



Jamol D. Ergashev¹ ✉, Sofia Santos², Andrés Soto², Shavkat E. Amonov¹

¹ Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

² University Clinic of Santiago de Compostela, Santiago de Compostela, Spain

Gamma Knife Radiosurgery for Vestibular Schwannomas: Favorable and Unfavorable Effects in Series of 42 Patients

Conflict of interest: nothing to declare.

Authors' contribution: research concept and design – Jamol D. Ergashev; collection of material – Jamol D. Ergashev; statistical processing of data, analysis and interpretation of results, text writing – Jamol D. Ergashev, Sofia Santos, Andrés Soto; editing – Jamol D. Ergashev, Shavkat E. Amonov.

The article is published in the author's edition.

Submitted: 04.03.2023

Accepted: 22.05.2023

Contacts: jamol.ergashev@tashpmi.uz

Abstract

Introduction. Gamma Knife radiosurgery (GKR) for vestibular schwannomas (VS) has been documented as an effective procedure based on works of majority authors worldwide. However, it introduces certain risks to the facial nerve and hearing and vestibular functions and may involve post-treatment complications such as pseudo-progression, hydrocephalus, and other cranial neuropathies.

Purpose. To analyze early and late complications of GKR based on 84 month of VS patients Post-treatment follow up.

Materials and methods. We conducted a retrospective review of 42 VS patients underwent Leksell Gamma Knife radiosurgery with the marginal dose of 13Gy and followed at the Clinical Hospital of Santiago de Compostela in the period between February 2009 and March 2019.

Results. Among 42 patients underwent GKR, 26 (61.90%) patients showed any post-radiosurgery complications. In 11 (26.1%) cases after 6 months of GKR we observed a surprising negative growth of tumor. In all other cases, the tumor remained steady. Only one (2.8%) patient presented regrowth of tumor after one year of GK Radiosurgery. In total 16 (38.1%) patients presented either type of complications including: facial paresis in 5 patients, complete deafness in 3 patients, vertigo in 2 patients, constant tinnitus in 2 patients, hearing loss more than 10dB and complete facial palsy in 1 patient, and cerebellar atrophy in 1 patient.

Conclusions. GKR is a primary treatment option for small and medium size VS, and rates of tumor control after radiosurgery are comparable to those after microsurgery. However, VS patients treated with GKR will experience certain post-treatment complications. Nevertheless, small sample size included to the study can affect the confidence and statistical interpretation of results. Therefore, further prospective studies with larger sample size should be designed to gain an accurate and deep understanding of long and short-term adverse effects of GKR.

Keywords: vestibular schwannoma, radiosurgery, gamma knife, complications, tumor control, tumor necrosis

Эргашев Ж.Д.¹ ✉, Сантос С.², Сото А.², Амонов Ш.Э.¹

¹ Ташкентский педиатрический медицинский институт, Ташкент, Узбекистан

² Университетская клиника Сантьяго-де-Компостела, Сантьяго-де-Компостела, Испания

Радиохирургия вестибулярных шванном гамма-ножом: благоприятные и неблагоприятные исходы на примере 42 пациентов

Конфликт интересов: не заявлен.

Вклад авторов: концепция и дизайн исследования – Эргашев Ж.Д.; сбор материала – Эргашев Ж.Д.; статистическая обработка данных, анализ и интерпретация результатов, написание текста – Эргашев Ж.Д., Сантос С., Сото А.; редактирование – Эргашев Ж.Д., Амонов Ш.Э.

Статья опубликована в авторской редакции.

Подана: 04.03.2023

Принята: 22.05.2023

Контакты: jamol.ergashev@tashpmi.uz

Резюме

Введение. Радиохирургия гамма-ножом (РГН) является эффективной процедурой в лечении вестибулярных шванном (ВШ), которая доказана в работах многочисленных авторов со всего мира. Однако процедура имеет определенные отрицательные воздействия, такие как парезы и параличи лицевого нерва, псевдопрогрессия опухоли, гидроцефалия и другие неврологические осложнения.

Цель. Анализ ранних и поздних осложнений после проведенной РГН, основанный на 84-месячных динамических наблюдениях за пациентами с ВШ.

Материалы и методы. В ретроспективном исследовании приняли участие 42 пациента с диагнозом ВШ, получивших лечение РГН с терапевтической дозой 13Гу и находившихся под динамическим наблюдением в отделении оториноларингологии, хирургии головы и шеи клинической больницы Сантьяго-де-Компостела в период с февраля 2009 г. по март 2019 г.

Результаты. Из 42 пациентов, перенесших радиохирургию, у 26 (61,90%) не наблюдалось никаких послеоперационных осложнений. У 11 (26,1%) пациентов после 6 месяцев мы наблюдали уменьшение размера опухоли. Во всех остальных случаях опухоли не показывали признаков роста. Только в одном (2,8%) случае был зарегистрирован рецидив опухоли через год. В общей сложности у 16 (38,1%) пациентов были выявлены те или иные послеоперационные осложнения, в том числе парез лицевого нерва – у 5 (11,9%) пациентов, полная глухота – у 3 (7,1%), головокружение – у 2 (4,7%); постоянный шум в ушах – у 2 (4,7%); потеря слуха более 10 дБ, полный односторонний паралич лицевого нерва – у 1 (2,3%); атрофия мозжечка – у 1 (2,3%).

Выводы. Радиохирургия является первостепенной терапией выбора ВШ малых и средних размеров с относительно одинаковыми результатами микрохирургии. Тем не менее как традиционная микрохирургия, так и радиохирургия гамма-ножом имеют послеоперационные осложнения. Однако количество исследованных пациентов может влиять на достоверность статистических результатов. Таким образом, проведение дальнейших проспективных исследований с большим количеством пациентов позволяет получить точное понимание долгосрочных и краткосрочных побочных эффектов от радиохирургии с использованием гамма-ножа.

Ключевые слова: вестибулярная шваннома, радиохирургия, гамма-нож, осложнение, контроль роста, некроз опухоли

■ INTRODUCTION

Vestibular schwannoma (VS) is a benign tumor arising from Schwann cells responsible for wrapping around the axons of motor and sensory neurons to form the myelin sheath. There are three main types of treatment modalities developed throughout history: conservative management, radiosurgery, and conventional microsurgery. Usually, the three above-mentioned treatment modalities are performed by three different specialists: conservative management for instance by otolaryngologists, radiosurgery by radiologists, and conventional microsurgery by neurosurgeons. Therefore, each treatment option has its advantages and disadvantages for a certain type of patient, and choosing the optimal treatment option is still controversial. It is also important to note that the lack of positive feedback mechanisms between above mentioned three specialists the available literature full of controversy. Small VS in elderly patients can be managed conservatively, and tumors with a medium size may require radiosurgery or microsurgery [1, 2]. Complete removal of tumor is a good option due to its excellent growth control. However, microsurgery may result in facial nerve palsy, cerebrospinal fluid leak, hearing loss and other postoperative complications. On the other hand partial tumor removal usually result good hearing and facial nerve preservation at the expense of tumor growth control. Since both recurrent and primary VS of small size have responded well to Gamma Knife radiosurgery (GKR) in terms of effective local tumor control and minimal side effects [1, 2]. GKR has become a valuable upfront treatment option for patients with small or medium sized tumors because of its minimal invasiveness in contrast to traditional neurosurgery. According to Noren G., from New England Gamma Knife Center GNR gained significant experience since 1969 and this experience demonstrates long-term growth control, usually with shrinkage, in 95% of unilateral tumors. At the beginning of GNR's introduction to the clinical practice, early facial weakness occurred in 38% and facial numbness in 33% and nowadays it gradually decreased to less than 2%. Hearing preservation is currently achieved to 70% and tinnitus, unfortunately, is rarely changed even by treatment [2, 3]. Therefore rational selection of certain treatment modality and prevention of complications is an important issue in the management of VS. Factors influencing to the selection of treatment modalities of VS includes age of the patients, size of the tumor, and location of the tumor and type of the tumor. Unlike malignant tumors, the sporadic VS growth slows down with advancing patients age. Majority of studies on the natural history of VS in last decades mostly excluded patients with Neurofibromatosis type 2 (NF2). However, Sebök M and colleagues 2018 reported a case of NF2-related VS regression and they emphasize conservative treatment in older patients even with long-term tumor progression without significant compression-related clinical symptoms. Large sample size studies including NF-related VS revealed that about half of the observed tumors usually no growth during an average observation period of 3–5 years [2, 3, 5]. Performing a conventional microsurgery in patients with NF2-related VS requires special attention and caution as it may result not only a hearing loss on the side of the tumor, but sometimes may result contralateral side sensorineural hearing loss [6]. A sufficient local tumor control and good facial and hearing nerve preservation in all above mentioned cases can be reached via combined treatment regimen.

Recent studies implicate that deregulation of the Hippo signaling pathway may suggest inhibition of Schwann cells proliferation as a potential treatment strategy in VS sight. However, up to the present time the radiosurgery is a more effective and time-tested treatment option for small and medium sized VSs. Radiosurgery or GKR doesn't involve surgical incisions, therefore it is usually less risky than conventional neurosurgery. Nevertheless, GKR includes certain types of short and long term complications affecting on quality of life in patients with VS.

■ PURPOSE OF THE STUDY

To evaluate tumor control and complication rates vestibular schwannoma patients who underwent Gamma Knife radiosurgery.

■ MATERIALS AND METHODS

Materials

Records of forty-two (42) patients with vestibular schwannoma patients who underwent Gamma Knife radiosurgery and attended to Santiago de Compostela University Hospital from the period between February 21, 1992 and April 2014 included to the study. Among them there were 26 (61.90%) females and 16 (38.0%) males.

Methods

- Audiometer: "Audiotest340" (Interacoustic Incidencia).
- Dynamic Craniocorpography (CCG): Eymasa with Polaroid®.
- Computerized Dynamic Posturography (CDP): Neurocom®.
- Caloric testing tool: "Nystar plus" from Nicolet Instrumental® and VNG "VN415" from "Intracoustics®".
- Otoacoustic Emission: Echoport. "ILO 292". Otodynamics.
- Vestibular Evoked Myogenic Potential: "Intelligent Hearing Systems".
- Magnetic Resonance Imaging (MRI) "MAGNETOM", Siemens.

■ RESULTS

According to patient records in total 42 (100%) patients underwent to GK Radiosurgery with 13-Gy. Among them there were 26 (61.90%) females and 16 (38.0%) males. The average age of patients in this group was 56.82 ± 14.30 (Range 24.75–78.48). The overall average PTA and size of the VS is presented in following table.

The size of tumors between females and males was slightly different and it was higher in females 14.86 ± 8.06 than males 17.72 ± 6.88 ($p=0.064$). The localization of VS: intracanalicular tumors 7 (25.9%), extracanalicular tumors 9 (33.3%), and intra-extracanalicular tumors were in 11 (40.74%) of the cases.

In caloric testing we found 23 (55.0%) pathologic responses and 18 (42.8%) normal bithermal caloric responses. Among patients with pathologic responses, there were 4 (5.9%) patients with vestibular areflexia.

Table 1
PTA average and size of VS

	Average/ $\pm$	Range
PTA	59.80 ± 26.86	16.25–120
MRI	16.13 ± 7.56	5–30

Twenty-three (57.7%) patients presented with paper-based CDP results performed at the time of diagnosis. We have analyzed the data from the different conditions, and sensory analysis by gender and age within these groups. We have compared the number of normal CDP results with the pathologic balance in different conditions of SOT. In the global balance cases, there are 27 (64.3%) patients who have had normal overall balance and in case of 15 (36.0%) patients, the overall balance was pathologic. We revealed existence of significant difference for the condition 6 and chart 5, showing that percentage of balance slightly higher for males among the population.

Complications of GKR

According to the patient records and test results after first review (after one month of GK Radiosurgery), there were 61.90% (26/42) who did not present with any post-radiosurgery complications. However 38.1% (16/42) of the patients presented with either type of complications. Among them, the 11.09% (5/42) of patients presented with facial paresis, 2.3% (1/42) had facial palsy, 6.9% (3/42) became completely deaf, 2.3% (1/42) suffered significant hearing loss (more than 10dB), and 4.76% of the patients (2/42) complained of vertigo, which was not observed before the GK Radiosurgery. Two patients 4.76% complained for increased tinnitus after GK Radiosurgery. Also one (2.3%) patient complained of a resistant holocraneal headache after one week of GK Radiosurgery and later presented with atrophy of the cerebellar hemisphere in the revised MRI. In addition to the main complications, all the above-mentioned patients presented with headaches in varying intensities.

Follow-up

Tumor size. In the GK radiosurgery group, 66.0% patients presented VS shrinkage, 33.0% were stable and 4.76% of the patients presented with growth of the VS even after GK radiosurgery.

Hearing function. The overall average initial PTA for the radiosurgery group was 59.80 ± 26.86 . After each year, the hearing loss gradually increased. At the diagnostic stage, there are 20 out of 42 patients who presented the overall average PTA ≤ 50 dB (useful

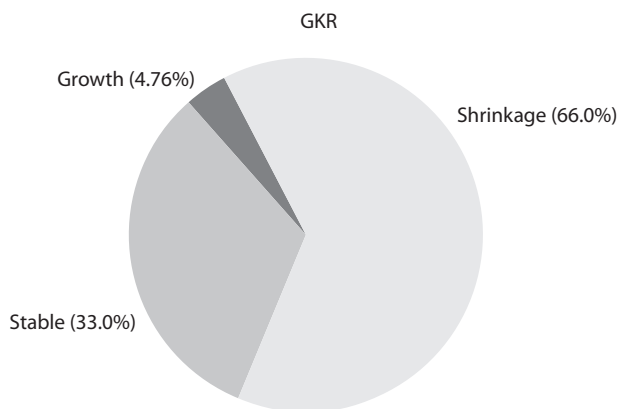


Fig. 1. Evolution of VS size over the follow up year

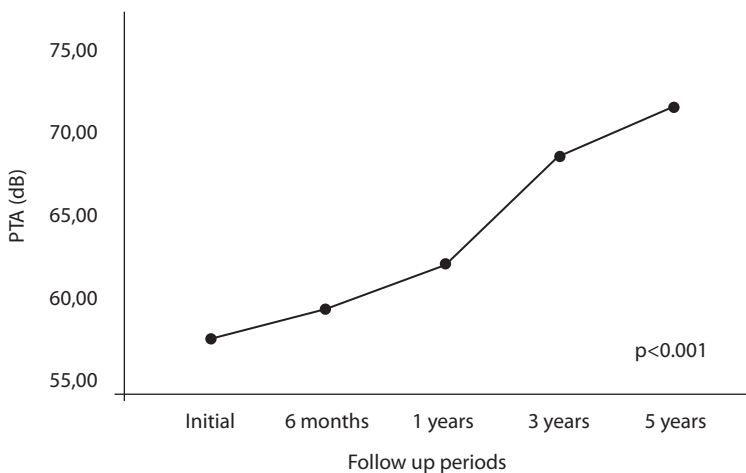
Table 2
Variations of the PTA average over the follow-up years after GKR

Follow up time	Average PTA $\pm$	95% CI	
		Lower Bound	Upper Bound
Initial	59.80 $\pm$ 26.86	49.18	70.43
6 months	69.18 $\pm$ 26.28	58.78	79.58
1 year	74.71 $\pm$ 24.42	86.04	84.37
3 years	78.96 $\pm$ 24.95	69.09	88.83
5 years	81.58 $\pm$ 23.66	72.22	90.94

hearing), after six months, one year, three years and five years, the average was 75.0%, 60.0%, 50.0% and 35.0%, respectively (As-treated cohort). Also, in the diagnostic stage, there were 30.9% (13/42) of patients with flat or pantonal audiometric configuration, but at the end of the last follow-up study, there were 50.0% (21/42) versus patients who presented flat audiometric configurations $p < 0.0001$ (t-test). The comparative analyzes of the average in the follow-up years is presented in the following Table 2.

As we see from table above, the average PTA in the GK Radiosurgery group over the follow up times changes in a more pronounced way. The graphical illustration of the overall average PTA presented in fig. 1.

Fig. 2 shows that the mean value of the PTA changes in each observation period. Repeated Measures ANOVA detected that in six months after initial diagnosis, there is no significant ($p = 0.19$) change in the average PTA, but following after one year, the difference of the PTA between the initial diagnosis was significant ($p = 0.013$). In the same way, in the third and fifth years after initial diagnosis, the hearing deterioration was more expressed and the difference between each follow-up stage was statistically and significantly different ($p < 0.001$). Also the Bonferroni multiple comparison revealed that there are more statistically and significantly differences between other follow-up levels, including the six months versus the fifth year $p < 0.000$ and the third year versus the fifth year $p = 0.038$.

**Fig. 2. The post-radiosurgery evolution of a PTA over follow-up years**

■ DISCUSSION

GK Radiosurgery has often been cited as a safe and effective treatment for small and medium sized VSs. But sometimes this safety and effectiveness may be questioned due to the lack of comparison with the natural course of other studies.

Niranjan A., Kondziolka D., Lunsford L.D. and their colleagues studied 5 to 10 year outcomes in 162 patients with VS who had undergone radiosurgery. In this study, a long-term 98.0% tumor control rate was reported. In another study performed by the same authors in 157 patients, there was a decrease in tumor size in 114 patients (73.0%), no change in 40 patients (25.5%), and an increase in 3 patients who later underwent resection (1.9%). In their series, only 2.0% of patients required tumor resection after radiosurgery [7].

In our series, a total of 42 patients underwent GK Radiosurgery and among them, only one (2.8%) patient presented the tumor growths after they were treated with GK Radiosurgery. In 26.1% (11/42) of cases, we have observed negative growth after GK Radiosurgery and in all other cases, the tumor remained steady.

Some studies have reported about malignant transformation of VS after performed GK Radiosurgery, has been performed, but in our series, we did not observe cases of a VS transforming into a malignant tumor. According to certain authors, after fractionated external-beam radiation therapy, the risk of malignant transformation may be as high as 2.0%, as has been reported many years after such radiation therapy for pituitary tumors

Hearing preservation is an important and critical issue for patients with VS undergoing GKS. The literature to the topic contains controversies, and a large number of individual results have been reported, but to date there have been few efforts to aggregate this research to achieve statistical power.

According to our follow-up results, the initial and final PTA average were significantly different ($p < 0.001$). At the diagnostic stage, there were 20 (41.6%) patients who presented useful hearing ($PTA \leq 50$ dB), and the rate of useful hearing preservation in six months, one, three and five years were at 75.0%, 60.0%, 50.0%, and 35.0% respectively. Also, in diagnostic stage, there were 30.9% (13/42) (As-treated cohort) patients who presented the flat audiometric configuration, but at the end of the last follow-up study, there were 50.0% (21/42) VS patients who presented with a flat audiometric configuration $p < 0.0001$. We have observed statistically significantly different hearing degradation in all patients who underwent GK radiosurgery, and the overall average PTA at the follow-up points were also statistically significantly different (initial vs. one year $p = 0.01$, initial vs. third and five years $p < 0.001$). Of the 42 patients treated with GK radiosurgery, one (2.3%) patient failed to complete the radiosurgery as a result of tumor growth after the GK radiosurgery. The patient was then directed to Neurosurgery.

Unlike our studies, some GK Radiologists, in their studies, reported the useful hearing preservation to be 61.0% to 80.0% in the third and five years after GK radiosurgery [7]. But the results of large meta-analysis performed by Yang and his colleagues (USA, 2010) are close to our results [6, 7].

Facial nerve impairment

Literature regarding the facial nerve preservation after GK remains controversial and it occurs in 0% to 13% of cases [6–8]. Kim J.H., Jung H.H., Chang J.H., and others reported a low occurrence of facial nerve weakness. However, they found no factors associated with facial nerve weakness after GK radiosurgery [7, 8].

In our series 38.1% (16/42) of the patients presented either type of complications. Including 11.09% (5/42) of patients presented with facial paresis, 2.3% (1/42) had facial palsy, 6.9% (3/42) became completely deaf, 2.3% (1/42) suffered significant hearing loss (more than 10dB), and 4.76% of the patients (2/42) complained of vertigo, which was not observed before the GK Radiosurgery. Two patients 4.76% complained for increased tinnitus after GK Radiosurgery. Also one (2.3%) patient complained of a resistant holocraneal headache after one week of GK Radiosurgery and later presented with atrophy of the cerebellar hemisphere in the revised MRI.

■ CONCLUSIONS

Initial wait-and-watch strategy considering the tumor size and age of the patient may prevent unfavorable complications of related with GR radiosurgery. As wait-and-watch strategy serves as a screening tool for the management of VSs because there aren't any effective criteria to consider GK radiosurgery or Conventional Neurosurgery at the diagnostic stage.

Patients who underwent GK Radiosurgery, over the follow-up years, show tumor shrinkage more than those patients included in the wait-and-watch group. However, in those patients who underwent GK Radiosurgery, the hearing deterioration observed during follow-up is higher than those included in the wait-and-watch group.

The vestibular schwannoma's peak incidence is in the sixth decades of life however, significant statistical results including favorable and unfavorable effects of GK radiosurgery needs a large sample size studies.

The instrumental tests for vestibular functions tend to show abnormal results in those patients who presented with vestibular symptoms at the diagnostic stage and the tests are usually normal in those patients who do not present with vestibular symptoms at the time of diagnosis.

■ REFERENCES

1. Brokinkel B, Sauerland C, Holling M, Ewelt C, Horstmann G, van Eck AT, Stummer W. Gamma Knife radiosurgery following subtotal resection of vestibular schwannoma. *Journal of Clinical Neuroscience*. 2014 Dec 1;21(12):2077–82.
2. Ergashev J, Santos S, Soto A, Amonov S, Shavkatov T. The assessment of state of hearing and audiometric configuration of patients with vestibular schwannoma before and after gamma knife radiosurgery. *Otorinolaringologiya. Vostochnaya Evropa*, 2017;7(1):31–8.
3. Noren G. Long-term complications following gamma knife radiosurgery of vestibular schwannomas. *Stereotactic and functional neurosurgery*. 1998;70(Suppl. 1):65–73.
4. Ng IB, Heller RS, Heilman CB, Wu JK. Facial nerve outcomes following gamma knife radiosurgery for subtotally resected vestibular schwannomas: early versus delayed timing of therapy. *Clinical Neurology and Neurosurgery*. 2020 Nov 1;198:106148.
5. Sebök M, van Niftrik CH, Bozinov O. Bilateral Spontaneous Regression of Vestibular Schwannoma in Neurofibromatosis Type 2. *World neurosurgery*. 2018 May 1;113:195–7.
6. Tripathi M, Satapathy A, Chauhan RB, Batish A, Gupta SK. Contralateral hearing loss after resection of vestibular schwannoma in a patient with neurofibromatosis 2: case report and literature review. *World Neurosurgery*. 2018 Sep 1;117:74–9.
7. Niranjana A, Kondziolka D, Lunsford LD. Neoplastic transformation after radiosurgery or radiotherapy: risk and realities. *Otolaryngologic Clinics of North America*. 2009 Aug 1;42(4):717–29.
8. Kim JH, Jung HH, Chang JH, Chang JW, Park YG, Chang WS. Predictive factors of unfavorable events after gamma knife radiosurgery for vestibular schwannoma. *World Neurosurgery*. 2017 Nov 1;107:175–84.
9. Régis J, Roche P-H, Delsanti C, Thomassin J, Ouaknine M, Gabert K, et al. Modern management of vestibular schwannomas. In: *Radiosurgery and pathological fundamentals*, vol. 20. Karger Publishers; 2007:129–141.
10. Rykaczewski B, Zabek M. A meta-analysis of treatment of vestibular schwannoma using Gamma Knife radiosurgery. *Contemporary Oncology/ Współczesna Onkologia*. 2014 Jan 25;18(1):60–6.
11. Zou P, Zhao L, Chen P, Xu H, Liu N, Zhao P, Lu A. Functional outcome and postoperative complications after the microsurgical removal of large vestibular schwannomas via the retrosigmoid approach: a meta-analysis. *Neurosurgical review*. 2014 Jan;37:15–21.