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Risk analysis of radiosurgery for vestibular schwannoma: Systematic review and comparative study of 10-year outcomes

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Abstract

Background. Determine the benefit of stereotactic radiosurgery (SRS) compared to no treatment for sporadic vestibular schwannoma (VS) by calculating epidemiologic risk using 10-year data; apply the analysis to VS that have demonstrated linear growth.

Methods. PubMed, Google Scholar, Web of Science, and Cochrane Library are systematically reviewed for VS tumor control 10 years after SRS and compared to a historical cohort of untreated VS (primary risk analysis). Subgroups of VS limited by size and observed growth are compared to the untreated cohort (secondary analysis).

Results. Twenty-four studies of 4079 SRS-treated VS exhibited tumor control in 90.93% (87.0%–100%; SD 4.1%), while 1959 untreated VS exhibited control in 65.24%. SRS reduces the absolute risk (ARR) of tumor progression by 25.7% compared to no treatment. The number needed to treat (NNT) is 4 (3.892, 95% CI: 3.619–4.210). Subgroup analyses of (1) VS with definite linear growth before SRS result in a similar ARR of 29.4% and NNT 4 (3.395, 95% CI: 2.966–3.968), and (2) Koos 1 VS result in lower ARR 18.31% and higher NNT 6 (5.209; 95% CI: 4.018–7.401).

Conclusions. This "best-available" case–control study of 10-year data reveals that ARR and NNT are similar for VS with and without definite pretreatment linear growth. These comparisons may be applied to CPA diameters less than 2 cm. Results for Koos 1 tumors are different. This analysis quantifies the therapeutic benefit of SRS by comparative risk analysis. The level of evidence on this topic is low.

Key Points

- Ten-year outcomes after radiosurgery are compared to a natural history cohort.
- Absolute risk reduction after radiosurgery for all tumors (26%) is similar to "growing" tumors (29%); the number needed to treat is 4; the therapeutic effect is less for intrameatal tumors.

It is generally accepted that large vestibular schwannomas (VS) should be treated, while the superiority of stereotactic radiosurgery (SRS) or surgical excision remains debated.[1] An understanding of natural history makes observation a viable first-line option for small and medium-sized VS.[2] The reality is that most people with VS experience hearing loss[3] and about half have balance problems of varying degrees.[4] The ideal management strategy should maximize tumor control and reduce the chances of additional neurological morbidity or mortality.[2] The optimal management remains controversial. The most recent, high-quality evidence for SRS favors treatment after diagnosis, without observation, to achieve superior tumor control; but not other symptom measures.[5,6] Considering cumulative risk and long-term outcomes of tumor control, with other measures equal, there are no comparative studies to inform the clinician's perspective on tumor control,

Importance of the Study

This "best-available" case–control study of 10-year data reveals that absolute risk reduction and the number needed to treat are similar for vestibular schwannoma with and without definite pretreatment linear growth. These comparisons are applicable to tumors with cerebellopontine angle diameters less than 2 cm. The risk reduction after radiosurgery is less for Koos 1 tumors. Our calculated treatment effect, based on a systematic review and historical controls, is similar to that of a recently published randomized controlled trial. This analysis quantifies the therapeutic benefit of radiosurgery for the purpose of tumor control, providing useful information to clinicians about the effect of radiosurgery on absolute risk reduction, relative risk reduction, and the number needed to treat.

our most basic management goal. A further relevant, and unsettled question is whether there is added benefit (or harm) when SRS is withheld until a VS has grown during a period of observation.

It is important to recognize the apparent paradoxes that exist with regard to VS tumor control. A long-held belief that most tumors are "non-growing" is falsified by volumetric evidence that "non-growing" tumors are actually a small minority, and consequently linear measurements of tumor growth lose relevance.[7] If the "non-growing" tumors in the literature of years past were in fact growing, then veritable (volumetric) "tumor growth" does not necessarily equate to "clinically significant progression."[7] Because there remains an interest in analysis of long-term data, this framework requires the reader to carefully consider the definitions of tumor control.

Traditionally, *tumor control* is defined as little to no linear tumor growth observed over time, with the concept of a quiescent VS serving as a basis for withholding treatment.[8] Linear measurements of growth are derived from magnetic resonance imaging (MRI) [or in the more distant past, computerized tomography (CT)]. Today, volumetric tumor analyses prove that most VS grow at variable rates, intermixed with periods of stability and/or shrinkage; and there is no consensus regarding the definition of "clinically significant" tumor growth.[8,9] Consequently, while the concept of a "non-growing" VS is erroneous in most cases, the fact that many small and medium-sized VS do not require intervention over the long term remains true.[2]

Consider a working definition of VS *tumor control*, then, include some tumors that are slowly (volumetrically) growing, but not threatening. Because quality-of-life studies show similar outcomes across modalities—even beyond 10 years[10]—any management (observation, SRS, or surgical excision) can be considered successful if no additional intervention or neurological morbidity occurs in spite of small, incremental changes in tumor size.

SRS, while not risk-free, is a primary treatment modality and is considered safe. *Treatment success* with SRS occurs when a treated tumor does not grow substantially, causes morbidity, or requires secondary treatment.[11] Clinical investigations have found very high rates of favorable outcomes by applying these benchmarks (**Table 1**). Since many untreated tumors do not require intervention, it would serve the medical community to quantify the margin of benefit attributable to SRS.[2] Yet, studies comparing long-term outcomes between cohorts with untreated (observed) vestibular schwannomas and SRS-treated tumors are few.[5,35] No effort has been made to quantify the benefit of the SRS intervention in epidemiological terms, because of numerous challenges: heterogeneous patient and tumor factors that hinder large-scale analysis, such as tumor characteristics and selection for treatment; study designs; and the variable growth patterns of untreated vestibular schwannoma.

The present study thus aims to quantify the benefit of SRS in achieving a favorable outcome (absence of tumor progression). This is done by comparing the rates of favorable outcomes (or, *tumor control* defined in a variety of ways) between cohorts managed by either observation or SRS. A casual survey of the literature suggests that about 2/3 observed, untreated tumors exhibit favorable outcomes and that about 9/10 tumors treated with SRS exhibit favorable outcomes. Considering the difference between these simple proportions, we hypothesized that the risk reduction afforded by SRS would be in the range of 20%–30%. This estimation of marginal benefit is not a new concept.[36] The added risk reduction may be considered the clinically relevant benefit of SRS and should help providers counsel patients with a new diagnosis of small and medium-sized VS about the long-term cumulative risk of progressive disease.

The analysis undertaken here has clearly stated limitations. Our scope did not include a study of functional outcomes, although these data were collected and are included in Appendix 3. Framed in terms of risk, and with large control and comparison groups, the study provides a novel perspective and generalizable data to inform clinical decision-making and patient counseling. Although the long-term results obtained herein from the systematically reviewed literature are based upon linear measurements, we consider the data to be valid in its separation of VS tumors that are "controlled" or "uncontrolled" (or having failed treatment). It must be acknowledged that, in the background, slow volumetric growth may be occurring in tumors that are clinically considered "controlled."

Materials and Methods

This systematic review is comprised of a literature search via the PubMed, Google Scholar, Web of Science, and Cochrane Library databases and is conducted in

Table 1. Author, Publication Year, and Study Characteristics

Study details		Study subjects (tumors)				Outcome		Confounders incl. in *N* (basis, 10-yr control)			
Year	First author	Categorical tumor size [Koos Grade(s)]	Age (median)	SRS Marginal Dose (Mean, Gy)	*N* (basis for 10-year control)	10-year Tumor Control	Control criteria*	*N* observed prior to SRS	*N* surgery prior to SRS	*N* treated with FSRT, not SRS	*N* (%) with NF2
2023	**Pikis et al**[1]	IV only	54	12.0	627	**87.6%**	**G(0)**	0	0	0	0
2021	**Villafuerte et al.**[12]	All	60	12.0	509	**94.6%**	**G(36) or 2T**	509	0	0	0
2022	**Umekawa et al.**[13]	All	58	12	452	**92.2**	**G(0)**	0	93	0	0
2018	**Rueß et al.**[14]	All	58	12.0	335	**87.0%**	**G(0) or 2T**	262	70	0	0
2020	**Hasegawa et al.**[15]	All	58	12.0	291	**91.0%**	**G(0)**	0	Unspecified	0	0
2021	**Ogino et al. (Koos I/Intrameatal)**[16]	I only	54	12.5	209	**92.1%**	**G(0)**	44	0	0	0
2019	**Johnson et al.**[17]	All	57	13.0	191	**94.0%**	**G(0)**	0	0	0	0
2016	**Watanabe et al.**[18]	All	56	14.8	183	**87.0%**	**G(0)**	57	56	0	10 (5)
2021	**Ogino et al. (Koos IV/Extrameatal)**[19]	IV only	61	12.5	170	**89.4%**	**G(0)**	0	0	0	0
2015	**Arribas et al.**[20]	All	60	12.0	167	**90.0%**	**G(0)**	21	0	12	6 (3.6)
2018	**Lo et al. (SRS)**[21]	All	65	12.0	136	**90.0%**	**G(0)**	69	31	0	5 (3.7)
2021	**Wage et al.**[22]	All	61	12.5	112	**90.0%**	**2T**	0	19	0	3 (2.9)
2019	**Frischer et al.**[23]	All	58	12.0	106	**91.0%**	**G(0)**	0	Unspecified	0	0
2023	**Park et al.**[24]	All	50	12.5†	106	**87.7%**	**G(0)**	0	0	0	0
2021	**Ogino et al.**[25]	All	55	12.5	100	**92.2%**	**G(0)**	0	0	0	0
2013	**Combs et al.**[26]	All	53	13.0	86	**93.0%**	**G(0)**	0	0	62	2 (2.3)
2014	**Bir et al.**[27]	All	62	12.0	82	**95.0%**	**G(0)**	0	20	0	0
2016	**Iorio-Morin et al.**[28]	IV only	58	12	68	**92.00%**	**G(24) or 2T**	0	13	0	0
2012	**Roos et al.**[29]	All	63	12	35	**97.10%**	**G(0)**	0	0	0	0
2019	**Anselmo et al.**[30]	All	59	16.5	35	**100.00%**	**G(0)**	0	0	0	0
2008	**Iwai et al.**[31]	I only	48	12.0	25	**96.0%**	**G(0)**	0	0	0	0
2022	**Chew et al**[32]	All	58	12.0	22	**98.0%**	**G(0)**	16	1	0	0
2017	**Putz et al.**[33]	All	62	13.0	19	**100.0%**	**G(0)**	0	0	0	0
2014	**Su et al.**[34]	I only	60	12.4	13	**100.0%**	**G(0)**	0	0	0	1 (0.8)

*Treatment failure was either defined as growth after SRS or need for a secondary treatment: G(N) represents treatment failure as growth observed after N months; G(0) represents treatment failure as any growth without a time constraint; 2T denotes treatment failure defined as the need for secondary treatment.
†median value is reported. N, number of subjects (tumors); SRS, Sterotactic Radiosurgery; FSRT, Fractionated Sterotactic Radiotherapy; NF2, Neurofibromatosis type II.

accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**, Appendix 1).[37] This systematic review is approved by the Eastern Virginia Medical School Institutional Review Board (EVMS IRB) as non-human subjects research and can be accessed through the EVMS IRB manager website. This study is also approved by the research ethics board of the University Health Network for the component

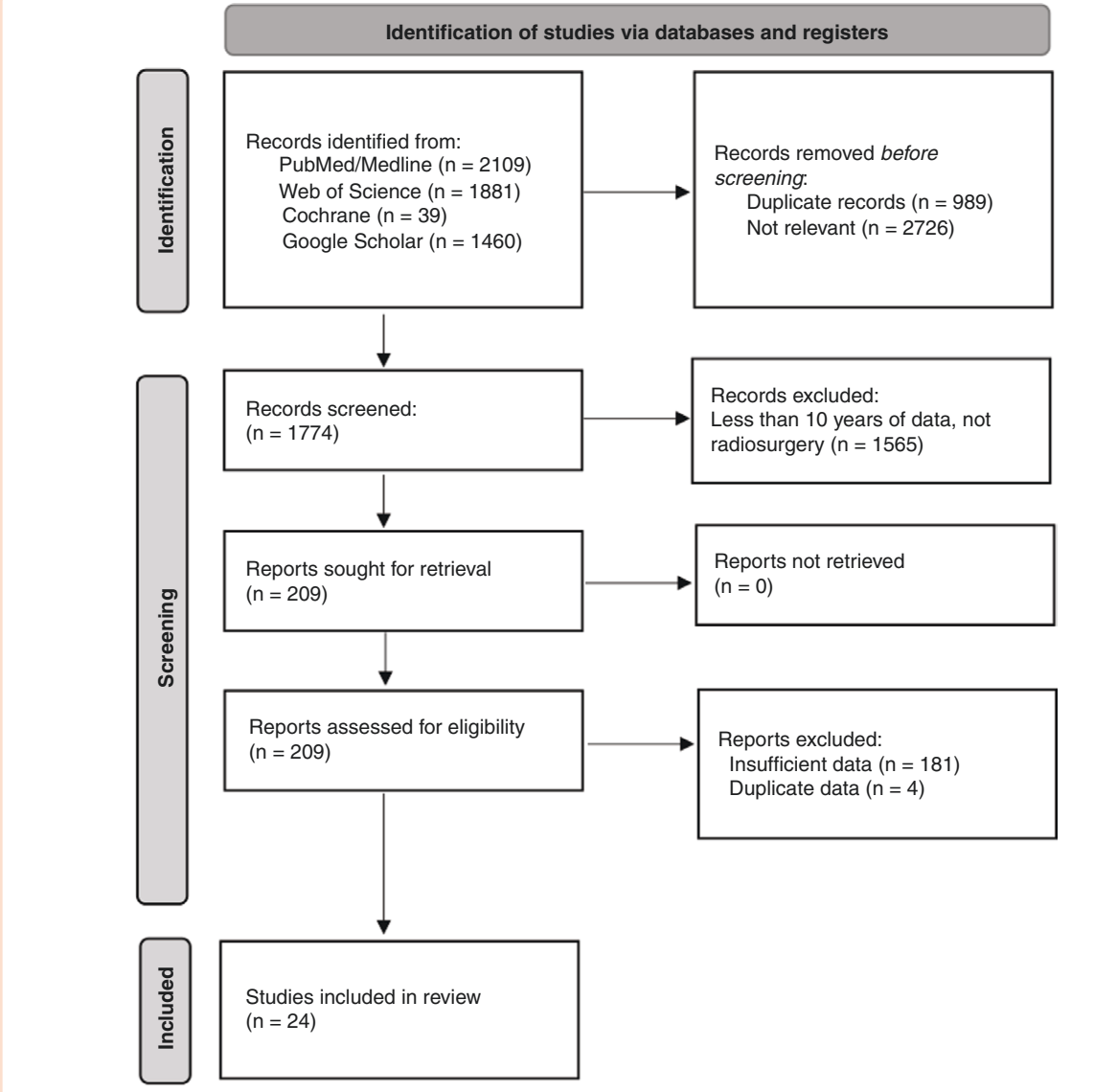

Figure 1. PRISMA flow diagram illustrating searches and screening of studies for inclusion in systematic review.

of the study involving de-identified individual patient data (22-5490). The data used to support the findings of this study are available from the corresponding author upon request.

Search Methods

We performed a search of the literature for studies of SRS and VS. The following inclusion criteria were applied: (1) tumor control rate or outcome reported with 10 or more years of follow-up, (2) a study population comprising a majority of tumors treated with SRS as primary modality, and (3) fewer than 10% of tumors with neurofibromatosis 2 (NF2). Studies were excluded if they did not meet the inclusion criteria or contained insufficient data for systematic review. Four databases, PubMed, Web of Science, the Cochrane Library, and Google Scholar, were systematically searched using MeSH terms when available and keyword terms with no date or language restrictions. The searches were performed in September 2022 (9/06 through 9/11) and updated in July 2024. The specific search criteria and date of search for each database are included in Appendix 2.

Data Acquisition

Data was collected by a 2-reviewer method. Two authors (K.M.G. and P.G.V) independently collected data from studies resulting from the literature search. The final review of collected data was performed by 3 authors (K.M.G., A.A.P., P.G.V) to verify accuracy. Data points collected included: first author, year of publication, categorical tumor size, median age, mean or median marginal dose, number of VS receiving SRS, the 10-year control rate, criteria for tumor control, numbers of VS observed or operated

on prior to SRS or treated with FSRT, and the number of NF2 cases. Supplemental clinical data was also tabulated (Appendix 3).

Individual patient data (IPD) records from the second-largest dataset of 612 tumors[12] were collected to create a subgroup of patients with richly annotated local control data. This permitted the exclusion of NF2 cases and VS with treatment prior to SRS. A total of 509 tumors met the above criteria. In that study, only tumors that were growing (at least a 2 mm increase in linear tumor size across 2 or more MR studies) or were approaching the institutional size cutoff for treatment (~3 cm in maximal diameter) were offered SRS.

Methods for Assessing Level of Evidence and Bias

Validated instruments, designed to assess the quality and risk of bias of non-randomized studies (including uncontrolled studies),[38,39] are applied, specifically, the Methodological Index for Non-Randomized Studies (MINORS) checklist and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series.

The MINORS checklist consists of 8 items for non-comparative studies with an additional 4 questions for comparative studies that assess the methodological quality of non-randomized studies. Each item is scored on a scale of 0–2, with a maximum possible score of 16 for non-comparative studies, and 24 for comparative studies.

The JBI checklist consists of 10 criteria that assess the methodological quality of case series studies. Many of the checklist items are consistent with the MINORS checklist, but the JBI includes questions about the reporting quality of patient demographics and clinical outcomes that are important to this review.

Both the MINORS and JBI tools provide a structured and standardized approach to evaluating the methodological quality of non-randomized studies and ensure that the studies included in the review were of high quality with a low risk of bias.

For the purpose of this systematic review, each included study is assessed using the MINORS checklist along with 3 additional questions from the JBI checklist. Any discrepancies or disagreements between the review team members are resolved through discussion and consensus (**Table 2**, **Supplementary Figure 1**).

Method for Statistical Analysis

Summary data are examined between the 2 groups using the Chi-square test for categorical variables and the Student *t*-test for continuous variables. Summary descriptive statistics are presented as mean ± standard deviation (SD) and/or median for continuous variables and as frequency (%) for categorical variables. Comparisons between the data sets are presented as relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) with their confidence intervals (CI). Statistical analyses are conducted using SAS statistical software version 9.4 (SAS Institute Inc.) and GraphPad Prism 9. All comparisons are 2-sided and $P < .05$ is considered statistically significant.

Results

Literature Search

The literature search of PubMed, Google Scholar, Web of Science, and the Cochrane Library yielded 5489 articles. Of these, 3715 were removed before screening (989 duplicates; 2726 not relevant), leaving 1774 articles to be screened for inclusion. Of these, 1565 either did not include 10 years of follow-up data or did not utilize SRS as the intervention and were therefore excluded. The remaining 209 articles were evaluated using a 2-reviewer system for inclusion in this systematic review. A 3-reviewer process was used for the final review of included studies to verify accuracy. Reference lists of articles were also cross-checked for additional studies, but no new studies were identified. After the final review, 24 unique records were found to fulfill all inclusion criteria (Figure 1).

An example excluded study is that of Rowe, et al. which does contain long-term tumor control data; however, the patient population is solely those with NF2.[40] Another, Przybylowski, et al., does not report a 10-year tumor control rate, although 1 or 2 subjects remain at risk at or beyond the 120-month timeline.[41]

Study Cohort Description

Retrieved studies, population characteristics, and other relevant data points are displayed in **Table 1**. These 24 studies comprise 4079 VS. The median age ranges from 48 to 65 years. Tumor sizes vary: 3 studies contain Koos I tumors only,[16,31,34] 3 studies contain Koos IV tumors only.[1,19,28] The remaining studies contain tumors of all Koos classes. The data cited by Villafuerte, et al.[12] is used for the secondary analysis with IPD acquired in collaboration with the principal investigator responsible for publication (D.S.T.; **Table 3**).

Control Cohort Description

The control group is a cohort of 2312 intent-to-observe VS accrued by the Danish national health system since 1976. This cohort is the largest available in the current literature and has the added benefit of minimizing selection and referral bias because it is a national health system. The authors consider it "close to ideal" for studying the natural history of VS. In Copenhagen, the current practice (with few[42] exceptions) is to observe tumors that have a diameter less than 15–20 mm in the cerebellopontine angle (CPA).[2,43]

The Danish cohort's growth results are obtained from 1959 tumors.[2] "Growth" is defined by the authors either by expansion of the maximal CPA linear measurement more than 2 mm or when a tumor previously limited to the internal auditory canal (IAC) expands into the CPA. The percentage of tumors with linear growth at 10 years is 34.8% overall with an inverse (no-growth) rate of 65.2% (**Table 4**).

Table 2. Risk of Bias Assessment; MINORS and JBI Checklists[20,29]

	Clear study aim	Inclusion of consecutive patients	Prospective data collection	Appropriate endpoints	Unbiased assessment of study endpoint	Follow-up period appropriate	Loss to follow-up less than 5%	Prospective calculation of the study size	Clear reporting of patient demographics (JBI)	Clear reporting of patient clinical information (JBI)	Clear reporting of outcomes (JBI)	MINORS	Total (MINORS and JBI)
Anselmo	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Arribas	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Birr	2	1	0	2	1	2	2	0	2	1	2	10/16	15/22
Chew	2	1	0	2	1	2	1	0	2	2	2	9/16	15/22
Combs	2	1	0	2	1	2	1	0	2	2	2	9/16	15/22
Frischer	2	2	0	2	1	2	1	0	1	1	2	10/16	14/22
Hasegawa	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Iorio-Morin	2	1	0	2	1	2	1	0	2	1	2	9/16	14/22
Iwai	2	2	0	2	1	2	2	0	1	1	1	11/16	14/22
Johnson	2	2	0	2	2	2	2	0	2	2	1	12/16	17/22
Lo	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Ogino[16]	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Ogino[19]	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Ogino[25]	2	1	0	2	1	2	1	0	2	2	2	10/16	15/22
Park	2	1	0	2	1	2	2	0	2	2	2	10/16	16/22
Pikis	2	1	0	2	1	2	1	0	2	2	2	9/16	14/22
Putz	2	1	0	2	1	2	1	0	2	2	2	9/16	15/22
Roos	2	2	0	2	1	2	2	0	1	1	2	11/16	15/22
Rueß	2	2	0	2	2	2	2	0	2	1	2	12/16	17/22
Su	2	2	2	2	1	2	2	0	2	2	2	13/16	19/22
Umekawa	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Villafuerte	2	2	0	2	1	2	1	0	2	1	1	10/16	14/22
Wage	2	2	0	2	1	2	1	0	2	2	2	10/16	16/22
Watanabe	2	2	0	2	1	2	1	0	2	1	2	10/16	15/22

Key: 2 = Adequately reported; 1 = Reported but inadequately; 0 = Not reported. MINORS: Additional criteria for comparative studies (Chew, et al.24): An adequate control group 2; Contemporary groups (vs. historic cohort) 1; Baseline equivalence of groups 2; Adequate statistical analysis 2.

The cohort has 333 VS with observation continuing beyond 10 years.

SRS Technique and "Tumor Control"

SRS is the primary intervention for all patients in the 24 included studies. The different modalities of SRS (eg Gamma knife, LINAC) used in each study are included in Appendix 3. The median tumor marginal dose ranges from 12.0 to 16.5 Gy. For a majority of the comprised studies, tumor control is defined as progression-free survival. A few studies define control as freedom from a second intervention. The tumor control rates of the 24 studies have a mean of 92.8% and a median of 92.2% (range 87%–100% SD 4.1%). If tumor control percentages are individually applied to the number of VS in each study (total 4079 VS), this proportioned aggregate tumor control rate is 90.93%. While the data resulting from the systematic review is not sufficiently homogenous to permit meta-analysis of SRS outcomes, this manipulation more accurately reflects the tumor control rates by accounting for study size and is used in the primary and secondary risk analyses.

University Health Network Subgroup

One of the authors (D.S.T.) is the principal investigator of University Health Network, cited as Villafuerte, et al.,[12] and possesses IPD that allows the exclusion of any cases of NF2 or any VS not treated with primary SRS. This cohort contains only VS that exhibited linear growth of at least 2 mm on 2 or more consecutive MRIs, or were approximately 3 cm maximal diameter (including IAC) prior to treatment.

Table 3. Baseline Characteristics of VS Cohort From *Villafuerte* et al.[12]

Variable	*N* = 509 patients	
Age at SRS, median, years (range)	61 (21–90)	
Sex	Male	237 (47%)
	Female	272 (53%)
Tumor appearance	Cystic	137 (27%)
	Solid	372 (73%)
VP shunt insertion	Pre-SRS	6 (1%)
	Post-SRS	20 (4%)
SRS equipment	Gamma Knife 4C	232 (46%)
	Perfexion	277 (54%)
SRS dose prescription	11 Gy	5 (1%)
	12 Gy	504 (9%)
Diameter, mm, median (range)	20.7 (2.22–37.1)	
Volume, cc, median (range)	1.48 (0.08–13.5)	
Dose rate, Gy/min, median (range)	2.4 (1.3–3.7)	
BED, $Gy_{\alpha/\beta = 2.47}$	57.1 (40.4–64.0)	
Integral dose to lesion, mJ, median (range)	25.6 (1.45-220.0)	

Key: BED, biologically effective dose; VP, ventriculoperitoneal.

Table 4. Study Characteristics of the Control Cohort, Reznitsky et al.[2]

Study details		Study subjects			Outcome
Year	First author	Categorical tumor size [Koos grade(s)]	**Age (median)**	**N (basis for 10-year control)**	10-year no growth rate
2021	Reznitsky[2]	All		1959	65.237% *

Key: * 25.4% growth rate of 868 Koos I tumors at 10 years, 42.3% growth rate of 1091 Koos II-IV tumors at 10 years, yields 681/1959 tumors with definite (linear) growth, a collective growth rate of 34.8%. The inverse (no-growth) rate is 65.2% at 10 years.
N, number of VS.

Statistical Analysis, Primary Endpoints, Subgroup Analyses

The risk analysis is calculated by comparing the study group and subgroups against the control cohort[2] as displayed in **Table 5**. For the primary analysis including all VS represented by the systematic review, the RR and RRR are 0.7175 (95% CI: 0.6936–0.7421) and 0.2850 ($P < .0001$), respectively. The RR indicates the proportion of "uncontrolled" VS after receiving SRS, which is decreased (value < 1). The ARR, 0.257 or 25.7%, reflects the magnitude of reduced risk of VS growth compared to no intervention. The reciprocal of ARR, the NNT, is 3.892, which rounds to 4 (since people are counted as whole numbers).

A secondary analysis uses the Villafuerte, et al[15] IPD. The 10-year 'tumor control' rate for this cohort is 94.6%. This results in a similar ARR of 29.36% and NNT of 4 (3.395 95% CI: 2.966–3.968; **Table 5**).

A tertiary analysis is applied to studies solely containing Koos I[16,31,34] tumors, which have a 10-year favorable outcome rate of 92.9%. Comparison to Koos I controls[2] (74.6%) yields ARR 18.31% and NNT 6 (5.209 95% CI: 4.018–7.401; **Table 5**).

Comparison to V-REX Trial

It is noteworthy to make a timely comparison to a recent and important randomized clinical trial, the first to compare upfront SRS with an observational "wait and scan" approach. This "V-REX Trial" included a population of 100 patients followed for 4 years.[5] The primary outcome is the ratio of tumor volume change at 4 years expressed as a geometric mean. The geometric mean change reported is 0.87 (CI: 0.66–1.15) in the upfront SRS group and 1.51 (CI: 1.23–1.84) in the wait and scan group. Our application of Cochrane's methods for calculating SD from confidence intervals produces a Cohen's d of 0.6465, and Furukawa's method to calculate an NNT of 3 for this comparison.[44,45]

Quality of Evidence

The level of evidence for the studies in this review is low with all but one[32] of the studies a descriptive, non-comparative study. Our search for studies with long-term outcomes of SRS for VS found no randomized controlled trials (RCT) and only 1 analytic cohort study that compares

Table 5. Analyses by Population Cohort

Comparisons	Study group N (mean TC rate)	Control group N (Reported TC rate, or % tumors with no growth at 10 years)	Relative risk (RR)	95% CI for RR	RRR	Significance level	ARR	NNT	95% CI for NNT
Entire Systematic Review cohort versus Reznitsky et al.[2]	4079 (0.90932)	1959 (0.65237)	0.7175 (71.8%)	0.6936 - 0.7421	0.285 (28.50%)	$P < .0001$	0.257 (25.7%)	4 (3.892)	3.619–4.210
Villafuerte cohort versus Reznitsky et al.*[2,12]	509 (0.946)	1959 (0.65237)	0.6889 (68.9%)	0.6630 - 0.7158	0.3111 (31.11%)	$P < .0001$	0.2936 (29.36%)	4 (3.395)	2.966–3.968
Koos I cohort versus Koos I in Reznitsky et al.*[2,16,31,34]	247 (0.929105263)	868 (0.746)	0.7954 (79.6%)	0.7564 - 0.8365	0.2046 (20.46%)	$P < .0001$	0.1831 (18.31%)	6 (5.209)	4.018–7.401

Key: * Subgroup analyses of special populations.
N, number of VS; TC, tumor control; RR, relative risk; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat.

SRS margin doses (high ≥ 12 Gy vs. low < 12 Gy).[32] A Cochrane Review also shows that there is no RCT data comparing long-term SRS outcomes in patients with vestibular schwannoma to other treatment options including observation.[46] (The aforementioned RCT[5] is recently published and only includes 4 years of follow-up data.) (A descriptive study design may be appropriate for answering a question about long-term outcomes in patients treated with SRS, but cannot be used to make causal inferences or provide evidence for the effectiveness of SRS over observation necessitating the use of the independent, best available natural history cohort for our analyses.

The review includes various study designs: one cohort study,[32] one case series,[34] twenty descriptive cohort studies, and a study that employed a cross-sectional design along with a descriptive cohort study.[26] Many neurosurgery studies confuse descriptive cohort designs with case series and mislabel these studies.[47] We define descriptive cohort studies as studies with a population sample based on exposure (SRS) that is followed over time without a control group.

We also assess the risk of bias for each individual study using validated tools (MINOR, JBI) specifically designed for non-comparative studies.[38,39] Our findings indicate a moderate risk of bias in the included studies, with the main sources being: retrospective versus prospective data gathering in 23 out of 24 studies, lack of sample size estimation in all studies, and unclear reporting on some validity attributes including loss to follow-up and assessment of study endpoints. The risk of bias assessment for each study is included in **Table 2** and the overall assessment of bias is in **Supplementary Figure 1**.

For our combined tool, the maximum number of points is 22 for non-comparative studies. Our included studies score from 13 to 19 with a mean of 15.35 (±1.3), a median of 15, and a mode of 16. For the MINORS component, the maximum is 16 for non-comparative studies. Our included studies score from 9 to 13 points with a mean of 10.17 (±1.03) and a median and mode of 10. One analytic cohort study[32] receives 7 of the 8 points from the additional questions for comparative studies. No studies report any relevant conflict of interest.

Heterogeneity of Studies Reviewed

The heterogeneity between studies for our primary outcome, long-term tumor control after SRS, cannot be calculated because of the limitations in the data provided in the individual studies. We would expect clinical heterogeneity in reviews of radiosurgery for vestibular schwannomas to arise from the following:

- Variation in patient characteristics including age, gender, and tumor size.
- Differences in treatment modalities: type and dosage of radiation.
- Variation in follow-up time (for which we controlled in this review).
- Differences in the definition and reporting of outcome measures.
- Variation in study design including differences in the inclusion criteria and exclusion criteria.

Long-term tumor control outcomes appear to be robust across the included studies with the majority of the studies reporting no differences in tumor control rate across subgroups. There are different definitions of treatment failure contributing to differences in the rate of tumor control beyond chance. The following definitions of failure are used in the included studies: >15% increase in volume[16,17,19]; ≥15% increase in volume[25]: >2 mm increase in diameter[29]; >2mm increase in any dimension after 2 MRIs[20]; 20% increase in largest diameter[23]; 20% increase in the sum of diameters (RECIST criteria)[26]; ≥25% increase in volume[15]; ≥25% increase in diameter or ≥10% in volume[18]; ≥3 mm in tumor growth[14]; any increase in volume[27]; any growth[13,31]; progressive enlargement in 2 MRIs[21]; any recurrence[33]; and any tumor requiring salvage treatment.[22]

Factors reported as not having an association with tumor control rates include the following: age, sex, trigeminal sensory loss, facial weakness, hearing status, presence of tinnitus, presence of vertigo, cobalt-60 dose rate, and other adverse effects. Park, et al.[24] found no associations with tumor volume >7.8 mL, marginal dose <11 Gy, transient volume expansion, and loss of central enhancement. The majority of studies also report that tumor volumes, Koos grade, prescribed radiation dose, and previous surgery do not have a significant effect on tumor control.

The factors that do have a significant association with tumor control rates after multivariate analysis include the following:

- Johnson: Progression-free survival is better with smaller tumors (<0.56 cm^3)[17]
- Ogino: A higher margin dose (≥12.0 Gy) is significantly associated with better tumor control[19]
- Watanabe: Cystic type tumors are more likely to require a follow-up procedure (univariate analysis)[18]
- Hasegawa: Tumor volume <10 cm^3 is associated with higher 10-year progression free survival[15]
- Villafuerte: Salvage SRS is associated with lower tumor control rates; cystic type tumors are associated with better tumor control (in contrast to Watanabe)[12,18]
- Pikis: Early tumor expansion, occurring in 10.7% of patients at a median of 12 months post-SRS, is associated with SRS failure at the last follow-up.[1]
- Umekawa: "Prior direct surgery" is associated with tumor progression[13]

None of the above factors are reported in more than one study, unless "prior direct surgery" is equivalent to "salvage SRS."[12,13]

Discussion

Deciding the correct primary management for VS is challenging and requires integration of individual patient goals, risk of tumor progression, risk of treatment side effects, and patient psychology. Current practice guidelines by the Congress of Neurological Surgeons (CNS) and the European Association of Neuro-oncology (EANO) agree that observation is appropriate for patients with small asymptomatic VS; however, EANO guidelines do mention that SRS can be performed as an alternative.[48,49] These recommendations cite Level 3 evidence. Despite these recommendations, many VS are treated primarily and "successfully" with SRS with favorable outcomes, as noted above. Although the risk of cranial nerve dysfunction is low, undesired effects of SRS impact quality of life and must be considered in discussions of treatment options.[50]

Existing data has limitations, as evidenced by the reviewed studies. One cannot ignore that a majority of observed, small, and medium-sized VS require no treatment when watched over an extended period.[2] Still, the results of this analysis provide a quantitative representation of the added margin of benefit afforded by treatment with SRS. The results of the NNT calculations are comparable to the recently published V-REX RCT which only has 4 years follow-up.[5]

A remarkable finding of this study's University Health Network subgroup analysis is that, compared to "all comers," no greater benefit (with regard to tumor control) was derived from using diametric growth (>2 mm) and overall size (3 cm maximal diameter) as a threshold for treatment. This subgroup informs our discussion since, in practice, some providers prefer to treat tumors without first observing growth, and some only treat growing tumors. The variability in VS tumor growth, further reinforced by the recent findings of Marinelli, et al.,[8,51] may nullify the value of observed linear growth as a criterion for treatment. We can only speculate, but it also suggests that observed linear growth changes nothing about the radiobiological effectiveness of SRS. Respective of the findings of this study, the benefit of SRS appears unaffected by evidence of prior linear growth (below a certain tumor size). There is also no added harm in delaying SRS until linear growth is evident since symptom measures and hearing loss for up-front SRS are no better.[5,6] A decision to treat should not universally rest on the finding of linear growth, nor do the data justify pre-emptive treatment of all newly diagnosed small and medium VS, given the smaller margin of benefit that SRS provides intra-meatal versus extra-meatal tumors (NNT 6 vs. 4). A continuum of risk, thus far unelucidated, likely exists. Currently, placement of a patient's given tumor, SRS, and surgical excision along this continuum is subject to the expert opinion and experience of individual providers and patient values.

We may consider treatment decisions based on tumor characteristics. For example, an intra-meatal, asymptomatic vestibular schwannoma (VS) with an excellent word discrimination score falls on the low-risk end, where observation may be appropriate due to its stability. In contrast, a Koos II or Koos III tumor smaller than 2 cm represents a middle ground. In these cases, when surgery is not desired, stereotactic radiosurgery (SRS) is often more beneficial compared to treating Koos I tumors, as it offers better outcomes with fewer complications.

Extension of this risk continuum to larger tumors is a necessity. A recent study of 214 Koos Grade 4 VS in the Netherlands revealed growth of 61%, shrinkage of 34%, stability of 4%, and 2% outliers with a 10-year growth-free rate of 27%.[52] Perhaps an absolute diameter or volume is the desired target for a future benefit/harm analysis to serve as the principal criterion for/against treatment. Such a criterion could be stratified by the degree of hearing loss. Using limits such as these in practice should reduce over-treatment over time. A threshold of 15 mm diameter has been suggested as the limit of tolerable CPA extension without increasing the risk of treatment-related complications.[30] Determining the levels of risk equivalence regarding tumor control and morbidity or undesirable symptoms on the basis of pretreatment variables is needed, yet highly improbable to achieve with the lack of VS data reporting standards. Further investigations of risk, including numbers needed to harm (NNH) analysis of studies detailing complications of SRS and surgery, stratified by pretreatment tumor size and observed growth rate of VS may guide better counseling and treatment decisions.

There are several investigative needs. Risk analyses stratified by tumor size and growth and a standardized definition of tumor progression, reported as mean tumor control rate with SD, are essential. The definition should apply to pretreatment as well as post-treatment scenarios and account for pseudo-progression post-SRS, which can confound the reporting of outcomes.[22] Validation of this definition using linear and volumetric measurements would be required in future studies.

While this study demonstrates interesting findings regarding the treatment of VS with SRS, there are clear limitations. First, control data used in this analysis was based on a large single population study, and the criteria by which patients were selected for observation versus initial surgical treatment were not explicit; however, the authors' treatment algorithm[2] as well as prior publications[43] are to advise treatment for >15–20 mm extra-meatal tumor size. More long-term natural history studies of diverse populations are needed to confirm the natural progression of VS when observed over many years. On this note, no studies included in this systematic review contained a control cohort of observed tumors; all control data were gathered from Reznitsky, et al.,[2] including the use of computerized tomography in the earlier years (the confounding effect of which is indeterminate).

An important, recently published comparative analysis based on volumetric measurements, the VISAS study,[6] affirmed superior tumor control with SRS over observation, and no differences in hearing and cranial nerve outcomes.

Second, this best available control cohort has been criticized for underestimating tumor growth, since the growth of tumors limited to the IAC (intra-meatal) is not reported. [This question is answered elsewhere. Another focused study by the same investigators shows that a minority of their intra-meatal VS enlarge sufficiently to result in treatment over 9.5 years: 37% exhibit growth within the IAC, and 23% develop extra-meatal extension.[53]] Further considering the recent evidence that, as a rule, VS grow volumetrically this criticism of growth underestimation is less valid (since all linear measurements are under-estimates). Indeed, it favors reversion of the paradigm to consider intra-meatal tumors as "controlled," regardless of size, since they cannot cause mortality or morbidity to the central nervous system. Treatment decisions for this subset of patients, then, must be based upon secondary criteria—symptoms, or auditory and vestibular function—still controversial.

Finally, several studies in this analysis include a minor fraction of VS with NF2, a history of prior surgery, or treatment with fractionated stereotactic radiotherapy that may skew the results. This bias is likely very small given that each of these confounders represented less than 10% of the total number of VS in this systematic review. We attempt to mitigate these confounders with the subgroup analysis using IPD excluding individuals with NF2 or prior radiotherapy, which confirms our primary results.

Conclusion

For VS that do not cause significant brainstem compression and do not extend more than 15–20 mm into the CPA, this study demonstrates the therapeutic benefit of SRS in 3 ways: (1) for all tumors (regardless of known growth), SRS reduces the absolute risk of tumor progression by 25.7% compared to no treatment; (2) the absolute risk reduction is similar (29.4%) if SRS is used to treat VS with definite linear growth; and (3) the risk reduction is less (18.3%) for Koos I tumors. Limitations of the data exist, and further analysis of treatment outcomes and complications stratified by pretreatment variables are needed to understand the undesirable effects of over-treatment.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

absolute risk reduction | comparative studies | natural history | stereotactic radiosurgery | vestibular schwannoma

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Authorship statement

K.M.G.: Data collection, interpretation of results, manuscript preparation. A.A.P.: Study design, analysis of results, manuscript preparation. D.S.T.: Data collection, manuscript preparation. P.G.V.: Study conception and design, data collection, interpretation of results, manuscript preparation.

Data availability

The data used to conduct this systematic review will be made available upon reasonable request.

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