(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 6 , Page No: 149-154
November-December 2023

IJMSCR

Treatment Outcomes Following Cyberknife Radiosurgery for Refractory Trigeminal Neuralgia.

[1]Marina Amorim[*], [2]Catarina Silva, [3]Maria Adelina Costa, [4]Graça Fonseca, [5]Cármen Calçada, [6]Sofia Ramos, [7]Joana Vale, [8]Ana Cavaco, [9]Pedro Vieira, [10]Paula Genésio, [11]Paulo Costa

[1,2,5,6,11] Radiotherapy Department - Hospital de Braga, Portugal
[3,4,7,8,9,10,11] Júlio Teixeira S.A - CUF Institute, Porto, Portuga

***Corresponding Author:**
Marina Amorim
Radiation Oncologist at Radiation Therapy Department – Hospital de Braga, Portugal

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Introduction: Trigeminal Neuralgia (TN) is a debilitating condition characterized by paroxysmal and lancinating facial pain. Cyberknife® radiosurgery (CKRS) consists of a radiotherapy non-invasive image-guided procedure. Our aim is to evaluate the effectiveness and safety of CKRS for medically and surgically intractable TN.

Materials and methods: We retrospectively evaluated 15 patients with uncontrolled/recurrent TN, submitted to CKRS from March 2016 - June 2021, at our institution. Patients received CKRS with a dose of 70 Gy applied to a median 77% isodose line on the affected trigeminal nerve. Trigeminal pain and hypoesthesia were classified according to the Barrow Neurological Institute (BNI). The pain-free interval was investigated using Kaplan-Meier analysis.

Results: The median age was 68 (44-81) years old. The median follow-up was 36,5 months (4-67). All the patients reported pain relief within the first 3 months after treatment. The majority (62%) were free of antalgic medication (BNI I/II) for a median period of 34 months (1-64 months). In the last follow-up, 38% of the patients reported controlled pain with medication (BNI III) and there were no cases of inadequately controlled or severe pain (BNI IV-V). We observed facial hypoesthesia in 28% of the patients, half of them with bothersome facial numbness (BNI IV).

Conclusion: Frameless image-guided robotic radiosurgery provided excellent pain control rates in the absence of major neurological complications. Even patients with severely debilitating symptoms may experience significant and sustained pain relief after CKRS. Thus, it should be considered a viable alternative to more invasive treatments.

Keywords: Cyberknife, Pain, Robotic, Stereotactic Radiosurgery, Trigeminal Neuralgia

Introduction

Trigeminal Neuralgia (TN) is the most common craniofacial pain syndrome. Medical therapy consists of the first-line treatment option, but effective pain control often requires high doses of drugs, usually associated with severe side effects. Surgery is necessary when drug therapy is deemed ineffective in controlling pain and/or it causes severe side effects(1). In case of a neurovascular conflict, microvascular decompression is indicated (2). Nonetheless, microvascular decompression is not always applicable due to a lack of neurovascular conflict, contraindications for major surgery, or patient preference. In combination with medical management, stereotactic radiosurgery (SRS) has evolved as one of the main treatments for TN. GammaKnife, an isocentric Cobalt radiation unit

(GK)(Elekta, Stockholm Sweden) was the initial radiosurgery method available for providing a highly focused isocentric radiation dose to a small target limited to 4-6 mm along the trigeminal nerve(3,4). The initial treatment dosage proved to be a crucial variable, ranging from 70 Gy to 90 Gy. While 90 Gy exhibited improved pain control, it was also linked to a higher occurrence of numbness(5). Experience has improved through the adoption of alternative radiosurgery systems, such as the non-isocentric robotic arm CyberKnife® (CK) (Accuray, Sunnyvale, California). Earlier reports on CyberKnife radiosurgery (CKRS) for Trigeminal Neuralgia (TN) were all retrospective studies, constrained either by small sample sizes and non-uniform imaging/treatment characteristics, or in the case of multicentric studies, by the absence of standardized protocols regarding patient selection, planning methods, target volumes, or delivered doses. Our purpose is to evaluate the effectiveness and safety of CKRS for medically and surgically intractable TN in a single department.

Materials And Methods

The research comprises individuals who experienced trigeminal neuralgia (TN) characterized by sharp, shooting, electric shock-like pain, with pain-free periods between the episodes. We conducted a retrospective analysis of 15 patients (3 male and 12 female) suffering from medically refractory TN (meaning the condition did not respond to standard medications or other treatments, or the patients declined invasive procedures). These patients underwent radiosurgery using CyberKnife® at our institution between March 2016 and June 2021. Among them, 9 had left-sided TN, 5 had right-sided TN, and 1 had bilateral TN. Before the treatment, a custom-made thermoplastic mask was performed on each patient to immobilize them during the procedure. This was done before conducting high-resolution thin-slice (0.6 mm) computed tomography (CT) scans. The process of treatment planning, which involved defining the target volume, determining the dosage, and optimizing the distribution of the dose, was conducted collaboratively by a team consisting of two physicians - a Radiation Oncologist and a Neurosurgeon - along with the assistance of a Medical Physicist. The treatment target encompasses a segment of the trigeminal nerve, ranging from 4 to 6 millimeters. However, it is important to mention medical centers may choose to extend the treatment target beyond this range. In such cases, they may include an additional 1 to 2 millimeters of the trigeminal root entry zone located in the pons, as part of their treatment approach for patients with TN. This decision is based on individualized considerations and may vary depending on the specific circumstances and expertise of the medical team at each center(6). A 6 mm elongated retrogasserian target was delineated on 3 slices, following the major axis of the trigeminal nerve. To minimize radiation dose with the inverse planning algorithm, critical structures such as the brainstem, gasserian ganglion, 7th and 8th cranial nerves, cochlea, and nearby vessels were specifically outlined. Additionally, other critical volumes such as the eyes, lenses, and optic chiasm were also delineated to avoid incident beams passing through them. A treatment plan was established using a fixed collimator with a 5 mm diameter, defined at Source-to-Axis Distance (SAD) of 800 mm. Dose constraints for the brainstem were set as follows: a volume equal to or smaller than 1 cm^3 could receive a dose of 15 Gy, with a maximum point dose (0.035 cm^3) not exceeding 30% of the prescription dose. For the gasserian ganglion, a mean dose below 20 Gy and a maximum point dose below 35 Gy were deemed acceptable. The maximum doses allowed for the cranial nerves and acoustic apparatus were 6 Gy and 4 Gy, respectively. The prescription dose for the treatment was 70 Gy delivered in a single fraction, prescribed to the 80-90% isodose line. To ensure accuracy during treatment, live images were acquired at a frequency of 30-45 seconds for all patients, reducing intrafraction inaccuracy. On average, the treatment delivery process took approximately 45-50 minutes. CKRS treatment plan is represented in Figure 1. The Barrow Neurologic Institute (BNI) scale is used to assess pain in TN(7). This scale categorizes patients from 0 to V based on the degree of pain and use of medication both before and after treatment. Results are classified as excellent or good when falling within the BNI 0-III range, indicating either no pain or mild/ intermittent pain that is controlled with medication. Post-procedure follow-up results are also evaluated on the same BNI scale. In this study, the effectiveness of the pain response following Stereotactic Radiosurgery was categorized as favorable when patients indicated BNI pain scores I-III, and as insufficient when they

Volume 6, Issue 6; November-December 2023; Page No 149-154

reported scores of IV-V. Similarly, clinically not significant or bothersome hypoesthesia was defined as BNI grades I-II and III-IV, respectively. The pain-free interval was assessed using Kaplan-Meier analysis, and statistical analysis was performed using IBM SPSS (Version 25.0). A p-value ≤ 0.05 was considered statistically significant.

Results

The median age was 68 years old, ranging from 44 to 81 years. Before radiosurgery, all patients experienced uncontrolled or recurrent pain despite medication. The most commonly prescribed antalgic drugs for pain management were carbamazepine and pregabalin. One patient had TN secondary to multiple sclerosis. One patient had been previously submitted to surgery (microvascular decompression) and one patient had previously undergone CKRS one year before, with a dose of 70 Gy delivered in a single fraction. Before undergoing Stereotactic Radiosurgery (SRS), all patients were classified as BNI class V, indicating severe pain with no relief from medication. The pain was localized on the right side in 35% of the patients and on the left side in 65%. The patients received CKRS with a prescribed dose of 70 Gy, delivered to the affected trigeminal nerve at a median isodose line of 77% (ranging from 57% to 85%). The median target volume was 0.08 cm^3 (ranging from 0.05 cm^3 to 0.21 cm^3). The median normalized conformation index (nCI) was 1.83 (ranging from 1.34 to 2.71). Median follow-up was 36,5 (4-67) months. Pain relief at 6, 12, 24, 36, 48 and ≥60 months was respectively 93%; 93%; 67%; 47%; 13% and 13%. The median time until pain relief was 2 (ranging from 1 to 3) months after radiosurgery. The median pain-free interval was 34 months (ranging from 1 to 64). In the last follow-up, 62% were free of antalgic medication (BNI I/II); 38% of the patients reported controlled pain with medication (BNI III). We haven't observed cases of inadequately controlled or severe pain (BNI IV-V). Figure 2 shows pain control over time after CKRS treatment. We evaluated hypoesthesia outcomes following the procedure. In the last follow-up, 72% of the patients did not experience facial hypoesthesia. However, 28% of the patients developed facial hypoesthesia, half of them (14%) reporting bothersome hypoesthesia classified as Grade IV on the BNI scale. In this present series, no additional complications were reported, such as temporal lobe radionecrosis, lockjaw, weakness of the mandible, diplopia or hearing loss.

Discussion

TN is an entity that is occasionally treated with radiotherapy, typically reserved for cases that are refractory to medical and surgical treatment(8). To our knowledge, there are some retrospective studies described in the literature, and there are no prospective trials due to the rarity of these events (1,3–6,8–15). Fifteen patients with refractory TN were treated with CKRS at our institution, a robotic image-guided linear accelerator that provides non-isocentric beam delivery, allowing for a homogeneous dose distribution across an extended segment of the trigeminal nerve. Clinical outcomes were evaluated over a median of 36.5 months post-treatment. The pain relief rate six months to one year after the procedure was 93%, with 47% and 13% of patients experiencing sustained benefit (BNI class I-III) at three and five years after treatment, respectively. 14% reported Grade IV hypoesthesia. In 2016, Jean Régis and his team conducted a study to evaluate frame-based radiosurgery Gamma Knife surgery (GKS) as a treatment option for 497 patients with medically refractory TN who had not previously received this technique. They prescribed a higher-than-usual median dose of 85 Gy (ranging from 70 to 90 Gy). The median follow-up period was 43.8 months (ranging from 12 to 174.4 months). 91.75% were pain-free within a median time of 10 days (ranging from 1 to 180 days). The actuarial probabilities of remaining pain-free without medication at 3, 5, 7, and 10 years were 71.8%, 64.9%, 59.7%, and 45.3%, respectively. Regarding the hypesthesia rate, it was 20.4% at 5 years and increased to 21.1% at 7 years. Three patients (0.6%) reported bothersome facial hypesthesia.(9) Subsequently, articles emerged in the literature about the treatment of TN with a frameless non-isocentric stereotactic radiotherapy approach. In 2019, Romanelli and colleagues published a study on the clinical outcomes of 527 patients with refractory TN who underwent CKRS with a dose of 60 Gy. The pain relief rates at 6, 12, 18, 24, 30, and 36 months were 92%, 87%, 87%, 82%, 78%, and 76%, respectively. During the observed period, 12.8% of the patients required a second treatment. At 36 months post-treatment, 21 patients (6.1%) reported bothersome facial hypoesthesia, 18 of whom (85.7%)

Volume 6, Issue 6; November-December 2023; Page No 149-154

developed this complication after re-treatment (12). In 2020, Alfredo Conti and colleagues evaluated the outcomes of 262 patients submitted to CKRS with a prescription median maximal dose of 72.4 Gy. Pain control rates (BNI I-III) at 6, 12, 24, 36, 48, and 60 months were 96.8%, 90.9%, 84.2%, 81.4%, 74.2%, and 71.2%, respectively. 18% of the patients experienced sensory disturbances after treatment. Although the retrospective design and the lack of prolonged follow-up, patients with a treatment volume ≥ 30mm3 were more likely to maintain pain relief ($p = 0.031$) (13). Most of the reported studies depict multi-institutional results, with hundreds of treated patients. We believe that the pain control rate in our study was slightly lower than described in the literature, especially after the 2nd year, due to the small sample size. Future work will allow us to establish the relationship between the dose received by the trigeminal nerve and clinical outcomes, specifically cumulative doses after retreatments.

Conclusion

SRS is emerging as a valid treatment option for TN. Frameless image-guided robotic radiosurgery in experienced hands provides excellent pain control rates in the absence of major neurological complications. Even patients with severely debilitating symptoms may experience significant and sustained pain relief after CKRS. It should be considered as a viable alternative to more invasive treatments. As part of our future perspectives, we plan to enlarge our patient cohort and evaluate the impact of robotic radiosurgery on quality of life. Further studies involving a larger number of patients will be necessary, and ideally, despite the challenges posed by the rarity of the condition, prospective trials should be conducted to validate this treatment approach.

Acknowledgments: We acknowledge all the medical staff and patients who participated in this study.

Conflicts of interest: The authors have nothing to disclose.

Ethical approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

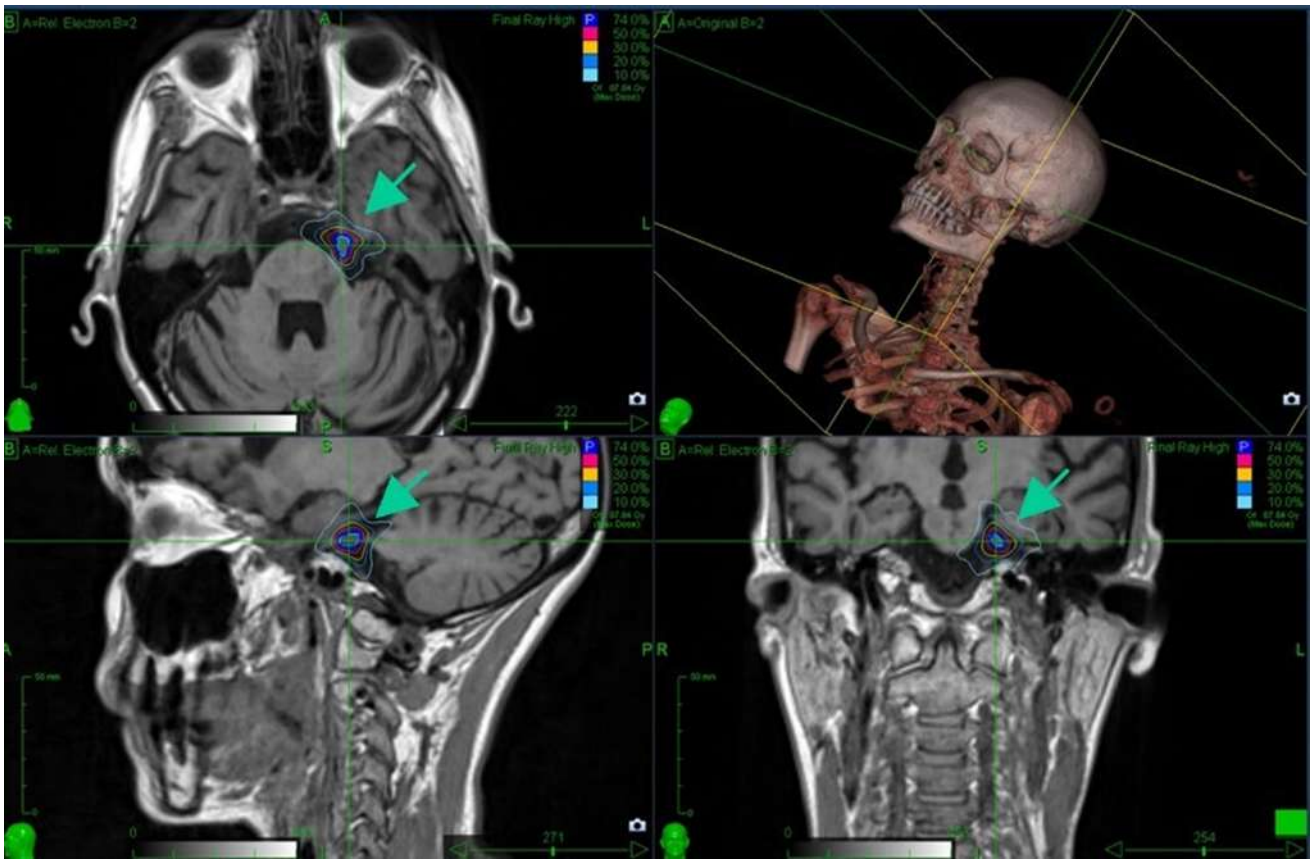
References

1. Bennetto L, Patel NK, Fuller G. Trigeminal neuralgia and its management. BMJ 2007; 334(7586):201.
2. Tomasello F, Esposito F, Abbritti R V., Angileri FF, Conti A, Cardali SM, et al. Microvascular Decompression for Trigeminal Neuralgia: Technical Refinement for Complication Avoidance. World Neurosurg 2016; 94:26–31.
3. Verheul JB, Hanssens PEJ, Lie S Te, Leenstra S, Piersma H, Beute GN. Gamma Knife surgery for trigeminal neuralgia: a review of 450 consecutive cases. J Neurosurg 2010; 113:160–7.
4. Singh R, Davis J, Sharma S. Stereotactic Radiosurgery for Trigeminal Neuralgia: A Retrospective Multi-Institutional Examination of Treatment Outcomes. Cureus 2016; 8(4).
5. Dhople AA, Adams JR, Maggio WW, Naqvi SA, Regine WF, Kwok Y. Longterm outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: Implications of treatment and critical review of the literature. J Neurosurg 2009; 111(2):351–8.
6. Berti A, Ibars G, Wu X, Sabo A, Granville M, Suarez G, et al. Evaluation of CyberKnife Radiosurgery for Recurrent Trigeminal Neuralgia. Cureus. 2018; 10(5):e2598.
7. Rogers CL, Shetter AG, Fiedler JA, Smith KA, Han PP, Speiser BL. Gamma knife radiosurgery for trigeminal neuralgia: The initial experience of the Barrow Neurological Institute. Int J Radiat Oncol Biol Phys. 2000; 47(4):1013–9.
8. Lazzara BM, Ortiz O, Bordia R, Witten MR, Haas JA, Katz AJ, et al. Cyberknife radiosurgery in treating trigeminal neuralgia. J Neurointerv Surg 2013; 5(1):81–5.
9. Regis J, Tuleasca C, Resseguier N, Carron R, Donnet A, Gaudart J, et al. Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. J Neurosurg 2016; 124(4):1079–87.
10. Mousavi SH, Niranjan A, Huang MJ, Laghari FJ, Shin SS, Mindlin JL, et al. Early radiosurgery provides superior pain relief for

Volume 6, Issue 6; November-December 2023; Page No 149-154

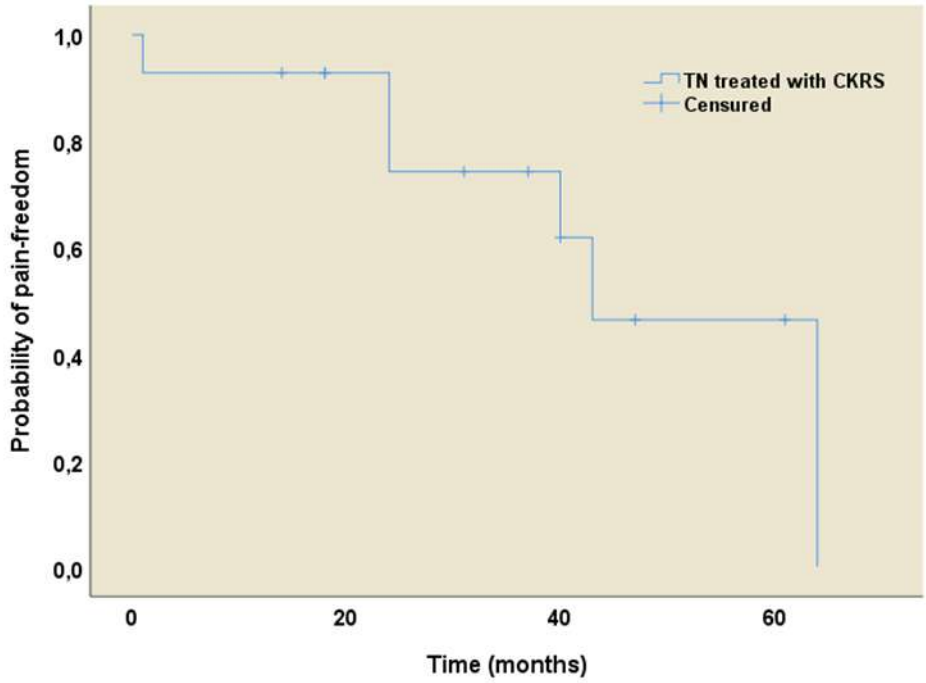
trigeminal neuralgia patients. Neurology 2015; 85(24):2159–65.
11. Karam SD, Tai A, Snider JW, Bhatia S, Bedrick EJ, Rashid A, et al. Refractory trigeminal neuralgia treatment outcomes following CyberKnife radiosurgery. Radiat Oncol 2014; 9:257.
12. Romanelli P, Conti A, Redaelli I, Martinotti AS, Bergantin A, Bianchi LC, et al. Cyberknife Radiosurgery for Trigeminal Neuralgia. Cureus 2019; 11(10):e6014.
13. Conti A, Acker G, Pontoriero A, Hardt J, Kluge A, Cacciola A, et al. Factors affecting outcome in frameless non-isocentric stereotactic radiosurgery for trigeminal neuralgia: A multicentric cohort study. Radiat Oncol 2020; 15(1):115.
14. Sudahar H, Kurup PGG, Murali V, Velmurugan J. Dosimetric analysis of trigeminal nerve, brain stem doses in CyberKnife radiosurgery of trigeminal neuralgia. J Med Phys 2012; 37(3):124–8.
15. Karam SD, Tai A, Snider JW, Bhatia S, Bedrick EJ, Rashid A, et al. Refractory trigeminal neuralgia treatment outcomes following CyberKnife radiosurgery. Radiat Oncol 2014; 9:257.

Figure 1. Cyberknife® treatment plan and isodose curves. The green arrow indicates the target treatment volume.



Volume 6, Issue 6; November-December 2023; Page No 149-154

Figure 2. Pain relief Kaplan Meier curve.



Volume 6, Issue 6; November-December 2023; Page No 149-154