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# Exploring long-term outcomes following CyberKnife robotic radiosurgery for trigeminal neuralgia

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ABSTRACT

*Background and purpose:* Radiosurgery has been extensively studied for its efficacy and safety in the management of trigeminal neuralgia (TN). However, among the plethora of relevant studies in the literature, only a restricted number have been conducted targeting an elongated trigeminal nerve segment with the CyberKnife radiosurgery (CKRS) system. Herein, we report long-term clinical outcomes of TN patients treated with CKRS.
*Materials and methods:* Fifty patients treated with CKRS for medically refractory TN were analyzed. Pain response and sensory dysfunction post CKRS were assessed using the Barrow Neurological Institute (BNI) scale. Kaplan-Meier analysis was used to assess the maintenance of pain control and the risk of onset of facial numbness. The Cox proportional hazards regression model was employed for both univariate and multivariate analyses to identify predictive factors among the collected variables.
*Results:* The median follow-up period was 63 months (range: 12–174 months). The median values of treated nerve volume, prescription dose, and integral dose were 59 $mm^3$, 60 Gy and 3.9 mJ, respectively. Pain control (BNI I-III) was achieved in 37 patients (74%). Among them, the actuarial freedom from pain (FFP) rate was 82%, 78% and 74% at 24, 36 and beyond 48 months post-CKRS, respectively. A correlation of FFP rate with patient gender, treated nerve volume, and mean dose was revealed in multivariate analysis. Twenty-three patients (62%) reported onset of new or aggravation of pre-existing, facial numbness with twenty-one of them (57%) characterizing it as "mild facial numbness, not bothersome" (BNI-II) and two (5%) as "somewhat bothersome" (BNI-III). We did not encounter any case with very bothersome facial numbness (BNI-IV).
*Conclusions:* Long-term results of this work contribute to the body of evidence supporting the safety and efficacy of CKRS in the treatment of TN patients, in view of excellent pain control for an acceptable toxicity profile.

## 1. Introduction

Trigeminal neuralgia (TN) is a disorder characterized by recurrent, usually unilateral, brief electric shock-like pain that is abrupt in onset and termination [1,2]. The pain is limited to the distribution of one or more divisions of the trigeminal nerve and is triggered by innocuous stimuli. The first therapeutic line of treatment is pharmacological using antiepileptics drugs, such as carbamazepine and oxcarbazepine [3]. For patients who do not respond to pharmacological treatment, or who experience intolerable side effects, invasive approaches could be considered. These approaches include percutaneous procedures (radiofrequency thermocoagulation, balloon compression, glycerol lesioning), microvascular decompression (MVD) and stereotactic radiosurgery (SRS) [4,5].

SRS is a non-invasive treatment that modulates the function of the sensory root of the trigeminal nerve using multiple precisely focused radiation beams. These beams can be delivered using an isocentric or a non-isocentric approach. The isocentric approach is used by the Gamma Knife system (Elekta AB, Stockholm, Sweden) and isocentric linear accelerators (Linacs). In Gamma Knife radiosurgery (GKRS) multiple cobalt-60 beams are focused to a specific point of the trigeminal nerve creating an almost spherical dose distribution ("shot") with a full width half maximum of about 4 mm [5]. The CyberKnife radiosurgery (CKRS) (Accuray, Inc., CA, USA) employes robotic and frameless image guidance technologies to deliver multiple 6 MV x-rays to the target [6,7]. In CKRS the nonisocentric approach is used enabling the irradiation of an extended segment of the trigeminal nerve with a relative homogeneous dose distribution [8]. The majority of clinical experience regarding SRS

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for TN treatment is based on GKRS and it is supported by an increasing volume of clinical data over prolonged observation periods [5]. Evidence supporting the efficacy and safety of CKRS for TN is limited in comparison to the available evidence of GKRS [9–12].

In this study, the clinical data of patients treated for TN with CKRS in our institution over a 14-year period are retrospectively reviewed, and long-term pain control and toxicity results are presented.

## 2. Methods and materials

### *Patient population*

The demographic and clinical details of patients with medication-refractory TN treated at our clinic between 2008 and 2022 with CKRS were retrospectively reviewed. Exclusion criteria comprised patients with intracranial benign tumors compressing the trigeminal nerve, and patients lacking follow-up data.

### *Variables*

Pain control, presence of multiple sclerosis (MS), previous treatments and therapy associated morbidity focusing on sensory dysfunctions were evaluated. In addition, the target nerve volume, prescription dose (PD), prescription isodose line, mean and maximum dose ($D_{mean}$, $D_{max}$), and the integral dose (ID) of the target – calculated as the product of the volume of the cisternal portion of the trigeminal nerve contoured multiplied by the mean dose [13] – were also retrieved from the delivered treatment plans to investigate factors affecting the clinical outcome.

### *Radiosurgery treatment*

Radiosurgery was performed using a CyberKnife G4 model which in 2010 was upgraded to the CyberKnife VSI model [14]. Before treatment, patients were positioned supine on the treatment couch, and a custom-fitted thermoplastic mask was applied. Each patient underwent multi-slice Computed Tomography (CT) scanning and Magnetic Resonance Imaging (MRI). The CT acquisition protocol adhered to CyberKnife-specific requirements, including 120 kV tube high voltage, 390 mAs exposure and a pitch of 0.55. High Resolution axial CT slices of 1 mm thickness without gap were reconstructed, utilizing a smooth reconstruction kernel (H22) [15]. MRI involved the acquisition of: 1) a three dimensional (3D) T1 weighted (T1w) magnetization-prepared rapid gradient echo pulse sequence (MPRAGE) of 1x1x1 $mm^3$ voxel size, and 2) a constructive interference in steady state (CISS) T2 weighted (T2w) sequence or a T2w Sampling Perfection with Application optimized Contrast using different flip angle Evolution (SPACE) sequence of 0.8x0.8x1 $mm^3$ voxel size covering the skull base region. Identification of potential neurovascular conflicts were assessed either by repeating the T1w MPRAGE MR scan using gadolinium contrast media or, by using the CISS images for the patients with a known reaction to gadolinium-based contrast agents [3]. All images were transferred to the CyberKnife workstation for treatment planning (MultiPlan™ treatment planning system, Accuray Inc).

Target and critical structures were delineated on the co-registered CT and MRI scans. The target comprised the entire nerve diameter over a length of 5–6 mm of the cisternal portion of the trigeminal nerve, depending on patient's anatomy (Fig. 1) [16]. The brainstem, ipsilateral hippocampal region, acoustic and facial nerves, were additionally delineated and used as critical structures during dose optimization. Other critical volumes included the eyes to restrict beams passing through them, the optic nerves, the optic chiasm, and the skin. Furthermore, two ring-shaped tuning structures distancing 1.5 mm and 8 mm from the target were used to conform the prescription isodose surface with the target shape and maximize dose fall-off outside the target, respectively. All treatments were planned using either the "trigeminal_path" or the "1path_head" CK robot path node set and the 5 mm nominal diameter collimator [14]. It must be noted that the actual field size defined by the 5 mm collimator at the isocenter is different between the two path node sets employed; in the "1path_head" a circular 5 mm field is generated, whereas in the "trigeminal_path" a circular field of 4.1 mm diameter is defined. This difference stems from the smaller source-to-isocenter distance of 650 mm in the "trigeminal_path", as opposed to that of 800 mm in the "1path_head". A non-isocentric beam distribution was selected for treatment planning in each TN case. The "1path_head" path node set was used for treatment planning since it allows the robot to correct for patient rotations during treatment delivery. If planning objectives could not be met, the "trigeminal_path" was used instead, with guidelines provided to the operator to monitor and maintain all patient rotations below 0.5° throughout the treatment. If patient rotations exceeded 0.5° the patient was repositioned prior resuming treatment. The temporal resolution for kV image acquisition was controlled by the operator and was 45 s for all TN patients to reduce intrafraction uncertainty. Dose constraints for the brainstem were as follows: a volume equal or less than 500 $mm^3$ could receive a dose of 10 Gy or higher, with a maximum dose (defined at a volume of 35 $mm^3$) of less than 15 Gy [17,18]. The maximum dose for cranial nerves, acoustic apparatus and ipsilateral hippocampal region was constrained to less than 8 Gy. While a specific dose constraint was not applied for the ipsilateral temporal lobe, care was taken during optimization to minimize the received dose. No specific dose constraint was set for vessels.

### *Follow-up and assessment of outcome*

Patient follow-up data were collected from corresponding medical records available in our clinic. These included clinical follow-up data recorded at 3–6 months post-CKRS and then annually, supported by MR imaging studies if deemed necessary. The data were supplemented by

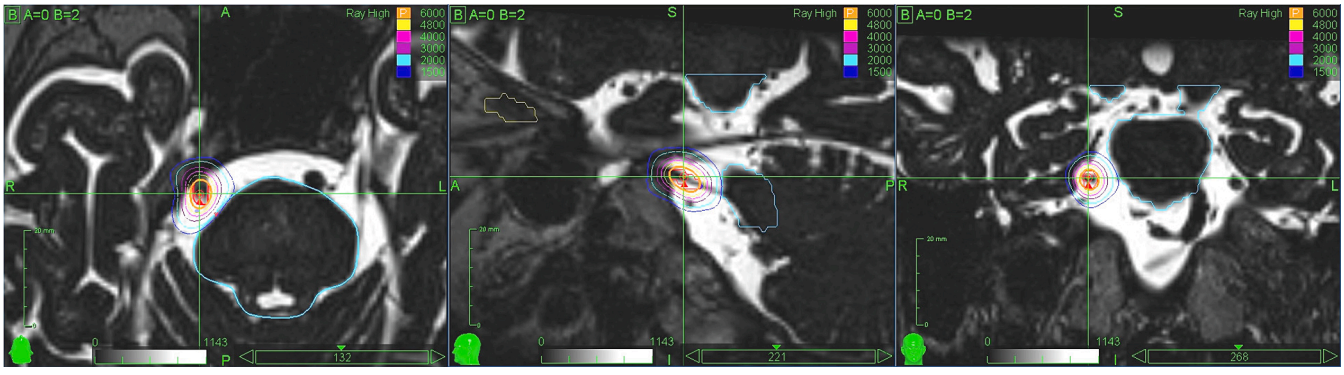


**Fig. 1.** Axial (left), sagittal (middle) and coronal (right) T2 weighted MR images of an indicative case showing the retrogasserian section of the trigeminal nerve that was targeted, excluding the root entry zone. The brainstem was kept outside the 15 Gy isodose line.

telephone interviews conducted by a physician who was not involved in the patients' management. In the latest follow-up of each patient, pain control, medication and complications were evaluated. Pain intensity was assessed using the Barrow Neurological Institute Pain Scale (BNI-PS), in which a score of I indicates no trigeminal pain without medication, II indicates occasional pain but not requiring medication, III indicates some pain adequately controlled with medication, IV indicates some pain not adequately controlled with medication, and V indicates severe pain or no pain relief. Trigeminal sensory loss after CKRS was evaluated using the BNI Numbness Scale (BNI-NS), in which a score of I indicates no facial numbness, II indicates mild but not bothersome facial numbness, III indicates somewhat bothersome facial numbness, and IV indicates very bothersome facial numbness. Recurrence was defined as any worsening of pain from the maximum level of response. Successful pain control was associated with BNI-PS scores of I–III, while trigeminal sensory dysfunction was related to BNI-NS scores of III-IV.

*Statistical methods*

Kaplan-Meier analysis was used to determine the time to event, which included pain recurrence or facial numbness. Pain recurrence and facial numbness were defined from treatment delivery until the date of the latest follow-up or the date of death. Maintenance of pain control, i.e., freedom from pain (FFP), was associated with BNI-PS scores of I–III, while bothersome facial numbness was related to BNI-NS scores of III-IV. The Cox proportional hazards regression model was employed for both univariate and multivariate analyses to identify predictive factors among the collected variables. The variables included in these analyses were selected based on prior knowledge from the literature and their availability from the recorded clinical, treatment planning, and follow-up data. All statistical analyses were performed using RStudio: Integrated Development for R (PBC, Boston, MA). A two-tailed p-value $< 0.05$ was considered statistically significant.

## 3. Results

*Patient population and treatment data*

Demographic and treatment planning details of the evaluated population consisting of 50 patients are presented in Table 1. The median age was 65 years (range: 38–85 years), with 24 females and 26 males. Of the patients, twenty-four (48%) had left-sided TN and twenty-six (52%) had right-sided TN; none had bilateral neuralgia. Twelve patients (24%) had MS, and eighteen had previously undergone percutaneous rhizotomy (36%). The median follow-up time was 63 months (range: 12–174 months).

The median volume of the delineated target was 59 $mm^3$ (range: 25–125 $mm^3$), with the "trigeminal_path" employed in 70% and the "1path_head" in 30% of the cases. A median dose of 60 Gy (range: 50–60 Gy), defined at the 80% median isodose line (range: 70 − 80%), was prescribed. The median maximum voxel dose was 75 Gy (range: 63–86 Gy). The median number of non-zero Monitor Unit (MU) beams was 191 (range: 56–267) resulting to a median treatment delivery time of 53 min (range: 30–76 min). The integral dose was found to vary linearly with the target volume as depicted in Fig. 2, with a median value of 3.9 mJ (range: 1.8–8.1 mJ). A least square regression analysis was performed on the presented data, yielding a linear polynomial function of: ID (mJ) = 0.066·Volume ($mm^3$), $R^2 = 0.99$.

*Pain response*

Before undergoing CKRS, all patients rated their pain as severe (BNI-PS V). Following CKRS, 42 out of 50 patients (84%) experienced an improvement in their pain level. Among them, 23 (55%) achieved complete pain relief and discontinued all TN medications (BNI-PS I). Additionally, 6 patients (14%) ceased all medications after experiencing excellent pain relief, with only occasional tolerable pain (BNI-PS II). Another 8 patients (19%) remained on medications but reported adequately controlled pain (BNI-PS III). Five patients (12%) noted pain improvement post-CKRS, although they did not consider their pain adequately controlled (BNI-PS IV). Overall, successful pain control (BNI-PS I-III) was achieved in 37 out of 50 patients (74%). Fig. 3a illustrates the actuarial FFP (BNI-PS I-III) rate following CKRS over an extended time-period of 173 months. As can be seen, the actuarial FFP rate is 82% (CI95%: 74–90%), 78% (CI95%: 69–88%) and 74% (CI95%: 63–85%) at 24, 36 and greater than 48 months post-CKRS, respectively. Moreover, when restricting the analysis to patients with longer follow-up, it was found that only 12 out of 37 retained pain control for more than 5 years. The actuarial FFP rate for this group of patients remained stable until they were censored.

**Table 1**
Demographic and treatment planning details for the analyzed patient population.

| Characteristic/Parameter | Value[a)] |
|---|---|
| Number of patients | 50 |
| Gender | |
| Female | 24 (48%) |
| Male | 26 (52%) |
| Age (years) | 65 (38–85) |
| Location | |
| Left | 24 (48%) |
| Right | 26 (52%) |
| Multiple sclerosis | 12 (24%) |
| Previous treatments[b)] | 18 (36%) |
| Target volume ($mm^3$) | 59 (25–125) |
| Robot path | |
| trigeminal_path | 35 (70%) |
| 1path_head | 15 (30%) |
| Number of beams | 191 (56–267) |
| Monitor Units | 23,882 (14,333–40,219) |
| Prescription isodose (%) | 80 (70–80) |
| Prescribed dose (Gy) | 60 (50–60) |
| Mean dose (Gy) | 66 (55–71) |
| Maximum dose (Gy) | 75 (63–86) |
| Integral dose (mJ) | 3.9 (1.8–8.1) |
| Treatment time (min) | 53 (30–76) |
| Follow-Up (months) | 63 (12–174) |

[a)] Frequency (%) or median (Range).
[b)] Besides medication, previous treatments include MVD (n = 2), balloon compression (n = 2), thermocoagulation (n = 7) and glycerol lesioning (n = 1).

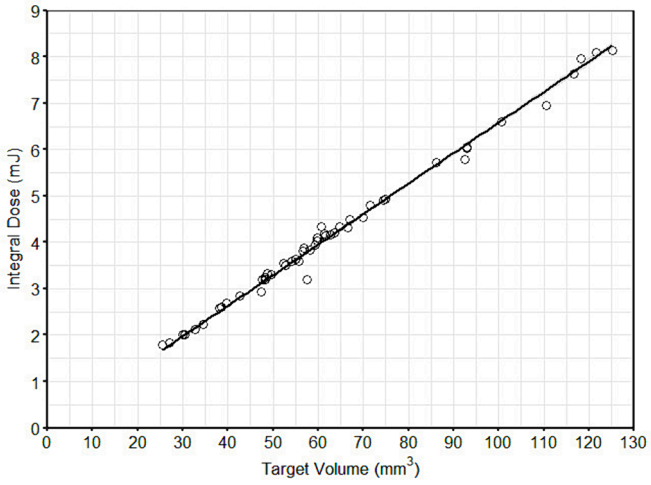


**Fig. 2.** Integral dose (calculated as the product of the mean dose to the targeted intracisternal nerve segment multiplied by its volume) data for the target plotted as a function of target volume of the patient cohort.

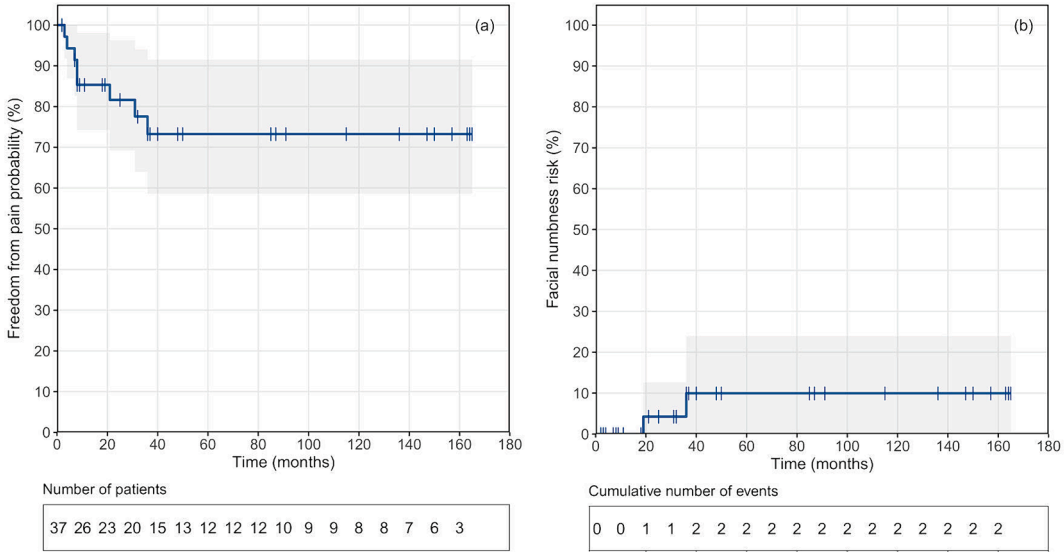


**Fig. 3.** Kaplan Meier data showing a) the freedom from pain probability (BNI-PS I-III) and b) the bothersome facial numbness risk defined as BNI-NS III-IV. Patients were censored at the last follow-up.

*Latency period*

Patients were queried about the timing of the initial onset of pain relief and maximum relief. Initial pain relief spanned from early (≤30 days) to 180 days, with a median of 30 days. Thirty-five patients out of fifty (70%), reported early (≤30 days) pain improvement following CKRS.

*Pain recurrence*

Recurrence was observed in thirteen patients out of 42 (31%). For these patients, the median time to recurrence was 8 months, (range: 2–36 months). Of the patients with pain recurrence, five were treated with radiofrequency thermocoagulation, two had MVD, one repeated SRS and the rest were under pharmacological treatment. Restricting the analysis to patients with more than 5 years of follow-up, no onset of new bothersome facial numbness was observed.

*Sensory dysfunctions*

The only complication observed was delayed, partial facial sensory loss (facial numbness). Among the patients achieving pain control (n = 37), fourteen (38%) experienced no facial numbness post-CKRS, while twenty-three patients (62%) developed new or aggravation of pre-existing numbness. Among these patients, twenty-one (57%) rated it as "mild facial numbness, not bothersome" (BNI-NS II), whereas two patients (5%) rated it as "somewhat bothersome facial numbness" (BNI-NS III). We did not encounter any case with very bothersome facial numbness (BNI-NS IV). Fig. 3b, illustrates the actuarial bothersome facial numbness risk (BNI-NS III-IV) for the patients achieving pain control following CKRS for the studied follow-up time. As can be seen the bothersome facial numbness risk is 4% (CI95%: 0–8%) at 24 and 36 months increasing to 9% (CI95%: 2–16%) beyond 48 months post-CKRS.

*Factors affecting pain control and sensory dysfunction*

Table 2 provides a summary of the univariate and multivariate analysis performed to identify factors affecting pain control. In analyzing the impact of ID a cutoff threshold of 2.7 mJ was used to distinguish medium and high ID values [10,19]. As can be seen, none of the analyzed factors had a statistically significant effect on the FFP probability in univariate analysis. However, in multivariance analysis gender, target volume and mean dose to the target were found to affect the FFP probability. Moreover, the presence of MS was not found to affect FFP probability in both univariate and multivariate analysis. A similar analysis for the facial numbness failed to reveal any correlation between the same parameters and the risk for bothersome facial numbness in both univariate and multivariate analysis (data not shown).

**Table 2**
Univariate and multivariate Cox regression analyses for factors affecting freedom from pain (BNI-PS I-III) probability.

| Variable | Univariate Analyses | | | Multivariate Analyses | | |
|---|---|---|---|---|---|---|
| | HR[a)] | 95% CI[b)] | p-value | HR[a)] | 95% CI[b)] | p-value |
| Age | 0.97 | 0.91–1.04 | 0.423 | 0.97 | 0.91–1.04 | 0.413 |
| Gender[c)] | 1.96 | 0.46–8.26 | 0.362 | 39.6 | 1.57–996.5 | **0.025** |
| Location[d)] | 1.18 | 0.28–4.93 | 0.823 | 1.13 | 0.17–7.29 | 0.899 |
| Target Volume ($mm^3$) | 0.98 | 0.95–1.01 | 0.193 | 0.90 | 0.82–0.99 | **0.032** |
| 1path_head[e)] | 0.85 | 0.17–4.19 | 0.837 | 8.37 | 0.43–164 | 0.162 |
| Number of Beams | 0.99 | 0.97–1.01 | 0.331 | 1.00 | 0.97–1.03 | 0.963 |
| Prescription Isodose (%) | 0.95 | 0.68–1.33 | 0.765 | 2.87 | 0.13–74.3 | 0.525 |
| Maximum Dose (Gy) | 1.08 | 0.83–1.41 | 0.544 | 3.01 | 0.12–76.1 | 0.504 |
| Mean Dose (Gy) | 0.99 | 0.76–1.30 | 0.958 | 0.46 | 0.22–0.94 | **0.033** |
| Integral Dose (mJ)[f)] | 0.56 | 0.11–2.76 | 0.474 | 0.88 | 0.06–13.11 | 0.923 |

a) HR = Hazard Ratio.
b) CI = Confidence Interval.
c) Female set as reference.
d) Left side set as reference.
e) "trigeminal_path" set as reference.
f) Integral Dose (ID) was factorized to medium and high ID values applying a cut off value of 2.7 mJ [10,19] and medium ID values were considered as reference.

## 4. Discussion

Institutional data on pain response and side effects for fifty patients with medically refractory TN treated using CKRS were presented. Pain control (BNI-PS I-III) was achieved in 37 out of 50 patients (74%). Of the patients who responded to CKRS, the majority (70%) noted

improvement in symptoms within the first month and all reported improvement within 6 months. Moreover, actuarial FFP rates of 82%, 78% and 74% at 24, 36 and beyond 48months post-CKRS were found. Twelve out of 37 remained pain free for more than 5 years and until they were censored. An actuarial bothersome facial numbness risk of 9% at 48 months was observed. No other toxicities, such as seizures or edema, were noted.

Targeting the trigeminal nerve with CKRS was initially applied by Romanelli et al. [8] in 2003 and Lim et al. [20] in 2005, both irradiating a nerve segment 5–12 mm long localized in the cisternal portion with an average marginal dose of 64.4 Gy and median marginal dose of 65.5 Gy, respectively. While CKRS was proved an efficient technique for the treatment of TN offering almost immediate pain relief, irradiating such lengthy nerve segments led to increased incidence of bothersome numbness (51.2%) [20]. These findings prompted an investigational study to determine the optimal dose parameters and trigeminal nerve length to be targeted in CKRS, which concluded on maximum and marginal dose values of 75–78 Gy and 60–62 Gy, respectively, delivered to a trigeminal nerve segment of 6 mm long [16]. Similar dose parameters were also reported by Fariselli et al. [11] in an independent dose escalation study, using trigeminal nerve segments 3–5 mm long. Using the above dose parameters and treated nerve segments, good to excellent pain control probabilities ranging from 77 to 96% have been reported at the one year follow-up [9,10,12,21]. On the longer run however, pain control (BNI-PS I-III) probabilities reduce and range from 67 to 84%, 72 to 81%, 72 to 76% and 71 to 72% at 24, 36, 48 and 60 months, respectively [9–11,22]. Pain control rates found in our study agree with the corresponding data in the literature, thus further supporting the effectiveness of CKRS for the management of TN, even for a follow-up time reaching 14 years.

Guillemette et al. used CKRS to register a single-shot at the cisternal portion of the trigeminal nerve [12]. A median maximum dose of 80 Gy was delivered to the nerve achieving pain control in 86.9% of the cases. Pain control was maintained to 77%, 62.5% and 50.2% of the cases at 12, 36, and 60 months from the treatment date, respectively. The relatively lower pain control rates reported by Guillemette *et al*, compared to studies that treat a nerve segment, could be attributed to the fact that maximum point doses greater than 85 Gy are required in single-shot SRS for maintaining pain control [5].

Regarding sensory dysfunctions, 62% of the patients reported onset of new facial numbness or aggravation of pre-existing numbness. This risk is higher than the 26.2% reported by Guillemette et al. [12] and could be attributed to corresponding differences in the nerve volume receiving high doses. However, it is noted that the higher numbness risk in our study is associated with increased probability of maintaining pain control (74% versus 50% at 60 months post-CKRS). The risk for onset of significant facial numbness (BNI-NS $\geq$ III) was found to be equal to 4% at 24 months increasing to 9% beyond 48 months post-CKRS. These findings are in agreement with corresponding BNI-NS $\geq$ III facial numbness risk values of 5%, 15% and 18% reported by Romanelli et al. [9], Adler et al. [21] and Conti et al. [10], respectively, indicating that CKRS for TN treatment is associated with acceptable toxicity rates.

Univariate and multivariate analysis was used to identify factors affecting the clinical outcome of the evaluated patient cohort. Regarding pain control, while univariate analysis failed to show any correlation with the endorsed factors, multivariate analysis revealed a correlation between the FFP rate and the gender, the target nerve volume, and the mean target dose. Specifically, males were found to have worse pain control probability compared to females. Moreover, the pain control probability was found to increase with target volume and mean dose, in agreement with corresponding findings reported in the literature [9,10]. Regarding the presence of MS, our study failed to confirm the reported worse outcome of patients having MS [10,12]. This could be attributed to the small number of patients with MS in the analyzed patient cohort.

The performed analysis failed to reveal a correlation of the pain control with the ID. This is probably due to the fact that relatively larger ID values were delivered in our study (median: 3.9 mJ) compared to the corresponding data reported by Conti et al. [10] using CKRS and a similar treatment protocol (median: 1.6 mJ). Nevertheless, two independent studies using GKRS [19] and CKRS [10], each analyzing a sufficient number of patient data, have shown a correlation between pain control and ID. It is noted that this variable combines the information of the target volume and the dose distribution within the target. In this work, a linear function was proposed to calculate ID given the delineated target volume (see Fig. 2). Notably, the slope of the linear function is in close agreement (within 2.3%) with the slope of the corresponding linear function reported by Mousavi et al. [19] using GKRS and a different radiosurgery machine and treatment protocol, which involves a single isocenter with the 4 mm collimator and a median prescription dose of 80 Gy at the 100% isodose. This finding implies that the isocentric GKRS and the non-isocentric and more homogeneous CKRS protocols lead to similar ID values for the same treated nerve volumes and, therefore, to similar clinical outcomes.

As far as facial numbness is concerned, both univariate and multivariate analysis failed to reveal a correlation with the studied parameters. This could be attributed to the small size of the patient cohort presented with bothersome or somewhat bothersome numbness. Other studies using CKRS have reported correlations between facial numbness and re-irradiation, prescription isodose line and the presence of MS [9,10,20].

Finally, in a recent systematic review Tuleasca et al. [5], analyzed 65 studies presenting data for a total number of 6461 patients. Most of the patients were treated using GKRS (88%). Reported actuarial initial FFP without medication median rates were 52.1% (range: 28.6–100%) for GKRS, 43.2% (range: 17.3–76%) for LINAC based radiosurgery, and 58% (range: 40 to 72%) for CKRS. Specific to facial numbness, median crude rates of 19% (range: 0 – 68.8%) for GKRS, of 28.5% (range: 11.4–49.7%) for LINAC, and 18.7% (range: 11.8–51.2%) for CKRS. Results presented in our study fall well within the data of this systematic review and suggest that CKRS is an effective treatment of TN.

This study contains some intrinsic limitations due to its design. Firstly, since this is a retrospective study, it is subject to a recall bias. Secondly, certain radiosurgical data were not analyzed in detail, including heterogeneous target delineation, latency of sensory dysfunctions (e.g., exact time of onset of new or aggravation of existing mild facial numbness) and the differences in treatment delivery times using different CyberKnife models during the study period. Those parameters may influence the treatment outcomes. Lastly, although the follow-up period was reasonably long, a larger number of patients with extended follow-up period would be preferable.

## 5. Conclusion

Stereotactic radiosurgery is emerging as a valid first-line treatment option for medically refractory TN patients. This study presents pain control and facial numbness outcomes for patients treated with CKRS, with a follow-up period extending up to 14 years. The probability of achieving pain control was found to be 74%. Pain control was maintained in 82%, 78%, and 74% of the patients at 24, 36, and beyond 48 months post-CKRS, respectively, with a 9% risk of bothersome facial numbness. These findings corroborate and augment existing literature, suggesting that CKRS is a favorable treatment option for patients with TN, associated with an acceptable toxicity profile.

## CRediT authorship contribution statement

**Anastasia Stergioula:** Conceptualization, Data curation, Writing – review & editing. **Argyris Moutsatsos:** Writing – review & editing. **Evaggelos Pantelis:** Formal analysis, Visualization, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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