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REVIEW ARTICLE - BRAIN TUMORS

Radiosurgery treatment is associated with improved facial nerve preservation versus repeat resection in recurrent vestibular schwannomas

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Abstract

Background Vestibular schwannomas (VSs) are benign neoplasms of the Schwann cells of cranial nerve VIII, and treatment of VS typically involves surgical resection. However, tumor recurrence may necessitate reintervention, and secondary treatment modalities include repeat surgical resection or adjuvant radiosurgery. The purpose of this study is to examine the scientific literature in order to determine whether surgical resection or radiosurgery for recurrent VS results in better tumor control, hearing preservation, and preservation of facial nerve function.

Methods The PubMed, Scopus, Embase, Cochrane, and Web of Science databases were searched for studies reporting on patients undergoing either radiosurgery or repeat surgical resection after primary surgical resection for recurrent VS. Statistical analyses were performed on the compiled data, primarily outcome data involving tumor control, hearing preservation, and preservation of facial nerve function.

Results We analyzed the data of 15 individual studies involving 359 total patients, and our results reveal that tumor control rates are comparable between adjuvant radiosurgery (91%, CI: 88–94%) and secondary resection (92%, CI 75–98%). However, adjuvant radiosurgery was shown to preserve good facial nerve function better (94%, CI 84–98%) compared to secondary surgical resection (56%, CI 41–69%).

Conclusion With comparable tumor control rates and better preservation of good facial nerve function, this study suggests that secondary radiosurgery for recurrent VS is associated with both optimal tumor control and preservation of good facial nerve function.

Keywords Facial nerve function · Stereotactic radiosurgery · Vestibular schwannoma

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Introduction

Vestibular schwannomas (VSs) are benign neoplastic growths of the Schwann cells surrounding cranial nerve VIII [8, 18]. Being the most common tumor of the cerebellopontine angle, VS typically presents with symptoms such as tinnitus, disequilibrium, and unilateral sensorineural hearing loss. These symptoms arise from a nexus of the vestibular, acoustic, trigeminal, and facial nerves [10, 15, 19, 27]. Although novel nonsurgical treatments are being investigated for VS, including bevacizumab, trastuzumab, erlotinib, and lapatinib [8], neurosurgical resection and radiotherapy are typically used as primary treatments [3, 21]. Surgical resection may be performed via retrosigmoid, translabyrinthine, or middle cranial fossa approaches with each approach having its own advantages and disadvantages [6], and a staged resection can also be performed for larger lesions [31].

Primary radiotherapy is also a viable treatment option for VS, and typical modalities include gamma-knife (GSK), cyber-knife (CYK), and linear particle acceleration (LINAC) [5, 23, 33]. In one study, primary GSK for VS resulted in successful tumor control in 97.1% of cases at mean follow up of 75.7 months [7], and another study involving LINAC for small VS demonstrated local tumor control in 88% of patients with a median follow up of 40 months [4].

In traditional surgical resection, the possibility of tumor recurrence can be as high as 7.7% depending on the particular surgical approach [1, 20]. In these instances, repeat surgery may be performed in order to resect the recurrent tumor; however, radiosurgical treatment of the recurrent schwannoma is an alternative to traditional repeat surgery that may result in better facial nerve function preservation, hearing preservation, and tumor control.

Facial nerve function preservation is defined using the House-Brackmann scale, which uses measurements to quantify facial nerve function; grade I is described as normal function and grade VI is described as flaccid paralysis [32]. Hearing preservation is defined using pure tone averages and speech discrimination percentages according to the Gardner-Robinson classification or the equivalent American Academy of Otolaryngology-Head and Neck Surgery classification, where grade I is defined as good or excellent hearing and grade V is defined as complete hearing loss [2].

The purpose of this systematic analysis is to assess adjuvant radiotherapy for recurrent VS results in better tumor control, facial nerve function preservation, and hearing preservation.

Methods

This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34]. A search through the scientific literature (PubMed, Scopus, Embase, Web of Science, and Cochrane databases) was performed in August 2018 using a combination of keywords—"((acoustic neuroma[tw]) OR (vestibular schwannoma[tw]) OR (acoustic schwannoma[tw])) AND ((revision[tw]) OR (residual[tw]) OR (recur*[tw]) OR (salvage[tw]) OR (postoperative[tw]) OR (post-operative[tw])) AND ((resection[tw]) OR (removal[tw]) OR (radiosurgery[tw]))". The articles that were included were full-text, clinical articles with data on patients receiving either microsurgery followed by adjuvant radiotherapy or two sessions of microsurgery. Patients who received radiosurgery as their initial treatment or with residual tumor were excluded. Additionally, case reports, cadaveric articles, non-human articles, articles with neurofibromatosis type 2 patients unable to be disaggregated, studies with residual and recurrent tumors unable to separated, and non-English articles were excluded (Fig. 1).

Data was extracted from the articles selected for inclusion including parameters of the primary and secondary treatment, patient demographics, patient characteristics prior to and after the secondary therapy, and follow up length. Patients with neurofibromatosis type 2 were not included in data processing. The outcomes that were examined in this study include tumor recurrence, facial nerve function (FNF) preservation, and hearing preservation. Good FNF was defined as grades I and II on the House-Brackmann scale, whereas serviceable FNF was defined as grades I, II, and III. Serviceable hearing was defined as grades I and II on the Gardner-Robinson scale or class A and B on the AAO-HNS scale [2, 32].

R (R Foundation ®, Vienna, Austria) was used to conduct all statistical analysis and generate the forest plots and proportions using a logit transformation. The 95% confidence intervals were produced using the Clopper–Pearson interval method. *P* values under 0.05 were considered significant, and heterogeneity analysis was performed using τ^2, Cochran's Q, and I^2 statistics. A significant I^2 value was considered 25% or greater and served as the cutoff when comparing fixed vs. random effects. Semi-logarithmic funnel plots were constructed to determine publication bias with Egger's test reported.

Results

Fifteen articles were selected for inclusion in this study: 7 examining adjuvant radiosurgery [5, 9, 12–14, 24, 35] and 8 examining secondary microsurgery [11, 16, 17, 22, 25, 26, 28, 30] after primary surgical resection.

Group A: secondary radiosurgery

There were 275 patients in total in the group that received radiosurgery for the recurrent tumor (group A, Table 1). Within this group, 73 patients underwent a primary gross total resection (26.5%) and 196 patients underwent a primary

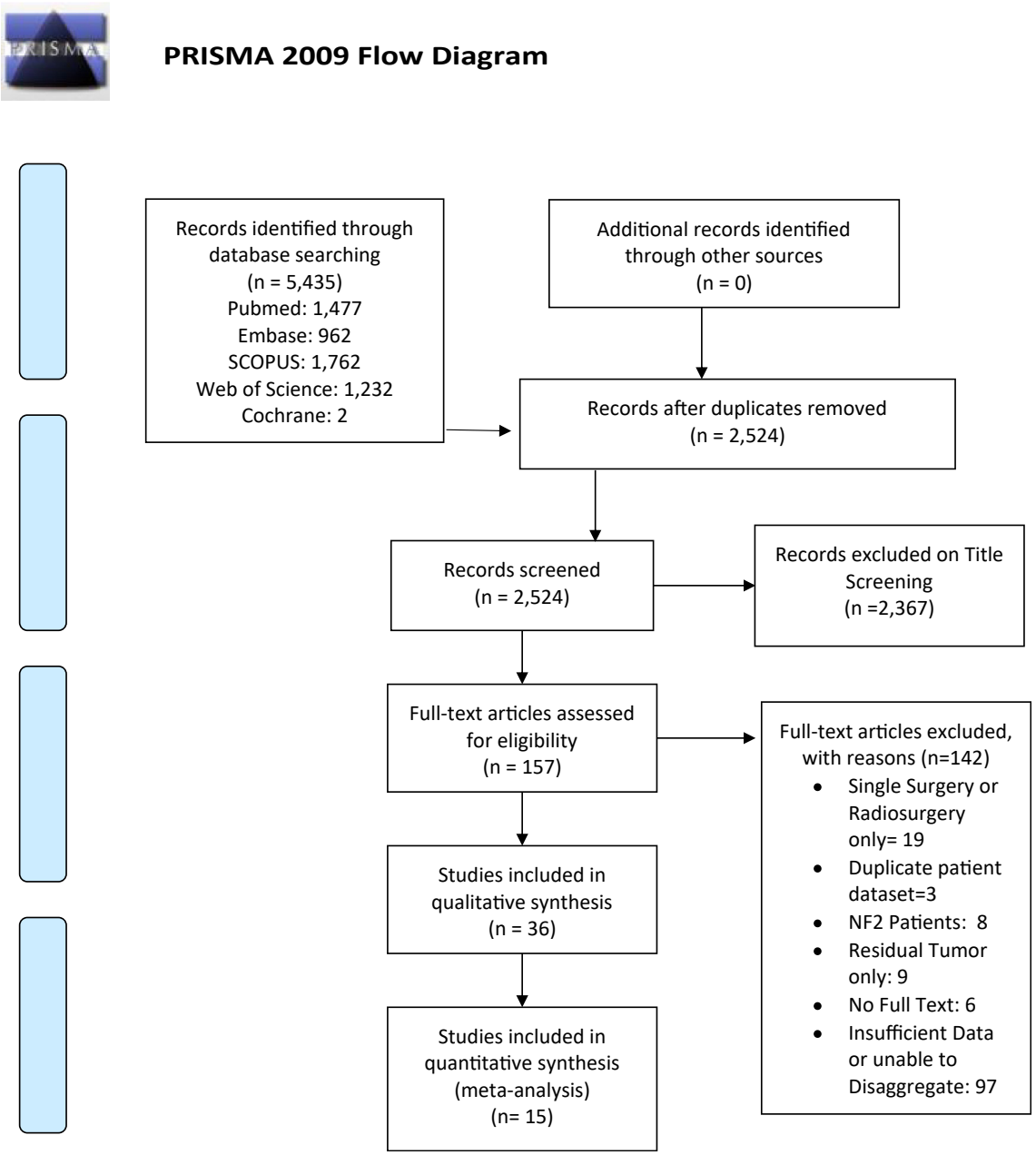

Fig. 1 PRISMA flow diagram illustrating approach used to isolate eligible articles for this study

subtotal resection (71.3%). For the remaining patients, the type of resection was not explicitly stated in the corresponding studies (2.2%). In addition, 99 patients underwent a single resection (36%), whereas 19 patients underwent more than one resection (6.9%), and for the remaining 118 patients, the number of primary resections performed was not explicitly stated (42.9%).

Patients within this group received either Gamma-Knife (246 patients, 89.5%) or LINAC (28 patients, 10.2%) radiosurgery, and for one of the patients in this group, the type of radiosurgery was not explicitly stated. Median time between resection and radiosurgery ranged from 31 months to 59 months (four studies, 253 patients), and median marginal radiosurgery dosage ranged from 13 Gy to 30 Gy (5 studies, 137 patients). Mean follow up time after SRS was 74.5 months (6 studies, 139 patients).

Within group A, 260 of the tumors were controlled after secondary radiosurgery (94.5%). The tumor control in the adjuvant radiosurgery group was 91% (CI: 88–94%). FNF improved or stayed the same in 97% of patients based on HB grade (3 studies, 99 patients total), and in 1 study in particular [13], 93.9% of patients had preservation of good FNF (66 patients total, grade I and grade II on HB scale). Adjuvant radiosurgery was shown to preserve good facial nerve function 94% (CI 84–98%). With regard to serviceable hearing preservation after SRS, one study [5] reported a serviceable hearing preservation rate of 40% (90 patients in total).

Table 1 Basic patient characteristics in the adjuvant radiosurgery group

Author and year published	No. of patients	Mean age	Mean tumor volume (cm^3)	Mean follow-up, months
Valentino et al. (1995)	6	43.5	10	40
Raftopoulos et al. (2005)	3	38[a]	–	55
Hsu et al. (2010)	46	52.4	1.5[a]	97.8
Haque et al. (2011)	20	47	3.6	72
Jeltema et al. (2015)	7	44.4	0.55	35.4
Bailo et al. (2017)	90	53.5[a]	2.5	77.2
Huang et al. (2017)	168	57[a]	2.7[a]	74[a]

[a] Median value

Group B: secondary surgical resection

There were 84 patients in the group that underwent repeat surgery for recurrent tumor (group B, Table 2). Within this group, 54.3% of patients underwent primary gross total resection, whereas 40% of patients underwent primary subtotal resection (5 studies, 35 patients in total). For the remaining 5.7% of patients, it was unclear as to whether or not they underwent gross total resection or subtotal resection as their primary treatment. In addition, 46.2% of patients underwent a retrosigmoid approach for their primary resection while 53.8% of patients underwent a translabyrinthine approach, and no patients within this group underwent a middle cranial fossa approach for their primary resection (5 studies, 26 patients total).

For their secondary resection, 95.9% of patients underwent gross total resection, whereas 4.1% of patients underwent subtotal resection (7 studies, 74 patients in total). The most common approach for the secondary resection was retrosigmoid (70.3%), followed by translabyrinthine (28.4%) and middle cranial fossa (1.4%) (7 studies, 74 patients in total). The mean time between primary and secondary resection was 56.4 months (4 studies, 60 patients in total), and mean follow up time was 59.5 months (5 studies, 41 patients in total). For tumor control, a rate of 92% (CI: 75–98%) was reported.

Within group B, 100% of tumors were controlled after repeat resection of the recurrent tumor (5 studies, 26 patients in total). FNF improved or stayed the same in 68.1% of patients (6 studies, 69 patients total). Good FNF was preserved in 56% (CI 41–69%) of patients (eight studies), whereas serviceable FNF was preserved in 72.2% of patients (7 studies). None of the studies within this group reported on hearing preservation.

Heterogeneity assessment

A fixed-effects model was used to assess the weight of the individual studies included in this systematic review in order to investigate the magnitude of any study heterogeneity that may be present [29]. There was no significant study heterogeneity observed in the proportions included in this study, with an I^2 ranging from 0 to 7%, for both the secondary radiosurgery and resection groups respectively. (Figs. 2 and 3).

Publication bias assessment

Semi-logarithmic funnel plots were used to assess publication bias, utilizing deviations of tumor control and preservation of good FNF from a line of fixed effect estimate. Due to inclusion of a greater range of functioning, only a “serviceable” rating on

Table 2 Basic patient characteristics in the secondary microsurgery group

Author and year published	No. of patients	Mean age	Mean tumor volume (cm^3)	Mean follow-up, months
Shelton et al.,1995)	5	32.8	3 cm diameter	33.5
Ramina et al.,(2007)	12	36.5[a]	4.4 cm diameter	69
Roche et al.,(2008)	9	54[a]	–	37
Hong et al.,(2014)	10	34.9	16.4	80
Kunert et al.,(2016)	5	38	4.24*	62
Samii et al.,(2016)	36	45	–	>12
Lee et al.,(2017)	3	46.7	–	>12
Perry et al.,(2017)	4	42.8	3.2	59[a]

[a] Median value

[b] Diameter (cm)

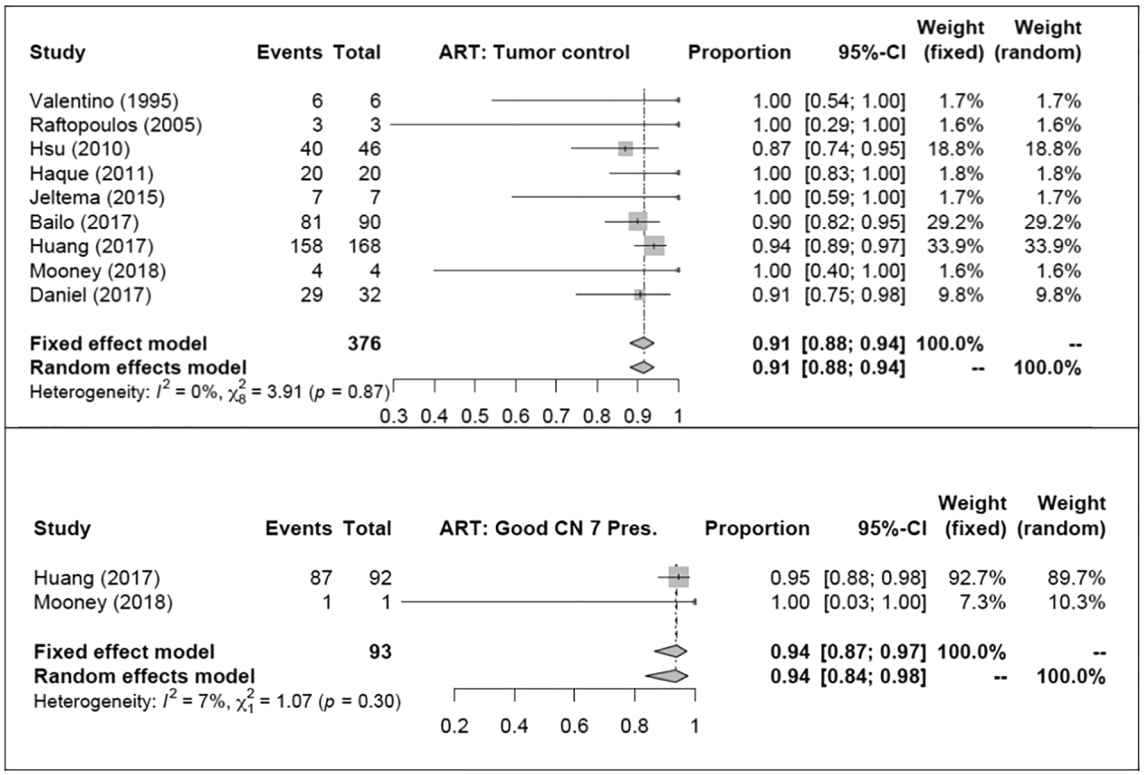

Fig. 2 Forest plot for adjuvant radiosurgery tumor control showing lack of significant heterogeneity

the House-Brackmann scale was used for analysis. Results of the funnel plots were determined by Egger's test. For serviceable hearing, neither the adjuvant radiosurgery group nor the double radiosurgery group showed evidence of publication bias. The same finding held true when the studies were combined ($t(6) = 0.692$, $P = 0.515$) (Fig. S1). Considering the effect of publication bias on tumor control, it was found that the combined adjuvant radiosurgery and double surgery groups did not significantly differ from the tumor control predicted by the fixed-effects estimate ($t(12) = 0.22$, $P = 0.83$) (Fig. S2).

Discussion

The purpose of this study was to analyze secondary radiosurgery or surgical resection for tumor control, facial nerve function preservation, and hearing preservation for recurrent VS. A search of the scientific literature resulted in the selection of 15 studies for inclusion in this systematic review, 7 examining secondary radiosurgery, and 8 examining secondary surgical resection, with a total of 359 patients. One or more studies were omitted when calculating certain statistical values due to lack of data or inability to disaggregate patients with neurofibromatosis type 2. Within these two groups of studies, tests for heterogeneity demonstrated virtually no heterogeneity ($I^2 = 0\%$ for all groups and all P values over 0.05), and tumor control, FNF preservation, and hearing preservation were the primary outcomes examined in this systematic review through means of proportions and confidence intervals.

Tumor control

Tumor control was defined as decreased or unchanged tumor volume following treatment for at least 1 year. Within group A, 94.5% of the tumors were controlled with adjuvant radiosurgery, whereas in group B, 100% of the tumors were controlled with secondary surgical resection. Proportionally, the results between adjuvant radiosurgery and secondary resection were 91% (CI 88–94%) and 92% (CI 75–98%), respectively. This implies that both radiosurgery and surgical resection are viable treatment options for recurrent VS when tumor control is the primary desired outcome.

Hearing preservation

Hearing preservation is assessed according to the Gardner-Robinson classification system, or the equivalent American Academy of Otolaryngology-Head and Neck Surgery system. Serviceable hearing is defined as grades I and II on the Gardner-Robinson classification system, or class A and class B on the AAO-HNS scale. Although one study in group A reported a serviceable hearing preservation rate of 40% after

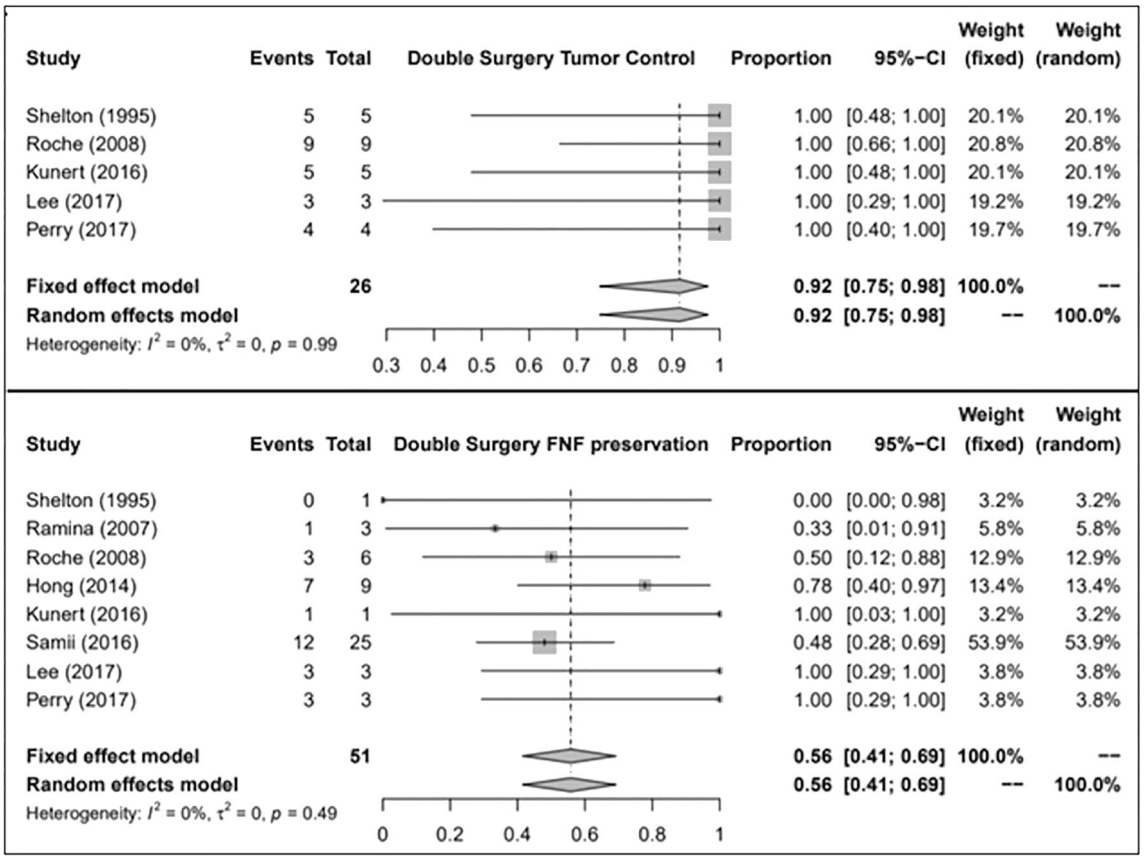

Fig. 3 Forest plots for secondary surgical resection tumor control and facial nerve preservation showing lack of significant heterogeneity in each group of studies

radiosurgery, there was no corresponding data reported in group B in order to determine valid differences. In order to further explore this aspect of treatment outcomes and prognosis, further studies must be performed so that patients and providers can be made aware of which treatment approaches yield the best results for hearing preservation after treatment for recurrent VS.

Facial nerve function preservation

FNF preservation is assessed utilizing the House-Brackmann scale, where grade I represents normal function and grade VI represents complete loss of function. Good FNF is defined as grades I and II on this scale, and serviceable FNF is defined as grades I, II, and III. There was a difference in preservation of good FNF between group A and group B, with adjuvant radiosurgery preserving good facial nerve function better (94%, CI 84–98%) compared to secondary surgical resection (56%, CI 41–69%). Although only two studies from group A was eligible for inclusion in the reporting of preservation of good FNF, patients and providers seeking better preservation of good FNF should consider radiosurgical intervention for treatment of recurrent VS. Further studies should be performed in order to provide additional information on preservation of FNF after secondary radiosurgery for recurrent VS, and future studies comparing radiosurgery and surgical resection for recurrent VS should also examine VS symptoms such as tinnitus, disequilibrium, vertigo, and trigeminal neuropathy in order to determine if one modality is more effective than the other at alleviating these symptoms.

Limitations

One possible limitation of this study could be the search keywords that were used to locate articles in the five databases that were examined. Certain full-text articles may have been missed due to this reason. Secondly, the short observation times noted in some studies can be a factor in the overall tumor control rate reported by this meta-analysis. The tumor control rate could potentially decrease given a longer follow-up time. Another possible limitation is the fact that errors may have been made when disaggregating patients with neurofibromatosis type 2 or patients with residual tumor after primary surgical resection. This would affect the statistical calculations that were performed and negatively affect the accuracy of our results. Lastly, certain statistical calculations involved lower numbers of patients relative to other calculations, due to lack of clarity with reported data or lack of data itself. The lack of

individualized patient data in the literature also limits the strength and results of the statistical analyses performed. For example, there were limited studies commenting on good FNF preservation in the adjuvant radiosurgery group, and the results from this study would be stronger if there were more eligible studies available in the scientific milieu. Heterogeneity and publication bias were addressed through forest plots and funnel plots respectively.

Conclusion

Treatment of recurrent VS typically involves either adjuvant radiosurgery or repeat surgical resection of the recurrent tumor. Our data suggests that there is minimal difference in tumor control between these two treatment modalities. Adjuvant radiosurgery is associated with improved good facial nerve function versus secondary surgical resection. As a result, patients and providers should consider radiosurgery as a treatment modality when treating recurrent VS, due to equivalent tumor control rates and improved preservation of facial nerve function.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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