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Peer reviewed

Management of sporadic intracanalicular vestibular schwannomas: A critical review and International Stereotactic Radiosurgery Society (ISRS) practice guidelines

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Abstract

Background. The choice of an appropriate strategy for intracanalicular vestibular schwannoma (ICVS) is still debated. We conducted a systematic review and meta-analysis with the aim to compare treatment outcomes amongst management strategies (conservative surveillance (CS), microsurgical resection (MR), or stereotactic radiosurgery (SRS)) aiming to inform guideline recommendations on behalf of the International Stereotactic Radiosurgery Society (ISRS).

Methods. Using PRISMA guidelines, we reviewed manuscripts published between January 1990 and October 2021 referenced in PubMed or Embase. Inclusion criteria were peer-reviewed clinical studies or case series reporting a cohort of ICVS managed with CS, MR, or SRS. Primary outcome measures included tumor control, the need for additional treatment, hearing outcomes, and posttreatment neurological deficits. These were pooled using meta-analytical techniques and compared using meta-regression with random effect.

Results. Forty studies were included (2371 patients). The weighted pooled estimates for tumor control were 96% and 65% in SRS and CS series, respectively ($P < .001$). Need for further treatment was reported in 1%, 2%, and 25% for SRS, MR, and CS, respectively ($P = .001$). Hearing preservation was reported in 67%, 68%, and 55% for SRS, MR, and CS, respectively ($P = .21$). Persistent facial nerve deficit was reported in 0.1% and 10% for SRS and MR series, respectively ($P = .01$).

Conclusions. SRS is a noninvasive treatment with at least equivalent rates of tumor control and hearing preservation as compared to MR, with the caveat of better facial nerve preservation. As compared to CS, upfront SRS is an effective treatment in achieving tumor control with similar rates of hearing preservation.

Key Points

- We conducted a meta-analysis with the aim to compare treatment outcomes for intracanalicular vestibular schwannoma aiming to inform guideline recommendations for the International Stereotactic Radiosurgery Society.
- Stereotactic radiosurgery was associated with reduced treatment-related adverse effects versus microsurgical resection and similar hearing preservation versus conservative surveillance.

Importance of the Study

Management approaches for intracanalicular vestibular schwannoma are controversial, with no current international multidisciplinary consensus guidelines. The challenge lies in that high-quality evidence, such as those derived from randomized controlled trials is limited. We present in this study the management guidelines on behalf of the International Stereotactic Radiosurgery Society based on the results of our meta-analysis and review of the literature. We conclude that although

microsurgical resection and stereotactic radiosurgery (SRS) are associated with high rates of local control and equivalent hearing preservation, improved facial nerve preservation rates are observed. As compared to conservative surveillance (CS), upfront SRS is an effective treatment in achieving tumor control with similar rates of hearing preservation. CS should be considered as the recommended approach for older patients and no appreciable tumor growth regardless of hearing status.

The incidence of vestibular schwannoma (VS) has increased over the past few decades mainly due to improved access to modern imaging techniques, and awareness of potential tumor-related etiologies in patients who present with unilateral hearing loss.^{1,2} Consequently, the diagnoses of intracanalicular VS (ICVS) have increased, representing ~8–33% of all VS,^{1,3} with most patients suffering from only minor clinical symptoms or even being asymptomatic. ICVS has always been considered distinct from larger more complex VS, given the lack of extracanalicular extension that can result in symptomatic mass effect on the cerebellopontine angle. When there is no compelling need for urgent upfront surgical resection, the optimal management approach to patients presenting with ICVS is considered controversial with no current international multidisciplinary consensus guidelines.

Upfront treatment is generally considered a reasonable option for patients with ICVS given the risk of hearing loss and other neurological manifestations associated with tumor progression. However, these arguments must be balanced against the risk of delivering a treatment that may not be necessary or could be delayed, given the typically slow progression of these tumors over years. Therefore, upfront treatment should provide at least equivalent if not better results, as compared to those expected risks associated with conservative surveillance (CS), in order to be justified.

Although factors including age, tumor size, symptomatology, hearing status of both ears and overall health status are the primary considerations driving treatment recommendations, decisions regarding care are highly nuanced and VS management philosophies vary substantially between countries, institutions, and even caregivers.^{4,5} The challenge lies in that high-quality evidence, such as those derived from randomized controlled trials, is limited.⁶ The purpose of this study was to perform a systematic review and meta-analysis specific to ICVS, with the aim to compare treatment options, and provide management recommendations on behalf of the International Stereotactic Radiosurgery Society (ISRS).

acoustic neuroma OR vestibular schwannoma) AND (small OR intracanalicular). Search filters were set to English-language studies only. Articles published before 1990, and radiosurgical series using high single marginal doses (>14 Gy), were excluded to maintain relevance to current standards of practice. Inclusion criteria required that each article be a peer-reviewed clinical study or a case series focusing on ICVS or reporting a cohort of ICVS. We included only those series reporting the results for tumor control, hearing preservation or facial nerve deficit associated with a strategy of single fraction radiosurgery (SRS), microsurgical resection (MR), CS, or hypofractionated radiotherapy. Case reports or series of <10 patients with ICVS, series including patients with neurofibromatosis, small VS without reporting specifically the results for ICVS, salvage treatment only, lesions partially removed, and inclusion of patients under the age of 18 were excluded. When multiple publications from the same authors or center were eligible for inclusion, we selected the study with the longest follow-up. This study was performed in accordance with the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁷ (Figure 1). Data extraction was performed from each study, with special attention to the primary outcome variables of tumor control, need for further treatment, hearing outcome, and facial nerve deficit.

Statistical Analysis

Only studies reporting individual data were selected. Due to high variations in study characteristics, a statistical analysis using a binary random-effects model (Der Simonian-Laird method) was performed using R 4.1.3 (Meta/Metafor package for forest and funnel plots). Weighted summary rates were determined using meta-analytical models. Pooled estimates using meta-analytical techniques were obtained for all outcomes previously described. Testing for heterogeneity was performed for each meta-analysis and the LFK index was reported.⁸ The Doi plots with a quantitative measure (LFK index) are used to detect study asymmetry in our meta-analysis. The closer the value of the LFK index to zero, the more symmetrical the Doi plot would be and zero represents complete symmetry. Values beyond ± 1 were deemed consistent with minor asymmetry and values beyond ± 2 were deemed with major asymmetry. STATA 17 was used for the LFK index. Results of series reporting tumor control, need for further treatment, hearing outcome, postoperative, and

Methods

Article Selection and Data Extraction

PubMed and Embase searches were performed for entries between January 1990 and October 2021 using the following query guidelines: (acoustic schwannoma OR

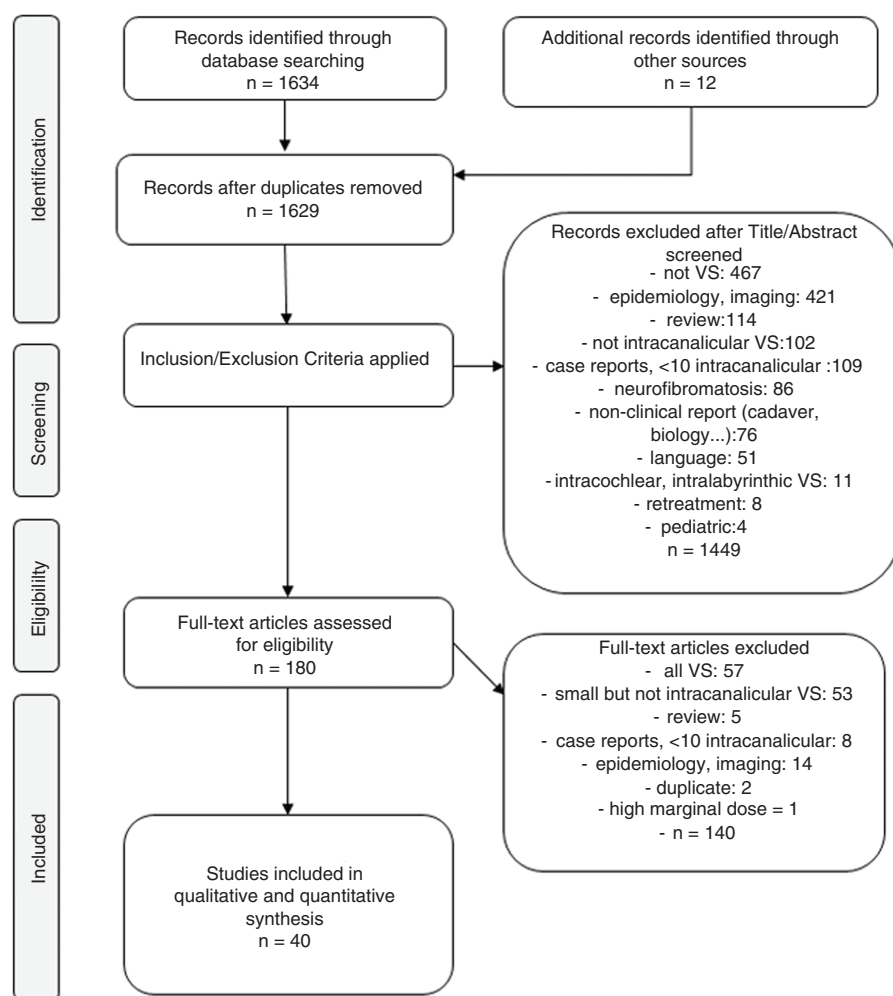


Figure 1. PRISMA⁷ flow diagram with study selection details. Studies included in qualitative synthesis correspond to peer-reviewed clinical studies or case series of ICVS treated by MR, SRS, or CS. Studies included in quantitative synthesis correspond to the subset of those at least reporting tumor control, need for further treatment, hearing outcome, or facial nerve deficit; different subsets have been used for meta-analyses focusing on each topic based on available respective rates.

persistent facial nerve deficit were compared using a meta-regression with random effect. A P -value $< .05$ was considered statistically significant.

Quality of the Meta-Analysis and Recommendations

The quality of the systematic review was assessed using the AMSTAR-2 scale.⁹ The quality of evidence and strength of recommendations were rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for clinical practice guidelines.^{10–12}

Results

Study Selection

Forty studies met the inclusion criteria (2371 patients)^{3,13–51}: 6 studies for SRS (550 patients),^{3,21,27,36,49,51} 19 studies for MR

(890 patients),^{13–17,20,22,24,26,31,33–35,37,39,40,42,43,45} and 14 studies for CS (863 patients,^{18,19,23,25,28,29,32,38,41,44,46–48,50} Tables 1–4). One observational study³⁰ compared the results of upfront SRS to CS. No series of hypofractionated radiotherapy was included. All SRS series were Gamma Knife® (Elekta AB, Stockholm, Sweden) based. The mean marginal dose for SRS studies was 12 Gy (range: 9–13.8 Gy). Mean follow-up for SRS and CS series were 68 and 52 months, respectively. Mean follow-up was scarcely reported in the MR series, with only 4 series^{15,37,39,40} reporting follow-up that ranged from 1 to 144 months. Most MR series reported only immediate postoperative results. The overall confidence in the results of the review was rated as moderate based on the AMSTAR-2 rating⁹ (Supplementary material Figure S1).

Tumor Control

Tumor control was achieved in 96% (95% CI: 90–98%) and 65% (95% CI: 55–74%) of the SRS and CS series, respectively (Figure 2). The difference observed was statistically

Table 1. Description of the Selected Studies, Treatment Strategy, and Definition of Tumor Growth and Hearing Preservation

Author, year	Institution	Location	Study Type/ Level of Evidence	Year	Method	Inclusion Criteria	Definition of Tumor Growth	Definition of Serviceable Hearing
Haines, ⁹ 1993	University of Minnesota	Minneapolis, United States	RS, low	1986–1991	MR	ICVS; serviceable hearing	NS	GR grade 1 & 2
Rowed, ¹⁰ 1997	Sunnybrook Health Science Centre	Toronto, Canada	RS, low	1985–1996	MR	VS with extra-meatal extension < 1.5 cm; serviceable hearing; RS approach	NS	PTA of less than 50 dB and an SD of greater than 50%
Irving, ¹¹ 1998	University of California	San Francisco, USA	RS, low	1987–1996	MR	Small VS; serviceable hearing	NS	AAO–HNS class A–B
Koos, ¹² , 1998	University of Vienna	Vienna, Austria	RS, low	1980–1996	MR	Koos I & II VS	NS	PTA of less than 50 dB and an SD of greater than 50%
Kumon, ¹³ 2000	Ehime University School of Medicine	Ehime, Japan	RS, low	1988–1997	MR	VS < 2 cm	NS	AAO–HNS class A to B
O'Reilly, ¹⁴ 2000	Southern General Hospital	Glasgow, Ireland	RS, low	1989–1998	CS	All VS	Increase of 1 mm in either the tangential or perpendicular planes	NS
Thomsen, ¹⁵ 2000	Gentofte University Hospital	Hellerup, Denmark	RS, low	1973–1996	CS	Intracanalicular VS	NS	NS
Magnan, ¹⁶ 2002	AP-HM	Marseille, France	RS, low	1993–1998	MR	VS < 2.5 cm	NS	Shelton classification type A & B
Litvack, ¹⁷ 2003	Rhode Island Hospital	Rhode Island, United States	RS, low	1994–2000	SRS	All VS	increase > 2 mm in mean diameter	GR grade I&II
Darrouzet, ¹⁸ 2004	Hôpital Pellegrin	Bordeaux, France	RS, low	1984–2000	MR	All VS	NS	AAO–HNS class A–B
Raut, ¹⁹ 2004	New Cross Hospital	Wolverhampton, United Kingdom	RS, low	1987–2002	CS	All VS	tumour growth > 1 mm/year	AAO–HNS class A to B
Colleti, ²⁰ 2005	General Hospital G.B. Rossi	Verona, Italy	PS comparative study, medium	1991–2002	MR	ICVS; serviceable hearing	NS	AAO–HNS class A–B
Ferri, ²¹ 2008	Orsola-Malpighi University Hospital	Bologna, Italy	RS, low	1981–2006	CS	Small & medium VS	Increase of 2 mm or more in comparison with the previous MRI scan	AAO–HNS class A–B
Gjuric, ²² 2008	KBC Zagreb	Zagreb, Croatia	RS, low	NS	MR	VS < 1.5 extra-meatal	NS	AAO–HNS class A–B
Iwai, ²³ 2008	Osaka City General Hospital	Osaka, Japan	RS, low	1994–2003	SRS	ICVS; serviceable hearing	NS	NS
Solares, ²⁴ 2008	Princess Alexandra Hospital	Brisbane, Australia	RS, low	NS	CS	All VS	An increase in diameter of greater than 2 mm	NS

Table 1. Continued

Author, year	Institution	Location	Study Type/ Level of Evidence	Year	Method	Inclusion Criteria	Definition of Tumor Growth	Definition of Serviceable Hearing
Godefroy, ²⁵ 2009	Leiden University Medical Centre	Leiden, The Netherlands	RS, low	2002–2003	CS	All VS	Increase of 2 mm or more in comparison with the previous MRI scan	AAO–HNS class A–B
Regis, ²⁶ 2010	AP-HM, La Timone	Marseille, France	PS comparative study, medium	1981–1999	CS vs SRS	ICVS	need for 2nd treatment	GR grades 1 & 2
Falcioni, ²⁷ 2011	University of Parma	Parma, Italy	RS, low	1987–2007	MR	All VS; no previous surgery or radiosurgery	NS	NS
Pennings, ²⁸ 2011	Maritime Lateral Skull Base Clinic	Halifax, Canada	RS, low	1998–2007	CS	ICVS; follow-up > 2 y	Increase of 2 mm or more in comparison with the previous MRI scan	AAO–HNS class A–B
Rabelo de Freitas, ²⁹ 2011	Gruppo Otologico Piacenza	Roma, Italy	RS, low	1988–2008	MR	All VS; follow-up > 1 y; MCF or RS approach	NS	AAO–HNS class A–B
Nguyen, ³⁰ 2012	Kaiser Permanente	San Diego, USA	RS, low	2001–2010	MR	ICVS; serviceable hearing	NS	AAO–HNS class A–B
Springborg, ³¹ 2012	Copenhagen University Hospital	Copenhagen, Denmark	RS, low	1976–2009	MR	All VS; TL approach	NS	NS
Kim, ³² 2013	Seoul National University College of Medicine	Seoul, Korea	RS, low	1998–2009	SRS	ICVS; serviceable hearing	Volume > 120%	GR grades 1 & 2
Wang, ³³ 2013	University of Michigan	Ann Arbor, United States	RS, low	1999–2008	MR	ICVS	NS	NS
Lee, ³⁴ 2014	Sungkyunkwan University School of Medicine	Seoul, Korea	RS, low	2001–2012	CS	ICVS; follow-up > 1 year	Increase of 2 mm or more in comparison with the previous MRI scan	AAO–HNS class A–B
Aihara, ³⁵ 2015	Nagoya City University Medical School	Nagoya, Japan	RS, low	2004–2013	MR	ICVS	NS	AAO–HNS class A–B
Raheja, ³⁶ 2016	University of Utah School of Medicine	Salt Lake City, USA	RS, low	2000–2015	MR	ICVS	NS	AAO–HNS class A–B
van Linge, ³⁷ 2016	Institute of Public Health, Erasmus MC	Rotterdam, The Netherlands	RS, low	2000–2010	CS	All VS	≥2-mm increase in any tumor diameter in 3 planes	AAO–HNS class A–B
Zhang, ³⁸ 2016	AP-HP	Paris, France	RS, low	1990–2006	MR	All VS	NS	AAO–HNS class A–B
Kang, ³⁹ 2017	Asan Medical Center, University of Ulsan College of Medicine,	Seoul, South Korea	RS, low	2002–2005	MR	ICVS; serviceable hearing	NS	AAO–HNS class A–B
Kirchman, ⁴⁰ 2017	Copenhagen University Hospital	Copenhagen, Denmark	RS, low	1976–2004	CS	ICVS	≥2-mm increase in any tumor diameter in 3 planes	AAO–HNS class A–B

Table 1. Continued

Author, year	Institution	Location	Study Type/ Level of Evidence	Year	Method	Inclusion Criteria	Definition of Tumor Growth	Definition of Serviceable Hearing
Samii, ⁴¹ 2017	International Neuroscience Institute	Hannover, Germany	RS, low	NS	MR	ICVS; vertigo	NS	New Hannover classification—class H1 & 2
Younes, ⁴² 2017	AP-HM, La Conception	Marseille, France	RS, low	2010–2015	CS	ICVS	increase of 2 mm/1 year	AAO-HNS class A to B
Prasad, ⁴³ 2018	Gruppo Otologico, Piacenza	Rome, Italy	RS, low	1986–2013	CS	All VS	>1 mm increase	Classes A&B of the Modified Sanna classification
Zanoletti, ⁴⁴ 2019	University of Padua	Padua, Italy	RS, low	2012–2016	CS	Small VS; <1cm in the CPA	Increase of 2 mm or more in comparison with the previous MRI scan	AAO-HNS class A–B
Dzierżęcki, ³ 2020	Brodno Masovian Hospital	Warsaw, Poland	RS, low	2011–2015	SRS	ICVS	NS	GR grades 1 & 2
Hasegawa, ⁴⁵ 2020	Komaki City Hospital	Komaki, Japan	RS, low	1991–2013	SRS	All VS; marginal dose < 14 Gy; follow-up > 5 y	Increase of tumor volume \geq 25%	GR grade s 1 & 2
Sethi, ⁴⁶ 2020	Cambridge University Hospitals	Cambridge, United Kingdom	RS, low	2005–2014	CS	VS < 20mm; follow-up > 5 y	\geq 2-mm increase in any tumor diameter in 3 planes	NS
Ogino, ⁴⁷ 2021	Presbyterian University Hospital	Pittsburgh, United States	RS, low	1987–2017	SRS	ICVS	Increase of tumor volume \geq 15%	GR grades 1 & 2

Abbreviations: AAO-HNS Stands for American Association of Otolaryngology–Head and Neck Surgery, GR for Gardner–Robertson Scale, ICVS for Intracanalicular Vestibular Schwannoma, NS for Not Specified, PS for Prospective Study, PTA for Pure Tone Average, RS for retrospective study, SD for Speech Discrimination, SRS for Stereotactic Radiosurgery, TL for Translabyrinthine, and VS for Vestibular Schwannoma

significant ($P < .001$), with higher rates of tumor growth following CS. Major asymmetry was observed between the studies (LFK = -6.05). The gross total resection rate ranged from 86% to 100% in the MR series. Local tumor control for those series reporting on MR could not be established, since only 4 out of the 19 studies presented described follow-up after surgery, with 1 study reporting only 1-month follow-up.

Additional treatment, following the initial proposed management for ICVS, secondary to tumor growth was reported in 1% (95% CI: 0–6%), 2% (95% CI: 0–7%), and 25% (95% CI: 15–38%) in those SRS, MR, and CS series, respectively. The difference observed was statistically significant ($P = .001$), with higher rates of additional treatment for CS vs those SRS or MR series. Major asymmetry was observed between the studies (LFK = 4.88).

Hearing Preservation

Twenty-five studies (4 SRS series^{3,21,27,36} including 165 patients, 15 MR series^{13–17,20,24,26,33,35,37,39,40,43,45} including 621 patients, and 6 CS series^{30,32,38,44,46,48} including 217 patients) reported crude hearing preservation rates and 2 reported

actuarial rates.^{30,51} Considering the actuarial rates, overall serviceable hearing preservation rates were 76.6–77% at 3 years, 63.5–65% at 5 years, and 27.3% at 10 years for SRS studies,^{30,51} respectively, and 75% at 3 years and 41% at 5 years for CS series,³⁰ respectively. Crude hearing preservation rates were reported as 67.0% (95% CI: 55–77%), 68.0% (95% CI: 56–79%) and 55% (95% CI: 38–71%) for SRS, MR, and CS series, respectively. Minor asymmetry was observed between the studies (LFK = -1.2). The difference observed was not statistically significant ($P = .21$). Yet, the mean follow-up for MR studies was <1 month, 68 months for SRS and 52 months for CS. The one comparative nonrandomized study evaluating SRS to CS reported a significant difference in hearing preservation in favor of upfront SRS.³⁰

Differences observed according to the MR approach were not statistically significant ($P = .53$), yet 2 series^{15,33} reported significantly higher hearing preservation rates for middle cranial fossa (MCF) compared to a retrosigmoid (RSi) surgical approach. Differences observed between studies reporting immediate postoperative hearing preservation^{13,14,16,20,24,33,39,43,45} or longer-term results^{15,17,26,34,37,40} were also not statistically significant

Table 2. Study Criteria, Tumor Control, Need for Additional Treatment from Initial Management, Postoperative and Persistent Facial Nerve Palsy, and Hearing Preservation among the Selected SRS Series. Only Gamma Knife (GK) Studies Met the Inclusion Criteria. NS Stands for Not Specified and SRS for Stereotactic Radiosurgery

Author, Year	Patients (All Cohort*)	Median Age (Range; Mean)	SRS Technique	Median Follow-Up months (Range; Mean)	Median Size (Range; Mean)	Tumor Control (%)	Need for Additional Treatment (%)	Post-operative Facial Palsy (%)	Persistent Facial Palsy (%)	Hearing Preservation (%)	Other Complications
Litvack, ¹⁷ 2003	23(134*)	NS (13–86;55) *	GK	NS (12–72;32) *	NS	100	0	NS	NS	63.6	
Iwai, ²³ 2008	25	NS (25–66;48)	GK	NS (36–132;89)	0.27(0.07–0.8; NS)	96	0	0	0	63	Vertigo 8%, hemifacial spasm 4%
Regis (2), ²⁶ 2010	34	NS (NS;51)	GK	NS	NS(NS;112.5 mm ³)	NS	2.9	NS	NS	77%-3 y, 70%-4 y, and 64%-5 y	
Kim, ³² 2013	60	NS (21–69;50)	GK	NS (36–141;62)	NS (0.03–1.00;0.34)	88	0	NS	NS	57	
Dzierżęcki, ³ 2020	136	NS(NS;54)	GK	NS (6–83;52)	NS (0.015–0.47; 0.16)	91.2	8.8	0.74	0	78.2	Hemifacial spasm 2.2%
Hasegawa, ⁴⁵ 2020	87(615*)	58(13–86; NS) *	GK	158*	2(0.02–28.9; NS) *	100	0	NS	0	NS	
Ogino, ⁴⁷ 2021	209	NS(NS;54)	GK	49 (6–350; NS)	0.17 (0.015–0.63)	95.7	1.4	0.47	0	76.6%-3 y, 63.5%-5 y, 27.3%-10 y	Tinnitus 5.3%, vertigo 4.3%

*Corresponds to the entire cohort.

($P = .65$). Minor asymmetry was observed between the studies (LFK = -1.63).

Facial Outcome

The House–Brackmann scale⁵² was used to assess facial nerve function. Facial nerve deficit was defined as House–Brackmann (HB) > grade II. Seventeen studies (3 SRS^{3,27,51}–370 patients and 13 MR^{13,15–17,20,22,24,26,31,33,37,40,45} series–723 patients) reported transient facial nerve deficit rates and long-term facial nerve deficit rates.

Facial nerve function was preserved in all observational studies. Posttreatment facial nerve deficit was reported in 1% (95% CI: 0–2%) and 14% (95% CI: 8–23%) for SRS and MR series, respectively. The difference observed between SRS and MR series was statistically significant ($P = .022$). Major asymmetry was observed between the studies (LFK = 5.92).

Considering MR approaches, transient postoperative facial nerve deficit was observed with a higher trend for the MCF approach ($P = .06$). Concerning the comparative studies of MR approaches, only one series²⁴ reported a significantly higher postoperative facial nerve deficit rate for MCF compared to the RSi surgical approach, albeit were not maintained on long-term follow-up.

Persistent facial nerve deficit was reported in 0.1% (95% CI: 0–0.2%) and 10% (95% CI: 6–16%) of SRS and MR series, respectively (Supplementary material Figure S2).

The difference observed between SRS and MR series was statistically significant ($P = .01$). Major asymmetry was observed between the studies (LFK = 7.24).

Other Complications

Vertigo was reported in 2 out of 8 SRS series^{27,51} with a mean rate of 6.2% (range: 4.3–8%) and in 2 out of 19 MR series^{13,22} with a mean rate of 26.9% (range: 8.3–45.5%). On the contrary, Samii et al. in a series evaluating the efficacy of microsurgery for ICVS presenting with disabling vestibular symptoms, showed that in 63% of patients, vertigo completely resolved.⁴⁵ Tinnitus was reported in 1 out of 8 SRS series⁵¹ with a rate of 5.3%, and in 1 out of 19 surgical series with a rate of 8.3%.¹³ Specific to the SRS series, hemifacial spasm was reported in 2 out of 8 series^{3,27} with a mean rate of 3.1% (range: 2.2–4%).

Considering the MR series, CSF leak was reported in 7 series^{13,22,24,37,42,43,45} with a mean rate of 6.9% (range: 4.7–9%), and hydrocephalus in 2 series^{22,26} with a mean rate of 1.75% (range: 1.5–2%). Wound infection was reported in 2 series^{22,40} with a mean rate of 5% (range: 3.8–6.2%) and meningitis in one series with a rate of 5.5%.²² Postoperative stroke was reported in 2 series^{22,37} with a mean rate of 0.75% (range: 0.5–1%), hematoma (extradural, temporal, cerebellopontine hematoma or superficial) in 3 series^{22,24,26} with a rate of 2.7% (range: 0.5–6%), cerebellar edema in

Table 3. Study Criteria, Tumor Control, Need for Second Treatment, Postoperative and Persistent Facial Nerve Palsy, and Hearing Preservation among the Selected Surgical Series.

Author, Year	Patients (All Cohort*)	Median Age (Range; Mean)	Surgical Approach	Median Follow-up Months (Range; Mean)	Median Size (Range; Mean)	GTR (%)	Need for Additional Treatment (%)	Postoperative Facial Palsy > HB II (%)	Persistent Facial Palsy > HB II (%)	Hearing Preservation	Other Complications
Haines, ⁹ 1993	14	NS (26–70;48)	MCF; RSi; TL	NS	NS (4–10 mm; NS)	NS	NS	14.3	14.3	90.9	CSF leak 8.3%; seizure 8.3%; vertigo 8.3%; tinnitus 8.3%
Rowed, ¹⁰ 1997	26	NS	RS	NS	NS	NS	NS	NS	3.8	47.8	NS
Irving, ¹¹ 1998	42	NS (14–69;48)	MCF vs RSi	NS (1–96;10)	42	NS	NS	22.0	2.6	54.8	NS
Koos, ¹² 1998	14(115*)	NS	RSi	NS	NS	NS	NS	0	0	100	NS
Kumon, ¹³ 2000	15(53*)	NS	MCF	NS	NS	100	NS	60	26.7	66.7	NS
Magnan, ¹⁶ 2002	20(119*)	NS	RSi	NS	NS	NS	NS	0	0	55	NS
Darrouzet, ¹⁸ 2004	39 (400*)	NS (11–78;54) *	TL; RL	NS	NS	NS	NS	2.6	NS	NS	VP shunt 2%*, cerebellopontine hematoma 0.5%*, postoperative stroke 0.5%*, CSF leak 4.7%, meningitis 5.5%*, wound infection 6.2%; acute vestibular complaint 45.5%; death 0.7%
Colletti, ²⁰ 2005	70	NS (21–68; NS)	MCF vs RSi	NS	NS (4–12 mm; NS)	NS	NS	32.9	17.1	45.7	Cerebellar edema 15.7%; CSF leak 9%; extradural hematoma 6%
Gjuric, ²² 2008	67(205*)	NS	MCF	NS	NS	98.5	NS	6	0	62.3	Epidural hemorrhage 0.5%*, temporal muscle hematoma 1%*, meningitis 1%*, VP shunt 1.5%*, pneumocephaly 1.5%*, diplopia 1.5%*
Falcioni, ²⁷ 2011	161 (1151*)	NS	MCF; TL; RSi	NS	NS (16–82;51) *	NS	NS	9.93	NS	NS	NS
Rabelo de Freitas, ²⁹ 2011	94(175*)	NS	MCF vs RSi	NS	NS	NS	NS	14.9	NS	18.1	NS
Nguyen, ³⁰ 2012	53	NS(NS;53)	RSi	NS	NS(3–10 mm;72)	NS	NS	NS	NS	75.5	NS
Springborg, ³¹ 2012	13(1244*)	NS(NS;53*)	TL	NS	NS	NS	NS	NS	7.7	NS	NS
Wang, ³³ 2013	103	NS	MCF	6(NS;48)	NS	98	1.9	31	9	82.1	CSF leak 9%; petrosal venous occlusive infarction 1%
Aihara, ³⁵ 2015	48	NS (31–64;48)	MCF	NS (16–144;70)	NS	NS	NS	NS	NS	72.3	NS
Raheja, ³⁶ 2016	78	NS (21–70;49)	MCF	NS(NS;15)	NS(1–172;75 mm)	100	NS	10.6	NS	75.5	wound infection 3.8%
Zhang, ³⁸ 2016	88(1006*)	NS(NS;56) *	TL; RSi; MCF	NS	NS	NS	NS	NS	8.3	NS	CSF leak 5%
Kang, ³⁹ 2017	14	46(29–57; NS)	MCF	NS	NS	86	0	NS	7.6	85.7	CSF leak 7.6%
Samii, ⁴¹ 2017	19	NS (39–70;47)	RSi	NS	NS	NS	NS	21.1	0	76	CSF leak 5%

CSF, cerebrospinal fluid leak; MCF, middle cranial fossa approach; NS, not specified; RSi, retrosigmoid approach; TL, translabirithine

*Corresponds to the entire cohort.

Table 4. Study Criteria, Tumor Control, Need for Second Treatment, and Hearing Preservation Among the Selected Observational Series. NS Stands for Not Specified

Author	Patients (All Cohort*)	Median Age (Range; Mean)	Median Follow-up Months (Range; Mean)	Median Tumor Size (Range; Mean)	Tumor Control (%)	Need for Additional Treatment (%)	Annual Growth Rate/Actuarial Control Rate	Hearing Preservation	Hearing Preservation (Actuarial Rates)
O'Reilly, ¹⁴ 2000	20(44) *	NS (30–85;64) *	NS (13–120;34)	NS	70	5	NS	NS	NS
Thomsen, ¹⁵ 2000	40	NS (17–77;57)	NS (6–132;44)	NS	32.5	32.5	3.2 mm/year	NS	NS
Raut, ¹⁹ 2004	18(72*)	NS (38–71;58)	NS (53–148;81)	NS(3–16;8 mm)	94.5	NS	0 ± 0.2 mm/year	NS	NS
Ferri, ²¹ 2008	59(123*)	NS (25–84;61)	NS (6–182;57) *	NS(2–28;11 mm)	69.5	NS	NS	NS	NS
Solares, ²⁴ 2008	32 (110*)	NS (32–91;62) *	NS (6–56;31) *	NS	84.4	15.6	NS	NS	NS
Godefroy, ²⁵ 2009	30(70*)	NS (35–82;60) *	NS (11–67;32) *	NS (2–27;10) *	73.3	26.6	0.45 mm/year	NS	NS
Regis (1), ²⁶ 2010	47	NS (20–71;54)	35(9–222;44)	8.1 ± 2.5 mm/84.5 ± 48.9 mm ³	23.4	74.5	0.12cm3/year	68	75%-3 y, 52%-4 y, 41%-5 y
Pennings, ²⁸ 2011	47	58(23–80; NS)	NS (0.7–84; 43)	NS	59.6	17	NS	74	NS
Lee, ³⁴ 2014	31	54(20–74; NS)	31(12–84; NS)	7(3–13 mm; NS)	77.4	16.1	NS	45.5	NS
van Linge, ³⁷ 2016	69(155) *	NS(NS;58) *	40(9–140; NS) *	NS	67	NS	NS	NS	NS
Kirchman, ⁴⁰ 2017	156	57(15–77; NS)	NS (12–300;114)	NS	62.8	14.7	NS	32.9	NS
Younes, ⁴² 2017	53	NS (18–82;55)	24(12–60;32)	NS	68	22.6	NS	74	NS
Prasad, ⁴³ 2018	95(154*)	NS (20–89;59)	NS (20–89;59) *	NS	62.1	22.2	1.07 ± 2.17 mm	NS	NS
Zanoletti, ⁴⁴ 2019	34(91*)	NS(NS;56) *	NS	NS	79.4	11.7	NS	26.7	NS
Sethi, ⁴⁶ 2020	166 (341*)	NS (33–63;67) *	NS	NS	64.5	NS	NS	NS	NS

*Corresponds to the entire cohort.

1 series²⁴ with an incidence of 15.7%, and seizure in one series with a rate of 8.3%.¹³

No complications besides tumor progression were reported for CS.

Discussion

General Interpretation

We present a systematic review and meta-analysis comparing treatment outcomes between SRS, MR and CS specific to ICVS, and international multidisciplinary consensus management guidelines (Table 5).

MR for VS was first described in 1894 and consisted at that time of a life-saving surgery despite high rates of complications.⁵³ Over the past few decades, postoperative

complications have decreased drastically in part due to the use of surgical microscopes, cranial nerve monitoring and functional sparing guided surgery.⁵⁴ Given that safe complete tumor removal is routinely expected, the primary issues affecting treatment decision-making for ICVS are preservation of functional hearing, facial nerve function and quality of life. Our meta-analysis showed that complete resection was generally obtained and tumor growth requiring an additional treatment was rarely observed (2%) following MR. However, long-term results were infrequently reported, which represents a shortcoming in the surgical literature.

The selection of the optimal microsurgical approach for ICVS remains a matter of debate. The decision is mainly based on the hearing status of the patient, the position of the tumor in the auditory canal, surgeon bias and the patient's preference and attributes. In this meta-analysis, hearing preservation was observed in 68% of the sample

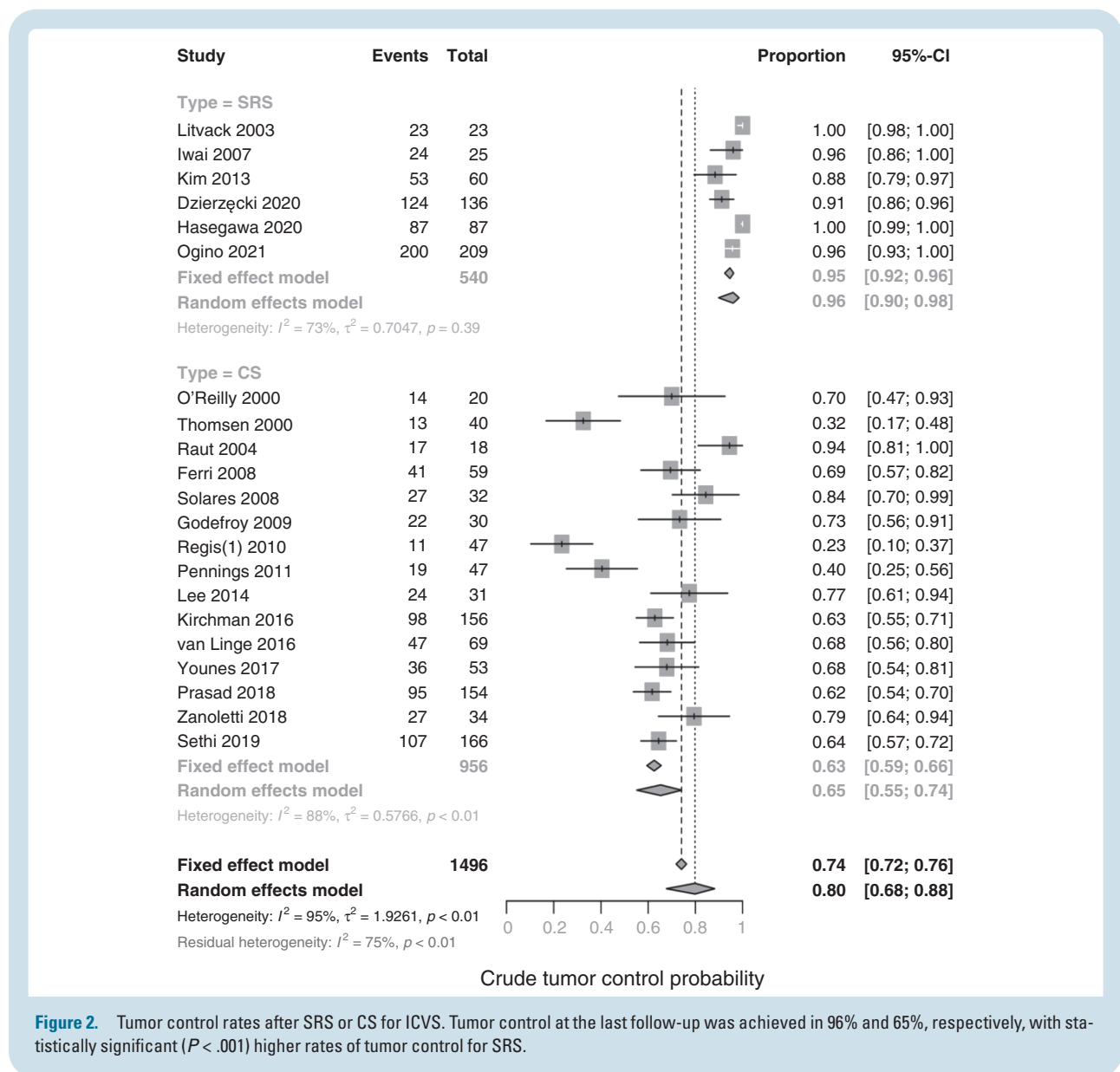


Figure 2. Tumor control rates after SRS or CS for ICVS. Tumor control at the last follow-up was achieved in 96% and 65%, respectively, with statistically significant ($P < .001$) higher rates of tumor control for SRS.

with no statistically significant difference between the various microsurgical approaches reported. However, the likelihood of successful preservation of cochlear nerve function during VS surgery has been improved by the advent of intraoperative monitoring techniques.⁵⁵ Several factors may also predict better postoperative hearing outcomes: the origin of the tumor,³⁹ the enlargement of the inferior portion of the internal canal,³⁹ fundal extensions,^{24,34,43} tumor size,^{16,24,26} preoperative hearing threshold,^{16,20,40} presence of synchronized auditory evoked potentials or preoperative otoacoustic emission,^{20,45} and neurotopographic relationship of the tumors to the cochlear nerve.¹⁶

With respect to facial nerve complications, postoperative and persistent facial nerve deficits were reported in 14% and 10%, respectively, in the MR series for ICVS. Factors affecting facial nerve preservation include tumor size and surgical approach. Other adverse events associated with

MR include CSF leak, hydrocephalus, wound infection, and vascular complications, and these should be carefully considered in the decision-making process. On the contrary, one special indication for surgical resection might be intractable dizziness which generally does not improve after SRS or CS.⁴⁵

SRS for VS was first used in 1969.⁵⁶ Since then, the efficacy of SRS in tumor control of small to medium VS has been well documented with less frequent and severe complications than conventional MR.^{57–60} Yet, its role in the management of ICVS remains controversial. In this meta-analysis, tumor control was achieved in 96% of ICVS with a need for an additional treatment observed in 1%. Hearing preservation was achieved in 67%, consistent with those series of small to medium VS.⁶¹ The main prognostic factors for hearing preservation include younger age,⁵¹ smaller tumor volume at SRS,⁵¹ lower mean cochlear dose,^{3,36} good pre-SRS hearing status,^{3,36,51} transient

Table 5. ISRS Management Guidelines are Based on the Current Meta-Analysis with Strength of Recommendation and Quality of Evidence**Patient Selection**

1. Treatment choice should be based on the hearing status, age, and overall condition of the patient (strong recommendation and low quality of evidence).
2. Patients with ICVS should be proposed upfront SRS irrespective of their hearing status (strong recommendation and low quality of evidence)
 - a. SRS results in greater rates of tumor control and equivalent hearing preservation rates as compared to CS. (strong recommendation and high quality of evidence)
 - b. Hearing preservation is achieved in approximately ~50–66% of patients after SRS
 - c. The risk of facial nerve deficit is lower after SRS than MR.
3. CS or SRS vs MR can be considered for elderly patients (>80 y old) with or without a serviceable hearing. (weak recommendation and low quality of evidence).

Treatment

1. A high-resolution volumetric treatment planning MRI with at least a volumetric T1 postgadolinium, high-resolution T2 (for example FIESTA/CISS) pre and postgadolinium and a CT scan (contrast optional) should be performed at the time of SRS to ensure accurate target volume delineation. (strong recommendation, low quality of evidence).
2. A marginal single fraction dose of 11–13 Gy is recommended (strong recommendation, moderate quality of evidence).
3. The cochlear dose should be kept as low as possible (eg maximum or mean dose < 4 Gy) to optimize serviceable hearing outcomes (weak recommendation and low quality of evidence).

Follow-up

1. Patients treated with SRS should undergo lifelong routine clinical follow-up, including audiometry, cranial nerve examination, and imaging surveillance. A schedule of every 6 months for the first year, annually for up to 5 y, every 2 y until 10 y follow-up, and every 5 y thereafter is reasonable (weak recommendation, low quality of evidence).

Abbreviations: CT, computerized tomography; CS, conservative surveillance; ICVS, stands for intracanalicular vestibular schwannoma; MR, microsurgical resection; SRS, stereotactic radiosurgery

volume enlargement < 20% of tumors³⁶ and smaller tumor volume³ at the last follow-up. Groups have demonstrated favorable results of early intervention for hearing preservation compared with untreated controls.³⁰ Post-SRS persistent facial nerve deficit was observed in less than 1%. Other complications such as hemifacial spasm, trigeminal neuropathy, vertigo, hydrocephalus and tinnitus have been reported.

Precision of tumor delineation is one of the cornerstones of SRS treatments. Targeting errors in the range of 1 mm may cause a significant reduction in the dose delivered to small targets, and increase the dose delivered to the critical surrounding structures. In order to improve accuracy, contouring should be based on a T1-weighted contrast-enhanced volumetric MRI (3DT1), a high-resolution T2-weighted volumetric sequence (for example FIESTA or CISS) without and with gadolinium and a high-resolution CT scan.⁶² Together, this approach minimizes partial volume effects and distortions, allows direct identification of the nerve, and enables improved delineation of the tumor in the IAC⁶³ and cochlea. The importance of slice thickness to SRS dosimetry was also a major issue historically but has been obviated with improved imaging protocols such as those recommended above.^{64,65} Although performing a CT scan is not systematically done for SRS (only 2^{30,51} out of 6 series in this meta-analysis), it might provide in this specific indication an additional quality assurance (Figure S3 Supplementary material). In a study evaluating the discrepancy between the targets relying on MRI and CT scans, Borden et al. reported average shifts of 0.9 mm in y-axis and 0.8 mm in z-axis; the corresponding percentage of tumor coverage subsequently decreased from 98% to 77%.⁶⁶ Based on the importance of the precision of the

targeting in these small tumors, important considerations for patient immobilization should include patient comfort, end-to-end accuracy testing, whether a set-up margin is added to the volume, and overall time treatment.^{67,68}

CS via serial radiological studies for VS was first proposed in the mid-1980s.⁶⁹ CS has become increasingly popular in patients with small asymptomatic tumors.⁷⁰ The basic premise of this option is that even if some growth is confirmed, the patient will maintain a higher level of function than if upfront treatment is performed.⁷¹ CS has been an accepted management strategy for those minimally symptomatic or mildly symptomatic Koos 1 or 2 VS. The pitfalls of CS include noncompliant patients who fail to get follow-up scans, that the growth of VS is not always linear, that mild volumetric changes in the tumor can lead to appreciable signs or symptoms which can be irreversible, and that some VS grow significantly even after several years of stability. Although the growth during the first year after diagnosis may be predictive of total growth, conflicting results have been reported regarding whether tumors that show no growth over 5 years will subsequently grow in later years,^{25,46,72,73} in which case lifelong follow-up is then recommended.⁷³ Recent meta-analyses evaluating the growth rate of VS have demonstrated that growth can vary significantly among patients who undergo CS ranging from 0.3 to 4.8 mm/year. Some authors have advocated that ICVS may be associated with lower growth rates than VS with extra-meatal extension,^{44,48,60} but this is still a matter of debate.⁷⁴

A recent landmark randomized controlled trial (reported after our meta-analysis window of eligible papers) consisting of 100 patients, of which 50 were randomized to CS and 50 to upfront SRS (V-REX trial), requires discussion

as highly relevant to our analyses.⁷⁵ Forty-four percent of patients in the wait-and-see group were treated for tumor growth, within the 4-year follow-up window, of which 42% received SRS. However, in the upfront SRS group, only 6% received additional treatment 4 years post-SRS due to persistent growth. Upfront SRS demonstrated a significantly greater tumor volume reduction than their CS approach, however, no significant differences were observed within the first year.⁷⁵ Importantly, other than the increased risk of reduced facial sensation (6/50, 12%), there were no significant differences in hearing acuity (equivalent rates of decline), vestibular function or quality of life between the two cohorts. With respect to post hoc analyses, 54% in the CS cohort and 53% in the SRS cohort developed nonserviceable hearing. These data counter the notion that upfront SRS may be detrimental to hearing secondary to radiation-induced neuropathy. Of note, long-term follow-up is required to ensure these rates remain equivalent, as worse hearing outcomes may be observed in either arm given that hearing loss can occur gradually or suddenly with tumor growth,^{41,44,46} or can be independent of tumor growth.^{25,30,47,48,55} An additional randomized controlled trial (NCT01938677), evaluating the role of upfront SRS vs CS in patients with newly diagnosed VS (less than 2 cm in diameter) with preserved hearing, with the primary endpoint of hearing preservation, is awaited.

Long-Term Outcomes

Long-term rates of tumor progression after MR were scarcely reported, which represents a shortcoming in the surgical literature. Based on the limited data, this risk has been evaluated to be 4% at 5 years, 18% at 10 years, and up to 27% at 15 years for all VS.^{76,77} Long-term tumor control after SRS is estimated at 95–98% with very few recurrences/tumor progression after 10–15 years follow-up. Concerning CS, although the growth during the first year after diagnosis may be predictive of total growth, conflicting results have been reported regarding whether tumors that show no growth over 5 years will grow in later years^{25,46} and, hence, lifelong follow-up is recommended.

Hearing preservation for MR studies is often reported based on the immediate postoperative assessment alone, which also represents a shortcoming of the surgical literature given that patients with intact postoperative hearing may subsequently experience hearing decline.^{26,37} In the series by Shelton et al.,⁷⁸ as many as 56% of patients were found to experience a decline in hearing quality with a follow-up ranging from 8 to 20 years. Although long-term data remain scarce, hearing preservation after SRS is estimated at 60% with at least 6 years of follow-up.⁶¹ For CS, the probability of keeping serviceable hearing also likely diminishes with time. In a recent meta-analysis including 15 series and 2142 patients initially observed, the probability of keeping serviceable hearing at a 5-year follow-up was evaluated to be 50%.⁷⁹ Kirchmann et al. prospectively examined the spontaneous course of 156 patients with ICVS and found that 37% of the tumors had increased at a mean follow-up of 9.5 years. In their study, hearing deterioration correlated positively with the mean absolute growth rate.⁴⁴ On the contrary, Regis et al. showed that

hearing can deteriorate without tumor growth,³⁰ and that upfront SRS improved the outcome; however, this was not confirmed in the V-REX study.⁷⁵ In this meta-analysis we also did not find significant differences in hearing preservation between the different approaches, with the caveat that longer mean length of follow-up with SRS studies may introduce bias.

Limitations of the Review Process

This meta-analysis suffers from several limitations. Only English-language articles were selected. Patients included in the series varied on several criteria (eg marginal doses for SRS, and different surgical approaches within the MR series). The indication for active treatment varied upon centers, with some teams proposing upfront SRS^{30,51} or surgery, some leaving the treatment choice to the patient, and some waiting for clinical deterioration or radiological progression.^{3,19,25,29,46,48,49} The definition of tumor volume and tumor growth also greatly varied across series and was pooled in this series as a crude rate, instead of 1-, 5- and 10-year time-dependent actuarial outcomes. Overall, this disparity engenders high heterogeneity among the pooled data limiting the prediction quality of such analysis. Unfortunately, there also are many sources of heterogeneity that cannot be controlled and are linked to the variety of practice among centers and inherent to the type of articles published (retrospective case series).

Limitations of Evidence

This meta-analysis suffers from bias that may be explained by various factors. The number of patients per study ranged from 14 to 209. The number of studies reporting a number of zero events was high for each analysis. To assess the evolution of hearing preservation over time, extraction of raw individual patient data from published Kaplan–Meier estimators would have been a useful method to calculate pooled actuarial rates.^{80,81} Given that only 2 SRS, 1 CS and no MR series reported Kaplan–Meier estimators, pooling Kaplan–Meier data was not possible. In general, actuarial outcomes in future series are needed to help define time-dependent outcomes for pooled series.

Implications

Early detection of ICVS raises the issue of whether upfront treatment is required, and which is the most appropriate treatment option (MR vs SRS). Excellent MR results have been reported with respect to tumor control and hearing preservation. However, facial nerve functional preservation rates of around 90% are observed. SRS is typically safer than MR with less serious adverse events and at least equivalent tumor control and hearing preservation rates, with a significantly lower risk of facial nerve deficit. One major argument supporting CS remains the absence of complications associated with any treatment and the typical slow growth rate. This strategy can then be of interest to elderly patients that may die of other causes before the tumor grows to a size that requires treatment (Table 5).

Conclusion

As compared to MR, SRS is a noninvasive treatment with at least equivalent rates of tumor control and hearing preservation through better facial nerve preservation. As compared to CS, upfront SRS is an effective treatment in achieving tumor control with at least equivalent rates of hearing preservation. The outcomes of this meta-analysis and the recently reported V-REX randomized trial should be discussed with patients when making treatment decisions. CS is considered the recommended approach for older patients with ICVS and no appreciable tumor growth, given the competing risk of death from other causes.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<https://academic.oup.com/neuro-oncology>).

Keywords

conservative surveillance | intracanalicular | microsurgical resection | radiosurgery | vestibular schwannoma

Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods of care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on the characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Society of Stereotactic Radiosurgery assume no liability for the information, conclusions, and recommendations contained in this report.

Conflicts of interest statement

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Authorship statement

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Data availability

Data used for the meta-analysis can be available under request to the corresponding author.

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