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CyberKnife for Treatment of Vestibular Schwannoma: A Meta-analysis

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Abstract

Objectives. (1) Perform a meta-analysis of the available data on the outcomes of CyberKnife radiosurgery for treatment of vestibular schwannomas (VSs) in the published English-language literature and (2) evaluate the collective outcomes of CyberKnife treatment with respect to tumor control and hearing preservation.

Data Sources. A thorough literature search of published English-language articles was performed in the PubMed, Ovid, and Cochrane databases.

Review Methods. A database search was conducted with the keywords "CyberKnife" and "vestibular schwannoma" or "acoustic neuroma." A total of 25 papers were found and reviewed. Data were extracted for patient demographics, number of patients with neurofibromatosis type 2, pretreatment hearing status, tumor size, margin dose, and follow-up duration. The primary outcome variables evaluated were tumor control and hearing preservation.

Results. After careful review of the published articles, 11 papers reported data on outcomes of CyberKnife treatment for VS and were included in the analysis, comprising 800 patients studied during 1998 to 2012. The reported mean tumor volume ranged from 0.02 to 19.8 cm³, and the follow-up duration ranged from 6 to 120 months. Margin dose varied from 14 to 25 Gy. The collective mean tumor control rate was 96.3% (95% CI: 94.0%-98.5%). The collective hearing preservation rate was 79.1% (95% CI: 71.0%-87.3%) in 427 patients with measurable hearing.

Conclusion. Clinical data on outcomes of CyberKnife radiosurgery for treatment of VSs are sparse and primarily limited to single-institution analyses, with considerable variation in tumor volume and follow-up time. This meta-analysis not only provides an in-depth analysis of available data in the literature but also reviews reported outcomes and complications.

Keywords

vestibular schwannoma, acoustic neuroma, CyberKnife, radiosurgery, stereotactic surgery, radiation therapy

Radiosurgery was developed in 1952 by the Swedish neurosurgeon Lars Leksell to noninvasively target specific intracranial targets with high doses of precisely localized radiation. The first patient was successfully treated in 1967, and since then, radiosurgery has evolved into a widely used treatment modality.[1] Initially, single fractionation procedures were used to eradicate target tissue while leaving surrounding tissues unharmed, but recent advancements have allowed the delivery of multiple doses of radiation to target tissues with the guidance of a stereotactic frame or mask system.[2]

CyberKnife (Accuray Incorporated, Sunnyvale, California) is a maneuverable robotic radiotherapy unit that delivers stereotactic, hypofractionated radiation without requiring skeletal fixation. It utilizes real-time x-ray image-guidance and dedicated computerized 3-dimensional treatment planning for precise single-session or staged irradiation without a stereotactic head frame.[3,4] The CyberKnife uses a 6-MV linear accelerator mounted to a computerized robotic manipulator with 6 degrees of freedom that offers fractionated irradiation of large and irregularly shaped tumors with respiratory tracking capabilities.[5-7] The Gamma Knife (Elekta, Sweden) and Novalis Tx (BrainLabs, Munich, Germany) are alternative

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radiosurgery units that offer similar capabilities and also use convergent beam techniques. Although each radiosurgery unit has unique advantages, a majority of Gamma Knife units in the world currently lack real-time image verification during treatment, while Novalis Tx offers less dose conformity than CyberKnife.[8]

CyberKnife has been widely used to treat numerous pathologies and widely demonstrated to be an efficacious and safe treatment modality for patients who are candidates for radiosurgery.[9,10] In particular, CyberKnife has been shown to be effective in the treatment of sporadic vestibular schwannomas (VSs) and neurofibromatosis type 2 (NF2), yielding satisfactory growth control and preservation of hearing, facial, and trigeminal nerve function.[11-16] VSs are benign tumors arising from Schwann cells of the vestibulocochlear nerve and constitute 6% of intracranial neoplasms, at an incidence of 9 to 13 per million individuals annually.[17] Neurotologists are increasingly using single- or multisession stereotactic radiosurgery to treat VS, with 37% of VS patients seen by neurotologists receiving either Gamma Knife or CyberKnife therapy with a tumor control rate of 74% to 100%.[18-22] To date, investigations on CyberKnife-based treatments for VS are primarily single-institution studies with relatively small sample sizes. No meta-analysis has been performed exclusively examining VS treatment with CyberKnife, although similar studies have been conducted on Gamma Knife radiosurgery.[23] In this meta-analysis, we aimed to (1) perform a meta-analysis of the available data on the outcomes of CyberKnife radiosurgery for treatment of VSs in the published English-language literature and (2) evaluate the collective outcomes of CyberKnife treatment with respect to tumor control and hearing preservations.

Methods

A thorough literature search of published English-language literature was performed in the PubMed, Ovid, and Cochrane databases with the keywords ''CyberKnife'' and ''vestibular schwannoma'' or ''acoustic neuroma.'' Each manuscript was independently reviewed for relevance by 2 authors. If disagreement occurred for inclusion, the senior author acted as the final arbiter. This study was exempt from Institutional Review Board evaluation, given investigation of published literature and noninvolvement of human subjects. This study was conducted in accordance with the PRISMA guidelines statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[24]

A total of 25 papers were found and reviewed (**Figure 1**). The abstracts were screened, and review articles and studies in languages other than English were excluded. Twenty papers remained, the full text of which was independently assessed by 2 authors. Studies were included in the meta-analysis if the patients had a diagnosis of VS and underwent CyberKnife treatment. Furthermore, studies should have reported data on treatment outcomes. Data were extracted for patient demographics, number of NF2 patients, pretreatment hearing status, tumor size, margin
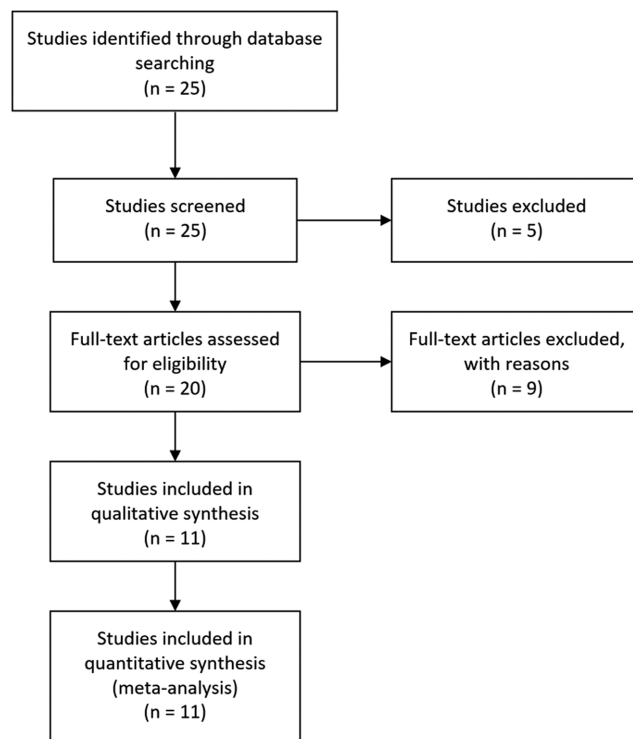

Figure 1. Flow diagram of study selection.

dose, and follow-up duration. The primary outcome variables interrogated were tumor control and hearing preservation. For each study, tumor control was unanimously defined as arrest of tumor growth or decrease in tumor volume, and hearing preservation was defined as preservation of ''useful'' hearing (pure tone average <50 dB and speech discrimination >50%). The Gardner-Robertson classification system was used in 8 studies (73%), which defines serviceable hearing as grade I-II and nonserviceable hearing as grade III-IV. Two studies (18%) implemented the American Academy of Otolaryngology–Head and Neck Surgery hearing classification system (class A-D), in which class A or B constitutes serviceable hearing. One study reported useful hearing to be <50 dB HL.

Complications were also assessed, where available, as secondary outcome variables. Facial nerve neuropathy, trigeminal nerve neuropathy, and cerebellar/brainstem toxicity were reported in the majority of the studies. Statistical analyses were performed with OpenMeta[Analyst] (Brown University, Providence, Rhode Island) via the random effect model. The collective mean and 95% CI were calculated for primary and secondary outcome variables.

Results

After careful review of the published studies, 11 articles were identified to report data on the outcomes of CyberKnife treatment for VS and were included in the analysis, comprising 800 patients studied during 1998 to 2012. A list of the included studies with their sample sizes and patient demographics is presented in **Table 1**. The mean sample size was

Table 1. Details of Published Studies on Outcomes of CyberKnife for Vestibular Schwannomas.

Study	Institution; Study Years	Design; Sample, n	Mean Age, y (Range); Female, %	# of NF2 patients	Number of patients with prior surgical resection and/or radiosurgery (%)	Pretreatment Hearing Levels	Definition of hearing preservation
Ishihara (2004)[14]	Yamaguchi University, Japan; 1998-2002	PRO; 40	53 (13-80); 53	0	11 (27.5) underwent prior microsurgery	14 (I-II) 24 (III-V)	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable
Chang (2005)[20]	Stanford University School of Medicine, US; 1999-2001	PRO; 61	54 (27-59); 51	0	8 (13) underwent prior microsurgery	48 (I-III) 13 (V)	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable
Ju (2008)[15]	National Yang-Ming University, Taiwan; 2005-2007	PRO; 21	54 (27-79); 52	7	1 (4.7%) underwent prior microsurgery	18 (I-IV) 3 (V)	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable
Mahadevan (2011)[25]	Beth Israel Deaconess Medical Center, US; 2005-2010	RET; 10	N/A; N/A	0	0 (0%)	10 (I-III)	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable Preserved objective hearing is I-III
Hansasuta (2011)[22]	Stanford University School of Medicine, US; 1999-2007	PRO; 383	53[a] (11-91); 47	15	41 (11%) underwent prior microsurgery	287 (I-II) 96 (III-V)	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable
Tsai (2013)[26]	National Defense Medical Center, Taiwan; 2006-2012	RET; 117	57.3 (24-90); 51	0	24 (20.5%)	65 (I-II) 52 (III-IV)	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable

(continued)

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Table I. (continued)

Study	Institution; Study Years	Design; Sample, n	Mean Age, y (Range); Female, %	# of NF2 patients	Number of patients with prior surgical resection and/or radiosurgery (%)	Pretreatment Hearing Levels	Definition of hearing preservation
Morimoto (2013)[27]	Osaka University Hospital, Japan; 1998-2011	PRO; 25	59[a] (15-81); 60	5	6 (24%) underwent prior microsurgery	12 had hearing levels < 50 dB	Only reported dB not GR
Karam (2013)[21]	MedStar Georgetown University Hospital, US; 2002-2011	RET; 32	58[a] (31-85); 30	0	0 (0%)	14 (I-II) 5 (III-V) Rest unknown	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable
Lin (2013)[28]	National Taiwan University Hospital, Taiwan; N/A	PRO; 20	56 (29-82); 50	0	0 (0%)	3 (Class A) 7 (Class B) 10 (Class C)	AAO-HNS hearing classification system class A, B, C, or D Class A or B is serviceable
Vivas (2014)[29]	University of Pittsburgh Medical Center, US; 2005-2011	RET; 58	59[a] (23-86); 56	0	10 (17%) subtotal resections	13 (Class A) 15 (Class B) 30 (Class C-D)	AAO-HNS hearing classification system class A, B, C, or D Class A or B is serviceable
Casentini (2015)[30]	S. Bortolo City Hospital, Italy; 2003-2011	PRO; 33	63 (28-85); 55	2	5 (15%) had prior resection or recurrence	8 (II) 25 (III-V)	Gardner-Robertson classification system (GR) I-II is serviceable III-V is nonserviceable

Abbreviations: N/A, not available; NF2, neurofibromatosis type 2; PRO, prospective; RET, retrospective.
[a]Median was reported instead of mean.

73 (range, 10-383); ages ranged from 11 to 91 years; and there were a total of 29 (3.8%) NF2 patients. **Table 1** also presents data on history of prior surgical resection and/or radiosurgery, as well as definition of hearing preservation and pretreatment hearing status.

Table 2 presents the outcomes of the CyberKnife treatment for VS. The reported mean tumor volume ranged from 0.02 to 19.8 cm^3, and the follow-up duration ranged from 6 to 120 months. The number of fractionated sessions ranged from 1 to 5. Tumor growth prior to treatment was not documented in all studies. Additionally, dosing strategies varied for each study. In all studies reviewed, no mention of attrition rate was included. Marginal dose varied from 14 to 25 Gy. The meta-analysis revealed the collective mean tumor control rate to be 96.3% (95% CI: 94.0%-98.5%; **Figure 2**). The collective hearing preservation rate was 79.1% (95% CI: 71.0%-87.3%) in 427 patients with measurable hearing (**Figure 3**). The trigeminal neuropathy rate was 2.0% (95% CI: 0.1%-3.1%); facial neuropathy rate, 2.0% (95% CI: 0.1%-3.0%); and cerebellar/brainstem toxicity rate, 1.8% (95% CI: 0.1%-3.4%).

Discussion

In this study, we analyzed the results of CyberKnife treatment on 800 patients between 1998 and 2012. The ultimate treatment goals for VS include controlling tumor growth and, ideally, shrinking it while preserving functionality of the vestibulocochlear nerve and the surrounding cranial nerves and quality of life. CyberKnife treatment met these standards for treating VS, with good tumor control over a wide range follow-up (range, 6-120 months) and with minimal treatment side effects. Similar results have been reported with Gamma Knife–based stereotactic radiosurgery.[17,31] The radiographic control rate following CyberKnife ranged from 74% to 100% in the included studies in this meta-analysis, with a collective control rate of 96.3% (95% CI: 94.0%-98.5%). Tumor control rates in the literature are generally higher for smaller tumors (Koos grade I) as compared with larger ones (Koos grade ≥2), with hearing preservation rates of 85% and 75%, respectively.[21,22] These correspond well with the 79.1% hearing preservation rate that we found collectively (95% CI: 71.0%-87.3%). A breakdown of the rates according to tumor size was not feasible due to unavailability of the response rates based on tumor size in the included studies. The majority of the studies did not report standard deviation for continuous variables such as age or tumor volume, and a meta-analysis of these variables could not be performed. In addition, some studies included NF2 patients, while others excluded them. VSs associated with NF2 oftentimes invade the cochlear nerve to a greater degree, leading to significant hearing impairment.[12,32] Radiosurgery of NF2 tumors has been associated with a higher likelihood of malignant transformation.[33] Based on the published data, it was not possible to separate these patients from sporadic ones. Therefore, the actual tumor control and preservation rates for sporadic VS might be higher than the rate calculated in this study.

The management of VS has evolved significantly since Harvey Cushing performed a bilateral suboccipital craniectomy with subtotal intracapsular VS resection in 1906.[34] This procedure decreased the mortality from 50% to 10% for VS resection. The introduction of the translabyrinthine approach by House in 1964 and the transmeatal posterior fossa approach by Rand and Kurze in 1965 further optimized the microsurgical management of VS. However, due to microsurgical complication rates, there has been a trend toward stereotactic radiation therapy, which has emerged an effective alternative with reportedly lower complication rates in select patients.[16,35-38] Preservation of hearing and minimizing cranial nerve damage have guided therapeutic options, and radiosurgery is being used more frequently by neurotologists in VS treatment.[18]

Recent studies have shown a trend in management toward observation instead of treatment, especially with smaller tumors.[39] Studies comparing the use of radiosurgery versus watchful observation provide mixed results. In a nationwide series of Danish VS patients who underwent observation, 49% with American Academy of Otolaryngology–Head and Neck Surgery class A or B hearing maintained their serviceable hearing over a mean observation period of 3.9 years.[40] Furthermore, 62.9% of the observed tumors did not require a change in management, as there was no substantial tumor growth. A larger study of the same population showed that 59% of those with serviceable hearing maintained good hearing after 4.7 years.[41] The same group also investigated the natural history of VSs <2 cm and found that only 17% of intrameatal tumors and 28.9% of extrameatal tumors grew. This growth exclusively occurred within 5 years of the diagnosis.[42] Another study showed an overall growth rate of 47% in small tumors conservatively managed.[43] Some have demonstrated a clear disadvantage in choosing observational treatment. Shirato et al found a 2% growth rate after stereotactic radiotherapy versus a 41% growth rate in the observed group.[44] Therefore, the possibility of hearing preservation and tumor growth arrest as a part of the natural disease process needs to be considered when counseling patients regarding treatment options such as CyberKnife.

Fractionation and radiation dosing have unclear influences on tumor control rates, but lower radiation doses have been shown to improve hearing preservation, plausibly due to less damage to the surrounding cochlea and brainstem.[45] Fractionated regimens allow for highly conformal target treatment while mitigating injury to the surrounding structures. In the current meta-analysis, 6 of 11 studies provided the dosing strategy justification (**Table 2**): hearing ability in 3 studies, tumor size in 1 study, pathology in 1 study, and the literature in 1 study. The extent of the available data in the literature limits the possibility of effective comparison among various fractionation regimens, and further investigation and optimization of the protocols are warranted. Proper planning may allow delivery of lower doses to the cochlea when compared with other radiosurgery units.[46] Despite dosimetric variations, facial and trigeminal nerve toxicity

Table 2. Treatment Outcomes of CyberKnife for Vestibular Schwannomas.

Study	n	Tumor Volume, cm³ [a]	Marginal Dose, Gy [a]	Dosing Strategy; Fractionated Sessions	Mean Follow-up (Range), mo	Patients, n (%): Tumor Control	Patients, n (%): Hearing Preservation	Major Complications, n (%)
Ishihara (2004)[14]	40	4.4 (0.5-24) in serviceable hearing group; 8.8 (0.2-41.3) in nonserviceable group	17 (15-20.5) in serviceable hearing group; 16.9 (1.9-20.1) in nonserviceable group	Determined by hearing ability; 1-3	31.9 (12-59)	38 of 40 (95)	14 of 14 (100)	Trigeminal neuropathy, 1 of 40 (3); facial neuropathy, 1 of 40 (3)
Chang (2005)[20]	61	18.5 mm (5-32)[b]	21 for first 14 patients; 18 for remaining 47 patients	Determined from literature; 3	48 (36-62)	60 of 61 (98)	43 of 48 (90)	No trigeminal or facial neuropathy; brainstem of cerebellar edema, 1 of 61 (2)
Ju (2008)[15]	21	5.4 (0.13-24.8)	18 for hearing GR I-IV; 20 for hearing GR V	Determined by hearing ability; 3	15 (6-25)	21 of 21 (100)	13 of 18 (72)	No trigeminal or facial neuropathy; no brainstem of cerebellar edema
Mahadevan (2011)[25]	10	1.9 (0.8-3.2)	25 for all	Determined by pathology; 5	19[c]	10 of 10 (100)	10 of 10 (100)	No trigeminal or facial neuropathy
Hansasuta (2011)[22]	383	1.1[c] (0.02-19.8)	18-21, multisession for GR I-II; 12-15, single session for GR III-V	Determined by hearing ability; 3	43.2 (12-120)	373 of 383 (97)	151 of 200 (76)	Trigeminal neuropathy, 8 of 383 (2.0); facial neuropathy, 8 of 383 (2.0); hydrocephalus, 4 of 383 (1.0)
Tsai (2013)[26]	117	4.7 (0.02-19.8)	N/A	N/A; 3	64.5 (21-89)	116 of 117 (99)	53 of 65 (82)	N/A
Morimoto (2013)[27]	25	2.6 (0.3-15.4)	21 (18-25)	Determined by tumor size; 3-5	80[c] (6-167)	24 of 25 (96)	6 of 12 (50)	No trigeminal neuropathy; facial neuropathy, 2 of 25 (8); hydrocephalus, 1 of 25 (4)
Karam (2013)[21]	32	1.03[c] (0.14-7.6)	21 for 2 patients, 25 for rest	N/A; 5	36[c] (15-108)	29 of 32 (91)	11 of 14 (79)	Trigeminal neuropathy, 2 of 32 (6); facial neuropathy, 2 of 32 (6); ataxia of disequilibrium, 1 of 32 (3)
Lin (2013)[28]	20	1.49[c] (0.17-11.93)	Mean, 18	N/A; 3	24 for all	19 of 20 (95)	5 of 10 (50)	Facial neuropathy, 1 of 20 (5)
Vivas (2014)[29]	58	0.81[c]	18 for all	N/A; 3	40 (6-81)	43 of 58 (74)	15 of 28 (54)	N/A
Casentini (2015)[30]	33	11 (8-24)	18.75-25.78	N/A; 2-5	48[c] (12-111)	31 of 33 (94)	7 of 8 (88)	Trigeminal neuropathy, 2 of 33 (6)

Abbreviations: GR, Gardner-Robertson classification system (I-II, serviceable; III-V, nonserviceable); N/A, not available.
a Mean (range) is reported wherever available.
b Reported as maximal diameter (mm).
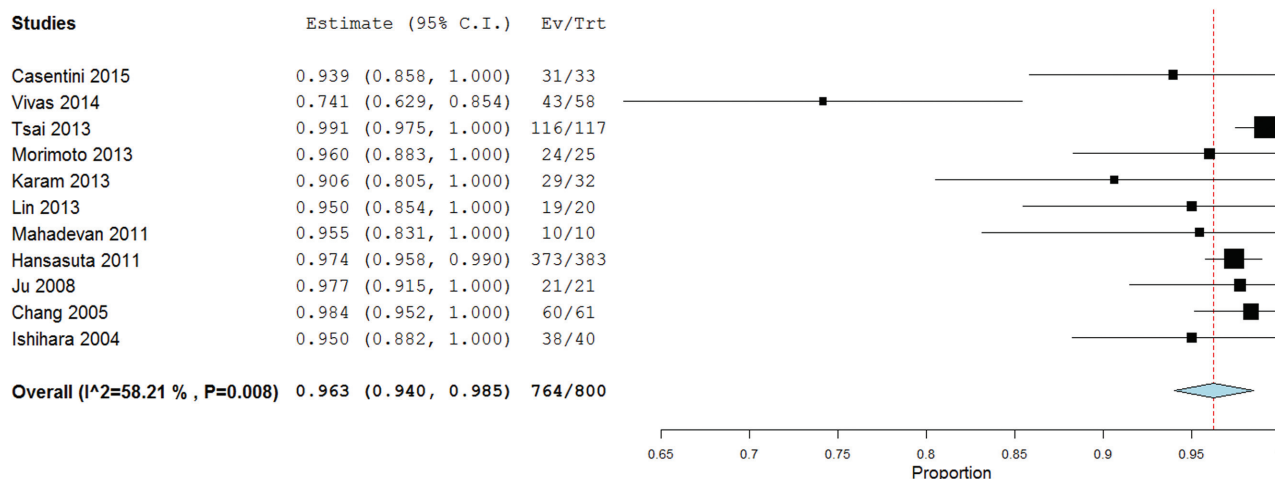c Median is reported instead of mean.

Figure 2. Forest plot demonstrating a 96.3% overall tumor control rate, with each line representing the 95% CI. Each box represents a tumor control rate, with its size correlating to the study's effect size.
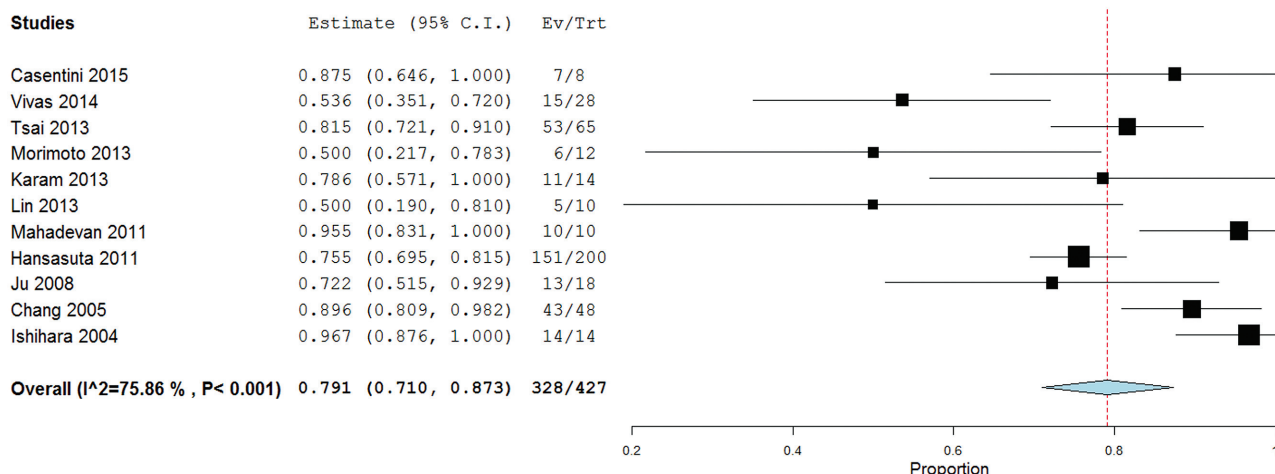

Figure 3. Forest plot demonstrating a 79.1% overall hearing preservation rate, with each line representing the 95% CI. Each box represents a hearing preservation rate, with its size correlating to the study's effect size.

following CyberKnife can range from 0% to 8% and 6%, respectively, while permanent or transient facial nerve paralysis was reported to range from 0%-5% to 1%-10% after Gamma Knife radiosurgery.[17,47] A supplementary measure of treatment effectiveness is self-reported and objective quality-of-life measurements in patients who have undergone various therapies.[48] The Penn Acoustic Neuroma Quality of Life scale, developed at the University of Pennsylvania, is a validated quality-of-life measure specific to VS that can be employed to quantify subjective treatment outcomes and augment therapeutic decision making.[49]

There were a number of limitations in this study. The heterogeneous methodology of the published papers in reporting their outcomes limited the ability to perform meta-analysis on all variables. Despite this heterogeneity, each study's methodology was evaluated to determine if differences exist. Classification of inclusion criteria,

dosing strategy, and number of fractionation sessions did not better characterize the population that benefits most form Cyberknife. Several studies had low sample sizes, and breakdown of data per patient type was not available. This meta-analysis can lay a foundation for future studies to recruit more patients and evaluate differences in response rate with respect to patient demographics and disease characteristics. In addition, all evaluated studies were case series that did not have control groups. This is an inherent limitation that constrains the conclusions that can be drawn regarding Cyberknife treatment. Nonetheless, analysis of the available data in the literature on CyberKnife treatment of VS undoubtedly supports the efficacy of this radiosurgical modality and offers patients clinically significant tumor control while maximizing hearing preservation. This study is the first to perform a meta-analysis of CyberKnife treatment outcomes for VS.

Conclusion

CyberKnife has been widely used to treat numerous pathologies and has been demonstrated to be an efficacious and safe treatment modality. This meta-analysis presents the results of CyberKnife treatment of VS on 800 patients between 1998 and 2012. CyberKnife treatment was reported to be effective in controlling VS growth and preserving functionality of the vestibulocochlear nerve and surrounding cranial nerves, with minimal treatment side effects.

Author Contributions

Hossein Mahboubi, designing, analysis and interpretation of data, drafting the article and final approval of the version to be published; **Ronald Sahyouni**, designing, acquisition of data, drafting the article, and final approval of the version to be published; **Omid Moshtaghi**, designing, analysis and interpretation of data, drafting the article and final approval of the version to be published; **Kent Tadokoro**, designing, acquisition of data, drafting the article, and final approval of the version to be published; **Yaser Ghavami**, analysis and interpretation of data, drafting the article and final approval of the version to be published; **Kasra Ziai**, analysis and interpretation of data, drafting the article and final approval of the version to be published; **Harrison W. Lin**, analysis and interpretation of data, drafting the article and final approval of the version to be published; **Hamid R. Djalilian**, designing, analysis and interpretation of data, drafting the article and final approval of the version to be published.

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