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# Predictors of Trigeminal Neuropathy after Radiosurgery for Vestibular Schwannomas

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None

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**Summary ( 74 words) :**

The incidence of trigeminal neuropathy after vestibular schwannomas (VS) radiosurgery (RS) varies between 0 and 29 % across series probably due to the lack of Vth nerve dedicated guidelines.

Retrospective multivariate analyses on 179 patients showed that the volume of the cisternal portion of the Vth nerve receiving at least 11Gy, volume of the cisternal Vth nerve and maximal dose to the Vth nerve nucleus and intra-axial portion should be precisely restricted when designing dosimetry for VS RS.

**Abstract (287 words):****Objectives :**

The incidence of trigeminal neuropathy (TN) after vestibular schwannomas (VS) radiosurgery (RS) varies between 0 and 29 % across recent series. The lack of detailed guidelines regarding dosimetry in order to avoid TN after VS RS may account for it. The primary objective of this study is to analyze relationship between dosimetrical characteristics and symptoms related to TN observed after RS.

Secondary objectives are to propose guidelines to optimize planification in VS RS regarding trigeminal nerve preservation and to precise the mechanism of trigeminal nerve impairment after VS RS.

**Methods and Materials :**

One hundred and seventy nine patients treated between 2011 and 2013 for VS RS and without trigeminal impairment before RS were included in a retrospective study. Univariate and multivariate analysis were performed in order to determine predictors of TN among characteristics of the patients, the dosimetry and the VS.

**Results :**

There were 20 grade I, 99 grade II, 57 grade III and 3 grade IV KOOS.

Fourteen patients (7.8%) presented a transitory or permanent TN.

Between the patients with and without TN after VS RS, there was no significant

difference regarding dosimetry or VS volume itself. Significant differences (univariate analysis  $p < 0.05$ , Mann-Whitney test) were found for parameters related to cisternal portion of the trigeminal nerve: total integrated dose, maximum dose, mean dose, volume of the Vth nerve ( $Vol_v$ ), volume of the Vth nerve receiving at least 11Gy ( $Vol_{V_{cist>11Gy}}$ ) but also for maximal dose to the Vth nerve nucleus and intra-axial portion ( $Dose\ max_{V_{ax}}$ ). After multivariate analysis, the best model predicting TN included:  $Vol_{V_{cist>11Gy}}$  ( $p=0.0045$ ),  $Dose\ max_{V_{ax}}$  ( $p=0,0006$ ) and  $Vol_v$ . ( $p=0.0058$ ). The negative predictive value of this model was 97%.

### **Conclusions :**

$Vol_{V_{cist>11Gy}}$ ,  $Dose\ max_{V_{ax}}$  and  $Vol_v$  should be checked when designing dosimetry for VS RS.

## INTRODUCTION

Radiosurgery (RS) for selected vestibular schwannoma (VS) is a recognized alternative to microsurgery (MS) (1-11). For selected VS, RS should be at least as efficient and as safe as MS. Studies have focused mainly on facial nerve preservation since it may be impaired in up to 27% of cases of MS (12). Yet, any adverse radiation event (ARE) should be minimized for the patient's sake and for justifying the use of RS vs MS.

Trigeminal neuropathy (TN) following MS is estimated to occur in less than 2 % of cases (13). This is low compared to facial nerve neuropathy post MS. Yet the incidence of TN after VS radiosurgery varies between 0 and 29 % across series (14-22). The lack of detailed guidelines focusing on dosimetry in order to avoid TN after VS radiosurgery may account for this. A recent study proposing a volume and dosimetric analysis in order to predict non auditory adverse radiation effects following radiosurgery found VS volume and maximum dose to the Vth nerve to be significant predictors of TN, with a threshold of 9 Gy (19). But this study did not focus on TN and several dosimetric parameters which may be relevant both for predicting occurrence of TN and understanding its mechanism were not included. Moreover, an earlier study for which higher treatment doses than today were used, concluded that the pons-petrous length of the TN was the best predictor of TN. Finally the volumes of VS treated by gamma knife radiosurgery tend to increase in the series reported (23-25). So predictors of TN after VS radiosurgery should be assessed with actual treatment doses and sizes of treated VS, and the underlying mechanism should be investigated using the more detailed dosimetry planning software that now exist. For

instance, the total integrated dose on organs at risk, or volume of tissue receiving 12Gy or more, have been shown to be critical for complications after radiosurgery for various conditions (26, 27).

The primary objective of this study was to identify predictors of TN after radiosurgery for VS. Secondary objectives were to propose guidelines regarding dosimetry in order to avoid TN, and to specify the mechanisms by which TN may occur after radiosurgery for VS.

## **MATERIAL & METHODS**

### **1. Patients**

Between 2011 and 2013, 179 patients presenting without TN before radiosurgery were treated by GK for vestibular schwannoma and were included in this retrospective study. They all completed at least 20 months of clinical and radiological follow-up, scheduled at 1, 6 and 12 months post radiosurgery, and then annually.

### **2. Analysis variables**



The patient variables included: age, gender, body mass index, diabetes, hypertension, thrombosis, hypercholesterolemia, chronic inflammatory disease, cancer, migraine, antiagregant or anticoagulant treatment.

The dosimetric variables regarding the cisternal portion of the trigeminal nerve included: pons-petrous length and volume of the trigeminal nerve, integrated, maximum, minimum, mean doses received by the trigeminal nerve. Several parameters were expressing volume of a given organ-at-risk receiving specific doses (6, 8, 10, 11, 12 Gy) as determined by dose-volume histogram.

The dosimetric variables regarding the estimated intra-axial portion of the trigeminal nerve included: volume, maximum, minimum, mean doses received, volumes receiving at least 10, 11, 12, 13 Gy.

The estimated intra-axial portion of the trigeminal nerve was 1) thought to be smaller than the volume of the cerebral trunk, which is usually used in studies as a gross estimation of the intra-axial portion of the trigeminal nerve, in order to increase sensitivity and specificity of this parameter, 2) drawn large enough in order to include the intra-axial portion of the Vth nerve and its somatosensory nucleus.

The region of interest (ROI) was defined by using a combination of anatomical landmarks (28, 29, 30) and individual anatomical analysis in magnetic resonance imaging studies. In the absence of registration between the anatomical and imaging data, these limits were large enough to ensure the reliability of the method. The ROI was centered on intra-axial path of the trigeminal nerve visible on an axial plane of the pons.

- The medial boundary was traced by a straight line connecting a ventral point, medial to the emergence of the trigeminal nerve and a dorsal point medial to the abducens nucleus in the floor of the fourth ventricle.
- The lateral boundary, parallel to the previous one, was traced rostrally from the cerebellopontine junction.

Among the internal structures, it included rostrocaudally the following structures: the pontocerebellar fibers (Pcb), the lateral Lemniscus (ll), the spinothalamic tract of the pons (stp), the motor nucleus of the trigeminal nerve (Mo5), the mesencephalic nucleus (Me5) and caudally the principal sensory nucleus of the of the trigeminal nerve, the tegmental central tract (ctg ), the dorsal trigeminal tract (d5), the medial longitudinal tract (MLF) and the dorsal longitudinal fasciculus (dlf) and caudally the abducens nucleus.

All the contours were drawn by SS, resident, and CAV, senior neurosurgeon.

Dosimetric variables regarding the VS included: volume, maximum diameter parallel to the petrous bone, integrated, maximum, minimum, mean doses received, number of shots, gradient PIV25/PIV50, conformity, selectivity and Paddick indexes.

### **3. Dosimetry**

Dosimetry was designed with Gammaplan software. RS was performed using a Leksell frame and an Elekta Gamma-knife. The prescribed dose at the 50% isodose was 12 Gy except for cases with useful hearing when a slightly lower dose (min 11 Gy) could achieve hearing preservation.

Treatments were co-defined on both stereotactic CT and stereotactic contrast enhanced MRI. Sequences were 1.5-mm section T1 co-registered with FIESTA

(Figure 1). After delineation of the tumor and organs at risk (OAR), dosimetry was carried out, taking into account selectivity, coverage, gradient index, maximum doses to OAR.

#### **4. Trigeminal neuropathy post radiosurgery**

At each out-patient clinic, patients were asked for subjective signs of TN that were transitory or still present. Objective signs that were looked for were facial hypoesthesia, paresthesia or pain. Dates of beginning, end and evolution of these clinical signs were recorded. BNI facial numbness scale was used (31).

#### **5. Statistical analysis**

Descriptive statistics used means and ranges, or medians and ranges, for quantitative variables, and numbers and percentages for qualitative variables.

Predictors of post radiosurgery TN were assessed by a univariate analysis with Mann-Whitney tests for quantitative variables and with chi2 tests or Fisher's exact tests for qualitative variables. Multiple comparisons were addressed by a Bonferoni protection.

A predictive risk of post radiosurgery trigeminal neuropathy was determined using a multivariate logistic model. Variable selection was based upon a cross-validation controlled lasso logistic regression, in order to take into account correlations between potential predictors. The final multidimensional logistic predictive model was based on the selected variables which were entered in a stepwise forward model-building

procedure. The volume and the size of the lesion, two variables described elsewhere as predictive, were added to all tested models.

The model discrimination power was described by a ROC curve and the model calibration was assessed by Hosmer and Lemeshow method, that is a plot of predicted and observed proportions of neuropathy in each estimated decile of risk. Point estimate and 95% confidence interval of the area under the ROC curve were based on Unrestricted Random Sampling bootstrap. All computations were carried out using macros R and the SAS V9.3 statistical package.

## RESULTS

### 1. Sample characteristics (Supplementary Table 1)

89 (49.8%) women and 90 (50.2%) men were included. Mean age at treatment was 62 years (range, 17-87).

There were 20 (11.2%) grade I, 99 (55.3%) grade II, 57 (31.8%) grade III, 3 (1.7%) grade IV Koos.

There were 19 (11.4%) grade I, 65 (38.9%) grade II, 47 (28.1%) grade III, 22 (13.2%) grade IV and 14 (8.4%) grade V GR.

Mean and median tumor diameters were respectively 12 and 12.3 mm (range 3.7-25.2 mm). Mean and median tumor volumes were respectively 1092 and 922 mm<sup>3</sup> (range, 63.2-6460 mm<sup>3</sup>).

Median follow-up was 31.9 months (range 20-48 months).

Control rate was 93.3 % (41.3 % VS size decrease on last MRI, 52% VS size stability on last MRI, 6.7% VS size increase on last MRI). T2 signal changes were seen in the brainstem in two cases, but none of them developed TN.

## **2. Trigeminal neuropathy post radiosurgery (Table 1)**

TN developed in 14 patients (7.8 %) after radiosurgery for VS.

It was transitory in 7 (50%) cases, and permanent in 7 (50%) cases.

For transitory cases, it started 6.3 months (range, 1-13) and ended 13.8 months (range, 12-17) after RS. Median duration of symptoms was 7 months. There were respectively 1 (14.3%), 4 (57.1%), 2 (28.6%) cases of hypoesthesia, paresthesia or pain.

For permanent cases, it started 4.5 months (range, 1-6) after RS. There were respectively 5 (71.4%), 1 (14.3%), 1 (14.3%) cases of hypoesthesia, paresthesia or pain respectively. The median of last check-up time and duration of symptoms were respectively 38 months after radiosurgery, and 34 months. The patients with hypoesthesia did not receive any treatment. The patients with paresthesia and pain were treated respectively by laroxyll and rivotril, with a mild efficacy for the first one, and a fair efficacy for the latest one.

Using BNI facial numbness scale, among transitory cases, there were 5 cases with score 2 (71.4%), 2 cases with score 3 (28.6%), and among permanent cases, there were 5 cases with score 2 (71.4%) and 2 cases with score 3 (28.6%).

There were 151 patients for whom VS was not impinging on the root entry zone : they developed 10 TN, so 6.6% of these cases. Among the 28 patients for whom VS was impinging on the root entry zone, 4 TN occurred, i.e. in 14.2% of these cases.

### **3. Predictors of trigeminal neuropathy post radiosurgery according to univariate analysis**

On univariate analyses, several variables were predictors of TN after radiosurgery for vestibular schwannoma, including inflammatory diseases, and cancers (Table 2).

No variable related to the treated schwannoma itself was a predictor of TN. Vascular accidents or common cardiovascular risk factors were not predictors either.

After Bonferoni correction for multiple comparisons, only volume of the cisternal portion of the Vth nerve receiving at least 12 Gy remained a significant predictor of TN after radiosurgery for vestibular schwannoma.

### **4. Predictors of trigeminal neuropathy post radiosurgery according to multivariate analysis**

Multivariate analysis provided a model including three variables, in addition to volume and size of the lesion : volume of the cisternal portion of the Vth nerve receiving at least 11 Gy ( $Vol_{V_{cist>11Gy}}$ ) ( $p= 0.0045$ ), maximum dose on the Vth nerve nucleus and Vth nerve-intraxial portion ( $Dose\ max_{V_{ax}}$ ) ( $p=0.0006$ ) and volume of the cisternal portion of the nerve ( $Vol_v$ ) ( $p=0.0058$ ) (Table 3).

The p-value of the Hosmer and Lemeshow test is 0.78, which corresponds to good model fit.

According to the results showed on Table 3, we can compute the probability of occurrence of TN by the logistic model.

The ROC curve is displayed in figure 2. Its AUC is 0.89. We obtained 0.89 (0.80-0.97) as bootstrap point and 95% confidence interval estimates for this AUC. An optimal threshold was computed by maximization of the (Sensitivity + Specificity) criterion. The optimal threshold score value is -2.3. With this threshold, the diagnostic parameters values are: Sensitivity = 0.714, specificity = 0.867, positive predictive value = 0.313, negative predictive value = 0.973.

## DISCUSSION

After multivariate analysis on a series of 179 patients, we were able to determine the three most relevant predictors of TN after radiosurgery for VS: volume of the cisternal portion of the Vth nerve receiving at least 11 Gy, maximum dose on a “region at risk” including both the Vth nerve nucleus and the intra-axial portion of the Vth nerve and volume of the cisternal portion of the Vth nerve.

Our model offers a negative predictive value as high as 0.97. Dose the cisternal portion of the Vth nerve should receive on a limited volume is 11 Gy. This dose is in the range of doses usually considered to be deleterious for cranial nerves in general (19, 21, 2, 16).

TN after radiosurgery for VS was rather low (7.4%) in our series including 1.7% grade IV Koos schwannomas. More precisely, the rate of permanent neuropathy was

3.9 %. Moreover, there is a current trend to treat larger VS with radiosurgery. So these new guidelines with high negative predictive value may be helpful for clinicians.

To our knowledge no study has ever focused on studying predictors of TN alone after radiosurgery for VS. Other non-auditory complications of radiosurgery have been reported in previous papers. But these studies did not consider the analysed variables we included, focusing on potential mechanisms of TN after radiosurgery. In addition, some of the previous studies were carried out at a time when prescribed doses were higher, dosimetry planning software did not enable all the computations we could perform in this study, and neuroimaging did not enable proper visualisation of the Vth nerve (32, 16). The Vth nerve is thicker than the VIIth or VIIIth nerve: for this reason, considering only maximal dose on the Vth nerve may not have been as relevant as for the other nerves. That is why we decided to study not only the length of the nerve, but also the volume of the Vth nerve, as suggested by Linskey (32). What is more, the Integrated dose represents the whole dose delivered to a certain amount of tissue. Measurement of this parameter is available on dosimetric software and has been successfully linked to hearing outcome after radiosurgery for VS (26). For a thick nerve such as the Vth, a moderate dose delivered to huge amount of tissue may be as deleterious as a high dose to a limited portion of a thin nerve. As a matter of fact, we delineated the cisternal portion of the Vth nerve on FIESTA sequences, and we found this volume and a parameter linked to both integrated dose and to volume of an organ at risk receiving this dose, i.e. the volume of the cisternal Vth nerve receiving at least 11 Gy, to be significantly linked to occurrence of TN in multivariate analysis. On the contrary, maximum dose was not correlated with TN.



The Vth nerve, because of its structure, may therefore behave as an organ at risk organized in a parallel structure and not in a serial structure.

In addition, central myelin of the intra-axial portion of the trigeminal nerve is followed by peripheral myelin surrounding the cisternal portion of the trigeminal nerve.

Respective radiosensitivity of these structures may differ significantly.

With current MRI sequences, an exact segmentation of the Vth nucleus and its intra-axial portion is impossible. Previous studies (19, 2) have therefore considered dose delivery on the whole brainstem. With current prescription doses, it has not been possible to highlight a possible relationship between occurrence of TN and dose to the brainstem. One possible explanation may be that using a too large volume, including the Vth nerve nucleus and the Vth nerve intra-axial portion, may decrease sensitivity. We successfully decided to restrict our computations to a smaller volume of interest still including the Vth nerve nucleus and the Vth nerve intra-axial portion according to histological atlases in order to better illustrate the deleterious effect of radiation on these structures.

Unlike other studies (17-19), we did not find a significant relationship between size or volume of the lesion and risk of Vth nerve neuropathy. This discrepancy may have been due to anatomical considerations such as cisternal size, distance between schwannomas and Vth nerve or brainstem and the fact that our study is the one with the smallest average and median tumor volumes published in the literature dealing with TN. The dose delivered to the cisternal Vth nerve is probably not only correlated to the prescribed dose to the tumor and to the tumoral volume : the surface of the « contact » nerve-tumor may also be an important factor, as suggested by Linskey et

al (32). No study ever proposed a parameter quantifying distance between schwannomas and a given organ at risk.

Our results may provide clues about structures and mechanisms involved in the TN after radiosurgery for VS. Acute interruption of neuronal fibers *per se* may not be the most important mechanism, since the median delay between treatment and occurrence of neuropathy was relatively short. On the other hand, a vascular mechanism may be involved. That is why our study considered the possible role of the general medical history of patients in the occurrence of TN after gamma knife radiosurgery for VS. Classic cardiovascular risk factors were not found to be significant predictors of TN according to univariate analysis, but patients with such factors were treated with antiagregants or anticoagulants. Nevertheless, histories of cancer or inflammatory vascularitis were shown to be significant predictors of TN according to univariate analysis. This may indicate a vascular component in the mechanism of occurrence of TN after radiosurgery for VS. This is in agreement with the hypotheses formulated by Linskey et al. in 1993 and animal experimentations (33-35): segmental demyelination and ischemic neuropathy may be crucial. The influence of individual genetic radiosensitivity on occurrence of TN could not be assessed in our study. What is more, another mechanism for TN to occur post VS radiosurgery could be decompensation of physical compression of the trigeminal nerve by the VS. But only 14.2% of cases where VS was impinging on the root entry zone developed trigeminal neuropathy.

Limitations of the study are low number of patients with TN after radiosurgery for VS, poor visualization of the intra-cisternal portion of the Vth nerve in grade III-IV VS

where it is compressed along the brainstem by the tumor and impossible precise segmentation of the Vth nerve nucleus and the Vth nerve intra-axial portion.

Development of very high field MRI sequences for anatomical imaging and diffusion weighted imaging with tractography reconstruction might be of interest to study the role of radiations on the intra-axial portions and nuclei of various cranial nerves.

Moreover, model discrimination power could not be validated by splitting the sample into a training and testing set because of the limited number of cases.

## **CONCLUSION**

The volume of the cisternal portion of the Vth nerve receiving at least 11 Gy, the volume of the cisternal portion of the Vth, and the maximum dose on the Vth nerve nucleus and the intra-axial portion of the Vth nerve, as defined in our study, are good predictors and indicators of possible mechanisms of TN after radiosurgery for VS.

They should be taken into account in dosimetry guidelines for radiosurgery when treating VS.

## **REFERENCES**

- 1 : Flickinger JC, Kondziolka D, Niranjan A, et al. Results of acoustic neuroma radiosurgery: An analysis of 5 years' experience using current methods. *J Neurosurg* 2001;94:1–6
- 2 : Foote KD, Friedman WA, Buatti JM, et al. Analysis of risk factors associated with radiosurgery for vestibular schwannoma. *J Neurosurg* 2001;95:440–449.
- 3 : Ito K, Shin M, Matsuzaki M, et al. Risk factors for neurological complications after acoustic neurinoma radiosurgery: Refinement from further experiences. *Int J Radiat Oncol Biol Phys* 2000;48:75–80.
- 4 : Kobayashi T, Tanaka T, Kida Y. The early effects of gamma knife on 40 cases of acoustic neurinoma. *Acta Neurochir Suppl* 1994;62:93–97.
- 5 : Lunsford LD, Niranjan A, Flickinger JC, et al. Radiosurgery of vestibular schwannomas: Summary of experience in 829 cases. *J Neurosurg* 2005;102(Suppl.):195–199.
- 6 : Miller RC, Foote RL, Coffey RJ, et al. Decrease in cranial nerve complications after radiosurgery for acoustic neuromas: A prospective study of dose and volume. *Int J Radiat Oncol Biol Phys* 1999;43:305–311.
- 7 : Noren G, Greitz D, Hirsch A, et al. Gamma knife surgery in acoustic tumours. *Acta Neurochir Suppl (Wien)* 1993;58:104–107.

8 : Prasad D, Steiner M, Steiner L. Gamma surgery for vestibular schwannoma. *J Neurosurg* 2000;92:745–759.

9 : Spiegelmann R, Gofman J, Alezra D, et al. Radiosurgery for acoustic neurinomas (vestibular schwannomas). *Isr Med Assoc J* 1999;1:8–13.

10 : Spiegelmann R, Lidar Z, Gofman J, et al. Linear accelerator radiosurgery for vestibular schwannoma. *J Neurosurg* 2001;94: 7–13.

11 : Valentino V, Raimondi AJ. Tumour response and morphological changes of acoustic neurinomas after radiosurgery. *Acta Neurochir (Wien)* 1995;133:157–163.

12 : Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): the facial nerve—preservation and restitution of function. *Neurosurgery* 1997;40:684–694. Discussion 694–685.

13 : Ansari SF, Terry C, Cohen-Gadol AA. Surgery for vestibular schwannomas: a systematic review of complications by approach. *Neurosurg Focus*. 2012;33(3):E14.

14 : Chopra R, Kondziolka D, Niranjan A, et al. Long-term follow-up of acoustic schwannoma radiosurgery with marginal tumor doses of 12 to 13 Gy. *Int J Radiat Oncol Biol Phys* 2007;68:845–851.

15 : Flickinger JC, Lunsford LD, Linskey ME, et al. Gamma knife radiosurgery for acoustic tumors: Multivariate analysis of four year results. *Radiother Oncol* 1993;27:91–98.

16 : Flickinger JC, Kondziolka D, Lunsford LD. Dose and diameter relationships for facial, trigeminal, and acoustic neuropathies following acoustic neuroma radiosurgery. *Radiother Oncol* 1996;41:215–219.

17 :Flickinger JC, Kondziolka D, Niranjan A, et al. Acoustic neuroma radiosurgery with marginal tumor doses of 12 to 13 Gy. *Int J Radiat Oncol Biol Phys* 2004;60:225–230.

18 : Friedman WA, Bradshaw P, Myers A, et al. Linear accelerator radiosurgery for vestibular schwannomas. *J Neurosurg* 2006; 105:657–661.

19 : Hayhurst C, Monsalves E, Bernstein M et al. Predicting non auditory adverse radiation effects following radiosurgery for vestibular schwannoma : a volume and dosimetric analysis. *Int. J. Radiation Oncology Biol. Phys.* 2012 ; 82(5):2041–2046.

20 : Lobato-Polo J, Kondziolka D, Zorro O, et al. Gamma knife radiosurgery in younger patients with vestibular schwannomas. *Neurosurgery* 2009;65:294–300. discussion 300–291.

21 : Regis J, Metellus P, Hayashi M, et al. Prospective controlled trial of gamma knife surgery for essential trigeminal neuralgia. *J Neurosurg* 2006;104:913–924.

22 : Sughrue ME, Yang I, Han SJ, et al. Non-audiofacial morbidity after gamma knife surgery for vestibular schwannoma. *Neurosurg Focus* 2009;27:E4.

23 : Williams BJ, Xu Z, Salvetti DJ, et al. Gamma Knife surgery for large vestibular schwannomas: a single-center retrospective case-matched comparison assessing the effect of lesion size. *J Neurosurg*. 2013 Aug;119(2):463-71.

24 : Zeiler FA, Bigder M, Kaufmann A, et al. Gamma knife radiosurgery for large vestibular schwannomas: a Canadian experience. *Can J Neurol Sci*. 2013 ;40(3):342-7.

25 : Inoue HK. Low-dose radiosurgery for large vestibular schwannomas: long-term results of functional preservation. *J Neurosurg*. 2013 Dec;119 Suppl:111-3.

26 : Massager N, Nissim O, Delbrouck C, et al. Irradiation of cochlear structures during vestibular schwannoma radiosurgery and associated hearing outcome. *J Neurosurg*. 2007 Oct;107(4):733-9.

27 : Flickinger JC, Kondziolka D, Lunsford LD, et al. Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. Arteriovenous Malformation Radiosurgery Study Group. *Int J Radiat Oncol Biol Phys*. 2000 Mar 15;46(5):1143-8.

- 28 : Duvernoy, H. M. (1995). THE HUMAN BRAIN STEM AND CEREBELLUM : Surface, structure, vascularization, and three-dimensional sectional anatomy with MRI. Wien; New York: Springer Verlag GmbH.
- 29 : Koutcherov Y., Halliday G., Paxinos G., et al. Organization of Human Brain Stem Nuclei. In The Human Nervous System (Second Edition) (pp. 267–320). San Diego: Academic Press. 2004.
- 30 : Mai J.K., Paxinos G. The Human Nervous System. Academic Press. 2011.
- 31 : Pollock BE. Contemporary stereotactic radiosurgery. Wiley-Blackwell. 2002.
- 32 : Linskey ME, Flickinger JC, Lunsford LD. Cranial nerve length predicts the risk of delayed facial and trigeminal neuropathies after acoustic tumor stereotactic radiosurgery. J Rad Oncology Biol Phys 1993 ; 25:227-233.
- 33 : Bergström R. Changes in peripheral nerve tissue after irradiation with high energy protons. Acta radiol. 1962 ;58:301-12.
- 34 : Kinsella TJ, DeLuca AM, Barnes M, et al. Threshold dose for peripheral neuropathy following intraoperative radiotherapy (IORT) in a large animal model. Int J Radiat Oncol Biol Phys. 1991 Apr;20(4):697-701.
- 35 : Kinsella TJ, Sindelar WF, DeLuca AM, et al. Tolerance of peripheral nerve to



intraoperative radiotherapy (IORT): clinical and experimental studies. Int J Radiat Oncol Biol Phys. 1985 Sep;11(9):1579-85.

## TABLES LEGENDS

**Table 1:** Characteristics of patients with trigeminal neuropathy post GK-radiosurgery for vestibular schwannoma

**Table 2:** Predictors of trigeminal neuropathy post GK-radiosurgery for vestibular schwannomas-Univariate analysis

**Table 3:** Predictive model of risk\* of trigeminal neuropathy post radiosurgery for vestibular schwannomas

\*Risk=1/(1+exp(-score), with (rounded values for simplicity):  
Score=-7.9 +0.4 Dosemax<sub>Vax</sub>+1.1 Vol<sub>Vcis>11Gy</sub> +0.06 Vol<sub>v</sub> -0.00025 volume of schwannoma – 0.22 diameter.

**Supplementary Table 1:** Sample characteristics

## FIGURES DESCRIPTION

### Figure1:

MRI FIESTA axial (a) and sagittal (c) slices of brainstem showing the cisternal portion of the Vth nerve (orange), the vestibular schwannoma (red), the 50% isodose with 11 Gy prescription dose (yellow), the region at risk including the Vth nerve nucleus and the Vth nerve intra-axial portion (green) and the VIIth nerve (pink).

Atlas axial slice of the brainstem (b), centered on the motor of the Vth nerve. In black is drawn the region at risk including the Vth nerve nucleus and the Vth nerve intra-axial portion. csp : corticospinal tract, ctg : tegmental central tract, d5 : dorsal trigeminal tract, dlf : dorsal longitudinal fasciculus, ll : lateral Lemniscus, m5 : motor root of the trigeminal nerve, mcp : middle cerebellar peduncle, Me5 : mesencephalic nucleus of the trigeminal nerve, me5 : mesencephalic tract of the trigeminal nerve, ml : médial lemniscus, MLF : medial longitudinal tract, Mo5 : motor nucleus of the trigeminal nerve, Pcb : pontocerebellar fibers, Pn : pontine nuclei, Pr5 : principal sensory nucleus of the trigeminal nerve, PRF : pontine reticular formation, rs : rubrospinal tract, s5 : sensory root of the trigeminal nerve, scp : superior cerebellar peduncle, sctv : ventral spinocerebellar tract, sp5 : spinal trigeminal tract, stp : spinothalamic tract of the pons, SUV : superior vestibular nucleus, v5 : ventral trigeminal tract.

**Figure 2:**

ROC curve for the model of prediction of Trigeminal Neuropathy after radiosurgery for Vestibular Schwannomas

**Table 1 : Characteristics of patients with trigeminal neuropathy post gamma-knife radiosurgery for vestibular schwannoma**

<b>Analysis Variable</b>	<b>Value</b>
Number of patients with Trigeminal Neuropathy (TN)	14
Number of patients Koos II with TN	6
Number of patients Koos III with TN	8
Number of transitory TN (TTN)	7
Number of permanent TN (PTN)	7
Mean onset of TTN (months)	6.3
Mean end of TTN (months)	13.8
Number of patients with TTN having Hypoesthesia	1
Number of patients with TTN having Paresthesia	4
Number of patients with TTN having Pain	2
Mean onset of PTN (months)	4.5
Number of patients with PTN having Hypoesthesia	5
Number of patients with PTN having Paresthesia	1
Number of patients with PTN having Pain	1
Number of patients with TTN having BNI score = 2	5
Number of patients with TTN having BNI score = 3	2
Number of patients with PTN having BNI score = 2	5
Number of patients with PTN having BNI score = 3	2

**Table 2 : Predictors of trigeminal neuropathy post gamma-knife radiosurgery for vestibular schwannomas- univariate analysis**

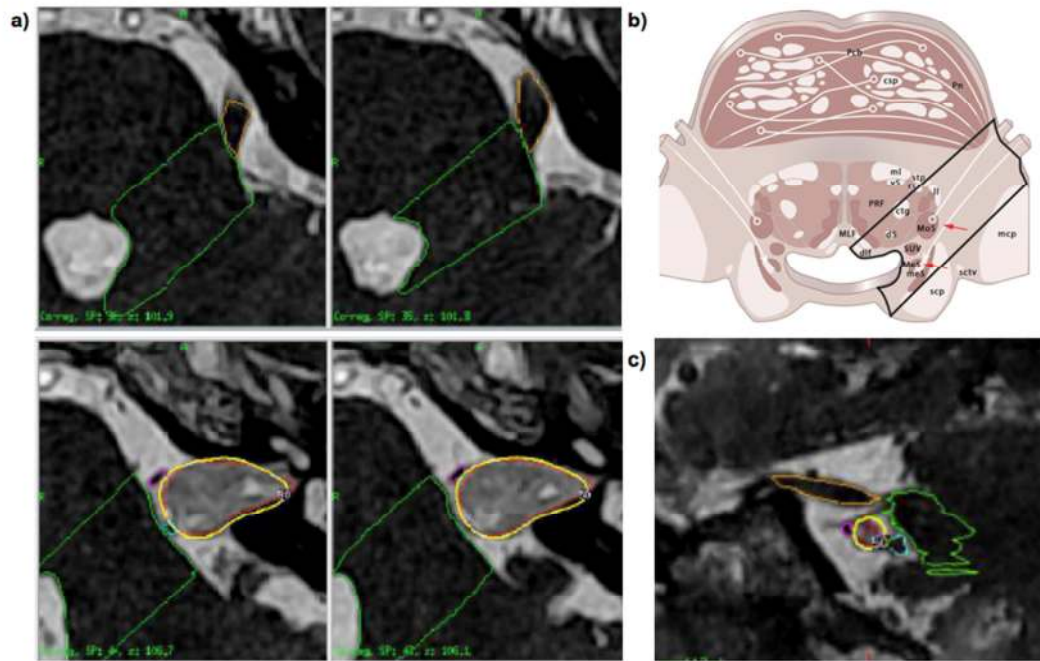
Variable	Patients without trigeminal neuropathy (n=165)	Patients with trigeminal neuropathy (n=14)	p
<b>Clinical data</b>			
Age (years)	62.3 ± 12.6	58.5 ± 10.5	0.2
Body mass index (kg/m <sup>2</sup> )	25.3 ± 4.14	25.1 ± 3.4	0.8
Inflammatory disease (%)	1(1)	2 (14)	0.02
Cancer (%)	13 (8)	3(21)	0.12
Diabetes (%)	11(7)	1(7)	1.0
Arterial hypertension (%)	57(35)	5(36)	1.0
Arterial thrombosis (%)	8(5)	0(0)	1.0
Venous thrombosis (%)	2 (1)	1 (7)	0.22
Hypercholesterolemia (%)	51(31)	3 (21)	(0.55)
<b>Vth nerve-cysternal portion</b>			
Integrated dose (mJ)	0.14 ± 0.09	0.29 ± 0.16	0.0003
Length (mm)	12.5 ± 2.3	12.7 ± 2.2	0.45
Volume (mm <sup>3</sup> )	47.2 ± 15.2	59.6 ± 20.5	0.002
Minimum dose (Gy)	1.6 ± 1.0	2.3 ± 1.4	0.053
Maximum dose (Gy)	6.3 ± 3.8	9.9 ± 3.8	0.002
Mean dose (Gy)	3.2 ± 1.9	5.0 ± 2.8	0.016
Volume of Vth nerve receiving at least 10 Gy	0.48 ± 1.5	5.2 ± 8.2	0.002
Volume of Vth nerve receiving at least 11 Gy	0.11 ± 0.47	2.95 ± 5.6	0.0002
Volume of Vth nerve receiving at least 12 Gy	0.028 ± 0.16	1.12 ± 3.5	0.0001
<b>Vth nerve nucleus and Vth nerve intra-axial portion</b>			
Minimum dose (Gy)	0.33 ± 0.29	0.49 ± 0.39	0.053
Maximum dose (Gy)	9.1 ± 4.7	12.8 ± 3.2	0.004
Mean dose (Gy)	1.9 ± 1.2	2.6 ± 1.0	0.022
Volume of Vth nerve receiving at least 10 Gy	23.5 ± 50.9	30.6 ± 27.8	0.019
Volume of Vth nerve receiving at least 11 Gy	10.3 ± 31	12.7 ± 15.9	0.021
Volume of Vth nerve receiving at least 12 Gy	4.3 ± 19	5.1 ± 10.7	0.010
Volume of Vth nerve receiving at least 13 Gy	1.9 ± 10.9	2.6 ± 7.6	0.043
<b>Schwannoma</b>			
Integrated dose (mJ)	16.8 ± 15.7	20.3 ± 15.9	0.24
Volume (mm <sup>3</sup> )	1077 ± 1032	1276 ± 998	0.26
Minimum dose (Gy)	8 ± 1.8	7.4 ± 2.4	0.36
Maximum dose (Gy)	22.9 ± 1.1	23.0 ± 1.2	0.92
Mean dose (Gy)	15.8 ± 1.3	15.9 ± 0.7	0.87
Diameter antero-posterior (mm)	12.0 ± 4.8	13.2 ± 4.2	0.29
Shots number	18.3 ± 11.4	21.7 ± 7.2	0.08
Gradient	2.8 ± 0.4	2.9 ± 0.2	0.6
Conformity index	0.97 ± 0.03	0.97 ± 0.03	0.65
Selectivity index	0.79 ± 0.10	0.83 ± 0.07	0.09
Paddick index	0.76 ± 0.10	0.80 ± 0.08	0.12

**Table 3. Predictive model of risk\* of trigeminal neuropathy post radiosurgery for vestibular schwannomas.**

Variable	Estimate	Std.err	OR [95% CI]	p-value
(Intercept)	-7.87	2.4184		0.001
Maximum dose in the intra-axial portion (Gy), Dose max <sub>vax</sub>	0.42	0.12	1.525 [1.200 - 1.939]	0.0006
Volume of the nerve receiving at least 11 Gy in the cisternal portion (mm <sup>3</sup> ), Vol <sub>vcis&gt;11Gy</sub>	1.16	0.41	3.186 [1.433 - 7.080]	0.0045
Volume of the cisternal portion (mm <sup>3</sup> ), Vol <sub>v</sub>	0.06	0.022	1.062 [1.018 - 1.109]	0.0058
Volume of schwannoma (mm <sup>3</sup> )	-0.00025	0.000682	0.9998 [0.998 - 1.001]	0.72
Antero-posterior diameter (mm)	-0.2223	0.1844	0.801 [0.558 - 1.149]	0.23

\*Risk=1/(1+exp(-score)), with (rounded values for simplicity):

Score=-7.9 +0.4 Dosemax<sub>vax</sub>+1.1 Vol<sub>vcis>11Gy</sub> +0.06 Vol<sub>v</sub> -0.00025 volume of schwannoma - 0.22 diameter.



**ROC Curve for Model**  
Area Under the Curve = 0.8939

