SCIE DOI: 10.14744/scie.2022.50102
South. Clin. Ist. Euras. 2022;33(2):203-208

Original Article

Long-term Outcomes of Gamma-Knife Radiosurgery for Intracanalicular Vestibular Schwannomas

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Submitted: 13.04.2022
Accepted: 27.04.2022

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Keywords: Gamma-knife radiosurgery; hearing preservation; intracanalicular; tumor control; vestibular schwannoma.

ABSTRACT

Objective: Intracanalicular vestibular schwannomas (IVS) constitute a small percentage of all vestibular schwannomas (VS). Hearing preservation is one of the most important goals in IVS management. The aim of this study was to delineate the long-term outcomes of gamma-knife radiosurgery (GKR) for IVS regarding tumor control and hearing preservation.

Methods: Patients with IVS who were irradiated at our Gamma-Knife Radiosurgery Center between January 2010 and January 2020 with clinical, audiometric, and radiological follow-up were included in this retrospective study. Tumor control was evaluated with magnetic resonance imaging by tumor dimensions. Hearing status was classified according to Gardner–Robertson (GR) classification system.

Results: Tumor control was achieved in 44 of 45 eligible patients by dimensional measuring (97.8%), and the remaining patient did not require further treatment (2.2%). In 29 patients who had functional hearing (GR grades I and II), only 13 patients preserved their functional hearing with a mean of 70.42 months follow-up (44.8%). A GR grade loss in hearing was correlated with a high GR grade preoperatively (Rs=0.459, p=0.002). Treatment dose was also found to be correlated with hearing loss, and higher doses resulted in worse outcomes (Rs=0.459, p=0.002).

Conclusion: GKR has excellent results on tumor control on long-term follow-up in IVS. Follow-up duration over 5 years may diminish functional hearing preservation rates, and more studies are needed with long-term follow-up to clarify the actual course of hearing status after GKR in IVS.

INTRODUCTION

Vestibular schwannomas (VS) are the most common tumors of cerebellopontine angle which usually arise from the eighth cranial nerve. Their first presenting sign is usually hearing loss. With the wide use of cranial magnetic resonance imaging (MRI), the diagnosis of vestibular schwannoma has been increased together with a tendency of smaller-sized tumors.[1] Intracanalicular vestibular schwannomas (IVS) constitute a small percentage of all VS,[2] but they have their own challenges. Because of the higher percentage of patients with functional hearing at the time of diagnosis, treatment modalities and choices have to not only focus on the control of tumor growth but also preserve functional hearing and quality of life.

Today, three main therapeutic options are available for VS: observation (wait and scan), microsurgical excision, and stereotactic radiosurgery (SRS). The main goals for IVS treatment today are tumor control, preservation of facial function, and avoiding hearing loss. SRS has different modalities, and gamma-knife radiosurgery (GKR) is one of the most precise and commonly used methods of SRS for VS with its frame-based nature and ultimate precision capability.[3] GKR can be a reasonable alternative to microsurgery and observation or wait and scan strategies in patients with IVS. As long-term results indicate good tumor control and functional stability, GKR is now a reliable and effective modality in small and medium-sized VS.[3,4] It can also offer a less invasive treatment option that avoids major neurosurgical interventions for the elderly and patients with comorbidities.[5]

The aim of this study was to delineate the result for tumor control and hearing preservation in patients with IVS who were treated with GKR.

MATERIALS AND METHODS

This retrospective study was approved by Institutional Review Board with decision number 09.2022.281. The study was performed in accordance with the "Declaration of Helsinki".

Patient selection and follow-up

This study included patients who were diagnosed with IVS and treated with GKR in our institution between January 2010 and January 2020. Patients with multiple VS, with a diagnosis of neurofibromatosis, harboring other intracranial and/or spinal tumors were excluded. There were 1138 patients left after this initial exclusion from a total of 1211 patients with VS. The pretreatment MRIs of these 1138 patients were evaluated by three neurosurgeon authors (M.S., F.B., Y.B.) separately, and the patients who were all classified as Samii T1[6] and Koos grade 1[7] were selected, yielding a total of 62 patients. Of these 62 patients, 45 were found to have a clinical, audiometric, and radiological follow-up, and were included in the study (Fig. 1).

After GKR, patients were radiologically followed up every 3 months in the first year, every 6 months up to the third year, and annually up to the fifth year. Patients without tumor progression continued radiological follow-up every 2–3 years thereafter. Clinical follow-up took place annually up to the fifth year and together with imaging studies thereafter. Audiometric tests were taken pre-GKR and were followed up yearly thereafter whenever possible and recorded at clinical follow-ups.

Radiosurgery technique

GKR was performed using Model B Leksell Gamma Knife (Elekta, Inc.). The stereotactic frame was attached to the patient's head with four pins of rigid fixation placed on the skull base, and the whole procedure was applied under local anesthesia. The target was localized in the three-dimensional stereotactic system, by contrast-enhanced MRI with T1- and/or T2-weighted images. The dose planning was performed with the Gamma Plan System v.3.2.1, and planning was done using axial, sagittal, and coronal series. Determination of stereotactic coordinates for irradiation isocenters was performed, and the appropriate conformal isodose configuration, total dosage, and irradiation time were calculated in the planning system. In most of the cases, a 50% isodose line was used for dose prescription (Fig. 2). All patients were admitted for radiosurgery on the day of their scheduled procedure. All patients received intravenous 40 mg of methylprednisolone after the procedure and were discharged from the hospital within 24 h of the procedure.

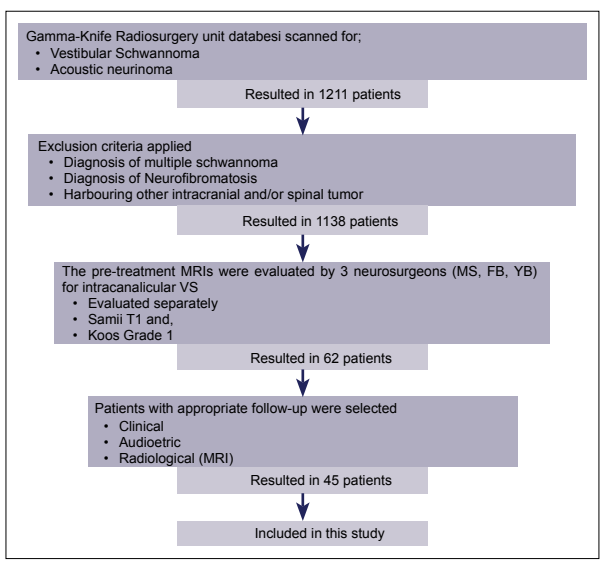

Figure 1. Flowchart of cohort inclusion.

Tumor growth and hearing assessment

Tumor growth was assessed by linear measurements of the lesion in all dimensions by the same radiologist throughout the study, and tumor enlargement over 1 mm in any dimension was regarded as tumor growth. Other qualitative characteristics of the lesions were also noted including contrast enhancement and cyst development.

Patients underwent follow-up with an audiometric test and their hearing status was graded according to GR modification of the Silverstein and Norrell classification (GR grade).[8] Pure tone average and speech discrimination scores were evaluated according to this system and the worst score of the two was chosen as the GR grade of the patient. Grade I and grade II were regarded as functional hearing.

Statistical analysis

Using normally distributed variables and binary variables, Pearson's correlation was performed. Spearman's rank correlation was used for ordinal data and not normally distributed variables, and Kendall's rank correlation was used for ordinal data and binary variables. Statistical analysis was performed using SPSS (version 22, IBM Corp.). $P<0.05$ was considered statistically significant.

RESULTS

A total of 45 patients satisfied the inclusion criteria in this study. There were 22 male and 23 female patients. The mean age at GKR was 46.76 years. The mean radiological follow-up was 48.23 months, mean audiometric follow-up was 70.42 months, and mean clinical follow-up was 82.60 months (radiological follow-up was hindered by the circumstances caused by the COVID-19 pandemic although other means of follow-up continued to some degree). The median treatment dose was 12.50 Gy (min–max, 8.00–12.50), and the mean treatment dose was 12.13 Gy (mean±SD, 12.13±0.78) for the 50% isodose line.

Tumor control

Of these 45 patients, only one patient showed tumor growth which then stabilized and required no further

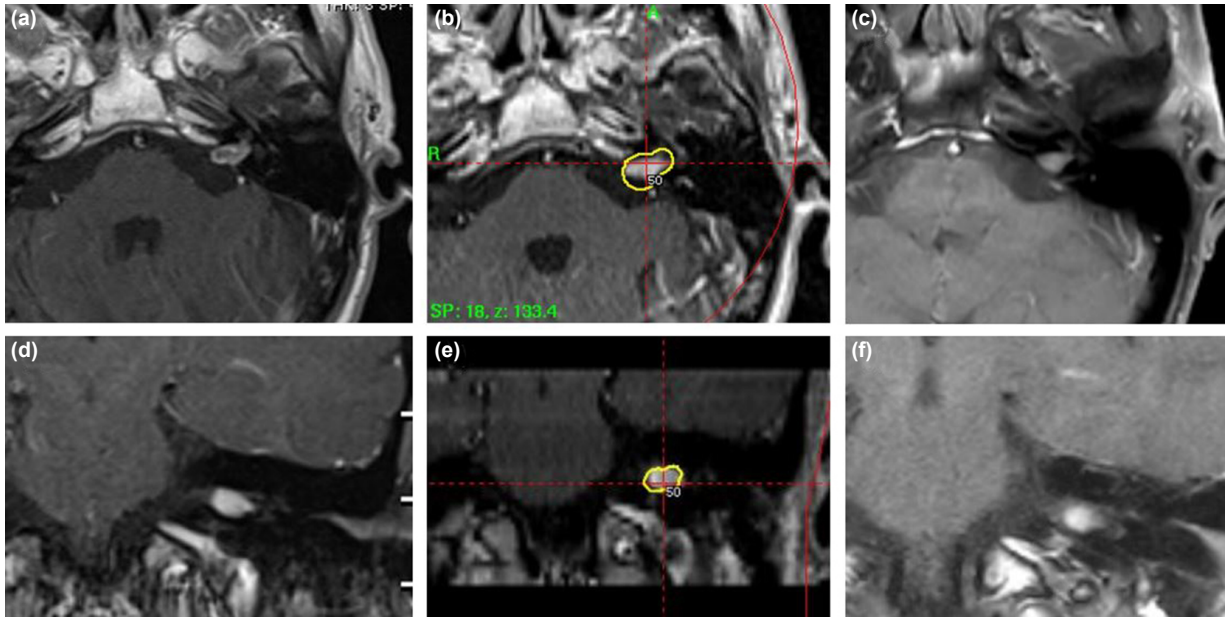

Figure 2. Radiological imaging documentation of 2 index patients. Upper row, 70 years old, male patient, 83 months follow-up duration, magnetic resonance imaging (MRI). **(a)** At the time of diagnosis. **(b)** On the day of treatment. **(c)** At the time of the last follow-up. Lower row, 50 years old, female patient, 117 months of follow-up duration, MRI. **(d)** At the time of diagnosis. **(e)** On the day of treatment. **(f)** At the time of the last follow-up.

treatment. This gave a tumor control rate of 97.8% with GKR in patients with IVS. None of the 45 patients required further intervention (0%). Two index patients are presented with their radiological images shown in Figure 2. While there was no change in tumor size in 20 patients (44.4%), 11 patients showed shrinkage of less than 1 mm (24.4%) and 13 patients showed shrinkage of more than 1 mm (28.9%). Overall, no patient in this series required further intervention after GKR for IVS.

Regarding qualitative characteristics and contrast enhancement of the lesions in MRI, 30 were found to be unchanged, 8 lesions were showing a peripheral and/or nodular contrast enhancement, and 5 lesions were showing a heterogenous and/or low contrast enhancement compared with preoperative assessments. There were 2 lesions that showed an apparent cyst formation.

Hearing results

Regarding functional hearing, 6 patients had GR grade I and 23 patients had GR grade II hearing preoperatively. All 6 GR grade I patients showed a GR grade loss at the last follow-up, and only 2 of them had a functional hearing with GR grade II at the last follow-up. Of the 23 patients who had GR grade II hearing preoperatively, 1 patient had GR grade I hearing and 10 patients had GR grade II hearing at the last follow-up. Functional hearing preservation was 33.3% and 47.8% in patients with GR grade I and GR grade II preoperatively, respectively. Overall, preservation of functional hearing was 44.8% in patients with functional hearing preoperatively. Detailed GR grades are depicted in Table 1 for all patients.

Several correlations were investigated between patients' characteristics and final hearing status (Table 2). Regarding age, mean age of patients whose hearing got worse after GKR (49.5 years old) was greater than the mean age of patients whose hearing did not get worse; however, this was not statistically significant (p=0.172). Older age was not correlated with having a greater preoperative GR grade (Rs=0.069, p=0.651); however, it was significantly correlated with having a higher GR grade at the last follow-up af-

Table 1. Hearing grades as Gardner–Robertson classification preoperatively and after GKR at the last follow-up

	At last follow-up					
Preop.	**Grade I**	**Grade II**	**Grade III**	**Grade IV**	**Grade V**	**Total**
Grade I	0	2	2	1	1	6
Grade II	1	10	8	2	2	23
Grade III	0	0	5	4	0	9
Grade IV	0	0	0	4	1	5
Grade V	0	0	0	0	2	2
Total	1	12	15	11	6	45

Table 2. Correlation among variables

	Age	Gender	Side of tumor	Follow-up (months)	Dose (Gy)	Preop. GR grade	Postop. GR grade
Age							
Gender	−0.22						
Side of tumor	−0.12	−0.07					
Follow-up (months)	0.07	−0.03	0.29				
Dose (Gy)	0.35*	−0.11	0.29	−0.25			
Pre-op. GR grade	0.07	−0.19	−00	0.01	0.20		
Post-op. GR grade	0.33**	−0.11	0.23	−0.07	0.42**	0.46**	

*P<0.05. **P<0.01.

ter GKR (Rs=0.330, p=0.03). Regarding other descriptive terms, the gender of patients and side of the tumor did not seem to have any correlation with the hearing results of the patients at the last follow-up after GKR.

A high preoperative GR grade (a patient with a preoperative hearing loss) is significantly correlated with a higher postoperative GR grade (Rs=0.459, p=0.002). Treatment dose also had an effect on the hearing status of patients. Higher doses in this series are significantly associated with higher GR grades at the last follow-up (Rs=0.415, p=0.005). When a cut off value was chosen regarding treatment dose at 12 Gy, patients having a greater dose of 12 Gy had higher GR grades than patients having a treatment dose of ≤12 Gy, and this reached statistical significance (p=0.039).

Overall, GR grades increased significantly after GKR in this series (p<0.001). In patients having functional hearing as GR grade I and grade II, only 13 of 29 patients (44.8%) preserved functional hearing at the last follow-up.

Other

Five patients had facial paralysis preoperatively. Two of them had fully recovered and 3 of them persisted at the last follow-up after GKR. Three patients in this series had newly developed facial paralysis after GKR in the first year of treatment, and they were given a course of steroids. These 3 patients fully recovered, and they did not have symptoms thereafter. One patient developed a hemifacial spasm on the same side of VS which did not respond to medical therapy. The patient had a second GKR for hemifacial spasm at a different center and lost follow-up thereafter.

Twenty-nine out of 45 patients had tinnitus as a presenting sign in this series (64.4%). Of these, 18 patients reported better or resolved of their tinnitus (62.1%), and the rest reported unchanged or worse.

DISCUSSION

The diagnosis of IVS is increasing due to the widespread availability of high-quality central nervous system imaging together with an improved awareness regarding early symptoms and signs.[2,9,10] There are several factors that contribute to the challenging difficulties regarding the best management of IVS. Today, most patients have no or minor clinical symptoms at the time of diagnosis,[2] and the natural course of the disease is somewhat debatable.

Most of the earlier studies include different-sized tumors.[2] There are now more recent reports that focus on IVS. Different studies report conflicting results on the growth of IVS. In a natural course study with a maximum number of patients and with a follow-up duration of 3.6 years, it was reported that only 17% of intracanalicular tumors show growth.[11] Another study also reported that growth rates are lower in the elderly than in younger age groups, with 5.17% in the elderly versus 26%–60% with different follow-up duration in the whole study group.[12] On the other hand, several reports show significant growth ratios for IVS in their natural course. Régis et al.[13] analyzed 2- and 5-year results of natural course and reported high growth rates of 74%. For a very long-term natural course, Charabi et al.[14] reported their findings from 10 to 20 years. They reported different follow-up times from 10 to 20 years, and all resulted in over 80% growth rate of VS, and conclude that the growth of these tumors was time dependent. It is obvious that shorter-term follow-up results in lower growth rates, and there is a tendency that higher rates of tumor growth are seen for longer-term follow-ups. This may also indicate a major problem of losing close monitoring in areas and/or countries of lower social and economic development levels. A study on the natural course of VS focused on this aspect of follow-up and reported a 17% of losing follow-up in 33 months.[15] Although the natural course of IVS is controversial with the information at hand, high growth rates with longer follow-up duration are undeniable.

The reports on SRS as the initial management of IVS show excellent results when it comes to tumor control. Most studies report over 90% tumor control with SRS at various follow-up times.[16–20] A study by Frischer et al.[16] reported on the very long-term result of VS of all Koos grades and found excellent growth control regardless of the tumor size. Their results indicate 92%, 91%, and 91% for 5, 10, and 15 years of follow-up, respectively. When tumor control is defined as no need for further intervention, their results got even higher and reached 99%. Studies that report solely on IVS also reported high tumor

control rates (>90%) after GKR.[2,9,17,19] In our series, in 44 out of 45 patients, tumor size was stable or smaller, which is comparable to the literature, and when tumor control is defined as no need for further intervention, tumor control rate reached 100% with a mean radiological follow-up of 48.23 months. Considering the results of published literature and the present series, it is obvious that SRS and particularly GKR have excellent tumor growth control in IVS.

The preservation of functional hearing in patients diagnosed with IVS is another important topic. Although there are numerous reports on functional hearing, many of them report on mixed groups or tumor size, or even different treatment modalities including GKR and microsurgery. There are few reports on IVS only, and most of them have relatively short follow-up duration. How hearing preservation was reported is also somewhat confusing. Some studies report this finding as a loss of grade(s) in GR or AAO–HNS (American Academy of Otolaryngology–Head and Neck Surgery Class) classification systems and others report the percentage of functional hearing after treatment in patients with functional hearing preoperatively.

Early reports from the late 1990s usually include small patient numbers. Two studies from this era that only included IVS reported 100%[19] and 86%[21] preservation of functional hearing in less than 15 patients with a follow-up duration of 12 and 18 months, respectively. Niranjan et al.[18] reported on 15 patients with a follow-up duration of 33 months and found 73% functional hearing preservation. They also focused on dosimetric analysis and reported that patients having over 14 Gy to the tumor margin had worse results on the preservation of functional hearing. There are other studies focused on dosimetric analysis, and better hearing preservation rates were reported with lower marginal dose plans without compromising tumor control.[22,23] Cochlear dose was also reported to have an effect on the preservation of functional hearing in VS both in a single session and fractionated SRS.[24–26] Although we did not calculate the cochlear dose in our study, we have used a mean of 12.13 Gy and a median of 12.50 Gy (range, 8.00–12.50) of marginal dose in our patients. Higher doses were associated with higher postoperative GR grades at the last follow-up. These findings indicate that the preservation of functional hearing is associated with irradiation doses even below 13 Gy although the exact mechanism of hearing loss after radiosurgery is still unclear. There are very few reports on the long-term follow-up of GKR in IVS over 5 years. In a study including 96 patients with IVS who were treated with GKR, Niranjan et al.[9] reported 64.5% preservation of functional hearing in patients who had GR grade I and II hearing preoperatively. Their mean follow-up duration was 42 months which ranged between 12 and 144. Interestingly, they reported 2 patients having a delayed functional hearing loss after 77 and 88 months, which puts emphasis on the long-term follow-up in these tumors. In our series, we reached a 44.8% rate of functional hearing preservation. Our follow-up duration was 70.42 months, which is relatively high compared with the published literature. Our results may indicate the importance of longer follow-up durations in patients with IVS when considering the preservation of functional hearing.

In conclusion, tumor control and preservation of functional hearing are the main goals of treatment in patients with IVS. GKR has excellent results on tumor control on the long-term follow-up. Preservation of functional hearing after GKR seems to be dose dependent, and long-term results over 5 years are lacking. There can be a delayed loss of functional hearing in the long term, and more studies are needed to clarify the actual course of hearing status during the follow-up period.

Ethics Committee Approval

This study approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (Date: 11.02.2022, Decision No: 09.2022.281).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: M.S., E.P., C.K., Y.B., F.B., B.A., İ.Z.; Design: M.S., Y.B., F.B., B.A.; Supervision: M.S., E.P., B.A., İ.Z.; Data: M.S., E.P., C.K., Y.B., F.B.; Analysis: M.S., E.P., C.K.; Literature search: M.S., E.P., C.K., B.A.; Writing: M.S., E.P., C.K.; Critical revision: B.A., Y.B., F.B., İ.Z.

Conflict of Interest

None declared.

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Kanal İçi Vestibüler Schwannomalarda Gamma-Knife Radyocerrahinin Uzun Dönem Takip Sonuçları

Amaç: Kanal içi vestibüler schwannomalar, tüm vestibüler schwannomalar içerisinde küçük bir yüzdeye sahiptir. Kanal içi vestibüler schwannomalarda işitmenin korunması, hasta yönetiminin temel amaçlarındandır. Bu çalışmanın amacı, kanal içi vestibüler schwannomalarda Gamma-Knife radyocerrahinin (GKR) tümör kontrolü ve işitmenin korunması üzerine etkisinin incelenemesidir.

Gereç ve Yöntem: Bu geriye dönük çalışmada, Gamma-Knife Radyocerrahi Merkezi'mizde Ocak 2010–Ocak 2020 arasında kanal içi vestibüler schwannoma tanısı ile stereotaksik radyocerrahi almış, klinik, odyometrik ve radyolojik takibi bulunan hastalar değerlendirildi. Tümör kontrolü manyetik rezonans görüntüleme yönteminde tümör boyutlarının ölçülmesi ile takip edildi. İşitme seviyeleri Gardner-Robertson (GR) işitme sınıflaması yöntemine göre değerlendirildi.

Bulgular: Ortalama 48.23 aylık takipte, çalışmaya dahil edilen toplam 45 hastadan 44'ünde tümör kontrolü sağlandığı görüldü (%97.7). Tümör büyümesi görülen bir hastada ise, ek bir tedavi uygulanması gerekmedi. Ek tedavi gerekliliğine göre değerlendirildiğinde tüm hastalarda tümör kontrolü sağlandı (%100). Tedavi öncesi fonksiyonel işitmesi olan (GR derece I ve II) toplam 29 hastadan, ortalama 70.42 aylık takip sonrasında, toplam 13 hastada fonksiyonel işitme korundu (%44.8). GR derecesinde kayıp, ameliyat öncesinde yüksek GR derecesine sahip olmak ile korelasyon gösterdi (Rs=0.459, p=0.002). Tedavi dozu işitme kaybı ile korelasyona sahipti ve daha yüksek doz alan hastalar daha kötü sonuçlara sahipti (Rs=0.459, p=0.002).

Sonuç: Kanal içi vestibüler schwannomalarda GKR uzun dönemli takiplerde mükemmel tümör kontrolü sağlamaktadır. Beş yılın üzerindeki takip sürelerinde fonksiyonel işitmenin korunma oranı azalabilir. Kanal içi vestibüler schwannomalarda GKR sonrası işitmenin seyrini ortaya koyabilmek için uzun takip süreli daha fazla çalışma gerekmektedir.

Anahtar Sözcükler: Gamma-knife radyocerrahi; işitmenin korunması; kanal içi; tümör kontrolü; vestibüler schwannoma.