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RESEARCH

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

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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. Progression-free survival rates were 91% at 5 and 10 years for Koos grade IV VSs, and 95% and 92%, respectively, for Koos grade I−III VSs ($p=0.278$). 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.

Keywords Vestibular schwannomas · Koos grade IV · Stereotactic radiosurgery · Gamma Knife radiosurgery

Introduction

Vestibular schwannomas (VSs) are relatively common, benign brain tumors originating from the vestibulocochlear nerve. Tumor size is important 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 [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 group and 47% in the subtotal resection group, respectively [2]; in contrast, reported facial nerve preservation rates were 47−89% and 47−93%, respectively [3–5].

SRS may be effective and safe for larger VSs, with tumor control rates of 80%−98%, 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. Additionally, hypofractionated SRS has similar outcomes to single-session SRS for VSs and is applicable for larger tumors [17–19]. However, there is a paucity of

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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 an institutional database. Exclusion criteria were: (i) < 6 months' 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) [20].

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, as previously described [21, 22]. 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 planned radiosurgery via commercially available software (the KULA planning system [Elekta Instruments] until 1998, Leksell Gamma Plan [Elekta Instruments] thereafter). In principle, 12–14 Gy was prescribed to the tumor margin with a 50% ± 5% isodose line. Prescription doses > 12 Gy were used to treat VSs before 2000; thereafter, 12 Gy was used for all treatments [21].

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. Tumor responses were monitored according to the Response Assessment in Neuro-Oncology criteria [23]; tumor progression was defined as an enlargement in volume of ≥ 25% upon two or more consecutive post-SRS imaging studies [24, 25]. Transient expansion was meticulously distinguished from actual tumor progression by evaluation of consecutive MRIs [26, 27]. 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 [28]. Facial nerve function was evaluated with House-Brackmann (HB) grading [29]. A Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grade was retrospectively assigned based on the descriptions of adverse events. Data for 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. For illustrative cases, see 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. Progression-free survival rates (PFRs), 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 PFRs 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).

Results

Baseline characteristics and neurological symptoms

Patient characteristics and neurological status before SRS are summarized in Table 1. The median post-SRS

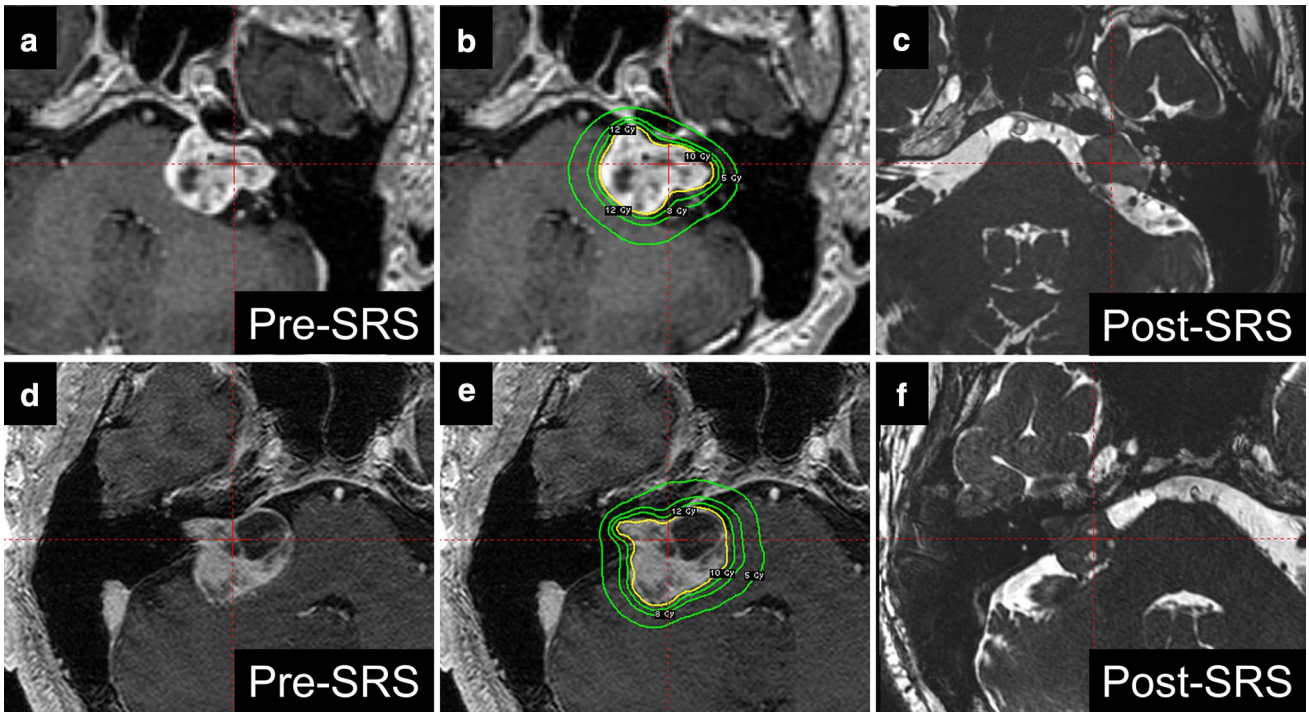

Fig. 1 Illustrative cases of stereotactic radiosurgery (SRS) for Koos grade IV vestibular schwannomas (VSs). A 57-year-old man presented with hearing loss on the left side, and magnetic resonance imaging (MRI) revealed a Koos grade IV VS (maximum diameter: 32 mm, tumor volume: 6.8 mL), causing considerable 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**)

follow-up period was 68 (range, 6–361) months overall, and 63 (range, 6–324) 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%; $p < 0.001$). Among the 93 patients who underwent resection before SRS, planned adjuvant SRS was performed in 28 (30%) and salvage SRS for regrowth after surgery in 65 (70%). Neurological symptoms were also compared between the groups (Table 1). A smaller proportion of patients in the Koos grade IV group than that 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%, $p = 0.034$).

Tumor progression

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 re-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 PFR was 94.7% at 5 years and 92.2% at 10 and 15 years (Fig. 2a). In the Koos grade IV group, the PFR was 90.6% at 5, 10, and 15 years, and no differences were observed with the Koos grade I−III group (95.1%, 92.4%, and 92.4% at the respective intervals; $p = 0.278$; Fig. 2b). Koos grade IV VSs were not associated with tumor progression in the bivariate or multivariable analyses. Only prior direct surgery was associated with tumor progression in the bivariate (HR = 2.96, 95% CI = 1.31–6.66, $p = 0.009$) and multivariable (HR = 2.85, 95% CI = 1.25–6.49, $p = 0.013$) analyses (Table 2).

Among the 14 patients with Koos grade IV VSs with a maximum tumor diameter ≥ 30 mm (median follow-up

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 [range]				Wilcoxon rank-sum test
Age, years	58 [14–93]	57 [28–86]	58 [14–93]	0.919
Follow-up, months	68 [6–361]	63 [6–324]	69 [6–361]	0.291
Maximum diameter, mm	18 [4–37]	26 [20–37]	17 [4–26]	< 0.001*
Target volume, mL	1.3 [0.1–17.0]	5.3 [2.0–17.0]	1.2 [0.1–6.0]	< 0.001*
Prescription dose, Gy	12 [8–25]	12 [12–18]	12 [8–25]	0.683
Central dose, Gy	24 [16–40]	24 [22–38]	24 [16–40]	0.401
Cochlear dose (mean), Gy	3.5 [1.1–7.2]	4.6 [1.8–6.0]	3.5 [1.1–7.2]	0.137
Cochlear dose (maximum), Gy	6.3 [2.0–14.5]	7.6 [2.3–8.4]	6.2 [2.0–14.5]	0.499
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

*Significant at $p < 0.05$

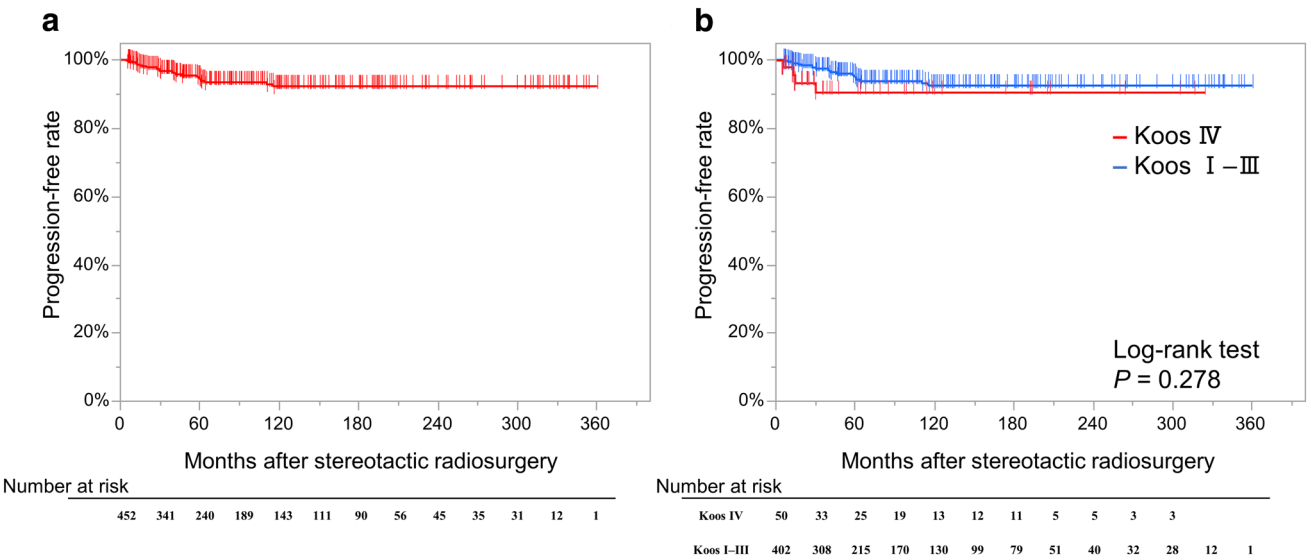

Fig. 2 Kaplan–Meier curves are indicated for (**a**) progression-free survival rates for the entire cohort and **b** progression-free survival rates of the groups with Koos grade IV and Koos grade I–III vestibular schwannomas

period of 60 months), 1 was treated with surgical resection for cystic expansion 5 months after SRS, and all 4 patients (8%, median follow-up period of 123 months) with a tumor volume ≥ 10 mL exhibited tumor shrinkage.

Hearing preservation

Among 199 patients with serviceable hearing function before SRS, hearing function was preserved in 119 (59.8%).

Table 2 Multivariable analysis for factors associated with tumor progression

Factor	Bivariate		Multivariable	
	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Age at SRS > 60 years	1.10 [0.48–2.52]	0.819		
Male sex	0.51 [0.22–1.18]	0.116	0.52 [0.22–1.21]	0.129
Koos grade IV (vs. Koos grade I–III)	1.80 [0.61–5.26]	0.285	1.37 [0.46–4.07]	0.575
Maximum diameter ≥ 30 mm	1.57 [0.21–11.66]	0.657		
Target volume ≥ 4 mL	2.06 [0.82–5.18]	0.126		
Prescription dose ≤ 12 Gy	0.62 [0.28–1.39]	0.248		
Central dose ≤ 24 Gy	0.81 [0.36–1.84]	0.616		
Prior direct surgery	2.96 [1.31–6.66]	0.009*	2.85 [1.25–6.49]	0.013*
Transient tumor expansion	0.40 [0.09–1.68]	0.210		

* Significant at $p < 0.05$. HR, hazard ratio; CI, confidence interval; SRS, stereotactic radiosurgery

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. 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, similar to those in the Koos grade I−III group (respective rates of 78.3%, 68.1%, and 53.0%; $p = 0.645$). Upon multivariable analysis, Koos grade did not exhibit significant associations with hearing outcomes; however, a mean cochlear dose of ≤ 5 Gy was significantly associated with better hearing preservation (HR = 1.97, 95% CI = 1.06–3.65, $p = 0.033$; 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 10/11 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. In the Koos grade IV group, the preservation rates were 95.5% at 5, 10, and 15 years, similar to those in the Koos grade I−III group, (97.7% at each time point; $p = 0.410$). Koos grade was not a risk factor for poor facial nerve preservation (Supplementary Table 1 in Online Resource 1). However, a prescription dose of ≤ 12 Gy was independently associated with better facial nerve preservation (HR = 6.52, 95% CI = 1.73–24.61, $p = 0.006$).

Trigeminal nerve preservation

New or worsened trigeminal nerve deficits after SRS were observed in 12 patients, overall (2.7%). The trigeminal nerve preservation rates were 97.5% at 5 years and 97.1% at 10 and 15 years. In the Koos grade IV group, the preservation rates were 96.1% at 5 years and 91.6% at 10 and 15 years, similar to those in the Koos grade I−III group, (97.7% at each time point; $p = 0.107$). Koos grade was not a risk factor for poor trigeminal nerve preservation (Supplementary Table 1 in Online Resource 1). However, a prescription dose of ≤ 12 Gy was independently associated with better trigeminal nerve preservation (HR = 6.71, 95% CI = 1.81–24.87, $p = 0.004$), and prior direct surgery was associated with poorer preservation (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. Age > 60 years was the only factor independently associated with post-SRS hydrocephalus (HR = 4.38, 95% CI = 1.16–16.59, $p = 0.030$; Supplementary Table 1 in Online Resource 1).

TTE

TTE was 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 (range, 1−47) months after SRS, and that to the end of TTE was 12 (range, 2−68) months. Compared with the start of tumor expansion in 24 patients with true tumor progression (median, 30 months), TTE in the above 80 patients started earlier (median: 6 months; $p < 0.001$). Symptomatic TTE occurred in 14 patients (3.1%), more commonly in patients

with Koos grade IV VSs (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 [1.1%]), and vertigo (eight [1.8%]). All symptoms were mild and disappeared as the tumor stopped expanding.

Primary vs. post-resection SRS

Details are described in Online Resource 2 and Supplementary Tables 3−5 in Online Resource 1.

Discussion

In this study, SRS yielded long-term tumor control and low complication rates in patients with Koos grade IV VSs. PFRs were satisfactory, at 90.6%, 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 the abovementioned previous studies in terms of tumor control and preservation of neurological function, as well as to patients with Koos grade I−III VSs in our cohort.

In terms of tumor control, the validity of SRS for larger VSs is controversial. Larger tumor volume correlated with control failure in several reports [8, 9, 12, 30]; in others, no correlation was observed 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. In other studies, lower prescription doses (≤ 12 Gy) yielded equivalent tumor control to higher doses [8, 12, 21, 30]. 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 PFR (90.6%) was similar to those in previous studies, and, among factors that were previously associated with tumor progression, previous resection was the only such factor in our cohort [8, 15]. Tumors that exhibit progression after resection may be aggressive, resulting in poorer control with SRS. Moreover, Koos grade was not associated with tumor progression in the primary SRS cohort in our study, with none of the Koos grade IV tumors exhibiting progression. Thus, the choice of SRS for primary treatment should not be made based on Koos grade.

In several studies, SRS provided comparable tumor control and cranial nerve preservation to surgery for Koos grade IV tumors [4, 5, 31]. 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 other studies of large-VS cohorts treated with SRS [11, 13, 16]. 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 tumor control and cranial nerve preservation [32–34]. Such combined treatment may compensate for the disadvantages of surgery for large VSs, yielding 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 TTE was significantly more common with Koos grade IV than with grade I–III VSs in our cohort. Therefore, patients with Koos grade IV VSs may require careful observation in terms of symptomatic TTE. Additionally, TTE needs to be differentiated from true tumor progression to avoid unnecessary surgery. Most TTE occurs approximately 6−18 months after SRS and true tumor progression generally occurs 24 months after SRS [27, 35–37]. Similarly, in this study, TTE occurred approximately

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, %	PFR, %	Hearing preservation, %	Facial nerve preservation, %	VPS, %
Yang et al., 2011	65	3−4 cm	12	36	26	89 (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	91 (3 y)	65.8 (3 y)	100	1.2
Hasegawa et al., 2021	203	Koos grade IV	12	152	25	82 (10 y)	39 (5 y)	100	3
Ogino et al., 2021	170	Koos grade IV	12.5	61.2	0	91 (10 y)	36 (7 y)	96	5
Present study	50	Koos grade IV	12	63	44	91 (10 y)	61.1 (10 y)	96	4

F/U follow up; *m* months; *N* number; *NA* not available; *PFR* progression-free survival rate; *SRS* stereotactic radiosurgery; *VPS* ventriculo-peritoneal shunt; *VS* vestibular schwannoma; *y* year

6 months after SRS, and true progression at 28 months. However, especially in the Koos IV group, there was a tendency for tumors to be resected during TTE, before they could stabilize or shrink, resulting in control failure, and these facts should still be fully considered.

The effect of tumor size on post-SRS neurological outcomes remains controversial. Johnson et al. [38] reported that smaller tumors (≤ 1.2 mL) were associated with better hearing preservation; however, this was not confirmed in previous studies [39, 40] or in ours. Indeed, the hearing preservation rate (61% at 10 years) in our study was comparable to those other studies (34–66% at 2–7 years after SRS), and suppression of the mean cochlear dose ≤ 5 Gy contributed to better hearing preservation, as in previous studies. [8, 11, 13, 15, 16, 41, 42]. 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 such deficits. Moreover, we demonstrated that a lower prescription dose was associated with better trigeminal nerve preservation [21]. These results suggest that a modest prescription dose (12 Gy) may be a suitable treatment even for larger VSs; validation with larger samples is needed.

Hydrocephalus is a major complication of SRS for VSs, with an incidence of 5.6%–11% [43, 44]. While older age is a well-known risk factor for post-SRS hydrocephalus, tumor size is not a clear risk. In this study, larger 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. First, this was a retrospective, single-center study, which might have introduced a selection bias. Second, the small numbers of patients with Koos grade IV VSs (50) and treatment failure may have led to inaccurate assessment of risk factors. Third, we did not analyze the size limit of SRS treatment in this group. Future studies are warranted to determine the highest VS volume for which SRS is practical and safe in the long term. Finally, 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 such tumors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11060-022-04058-9.

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Author contributions Conceptualization: MU and YS; Methodology: MUand YS; Formal analysis and investigation: MU and YS; Writing—original draft preparation: MU; Writing—review and editing: YS, HH, MK, MS, AK, MM, AK, KK, and NS; Funding acquisition: YS; Resources: YS, HH, AK, and MM; Supervision: NS.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Competing interest 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.

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