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ORIGINAL ARTICLE

Large vestibular schwannomas: long-term outcomes after stereotactic radiosurgery

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Abstract

OBJECTIVES: Stereotactic radiosurgery (SRS) is an established treatment option of small/medium-sized vestibular schwannomas (VSs). Concerning management of the large VSs, primary SRS remains a controversial option. Our retrospective study analyzes long-term radiological and clinical outcomes of SRS in large VSs.
MATERIAL AND METHODS: We retrospectively analyzed 73 patients with single large VS, treated with SRS. Inclusion criteria were: tumor volume >4 cm^3, follow-up >2 years, radiological (3D-volumetric studies) and clinical follow-up. SRS was either primary (94.5%) or secondary (5.5%) treatment. The median marginal dose (50%-isodose line) was 12Gy (11.5-12Gy). Fisher exact test, t-test, ANOVA, Kaplan-Meier and Cox regression models were performed when appropriate
RESULTS: The median follow-up was 5.5 years. The median VS volume at SRS was 6.5 cm^3 (range 4–14.2 cm^3). The tumor control rates assessed from Kaplan-Meier curve were 88.3%, 82.4% and 74.7% 5.8 and 10 years after SRS, respectively. Tumor shrinkage was observed in 83.6% of patients (n=61), unchanged volume in 4.1% patients (n=3) and progression in 12.3% (n=9). The median tumor volume significantly decreased to 4.0 cm^3, measured at 5-year follow-up (p<0.0001). Large cystic VSs responded better to SRS then homogeneous. Pre-SRS serviceable hearing was present in 37% of patients; 55% of these had hearing preserved after treatment. After SRS, new facial palsy (House-Brackmann gr. III-VI) appeared in 4.1% of patients; 9.6% of patients had transient brainstem/cranial nerves edema. For tumor progression, 8.2% of patients underwent resection, 2.8% of patients repeated SRS.
CONCLUSION: Our results are showing that SRS might be safe and effective primary treatment even in large VSs. However, long-term tumor control rates are lower in comparison with small/medium-sized VSs. Thus, closer follow-up should be applied.

Abbreviations:
CN - cranial nerve
GR - Gardner-Robertson grade
HB - House-Brackmann grade
SRS - stereotactic radiosurgery
VPS - ventriculo-peritoneal shunt
VS - vestibular schwannoma

INTRODUCTION

Vestibular schwannomas (VSs) are benign tumors arising from vestibular portion of vestibulocochlear nerve, representing 75–90% of cerebellopontine angle lesions. They are slowly progressing tumors, with rates varying between 0 and 3.9 mm per year (Bowden *et al.* 2017). Main clinical symptoms are ipsilateral hearing loss, tinnitus, dizziness, gait disturbances, with later progression of tumor signs of hydrocephalus and brainstem compression.

Besides surgical resection, stereotactic radiosurgery (SRS) is an established treatment option of small and medium-sized VS and postoperative tumor residues (Hasegawa *et al.* 2005; Lunsford *et al.* 2005; Williams *et al.* 2013). Long-term control rates of these VS treated with SRS vary between 90 and 98% (Kondziolka *et al.* 1998; Murphy *et al.* 2011). SRS achieves a good preservation of function of cranial nerves (CNs): trigeminal (V), facial (VII) and vestibulocochlear (VIII) (Regis *et al.* 2002; Pollock *et al.* 2006).

Treatment of large vestibular schwannomas remained microsurgical until recently, mostly because of the brainstem compression and hydrocephalus. But growing evidence in recent literature reveals that SRS might be another treatment option. In general, tumor control rates of large VSs are lower than for small tumors, but vary between 70–94% (Litvack *et al.* 2003; Inoue 2005; Chung *et al.* 2010; van de Langenberg *et al.* 2011; Yang *et al.* 2011; Milligan *et al.* 2012; Zeiler *et al.* 2013; Casentini *et al.* 2015; Huang *et al.* 2017).

METHODS

Patient population, follow-up

We retrospectively analyzed data of 73 patients with single large VS, treated with LGK SRS in our center between years January 2004 and December 2012. The retrospective study was approved by our institutional review board (Etická komise Nemocnice Na Homolce), with a consent waiver. We defined "large VS" as tumor with volume >4 cm^3 and at least one diameter > 2.5 cm. SRS was performed as either primary (94.5%) or secondary/post-surgery (5.5%) treatment. Another inclusion criterion was minimal follow-up period of 24 months after SRS. 43 patients with neurofibromatosis 2 or lacking imaging were not included. Clinical and radiological evaluation was performed at follow-up check-points every 2–3 years after SRS. In the case of significant regression of VS, further follow-up interval was 5 years. An earlier follow-up visit was performed in the case of symptomatic progression.

SRS parameters

Stereotactic radiosurgery was performed using a Leksell Gamma Knife (Elekta AB), a technique described elsewhere (Liscak *et al.* 2009). Treatment planning and further volumetric measurements were performed with Leksell GammaPlan software (Elekta), using precontrast and postcontrast 1 mm thin-slice axial 1.5T MR images. The marginal dose was prescribed at 50% isodose level, its median value was 12Gy (range 11.5–12 Gy). The median maximal dose was 24 Gy (range 23–24 Gy). The median maximal dose to the brainstem was 10 Gy (range 2.5–12.5Gy), median dose for cochlea was 5.0Gy (range 3.1–8.1Gy) and median dose for trigeminal nerve was 8.0 Gy (range 2–12 Gy). Median number of isocenters was 18 (range 6–27). Median conformity index was 98% (range 95–100%) (Table 1).

Tab. 1. Demographic, radiological and radiosurgical features

Demographic features	
Number of patients	73
Gender, female: male (%)	60.3 : 39.7
Age in years, median (range)	61 (23-84)
Follow-up in years, median (range)	5.5 (2.1-14.8)
Tumor characteristics	
Side of tumor, right: left (%)	49.2: 50.8
Tumor volume in cm^3, median (range)	6.5 (4-14.2)
Volumetric subgroups	
A subgroup "4-8 cm^3" ,	59/73 (80.8%)
B subgroup " >8 cm^3",	14/73 (19.2%)
Initial tumor volume, in cm^3, median (range)	6.5 (4-14.2)
A subgroup "4-8cm^3", (cm^3)	5.4 (4-7.7)
B subgroup " >8cm^3", (cm^3)	9.75 (8-14.2)
Radiological morphology of VS	
cystic, No(%)	27 (37%)
homogeneous, N (%)	26 (35.6 %)
heterogenous, N (%)	20 (27.4%)
SRS parameters	
SRS primary : secondary, (%)	94.5 : 5,5
Maximal dose to VS (Gy), median(range)	24 (23-24)
Marginal dose to VS (Gy), median(range)	12 (11.5-12)
Isodose line (%), median(range)	50 (50)
Number of isocenters, median (range)	18 (6-27)
Conformity index (%), median (range)	98 (95-100)
Maximal dose to cochlea, (Gy), median(range)	5 (3.1-8.1)
Maximal dose to brainstem, (Gy), median(range)	10 (2.5-12.5)

*SRS :stereotactic radiosurgery

Radiological parameters, tumor control rate

3D-volumetric measurements were performed on gadolinium-enhanced axial T1-weighted MR images (Gd-T1wMRI) at the time of SRS (Vo) and at the time of follow-up (Vn). The slice thickness of Gd-T1wMRI was 1 mm, the volume was manually contoured using GammaPlan software. Absolute tumor volume was assessed at each follow-up check-point.

The VS volume was considered as "stable" if relative volume change, calculated as (Vn-Vo)/Vo*100%, was within ±10%. We defined radiological control rate (%) as a fraction of schwannomas with stable or regressing volume. To better assess the influence of initial tumor volume, we divided cohort into 2 volumetric subgroups: A-group with volume 4–8 cm^3 (n=59 patients) and B-group with 8–14.2 cm^3 (n=14).

We distinguished also pre-SRS radiological appearance of VS as cystic, homogeneous and heterogeneous. Cystic VS were defined by presence of the cystic non-enhancing area, hypointense on T1-weighted (T1w) MRI and hyperintense on T2-weighted (T2w) MRI. In contrast, heterogeneous VS contained non-enhancing regions which were hypointense on both T1w and T2w MRI. According to radiologic appearance, 27 patients (37%) presented with cystic VS, 26 patients (35.6%) homogeneous and 14 patients (27.4%) heterogeneous VS (Table 1).

Clinical variables

Karnofsky score, functions of cranial nerves including CN V (trigeminal), CN VI (abducens), CN VII (facial) and CN VIII (vestibulocochlear), cerebellar function were assessed before SRS and on follow-up visits. Most of the clinical variables were evaluated as improved, unchanged or deteriorated. Serviceable hearing was considered as Gardner-Robertson I and II grade (Gardner & Robertson,1988). House-Brackmann scale was used to score facial nerve function (House & Brackmann, 1985). Due to retrospective analyses, we couldn't distinguish between cerebellar and CN VIII etiology of vertigo/imbalance. Eventual clinical signs of hydrocephalus and complications (post-SRS brainstem edema or CN deficit) were also noted.

Statistics

Repeated measurement ANOVA test with Bonferroni corrections was used to analyze volume changes of defined cohort during follow-up time. Kaplan-Meier analysis with log-rank test was also performed to calculate estimated rates of tumor control during follow-up. The Fisher's exact test for small sample categorical data, univariate and multivariate Cox proportional hazards analysis of potential risk factors were performed. For all tests, $p<0.05$ indicated statistical significance. All

Tab. 2. Radiological and clinical outcomes after SRS

Radiologic tumor control after SRS						
	All patients		**A-group (4-8cm3)**		**B-group (>8cm³)**	
Tumor control (shrinkage +stable)	64/73 (87.7%)		52/59 (88.1%)		12/14(85.7%) ¥	
Tumor growth	9/73 (12.3 %)		7/59 (11.9%)		2/14 (14.3%)	
Clinical outcome after SRS						
Clinical features	**Pre-SRS**	**Post-SRS**	***De novo palsy***	***Worsened***	***Unchanged***	***Improved***
Karnofsky score, median (range)	90 (70-100)	90 (60-100)		8/67 (12%)	55/67 (82%)	4/67 (6%)
Hearing N, (%)			0	18/73 (24.6%)	54/73 (74%)	1/73 (1.4%)
Serviceable hearing (GR I-II)	27 (36.9%)	16 (21.9%)	0	11/27 (40.7%)	15/27 (55.6%)	1/27 (3.7%)
Non-serviceable hearing (GR III-IV)	28 (38.4%)	32 (43.9%)	0	7/28 (25%)	21/27 (75%)	0
Deaf	18 (24.7%)	25 (34.2%)				
Tinnitus, N (%)	62/72 (86.1%)	40/70 (57.1%)	3/70 (4.3%)	3/70 (4.3%)	42/70 (60%)	22/70 (31.4%)
Vertigo/dizziness , N (%)	52/72 (72.2%)	34/71 (47.9%)	7/71 (9.9%)	10/71 (14.1%)	29/71 (40.8%)	25/71 (35.2%)
Facial function, N (%)			3/73 (4.1%)	0	70/73 (95.9%)	0
Facial function (HB I-II)	68/73 (93.2%)	65/73 (89.1%)				
Facial function/palsy (HB III-VI)	5/73 (6.8%)	8/73 (10.9%)				
Dysfunction of CN V, (%)						
hypo/paresthesia	8/73 (10.9%)	11/73 (15%) *	6/73 (8.2%) *	0	64/73 (87.7%)	3/73 (4.1%)
pain	2/73 (2.8%)	7/73 (9.6%) *	5/73 (6.8%) *	0	68/73 (93.2%)	0
Ventriculoperitoneal shunt	13/73 (17.8%)	4/73 (5.5%)				

¥ Fisher exact probability test comparing tumor control between volumetric subgroups A ("4-8 cm^3") and B (" >8 cm^3"), two-tailed p value = 1.0000, Odds ratio 0,8077 (.95 CI 0,1487-4,387)
(CN V: trigeminal nerve; GR: Gardner-Robertson grade; HB: House-Brackmann grade; Vo: initial tumor volume at SRS; * temporary palsy)

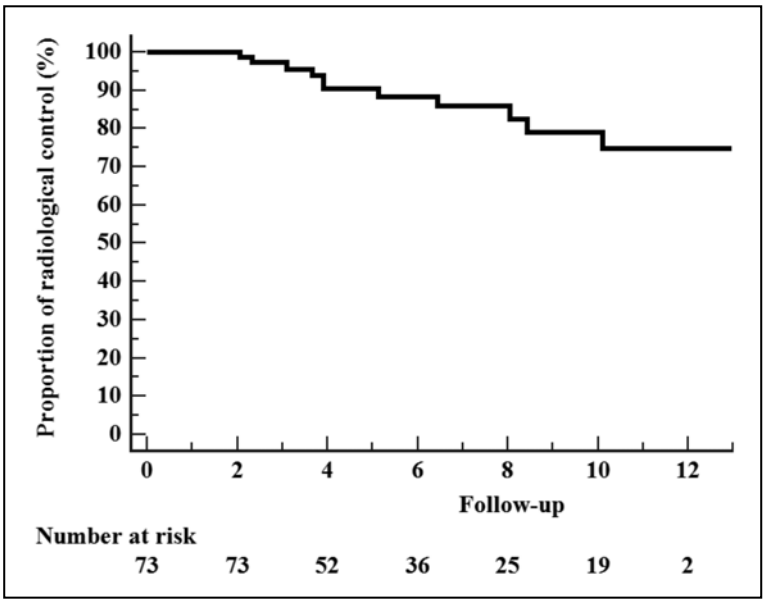

Fig. 1. Radiological tumor control rate
Kaplan-Meier plot of radiological tumor control rate (%) against follow-up time for all large vestibular schwannomas.

analyses were performed using MedCalc software (MedCalc, Version 18.10.2, Inc, South Korea).

RESULTS

Patient cohort

Our cohort included 73 patients with single large VS treated with SRS as primary or secondary treatment. There was a predominance of women (60,3%), median of age was 61 years (range 23-84 years). Median follow-up was 5.5 years (range 2.1–14.8). Median tumor volume of all cohort was 6.5 cm^3 (range 4–14.2) (Table 1).

Radiological outcome, control rate in time

Radiological control rate at the last follow-up was 87.7% (64/73 patients). Altogether we noticed tumor shrinkage in 61 patients (83.6%), unchanged tumor volume in 3 patients (4.1%) and tumor progression in 9 patients (12.3%). There was no significant difference in response to SRS between volumetric subgroups A ("4-8 cm^3") and B (">8 cm^3") with Fisher exact probability test, (two-tailed *p*-value =1.0000, Odds ratio 0.8077, .95 CI 0.1487–4.387) (Table 2).

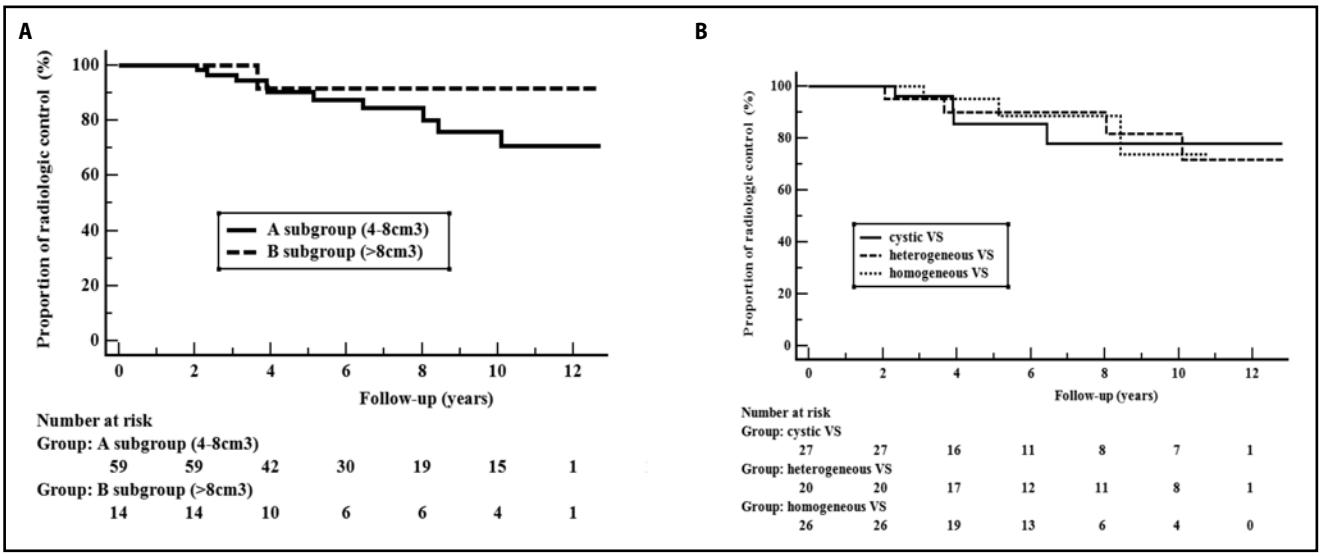

Fig. 2a,b. Radiological tumor control rates in relation to the tumor size and morphology
Kaplan-Meier plot of a) radiological tumor control (in %) against follow-up time for volumetric subgroups of vestibular schwannomas (log-rank test, p = 0,6013) and b) radiological tumor control for morphologic subgroups (heterogeneous, homogeneous and cystic), (log-rank test, p= 0,8784).

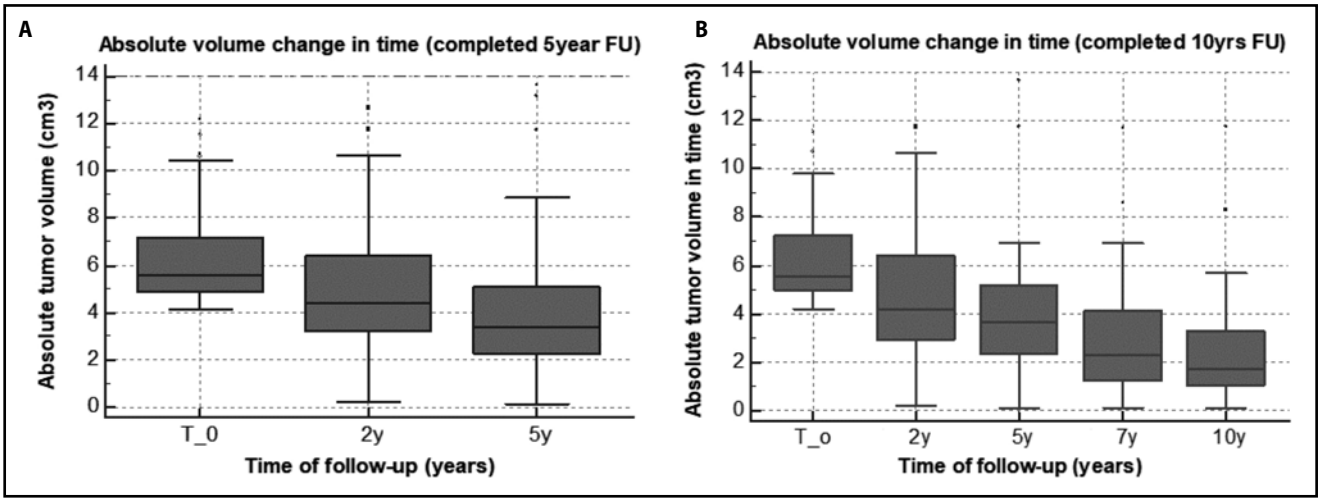

Fig. 3a,b. Volumetric changes of the VSs after the SRS
Whisker plots for tumor volumetric changes after SRS in a) cohort of 49 patients who achieved 5-year follow-up (FU) and b) cohort of 24 patients who achieved 10-year FU, repeated measurement ANOVA test, for both $p<0.0001$ (T_0 time at SRS).

Kaplan-Meier analysis with log-rank test was used to assess radiologic tumor control during follow-up for all cohort and volumetric or morphologic subgroups separately (Figure 1, 2a,b).

The radiological control rate for all cohort was 88,3%, 82.4% and 74.7% at follow-up points 5.8 and 10 years after SRS, respectively (Figure 1). The differences in tumor control between volumetric subgroups were non-significant, log-rank test $p = 0.6013$ (Figure 2a). Concerning control rates, no significant difference was observed among different morphologic subgroups of VS $p=0.6170$ (Figure 2b).

Tumor volume changes in time

The median tumor volume at SRS was 6.5 cm^3 (range 4-14.2 cm^3). In detail, median tumor volume in A-subgroup „4–8 cm^3" was 5.4 cm^3 (range 4–7.7 cm^3) and in B-group „>8 cm^3" was 9.75 cm^3 (range 8-14.2 cm^3) (Table 1).

We performed repeated measurement ANOVA analysis of absolute tumor volume for all patients who achieved follow-up 5 years (49 patients) and 10 years (24 patients). Significant volume regressions were observed in all cases (Figure 3a, b). Mean volume of 49 patients with 5 years follow-up decreased from pre-SRS 6.4 cm^3 to 4.0 cm^3 and in 24 patients with achieved 10 years follow-up to 2.64 cm^3 (both $p<0.0001$). Similar analysis was performed for 10 patients from B ">8 cm^3 subgroup, significant volume regression at 5 years follow-up was noted ($p=0.0019$) (Figure 4).

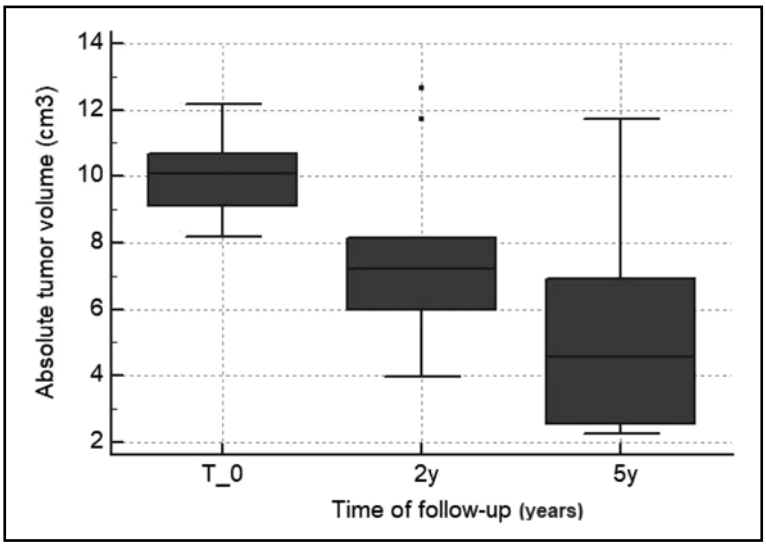

Fig. 4. Volumetric changes in the subgroup of VSs with initial volume >8 cm^3
Whisker plots for tumor volumetric changes in subgroup B ">8cm3" during time of follow-up. Cohort of 10 patients who achieved 5 years of follow-up (FU), repeated measurement ANOVA, p = 0,0019. (T_0 time at SRS).

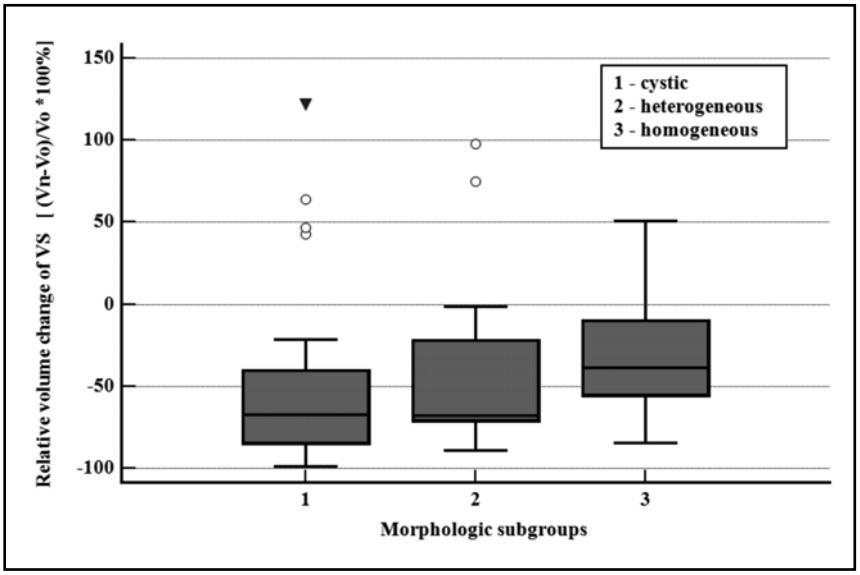

Fig. 5. Relative tumor volume changes in relation to the morphology
Whisker plots for relative tumor volume changes at last follow-up, calculated as [(Vn-Vo)/Vo*100%], in relation to morphologic subgroups of VS, (univariate ANOVA test, p=0.422).

Concerning morphologic appearance of VS, tumor shrinkage expressed as relative volume change at last follow-up was highest in sequence: cystic>heterogeneo us>homogeneous, p=0.422 (Figure 5).

Pre-SRS clinical parameters and clinical outcome

The most frequent initial symptoms were tinnitus, hearing loss, vertigo and gait disturbances. Median duration of symptoms before SRS was 24 months (range 3–120). Pre-SRS serviceable hearing (Gardner-Robertson I-II) was present in 27 patients (36.9%). After SRS, 15 of those patients (55.6%) preserved initial hearing, 11 patients (40.7%) progressed into non-serviceable hearing, one patient even improved at last follow-up (Table 2). Tinnitus and vertigo were present in 86.1% and 72.2% patients at the time of SRS, respectively. At the last follow-up, important regression of tinnitus and vertigo rates were observed; tinnitus remained in 57.1% of patients and vertigo in 47.9% of patients (Table 2).

Significant pre-SRS facial palsy (defined by House-Brackmann HB grade III-VI) was present in 6.8% patients mostly due to previous surgery. New facial palsy grade III-VI occurred in 3 patients (4.1%) after SRS, either de novo or either as progression of initial II grade palsy. One patient presented with 2 episodes of hemifacial spasm, not requiring corticosteroids.

Pre-SRS impairment of trigeminal nerve (CN V) function occurred in 10 patients (13.7%); 8 patients with paresthesia and 2 patients with intermittent pain. During follow-up after SRS, trigeminal paresthesia disappeared in 3 patients (4.1%), but 6 patients (8.2%) developed new transient facial paresthesia and 5 patients (6.8%) presented with transient facial pain. No abducens nerve palsy was noted in cohort. After SRS, 7 patients (9.6%) had corticosteroids for transient adverse effects of SRS; of those, 1 patient with brainstem edema and 6 patients with cranial nerve edema (transient facial palsy, trigeminal pain/paresthesia, transient worsening of vertigo).

Overall 23.3% of patients presented with symptomatic hydrocephalus requiring implantation of ventriculoperitoneal-shunt (VPS); pre-SRS implantation in 13 patients (17.8%) and post-SRS implantation in 4 patients (5.5%). The median initial Karnofsky score was 90 (70-100), which remained unchanged in 75% of patients at the last follow-up.

Tumor progression, risk factors for progression

Tumor volume progression occurred in 9 patients (12.3%), the median time of tumor growth was 2.7 years after SRS (range 0.7–8.9 years). The median relative tumor volume increase was +13.8% per year. We proposed re-treatment to all nine patients with growing tumor. Six patients (8.2% of all cohort) underwent microsurgery, one patient (1.4%) repeated SRS and another one (1.4%) repeated SRS after stereotactic puncture of cystic portion of VS. One patient refused any procedure. Even repeated SRS didn't increase morbidity during 12 months of the follow-up.

The only significant risk factor for tumor progression was previous microsurgery and progression of tumor residue preceding SRS, p=0.0373 (Table 3). All 4 patients (5.5%) who underwent pre-SRS microsurgery were irradiated because of tumor residue progression prior SRS, median tumor volume at SRS was 6.2 cm^3 (range 5.1–8.0). Two patients continued to progress despite SRS and underwent second microsurgery.

Tab. 3. Univariate and multivariate Cox proportional hazards regression analysis of possible risk factors of tumor growth after SRS

Characteristics	Radiological control	Radiological progression	Univariate			Multivariate		
			p	HR	95% CI of HR	p	HR	95% CI of HR
Age in years, mean, (±SD)	60,4 (±13,2)	59,1 (±15,7)	0,507	1,0158	0,9698 to 1,0641	0,5909	1,0148	0,9619 to 1,0707
Gender female, N(%)	40 (62,5%)	4 (44,4%)	0,301	1,873	0,5703 to 6,1517	0,3668	1,8686	0,4806 to 7,2644
male, N(%)	24 (37,5%)	5 (55,6%)						
Side of VS right ,N(%)	34 (53,1%)	4 (44,4%)	0,2107	2,1393	0,6503 to 7,0374	0,3192	2,1845	0,4695 to 10,1639
left, N(%)	30 (46,9%)	5 (55,6%)						
SRS primary, N (%)	62 (96,9%)	7 (77,8%)	0,0373	5,1303	1,1006 to 23,9147	0,227	3,1694	0,4877 to 20,5970
secondary, N(%)	2 (3,1%)	2 (22,2%)						
preSRS VS volume (cm^3), mean (±SD)	6,4 (±2,3)	6,0 (± 1,3)	0,5809	0,9999	0,9996 to 1,0002	0,7052	0,9999	0,9995 to 1,0003
Maximal dose on VS (Gy), mean,(±SD)	23,9 (± 0,3)	24 (± 0)	0,7613	1,5978	0,0777 to 32,8686	0,7552	1,7803	0,0474 to 66,8476
Radiological appearance (%)								
heterogeneous	18 (28,1%)	2 (22,2%)	0					
homogeneous	23 (35,95%)	3 (33,3%)	0,908	0,914	0,1990 to 4,1979	0,6475	0,678	0,1282 to 3,5870
cystic	23 (35,95%)	4 (44,5%)	0,7067	1,2881	0,3445 to 4,8161	0,6781	1,3401	0,3363 to 5,3392

* SD: standard deviation ; SRS: stereotactic radiosurgery; VS :vestibular schwannoma;

DISCUSSION

The definition of large VS in the literature remains debatable. In 2D measurement studies, threshold for largest tumor diameter varies from 2.5 cm to 3 cm. 3D volumetric studies consider VS as large with volume superior to 4-6 cm^3 (Table 4). Our threshold for large VS was volume >4 cm^3 and at least one diameter superior to 2.5 cm. To compare with other publications, we subdivided cohort into two volumetric subgroups: A subgroup („4–8 cm^3“) and B-subgroup („>8 cm^3”) and analyzed them separately.

Most of the studies reveal long-term radiologic tumor control rates between 82 to 94% for SRS of large VSs (Table 4). Our data are consistent with these results; with control rates 88.3% and 74.7% at follow-up points 5 and 10 years after SRS, respectively. The control rates of SRS for small/medium-sized VSs, reported to be superior to 90% at 5 years of follow-up, are higher in comparison to control rates of large VSs (Kondziolka *et al.* 1998; Lunsford *et al.* 2005; Murphy *et al.* 2011). Despite this lower efficiency of tumor control, SRS is still effective primary treatment of large VSs and might be considered in specific population of patients: elderly, patients with severe comorbidities or those refusing surgery.

The durability of SRS effect remains in question. Several studies report tumor control rates 88-98% even 10 years after SRS for small or medium size VSs (Kondziolka *et al.* 1998; Regis *et al.* 2002; Murphy *et al.* 2011). Literature lacks this evidence for large VSs, with the median of follow-up less than 50-60 months in most studies (Table 4). Inoue (2005) reported 93.3% control rate with follow-up more than 70 months (range 72–152). Williams *et al.* (2013) found control rate 82% during median follow-up 82 months. Our results show lower control rates, 74.7% 10 years after SRS.

Regarding possible role of VSs radiologic appearance in response to SRS, we found tumor shrinkage decreasing in following sequence of VS: cystic>heterogeneous> homogeneous, p=0.422 (Figure 5). Bowden *et al.* (2017) found that tumor shrinkage is decreasing in the same sequence: macrocystic VSs > microcystic VSs>homogeneous VSs. Our definition of heterogenous VS meets with description of above mentioned microcystic VSs.

The preservation of serviceable hearing after SRS of large VS varies between 28% and 100% (Table 4). In our cohort, 55.6% of patients with pre-SRS serviceable hearing preserved it. In contrast, the reported preservation rates of serviceable hearing in surgical resection of large VSs are 0-51% (Wiet *et al.* 2001; Samii *et al.* 2006).

Preservation of facial nerve function 5 years after SRS reported in literature varies between 70% and 100%

Tab. 4. Previous reports of radiosurgery for large VSs.

Authors	Technique	Tumor size criteria	Median tumor volume, range (cm^3)	N of patients	Tumor control rate (%)	Median of Follow-up (months)	CN VII function stability (%)	Serviceable hearing preservation rate (%)	Surgery post-SRS (%)	Repeated SRS (%)
Litvack *et al.* 2003	SRS (LGK)	>3 cm	NA	9	100	31.7 *	NA	33.3% (overall NA)	0	0
Inoue, 2005	SRS (LGK)	>3 cm	15.2	18	93.3	>70 (72-156)	100	80% (overall 22.2%)	6.6	0
Chung *et al.* 2010	SRS (LGK)	>3 cm	17.3 (12.7-25.2)	21	90.5	53	100	no HB I-II pre-SRS	9.5	4.7
Yang *et al.* 2011	SRS (LGK)	>3 cm	9 (5-22)	65	86.2	36	98	82% (overall 27.7%)	10.8	1.5
van de Langenberg *et al.* 2011	SRS (LGK)	>6 cm^3	8.8 (6.1-17.7)	33	88	30	91	58% (overall NA)	15	0
Milligan *et al.* 2012	SRS (LGK)	>2,5 cm	2.8 (2.5-3.8)	22	82	66	92	28% (overall NA)	9	0
Williams *et al.* 2013	SRS (LGK)	>3 cm	9.5 (3.1-24.7)	24	82	82.5	70	75% (overall 18%)	12.5	12.5
Zeiler *et al.* 2013	SRS (LGK)	>3 cm	9.6 (6.9-10.6)	28	92	34.5	100	100% (overall 28%)	3.6	0
Casentini *et al.* 2015	MRS (CK)	>8 cm^3	9.4 (8-24)	33	94	48	100	87.5% (overall 21%)	6	0
Huang *et al.* 2017	SRS (LGK)	>3 cm,>10 cm^3	14.8 (10.3-24.5)	35	85.7	48	100	33.3 (overall 8.7%)	14.3	0
Present study	SRS (LGK)	>2,5 cm,>4 cm^3	6.5 (4-14.2)	73	86.7	61	95.9	55.6 (overall 21.9%)	8.2	2.8

*Serviceable hearing rate is presented as rate of patients (%) with preserved initial serviceable hearing after SRS. Overall hearing preservation is calculated from whole analyzed cohort (Gardner-Robertson grades (I-V).
(Legend: CK Cyber Knife; LGK Leksell Gamma Knife; MRS multisession radiosurgery; NA not available; SRS stereotactic radiosurgery ;VS vestibular schwannoma; * mean (otherwise median value).

(Table 4). Our results are comparable, with unchanged facial nerve function noticed in 95.9% of patients. According to Gurgel *et al.* (2012) the preservation of good facial nerve function (HB I-II) after microsurgery of 1390 large VS (maximal diameter ≥ 2.5 cm) varied between 27.4 and 65.2%. Higher rate of preservation of facial nerve function (92.5%) was achieved with subtotal resection in contrast with gross-total resection where the preservation rate was 47.3%. In summary, recent literature concerning treatment of large VSs shows comparable and even higher preservation rates of audition and facial nerve function for SRS compared to microsurgery (Wiet *et al.* 2001; Pollock *et al.* 2006; Samii et at. 2006; Gurgel *et al.* 2012).

Vertigo/ imbalance reported after SRS varies between 28 to 36% of patients (Litvack *et al.* 2003; Inoue 2005; Chung *et al.* 2010; van de Langenberg *et al.* 2011; Yang *et al.* 2011; Milligan *et al.* 2012; Zeiler *et al.* 2013; Casentini *et al.* 2015; Huang *et al.* 2017). In our cohort, we found a higher pre-SRS rate of vertigo (72.2%), but after SRS vertigo improved in 35.2% of patients. Concerning the trigeminal nerve preservation, literature report unchanged function in 72–94% of patients and improvement of symptoms occurring in 36–66% of patients (Yang *et al.* 2011; Milligan *et al.* 2012; Zeiler *et al.* 2013; Casentini *et al.* 2015; Huang *et al.* 2017). Our results are in concordance with literature. We noticed de novo transient paresthesia in 8.2% of patients and transient trigeminal pain in 6.8% of patients. We conclude that SRS even as primary treatment for large VS is safe, with low morbidity especially regarding CNs function.

Literature report occurrence of hydrocephalus between 5 to 16% of patients (Lee *et al.* 2012; Williams *et al.* 2013; Zeiler *et al.* 2013). In our cohort, 5.5% of patients (n=4) had symptomatic hydrocephalus and required implantation of VPS after SRS. In all these patients with post-SRS hydrocephalus we noticed tumor shrinkage, but in 2 of them (50%) transient enlargement occurred within 2 years after SRS. Besides tumor obstruction, higher protein level in cerebrospinal fluid might be another cause of hydrocephalus (Mindermann & Schlegel 2014).

The rate of VS progression in recent literature varies between 6 and 25% (Table 4). In our study, tumor progression occurred in 12.3% of patients, requiring

either resection or repeated SRS. Our median time to progression was 32 months (range 8 to 107 months). Other studies reported similar progression intervals, varying from 8 to 72 months (Litvack *et al.* 2003; Inoue 2005; Chung *et al.* 2010; van de Langenberg *et al.* 2011; Yang *et al.* 2011; Milligan *et al.* 2012; Zeiler *et al.* 2013; Casentini *et al.* 2015; Huang *et al.* 2017). Literature also describes transient tumor enlargement with earlier occurrence, 6–18 months after SRS (Mindermann & Schlegel 2014). We had 4 cases of transient enlargement, occurring 14–59 months after SRS, which could have been observed and spontaneously shrunk during follow-up. Two symptomatic patients required transient steroids.

Risk factors of VS progression mentioned in literature are volume superior to 15cm^3 and brainstem compression (Hasegawa *et al.* 2005; Chung *et al.* 2010; Milligan *et al.* 2012). No other predictor factors for tumor progression were identified in the literature (van de Langenberg *et al.* 2011; Huang *et al.* 2017). In our study we found the only one significant risk factor: previous microsurgery and residue progression.

There is no clear consensus concerning definition of radiologic control and progression. The threshold for tumor progression in the literature concerning SRS varies from 10% to 25% of volume increase (Kondziolka *et al.* 1998; Chung *et al.* 2010; Williams *et al.* 2013). We have chosen lower 10% threshold for tumor progression, which may lead to higher progression rate in our cohort in comparison with other studies.

Moreover, our long-term radiologic control rates of shrinking VSs might be artificially lower after 5–8 years of follow-up, because of prolongation of the interval visit to 5 years, thus reducing follow-up data for log-rank test.

Another limitation of our study might be to distinguish tumor progression from transient enlargement (pseudo-progression). There is no consensus in the literature, only reported time of occurrence after SRS; 8–72 months for progression versus 6-18 months for pseudo-progression (Mindermann & Schlegel 2014). We observed 4 patients with early and transient enlargement. Another patient with early enlargement (8 months after SRS), required microsurgery, with significant relative volume increase (+75%). The other progressions were observed 2.1 to 8 years after SRS, which is more in favor of the tumor progression.

CONCLUSION

Despite fact that stereotactic radiosurgery achieves lower radiologic control in large VSs in comparison to small/medium-sized VSs, SRS still might be considered as effective treatment option in selected population of patients, e.g. refusing or non-eligible for surgery. Moreover, SRS is safe in regard to the preservation of cranial nerves function. Closer clinical and radiological follow-up should be applied.

Ethical approval and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional ethical committee (Etická komise Nemocnice Na Homolce) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Our institutional ethical committee (Etická komise Nemocnice Na Homolce) allowed us to perform our retrospective analysis, with consent waiver.

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