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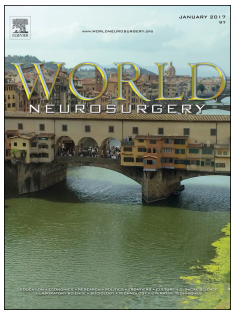

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Frameless stereotactic radiosurgery for the treatment of multiple sclerosis-related trigeminal neuralgia

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ABSTRACT

Background: Trigeminal neuralgia (TN) affects 7% of patients with multiple sclerosis (MS). In such patients, TN is difficult to manage either pharmacologically and surgically. Radiosurgical rhizotomy is an effective treatment option. The non-isocentric geometry of radiation beams of CyberKnife introduces new concepts in the treatment of TN. Its efficacy for MS-related TN has not yet been demonstrated.

Methods: Twenty-seven patients with refractory TN and MS were treated. A non-isocentric beams distribution was chosen; the maximal target dose was 72.5 Gy. The maximal dose to the brainstem was <12 Gy. Effects on pain, medications, sensory disturbance, rate and time of pain recurrence were analyzed.

Results: Median follow-up was 37 (18-72) months. Barrow Neurological Institute (BNI) pain scale score I-III was achieved in 23/27 (85%) patients within 45 days. Prescription isodose line (80%) accounting for a dose of 58 Gy incorporated an average of 4.85 mm (4-6 mm) of the nerve and mean nerve volume of 26.4 mm^3 (range 20-38 mm^3). Seven out of 27 (26%) patients had mild, not bothersome facial numbness (BNI numbness score II). The rate of pain control decreased progressively after the first year and only 44% of patient retained pain control 4 years later.

Conclusions: Frameless radiosurgery can be effectively used to perform retrogasserian rhizotomy. Pain relief was satisfactory and, with our dose/volume constraints, no sensory complications were recorded. Nonetheless, long-term pain control was possible in less than half of the patients. This is a limitation that Cyberknife radiosurgery shares with other techniques in MS patients.

Introduction

Trigeminal Neuralgia (TN) is the most common cranio-facial pain syndrome, with an incidence of up to 5 in 100,000. It is a severe condition requiring long-term medical treatment. Nonetheless, up to 10% of patients suffer major adverse drug-related events and requires some type of surgical treatment.(4,29) About 1-2% of TN cases are caused by demyelinating plaques of multiple sclerosis (MS) along the trigeminal pathway, nerve and brainstem. Trigeminal pain affects up to 7% of patients with MS and symptoms are often atypical or bilateral.(6) In such patients, TN is often difficult to manage either pharmacologically and surgically, with lower response rates than idiopathic TN(5,17,19).

Pioneered by Lars Leksell in 1951(21), stereotactic radiosurgery is a proven and valuable method to treat TN. A remarkable body of experience is available in the use of GammaKnife single isocenter treatments of TN(20,26,27,32-34,38,42,43). On the other hand, only a handful of dedicated studies about the treatment of MS-related TN are available to-date (2,10,15,36,44,46,47). Whether the radiosurgical rhizotomy for TN can be performed using a frameless technique is often questioned. The CyberKnife (Accuray Inc., Sunnyvale, California), is a frameless robotic system (1,7,8) whose use has been proposed also for the treatment of functional disorders. Because of the non-isocentric geometry of radiation beams delivery, it provides the possibility of homogeneous irradiation of an extended segment of the trigeminal nerve, so introducing new concepts for the radiosurgical treatment of TN. Despite the limited number of series reported to date, clinical results of CyberKnife radiosurgery seems to be satisfactory. Whether frameless radiosurgery can be successfully applied to patients with TN secondary to MS has yet to be demonstrated. We report our results on this issue.

MATERIAL AND METHODS

Patients Selection

Between September 2009 and November 2015, 27 patients presenting with medically intractable TN and MS were treated and followed up at the CyberKnife Center at the University of Messina, Italy. Patients fulfilling the criteria of the International Headache Society (2003)(23) were included. Evaluation of the type of trigeminal pain was made according to the classification proposed by Eller et al.(11) into idiopathic TN1 and TN2. Patients were categorized as having TN1 (typical) if pain was described as typically sharp, shooting, electrical shock-like, with pain free intervals between the attacks, and TN2 (atypical) if pain was described as an aching, throbbing or burning pain, for more than 50% of the time and constant in nature (constant background pain being the most significant attribute).

Clinical Characteristics

Table 1 summarizes demographic and preoperative clinical data. Pre-operatively, all patients had severe pain with numerical rating scale (NRS) score of 10 and were in BNI class IV (33%) or V (67%). Twenty-two out of 27 patients (81%) had typical (TN1) trigeminal neuralgia. Fifty-nine percent had V3 involvement (22% V3 alone, 33% V2 and V3, 4% V1-V2-V3); 88% had V2 involvement (22% V2 alone; 33% V2 and V3; 19% V1 and V2; 4% V1-V2-V3); 23% had V1 involvement (19% V1 and V2; 4% V1-V2-V3). Pain was referred to the left side in 39% of patients. All patients had taken pain medication for an average of 2.3 years (range, 11 months–7 years). One third of patients had undergone previous rhizotomy (radiosurgery or radiofrequency).

Five patients had visible signal anomalies on T2 weighed sequences in the brainstem. Seven patients had a neurovascular contact, visible on MRI, at the REZ on the symptomatic side

Radiosurgery Technique

Immobilization and Imaging

Patients were treated with SRS using a CyberKnife G4 model. Before the treatment, the patient lied supine on the treatment couch and a custom-fitted thermoplastic mask (Orfit® Industries America, New York) was molded. For all patients, a multislice computed tomography scanning (CT; Siemens Somatom Sensation 16 - Siemens AG Medical Solutions, Germany) and gadolinium enhanced magnetic resonance imaging (MRI; Siemens Magnetom 1.5-T) was performed. The CT protocol followed the CyberKnife-specific requirements, namely, acquisition 16 × 0.75 mm, Kv 120, effective mAs 320, rotation time 1 s, pitch 1.15. We choose the have reconstruction slice of 0.75 mm and reconstruction increments of 0.75 mm, filter reconstruction H31 (smooth), and 512 × 512 matrix.

The MRI was performed with the following parameters: a T1 volumetric sequence: matrix 512 × 512, flip angle 0°, effective thickness 0.88 mm, reconstruction slice 0.75 mm, and reconstruction increment 0 mm. A constructive interference in steady state (CISS) sequence: matrix 512x512, flip angle 60, reconstruction voxel size 0.35 mm.

3D time-of-flight (TOF): matrix 512x512, flip angle 60, reconstruction voxel size 0.39 mm. The axial source images were transferred to the CyberKnife workstation for treatment planning (Multiplan System).

The contouring of the target and critical volumes were defined on co-registered MRI and CT imaging. The 5-6 mm retroGasserian segment of the trigeminal nerve was used as target. This volume was delineated on the CISS sequence with the aid of the CT. On this latter exam, it was possible to clearly identify the bony landmarks of the nerve entrance in the Meckel's cave (figure 1).

Target and Doses Selection

Two surgeons (AC and AP) coregistered the CT and MRI datasets and checked the quality of co-registration visually using multiple views and transparency tools of the treatment planning system (Multiplan, Accuray Inc.) in the three projections. Afterwards, they identified the Gasser ganglion and the retrogasserian portion of the trigeminal nerve on the MRI and a bony canal on the edge of the petrous bone clearly identifying the entrance of the Meckel's cave. This point could be immediately and constantly identifiable on 0.75 mm thin CT slices in axial view and then checked on the sagittal and coronal view using a crosshair. Shifting the imaging from the CT to the CISS sequence, the pars triangularis was pointed out by the crosshair (Figure 1). An elongated target, 6 mm long and including the lateral margins of the nerve was drawn on 2 or 3 slices depending on the nerve thickness. The brainstem, the mesial temporal lobe, the acoustic and facial nerves, the cochlea and semicircular channels were specifically delineated as critical structures to minimize radiation dose with the inverse planning algorithm. Other critical volumes, including the eyes, lens, optic nerves, whole brain, and skin were also delineated for dose calculations. Furthermore, two tuning structures were delineated at 3 mm and 10 mm distance to restrict isodose distribution outside the target within a precise distance.

The treatment was planned using a "trigeminal node set", a specifically defined path of the robot, including a reduced source-axis distance, which provides an effective collimation diameter of 4 mm at the isocenter.

A non-isocentric beams distribution was chosen; the maximal dose delivered to the target was set at 72.5 Gy. The maximal point dose to the brainstem and the medial temporal lobe were set at 12 Gy and 36 Gy respectively. Eight Gy were the maximal dose allowed to the cranial nerves, whereas 4 Gy was the limit to the middle ear. The external most tuning structure (10 mm outside the target) had a dose limit of 14 Gy.

Once the calculation was obtained, we verified that a 4- to 6-mm segment of the trigeminal nerve were included in the 80% isodose line (58 Gy). The maximal length and the volume of the nerve that were eventually included into the 80% isodose line were determined by individual anatomy (length of the nerve and the relative dose received by the brainstem and the mesial temporal lobe). For shorter nerves, we moved the target forward, toward the Gasser ganglion, but always remaining into the root. If this was not sufficient to respect the dose limit to the brainstem, we forced the inverse planning accepting a smaller portion of the nerve to be included into a 58 Gy isodose line. The treatment plan was performed the 1-3 days after imaging acquisition and 1-3 day before the treatment delivery. Overall the planning procedure required 45-90 minutes.

Patient setup, treatment delivery, and quality assurance

Patients were set up on the treatment couch utilizing a mask that had been custom-formed at the time of simulation. In-room lasers define the center of the imaging system and provide the radiation therapists with an

estimate for patient initial alignment. For treatment tracking the *6D Skull Tacking* mode was used. The treatment location system (TLS) compares orthogonal kV x-ray pairs, so called live images, obtained during the patient set up to the planning system-generated digitally reconstructed radiographs (DRR) obtained from the stereotactic CT scan. Adjustments were then made to x-ray energy, mA, and pulse time to improve quality of the live images. The patient was then aligned to within a few millimeters of the final treatment location by a robotic couch. The system recommends shifts and rotations including pitch, roll and yaw, which are confirmed and initiated by the therapists. This process continues iteratively until the residual offsets are within acceptable values (<1 mm in translation and <0.5° in rotation that are within limits corrected by the robot during treatment). The TLS allows for an x-ray image and confirmation of the patients position at a defined time intervals. For the trigeminal neuralgia treatment, a frequency of 15 sec was used for all patients to reduce intrafraction inaccuracy. Any residual offset between the patient's simulation position and that at the time of treatment is accounted for through robotic positional adjustments. At each beam position, the robot adjusts the target location according to the patient offsets.

The accuracy of targeting of the *6D Skull Tacking* mode was verified by offsetting the anthropomorphic phantom used for the End-to-End (E2E) test by a known amount within this range, and then delivering the plan radiation in this or several similar offset positions. Such test was performed by dedicated medical physicists on a monthly basis. The median total treatment error (TTE) of the *6D Skull Tacking* mode was measured, using GAFchromic films for ballcube EBT3 phantom (Ashland Advanced Materials, Brigewaters, NJ), as 0.30±0.12 mm.

Assessments of MR image quality were performed on a monthly basis using special phantoms and included: geometric accuracy, slice thickness and intervals accuracy, slice position accuracy, image intensity uniformity, uniformity of signal-to-noise ratio, percent signal ghosting, and low-contrast object detectability. Values of spatial linearity or geometric distortion were represented as the maximal distance between rods of a reticle in a special phantom. The geometric distortion depends on the gradients linearity and magnetic field linearity. Median vertical deviation was measured as 0.4 mm; median horizontal deviation was 0.2 mm.

Follow-Up and Assessment of Outcome

Follow-up information was obtained by outpatient clinical evaluation or telephone interviews. The end-points analyzed were: i) effects on pain scores, ii) effects on medication, iii) latency to pain reduction, iv) occurrence of sensory disturbance, v) rate and time of pain recurrence. Pain level was scored using the Barrow Neurological Institute scale (BNI; class I: no trigeminal pain, no medication; II: occasional pain, not requiring medication; IIIa: no pain, continued medication; IIIb: controlled with medication; IV: some pain, not adequately controlled with medication; V: severe pain, no pain relief)(35). For hypoesthesia evaluation, we used the BNI facial hypoesthesia scale (class I: no facial numbness; II: mild facial numbness, not bothersome; III: facial numbness, somewhat bothersome; IV: facial numbness, very bothersome)(35).We also recorded any possible trigeminal motor deficits.

Statistical Analysis

First, a descriptive analysis of recorded data was realized among the MS-related TN population. For the evaluation of outcomes such as initial pain cessation and recurrence, time to event was estimated by using the

Kaplan-Meier method. A bivariate analysis was then performed to identify predictive factors among the collected variables. Contingency tables (Fisher's exact test) were used to compare categorical variables in univariate analysis. To perform univariate analysis the INSTAT 3.0 software (GRAPHPAD, San Diego, California, USA) application was used. Multivariate analysis was performed using the multiple logistic regression method. Variables resulting statistically significant in the univariate analysis were transformed into binary variables to be used in the logistic regression model. To perform multivariate analysis the STATCALC 7.1.1 software (AcaStat, Poinciana, Fl) was used. The values of $p<0.05$ were considered statistically significant.

RESULTS

Target and Treatment Data

All treatments were performed in a single session. Median prescription isodose line (80%) accounting for a dose of 58 Gy incorporated an average of 4.85 mm (4 to 6 mm) segment of the trigeminal nerve, with a mean nerve volume of 26.4 mm^3 (range 20-38 mm^3) (Figure 2). The median maximal dose was 72.5 Gy (range, 71.8–Gy74.4). Median number of beams was 105 (range 90-110); median number of nodes was 87 (range 85-90). Treatment time ranged 45-55 minutes with beam on time ranging 15-21 minutes. The average new conformation index (nCI) was 1.32 (range, 1.04– 2.17); the median homogeneity index (HI) was 1.25.

Pain Control and Sensory Dysfunctions

The median follow-up time was 37 months (range, 18-72 months). Significant pain relief (a decrease in NRS score of $\geq$5) was achieved in 23 out of 27 (85%) patients within 45 days. Twenty patients (74%) experienced pain cessation within 15 days after treatment.

Twenty-three patients (85%) were able to decrease the frequency of pain medication throughout follow-up and 7 (26%) patients ceased pain medication. Twelve months after treatment, the rate of patients with BNI score of II or III was 85%; at 24 months, it was 65%; at 36 months, it was 55%; at 48 months, it was 44%. Figure 3 shows the rate of pain control after treatment.

Seven out of 27 (26%) patients had mild, not bothersome facial numbness (BNI numbness score II); all these patients had previously received rhizotomy treatments ($p<0.001$). No patient reported bothersome numbness.

Statistical analysis showed that a shorter nerve length (4mm vs. 5 to 6 mm) and smaller nerve volume (<25 mm^3 versus $\geq$ 25mm^3) were associated to treatment failure ($p=0.02$ and $p=0.004$ respectively). These variables did not retained statistical significance in the multiple logistic analysis.

Multiple dermatomes involved in the trigeminal pain ($p = 0.97$), left side ($p = 0.16$), male gender ($p = 0.68$), atypical pain ($p = 0.55$), previous surgery ($p = 0.9$), ipsilateral neurovascular conflict ($p=0.55$), visible brainstem plaques ($p=0.14$), post-treatment hypoesthesia ($p = 0.43$) were not significantly associated to treatment failure.

Kaplan Meier analysis was performed to compare pain control in patients with typical vs. atypical neuralgia. The log rang test did not disclose a significant difference ($z=0.82$; $p=0.41$). Patient outcomes are listed in Table 2.

Salvage Therapy

Fifteen patients (66%) did not benefit from or experienced recurrence after the treatment. The median time to recurrent pain was of 24 months (range 18-42). Because of medically refractory pain, 10 (37%) patients required further surgeries. Five patients received radiofrequency retroGasserian rhizotomy, 3 patients underwent retreatment with Cyberknife, two patients underwent microvascular decompression and open retroGasserian rhizotomy. All 10 patients obtained pain control after the second treatment (BNI pain scores I-IIIa). All 10 patients reported new facial numbness (8 BNI numbness score II; 2 BNI numbness score III).

DISCUSSION

In our series, the first on the use of frameless, non-isocentric radiosurgery technique to treat MS-related TN, we observed initial pain relief in 85% of the patients. This result is consistent with the data of GammaKnife radiosurgery for idiopathic TN, in which initial pain relief has been reported in 50 to 96%(14,20,26,27,33,43). Overall, the studies specifically addressing the use of radiosurgery for TN cases associated to MS report clinically relevant benefits in 57-100% of the patients(2,15,36,44,46,47) (Table 3). On the other hand, pain recurrence remains the main limitation of radiosurgery for TN. In our series, pain control was retained in only 44% of the cases four years after the treatment, which is not different from what reported in GammaKnife series(14,20,26,27,33,43). Noteworthy, no patient in our series developed bothersome numbness as consequence of treatment.

The use of frameless stereotactic radiosurgery for the treatment of TN was first reported by Romanelli et al., at Stanford,(37) in a study that was the first clinical demonstration of the submillimetric accuracy of frameless radiosurgery. Almost immediate pain relief (within days) was found in this first cohort of patients following delivery of a prescribed dose ranging from 65 to 70 Gy to a nerve segment up to 11 mm. The irradiation of such a long nerve segment, however, caused a high rate of bothersome numbness that developed over time by these patients and suggested a reduction of doses and length of the nerve to be treated.

Indeed, the treatment planning for CyberKnife radiosurgical retroGasserian rhizotomy introduces a number of novel, yet highly critical treatment planning variables, in particular the necessity to identify a favorable proportion between the radiation dose and the target volume of trigeminal nerve.

It has been difficult to determine an optimal dose range for CyberKnife treatments (12,18,22,39,41) (Table 4). In 2008 Villavicencio et al.(45) published the results of a multicenter study illustrating the results of 95 patients who underwent CyberKnife radiosurgery. This heterogeneous study included patients treated with different modalities (isocentric and non-isocentric) and doses. The median dose used was 78 Gy. Certain variables were predictive of stable pain relief over pain recurrence including the median maximum dose (77.5 versus 65 Gy), median minimum dose (64 versus 52 Gy), and median nerve length treated (4 mm versus 6 mm). After 2 years, 50% in the population had excellent results, but 47% suffered new facial numbness.(45) An update from the Stanford series reported on 46 patients receiving a treatment delivered over a 6-mm segment of the nerve, with a mean marginal prescription dose of 58.3 Gy and a mean maximal dose of 73.5 Gy. (1) Symptoms disappeared completely in 39 patients (85%) after a mean latency of 5.2 weeks. In most of these patients, pain relief began within the first week. Pain recurred in 1 patient after a pain-free interval of 7 months and was resolved by a second treatment. Four additional patients repeated the treatment after failing to respond adequately to the first operation. After a mean follow-up period of 14.7 months, patient-reported outcomes that were excellent in 33 patients (72%), good in 11 patients (24%), and poor in 2 patients (4%). Nevertheless, significant ipsilateral facial numbness (Grade III on the BNI numbness scale) was reported in 7 patients (15%).(1)

The ability to define the target volume based on the individual patient's anatomy remains also a distinct advantage of the CyberKnife. The abovementioned studies show that CyberKnife radiosurgery to an elongated segment of the trigeminal nerve is associated with satisfactory pain control, but with still significant rate of patients suffering bothersome sensory disturbances. In our patients, the marginal dose was set to 58 Gy with a median length of the nerve receiving this dose of 5 mm. This seems a critical value, since a shorter length was associated to a lower probability of pain response. At the same time, we kept the maximal dose to 72.5 Gy. To get these goals, we selected an anterior target, just behind the Gasser ganglion, while sparing the proximal 5 mm of the nerve.

Beyond the length of the nerve, we would indeed emphasize the importance of the volume of the nerve receiving the prescription dose. During treatment planning, we worked on the size and the position of the prescription isodose line (corresponding to 58 Gy). We set the prescription isodose size to embrace a portion of the nerve of at least 4 mm. The length and the anatomical characteristics of the nerve and the relative distance from the brainstem, however, conditioned the final target volume. We set the minimum target volume to 20 mm^3, but a volume >25 mm^3 seems to be, according to our results, associated to a higher probability of pain control. We admitted a maximal dose to the brainstem as low as 12 Gy. This is much lower than reported all along the literature on the treatment of TN(13,16,20,25-27,30,31,40,42) , but we did set this limit considering that the dose to the brainstem is one major cause of sensory disturbances. Indeed, it has been demonstrated that the most significant predictive factor of numbness, in a series of 37 patients undergoing GammaKnife re-treatment for TN, was the cumulative pons surface dose (3). The incidence of numbness increased with dose escalation to the brainstem in the series by Smith et al. (40). At a maximum dose of 90 Gy, with the brainstem along either the 30% or 50% isodose line, the rate of grade 4–5 numbness was 10% and 17%, respectively. (40) The dose to the brainstem might be even more important in MS patients. Actually, patients affected by MS would be at increased risk of rare and high-grade treatment-related toxicity, in particular edema and demyelination, after radiosurgery (9,24). In a study on post-treatment edema in meningioma radiosurgery, Conti et al. reported the case of two patients' with MS who had unexpected demyelination of the brainstem and cerebellum along the distribution of the 30% isodose line.(9) Other evidence also supports the relevance of this point. Weller et al.(46) analyzed a series of 35 patients with MS-related TN. Initially, the target was the root entry zone, further on in the course of treatments the retroGasserian target was used. The overall initial response (BNI I–III) was 82% in a median time of 42 days (range 2–170). The rate of numbness was, however, rather high (39%); the authors considered this to be related to the use of higher doses and a root entry zone target early in their series. Accordingly, we recommend caution about the dose limits to the brainstem at the REZ. Actually, the length of the nerve and the consequent dose received by the pons remains the main limitation for radiosurgical rhizotomy.

There are some technical aspects that deserve also to be mentioned. With the inverse planning technique used by the CyberKnife treatment planning, all brain structures have to be contoured. Automatic contouring was used and each volume was carefully checked and corrected for individual anatomy. All DVH had to be

evaluated since the risk of high doses on sensitive structures, even though distant from the target, is remarkable because of the non-isocentric radiation beams distribution. In particular, the medial most portion of the temporal lobe can receive doses as high as 45 Gy after initial planning that was reduced to <15 Gy/1mm^3 to avoid late medio-temporal radionecrosis.

One of the main criticisms to the use of CyberKnife for TN is the necessity to plan on CT cisternography or on a MRI after a potentially inadequate fusion. We suggest that bony landmarks, indicating the entrance of the trigeminal nerve root into the Meckel's cave, are easily recognizable directly on a bone CT scan. The identification of these points greatly supports a precise co-registration of the CT with MR sequence stressing the T2 values between cerebrospinal fluid and cranial nerves and vessels. Magnetic distortion is a possible limit of functional treatments performed by MRI targeting; i.e. we measured a median maximal distortion of 0.4 mm. Nevertheless, this is a common limit of anatomical targeting in functional neurosurgery whose clinical impact appears negligible.

The major limitation of our treatment modality seems to be the durability of pain relief, with only 44% retaining effective pain control 4 years after the treatment. It appears that this is common to frame-based isocentric radiosurgical rhizotomy. Actually, in GammaKnife series specifically addressing the treatment of MS-related TN, the rate of recurrence ranged 33-61.5% in the long run(2,15,36,44,46,47). Unfortunately, other lesional techniques seem to have even worse results in terms of long-term pain relief. Recently Alvarez-Pinzon et al.(2) compared percutaneous retroGasserian balloon compression and GammaKnife radiosurgery in 202 patients with MS. Fewer complications and superior long-term relief were associated with GammaKnife. Similarly, radiosurgery demonstrated fewer complications than percutaneous retroGasserian glycerol rhizotomy for trigeminal neuralgia in patients with multiple sclerosis.(28) Therefore, radiosurgery may represent the best treatment option for the treatment of TN in patients with MS, while other more invasive rhizotomy techniques should be reserved for patients with acute, intractable pain requiring immediate postoperative relief.

In conclusion, frameless radiosurgery represents a safe technique to achieve trigeminal retroGasserian rhizotomy. In MS patients, results are satisfactory, with 85% of patients gaining pain control within few weeks. Furthermore, using our constraints for dose, volume of the nerve, and dose to the brainstem no bothersome hypoesthesia or other complications were recorded. In the long-term, however, pain control seems to be possible in less than half of the patients. This is a limit that radiosurgery shares with other retroGasserian rhizotomy techniques in MS patients. Higher doses delivered to a longer nerve portion would be possible with the CyberKnife resulting, according to the experience in patients with idiopathic TN, in a long-term pain control but a higher risk of sensory complications.

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FIGURE LEGENDS

Figure 1. The crosshair is positioned on the bony landmark that was used to localize the trigeminal nerve at the entrance in the Meckel's cave. Switching on the MRI, the crosshair is positioned on the retroGasserian portion of the nerve, namely on the target. The use of this bony landmark allowed the submillimetric precision in co-registration of the stereotactic CT used by the system for image-guidance and the MRI.

Figure 2. Frameless radiosurgery for Trigeminal Neuralgia treatment plan. The 4-6 mm (20-40 mm^3) retroGasserian section of the trigeminal nerve was targeted, excluding the REZ. The brainstem was kept outside the 10% isodose line. Cranial nerve VIII, the cochlea, and the inner ear received doses far below conventional tolerance limits.

Figure 3. Kaplan-Meier estimate of the probability of pain relief after treatment (A). Comparison between patients with typical (TN1) and atypical (TN2) trigeminal neuralgia (B)

Table 1. Preoperative characteristics of patients

Age/Sex	53 years 15 F/12 M
Type of Neuralgia	TN1 (typical) 22 (81%) TN2 (atypical) 5 (19%)
Pain Distribution Right/ Left V1 V2 V3 V1-V2 V2-V3 V1-V2-V3	 14/9 - 6 (22%) 6 (22%) 5 (19%) 9 (33%) 1 (4%)
Average Time from Onset (months)	27
BNI Pain Score IIIb IV V	 - 9 (33%) 18 (67%)
NRS Score	10

Abbreviations: numerical rating scale (NRS); Barrow Neurological Institute (BNI)

Table 2. Treatment parameters and clinical results

Patient no.	Previous Treatments (RF or RS)	Marginal Dose (Gy)	Type of Neuralgia	Dose Max (Gy)	Target Volume (mm^3)	Length of treated nerve (mm)	Dose to the brainstem	Pain NRS preop/ 6 m. postop	BNI scale class preop/ 6 m. postop	BNI Numbness Score
1	1	58	TN1	72.5	38	6	11	10/10	V/V	I
2	-	58	TN1	72.5	26	4	10	10/3	V/IIIA	II
3	-	58	TN1	72.5	20	4	11.2	10/10	V/V	I
4	-	58	TN1	72.5	28	5	11.1	10/3	IV/IIIa	I
5	1	58	TN2	72.5	24	5	7.2	10/3	IV/IIIa	II
6	-	58	TN2	71.8	39	6	8.9	10/1	V/II	I
7	-	58	TN1	72.5	27	5	9.20	10/1	V/II	I
8	-	58	TN1	72.5	26	5	10.8	10/5	IV/IIIb	I
9	2	58	TN1	72.5	30	6	10.9	10/5	V/IIIb	II
10	-	58	TN2	72.5	20	4	10.4	10/3	IV/IIIa	I
11	-	58	TN1	74.4	26	4	9.9	10/1	V/II	I
12	-	58	TN2	72.5	26	4	8.3	10/1	V/II	I
13	-	58	TN1	72.5	20	4	8.8	10/3	IV/IIIa	I
14	-	58	TN1	72.5	20	4	10.2	10/5	V/IIIb	I
15	1	58	TN1	72.5	21	4	10	10/5	V/IIIb	I
16	-	58	TN1	72.5	20	4	11.98	10/10	V/V	I
17	-	58	TN1	72.5	29	5	8.44	10/5	V/IIIb	I
18	-	58	TN1	72.5	25	5	8.77	10/5	IV/IIIb	I
19	2	58	TN1	72.5	22	5	8.67	10/1	V/II	II
20	1	58	TN1	72.5	38	6	9.45	10/3	IV/II	II
21	-	58	TN1	72.5	25	5	9.1	10/5	V/IIIb	I
22	1	58	TN1	72.5	23	4	9.76	10/5	V/V	I
23	-	58	TN1	72.5	30	6	10.98	10/5	IV/IIIa	I
24	2	58	TN1	72.5	31	6	12.1	10/10	V/IIIb	II
25	-	58	TN1	72.5	32	6	11	10/3	V/IIIa	I

26	1	58	TN2	72.5	28	5	10	10/1	V/II	II
27	-	58	TN1	72.5	20	4	11	10/5	IV/IIIb	I

Abbreviations: radiofrequency (RF), radiosurgery (RS); numerical rating scale (NRS); Barrow Neurological Institute (BNI)

Table 3. Radiosurgery for the treatment of TN secondary to MS

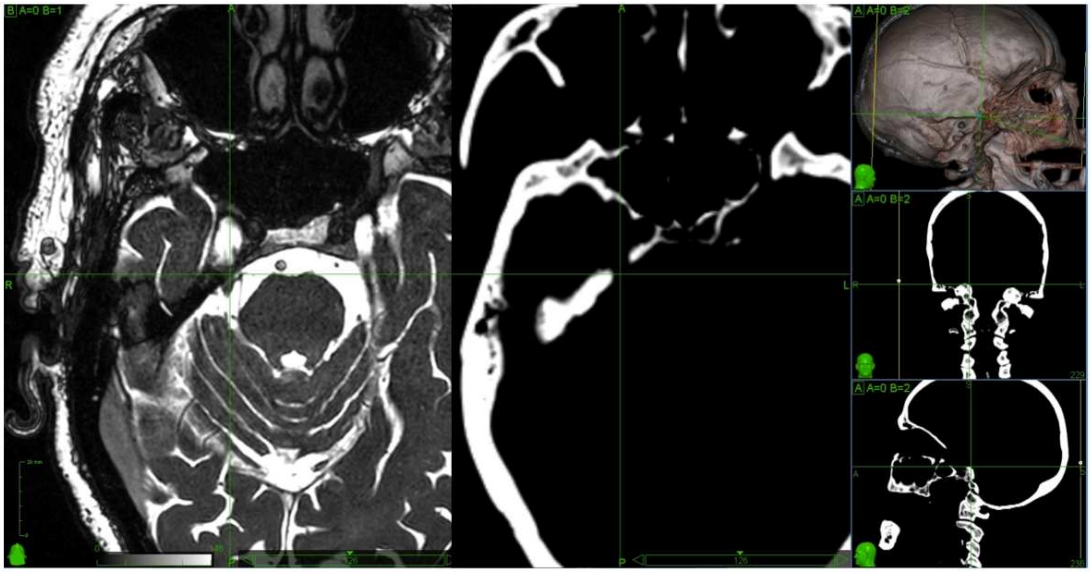
Authors	Patients N.	System	Median/Mean Age	Maximum Dose (Gy)	Target	Median FU (months)	Results (%)			Recurrence (%)
							No Pain	>90% Pain control	Side Effects	
Huang et al. (15), 2002	7	GKS	51 (40-63	80 (5 PTS), 90 (2 PTS)	REZ	28 (13-38)	100	-	57.1	14.3
Rogers et al. (35), 2002	15	GKS	-	70-80 (12), > 80 (3)	REZ	17 (6-38)		80	13	33.3
Zorro et al. (47), 2009	37	GKS	59 (38 – 74)	median 80	Pars triangularis	56.7 (6 – 174)	62.1	97.3	5.4	37.8
Diwanji et al. (10), 2010	13	GKS	-	median 75	REZ	67 (13 – 96)	42	57	7	-
Tuleasca et al.(43), 2014	43	GKS	57.2 (36.5 – 82.6)	70-80 (22 pts), >80 (31 pts)	Pars Triangularis	53.8 (12 – 157.1)	90.7	90.7	16	61.5
Weller et al. (46), 2014	35	GKS	62 (39 – 86)	median 90 (80 – 90)	Retrogasserian	39 (3 – 97)	35	88	39	-
Alvarez-Pinzon et al. (2), 2016	124	GKS	51	74	-	Mean 37.6		90	10	14.3
Conti et al. (Present series)	27	CKS	53.3 (36-62)	Median 72.5	Pars Triangularis	37 (18-72)	48	85	0	66

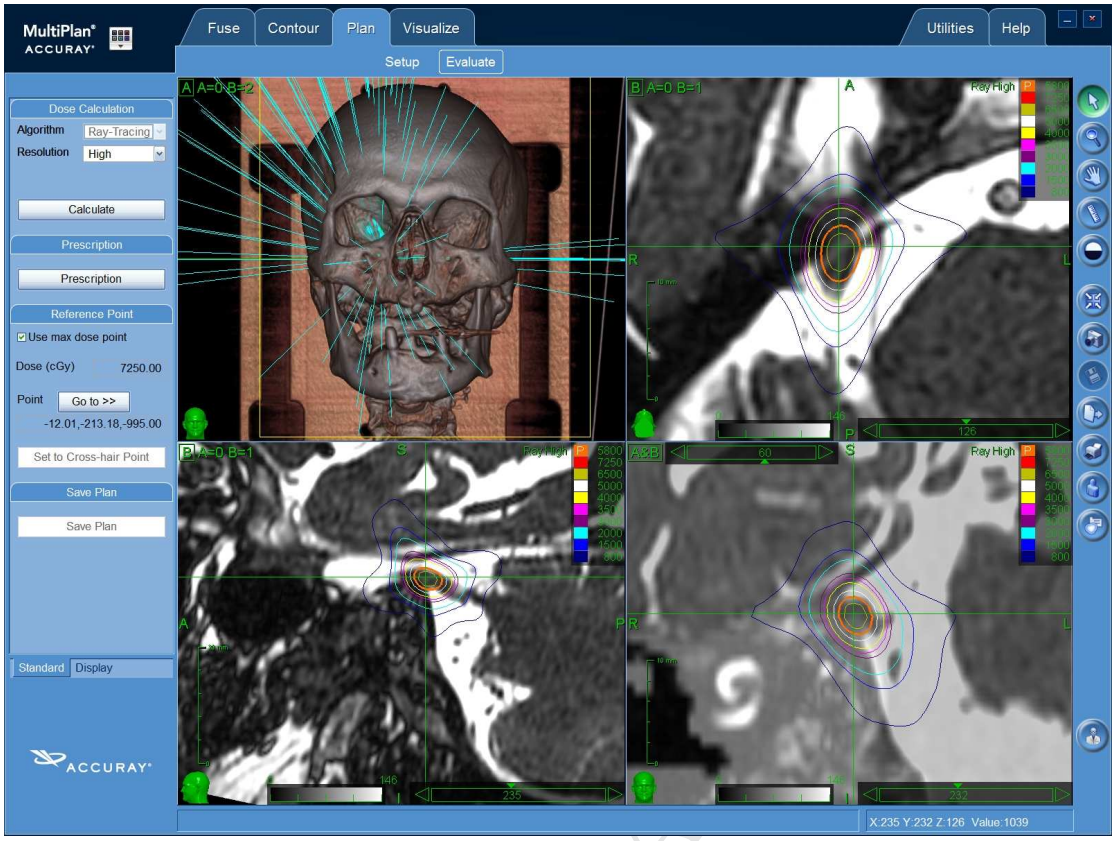
Abbreviations: GKS (GammaKnife surgery); CKS (CyberKnife surgery); REZ (root entry zone)

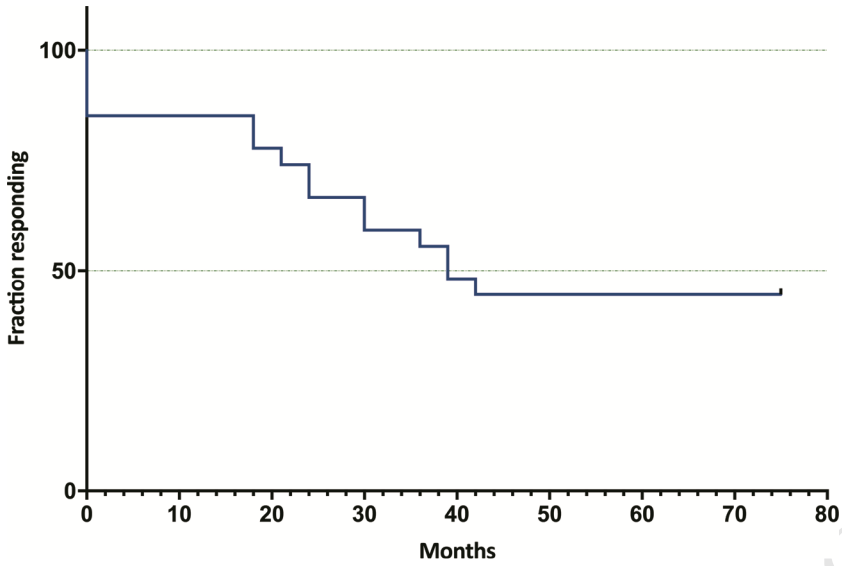
Table 4. Series reporting the non-isocentric CyberKnife radiosurgery for the treatment of idiopathic trigeminal neuralgia

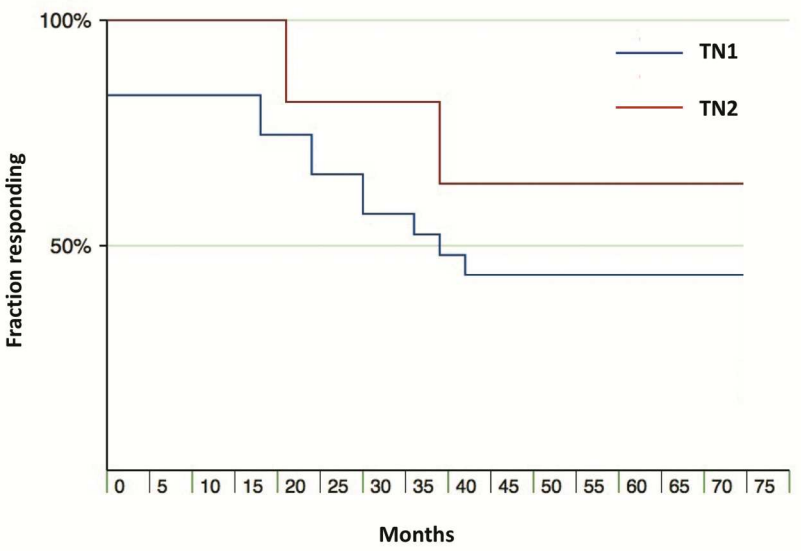
Authors	Patients N.	Median/Mean Age	Maximum Dose (Gy)	Target	Median FU (months)	Results			Recurrence
						No Pain	>90% Pain control	Side Effects	
Romanelli et al. (37), 2003	10	-	Mean 80	Retrogasserian (8 mm)	6	70	70	-	-
Lim et al. (22), 2005	41	68	78	Retrogasserian (mean 7.2 mm; range 5-12)	11	87.8%	92.7%	14.3%	15.8%
Villavicencio et al. (45), 2008	95	69.8	78	Retrogasserian (median 6 mm; range 5-12)	Mean 2 years	67%	92%	18%	28%
Fariselli et al. (12), 2009	33	74	55 (6 pts) 65 (10 pts) 75 (17 pts)	Retrogasserian (4 mm)	Mean 23	-	97%	0%	33%
Adler et al. (1), 2009	46	78	73.5	Retrogasserian	14.7	72%	96%	15%	10%
Tang et al. (41), 2011	14	67.8	80.5	Retrogasserian (mean 6.8 mm)	20.4	36%	100%	20%	-
Karam et al. (18), 2014	30	65	Marginal dose 64.5 (median isodose line 86%)	Retrogasserian (volume range, 25–71 mm3)	28	48%	72%	-	8%
Singh et al. (39), 2016	168	68.2 (TN1) 66.7 (TN2)	75	Retrogasserian Median volume: 8.5 mm3 (TN1) 10.7 mm3 (TN2)	-	82% (TN1) 72% (TN2)	.	18% (TN1) 11% (TN2)	-

Abbreviations:









Highlights

- Trigeminal neuralgia (TN) affects up to 7% of patients with multiple sclerosis (MS). In such patients, TN is difficult to manage either pharmacologically and surgically.
- Radiosurgical retroGasserian rhizotomy is an effective treatment option. Frameless radiosurgery provides a totally noninvasive method for retroGasserian rhizotomy.
- The non-isocentric geometry of radiation beams of the CyberKnife introduces different concepts for the treatment of TN andiIts efficacy for MS-related TN has not yet been proved.
- Using a maximal dose of 72.5 Gy and a prescription dose of 58 Gy delivered to a segment of the nerve long 5 mm with a volume of >25 mm3, pain relief can be obtained in 85% of patients without sensory complications.
- Long-term pain control was possible in less than half of the patients. Nevertheless, this is a limitation that Cyberknife radiosurgery shares with other techniques in MS patients.

Abbreviations

BNI: Barrow Neurological Institute

CISS: constructive interference in steady state

CT: Computed Tomography

DRR: digitally reconstructed radiographs

HI: Homogeneity Index

MR: Magnetic Resonance

MS: Multiple Sclerosis

nCI: New Conformation Index

NRS: Numerical Rating Scale

REZ: Root Entry Zone

TLS: treatment location system

TN: Trigeminal Neuralgia

TOF: Time-of-flight