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RESEARCH

Stereotactic radiosurgery for Koos grade IV vestibular schwannoma in young patients: a multi-institutional study

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Abstract

Purpose Surgery is the treatment of choice for large vestibular schwannomas (VS). Stereotactic radiosurgery (SRS) has been suggested as an alternative to resection in selected patients. However, the safety and efficacy of SRS in Koos grade IV patients ≤ 45 years old has not been evaluated. The aim of this study is to describe the clinical and radiological outcomes of Koos grade IV in young patient managed with a single-session SRS.

Methods This retrospective, multicenter analysis included SRS-treated patients, ≤ 45 years old presenting with non-life threatening or incapacitating symptoms due to a Koos Grade IV VS and with follow-up ≥ 12 months. Tumor control and neurological outcomes were evaluated.

Results 176 patients [median age of 36.0 (IQR 9) and median tumor volume of 9.3 cm^3 (IQR 4.7)] were included. The median prescription dose was 12 Gy (IQR 0.5). Median follow-up period was 37.5 (IQR 53.5) months. The 5- and 10-year progression-free survival was 90.9% and 86.7%. Early tumor enlargement occurred in 10.9% of cases and was associated with tumor progression at the last follow-up. The probability of serviceable hearing preservation at 5- and 10-years was 56.8% and 45.2%, respectively. The probability of improvement or preservation of facial nerve function was 95.7% at 5 and 10-years. Adverse radiation effects were noted in 19.9%. New-onset hydrocephalus occurred in 4.0%.

Conclusion Single-session SRS is a safe and effective alternative to surgical resection in selected patients ≤ 45 years old particularly those with medical co-morbidities and those who decline resection. Longer term follow up is warranted.

Keywords Koos grade IV · Vestibular schwannoma · Stereotactic radiosurgery · Young age

Abbreviations

ARE	Adverse radiation effect
CI	Confident interval
GR	Gardner–Robertson
HB	House-Brackmann
HR	Hazard-Ratio
IRRF	International Radiosurgery Research Foundation
SRS	Stereotactic radiosurgery
VPS	Ventriculoperitoneal shunt
VS	Vestibular schwannoma

Introduction

Vestibular schwannoma (VS) is the most common tumor of the cerebellopontine angle [1]. It can be treated by resection or stereotactic radiosurgery (SRS). The indication depends mainly on the tumor size, and SRS is often reserved for small and medium-sized tumor. Koos grade IV, i.e. tumor compressing the brainstem [2] are usually considered for surgery [3]. However, the management of patients with

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medical contraindications to or those who refuse surgery remains controversial. Literature reporting outcomes of SRS for Koos grade IV VS are limited mostly to single center series [4–7]. Recently, a multi-institutional, retrospective study was published showing good tumor control and facial nerve preservation, increasing the evidence for the effectiveness of SRS as an alternative to surgery in these cases [8].

Resection is frequently recommended to younger patients with Koos grade IV vestibular schwannomas. These patients often lack the medical contraindications that elderly patients with vestibular schwannoma patients harbor. However, the risks of mortality with microsurgery for larger VS vary from 0.4 to 2.1% [9–13] and long-term tumor control are between 83 and 96.5% [12, 14–16], mainly dependent of the extent of resection [17]. SRS is a definitive treatment in many elderly patients with VS's. The aim of this retrospective multicenter study was to evaluate the outcomes of single-session SRS for Koos grade IV VS in patients under 45 years old.

Materials and methods

Patient population and inclusion criteria

This study included patients ≤ 45 years old managed with a single-session SRS for a grade IV VS. It involved patients from ten participating centers through the International Radiosurgery Research Foundation [18]. Each center obtained review board approval for the study and for sharing the database.

The inclusion criteria were (1) Single-session SRS for Koos Grade IV VS, (2) at least 12 months of clinical and radiological follow-up, (3) age ≤ 45 years at treatment. Exclusion criteria were (1) history of prior resection, (2) history of neurofibromatosis, (3) presentation with life-threatening symptoms (i.e., acute hydrocephalus) or incapacitating symptoms (debilitating ataxia, refractory trigeminal neuralgia, incapacitating headaches). Following SRS, patients typically undergo clinical and brain MRI follow-ups every 6–12 months for the first 2 years and yearly thereafter.

The following clinical data were collected: patient age at SRS, performance status at diagnosis, SRS, and last follow-up, date of VS diagnosis and vestibulocochlear, trigeminal and facial nerve function at SRS and at last follow-up. Hearing was classified using the Gardner–Robertson (GR) hearing scale [19] and facial nerve functional status using the House-Brackmann classification [20].

The following SRS parameters were collected: tumor volume, margin dose, isodose line, number of isocenters, prescription volume, maximum treatment dose and maximum dose to the cochlea.

Follow-up data collected included tumor control rate, hearing, facial and trigeminal nerves outcome, occurrence of post-SRS hydrocephalus, overall survival, and any salvage therapy following SRS.

Adverse-radiation effects (ARE) included post-SRS T2 hyperintensities documented on images, cysts, and radiation necrosis. Local failure was defined as VS volume increase of > 20% from baseline at the last follow-up. Early VS expansion was defined as an increase in VS volume within the 36 months of treatment followed by tumor stability or regression. VS stability was defined as tumor volume within 20% from baseline at last radiological follow-up and VS regression as a decrease in tumor volume of > 20% from baseline.

SRS technique and treatment parameters

Single-session SRS was delivered using the Gamma Knife technology available at each center. The targeting used Stereotactic, high-resolution brain MRI and/or CT scanning. A dose plan was performed by the local multidisciplinary team to deliver an effective radiation dose to the target tumor. The median prescription dose used was 12 Gy (IQR 0.5) at a median isodose line of 50% (IQR 0; Table 1).

Statistical analysis

Statistical analysis were performed using R (R foundation of Statistical computing) [21]. A p-value < 0.05 was considered statistically significant. Kaplan–Meier analysis was performed to evaluate time-dependent tumor-control, hearing preservation and facial nerve preservation. Univariate and multivariate analysis were performed for outcome using Cox-regression analysis. Statistically significant factors and clinically relevant one with a p-value less than 0.20 were included in the multivariate analysis.

Results

Patient and tumor characteristics

176 patients [89 males (50.6%), median age 36.0 (IQR 9) years old]. Data on the indication of SRS were available for 146 patients; 3 (2.1%) patients were unfit to resection and 143 (97.9%) patients refused resection (Table 1). Three (1.7%) patients presented with hydrocephalus and underwent ventriculo-peritoneal shunt (VPS) insertion prior to SRS. The median tumor volume was 9.3 (IQR 4.7) cm^3.

Clinical and radiological outcomes

Radiological outcome data were available for 175 patients. At a median follow-up period of 37.5 (IQR 53.5) months, tumor stability and regression were noted in 38.9% (68/175)

Table 1 Characteristics of 176 young patients treated for Koos grade IV vestibular schwannoma

Variable	Value
Median age at SRS in years (IQR)	36.0 (9)
Gender, n (%)	
Male	89 (50.6)
Female	87 (49.4)
Symptoms at SRS, n (%)	
None	5 (2.8)
Facial palsy	16 (9.1)
Hemifacial spasm	1 (0.6)
Hearing deterioration	115 (65.3)
Tinnitus	104 (59.1)
Vertigo	22 (12.5)
Trigeminal nerve dysfunction	60 (34.1)
Gait disorder	23 (13.1)
Hydrocephalus	3 (1.7)
Visual distrubance	3 (1.7)
Hemiparesis	0
Sensory loss	4 (2.3)
Median tumor volume in cm^3 (IQR)	9.3 (4.7)
Median prescription dose in Gy (IQR)	12 (0.5)
Median isodose line in % (IQR)	50 (0)
Median cochlea dose in Gy (IQR)	4.5 (2.4)
Median clinical FU in month (IQR)	33 (29.3)
Median radiological FU in month (IQR)	37.5 (53.5)

n number, *SRS* stereotactic radiosurgery, *IQR* inter-quartile range, *FU* follow-up

Table 2 Tumor radiological outcomes for 175 young patients treated for Koos grade IV vestibular schwannoma

Outcome	Value
Regression, no. of patients (%)	95 (54.3)
Stable, no. of patients (%)	68 (38.9)
Progression, no. of patients (%)	12 (6.9)
Tumor control rate [CI 95%]	
5 years	90.9 [85.5–96.6]
10 years	86.7 [79.3–94.8]

n number, *CI 95%* 95% confident interval

and 54.3% (95/175) patients, respectively. Tumor progression was noted in 6.9% (12/175) patients. Of these with progression, eight underwent VS resection, one VPS insertion, and three were managed conservatively.

Early tumor enlargement occurred in 10.9% of the patients (19/175) necessitating VPS insertion in two and VS resection in five patients. The 12 remaining patients were treated medically typically with a short course of steroids (Table 2).

The probability of 5-year and 10-year progression free survival was 90.9 [CI 95% 85.5–96.6] and 86.7 [CI 95% 79.3–94.8], respectively (Fig. 1a). On multivariate analysis, early tumor enlargement was associated with tumor progression at the last follow-up ($p = 0.00002$, HR 19.6 [CI 95% 5.1–75.8]. Neither margin dose nor tumor volume were associated with tumor progression (Suppl. Table 1).

Cranial nerve outcomes

Median neurological follow-up was 33 (IQR 29.3) months and was available for 176 patients.

Vestibulocochlear outcomes

Serviceable hearing (i.e., GR classes 1 and 2) was present in 51.7% (91/176) patients at SRS and in 33.0% (58/176) at the last follow-up (Table 3). The serviceable hearing preservation rates at the 3-, 5-, and 10-year follow-up were 70.4% [CI 95% 60.6–81.8], 56.8% [CI 95% 45.6–70.8], and 45.2% [CI 95% 32.9–62.2] respectively (Fig. 1b, c).

Dose to cochlea was only available in 48 patients with serviceable hearing at SRS. The 48 patients were included in a multivariate analysis. Female sex was associated with serviceable hearing at last follow-up ($p = 0.0124$, HR 5.0 [CI 95% 1.4–17.8]) (Suppl. Table 2).

Facial and trigeminal nerves outcomes

Facial nerve neuropathy (i.e., HB grade > 1) was present in 8.5% (15/176) prior to SRS and in 7.4% (13/176) at last follow-up. At a median clinical follow-up of 33 [IQR 29.3] months, the facial nerve function was improved in 6.3% (11/176), stable in 90.9% (160/176) and worse in 2.8% (5/176) (Table 4). The 3-, 5-, 10-year of post-SRS facial nerve function improvement or preservation was 98.7% [CI 95% 97.0–1], 95.7% [CI 95% 91.2–1], and 95.7% [CI 95% 91.2–1] respectively (Fig. 1d). A margin dose > 13 Gy was associated with facial nerve deterioration at last follow-up in univariate but not in multivariate analysis (Suppl. Table 3).

Trigeminal neuropathy was present in 34.1% of patient in pre-SRS (60/176) and consisted in trigeminal neuralgia in 10, numbness in 44 and both for 6. At last follow-up, the trigeminal nerve status was improved, stable, and worsened in 14.8% (26/176), 80.1% (141/176), and 5.1% (9/176), respectively (Table 4.)

Adverse radiation effect was associated with deterioration of trigeminal nerve status at last follow-up in Cox multivariate analysis ($p = 0.03$, HR 5.2 [CI 95% 1.2–22.3]. (Suppl. Table 4).

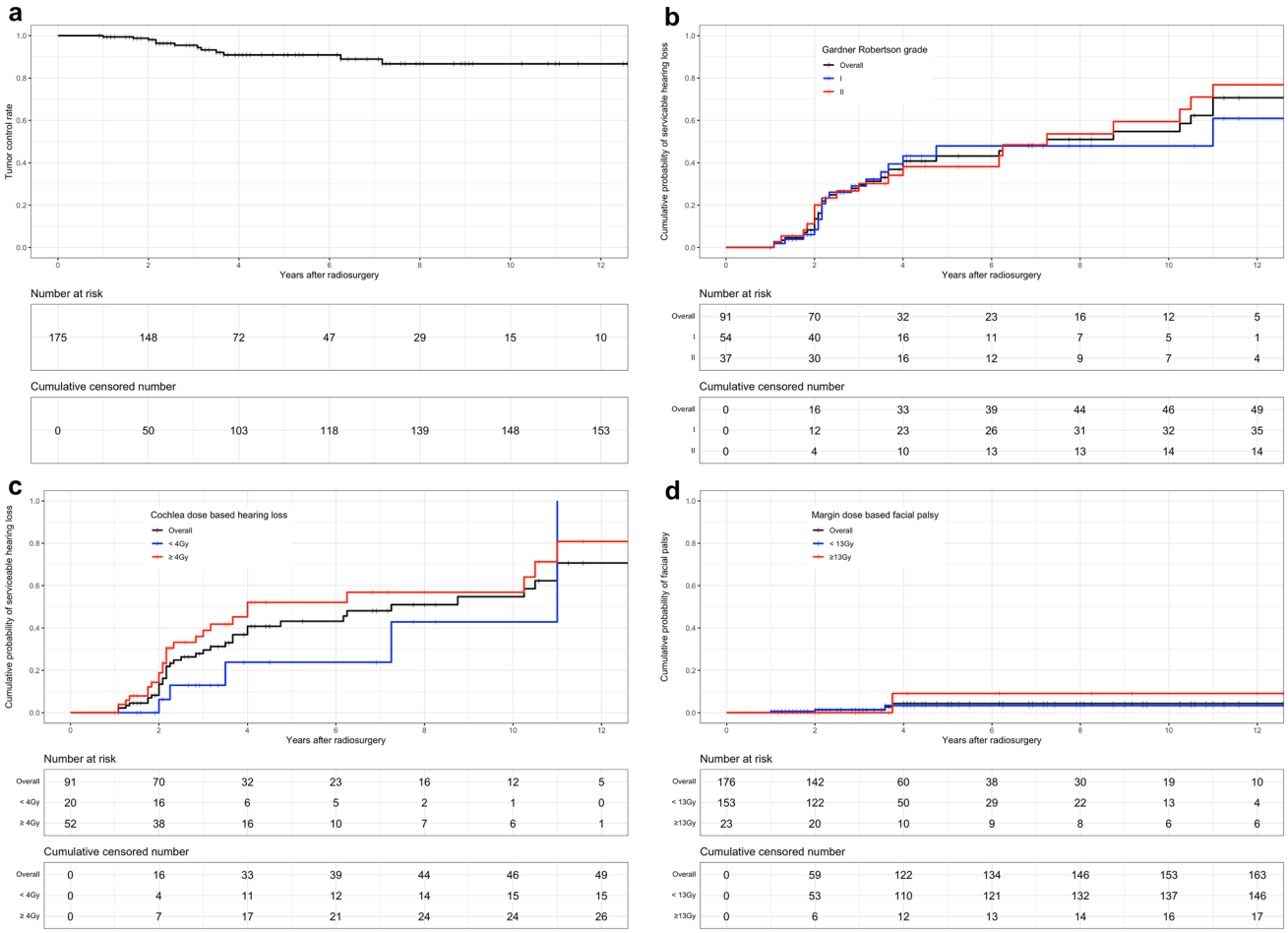

Fig. 1 Kaplan–Meier plots for tumor control rate (**a**), probability of serviceable hearing loss at last follow-up between patients with pre-SRS GR class I and II (**b**), probability of serviceable hearing loss at last follow-up between patients with cochlea dose < 4 Gy or ≥ 4 Gy (**c**), probability of facial palsy between patients treated with ≥ 13 Gy and < 13 Gy (**d**)

Table 3 Vestibulocochlear nerve function pre-SRS and at the last follow-up for 176 young patients

Serviceable hearing	Pre-SRS	Post-SRS	GR class	Pre-SRS	Post-SRS
Yes	91 (51.7)	58 (33.0)	1	54 (30.7)	33 (18.8)
			2	37 (21.0)	25 (14.2)
No	85 (48.3)	118 (67.0)	3	35 (19.9)	38 (21.6)
			4	16 (9.1)	24 (13.6)
			5	34 (19.3)	56 (31.8)

Data are expressed as number (percentages)

SRS stereotactic radiosurgery, *GR* Gardner–Robertson scale

Complications

ARE was noted in 19.9% (35/176) of the patients and included cyst formation in 9 patients, brainstem hyperintensities in 17 patients, and symptomatic enlargement in 9. Two of the patients with cyst formation were managed with resection of VS, the other managed conservatively. Among patients with brainstem hyperintensities, one patient was treated with surgical resection and the other medically. Seven of them were managed with resection of VS, 14 with usually short course of steroid therapy, and 14 with conservative management. Among the patients with symptomatic enlargement, four received surgical resection of VS and the other medically. Medical management include typically short course of steroids. In multivariate analysis, occurrence of ARE was inversely correlated to a margin dose > 11 Gy (p = 0.02, HR 0.4 [CI 95% 0.2–0.9]) (Suppl. Table 5).

New-onset hydrocephalus after SRS occurred in 4.0% (7/176) of the patients, and it was managed with VPS in 71.4% (5/7). A tumor volume at SRS > 10 cm^3 was associated with the occurrence of new hydrocephalus in multivariate analysis (p = 0.01, HR 24.06 [CI 95% 2.4–240.4] (Suppl. Table 6). No procedure or tumor-related mortality

Table 4 Cranial nerve status pre-SRS and at last follow-up for 176 young patients

	Pre-SRS	Post-SRS
Trigeminal neuropathy		
No	116 (65.9)	135 (76.7)
Yes	60 (34.1)	41 (23.3)
Pain	10 (5.7)	17 (9.7)
Sensation loss	44 (25.0)	24 (13.6)
Both	6 (3.4)	0
Trigeminal nerve function		
Improved		26 (14.8)
Stable		141 (80.1)
Deteriorated		9 (5.1)
Facial nerve function at the last follow-up		
Improved		11 (6.3)
Stable		160 (90.9)
Deteriorated		5 (2.8)
House-Brackmann scale		
I	161 (91.5)	163 (92.6)
II	5 (2.8)	6 (3.4)
III	7 (4.0)	7 (4.0)
IV	2 (1.1)	0
V	0	0
VI	1 (0.6)	0

Data are expressed as number (percentages)

SRS stereotactic radiosurgery

occurred during the follow-up. No malignant transformation was observed in this study.

Discussion

Single-session SRS appears to be a safe and effective option in selected young patients with Koos grade IV VS. In this analysis of 176 patients, at a median follow-up of 37.5 (IQR 53.5) months, tumor control was 93.2%. The actuarial tumor control at 5- and 10-years was 90.9% and 86.7%, respectively in accordance to previously reported tumor control rates ranging from 88 to 97.9% [4, 22–24]. Early tumor expansion is the sole risk factor of tumor progression, $p < 0.0001$, HR 19.6 [CI 95% 5.1–75.8]. In contrast to the study by Ogino et al. [4], the margin dose in this report was not identified as a risk factor for tumor progression. A recent study from Kawashima et al., shows a tumor control at 5 and 10 years of 90.2% and 85.4% in 49 young patients with primary or secondary SRS. Age was not a risk factor for tumor control in their series in multivariate analysis [25].

Early VS expansion, within 36 months of SRS, occurred in 10.9% of patients. Of these, 2.3% underwent VS resection and 1.2% VPS insertion. VS expansion occurs in 6–74% of patients after SRS for VS [26, 27]. In small VS, this growth is mostly followed by stability or regression during follow-up and is considered benign in most cases [28]. However, early, post-SRS tumor expansion in Koos grade IV patients may result in symptomatic brainstem compression and hydrocephalus requiring surgical intervention, especially in young patient. Symptomatic enlargement was noted in 5.1% of the patients, and resection of the VS was performed in 3.4%. We excluded the patient with a follow-up of less than 12 months, some of them could have early VS expansion with VS resection that are not captured in this study. Patient must be informed about the increased risk of neurologic deterioration due to tumor expansion, and, in case of tumor enlargement, rigorous follow-up should be instituted to promptly identify and manage life threatening signs and symptoms. Moreover, some centers have reported surgery can be more difficult after SRS than in naïve-patient [29] and functional sparing surgery must be discussed in these cases [30, 31].

Serviceable hearing (i.e., GR classes 1 and 2) was present in 51.7% of cases at SRS and in 33.0% at the last follow-up. The actuarial serviceable hearing preservation rates at 3-, 5-, 10-years follow-up were 70.4%, 56.8%, and 45.2%, respectively. Serviceable hearing preservation after SRS in large VS was reported between 0 and 82% [4–7, 23, 24, 32–34] and is similar to the young cohort recently published [25]. Pre-SRS GR class I [4, 35, 36], central cochlear dose < 4.2 Gy [36], mean cochlear dose < 6 Gy [35], and age < 60 years old were factors associated with hearing preservation [4]. In our study, female gender was the only factor to be associated with serviceable hearing at last follow-up in multivariate analysis.

Post-SRS facial nerve neuropathy was described between 0 and 4% in recent series for large vestibular schwannoma [4–7, 23]. In the present study, worsening of facial nerve function was reported in 2.8% of the patients at last follow-up. Post-SRS improvement or preservation of facial nerve function at 3-, 5-, and 10-years was 98.7%, 95.7%, and 95.7% respectively.

Trigeminal neuropathy defined as new-onset of facial pain and /or sensory loss after SRS for large VS was reported with a rate of 0–15% [4–7, 23, 24, 32, 33]. In the present study, 5.1% of patients had worsening of trigeminal neuropathy (trigeminal neuralgia, sensation loss or both) and 14.8% has improved symptoms. Adverse radiation effect was associated with worsening trigeminal neuropathy in multivariate analysis, $p = 0.03$, HR 5.2 [CI 95% 1.2–22.3]. In the all cohort analysis, age was not associated with facial or trigeminal neuropathy [18]. This is confirmed in the series of Kawashima et al. [25]

New-onset hydrocephalus after treatment was found in 4.0% of the young patients. Literature for large VS shows a rate between 1 and 19% [4, 6, 7, 23, 24, 34]. Kawashima

et al., found no impact of an age < 40 years old on the occurrence of hydrocephalus compared to older patient [25].

No radiation induced malignancy or mortality was found in this cohort of young patient, which is concordant with literature data showing a low complication rate for benign tumors [37, 38]. Further follow-up is needed as the median radiological follow-up was 37.5 (IQR 53.5) months in this series and the long-term survival of this young population.

Limitations

Due to the retrospective nature of the study, bias cannot be exclude concerning patient selection and evaluation. No centralized imaging data evaluation and follow-up were performed. Some radiological features as the presence of a cystic component were not captured. However, the consequences of a cystic tumor is not clearly understood and some recent studies shows good outcomes with SRS in these cases [39–41]. It is not clear how this can influence the results presented here. The case selection among the Koos grade IV is not captured, except for the inclusion of non-life threatening or debilitating symptoms prior to procedure. There was no comparison to the gold-standard treatment, surgical resection, which would be particularly interesting for this young age group. Moreover, the median follow-up was approximately 3 years which is insufficient to evaluate long-term control rate or radiation induced malignancy. Data about the outcome of some specific symptoms: gait disturbance, tinnitus and their impact on quality-of-life were not capture with enough precision to allow analysis. In the same way, dose and duration of steroid management were not captured. Complications due to steroid management were not specifically screened and should be an important point to evaluate in a future study.

Importance of the study

SRS can be a safe and valuable alternative to surgery for Koos Grade IV VS in selected patients younger than 45 years old. Further studies are warranted to best characterize clinical presentation and tumor imaging characteristics of VS that are more suitable for SRS.

Conclusion

SRS is a reasonable option with high-rate tumor control for selected Koos grade IV VS in a young population. Early tumor expansion may lead neurologic deterioration requiring surgical intervention. Further study to evaluate long-term outcomes and specific imaging features for selection of patient suitable for radiosurgery are warranted. Risk of radiation induced expansion must be explained to the patient prior to treatment as it can lead to resection.

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Declarations

Conflict of interest L. D. Lunsford is a shareholder in Elekta AB, the manufacturer of some radiosurgical devices; a consultant for Teledoc Inc.; and a chair for Insightec's data safety monitoring board. C. P. Cifarelli has received speaking honoria from Carl Zeiss. Zacharia is a consultant for Medtronic Inc. and a member of the speaker's bureau of NICO Corp., and has ownership in Decentramed LLC.

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