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Outcomes of stereotactic radiosurgery for large vestibular schwannomas: a systematic review and meta-analysis

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Abstract

Background. Large vestibular schwannomas (VS) pose a treatment challenge for both microsurgery (MS) and stereotactic radiosurgery (SRS). Technical developments have allowed for safer irradiation of large tumors. It remains unclear if SRS can achieve appropriate tumor control and acceptable cranial nerve toxicities. In this study, we assess outcomes of irradiation for large VS.

Methods. PubMed MEDLINE, EMBASE, Web of Science, and Cochrane were searched for all the studies assessing SRS outcome in large VS. Primary endpoints included clinical and radiographic tumor control, need for salvage surgery, serviceable hearing, cranial nerve V and VII impairment, presence of hydrocephalus requiring shunting, and presence of vertigo/dizziness.

Results. Twenty-two studies were identified that met selection criteria for analysis from an initial pool of 1272 reports. They were evaluated according to treatment protocol: 1) single-dose SRS (13 studies, 483 patients), 2) combination of MS and SRS (7 studies, 182 patients), and 3) fractionated SRS (3 studies, 82 patients). Tumor control was achieved in 89%, 94%, and 91% of patients, respectively. Odds ratios (ORs) of post- over pretreatment serviceable hearing were 0.42 ($P < .01$), 0.47 ($P = .05$), and 0.60 ($P = .22$); for facial nerve impairment, these ORs were 1.08 ($P = .69$), 3.45 ($P = .28$), and 0.87 ($P = .71$), respectively.

Conclusions. The management of large VS remains challenging. All treatment modalities resulted in high tumor control rates and worsening of pretreatment hearing. None, however, caused significant facial nerve impairment, suggesting that management strategies incorporating focal irradiation can be successful.

Keywords

acoustic neuroma | Koos IV | large vestibular schwannoma | radiosurgery | stereotactic radiosurgery

Vestibular schwannomas (VS) are benign tumors arising from the eighth cranial nerve (CN VIII).[1] They represent the most common tumor of the cerebellopontine angle (CPA).[2] Patients present with decreased hearing, tinnitus, and vestibular symptoms.[3] Tumor Koos grade is key in predicting symptomatology, as grade III (tumor in the CPA without cerebellopontine trunk displacement) and grade IV (cerebellopontine trunk displacement) tend to cause hydrocephalus and symptoms of

brainstem compression and vasogenic edema.[4] Large tumors can also cause deficits of other CNs including facial numbness, weakness, and swallowing difficulties.[5]

Concerns about iatrogenic morbidity are heightened in the case of large VS. Classic treatments that work well for smaller tumors are more challenging, and with higher morbidities. Both microsurgery (MS) and radiation therapy (XRT) are able to reduce tumor burden; MS can be curative in cases of complete resection.[6,7] Surgical complication rates are, however, higher for larger tumors.[8,9] XRT can be given either as a single high dose in the form of stereotactic radiosurgery (SRS) or under fractionation regimens, either via fractionated SRS (fSRS), for example, 6–7 Gy × 3, or via fractionated stereotactic radiotherapy (fSRT), for example, 25 fractions of 2 Gy each.[10] Neurosurgical complications are most commonly acute, while radiation complications may not be evident until years later.[11]

To maintain excellent tumor control and reduce CN impairment, some authors have advocated for a combination of subtotal resection and SRS, wherein the surgery is performed primarily to reduce the tumor size to a safe SRS target. Such a "nerve-centered" approach has reported excellent outcomes, with 93% tumor control and preservation of facial nerve function in 96% of patients, as found by a recent meta-analysis.[12–14]

An important question is whether large VS can successfully be treated with SRS as a single therapy. Contemporary radiosurgery platforms utilizes sophisticated planning software and high-resolution stereotactic MRI and CT which may facilitate safe and effective treatment of tumors with a diameter greater than 30 mm—historically considered the highest suitable dimension for SRS, given the risk of postradiation edema requiring surgical decompression.[8,15] Recent studies have, in fact, shown promise of this approach, with high tumor control rates and acceptable comorbidities.[16–18] The exact likelihood of tumor control and rate of CN toxicities remains unclear, given the lack of randomized controlled trials and significant variability in radiation regimens.[11,16,19–22]

In this study, we performed a systematic literature review to assess studies that utilize SRS on large VS. Given the high variability in the literature in defining "large" tumors, we included all studies where the authors claimed to be treating "large tumors," providing their cutoff measures. We focus our attention on the radiation parameters, tumor control, the need for other interventions, and CN toxicities. By performing a classical meta-analysis, we endeavored to characterize clinically relevant outcomes for differing radiotherapy regimens on large VS.

Methods

Research Protocol and Search Question

Systematic literature searches were conducted (March 30, 2020) in 4 databases for any publication types and reports of human studies written in English, with no filters on publication date or other search limits applied. The databases searched were: 1) MEDLINE (via PubMed), 2) Embase (via OVID), 3) The Cochrane Library (via Wiley), and 4) Web of Science (via Clarivate Analytics). Detailed key words are reported in the Supplementary Material. Search results were combined in a bibliographic management tool (EndNote) and duplicates were removed both electronically and through manual review. Search results were then imported into the systematic review support tool, Covidence, for further management and review which included title/abstract screening and full-text screening phases. A detailed search strategy is provided in the Supplementary Material.

In accordance with current guidelines, this meta-analysis followed the PRISMA Checklist (Supplementary Material) and has been registered in PROSPERO (https://www.crd.york.ac.uk/prospero/)—protocol #CRD42020187373.

Eligibility Criteria and Primary Outcomes

Following preliminary searches, 3 broad categories of studies were identified: 1) those where single-dose SRS was used, 2) those where SRS was used in conjunction with tumor removal (always done before SRS), and 3) those where SRS was given via fractionation. For a more comprehensive analysis, we included all peer-reviewed publications that met the following criteria: 1) studies were in English; 2) outcome was not limited to quality of life assessment but included, at least, either a functional (CN status) outcome or tumor control; 3) at least one of the primary outcomes of interest was reported in the population of interest; and 4) the authors specifically discussed "large" VS (either in the entire paper or in a subcohort). Studies where normal fractionation (fSRT) (eg, 2 Gy/fraction in 20 fractions) was utilized were excluded.

Primary outcomes assessed included rate of tumor control (defined as no need for further intervention or lack of symptom progression, as specified in each manuscript), need for salvage surgery, radiographic control (defined as tumors either remaining within 10% of their original size or decreasing in size[23,24]), trigeminal nerve impairment, facial nerve impairment, serviceable hearing, presence of vertigo and/or dizziness, and presence of hydrocephalus requiring a ventriculoperitoneal shunt (VPS).

Data Collection

Abstract and full-text review was carried out independently and blindly by 2 authors (A1 and A2). Conflicts were resolved with discussion. Data were then extracted manually from the included articles and stored electronically. Data fields extracted included study characteristics, patient biographical characteristics, tumor characteristics, treatment characteristics, tumor response, before- and after-treatment rate of serviceable hearing (either grade 1 or 2 on the Gardner–Robertson scale, or grade A or B on the American Academy Otolaryngology-Head and Neck Surgery [AAO-HNS] scale), trigeminal symptoms, facial nerve symptoms, and presence of hydrocephalus requiring VPS (Supplementary Material). Odds ratios (ORs) were calculated for each variable. Tumor control was broadly defined as no need for further intervention and no symptom progression; radiographic tumor control was defined as tumors either remaining within 10% of their original size

or decreasing in size at the time of the report made by the original authors.[23,24]

Statistical Analysis

Meta-analyses for the complication proportions were conducted for studies using fSRS, single-dose SRS, and MS and single-dose SRS. Statistical heterogeneity was tested through the Cochrane Q test, and a *P*-value ≤.20 was used to indicate the presence of heterogeneity (ie, a more conservative approach using a random-effects meta-analysis). Statistical heterogeneity was also assessed by the inconsistency statistic (I^2). However, regardless of the heterogeneity test *P*-value or I^2 statistic percentage, a random-effects analysis was used to calculate the pooled proportions.

For each meta-analysis of a specific complication type, the presence of publication bias was evaluated through a funnel plot (Supplementary Material). Egger's test and the Begg–Mazumdar rank-correlation test were used to statistically assess the presence of publication bias. All analyses were conducted with the use of R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria), packages *meta*, *metaphor*, and *dmetar*.

Results

Study Selection

A total of 1272 studies were identified. After de-duplication and initial screening, 664 full-text studies were assessed for eligibility, resulting in 22 studies included here. Of these, 13 studies assessed single-dose SRS,[15–18,23,25–32] 7 a combination of MS followed by SRS in all patients,[12,25,33–37] and 3 relied on fSRS.[38–40] One study had 2 subcohorts (Figure 1).[25] Of note, studies varied in how they defined "large VS," as shown in Tables 1–3.

Single-Dose SRS

Of the studies identified, 13 focused solely on single-dose SRS for a total of 483 patients (Table 1). Combining these studies, mean age was 56.6 (range: 18–91) years, mean tumor volume was 8.9 (range: 1.4–30.6) mL, mean tumor diameter was 27.9 (range: 20–40) mm, and mean follow-up was 59 (range: 1–222) months. Treatment was carried out with a mean marginal dose of 11.1 (range: 10–15) Gy and a mean maximal dose of 24.0 (range: 18.2–47) Gy; the mean isodose was at 53.8% (range: 49.2%–90%); an average of 15.1 (range: 2–41) isocenters was used. About 23.4% of patients had undergone prior surgery before SRS (range: 0%–80%).

Clinical control was achieved in 89% (95% CI: 85%, 94%) of patients with moderate heterogeneity (I^2 = 47%) (Figure 2A), and radiographic control in 92% (95% CI: 87%, 96%) with moderate heterogeneity (I^2 = 57%) (Figure 2B). Salvage surgery was required in 7% (95% CI: 4%, 10%) of patients because of recurrent tumor growth, with minimal heterogeneity (I^2 = 0%) (Figure 2C).

Significant morbidities were observed before and after treatment. For all primary endpoint morbidities, ORs were calculated as post- over pretreatment symptom incidence. With respect to serviceable hearing, 12 studies (459 patients) were included. Overall, low heterogeneity was observed (I^2 = 11%) for a combined OR of 0.42 (95% CI: 0.29, 0.60, *P* < .01; Figure 2D). Trigeminal nerve impairment was

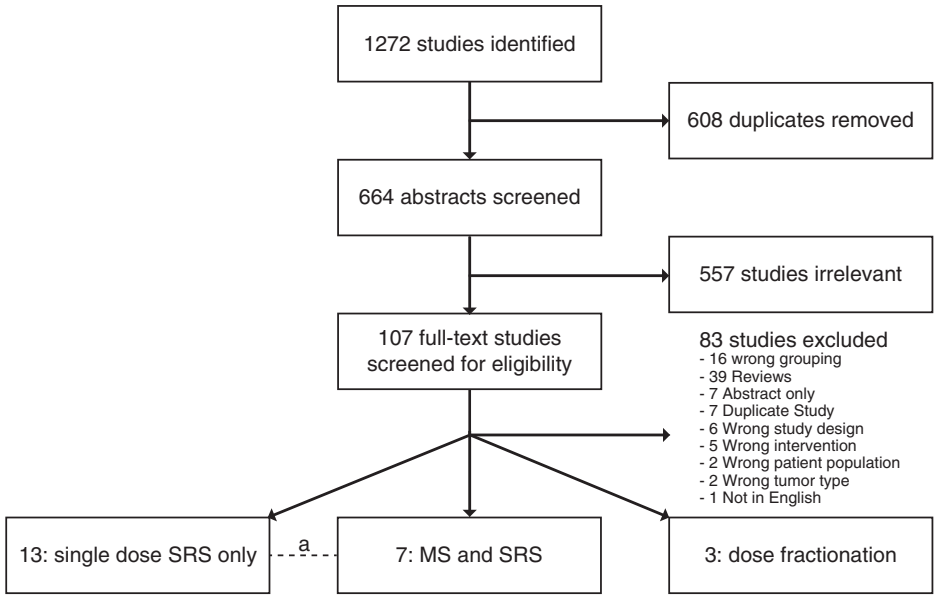

Figure 1. Scheme of search results and assessment of eligibility. a: one study in common with 2 arms.

Table 1. Summary of Studies Utilizing Single-Dose SRS for Large VS

Author, Year[a]	"Large VS" Definition	Patients/ Tumors (% NF2)	Mean Age (range)	Prior Surgery (%)	Mean Follow-up (range) (mo)	Mean Marginal Dose (range) (Gy)	Mean Max. Dose (range) (Gy)	Mean Isodose (%)	Mean Isocenters (range)	Mean Tumor Volume (range) (mL)	Mean Tumor Diameter (range) (mm)
Bailo,[20] 2016	>2.5 cm	59 (0)	63.8 (24–85)	0	79 (36–164)	13 (11–15)	26 (23.8–32.6)	50	20 (11–41)	5.98 (2.5–14.9)	28.5 (25.5–34.0)
Chung,[28] 2010	>3 cm	21 (N/A)	49.5 (27–77)	66.7	66 (12–155)	11.9 (11–14)	21.2 (19.2–28)	57	18 (10–27)	17.3 (12.7–25.2)	N/A
Huang,[14] 2018	>3 cm and >10 mL	35 (0)	49.7 (21–74)	25.7	48 (6–156)	11 (10–12)	22 (18.2–28.6)	50	17 (10–36)	14.8 (10.3–24.5)	N/A
Inoue,[30] 2004	>4 cm	5[b] (20)	58.8 (44–67)	66.7	106 (60–144)	11.5 (10–12)	25.67 (24–30)	50	N/A	21.0 (17.3–24.9)	N/A
Inoue,[31] 2005	>3 cm	18[c] (11.1)	N/A (33–81)	55	N/A (72–156)	11.5 (10–12)	N/A	N/A	N/A	15.2 (5.3–28.5)	N/A
Iorio-Morin,[32] 2016	Koos IV and >4 cm	68 (0)	58 (18–65)	19.1	47 (6–125)	12 (11–13)	N/A	50	N/A	7.4 (4–19)	27.0 (20.0–40.0)
Lefranc,[33] 2018	Koos IV	86 (N/A)	54.6 (23–84)	16.3	74.4 (36–192)	10.94 (8–13)	N/A	49.2	N/A	4.5 (1.4–8.7)	25.8 (16.3–35.0)
Milligan,[21] 2012	>2.5 cm	22 (4.5)	61 (N/A)	4.5	28 (25–38)	12 (12–14)	N/A	N/A	13 (8–22)	9.4 (5.3–19.1)	28 (25–38)
van de Langenberg,[34] 2011	>6 mL, indenting brainstem	33 (0)	54.8 (30–83)	0	30 (12–72)	11.6 (10.3–13)	20.79 (18.1–25.5)	90	9 (3–23)	8.8 (6.1–17.7)	30.0 (23.0–40.0)
Watanabe,[35] 2019	>8 mL	19 (0)	71 (29–91)	47.4	98 (49–204)	11.9 (10–12)	20.3 (20–24.8)	60	N/A	11.5 (8.0–30.6)	N/A
Williams,[36] 2013	>3 cm	24 (0)	61 (32–87)	37.5	82.5 (7–222)	11 (8–20)	30 (20–47)	N/A	8 (2–25)	9.5 (3.1–24.7)	N/A
Yang,[22] 2011	3–4 cm extracanalicular	65 (0)	51 (19–89)	26.2	36 (1–146)	12 (11–15)	N/A	50	N/A	9.0 (5.0–22.0)	N/A
Zeiler,[37] 2013	3–4 cm	28 (7)	56 (26–85)	42.9	34.5 (6–99)	N/A	25 (24–26)	50	N/A	N/A	32.8 (30.0–40.0)

Author, Year[a]	% R- CTRL, % C-CTRL (% re-op)	CN V Impairment (%)		CN VII Impairment (%)		Serviceable Hearing (%)		Hydrocephalus Requiring VPS (%)		Vertigo/ Dizziness (%)	
		Pre-SRS	Post-SRS	Pre-SRS	Post-SRS	Pre-SRS	Post-SRS	Pre-SRS	Post-SRS	Pre-SRS	Post-SRS
Bailo,[20] 2016	88.6, 98.3 (1.7)	27.1	20.3	15.3	8.5	35.6	8.5	8.5	25.4	10.2	6.8
Chung,[28] 2010	85.7, 76.2 (9.5)	38.1	38.1	57.1	57.1	4.8	0	0	9.5	N/A	N/A
Huang[14] 2018	85.7, 85.7 (11.4)	34.30%	11.40%	N/A	N/A	8.6	2.9	0	5.7	25.7	N/A
Inoue,[30] 2004	100, 100 (0)	N/A	N/A	80	80	16.7	16.7	N/A	N/A	N/A	N/A
Inoue,[31] 2005	93.3, 93.3 (5.6)	N/A	N/A	55	55	25	20	N/A	N/A	N/A	N/A
Iorio-Morin,[32] 2016	94.1, 94.1 (4.4)	51.5	57.4	8.8	8.8	58.8	29.4	7.4	11.8	11.8	11.8
Lefranc,[33] 2018	100, 90.7 (8.1)	1.2	1.2	0	0	44.2	29.1	18.6	19.8	7	15.1
Milligan,[21] 2012	90.9, 81.8 (9.1)	59.1	72.7	4.5	18.2	45.5	13.6	4.5	18.2	N/A	N/A
van de Langenberg,[34] 2011	87.9, 78.8 (15.2)	36.4	12.1	3	9.1	36.4	21.2	6.1	12.1	51.5	54.5
Watanabe,[35] 2019	83.3, 84.2 (15.8)	15.8	26.3	21.1	21.1	36.8	0	15.8	31.6	N/A	N/A
Williams,[36] 2013	88.9, 75.0 (12.5)	45.8	29.2	33.3	54.2	25	N/A	4.2	12.5	20.8	N/A
Yang,[22] 2011	89.2, 89.2 (10.8)	40	46.2	23.1	24.6	33.8	27.7	7.7	13.8	N/A	N/A
Zeiler,[37] 2013	92.0, 92.0 (4)	48	24	36	28	16	16	0	12	20	0

Abbreviations: C-CTRL, clinical control; CN, cranial nerve; N/A, not applicable; NF2, neurofibromatosis 2; R-CTRL, radiographic control; SRS, stereotactic radiosurgery; VS, vestibular schwannomas.
[a]All studies are retrospective.
[b]Five patients, 6 tumors.
[c]Eighteen patients, 20 tumors.

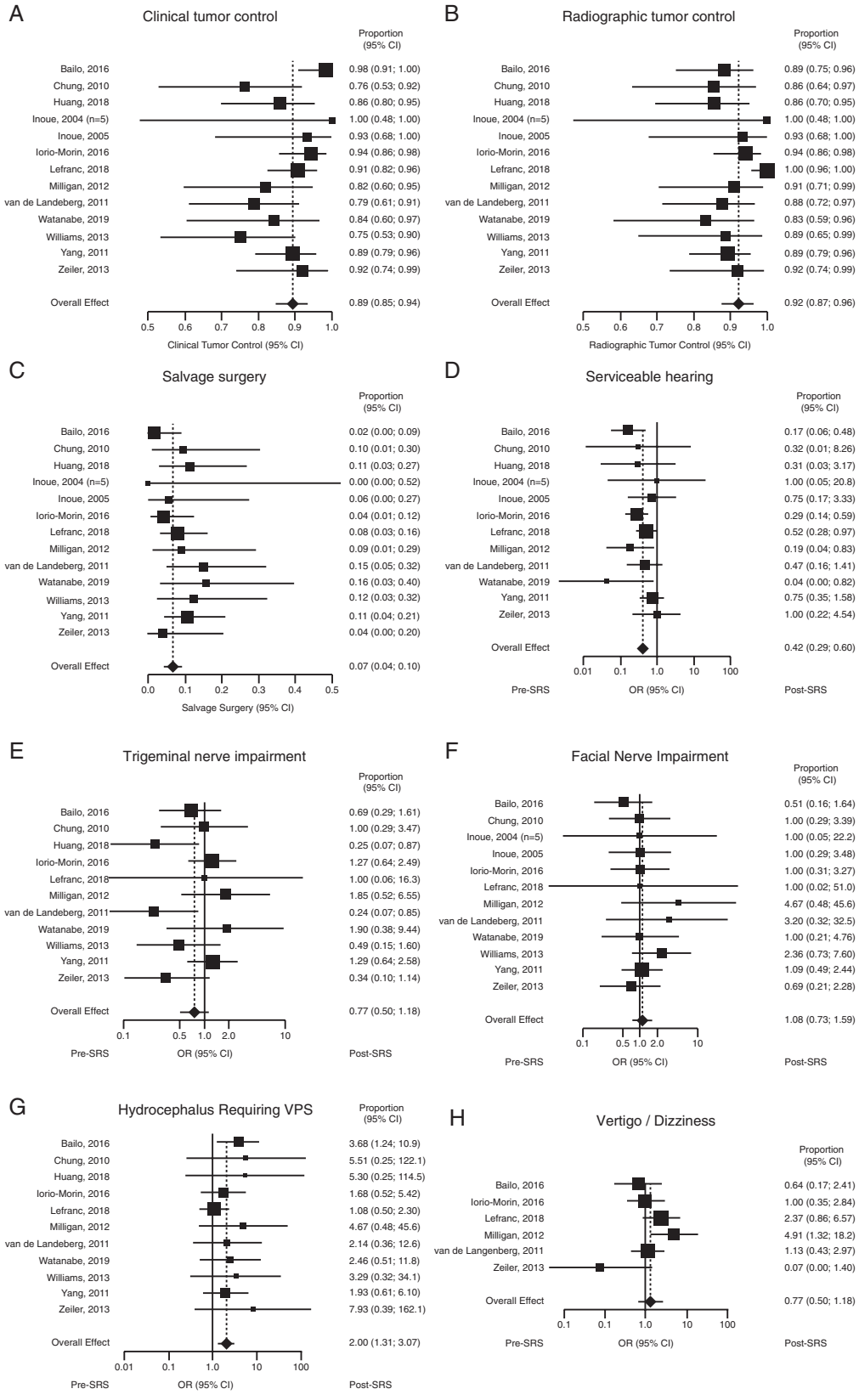

Figure 2. Single-dose stereotactic radiosurgery (SRS). Forest plots showing (A) clinical tumor control, (B) radiographic tumor control, and (C) rate of salvage surgery. Forest plots summarizing odds ratio (OR) of (D) serviceable hearing, (E) trigeminal nerve impairment, (F) facial nerve impairment, (G) hydrocephalus requiring ventriculoperitoneal shunt (VPS), and (H) vertigo/dizziness.

assessed in 11 studies (457 patients) for a combined OR of 0.77 (95% CI: 0.50, 1.18, $P = .23$; Figure 2E). Heterogeneity was moderate ($I^2 = 38\%$). Facial nerve impairment was assessed in 12 studies (447 patients) for a combined OR of 1.08 (95% CI: 0.73, 1.59, $P = .69$; Figure 2F). Heterogeneity was minimal ($I^2 = 0\%$). The presence of hydrocephalus requiring VPS was assessed in 11 studies (457 patients) for a combined OR of 2.00 (95% CI: 1.31, 3.07, $P < .01$; Figure 2G). Heterogeneity was minimal ($I^2 = 0\%$). The presence of vertigo or dizziness was assessed in 6 studies (293 patients) for a combined OR of 1.29 (95% CI: 0.62, 2.70, $P = .50$; Figure 2H). Heterogeneity was moderate ($I^2 = 52\%$). Overall, these results show that single-dose SRS results in a decrease in serviceable hearing and an increase in incidence of hydrocephalus requiring VPS. Funnel plots summarizing heterogeneity are shown in Supplementary Figure 1.

MS and SRS

Of the studies identified, 7 assessed the efficacy of MS followed by SRS, for a total of 182 patients in whom this combined approach was used (Table 2). Combining these studies, mean age was 53.0 (range: 18–85) years, mean tumor volumes before and after MS were 14.9 (range: 1.5–36.1) mL and 3.9 (range: 0.2–28.5) mL, respectively (ie, before SRS), mean tumor diameters before and after MS were 28.0 (range: 20–58) mm and 18.6 (range: 9–36.1) mm, respectively, and mean follow-up was 43.5 (range: 4–156) months. The average delay between MS and SRS was 5.8 (range: 1–24) months. Treatment was carried out with a mean marginal dose of 11.7 (range: 9.4–14.1) Gy and a mean maximal dose of 21.6 (range: 18–26) Gy; the mean prescription isodose was 66.7% (range: 50–90%); an average of 21.7 (range: 7–44) isocenters was used.

Overall clinical control (ie, after both procedures) was achieved in 94% (95% CI: 89%, 98%) of patients with minimal heterogeneity ($I^2 = 0\%$) (Figure 3A), and radiographic control in 95% (95% CI: 90%, 99%) with low heterogeneity ($I^2 = 16\%$) (Figure 3B). Salvage surgery was required in 3% (95% CI: 0%, 8%) of patients because of tumor recurrence with minimal heterogeneity ($I^2 = 0\%$) (Figure 3C).

To assess whether either treatment alone (MS or SRS) or their combinations resulted in significant worsening of serviceable hearing and facial nerve impairment (the only 2 metrics reliably assessed across studies), ORs were calculated as post- over pretreatment symptom incidence for the following pairs: pre-MS and post-MS, post-MS and post-SRS, and pre-MS and post-SRS. With respect to serviceable hearing, 6 studies were included, of which 1 had 2 arms (174 patients). Comparing pre-MS with post-MS, low heterogeneity was observed ($I^2 = 30\%$) for a combined OR of 0.55 (95% CI: 0.27, 1.16, $P = .12$; Figure 3D). Comparing post-MS with post-SRS, minimal heterogeneity was observed ($I^2 = 0\%$) for a combined OR of 0.83 (95% CI: 0.46, 1.52, $P = .55$; Figure 3E). Comparing pre-MS with post-SRS, moderate heterogeneity was observed ($I^2 = 31\%$) for a combined OR of 0.47 (95% CI: 0.22, 1.01, $P = .05$; Figure 3F).

With respect to facial nerve impairment, 6 studies were included, of which 1 had 2 arms (179 patients). Comparing pre-MS with post-MS, high heterogeneity was observed ($I^2 = 81\%$) for a combined OR of 5.28 (95% CI: 0.65, 43.25, $P = .12$; Figure 3G). Comparing post-MS with post-SRS, minimal heterogeneity was observed ($I^2 = 0\%$) for a combined OR of 0.49 (95% CI: 0.27, 0.90, $P = .02$; Figure 3H). Comparing pre-MS with post-SRS, high heterogeneity was observed ($I^2 = 81\%$) for a combined OR of 3.45 (95% CI: 0.36, 32.96, $P = .28$; Figure 3I). Overall, this shows that the combination of MS and SRS does not result in facial nerve impairment; rather, the use of SRS following MS is associated with some recovery of function.

The presence of hydrocephalus requiring VPS was assessed in 3 studies (125 patients), for a combined OR of 1.97 (95% CI: 0.60, 6.44, $P = .26$; Figure 3J). Heterogeneity was minimal ($I^2 = 0\%$). Funnel plots summarizing heterogeneity are shown in Supplementary Figure 2. The prevalence of trigeminal nerve impairment was assessed in only 2 studies.[12,36] The presence of vertigo/dizziness was assessed in only 1 study.[36]

Fractionated SRS

Of the studies identified, 3 utilized fSRS, for a total of 82 patients. Studies that relied on fSRT were excluded. These studies are summarized in Table 3. Combining these studies, mean age was 57.2 (range: 17–85) years, mean tumor diameter was 33.8 (range: 23–50) mm, and mean follow-up was 67.3 (range: 7–175) months. The mean prescription isodose was 80.2% (range: 70%–95%). About 28.0% of patients had undergone prior treatment before fSRS (range: 15.2%–36.8%).

Clinical control was achieved in 91% (95% CI: 76%, 100%) of patients, with moderate heterogeneity ($I^2 = 69\%$) (Figure 4A), and radiographic control in 83% (95% CI: 52%, 100%) with high heterogeneity ($I^2 = 89\%$) (Figure 4B). Salvage surgery was required for 4% (95% CI: 0%, 10%) of patients, with minimal heterogeneity ($I^2 = 0\%$) (Figure 4C). With respect to serviceable hearing, moderate heterogeneity was observed ($I^2 = 28\%$) for a combined OR of 0.60 (95% CI: 0.26, 1.36, $P = .22$; Figure 4D). With respect to facial nerve impairment, heterogeneity was minimal ($I^2 = 0\%$) for a combined OR of 0.87 (95% CI: 0.41, 1.83, $P = .71$; Figure 4E). Funnel plots summarizing heterogeneity are shown in Supplementary Figure 3.

Trigeminal nerve impairment was assessed in only 2 studies.[38,40] Vertigo/dizziness was assessed in only 1 study.[38] Hydrocephalus requiring VPS was assessed in only 2 studies.[38,39]

Discussion

The management of large VS remains a challenge, as bulky size increases the morbidity of MS and has historically hindered the delivery of XRT. In this study, we analyze the use of SRS in treating large VS and show how single-dose SRS, the combination of MS and SRS, and fractionated SRS result in excellent clinical (89%, 94%, and 91%, respectively) and radiographic (92%, 95%, and 83%, respectively) tumor control, with low incidence of salvage surgery (7%, 3%, and 4%, respectively). Both single-dose

Table 2. Summary of Studies Utilizing MS Followed by SRS

Author, Year	"Large VS" Definition	*N* (% NF2)[a]	Mean Age (range)	Surgical Approach	Mean Follow-up (range) (mo)	Mean Marginal Dose (range) (Gy)	Mean Max. Dose (range) (Gy)	Mean Isodose (%)	Mean Isocenters (range)	MS-SRS Delay (range) (mo)	Mean Tumor Volume (range) (mL)		Mean Tumor Diameter (range) (mm)		% R-CTRL, % C-CTRL (% re-op)	CN V Impairment (%)			CN VII Impairment (%)			Serviceable Hearing (%)			Hydrocephalus Requiring VPS (%)		Vertigo/ Dizziness (%)	
											Pre-MS	Pre-SRS	Pre-MS	Pre-SRS		Pre-MS	Post-MS	Post-SRS	Pre-MS	Post-MS	Post-SRS	Pre-MS	Post-MS	Post-SRS	Pre-MS	Post-SRS	Pre-MS	Post-SRS
Daniel,[17] 2017[b]	Koos IV	32 (0)	51.7 (32–85)	RS	29 (4–78)	12 (11–12)	N/A	50	20 (7–33)	6.3 (3.8–13.9)	12.5 (1.5–34.9)	3.5 (0.5–12.8)	33.2 (20–45)		90.6, 90.6 (9.4)	6.3	0	0	3.1	0	0	40.6	37.5	37.5	N/A	N/A	12.5	N/A
Fuentes,[38] 2008[b]	>3.5 cm	8 (N/A)	53 (24–78)	RS	46 (12–73)	11.8 (11–13)	23.75 (22–26)	N/A	N/A	9 (6–12)	N/A	1.16 (0.3–2.2)	40 (35–45)	18 (9–20)	100, 100 (0)	25	N/A	N/A	N/A	25	25	12.5	N/A	N/A	N/A	N/A	N/A	N/A
Inoue,[30] 2004[c]	>4 cm	3 (0)	51.3 (41–66)	N/A, ICD	34 (12–72)	12 (12-12)	23.3 (22–24)	50	N/A	3.67 (2–5)	N/A	17.1 (2.2–28.5)	N/A	N/A	100, 100 (0)	N/A	N/A	N/A	N/A	N/A	N/A	33.3	33.3	33.3	N/A	N/A	N/A	N/A
Iwai,[42] 2003[b]	>3 cm	14 (14.3)	47 (18–64)	RS	32 (12–72)	12.1 (10–14.1)	N/A	N/A	N/A	2.9 (1–6)	N/A	N/A	42 (30–58)	18.9 (9.8–36.1)	78.6, 92.9 (7.1)	50	N/A	N/A	0	28.6	28.6	21.4	7.1	7.1	N/A	N/A	N/A	N/A
Iwai,[39] 2015[b]	>2.5 cm	40 (N/A)	60.5 (33–82)	RS	65 (18–156)	12 (10–12)	N/A	N/A	N/A	3 (1–12)	N/A	N/A	32.5 (25–52)	18.6 (9.1–27.1)	90, 90 (10)	75	N/A	N/A	32.5	22.5	7.5	35	27.5	17.5	0	0	N/A	N/A
Pan,[40] 2012[b]	>3 cm	18 (N/A)	50 (N/A)	RS, ICD	57.7 (N/A)	12 (12-12)	N/A	50	N/A	3.6	17.5 (N/A)	9.35 (N/A)	N/A	N/A	100, 94 (N/A)	N/A	N/A	N/A	5.6	11.1	11.1	61.1	61.1	61.1	N/A	5.6	N/A	N/A
		17 (N/A)	49 (N/A)	RS, ECD	52.7 (N/A)	12 (12-12)	N/A	50	N/A	7	16.4 (N/A)	1.1 (N/A)	N/A	N/A	100, 94 (N/A)	N/A	N/A	N/A	0	88.2	88.2	64.7	0	0	N/A	5.9	N/A	N/A
van de Langenberg,[41] 2011[c]	Koos III or IV	50 (0)	52 (21–84)	TL (25) or RS (25)	33.8 (12–84)	11 (9.4–11.9)	21.1 (18–26)	90	22.8 (7–44)	8.5 (2–24)	14.9 (4.1–36.1)	3.34 (0.2–11.8)	35 (26–54)	N/A	90, 92, 2	28	30	30	2	40	18	8	2	2	4	8	48	48

Abbreviations: CN, cranial nerve; ECD, extracapsular decompression; ICD, intracapsular decompression; MS, microsurgery; N/A, not applicable; NF2, neurofibromatosis 2; RS, retrosigmoid; SRS, stereotactic radiosurgery; TL, translabyrinthine; VPS, ventriculoperitoneal shunt; VS, vestibular schwannomas.

[a]All studies had patients with 1 VS per patient.

[b]A prospective study.

[c]A retrospective study.

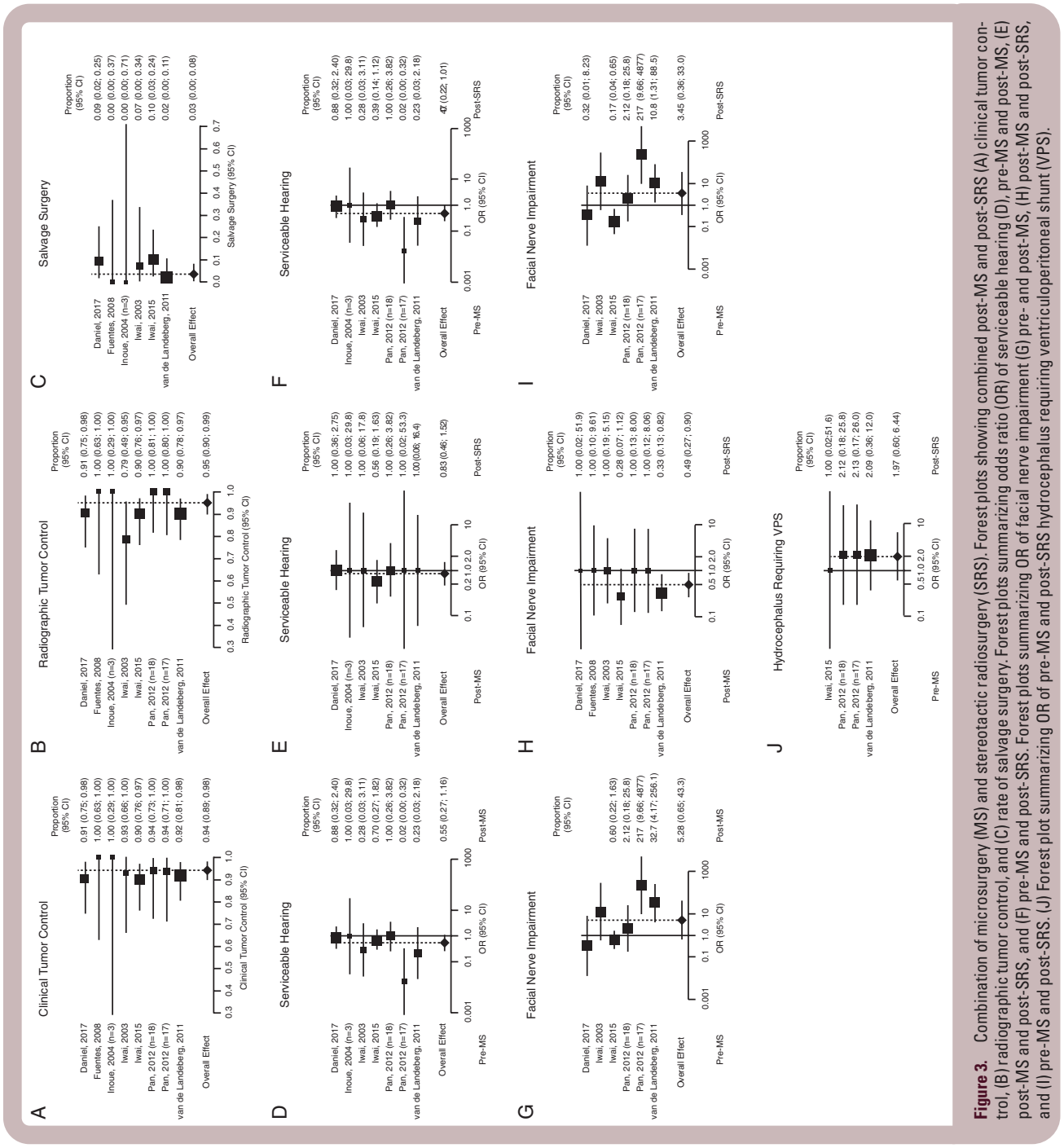

Figure 3. Combination of microsurgery (MS) and stereotactic radiosurgery (SRS). Forest plots showing combined post-MS and post-SRS (A) clinical tumor control, (B) radiographic tumor control, and (C) rate of salvage surgery. Forest plots summarizing odds ratio (OR) of serviceable hearing (D), pre-MS and post-MS, (E) post-MS and post-SRS, and (F) pre-MS and post-SRS. Forest plots summarizing OR of facial nerve impairment (G) pre- and post-MS, (H) post-MS and post-SRS, and (I) pre-MS and post-SRS. (J) Forest plot summarizing OR of pre-MS and post-SRS hydrocephalus requiring ventriculoperitoneal shunt (VPS).

SRS and the combination of MS with SRS resulted in significant worsening of pretreatment serviceable hearing; this finding was not seen for fractionated SRS, possibly because of small sample size. Trigeminal nerve impairment was assessed only by single-dose studies, which did not result in significant post-treatment impairment. Facial nerve impairment was not increased following any of these approaches. The incidence of hydrocephalus requiring VPS was increased following single-dose SRS but not after the combination of MS and SRS; however, in the latter case, only 3 studies assessed such a complication. Unfortunately, studies did not clearly associate toxicities with dose given, partly because of the wide range of treatment regimens.

It is important to note how the definition of "large VS" differed across studies: some authors used a maximal diameter cutoff, others used a volume cutoff; others yet used both metrics, with 5 studies relying on Koos grade. Such a

Table 3. Summary of Studies Utilizing Fractionated Radiation

Author, Year[a]	"Large VS" Definition	*N* (% NF2)	Mean Age (range)	Prior Surgery (%)	Mean Follow-up (range) (mo)	Fractionation Schedule	Mean Isodose (range) (%)	Mean Tumor Volume (range) (mL)	Mean Tumor Diameter (range) (mm)	% R-CTRL, % C- CTRL (% re-op)	CN V Impairment (%)		CN VII Impairment (%)		Serviceable Hearing (%)		Hydrocephalus Requiring VPS (%)		Vertigo/Dizziness (%)	
											Pre-SRS	Post-SRS	Pre-SRS	Post-SRS	Pre-SRS	Post-SRS	Pre-SRS	Post-SRS	Pre-SRS	Post-SRS
Casentini,[43] 2015	>8 mL	33 (6.1)	63 (28–85)	15.2	48 (12–111)	2–5 fr, total 14–19.5 Gy	77.6 (70–82)	11.0 (8.0–24.)	N/A	576, 87.9 (6.1)	21.2	24.2	27.3	27.3	24.2	21.2	15.2	21.2	12.1	9.1
Kalapurakal,[45] 1999	PP > 1 cm, MPTD > 2 cm	19 (N/A)	68 (34–84)	36.8	54 (34–65)	6 fr × 5 or 6 Gy each	85 (80–95)	N/A	35 (23–49)	100, 100 (0)	21.1	21.1	15.8	15.8	47.4	47.4	N/A	N/A	N/A	N/A
Teo,[44] 2016	Koos IV, >3 cm	30 (20)	44 (17–82)	36.7	97 (7–175)	3 fr × 6 Gy each	79.9 (71–90)	N/A	33.0 (25.0–50.0)	80.0, 80.0 (6.7)	N/A	N/A	83.3	76.7	43.3	16.7	0	10	N/A	N/A

Abbreviations: C-CTRL, clinical control; CN, cranial nerve; fr, fraction; MPTD, mid-porous transverse diameter; N/A, not applicable; NF2, neurofibromatosis 2; PP, pons-petrous distance; R-CTRL, radiographic control; Re-op, re-operation; SRS, stereotactic radiosurgery; VPS, ventriculoperitoneal shunt; VS, vestibular schwannomas.

[a]All studies are retrospective.

Figure 4. Fractionated stereotactic radiosurgery (SRS). Forest plots showing (A) clinical tumor control, (B) radiographic tumor control, (C) rate of salvage surgery, (D) odds ratio (OR) of serviceable hearing, and (E) OR of facial nerve impairment.

wide-ranging definition of large tumors indicates different levels of comfort with irradiating "borderline" tumors and can explain, at least in part, some of the variability here observed.

In recent years, XRT protocols have been applied to larger tumors, going beyond the historical limit of 2.5–3.0 cm in diameter.[19] A promising approach centered on the combination of MS with SRS—MS aimed at reducing the bulk of the tumor followed by SRS to target the remnant. As shown here, this approach achieves good tumor control despite the inherent difficulty in treating large VS without any significant worsening of pre-existing CN impairment, at the cost of reducing serviceable hearing. Our findings are consistent with another meta-analysis that solely focused on such a "nerve-centered approach."[14] Patient selection will have to be carefully carried out: one of the main reasons why SRS is chosen in the first place is to avoid surgery. On the other hand, surgical intervention in experienced centers can be associated with low morbidity and minimal need for any future treatments.[35,41] Noticeably, in this series, the use of MS and SRS did not result in a significant increase in hydrocephalus requiring VPS, thus indicating how decompression may prevent future hydrocephalus. Since such a measure was assessed in only 3 studies, more data are needed to determine if, in fact, this is the case.

In recent years, fSRS has been utilized for the treatment of VS and other tumors in the hope of reducing toxicities associated with high radiation doses without compromising tumor control. In this study, we show how a careful use of this treatment modality (ie, performed by an experienced practitioner with close postprocedural monitoring and assessment of acute complication development) is safe even for large VS.[42]

Currently, no definitive randomized clinical trial has shown the superiority of the treatment modalities here discussed over the others. The problem is further compounded by the wide range in treatment doses. Initially, VS were irradiated with marginal doses of 16 Gy and above, which achieved excellent tumor control (>95%) with significant cranial nuropathies.[11] Now, rarely do authors go above 14 Gy; however, such a regimen has not completely fallen out of practice.[11,16,18,31,43–49] Here, we have shown how different approaches can successfully achieve tumor control; further structured studies will be needed to better define a treatment paradigm in treatment of large VS.

Numerous limitations of the current study exist. The studies identified represent retrospective case series with no randomized clinical trials; data are further reported in a highly heterogenous manner. Furthermore, separating studies in subgroups based on treatment, albeit necessary to compare similar interventions, resulted in a limited sample size of each subgroup, with some with a limited number of studies and cases. Despite the limited size, statistical analysis was still possible and carried out, conscious of the fact that our conclusions will be strengthened by further studies with larger sample size. To understand how each treatment modality fares compared to the others, further structured studies are necessary.

In conclusion, large VS pose a therapeutic challenge given the high likelihood of compromise of local structures, the tendency to continue growing in size, and the difficulties associated with both MS and SRS. SRS, either as a single dose, in conjunction with MS, or fractionated, is a valid treatment alternative, as it achieves good tumor control with acceptable CN morbidity.

Conclusions

The radiosurgical treatment of large VS remains a technically challenging endeavor. However, thanks to novel low-dose radiation regimens (either single dose, fractionated, or in combination with surgical debulking) and accurate patient selection, it can provide excellent tumor control and low level of CN toxicities. Further structured studies, however, are urgently needed to determine the relative success of each of these different approaches and to reach a higher level of evidence.

Supplementary Material

Supplementary material is available *Neuro-Oncology Practice* online.

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