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TOPIC REVIEW

Facial nerve preservation after vestibular schwannoma Gamma Knife radiosurgery

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Abstract *Objective* Facial nerve preservation is a critical measure of clinical outcome after vestibular schwannoma treatment. Gamma Knife radiosurgery has evolved into a practical treatment modality for vestibular schwannoma patients, with several reported series from a variety of centers. In this study, we report the results of an objective analysis of reported facial nerve outcomes after the treatment of vestibular schwannomas with Gamma Knife radiosurgery. *Materials and methods* A Boolean Pub Med search of the English language literature revealed a total of 23 published studies reporting assessable and quantifiable outcome data regarding facial nerve function in 2,204 patients who were treated with Gamma Knife radiosurgery for vestibular schwannoma. Inclusion criteria for articles were: (1) Facial nerve preservation rates were reported specifically for vestibular schwannoma, (2) Facial nerve functional outcome was reported using the House–Brackmann classification (HBC) for facial nerve function, (3) Tumor size was documented, and (4) Gamma Knife radiosurgery was the only radiosurgical modality used in the report. The data were then aggregated and analyzed based on radiation doses delivered, tumor volume, and patient age. *Results* An overall facial nerve preservation rate of 96.2% was found after Gamma Knife radiosurgery for vestibular schwannoma in our analysis. Patients receiving less than or equal to 13 Gy of radiation at the marginal dose had a better facial nerve preservation rate than those who received higher doses ($\leq$13 Gy = 98.5% vs. >13 Gy = 94.7%, $P < 0.0001$). Patients with a tumor volume less than or equal to 1.5 cm^3 also had a greater facial nerve preservation rate than patients with tumors greater than 1.5 cm^3 ($\leq$1.5 cm^3 99.5% vs. >1.5 cm^3 95.5%, $P < 0.0001$). Superior facial nerve preservation was also noted in patients younger than or equal to 60 years of age (96.8 vs. 89.4%, $P < 0.0001$). The average reported follow up duration in this systematic review was 54.1 $\pm$ 31.3 months. *Conclusion* Our analysis of case series data aggregated from multiple centers suggests that a facial nerve preservation rate of 96.2% can be expected after Gamma knife radiosurgery for vestibular schwannoma. Younger patients with smaller tumors less than 1.5 cm^3 and treated with lower doses of radiation less than 13 Gy will likely have better facial nerve preservation rates after Gamma Knife radiosurgery for vestibular schwannoma.

Keywords Stereotactic radiosurgery · Vestibular schwannoma · Facial nerve preservation · Gamma knife · Acoustic neuroma

Introduction

Gamma Knife radiosurgery (GKRS) has evolved into a practical alternative treatment to open microsurgical resection of vestibular schwannoma (VS) [1–30]. GKRS as a treatment modality for VS typically does not require inpatient hospitalization, however acute and chronic complications can occur [31–33]. In particular, radiation toxicity of neuro-anatomic structures adjacent to the tumor may develop and manifest as impaired function of the

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facial nerve, hearing loss, or loss of equilibrium and balance. [14, 16, 17, 23, 27, 30, 34–41]. Hydrocephalus, cerebral edema, and other cranial neuropathies have also been documented after GKRS, and in some reported cases required shunting as a treatment for hydrocephalus [4, 23, 37, 42–49].

Despite the available data on facial nerve outcome in VS patients treated with GKRS, there is no consensus as to what reported clinical parameters relate to facial nerve function. Most reported studies to date have been small to modest in size, frequently from a single institution, and lacking the statistical power and freedom from potential practitioner bias to draw concrete conclusions. Our review of the literature revealed widely varying results with reported facial nerve preservation between 55 and 100% after GKRS for VS (Table 1). Due to these factors and the multitude of methods to assess facial nerve preservation in the reported literature, facial nerve preservation after GKRS has not yet been fully characterized.

Several potential factors affecting facial nerve preservation after GKRS have been suggested, including the dose of radiation delivered, tumor volume, and patient age. In this study, we performed an extensive review of the English Language literature to objectively analyze and methodically evaluate facial nerve outcomes of patients with VS treated with GKRS. The primary aims were to provide an objective summary of the published literature on facial nerve preservation and to evaluate specific prognostic factors that may influence facial nerve preservation after GKRS for VS.

Methodology

Article selection

Articles were identified via Boolean PubMed searches using key words "Gamma knife," "radiosurgery," "acoustic neuroma," "facial nerve," "vestibular schwannoma," and "facial nerve preservation," alone and in combination. This query identified 23 papers describing over 2,204 patients from which all quantifiable and assessable data regarding patients treated with radiosurgery were analyzed. Articles published up to and including the year 2007 were included in this analysis. Inclusion criteria for articles were: (1) Facial nerve preservation rates were reported specifically for VS before and after GKRS, (2) Facial nerve outcome was reported using the House–Brackmann classification (HBC) for facial nerve function [5, 50–54], (3) Tumor size was documented, and (4) GKRS was the only radiation modality used to treat the tumor. The data were then aggregated and analyzed based on radiosurgery dose delivered, size of the tumor, and patient age.

Data extraction

Data from individual and aggregated cases were extracted from each paper. Cases with pre-operative facial dysfunction (HBC 3 or higher) were excluded. All recent cases of open microsurgery and radiotherapy other than GKRS were also excluded. "Facial nerve preservation" was defined as having a grade I or II HBC at the last reported follow-up visit. Overall average for facial preservation, patient age, and radiation dose were weighted accordingly to their sample size, so that larger and smaller series had an appropriate impact on the overall data. Data were analyzed as a whole and stratified into three groups. (1) Radiosurgery marginal dose $\leq$13 versus >13 Gy, (2) Tumor size $\leq$1.5 versus >1.5 cm^3, and (3) Age $\leq$60 versus >60 years old.

Statistical analysis

The raw data were tabulated using Microsoft Excel (Microsoft Corp., Seattle, WA). All results were analyzed using a Fisher's exact test or a *t*-test when appropriate for statistical evaluation of the data. For these statistical investigations, tests for significance were two sided, with a (two tailed) *P*-value threshold of 0.05 considered statistically significant. Unless otherwise stated, all continuous values presented were mean $\pm$ standard deviation or standard error of measurement when appropriate.

Results

Results of comprehensive analysis

A total of 23 articles involving 2,204 patients with 1,908 patients meeting our inclusion criteria, were evaluated [1, 2, 11–13, 16, 17, 26, 41, 43, 44, 55–77] (Table 1). The overall facial nerve functional preservation rate in patients with VS treated with GKRS reported in the included studies was 96.2%. The mean of the reported average age of the patients in this analysis was 55.3 years ($\pm$10.8; SEM $\pm$ 2.3) with an average of reported length of follow up duration of 54.1 months ($\pm$31.4 months). Median length of follow up time in this analysis was 43.0 months. In this systematic analysis, the average of the published radiation doses used to treat these patients was 13.1 $\pm$2 Gy (SEM $\pm$ 0.4).

The effect of radiation dose on facial nerve preservation

A total of 1,038 reported patients were treated using an average marginal dose of $\leq$13 Gy, and 801 patients treated with an average marginal dose of >13 Gy. In this comparison, the group treated with lower dose radiosurgery (less than or equal to 13 Gy) had superior facial nerve preservation

Table 1 Data summary from papers listed by Pub Med ID and institution

PubMed ID		Total sample	CN VII intact	Avg age	Avg dose (Gy)	Avg tumor volume (cm^3)	Tumor ctrl rate (%)	Avg follow up (mo.)	CN VII preservation (%)
17379451	University of Pittsburgh	216	215	56.5	13.0	1.300	98.30	68.4	100.0
16741754	Ludwig Maximilians University	123	121	59	13.0	1.600	96.70	98.4	100.0
16094154	Komaki City Hospital	317	291	54	13.2	5.600	92.00	93.6	96.4
15854240	Haukeland University Hospital, Norway	103	102	59.7	12.2		89.20	70.8	94.8
15662791	Inst of Neural Org, Japan	18	9	–	–	15.200	93.33	72.0	100.0
15662787	Taipei Veterans Gen Hosp and Natl Yang Ming University	195	135	51	13.0	4.100	95.00	36.0	100.0
15354007	Medical College of Wisconsin	29	25	–	13.5		96.55	–	100.0
15337560	University of Pittsburgh	313	313	56	13.0	1.100	98.60	24.0	100.0
14617712	Royal Hallamshire Hospital, UK	232	179	56	14.6	3.350	92.00	35.0	99.1
14609174	Gunma Univ Sch of Med, Japan	1	1	63	12.0	0.520	0.00	27.0	0.0
14571654	Hospital Academique Erasme, Belgium	48	42	54.8	12.3	1.440	97.92	12.0	97.9
14519213	University of Pittsburgh	157	124	60	16.7	–	96.90	109.2	95.0
12520350	Addenbrooke's Hospital, England	5	5	29	–	–	0.00	–	80.0
12459364	Baylor memorial Hermann Hospital	72	58	61.6	14.5		91.00	48.0	97.4
12379008	Karl-Franzens University, Graz, Austria	60	52	58	13.0	3.400	96.00	76.0	85.0
11483338	Thomas Jefferson Univ Hosp, PA	69	57	61	12.0	2.920	98.00	119.0	98.0
11143268	University of Tokyo	1	1	25	14.0	0.180	100.00	60.0	100.0
10821551	Northwestern Hospital	9	9	39	19.6		74.00	–	55.6
10030254	Mayo Clinic and Mayo Foundation [reduced protocol]	40	33	65	16.0	3.700	97.44	27.6	92.0
10030254	Mayo Clinic and Mayo Foundation [standard protocol]	42	35	63	–	3.000	97.44	27.6	62.0
9833820	Mayo Clinic/University of Pittsburgh	76	35	58	15.0	2.800	94.00	43.0	83.0
9392535	University of Tokyo	46	46	54	16.8	–	96.00	39.0	80.0
8588625	House Ear Clinic and House Ear Institute	1	1	39	–	–	0.00	24.0	100.0
7826279	University of Pittsburgh	31	19	55	–	0.600	90.00	26.0	95.0
Totals and Avg		2,204	1,908	55.3	13.1	3.2	82.5	54.1	96.2

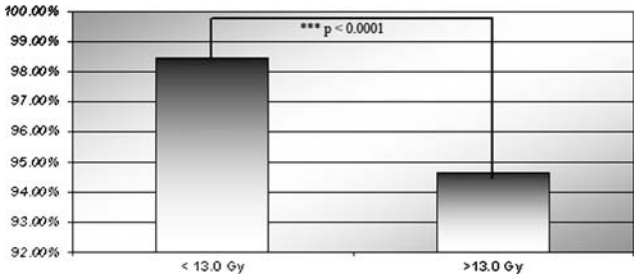

Fig. 1 Facial nerve preservation analyzed by radiation dose of radiosurgery (*P* value indicated)

rates [≤13 Gy = 98.5% vs. >13 Gy = 94.7%, $P < 0.0001$ (Fig. 1)]. Improved facial nerve preservation with low dose Gamma Knife radiosurgery suggests that radiation dose is a significant prognostic factor for facial nerve preservation with Gamma Knife radiosurgery. Patients with improved facial nerve preservation with low dose GKRS maintained good tumor control rates of 96.7%.

The effect of volume on facial nerve preservation

A total of 591 reported patients in our analysis had an average tumor volume of 1.5 cm^3 or less, and 947 patients

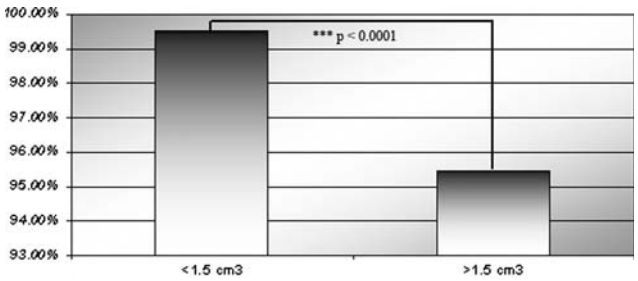

Fig. 2 Facial nerve preservation analyzed by tumor volume stratified by tumors larger and smaller then 1.5 cm^3 (*P* value indicated)

had an average tumor volume of >1.5 cm^3. The patients with the smaller tumors (measuring 1.5 cm^3 or less) had superior facial nerve preservation rates than those with larger tumors [≤1.5 cm^3 99.5% vs. >1.5 cm^3 95.5%, $P < 0.0001$ (Fig. 2)]. Smaller tumors were significantly associated with better facial nerve preservation after treatment with GKRS. The mean of the reported average radiation dose for smaller tumors was 12.9 ± 0.8 Gy which was less than the 13.7 ± 1.3 Gy that larger (>1.5 cm^3) tumors received on average ($P < 0.0001$).

The effect of age on facial nerve preservation

A total of 1,690 patients were reported to have an average age equal to or younger than 60 years, and 184 patients were reported to be older than 60 years on average at the time of Gamma Knife radiosurgery. Facial nerve preservation was noted to be worse in patients older than 60 years of age [≤60 years = 96.8% vs. >60 years = 89.4%, $P < 0.0001$ (Fig. 3)]. Younger and older patients had similar tumor sizes (2.31 vs. 2.54 cm^3) indicating that younger patient had improved facial nerve preservation despite tumor size. Furthermore older patients (>57 years old), treated with higher levels of radiation (>13 Gy) had significantly worse facial nerve outcomes than younger patient (<57 years old) treated with similarly higher radiation doses of greater than 13 Gy ($P < 0.0010$). Younger age may be an important prognostic factor for improved facial nerve preservations with GKRS for VS.

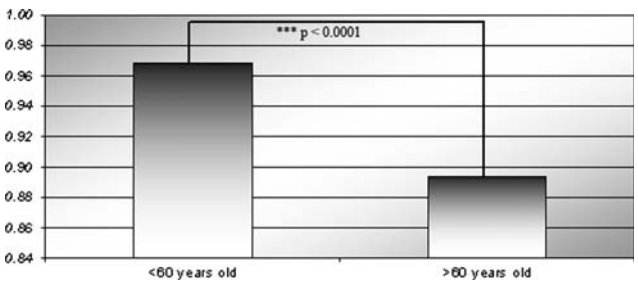

Fig. 3 Facial nerve preservation analyzed as a function of age with an age cut off of older or younger than 60 years old (*P* value indicated)

Discussion

Facial nerve preservation continues to be a primary concern of patients undergoing Gamma Knife radiosurgery for vestibular schwannomas. Despite the currently available data there have been few efforts to combine this research into accurate estimates of facial nerve preservation with GKRS for VS. In this study we performed a comprehensive analysis of facial nerve functional preservation in a large aggregated population of patients who underwent GKRS for vestibular schwannomas.

Our methodical analysis revealed that patients treated with a marginal dose of less than 13 Gy were more likely to preserve facial nerve function after GKRS treatment than studies that delivered higher doses of radiation. Higher doses of radiation are associated with higher rates of cranial nerve toxicity [67, 78–81]. One possible reason for this is the significant amount of fibrosis within and around the vestibular schwannoma, involving the adjacent cochlear and facial nerves. This finding has been noted in surgical salvage after failed irradiation [82, 83]. Several recent studies have demonstrated that low dose radiosurgery has a favorable efficacy/toxicity ratio as compared to higher doses [4, 23, 40, 44, 48, 57, 61, 84]. In our analysis patients treated with lower dose Gamma Knife radiosurgery (<13 Gy) had superior facial nerve preservation rates [<13 Gy = 98.5% vs. > 13 Gy = 94.7%, $P < 0.0001$ (Fig. 1)] with good tumor control rates of 96.7% at a reported average length of follow up duration of 54.1 months (Median 43.0 months).

In our objective analysis, patients with an average tumor volume of 1.5 cm^3 or less had a better facial nerve preservation rate compared to studies with tumors of larger volumes [<1.5 cm^3 99.5% vs. >1.5 cm^3 95.5%, $P < 0.0001$ (Fig. 2)]. Smaller tumors had improved facial preservation rates and lower average radiation doses for smaller tumors (12.9 ± 0.8 Gy vs. 13.7 ± 1.3 Gy, $P < 0.0001$). This data suggests that both smaller tumor size and lower radiosurgery dose are important risk factors for facial nerve preservation with Gamma knife radiosurgery treatment. Although it appears that radiation dose is an important associated factor with facial nerve preservation, our data does not permit the discrimination between size or radiation dose as the more significant parameter for facial nerve preservation as both smaller tumors and lower radiation doses both had improved outcomes. Our data does not clarify this ambiguity about whether size or radiation dose has a more significant impact on facial nerve preservation.

Older patients commonly have medically related comorbidities which can preclude them from open brain surgery. Our analysis indicates that older patients with age >60 years had inferior facial nerve preservation rates than younger patients [<60 years = 96.8% vs. >60 years = 89.4%, $P < 0.0001$ (Fig. 3)]. Age may be an important

prognostic factor for facial nerve preservation despite tumor size or radiation dose. Older patients had similar tumor sizes as younger patients (2.31 vs. 2.54 cm^3). Advanced age does appear to be a negative prognostic factor in facial nerve preservation outcomes in patients treated with GKRS for VS. Furthermore older patients (>57 years old), treated with high levels of radiation (>13 Gy) had significantly worse facial nerve outcomes than younger patient (<57 years old) treated with similarly high radiation doses of greater than 13 Gy ($P < 0.0010$). Our data suggests that older age may be significantly associated with worse facial nerve preservation independent of radiation dose because older patients did worse with high radiation doses than their younger counterparts who also received high radiation doses (>13 Gy).

The various methods of data presentation reported in the papers for our systematic analysis precluded us from further investigation to stratify other statistically significant data points. Unfortunately actuarial time dependant data was not possible in our retrospective, systematic analysis as this is an inherent limitation in the methodology of our study. Similarly, multi-variable analysis and a logistic regression analysis are also problematic across multiple studies which adhere to differing formats of data presentation.

Prospective studies could further elucidate the actuarial nature of facial nerve preservation over time after GKRS and may also provide further insight into the exact relationship between the prognostic variables we investigated here and facial nerve preservation. Our systematic analysis is the first reported attempt to comprehensively evaluate the overall impact of GKRS for VS on facial nerve function as described in the published literature.

There are some inherent limitations with systematic reviews and analysis [85]. One obvious limitation is that any aggregation of data is only as good as its composite studies. The quality of the data reported in the literature, the effect of failure to detect, or unwillingness to report complications, and other such omissions would inevitably change and skew the result reported in our aggregated analysis. Furthermore, small sample size reports that met our inclusion criteria were also included in our analysis. Although their contribution is small, we mitigated the effect of case reports and small samples by analyzing an aggregated database and by weighting the appropriate contribution of each paper by the number of patients with facial nerve intact before GKRS accordingly. Hence in our analysis, smaller sample sizes and case reports had a proportionate effect on our overall aggregated facial nerve preservation data. However, the large nature of our systematic review minimizes the biases and dilutes the inherent error of any individual study in our comprehensive report and also has the advantage of expansive results from multiple international centers.

In conclusion, we report the results from a large aggregated analysis of facial nerve outcomes in patients with vestibular schwannoma treated specifically with Gamma Knife radiosurgery. Utilizing this systematic data set from the available published literature, minimizes the effect of bias and dilutes the inherent error from individual institutions, increases the statistical power of our analysis, and aggregates expansive results to determine an accurate and overall facial nerve preservation for patients treated with Gamma Knife radiosurgery for vestibular schwannomas. This systematic analysis suggests that radiation dose is an important and critical prognostic factor for facial nerve outcomes in VS patients treated with GKRS. Our data also confirms that patients treated with 13 Gy or less of radiation, with tumors less than 1.5 cm^3 in size, and younger patients have improved facial nerve outcomes.

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