

Stereotactic radiosurgery ensures an effective and safe long-term control of Koos grade IV vestibular schwannomas: a single-center, retrospective, cohort study

Motoyuki Umekawa

Department of Neurosurgery, The University of Tokyo Hospital

Yuki Shinya (✉ yukishinya6155@gmail.com)

Department of Neurosurgery, The University of Tokyo Hospital

Hirotaaka Hasegawa

Department of Neurosurgery, The University of Tokyo Hospital

Mariko Kawashima

Department of Neurosurgery, The University of Tokyo Hospital

Masahiro Shin

Department of Neurosurgery, The University of Tokyo Hospital

Atsuto Katano

Department of Radiology, The University of Tokyo Hospital

Masanari Minamitani

Department of Radiology, The University of Tokyo Hospital

Akinori Kashio

Department of Otorhinolaryngology, The University of Tokyo Hospital

Kenji Kondo

Department of Otorhinolaryngology, The University of Tokyo Hospital

Nobuhito Saito

Department of Neurosurgery, The University of Tokyo Hospital

Research Article

Keywords: vestibular schwannomas, Koos grade IV, stereotactic radiosurgery, Gamma Knife radiosurgery

Posted Date: April 14th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1550679/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Purpose: Stereotactic radiosurgery (SRS) is a standard treatment modality for vestibular schwannomas (VSs). However, there is a paucity of data on tumor control and neurological preservation for larger VSs. We aimed to investigate the long-term effectiveness of SRS for Koos grade IV compared with I-III VSs.

Methods: We included 452 patients with VSs (50 Koos grade IV and 402 Koos grade I-III) who were treated with SRS at our institution from 1990 to 2021. Tumor control and functional preservation were calculated using the Kaplan-Meier method and compared between groups with the log-rank test.

Results: The median post-SRS follow-up period was 68 months. Tumor control rates were 96% at 5 and 10 years for Koos grade IV VSs, and 97% and 95%, respectively, for Koos grade I-III VSs ($p = 0.744$). In Koos grade IV VSs, functional preservation rates of the facial and trigeminal nerves were both 96% at 5 years (both 98% for Koos grade I-III VSs; facial, $p = 0.410$; trigeminal, $p = 0.107$). Hearing preservation rates were 61% at 5 years for Koos grade IV VSs and 78% for Koos grade I-III VSs ($p = 0.645$). Symptomatic transient tumor expansion was more common with Koos grade IV VSs (8.0% vs. 2.5%, $p = 0.034$), although all related symptoms diminished in accordance with tumor shrinkage.

Conclusion: SRS may contribute to long-term tumor control and adequate neurological preservation in the treatment of Koos grade IV VSs, comparable to those in the treatment of Koos grade I-III VSs.

Introduction

Vestibular schwannomas (VSs) are relatively common, benign brain tumors originating from the vestibulocochlear nerve. Tumor size is an important factor in determining the treatment strategy. For small- and medium-sized VSs, tumor control and preservation of the facial nerves and hearing function are the primary treatment goals, and stereotactic radiosurgery (SRS) is safe and effective for such purposes [1]. For larger VSs, surgical resection is the primary treatment to reduce the tumor mass effect. However, durable tumor control and satisfactory preservation of facial nerve function are not always achievable. In previous studies, 15-year tumor control rates were 73% in the gross total resection (GTR) group and 47% in the subtotal resection (STR) group, respectively [2]. In contrast, facial nerve preservation rates were reported as 47%–89% in the GTR group and 47%–93% in the STR group [3–5].

SRS may be effective and safe for larger VSs, with tumor control rates of 80%–98% and facial nerve preservation rates of 67%–100% [6–16], and serviceable hearing preservation [8, 11, 13]. These results are promising for selected patients with large VSs who have poor surgical tolerance, medical comorbidities, are of an advanced age, or decline surgery. However, there is a paucity of data on the long-term outcomes of SRS for larger VSs in terms of tumor control and preservation of neurological function. It also remains unclear how transient tumor expansion (TTE) affects patients with large VSs after SRS. Therefore, we aimed to confirm the long-term effectiveness and safety of SRS for large VSs.

Methods

Patients and tumors

The data of 536 consecutive patients with VSs, treated with SRS from June 1990 to December 2021 at our institution, were collected from the institutional Gamma Knife database. The exclusion criteria were: (i) < 6 months of

follow-up after SRS (n = 52), and (ii) having neurofibromatosis type 2 (n = 32). Accordingly, 452 patients were included for statistical analysis. Based on the Koos grading system, 68 tumors were classified as grade I (small intracanalicular type), 252 as grade II (small tumor with protrusion into the cerebellopontine angle without brainstem contact), 82 as grade III (tumor occupying the cerebellopontine cistern without brainstem displacement), and 50 as grade IV (large tumor with brain stem and cranial nerve displacement) [17].

Most diagnoses were radiographically determined (n = 359, 79%) without histological confirmation. All radiographic images were reviewed by two independent neuroradiologists and attending neurosurgeons. This study was conducted in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

SRS procedure

The Leksell Gamma Knife (Elekta Instruments, Stockholm, Sweden) was used for all SRS treatments. The detailed treatment process was previously described [18, 19]. After head fixation using a Leksell frame (Elekta Instruments), stereotactic imaging (CT until July 1996, MRI from August 1996 to January 2018, cone-beam CT thereafter) was performed to obtain precise tumor data. Neurosurgeons and radiation oncologists performed radiosurgical planning using commercially available software (the KULA planning system [Elekta Instruments] until 1998 and the Leksell Gamma Plan [Elekta Instruments] thereafter). In principle, 12–14 Gy was prescribed to the tumor margin with a 50% \pm 5% isodose line. Prescription doses > 12 Gy were used to treat VSs before 2000; thereafter, 12 Gy was used for all treatments, as previously described [18].

Follow-up and treatment outcomes

After SRS, MRI was performed every 6 months for 3 years and annually thereafter. Radiographic findings were independently assessed by neuroradiologists and neurosurgeons. Successful tumor control was defined as the absence of tumor progression requiring additional interventions. Tumor responses were monitored according to the Response Assessment in Neuro-Oncology criteria [20]; tumor progression was defined as a > 2-mm increase in tumor diameter in any direction observed upon two or more consecutive post-SRS imaging studies. Transient expansion, typically occurring in schwannomas owing to radiation-induced tumor swelling at around 6 months after SRS, followed by shrinkage at approximately 18 months, was meticulously distinguished from actual tumor progression by evaluation of consecutive MRIs [21, 22]. Patient neurological status and response to treatment were prospectively collected at each hospital visit. Hearing function was evaluated based on the Gardner-Robertson (GR) classification [23]. Facial nerve function was evaluated with House-Brackmann (HB) grading [24]. A Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grade was retrospectively assigned based on the descriptions of adverse events. Data on patients who did not attend regular follow-up at our institution were collected telephonically, and follow-up radiographic images were obtained for our independent review. Illustrative cases are provided in Fig. 1.

Statistical analysis

Baseline characteristics were compared between patients with Koos grade IV and those with Koos grade I–III VSs via chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Tumor control rates (TCRs), serviceable hearing, and facial and trigeminal nerve preservation rates were calculated using Kaplan–Meier analysis and compared between Koos grade IV and I–III tumors with log-rank tests. Factors associated with TCRs were examined using bivariate and multivariable Cox proportional-hazards analyses. Continuous variables were entered into models after being dichotomized using their median values. Post-SRS neurological outcomes were summarized, and factors associated with functional improvement, deterioration, and new deficits were examined

with logistic regression analysis. Statistical analyses were performed using JMP Pro 16 software (SAS Institute Inc., Cary, NC, USA).

Result

Baseline characteristics and neurological symptoms

Patient characteristics and neurological status before SRS are summarized in Table 1. The median post-SRS follow-up period was 68 (interquartile range [IQR], 31–153) months in the entire cohort, and 63 (IQR, 24–178) months in the Koos grade IV group. Between the Koos grade IV and I–III groups, the maximum tumor diameter (median, 26 vs. 17 mm; $p < 0.001$) and target volume (median, 5.3 vs. 1.2 mL; $p < 0.001$) were larger in the former. The median prescription (12 Gy) and central (24 Gy) dose did not differ between the groups. Patients in the Koos grade IV group more commonly underwent resection prior to SRS than those in the Koos grade I–III group (44% vs. 18%; $p < 0.001$). A smaller proportion of patients in the Koos grade IV group than in the Koos grade I–III group had serviceable hearing (26% vs. 46%; $p < 0.001$). Facial palsy, trigeminal dysfunction, and ataxia were observed more commonly in the Koos grade IV group than in the Koos grade I–III group (facial palsy: 30% vs. 9%, $p < 0.001$; trigeminal dysfunction: 28% vs. 6%, $p < 0.001$; ataxia: 8% vs. 2%, $p = 0.034$).

Table 1
Baseline characteristics of 452 patients with vestibular schwannomas according to Koos grading

Variables	All tumors (n = 452)	Koos grade IV (n = 50)	Koos grade I–III (n = 402)	p-value
Median [IQR]				Wilcoxon rank-sum test
Age, years	58 [48–66]	57 [50–67]	58 [48–66]	0.919
Follow-up, months	68 [31–153]	63 [24–178]	69 [32–153]	0.291
Maximum diameter, mm	18 [14–22]	26 [25–29]	17 [14–20]	< 0.001*
Target volume, mL	1.3 [0.7–2.7]	5.3 [4.1–6.8]	1.2 [0.6–2.1]	< 0.001*
Prescription dose, Gy	12 [12–14]	12 [12–14]	12 [12–14]	0.683
Central dose, Gy	24 [24–28]	24 [24–28]	24 [24–29]	0.401
n [%]				chi-square test
Male sex	222 [49]	24 [48]	198 [49]	0.867
Prior surgery	93 [21]	22 [44]	71 [18]	< 0.001*
Neurological status before SRS				
Serviceable hearing	199 [44]	13 [26]	186 [46]	< 0.001*
Facial palsy	51 [11]	15 [30]	36 [9]	< 0.001*
Trigeminal dysfunction	38 [8]	14 [28]	24 [6]	< 0.001*
Vertigo	75 [17]	10 [20]	65 [16]	0.492
Tinnitus	152 [34]	16 [32]	136 [34]	0.787
Ataxia	14 [3]	4 [8]	10 [2]	0.034*
Dysphagia	2 [0.4]	1 [2]	1 [0.2]	0.079
Hydrocephalus	1 [0.2]	0	1 [0.2]	0.724
IQR, interquartile range				
* Significant at $p < 0.05$.				

Tumor control

At the last follow-up, 276 (61%) tumors decreased in size, 152 (34%) remained unchanged, and 24 (5%) increased in size, with no difference between the groups. Among the latter 24 patients (4 with Koos grade IV VSs), 15 (2 with Koos grade IV VSs) were treated with surgical resection, and 1 was again treated with SRS. The other eight patients were only monitored because the tumor increase was mild and did not worsen their neurological states. The overall TCR was 96.8% at 5 years and 94.6% at both 10 and 15 years (Fig. 2a). In the Koos grade IV group, the TCR was 95.6% at 5, 10, and 15 years, and no differences were observed with the Koos grade I–III group, with TCRs of 96.9%, 94.6%, and 94.6% at the respective intervals ($p = 0.744$; Fig. 2b). Koos grade IV VSs were not associated with tumor control in the bivariate (hazard ratio [HR] = 0.78, 95% confidence interval [CI] = 0.18–3.4, $p = 0.745$) and multivariable (HR = 1.0, 95% CI = 0.23–4.6, $p = 0.964$) analyses, nor were any of the other factors (Table 2).

Table 2
Multivariable analysis for factors associated with better tumor control

Factor	Bivariate		Multivariable	
	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value
Age at SRS > 60 y	1.2 [0.42–3.5]	0.730		
Male sex	3.0 [0.96–9.2]	0.060	3.0 [0.96–9.3]	0.060
Koos grade IV (vs. Koos grade I–III)	0.78 [0.18–3.4]	0.745	1.0 [0.23–4.6]	0.964
Maximum diameter ≥ 25 mm	0.85 [0.20–3.7]	0.827		
Target volume ≥ 4 mL	0.49 [0.16–1.5]	0.217		
Prescription dose ≤ 12 Gy	1.5 [0.55–4.0]	0.439		
Central dose ≤ 24 Gy	1.2 [0.43–3.1]	0.766		
Prior direct surgery	0.40 [0.14–1.1]	0.075	0.40 [0.14–1.1]	0.076
Transient tumor expansion	3.4 [0.45–26]	0.236		
HR, hazard ratio; CI, confidence interval; SRS, stereotactic radiosurgery				

Hearing preservation

Among 199 patients with serviceable hearing function before SRS, hearing function was preserved in 119 (59.8%). Crude hearing preservation rates were 61.5% in the Koos grade IV group and 59.7% in the Koos grade I–III group. The hearing preservation rates were 88.7% at 3 years, 79.2% at 5 years, and 54.6% at 10 years (Fig. 3a). In the Koos grade IV group, the preservation rates were 91.7% at 3 years, 61.1% at 5 years, and 61.1% at 10 years, and no differences were observed compared with the Koos grade I–III group, with respective rates of 78.3%, 68.1%, and 53.0% ($p = 0.645$; Fig. 3b). Neither Koos grade nor other factors were risk factors for poor hearing outcomes (Supplementary Table 1 in Online Resource 1).

Facial nerve preservation

Overall, facial nerve functions were completely lost in five patients before SRS. Among the remaining 447 patients (HB grade other than V at SRS), 11 experienced new or worsened facial nerve deficits, and the crude preservation rate was 97.5%. Although 10 of the 11 patients' deficits were slight to mild (CTCAE grade 1/2), one patient experienced HB grade 4 facial palsy 10 months after SRS and was treated with dynamic and static reconstruction. The overall facial nerve preservation rate was 97.4% at 5, 10, and 15 years (Fig. 3c). In the Koos grade IV group, the preservation rate was 95.5% at 5, 10, and 15 years, and no differences were observed with the Koos grade I–III group, with a rate of 97.7% at each time point ($p = 0.410$; Fig. 3d). Koos grade was not a risk factor for poor facial nerve functional outcomes (Supplementary Table 1 in Online Resource 1). However, a prescription dose of ≤ 12 Gy was independently associated with better facial nerve functional outcomes (HR = 6.5, 95% CI = 1.7–25, $p = 0.006$).

Trigeminal nerve preservation

New or worsened trigeminal nerve deficits after SRS were observed in 12 patients overall (2.7%). The trigeminal nerve preservation rate was 97.5% at 5 years and 97.1% at 10 and 15 years (Fig. 3e). In the Koos grade IV group, the preservation rate was 96.1% at 5 years and 91.6% at 10 and 15 years, and no differences were observed with the

Koos grade I–III group, with a rate of 97.7% at each time point ($p = 0.107$; Fig. 3f). Koos grade was not a risk factor for poor trigeminal nerve functional outcomes (Supplementary Table 1 in Online Resource 1). However, a prescription dose of ≤ 12 Gy was independently associated with better facial nerve functional outcomes, and prior direct surgery was associated with poorer outcomes (prescription dose ≤ 12 Gy, HR = 6.7, 95% CI = 1.8–25, $p = 0.004$; prior surgery, HR = 0.31, 95% CI = 0.10–0.97, $p = 0.044$).

Other neurological symptoms

Changes in other neurological symptoms were compared before and after SRS (Supplementary Table 2 in Online Resource 1). Pre-SRS vertigo improved in a higher proportion of patients in the Koos grade IV group (Koos grade IV: 20% vs. Koos grades I–III: 2%, $p = 0.006$). Tinnitus, the second most common symptom before SRS, improved in 3.9% of the entire cohort, with no differences according to tumor size. Post-SRS worsening or new neurological symptoms were as follows: vertigo in 18 patients (4.0% of the entire cohort; 4 [8%] in Koos grade IV vs. 14 [3%] in Koos grades I–III, $p = 0.123$), tinnitus in 15 (3.3%; 2 [4%] vs. 13 [3%], $p = 0.776$), ataxia in 2 (0.4%; 0 vs. 2 [1%], $p = 0.617$), and hydrocephalus in 11 (2.4%; 2 [4%] vs. 9 [2%], $p = 0.446$). Age > 60 years was the only factor independently associated with post-SRS hydrocephalus (HR = 4.4, 95% CI = 1.2–17, $p = 0.030$; Supplementary Table 1 in Online Resource 1).

Transient tumor expansion

TTEs were observed in 80 patients (18%) overall; the proportion was similar between the groups: 11 patients (22%) in the Koos grade IV group and 69 (17%) in the Koos grade I–III group ($p = 0.398$). The median time to the start of TTE was 6 (IQR, 5–12) months after SRS, and that to the end of TTE was 12 (IQR, 12–23) months. This tendency was confirmed in both the Koos grade IV (true progression, median: 10 months vs. TTE, median: 6 months, $p = 0.049$) and Koos grade I–III (34 vs. 6 months, $p < 0.001$) groups.

Symptomatic TTEs occurred in 14 patients (3.1%), more commonly in patients with Koos grade IV VSs (Koos grade IV, 8.0% vs. Koos grades I–III, 2.5%, $p = 0.034$). Symptoms concomitant with TTEs were trigeminal dysesthesia (four patients [0.9%]), facial palsy or spasm (five patients [1.1%]), and vertigo (eight patients [1.8%]). All symptoms were mild and disappeared as the tumor stopped expanding and decreased in size.

Discussion

In this study, SRS yielded long-term tumor control and low complication rates in patients with Koos grade IV VSs. TCRs were satisfactory, at 95.6%, and the hearing, facial nerve, and trigeminal nerve preservation rates were 61.1%, 95.5%, and 91.6%, respectively. SRS was recently reported as an efficacious treatment for large VSs (Table 3) [8, 11, 13, 15, 16]. Outcomes of patients with Koos grade I–III VSs in this study are comparable to those of previous studies in terms of tumor control and preservation of neurological function, and also comparable to patients with Koos grade I–III VSs in our cohort.

Table 3
Previous studies of SRS for large VSs with 50 or more patients

Authors	N	Size	Prescription dose, Gy, median	F/U, m, median	Prior surgery, %	TCR, %	Hearing preservation, %	Facial nerve preservation, %	VPS, %
Yang et al., 2011	65	3–4 cm	12	36	26	87 (2 y)	34 (2 y)	98	5
Iorio-Morin et al., 2016	68	Koos grade IV	12	47	19	92 (10 y)	49 (5 y)	100	4.4
Lefranc et al., 2018	86	Koos grade IV	10.9	74.4	0	90.7 (3 y)	65.8 (3 y)	100	1.2
Hasegawa et al., 2021	203	Koos grade IV	12	152	25	85 (5 y)	39 (5y)	100	3
Ogino et al., 2021	170	Koos grade IV	12.5	61.2	0	93.7 (10 y)	36 (7 y)	96	5
Present study	50	Koos grade IV	12	63	44	95.6 (10 y)	61.1 (10 y)	96	4
F/U, follow up; m, months; N, number; NA, not available; SRS, stereotactic radiosurgery; TCR, tumor control rate; VPS, ventriculo-peritoneal shunt; VS, vestibular schwannoma; y, year									

In terms of tumor control, the validity of SRS for larger VSs has been controversial. There are several reports that larger tumor volume correlates with control failure [8, 9, 12, 25]; other reports noted no correlation between tumor size and tumor control [7, 11, 13, 16]. Ogino et al. [16] reported that a prescription dose > 12 Gy was associated with better tumor control of Koos grade IV VSs; however, they also reported a negative effect on the facial nerve at a prescription dose > 13 Gy. Other studies revealed that lower prescription doses (≤ 12 Gy) yield equivalent tumor control to higher doses [8, 12, 18, 25]. In recent years, the advancement of imaging modalities and planning software has contributed to more precise tumor targeting and better, more conformal, multi-isocenter-based planning. Even for large tumors, accurate targeting can lead to excellent tumor control with lower prescription doses. In fact, our tumor control rate of 95.6% was similar to those in previous studies, and other factors that were previously associated with control failure, such as younger age and previous resection, were not associated with tumor control in our cohort [8, 15].

In several studies, SRS provided comparable tumor control and cranial nerve preservation to surgery in the treatment of Koos grade IV tumors [4, 5, 26]. However, in neither those studies nor ours was a size limitation of VSs defined for SRS. Huang et al. [12] reported that SRS for VSs larger than 10 mL yielded 86% tumor control and 80% facial nerve preservation, inferior to those of another study with large-VS cohorts treated with SRS [11, 13, 16]. Accordingly, the size limit for SRS requires further validation. Furthermore, our SRS cohort might have caused a selection bias, as patients with larger VSs commonly experience severe brainstem compression and severe symptoms, leading to immediate surgery. Moreover, the efficacy of combined treatment with subtotal resection and subsequent SRS is comparable to primary SRS alone in terms of both tumor control and cranial nerve preservation [27–29]. Such

combined treatment may compensate for the disadvantages of surgery for large VSs, yielding both excellent tumor control and facial nerve preservation.

TTE after SRS for VS is not usually problematic but may be a symptomatic adverse effect of larger tumors. Although all symptoms were mild and transient, symptomatic TTEs were significantly more common in Koos grade IV VSs in our cohort. Therefore, certain patients with Koos grade IV VSs may require careful observation on symptomatic TTE. Additionally, TTE needs to be differentiated from true tumor progression to avoid unnecessary surgery. A useful distinguishing characteristic is that most TTE occurs approximately 6–18 months after SRS and true tumor progression generally occurs 24 months after SRS [22, 30–32]. In this study, TTE occurred approximately 6 months after SRS, and true progression occurred at 28 months, consistent with previous reports.

The effect of tumor size on post-SRS neurological outcomes remains controversial. Johnson et al. [33] reported that smaller tumors (≤ 1.2 mL) were associated with better hearing preservation; however, this was not confirmed in previous studies [34, 35] or in ours. Indeed, our hearing preservation rate (61% at 10 years) was comparable to those in other previous studies (34–66% at 2–7 years after SRS) [8, 11, 13, 15, 16]. Hence, further investigation of the association between tumor size and hearing preservation is necessary. Facial nerve preservation after SRS is generally excellent even in large tumors [6–8, 10–16], although Ogino et al. [16] reported an association between a worse facial nerve prognosis and a larger tumor as well as a higher prescription dose ($> 12/13$ Gy). Although our study did not confirm the association between post-SRS facial nerve deficits and Koos grade IV tumors, a prescription dose > 12 Gy was associated with the deficits. Moreover, our study demonstrated that a lower prescription dose was associated with better trigeminal nerve preservation [18]. These results suggest that a modest prescription dose (12 Gy) may be suitable for treating even those patients with large VSs; validation with larger samples is needed.

Hydrocephalus is a major complication of SRS for VSs, with an incidence of 5.6–11% [36, 37]. While older age is a well-known risk factor for post-SRS hydrocephalus, tumor size is not a clear risk. In this study, large tumor size was not a risk factor. In terms of hydrocephalus, although there may be no need to avoid SRS, we recommend careful follow-up in older patients or patients with enlarged ventricles before SRS.

This study has several limitations. This was a retrospective, single-center study, which might have introduced a selection bias. The small numbers of patients with Koos grade IV VSs (50) and treatment failure may have led to inaccurate assessment of risk factors. Additionally, only 93 patients were pathologically diagnosed; the other patients were treated based on a radiological diagnosis of VS, which might have increased the false positive rate and influenced our results.

Conclusion

We observed favorable long-term tumor control and neurological preservation with SRS for Koos grade IV VSs, suggesting that SRS may play an essential role in the treatment of large VSs.

Statements And Declarations

- **Acknowledgments:** None
- **Funding:** This work was supported by JSPS KAKENHI (grant number 20K17919 to Yuki Shinya).
- **Competing interests:** The authors have no conflicts of interest to declare that are relevant to the content of this article.

- **Ethics approval:** The study was approved by the Institutional Review Board of The University of Tokyo Hospital (approval #2231) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.
- **Informed consent:** All patients provided written informed consent for study participation.
- **Data availability:** The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.
- **Author contributions:** Conceptualization: Motoyuki Umekawa and Yuki Shinya; Methodology: Motoyuki Umekawa and Yuki Shinya; Formal analysis and investigation: Motoyuki Umekawa and Yuki Shinya; Writing - original draft preparation: Motoyuki Umekawa; Writing - review and editing: Yuki Shinya, Hirotaka Hasegawa, Mariko Kawashima, Masahiro Shin, Atsuto Katano, Masanari Minamitani, Akinori Kashio, Kenji Kondo, and Nobuhito Saito; Funding acquisition: Yuki Shinya; Resources: Yuki Shinya, Hirotaka Hasegawa, Atsuto Katano, and Masanari Minamitani; Supervision: Nobuhito Saito.

References

1. Goldbrunner R, Weller M, Regis J, Lund-Johansen M, Stavrinou P, Reuss D, Evans DG, Lefranc F, Sallabanda K, Falini A, Axon P, Sterkers O, Fariselli L, Wick W, Tonn JC (2020) EANO guideline on the diagnosis and treatment of vestibular schwannoma. *Neuro Oncol* 22:31–45. doi:10.1093/neuonc/noz153
2. Nakatomi H, Jacob JT, Carlson ML, Tanaka S, Tanaka M, Saito N, Lohse CM, Driscoll CLW, Link MJ (2017) Long-term risk of recurrence and regrowth after gross-total and subtotal resection of sporadic vestibular schwannoma. *J Neurosurg* 1–7. doi:10.3171/2016.11.JNS16498
3. Gurgel RK, Dogru S, Amdur RL, Monfared A (2012) Facial nerve outcomes after surgery for large vestibular schwannomas: do surgical approach and extent of resection matter? *Neurosurg Focus* 33:E16. doi:10.3171/2012.7.FOCUS12199
4. Chen Z, Prasad SC, Di Lella F, Medina M, Piccirillo E, Taibah A, Russo A, Yin S, Sanna M (2014) The behavior of residual tumors and facial nerve outcomes after incomplete excision of vestibular schwannomas. *J Neurosurg* 120:1278–1287. doi:10.3171/2014.2.JNS131497
5. Zumofen DW, Guffi T, Epple C, Westermann B, Krahenbuhl AK, Zabka S, Taub E, Bodmer D, Mariani L (2018) Intended Near-Total Removal of Koos Grade IV Vestibular Schwannomas: Reconsidering the Treatment Paradigm. *Neurosurgery* 82:202–210. doi:10.1093/neuros/nyx143
6. Chung WY, Pan DH, Lee CC, Wu HM, Liu KD, Yen YS, Guo WY, Shiau CY, Shih YH (2010) Large vestibular schwannomas treated by Gamma Knife surgery: long-term outcomes. *J Neurosurg* 113 Suppl:112–121. doi:10.3171/2010.8.GKS10954
7. van de Langenberg R, Hanssens PE, Verheul JB, van Overbeeke JJ, Nelemans PJ, Dohmen AJ, de Bondt BJ, Stokroos RJ (2011) Management of large vestibular schwannoma. Part II. Primary Gamma Knife surgery: radiological and clinical aspects. *J Neurosurg* 115:885–893. doi:10.3171/2011.6.JNS101963
8. Yang HC, Kano H, Awan NR, Lunsford LD, Niranjana A, Flickinger JC, Novotny J Jr, Bhatnagar JP, Kondziolka D (2011) Gamma Knife radiosurgery for larger-volume vestibular schwannomas. Clinical article. *J Neurosurg* 114:801–807. doi:10.3171/2010.8.JNS10674
9. Williams BJ, Xu Z, Salvetti DJ, McNeill IT, Lerner J, Sheehan JP (2013) Gamma Knife surgery for large vestibular schwannomas: a single-center retrospective case-matched comparison assessing the effect of lesion size. *J Neurosurg* 119:463–471. doi:10.3171/2013.4.JNS122195

10. Bailo M, Boari N, Franzin A, Gagliardi F, Spina A, Del Vecchio A, Gemma M, Bolognesi A, Mortini P (2016) Gamma Knife Radiosurgery as Primary Treatment for Large Vestibular Schwannomas: Clinical Results at Long-Term Follow-Up in a Series of 59 Patients. *World Neurosurg* 95:487–501. doi:10.1016/j.wneu.2016.07.117
11. Iorio-Morin C, AlSubaie F, Mathieu D (2016) Safety and Efficacy of Gamma Knife Radiosurgery for the Management of Koos Grade 4 Vestibular Schwannomas. *Neurosurgery* 78:521–530. doi:10.1227/NEU.0000000000001154
12. Huang CW, Tu HT, Chuang CY, Chang CS, Chou HH, Lee MT, Huang CF (2018) Gamma Knife radiosurgery for large vestibular schwannomas greater than 3 cm in diameter. *J Neurosurg* 128:1380–1387. doi:10.3171/2016.12.JNS161530
13. Lefranc M, Da Roz LM, Balossier A, Thomassin JM, Roche PH, Regis J (2018) Place of Gamma Knife Stereotactic Radiosurgery in Grade 4 Vestibular Schwannoma Based on Case Series of 86 Patients with Long-Term Follow-Up. *World Neurosurg* 114:e1192–e1198. doi:10.1016/j.wneu.2018.03.175
14. Watanabe S, Yamamoto M, Kawabe T, Koiso T, Aiyama H, Kasuya H, Barfod BE (2019) Long-term follow-up results of stereotactic radiosurgery for vestibular schwannomas larger than 8 cc. *Acta Neurochir (Wien)* 161:1457–1465. doi:10.1007/s00701-019-03951-z
15. Hasegawa T, Kato T, Naito T, Tanei T, Ishii K, Tsukamoto E, Okada K, Ito R, Kouketsu Y (2021) Predictors of long-term tumor control after stereotactic radiosurgery for Koos grade 4 vestibular schwannomas. *J Neurooncol* 151:145–156. doi:10.1007/s11060-020-03622-5
16. Ogino A, Lunsford LD, Long H, Johnson S, Faramand A, Niranjana A, Flickinger JC, Kano H (2021) Stereotactic radiosurgery as the primary management for patients with Koos grade IV vestibular schwannomas. *J Neurosurg* 1–9. doi:10.3171/2020.8.JNS201832
17. Koos WT, Day JD, Matula C, Levy DI (1998) Neurotopographic considerations in the microsurgical treatment of small acoustic neurinomas. *J Neurosurg* 88:506–512. doi:10.3171/jns.1998.88.3.0506
18. Kawashima M, Hasegawa H, Shin M, Takahashi W, Shinya Y, Iwasaki S, Kashio A, Nakatomi H, Saito N (2020) Long-term Outcomes of Gamma Knife Radiosurgery for Treating Vestibular Schwannoma With a Lower Prescription Dose of 12 Gy Compared With Higher Dose Treatment. *Otol Neurotol* 41:e1314–e1320. doi:10.1097/MAO.0000000000002885
19. Shinya Y, Hasegawa H, Shin M, Sugiyama T, Kawashima M, Takahashi W, Iwasaki S, Kashio A, Nakatomi H, Saito N (2019) Long-Term Outcomes of Stereotactic Radiosurgery for Vestibular Schwannoma Associated with Neurofibromatosis Type 2 in Comparison to Sporadic Schwannoma. *Cancers (Basel)* 11. doi:10.3390/cancers11101498
20. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 28:1963–1972. doi:10.1200/JCO.2009.26.3541
21. Mindermann T, Schlegel I (2014) How to distinguish tumor growth from transient expansion of vestibular schwannomas following Gamma Knife radiosurgery. *Acta Neurochir (Wien)* 156:1121–1123. doi:10.1007/s00701-014-2063-3
22. Nagano O, Higuchi Y, Serizawa T, Ono J, Matsuda S, Yamakami I, Saeki N (2008) Transient expansion of vestibular schwannoma following stereotactic radiosurgery. *J Neurosurg* 109:811–816. doi:10.3171/JNS/2008/109/11/0811

23. Gardner G, Robertson JH (1988) Hearing preservation in unilateral acoustic neuroma surgery. *Ann Otol Rhinol Laryngol* 97:55–66. doi:10.1177/000348948809700110
24. House JW, Brackmann DE (1985) Facial nerve grading system. *Otolaryngol Head Neck Surg* 93:146–147. doi:10.1177/019459988509300202
25. Johnson S, Kano H, Faramand A, Pease M, Nakamura A, Hassib M, Spencer D, Sisterson N, Faraji AH, Arai Y, Monaco E, Niranjana A, Flickinger JC, Lunsford LD (2019) Long term results of primary radiosurgery for vestibular schwannomas. *J Neurooncol* 145:247–255. doi:10.1007/s11060-019-03290-0
26. Won SY, Kilian A, Dubinski D, Gessler F, Dinc N, Lauer M, Wolff R, Freiman T, Senft C, Konczalla J, Forster MT, Seifert V (2020) Microsurgical Treatment and Follow-Up of KOOS Grade IV Vestibular Schwannoma: Therapeutic Concept and Future Perspective. *Front Oncol* 10:605137. doi:10.3389/fonc.2020.605137
27. Huang MJ, Kano H, Mousavi SH, Niranjana A, Monaco EA 3, Arai Y, Flickinger JC, Lunsford LD (2017) Stereotactic radiosurgery for recurrent vestibular schwannoma after previous resection. *J Neurosurg* 126:1506–1513. doi:10.3171/2016.5.JNS1645
28. Radwan H, Eisenberg MB, Sandberg Knisely JP, Ghaly MM, Schuller M (2016) Outcomes in Patients with Vestibular Schwannoma after Subtotal Resection and Adjuvant Radiosurgery. *Stereotact Funct Neurosurg* 94:216–224. doi:10.1159/000447520
29. Starnoni D, Daniel RT, Tuleasca C, George M, Levivier M, Messerer M (2018) Systematic review and meta-analysis of the technique of subtotal resection and stereotactic radiosurgery for large vestibular schwannomas: a "nerve-centered" approach. *Neurosurg Focus* 44:E4. doi:10.3171/2017.12.FOCUS17669
30. Breshears JD, Chang J, Molinaro AM, Sneed PK, McDermott MW, Tward A, Theodosopoulos PV (2019) Temporal Dynamics of Pseudoprogression After Gamma Knife Radiosurgery for Vestibular Schwannomas-A Retrospective Volumetric Study. *Neurosurgery* 84:123–131. doi:10.1093/neuros/nyy019
31. Hayhurst C, Zadeh G (2012) Tumor pseudoprogression following radiosurgery for vestibular schwannoma. *Neuro Oncol* 14:87–92. doi:10.1093/neuonc/nor171
32. Pollock BE (2006) Management of vestibular schwannomas that enlarge after stereotactic radiosurgery: treatment recommendations based on a 15 year experience. *Neurosurgery* 58: 241–248; discussion 241–248 doi:10.1227/01.NEU.0000194833.66593.8B
33. Johnson S, Kano H, Faramand A, Niranjana A, Flickinger JC, Lunsford LD (2019) Predicting hearing outcomes before primary radiosurgery for vestibular schwannomas. *J Neurosurg* 1–7. doi:10.3171/2019.5.JNS182765
34. Frischer JM, Gruber E, Schoffmann V, Ertl A, Hoftberger R, Mallouhi A, Wolfsberger S, Arnoldner C, Eisner W, Knosp E, Kitz K, Gatterbauer B (2018) Long-term outcome after Gamma Knife radiosurgery for acoustic neuroma of all Koos grades: a single-center study. *J Neurosurg* 1–10. doi:10.3171/2017.8.JNS171281
35. Ruess D, Pohlmann L, Grau S, Hamisch C, Hoevels M, Treuer H, Baues C, Kocher M, Ruge M (2020) Outcome and toxicity analysis of single dose stereotactic radiosurgery in vestibular schwannoma based on the Koos grading system. *Sci Rep* 10:9309. doi:10.1038/s41598-020-66213-4
36. Han JH, Kim DG, Chung HT, Paek SH, Park CK, Kim CY, Hwang SS, Park JH, Kim YH, Kim JW, Kim YH, Song SW, Kim IK, Jung HW (2012) The risk factors of symptomatic communicating hydrocephalus after stereotactic radiosurgery for unilateral vestibular schwannoma: the implication of brain atrophy. *Int J Radiat Oncol Biol Phys* 84:937–942. doi:10.1016/j.ijrobp.2012.01.048
37. Powell C, Micallef C, Gonsalves A, Wharram B, Ashley S, Brada M (2011) Fractionated stereotactic radiotherapy in the treatment of vestibular schwannoma (acoustic neuroma): predicting the risk of hydrocephalus. *Int J Radiat Oncol Biol Phys* 80:1143–1150. doi:10.1016/j.ijrobp.2010.04.019

Figures

Figure 1

Illustrative cases of stereotactic radiosurgery (SRS) for Koos grade IV vestibular schwannomas (VSs). A 57-year-old man presented with hearing loss on the left side, and magnetic resonance imaging (MRI) revealed a Koos grade IV VS (maximum diameter: 32 mm, tumor volume: 6.8 mL), causing considerable compression of the brainstem (a). SRS planning with a prescription dose of 12 Gy with a 50% isodose line (b); follow-up MRI revealed favorable tumor control and brainstem decompression 114 months after the SRS (c). A 51-year-old man with a Koos grade IV VS (maximum diameter: 30 mm, tumor volume: 7.4 mL) causing hearing loss and trigeminal dysesthesia on the right side (d), treated with SRS (prescription dose: 12 Gy, with a 50% isodose line; e). The tumor considerably decreased in size and the trigeminal dysesthesia was completely resolved 29 months after the SRS (f)

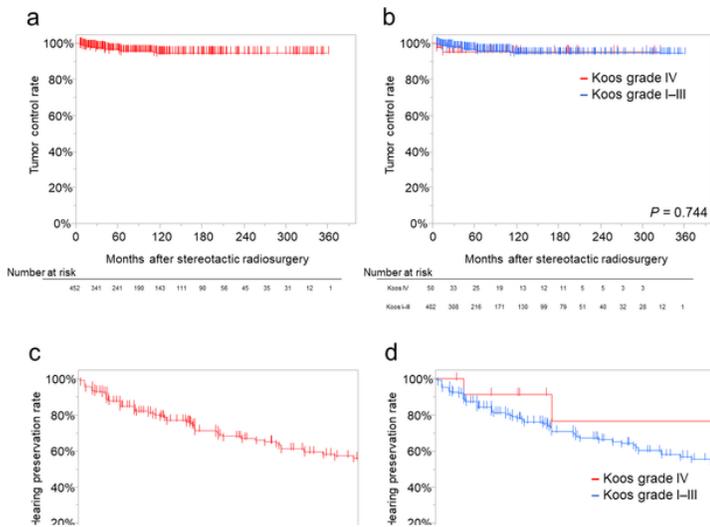


Figure 2

Kaplan–Meier curves are indicated for (a) tumor control rates for the entire cohort and (b) tumor control rates comparing the groups with Koos grade IV and Koos grade I–III vestibular schwannomas. Kaplan–Meier curves for functional preservation rates are indicated as follows: (c) Hearing preservation rates, (e) facial nerve preservation rates, and (g) trigeminal nerve preservation rates for the entire cohort; (d) hearing preservation rates, (f) facial nerve preservation rates, and (h) trigeminal nerve preservation rates comparing the groups with Koos grade IV and Koos grade I–III vestibular schwannomas

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTables.docx](#)