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ORIGINAL ARTICLE

Factors affecting long-lasting pain relief after Gamma Knife radiosurgery for trigeminal neuralgia: a single institutional analysis and literature review

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Abstract

Gamma Knife radiosurgery (GKRS) is a well-established safe and effective treatment for trigeminal neuralgia (TN) with high initial success rate (80–90%). Why the pain relief is progressively decreased with time is a matter of considerable debate. To investigate factors related to long-lasting pain relief, the authors conducted a retrospective analysis focusing on anatomical and radiosurgical related parameters, chosen according to literature review. One hundred and twelve patients with classical trigeminal neuralgia and follow-up longer than 12 months were selected from our institutional consecutive series of patients treated by GKRS. Patients were followed for a mean period of 61.5 ± 3.5 months (range, 12–126 months) to evaluate, as endpoints, long-term pain relief and hypoesthesia onset. The median maximum radiation dose was 80 Gy (range 70–90 Gy). Factors related to poor long-term pain relief were prescription dose < 80 Gy (p = 0.038), calibration dose rate < 2.5 Gy/min (p = 0.018), and distance between isocenter and trigeminal nerve emergence > 8 mm (p < 0.001). When analyzing patients who received 80 Gy as maximum dose without any sector blocking, we notice that ID_{50} < 2.7 mJ was predictive for longer period of pain control (p = 0.043). It was experienced also among patients in which a small volume of the nerve (< 35%) received more than 80% of the maximal dose, compared to those in which a larger volume of the nerve was irradiated with maximal dose (p 0.034). This last result was significant if the shot was 8 mm or less from the pons. Several single-patient anatomical and radiosurgical parameters should be considered to improve GKRS effectiveness.

Keywords Gamma Knife radiosurgery · Retrogasserian target · Trigeminal neuralgia · Integral dose · Dose rate · Ponto-trigeminal angle · Trigeminal length

Introduction

Gamma Knife radiosurgery (GKRS) is a well-accepted procedure for treating classical trigeminal neuralgia (CTN) [5, 10, 18, 20, 23, 24, 26, 34–37]. A recent systematic review reported its effectiveness by classifying patient outcomes according to the Barrow Neurological Institute (BNI) Pain Intensity scale: the initial freedom from pain (iFFP) without medication (BNI I-II) occurred in 53.1% of treated patients whereas the iFFP with or without medication (BNI I-IIIa) in 84.8% of cases [38, 41]. The most common adverse effect was facial hypoesthesia, evaluated according to the BNI Facial Numbness scale. Its overall incidence rate was 21.7%, whereas bothersome hypoesthesia (BNI III and IV) occurred in 3.1% of treated patients [41].

Unfortunately, patients with CTN successfully treated through different non-pharmacological approaches, including both radiosurgery and more invasive techniques, may experience pain recurrence during their life [5, 10, 20, 23, 26, 36, 37]. The case series with the longest reported follow-up shows a probability of achieving and maintaining pain relief, at 10 years after GKRS, of 45.3% and 67.7%, without the new use

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of medications or without any surgical interventions, respectively [37]. The following positive prognostic factors were suggested: advanced age, microvascular compression, latency between pain onset and GKRS < 3 years, high prescription dose, no previous surgical treatments, and classical trigeminal pain features [26, 41].

To understanding of why the rate of pain recurrence may be so high, several anatomical and radiosurgical planning parameters were investigated by reviewing the medical literature. When analyzing the anatomic variables, trigeminal length, ponto-trigeminal angle, trigeminal volume, target location (retrogasserian or root entry zone), shot-emergence distance, and ratio between nerve length and targeting length were evaluated [4, 16, 25, 33, 44]. With regard to the radiosurgical planning parameters, well-known factors such as the prescription dose, the number of isocenters and beam channel blocking (plug use) were considered; however, given more recent investigations on other contributes, such as the integral dose (depending on the volume of trigeminal nerve being examined), trigeminal volume receiving ≥ 80% of the maximal dose, calibration dose rate, and biologically effective dose (BED), these were taken into consideration too [11, 27–30, 42, 43].

To date, published data are not completely conclusive, but the latest evidences recommend a single subject-based targeting planned on the patient's anatomy and physical parameters like dose (maximal or integral) and time of delivery, rather than a standardized approach. In our study, we retrospectively reviewed our institutional series including both older and more recently introduced parameters with the aim of investigating whether anatomy- and planning-related factors could be predictive markers of long-lasting pain relief and/or trigeminal hypoesthesia.

Materials and methods

Study design

The study follows a retrospective observational cohort design and the principles outlined in the Declaration of Helsinki. Informed consent to GKRS treatment and data collection was signed by all patients and approved by the Institutional Review Board.

Patients' selection

Patients with trigeminal neuralgia or painful trigeminal neuropathy who consecutively underwent GKRS between 2009 and 2018 at the Department of Neurosurgery and Gamma Knife Radiosurgery, San Raffaele Scientific Institute (Milan, Italy), were considered for study enrollment (n = 244). GKRS was proposed in the case of medically refractory trigeminal pain, intolerance/serious side effects to drug treatment, and in the case of patient's preference.

For the purpose of this study, eligible patients were those with complete data (n = 204) extracted from our institutional database, prospectively recorded. Data were reviewed to include cases with follow-up longer than 12 months (n = 181), to avoid underestimating pain recurrence, and diagnosis of classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain (n = 148), according to International Classification of Headache Disorders (ICHD); so 33 patients, affected by painful cranial neuropathies (multiple sclerosis related and/or secondary to space occupying lesion or other factors), were not included [14]. Subsequently, we excluded 12 patients who received a computed tomography–based planning and 24 patients who were already treated by GKRS before 2009 (Fig. 1).

A total of 112 patients met the inclusion and exclusion criteria, 66.1% of them were female and 33.9% male (p = 0.01). The mean age at treatment was 63.9 ± 1.1 years with a peak (21%) between 65 and 70 years (median 66; range 28–92 years). The pain was equally distributed on the right and on the left in 53 patients (47.3%), on each side, and only 6 of 112 cases (5.4%) referred bilateral pain; the latter underwent GKRS bilaterally but at different times and only the first treatment was considered. In 79 cases (70.5%), pre-treatment MRI demonstrated a possible neurovascular conflict. GKRS was the first surgical procedure in 92 patients (82.1%). Nine patients (8%) had a trigeminal sensory loss secondary to a previous surgical procedure.

Gamma Knife radiosurgery technique

Patients underwent placement of the Leksell stereotactic head frame (model G; Elekta Instruments, Stockholm, Sweden) under mild sedation and after application of a local anesthetic agent. The following MRI sequences were carried out on MRI machine (Philips Achieva, 1,5 Tesla, Eindhoven, The Netherlands) to identify the trigeminal nerve: (i) three dimensional axial T2-weigheted turbo spin-echo (repetition time = 1500 ms, echo time = 250 ms, flip angle = 90°, slice thickness = 1.0 mm, voxel size 1.0 × 1.0 × 1.0 mm, matrix size = 256 × 256); (ii) three dimensional axial gadolinium-enhanced T1-weighted (repetition time =3 0 ms, echo time = 4605 ms, flip angle = 25°, slice thickness = 1.0 mm, voxel size 1.0 × 1.0 × 1.0 mm, matrix size = 256 × 256).

Treatment plans were performed using the Leksell Gamma Knife Perfexion model (Elekta Instruments AB, Stockholm, Sweden): one single shot via a 4-mm collimator was placed on the anterior cisternal portion of the trigeminal nerve (retrogasserian target), with a prescription dose of 90 Gy (isodose 100%). At our center, we limited irradiation to 10 mm^3 of the brainstem with a maximum dose of 12 Gy. According to the dose-volume histogram (DVH) and the nerve proximity,

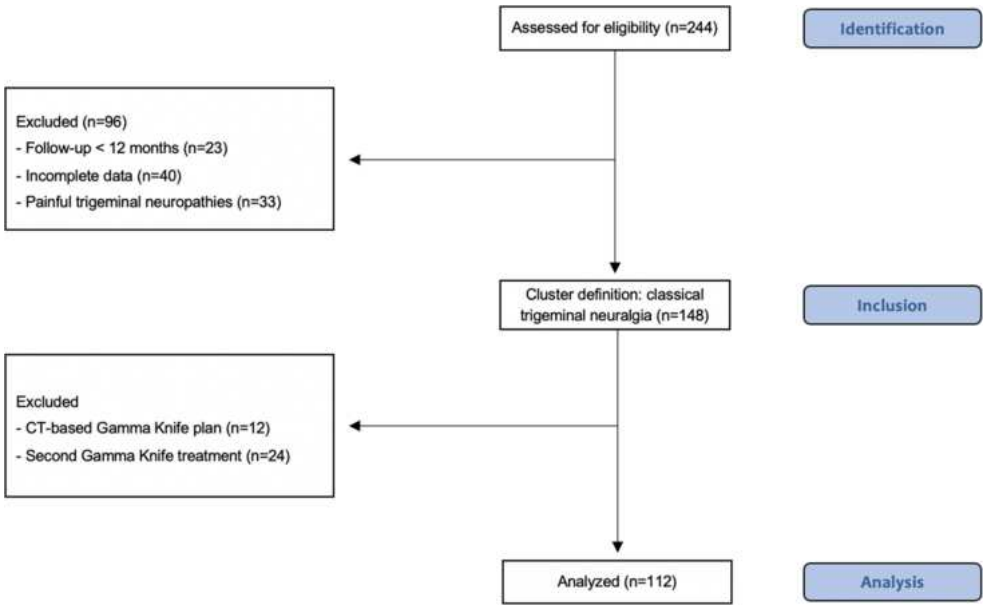

Fig. 1 Outline of patients' selection. Chart data for 244 patients with trigeminal neuralgia or painful trigeminal neuropathy who consecutively underwent GKRS between 2009 and 2018 at our department. We included in the study only cases with classical trigeminal neuralgia ($n = 148$) and analyzed 112 patients according to inclusion and exclusion criteria

prescription dose and/or shot location were therefore adjusted by decreasing the dose or moving few mm anteriorly the isocenter, along the nerve. The maximum dose (D_{max}) to the nerve always ranged between 70 and 90 Gy. Sector blocks of beam channels were adopted only as the last chance to limit doses to the brainstem and always keeping the prescription dose under 90 Gy (100%).

MRI measurements and variables definition

Single-patient MRIs were retrospectively reviewed on the Gamma Plan software (Elekta Instruments AB, Stockholm, Sweden) by two neurosurgeons. The following measurements were obtained:

1. Trigeminal nerve length into the anterior cistern (Trigeminal Cisternal Length, TCL) from the nerve's exit from the brainstem to the trigeminal incisura on the petrous bone along the major axis of the nerve (mm).
2. Distance between the middle of the isocenter and the nerve's exit from the brainstem (isocenter-emergence distance, IED), along the major axis of the nerve (mm).
3. Ponto-trigeminal angle computed by drawing a right-angled triangle between nerve and brainstem (PTA, degree°) [4].
4. Trigeminal cisternal volume (TCV, mm^3).
5. Trigeminal nerve volume inside the 50% isodose line (TV_{50}, mm^3).
6. Overall trigeminal integral dose (ID, mJ).
7. Integral dose of the TV_{50} (ID_{50}, mJ) [29].
8. Percentage of trigeminal volume receiving ≥ 80% of the D_{max} (%), using the trigeminal nerve DVH [43].
9. Dose rate at the time of treatment (Gy/min): calibration dose time (CDR), from treatment plan stored on database.
10. Dose administered to 10 mm^3 of brainstem, using the brainstem DVH (Gy).

In particular, the "line function" was used to define the aforementioned linear measures (points 1, 2, and 3); the nerve and the brainstem contours were drawn on the 3D T2-weighted sequences to calculate their volumes and more (points 4 and 5); the planning software was used to evaluate radiosurgical parameters like the integral doses (points 6 and 7) as mean dose × target volume.

Radiosurgery planning data and MRI measurements are summarized in Table 1.

Data collection and outcome evaluations

All included patients received clinical examination on hospital admission. Trigeminal pain was evaluated, according to the BNI Pain Intensity scale, at baseline (before GKRS), at 3- and 6-month intervals after radiosurgery for the first year and yearly thereafter for 5 years. After this period, a clinical control was scheduled at two-yearly intervals or when clinically indicated. In reference to the postoperative outcomes, BNI I-IIIb scores were considered as "good pain relief with or without medication" and BNI IV-V as "poor pain relief or failure." Long-lasting good pain control was defined as experiencing pain relief without subsequent pain recurrence during follow-up (when patients did not fall in BNI IV or V class or did not undergo to further invasive treatment as surgery, percutaneous procedures, or second GKRS). Development of hypoesthesia

Table 1 Gamma Knife planning data and MRI measurements of 112 patients with trigeminal neuralgia

	n	%	
Maximum dose (*n*, %)			
70–79 Gy	26	23.2%	
80 Gy	70	62.5%	
81–90 Gy	16	14.3%	
Plug (*n*, %)			
No	99	88.4%	
Yes	13	11.6%	
	Mean ± SE	Range	Median
Trigeminal nerve length	11.2 ± 0.2 mm	6.9–17 mm	11 mm
Trigeminal volume	51.1 ± 2.3 mm^3	7–160 mm^3	48 mm^3
Integral dose	2 ± 0.1 mJ	0.3–6.1 mJ	2 mJ
Trigeminal volume inside 50% isodose	22.5 ± 1.1 mm^3	2–68 mm^3	21.5 mm^3
Integral dose of trigeminal volume inside 50% isodose	1.5 ± 0.1 mJ	0.2–5.4 mJ	1.4 mJ
Distance middle of isocenter—emergence from the brainstem	8.1 ± 0.2 mm	4–12.7 mm	7.9 mm
Ponto-trigeminal angle*	36.5° ± 0.9°	16.3°–58.1°	36.2°
Dose to 10 mm^3 of the brainstem	10.6 ± 0.3 Gy	3.9–23.8 Gy	10.5 Gy
Calibration dose rate	2.2 ± 0.04 Gy/min	1.4–3.3 Gy/min	2.2 Gy/min
Percent of trigeminal volume receiving > 80% of dose	29.7 ± 1.1	1-69,2	29.85
Maximum dose	79.2 ± 0.5 Gy	70–90 Gy	80.1 Gy

* Angle between the brainstem and trigeminal nerve

after treatment was recorded during follow-up according to BNI Facial Numbness Scale.

We mainly focused on two clinical endpoints: long-term good pain control with or without medication among successfully treated patients and postoperative bothersome hypoesthesia onset (BNI score III-IV) in the whole cohort of patients.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics package (IBM Corporation, SPSS Statistics for Macintosh, Version 20, Armonk, NY, USA).

Continuous data was expressed as mean ± standard error (SE) and categorical variables as frequencies/percentages. The variable distribution was analyzed using Kolmogorov-Smirnov test, binominal test, or chi square. Continuous variables were compared adopting the Mann-Whitney *U* test or the Student *t* test. Categorical variables were compared with Pearson's chi square test or the Fisher exact test. Multinominal logistic regression tested variables achieving p value < 0.1.

For long-term pain control, the time-to-event was estimated using the Kaplan-Meier method stratified according to age (≥/< 65 years), previous microsurgery and percutaneous procedures or not, the presence on MRI of neurovascular conflict or not; we tested also the effect of latency of the response (≤/> 10 days, which was the median value in our population) and the entity of initial pain control (BNI I-II versus BNI IIIa-b).

Cox regression analysis was performed to test the relation between long-lasting pain control and patient's anatomic variables (continuous variables). A correlation between TNL, TNV, ID, and ID_{50} was demonstrated [29], A multicollinearity test, thus, was applied and the variance inflation factor (VIF) calculated for TNL, TVL, TNA, and percentage of TNV receiving ≥ 80% of the prescription dose. It resulted being < 1.5, excluding a significant interaction.

Cox regression analysis with a stepwise selection procedure was performed to identify significant covariates among GKRS planning parameters, including D_{max}, IED, ID, and CDR. Because there is a correlation between TNL, TNA, and IED, between TNL and D_{max}, and between ID and D_{max} [4, 29], a multicollinearity was tested by calculating the VIF (< 1.5). Stepwise Cox regression was repeated for testing significant covariates with categorical subdivision (prescription dose > 80 Gy versus dose = 80 Gy and < 80 Gy; CDR ≥ 2.5 Gy/min versus CDR < 2.5; IES ≤ 8 mm versus > 8 mm) also including the use or not of sector blocking.

The ID_{50} was not included in the Cox regression because strongly dependent on the TNV and D_{max} (VIF > 5). We tested a previously published cutoff (2.7 mJ) relative to patients treated at 80 Gy in a selected sub-group of our population.

A probability value < 0.05 was considered indicative of statistical significance or confidence intervals at 95% (CI95%) were reported.

Results

Initial pain control

Six months after GKRS, 89.3% of patients (n = 100) had good pain control with or without medication (BNI I-IIIb) and 84.8% of cases (n = 95) had pain relief (BNI I-IIIa). Moreover, 39 of 112 patients (34.8%) became pain free without therapy (BNI score of I-II). The mean time between radiosurgical treatment and initial pain relief was 35.3 ± 5.2 days. Time to response ranged widely (from 1 up to 180 days) with many cases of early pain relief and some with a very late response. Data distribution was therefore not normal: the 25th, 50th, and 75th percentiles were 2 days, 10 days, and 35 days, respectively.

Long-lasting pain control

The mean follow-up was 61.5 ± 3.5 months (median 58 months, range 12–126 months). The cumulative rate of long-lasting good pain control was 56.2% (C.I. 45.2–67.6%) and 47.7% (C.I. 34.3–61.1%) at 5 and 10 years, respectively. Age older than 65 years (p = 0.24), the absence of any previous invasive treatment (p = 0.59), and the presence of neurovascular conflict (p = 0.41) did not correlate with longer pain control (see Fig. 2). On the other hand, the 5-year cumulative rate of BNI I-IIIb maintenance in 39 cases achieving initial BNI I-II was 74.9% (91.3–58.5%), higher than 42% (57–27%) in 61 cases with initial BNI IIIa-IIIb (p = 0.04). Moreover, the 5-year cumulative rate of BNI I-IIIb maintenance in 49 slow responders was 69.1% (83.9–54.3%), higher than 42% (59.4–24.6%) in 51 fast responders (p = 0.02).

Anatomy-related variables and long-lasting pain control

We did not find any relation between pain recurrence and all continuous variables measured: TNL (p = 0.92, HR 1, IC95%

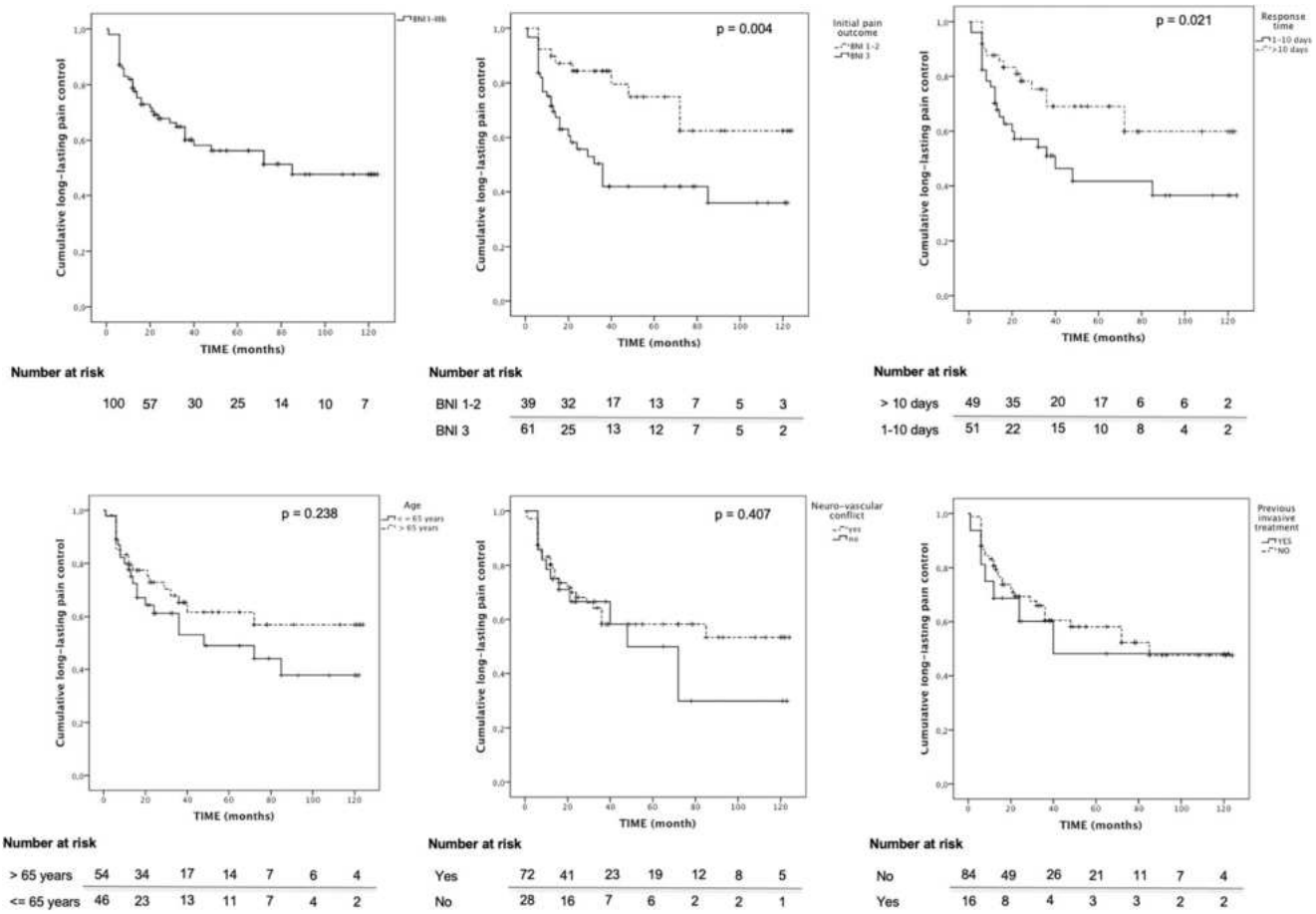

Fig. 2 Kaplan-Meier analysis: cumulative rate of long-lasting pain control considering 40 of 100 patients who fall in BNI IV or V scores during follow-up (pain recurrence). Analysis calculated in the overall population (top left) and in sub-groups according to age > 65 years (p = 0.24), the presence of neurovascular conflict (p = 041), and previous invasive treatments (p = 0.59; bottom from the left to the right). The maintenance of good pain control was longer when initial achievement of BNI I-II scores occurred (p = 0.04; top center) and when the latency between initial response and GKRS treatment was longer than 10 days (p = 0.021; top right).

0.8–1.2), TNA (p = 0.62, HR 1, IC95% 0.9–1.0), TNV (p = 0.96, HR 1, IC95% 0.9–1.0), and TNV receiving 80% of the prescription dose (p = 0.69, HR 1, IC95% 0.9–1).

Planning-related parameters and long-lasting pain control

Factors associated with long-term poor control of pain were the following: D_{max} (negative relation, p = 0.005; HR 0.89, IC95% 0.82–0.97), CDR (negative relation, p = 0.015; HR 0.44, IC95% 0.22–0.86), and IED (positive relation, p = 0.012; HR 1.29, IC95% 1.06–1.60), whereas ID was not significantly related (p = 0.937, HR 0.99, IC95% 0.69–1.4). No significant difference in long-term maintenance of pain relief was found neither in relation to the use of sector block or not, as shown in Table 2 and Fig. 3.

ID_{50} and TNV receiving 80% of D_{max} in a sub-population treated at constant dose

We selected patients treated through D_{max} equal to 80 Gy without sectors blocking in order to define a homogeneous population and thus to avoid any potential influence of the dose. This value was chosen not only because it was the most common but also due to previous publications which reported ID_{50} and TNV analyses referring mainly to prescription dose of 80 Gy (100%). Among 59 successfully treated patients, ID_{50} < 2.7 mJ was predictive of longer pain control (p = 0.043, HR 0.2, IC95% 0.05–0.9) as shown in Fig. 4.

In 66 of 100 patients (66%), treated with different doses, the volume of the trigeminal nerve receiving ≥ 80% of D_{max} was below 35% but there was no significant difference in terms of long-term pain relief between these patients and those whose volume of trigeminal nerve receiving ≥ 80% of the D_{max} was ≥ 35% (p = 0.739, HR 0.9, IC95% 0.4–1.9). On the contrary, a post hoc analysis including only patients treated with a constant dose demonstrated a significant difference (p = 0.034, HR 0.1, IC95% 0.02–1.2) between the two groups when the shot was 8 mm or less from the pons, with better outcome in patients whose small trigeminal volume was irradiated at 80% of the maximal dose (Fig. 4). No difference occurred when the shot was located 8 mm away from the pons or more (p = 0.477, HR 1.4, IC95% 0.5–4).

Table 2 Proportional Hazards Model for long-term poor pain control

Covariates	p	HR	IC95%
Isocenter-emergence distance ≤ 8 mm	< 0.001	0.3	0.1–0.6
Prescription dose < 80 Gy	0.038	3.4	1.2–10.8
Prescription dose = 80 Gy	0.064	2.8	0.9–8.3
Sectors blocking use	0.976	1.0	0.3–3
Calibration dose rate < 2.5 Gy/min	0.018	2.7	1.2–6.3

Factors predictive for good pain control ≥ 5 years

Twenty-five patients obtained a good pain control for 5 years or more. Adopting multinominal logistic regression, the factors resulting predictive for unfavorable pain control (< 5 years) were shot-emergence distance > 8 mm (p = 0.020) and dose < 80 Gy (p = 0.048).

Hypoesthesia

New onset of hypoesthesia during follow-up was recorded in 14 of 103 patients (13.6%) with normal trigeminal function before GKRS.

Severe hypoesthesia (BNI III-IV), as a new occurrence or worsening of a less severe symptom, was recorded in 6 out of 112 patients (5.4%). Table 3 shows possible relations between the incidence of severe hypoesthesia and anatomical parameters, GKRS planning variables, and patient's characteristics. Among 6 patients who developed severe hypoesthesia, the ID_{50} was < 1.4 mJ in 5 patients (83.3%) and between 1.4 and 2.7 mJ in one case (16.7%). The ponto-trigeminal angle proved to be the only significant factor. In particular, the mean angle between trigeminal nerve and pons was 29° ± 4.4° and 37° ± 0.9° in patients who developed severe hypoesthesia and in patients without trigeminal dysfunction, respectively (p = 0.045)

Discussion

In this study, we retrospectively looked at both well-established and widely analyzed variables (i.e., prescription dose, plug use, shot targeting) and recently published parameters related to trigeminal pain relief after GKRS, as ID_{50} and TNV.

We did not find any independent patient's characteristic or anatomy-related parameter predictive for long-lasting pain relief or for post-treatment hypoesthesia, with the exception of an excessive proximity between nerve and brainstem, measured by drawing the ponto-trigeminal angle, that should be kept in mind for the hypoesthesia risk.

Latency and type of initial pain response to GKRS

Tuleasca et al. described three time patterns of pain relief after GKRS for TN: early (≤ 48 h), intermediate (3–30 days), and late (> 30 days). They reported higher incidence of hypoesthesia in the late pattern and association between early pattern and higher pain recurrence crude rate, similarly to our results, showing the association between lower cumulative pain control and both a too early response (less than 10 days) and a suboptimal initial pain control (BNI IIIa and IIIb).

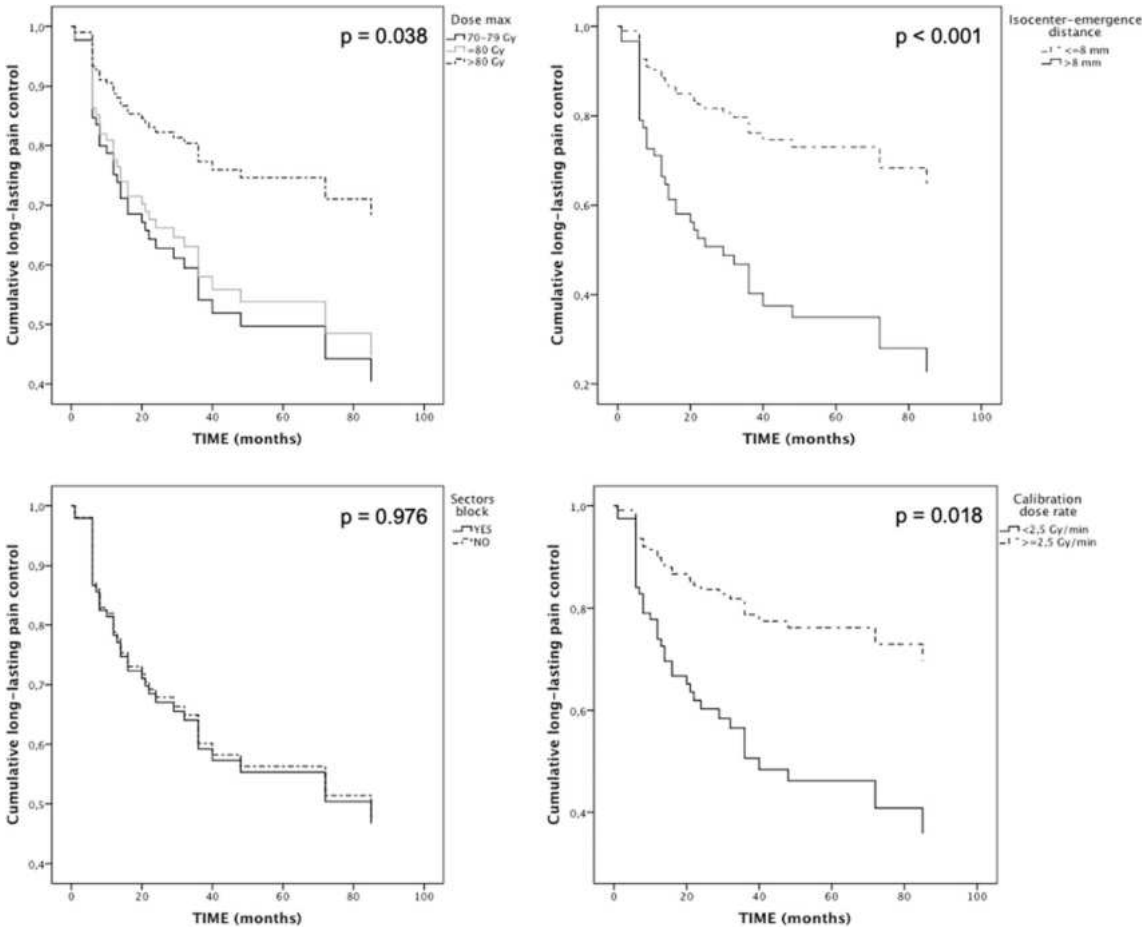

Fig. 3 Cox regression (see Table 2) showed an increased risk of pain recurrence when: the prescription dose was < 80 Gy (D_{max} > 80 Gy vs. < 80Gy $p = 0.038$; > 80 Gy vs. = 80Gy $p = 0.064$), the calibration dose rate was < 2.5 Gy/min (CDR < 2.5 vs ≥ 2.5 Gy/min, $p = 0.018$), and the isocenter-emergence distance > 8 mm (IED ≤ 8 mm vs > 8 mm; $p < 0.001$) adopting retrogasserian target. The sectors block use did not influence the pain recurrence risk ($p = 0.976$).

We can suppose that early and late response may represent two different mechanisms of radiosurgery function. The physiological effect of radiation on nerve is the conduction block; it could lead to a fast pain reduction by

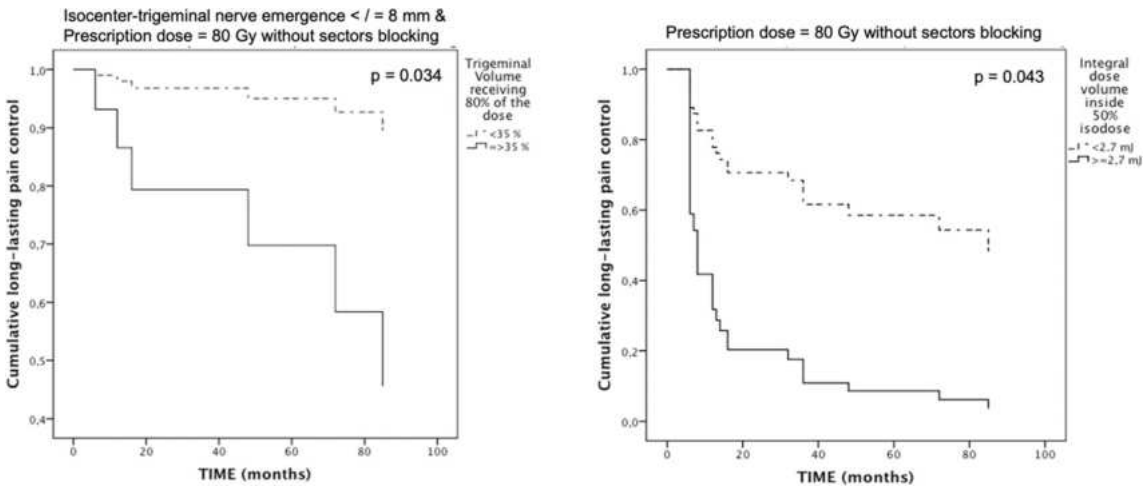

Fig. 4 Cox regression including patients treated with a maximum dose of 80 Gy without sectors blocking. On the left: when the shot was placed 8 mm or less from the pons, the pain relief was longer in patients with a small trigeminal volume receiving ≥ 80% of the dose (< 35%), compared to those with a volume ≥ 35% ($p = 0.034$). On the right: $ID_{50} \geq 2.7$ mJ was predictive of shorter pain control compared to $ID_{50} < 2.7$ mJ ($p = 0.043$)

Table 3 Factors related to severe hypoesthesia onset

	T test *p*	*U* test *p*	Chi square *p*
Trigeminal cisternal length	0.957		
Ponto-trigeminal angle	0.045		
Trigeminal nerve volume	0.129		
Integral dose	0.149		
Integral dose-volume inside 50% isodose	0.204		
Isocenter-emergence distance	0.781		
Prescription dose	0.843		
Dose administered to 10 mm^3 of the brain stem	0.223		
Calibration dose rate	0.543		
Sectors blocking			0.468
Age	0.690		
Presence of neurovascular conflict			0.480
Previous invasive treatment			0.309
BNI I-IIIb after GKRS			0.124
Response time		0.390	

impairing the trigeminal function through the distortion of sodium ion channels function (early response) [13]. An inflammation process probably occurs within the first few days after GKRS; however, it seems to be transient because no persistent inflammatory cells were found at 6 months after GKRS in some case reports with histopathological analysis [19, 39, 46]. What happens later is not clear. We would hypothesize that the subsequent chronic nerve changes (mainly in myelin) work in supporting a modulation or/and a plastic modification of cortical or basal ganglia areas (late response). In other words, focal axonal loss discovered 6 months after GKRS, when clinical benefit is achieved in most of patients, might be the direct local consequence of irradiation, but not the real mechanism related to pain relief. Axons irradiated might change their function and their connectivity with distant brain areas regulating thus neural circuits by activating/inhibiting mechanisms. In reference to patients with TN, modified gray matter volume and cortical thickness were identified in several brain regions involved in pain perception and modulation, in particular in primary and secondary somatosensory areas, in the insula, thalamus, cingulate and orbitofrontal cortex, hippocampus, and amygdala [7, 8, 22, 31, 32], Furthermore, MRI studies focused on white matter analysis of patients with TN reported some abnormalities both in trigeminal nerves and in the central nervous system: posterior corona radiate, corpus callosum, cingulum bundle, and contralateral superior longitudinal fasciculus [6]. Moreover, structural abnormalities at the trigeminal REZ and in the ventral anterior insular cortex reversed toward the level of healthy controls following effective, but not ineffective, neurosurgical treatment (microvascular decompression and GKRS) [9]. Finally, a resting-state functional connectivity analysis between TN patients and healthy control showed that preoperative abnormalities of two fronto-limbic circuits discovered in those affected by TN (left amygdala/left dorsolateral-prefrontal cortex and right amygdala/right prefrontal cortex) improved after an effective treatment [45].

Planning variables

Long-lasting poor pain control was related to low prescription doses (less than 80 Gy), CDR < 2.5 Gy/min, and IED > 8 mm (in case of retrogasserian target), whereas none factor was predictive of hypoesthesia.

Role of the maximal dose and integral dose on long-lasting pain control

The target dose is the most investigated parameter in the medical literature on radiosurgery for TN. Its role, based on animal models, was well established in the early 2000s [19, 46]. A target dose of 60 and 70 Gy can induce very mild nerve damage, consisting of axonal degeneration of few fibers. Nerves receiving 80 Gy showed focal axonal degeneration and, in addition, small foci of necrosis including Schwann cell nuclei. A selective effect among different kinds of fibers, like small myelinated, large myelinated and unmyelinated fibers, has not been detected. Nerves irradiated with 100 Gy showed both extensive demyelination and diffuse axonal loss. These evidences, corroborated by histopathological findings in some patients who suffered from TN and treated by radiosurgery [1, 12, 39], and combined with clinical studies demonstrated

that both pain relief and preservation of sensation were dose related. The lowest described effective dose is 70 Gy and the maximum accepted dose is 90 Gy. On the contrary, higher doses increase the chances of nerve damage and the incidence of postoperative facial sensory loss [11, 18–20, 24].

Axonal injury secondary to GKRS led some authors to assimilate radiosurgery to other ablative surgical techniques. However, the radiobiological mechanism of GKRS remains poorly understood and widely debated. Some authors support, in fact, the idea that GKRS does not work via tissue necrosis. First of all, Flickinger et al. described the "Flickinger's effect" in 2001 [11]. They supposed that clinical benefit was obtained increasing length of the nerve being irradiated but on the contrary they discovered that only the toxicity (expressed as trigeminal nerve dysfunction) increases with the length, whereas no additional effects were reported in terms of pain relief. In addition, several studies as well as our experience demonstrated that trigeminal dysfunction after GKRS was not essential to obtain pain relief, as opposed to initial published clinical series [34, 35, 41]. The low rate of facial hypoesthesia in the majority of successfully treated patients is expression, in fact, of uninjured axons. Furthermore, the beam channel blocking (plug use), increasing the irradiated volume of the nerve and the integral dose, is associated to an increased risk of facial hypoesthesia, and not to a better pain control [27, 28]. Mousavi et al. recently demonstrated that the ideal ID_{50} to achieve the best pain relief with the lowest risk of sensory loss ranges between 1.4 and 2.7 mJ. $ID_{50} > 2.7$ mJ is associated to an increased risk of trigeminal dysfunction and doses < 1.4 mJ or > 2.7 mJ to worse pain outcomes [29]. In other words, GKRS seems to relieve TN by acting on an undefined axon population; this allows for clinical pain relief while not causing diffuse axonal loss. Axonal injury should thus be minimal as shown also by our results demonstrating that $ID_{50} \geq 2.7$ mJ (using a prescription dose of 80 Gy) was a risk factor for pain recurrence. The interpretation of the recent paper of Wolf et al. is similar: they demonstrated that if a small volume of the nerve (< 35%) receives more than 80% of the maximal dose, the pain control is more long-lasting compared to patients with larger volumes of the nerve being irradiated at maximal dose [29]. Referring to our overall cohort of patients, we did not find this relationship, probably due to different doses adopted and shot location. To avoid these confounding factors, we selected only patients treated with the same dose (80 Gy without beam channel blocking) and we divided the population in two groups, according to their IED (≤ 8 mm and > 8 mm): cumulative curves of good pain control were quite similar to those published by Wolf et al. (who adopted root entry zone target, unlike us), only in our group of distance ≤ 8 mm, but not in the group of distance > 8 mm. We can suppose that close to the nerve emergence its section is smaller than more distally, and its fibers more compact; in this region or in the root entry zone (REZ), the volume receiving higher doses may, thus, be different from the retrogasserian distal region and consequently the cutoff.

Finally, more recent studies on MRI-based diffusion tensor imaging (DTI) delineated microstructural changes on cisternal portion, REZ, and pontine segment of trigeminal nerve in affected patients [8, 15, 17, 40]. The significant rise in radial diffusivity and the non-significant modification in axial diffusivity in the target area after GKRS point to changes in myelination as the main contributor of pain effect induced by radiosurgery as opposed to axonal damage (expressed by axial diffusivity) [15, 17].

Role of the nerve targeting on long-lasting pain control

With regard to the role of IED on long-term pain control, we would highlight that our patients were always treated by the retrogasserian target. This is an important limitation because we could not compare the proximal target (close to the REZ) and the distal one. Nevertheless, we demonstrated a relationship between the IED not exceeding 8 mm and long-term pain relief. This relationship was also confirmed in a multivariate analysis. The IED ≤ 8 mm should be kept in mind mainly in specific anatomical conditions, like a long nerve with a small ponto-trigeminal angle, where we can move the shot more anteriorly but not more than 8 mm to maintain a prescription dose ≥ 80 Gy and to gain a safe DVH of the brainstem.

Role of calibration dose rate on long-lasting pain control

Our analysis demonstrated that CDR plays a significant role on long-term pain control. We obtained this result evaluating the dose rate both as a continuous variable and as a categorical variable. The difference was significant when comparing values inferior and superior to 2.5 Gy/min. Balamucki et al. in 2006 and Arai et al. in 2010 concluded that there is no observable effect of dose rate and recommended no adjustment of the maximum dose to treat nerve at different CDR [2, 3]. Lee et al. in 2015 suggested that treatment with a CDR > 2 Gy/min produces an earlier and more long-lasting pain relief with a lower recurrence rate than a CDR of < 2 Gy/min; they analyzed a series of 133 patients treated with the same prescription dose of 80 Gy [21]. A recently published paper analyzing BED and prescription dose concluded that the best safety and efficacy of GKRS for TN might be achieved by prescribing a specific BED and not a common physical dose [42]. They demonstrated that BED is very important in relation to facial sensory loss: increasing the BED the risk of facial hypoesthesia increased exponentially. Furthermore, the authors calculated a range of optimal BED associated to both long-term pain-free incidence of 90% and low risk of hypoesthesia development (< 10%). BED values greater than the threshold were associated to an increased risk of sensory complications and not to a higher probability of pain control.

Our result confirmed the hypothesis that the extent of time during which radiation is delivered, and not only the prescription dose is an important factor. It should, thus, be considered during radiosurgical planning, even if the two variables, time and dose, can only be evaluated appropriately using the concept of BED. The value of 2.5 Gy/min that we found correlated with long-lasting pain control is quite large and higher than the value detected by Lee et al. Further studies will be needed to define an eventual correction of the dose based on CDR. Currently, we can propose a cutoff of 2.5 Gy/min to consider the need for changing the prescription dose, without overlooking anatomical and planning parameters, such us beam channels blocking or ID_{50}. The use of BED in the clinical practice may be difficult, but the reported prescription doses and treatment time combinations required for some Iso-BED (by Tuleasca et al.) should be used to adjust the prescription dose for very low/very high CDR [42].

Study limitations

Limitations of this study include its single-center design, exposing our analysis to bias errors, as aforementioned, concerning the relationship between the shot position and the effectiveness or the hypoesthesia risk. Another potential bias error could exist, due to retrospective selection of patients included in the study. Twenty-three patients were lost at follow-up or the latter was too short and forty cases were excluded because of incomplete availability of data, even if we know their responses, potentially causing both an overestimation and an underestimation of initial and long-lasting pain relief. Unfortunately, we did not prospectively register the latency of pain onset before GKRS in a large amount of our population. We cannot, thus, test this variable in the Cox regression analysis, although it is known as a prognostic factor related to pain control [26, 41].

In light of our experience and data analysis, we could not demonstrate any relationships between factors associated with the risk of severe hypoesthesia, except the narrow angle between trigeminal nerve and brainstem. It is likely that the limited number of cases (6) explains the absence of meaningful statistical analyses in association with a low frequency of sectors block use, a factor that potentially could increase the ID and the toxicity.

Conclusion

This study demonstrated the importance of the patient's anatomy and the role of treatment parameters, such as the physical dose and time of delivery, during GKRS planning to obtain better clinical effects in CTN. The ponto-trigeminal angle analysis might reduce the risk of hypoesthesia and anatomy evaluation indirectly influences both the isocenter location and the prescription dose. Adopting retrogasserian target, the IED $\leq$ 8 mm must be maintained to achieve a longer pain control. More long-lasting pain relief is associated either with doses $\geq$ 80 Gy, as is well known, and CDR $\geq$ 2.5 Gy/min, thus time of delivery or even BED should be considered during the planning. Factors predictive for pain control longer than 5 years were shot-emergence distance $\leq$ 8 mm and dose $\geq$ 80 Gy.

Finally, our results support the hypothesis of two different mechanisms of action in early and late responders by showing an inverse relation between time of response and pain recurrence. Focal demyelination and subsequent repair would be just the chronic and local result of GKRS; the real mechanism involved in pain relief would be a brain white and gray matter plasticity and reorganization, occurring several months after an effective treatment, rather than the small lesion effect. According to this theory, our data demonstrate that a small volume of the nerve have to receive 80% of the D_{max} to obtain a durable pain relief in a selected sub-group of patients (treated through the same dose, 80 unplugged Gy, and IED less than 8 mm). In the same homogeneous sub-population chosen according to the dose, an $ID_{50} \geq 2.7$ mJ was a risk factor for pain recurrence.

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Authors' contributions LRB: conceptualization, methodology, data collection, writing-original draft preparation, and editing; LA: methodology, reviewing, and editing; CS: data collection and reviewing; CRG: data collection and reviewing; ADV: supervision and validation; PM: supervision and validation

Data availability The clinical and planning data will be provided upon reasonable request to the corresponding author.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Code availability The statistical data will be provided upon reasonable request to the corresponding author

Ethics approval All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants involved in the study.

Consent to publication No individual or identifiable information is provided.

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