurgery, microvascular-decompression, balloon compression, radiofrequency rhizotomy, trigeminal nerve, brainstem.

SUMÁRIO

A radiocirurgia é uma técnica relativamente nova no armamentário terapêutico da neuralgia do trigêmio. Como cerca de 50% dos pacientes eventualmente requerem tratamento cirúrgico para obter alívio da dor, a seleção apropriada dos pacientes às diferentes técnicas cirúrgicas é uma questão muito relevante. As revisões sistemáticas da literatura e as maiores publicações de séries de tratamento cirúrgico da neuralgia do trigêmio refratária são discutidas considerando os prós e contras de cada técnica cirúrgica. As variações nos protocolos e resultados das séries radiocirúrgicas modernas são apresentados com foco nas doses aplicadas e alvos utilizados, objetivando uma melhor compreensão da técnica. Além disto, trials randomizados destinados a determinar a dose de radiação e o alvo ideal, podem otimizar os resultados radiocirúrgicos, procurando atingir resultados semelhantes aos obtidos com a descompressão microvascular, atualmente considerada o método "gold-standard".

Palavras-chave: Neuralgia do trigêmio, descompressão microvascular, compressão por balão, rizotomia por radiofrequência, nervo trigêmio, tronco encefálico.
INTRODUCTION

Trigeminal Neuralgia is the most common neuralgia with an annual incidence of 4-5/100,000 people. The International Headache Society classified TN in classical (synonym for idiopathic or essential) and symptomatic (synonym of secondary). The constellation of symptoms further allows for categorization into typical (sudden, lancinating, short-lasting, usually unilateral, recurrent pain in one or more trigeminal branches) or atypical.

Trigeminal Neuralgia is a medical condition with one of the broadest therapeutic armamentarium varieties. This reflects the fact that none of current therapeutic options leads to definitive and long lasting pain relief in the absence of significant toxicity or post-operative complications. A common consensus regarding the optimal timing for surgery and the optimal surgical procedure for different given contexts is, unfortunately, still lacking. The goal of this paper is to present evidence from our experience and from the literature on why, when and how radiosurgery could be offered to the population suffering from TN.

MEDICATION APPROACH:

Anticonvulsants are recommended for those initially diagnosed with this condition. Carbamazepine is the most effective drug. Pooled results from placebo controlled trials showed robust results, with the number needed to treat (NNT) to accomplish pain control of only 1.7-1.8. Unfortunately, toxicity threshold is also low. The number needed to harm (NNH) equals 3.4 for minor side effects and 24 for severe. Albeit classified as minor, these side effects significantly interfere with the quality of life in the long run.

Oxcarbazepine has become preferable to carbamazepine due to reduced toxicity, while maintaining comparable pain relief outcomes. Other second line options are baclofen, lamotrigine and pimozide. According to the American Academy of Neurology guidelines, there is insufficient data to conclude in favor or against the use of gabapentin, phenytoin, clonazepam, valproate and topical capsaicin.

About a quarter of the patients diagnosed with TN will not respond to medication, while another quarter will develop intolerance to medication. Therefore 50% of the patients diagnosed with TN seek for surgical options during their lifetime. Although half of the TN patients need surgical intervention, it has not been defined yet “when” is the best moment to refer them to the neurosurgeon. Studies evaluating quality of life in patients submitted to microvascular decompression showed that an absolute majority of the patients would have had surgery earlier.

SURGICAL TREATMENT FOR TRIGEMINAL NEURALGIA:

Microvascular decompression (MVD) is unique among all the surgical approaches available. It is the most invasive procedure; yet it is the only technique that is not ablative. It acts in the believed cause of the TN.

Minimally invasive approaches paralleled the technical development of MVD technique. The access of the gasserian ganglion through the foramen ovale led to the development of the percutaneous treatments. Selective radiofrequency rhizotomy came to scene due to the efforts of William Sweet. Glycerol injection was discovered surreptitiously by Leksell and co-workers while applying radiosurgery to the trigeminal ganglion in the early radiosurgery era. Percutaneous compression by inflating a balloon was later described and continues in favor in many centers.

Radiosurgery, after initial disappointing results when radiation was targeted to the gasserian ganglia, has become the most modern and least invasive tool of the surgical armamentarium. Due to its lack of invasiveness, it has become extremely attractive to patients and the trend shall become even stronger among patients with the possibility of frameless LINAC radiosurgery.

The immediate above 90% success observed with the multiple surgical modalities for trigeminal neuralgia is similar, including microvascular decompression (MVD), radiofrequency rhizolysis (RFR), balloon compression (BC), glycerol rhizolysis (GR) and stereotactic radiosurgery (SRS). The issue is the lack of uniformity on the definition of the parameters described in the surgical literature. Pain relief parameter is defined of multiple forms: as pain free and medication free in some series, as pain free with medication use, and even as eventual pain attacks appropriately controlled with medication after surgery. Recurrence is recognized, by some authors, only when additional surgery or increase in the medication dose is required. For others, recurrence means any drop from the best pain relief ever experienced after a surgical procedure, despite the need of additional treatment (medication modification or additional surgery). The patient populations are also not comparable. The follow-up protocols are also different and the detail level on identifying post-operative complications vary immensely. There are few studies comparing two techniques, but the patients were often the individuals preferring one approach to another rather than being randomized to surgery. Therefore, an undisputable scientific comparison of all the techniques regarding long term pain outcome, recurrence rate and complications is not possible. Zakrzewska et al suggested how the future surgical series should report their results and conduct follow-up based on a standardized protocol. It is observed in the most recent surgical series an attempt to follow these guidelines in the possible
extend, since many series are retrospective. It seems that better conclusions may be possible in the future when the comparison of the multiple approaches either through randomized prospective studies or formal meta-analysis will become possible. Hopefully, refined profiles of the subpopulations that may benefit more from one particular technique despite the others will be determined within appropriate scientific standards.

Two systematic literature reviews\textsuperscript{11,74} disclosed similar conclusions. MVD is the procedure leading to the higher long-lasting rate of pain control (65\% to 80\% in 10 years) with the lowest rate of trigeminal sensory root dysfunction (1 to 2\%). In experienced hands, complications can be minimized. Mortality rate is low, ranging from 0.2 to 1.4\%\textsuperscript{11,33,74}. This technique leads to the highest incidence of CSF leak and hearing loss (1-19\%) in comparison to the others\textsuperscript{2,6,11,80}. In summary, this approach requires that patients are eligible to receive general anesthesia and be submitted to a craniotomy. The results are the best among the surgical techniques leading to sustained pain relief and low incidence of facial numbness, the most frequent complication. However there is a small risk of more prominent complications as deafness, CSF leak, meningitis (aseptic and bacterial), stroke and an even lower risk of death.

Radiofrequency rhizotomy (RFR) leads to pain control in 50\% of the cases at mean 5 years follow-up according to the pooled results reported by Tatli et al\textsuperscript{74}. Although acute relief is uniformly reported by the multiple RFR series in the literature, sustained pain relief and recurrence rates are highly variable. For instance, 80\% pain relief rate has been observed in some series at average 10 years follow-up\textsuperscript{63}. This is probably related to variations in the surgical technique and surgical experience, besides the heterogeneity on follow-up protocols. Another systematic literature review\textsuperscript{86} reported RFR as the second most effective surgical technique after MVD. In the Tatli et al\textsuperscript{74} review, balloon compression was the second most effective technique. A possible explanation for the different findings in both systematic literature reviews is the inclusion criteria used in both studies. In Lopez et al\textsuperscript{39} studies with a minimum of 12 months median/mean follow-up were included, while in the Tatli et al\textsuperscript{74}, only studies with minimum 5 years median/mean follow-up were included. The very same fact possibly explains why balloon compression was the second most successful technique leading to sustained pain relief according to one publication and not into the other. One point of no controversy among the reviews is about the frequency and impact of the complications generated by RFR. It is definitely the technique that leads to the highest incidence of complications among all the percutaneous techniques and radiosurgery. Some of these complications are extremely relevant. The incidences of relevant complications are as follow: anaesthesia dolorosa about 1.6\%, bothersome dysesthesia in 3.7\% to 5\%, keratitis in 1.3\%, motor trigeminal root dysfunction in 10-12\%, meningitis in 0.2\% of the cases\textsuperscript{5,7,39,31,78}. In summary, the long term effectiveness of this technique is about 50\%, success is closely correlated with facial numbness occurrence\textsuperscript{2,44,78} and RFR carries the highest complication rate among all minimally invasive techniques; in special of anaesthesia dolorosa, a complication by far worse and more difficult to manage than the original pain condition. There is no agreement among the multiple trigeminal neuralgia experts about who should be indicated to this procedure. Our group never recommends RFR for V1 pain, due to the significant incidence of important corneal numbness (around 10\%) and keratitis. Broggi et al\textsuperscript{10} recently expressed their preference for balloon compression over RFR. Only patients who are willing to accept facial numbness as a consequence of the intervention should be offered with this option.

There are fewer studies reporting on balloon compression (BC) that meet the standards to be included in the systematic literature reviews in comparison to the number of studies on MVD and RFR. Considering this restriction, different systematic reviews\textsuperscript{39,74} placed this technique as the second or third most effective one but both acknowledged that BC leads to significantly fewer complications than RFR. The expected pain relief is about 80\% at 5 years and 68\% at mean 10.7 years follow-up\textsuperscript{63}. The incidence of facial numbness is variable (4-89\%) since it appears to subside overtime\textsuperscript{8,44,63}. BC is responsible for the highest incidence of trigeminal motor root weakness, which is about 66\%.\textsuperscript{74} The incidence of bothersome dysesthesia is around 10\%. In summary, balloon compression leads to satisfactory pain relief at the cost of lower complications in comparison to RFR and the incidence of facial numbness is variable, subsiding overtime. BC leads to the highest incidence of trigeminal motor root dysfunction, and mild transient mastiatory weakness is virtually present in all cases immediately post-operatively.

Glycerol injection leads to the lowest success rate of pain relief both at short term and mainly at long term. Recurrence rate is 62\% at actuarial 5 years\textsuperscript{74}. Anaesthesia dolorosa and bothersome dysesthesia have been reported in glycerol injection series. In summary, this technique leads to modest results regarding pain relief. In our experience we do not perform glycerol injection. We prefer to offer BC or RFR to patients with, respectively, V1 or V2/V3 pain. Some authors indicate glycerol for elderly patients.

SRS emerges as the least invasive technique leading to good pain outcomes and low complication rate. It will be discussed in detail in the next sections with. Facial numbness is the most common complication ranging from 2\% to 54\% according to the treatment protocol. Anaesthesia dolorosa has been reported by some authors\textsuperscript{34,52}, however the incidence is considerably lower than with RFR. Since MVD carries a low risk of major complications and all the other percutaneous techniques carry
a reasonable risk of important (anaesthesia dolorosa, bothersome dysesthesia, masticatory weakness) or minor (facial numbness) complications, there is room for new techniques to be brought to scene. SRS is not the “definitive” surgical procedure for this condition as none of the other procedures are as well. Sustained pain relief rates with SRS are not the highest ones but the lack of invasiveness associated to the low incidence of complications, mainly major ones, explain why this technique has gained increased acceptability.

RADIOSURGERY INDICATIONS:

As mentioned before, there is no agreement as when and which surgical technique should be indicated to a given patient accounting for age, general health status and previous surgical treatment. Radiosurgery was classically indicated for patients who failed previous treatments or were not suitable to undergo anesthesia due to fragile medical status. However, based on the initial series results and on the convenience of the technique, SRS has been increasingly indicated to patients not submitted to prior procedures.

At UCLA, we use the algorithm presented in Figure 1, previously discussed in one of our publications21. Elderly patients are offered radiosurgery as the initial surgical approach. Young patients and even older patients in good medical condition are recommended to have MVD, the gold-standard surgical procedure. Patients’ candidates to MVD that refuse surgery are recommended to have radiosurgery. In our experience, the amount of patients that are suitable to MVD but prefer to try a non-invasive procedure first is increasing. Patients are told that SRS requires a latency time to accomplish pain control and leads to a more modest rate of sustained pain relief. Also the incidence of facial numbness is higher than MVD. The intensity of facial numbness post-SRS is however subtle in the majority of the cases. Moreover, MVD following prior SRS is not more difficult to perform62 giving patients more confidence to attempt the least invasive method earlier on.

Patients in acute pain attack (i.e., not being able to eat or talk) receive intra-venous anticonvulsant infusion as the initial approach. If the pain is at V1, they are treated with BC; if the pain is at V2 or V3, they are treated with RFR. Those not presenting acute pain are offered radiosurgery option. Pain recurrence after MVD or any of the percutaneous techniques are also offered to be treated with radiosurgery at recurrence.

As can be noticed in Figure 1, patients have radiosurgery as the initial surgical procedure or at recurrence/failure of other surgical procedures. Our data66 and that of others30,40,48,52,66 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 two directions: either radiation works better in an intact nerve or patients having radiosurgery after a failure define a more “resistant” population to any treatment.

Figure 1: Algorithm used for selection of the surgical modalities among patients with refractory trigeminal neuralgia. Young patients are offered micro-vascular decompression as first line surgical modality. Elderly patients are offered radiosurgery as the initial surgical approach. Patients experiencing acute pain attacks are offered balloon compression when V1 branch is involved or radiofrequency rhizotomy when pain does not involve V1. Radiosurgery is also offered at recurrence of MVD or any percutaneous technique.

Other authors have different opinions based on their own experience. Just to cite few examples, Little et al36 described a similar approach about who are the candidates to SRS. They recommend SRS for elderly patients and for those refusing surgery since SRS offers a satisfactory rate of pain control and low rate of complication. Oh et al46 retrospectively reviewed the results of SRS and MVD on patients 65 years-old and older. Pain relief rate was higher in the MVD group at mean 2 years follow-up (63% vs. 56%). Complications, which included hearing disturbance, CSF leak, herpes zoster and subdural hematoma, were more frequent in the MVD group. Due to the increased fragility of the elderly individuals, SRS seems preferable to MVD. Broggi et al5 have an extensive experience with TN. They suggest MVD as the initial approach for all the cases, not considering age a limiting factor per se. BC is offered as the second surgical option. For those who failed MVD or BC and accept to have facial numbness, they perform RFR. This group has a Cyber-knife device in their Institution with a limited experience on TN patients. Besides this fact, Cyber-knife SRS results for TN are different from the results obtained with LINAC or Gamma-Knife based radiosurgery. All opinions deserve respect since they reflect what a particular neurosurgeon believes it is the best for the patient. However, different environments define different profiles of surgical experience. Also
the literature reporting on surgery for TN is extremely heterogeneous in terms of how to evaluate outcomes, report results, length of follow-up etc, making conclusions from erratic reading very dubious. This enhances the need for standardization on reports to allow future meta-analysis and prospective trials comparing the multiple techniques with long term follow-up.

**THE EARLY RADIOSURGERY PERIOD:**

Stereotactic Radiosurgery (SRS) initiated by Lars Leksell was actually first used in humans to treat Trigeminal Neuralgia. A focused dose of radiation was delivered concentrically with an X-ray tube attached to a stereotactic arc centered device to the trigeminal ganglion. The initial two patients had follow-up for up to 17 years and experienced sustained pain relief. Despite treating about 60 patients with SRS for TN, Lars Leksell wrote: “no definite conclusion should be drawn concerning the optimal dose of radiation or the exact mechanism and site of action in the root or the ganglion, or even the general applicability of the method”. The interest on radiosurgery was negligible for more than one decade.

In the nineties, thin cuts MRI and use of special sequences made possible radiosurgery to be the only minimally invasive technique modifying the trigeminal pathway at the same site modern microsurgery does.

**Figure 2:** Axial MRI scan, CISS (constructive interference steady state) images at the level of the trigeminal pathway allows exquisite visualization of the anatomical details and allow for optimized targeting for radiosurgery. (A) The main target locations used in modern SRS are shown. The REZ lies closely to the emergence of the trigeminal nerve from the pons. The far anterior cisternal target lays just-posterior to the gasserian ganglia (GG). The GG was initially used by Leksell and co-workers for TN SRS. (B) The superior imaging allows the recognition of the trigeminal rosettes and massager entry zone based on our data and others.

Recently, several authors reported their results of SRS for trigeminal neuralgia (Table 1). There is however disagreement on the SRS approaches, centering mostly on the location of the target within the trigeminal complex (Figure 2) and on the total radiation dose.

**ISOCENTER POSITIONING:**

The reports of radiosurgery for TN define the isocenter position based on the isodoseline touching the brainstem surface in an attempt to limit the radiation dose delivered to this structure. At UCLA, since March/2003, the isocenter is placed with a slightly encroachment of the 50% IDL into the pontine surface (Figure 3). When SRS for TN first started at UCLA, the 20% IDL was positioned touching the surface of the pons. There have been 249 patients treated with SRS for TN at UCLA since August/1995 until June/2008. Thirty-eight patients were treated with the 20% IDL tangential to the pons, 72 were treated with the 30% IDL tangential to the pons and the remaining were treated with the 50% IDL. As we accumulated experience, we felt more confident on bringing the isocenter closer to the REZ and brainstem based on our data and others.

Some authors, however, have the opinion that the increase in facial numbness is not worthy and optioned for a protocol with either a more distant isocenter positioning or a lower total radiation dose. Kondziolka et al defined the isocenter position by the 30% isodoseline (IDL) touching the pons. Pollock et al described the 20% as the median IDL at the brainstem surface when delivering 90 Gy and the 40% IDL when delivering 70 Gy. Nicol et al and Hasegawa et al also chose the 20% isodoseline tangential to the pons surface. Petit et al are among those also using the 50% IDL tangential to the brainstem surface.

Other groups propose to place the isocenter even further away the REZ, juxta-posterior to the gasserian ganglion. The results of the only prospective trial in SRS for TN showed that 58% were pain free and medication free at minimum 1 year follow-up. Numbness incidence was 10% in the series. Regis et al results in symptomatic TN 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 from 8 to 45 Gy) since in all but 7 cases the main goal was to treat the tumor rather than the trigeminal nerve. Massager et al treated classical TN patients delivering 90 Gy and the same isocenter positioning described by Regis, with mild variations from the original protocol. Pain improvement was observed in a lower percentage of the cases (71%) at a shorter mean follow-up (42 months), while numbness was reported by 38.3% of the patients, being bothersome in 4.25%.

The root entry zone (REZ), representing the transition areas between central and peripheral myelin, lies about 3mm away from the brainstem surface in the pre-pontine cistern in humans. The central myelin is more sensitive to diverse types.
of injury, including radiation induced injury. This is the area where the neuro-vascular conflict is noticed when MVD is performed. One can infer that damage to this portion of the trigeminal circuitry is responsible for abnormal conduction of the sensory stimuli thought the trigeminal pathway. MVD reaches success in controlling pain by modifying trigeminal function in this particular segment. This is the rational for our choice of placing the isocenter at the REZ, and therefore with the 50% IDL tangential to the brainstem surface (Figure 3). This rational is substantiated by evidence provided by different series, including ours, and is discussed below.

The analysis of our series at UCLA showed a positive correlation between brainstem enhancement post-radiosurgery and excellent pain outcome. This observation taken together with findings correlating proximity of the isocenter to the brainstem and better pain outcomes suggest that the magnitude of the dose delivered to the REZ is more important than the absolute dose delivered to the nerve itself. An increased incidence of facial numbness is noticed. A meta-analysis performed by Pollock showed a positive correlation between excellent pain outcomes and radiation total dose. Our data showed a positive correlation between dose to the brainstem and facial numbness (Gorgulho unpublished).

Given that radiosurgery is an ablative technique, it behaves as expected: the good results depend on the fine tuning between triggering pain relief vs. facial numbness. Bothersome dysesthesia and anaesthesia dolorosa have been reported in radiosurgery series but its incidence has been low in the LINAC and Gamma-Knife series. The levels were significantly higher in the Cyber-Knife series.

One group recently published a retrospective analysis of their series where either the REZ or the anterior cisternal portion of the trigeminal nerve (Figure 2) were used for targeting throughout different time periods. The aim of the paper was to compare pain outcomes and complications post-SRS targeting at either the anterior cisternal portion of the trigeminal nerve or the REZ. There are important limitations in this analysis, and some of them were acknowledged by the authors. First, the radiation dose also varies between the groups and dose is also known to modify the results obtained with SRS. The study is retrospective; the majority of the patients submitted to the anterior target were treated more recently leading to significantly different length of follow-up available for both groups. The study covers a times period of 9 years. It is very likely that the follow-up protocol changed overtime. In our institution, questions were added, other were rephrased over the years as part of a natural process of improvement of our follow-up standardized questionnaire. The same occurrence would lead to a bias on improving the sensitivity to detect complications in the group treated more recently (i.e. the group treated at the anterior portion of the trigeminal nerve). The authors concluded that excellent pain outcomes were initially higher in the group treated at the REZ. When they compared pain free results at last follow-up, there was no difference between the groups. But the length of follow-up was significantly different (25 months vs. 47 months), biasing the analysis towards the anterior target group. The Kaplan-Meier curves did not clearly account for the relapses described in the text. The conclusions were that the REZ target led to improved pain outcomes at short-term and to a lower rate of bothersome sensory complications. Since the mean total dose in the group treated at the anterior target was significantly higher (88 Gy vs. 80Gy), it is unclear to which extent each of these variables contributed to the finding, above and beyond the problem of the prolonged study duration. A key question arises at this point of discussion: where exactly lies the sweet spot triggering an optimal rate of pain relief without increasing sensory complications to unacceptable levels? Our experience and literature evidence points to the REZ but a definitive and properly designed trial comparing both radiosurgery protocols is lacking in the literature.

**RADIATION DOSE:**

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. The ideal dose
appears to be somewhere between 70 Gy and 90 Gy, since pain control was significantly poorer when less than 70 Gy (24) was delivered to patients, and 100 Gy caused nerve necrosis in baboons (23). Brisman et al series3 disclosed 57.7% of patients having 50% or more pain relief using a 4 mm collimator to deliver 75 Gy. The isocenter position was defined by the 40-50% isodoseline touching the pons. Dysesthesias were reported in 3.2% of the cases. Nicol et al45 delivered 90 Gy, also with a 4 mm collimator and the 20% isodoseline touching the brainstem. 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 per Brisman et al3. Petit et al48 delivered 70 to 80 Gy as the maximal dose to the REZ and obtained 70% of excellent and good outcomes at 1 year follow-up. Once again, a properly designed study has not been done to show the effect of dose variation in outcomes post-SRS. The evidence available is based on the comparison of the results among the different series treated with low or high dose, acknowledging to the fact that treated populations, criteria definitions and follow-up protocols significantly differ among these series. The conclusions point to the direction that higher doses lead to better pain relief and more sensory deficits. Although the frequency of facial numbness post-SRS differs substantially among the series41,45,66, bothersome numbness is consistently observed in a minority of the cases (4-12%)48,52,54,66 and so far could not be attributed to a minimal threshold dose.

The precise dose to achieve better results and less recurrence within acceptable rates of sensory complications is still to be defined. The definition of where to place the isocenter also impacts in the final decision of the dose prescription. UCLA studies support the prescription of 90 Gy due to the lack of bothersome dysesthesia and other major complications17,51. (Table 1).

### Table 1: Summary of Radiosurgery results for trigeminal neuralgia.

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<th>Authors</th>
<th>Nb Patients</th>
<th>Dose (Gy)</th>
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<th>Recurrence (%)</th>
<th>Numbness (%)</th>
<th>Follow-up (months)</th>
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* α Patients not submitted to prior procedures
† § Patients submitted to prior procedure
¶ Δ Mean follow-up
● ♦ Median follow-up
☆ Minimum follow-up
NA: information not available in the report

### Radiosurgery Treatment Protocol and Results:

Our protocol consists of 1 mm thickness T1 and CISS (constructive interference steady state) sequences MRI scan and 2 mm thickness CT scan. In our experience the CISS sequence offers an exquisite level of detailed anatomy of the trigeminal pathway from inside the Meckel’s cave through the pre-pontine cistern until its entrance in the pons (Figure 2). Accuracy remains an important aspect of the radiosurgery process since the target has a diameter of 3 mm and it is targeted by a 3 to 5 mm collimator. Therefore, every single detail counts to improve precision. The minimal inaccuracy can lead to the complete failure reaching the target and radiation being delivered to the cerebral spinal fluid in the pre-pontine cistern. High resolution imaging throughout the trigeminal nerve entry zone, multi MRI sequencing and multi image fusion in much improves the accuracy of the stereotactic technique10,13,28,68,69. Moreover, visualization of the trigeminal nerve and the encroaching vasculature in the root entry zone 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, i.e. targeting. We have reported on the importance of special MRI sequencing50 to improve the stereotactic targeting12,13.

Since January/2008 we use the 4 mm collimator. Before that we used the 5 mm collimator because we did not have a 4 mm collimator at UCLA. We performed SRS with the 3 mm collimator in a few cases which required SRS retreatment due to pain recurrence. The dosimetry of the 3 mm collimator is however challenging and the use of the 4 mm collimator, under this circumstance, is preferable.

We use 7 arcs to achieve a circular dose distribution. Some gamma-knife protocols use plugging to limit the dose to the brainstem. It is not clear whether this technique decreases incidence of facial numbness while maintaining pain control. This has been an explanation proposed by some authors42 to justify different results obtained with the same protocol but with different plugging41,55. Irradiation of a longer portion of the nerve either with 2 isocenters or with non-isocentric technique (i.e Cyber-Knife) resulted in increased incidence of sensory
disturbance without the benefit of improved pain relief. The non-isocentric technique reports have varied the length of trigeminal nerve treated (3 to 12mm) as well as the radiation dose. Pain outcomes have been similar to those reported by LINAC and gamma-knife series but the incidence of anaesthesia dolorosa, masticatory weakness and extra-trigeminal nerve complications were significantly higher. Complications such as hearing loss, foot paresis and diplopia have been described in non-isocentric series. A recent publication where the maximal nerve length was limited to 6mm and the average maximal dose was 73.5 Gy showed lower incidence of complications with absence of the extra-trigeminal system. The length of follow-up was too short to establish whether or not this protocol will lead to the similar sustained pain response observed in the isocentric series. Short-term pain control was satisfactory.

Figure 3 illustrates the treatment plan protocol currently used at UCLA. In summary, 90Gy are delivered with a 4mm collimator to the REZ by positioning the isocenter with the 50% IDL tangential to the pons using a circular dose distribution.

The results of our most recent series review on 179 patients treated at UCLA from August/1995 to January/2007 is presented in Figure 4 submitted. The median age was 74 years (range: 32-90). One hundred thirty had classical TN while 39 had symptomatic TN. Radiation dose ranged from 75 to 90Gy, the 5mm collimator was used in 90% of the cases. The isocenter positioning was progressive brought closer to the brainstem during different periods of time as prior detailed in the text. Mean latency to pain relief was 1.92 months. At mean 28.8 months follow-up 79.3% of the patients experienced excellent or good pain relief. The actuarial analysis (Figure 4) shows that excellent pain relief (defined as pain free and medication free) for those diagnosed as essential TN is 85% at 1 year and 65% at 3 years. These results are among the best ones achieved with SRS technique. Facial numbness was observed in 49.7% of the cases however it was mild in the majority of the cases. A five grading scale was used to rate the intensity of numbness with 1 being very faint numbness and 5 complete anesthesia. The median numbness score was 2. No masticatory weaknesses, anaesthesia dolorosa, hearing loss or keratitis were observed in our series.

REPEAT RADIOSURGERY:

There are few publications describing the use of different protocols in the retreatment of patients who failed or presented pain recurrence after initial SRS. It appears that recurrences after successful SRS respond well to retreatment while failures still do not significantly respond to a second radiosurgery. Some groups change the position of the isocenter to a more anterior target, others decrease the radiation dose and others use the same protocol for retreatment. We repeat SRS using the same treatment protocol. So far, we have retreated 16 patients. All the series uniformly describe the same findings: pain relief should be expected in about 80% of the patients, there is increased incidence of “new” facial numbness and intensification of “previous” facial numbness in some cases. Therefore, patients should be carefully informed that they should expect more sensory complications when submitted to repeat SRS. The technique is successful in the majority of the cases and safe to perform. The experience of the groups reporting repeated SRS is limited to few patients. Extended follow-ups are being acquired to establish the effectiveness and safety of repeated SRS in the long-run.
CONCLUSIONS

Radiosurgery is a good option in the surgical armamentarium available for TN treatment. Although there is no unique consensus, it seems that SRS is considered the first surgical option for the elderly by the majority of the surgical community. An increasing percentage of younger patients have been treated initially with SRS due to the fact that this technique is the least invasive among all, leading to satisfactory pain relief results and low complications rates. An indisputable fact considering surgical treatment of TN is that MVD achieves the best results, leading to the higher rates of sustained pain relief and lowest incidence of facial numbness. The only drawback of this technique is a reduced, but present, risk of serious complications and the invasive nature of the procedure. These observations allied to the fact that SRS does not increase the difficulty of performing MVD at a later time have attracted surgical candidates to attempt SRS as initial surgical modality.

Radiosurgery results are best in the group diagnosed with classical TN and in those not submitted to prior procedures. Facial numbness incidence varies considerably among the series in the literature and it correlates to pain relief, in similarity with other ablative techniques.

Carefully designed randomized trials comparing different SRS protocols that appear to lead to the most promising results are warranted. The present and future reports should follow the proposed guidelines in the literature to improve the level of evidence that can be obtained with the series analysis and to allow reliable comparisons among the different surgical techniques. Since SRS for TN has become common practice more recently in comparison to the other surgical modalities, studies describing long-term results are expected for the future.

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