


Original Article

Repeat CyberKnife Radiosurgery for Trigeminal Neuralgia: Outcomes and Complications

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ABSTRACT: Background: CyberKnife radiosurgery (RS), as an initial first treatment, is recognized as an efficient and safe modality for trigeminal neuralgia (TN). However, knowledge on repeat CyberKnife RS in refractory cases is limited. The objective was to evaluate the clinical outcomes of repeat CyberKnife RS for TN. **Methods:** A retrospective review of 33 patients with refractory TN treated a second time with CyberKnife RS from 2009 to 2021. The median follow-up period after the second RS was 26.0 months (range 0.3–115.8). The median dose for the repeat RS was 60 Gy (range 60.0–70.0). Pain relief after the intervention was assessed using the Barrow Neurological Institute scale for pain (I–V). Scores I to IIIb were classified as an adequate pain relief and scores IV–V were classified as a treatment failure. **Results:** After the second RS, initial adequate pain relief was achieved in 87.9% of cases. The actuarial probabilities of maintaining an adequate pain relief at 6, 12, 24, and 36 months were 92.1%, 74.0%, 58.2%, and 58.2%, respectively. Regarding sustained pain relief, there was no significant difference between the first and the second RS. Sensory toxicity after the first RS was predictive of a better outcome following the second RS. The onset of hypesthesia rate was the same after the first or the second RS (21%). **Conclusion:** Repeat RS is an effective and safe method for the treatment of refractory TN.

RÉSUMÉ : Les reprises du traitement de la névralgie du trijumeau par la radiochirurgie au cyberbistouri : résultats et complications.

Contexte : La radiochirurgie au cyberbistouri en traitement initial de la névralgie du trijumeau est reconnue comme une intervention sûre et efficace. Toutefois, on en sait peu sur les reprises de radiochirurgie au cyberbistouri dans les cas de névralgie réfractaire. L'étude ici présentée avait donc pour but d'évaluer les résultats cliniques des reprises de radiochirurgie au cyberbistouri dans les cas de névralgie du trijumeau. **Méthode :** Il s'agit d'un examen rétrospectif de dossiers de 33 patients souffrant d'une névralgie réfractaire du trijumeau, traitée une seconde fois par la radiochirurgie au cyberbistouri, de 2009 à 2021. La durée médiane du suivi après la deuxième intervention de radiochirurgie était de 26,0 mois (plage : 0,3-115,8), et la dose médiane de rayonnement pour les reprises de radiochirurgie, de 60 Gy (plage : 60,0-70,0). Le soulagement de la douleur après l'intervention a été quantifié selon l'échelle d'évaluation de la douleur du Barrow Neurological Institute (BNI) (I-V) : les niveaux de I à IIIb sont considérés comme un soulagement satisfaisant de la douleur, et les niveaux IV et V, comme un échec du traitement. **Résultats :** Un soulagement initial efficace de la douleur après la seconde intervention de radiochirurgie a été obtenu dans 87,9 % des cas. Les probabilités actuarielles de persistance d'un soulagement satisfaisant de la douleur au bout de 6, 12, 24 et 36 mois s'établissaient à 92,1 %, 74,0 %, 58,2 % et 58,2 %, respectivement. Quant au soulagement durable de la douleur, il n'y avait pas d'écart significatif entre la première et la seconde intervention de radiochirurgie. Pour ce qui est de la toxicité sensorielle après la première intervention de radiochirurgie, elle était prédictive d'un meilleur résultat après la seconde intervention. Enfin, le taux d'apparition d'hypoesthésie était le même après la première ou la seconde intervention de radiochirurgie (21 %). **Conclusion :** Les reprises de radiochirurgie s'avèrent un moyen sûr et efficace du soulagement de la névralgie réfractaire du trijumeau.

Keywords: Cyberknife; Repeat radiosurgery; Trigeminal neuralgia

(Received 2 September 2022; final revisions submitted 21 April 2023; date of acceptance 26 April 2023; First Published online 8 May 2023)

Introduction

Trigeminal neuralgia (TN) is the most severe and debilitating craniofacial pain with an incidence between 12.6 and 26.9 per

100 000.¹ According to the *International Classification of Headache Disorders-3*, TN is “a disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination,

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Cite this article: Guillemette A, Roberge D, Heymann S, Ménard C, Bahary J-P, and Fournier-Gosselin M-P. (2024) Repeat CyberKnife Radiosurgery for Trigeminal Neuralgia: Outcomes and Complications. *The Canadian Journal of Neurological Sciences* 51: 272–277, <https://doi.org/10.1017/cjn.2023.52>

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limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli".² The most widely accepted theory regarding the pathophysiology supports a neurovascular compression.³ TN can also be a symptomatic presentation of another disease such as multiple sclerosis (MS).² However, in many cases, the exact etiology is uncertain, and these cases are deemed idiopathic.

When the first line of treatment (pharmacological) is ineffective or associated with intolerable toxicity, more invasive approaches may be indicated such as percutaneous rhizotomy (PR), microvascular decompression (MVD), and radiosurgery (RS).⁴

RS consists of delivering highly targeted radiation to the cisternal portion of the trigeminal nerve. Most of the clinical experience and literature regarding RS treatment for refractory TN is based on Gamma Knife radiosurgery (GKRS), a technique that delivers a spherical or near-spherical radiation dose (Gamma Knife [Elekta, Stockholm, Sweden]).⁵ However, it is possible to use other radiosurgical techniques. Indeed, the CyberKnife (Accuray Inc., Sunnyvale, CA), a robotic and frameless technique can be used, and it allows the delivery of a customized non-spherical dose to an anatomically defined target.

Many large retrospective cohort studies have already been published supporting the efficacy and safety of GKRS. For example, in a cohort of 503 patients treated by GKRS, the actuarial probabilities of maintaining adequate pain relief at 12, 36, and 60 months were 80%, 71%, and 46%, respectively. Furthermore, this study demonstrated that 10.5 % of patients had a new or an increase in their facial sensitive dysfunction.⁶ Even though there is less literature specifically dedicated to CKRS, available studies do support its efficacy and safety. In a cohort of 262 patients, reported actuarial adequate pain control rates at 12, 36, and 60 months were 90.9%, 81.4%, and 71.2%, respectively.⁷ In a cohort of 496 patients with adequate follow-up, the rates of pain relief at 6, 12, 24 and, 36 months were 92%, 87%, 82%, and 76%, respectively. The onset of facial sensitive dysfunction was 20.1%.⁸

Although initial pain relief rates are high, up to half of patients will eventually experience recurrence of pain. For these patients, RS retreatment can be offered, especially when their first RS treatment was effective over an adequate period and/or when comorbidities preclude more invasive surgical treatments. The aim of this study is to evaluate CKRS, as a repeat RS treatment for patients with highly refractory TN.

Clinical knowledge of RS retreatment is not as extensive as for initial RS treatments. A limited number of systematic reviews and retrospective series report relevant findings.^{9–11} As with initial RS for TN, only a limited number of studies report CKRS in the setting of re-treatment.^{7,11}

The aims of this present study are: 1) to evaluate the efficacy of repeat CKRS on pain relief; 2) to compare the efficacy of repeat CKRS with the efficacy of initial RS treatment; 3) to identify potential predictive factors for the efficacy of a repeat CKRS; and 4) to evaluate the safety of repeat CKRS.

Methods

Patients' selection

The approval of our institutional ethics review board was obtained for this retrospective chart study. The inclusion criteria were as follows: (1) diagnosed medically refractory TN and (2) repeat RS performed at our institution. Thirty-three patients treated with a repeat CKRS at the Centre Hospitalier de l'Université de Montréal (CHUM) from 2009 to 2021 met these inclusion criteria. Of these

Table 1: Clinical and demographic data

Characteristic	Cases (% ^a)
Total number of cases:	33
Sex:	
Male	10 (30.3)
Female	23 (69.7)
Median age in years at first RS (range):	61 (42–88)
Median duration of symptoms in months before first RS (range):	72.0 (11–292)
Median interval in months between RS #1 and RS #2 (range):	31.6 (7.7–179.5)
Side of pain:	
Right	18 (54.5)
Left	14 (42.4)
Bilat	1 (3.0)
Pain distribution over the 3 branches of the V cranial nerve:	
V1	1 (3.0)
V2	4 (12.1)
V3	15 (45.5)
V1 + V2	1 (3.0)
V1 + V3	0 (0.0)
V2 + V3	8 (24.3)
V1 + V2 + V3	4 (12.1)
Classification of pain ^b :	
Idiopathic-TN1	14 (42.4)
Idiopathic-TN2	2 (6.1)
Symptomatic ^c	16 (48.5)
Neuropathic	1 (3.0)
Postherpetic	0 (0.0)
Etiology:	
Idiopathic	16 (48.5)
Multiple sclerosis	15 (45.5)
Other ^d	2 (6.1)
Vascular compression	7 (21.2)
Prior surgery:	
Percutaneous rhizotomy (PR)	2 (6.1)
Microvascular decompression (MVD)	0 (0.0)
Pre-RS hypesthesia (BNI numbness scale ^e):	a) RS # 1: b) RS # 2:
I	29 (87.9) 27 (81.8)
II	4 (12.1) 6 (18.2)
III	0 (0.0) 0 (0.0)
IV	0 (0.0) 0 (0.0)
Median maximal dose in Gy (range)	80 (70.0–85.0) 60 (60.0–70.0)

^a(%) is the number of cases in each category over the total number of cases (33).

^bAccording to the classification proposed by Eller et al. (2005).¹²

^cIncludes MS and infarct cases.

^dIncludes infarct and neuropathic cases.

^eBNI numbness scale: Barrow Neurological Institute facial hypesthesia scale.

33 cases, 9 had GKRS as their first treatment at a different institution, and 24 had CKRS as a first treatment at our institution.

Cases characteristics

Table 1 summarizes demographic and preoperative clinical data. Amongst the 33 cases, 10 (30.3%) were male and 23 (69.7%) were female; the median age was 61 years (range 42–88 years); the median duration of symptoms before their first RS was 72.0 months (range 11–292 months). The pain was left sided in 42.4%, right sided in 54.5%, and bilateral in 3.0%. The pain was most commonly limited to the V3 division of the trigeminal nerve

Table 2: Clinical outcomes following radiosurgery

Outcome	Cases (% ^a)	
	a) RS #1	b) RS #2
Median follow-up in months (range):	85.4 (12.0–192.0 ^b)	26.0 (0.3–115.8)
Median time (days) from RS to onset of adequate relief (range):	16 (0–202)	61 (0–221)
Failure of RS (BNI IV–V) after an adequate initial pain relief (BNI I–IIIb response) was obtained:	33 (100)	9 (27.3)
Median time (months) from adequate initial pain relief (BNI I–IIIb response) to failure of RS (range):	13.6 (4.0–170.6)	8.7 (3.1–13.3)

BNI: Barrow Neurological Institute pain intensity scale.

^aUnless otherwise indicated, (%) is the percentage of cases over the total number of cases (33).

^bFollow-up period longer than our study duration (2009–2021) is explained by patients having received prior GKRS at another institution before being treated for a repeat CKRS at our institution.

(45.5%), followed by V2V3 (24.3%), V1V2V3 or V2 (12.1%), and V1 or V1V2 (3.0%). The cases were idiopathic in 48.5%, followed by MS associated in 45.5%, and other etiologies in 6.1%. A TN1 pain presentation was among 42.4% of the cases and 7.0% had a TN2 presentation. MRI highlighted a vascular compression in 21.2%.

Details of previous surgery and prior facial hypesthesia

Prior to their first RS, 6.1% had had a PR. Facial hypesthesia was assessed with the Barrow Neurological Institute (BNI) scale. Before their first RS, 87.9% had no facial numbness (score of I), 12.1% had mild facial numbness that is not bothersome (score of II), none had somewhat bothersome facial numbness (score of III), and none had very bothersome facial numbness (score of IV)(11). Before their second CKRS, 81.8% had no facial numbness (score of I), and 18.2% had mild facial numbness that is not bothersome (score of II).

Dose selection and target planning

CKRS treatment was performed using CyberKnife G4 (2009–2012), VSI (2012–2017), or M6 (2017–2021) systems (Accuray Inc., Sunnyvale, USA). CT (high-resolution, slice thickness: 1 mm) and MRI (3D MPRAGE, T2-weighted) datasets were co-registered for treatment planning. Plans were optimized on the MultiPlan or Precision (Accuray Inc.) platforms. The location of the target was alongside the cisternal portion of the trigeminal nerve and precautions were made to minimize radiations on critical structures (e.g., brainstem, temporal lobe, and optic nerves). The median maximal dose of the first RS was 80.0 Gy (70.0–85.5 Gy), and the median maximal dose of the repeat CKRS was 60.0 Gy (60.0–70.0 Gy).

Statistical analysis and outcome measures

In order to evaluate facial pain, the BNI scale for pain (I–V) was employed. This scale is characterized as I – no trigeminal pain, no medications; II – occasional facial pain, not requiring medication; IIIa – no pain, continued medication; IIIb – persistent pain, controlled with medications; IV – some pain, not adequately controlled with medication; and V – severe pain/no pain relief. Adequate pain relief was obtained when the BNI score was I to IIIb, and treatment failure occurred when the BNI score was IV or V.¹³

The maintenance of pain relief and time to event were estimated using the Kaplan–Meier method. The event was the

treatment failure (BNI IV–V) and the patients were right-censored if they had adequate pain relief at their last follow-up. The comparison of maintenance of pain relief between groups was assessed using the log-rank method and it was also used to find potential predictive factors of efficacy. Univariate cox proportional hazards model was also used to evaluate potential predictive factors of efficacy for continuous covariables. The potential predictive factors evaluated were chosen based upon a previous systematic review.⁹

All statistical analyses were conducted using the open-source software Jamovi (The jamovi project [2021]. jamovi [Version 1.6] [Computer Software]. Retrieved from <https://www.jamovi.org>). The results were considered significant when *P* values were less than 0.05.

Results

Follow-up period and initial adequate pain relief

Table 2 shows the follow-up period and initial adequate pain relief rates after each RS. The median follow-up period was 85.4 months (range 12.0–192.2 months).

After the first RS, 100% had adequate pain relief; the median latency period before the onset of the pain relief was 16 days (range 0–202 days).

After the second RS, 87.9% had adequate pain relief; the median latency period before the onset of the pain relief was 61 days (range 0–221 days).

Treatment failure, recurrence of TN (BNI IV–V), and additional treatments

Table 2 shows recurrence rates of TN and additional treatment.

After the first RS, failure of pain relief occurred after a median of 13.6 months (range 4.0–170.6 months). Two patients (6.1%) had a PR before their second RS.

After the second RS, 27.3% of all cases had a failure after an adequate pain relief was reached, in a median time of 8.7 months (range 3.1–13.3 months). 39.4% of cases had a PR after their second RS for cases without any pain relief (12.1%) or with a failure of pain relief (27.3%).

Maintenance of adequate pain relief after RS

Figure 1 demonstrates the Kaplan–Meier curves for the maintenance of pain relief after each RS treatment. After the first RS, actuarial probabilities of maintaining pain relief at 6, 12, 24, and 36

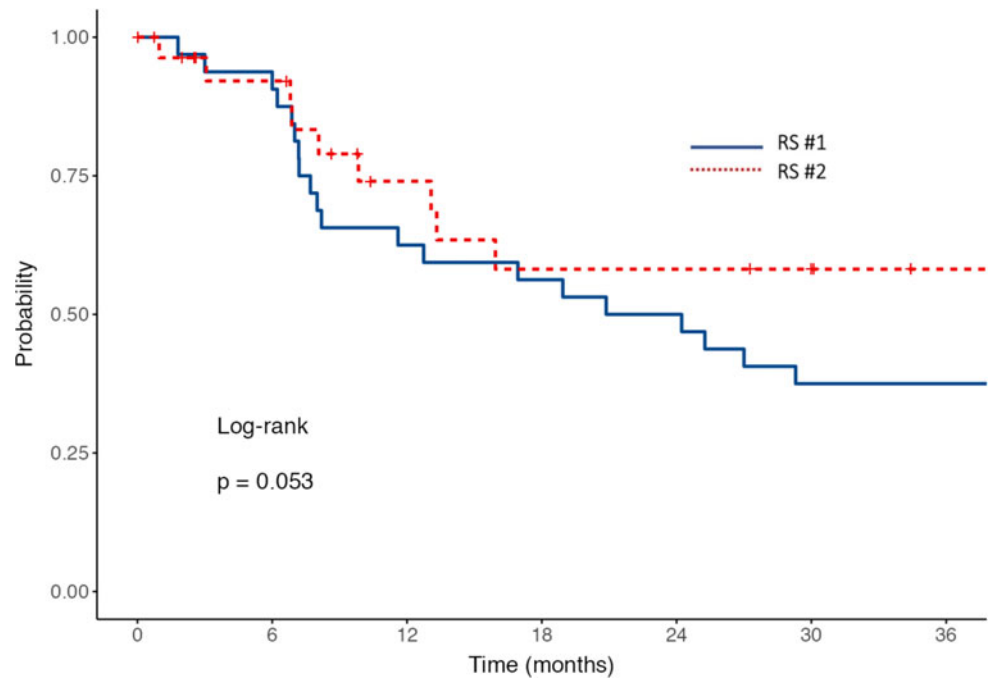


Figure 1: Kaplan-Meier survival curves for the maintaining of adequate pain relief after both RS treatments

Table 3: Clinical complications after radiosurgery

Complications:	Cases (% ^a)	
	a) RS #1	b) RS #2
Hypoesthesia onset/aggravation after RS (BNI numbness scale ^b):		
II	7 (21.2)	7 (21.2)
III	0 (0.0)	1 (3.0)
IV /anesthesia dolorosa	0 (0.0)	0 (0.0)
Facial spasm	1 (3.0)	0 (0.0)
Diminution of the corneal reflex	1 (3.0)	2 (6.1)
Keratitis/dry eye	0 (0.0)	1 (3.0)
Tinnitus	0 (0.0)	0 (0.0)
Facial motor deficit and TMJ ^c dysfunction	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)

^a(%) is the number of cases in each category over the total number of cases (33).

^bBNI numbness scale: Barrow Neurological Institute facial hypesthesia scale.

^cTMJ: Temporomandibular joint.

months were 90.6%, 62.5%, 50.0%, and 37.5%, respectively. After the second RS, actuarial probabilities of maintaining pain relief at 6, 12, 24, and 36 months were 92.1%, 74.0%, 58.2%, and 58.2%, respectively.

Maintenance of pain relief comparison between each RS treatment

Log-rank comparison between the first RS and the second RS treatment in group 2 was not significant ($P = 0.053$).

Predictive factors of the outcome for the repeat CKRS

The statistical difference was not significant for: pain relief duration after the first RS (HR: 0.98; 95% CI: 0.94–1.02; $P = 0.300$),

for patients with an idiopathic etiology (HR: 0.37; 95% CI: 0.05–3.04; $P = 0.356$), or with a MS-related etiology (HR: 1.82; 95% CI: 0.37–9.08; $P = 0.667$). There was a significant statistical difference for the hypesthesia onset/aggravation after the first RS ($P = 0.042$) as a predictor of efficacy for the repeat CKRS in the univariate log-rank comparison.

Clinical complications after RS

Table 3 shows the clinical complications after the RS treatments. After the first RS, seven cases (21.2 %) had a mild new onset or an aggravation of their facial numbness that is not bothersome (II). Other complications were present such as one case of facial spasm, one case of diminution of the corneal reflex, and one case of facial motor deficit/TMJ dysfunction. After the second RS, seven cases (21.2%) had a new onset or an aggravation of their facial hypesthesia. Of those cases, six cases (18.2%) had mild facial bothersome facial numbness (III). Other complications were present such as diminution of the corneal reflex in three cases, and Keratitis/dry eye in one case.

Discussion

In cases where TN is highly refractory to both the pharmacological and the initial radiosurgical approach, three treatment methods are usually available to patients depending on their clinical characteristics: PR (balloon compression, radiofrequency thermocoagulation, and glycerol lesioning), MVD, and repeat RS. The main objective was to assess the effectiveness, the safety, and the predictive factors of a repeat CKRS.

In this retrospective study, there were no significant differences between the efficacy of the first and the second treatment. Initial adequate pain relief was 87.9% and actuarial probabilities of maintenance of pain relief at 6, 12, 24, and 36 months were 92.1%, 74.0%, 58.2%, and 58.2%, respectively. The initial pain relief rate is similar to the rates available in other studies while the maintenance

of pain relief rates seems to be similar at 6 months but lower over time.^{7,9,10,14} However, the results need to be interpreted by taking into consideration that we have a larger proportion of MS cases (45.5%) in comparison to other studies where there was an absence or a smaller proportion of MS cases. Indeed, it is reported that in MS-related cases, long-term pain relief is significantly worse in comparison to idiopathic cases. It is also reported that for the MS-related cases treated twice, 46% experienced a freedom from recurrence at 5 years while it was at 75% for the idiopathic cases.¹⁵ Another study reports that MS-related cases appear to affect the durability of pain relief in their univariate analysis but not in their multivariate analysis.¹⁴ Further research is needed for this population in order to assess the efficacy and safety of repeat RS.

In this retrospective study, hypesthesia onset or aggravation after the first or the second RS was identical (21.2 %). The onset of hypesthesia rate seems to be lower than what can be found in other studies.^{9,10} Furthermore, because the rates of hypesthesia are similar after the first and second RS, the relation between re-irradiation and the occurrence of sensory disturbance is not supported by the current results, although this relation was supported in another study.⁷

In this retrospective study, only one factor was identified as a significant predictors of efficacy for the second RS. Indeed, the onset of hypesthesia after a first RS was predictive of a better outcome for the retreatment and it is consistent with what is reported in other studies.^{14,16–18} The duration of the pain relief after the first RS was not significant as a predictive factor, whereas it was significant in another previous cohort analysis.¹⁹ The etiology of the cases was also not statistically significant as a predictor of the outcome in the univariate analysis. The question remains on the importance of the etiology on the pain relief after a repeat RS, and further research is needed to ascertain its true impact on the clinical outcomes.^{14,15}

Many clinical retrospective trials support the utilization of repeat GKRS because of its efficacy and safety.^{9,10,14} In a systematic review comparing GKRS with MVD, it is reported that 83% of patients that underwent a repeat GKRS, as a salvage therapy, had an adequate pain relief 1 year after their treatment. These authors also reported, in their institutional retrospective study of 198 patients, adequate pain relief rates at 3, 6, 12, and 24 months of 93 %, 87 %, 80 %, and 67%, respectively. One year after the treatment, the facial numbness rate was 46.6%.¹⁰

In a systematic review, it is reported that the initial pain cessation rates were similar to those observed after a first GKRS. In this systematic review, the initial pain relief rate was 88% and the recurrences rates of pain varied between 5.3 and 32% in a median duration of 24 months. The maintenance of adequate pain relief rate, at 5 years, varied between 44.2% and 72.7%. The median rate for the onset of hypesthesia after the treatment was 33%, which is higher than the rates after a first GKRS treatment (6%–54%). Interestingly, hypesthesia onset was also a predictor of a better outcome. Other complications were also noted such as bothersome hypesthesia (16%), corneal numbness (11%), dry eye (10.9%), taste changes (8.7%), jaw weakness (4%), and anesthesia dolorosa.^{9,20–23} In a retrospective cohort study, authors reported that 84% of patients had an initial adequate pain relief. They also reported actuarial rates of adequate pain relief at 1, 3, and 5 years of 74%, 59%, and 46%, respectively. They also identified predictive factors for pain relief such as facial numbness after the first GKRS, and a positive pain response to the initial GKRS treatment.¹⁴

Only few studies reported results in regard to CKRS as salvage therapy after an initial RS failure.^{7,8,11} A series of 23 patients was

published but because of the limited sample size and numerous patients lost to follow-up, statistical evaluation was impossible to perform. However, this study reported that with patients with an available follow-up, 2–3 years of pain relief was obtained.¹¹ In a multicentric cohort study of CKRS cases (34 repeat treatments), reported actuarial adequate pain control rates for retreatment at 6, 12, 24, and 36 months were 91.2%, 88.1%, 88.1%, and 88.1%, respectively. No significant difference between the efficacy of a first or a second treatment was identified. Re-irradiation was a predictor in the apparition of bothersome hypesthesia in the univariate and multivariate analyses.⁷

Limitations

The population in this study is heterogeneous (idiopathic and MS cases) which limits the generalization and comparison of the findings in this study.

This study is also one of the largest on CKRS retreatment, but the total numbers of patients is still low (33 patients), which limits the analysis on different levels. For example, it prevents the use of a multivariate analysis to identify potential predictive factors.

Because of the single institution retrospective nature of this study, a selection bias is to be expected for this clinical review.

At our institution, clinical decision making to evaluate potential candidates for the repeat RS may differ than what is realized elsewhere. In our center, only patients with optimal outcomes after the first RS are considered for a repeat RS. In other centers, patients without pain relief after the first RS are sometimes considered for a repeat RS.

Also, it is common practice to wait at least 12 months before delivering another RS treatment. The reasoning behind this cautious approach is based on the latency period to achieve pain relief that varies from immediate to up to 6 months after RS (average of about six weeks), and the biphasic response experienced for some patients after RS.²⁴

However, in the literature, some studies offer a retreatment after a shorter period. In a systematic review, the median time reported between two RS was 17 months (range 3–146 months).⁹

At our institution, the median duration between the two RS is 31.6 months. Only four cases were retreated before 12 months (11.7 months, 11.2 months, 9.5 months, and 7.7 months). The clinical decision making for these particular cases was based on their initial optimal pain relief followed by recurrence with limited therapeutic options. It was deemed acceptable to offer earlier second RS in exceptional situations.

It is important to consider that these factors limit the generalization of these findings to a larger clinical setting because the clinical decision making may vary between different centers.

Conclusion

The present study is in line with the previous literature in terms of the efficacy and safety for CKRS retreatment in refractory TN. In this series of 33 patients, the profile of efficacy and safety of repeat CKRS for TN is similar to after a first RS treatment. There was no statistical difference between the duration of pain relief or occurrence of hypesthesia after first RS or the second CKRS. The onset or the aggravation of hypesthesia after the first RS was the only predictor of a better outcome after the second CKRS.

Acknowledgement. We gratefully thank the PREMIER-CRCHUM committee for their research grant.

Statement of Authorship. AG and MPFG designed the study. AG, DR, CM, JPB, SH, and MPFG collected the data for the study. AG, DR, and MPFG wrote the initial manuscript. All authors provided feedback during the writing process.

Disclosures. Under the supervision of MPFG, AG received a research grant from the Université de Montréal for this project. DR reports travel support from Accuray. The authors have no other relevant disclosures or conflicts of interest.

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